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A Glimpse of Ocean of Abundant Discoveries: Two-Way Cross Family Analysis of In-Silico Ranked 2nd Order Unexplored, ETC-1922159 Affected, Synergistic Combinations in CRC Cells

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Abstract: Often, in biology, we are faced with the problem of exploring relevant unknown biological hypotheses in the form of myriads of combination of factors that might be affecting the pathway under certain conditions. For example, Brancati *et al.* [1] observe that mutations in poliovirus receptor related protein 4 (PVRL4), encoding cell adhesion molecule nectin-4, causes Ectodermal dysplasia-syndactyly syndrome. Interaction with cad-herins also implies an influence of nectin-4 on Wnt signaling, which plays a relevant role in limb development (Brancati *et al.* [1]). However, not much work has been done to explore the relation of Wnts and PVR family. In CRC cells treated with ETC-1922159, both were found up regulated. In a recent unpublished work in Open Science Framework, Sinha [2], we had the opportunity to rank these unknown biological hypotheses for both up and down regulated genes at 2nd order level after drug administration. The search engine alloted high nu-merical valued rankings to some combinations of PVR-WNT, thus indicating a possibility of high combinatorial synergy also. The in-silico derived influences can be represented graphically as - • PVR w.r.t WNT with PVR <- WNT9A; and • WNT w.r.t PVR with WNT-7B/9A <- PVR and WNT4 <- PVRL2; In the light of the recent findings of PVR with IFN (interferon) and the known interactions between IFN and Wnts, there might be a possibilty to explore the bridge of PVR, IFN and WNTs. The 3 fold (PVR - IFN; IFN - WNT; WNT - PVR), 2 way cross family analysis might shed light on the possible combinations that might be of import. Here, we present a 2-way cross family analysis of multiple, such in-silico ranked 2^{nd} order synergistic combinations, after ETC-1922159 treatment of CRC cells. Via this 2-way cross family analysis, we are able to discover through majority voting, the combinations that might of interest to biologists and also derive plausible influences of components of combinations among themselves. Note that these form biological hypotheses which indicate whether a particular combination and the direction of influence within the combination, exist synergistically in CRC cells. Wet lab tests will indicate the veracity of these combinations and if proven true, will lead to further study of mechanism between the components. KEYWORDS - WNT, NF-κB, Ion Channels, Anthrax toxin recep-tors, Poliovirus receptors ,Porcupine inhibitor ETC-1922159, Sensitivity analysis, Colorectal cancer, Unknown biological hypotheses, Combinatorial search space, Support vector ranking

Key words: WNT; NF-κB, Ion Channels; Anthrax toxin recep- tors; Poliovirus receptors; Porcupine inhibitor ETC-1922159; Sensitivity analysis; Colorectal cancer; Unknown biological hypotheses; Combinatorial search space; Support vector ranking

Contents

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1 Introduction

We reproduce a part of the manuscript Sinha[3] before we delve into the details of the current work. In Sinha[2], a frame work of a search engine is developed which can rank combinations of factors in a signaling pathway. Such combinations are of import due to the vast search space in which they exist and the difficulty to find them. The search engine facilitates in prioritizing the combinations as ranked biological hypotheses which the biologists might want to test in wet lab, to know if a synergistic combination is prevalent in a signaling pathway, in a (in)direct manner. Interested readers are advised to go through Sinha[2] for details regarding the search engine and the discoveries mentioned in there.

We present a 2-way cross family analysis of multiple, such in-silico ranked 2^{nd} order synergistic combinations, after ETC-1922159 treatment of CRC cells. Via this 2-way cross family analysis, we are able to discover through majority voting, the combinations that might of interest to biologists and also derive plausible influences of components of combinations among themselves. Note that these form biological hypotheses which indicate whether a particular combination and the direction of influence within the combination, exist synergistically in CRC cells. Wet lab tests will indicate the veracity of these combinations and if proven true, will lead to further study of mechanism between the components.

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1.1 PORCN-WNT inhibitors

The regulation of the Wnt pathway is dependent on the production and secretion of the WNT proteins. Thus, the inhibition of a causal factor like PORCN which contributes to the WNT secretion has been proposed to be a way to interfere with the Wnt cascade, which might result in the growth of tumor. Several groups have been engaged in such studies and known PORCN-WNT inhibitors that have been made available till now are IWP-L6 Chen *et al.*[4] & Wang *et al.*[5], C59 Proffitt *et al.*[6], LGK974 Liu *et al.*[7] and ETC-1922159 Duraiswamy *et al.*[8]. In this study, the focus of the attention is on the implications of the ETC-1922159, after the drug has been administered. The drug is a enantiomer with a nanomolar activity and excellent bioavailability as claimed in Duraiswamy *et al.*[8].

1.2 Combinatorial search problem and a possible solution

We have already addressed the issue of combinatorial search problem and a possible solution in Sinha[9] and Sinha[3]. The details of the methodology of this manuscript have been explained in great detail in Sinha[9] & its application in Sinha[3] and the walk-through of the code has been made available in Sinha[2]. Readers are requested to go through the same for gaining deeper insight into the working of the pipeline and its use of published data set generated after administration of ETC-1922159. In order to understand the significance of the solution proposed to the problem of combinatorial search that the biologists face in revealing unknown biological search problem, these works are of importance. Using the same code Sinha[2], with minor modifications in Sinha[9] and Sinha[3], it was possible to generate the rankings for 3^{rd} order combinations also. 100 genes were randomly selected from the list of down regulated genes, by the pipeline and a 3^{rd} order combination was generated from those 100 genes. The total number of gene combination with $C_3^{100} = 161700$. Out of these the WNT10B associated 3^{rd} order combinations were selected, which account to a total of 4851 combinations.

1.3 Wnt signaling and secretion

Sharma[10]'s accidental discovery of the Wingless played a pioneering role in the emergence of a widely expanding research field of the Wnt signaling pathway. A majority of the work has focused on issues related to • the discovery of genetic and epigenetic factors affecting the pathway Thorstensen *et al.*[11] & Baron and Kneissel[12], • implications of mutations in the pathway and its dominant role on cancer and other diseases Clevers[13], • investigation into the pathway's contribution towards embryo development Sokol[14], homeostasis Pinto *et al.*[15] & Zhong *et al.*[16] and apoptosis Pećina-Šlaus[17] and • safety and feasibility of drug design for the Wnt pathway Kahn[18], Garber[19], Voronkov and Krauss[20], Blagodatski *et al.*[21] & Curtin and Lorenzi[22].

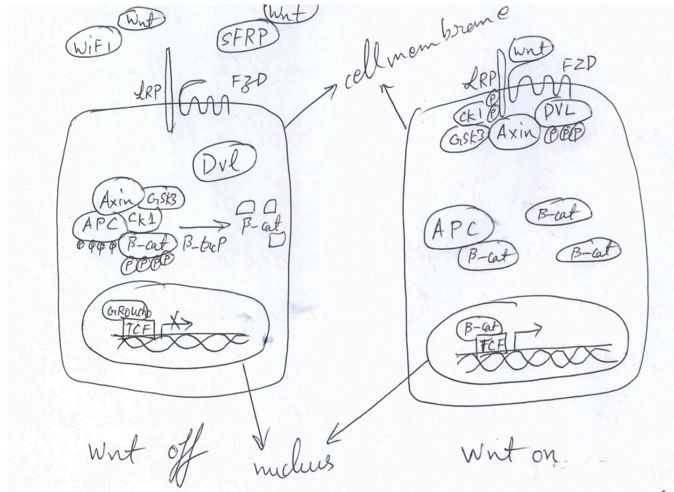

Fig. 1 Cartoon of Wnt Signaling from Sinha[3].

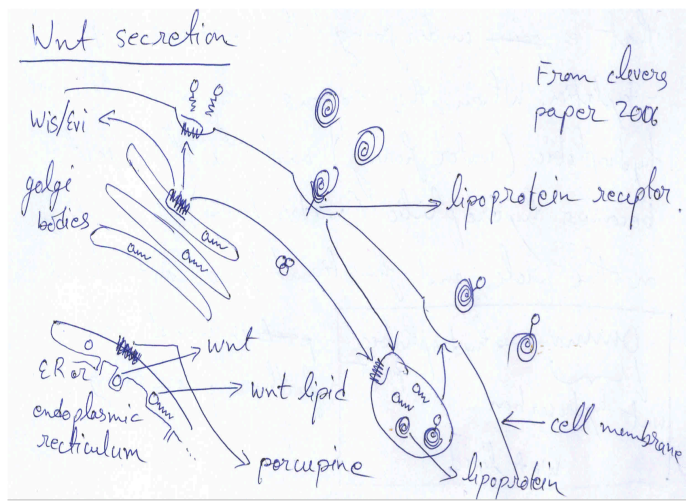

Fig. 2 Cartoon of Wnt Secretion from Sinha[3].

The Wnt phenomena can be roughly segregated into signaling and secretion part. The Wnt signaling pathway works when the WNT ligand gets attached to the Frizzled(FZD)/LRP coreceptor complex. FZD may interact with the Dishevelled (DVL) causing phosphorylation. It is also thought that Wnts cause phosphorylation of the LRP via casein kinase 1 (CK1) and kinase GSK3. These developments further lead to attraction of Axin which causes inhibition of the formation of the degradation complex. The degradation complex constitutes of AXIN, the β-catenin transportation complex APC, CK1 and GSK3. When the pathway is active the dissolution of the degradation complex leads to stabilization in the concentration of β-catenin in the cytoplasm. As β-catenin enters into the nucleus it displaces the GROUCHO and binds with transcription cell factor TCF thus instigating transcription of Wnt target genes. GROUCHO acts as lock on TCF and prevents the transcription of target genes which may induce cancer. In cases when the Wnt ligands are not captured by the coreceptor at the cell membrane, AXIN helps in formation of the degradation complex. The degradation complex phosphorylates β-catenin which is then recognised by F BOX/WD repeat protein β-TRCP. β-TRCP is a component of ubiquitin ligase complex that helps in ubiquitination of β-catenin thus marking it for degradation via the proteasome. A cartoon of the signaling transduction snapshot is shown in figure 1.

Contrary to the signaling phenomena, the secretion phenomena is about the release and transportation of the WNT protein/ligand in and out of the cell, respectively. Briefly, the WNT proteins that are synthesized with the endoplasmic reticulum (ER), are known to be palmitoyleated via the Porcupine (PORCN) to form the WNT ligand, which is then ready for transportation Tanaka *et al.*[23]. It is believed that these ligands are then transported via the EVI/WNTLESS transmembrane complex out of the cell Bänziger *et al.*[24] & Bartscherer *et al.*[25]. The EVI/WNTLESS themselves are known to reside in the Golgi bodies and interaction with the WNT ligands for the later's glycosylation Kurayoshi *et al.*[26] & Gao and Hannoush[27]. Once outside the cell, the WNTs then interact with the cell receptors, as explained in the foregoing paragraph, to induce the Wnt signaling. Of importance is the fact that the EVI/WNTLESS also need a transporter in the from of a complex termed as Retromer. A cartoon of the signaling transduction snapshot is shown in figure 2.

2 Results & discussion

2.1 WNT related synergies

2.1.1 WNT10B-ASCL2

WNT10B has been found to be implicated in a range of cancers. In gastric cancer, the knockdown of WNT10B showed reduced expression of cell proliferation and migration as well as inhibition of epithelial-mesenchymal transition Wu *et al.*[28]. On the other hand, WNT10B is also involved in the formation of bone mass and progenitor maintenance of various kinds of tissue, while deletion of the same leads to loss of bone mass and mesenchymal progenitor cells Stevens *et al.*[29]. Their contribution is also reported in axonal regeneration in injured CNS Tassew *et al.*[30]. Furthermore, like WNT10B, WNT10A and WNT6 have shown to play a major role in inhibiting adipogenesis and stimulates osteoblastogenesis while regulating the mesenchymal stem cells Cawthorn *et al.*[31] & Collins *et al.*[32]. Involvement in heptocellular carcinoma of WNT10B has been found wherein it is shown that stable silencing of WNT10B leads to significant reduction in proliferation, colony formation, migration and invasion in HepG2 HCC cell line Wu *et al.*[33]. Its implication in breast cancer Wend *et al.*[34] & Chen *et al.*[35] as well as endometrial cancer Chen *et al.*[36] has also been reported.

In colorectal cancer, WNT10B has shown to play a dual function of both oncogenesis promotion via β-catenin/TCF pathway and the inhibition of cell growth, possibly via FGF family of proteins Yoshikawa *et al.*[37]. Methylation of WNT10B has been found in the some of the cancer cell lines while its reversal has lead to over-expression of the WNT10B. However, the over-expression of WNT10B has lead to reduced cell growth in cancer, indicating a β-catenin independent component to be behind such a phenomena. Methylation of over-expressed WNT10B and synergistic work with FGF family of proteins later indicate the promotion of oncogenesis, as has been demonstrated in Yoshikawa *et al.*[37].

In a more recent work, ASCL2 has been found to play a major role in stemness in colon crypts and is implicated in colon cancer Zhu *et al.*[38]. Switching off the ASCL2 leads to a literal blockage of the stemness process and vice versa. At the downstream level, ASCL2 is regulated by TCF4/β-catenin via non-coding RNA target named WiNTRLINC1 Giakountis *et al.*[39]. Activation of ASCL2 leads to feedforward transcription of the non-coding RNA and thus a loop is formed which helps in the stemness and is highly effective in colon cancer. At the upstream level, ASCL2 is known act as a WNT/RSPONDIN switch that controls the stemness Schuijers *et al.*[40]. It has been shown that removal of RSPO1 lead to decrease in the Wnt signaling due to removal of the FZD receptors that led to reduced expression of ASCL2. Also, low levels of LGR5 were observed due to this phenomena. The opposite happened by increasing the RSPO1 levels. After the drug treatment, it was found that ASCL2 was highly suppressed pointing to the inhibition of stemness in the colorectal cancer cells. Also, Schuijers *et al.*[40] show that by genetically disrupting PORCN or inducing a PORCN inhibitor (like IWP-2), there is loss of stem cell markers like LGR5 and RNF43, which lead to disappearance of stem cells and moribund state of mice. A similar affect can be found with ETC-1922159, where there is suppression of RNF43 and LGR5 that lead to inhibition of the Wnt pathway and thus the ASCL2 regulation. These wet lab evidences are confirmed in the relatively low ranking of the combination ASCL2-RNF43 via the inhibition of PORCN-WNT that leads to blocking of the stemness that is induced by ASCL2. Since ASCL2 is directly mediated by the WNT proteins, the recorded ASCL2-WNT10B combination showed low priority ranking of 488, 497 and 321 for rbf, laplace and linear kernels, respectively, thus indicating a possible connection between WNT10B and ASCL2 activation. WNT10B might be playing a crucial role in stemness. This is further confirmed by wet lab experiments in Reddy *et al.*[41], which show BVES deletion results in amplified stem cell activity and Wnt signaling after radiation. WNT10B has been implicated in colorectal cancer Yoshikawa *et al.*[37].

2.1.2 ABC transporters - WNT cross family analysis

Hlavata *et al.*[42] have shown the role of ABC transporters in progression and clinical outcome of colorectal cancer. Work by Kobayashi *et al.*[43] show that Wnt-β catenin signaling regulates ABCC3 (MRP3) transporter expression in colorectal cancer. ABCA2 belongs to the category of ABC transporters that play an essential role in the development of resistance by the efflux of anticancer agents outside of cancer cells Hlavata *et al.*[42]. Hlavata *et al.*[42] observed that ABCA2 had no significant change/affect in colorectal cancer cases. Kobayashi *et al.*[43] found ABCA2 to be downregulated in colorectal cancer case. In ETC-1922159 affected CRC cells, down regulation of ABCA2 was observed, after the inhibition of proliferation in respective cells. Multiple members of ABC transporters and WNTs were found to be UP regulated after ETC-159 in CRC cells and WNTs are known to regulate ABCs. Below, we show a range of up regulated, possible unknown and unexplored synergistic 2^{nd} order combinations that were ranked by the search engine. Note that the high numerical valued ranks (i.e nearing to 1800/2000 and above) indicate high potential of synergy that might be existing in CRC cells after the drug administration. Majority voting of rankings across the three different kernels point to the potential of the synergistic discovery. Wet labs investigations will assist in confirmation of these discoveries and if proven true, might lead to understanding of further mechanism between the components.

Tables 1 and 2 show the rankings of ABC family w.r.t to WNT family members and WNT family w.r.t to ABC family members, respectively. From these two tables, we derive the plausible influences that might be existing in a two way format that is depicted in table 3. In table 1, WNT2B - ABC-C3 combination shows a majority voting of 1853 (laplace) and 2498 (rbf). Similarly, WNT7B - ABC-C13 shows a majority voting of 2245 (linear) and 2298 (rbf). These two combinations are depicted in table 3 as ABC members influenced by WNT members (see under ABC w.r.t WNT). Reversibily, in table 2 ABC-A5 - WNT2B shows a majority voting of 2018 (linear) and 2132 (rbf), ABC-A5 - WNT4 shows a majority voting of 2436 (linear) and 2449 (rbf), ABC-A5 - WNT9A shows a majority voting of 1989 (laplace), 2209 (linear) and 2365 (rbf), WNT2B - ABC-C5 shows a majority voting of 1970 (laplace), 2309 (linear) and 2248 (rbf), ABC-C5 - WNT9A shows a majority voting of 2183 (linear) and 2480 (rbf), WNT2B - ABC-C13 shows a majority voting of 2150 (linear) and 2048 (rbf), WNT7B - ABC-C13 shows a majority voting of 2508 (laplace) and 1830 (linear), WNT7B - ABC-D1 shows a majority voting of 2238 (laplace) and 2021 (linear), WNT7B - ABC-G1 shows a majority voting of 1808 (linear) and 1866 (rbf), WNT7B - ABC-G2 shows a majority voting of 2334 (linear) and 2145 (rbf) and WNT9A - ABC-G2 shows a majority voting of 1919 (laplace) and 2003 (rbf). These point to WNT members influenced by ABC members (see under WNT w.r.t ABC). Hypothetically, what we find is that the synergies can be bi-directional also and might contain various intermitent factors through which the factors might be working synergistically. These hypothese form present themselves as important combinations that might be of interest to biologists/oncologists.

One can also interpret the results of the table 3 graphically, with the following influences - • ABC w.r.t WNT with WNT-2B -> ABC-C3; WNT-7B -> ABC-C13; and • WNT w.r.t ABC with ABC-A5 <- WNT-2B/4/9A; WNT-2B/9A <- ABC-C5; WNT-2B/7B <- ABC-C13; WNT-7B <- ABC-D1; WNT-7B <- ABC-G1; WNT-7B/9A <- ABC-G2. Thus, in this way, we can utilize the search engine to derive the various probable combinations between the factors of interest and their interdependent influences through the two-way

Ranking ABC family w.r.t WNT family

Ranking of ABC family w.r.t WNT-2B	laplace	linear	rbf	Ranking of ABC family w.r.t WNT4	laplace	linear	rbf
WNT2B - ABC-A5	2108	310	72	ABC-A5 - WNT4	359	1285	433
ABC-B11 - WNT2B	319	2132	18	ABC-B11 - WNT4	872	1284	867
WNT2B - ABC-C3	1853	262	2498	ABC-C3 - WNT4	10	617	296
WNT2B - ABC-C5	2213	1685	840	WNT4 - ABC-C5	1383	2119	215
WNT2B - ABC-C13	1149	1191	2175	WNT4 - ABC-C13	1649	1814	542
WNT2B - ABC-D1	1119	177	2163	ABC-D1 - WNT4	1041	1171	1740
WNT2B - ABC-G1	1068	1583	214	ABC-G1 - WNT4	1020	1146	2025
WNT2B - ABC-G2	1500	1533	172	ABC-G2 - WNT4	784	1431	435
Ranking of ABC family w.r.t WNT-7B	laplace	linear	rbf	**Ranking of ABC family w.r.t WNT-9A**	laplace	linear	rbf
ABC-A5 - WNT7B	1550	516	995	ABC-A5 - WNT9A	735	349	1479
ABC-B11 - WNT7B	968	599	324	ABC-B11 - WNT9A	843	1647	689
ABC-C3 - WNT7B	694	1668	695	ABC-C3 - WNT9A	1590	359	2136
WNT7B - ABC-C5	979	1715	2268	ABC-C5 - WNT9A	1295	368	2265
WNT7B - ABC-C13	950	2245	2298	ABC-C13 - WNT9A	1394	2294	1134
ABC-D1 - WNT7B	252	850	1215	ABC-D1 - WNT9A	910	2367	675
ABC-G1 - WNT7B	269	733	1160	ABC-G1 - WNT9A	426	2457	1074
ABC-G2 - WNT7B	1717	224	264	ABC-G2 - WNT9A	1108	2350	960

Table 1 2^{nd} order interaction ranking between ABC w.r.t WNT family members.

Ranking WNT family w.r.t ABC family

Ranking of WNT family w.r.t ABC-A5	laplace	linear	rbf	Ranking of WNT family w.r.t ABC-B11	laplace	linear	rbf
ABC-A5 - WNT2B	1549	2018	2132	WNT2B - ABC-B11	1083	703	1887
ABC-A5 - WNT4	1375	2436	2449	WNT4 - ABC-B11	156	298	1517
ABC-A5 - WNT7B	2420	1527	460	WNT7B - ABC-B11	1134	204	2323
ABC-A5 - WNT9A	1989	2209	2365	WNT9A - ABC-B11	226	2134	1480
Ranking of WNT family w.r.t ABC-C3	laplace	linear	rbf	**Ranking of WNT family w.r.t ABC-C5**	laplace	linear	rbf
ABC-C3 - WNT2B	1127	1482	1905	WNT2B - ABC-C5	1970	2309	2248
ABC-C3 - WNT4	897	1454	489	WNT4 - ABC-C5	2129	229	230
ABC-C3 - WNT7B	656	2080	772	WNT7B - ABC-C5	1539	756	1258
ABC-C3 - WNT9A	2339	1616	814	ABC-C5 - WNT9A	213	2183	2480
Ranking of WNT family w.r.t ABC-C13	laplace	linear	rbf	**Ranking of WNT family w.r.t ABC-D1**	laplace	linear	rbf
WNT2B - ABC-C13	950	2150	2048	WNT2B - ABC-D1	1751	1370	1174
WNT4 - ABC-C13	538	326	2242	WNT4 - ABC-D1	45	1784	101
WNT7B - ABC-C13	2508	1830	1219	WNT7B - ABC-D1	2238	2021	1121
WNT9A - ABC-C13	738	2501	634	WNT9A - ABC-D1	732	1526	1759
Ranking of WNT family w.r.t ABC-G1	laplace	linear	rbf	**Ranking of WNT family w.r.t ABC-G2**	laplace	linear	rbf
WNT2B - ABC-G1	318	775	2040	WNT2B - ABC-G2	1342	1987	1230
WNT4 - ABC-G1	2169	157	39	WNT4 - ABC-G2	862	1352	1985
WNT7B - ABC-G1	587	1808	1866	WNT7B - ABC-G2	2334	2145	1526
WNT9A - ABC-G1	856	2350	920	WNT9A - ABC-G2	1919	1284	2003

Table 2 2^{nd} order interaction ranking between WNT w.r.t ABC family members.

Unexplored combinatorial hypotheses	
ABC w.r.t WNT	
WNT-2B	ABC-C3
WNT-7B	ABC-C13
WNT w.r.t ABC	
ABC-A5	WNT-2B/4/9A
WNT-2B/9A	ABC-C5
WNT-2B/7B	ABC-C13
WNT-7B	ABC-D1
WNT-7B	ABC-G1
WNT-7B/9A	ABC-G2

Table 3 2^{nd} order combinatorial hypotheses between ABC and WNT family members.

Ranking IL family VS WNT family							
Ranking of IL family w.r.t WNT-2B				Ranking of WNT-2B w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - WNT2B	6	2363	924	IL1A - WNT2B	2290	1360	2427
IL1B - WNT2B	1015	1278	794	IL1B - WNT2B	847	2168	1369
IL1RAP - WNT2B	1481	1391	799	IL1RAP - WNT2B	2488	35	1892
IL1RN - WNT2B	1229	1967	1582	IL1RN - WNT2B	1307	43	2514
IL2RG - WNT2B	1434	1100	2335	IL2RG - WNT2B	1384	1255	1283
IL6ST - WNT2B	1157	1797	2088	IL6ST - WNT2B	776	242	1481
IL8 - WNT2B	2107	1817	2251	IL8 - WNT2B	2157	2025	593
IL10RB - WNT2B	961	2494	512	IL10RB - WNT2B	2419	856	1419
IL15 - WNT2B	1008	1214	1714	IL15 - WNT2B	1171	625	1215
IL15RA - WNT2B	728	1782	1382	IL15RA - WNT2B	2262	1021	657
IL17C - WNT2B	477	2357	1483	IL17C - WNT2B	1947	1304	1331
IL17REL - WNT2B	1824	12	2241	IL17REL - WNT2B	1980	919	1617
Ranking of IL family w.r.t WNT-4				Ranking of WNT-4 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - WNT4	2500	1346	955	IL1A - WNT4	507	221	91
IL1B - WNT4	1867	1976	1682	IL1B - WNT4	129	250	291
IL1RAP - WNT4	2302	1826	803	IL1RAP - WNT4	74	19	1553
IL1RN - WNT4	1314	856	104	IL1RN - WNT4	851	1218	2029
IL2RG - WNT4	1289	590	319	IL2RG - WNT4	520	920	424
IL6ST - WNT4	1315	273	2422	IL6ST - WNT4	991	1443	2454
IL8 - WNT4	1722	549	11	IL8 - WNT4	1980	2144	1267
IL10RB - WNT4	1700	153	1055	IL10RB - WNT4	1828	2259	1993
IL15 - WNT4	1012	871	1658	IL15 - WNT4	959	553	448
IL15RA - WNT4	1987	2265	819	IL15RA - WNT4	788	139	645
IL17C - WNT4	2018	1639	1881	IL17C - WNT4	406	276	232
IL17REL - WNT4	1019	425	893	IL17REL - WNT4	955	595	1689
Ranking of IL family w.r.t WNT-7B				Ranking of WNT-7B w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - WNT7B	662	950	149	IL1A - WNT7B	1058	2134	2312
IL1B - WNT7B	290	167	502	IL1B - WNT7B	1683	1871	1575
IL1RAP - WNT7B	872	1976	789	IL1RAP - WNT7B	381	1728	1517
IL1RN - WNT7B	1882	1796	503	IL1RN - WNT7B	1907	2162	1605
IL2RG - WNT7B	1381	446	482	IL2RG - WNT7B	1070	1695	2245
IL6ST - WNT7B	819	1284	1528	IL6ST - WNT7B	1268	1881	2020
IL8 - WNT7B	2232	220	701	IL8 - WNT7B	1551	58	2149
IL10RB - WNT7B	1318	1198	656	IL10RB - WNT7B	375	2145	803
IL15 - WNT7B	1000	290	245	IL15 - WNT7B	2307	1524	1687
IL15RA - WNT7B	1535	1054	2204	IL15RA - WNT7B	1575	191	1949
IL17C - WNT7B	515	263	113	IL17C - WNT7B	1956	2388	1982
IL17REL - WNT7B	2053	2445	2489	IL17REL - WNT7B	322	859	1631
Ranking of IL family w.r.t WNT-9A				Ranking of WNT-9A w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - WNT9A	199	2228	1270	IL1A - WNT9A	597	1322	469
IL1B - WNT9A	305	2266	466	IL1B - WNT9A	776	652	1010
IL1RAP - WNT9A	1773	2273	2159	IL1RAP - WNT9A	2003	2179	964
IL1RN - WNT9A	2479	1506	1503	IL1RN - WNT9A	1363	1829	1632
IL2RG - WNT9A	1489	598	865	IL2RG - WNT9A	186	260	1276
IL6ST - WNT9A	2229	761	1103	IL6ST - WNT9A	2099	1416	1674
IL8 - WNT9A	346	1103	1910	IL8 - WNT9A	589	1751	1529
IL10RB - WNT9A	1836	1556	1006	IL10RB - WNT9A	1021	2127	1534
IL15 - WNT9A	168	1445	855	IL15 - WNT9A	1357	1025	1709
IL15RA - WNT9A	1776	206	2380	IL15RA - WNT9A	2149	2362	737
IL17C - WNT9A	72	2442	569	IL17C - WNT9A	1532	2465	1607
IL17REL - WNT9A	2512	24	580	IL17REL - WNT9A	2101	1940	313

Table 4 2^{nd} order interaction ranking between ABC w.r.t IL family members.

cross family analysis.

2.1.3 IL - WNT cross family analysis

Interleukin (IL) has been found in cross talk with WNT pathway. Kaler *et al.*[44] show that NFκB induced WNT signaling in colorectal cancer via interleukin-1β IL1B. Further, Zhong *et al.*[45] have shown that nitric oxide mediates crosstalk between interleukin 1β and Wnt signaling in primary human chondrocytes by reducing DKK1 and FRZB expression. The role of IL-17 (Interleukin-17) family is known to be controversial in CRC, however there are cases were it has been reported to be a prognostic marker for colorectal cancer Lin *et al.*[46] & Housseau *et al.*[47]. A homologue of the family, IL-17D a novel cytokine has been discovered Starnes *et al.*[48] and found to play a role in many of the cancers. In cells treated with ETC-1922159, IL-17D was found to be down regulated and reversibly it must have been regulated in the colorectal cancer cases. Recently, crosstalk between WNT/β-Catenin and NF-κB signaling pathway during inflammation has been reported by Ma and Hottiger[49]. Ma *et al.*[50] also show WNT/β-catenin negative feedback loop inhibits IL-1 induced matrix metalloproteinase expression in human articular chondrocytes. Masckauchán *et al.*[51] conclude that WNT/β-catenin signaling promotes angiogenesis possibly via the induction of known angiogenic regulators such as Interleukin-8. In mouse colon, Interleukin-1 signaling is shown to mediate obesity-promoted elevations in inflammatory cytokines, WNT activation, and epithelial proliferation by Pfalzer *et al.*[52]. In pulmonary fibrosis, Aumiller *et al.*[53] show that WNT/β-Catenin signaling induces IL-1β expression by alveolar epithelial cells. Chen *et al.*[54] show that IL-23 promotes the epithelial-mesenchymal transition of oesophageal carcinoma cells via the WNT/β-catenin pathway. Finally, Malysheva *et al.*[55] show that IL-6/WNT interactions in rheumatoid arthritis.

Family members belonging to each of the factors like WNT, IL etc, might be involved synergistically in pathological case or otherwise. IL and WNT members were found to be up regulated after the treatment of ETC-1922159 in colorectal cancer cells. We present here, multiple plausible and alternative synergistic combinatorial biological hypotheses for IL-WNT combination, which emerge after a cross family member analysis of the in silico revelations pertaining to the components under investigation.

Table 4 shows IL-WNT two way cross family analysis. The left side of the table contains rankings of IL family with respect to WNTs and the right side of the table contains rankings of WNT family with respect to ILs. Depicted in table are the plausible combinatorial hypotheses derived from majority voting of the rankings in table 4. On the left half, **w.r.t WNT2B**, IL-6ST/8/17REL show a synergy with WNT2B. These are reflected with rankings of 1797 (linear) and 2088 (rbf) for IL-6ST - WNT2B; rankings of 2107 (laplace), 1817 (linear) and 2088 (rbf) for IL-8 - WNT2B and rankings of 1824 (laplace) and 2241 (rbf) for IL-17REL - WNT2B, respectively. **W.r.t WNT4**, IL-1B/1RAP/15RA/17C show a synergy with WNT4. These are reflected with rankings of 1867 (laplace) and 1976 (linear) for IL-1B - WNT4; rankings of 2302 (laplace) and 1826 (linear) for IL-1RAP - WNT4; rankings of 1987 (laplace) and 2265 (linear) for IL-15RA - WNT4 and rankings of 2018 (laplace) and 1881 (linear) for IL-17C - WNT4, respectively. **W.r.t WNT7B**, IL-1RN/17REL show a synergy with WNT7B. These are reflected with rankings of 1882 (laplace) and 1796 (linear) for IL-1RN - WNT7B and rankings of 2053 (laplace), 2445 (linear) and 2489 (rbf) for IL-17REL - WNT4, respectively. **W.r.t WNT9A**, IL-1RAP/15RA show a synergy with WNT9A. These are reflected with rankings of 2273 (linear) and 2159 (rbf) for IL-1RAP - WNT9A and rankings of 1776 (laplace) and 2380 (linear) for IL-15RA - WNT9A, respectively.

UNEXPLORED COMBINATORIAL HYPOTHESES	
IL w.r.t WNT	
IL-6ST/8/17REL	WNT-2B
IL-1B/1RAP/15RA/17C	WNT-4
IL-1RN/17REL	WNT-7B
IL-1RAP/15RA	WNT-9A
WNT w.r.t IL	
IL-1A/1RAP/8	WNT-2B
IL-8/10RB	WNT-4
IL-1A/1RN/6ST/17C	WNT-7B
IL-1RAP/15RA/17REL	WNT-9A

Table 5 2^{nd} order combinatorial hypotheses between IL and WNT family members.

On the right half, **WNT2B w.r.t IL family**, IL-1A/1RAP/8 show a synergy with WNT2B. These are reflected with rankings of 2290 (laplace) and 2427 (rbf) for IL-1A - WNT2B; rankings of 2488 (laplace) and 1892 (rbf) for IL-1RAP - WNT2B and rankings of 2157 1824 (laplace) and 2025 (linear) for IL-8 - WNT2B, respectively. **WNT4 w.r.t IL family**, IL-8/10RB show a synergy with WNT4. These are reflected with rankings of 1980 (laplace) and 2144 (linear) for IL-8 - WNT4 and rankings of 1828 (laplace), 2259 (linear) and 1993 (rbf) for IL-10RB - WNT4; respectively. **WNT7B w.r.t IL family**, IL-1A/1RN/6ST/17C show a synergy with WNT7B. These are reflected with rankings of 2134 (linear) and 2312 (rbf) for IL-1A - WNT7B; rankings of 1907 (laplace) and 2162 (linear) for IL-1RN - WNT7B; rankings of 1881 (linear) and 2020 (rbf) for IL-ST - WNT7B; and rankings of 1956 (laplace), 2388 (linear) and 1982 (rbf) for IL-17C - WNT7B, respectively. **WNT9A w.r.t IL family**, IL-1RAP/15RA/17REL show a synergy with WNT9A. These are reflected with rankings of 2003 (laplace) and 2179 (linear) for IL-1RAP - WNT9A; rankings of 2149 (laplace) and 2362 (linear) for IL-15RA - WNT9A; and rankings of 2101 (laplace) and 1940 (linear) for IL-17REL - WNT9A, respectively. One can also interpret the results of the table 5 graphically, with the following influences - • IL w.r.t WNT with IL-6ST/8/17REL <- WNT-2B; IL-1B/1RAP/15RA/17C <- WNT-4; IL-1RN/17REL <- WNT-7B; IL-1RAP/15RA <- WNT-9A and • WNT w.r.t IL with IL-1A/1RAP/8 -> WNT-2B; IL-8/10RB -> WNT-4; IL-1A/1RN/6ST/17C -> WNT-7B and IL-1RAP/15RA/17REL -> WNT-9A.

2.1.4 UBE2 - WNT cross family analysis

Mukai *et al.*[56] observed balanced ubiquitylation and deubiquitylation of Frizzled regulate cellular responsiveness to Wg/Wnt. Family members belonging to each of the factors like UBE2, WNT etc, might be involved synergistically in pathological case or otherwise. UBE2 and WNT members were found to be up regulated after the treatment of ETC-159 in colorectal cancer cells. However, not much is known about interation between the UBE2 family members and WNTs. Here we present a range of synergies that were ranked highly for up regulation. Table 6 presents the rankings of UBE family VS WNT family. Following this, is the table 7 which derives the necessary influences via majority voting of rankings in table 6.

On the left half, **w.r.t WNT family**, UBE2A show a synergy with WNT4. These are reflected with rankings of 2314 (linear) and 2279 (rbf) for UBE2A - WNT4; UBE2B show a synergy with WNT4/7B. These are reflected with rankings of 2260 (laplace), 2008 (linear) and 2141 (rbf) for UBE2B - WNT4 and rankings of 2116 (laplace) and 2206 (rbf) for UBE2B - WNT7B, respectively; UBE2F show a synergy with WNT4/7B. These are reflected with rankings of 2135 (laplace) and 2505 (linear) for UBE2F - WNT4 and rankings of 2423 (laplace) and 2077 (rbf) for UBE2F - WNT7B, respectively; UBE2H show a synergy with WNT2B. These are reflected with rankings of 1841 (laplace) and 2178 (linear) for UBE2H - WNT2B; UBE2J1 show a synergy with WNT-7B/9A. These are reflected with rankings of 2349 (laplace) and 2183 (rbf) for UBE2J1 - WNT7B and rankings of 1835 (laplace) and 2053 (rbf) for UBE2J1 - WNT9A, respectively. UBE2Z show a synergy with WNT-2B/4/9A. These are reflected with rankings of

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Ranking UBE2 family VS WNT family

Ranking of UBE2-A w.r.t WNT family				Ranking of WNT family w.r.t UBE2-A			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - UBE2A	1608	203	181	WNT2B - UBE2A	1677	899	1671
WNT4 - UBE2A	1293	2314	2279	WNT4 - UBE2A	424	1062	545
WNT7B - UBE2A	1139	1217	1961	WNT7B - UBE2A	392	2345	2151
WNT9A - UBE2A	443	1705	287	WNT9A - UBE2A	806	1581	1098
Ranking of UBE2-B w.r.t WNT family				Ranking of WNT family w.r.t UBE2-B			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - UBE2B	1473	2220	599	WNT2B - UBE2B	2020	553	73
WNT4 - UBE2B	2260	2008	2141	WNT4 - UBE2B	301	334	47
WNT7B - UBE2B	2116	2206	1454	WNT7B - UBE2B	1336	2052	1903
WNT9A - UBE2B	2291	79	1381	WNT9A - UBE2B	2300	2476	2326
Ranking of UBE2-F w.r.t WNT family				Ranking of WNT family w.r.t UBE2-F			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - UBE2F	1246	833	2387	WNT2B - UBE2F	1006	1917	49
WNT4 - UBE2F	2135	2505	1762	WNT4 - UBE2F	63	1109	664
WNT7B - UBE2F	2423	1673	2077	WNT7B - UBE2F	2236	1660	1751
WNT9A - UBE2F	2032	1165	128	WNT9A - UBE2F	1014	2251	2179
Ranking of UBE2-H w.r.t WNT family				Ranking of WNT family w.r.t UBE2-H			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - UBE2H	1841	351	2178	WNT2B - UBE2H	2015	1019	1331
WNT4 - UBE2H	1090	778	1224	WNT4 - UBE2H	218	2248	2155
WNT7B - UBE2H	1505	1215	527	WNT7B - UBE2H	2294	1209	1367
WNT9A - UBE2H	605	332	2479	WNT9A - UBE2H	437	1202	2379
Ranking of UBE2-J1 w.r.t WNT family				Ranking of WNT family w.r.t UBE2-J1			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - UBE2J1	1539	1251	1814	WNT2B - UBE2J1	1500	1562	1255
WNT4 - UBE2J1	1583	2478	1604	WNT4 - UBE2J1	292	62	65
WNT7B - UBE2J1	2349	1207	2183	WNT7B - UBE2J1	552	1877	1846
WNT9A - UBE2J1	1835	2053	1652	WNT9A - UBE2J1	2471	2137	2469
Ranking of UBE2-Z w.r.t WNT family				Ranking of WNT family w.r.t UBE2-Z			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - UBE2Z	58	1756	1878	WNT2B - UBE2Z	1576	1171	1543
WNT4 - UBE2Z	2195	2468	938	WNT4 - UBE2Z	896	132	186
WNT7B - UBE2Z	2343	1973	723	WNT7B - UBE2Z	1972	1800	1399
WNT9A - UBE2Z	136	1986	4	WNT9A - UBE2Z	1149	865	813

Table 6 2^{nd} order interaction ranking between WNT w.r.t UBE2 family members.

1756 (linear) and 1878 (rbf) for UBE2J1 - WNT2B, rankings of 2195 (laplace) and 2468 (rbf) for UBE2J1 - WNT4, and 2343 (laplace) and 1973 (rbf) for UBE2J1 - WNT9A, respectively.

On the right half, **w.r.t UBE2**, UBE2A shows a synergy with WNT4. These are reflected with rankings of 2345 (linear) and 2151 (rbf) for UBE2A - WNT7B; UBE2B shows a synergy with WNT-7B/9A. These are reflected with rankings of 2052 (linear) and 1903 (rbf) for UBE2B - WNT7B and rankings of 2300 (laplace), 2476 (linear) and 2326 (rbf) for UBE2B - WNT9A, respectively; UBE2F shows a synergy with WNT-7B/9A. These are reflected with rankings of 2236 (laplace) and 1751 (rbf) for UBE2F - WNT7B and rankings of 2251 (linear) and 2179 (rbf) for UBE2F - WNT9A, respectively; UBE2H shows a synergy with WNT4. These are reflected with rankings of 2248 (linear) and 2155 (rbf) for UBE2H - WNT4; UBE2J1 shows a synergy with WNT-7B/9A. These are reflected with rankings of 1877 (llinear) and 1846 (rbf) for UBE2J1 - WNT7B and rankings of 2471 (laplace), 2137 (linear) and 2469 (rbf) for UBE2J1 - WNT9A, respectively. UBE2Z shows a synergy with WNT-9A. These are reflected with rankings of 1972 (laplace) and 1800 (linear) for UBE2Z - WNT7B, respectively.

One can also interpret the results of the table 7 graphically,

Unexplored combinatorial hypotheses

UBE2 w.r.t WNT	
WNT-4	UBE2-A
WNT-4/7	UBE2-B
WNT-4/7B	UBE2-F
WNT-2B	UBE2-H
WNT-7B/9B	UBE2-J1
WNT-2B/4/7B	UBE2-Z
WNT w.r.t UBE2	
WNT-7B	UBE2-A
WNT-7B/9A	UBE2-B
WNT-7B/9A	UBE2-F
WNT-4	UBE2-H
WNT-7B/9A	UBE2-J1
WNT-7B	UBE2-Z

Table 7 2^{nd} order combinatorial hypotheses between UBE2 and WNT family members.

with the following influences - • UBE2 w.r.t WNT with WNT-4 -> UBE2-A; WNT-4/7 -> UBE2-B; WNT-4/7B -> UBE2-F; WNT-2B -> UBE2-H; WNT-7B/9B -> UBE2-J1; WNT-2B/4/7B -> UBE2-Z and • WNT w.r.t UBE2 with WNT-7B <- UBE2-A; WNT-7B/9A <- UBE2-B; WNT-7B/9A <- UBE2-F; WNT-4 <- UBE2-H; WNT-7B/9A <- UBE2-J1; WNT-7B <- UBE2-Z;

2.1.5 EXOSC - WNT10B cross family analysis

Ranking EXOSC family VS WNT10B

Ranking of WNT10B w.r.t EXOSC family				Ranking of EXOSC family w.r.t WNT10B			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC2 - WNT10B	221	433	699	EXOSC2 - WNT10B	1695	1077	992
EXOSC3 - WNT10B	906	1292	860	EXOSC3 - WNT10B	610	2496	2428
EXOSC5 - WNT10B	919	484	997	EXOSC5 - WNT10B	832	1445	1589
EXOSC6 - WNT10B	407	1195	1747	EXOSC6 - WNT10B	1319	1738	1689
EXOSC7 - WNT10B	2599	2571	2584	EXOSC7 - WNT10B	2710	13	4
EXOSC8 - WNT10B	336	1437	391	EXOSC8 - WNT10B	451	2284	2493
EXOSC9 - WNT10B	222	701	732	EXOSC9 - WNT10B	1378	1501	1651

Table 8 2^{nd} order interaction ranking between WNT w.r.t EXOSC family members.

Recently, emerging role of exosome (EXOSC) has been studied in WNT secretion and transportation by Zhang and Wrana[57]. It has been found that exosomes play a critical role in morphogen signaling during embryonic development and cancer progression. In injured CNS, exosomes mediate mobilization of WNT10B to promote axonal regeneration as shown by Tassew *et al.*[58]. Koles and Budnik[59] show the importance of exsosomes in WNT transportation. Emerging on these lines, we conducted a small two-way analysis of EXOSC components and WNT10B which were found to be down regulated in CRC cells after administration of ETC-1922159. Note that here, the interpretation of the rankings changes as the low numerical valued ranks (nearing to 1) are considered of high importance as they point to the synergistic down regulation after the drug administration. In line with the experiments, as ETC-1922159 a PORCN-WNT inhibitor block the transportation of WNTs, it might be that the affects of EXOSC components are also down regulated. These were rightly allocated with the low numerical valued in-silico ranks by the engine, thus pointing to the experimental down regulation in cells also. This confirmatory results also helps us in exploring the unknown combinations that might be prevailing synergistically when the WNT-EXOSC were up regulated before the administration of ETC-1922159 in CRC cells.

Table 8 shows the rankings of EXOSC family w.r.t WNT10B and vice versa. Followed by this is the unexplored combinatorial hypotheses in table 9 generated from two-way analysis of the ranks in table 8. On the left half of the table 8, except for EXOSC7 - WNT10B, all other combinations of EXOSC family show high synergy with WNT10B. This is depicted by the low numerical valued ranks allocated by the search engine for EXOSC-2/3/5/6/8/9 with WNT10B, via majority voting across the ranking methods using laplace, linear and rbf kernels. This shows that EXOSC-2/3/5/6/8/9 had a critical role in the transport of WNT10B. On the right half of the same table, EXOSC-2/5/6/7/9 show synergistic affiliation with respect to WNT10B, via low numerical valued ranks. These are translated to graphical influences in table 9. One can also interpret the results of the table 9 graphically, with the following influences - • EXOSC w.r.t WNT10B with EXOSC-2/5/6/7/9 <- WNT10B and • WNT10B w.r.t EXOSC with EXOSC-2/3/5/6/8/9 -> WNT10B. Further analyses of these combinations in wet lab might help biologists explore the deeper mechanism of exosome components and WNT10B in CRC cells.

UNEXPLORED COMBINATORIAL HYPOTHESES	
EXOSC w.r.t WNT10B	
EXOSC-2/5/6/7/9	WNT10B
WNT10B w.r.t EXOSC	
EXOSC-2/3/5/6/8/9	WNT10B

Table 9 2^{nd} order combinatorial hypotheses between EXOSC and WNT10B family members.

2.1.6 CASP - WNT cross family analysis

Wu *et al.*[60] show that a caspase-dependent pathway is involved in Wnt/β-catenin signaling promoted apoptosis in Bacillus Calmette-Guerin infected RAW264.7 macrophages. Abdul-Ghani *et al.*[61] have shown that WNT11 promotes cardiomyocyte development by caspase-mediated suppression of canonical WNT signals. Additionally, Bisson *et al.*[62] show that Wnt5a and Wnt11 inhibit the canonical Wnt pathway and promote cardiac progenitor development via the Caspase-dependent degradation of AKT. These findings indicate probable interplay of Caspase and WNTs in various pathological cases. In mice, caspase-1 activation and IL-1Îš secretion together have shown to contribute to inflammatory condition of acute arthritis (see Singh *et al.*[63]). Recently, Caspase-3 inhibition has been found to be a therapeutic approach in colorectal cancer as shown by Flanagan *et al.*[64]. Yao *et al.*[65] also show synergistic role of Caspase-8 and Caspase-3 expressions as biomarkers in colorectal cancer. Family members belonging to each of the factors like CASP, WNT etc, might be involved synergistically in pathological case or otherwise. CASP and WNT members were found to be up regulated after the treatment of colorectal cancer cells with ETC-1922159.

Table 10 shows the rankings of CASP family w.r.t WNTs and vice versa. Followed by this is the unexplored combinatorial hypotheses in table 11 generated from two-way analysis of the ranks in table 10. On the first three tabular rows of the table 10 show rankings of CASP family w.r.t WNT family. Here we present the possible interdependent WNT-CASP combinations that might be working synergistically in CRC cells. Considering CASP5 w.r.t WNTs, CASP5 - WNT2B show up regulated synergy through rankings of 2171 (laplace) and 2366 (linear). Considering CASP9 w.r.t WNTs, CASP9 - WNT-4/7B/9A show up regulated synergy through rankings of 2472 (laplace) and 2200 (linear) for CASP9 - WNT4; 2196 (laplace) and 1935 (linear) for CASP9 - WNT7B; and 1863 (laplace) and 2002 (linear) for CASP9 - WNT9A, respectively. Finally, considering CASP16 w.r.t WNTs, CASP16 - WNT4 showed up regulated synergy with rankings of 2070 (laplace) and 1783 (linear).

The next three tabular rows show rankings of WNT family w.r.t CASP family. **W.r.t CASP4**, WNT-7B/9A show promise of up regulation. These are reflected with rankings of 2479 (linear) and 1739 (rbf) for WNT7B - CASP4 and rankings of 2278 (linear) and 1939 (rbf) for WNT9A - CASP4, respectively. **W.r.t CASP5**, WNT-7B shows promise of up regulation. This is reflected with rankings of 2112 (laplace), 1919 (linear) and 2440 (rbf) for WNT7B - CASP5. **W.r.t CASP7**, WNT-2B/4/9A show promise of up regulation. These are reflected with rankings of 2505 (laplace) and 1891 (linear) for WNT2B - CASP7; rankings of 2456 (linear) and 2455 (rbf) for WNT4 - CASP7; and rankings of 2183 (laplace) and 1941 (linear) for WNT9A - CASP7, respectively. **W.r.t CASP9**, WNT-9A shows promise of up regulation. This is reflected with rankings of 2378 (laplace), 2396 (linear) and 2058 (rbf) for WNT9A - CASP9. **W.r.t CASP10**, WNT-4/9A show promise of up regulation. These are reflected with rankings of 1830 (laplace), 2229 (linear) and 1847 (rbf) for WNT4 - CASP10; and rankings

RANKING CASP FAMILY VS WNT FAMILY

RANKING OF CASP4 W.R.T WNTS FAMILY				RANKING OF CASP5 W.R.T WNTS FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - WNT2B	2265	320	1517	CASP5 - WNT2B	975	2171	2366
CASP4 - WNT4	1050	1081	558	CASP5 - WNT4	1788	1356	569
CASP4 - WNT7B	622	9	632	CASP5 - WNT7B	716	978	606
CASP4 - WNT9A	446	1413	583	CASP5 - WNT9A	383	808	147
RANKING OF CASP7 W.R.T WNTS FAMILY				RANKING OF CASP9 W.R.T WNTS FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
CASP7 - WNT2B	1152	305	248	CASP9 - WNT2B	1345	1501	1328
CASP7 - WNT4	936	1260	1787	CASP9 - WNT4	1344	2472	2200
CASP7 - WNT7B	901	1403	1303	CASP9 - WNT7B	2196	1935	1713
CASP7 - WNT9A	1330	1527	2436	CASP9 - WNT9A	1863	428	2002
RANKING OF CASP10 W.R.T WNTS FAMILY				RANKING OF CASP16 W.R.T WNTS FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
CASP10 - WNT2B	1607	1108	739	CASP16 - WNT2B	240	621	193
CASP10 - WNT4	432	689	132	CASP16 - WNT4	2070	1783	711
CASP10 - WNT7B	1906	1171	1165	CASP16 - WNT7B	411	713	103
CASP10 - WNT9A	1611	2152	1451	CASP16 - WNT9A	14	2512	181
RANKING OF WNTS FAMILY W.R.T CASP4				RANKING OF WNTS FAMILY W.R.T CASP5			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - WNT2B	609	1317	2372	CASP5 - WNT2B	1849	1192	1590
CASP4 - WNT4	105	711	1062	CASP5 - WNT4	890	682	714
CASP4 - WNT7B	1093	2479	1739	CASP5 - WNT7B	2112	1919	2440
CASP4 - WNT9A	456	2278	1939	CASP5 - WNT9A	315	1880	1437
RANKING OF WNTS FAMILY W.R.T CASP7				RANKING OF WNTS FAMILY W.R.T CASP9			
	laplace	linear	rbf		laplace	linear	rbf
CASP7 - WNT2B	2505	1891	1120	CASP9 - WNT2B	282	639	1414
CASP7 - WNT4	108	2456	2455	CASP9 - WNT4	572	1788	378
CASP7 - WNT7B	1380	1559	1681	CASP9 - WNT7B	979	901	676
CASP7 - WNT9A	2183	1941	1632	CASP9 - WNT9A	2378	2396	2058
RANKING OF WNTS FAMILY W.R.T CASP10				RANKING OF WNTS FAMILY W.R.T CASP16			
	laplace	linear	rbf		laplace	linear	rbf
CASP10 - WNT2B	625	1471	81	CASP16 - WNT2B	2197	2489	1775
CASP10 - WNT4	1830	2229	1847	CASP16 - WNT4	1382	954	1017
CASP10 - WNT7B	1965	937	147	CASP16 - WNT7B	2508	1820	1867
CASP10 - WNT9A	2185	1977	1350	CASP16 - WNT9A	1943	1154	1839

Table 10 2^{nd} order interaction ranking between WNT VS CASP family members.

of 2185 (laplace) and 1977 (linear) for WNT9A - CASP10, respectively. Finally, **w.r.t CASP16**, WNT-2B/4/9A show promise of up regulation. These are reflected with rankings of 2197 (laplace), 2489 (linear) and 1775 (rbf) for WNT2B - CASP16; rankings of 2508 (laplace), 1820 (linear) and 1867 (rbf) for WNT7B - CASP16; and rankings of 1943 (laplace) and 1839 (linear) for WNT9A - CASP16, respectively.

One can also interpret the results of the table 11 graphically, with the following influences - • CASP w.r.t WNT with CASP5 <- WNT2B; CASP9 <- WNT-4/7B/9A; CASP16 <- WNT4 and • WNT w.r.t CASP with. WNT-7B/9A <- CASP4; WNT7B <- CASP5; WNT-2B/4/9A <- CASP7; WNT9A <- CASP9; WNT-4/9A <- CASP10; WNT-2B/7B/9A <- CASP16.

2.1.7 TP53 - WNT cross family analysis

Sadot *et al.*[66] have shown that down regulation of β-catenin is activated by TP53. Wnt/β-catenin signaling is known to regulate the proliferation and differentiation of mesenchymal progenitor cells through the TP53 Pathway, as shown by Peng *et al.*[67]. Zhukova *et al.*[68] show that WNT activation by lithium abrogates TP53 mutation associated radiation resistance in medulloblastoma. In mouse cochlea, Liu *et al.*[69] show that WNT signaling ac-

UNEXPLORED COMBINATORIAL HYPOTHESES

CASP w.r.t WNT	
CASP5	WNT2B
CASP9	WNT4/WNT7B/WNT9A
CASP16	WNT4
WNT w.r.t CASP	
WNT7B/WNT9A	CASP4
WNT7B	CASP5
WNT2B/WNT4/WNT9A	CASP7
WNT9A	CASP9
WNT4/WNT9A	CASP10
WNT2B/WNT7B/WNT9A	CASP16

Table 11 2^{nd} order combinatorial hypotheses between CASP and WNT family members.

tivates TP53-induced glycolysis and apoptosis regulator and protects against cisplatin-induced spiral ganglion neuron damage. These range of interactions of TP53 with WNT points towards definite synergy. Okayama *et al.*[70] show that TP53 protein regulates Hsp90 ATPase activity and thereby Wnt signaling by modulating Aha1 expression. Family members belonging to each of the factors like TP53, WNT etc, might be involved synergistically in pathological case or otherwise. TP53 and WNT members were found to be up regulated after the treatment of ETC-159 in colorectal cancer cells.

Table 12 contains rankings of TP53 w.r.t WNTs and vice versa. Followed by this is the unexplored combinatorial hypotheses in table 13 generated from two-way analysis of the ranks in table 12. On the left half of table 12 are rankings of TP53 w.r.t WNTs and on the right half are the rankings of WNTs w.r.t TP53 family. Beginning with the left half, TP53I3 - WNT2B shows synergistic up regulation with rankings of 2056 (laplace) and 1712 (linear); TP53INP1 - WNT2B shows synergistic up regulation with rankings of 1805 (linear) and 2056 (rbf) and TP53BP2 - WNT9A shows synergistic up regulation with rankings of 2232 (linear) and 2143 (rbf). On the right half the table, TP53INP1 - WNT2B shows synergistic up regulation with rankings of 1853 (laplace) and 2089 (linear); TP53INP2 - WNT2B shows synergistic up regulation with rankings of 1723 (linear) and 2335 (rbf); TP53INP1 - WNT4 shows synergistic up regulation with rankings of 2414 (linear) and 2493 (rbf); TP53I3 - WNT7B shows synergistic up regulation with rankings of 1988 (laplace) and 2393 (rbf) and finally, TP53INP1 - WNT9A shows synergistic up regulation with rankings of 2045 (linear) and 2437 (rbf).

One can also interpret the results of the table 11 graphically, with the following influences - • TP53 family w.r.t WNTs with TP53I3 <- WNT2B; TP53INP1 <- WNT2B and TP53BP2 <-

Ranking TP53 family VS WNT

Ranking of TP53 family w.r.t WNT2B				Ranking of WNT2B w.r.t TP53 family			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - WNT2B	2286	234	1550	TP53BP2 - WNT2B	313	908	2457
TP53I3 - WNT2B	2056	1712	1461	TP53I3 - WNT2B	713	1223	1720
TP53INP1 - WNT2B	945	1805	2056	TP53INP1 - WNT2B	1853	2089	762
TP53INP2 - WNT2B	369	1277	453	TP53INP2 - WNT2B	754	1723	2335
Ranking of TP53 family w.r.t WNT4				Ranking of WNT4 w.r.t TP53 family			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - WNT4	1034	315	1734	TP53BP2 - WNT4	678	1464	2500
TP53I3 - WNT4	1738	1631	232	TP53I3 - WNT4	297	319	493
TP53INP1 - WNT4	645	498	450	TP53INP1 - WNT4	131	2414	2493
TP53INP2 - WNT4	671	1440	405	TP53INP2 - WNT4	529	467	154
Ranking of TP53 family w.r.t WNT7B				Ranking of WNT7B w.r.t TP53 family			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - WNT7B	2333	1282	1673	TP53BP2 - WNT7B	1442	2217	1068
TP53I3 - WNT7B	324	712	284	TP53I3 - WNT7B	1712	1988	2393
TP53INP1 - WNT7B	1227	1585	1019	TP53INP1 - WNT7B	1226	1685	1497
TP53INP2 - WNT7B	845	1004	470	TP53INP2 - WNT7B	1017	1746	1925
Ranking of TP53 family w.r.t WNT9A				Ranking of WNT9A w.r.t TP53 family			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - WNT9A	908	2232	2143	TP53BP2 - WNT9A	1035	371	1218
TP53I3 - WNT9A	1707	2297	1018	TP53I3 - WNT9A	1351	1281	1695
TP53INP1 - WNT9A	447	243	1245	TP53INP1 - WNT9A	295	2045	2437
TP53INP2 - WNT9A	22	2497	1138	TP53INP2 - WNT9A	421	1765	1121

Table 12 2^{nd} order interaction ranking between WNT VS TP53 family members.

Unexplored combinatorial hypotheses

TP53 family w.r.t WNT	
TP53I3	WNT2B
TP53INP1	WNT2B
TP53BP2	WNT9A
WNT family w.r.t TP53	
TP53INP1	WNT2B
TP53INP2	WNT2B
TP53INP1	WNT4
TP53I3	WNT7B
TP53INP1	WNT9A

Table 13 2^{nd} order combinatorial hypotheses between TP53 and WNT family members.

WNT9A; and • WNT family VS TP53 with TP53INP1 -> WNT2B; TP53INP2 -> WNT2B; TP53INP1 -> WNT4; TP53I3 -> WNT7B and TP53INP1 -> WNT9A.

2.1.8 BCL - WNT cross family analysis

Wang *et al.*[71] observed that silencing Wnt2B by siRNA interference inhibits metastasis and enhances chemotherapy sensitivity in ovarian cancer. More specifically, Wang *et al.*[71] show that in the presence of Wnt2B siRNA treatment, the caspase-9/B-cell lymphoma 2 (BCL2)/B-cell lymphoma-xL (BCL-xL) pathway and the epithelial-mesenchymal transition/phosphorylated protein kinase B pathway were inhibited. Takada *et al.*[72] show that targeted disruption of the BCL9/β-catenin complex inhibits oncogenic WNT signaling. CDK1-mediated BCL9 phosphorylation inhibits clathrin to promote mitotic Wnt signaling as shown by Chen *et al.*[73]. These findings point to the existing synergy of BCL family with WNTs. Family members belonging to each of the factors like BCL, WNT etc, might be involved synergistically in pathological case or otherwise. BCL and WNT members were found to be up regulated after the treatment of ETC-159 in colorectal cancer cells.

Table 14 contains rankings of BCL w.r.t WNTs and vice versa. Followed by this is the unexplored combinatorial hypotheses in table 15 generated from two-way analysis of the ranks in table 14. On the left half of table 14 are rankings of BCL w.r.t WNTs. WNT4 - BCL2L2 shows high ranking with 2364 (laplace) and 2042 (linear); WNT7B - BCL2L2 shows high ranking with 1877 (laplace) and 2456 (linear); WNT9A - BCL2L2 shows high ranking with 1877 (laplace) and 2447 (linear); WNT4 - BCL2L13 shows high ranking with 1938 (laplace), 2425 (linear) and 1900 (rbf); WNT7B - BCL2L13 shows high ranking with 1993 (linear) and 2284 (rbf) and WNT2B - BCL10 shows high ranking with 2321 (laplace) and 2023 (linear).

On the right side are rankings of WNTs w.r.t BCL. WNT7B - BCL2L1 shows high ranking with 2213 (laplace) and 2266 (linear); WNT7B - BCL2L2 shows high ranking with 2456 (laplace), 2512 (linear) and 2286 (rbf); WNT9A - BCL2L2 shows high ranking with 1868 (laplace) and 2333 (rbf); WNT9A - BCL2L13 shows high ranking with 1858 (laplace), 2422 (linear) and 1934 (rbf); WNT2B - BCL3 shows high ranking with 1846 (laplace), 2056 (linear) and 1896 (rbf); WNT4 - BCL6 shows high ranking with 2483 (laplace) and 2488 (linear); WNT7B - BCL6 shows high ranking with 1893 (laplace) and 2284 (linear); WNT9A - BCL6 shows high ranking with 2098 (linear) and 1905 (rbf); WNT2B - BCL9L shows high ranking with 1918 (laplace) and 1882 (rbf) and WNT4 - BCL9L shows high ranking with 2498 (linear) and 2509 (rbf); One can also interpret the results of the table 15 graphically, with the following influences - • BCL family w.r.t WNTs with WNT4 -> BCL2L2; WNT7B -> BCL2L2; WNT9A -> BCL2L2; WNT4 -> BCL2L13; WNT7B -> BCL2L13; WNT2B -> BCL10 and • WNT family w.r.t BCL with WNT7B <- BCL2L1; WNT7B <- BCL2L2; WNT9A <- BCL2L2; WNT9A <- BCL2L13; WNT2B <- BCL3; WNT4 <- BCL6; WNT7B <- BCL6; WNT9A <- BCL6; WNT2B <- BCL9L; WNT4 <- BCL9L.

2.2 NF-κB related synergies

2.2.1 CASP - RIPK cross family analysis

The caspase - receptor interacting protein kinases (RIPK) has an intricate mechanism which has not yet been discovered and many views exist about their synergistic interaction. Green *et al.*[74] presents a review of RIPK-dependent necrosis and its regulation by CASPs. Furthermore, Lin *et al.*[75] show that cleavage of the

Ranking BCL family VS WNT

Ranking of BCL2L1 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t BCL2L1	laplace	linear	rbf
WNT2B - BCL2L1	1884	101	966	WNT2B - BCL2L1	1854	1666	1699
WNT4 - BCL2L1	98	1162	719	WNT4 - BCL2L1	21	107	16
WNT7B - BCL2L1	1434	1891	620	WNT7B - BCL2L1	2213	2266	1511
WNT9A - BCL2L1	1088	1020	1318	WNT9A - BCL2L1	1019	1462	1345
Ranking of BCL2L2 w.r.t WNT family				Ranking of WNT family w.r.t BCL2L2			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - BCL2L2	625	2204	1677	WNT2B - BCL2L2	1574	2206	955
WNT4 - BCL2L2	2364	2042	1610	WNT4 - BCL2L2	160	590	316
WNT7B - BCL2L2	843	1877	2456	WNT7B - BCL2L2	2456	2512	2286
WNT9A - BCL2L2	1877	538	2447	WNT9A - BCL2L2	1868	2333	990
Ranking of BCL2L13 w.r.t WNT family				Ranking of WNT family w.r.t BCL2L13			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - BCL2L13	201	1862	1353	WNT2B - BCL2L13	1256	1254	1490
WNT4 - BCL2L13	1938	2425	1900	WNT4 - BCL2L13	922	270	187
WNT7B - BCL2L13	1105	1993	2284	WNT7B - BCL2L13	1610	1319	954
WNT9A - BCL2L13	1855	268	2387	WNT9A - BCL2L13	1858	2422	1934
Ranking of BCL3 w.r.t WNT family				Ranking of WNT family w.r.t BCL3			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - BCL3	950	1328	2482	WNT2B - BCL3	1846	2056	1896
WNT4 - BCL3	1228	1562	1353	WNT4 - BCL3	591	359	1932
WNT7B - BCL3	591	615	553	WNT7B - BCL3	1687	2160	1428
WNT9A - BCL3	1037	1410	1102	WNT9A - BCL3	1539	1424	398
Ranking of BCL6 w.r.t WNT family				Ranking of WNT family w.r.t BCL6			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - BCL6	455	2426	1529	WNT2B - BCL6	52	107	170
WNT4 - BCL6	256	486	787	WNT4 - BCL6	2483	2488	1273
WNT7B - BCL6	2147	1466	1105	WNT7B - BCL6	975	1893	2284
WNT9A - BCL6	1547	734	2012	WNT9A - BCL6	1558	2098	1905
Ranking of BCL9L w.r.t WNT family				Ranking of WNT family w.r.t BCL9L			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - BCL9L	2348	804	1558	WNT2B - BCL9L	1918	700	1882
WNT4 - BCL9L	1446	657	309	WNT4 - BCL9L	303	2498	2509
WNT7B - BCL9L	1539	253	1279	WNT7B - BCL9L	1608	811	2168
WNT9A - BCL9L	1923	677	688	WNT9A - BCL9L	941	1843	1238
Ranking of BCL10 w.r.t WNT family				Ranking of WNT family w.r.t BCL10			
	laplace	linear	rbf		laplace	linear	rbf
WNT2B - BCL10	2321	69	2023	WNT2B - BCL10	1951	1101	1599
WNT4 - BCL10	285	1170	465	WNT4 - BCL10	2032	34	406
WNT7B - BCL10	1847	606	1252	WNT7B - BCL10	1297	74	2009
WNT9A - BCL10	217	798	1649	WNT9A - BCL10	1771	335	861

Table 14 2^{nd} order interaction ranking between WNT VS BCL family members.

death domain RIPK by CASP-8 prompts TNF-induced apoptosis. RIPK1 is known to promote death receptor-independent CASP-8 mediated apoptosis under unresolved ER stress conditions, as shown by Estornes *et al.*[76]. Weng *et al.*[77] show that CASP-8 and RIPK regulate bacteria-induced innate immune responses and cell death. Also, Moriwaki *et al.*[78] show that RIPK3-CASP8 complex mediates atypical pro-IL-1β processing. Recent work by Declercq *et al.*[79] shows RIPK importance in cell death and survival along with CASP influence. These interactions point to a definite synergy between the CASP - RIPK. Chaudhary *et al.*[80] showed activation of NF-κB pathway via Caspase-8 (CASP-8) and its homologs. Additionally, Caspase-8 was found to interact with Receptor-interacting serine/threonine-protein kinase 1 (RIPK1). Family members belonging to each of the factors like CASP, RIPK etc, might be involved synergistically in pathological case or otherwise. CASP and RIPK members were found to be up regulated after the treatment of ETC-1922159 in colorectal cancer cells.

Tables 16 and 17 show the rankings of CASP family w.r.t RIPK and vice versa, respectively. Followed by this is the derived influences between CASP and RIPK via two way analysis of majority voting of rankings in the two foregoing tables. These influences are tabulated in table 18. In table 16, only CASP9 - RIPK3 combination showed up regulation with rankings of 2133 (laplace), 2030 (linear) and 2295 (rbf). In table 17, RIPK1 showed up regulation with CASP-4/10 with rankings of 2363 (laplace) and 1805 (rbf) for CASP4 - RIPK1; and 2438 (laplace) and 1915 (linear) for CASP10 - RIPK1, respectively. RIPK2 showed up regulation with CASP-5/9/16 with rankings of 1776 (linear) and 2247 (rbf) for CASP5 - RIPK2; 2000 (laplace), 2476 (linear) and 2138 (rbf) for CASP9 - RIPK2; and 2006 (linear) and 2046 (rbf) for CASP16 - RIPK2; Finally, RIPK4 showed up regulation with CASP-16 with rankings of 2273 (laplace) and 2023 (linear) for CASP16 - RIPK4.

One can also interpret the results of the table 18 graphically,

Unexplored combinatorial hypotheses

BCL w.r.t WNT family	
WNT-4/7B/9A	BCL2L2
WNT-4/7B	BCL2L13
WNT-2B	BCL10
WNT family w.r.t BCL	
WNT-7B	BCL2L1
WNT-7B/9A	BCL2L2
WNT-9A	BCL2L13
WNT-2B	BCL3
WNT-4/7B/9A	BCL6
WNT-2B/4	BCL9L

Table 15 2^{nd} order combinatorial hypotheses between TP53 and WNT family members.

Ranking CASP family w.r.t RIPK family

Ranking of CASP4 w.r.t RIPK family	laplace	linear	rbf	Ranking of CASP5 family w.r.t RIPK	laplace	linear	rbf
CASP4 - RIPK1	1154	1259	147	CASP5 - RIPK1	490	152	1818
CASP4 - RIPK2	559	2147	434	CASP5 - RIPK2	1274	2485	608
CASP4 - RIPK3	111	131	41	CASP5 - RIPK3	523	1047	317
CASP4 - RIPK4	187	1048	1039	CASP5 - RIPK4 7 1176	2361	1292	
Ranking of CASP7 w.r.t RIPK family				Ranking of CASP9 family w.r.t RIPK			
	laplace	linear	rbf		laplace	linear	rbf
CASP7 - RIPK1	2445	1289	1253	CASP9 - RIPK1	1726	1304	1480
CASP7 - RIPK2	1584	406	155	CASP9 - RIPK2	2079	291	1647
CASP7 - RIPK3	1406	1057	2091	CASP9 - RIPK3	2133	2030	2295
CASP7 - RIPK4	1739	231	2332	CASP9 - RIPK4	2037	1627	363
Ranking of CASP10 w.r.t RIPK family				Ranking of CASP16 family w.r.t RIPK			
	laplace	linear	rbf		laplace	linear	rbf
CASP10 - RIPK1	758	846	1405	CASP16 - RIPK1	73	1046	1887
CASP10 - RIPK2	1535	2312	884	CASP16 - RIPK2	20	932	1189
CASP10 - RIPK3	1530	250	2181	CASP16 - RIPK3	30	359	717
CASP10 - RIPK4	954	415	1547	CASP16 - RIPK4	493	2507	519

Table 16 2^{nd} order interaction ranking between CASP w.r.t RIPK family members.

RANKING RIPK FAMILY W.R.T CASP FAMILY

Ranking of RIPK family w.r.t CASP4	laplace	linear	rbf	Ranking of RIPK family w.r.t CASP5	laplace	linear	rbf
CASP4 - RIPK1	2363	1374	1805	CASP5 - RIPK1	7	82	131
CASP4 - RIPK2	1713	2349	1261	CASP5 - RIPK2	1577	1776	2247
CASP4 - RIPK3	1397	768	1008	CASP5 - RIPK3	574	14	30
CASP4 - RIPK4	2215	1334	1425	CASP5 - RIPK4	2448	1178	810
Ranking of RIPK family w.r.t CASP7	laplace	linear	rbf	**Ranking of RIPK family w.r.t CASP9**	laplace	linear	rbf
CASP7 - RIPK1	1341	2005	1131	CASP9 - RIPK1	820	140	611
CASP7 - RIPK2	1287	727	1143	CASP9 - RIPK2	2000	2476	2138
CASP7 - RIPK3	579	595	775	CASP9 - RIPK3	1550	430	97
CASP7 - RIPK4	852	1586	595	CASP9 - RIPK4	1565	862	209
Ranking of RIPK family w.r.t CASP10	laplace	linear	rbf	**Ranking of RIPK family w.r.t CASP16**	laplace	linear	rbf
CASP10 - RIPK1	2438	1915	1039	CASP16 - RIPK1	924	686	587
CASP10 - RIPK2	1526	1800	1228	CASP16 - RIPK2	1613	2006	2046
CASP10 - RIPK3	419	1481	2001	CASP16 - RIPK3	827	494	328
CASP10 - RIPK4	1303	947	785	CASP16 - RIPK4	2273	2023	1698

Table 17 2^{nd} order interaction ranking between RIPK w.r.t CASP family members.

UNEXPLORED COMBINATORIAL HYPOTHESES

CASP w.r.t RIKP family	
CASP9	RIPK3
RIPK w.r.t CASP family	
RIPK1	CASP4/CASP10
RIPK2	CASP5/CASP9/CASP16
RIPK4	CASP16

Table 18 2^{nd} order combinatorial hypotheses between CASP and RIPK.

with the following influences - • CASP w.r.t RIKP family with CASP9 <- RIPK3 and • RIPK w.r.t CASP family with RIPK1 <- CASP-4/10; RIPK2 <- CASP-5/9/16 and RIPK4 <- CASP16.

2.2.2 MUC - RIPK cross family analysis

In a recent work Sheng *et al.* [81] show that MUC13 promoted tumor necrosis factro (TNF)-induced NF-κB activation by interacting with TNFR1 and the E3 ligase, cIAP1, to increase ubiquitination of Receptor-interacting serine/threonine-protein kinase 1 (RIPK1). Family members belonging to each of the factors like MUC, RIPK etc, might be involved synergistically in pathological case or otherwise. MUC and RIPK members were found to be up regulated after the treatment of ETC-1922159 in colorectal cancer cells.

Tables 19 and 20 show the rankings of MUC family w.r.t RIPK family and vice versa, respectively. Followed by this is the derived influences between MUC and RIPK. In table 19, MUC1 was found to be highly upregulated with RIPK1. This is reflected in the rankings of 2027 (linear) and 2249 (rbf) for MUC1 - RIPK1. MUC3A was found to be highly upregulated with RIPK3. This is reflected in the rankings of 2208 (laplace) and 2017 (rbf) for MUC3A - RIPK3. MUC12 was found to be highly upregulated with RIPK4. This is reflected in the rankings of 2249 (linear) and 2130 (rbf), for MUC12 - RIPK4. MUC20 was found to be highly upregulated with RIPK3. This is reflected in the rankings of 2192 (laplace), 2288 (linear) and 1796 (rbf) for MUC20 - RIPK3.

RANKING MUC FAMILY W.R.T RIPK FAMILY

Ranking of MUC1 w.r.t RIPK family	laplace	linear	rbf	Ranking of MUCA3 w.r.t MUC3A	laplace	linear	rbf
MUC1 - RIPK1	2027	2249	218	MUC3A - RIPK1	945	186	1508
MUC1 - RIPK2	248	1802	389	MUC3A - RIPK2	840	2390	1653
MUC1 - RIPK3	342	410	342	MUC3A - RIPK3	2208	2017	689
MUC1 - RIPK4	176	162	853	MUC3A - RIPK4	714	1494	797
Ranking of MUC4 w.r.t RIPK family	laplace	linear	rbf	**Ranking of MUC12 w.r.t RIPK family**	laplace	linear	rbf
MUC4 - RIPK1	358	2384	690	MUC12 - RIPK1	317	2437	167
MUC4 - RIPK2	371	500	408	MUC12 - RIPK2	286	2178	76
MUC4 - RIPK3	809	371	1096	MUC12 - RIPK3	747	366	136
MUC4 - RIPK4	652	1863	1248	MUC12 - RIPK4	176	2249	2130
Ranking of MUC13 w.r.t RIPK family	laplace	linear	rbf	**Ranking of MUC17 w.r.t RIPK family**	laplace	linear	rbf
MUC13 - RIPK1	379	2241	227	MUC17 - RIPK1	858	932	1503
MUC13 - RIPK2	824	2483	227	MUC17 - RIPK2	248	934	37
MUC13 - RIPK3	1687	19	24	MUC17 - RIPK3	342	64	329
MUC13 - RIPK4	562	532	184	MUC17 - RIPK4	209	2335	1080
Ranking of MUC20 w.r.t RIPK family	laplace	linear	rbf				
MUC20 - RIPK1	1419	760	1794				
MUC20 - RIPK2	948	2482	137				
MUC20 - RIPK3	2192	2288	1796				
MUC20 - RIPK4	1564	1619	2179				

Table 19 2^{nd} order interaction ranking between MUC w.r.t RIPK family members.

RANKING RIPK FAMILY W.R.T MUC FAMILY

Ranking of RIPK family w.r.t MUC1	laplace	linear	rbf	Ranking of RIPK family w.r.t MUC3A	laplace	linear	rbf
MUC1 - RIPK1	1839	58	2421	MUC3A - RIPK1	783	1668	1842
MUC1 - RIPK2	1913	2091	954	MUC3A - RIPK2	758	2301	459
MUC1 - RIPK3	1038	268	295	MUC3A - RIPK3	268	1595	1893
MUC1 - RIPK4	1385	2246	1298	MUC3A - RIPK4	1770	1109	1461
Ranking of RIPK family w.r.t MUC4	laplace	linear	rbf	**Ranking of RIPK family w.r.t MUC12**	laplace	linear	rbf
MUC4 - RIPK1	562	1621	2216	MUC12 - RIPK1	1462	682	2351
MUC4 - RIPK2	383	924	494	MUC12 - RIPK2	989	597	1798
MUC4 - RIPK3	541	43	129	MUC12 - RIPK3	2158	1286	1636
MUC4 - RIPK4	1981	1949	2028	MUC12 - RIPK4	1577	975	976
Ranking of RIPK family w.r.t MUC13	laplace	linear	rbf	**Ranking of RIPK family w.r.t MUC17**	laplace	linear	rbf
MUC13 - RIPK1	1961	1535	32	MUC17 - RIPK1	260	446	260
MUC13 - RIPK2	784	494	1467	MUC17 - RIPK2	1021	1114	2355
MUC13 - RIPK3	860	1514	1425	MUC17 - RIPK3	427	223	128
MUC13 - RIPK4	107	1387	1972	MUC17 - RIPK4	1567	2225	2048
Ranking of RIPK family w.r.t MUC20	laplace	linear	rbf				
MUC20 - RIPK1	514	2042	420				
MUC20 - RIPK2	1039	1751	1950				
MUC20 - RIPK3	303	2504	280				
MUC20 - RIPK4	794	1193	989				

Table 20 2^{nd} order interaction ranking between RIPK w.r.t MUC family members.

In table 20, RIPK-1/2 was found to be highly upregulated with MUC1. This is reflected in the rankings of 1839 (laplace) and 2421 (rbf) for MUC1 - RIPK1; and 1913 (laplace) and 2091 (lin-

Unexplored combinatorial hypotheses	
MUC w.r.t RIKP family	
MUC1	RIPK1
MUC3A	RIPK3
MUC12	RIPK4
MUC20	RIPK3
RIPK w.r.t MUC family	
MUC1	RIPK1/RIPK2
MUC4	RIPK4
MUC17	RIPK4
MUC20	RIPK2

Table 21 2^{nd} order combinatorial hypotheses between MUC and RIPK.

ear) for MUC1 - RIPK2. RIPK4 was found to be highly upregulated with MUC4. This is reflected in the rankings of 1981 (laplace), 1949 (linear) and 2028 for MUC4 - RIPK4. RIPK4 was found to be highly up regulated with MUC17. This is reflected in the rankings of 2225 (linear) and 2048 (rbf) for MUC17 - RIPK4. RIPK2 was found to be highly up regulated with MUC20. This is reflected in the rankings of 1751 (linear) and 1950 (rbf) for MUC20 - RIPK2.

One can also interpret the results of the table 21 graphically, with the following influences - • MUC w.r.t RIKP family with MUC1 <- RIPK1; MUC3A <- RIPK3; MUC12 <- RIPK4; MUC20 <- RIPK3 and • RIPK w.r.t MUC family with MUC1 -> RIPK-1/2; MUC4 -> RIPK4; MUC17 -> RIPK4; MUC20 -> RIPK2.

2.2.3 TNF - NF-κB-2/I cross family analysis

The NF-κB family and NF-κB-Inhibitor i.e NF-κB-I play a significant role in immune response to infection. Problems in its functioning leads to cancer, infections, inflammatory and autoimmune diseases. The discovery and seminal work by Sen and Baltimore[82] on NF-κB lead to range of research on immune responses and study of related pathological cases. Tanaka and Nakano[83] have shown that NF-κB2 limits TNF-α induced osteoclastogenesis. Recently, in Japanese population, Imamura *et al.*[84] show that the impaired NF-κBIE gene function decreases cellular uptake of methotrexate by down-regulating SLC19A1 expression in a human rheumatoid arthritis cell line. They postulate that NF-κBIE could be closely related to NF-κB activity. Also, Lee *et al.*[85] show through deep study of fold-change analysis of the interrelation between NF-κB and TNFs. However, the synergy between these members has yet not been explored completely. We found some interesting combinations that were allocated high numerical ranking (in silico) to indicate synergistic up regulation in CRC cells after ETC-1922159 treatment, apart from the individual up regulation that was observed in wet experiements.

Ranking TNF family w.r.t NFκB-2/I family

Ranking of TNF family w.r.t NFκB2	laplace	linear	rbf	Ranking of TNF family w.r.t NFκBI-A	laplace	linear	rbf
NFkB2 - TNF	1620	615	1897	NFkBI-A - TNF	820	1495	1109
NFkB2 - TNF-AIP1	324	649	1387	NFkBI-A - TNF-AIP1	1779	1904	1400
NFkB2 - TNF-AIP2	1437	715	1986	NFkBI-A - TNF-AIP2	1247	217	766
NFkB2 - TNF-AIP3	1272	1574	441	NFkBI-A - TNF-AIP3	776	981	212
NFkB2 - TNF-RSF1A	30	2465	575	NFkBI-A - TNF-RSF1A	1580	1422	43
NFkB2 - TNF-RSF10A	2095	817	2509	NFkBI-A - TNF-RSF10A	2499	1438	2191
NFkB2 - TNF-RSF10B	37	1411	250	NFkBI-A - TNF-RSF10B	2075	1555	1401
NFkB2 - TNF-RSF10D	2473	12	1499	NFkBI-A - TNF-RSF10D	2498	2344	2501
NFkB2 - TNF-RSF12A	1813	824	1893	NFkBI-A - TNF-RSF12A	2337	1101	1491
NFkB2 - TNF-RSF14	1799	834	302	NFkBI-A - TNF-RSF14	1974	2045	1136
NFkB2 - TNF-RSF21	332	1973	1719	NFkBI-A - TNF-RSF21	1119	951	903
NFkB2 - TNF-SF10	1627	1614	1299	NFkBI-A - TNF-SF10	2185	499	2316
NFkB2 - TNF-SF15	564	2437	1064	NFkBI-A - TNF-SF15	564	1684	1473

Ranking of TNF family w.r.t NFκBI-E	laplace	linear	rbf	Ranking of TNF family w.r.t NFκBI-Z	laplace	linear	rbf
NFkBI-E - TNF	2443	925	228	NFkBI-Z - TNF	851	776	850
NFkBI-E - TNF-AIP1	1720	685	971	NFkBI-Z - TNF-AIP1	153	397	621
NFkBI-E - TNF-AIP2	2347	1863	964	NFkBI-Z - TNF-AIP2	2188	432	566
NFkBI-E - TNF-AIP3	559	1663	280	NFkBI-Z - TNF-AIP3	775	10	2362
NFkBI-E - TNF-RSF1A	846	1624	176	NFkBI-Z - TNF-RSF1A	399	2006	93
NFkBI-E - TNF-RSF10A	840	359	952	NFkBI-Z - TNF-RSF10A	1380	2004	1540
NFkBI-E - TNF-RSF10B	835	2257	1294	NFkBI-Z - TNF-RSF10B	2204	1438	1991
NFkBI-E - TNF-RSF10D	2454	1018	1566	NFkBI-Z - TNF-RSF10D	2214	2033	2514
NFkBI-E - TNF-RSF12A	383	166	1464	NFkBI-Z - TNF-RSF12A	1638	2370	1841
NFkBI-E - TNF-RSF14	1877	2282	1426	NFkBI-Z - TNF-RSF14	1120	1505	1899
NFkBI-E - TNF-RSF21	2129	1293	831	NFkBI-Z - TNF-RSF21	207	804	344
NFkBI-E - TNF-SF10	890	1096	1816	NFkBI-Z - TNF-SF10	609	1088	1344
NFkBI-E - TNF-SF15	523	1957	32	NFkBI-Z - TNF-SF15	1237	1375	2196

Table 22 2^{nd} order interaction ranking between TNF w.r.t NFkB-2/I family members.

Tables 22 and 23 depict the rankings of TNF family w.r.t to NF-κB-2/I and vice versa, respectively. Followed by this is table 24 that contains the derived influences via majority voting of the rankings in the tables containing two-way cross family rankings.

In table 22 we find TNF-RSF10A/RSF12A up regulated with NFkB2. These are reflected in rankings of 2095 (laplace) and 2509 (rbf) for NFkB2 - TNFRSF10A; and 1813 (laplace) and 1893 (rbf) for NFkB2 - TNFRSF12A. TNF-AIP1/RSF10A/RSF10D/RSF14/SF10 were found to be up regulated with NFkBI-A. These are reflected in rankings of 1779 (laplace) and 1904 (linear) for NFkBI-A - TNF-AIP1; 2499 (laplace) and 2191 (rbf) for NFkBI-A - TNFRSF10A; 2498 (laplace), 2344 (linear) and 2501 (rbf) for NFkBI-A - TNFRSF10D; 1974 (laplace) and 2045 (linear) for NFkBI-A - TNFRSF14; and 2185 (laplace) and 2316 (rbf) for NFkBI-A - TNFSF10, respectively. TNF-AIP2/RSF14 were found to be up regulated with NFkBI-E. These are reflected in rankings of 2347 (laplace) and 1863 (linear) for NFkBI-E - TNFAIP2; and 1877 (laplace) and 2282 (linear) for NFkBI-E - TNFRSF14, respectively. Finally, TNF-RSF10B/RSF10D/RSF12A were found to be up regulated with NFkBI-Z. These are reflected in rankings of 2204 (laplace) and 1991 (rbf) for NFkBI-Z - TNFRSF10B; 2214 (laplace), 2033 (linear) and 2514 (rbf) for NFkBI-Z - TNFRSF10D; and 2370 (linear) and 1841 (rbf) for NFkBI-Z - TNFRSF12A, respectively. In table 23 we find NFkB-2 to be up regulated along with TNF-AIP1/AIP2/AIP3. These are reflected in rankings of 2027 (linear) and 1807 (rbf) for NFkB2 - TNFAIP1;

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Ranking NFkB-2/I family w.r.t TNF family

Ranking of NFkB-2/I family w.r.t TNF				Ranking of NFkB-2/I family w.r.t TNF-AIP1			
	laplace	linear	rbf		laplace	linear	rbf
NFkB-2 - TNF	1632	989	1453	NFkB-2 - TNF-AIP1	2027	1807	1140
NFkBI-A - TNF	904	561	658	NFkBI-A - TNF-AIP1	2072	349	1218
NFkBI-E - TNF	2116	1247	803	NFkBI-E - TNF-AIP1	56	420	1551
NFkBI-Z - TNF	691	51	265	NFkBI-Z - TNF-AIP1	499	1648	646
Ranking of NFkB-2/I family w.r.t TNF-AIP2				Ranking of NFkB-2/I family w.r.t TNF-AIP3			
	laplace	linear	rbf		laplace	linear	rbf
NFkB-2 - TNF-AIP2	2077	1027	2224	NFkB-2 - TNF-AIP3	1042	2336	2130
NFkBI-A - TNF-AIP2	499	22	1192	NFkBI-A - TNF-AIP3	1452	411	637
NFkBI-E - TNF-AIP2	526	1755	338	NFkBI-E - TNF-AIP3	711	1686	2041
NFkBI-Z - TNF-AIP2	452	988	1617	NFkBI-Z - TNF-AIP3	1979	886	278
Ranking of NFkB-2/I family w.r.t TNF-RSF1A				Ranking of NFkB-2/I family w.r.t TNF-RSF10A			
	laplace	linear	rbf		laplace	linear	rbf
NFkB-2 - TNF-RSF1A	648	164	990	NFkB-2 - TNF-RSF10A	611	1007	454
NFkBI-A - TNF-RSF1A	435	1454	130	NFkBI-A - TNF-RSF10A	458	190	1412
NFkBI-E - TNF-RSF1A	431	980	1417	NFkBI-E - TNF-RSF10A	1719	263	374
NFkBI-Z - TNF-RSF1A	550	2213	1447	NFkBI-Z - TNF-RSF10A	342	742	732
Ranking of NFkB-2/I w.r.t TNF-RSF10B				Ranking of NFkB-2/I w.r.t TNF-RSF10D			
	laplace	linear	rbf		laplace	linear	rbf
NFkB-2 - TNF-RSF10B	713	1408	2397	NFkB-2 - TNF-RSF10D	123	1939	543
NFkBI-A - TNF-RSF10B	1237	1054	562	NFkBI-A - TNF-RSF10D	371	948	584
NFkBI-E - TNF-RSF10B	1352	931	2142	NFkBI-E - TNF-RSF10D	2136	621	1811
NFkBI-Z - TNF-RSF10B	165	2407	361	NFkBI-Z - TNF-RSF10D	259	400	1341
Ranking of NFkB-2/I family w.r.t TNF-RSF12A				Ranking of NFkB-2/I family w.r.t TNF-RSF14			
	laplace	linear	rbf		laplace	linear	rbf
NFkB-2 - TNF-RSF12A	250	341	1232	NFkB-2 - TNF-RSF14	299	1253	543
NFkBI-A - TNF-RSF12A	689	2225	17	NFkBI-A - TNF-RSF14	280	1126	277
NFkBI-E - TNF-RSF12A	1188	1133	765	NFkBI-E - TNF-RSF14	278	2025	1557
NFkBI-Z - TNF-RSF12A	973	1590	2298	NFkBI-Z - TNF-RSF14	131	893	1953
Ranking of NFkB-2/I family w.r.t TNF-RSF21				Ranking of NFkB-2/I family w.r.t TNF-SF10			
	laplace	linear	rbf		laplace	linear	rbf
NFkB-2 - TNF-RSF21	250	341	1232	NFkB-2 - TNF-SF10	1643	496	743
NFkBI-A - TNF-RSF21	689	2225	17	NFkBI-A - TNF-SF10	262	1238	1352
NFkBI-E - TNF-RSF21	1188	1133	765	NFkBI-E - TNF-SF10	985	1090	158
NFkBI-Z - TNF-RSF21	973	1590	2298	NFkBI-Z - TNF-SF10	537	1557	2104
Ranking of NFkB-2/I family w.r.t TNF-SF15							
	laplace	linear	rbf				
NFkB-2 - TNF-SF15	1521	786	1211				
NFkBI-A - TNF-SF15	2367	325	1079				
NFkBI-E - TNF-SF15	97	1868	1195				
NFkBI-Z - TNF-SF15	774	407	372				

Table 23 2^{nd} order interaction ranking between NFkB-2/I family w.r.t TNF family members.

2077 (laplace) and 2224 (rbf) for NFkB2 - TNFAIP2; and 2336 (linear) and 2130 (rbf) for NFkB2 - TNFAIP3, respectively. Finally, NFkBI-E was found to be up regulated with TNFRSF10D. These are reflected in rankings of 2136 (laplace) and 1811 (rbf) for NFkBI-E - TNFRSF10D.

One can also interpret the results of the table 24 graphically, with the following influences - • TNF w.r.t NFkB family with NFkB2 -> TNF-RSF10A/RSF12A; NFkBI-A -> TNF-AIP1/RSF10A/RSF10D/RSF14/SF10; NFkBI-E -> TNF-AIP2/RSF14; NFkBI-Z -> TNF-RSF10B/RSF10D/RSF12A; and • NFkB w.r.t TNF family with NFkB-2 <- TNF-AIP1/AIP2/AIP3 and NFkBI-E <- TNF-RSF10D.

2.2.4 NFkB-2/I - STAT cross family analysis

Grivennikov and Karin[86] show the potent collaboration and cross talk of STAT3 and NF-κB in cancer. In chronic lymphocytic leukemia cells, Liu *et al.*[87] observe that STAT-3 activates NF-κB. Co-opertion between STAT3 and NF-κB pathways has been observed in subtypes of diffuse large B Cell Lymphoma by Lam *et al.*[88]. Lee *et al.*[89] also shows a signal network involving coactivated NF-κB and STAT3 and altered p53 modulates BAX/BCL-XL expression and promotes cell survival of head and neck squamous cell carcinomas. These observations show a definite, concommitent functioning of the two pathways and we further found that some of them were up regulated synergistically in CRC cells after ETC-1922159 treatment, via in silico ranking of the combinations. Tables 25 and 26 show ranking of STAT family w.r.t NFkB-2/I and vice versa, respectively. Followed by this is the derived influences from majority voting of rankings in the two foregoing tables, which is shown in table 27.

Unexplored combinatorial hypotheses

TNF w.r.t NFkB-2/I	
NFkB2	TNF-RSF10A/RSF12A
NFkBI-A	TNF-AIP1/RSF10A/RSF10D/RSF14/SF10
NFkBI-E	TNF-AIP2/RSF14
NFkBI-Z	TNF-RSF10B/RSF10D/RSF12A
NFkB-2/I w.r.t TNF	
NFkB-2	TNF-AIP1/AIP2/AIP3
NFkBI-E	TNF-RSF10D

Table 24 2^{nd} order combinatorial hypotheses between NFkB-2/I and TNF

.

Ranking STAT family w.r.t NFkB-2/I family

Ranking of STAT2 w.r.t NFkB-2/I family				Ranking of STAT3 w.r.t NFkB-2/I family			
	laplace	linear	rbf		laplace	linear	rbf
NFkB2 - STAT2	2220	1068	1207	NFkB2 - STAT3	2125	252	1453
NFkBIA - STAT2	2211	1253	2402	NFkBIA - STAT3	1614	702	1333
NFkBIE - STAT2	1809	512	1207	NFkBIE - STAT3	1493	211	1850
NFkBIZ - STAT2	802	2121	1862	NFkBIZ - STAT3	1633	1679	2122
Ranking of NFkB-2/I family w.r.t STAT5A							
	laplace	linear	rbf				
NFkB2 - STAT5A	2034	1321	1502				
NFkBIA - STAT5A	490	2215	283				
NFkBIE - STAT5A	578	1969	2485				
NFkBIZ - STAT5A	2286	473	1409				

Table 25 2^{nd} order interaction ranking between STAT w.r.t NFkB-2/I family members.

Tables 25 and 26 show the rankings of STAT family w.r.t NFkB-2/I and vice versa, respectively. Followed by this is the influence between the components in table 27, via majority voting of the rankings. In the drug treated CRC cells, we found members of the STAT family to be up regulated with NFkB-2/I. These are reflected with rankings of 2211 (laplace) and 2402 (rbf) for NFkBIA -> STAT2; 2121 (linear) and 1862 (rbf) for NFkBIZ -> STAT2; and 1969 (linear) and 2485 (rbf) for NFkBIE -> STAT5A, respectively. One can also interpret the results of the table 27 graphically, with the following influences - • STAT w.r.t NFkB-2/I with NFkBIA -> STAT2; NFkBIZ -> STAT2; and NFkBIE -> STAT5A;

2.2.5 IKBKE and STAT cross family analysis

Ng *et al.*[90] show that phosphorylation of STAT1 by IκB kinase ε (IKBKE) inhibits STAT1 homodimerization, and thus assembly of GAF, but does not disrupt ISGF3 formation. Furthermore, Guo

Ranking NFkB-2/I family w.r.t STAT family

Ranking of NFkB-2/I family w.r.t STAT2	laplace	linear	rbf	Ranking of NFkB-2/I family w.r.t STAT3	laplace	linear	rbf
NFkB2 - STAT2	935	952	86	NFkB2 - STAT3	858	606	162
NFkBIA - STAT2	543	36	1180	NFkBIA - STAT3	1547	88	476
NFkBIE - STAT2	1449	1861	1262	NFkBIE - STAT3	1731	1063	509
NFkBIZ - STAT2	483	1150	262	NFkBIZ - STAT3	1262	489	1145
Ranking of NFkB-2/I family w.r.t STAT3	laplace	linear	rbf				
NFkB2 - STAT5A	558	1070	670				
NFkBIA - STAT5A	1509	1020	81				
NFkBIE - STAT5A	18	854	1052				
NFkBIZ - STAT5A	83	1208	240				

Table 26 2^{nd} order interaction ranking between NFkB-2/I family w.r.t STAT members.

Unexplored combinatorial hypotheses

STAT w.r.t NFkB-2/I	
NFkBIA	STAT2
NFkBIZ	STAT2
NFkBIE	STAT5A

Table 27 2^{nd} order combinatorial hypotheses between NFkB-2/I and TNF

Ranking STAT family vs IKBKE

Ranking of STAT family w.r.t IKBKE family	laplace	linear	rbf	Ranking of IKBKE w.r.t STAT family	laplace	linear	rbf
STAT2 - IKBKE	1267	2033	1892	STAT2 - IKBKE	1604	554	2108
STAT3 - IKBKE	1055	2144	1672	STAT3 - IKBKE	1442	2179	1976
STAT5A - IKBKE	178	1687	1183	STAT5A - IKBKE	2085	2409	2277

Table 28 2^{nd} order interaction ranking between STAT family w.r.t IKBKE.

et al.[91] show that IKBKE is induced by STAT3 and tobacco carcinogen and determines chemosensitivity in non-small cell lung cancer. It has already been established in some cases that IKBKE has a confirmed role with one of the STAT members. Here we found that both IKBKE and STAT were up regulated after ETC-1922159 treatment of CRC cells. Table 28 shows ranking of STAT family vs IKBKE and vice versa. Table 29 shows the dervied influences from majority voting of the rankings. On the left half of table 28 we find STAT2 to be up regulated w.r.t IKBKE. This is reflected with the rankings of 2033 (linear) and 1892 (rbf) for STAT2 - IKBKE. On the right half of the same table we find IKBKE being up regulated w.r.t STAT-3/5A. These are reflected in rankings of 2179 (linear) and 1976 (rbf) for STAT3 - IKBKE; and 2085 (laplace), 2409 (linear) and 2277 (rbf) for STAT5A - IKBKE, respectively. One can also interpret the results of the table 29 graphically, with the following influences - • STAT w.r.t IKBKE with STAT2 <- IKBKE; and • IKBKE w.r.t STAT with STAT3 -> IKBKE and STAT5A -> IKBKE;

Unexplored combinatorial hypotheses

STAT w.r.t IKBKE	
STAT2	IKBKE
IKBKE w.r.t STAT	
STAT3	IKBKE
STAT5A	IKBKE

Table 29 2^{nd} order combinatorial hypotheses between NFkB-2/I and TNF

Ranking TRAF family vs IKBKE

Ranking of IKBKE w.r.t TRAF family	laplace	linear	rbf	Ranking of TRAF family w.r.t IKBKE	laplace	linear	rbf
TRAF4 - IKBKE	1235	2158	2416	TRAF4 - IKBKE	1606	461	1330
TRAF6 - IKBKE	1694	389	1554	TRAF6 - IKBKE	2105	1376	1819
TRAFD1 - IKBKE	1687	532	1793	TRAFD1 - IKBKE	866	733	496
TRAF3IP2 - IKBKE	1349	738	1987	TRAF3IP2 - IKBKE	924	1966	334

Table 30 2^{nd} order interaction ranking between STAT family w.r.t IKBKE.

2.2.6 IKBKE - TRAF cross family analysis

Shen *et al.*[92] show interaction of IKBKE with TRAF2, by observing that IκB kinase ε phosphorylates TRAF2 to promote mammary epithelial cell transformation. Zhou *et al.*[93] observe IKKε-mediated tumorigenesis requires K63-linked polyubiquitination by a cIAP1/cIAP2/TRAF2 E3 ubiquitin ligase complex. Also, Nakanishi and Akira[94] show NF-κB activation through IKK-i-dependent I-TRAF/TANK phosphorylation. These findings suggest interaction between IKBKE - TRAF family members. IKBKE and TRAF members were found to be up regulated in CRC cells treated with ETC-1922159. Their combinations were allocated with high numerical ranks indicating synergistic up regulation. Table 30 rankings between TRAF and IKBKE, both ways. TRAF4 was found to up regulated with IKBKE and the rankings reflect the same with 2158 (linear) and 2416 (rbf). Also IKBKE was found to be up regulated with TRAF6 and the rankings reflect the same with 2105 (laplace) and 1819 (rbf). Table 31 reflects the derived influences graphically for - • TRAF w.r.t IKBKE with TRAF6 <- IKBKE and • IKBKE w.r.t TRAF with TRAF4 -> IKBKE.

2.2.7 ABC transporters - NFkB cross family analysis

Gerbod-Giannone *et al.*[95] observe that TNFα induces ABCA1 through NF-κB in macrophages and in phagocytes ingesting apoptotic cells. ABCA1 has also been found to be a key regulator in cholesterol related problems. Van Eck *et al.*[96] report leukocyte ABCA1 controls susceptibility to atherosclerosis and macrophage recruitment into tissues. The macrophage cholesterol exporter ABCA1 functions as an anti-inflammatory receptor, as shown by Tang *et al.*[97]. Furthermore, macrophage ABCA1 reduces MyD88-

Unexplored combinatorial hypotheses	
TRAF w.r.t IKBKE	
TRAF6	IKBKE
IKBKE w.r.t TRAF	
TRAF4	IKBKE

Table 31 2^{nd} order combinatorial hypotheses between NFkB-2/I and TNF

dependent Toll-like receptor trafficking to lipid rafts by reduction of lipid raft cholesterol, as shown by Zhu *et al.*[98]. These findings suggest the intricate role of NFκB family components play with ABC transporters. Both were up regulated in CRC cells after treatment with ETC-1922159. Our search engine allocated numerically high rank to several of the combinations in silico. These have been tabulated in tables 32 and 33, i.e rankings of ABC transporters w.r.t NFkB members and vice versa, respectively. Table 34 shows the un explored hypotheses between the two in the form of the derived influences after majority voting of the two-way cross family the rankings.

In table 32, we find ABC-C13/ABC-D1 to be up regulated w.r.t. NFkBIE. These are reflected in rankings of 2048 (linear) and 1735 (rbf) for ABC-C13 - NFkBIE and 2380 (laplace) and 1795 (linear) for ABC-D1 - NFkBIE, respectively. In table 33, we find NFkB2 to be up regulated w.r.t ABC-A5/ABC-B11. These are reflected in rankings of 2097 (laplace), 1772 (linear) and 2086 (rbf) for NFkB2 - ABC-A5; and 1916 (linear) and 1955 (rbf) for NFkB2 - ABC-B11, respectively. NFkBIE was up regulated with ABC-C13 and the rankings for the same are reflected in 2318 (laplace) and 2513 (rbf). Also, NFkBIZ was up regulated with ABC-C13 and the rankings for the same are reflected in 1799 (laplace) and 2175 (linear). NFkB2 was up regulated with ABC-G1 and the rankings for the same are reflected in 1951 (laplace), 2240 (linear) and 2215 (rbf).

Finally, 34 shows derived influences which can be represented graphically, with the following influences - • ABC w.r.t NFkB-2/I family with NFkIBE -> ABC-C13/ABC-D1 and • NFkB-2/I w.r.t ABC family with NFkB2 <- ABC-A5/ABC-B11; NFkBIE <- ABC-C13; NFkBIZ <- ABC-C13 and NFkB2 <- ABC-G1;

2.2.8 IKBKE - UBA/UBE cross family analysis

Not much is known about IKBKE and Ubiquitination modifier enzyme and ubiquitination conjugating enzymes interaction. They were found them to be up regulated in CRC cells after ETC-1922159 treatment. Our search engine allocated high ranks to some of the combinations between IKBKE and UBA/UBE family members. These combinations might be worth exploring if it is of interest. Tables 35 shows the rankings of UBE/A w.r.t to IKBKE

Ranking ABC family w.r.t NFkB-2/I family

Ranking of ABC family w.r.t NFkB2	laplace	linear	rbf	Ranking of ABC family w.r.t NFkBI-A	laplace	linear	rbf
NFkB2 - ABC-A5	851	1517	350	ABC-A5 - NFkBIA	398	365	1660
ABC-B11 - NFkB2	1684	400	412	ABC-B11 - NFkBIA	1079	566	104
NFkB2 - ABC-C3	127	2031	6	ABC-C3 - NFkBIA	601	1048	1760
NFkB2 - ABC-C5	1035	1431	889	NFkBIA - ABC-C5	1683	2404	1341
NFkB2 - ABC-C13	1399	1951	747	NFkBIA - ABC-C13	200	886	1275
NFkB2 - ABC-D1	1317	1133	1773	ABC-D1 - NFkBIA	1361	1361	1432
NFkB2 - ABC-G1	1983	1343	1140	ABC-G1 - NFkBIA	21	313	461
NFkB2 - ABC-G2	1322	955	1292	ABC-G2 - NFkBIA	809	613	48

Ranking of ABC family w.r.t NFkBI-E	laplace	linear	rbf	Ranking of ABC family w.r.t NFkBI-Z	laplace	linear	rbf
ABC-A5 - NFkBIE	1445	1662	679	ABC-A5 - NFkBIZ	699	1806	1290
ABC-B11 - NFkBIE	2285	1154	54	ABC-B11 - NFkBIZ	1240	37	803
ABC-C3 - NFkBIE	1547	2168	355	ABC-C3 - NFkBIZ	468	1366	1571
NFkBIE - ABC-C5	876	2048	1735	ABC-C5 - NFkBIZ	1278	1714	1065
NFkBIE - ABC-C13	623	1992	2351	ABC-C13 - NFkBIZ	1083	1063	1386
ABC-D1 - NFkBIE	2380	1795	861	ABC-D1 - NFkBIZ	1677	1688	794
ABC-G1 - NFkBIE	2193	251	208	ABC-G1 - NFkBIZ	979	2373	590
ABC-G2 - NFkBIE	2124	383	766	ABC-G2 - NFkBIZ	86	77	845

Table 32 2^{nd} order interaction ranking between ABC w.r.t NFkB-2/I family members.

Ranking NFkB-2/I family w.r.t ABC family

Ranking of NFkB-2/I family w.r.t ABC-A5	laplace	linear	rbf	Ranking of NFkB-2/I family w.r.t ABC-B11	laplace	linear	rbf
ABC-A5 - NFkB2	2097	1772	2086	NFkB2 - ABC-B11	1916	1955	1020
ABC-A5 - NFkBIA	827	1142	379	NFkBIA - ABC-B11	365	1702	602
ABC-A5 - NFkBIE	1276	1749	1795	NFkBIE - ABC-B11	893	1285	1173
ABC-A5 - NFkBIZ	778	272	930	NFkBIZ - ABC-B11	683	254	421

Ranking of NFkB-2/I family w.r.t ABC-C3	laplace	linear	rbf	Ranking of NFkB-2/I family w.r.t ABC-C5	laplace	linear	rbf
ABC-C3 - NFkB2	1225	936	281	NFkB2 - ABC-C5	1510	1712	939
ABC-C3 - NFkBIA	782	271	1996	NFkBIA - ABC-C5	2017	953	1649
ABC-C3 - NFkBIE	1071	1094	308	NFkBIE - ABC-C5	567	615	1600
ABC-C3 - NFkBIZ	546	653	841	ABC-C5 - NFkBIZ	1978	943	160

Ranking of NFkB-2/I family w.r.t ABC-C13	laplace	linear	rbf	Ranking of NFkB-2/I family w.r.t TNF-ABC-D1	laplace	linear	rbf
NFkB2 - ABC-C13	618	1423	1550	NFkB2 - ABC-D1	2094	1655	318
NFkBIA - ABC-C13	1499	1092	456	NFkBIA - ABC-D1	613	1812	1581
NFkBIE - ABC-C13	2318	586	2513	NFkBIE - ABC-D1	806	2204	410
NFkBIZ - ABC-C13	1799	2175	1068	NFkBIZ - ABC-D1	16	1723	955

Ranking of NFkB-2/I family w.r.t ABC-G1	laplace	linear	rbf	Ranking of NFkB-2/I family w.r.t ABC-G2	laplace	linear	rbf
NFkB2 - ABC-G1	1951	2240	2215	NFkB2 - ABC-G2	957	1427	788
NFkBIA - ABC-G1	1155	258	238	NFKBIA - ABC-G2	508	417	686
NFkBIE - ABC-G1	2034	612	490	NFKBIE - ABC-G2	2223	806	685
NFkBIZ - ABC-G1	1146	324	900	NFkBIZ - ABC-G2	229	221	1196

Table 33 2^{nd} order interaction ranking between NFkB-2/I w.r.t ABC family members.

Unexplored combinatorial hypotheses	
ABC w.r.t NFkB-2/I family	
NFkIBE	ABC-C13/ABC-D1
NFkB-2/I w.r.t ABC family	
NFkB2	ABC-A5/ABC-B11
NFkBIE	ABC-C13
NFkBIZ	ABC-C13
NFkB2	ABC-G1

Table 34 2^{nd} order combinatorial hypotheses between NFkB-2/I and ABC

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and vice versa. We find IKBKE to be up regulated w.r.t UBA/E2 family. These are reflected with rankings of 2327 (laplace), 1807 (linear) and 2066 (rbf) for IKBKE - UBA-1; 2326 (linear) and 2456 (rbf) IKBKE - UBA-7; 2162 (laplace) and 1817 (linear) for IKBKE - UBA-P1; 2422 (laplace) and 2328 (rbf) for IKBKE - UBE2-A; 2367 (linear) and 2427 (rbf) for IKBKE - UBE2-B; and finally 2366 (laplace) and 1909 (rbf) for IKBKE - UBE2-Z; We also find UBA/E2 family to be up regulated w.r.t IKBKE also. This is reflected in rankings of 2189 (laplace) and 2271 (linear) for IKBKE - UBA-7; 2262 (laplace), 1901 (linear) and 2341 (rbf) for IKBKE - UBA-P1; 2293 (laplace), 2319 (linear) and 2396 (rbf) for IKBKE - UBE2-A; 2129 (laplace) and 1795 (linear) for IKBKE - UBE2-B; 2494 (laplace), 2233 (linear) and 1896 (rbf) for IKBKE - UBE2-F; 2016 (laplace) and 2103 (linear) for IKBKE - UBE2-Z;

Ranking UBA/E2 family vs IKBKE

Ranking of UBA/E2 family w.r.t IKBKE				Ranking of IKBKE w.r.t UBA/E2 family			
	laplace	linear	rbf		laplace	linear	rbf
IKBKE - UBA-1	1752	785	966	UBA-1 - IKBKE	2327	1807	2066
IKBKE - UBA-7	2189	2271	1335	IKBKE - UBA-7	1134	2326	2456
IKBKE - UBA-P1	2262	1901	2341	IKBKE - UBA-P1	2162	1817	1407
IKBKE - UBA-LD2	2034	1773	1409	IKBKE - UBA-LD2	1381	1647	556
IKBKE - UBE2-A	2293	2319	2396	IKBKE - UBE2-A	2422	536	2328
IKBKE - UBE2-B	2129	1516	1795	IKBKE - UBE2-B	680	2367	2427
IKBKE - UBE2-F	2494	2233	1896	IKBKE - UBE2-F	2309	181	24
IKBKE - UBE2-H	1265	1666	1257	IKBKE - UBE2-H	385	710	746
IKBKE - UBE2-J1	905	1936	1046	IKBKE - UBE2-J1	903	1729	2215
IKBKE - UBE2-Z	2016	2103	481	IKBKE - UBE2-Z	783	2366	1909

Table 35 2^{nd} order interaction ranking between UBA/E2 family w.r.t IKBKE.

Table 36 shows the derived influences which can be represented graphically, with the following influences - • UBA/E2 w.r.t IKBKE with IKBKE -> UBA-1; IKBKE -> UBA-7; IKBKE -> UBA-P1; and IKBKE -> UBE2-A; IKBKE -> UBE2-B; IKBKE -> UBE2-Z •; IKBKE w.r.t UBE/A2 with IKBKE <- UBA-7; IKBKE <- UBA-P1; IKBKE <- UBA-LD2; and IKBKE <- UBE2-A; IKBKE <- UBE2-B; IKBKE <- UBE2-F; IKBKE <- UBE2-Z;

2.2.9 REL-A/B - NF-kB cross family analysis

REL-A is known to be associated with NF-κB and most deeply studied member of the NF-κB. Tian *et al.* [99] observe that the NFkB subunit RELA is a master transcriptional regulator of the committed epithelial-mesenchymal transition in airway epithelial cells. Ke *et al.* [100] observe that inactivation of NF-κB p65 (RelA) in liver improves insulin sensitivity and inhibits cAMP/PKA pathway. Weichert *et al.* [101] observe that high expression of RelA/p65 is associated with activation of NF-κB-dependent signaling in pancreatic cancer. These findings and many others not cited here show the deep interaction between REL and NF-κB members. Table 37 shows rankings of RELA w.r.t NFkB members and vice versa. Table 38 shows rankings of RELB w.r.t NFkB members and vice versa. Finally, table 39 shows the hypotheses generated from majority voting of the ranks. In table 37 we find RELA to be

Unexplored combinatorial hypotheses

UBA/E2 w.r.t IKBKE	
IKBKE	UBA-1/7/P1
IKBKE	UBE2-A/B/Z
IKBKE w.r.t UBE/A2	
IKBKE	UBA-7/P1/LD2
IKBKE	UBE2-A/B/F/Z

Table 36 2^{nd} order combinatorial hypotheses between NFkB-2/I and TNF

Ranking NFkB-2/I vs REL-A

Ranking of NFkB-2/I family w.r.t REL-A				Ranking of REL-A w.r.t NFkB-2/I family			
	laplace	linear	rbf		laplace	linear	rbf
NFkB2 - RELA	664	420	271	NFkB2 - RELA	2454	794	2307
NFKBIA - RELA	198	205	190	NFKBIA - RELA	2106	2305	1153
NFKBIE - RELA	1503	2321	331	NFKBIE - RELA	1664	456	1926
NFKBIZ - RELA	323	1714	619	NFKBIZ - RELA	1924	1687	1584

Table 37 2^{nd} order interaction ranking between NFkB-2/I VS REL-A family members.

Ranking REL-B vs NFkB-2/I family

Ranking of NFKB-2/I w.r.t REL-B				Ranking of REL-B w.r.t NFKB-2/I			
	laplace	linear	rbf		laplace	linear	rbf
NFkB2 - RELB	503	2146	1788	NFkB2 - RELB	1156	1346	2184
NFKBIA - RELB	239	1576	924	NFKBIA - RELB	968	424	1725
NFKBIE - RELB	1203	714	2200	NFKBIE - RELB	1414	2228	800
NFKBIZ - RELB	1776	2244	1869	NFKBIZ - RELB	746	1281	1055

Table 38 2^{nd} order interaction ranking between NFkB-2/I VS REL-B family members.

up regulated w.r.t NFKB2. This is reflected in rankings of 2454 (laplace) and 2307 (rbf) for NFkB2 - RELA. Similarly, NFKBIA was found to be up regulated w.r.t RELA. This is reflected in rankings of 2106 (laplace) and 2305 (linear) for NFKBIA - RELA. In table 38 we find NFkB2 to be up regulated RELB. This is reflected in 2146 (laplace) and 1788 (rbf) for NFkB2 - RELB. Similarly, we find NFKBIZ to be 1776 (laplace), 2244 (linear) and 1869 (rbf) for NFKBIZ - RELB. Table 39 shows the derived influences which can be represented graphically, with the following influences - • NFkB-2/I family w.r.t REL-B with NFkB2 <- REL-B and NFKBIZ <- RELB and • REL-A w.r.t NFkB-2/I family with NFkB2 -> RELA and NFKBIA -> RELA.

2.3 Tumor necrosis factor related synergies

2.3.1 TNF - WNT cross family analysis

Brooks *et al.* [102] observed TNF-α induced alterations in the Wnt signaling cascade as a potential mechanism for obesity-associated colorectal tumorigenesis. Effects of TNF inhibitors on parathyroid

Unexplored combinatorial hypotheses	
NFkB-2/I family w.r.t REL-B	
NFkB2	RELB
NFKBIZ	RELB
REL-A w.r.t NFkB-2/I family	
NFkB2	RELA
NFKBIA	RELA

Table 39 2^{nd} order combinatorial hypotheses between NFkB-2/I and ABC

hormone and Wnt signaling antagonists in rheumatoid arthritis have been studies in Adami *et al.*[103]. A complex interaction between Wnt signaling and TNF-α in nucleus pulposus cells has been studied by Hiyama *et al.*[104]. Ma and Hottiger[49] study the crosstalk between Wnt/β-catenin and NF-κB signaling pathway during inflammation. Roubert *et al.*[105] study the influence of tumor necrosis factor-α on the tumorigenic Wnt-signaling pathway in human mammary tissue from obese women. Jang *et al.*[106] observe that WNT/β-catenin pathway modulates the TNF-α-induced inflammatory response in bronchial epithelial cells. These studies suggest already existing synergistic roles of WNTs and TNFs. In CRC cells affected with ETC-1922159, members of TNF and WNT family were found to be up regulated. Our search engine alloted high numerical valued ranks to some of the combinations between WNTs and TNFs. Table 40 shows rankings of TNF w.r.t to WNTs on the left half and vice verse on the right half.

On the left half, we found **TNF-RSF1A/RSF10A/RSF10B/SF15** to be up regulated w.r.t WNT2B. These were reflected in rankings of 2170 (laplace) and 2127 (linear) for TNFRSF1A - WNT2B; 1861 (laplace), 2367 (linear) and 1800 (rbf) for TNFRSF10A - WNT2B; 2020 (laplace) and 1881 (rbf) for TNFRSF10B - WNT2B and 2476 (laplace) and 2073 (rbf) for TNFSF15 - WNT2B. **TNF-RSF10A/RSF10D/RSF12A/SF10** were found to be up regulated w.r.t WNT4. These were reflected in rankings of 2509 (laplace) and 2460 (linear) for TNFRSF10A - WNT4; 2233 (linear) and 2126 (rbf) for TNFRSF10D - WNT4; 2294 (linear), 1775 (linear) and 2384 (rbf) for TNFRSF12A - WNT4 and 2451 (linear) and 1782 (rbf) for TNFSF10 - WNT4. **TNF-RSF12A/SF10** were found to be up regulated w.r.t WNT7B. These were reflected in rankings of 2100 (laplace) and 1983 (rbf) for TNFRSF12A - WNT7B and 2462 (laplace) and 2179 (rbf) for TNFSF10 - WNT7B. **TNFRSF21** were found to be up regulated w.r.t WNT9A. These were reflected in rankings of 1805 (laplace) and 1999 (linear) for TNFRSF21 - WNT9A.

On the left half, we found **WNT2B** to be up regulated w.r.t **TNF-RSF10B/RSF10D/RSF14**. These were reflected in rankings of 1797 (laplace) and 2056 (rbf) for TNFRSF10B - WNT2B; 1989 (linear) and 2130 (rbf) for TNFRSF10D - WNT2B and 1932 (laplace) and 2399 (rbf) for TNFRSF14 - WNT2B. **WNT4** was upregulated w.r.t **TNF-AIP3/RSF10B**. These are refliected in rankings of 2336 (laplace), 2511 (linear) and 2342 (rbf) for TNFAIP3 - WNT4 and 2105 (linear) and 2264 (rbf) for TNFRSF10B - WNT4. **WNT7B** was upregulated w.r.t **TNF, TNF-RSF1A/RSF14**. These are reflected in rankings of 2511 (linear) and 2210 (rbf) for TNF - WNT7B; 2084 (laplace), 1975 (linear) and 2154 (rbf) for TNFRSF1A - WNT7B and 2079 (laplace) and 1928 (rbf) for TNFRSF14 - WNT7B. **WNT9A** was upregulated w.r.t **TNF-AIP2/AIP3/RSF10A/RSF12A/SF10**. These are reflected in rankings of 2125 (laplace) and 2437 (linear) for TNFAIP2 - WNT9A; 1764 (laplace) and 2460 (linear) for TNFAIP3 - WNT9A; 2259 (laplace) and 2413 (linear) for TNFRSF10A - WNT9A; 2345 (laplace) and 2466 (rbf) for TNFRSF12A - WNT9A and 2054 (laplace) and 2338 (linear) for TNFSF10 - WNT9A.

Table 41 shows the derived influences which can be represented graphically, with the following influences - • TNF w.r.t WNT with TNF-RSF1A/RSF10A/RSF10B/SF15 <- WNT2B; TNF-RSF10A/RSF10D/RSF12A/SF10 <- WNT4; TNF-RSF12A/SF10 <- WNT7B and TNF-RSF21 <- WNT9A; and • WNT w.r.t TNF with TNF-RSF10B/RSF10D/RSF14 -> WNT2B; TNF-AIP3/RSF10B -> WNT4; TNF, TNF-RSF1A/RSF14 -> WNT7B; and TNF-AIP2/AIP3/RSF10A/RSF12A/SF10 -> WNT9A.

2.3.2 MUC - TNF cross family analysis

In a recent development in Sheng *et al.*[81] MUC13 promoted tumor necrosis factro (TNF)-induced NFkB activation by interacting with TNFR1 and the E3 ligase, cIAP1, to increase ubiquitination of RIPK1. Dharmani *et al.*[107] show that TNF-α and MUC2 (Mucin 2) play major roles in disease onset and progression in dextran sodium sulphate-induced colitis. TNF-α is also shown to induce mucin hypersecretion and MUC2 gene expression by human airway epithelial cells by Levine *et al.*[108]. Also, inhibition of TNF-α induced MUC5AC expression and production by wogonin through the inactivation of NF-κB signaling in airway epithelial cells, as shown by Sikder *et al.*[109]. Similarly, neutrophil elastase induces MUC5AC production in human airway epithelial cells via a cascade involving protein kinase-C, reactive oxygen species, and TNF-α- converting enzyme, as shown by Shao and Nadel[110]. TNF-α or transforming growth factor-α stimulation of human epithelial cells resulted in mucus secretion as measured by MUC5AC mRNA and protein (Lora *et al.*[111]). In earlier experiments by Fischer *et al.*[112], TNF-α was found to stimulate mucin secretion and cyclic GMP production by guinea pig tracheal epithelial cells in vitro. Similar earlier experiments by Lin *et al.*[113], induction of mucin gene expression in middle ear of rats by TNF-α was the potential cause for mucoid otitis media. Effects of TNF-α and IL-1β

Ranking TNF family vs WNT family

Ranking of TNF family w.r.t WNT2B				Ranking of WNT2B w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
TNF - WNT2B	503	893	1656	TNF - WNT2B	1341	808	1366
TNFAIP1 - WNT2B	235	156	1811	TNFAIP1 - WNT2B	1671	1434	1404
TNFAIP2 - WNT2B	868	527	2439	TNFAIP2 - WNT2B	1130	218	1105
TNFAIP3 - WNT2B	1135	2381	1688	TNFAIP3 - WNT2B	997	1280	1902
TNFRSF1A - WNT2B	2170	2127	1628	TNFRSF1A - WNT2B	1747	1857	1550
TNFRSF10A - WNT2B	1861	2367	1800	TNFRSF10A - WNT2B	100	464	1162
TNFRSF10B - WNT2B	2020	615	1881	TNFRSF10B - WNT2B	1797	120	2056
TNFRSF10D - WNT2B	29	2515	1174	TNFRSF10D - WNT2B	1348	1989	2130
TNFRSF12A - WNT2B	1072	2061	1109	TNFRSF12A - WNT2B	1595	298	1432
TNFRSF14 - WNT2B	333	1585	1247	TNFRSF14 - WNT2B	1932	277	2399
TNFRSF21 - WNT2B	1275	648	1114	TNFRSF21 - WNT2B	1396	620	2136
TNFSF10 - WNT2B	1204	2287	1396	TNFSF10 - WNT2B	1732	738	1751
TNFSF15 - WNT2B	2476	359	2073	TNFSF15 - WNT2B	402	128	1875
Ranking of TNF family w.r.t WNT4				Ranking of WNT4 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
TNF - WNT4	1982	1301	928	TNF - WNT4	1021	420	864
TNFAIP1 - WNT4	1434	1078	804	TNFAIP1 - WNT4	1114	337	1015
TNFAIP2 - WNT4	1810	1047	330	TNFAIP2 - WNT4	1611	1341	423
TNFAIP3 - WNT4	646	1955	1534	TNFAIP3 - WNT4	2336	2511	2342
TNFRSF1A - WNT4	915	545	829	TNFRSF1A - WNT4	132	333	1321
TNFRSF10A - WNT4	2509	2460	897	TNFRSF10A - WNT4	535	202	582
TNFRSF10B - WNT4	517	875	1365	TNFRSF10B - WNT4	320	2105	2264
TNFRSF10D - WNT4	1719	2233	2126	TNFRSF10D - WNT4	660	49	341
TNFRSF12A - WNT4	2294	1775	2384	TNFRSF12A - WNT4	649	1756	780
TNFRSF14 - WNT4	1608	2284	1436	TNFRSF14 - WNT4	61	519	1542
TNFRSF21 - WNT4	1915	1596	93	TNFRSF21 - WNT4	201	533	657
TNFSF10 - WNT4	1747	2451	1782	TNFSF10 - WNT4	904	1511	2280
TNFSF15 - WNT4	1542	806	2439	TNFSF15 - WNT4	64	709	793
Ranking of TNF family w.r.t WNT7				Ranking of WNT7 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
TNF - WNT7B	815	381	47	TNF - WNT7B	1530	2511	2210
TNFAIP1 - WNT7B	313	1438	992	TNFAIP1 - WNT7B	2196	519	1058
TNFAIP2 - WNT7B	1897	85	631	TNFAIP2 - WNT7B	2121	599	1313
TNFAIP3 - WNT7B	577	1807	1251	TNFAIP3 - WNT7B	1901	1357	830
TNFRSF1A - WNT7B	165	844	353	TNFRSF1A - WNT7B	2084	1975	2154
TNFRSF10A - WNT7B	1084	1341	2119	TNFRSF10A - WNT7B	1301	1120	1663
TNFRSF10B - WNT7B	1274	1980	744	TNFRSF10B - WNT7B	1209	908	1075
TNFRSF10D - WNT7B	1314	774	1928	TNFRSF10D - WNT7B	1252	2301	1250
TNFRSF12A - WNT7B	2100	1332	1983	TNFRSF12A - WNT7B	1104	22	1879
TNFRSF14 - WNT7B	1576	981	1811	TNFRSF14 - WNT7B	2079	1028	1928
TNFRSF21 - WNT7B	1565	798	720	TNFRSF21 - WNT7B	2114	1219	737
TNFSF10 - WNT7B	1598	2462	2179	TNFSF10 - WNT7B	2129	763	204
TNFSF15 - WNT7B	1026	756	621	TNFSF15 - WNT7B	130	1599	2504
Ranking of TNF family w.r.t WNT9A				Ranking of WNT9A w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
TNF - WNT9A	1624	2025	799	TNF - WNT9A	1121	1930	1400
TNFAIP1 - WNT9A	1433	839	465	TNFAIP1 - WNT9A	1254	569	394
TNFAIP2 - WNT9A	40	2167	397	TNFAIP2 - WNT9A	2125	2437	1605
TNFAIP3 - WNT9A	1427	1109	2040	TNFAIP3 - WNT9A	1764	2460	1032
TNFRSF1A - WNT9A	1470	719	1933	TNFRSF1A - WNT9A	1645	58	1419
TNFRSF10A - WNT9A	2272	1234	918	TNFRSF10A - WNT9A	2259	2413	1204
TNFRSF10B - WNT9A	2249	1222	1071	TNFRSF10B - WNT9A	882	566	813
TNFRSF10D - WNT9A	410	2132	968	TNFRSF10D - WNT9A	1808	1055	568
TNFRSF12A - WNT9A	1080	373	1120	TNFRSF12A - WNT9A	2345	1211	2466
TNFRSF14 - WNT9A	1106	2166	198	TNFRSF14 - WNT9A	1127	1147	1191
TNFRSF21 - WNT9A	1805	1999	986	TNFRSF21 - WNT9A	1265	832	1098
TNFSF10 - WNT9A	1258	864	1839	TNFSF10 - WNT9A	2054	2338	1523
TNFSF15 - WNT9A	1621	1129	1139	TNFSF15 - WNT9A	37	1105	1076

Table 40 2^{nd} order combinatorial hypotheses between ABC and IL

on mucin, lysozyme, IL-6 and IL-8 in passage-2 normal human nasal epithelial cells have been stuided by Yoon *et al.*[114]. Also, Mercogliano *et al.*[115] show that TNF-α induced MUC4 expression elicits trastuzumab resistance in HER2-$+ive$ breast cancer. These findings suggest deep synergy between Mucin family and TNF family members. However, not all synergies might have been explored till now. A set of family members of MUC and TNFs were found to be UP regulated after ETC-1922159 treatment in CRC cells.

Tables 42 and 43 show the additional range of TNFs and MUCs that might be engaged in CRC through the NFkB pathway, in the

Unexplored combinatorial hypotheses

TNF w.r.t WNT	
TNF-RSF1A/RSF10A/RSF10B/SF15	WNT2B
TNF-RSF10A/RSF10D/RSF12A/SF10	WNT4
TNF-RSF12A/SF10	WNT7B
TNF-RSF21	WNT9A
WNT w.r.t TNF	
TNF-RSF10B/RSF10D/RSF14	WNT2B
TNF-AIP3/RSF10B	WNT4
TNF, TNF-RSF1A/RSF14	WNT7B
TNF-AIP2/AIP3/RSF10A/RSF12A/SF10	WNT9A

Table 41 2^{nd} order combinatorial hypotheses between TNF and WNT family.

light of the recent findings of MUC13 and TNFRSF1A in Sheng *et al.*[81]. Table 42 shows the rankings of the TNF family w.r.t to MUCIN family and table 43 shows the rankings of the MUCIN family w.r.t to TNF family. Followed by this are the derived influences from the majority votings of the rankings in the foregoing tables, which are depicted in table 44.

Considering table 42, **TNF family w.r.t MUC1**, we find TNFAIP3, TNFRSF-10D/12A/14 to be highly up regulated. These are reflected in the rankings of 2115 (laplace) and 1882 (rbf) for MUC1 - TNFAIP3; 2303 (laplace) and 2154 (linear) for MUC1 - TNFRSF10D; 2019 (laplace) and 2009 (linear) for MUC1 - TNFRSF12A; and 1955 (laplace) and 1899 (linear) for MUC1 - TNFRSF14. **TNF family w.r.t MUC3A**, we find TNFRSF-10A/10D to be highly up regulated. These are reflected in the rankings of 2237 (laplace) and 1910 (linear) for MUC3 - TNFRSF10A; 1678 (laplace) and 2049 (linear) for MUC3 - TNFRSF10D. **TNF family w.r.t MUC4** we find TNFRSF10D/TNFSF10 to be highly up regulated. These are reflected in the rankings of 2503 (laplace), 2403 (linear) and 2356 (rbf) for MUC4 - TNFRSF10D and 2134 (laplace) and 1957 (linear) for MUC4 - TNFSF10. **TNF family w.r.t MUC12** we find TNFRSF21/TNFSF10 to be highly up regulated. These are reflected in the rankings of 1795 (laplace) and 2438 (linear) for MUC12 - TNFRSF21 and 1795 (linear) 2435 (rbf) for MUC12 - TNFSF10. **TNF family w.rt MUC13** we find TNFRSF10A/TNFRSF10D to be highly up regulated. These are reflected in the rankings of 2500 (laplace) and 1844 (rbf) for MUC13 - TNFRSF10A and 2263 (linear) and 2294 (rbf) for MUC13 - TNFRSF10D. **TNF family w.r.t MUC17** we find TNFRSF-10A/10D/12A to be highly up regulated. These are reflected in the rankings of 2269 (laplace) 2364 (linear) and 2005 (rbf) for MUC17 - TNFRSF10A; 1798 (laplace) and 2302 (rbf) for MUC17 - TNFRSF10D and 2041 (laplace) and 2303 (linear) for

RANKING TNF FAMILY W.R.T MUC FAMILY

RANKING OF TNF FAMILY W.R.T MUC1				RANKING OF TNF FAMILY W.R.T MUC3A			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - TNF	112	72	88	MUC3A - TNF	1353	1659	1479
MUC1 - TNFAIP1	1193	1603	997	MUC3A - TNFAIP1	2178	1209	1347
MUC1 - TNFAIP2	716	405	2340	MUC3A - TNFAIP2	1075	1614	1158
MUC1 - TNFAIP3	2115	1636	1882	MUC3A - TNFAIP3	962	1020	2491
MUC1 - TNFRSF1A	1380	422	1390	MUC3A - TNFRSF1A	461	1708	189
MUC1 - TNFRSF10A	1009	2180	1095	MUC3A - TNFRSF10A	2237	1910	335
MUC1 - TNFRSF10B	1923	732	88	MUC3A - TNFRSF10B	450	1443	2040
MUC1 - TNFRSF10D	2303	2154	376	MUC3A - TNFRSF10D	1678	2049	102
MUC1 - TNFRSF12A	2019	2009	1700	MUC3A - TNFRSF12A	2349	1315	382
MUC1 - TNFRSF14	1955	1899	1429	MUC3A - TNFRSF14	956	1442	1953
MUC1 - TNFRSF21	337	477	968	MUC3A - TNFRSF21	1297	1492	1959
MUC1 - TNFSF10	1111	1592	1198	MUC3A - TNFSF10	891	257	798
MUC1 - TNFSF15	936	986	2391	MUC3A - TNFSF15	2285	795	1164
RANKING OF TNF FAMILY W.R.T MUC4				RANKING OF TNF FAMILY W.R.T MUC12			
	laplace	linear	rbf		laplace	linear	rbf
MUC4 - TNF	1896	231	1355	MUC12 - TNF	1862	102	135
MUC4 - TNFAIP1	864	397	987	MUC12 - TNFAIP1	1386	479	942
MUC4 - TNFAIP2	73	1011	1087	MUC12 - TNFAIP2	1056	303	1587
MUC4 - TNFAIP3	1159	1751	179	MUC12 - TNFAIP3	2493	1259	1330
MUC4 - TNFRSF1A	179	71	16	MUC12 - TNFRSF1A	1709	1440	837
MUC4 - TNFRSF10A	1668	1892	1652	MUC12 - TNFRSF10A	598	531	363
MUC4 - TNFRSF10B	2024	1396	331	MUC12 - TNFRSF10B	409	1572	1297
MUC4 - TNFRSF10D	2503	2403	2356	MUC12 - TNFRSF10D	30	102	149
MUC4 - TNFRSF12A	1684	700	745	MUC12 - TNFRSF12A	298	882	153
MUC4 - TNFRSF14	1675	2029	1146	MUC12 - TNFRSF14	1749	2237	135
MUC4 - TNFRSF21	647	326	323	MUC12 - TNFRSF21	1795	607	2438
MUC4 - TNFSF10	936	2134	1957	MUC12 - TNFSF10	801	1795	2435
MUC4 - TNFSF15	1440	1180	1627	MUC12 - TNFSF15	1741	889	1098
RANKING OF TNF FAMILY W.R.T MUC13				RANKING OF TNF FAMILY W.R.T MUC17			
	laplace	linear	rbf		laplace	linear	rbf
MUC13 - TNF	2282	220	127	MUC17 - TNF	683	362	515
MUC13 - TNFAIP1	378	230	1935	MUC17 - TNFAIP1	117	188	272
MUC13 - TNFAIP2	2464	220	697	MUC17 - TNFAIP2	1311	414	351
MUC13 - TNFAIP3	2274	1233	1446	MUC17 - TNFAIP3	1589	1547	1539
MUC13 - TNFRSF1A	274	2152	514	MUC17 - TNFRSF1A	428	205	329
MUC13 - TNFRSF10A	2500	938	1844	MUC17 - TNFRSF10A	2269	2364	2005
MUC13 - TNFRSF10B	1891	1497	225	MUC17 - TNFRSF10B	1199	1323	2120
MUC13 - TNFRSF10D	1191	2263	2294	MUC17 - TNFRSF10D	1798	1378	2302
MUC13 - TNFRSF12A	460	1753	1704	MUC17 - TNFRSF12A	2041	2303	1049
MUC13 - TNFRSF14	2220	1602	1359	MUC17 - TNFRSF14	2043	825	1700
MUC13 - TNFRSF21	1612	1673	127	MUC17 - TNFRSF21	2013	393	119
MUC13 - TNFSF10	2236	1598	1495	MUC17 - TNFSF10	280	1025	817
MUC13 - TNFSF15	2423	1488	1292	MUC17 - TNFSF15	833	967	950
RANKING OF TNF FAMILY W.R.T MUC20							
	laplace	linear	rbf				
MUC20 - TNF	2267	262	145				
MUC20 - TNFAIP1	1273	2296	178				
MUC20 - TNFAIP2	1062	598	339				
MUC20 - TNFAIP3	2205	435	2136				
MUC20 - TNFRSF1A	483	2346	145				
MUC20 - TNFRSF10A	100	2305	917				
MUC20 - TNFRSF10B	775	1578	1556				
MUC20 - TNFRSF10D	200	1487	799				
MUC20 - TNFRSF12A	318	1607	2258				
MUC20 - TNFRSF14	410	1832	745				
MUC20 - TNFRSF21	1686	2259	164				
MUC20 - TNFSF10	1005	2139	1548				
MUC20 - TNFSF15	2493	387	2108				

Table 42 2^{nd} order interaction ranking between TNF w.r.t MUC family members.

RANKING MUC FAMILY W.R.T TNF FAMILY

RANKING OF MUC1 W.R.T TNF FAMILY				RANKING OF MUC3A W.R.T TNF FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - TNF	368	142	21	MUC3A - TNF	1478	985	2373
MUC1 - TNFAIP1	692	91	1591	MUC3A - TNFAIP1	1485	536	1698
MUC1 - TNFAIP2	2290	476	398	MUC3A - TNFAIP2	1254	1265	75
MUC1 - TNFAIP3	810	492	748	MUC3A - TNFAIP3	1844	960	243
MUC1 - TNFRSF1A	1089	2344	2312	MUC3A - TNFRSF1A	496	574	792
MUC1 - TNFRSF10A	1263	351	826	MUC3A - TNFRSF10A	1315	1525	1815
MUC1 - TNFRSF10B	1630	1604	2103	MUC3A - TNFRSF10B	351	1920	1489
MUC1 - TNFRSF10D	975	1026	984	MUC3A - TNFRSF10D	596	950	1016
MUC1 - TNFRSF12A	1597	1811	1078	MUC3A - TNFRSF12A	436	595	2124
MUC1 - TNFRSF14	739	2119	938	MUC3A - TNFRSF14	1612	1383	329
MUC1 - TNFRSF21	766	1495	2322	MUC3A - TNFRSF21	1254	1357	1162
MUC1 - TNFSF10	1360	1969	477	MUC3A - TNFSF10	774	980	2053
MUC1 - TNFSF15	424	1183	542	MUC3A - TNFSF15	75	1261	624
RANKING OF MUC4 W.R.T TNF FAMILY				RANKING OF MUC12 W.R.T TNF FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
MUC4 - TNF	1656	777	565	MUC12 - TNF	266	1223	628
MUC4 - TNFAIP1	2483	895	390	MUC12 - TNFAIP1	2321	668	2457
MUC4 - TNFAIP2	1875	1792	180	MUC12 - TNFAIP2	281	1829	1913
MUC4 - TNFAIP3	54	498	464	MUC12 - TNFAIP3	2353	153	576
MUC4 - TNFRSF1A	1074	753	68	MUC12 - TNFRSF1A	1481	1952	1406
MUC4 - TNFRSF10A	683	311	997	MUC12 - TNFRSF10A	445	337	888
MUC4 - TNFRSF10B	98	1413	704	MUC12 - TNFRSF10B	792	164	133
MUC4 - TNFRSF10D	1916	230	80	MUC12 - TNFRSF10D	167	193	521
MUC4 - TNFRSF12A	1321	2190	150	MUC12 - TNFRSF12A	216	2093	302
MUC4 - TNFRSF14	606	704	1493	MUC12 - TNFRSF14	105	59	69
MUC4 - TNFRSF21	1225	1967	1093	MUC12 - TNFRSF21	1471	1975	1769
MUC4 - TNFSF10	815	1108	1906	MUC12 - TNFSF10	662	2135	2255
MUC4 - TNFSF15	1141	1841	920	MUC12 - TNFSF15	1619	2204	1257
RANKING OF MUC13 W.R.T TNF FAMILY				RANKING OF MUC17 W.R.T TNF FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
MUC13 - TNF	623	292	295	MUC17 - TNF	203	811	57
MUC13 - TNFAIP1	823	755	81	MUC17 - TNFAIP1	381	193	118
MUC13 - TNFAIP2	1118	2464	116	MUC17 - TNFAIP2	1069	822	136
MUC13 - TNFAIP3	1189	546	541	MUC17 - TNFAIP3	2132	47	937
MUC13 - TNFRSF1A	978	1506	490	MUC17 - TNFRSF1A	120	497	864
MUC13 - TNFRSF10A	1180	540	1926	MUC17 - TNFRSF10A	852	218	346
MUC13 - TNFRSF10B	280	1105	190	MUC17 - TNFRSF10B	933	1667	1166
MUC13 - TNFRSF10D	655	725	1668	MUC17 - TNFRSF10D	546	133	304
MUC13 - TNFRSF12A	401	1242	999	MUC17 - TNFRSF12A	18	1675	86
MUC13 - TNFRSF14	1324	374	389	MUC17 - TNFRSF14	819	296	1014
MUC13 - TNFRSF21	690	2337	107	MUC17 - TNFRSF21	1659	814	889
MUC13 - TNFSF10	1146	1208	2159	MUC17 - TNFSF10	387	1542	156
MUC13 - TNFSF15	1633	314	155	MUC17 - TNFSF15	1207	1040	522
RANKING OF MUC20 W.R.T TNF FAMILY							
	laplace	linear	rbf				
MUC20 - TNF	57	216	903				
MUC20 - TNFAIP1	1265	2266	2057				
MUC20 - TNFAIP2	241	2404	2157				
MUC20 - TNFAIP3	484	1012	513				
MUC20 - TNFRSF1A	748	173	2193				
MUC20 - TNFRSF10A	620	427	1054				
MUC20 - TNFRSF10B	765	1563	790				
MUC20 - TNFRSF10D	509	2185	794				
MUC20 - TNFRSF12A	216	2093	302				
MUC20 - TNFRSF14	2298	651	1368				
MUC20 - TNFRSF21	2374	1611	1140				
MUC20 - TNFSF10	1257	1088	1031				
MUC20 - TNFSF15	142	2159	7				

Table 43 2^{nd} order interaction ranking between MUC w.r.t TNF family members.

MUC17 - TNFRSF12A. **TNF family w.r.t MUC20** we find TNFAIP3/TNFSF15 to be highly up regulated. These are reflected in the rankings of 2205 (laplace) and 2136 (rbf) for MUC20 - TNFAIP3 and 2493 (laplace) and 2108 (rbf) for MUC20 - TNFSF15.

Considering table 43, **MUC1 w.r.t TNF family**, we find TNFRSF1A to be highly up regulated. These are reflected in the rankings of 2344 (linear) and 2312 (rbf) for MUC1 - TNFRSF1A. **MUC4 w.r.t TNF family**, we find TNFAIP2 to be highly up regulated. These are reflected in the rankings of 1875 (laplace) and 1792 (linear) for MUC4 - TNFAIP2. **MUC12 w.r.t TNF family** we find TNFAIP1/TNFAIP2/TNFRSF21/TNFSF10 to be highly up regulated. These are reflected in the rankings of 2321 (laplace) and 2457 (rbf) for MUC12 - TNFAIP1; 1829 (linear) and 1913 (rbf) for MUC12 - TNFAIP2; 1975 (linear) and 1769 (rbf) for MUC12 - TNFRSF21; 2135 (linear) and 2255 (rbf) for MUC12 - TNFSF10. **MUC12 w.r.t TNF family** we find TNFRSF21/TNFSF10 to be highly up regulated. These are reflected in the rankings of 1795 (laplace) and 2438 (linear) for MUC12 - TNFRSF21 and 1795 (linear) and 2435 (rbf) for MUC12 - TNFSF10. **MUC20 w.r.t TNF family** we find TNFAIP1/TNFAIP2 to be highly up regulated.

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UNEXPLORED COMBINATORIAL HYPOTHESES

TNF w.r.t MUC	
MUC1	TNFAIP3/TNFRSF10D/TNFRSF12A/TNFRSF14
MUC3A	TNFRSF10A/TNFRSF10D
MUC4	TNFRSF10D/TNFSF10
MUC12	TNFRSF21/TNFSF10
MUC13	TNFRSF10A/TNFRSF10D
MUC17	TNFRSF10A/TNFRSF10D/TNFRSF12A
MUC20	TNFAIP3/TNFSF15
MUC w.r.t TNF	
MUC1	TNFRSF1A
MUC4	TNFAIP2
MUC12	TNFAIP1/TNFAIP2/TNFRSF21/TNFSF10
MUC13	TNFAIP1/TNFAIP2

Table 44 2^{nd} order combinatorial hypotheses between MUC and TNF.

These are reflected in the rankings of 2266 (laplace) and 2057 (rbf) for MUC20 - TNFAIP1 and 2404 (linear) and 2157 (rbf) for MUC20 - TNFAIP2.

One can also interpret the results of the table 44 graphically, with the following influences - • TNF family w.r.t MUC family with MUC1 -> TNFAIP3/TNFRSF-10D/12A/14; MUC3A -> TNFRSF-10A/10D; MUC4 -> TNFRSF10D/TNFSF10; MUC12 -> TNFRSF21/TNFSF10; MUC13 -> TNFRSF-10A/10D; MUC17 -> TNFRSF-10A/10D/12A; MUC20 -> TNFAIP3/TNFSF15 and • MUC family w.r.t TNF family with MUC1 <- TNFRSF1A; MUC4 <- TNFAIP2; MUC12 <- TNFAIP1/TNFAIP2/TNFRSF21/TNFSF10 and MUC13 <- TNFAIP1/TNFAIP2.

2.3.3 STEAP4 - TNF cross family analysis

STEAP4 or six transmembrane epithelial antigen of prostate 4, resides in the golgi apparatus and functions as a metalloreductase with the capacity to reduce insoluble ferric ions Fe^{3+} to soluble ferrous ions Fe^{2+}. Emerging role of STEAP4 in metabolism and homeostasis of cellular iron and copper in metabolism and homeostasis of cellular iron and copper has been studied in Scarl *et al.* [116]. STEAP4 was first identified as a novel gene induced by TNF-α during adipose differentiation by Moldes *et al.* [117]. Zhang *et al.* [118] observe that STEAP4 was up-regulated by LPS at a very early time point, consistent with reports that STEAP4 could be up-regulated by tumor necrosis factor-alpha. Tanaka *et al.* [119] show that STEAP4 is expressed on monocytes/neutrophils, and is regulated by TNF antagonist in patients with rheumatoid arthritis. Also, Tanaka *et al.* [120] show STEAP4 is a tumor necrosis factor alpha-induced protein that regulates IL-6, IL-8, and cell proliferation in synovium from patients with rheumatoid arthritis. Gauss *et al.* [121] observe that the STEAP4 expression in adipocytes is normally induced by nutritional stress, leptin, and proinflammatory cytokines, including TNF-α, interleukin-1β, and interleukin-6. ZHANG *et al.* [122] show that the downregulation of STEAP4, a

RANKING TNF FAMILY VS STEAP4 FAMILY

RANKING OF TNF FAMILY W.R.T STEAP4				RANKING OF STEAP4 W.R.T IL FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
TNF - STEAP4	1579	1914	2130	TNF - STEAP4	1116	1482	999
TNFAIP1 - STEAP4	2189	1293	1910	TNFAIP1 - STEAP4	691	611	1105
TNFAIP2 - STEAP4	1172	2002	1840	TNFAIP2 - STEAP4	228	1747	2463
TNFAIP3 - STEAP4	1458	1882	2197	TNFAIP3 - STEAP4	159	727	219
TNFRSF1A - STEAP4	803	75	1086	TNFRSF1A - STEAP4	1483	408	1966
TNFRSF10A - STEAP4	239	1949	339	TNFRSF10A - STEAP4	1512	1796	2026
TNFRSF10B - STEAP4	2210	1717	1827	TNFRSF10B - STEAP4	565	571	248
TNFRSF10D - STEAP4	510	2192	1797	TNFRSF10D - STEAP4	1018	2339	2405
TNFRSF12A - STEAP4	757	338	1497	TNFRSF12A - STEAP4	1495	1430	581
TNFRSF14 - STEAP4	1323	1512	792	TNFRSF14 - STEAP4	1363	1956	2256
TNFRSF21 - STEAP4	1643	1920	165	TNFRSF21 - STEAP4	1646	802	160
TNFSF10 - STEAP4	2083	544	1773	TNFSF10 - STEAP4	845	675	2468
TNFSF15 - STEAP4	631	1296	1020	TNFSF15 - STEAP4	1558	600	784

Table 45 2^{nd} order combinatorial hypotheses between STEAP4 and TNF

highly-expressed TNF-α-inducible gene in adipose tissue, is associated with obesity in humans 1. Liang *et al.* [123] show that STEAP comprises a novel inflammatory nexus in patients with pustular skin disorders. They show that in primary human keratinocytes STEAP4 expression was induced by TNF-α, IL-1β, IL-36α, IL-36γ, IL-17A, and IL-17A combined with TNF-α or IL-22. Gomes *et al.* [124] further show the TNF STEAP interactions while studying the structure of STEAP proteins and its applications to cancer therapy. Such interactions point to the existing synergy between STEAP4 and TNF-α. In CRC cells treated with ETC-1922159, both TNF members and STEAP4 were found to be up regulated. Our search engine alloted the dual combinations with numerically high ranked values thus pointing to the possible synergies that might be existing in the cells and may not have been explored. Table 45 shows the rankings of each with the other. On the left we found, **TNF, TNF-AIP1/AIP2/AIP3/RSF10B/RSF10D/SF10** to be up regulated w.r.t STEAP4. These are reflected in rankings of 1914 (linear) and 2130 (rbf) for TNF - STEAP4; 2189 (laplace) and 1910 (rbf) for TNFAIP1 - STEAP4; 2002 (linear) and 1840 (rbf) for TNFAIP2 - STEAP4; 1882 (linear) and 2197 (rbf) for TNFAIP3 - STEAP4; 2210 (laplace), 1717 (linear) and 1827 (rbf) for TNFRSF10B - STEAP4; 2192 (linear) and 1797 (rbf) for TNFRSF10D - STEAP4; and 2083 (laplace) and 1773 (rbf) for TNFSF10 - STEAP4. On the right we found, **STEAP4** to be up regulated w.r.t TNF-RSF10A/RSF10D/RSF14. These are reflected in rankings of 1796 (linear) and 2026 (rbf) for TNFRSF10A - STEAP4; 2339 (linear) and 2405 (rbf) for TNFRSF10D - STEAP4; and 1956 (linear) and 2256 (rbf) for TNFRSF14 - STEAP4.

One can also interpret the results of the table 44 graphically, with the following influences - • TNF w.r.t STEAP4 with TNF, TNF-AIP1/AIP2/AIP3/RSF10B/RSF10D/SF10 <- STEAP4 and • STEAP4 w.r.t TNF with TNF-RSF10A/RSF10D/RSF14 -> STEAP4.

2.3.4 TNF - UBE2 cross family analysis

Fu *et al.* [125] show that the ubiquitin conjugating enzyme UBE2L3 regulates TNFα-induced linear ubiquitination. They show by western blotting of HOIL-1L immunoprecipitates demonstrates

Unexplored combinatorial hypotheses	
TNF w.r.t STEAP4	
TNF, TNF-AIP1/AIP2/AIP3/RSF10B/RSF10D/SF10	STEAP4
STEAP4 w.r.t TNF	
TNF-RSF10A/RSF10D/RSF14	STEAP4

Table 46 2^{nd} order combinatorial hypotheses between TNF and STEAP4 family.

that endogenous HOIL-1L interacts with endogenous UBE2L3 in vivo and these associations are stable following TNFα stimulation. Through various hypotheses, the authors show the interaction of UBE2L3 with TNF. In conclusion, the authours state that increased UBE2L3 expression enhances NF-ÎžB activation, and increased levels of NF-ÎžB activity are linked to inflammatory and autoimmune diseases. Li *et al.* [126] show that TNF-α increases ubiquitin-conjugating activity in skeletal muscle by up-regulating UBCH2/E2$_{20k}$. Shembade *et al.* [127] show that IL-1β or TNF induce late depletion of UBE2D3 (UBCH5C) and UBE2N (UBC13) in mouse embryonic fibroblasts. These studies show a definite synergy between UBE family and TNFs. In CRC cells treated with ETC-1922159, both TNF members and UBE2 were found to be up regulated. Our search engine alloted the dual combinations with numerically high ranked values thus pointing to the possible synergies that might be existing in the cells and may not have been explored. Tables 47 and 48 shows the rankings of each with the other.

On the left side is the ranking of UBE2 family w.r.t TNF family. We found **UBE2A** to be up regulated w.r.t TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF10D/RSF12A/RSF14/RSF21/SF15. These are reflected in rankings of 2357 (linear) and 2455 (rbf) for TNFAIP1 - UBE2A; 2457 (laplace) and 2020 (rbf) for TNFRSF1A - UBE2A; 2164 (laplace) and 2126 (linear) for TNFRSF10A - UBE2A; 2284 (laplace) and 1901 (linear) for TNFRSF10B - UBE2A; 1989 (laplace) and 2291 (linear) for TNFRSF10D - UBE2A; 2484 (laplace) and 2427 (linear) for TNFRSF12A - UBE2A; 2301 (laplace), 2180 (linear) and 2323 (rbf) for TNFRSF14 - UBE2A; 2419 (laplace) and 2035 (linear) for TNFRSF21 - UBE2A; 1768 (laplace) and 1942 (rbf) for TNFSF15 - UBE2A. **UBE2B** to be up regulated w.r.t TNF-RSF10A/RSF10B/RSF10D/RSF14/RSF21. These are reflected in rankings of 2132 (laplace) and 2184 (rbf) for TNFRSF10A - UBE2B; 2399 (laplace) and 2000 (linear) for TNFRSF10B - UBE2B; 1959 (laplace) and 2232 (rbf) for TNFRSF10D - UBE2B; 2297 (linear) and 2373 (rbf) for TNFRSF14 - UBE2B; and 1986 (laplace) and 1754 (rbf) for TNFRSF21 - UBE2B. **UBE2F** to be up regulated w.r.t TNF, TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF12A/SF15. These are reflected in rankings of 2162 (laplace), 2484 (linear) and 2500 (rbf) for TNF - UBE2F; 1732 (laplace), 2239 (linear) and 2003 (rbf) for TNFAIP1 - UBE2F; 1980 (laplace), 2255 (linear) and 1872 (rbf) for TNFRSF1A - UBE2F; 2085 (laplace), 2218 (linear) for TNFRSF10A - UBE2F; 2432 (laplace), 2011 (linear) and 2144 (rbf) for TNFRSF10B - UBE2F; 2458 (laplace) and 2336 (linear) for TNFRSF12A - UBE2F; 1910 (laplace) and 2353 (rbf) for TNFSF15 - UBE2F; **UBE2H** to be up regulated w.r.t TNF-RSF12A/RSF14/RSF21. These are reflected in rankings of 1950 (laplace), 1793 (linear) and 1851 (rbf) for TNFRSF12A - UBE2H; 2297 (laplace) and 2385 (rbf) for TNFRSF14 - UBE2H; and 2022 (laplace) and 2231 (rbf) for TNFRSF21 - UBE2H; **UBE2J1** to be up regulated w.r.t TNF, TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF12A/RSF14/RSF21/SF15. These are reflected in rankings of 2308 (linear) and 2336 (rbf) for TNF - UBE2J1; 2292 (linear) and 1756 (rbf) for TNFAIP1 - UBE2J1; 1992 (laplace) and 2268 (rbf) for TNFRSF1A - UBE2J1; 1893 (laplace), 2090 (linear) and 2363 (rbf) for TNFRSF10A - UBE2J1; 1913 (laplace) and 1838 (rbf) for TNFRSF10B - UBE2J1; 2401 (laplace) and 1901 (linear) for TNFRSF12A -

Ranking TNF family vs UBE2 family							
Ranking of UBE2A w.r.t TNF family				Ranking of TNF family w.r.t UBE2A			
	laplace	linear	rbf		laplace	linear	rbf
TNF - UBE2A	1360	2307	1720	TNF - UBE2A	499	1379	750
TNFAIP1 - UBE2A	498	2357	2455	TNFAIP1 - UBE2A	1340	2494	578
TNFAIP2 - UBE2A	524	1161	2385	TNFAIP2 - UBE2A	441	1852	691
TNFAIP3 - UBE2A	855	1642	812	TNFAIP3 - UBE2A	1157	1048	207
TNFRSF1A - UBE2A	2457	1087	2020	TNFRSF1A - UBE2A	1066	655	1701
TNFRSF10A - UBE2A	2164	2126	621	TNFRSF10A - UBE2A	2116	858	2376
TNFRSF10B - UBE2A	2284	1901	1203	TNFRSF10B - UBE2A	362	1083	756
TNFRSF10D - UBE2A	1989	2291	677	TNFRSF10D - UBE2A	1848	1336	903
TNFRSF12A - UBE2A	2484	2427	339	TNFRSF12A - UBE2A	1537	1304	629
TNFRSF14 - UBE2A	2301	2180	2323	TNFRSF14 - UBE2A	908	1519	1945
TNFRSF21 - UBE2A	2419	2035	1169	TNFRSF21 - UBE2A	605	2245	60
TNFSF10 - UBE2A	832	2202	1036	TNFSF10 - UBE2A	1520	44	2125
TNFSF15 - UBE2A	1768	1184	1942	TNFSF15 - UBE2A	545	580	1448
Ranking of UBE2B w.r.t TNF family				Ranking of TNF family w.r.t UBE2B			
	laplace	linear	rbf		laplace	linear	rbf
TNF - UBE2B	1072	2046	1316	TNF - UBE2B	1719	218	346
TNFAIP1 - UBE2B	1097	744	1295	TNFAIP1 - UBE2B	920	90	1028
TNFAIP2 - UBE2B	669	1158	2407	TNFAIP2 - UBE2B	1680	147	45
TNFAIP3 - UBE2B	470	1528	1388	TNFAIP3 - UBE2B	2259	742	1610
TNFRSF1A - UBE2B	937	1473	2390	TNFRSF1A - UBE2B	1277	1454	1258
TNFRSF10A - UBE2B	2132	1128	2184	TNFRSF10A - UBE2B	551	2318	2265
TNFRSF10B - UBE2B	2399	2000	402	TNFRSF10B - UBE2B	2272	1268	1080
TNFRSF10D - UBE2B	1959	1562	2232	TNFRSF10D - UBE2B	1157	207	1729
TNFRSF12A - UBE2B	1632	12	2259	TNFRSF12A - UBE2B	1940	1868	1758
TNFRSF14 - UBE2B	1137	2297	2373	TNFRSF14 - UBE2B	1143	1657	1507
TNFRSF21 - UBE2B	1986	1439	1754	TNFRSF21 - UBE2B	1291	569	17
TNFSF10 - UBE2B	2265	1488	769	TNFSF10 - UBE2B	2208	2326	2470
TNFSF15 - UBE2B	1432	2460	1655	TNFSF15 - UBE2B	2055	1964	183
Ranking of UBE2F w.r.t TNF family				Ranking of TNF family w.r.t UBE2F			
	laplace	linear	rbf		laplace	linear	rbf
TNF - UBE2F	2162	2484	2500	TNF - UBE2F	638	435	1471
TNFAIP1 - UBE2F	1732	2239	2003	TNFAIP1 - UBE2F	447	1376	1357
TNFAIP2 - UBE2F	693	1446	1706	TNFAIP2 - UBE2F	900	208	883
TNFAIP3 - UBE2F	498	2265	1264	TNFAIP3 - UBE2F	1881	113	1185
TNFRSF1A - UBE2F	1980	2255	1872	TNFRSF1A - UBE2F	368	1756	266
TNFRSF10A - UBE2F	2085	2218	179	TNFRSF10A - UBE2F	1767	1599	781
TNFRSF10B - UBE2F	2432	2011	2144	TNFRSF10B - UBE2F	1413	1157	1510
TNFRSF10D - UBE2F	1164	1400	2150	TNFRSF10D - UBE2F	389	206	2481
TNFRSF12A - UBE2F	2458	2336	531	TNFRSF12A - UBE2F	581	2022	630
TNFRSF14 - UBE2F	1757	574	1070	TNFRSF14 - UBE2F	2324	1924	1954
TNFRSF21 - UBE2F	1056	2498	1418	TNFRSF21 - UBE2F	718	2123	1022
TNFSF10 - UBE2F	1710	2365	1691	TNFSF10 - UBE2F	1656	1584	810
TNFSF15 - UBE2F	1910	1171	2353	TNFSF15 - UBE2F	1224	1637	394

Table 47 2^{nd} order combinatorial hypotheses between UBE2 and TNF

Ranking TNF family vs UBE2 family

Ranking of UBE2H w.r.t TNF family				Ranking of TNF family w.r.t UBE2H			
	laplace	linear	rbf		laplace	linear	rbf
TNF - UBE2H	967	1966	1018	TNF - UBE2H	2277	770	640
TNFAIP1 - UBE2H	1235	1484	817	TNFAIP1 - UBE2H	883	2396	608
TNFAIP2 - UBE2H	1251	978	2517	TNFAIP2 - UBE2H	762	1362	593
TNFAIP3 - UBE2H	889	1055	1837	TNFAIP3 - UBE2H	1942	1421	1467
TNFRSF1A - UBE2H	589	1498	1428	TNFRSF1A - UBE2H	1134	2154	182
TNFRSF10A - UBE2H	1317	905	2229	TNFRSF10A - UBE2H	1139	202	1061
TNFRSF10B - UBE2H	33	2128	1725	TNFRSF10B - UBE2H	1053	539	1207
TNFRSF10D - UBE2H	1326	1814	1657	TNFRSF10D - UBE2H	2227	926	791
TNFRSF12A - UBE2H	1950	1793	1851	TNFRSF12A - UBE2H	1347	776	1899
TNFRSF14 - UBE2H	2297	1601	2385	TNFRSF14 - UBE2H	2244	703	1208
TNFRSF21 - UBE2H	2022	1131	2231	TNFRSF21 - UBE2H	827	880	672
TNFSF10 - UBE2H	2387	7	760	TNFSF10 - UBE2H	1313	1169	2002
TNFSF15 - UBE2H	125	58	96	TNFSF15 - UBE2H	350	2416	1960
Ranking of UBE2J1 w.r.t TNF family				Ranking of TNF family w.r.t UBE2J1			
	laplace	linear	rbf		laplace	linear	rbf
TNF - UBE2J1	1289	2308	2336	TNF - UBE2J1	1101	1549	105
TNFAIP1 - UBE2J1	1109	2292	1756	TNFAIP1 - UBE2J1	329	1971	252
TNFAIP2 - UBE2J1	1379	1516	1696	TNFAIP2 - UBE2J1	112	22	969
TNFAIP3 - UBE2J1	187	1261	1065	TNFAIP3 - UBE2J1	289	891	1202
TNFRSF1A - UBE2J1	1992	326	2268	TNFRSF1A - UBE2J1	1422	624	73
TNFRSF10A - UBE2J1	1893	2090	2363	TNFRSF10A - UBE2J1	2379	2213	2135
TNFRSF10B - UBE2J1	1913	1299	1838	TNFRSF10B - UBE2J1	807	1793	1231
TNFRSF10D - UBE2J1	325	1500	588	TNFRSF10D - UBE2J1	2393	1360	2102
TNFRSF12A - UBE2J1	2401	1901	437	TNFRSF12A - UBE2J1	380	1284	650
TNFRSF14 - UBE2J1	2277	2347	1943	TNFRSF14 - UBE2J1	1614	2133	2313
TNFRSF21 - UBE2J1	1976	2333	1681	TNFRSF21 - UBE2J1	1315	1266	1070
TNFSF10 - UBE2J1	511	2508	506	TNFSF10 - UBE2J1	1322	203	1148
TNFSF15 - UBE2J1	2021	2013	2515	TNFSF15 - UBE2J1	678	886	1128
Ranking of UBE2Z w.r.t TNF family				Ranking of TNF family w.r.t UBE2Z			
	laplace	linear	rbf		laplace	linear	rbf
TNF - UBE2Z	2264	2505	2479	TNF - UBE2Z	739	701	1241
TNFAIP1 - UBE2Z	1283	2055	2332	TNFAIP1 - UBE2Z	1198	1213	226
TNFAIP2 - UBE2Z	2404	1625	2139	TNFAIP2 - UBE2Z	1281	1431	492
TNFAIP3 - UBE2Z	1066	1152	1627	TNFAIP3 - UBE2Z	530	51	972
TNFRSF1A - UBE2Z	2473	2194	2405	TNFRSF1A - UBE2Z	692	43	1382
TNFRSF10A - UBE2Z	2234	2152	713	TNFRSF10A - UBE2Z	2410	2103	1513
TNFRSF10B - UBE2Z	1501	451	2081	TNFRSF10B - UBE2Z	948	1369	403
TNFRSF10D - UBE2Z	2264	2360	2278	TNFRSF10D - UBE2Z	1786	661	1746
TNFRSF12A - UBE2Z	2207	2149	353	TNFRSF12A - UBE2Z	1621	2010	1448
TNFRSF14 - UBE2Z	1683	1983	705	TNFRSF14 - UBE2Z	1779	1360	2100
TNFRSF21 - UBE2Z	994	604	219	TNFRSF21 - UBE2Z	459	1030	584
TNFSF10 - UBE2Z	516	2374	2235	TNFSF10 - UBE2Z	1100	2047	168
TNFSF15 - UBE2Z	2081	1037	2102	TNFSF15 - UBE2Z	1342	1180	536

Table 48 2^{nd} order combinatorial hypotheses between UBE2 and TNF

Unexplored combinatorial hypotheses

UBE2 w.r.t TNF	
TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF10D/RSF12A/RSF14/RSF21/SF15	UBE2A
TNF-RSF10A/RSF10B/RSF10D/RSF14/RSF21	UBE2B
TNF, TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF12A/SF15	UBE2F
TNF-RSF12A/RSF14/RSF21	UBE2H
TNF, TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF12A/RSF14/RSF21/SF15	UBE2J1
TNF, TNF-AIP1/AIP2/RSF1A/RSF10A/RSF10D/RSF12A/SF10/SF15	UBE2Z
TNF w.r.t UBE2	
TNF-RSF10A	UBE2A
TNF-RSF10A/RSF12A/SF10/SF15	UBE2B
TNF-RSF14	UBE2F
TNF-SF15	UBE2H
TNF-RSF10A/RSF10D/RSF14	UBE2J1
TNF-RSF10A/RSF14	UBE2Z

Table 49 2^{nd} order combinatorial hypotheses between TNF and UBE2 family.

UBE2J1; 2277 (laplace), 2347 (linear) and 1943 (rbf) for TNFRSF14 - UBE2J1; 1976 (laplace), 2333 (linear) for TNFRSF21 - UBE2J1; and 2021 (laplace), 2013 (linear) and 2515 (rbf) for TNFSF15 - UBE2J1; **UBE2Z** to be up regulated w.r.t TNF, TNF-AIP1/AIP2/RSF1A/RSF10A/RSF10D/RSF12A/SF10/SF15. These are reflected in rankings of 2264 (laplace), 2505 (linear) and 2479 (rbf) for TNF - UBE2Z; 2055 (linear) and 2332 (rbf) for TNFAIP1 - UBE2Z; 2404 (laplace) and 2139 (rbf) for TNFAIP2 - UBE2Z; 2473 (laplace), 2194 (linear) and 2405 (rbf) for TNFRSF1A - UBE2Z; 2234 (laplace) and 2152 (linear) for TNFRSF10A - UBE2Z; 2264 (laplace), 2360 (linear) and 2278 (rbf) for TNFRSF10D - UBE2Z; 2207 (laplace) and 2149 (linear) for TNFRSF12A - UBE2Z; 2374 (linear) and 2235 (rbf) for TNFSF10 - UBE2Z; and 2081 (laplace) and 2102 (rbf) for TNFSF15 - UBE2Z;

One the right side is the ranking of TNF family w.r.t UBE2 family. We found **TNF-RSF10A** to be up regulated w.r.t UBE2A. This is reflected in rankings of 2116 (laplace) and 2376 (rbf) for TNFRSF10A - UBE2A. **TNF-RSF10A/RSF12A/SF10/SF15** were up regulated w.r.t UBE2B. These are reflected in rankings of 2318 (linear) and 2265 (linear) for TNFRSF10A - UBE2B; 1940 (laplace); 1868 (linear) and 1758 (linear) for TNFRSF12A - UBE2B; 2208 (laplace); 2326 (linear) and 2470 (linear) for TNFSF10 - UBE2B; and 2055 (laplace) and 1964 (linear) for TNFSF15 - UBE2B. **TNF-RSF14** were up regulated w.r.t UBE2F. These is reflected in rankings of 2324 (laplace) and 1924 (linear) for TNF-RSF14 - UBE2F. **TNF-SF15** were up regulated w.r.t UBE2H. These is reflected in rankings of 2416 (linear) and 1960 (rbf) for TNF-SF15 - UBE2H. **TNF-RSF10A/RSF10D/RSF14** were up regulated w.r.t UBE2J1. These are reflected in rankings of 2379 (laplace), 2213 (linear) and 2135 (rbf) for TNFRSF10A - UBE2J1; 2393 (laplace) and 2102 (rbf) for TNFRSF10D - UBE2J1; and 2133 (linear) and 2313 (rbf) for TNFRSF14 - UBE2J1. **TNF-RSF10A/RSF14** were up regulated w.r.t UBE2Z. These are reflected in rankings of 2410 (laplace) and 2103 (laplace) for TNFRSF10A - UBE2Z and 1779 (laplace) and 2100 (rbf) for TNFRSF14 - UBE2Z.

One can also interpret the results of the table 49 graphically, with the following influences - • UBE2 w.r.t TNF with TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF10D/RSF12A/RSF14/RSF21/SF15 -> UBE2A; TNF-RSF10A/RSF10B/RSF10D/RSF14/RSF21 -> UBE2B; TNF, TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF12A/SF15 -> UBE2F; TNF-RSF12A/RSF14/RSF21 -> UBE2H; TNF, TNF-AIP1/RSF1A/RSF10A/RSF10B/RSF12A/RSF14/RSF21/SF15 -> UBE2J1; and TNF, TNF-AIP1/AIP2/RSF1A/RSF10A/RSF10D/RSF12A/SF10/SF15 -> UBE2Z • TNF w.r.t UBE2 with TNF-RSF10A <- UBE2A; TNF-RSF10A/RSF12A/SF10/SF15 <- UBE2B; TNF-RSF14 <- UBE2F; TNF-SF15 <- UBE2H; TNF-RSF10A/RSF10D/RSF14 <- UBE2J1; TNF-RSF10A/RSF14 <- UBE2Z.

2.3.5 TNF - BCL cross family analysis

Tamatani *et al.* [128] observe that tumor necrosis factor induces BCL-2 and BCL-x expression through NFκB activation in primary hippocampal neurons. The role of Bcl-2 Expression in EGF Inhibition of TNF-α/IFN-γ-induced Villous Trophoblast Apoptosis has been studied by Ho *et al.*[129]. Genestier *et al.*[130] show that tumor necrosis factor-α up-regulates BCL-2 expression and decreases calcium-dependent apoptosis in human B cell lines. In breast carcinoma cells, Bcl-x and Bcl-2 inhibit TNF and FAS-induced apoptosis and activation of phospholipase A2 (Jäättelä *et al.*[131]). Kim *et al.*[132] show that TNF-α-induced ROS production triggering apoptosis is directly linked to Romo1 and BCL-X_L. Kuwata *et al.*[133] showed that IL-10-inducible BCL-3 negatively regulates LPS-induced TNF-α production in macrophages. Esche *et al.*[134] showed that tumor necrosis factor-α-promoted expression of BCL-2 and inhibition of mitochondrial cytochrome c release mediate resistance of mature dendritic cells to melanoma-induced apoptosis. These studies show a definite synergy between BCL family and TNFs. In CRC cells treated with ETC-1922159, both TNF members and BCL were found to be up regulated. Our search engine alloted the dual combinations with numerically high ranked values thus pointing to the possible synergies that might be existing in the cells and may not have been explored. Table 50 and 51 show the rankings of each with the other.

On the left side is the ranking of BCL family w.r.t TNF family. We found **BCL2L2** to be up regulated w.r.t TNF, TNF-AIP1/RSF1A/RSF10B/RSF10D/RSF12A/RSF14/RSF21/SF10/SF15. These are reflected in rankings of 1822 (laplace), 1926 (linear) and 2359 (rbf) for TNF - BCL2L2; 2266 (laplace), 2478 (linear) and 1847 (rbf) for TNFAIP1 - BCL2L2; 2311 (linear) and 1920 (rbf) for TNFRSF1A - BCL2L2; 2478 (laplace) and 2239 (rbf) for TNFRSF10B - BCL2L2; 2278 (linear) and 2237 (rbf) for TNFRSF10D - BCL2L2; 1945 (laplace) and 2484 (rbf) for TNFRSF12A - BCL2L2; 2358 (laplace) and 2310 (rbf) for TNFRSF14 - BCL2L2; 2292 (laplace) and 1850 (linear) for TNFRSF21 - BCL2L2; 2438 (laplace) and 2013 (rbf) for TNFSF10 - BCL2L2 and 2443 (linear) and 2350 (rbf) for TNFSF15 - BCL2L2; **BCL2L3** was up regulated w.r.t TNF, TNF-AIP1/RSF1A/RSF10A/RSF10D/RSF12A/RSF14/RSF21/SF10/SF15. These are reflected in rankings of 2437 (laplace), 2482 (linear) and 2482 (rbf) for TNF - BCL2L13; 1863 (laplace) and 2386 (linear) for TNFAIP1 - BCL2L13; 1962 (linear) and 2489 (rbf) for TNFRSF1A - BCL2L13; 2055 (linear) and 2499 (rbf) for TNFRSF10A - BCL2L13; 2204 (laplace), 2159 (linear) and 2343 (rbf) for TNFRSF10D - BCL2L13; 2183 (laplace), 2509 (linear) for TNFRSF12A - BCL2L13; 1852 (laplace), 1974 (linear) and 2339 (rbf) for TNFRSF14 - BCL2L13; 2280 (laplace), 2424 (linear) and 2301 (rbf) for TNFRSF21 - BCL2L13; 2429 (linear) and 1803 (rbf) for TNFSF10 - BCL2L13; and 2438 (linear) and 2252 (rbf) for TNFSF15 - BCL2L13; **BCL3** was up regulated w.r.t TNFRSF10B. This is reflected in rankings of 2427 (laplace) and 1868 (rbf). **BCL6** was up regulated w.r.t TNF, TNF-AIP1/AIP2/RSF1A/RSF10A/RSF10D/RSF21. These are reflected in rankings of 2271 (laplace), 2071 (linear) and 1810 (rbf) for TNF - BCL6; 2135 (laplace) and 2158 (linear) for TNFAIP1 - BCL6; 2340 (laplace) 1808 (rbf) for TNFAIP2 - BCL6; 1771 (linear) and 2503 (rbf) for TNFRSF1A - BCL6; and 1831 (linear) and 2096 (rbf) for TNFRSF10A - BCL6; and 2213 (laplace) and 2188 (rbf) for TNFRSF10D - BCL6; and 2071 (linear) and 2335 (rbf) for TNFRSF21 - BCL6; **BCL10** was up regulated w.r.t TNF-RSF10D/RSF12A. These are reflected in rankings of 1831 (laplace) and 2040 (rbf) for TNFRSF10D - BCL10; and 2015 (laplace) and 1883 (rbf) for TNFRSF12A - BCL10;

RANKING TNF FAMILY VS BCL FAMILY

RANKING OF BCL2L1 W.R.T TNF FAMILY				RANKING OF TNF FAMILY W.R.T BCL2L1			
	laplace	linear	rbf		laplace	linear	rbf
TNF - BCL2L1	174	14	235	TNF - BCL2L1	56	1101	294
TNFAIP1 - BCL2L1	1527	435	791	TNFAIP1 - BCL2L1	1497	1150	74
TNFAIP2 - BCL2L1	2142	1735	798	TNFAIP2 - BCL2L1	1485	1735	400
TNFAIP3 - BCL2L1	2467	842	867	TNFAIP3 - BCL2L1	1109	1939	1553
TNFRSF1A - BCL2L1	1004	1558	383	TNFRSF1A - BCL2L1	492	376	1016
TNFRSF10A - BCL2L1	1906	1270	1222	TNFRSF10A - BCL2L1	2273	1928	508
TNFRSF10B - BCL2L1	1506	2235	589	TNFRSF10B - BCL2L1	1003	2252	2217
TNFRSF10D - BCL2L1	1920	1555	1787	TNFRSF10D - BCL2L1	1868	2420	2392
TNFRSF12A - BCL2L1	1254	1388	1319	TNFRSF12A - BCL2L1	1923	53	1936
TNFRSF14 - BCL2L1	688	237	2009	TNFRSF14 - BCL2L1	340	2350	2414
TNFRSF21 - BCL2L1	1465	1269	100	TNFRSF21 - BCL2L1	2139	718	289
TNFSF10 - BCL2L1	532	560	2332	TNFSF10 - BCL2L1	2115	2299	1307
TNFSF15 - BCL2L1	1026	1551	1134	TNFSF15 - BCL2L1	453	423	25
RANKING OF BCL2L2 W.R.T TNF FAMILY				RANKING OF TNF FAMILY W.R.T BCL2L2			
	laplace	linear	rbf		laplace	linear	rbf
TNF - BCL2L2	1822	1926	2359	TNF - BCL2L2	2140	109	1062
TNFAIP1 - BCL2L2	2266	2478	1847	TNFAIP1 - BCL2L2	2235	1607	712
TNFAIP2 - BCL2L2	823	535	1117	TNFAIP2 - BCL2L2	109	1002	54
TNFAIP3 - BCL2L2	1201	1103	1511	TNFAIP3 - BCL2L2	1470	1696	1276
TNFRSF1A - BCL2L2	1124	2311	1920	TNFRSF1A - BCL2L2	1912	169	1531
TNFRSF10A - BCL2L2	1063	1532	2458	TNFRSF10A - BCL2L2	1643	1095	953
TNFRSF10B - BCL2L2	2478	739	2239	TNFRSF10B - BCL2L2	2153	1164	1983
TNFRSF10D - BCL2L2	910	2278	2237	TNFRSF10D - BCL2L2	35	1012	1905
TNFRSF12A - BCL2L2	1945	240	2484	TNFRSF12A - BCL2L2	1971	1633	975
TNFRSF14 - BCL2L2	2358	1648	2310	TNFRSF14 - BCL2L2	1027	825	1228
TNFRSF21 - BCL2L2	2292	1850	1014	TNFRSF21 - BCL2L2	1138	486	554
TNFSF10 - BCL2L2	2438	547	2013	TNFSF10 - BCL2L2	2212	902	169
TNFSF15 - BCL2L2	1196	2443	2350	TNFSF15 - BCL2L2	2285	165	1330
RANKING OF BCL2L13 W.R.T TNF FAMILY				RANKING OF TNF FAMILY W.R.T BCL2L13			
	laplace	linear	rbf		laplace	linear	rbf
TNF - BCL2L13	2437	2482	2482	TNF - BCL2L13	1162	103	462
TNFAIP1 - BCL2L13	1863	2386	989	TNFAIP1 - BCL2L13	852	606	787
TNFAIP2 - BCL2L13	793	293	1846	TNFAIP2 - BCL2L13	438	479	742
TNFAIP3 - BCL2L13	1350	1030	2129	TNFAIP3 - BCL2L13	1804	879	626
TNFRSF1A - BCL2L13	1173	1962	2489	TNFRSF1A - BCL2L13	1577	1512	476
TNFRSF10A - BCL2L13	737	2055	2499	TNFRSF10A - BCL2L13	1534	2360	1105
TNFRSF10B - BCL2L13	1992	885	906	TNFRSF10B - BCL2L13	2177	960	1053
TNFRSF10D - BCL2L13	2204	2159	2343	TNFRSF10D - BCL2L13	171	1983	960
TNFRSF12A - BCL2L13	2183	2509	241	TNFRSF12A - BCL2L13	59	1706	2046
TNFRSF14 - BCL2L13	1852	1974	2339	TNFRSF14 - BCL2L13	2459	2381	1187
TNFRSF21 - BCL2L13	2280	2424	2301	TNFRSF21 - BCL2L13	52	1054	394
TNFSF10 - BCL2L13	1088	2429	1803	TNFSF10 - BCL2L13	1764	1186	1227
TNFSF15 - BCL2L13	1286	2438	2252	TNFSF15 - BCL2L13	638	1962	814

Table 50 2^{nd} order combinatorial hypotheses between BCL and TNF

On the right side is the ranking of TNF family w.r.t BCL family. We found **TNF-RSF10A/RSF10B/RSF10D/RSF12A/RSF14/SF10** to be up regulated w.r.t BCL2L1. These are reflected in rankings of 2273 (laplace) and 1928 (linear) for TNFRSF10A - BCL2L1; 2252 (linear) and 2217 (rbf) for TNFRSF10B - BCL2L1; 1868 (laplace), 2420 (linear) and 2392 (rbf) for TNFRSF10D - BCL2L1; 1923 (laplace) and 1936 (rbf) for TNFRSF12A - BCL2L1; 2350 (linear)

Ranking TNF family vs BCL family

Ranking of BCL3 w.r.t TNF family	laplace	linear	rbf	Ranking of TNF family w.r.t BCL3	laplace	linear	rbf
TNF - BCL3	652	370	642	TNF - BCL3	598	311	2473
TNFAIP1 - BCL3	168	723	124	TNFAIP1 - BCL3	596	500	158
TNFAIP2 - BCL3	642	856	1098	TNFAIP2 - BCL3	59	776	323
TNFAIP3 - BCL3	2377	534	567	TNFAIP3 - BCL3	300	940	1527
TNFRSF1A - BCL3	163	206	740	TNFRSF1A - BCL3	83	476	1355
TNFRSF10A - BCL3	799	865	1044	TNFRSF10A - BCL3	2388	2493	88
TNFRSF10B - BCL3	1632	2427	1868	TNFRSF10B - BCL3	757	1508	1062
TNFRSF10D - BCL3	1110	858	714	TNFRSF10D - BCL3	2213	1091	1972
TNFRSF12A - BCL3	273	931	623	TNFRSF12A - BCL3	671	1869	1286
TNFRSF14 - BCL3	232	85	1422	TNFRSF14 - BCL3	2149	1311	1650
TNFRSF21 - BCL3	340	1384	2474	TNFRSF21 - BCL3	411	729	998
TNFSF10 - BCL3	1537	1753	1638	TNFSF10 - BCL3	1926	1523	2107
TNFSF15 - BCL3	129	284	729	TNFSF15 - BCL3	1649	1032	2122
Ranking of BCL6 w.r.t TNF family	laplace	linear	rbf	Ranking of TNF family w.r.t BCL6	laplace	linear	rbf
TNF - BCL6	2271	2071	1810	TNF - BCL6	806	437	1411
TNFAIP1 - BCL6	2135	2158	1330	TNFAIP1 - BCL6	1089	850	372
TNFAIP2 - BCL6	2340	1428	1808	TNFAIP2 - BCL6	152	334	703
TNFAIP3 - BCL6	267	1336	1219	TNFAIP3 - BCL6	1884	1935	855
TNFRSF1A - BCL6	1598	1771	2503	TNFRSF1A - BCL6	788	741	1130
TNFRSF10A - BCL6	1327	1831	2096	TNFRSF10A - BCL6	607	1249	2360
TNFRSF10B - BCL6	1373	1873	1264	TNFRSF10B - BCL6	1746	1282	361
TNFRSF10D - BCL6	2213	2188	788	TNFRSF10D - BCL6	1540	1301	2008
TNFRSF12A - BCL6	1867	99	2261	TNFRSF12A - BCL6	545	2200	1910
TNFRSF14 - BCL6	1409	1337	2028	TNFRSF14 - BCL6	731	1302	1902
TNFRSF21 - BCL6	645	2071	2335	TNFRSF21 - BCL6	40	1850	50
TNFSF10 - BCL6	919	445	99	TNFSF10 - BCL6	2119	1102	1626
TNFSF15 - BCL6	2106	1692	1451	TNFSF15 - BCL6	969	1475	226
Ranking of BCL9L w.r.t TNF family	laplace	linear	rbf	Ranking of TNF family w.r.t BCL9L	laplace	linear	rbf
TNF - BCL9L	1964	1172	1478	TNF - BCL9L	2218	98	425
TNFAIP1 - BCL9L	439	1445	264	TNFAIP1 - BCL9L	766	2470	1802
TNFAIP2 - BCL9L	1250	1473	696	TNFAIP2 - BCL9L	646	567	85
TNFAIP3 - BCL9L	534	630	618	TNFAIP3 - BCL9L	1046	1223	2296
TNFRSF1A - BCL9L	2050	1096	978	TNFRSF1A - BCL9L	863	500	825
TNFRSF10A - BCL9L	212	1682	980	TNFRSF10A - BCL9L	2140	241	1547
TNFRSF10B - BCL9L	952	698	685	TNFRSF10B - BCL9L	286	414	2046
TNFRSF10D - BCL9L	1315	181	1423	TNFRSF10D - BCL9L	1956	112	990
TNFRSF12A - BCL9L	430	1167	1470	TNFRSF12A - BCL9L	1797	1280	1699
TNFRSF14 - BCL9L	1433	635	1497	TNFRSF14 - BCL9L	670	1055	1540
TNFRSF21 - BCL9L	495	2326	468	TNFRSF21 - BCL9L	1291	1378	246
TNFSF10 - BCL9L	1889	974	183	TNFSF10 - BCL9L	1812	1796	2095
TNFSF15 - BCL9L	878	2389	71	TNFSF15 - BCL9L	1939	2114	2405
Ranking of BCL10 w.r.t TNF family	laplace	linear	rbf	Ranking of TNF family w.r.t BCL10	laplace	linear	rbf
TNF - BCL10	708	79	979	TNF - BCL10	1931	114	1573
TNFAIP1 - BCL10	1657	805	1298	TNFAIP1 - BCL10	690	1941	7
TNFAIP2 - BCL10	1101	2197	312	TNFAIP2 - BCL10	523	2099	339
TNFAIP3 - BCL10	985	813	767	TNFAIP3 - BCL10	935	595	1870
TNFRSF1A - BCL10	745	1191	1288	TNFRSF1A - BCL10	362	173	448
TNFRSF10A - BCL10	451	819	954	TNFRSF10A - BCL10	1547	415	2426
TNFRSF10B - BCL10	791	537	1446	TNFRSF10B - BCL10	582	658	1464
TNFRSF10D - BCL10	1831	1694	2040	TNFRSF10D - BCL10	302	19	2497
TNFRSF12A - BCL10	2015	1072	1883	TNFRSF12A - BCL10	1865	1234	1540
TNFRSF14 - BCL10	254	1400	847	TNFRSF14 - BCL10	1175	1894	2227
TNFRSF21 - BCL10	1912	571	958	TNFRSF21 - BCL10	848	1943	418
TNFSF10 - BCL10	1743	931	1657	TNFSF10 - BCL10	2020	1522	1054
TNFSF15 - BCL10	254	1469	577	TNFSF15 - BCL10	1256	188	1074

Table 51 2^{nd} order combinatorial hypotheses between BCL and TNF

and 2414 (rbf) for TNFRSF14 - BCL2L1 and 2115 (laplace) and 2299 (linear) for TNFSF10 - BCL2L1; **TNFRSF10B** was up regulated w.r.t BCL2L2. This is reflected in rankings of 2153 (laplace) and 1983 (rbf) for TNFRSF10B - BCL2L2; **TNFRSF14** was up regulated w.r.t BCL2L13. This is reflected in rankings of 2459 (laplace) and 2381 (linear) for TNFRSF14 - BCL2L13; **TNF-RSF10A/SF10D/SF10** were up regulated w.r.t BCL3. These are reflected in rankings of 2388 (laplace) and 2493 (linear) for TNFRSF10A - BCL3; 2213 (laplace) and 1972 (rbf) for TNFRSF10D - BCL3 and 1926 (laplace) and 2107 (rbf) for

Unexplored combinatorial hypotheses

BCL w.r.t TNF	
TNF, TNF-AIP1/RSF1A/RSF10B/RSF10D/RSF12A/RSF14/RSF21/SF10/SF15	BCL2L2
TNF, TNF-AIP1/RSF1A/RSF10A/RSF10D/RSF12A/RSF14/RSF21/SF10/SF15	BCL2L13
TNFRSF10B	BCL3
TNF, TNF-AIP1/AIP2/RSF1A/RSF10A/RSF10D/RSF21	BCL6
TNF-RSF10D/RSF12A	BCL10
TNF w.r.t BCL	
TNF-RSF10A/RSF10B/RSF10D/RSF12A/RSF14/SF10	BCL2L1
TNF-RSF10B	BCL2L2
TNF-RSF14	BCL2L13
TNF-RSF10A/SF10D/SF10	BCL3
TNF-RSF12A	BCL6
TNF-AIP1	BCL9L
TNF-SF10/SF15	BCL9L
TNF-RSF14	BCL10

Table 52 2^{nd} order combinatorial hypotheses between TNF and BCL family.

TNFSF10 - BCL3; **TNFRSF12A** was up regulated w.r.t BCL6. This is reflected in rankings of 2200 (linear) and 1910 (rbf) for TNFRSF12A - BCL6; **TNF-AIP1/SF10/SF15** was up regulated w.r.t BCL9L. This is reflected in rankings of 2470 (linear) and 1802 (rbf) for TNFAIP1 - BCL9L; 1812 (laplace), 1796 (linear) and 2095 (rbf) for TNFSF10 - BCL9L; and 1939 (laplace), 2114 (linear) and 2405 (rbf) for TNFSF15 - BCL9L; **TNFRSF14** was up regulated w.r.t BCL10. This is reflected in rankings of 1894 (linear) and 2227 (rbf) for TNFRSF14 - BCL10;

One can also interpret the results of the table 111 graphically, with the following influences - • BCL w.r.t TNF with TNF, TNF-AIP1/RSF1A/RSF10B/RSF10D/RSF12A/RSF14/RSF21/SF10/SF15 -> BCL2L2; TNF, TNF-AIP1/RSF1A/RSF10A/RSF10D/RSF12A/RSF14/RSF21/SF10/SF15 -> BCL2L13; TNFRSF10B -> BCL3; TNF, TNF-AIP1/AIP2/RSF1A/RSF10A/RSF10D/RSF21 -> BCL6; TNF-RSF10D/RSF12A -> BCL10; • TNF w.r.t BCL with TNF-RSF10A/RSF10B/RSF10D/RSF12A/RSF14/SF10 <- BCL2L1; TNF-RSF10B <- BCL2L2; TNF-RSF14 <- BCL2L13; TNF-RSF10A/SF10D/SF10 <- BCL3; TNF-RSF12A <- BCL6; TNF-AIP1 <- BCL9L; TNF-SF10/SF15 <- BCL9L and TNF-RSF14 <- BCL10.

2.4 DNA repair related synergies

2.4.1 XRCC - RAD cross family analysis

X-ray repair cross-complementing protein (XRCC) plays major role in DNA repair process, especially in Double Strand Repair (DBS) Thacker and Zdzienicka [135] and Thacker and Zdzienicka [136]. Sultana *et al.* [137] observe that ataxia telangiectasia mutated and RAD3 related (ATR) protein kinase inhibition is synthetically lethal in XRCC1 deficient ovarian cancer cells. Della-Maria *et al.* [138] observe that human Mre11/human RAD50/Nbs1 and DNA ligase IIIα/XRCC1 protein complexes act together in an alternative nonhomologous end joining pathway. These findings along with multiple published work indi-

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cate the joint synergy of XRCC - RAD family. In colorectal cancer cell lines treated with ETC-1922159, both XRCC and RAD members were found to be down regulated. The search engine gave the 2^{nd} order synergies between XRCC - RAD families, low numerical valued ranks to signify plausible synergistic down regulations that might not have been explored. Table 53 shows the rankings of RAD family w.r.t XRCC family and 54 shows the rankings of the XRCC family w.r.t RAD family. In table 53 we found RAD-18/51/51AP1/51C/54B/54L to be down regulated **w.r.t XRCC1**. These are reflected with rankings of 1027 (laplace), 456 (linear) and 1355 (rbf) for RAD-18 - XRCC1; 282 (laplace), 365 (linear) and 1003 (rbf) for RAD51 - XRCC1; 753 (laplace), 5 (linear) and 27 (rbf) for RAD51AP1 - XRCC1; 337 (laplace), 111 (linear) and 968 (rbf) for RAD51C - XRCC1; 175 (laplace), 224 (linear) and 78 (rbf) for RAD54B - XRCC1; and 327 (laplace), 889 (linear) and 709 (rbf) for RAD54L - XRCC1. RAD-18/51/51AP1/51C/54B/54L were also found to be down regulated **w.r.t XRCC2**. These are reflected in 1388 (laplace), 847 (linear) and 765 (rbf) for XRCC2 - RAD18; 1247 (laplace), 1033 (linear) and 629 (rbf) for XRCC2 - RAD51; 302 (laplace); 247 (linear) and 42 (rbf) for XRCC2 - RAD51AP1; 1079 (laplace), 674 (linear) and 323 (rbf) for XRCC2 - RAD51C; 387 (laplace), 566 (linear) and 506 (rbf) for XRCC2 - RAD54B; and 976 (laplace), 918 (linear) and 847 (rbf) for XRCC2 - RAD54L. RAD-18/51/51AP1/51C/54B/54L were found to be down regulated with **w.r.t XRCC6**. These are reflected in 541 (laplace), 25 (linear) and 1068 (rbf) for RAD18 - XRCC6; 608 (laplace), 425 (linear) and 900 (rbf) for RAD51 - XRCC6; 216 (laplace), 67 (linear) and 83 (rbf) for RAD51AP1 - XRCC6; 426 (laplace), 865 (linear) and 503 (rbf) for RAD51C - XRCC6; 3 (laplace), 610 (linear) and 112 (rbf) for RAD54B - XRCC6; and 85 (laplace), 252 (linear) and 432 (rbf) for RAD54L - XRCC6. RAD-1/18/50/51/51AP1/51C/54B/54L were found to be down regulated **w.r.t XRCC6BP1**. These are reflected in 1167 (laplace) and 308 (rbf) for RAD1 - XRCC6BP1; 656 (linear) and 1612 (rbf) for RAD18 - XRCC6BP1; 1302 (laplace) and 328 (rbf) for XRCC6BP1 - RAD50; 435 (laplace), 495 (linear) and 1275 (rbf) for RAD51 - XRCC6BP1; 81 (laplace), 177 (linear) and 73 (rbf) for RAD51AP1 - XRCC6BP1; 645 (laplace), 1366 (linear) and 1414 (rbf) for RAD51C - XRCC6BP1; 154 (laplace), 693 (linear) and 1398 (rbf) for RAD54B - XRCC6BP1; and 420 (linear) and 1060 (rbf) for RAD54L - XRCC6BP1;

In table 54 we found XRCC-2/6BP1 to be down regulated **w.r.t RAD1**. These are reflected in 62 (laplace), 498 (linear) and 1231 (rbf) for RAD1 - XRCC2; and 764 (laplace) and 1325 (rbf) for RAD1 - XRCC6BP1. XRCC-1/2/6 were found to be down regulated with **w.r.t RAD18**. These are reflected in 927 (laplace) and 200 (rbf) for RAD18 - XRCC1; 506 (laplace) and 1517 (rbf) for RAD18 - XRCC2; and 279 (laplace) and 804 (rbf) for RAD18 - XRCC6; XRCC-2/6BP1 were found to be down regulated **w.r.t RAD50**. These are reflected in rankings of 53 (laplace), 244 (linear) and 147 (rbf) for XRCC-2 - RAD50; and 1375 (linear) and 1366 (rbf) for RAD50 - XRCC6BP1. XRCC-6/6BP1 were found to be down regulated **w.r.t RAD51**; These are reflected in rankings of 80 (laplace) and 1244 (linear) for XRCC6 - RAD51; and 792 (laplace), 951 (linear) and 1595 (rbf) for XRCC6BP1 - RAD51. XRCC-2/6BP1 were found to be down regulated **w.r.t RAD51AP1**. These were reflected in 78 (laplace), 112 (linear) and 351 (rbf) for XRCC2 - RAD51AP1; and 936 (linear) and 974 (rbf) for XRCC6BP1 - RAD51AP1; XRCC2 was found to be down regulated **w.r.t RAD51C**. This are reflected in 1695 (laplace), 932 (linear) and 520 (rbf) for XRCC2 - RAD51C. XRCC2 was found to be down regulated **w.r.t RAD54B**. This is reflected in rankings of 1554 (laplace), 744 (linear) and 620 (rbf) for XRCC2 - RAD54B. XRCC-1/2/6/6BP1 were found to be down regulated **w.r.t RAD54L**. These are reflected in rankings of 657 (linear) and 525 (rbf) for XRCC1 - RAD54L; 167 (laplace) and 565 (rbf) for XRCC2 - RAD54L; 496 (linear) and 1247 (rbf) for XRCC6 - RAD54L; and 1389 (laplace), 1227 (linear) and 1454 (rbf) for RAD54L - XRCC6BP1;

Ranking RAD family w.r.t XRCC family

Ranking of RAD family w.r.t XRCC1				Ranking of RAD family w.r.t XRCC2			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - XRCC1	1922	1658	1771	XRCC2 - RAD1	1921	893	1774
RAD18 - XRCC1	1027	456	1355	XRCC2 - RAD18	1388	847	765
XRCC1 - RAD50	2459	2254	2082	XRCC2 - RAD50	1877	2185	2546
RAD51 - XRCC1	282	365	1003	XRCC2 - RAD51	1247	1033	629
RAD51AP1 - XRCC1	753	5	275	XRCC2 - RAD51AP1	302	247	42
RAD51C - XRCC1	337	111	968	XRCC2 - RAD51C	1079	674	323
RAD54B - XRCC1	175	224	782	XRCC2 - RAD54B	387	566	506
RAD54L - XRCC1	327	889	709	XRCC2 - RAD54L	976	918	847
Ranking of RAD family w.r.t XRCC6				**Ranking of RAD family w.r.t XRCC6BP1**			
	laplace	linear	rbf		laplace	linear	rbf
XRCC6 - RAD1	1929	2029	2627	RAD1 - XRCC6BP1	1167	2417	308
RAD18 - XRCC6	541	25	1068	RAD18 - XRCC6BP1	656	1612	2271
XRCC6 - RAD50	2434	2043	2603	XRCC6BP1 - RAD50	1302	2263	328
RAD51 - XRCC6	608	425	900	RAD51 - XRCC6BP1	435	495	1275
RAD51AP1 - XRCC6	216	67	83	RAD51AP1 - XRCC6BP1	81	177	73
RAD51C - XRCC6	426	865	503	RAD51C - XRCC6BP1	645	1366	1414
RAD54B - XRCC6	3	610	112	RAD54B - XRCC6BP1	154	693	1398
RAD54L - XRCC6	85	252	432	RAD54L - XRCC6BP1	420	1060	2542

Table 53 2^{nd} order interaction ranking between RAD w.r.t XRCC family members.

Table 55 shows the derived influences which can be represented graphically, with the following influences - • RAD w.r.t XRCC with RAD-18/51/51AP1/51C/54B/54L <- XRCC1; RAD-18/51/51AP1/51C/54B/54L <- XRCC2; RAD-18/51/51AP1/51C/54B/54L <- XRCC6 and RAD-1/18/50/51/51AP1/51C/54B/54L <- XRCC6BP1; •; XRCC w.r.t RAD with RAD1 -> XRCC-2/6BP1; RAD18 -> XRCC-1/2/6; RAD50 -> XRCC-2/6BP1; RAD51 -> XRCC-6/6BP1; RAD51AP1 -> XRCC-2/6BP1; RAD51C -> XRCC-2; RAD54B -> XRCC-2; RAD54L -> XRCC-1/2/6/6BP1;

RANKING XRCC FAMILY W.R.T RAD FAMILY

Ranking of XRCC w.r.t RAD1	laplace	linear	rbf	Ranking of XRCC w.r.t RAD18	laplace	linear	rbf
RAD1 - XRCC1	1751	1808	793	RAD18 - XRCC1	927	2669	200
XRCC2 - RAD1	62	498	1231	XRCC2 - RAD18	506	1844	1517
XRCC6 - RAD1	2736	2511	1284	RAD18 - XRCC6	279	2193	804
RAD1 - XRCC6BP1	764	2108	1325	RAD18 - XRCC6BP1	819	1954	1976
Ranking of XRCC w.r.t RAD50	laplace	linear	rbf	**Ranking of XRCC w.r.t RAD51**	laplace	linear	rbf
XRCC1 - RAD50	2573	2374	2497	RAD51 - XRCC1	1673	1818	2611
XRCC2 - RAD50	53	244	147	XRCC2 - RAD51	472	2348	1973
XRCC6 - RAD50	2615	2568	2582	RAD51 - XRCC6	80	1244	2595
RAD50 - XRCC6BP1	1962	1375	1366	RAD51 - XRCC6BP1	792	951	1595
Ranking of XRCC w.r.t RAD51AP1	laplace	linear	rbf	**Ranking of XRCC w.r.t RAD51C**	laplace	linear	rbf
XRCC1 - RAD51AP1	1802	2732	801	RAD51C - XRCC1	2282	1846	2026
XRCC2 - RAD51AP1	78	112	351	XRCC2 - RAD51C	1695	932	520
XRCC6 - RAD51AP1	2653	2439	347	RAD51C - XRCC6	2545	1848	1858
RAD51AP1 - XRCC6BP1	1790	936	974	RAD51C - XRCC6BP1	2325	1070	1844
Ranking of XRCC w.r.t RAD54B	laplace	linear	rbf	**Ranking of XRCC w.r.t RAD54L**	laplace	linear	rbf
XRCC1 - RAD54B	2475	2670	1824	RAD54L - XRCC1	1834	657	525
XRCC2 - RAD54B	1554	744	620	XRCC2 - RAD54L	2564	167	565
XRCC6 - RAD54B	2505	2709	2604	RAD54L - XRCC6	2597	496	1247
RAD54B - XRCC6BP1	1932	2504	2170	RAD54L - XRCC6BP1	1389	1227	1454

Table 54 2^{nd} order interaction ranking between XRCC w.r.t RAD family members.

UNEXPLORED COMBINATORIAL HYPOTHESES

RAD w.r.t XRCC family	
RAD-18/51/51AP1/51C/54B/54L	XRCC1
RAD-18/51/51AP1/51C/54B/54L	XRCC2
RAD-18/51/51AP1/51C/54B/54L	XRCC6
RAD-1/18/50/51/51AP1/51C/54B/54L	XRCC6BP1
XRCC w.r.t RAD family	
RAD1	XRCC-2/6BP1
RAD18	XRCC-1/2/6
RAD50	XRCC-2/6BP1
RAD51	XRCC-6/6BP1
RAD51AP1	XRCC-2/6BP1
RAD51C	XRCC-2
RAD54B	XRCC-2
RAD54L	XRCC-1/2/6/6BP1

Table 55 2^{nd} order combinatorial hypotheses between RAD and XRCC.

2.4.2 XRN2 - RAD cross family analysis

XRN2 (5'-3' exoribonuclease 2) is involved in RNA synthesis/trafficking and termination. Morales *et al.*[139] observe that XRN2 links transcription termination to DNA damage and replication stress. They found an increase in the amount of RAD51 foci in shXRN2 cells compared to controls, suggesting that cells depleted of XRN2 are subjected to an increased level of basal DNA damage and show that loss of XRN2 also leads to the focal accumulation of several factors required for homologous recombination, such as ATM, BRCA1 and RAD51. This definitely shows that there is synergy between the XRN2 and RAD51. We found that both the XRN2 and RAD families were down regulated in CRC cell after ETC-1922159 treatment. The search en-

RANKING XRN2 W.R.T RAD FAMILY

Ranking of RAD family w.r.t XRN2	laplace	linear	rbf	Ranking of XRN2 w.r.t RAD family	laplace	linear	rbf
XRN2 - RAD51AP1	340	545	290	XRN2 - RAD51AP1	1905	1256	852
XRN2 - RAD51	387	560	605	XRN2 - RAD51	786	2647	1995
XRN2 - RAD54L	594	827	879	XRN2 - RAD54L	1541	1246	1819
XRN2 - RAD51C	639	1236	745	XRN2 - RAD51C	1037	1777	2228
XRN2 - RAD18	794	688	804	XRN2 - RAD18	904	2403	1801
XRN2 - RAD1	898	1955	2506	XRN2 - RAD1	255	122	2557
XRN2 - RAD54B	951	165	343	XRN2 - RAD54B	1818	2381	2603
XRN2 - RAD50	1330	2312	2295	XRN2 - RAD50	504	2100	1842

Table 56 2^{nd} order interaction ranking between RAD family vs XRN2.

UNEXPLORED COMBINATORIAL HYPOTHESES

RAD w.r.t XRN2	
XRN2	RAD-51AP1/51/54L/51C/18/54B
XRN2 w.r.t RAD	
XRN2	RAD1
XRN2	RAD51AP1
XRN2	RAD54L
XRN2	RAD51C

Table 57 2^{nd} order combinatorial hypotheses between RAD and XRN2.

gine gave rankings to the combinations of the XRN2 and RAD family members with low numerical valued in silico ranks. Table 56 shows the rankings of XRN2 w.r.t RAD family and vice versa. Following this is the derived influences in table 57. We find RAD-51AP1/51/54L/51C/18/54B to be down regulated w.r.t XRN2. These are reflected in rankings of 340 (laplace), 545 (linear) and 290 (rbf) for RAD51AP1 - XRN2; 387 (laplace), 560 (linear) and 605 (rbf) for XRN2 - RAD51; 594 (laplace), 827 (linear) and 879 (rbf) for XRN2 - RAD54L; 639 (laplace), 1236 (linear) and 745 (rbf) for XRN2 - RAD51C; 794 (laplace), 688 (linear) and 804 (rbf) for XRN2 - RAD18; 255 (linear) and 122 (rbf) for XRN2 - RAD1 and 951 (laplace), 165 (linear) and 34 (rbf) for XRN2 - RAD54B; On the other hand, XRN2 was found to be down regulated w.r.t RAD family. These are reflected in rankings of 255 (laplace) and 122 (rbf) for XRN2 - RAD1; 1256 (linear) and 852 (rbf) for XRN2 - RAD51AP1; 1541 (laplace) and 1246 (linear) for XRN2 - RAD54L and 1037 (laplace) and 1777 (linear) for XRN2 - RAD51C. Graphical depiction of XRN2 and RAD family dependencies is shown as • RAD w.r.t XRN2 with XRN2 -> RAD-51AP1/51/54L/51C/18/54B and • XRN2 w.r.t RAD with XRN2 <- RAD1; XRN2 <- RAD51AP1; XRN2 <- RAD54L; XRN2 <- RAD51C;

Table 57 shows the derived influences which can be represented graphically, with the following influences - • RAD w.r.t XRN2 with XRN2 -> RAD-51AP1/51/54L/51C/18/54B; and • XRN2 w.r.t RAD with XRN2 <- RAD-1/51AP1/54L/51C.

Ranking NKRF w.r.t RAD family

Ranking of NFRK w.r.t RAD family	laplace	linear	rbf	Ranking of RAD family w.r.t NKRF	laplace	linear	rbf
RAD51AP1 - NKRF	1724	1642	649	RAD51AP1 - NKRF	157	553	2561
RAD51 - NKRF	982	1724	1352	RAD51 - NKRF	439	1441	1606
RAD54L - NKRF	1727	1387	1120	RAD54L - NKRF	117	1175	1415
RAD51C - NKRF	1568	472	1505	RAD51C - NKRF	418	2178	1653
RAD18 - NKRF	1508	615	405	RAD18 - NKRF	164	2306	1509
RAD1 - NKRF	2667	2222	1181	NKRF - RAD1	1391	1115	735
RAD54B - NKRF	1476	1189	1534	RAD54B - NKRF	207	1869	2244
RAD50 - NKRF	2003	2343	2511	NKRF - RAD50	1354	851	824

Table 58 2^{nd} order interaction ranking between RAD family vs NKRF.

Unexplored combinatorial hypotheses

RAD w.r.t NKRF	
RAD51AP1	NKRF
RAD51	NKRF
RAD54L	NKRF
RAD51C	NKRF
RAD18	NKRF
RAD1	NKRF
RAD54B	NKRF
NKRF w.r.t RAD	
RAD51AP1	NKRF
RAD51	NKRF
RAD54L	NKRF
RAD51C	NKRF
RAD18	NKRF
NKRF	RAD1
NKRF	RAD50

Table 59 2^{nd} order combinatorial hypotheses between RAD and XRN2.

2.4.3 NKRF - RAD cross family analysis

Not much is known about the NKRF (NF-κB-repressing factor) and RAD members. We found the combinations to be down regulated by the search engine between NKRF and RAD family. Table 58 shows the rankings of NKRF and RAD family. We found NKRF down regulated w.r.t RAD family. These are reflected in rankings of 1724 (laplace), 1642 (linear) and 649 (rbf) for RAD51AP1 <- NKRF; 982 (laplace), 1724 (linear) and 1352 (rbf) RAD51 <- NKRF; 1727 (laplace), 1387 (linear) and 1120 (rbf) for RAD54L <- NKRF; 1568 (laplace), 472 (linear) and 1505 (rbf) for RAD51C <- NKRF; 1508 (laplace), 615 (linear) and 405 (rbf) for RAD18 <- NKRF; and 1476 (laplace), 1189 (linear) and 1534 (rbf) for RAD54B <- NKRF;

Also, we found RAD family to be down regulated w.r.t NKRF. These are reflected in rankings of 157 (laplace) and 553 (linear) for RAD51AP1 - NKRF; 439 (laplace), 1441 (linear) and 1606 (rbf) for RAD51 - NKRF; 117 (laplace), 1175 (linear) and 1415 (rbf) for RAD54L - NKRF; 418 (laplace), and 1653 (rbf) for RAD51C - NKRF; 164 (laplace) and 1509 (rbf) for RAD18 - NKRF; 1391 (laplace), 1115 (linear) and 735 (rbf) NKRF - RAD1; 1354 (laplace), 851 (linear) and 824 (rbf) for NKRF - RAD50;

Table 59 shows the derived influences which can be represented graphically, with the following influences - • RAD w.r.t NKRF with RAD51AP1 <- NKRF; RAD51 <- NKRF; RAD54L <- NKRF; RAD51C <- NKRF; RAD18 <- NKRF; RAD1 <- NKRF; RAD54B <- NKRF and • NKRF w.r.t RAD with RAD51AP1 -> NKRF; RAD51 -> NKRF; RAD54L -> NKRF; RAD51C -> NKRF; RAD18 -> NKRF; NKRF -> RAD1; NKRF -> RAD50.

2.4.4 RAD - BCL cross family analysis

Saintigny *et al.* [140] show a specific role of BCL2 in suppression of the RAD51 recombination pathway. They observe that BCL2 consistently inhibits recombination stimulated by RAD51 overexpression and alters RAD51 protein by post-translation modification. Based on the findings that CARD9 and BCL10 acted together to activate NF-ÎžB following cytosolic DNA sensing, Meng *et al.* [141] demonstrated that BCL10 was recruited to the dsDNAâĂŞRAD50 complexes in a CARD9-dependent manner. These mechanisms point to a synergy between BCL and RAD family. In CRC cells treated with ETC-1922159, BCL and RAD family members were found to be down regulated. The search engine alloted the combinations of RAD and BCL low numerical valued ranks pointing to possible synergistic down regulations. Table 60 shows rankings of BCL and RAD w.r.t to each other. The left half of the table points to rankings of BCL family w.r.t RAD family. The right half of the table points to rankings of RAD family w.r.t BCL family.

On the left side, **BCL2L12** was found to be down regulated w.r.t RAD-1/18/50/51/51C/54B/54L. These are reflected in rankings of 1530 (linear) and 1401 (rbf) for RAD1 - BCL2L12; 675 (laplace) and 1312 (rbf) for RAD18 - BCL2L12; 1151 (linear) and 929 (rbf) for RAD50 - BCL2L12; 1234 (laplace) and 1334 (linear) for RAD51 - BCL2L12; 1561 (laplace) and 1647 (rbf) for RAD51C - BCL2L12; 1329 (linear) and 1625 (rbf) for RAD54B - BCL2L12, and 821 (linear) and 210 (rbf) for RAD54L - BCL2L12; **BCL6B** was found to be down regulated w.r.t RAD-1/18/50/51/51AP1/51C/54B/54L. 194 (laplace), 481 (linear) and 102 (rbf) for RAD1 - BCL6B; 176 (linear) and 929 (rbf) for RAD18 - BCL6B; 860 (laplace), 87 (linear) and 74 (rbf) for RAD50 - BCL6B; 263 (linear) and 58 (rbf) for RAD51 - BCL6B; 723 (laplace), 428 (linear) and 579 (rbf) for RAD51AP1 - BCL6B; 660 (laplace), 521 (linear) and 1609 (rbf) for RAD51C - BCL6B; 708 (laplace), 596 (linear) and 647 (rbf) for RAD54B - BCL6B; and 108 (laplace) and 1326 (rbf) for RAD54L - BCL6B; **BCL7A**

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was found to be down regulated w.r.t RAD-1/18/50/51/54L. These are reflected in rankings of 690 (laplace) and 1202 (rbf) for BCL7A - RAD1; 385 (laplace) and 185 (rbf) for BCL7A - RAD18; 137 (laplace), 601 (linear) and 41 (rbf) for RAD50 - BCL7A; 514 (laplace) and 1694 (linear) for BCL7A - RAD51; 1519 (laplace), 418 (linear) and 842 (rbf) for RAD54L - BCL7A; **BCL9** was found to be down regulated w.r.t RAD-18/51/51C/54L. These are reflected in rankings for 461 (laplace) and 1453 (linear) for RAD18 - BCL9; 1143 (linear) and 95 (rbf) for RAD51 - BCL9; 956 (laplace) and 376 (rbf) for RAD51C - BCL9; 1450 (laplace), 1096 (linear) and 400 (rbf) for RAD54L - BCL9; **BCL11A** was found to be down regulated w.r.t RAD-1/18/50/51/51AP1/51C/54B. These are reflected in rankings of 1069 (laplace), 507 (linear) and 1267 (rbf) for RAD1 - BCL11A; 1561 (laplace), 169 (linear) and 692 (rbf) for RAD18 - BCL11A; 582 (laplace), 1144 (linear) and 1047 (rbf) for RAD50 - BCL11A; 1120 (laplace), 752 (linear) and 645 (rbf) for RAD51AP1 - BCL11A; 1024 (laplace), 199 (linear) and 899 (rbf) for RAD51C - BCL11A; and 1037 (laplace), 917 (linear) and 867 (rbf) for RAD54B - BCL11A. **BCL11B** was found to be down regulated w.r.t RAD-50/51/51AP1/54B/54L. These are reflected in rankings of 1198 (linear) and 903 (rbf) for RAD50 - BCL11B; 449 (linear) and 971 (rbf) for RAD51 - BCL11B; 1247 (laplace), 908 (linear) and 1671 (rbf) for RAD51AP1 - BCL11B; 1193 (laplace), 1192 (linear) and 832 (rbf) for RAD54B - BCL11B and 1421 (laplace) and 1385 (linear) for RAD54L - BCL11B.

On the right side, **w.r.t BCL2L12**, RAD-18/50/51/51AP1/51C/54B/54L were found to be down regulated. These are found in the rankings of 779 (laplace), 652 (linear) and 1388 (rbf) for RAD18 - BCL2L12; 1668 (laplace), 2566 (linear) and 1703 (rbf) for RAD50 - BCL2L12; 1164 (laplace), 365 (linear), 1213 (rbf) for RAD51 - BCL2L12; 306 (laplace), 57 (linear) and 28 (rbf) for RAD51AP1 - BCL2L12; 495 (laplace), 1191 (linear) and 429 (rbf) for RAD51C - BCL2L12; 678 (laplace), 432 (linear) and 787 (rbf) for RAD54B - BCL2L12; and 901 (laplace), 1128 (linear) and 263 (rbf) for RAD54L - BCL2L12; **w.r.t BCL6B**, RAD-18/51/51AP1/51C/54B/54L were found to be down regulated. These are reflected in rankings of 1113 (laplace), 640 (linear) and 482 (rbf) for RAD18 - BCL6B; 287 (laplace), 681 (linear) and 497 (rbf) for RAD51 - BCL6B; 1607 (laplace), 1638 (linear) and 916 (rbf) for RAD51AP1 - BCL6B; 43 (laplace), 871 (linear) and 999 (rbf) for RAD51C - BCL6B; 1212 (laplace), 1392 (linear) and 1170 (rbf) for RAD54B - BCL6B; and 1009 (linear) and 785 (rbf) for RAD54L - BCL6B; **w.r.t BCL7A**, RAD-18/51/51AP1/51C/54B/54L were found to be down regulated. These are reflected in rankings of 1514 (laplace), 1515 (linear), 783 (rbf) for RAD18 - BCL7A; 879 (laplace), 274 (linear) and 639 (rbf) for RAD51 - BCL7A; 412 (laplace), 416 (linear) and 4 (rbf) for RAD51AP1 - BCL7A; 215 (laplace), 394 (linear) and 461 (rbf) for RAD51C - BCL7A; 809 (laplace), 1407 (linear) and 213 (rbf) for RAD54B - BCL7A and

Ranking RAD family VS BCL family

Ranking of BCL2L12 w.r.t RAD family				Ranking of RAD family w.r.t BCL2L12			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - BCL2L12	1797	1530	1401	RAD1 - BCL2L12	1958	2120	1957
RAD18 - BCL2L12	675	2437	1312	RAD18 - BCL2L12	779	652	1388
RAD50 - BCL2L12	2080	1151	929	RAD50 - BCL2L12	1668	2566	1703
RAD51 - BCL2L12	1234	1334	2350	RAD51 - BCL2L12	1164	365	1213
RAD51AP1 - BCL2L12	2267	2500	2265	RAD51AP1 - BCL2L12	306	57	28
RAD51C - BCL2L12	1561	2384	1647	RAD51C - BCL2L12	495	1191	429
RAD54B - BCL2L12	1979	1329	1625	RAD54B - BCL2L12	678	432	787
RAD54L - BCL2L12	2446	821	210	RAD54L - BCL2L12	901	1128	263
Ranking of BCL6B w.r.t RAD family				Ranking of RAD family w.r.t BCL6B			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - BCL6B	194	481	102	RAD1 - BCL6B	2110	2151	2059
RAD18 - BCL6B	1790	176	929	RAD18 - BCL6B	1113	640	482
RAD50 - BCL6B	860	87	74	RAD50 - BCL6B	2164	2412	2581
RAD51 - BCL6B	2324	263	58	RAD51 - BCL6B	287	681	497
RAD51AP1 - BCL6B	723	428	579	RAD51AP1 - BCL6B	1607	1638	916
RAD51C - BCL6B	660	521	1609	RAD51C - BCL6B	43	871	999
RAD54B - BCL6B	708	596	647	RAD54B - BCL6B	1212	1392	1170
RAD54L - BCL6B	108	2684	1326	RAD54L - BCL6B	1867	1009	785
Ranking of BCL7A w.r.t RAD family				Ranking of RAD family w.r.t BCL7A			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - BCL7A	690	1791	1202	RAD1 - BCL7A	1989	2101	1804
RAD18 - BCL7A	385	2366	185	RAD18 - BCL7A	1514	1515	783
RAD50 - BCL7A	137	601	417	RAD50 - BCL7A	2123	1771	2085
RAD51 - BCL7A	514	1694	2361	RAD51 - BCL7A	879	274	639
RAD51AP1 - BCL7A	2440	2609	774	RAD51AP1 - BCL7A	412	416	4
RAD51C - BCL7A	2726	2448	983	RAD51C - BCL7A	215	394	461
RAD54B - BCL7A	2729	1830	2743	RAD54B - BCL7A	809	1407	213
RAD54L - BCL7A	1519	418	842	RAD54L - BCL7A	435	783	1499
Ranking of BCL9 w.r.t RAD family				Ranking of RAD family w.r.t BCL9			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - BCL9	1296	2418	1775	RAD1 - BCL9	1749	2528	1391
RAD18 - BCL9	461	1952	1453	RAD18 - BCL9	656	1194	482
RAD50 - BCL9	2338	2653	2559	RAD50 - BCL9	2220	1441	1098
RAD51 - BCL9	1748	1143	952	RAD51 - BCL9	622	929	860
RAD51AP1 - BCL9	1861	2280	786	RAD51AP1 - BCL9	331	61	102
RAD51C - BCL9	956	2741	376	RAD51C - BCL9	1113	417	1154
RAD54B - BCL9	2063	2375	1050	RAD54B - BCL9	1045	53	650
RAD54L - BCL9	1450	1096	400	RAD54L - BCL9	636	602	934
Ranking of BCL11A w.r.t RAD family				Ranking of RAD family w.r.t BCL11A			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - BCL11A	1069	507	1267	RAD1 - BCL11A	1430	1475	1584
RAD18 - BCL11A	1561	169	692	RAD18 - BCL11A	465	164	1952
RAD50 - BCL11A	582	1144	1047	RAD50 - BCL11A	2649	875	1226
RAD51 - BCL11A	1722	2073	339	RAD51 - BCL11A	255	2064	2461
RAD51AP1 - BCL11A	1120	752	645	RAD51AP1 - BCL11A	659	388	496
RAD51C - BCL11A	1024	199	899	RAD51C - BCL11A	363	1673	97
RAD54B - BCL11A	1037	917	867	RAD54B - BCL11A	581	2743	799
RAD54L - BCL11A	172	2193	2318	RAD54L - BCL11A	846	2733	209
Ranking of BCL11B w.r.t RAD family				Ranking of RAD family w.r.t BCL11B			
	laplace	linear	rbf		laplace	linear	rbf
RAD1 - BCL11B	2371	2360	43	RAD1 - BCL11B	2571	230	1373
RAD18 - BCL11B	1741	993	2677	RAD18 - BCL11B	1747	2028	14
RAD50 - BCL11B	2010	1198	903	RAD50 - BCL11B	919	860	2263
RAD51 - BCL11B	2067	449	971	RAD51 - BCL11B	1095	1238	2373
RAD51AP1 - BCL11B	1247	908	1671	RAD51AP1 - BCL11B	196	2646	987
RAD51C - BCL11B	1736	1234	2282	RAD51C - BCL11B	1122	1844	1161
RAD54B - BCL11B	1193	1192	832	RAD54B - BCL11B	363	2150	1561
RAD54L - BCL11B	1421	1385	1854	RAD54L - BCL11B	579	2543	159

Table 60 2^{nd} order interaction ranking between RAD and BCL family members.

435 (laplace), 783 (linear) and 1499 (rbf) for RAD54L - BCL7A. **w.r.t BCL9**, RAD-18/50/51/51AP1/51C/54B/54L were found to be down regulated. These are reflected in the rankings of 656 (laplace), 1194 (linear) and 482 (rbf) for RAD18 - BCL9; 1441 (linear) and 1098 (rbf) for RAD50 - BCL9; 622 (laplace), 929 (linear), 860 (rbf) for RAD51 - BCL9; 331 (laplace), 61 (linear) and 102 (rbf) for RAD51AP1 - BCL9; 1113 (laplace), 417 (linear) and 1154 (rbf) for RAD51C - BCL9; 1045 (laplace), 53 (linear) and 650 (rbf) for RAD54B - BCL9 and 636 (laplace), 602 (linear) and 934 (rbf) for RAD54L - BCL9. **w.r.t BCL11A**,

UNEXPLORED COMBINATORIAL HYPOTHESES

RAD w.r.t BCL	
RAD-18/50/51/51AP1/51C/54B/54L	BCL-2L12
RAD-18/51/51AP1/51C/54B/54L	BCL-6B
RAD-18/51/51AP1/51C/54B/54L	BCL-7A
RAD-18/50/51/51AP1/51C/54B/54L - BCL-9	
RAD-1/18/50/51/51AP1/51C/54B/54L	BCL-11A
RAD-1/50/51/51AP1/51C/54B/54L	BCL-11B
BCL w.r.t RAD	
RAD-1/18/50/51/51C/54B/54L	BCL-2L12
RAD-1/18/50/51/51AP1/51C/54B/54L	BCL-6B
RAD-1/18/50/51/54L	BCL-7A
RAD-18/51/51C/54L	BCL-9
RAD-1/18/50/51/51AP1/51C/54B	BCL-11A
RAD-50/51/51AP1/54B/54L	BCL-11B

Table 61 2^{nd} order combinatorial hypotheses between RAD and BCL members.

RAD-1/18/50/51/51AP1/51C/54B/54L were found to be down regulated. These are reflected in 1430 (laplace), 1475 (linear) and 1584 (rbf) for RAD1 - BCL11A; 465 (laplace) and 164 (linear) for RAD18 - BCL11A; 875 (linear) and 1226 (rbf) for RAD50 - BCL11A; 659 (laplace), 388 (linear) and 496 (rbf) for RAD51AP1 - BCL11A; 363 (laplace), 1673 (linear) and 97 (rbf) for RAD51C - BCL11A; 581 (laplace) and 799 (rbf) for RAD54B - BCL11A; and 846 (laplace) and 209 (rbf) for RAD54L - BCL11A; **w.r.t BCL11B**, RAD-1/50/51/51AP1/51C/54B/54L were found to be down regulated. These are reflected in rankings of 230 (linear) and 1373 (rbf) RAD1 - BCL11B; 919 (laplace) and 860 (linear) for RAD50 - BCL11B; 1095 (laplace) and 1238 (linear) RAD51 - BCL11B; 196 (laplace) and 987 (rbf) for RAD51AP1 - BCL11B; 1122 (laplace) and 1161 (rbf) for RAD51C - BCL11Bl; 363 (laplace) and 1561 (rbf) for RAD54B - BCL11B; 579 (laplace), 2543 (linear) and 159 (rbf) for RAD54L - BCL11B.

Table 61 shows the derived influences which can be represented graphically, with the following influences - • RAD w.r.t BCL with RAD-18/50/51/51AP1/51C/54B/54L <- BCL-2L12; RAD-18/51/51AP1/51C/54B/54L <- BCL-6B; RAD-18/51/51AP1/51C/54B/54L <- BCL-7A; RAD-18/50/51/51AP1/51C/54B/54L <- BCL-9; RAD-1/18/50/51/51AP1/51C/54B/54L <- BCL-11A; RAD-1/50/51/51AP1/51C/54B/54L <- BCL-11B; and • BCL w.r.t RAD with RAD-1/18/50/51/51C/54B/54L -> BCL-2L12; RAD-1/18/50/51/51AP1/51C/54B/54L -> BCL-6B; RAD-1/18/50/51/54L -> BCL-7A; RAD-18/51/51C/54L -> BCL-9; RAD-1/18/50/51/51AP1/51C/54B -> BCL-11A; and RAD-50/51/51AP1/54B/54L -> BCL-11B.

2.4.5 RAD - EXOSC cross family analysis

Marin-Vicente *et al.*[142] show that RRP6/EXOSC10 is required for the repair of DNA double-strand breaks by homologous recombination. The authors results suggest that ribonucleolytic activity of RRP6/EXOSC10 is required for the recruitment of RAD51 to DSBs. The therapeutic potential of exosome-mediated siRNA delivery was demonstrated in vitro by the strong knockdown of RAD51, a prospective therapeutic target for cancer cells (Shtam *et al.*[143]). These findings point to the synergy between EXOSC and RAD family. In CRC cells treated with ETC-1922159, they were down regulated and the search engine allocated low numerical rankings for combinations, thus pointing to possible synergistic down regulation. Table 62 shows the rankings of the EXOSC and RAD family w.r.t to each other. On the left half of the table is the rankings of EXOSC w.r.t RAD family. **EXOSC2** was found to be down regulated w.r.t RAD-1/18/50/51/51AP1/51C/54B/54L. These are reflected in rankings of 1033 (laplace), 1311 (linear) and 1207 (rbf) for EXOSC2 - RAD1; 1210 (laplace) and 995 (linear) for EXOSC2 - RAD18; 1124 (laplace), 698 (linear) and 629 (rbf) for EXOSC2 - RAD50; 1754 (laplace), 191 (linear)and 633 (rbf) and for EXOSC2 - RAD51; 198 (laplace) and 1462 (linear) for EXOSC2 - RAD51AP1; 87 (laplace), 463 (linear) and 1130 (rbf) for EXOSC2 - RAD51C; 351 (laplace), 135 (linear) and 142 (rbf) for EXOSC2 - RAD54B; and 1131 (laplace), 1652 (linear) and 320 (rbf) for EXOSC2 - RAD54L. **EXOSC3** was found to be down regulated w.r.t RAD-1/18/51/51AP1/54L. These are reflected in rankings of 1677 (linear) and 549 (rbf) for EXOSC3 - RAD1; 1676 (laplace) and 184 (rbf) for EXOSC3 - RAD18; 894 (laplace) and 1066 (linear) for EXOSC3 - RAD51; 1037 (linear) and 804 (rbf) for EXOSC3 - RAD51AP1, and 469 (linear) and 736 (rbf) for EXOSC3 - RAD54L. **EXOSC5** was found to be down regulated w.r.t RAD-1/18/50/51/51AP1/51C/54B/54L. These are reflected in rankings of 568 (laplace), 1169 (linear) and 1699 (rbf) for EXOSC5 - RAD1; 219 (linear) and 1652 (rbf) for EXOSC5 - RAD18; 447 (laplace), 195 (linear) and 475 (rbf) for EXOSC5 - RAD50; 431 (linear) and 1121 (rbf) for EXOSC5 - RAD51; 1290 (laplace), 487 (linear) and 430 (rbf) for EXOSC5 - RAD51AP1; 1284 (laplace) and 1264 (linear) for EXOSC5 - RAD51C; 940 (laplace), 812 (linear) and 1036 (rbf) for EXOSC5 - RAD54B; and 408 (laplace) and 1407 (rbf) for EXOSC5 - RAD54L; **EXOSC6** was found to be down regulated w.r.t RAD-18/51/54L. These were reflected in rankings of 1637 (laplace), 1599 (linear) and 2254 (rbf) for EXOSC6 - RAD18; 1056 (laplace), 1482 (linear) and 1007 (rbf) for EXOSC6 - RAD51; and 987 (laplace) and 1642 (rbf) for EXOSC6 - RAD54L; **EXOSC7** was found to be down regulated w.r.t RAD-1/18/51C/54B/54L. These are reflected in rankings of 1735 (linear) and 1210 (rbf) for EXOSC7 - RAD1; 490 (laplace), 1688 (linear) and 1331 (rbf) for EXOSC7 - RAD18; 1113 (laplace), 1623 (linear) and 530 (rbf) for EXOSC7

- RAD51C; 1612 (linear) and 1191 (rbf) for EXOSC7 - RAD54B; and 1550 (laplace), 1754 (linear) and 1728 (rbf) for EXOSC7 - RAD54L; **EXOSC8** was found to be down regulated w.r.t RAD-18/51/51AP1/54B/54L. These are reflected in 805 (laplace) and 1564 (rbf) for EXOSC8 - RAD18; 404 (laplace) and 1630 (linear) for EXOSC8 - RAD51; 1567 (linear) and 1701 (rbf) for EXOSC8 - RAD51AP1; 1562 (laplace) and 1736 (rbf) for EXOSC8 - RAD54B; and 1248 (laplace), 622 (linear) and 239 (rbf) for EXOSC8 - RAD54L; **EXOSC9** was found to be down regulated w.r.t RAD-1/18/50/51/51C/54B/54L. These are reflected in rankings of 175 (linear) and 1648 (rbf) for EXOSC9 - RAD1; 1533 (laplace), 774 (linear) and 1180 (rbf) for EXOSC9 - RAD18; 545 (laplace), 183 (linear) and 467 (rbf) for EXOSC9 - RAD50; 866 (laplace), 106 (linear) and 99 (rbf) for EXOSC9 - RAD51; 110 (laplace), 742 (linear) and 200 (rbf) for EXOSC9 - RAD51C; 179 (laplace), 178 (linear) and 84 (rbf) for EXOSC9 - RAD54B and 1113 (laplace) and 22 (rbf) for EXOSC9 - RAD54L;

On the right half of the table is the rankings of RAD family w.r.t EXOSC. **RAD-18/51/51C/54B/54L** was found to be down regulated w.r.t EXOSC2. These are reflected in rankings of 1115 (laplace), 979 (linear) and 654(rbf) for EXOSC2 - RAD18; 795 (laplace), 1332 (linear) and 441(rbf) for EXOSC2 - RAD51; 636 (laplace), 564 (linear) and 152(rbf) for EXOSC2 - RAD51C; 278 (laplace), 132 (linear) and 282(rbf) for EXOSC2 - RAD54B and 125 (laplace), 888 (linear) and 545(rbf) for EXOSC2 - RAD54L. **RAD-18/50/51/51AP1/51C/54B/54L** was found to be down regulated w.r.t EXOSC3. These are reflected in rankings of 1468 (linear) and 767 (rbf) for EXOSC3 - RAD18; 1062 (laplace) and 596 (linear) for EXOSC3 - RAD50; 727 (laplace), 583 (linear) and 963 (rbf) for EXOSC3 - RAD51; 100 (laplace), 49 (linear) and 219 (rbf) for EXOSC3 - RAD51AP1; 663 (laplace), 869 (linear) and 887 (rbf) for EXOSC3 - RAD51C; 384 (laplace), 277 (linear) and 310 (rbf) for EXOSC3 - RAD54B and 546 (laplace), 1117 (linear) and 808 (rbf) for EXOSC3 - RAD54L; **RAD-1/18/51/51AP1/51C/54B/54L** was found to be down regulated w.r.t EXOSC5. These are reflected in rankings of 1716 (linear) and 1718 (rbf) for EXOSC5 - RAD1; 1026 (laplace), 550 (linear) and 253 (rbf) for EXOSC5 - RAD18; 260 (laplace), 1095 (linear) and 137 (rbf) for EXOSC5 - RAD51; 1555 (laplace) and 976 (rbf) for EXOSC5 - RAD51AP1; 233 (laplace), 1003 (linear) and 359 (rbf) for EXOSC5 - RAD51C; 834 (laplace), 1825 (linear) and 335 (rbf) for EXOSC5 - RAD54B; and 248 (laplace), 197 (linear) and 39 (rbf) for EXOSC5 - RAD54L. **RAD-1/18/50/51AP1/51C/54L** was found to be down regulated w.r.t EXOSC6. These are reflected in rankings of 142 (linear) and 639(rbf) for EXOSC6 - RAD1; 1118 (laplace), 1313 (linear) and 1549(rbf) for EXOSC6 - RAD18; 1722 (linear) and 575(rbf) for EXOSC6 - RAD50; 149 (laplace) and 1060 (linear) for EXOSC6 - RAD51AP1; 500 (laplace) and 1628 (linear) for EXOSC6 - RAD51C; and 885 (laplace), 271 (linear) and 1224(rbf) for EXOSC6 - RAD54L; **RAD-18/51/51AP1/51C/54B/54L** was found to be down regulated w.r.t EXOSC7. These were reflected in rankings of 441 (laplace), 385 (linear) and 1542(rbf) for EXOSC7 - RAD18; 376 (laplace), 1180 (linear) and 550(rbf) for EXOSC7

Ranking RAD family VS EXOSC family

Ranking of EXOSC2 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC2			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC2 - RAD1	1033	1311	1207	EXOSC2 - RAD1	2456	1368	2292
EXOSC2 - RAD18	1210	995	1906	EXOSC2 - RAD18	1115	979	654
EXOSC2 - RAD50	1124	698	629	EXOSC2 - RAD50	1647	2495	2375
EXOSC2 - RAD51	1754	191	633	EXOSC2 - RAD51	795	1332	441
EXOSC2 - RAD51AP1	198	1462	2718	EXOSC2 - RAD51AP1	2320	1316	2127
EXOSC2 - RAD51C	87	463	1130	EXOSC2 - RAD51C	636	564	152
EXOSC2 - RAD54B	351	135	142	EXOSC2 - RAD54B	278	132	282
EXOSC2 - RAD54L	1131	1652	320	EXOSC2 - RAD54L	125	888	545
Ranking of EXOSC3 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC3			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC3 - RAD1	2492	1677	549	EXOSC3 - RAD1	2200	1243	2711
EXOSC3 - RAD18	1676	2516	184	EXOSC3 - RAD18	2024	1468	767
EXOSC3 - RAD50	2368	1892	2204	EXOSC3 - RAD50	1062	596	2346
EXOSC3 - RAD51	894	1066	2463	EXOSC3 - RAD51	727	583	963
EXOSC3 - RAD51AP1	1884	1037	804	EXOSC3 - RAD51AP1	100	49	219
EXOSC3 - RAD51C	2499	2356	1248	EXOSC3 - RAD51C	663	869	887
EXOSC3 - RAD54B	2183	2518	2360	EXOSC3 - RAD54B	384	277	310
EXOSC3 - RAD54L	1735	469	736	EXOSC3 - RAD54L	546	1117	808
Ranking of EXOSC5 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC5			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC5 - RAD1	568	1169	1699	EXOSC5 - RAD1	2405	1716	1718
EXOSC5 - RAD18	2481	219	1652	EXOSC5 - RAD18	1026	550	253
EXOSC5 - RAD50	447	195	475	EXOSC5 - RAD50	1596	1952	2271
EXOSC5 - RAD51	2548	431	1121	EXOSC5 - RAD51	260	1095	137
EXOSC5 - RAD51AP1	1290	487	430	EXOSC5 - RAD51AP1	1555	1860	976
EXOSC5 - RAD51C	1284	1264	1790	EXOSC5 - RAD51C	233	1003	359
EXOSC5 - RAD54B	940	812	1036	EXOSC5 - RAD54B	834	1825	335
EXOSC5 - RAD54L	408	2539	1407	EXOSC5 - RAD54L	248	197	39
Ranking of EXOSC6 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC6			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC6 - RAD1	2283	2490	1228	EXOSC6 - RAD1	2405	142	639
EXOSC6 - RAD18	1637	1599	2254	EXOSC6 - RAD18	1118	1313	1549
EXOSC6 - RAD50	2289	1969	1797	EXOSC6 - RAD50	2309	1722	575
EXOSC6 - RAD51	1056	1482	1007	EXOSC6 - RAD51	998	2297	2219
EXOSC6 - RAD51AP1	1854	2480	1827	EXOSC6 - RAD51AP1	149	1060	2731
EXOSC6 - RAD51C	1996	940	1842	EXOSC6 - RAD51C	500	1628	2409
EXOSC6 - RAD54B	2289	2312	2005	EXOSC6 - RAD54B	262	2703	2465
EXOSC6 - RAD54L	987	2240	1642	EXOSC6 - RAD54L	885	271	1224
Ranking of EXOSC7 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC7			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC7 - RAD1	2559	1735	1210	EXOSC7 - RAD1	2079	2308	1604
EXOSC7 - RAD18	490	1688	1331	EXOSC7 - RAD18	441	385	1542
EXOSC7 - RAD50	2661	1939	2021	EXOSC7 - RAD50	1840	406	2100
EXOSC7 - RAD51	842	1900	1876	EXOSC7 - RAD51	376	1180	550
EXOSC7 - RAD51AP1	2446	349	2374	EXOSC7 - RAD51AP1	35	97	786
EXOSC7 - RAD51C	1113	1623	530	EXOSC7 - RAD51C	854	671	1459
EXOSC7 - RAD54B	2431	1612	1191	EXOSC7 - RAD54B	458	260	646
EXOSC7 - RAD54L	1550	1754	1728	EXOSC7 - RAD54L	464	528	790
Ranking of EXOSC8 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC8			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC8 - RAD1	2380	2442	2630	EXOSC8 - RAD1	1928	151	1563
EXOSC8 - RAD18	805	2287	1564	EXOSC8 - RAD18	764	523	29
EXOSC8 - RAD50	1798	1830	1893	EXOSC8 - RAD50	2103	2649	1822
EXOSC8 - RAD51	404	1630	2092	EXOSC8 - RAD51	98	1161	902
EXOSC8 - RAD51AP1	1932	1567	1701	EXOSC8 - RAD51AP1	408	1824	541
EXOSC8 - RAD51C	2439	1576	2554	EXOSC8 - RAD51C	906	738	1052
EXOSC8 - RAD54B	1562	2542	1736	EXOSC8 - RAD54B	23	1578	130
EXOSC8 - RAD54L	1248	622	239	EXOSC8 - RAD54L	651	1384	1047
Ranking of EXOSC9 w.r.t RAD family				Ranking of RAD family w.r.t EXOSC9			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC9 - RAD1	2240	175	1648	EXOSC9 - RAD1	1335	1799	978
EXOSC9 - RAD18	1533	774	1180	EXOSC9 - RAD18	2529	54	540
EXOSC9 - RAD50	545	183	467	EXOSC9 - RAD50	211	2217	1377
EXOSC9 - RAD51	866	106	99	EXOSC9 - RAD51	807	74	429
EXOSC9 - RAD51AP1	1570	1819	1807	EXOSC9 - RAD51AP1	2480	103	1210
EXOSC9 - RAD51C	110	742	200	EXOSC9 - RAD51C	399	844	69
EXOSC9 - RAD54B	179	178	84	EXOSC9 - RAD54B	2385	466	1286
EXOSC9 - RAD54L	1113	2436	22	EXOSC9 - RAD54L	536	724	414

Table 62 2^{nd} order interaction ranking between RAD and EXOSC family members.

- RAD51C; and 885 (laplace), 271 (linear) and 1224(rbf) for EX-

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- RAD51; 35 (laplace), 97 (linear) and 786(rbf) for EXOSC7 - RAD51AP1; 854 (laplace), 671 (linear) and 1459(rbf) for EXOSC7 - RAD51C; 458 (laplace), 260 (linear) and 646(rbf) for EXOSC7 - RAD54B; and 464 (laplace), 528 (linear) and 790(rbf) for EXOSC7 - RAD54L; **RAD-1/18/51/51AP1/51C/54B/54L** was found to be down regulated w.r.t EXOSC8. These were reflected in rankings of 151 (linear) and 1563 (rbf) for EXOSC8 - RAD1; 764 (laplace), 523 (linear) and 29 (rbf) for EXOSC8 - RAD18; 98 (laplace), 1161 (linear) and 902 (rbf) for EXOSC8 - RAD51; 408 (laplace) and 541 (rbf) for EXOSC8 - RAD51AP1; 906 (laplace), 738 (linear) and 1052 (rbf) for EXOSC8 - RAD51C; 23 (laplace), 1578 (linear) and 130 (rbf) for EXOSC8 - RAD54B; and 651 (laplace), 1384 (linear) and 1047 (rbf) for EXOSC8 - RAD54L; **RAD-1/18/50/51/51AP1/51C/54B/54L** was found to be down regulated w.r.t EXOSC9. These were reflected in rankings of 1335 (laplace) and 978 (rbf) for EXOSC9 - RAD1; 54 (linear) and 540 (rbf) for EXOSC9 - RAD18; 211 (laplace) and 1377 (rbf) for EXOSC9 - RAD50; 807 (laplace), 74 (linear) and 429 (rbf) for EXOSC9 - RAD51; 103 (linear), 1210 (rbf) for EXOSC9 - RAD51AP1; 399 (laplace), 844 (linear) and 69 (rbf) for EXOSC9 - RAD51C; 466 (linear), 1286 (rbf) for EXOSC9 - RAD54B; and 536 (laplace), 724 (linear) and 414 (rbf) for EXOSC9 - RAD54L;

Table 63 shows the derived influences which can be represented graphically, with the following influences - • RAD w.r.t EXOSC with EXOSC-2 -> RAD-18/51/51C/54B/54L; EXOSC-3 -> RAD-18/50/51/51AP1/51C/54B/54L; EXOSC-5 -> RAD-1/18/51/51AP1/51C/54B/54L; EXOSC-6 -> RAD-1/18/50/51AP1/51C/54L; EXOSC-7 -> RAD-18/51/51AP1/51C/54B/54L; EXOSC-8 -> RAD-1/18/51/51AP1/51C/54B/54L; EXOSC-9 -> RAD-1/18/50/51/51AP1/51C/54B/54L; and • EXOSC w.r.t RAD with EXOSC-2 <- RAD-1/18/50/51/51AP1/51C/54B/54L; EXOSC-3 <- RAD-1/18/51/51AP1/54L; EXOSC-5 <- RAD-1/18/50/51/51AP1/51C/54B/54L; EXOSC-6 <- RAD-18/51/54L; EXOSC-7 <- RAD-1/18/51C/54B/54L; EXOSC-8 <- RAD-18/51/51AP1/54B/54L; and EXOSC-9 <- RAD-1/18/50/51/51C/54B/54L.

UNEXPLORED COMBINATORIAL HYPOTHESES

RAD w.r.t EXOSC	
EXOSC-2	RAD-18/51/51C/54B/54L
EXOSC-3	RAD-18/50/51/51AP1/51C/54B/54L
EXOSC-5	RAD-1/18/51/51AP1/51C/54B/54L
EXOSC-6	RAD-1/18/50/51AP1/51C/54L
EXOSC-7	RAD-18/51/51AP1/51C/54B/54L
EXOSC-8	RAD-1/18/51/51AP1/51C/54B/54L
EXOSC-9	RAD-1/18/50/51/51AP1/51C/54B/54L
EXOSC w.r.t RAD	
EXOSC-2	RAD-1/18/50/51/51AP1/51C/54B/54L
EXOSC-3	RAD-1/18/51/51AP1/54L
EXOSC-5	RAD-1/18/50/51/51AP1/51C/54B/54L
EXOSC-6	RAD-18/51/54L
EXOSC-7	RAD-1/18/51C/54B/54L
EXOSC-8	RAD-18/51/51AP1/54B/54L
EXOSC-9	RAD-1/18/50/51/51C/54B/54L

Table 63 2^{nd} order combinatorial hypotheses between RAD and EXOSC members.

2.4.6 XRCC - EXOSC cross family analysis

Not much is known about XRCC - EXOSC synergy, however both were found to be down regulated in CRC cells after treatment with ETC-1922159. The search engine also allocated rankings of low numerical values to several combinations thus indicating plausible synergistic down regulations. Table 64 shows the rankings of XRCC vs EXOSC family members.

On the left half of the table is the rankings of EXOSC w.r.t XRCC family. **EXOSC2** was found to be down regulated w.r.t XRCC-1/2/6/6BP1. These are reflected in rankings of 277 (laplace), 176 (linear) and 423 (rbf) for EXOSC2 - XRCC1; 8 (laplace), 38 (linear) and 100 (rbf) for EXOSC2 - XRCC2; 1252 (laplace), 398 (linear) and 623 (rbf) for EXOSC2 - XRCC6; and 935 (laplace) and 905 (linear) for EXOSC2 - XRCC6BP1; **EXOSC3** was found to be down regulated w.r.t XRCC-6BP1. These are reflected in rankings of 1523 (linear) and 1356 (rbf) for EXOSC3 - XRCC6BP1; **EXOSC5** was found to be down regulated w.r.t XRCC-1/2/6/6BP1. These are reflected in rankings of 741 (laplace), 291 (linear) and 8 (rbf) for EXOSC5 - XRCC1; 1244 (laplace), 791 (linear) and 702 (rbf) for EXOSC5 - XRCC2; 65 (laplace), 1064 (linear) and 322 (rbf) for EXOSC5 - XRCC6; and 416 (laplace), 880 (linear) and 1434 (rbf) for EXOSC5 - XRCC6BP1. **EXOSC6** was found to be down regulated w.r.t XRCC-1/2. These are reflected in rankings of 985 (linear) and 1163 (rbf) for EXOSC6 - XRCC1 and 1512 (laplace), 648 (linear) and 1458 (rbf) for EXOSC6 - XRCC2; **EXOSC7** was found to be down regulated w.r.t XRCC-1/6/6BP1. These are reflected in rankings of 1510 (linear) and 1603 (rbf) for EXOSC7 - XRCC1; 584 (laplace), 1523 (linear) and 1018 (rbf) for EXOSC7 - XRCC6; and 1419 (laplace) and 876 (rbf) for EXOSC7 - XRCC6BP1. **EXOSC8** was found to be down regulated w.r.t XRCC-1. These are reflected in rankings of 1373 (laplace) and 1515 (linear) for EXOSC8 - XRCC1; **EXOSC9** was found to be down regulated w.r.t XRCC-1/2/6/6BP1. These are reflected in rankings of 44 (laplace), 1214 (linear) and 1410 (rbf) for EXOSC9 - XRCC1; 496 (laplace), 672 (linear) and 840 (rbf) for EXOSC9 - XRCC2; 1121 (laplace), 151 (linear) and 689 (rbf) for EXOSC9 - XRCC6 and 362 (laplace), 463 (linear) and 1741 (rbf) for EXOSC9 - XRCC6BP1.

On the right half of the table is the rankings of XRCC w.r.t EXOSC family. **W.r.t EXOSC2**, XRCC-2 was found to be down regulated. These are reflected in rankings of 166 (laplace), 417

Ranking XRCC family VS EXOSC family

Ranking of EXOSC2 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC2			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC2 - XRCC1	277	176	423	EXOSC2 - XRCC1	2708	2386	2634
EXOSC2 - XRCC2	8	38	100	EXOSC2 - XRCC2	166	417	56
EXOSC2 - XRCC6	1252	398	623	EXOSC2 - XRCC6	2678	2504	2576
EXOSC2 - XRCC6BP1	935	905	1755	EXOSC2 - XRCC6BP1	1740	1842	2177
Ranking of EXOSC3 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC3			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC3 - XRCC1	1551	2256	1974	EXOSC3 - XRCC1	2217	1418	2041
EXOSC3 - XRCC2	2462	2553	2329	EXOSC3 - XRCC2	125	15	194
EXOSC3 - XRCC6	1720	1716	2398	EXOSC3 - XRCC6	2742	2608	2193
EXOSC3 - XRCC6BP1	2506	1523	1356	EXOSC3 - XRCC6BP1	2561	2154	2406
Ranking of EXOSC5 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC5			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC5 - XRCC1	741	291	8	EXOSC5 - XRCC1	2578	2568	1910
EXOSC5 - XRCC2	1244	791	702	EXOSC5 - XRCC2	1559	1857	866
EXOSC5 - XRCC6	65	1064	322	EXOSC5 - XRCC6	2410	2465	2190
EXOSC5 - XRCC6BP1	416	880	1434	EXOSC5 - XRCC6BP1	1907	2029	1394
Ranking of EXOSC6 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC6			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC6 - XRCC1	1890	985	1163	EXOSC6 - XRCC1	509	2373	1046
EXOSC6 - XRCC2	1512	648	1458	EXOSC6 - XRCC2	486	2564	1901
EXOSC6 - XRCC6	2304	1719	2690	EXOSC6 - XRCC6	2576	35	188
EXOSC6 - XRCC6BP1	2428	492	2112	EXOSC6 - XRCC6BP1	1753	1295	366
Ranking of EXOSC7 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC7			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC7 - XRCC1	1907	1510	1603	EXOSC7 - XRCC1	1844	1229	987
EXOSC7 - XRCC2	1369	2555	2124	EXOSC7 - XRCC2	176	436	788
EXOSC7 - XRCC6	584	1523	1018	EXOSC7 - XRCC6	1074	242	288
EXOSC7 - XRCC6BP1	1419	1944	876	EXOSC7 - XRCC6BP1	2144	1577	2038
Ranking of EXOSC8 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC8			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC8 - XRCC1	1373	1515	2103	EXOSC8 - XRCC1	1769	2151	1435
EXOSC8 - XRCC2	1086	2309	2435	EXOSC8 - XRCC2	13	1932	6
EXOSC8 - XRCC6	1820	2542	2693	EXOSC8 - XRCC6	1869	1233	2625
EXOSC8 - XRCC6BP1	2112	1994	2699	EXOSC8 - XRCC6BP1	2305	2461	2319
Ranking of EXOSC9 w.r.t XRCC family				Ranking of XRCC family w.r.t EXOSC9			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC9 - XRCC1	44	1214	1410	EXOSC9 - XRCC1	1804	2696	1629
EXOSC9 - XRCC2	496	672	840	EXOSC9 - XRCC2	1793	655	1526
EXOSC9 - XRCC6	1121	151	689	EXOSC9 - XRCC6	1882	2188	2404
EXOSC9 - XRCC6BP1	362	463	1741	EXOSC9 - XRCC6BP1	1206	1776	1626

Table 64 2^{nd} order interaction ranking between RAD and EXOSC family members.

(linear) and 56 (rbf) for EXOSC2 - XRCC2. W.r.t **W.r.t EXOSC3**, XRCC-2 was found to be down regulated. These are reflected in rankings of 166 (laplace), 417 (linear) and 56 (rbf) for EXOSC3 - XRCC2. **W.r.t EXOSC5**, XRCC-2 was found to be down regulated. These are reflected in rankings of 1559 (laplace) and 56 (rbf) for EXOSC5 - XRCC2. **W.r.t EXOSC6**, XRCC-1/2/6/6BP1 were found to be down regulated. These are reflected in rankings of 509 (laplace) and 1046(rbf) for EXOSC6 - XRCC1; 486 (laplace) and 1901(rbf) for EXOSC6 - XRCC2; 35 (linear) and 188(rbf) for EXOSC6 - XRCC6; 1295 (linear) and 366 (rbf) for EXOSC6 - XRCC6BP1. **W.r.t EXOSC7**, XRCC-6 was found to be down regulated. These are reflected in rankings of 1229 (linear) and 987(rbf) for EXOSC7 - XRCC1; 176 (laplace), 436 (linear) and 788 (rbf) for EXOSC7 - XRCC2; and 1074 (laplace), 242 (linear) and 288(rbf) for EXOSC7 - XRCC6. **W.r.t EXOSC8**, XRCC-2 was found to be down regulated. These are reflected in rankings of 13 (laplace) and 6 (rbf) for EXOSC8 - XRCC2. **W.r.t EXOSC9**, XRCC-2 was found to be down regulated. These are reflected in rankings of 655 (linear) and 1526 (rbf) for EXOSC9 - XRCC2 and 1206 (laplace) and 1626 (rbf) for EXOSC9 - XRCC6BP1;

Unexplored combinatorial hypotheses	
XRCC w.r.t EXOSC	
EXOSC-2	XRCC-2
EXOSC-3	XRCC-2
EXOSC-5	XRCC-2
EXOSC-6	XRCC-6
EXOSC-7	XRCC-1/2/6
EXOSC-8	XRCC-2
EXOSC-9	XRCC-2/6BP1
EXOSC w.r.t XRCC	
EXOSC-2	XRCC-1/2/6/6BP1
EXOSC-3	XRCC-6/6BP1
EXOSC-5	XRCC-1/2/6/6BP1
EXOSC-6	XRCC-1/2
EXOSC-7	XRCC-1/6/6BP1
EXOSC-8	XRCC-1
EXOSC-9	XRCC-1/2/6/6BP1

Table 65 2^{nd} order combinatorial hypotheses between XRCC and EXOSC members.

Table 65 shows the derived influences which can be represented graphically, with the following influences - • XRCC w.r.t EXOSC with EXOSC-2 -> XRCC-2; EXOSC-3 -> XRCC-2; EXOSC-5 -> XRCC-2; EXOSC-6 -> XRCC-6; EXOSC-7 -> XRCC-1/2/6; EXOSC-8 -> XRCC-2; EXOSC-9 -> XRCC-2/6BP1; and • EXOSC w.r.t XRCC with EXOSC-2 <- XRCC-1/2/6/6BP1; EXOSC-3 <- XRCC-6/6BP1; EXOSC-5 <- XRCC-1/2/6/6BP1; EXOSC-6 <- XRCC-1/2; EXOSC-7 <- XRCC-1/6/6BP1; EXOSC-8 <- XRCC-1; and EXOSC-9 <- XRCC-1/2/6/6BP1.

2.4.7 RAD - FANC cross family analysis

Fanconi Anemia (FA) is rare genetic disorder that happens mainly due to defects in proteins responsible for DNA repair via homologous recombination (Walden and Deans [144]). Cohn and D'Andrea [145] provides a review on the recent discoveries in the Fanconi Anemia and DNA double-strand break (DSB) repair pathways, which underscore the importance of regulated chromatin loading in the DNA damage response. Romick-Rosendale *et al.* [146] study the role Fanconi anemia pathway in squamous Cell Carcinoma. A review of the interplay between Fanconi anemia and homologous recombination pathways in genome integrity has been conducted by Michl *et al.* [147]. Liang *et al.* [148] observe the role of trimeric RAD51 and RAD51AP1-UAF1 complex in FANCD2. Taniguchi *et al.* [149] observe S-phase-specific interaction

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of the Fanconi anemia protein, FANCD2, with BRCA1 and RAD51. Zadorozhny *et al.* [150] show Fanconi anemia associated mutations destabilize RAD51 filaments and impair replication fork protection. Geng *et al.* [151] find RAD18-mediated ubiquitination of PCNA activates the Fanconi anemia DNA repair network. Rad18 E3 ubiquitin ligase activity mediates Fanconi anemia pathway activation and cell survival following DNA topoisomerase 1 inhibition as shown by Palle and Vaziri [152]. García-Luis and Machín [153] observe that Fanconi anaemia-like Mph1 helicase backs up RAD54 and RAD5 to circumvent replication stress-driven chromosome bridges. These findings suggest deep interactive role between the RAD and FA family. In colorectal cancer cell treated with ETC-1922159 these were found to both families were found to be down regulated. Our search engine alloted low laved numerical ranks to many of the 2^{nd} order combinations between the RAD - FANC family. This signifies possible synergistic mechanism between the two in CRC cells. Table 67 shows the rankings of each, with respect to the other. On the left half is the rankings of RAD family w.r.t FANC family and vice versa on the right half.

On the left half, we find, **RAD-18/51/51AP1/51C/54B/54L** were found to be down regulated w.r.t FANCB. These are reflected in rankings of 10 (laplace), 2219 (linear) and 625 (rbf) for RAD18 - FANCB; 247 (laplace), 73 (linear) and 610 (rbf) for RAD51 - FANCB; 479 (laplace), 1667 (linear) and 663 (rbf) for RAD51AP1 - FANCB; 769 (laplace), 536 (linear) and 887 (rbf) for RAD51C - FANCB; 468 (laplace), 133 (linear) and 438 (rbf) for RAD54B - FANCB; and 583 (laplace), 2131 (linear) and 160 (rbf) for RAD54L - FANCB. **RAD-18/51/51AP1/54B/54L** were found to be down regulated w.r.t FANCD2. These are reflected in rankings of 1035 (laplace), 1271 (linear) and 405 (rbf) for RAD18 - FANCD2; 885 (laplace) and 1383 (rbf) for RAD51 - FANCD2; 1734 (laplace), 644 (linear) and 1291 (rbf) for RAD51AP1 - FANCD2; 275 (laplace), 2460 (linear) and 478 (rbf) for RAD54B - FANCD2; and 493 (laplace) and 203 (rbf) for RAD54L - FANCD2; **RAD-1/18/50/51/51C/54B/54L** were found to be down regulated w.r.t FANCD2OS. These are reflected in rankings of 693 (laplace) and 1146 (rbf) for RAD1 - FANCD2OS; 1472 (laplace), 526 (linear) and 239 (rbf) for RAD18 - FANCD2OS; 178 (laplace) and 1534 (linear) for RAD50 - FANCD2OS; 1080 (linear) and 1226 (rbf) for RAD51 - FANCD2OS; 1297 (laplace), 977 (linear) and 1237 (rbf) for RAD51C - FANCD2OS; 475 (laplace), 1367 (linear) for RAD54B - FANCD2OS; 1227 (linear) and 252 (rbf) for RAD54L - FANCD2OS; **RAD-1/18/50/51/51AP1/51C/54B/54L** were found to be down regulated w.r.t FANCF. These are reflected in rankings of 1582 (linear) and 285 (rbf) for RAD1 - FANCF; 770 (laplace), 1329 (linear) and 1445 (rbf) for RAD18 - FANCF; 1403 (laplace), 1684 (linear) and 803 (rbf) for RAD50 - FANCF; 209 (laplace), 1247 (linear) for RAD51 - FANCF; 1681 (laplace), 13 (linear) for RAD51AP1 - FANCF; 1493 (laplace) and 224 (linear) for RAD51C - FANCF; 401 (laplace) and 143 (linear) for RAD54B - FANCF; for 690 (laplace), 829 (linear) for RAD54L - FANCF; **RAD-1/18/50/51/51AP1/51C/54B/54L** were found to be down regulated w.r.t FANCG. These are reflected in rankings of 755 (laplace), 393 (linear) and 82 (rbf) for RAD18 - FANCG; 345 (laplace), 114 (linear) and 295 (rbf) for RAD51 - FANCG; 957 (laplace), 218 (linear) and 1360 (rbf) for RAD51C - FANCG; 17 (laplace), 182 (linear) and 423 (rbf) for RAD54B - FANCG; and 1058 (laplace), 701 (linear) and 581 (rbf) for RAD54L - FANCG. **RAD-18/50/51/51C/54B/54L** were found to be down regulated w.r.t FANCG. These are reflected in rankings of 1693 (laplace)and 436 (rbf) for RAD18 - FANCI; 1703 (laplace) and 1458 (rbf) for RAD50 - FANCI; 1038 (laplace), 1668 (linear) and 310 (rbf) for RAD51 - FANCI; 597 (laplace) and 165 (linear) for RAD51C - FANCI; 557 (laplace) and 84 (linear) for RAD54B - FANCI; and 468 (laplace), 606 (linear) for RAD54L - FANCI.

On the right half, we find, **FANCB** to be down regulated w.r.t RAD-1/50/51/51AP1/51C/54B/54L. These are reflected in rankings of 1499 (laplace), 656 (linear) and 340 (rbf) for RAD1 - FANCB; 133 (laplace), 234 (linear) and 73 (rbf) for RAD50 - FANCB; 378 (linear) and 8 (rbf) for RAD51 - FANCB; 89 (laplace), 562 (linear) and 2 (rbf) for RAD51AP1 - FANCB; 460 (laplace), 187 (linear) and 86 (rbf) for RAD51C - FANCB; 486 (laplace), 891 (linear) and 568 (rbf) for RAD54B - FANCB and 41 (laplace) and 692 (rbf) for RAD54L - FANCB; **FANCD2** was found to be down regulated w.r.t RAD-1/50/51/51AP1/51C/54B/54L. These are reflected in rankings of 1451 (laplace), 1605 (linear) and 796 (rbf) for RAD1 - FANCD2; 403 (linear) and 1299 (rbf) for RAD18 - FANCD2; 646 (laplace), 357 (linear) and 769 (rbf) for RAD50 - FANCD2; 591 (laplace) and 85 (rbf) for RAD51 - FANCD2; 993 (laplace) and 603 (linear) for RAD51AP1 - FANCD2; 629 (laplace), 656 (linear) and 620 (rbf) for RAD51C - FANCD2; 227 (laplace), 230 (linear) and 131 (rbf) for RAD54B - FANCD2. **FANCD2OS2** was found to be down regulated w.r.t RAD-1/18/5051C/54B. These are reflected in rankings of 1455 (laplace) and 1624 (rbf) for RAD1 - FANCD2OS; 851 (laplace), 1457 (linear) and 653 (rbf) for RAD18 - FANCD2OS; 1477 (linear) and 1372 (rbf) for RAD50 - FANCD2OS; 1729 (laplace) and 779 (linear) for RAD51C - FANCD2OS; 1241 (linear) and 1637 (rbf) for RAD54B - FANCD2OS; **FANCF** was found to be down regulated w.r.t RAD-1/18/50/51C/54B. These are reflected in rankings of 1063 (laplace) and 196 (rbf) for RAD18 - FANCF; 1419 (linear) and 1676 (rbf) for RAD50 - FANCF; 1222 (laplace) and 1060 (linear) for RAD51 - FANCF; and 716 (linear) and 1262 (rbf) for RAD54L - FANCF; **FANCG** was found to be down regulated w.r.t RAD-1/50/51/51AP1/51C/54B. These are reflected in rankings of 825 (linear) and 843 (rbf) for RAD1 - FANCG; 695 (laplace), 511 (linear) and 933 (rbf) for RAD50 - FANCG; 1 (linear) and 397 (rbf) for RAD51 - FANCG; 661 (laplace), 400 (linear) and 23 (rbf) for RAD51AP1 - FANCG; 450 (laplace) and 1122 (rbf) for RAD51C - FANCG; 140 (laplace), 194 (linear) and

Ranking RAD family VS FANC family

Ranking of RAD family w.r.t FANCB	laplace	linear	rbf	Ranking of FANCB w.r.t RAD family	laplace	linear	rbf
RAD1 - FANCB	2431	400	2553	RAD1 - FANCB	1499	656	340
RAD18 - FANCB	10	2219	625	RAD18 - FANCB	2708	383	2298
RAD50 - FANCB	2419	915	2556	RAD50 - FANCB	133	234	73
RAD51 - FANCB	247	73	610	RAD51 - FANCB	2444	378	8
RAD51AP1 - FANCB	479	1667	663	RAD51AP1 - FANCB	89	562	2
RAD51C - FANCB	769	536	887	RAD51C - FANCB	460	187	86
RAD54B - FANCB	468	133	438	RAD54B - FANCB	486	891	568
RAD54L - FANCB	583	2131	160	RAD54L - FANCB	41	2675	692
Ranking of RAD family w.r.t FANCD2	laplace	linear	rbf	Ranking of FANCD2 w.r.t RAD family	laplace	linear	rbf
RAD1 - FANCD2	1935	332	2102	RAD1 - FANCD2	1451	1605	796
RAD18 - FANCD2	1035	1271	405	RAD18 - FANCD2	2356	403	1299
RAD50 - FANCD2	2109	436	2038	RAD50 - FANCD2	646	357	769
RAD51 - FANCD2	885	1995	1383	RAD51 - FANCD2	591	1938	85
RAD51AP1 - FANCD2	1734	644	1291	RAD51AP1 - FANCD2	993	603	2684
RAD51C - FANCD2	54	2399	2566	RAD51C - FANCD2	629	656	620
RAD54B - FANCD2	275	2460	478	RAD54B - FANCD2	227	230	131
RAD54L - FANCD2	493	2530	203	RAD54L - FANCD2	2457	1369	1816
Ranking of RAD family w.r.t FANCD2OS	laplace	linear	rbf	Ranking of FANCD2OS w.r.t RAD family	laplace	linear	rbf
RAD1 - FANCD2OS	693	1926	1146	RAD1 - FANCD2OS	1455	2445	1624
RAD18 - FANCD2OS	1472	526	239	RAD18 - FANCD2OS	851	1457	653
RAD50 - FANCD2OS	178	1534	2141	RAD50 - FANCD2OS	1763	1477	1372
RAD51 - FANCD2OS	2061	1080	1226	RAD51 - FANCD2OS	2007	2336	1739
RAD51AP1 - FANCD2OS	637	2050	2660	RAD51AP1 - FANCD2OS	2209	2376	1722
RAD51C - FANCD2OS	1297	977	1237	RAD51C - FANCD2OS	1729	779	2596
RAD54B - FANCD2OS	475	1367	2571	RAD54B - FANCD2OS	2032	1241	1637
RAD54L - FANCD2OS	2557	1227	252	RAD54L - FANCD2OS	1671	1830	1839
Ranking of RAD family w.r.t FANCF	laplace	linear	rbf	Ranking of FANCF w.r.t RAD family	laplace	linear	rbf
RAD1 - FANCF	1817	1582	285	RAD1 - FANCF	529	2198	1997
RAD18 - FANCF	770	1329	1445	RAD18 - FANCF	1063	2186	196
RAD50 - FANCF	1403	1684	803	RAD50 - FANCF	2205	1419	1676
RAD51 - FANCF	209	1247	2221	RAD51 - FANCF	1222	1060	2251
RAD51AP1 - FANCF	1681	13	2619	RAD51AP1 - FANCF	1963	2372	107
RAD51C - FANCF	1493	224	2051	RAD51C - FANCF	2062	1904	2386
RAD54B - FANCF	401	143	2359	RAD54B - FANCF	1903	1936	2026
RAD54L - FANCF	690	829	2120	RAD54L - FANCF	2529	716	1262
Ranking of RAD family w.r.t FANCG	laplace	linear	rbf	Ranking of FANCG w.r.t RAD family	laplace	linear	rbf
RAD1 - FANCG	2013	2215	2328	RAD1 - FANCG	1938	825	843
RAD18 - FANCG	755	393	82	RAD18 - FANCG	2352	878	2574
RAD50 - FANCG	2652	2408	2663	RAD50 - FANCG	695	511	933
RAD51 - FANCG	345	114	295	RAD51 - FANCG	2163	1	397
RAD51AP1 - FANCG	1743	749	1984	RAD51AP1 - FANCG	661	400	23
RAD51C - FANCG	957	218	1360	RAD51C - FANCG	450	2319	1122
RAD54B - FANCG	17	182	423	RAD54B - FANCG	140	194	64
RAD54L - FANCG	1058	701	581	RAD54L - FANCG	2167	1968	2344
Ranking of RAD family w.r.t FANCI	laplace	linear	rbf	Ranking of FANCI w.r.t RAD family	laplace	linear	rbf
RAD1 - FANCI	1919	2263	2286	RAD1 - FANCI	2496	897	664
RAD18 - FANCI	1693	2466	436	RAD18 - FANCI	1601	1161	1668
RAD50 - FANCI	1703	2074	1458	RAD50 - FANCI	1133	1211	1238
RAD51 - FANCI	1038	1668	310	RAD51 - FANCI	1612	2724	1187
RAD51AP1 - FANCI	2496	2517	383	RAD51AP1 - FANCI	1513	1211	65
RAD51C - FANCI	597	165	2447	RAD51C - FANCI	143	137	87
RAD54B - FANCI	557	84	2055	RAD54B - FANCI	178	350	76
RAD54L - FANCI	468	606	2461	RAD54L - FANCI	211	2304	1128

Table 66 2^{nd} order combinatorial hypotheses between RAD and FANC members.

64 (rbf) for RAD54B - FANCG; **FANCI** was found to be down regulated w.r.t RAD-1/18/50/51/51AP1/51C/54B/54L. These are reflected in 897 (linear) and 664 (rbf) for RAD1 - FANCI; 1601 (laplace), 1161 (linear) and 1668 (rbf) for RAD18 - FANCI; 1133 (laplace), 1211 (linear) and 1238 (rbf) for RAD50 - FANCI; 1612 (laplace) and 1187 (rbf) for RAD51 - FANCI; 1513 (laplace), 1211 (linear) and 65 (rbf) for RAD51AP1 - FANCI; 143 (laplace), 137 (linear) and 87 (rbf) for RAD51C - FANCI; 178 (laplace), 350 (linear) and 76 (rbf) for RAD54B - FANCI; 211 (laplace) and 1128 (rbf) for RAD54L - FANCI.

Table 67 shows the derived influences which can be represented graphically, with the following influences -

Unexplored combinatorial hypotheses

RAD w.r.t FANC	
RAD-18/51/51AP1/51C/54B/54L	FANCB
RAD-18/51/51AP1/54B/54L	FANCD2
RAD-1/18/50/51/51C/54B/54L	FANCD2OS
RAD-1/18/50/51/51AP1/51C/54B/54L	FANCF
RAD-1/18/50/51/51AP1/51C/54B/54L	FANCG
RAD-18/50/51/51C/54B/54L	FANCI
FANC w.r.t RAD	
FANCB	RAD-1/50/51/51AP1/51C/54B/54L
FANCD2	RAD-1/50/51/51AP1/51C/54B/54L
FANCD2OS	RAD-1/18/5051C/54B
FANCF	RAD-1/18/50/51C/54B
FANCG	RAD-1/50/51/51AP1/51C/54B
FANCI	RAD-1/18/50/51/51AP1/51C/54B/54L

Table 67 2^{nd} order combinatorial hypotheses between RAD and FANC family.

• RAD w.r.t FANC with RAD-18/51/51AP1/51C/54B/54L <- FANCB; RAD-18/51/51AP1/54B/54L <- FANCD2; RAD-1/18/50/51/51C/54B/54L <- FANCD2OS; RAD-1/18/50/51/51AP1/51C/54B/54L <- FANCF; RAD-1/18/50/51/51AP1/51C/54B/54L <- FANCG; and RAD-18/50/51/51C/54B/54L <- FANCI, and • FANC w.r.t RAD with FANCB <- RAD-1/50/51/51AP1/51C/54B/54L; FANCD2 <- RAD-1/50/51/51AP1/51C/54B/54L; FANCD2OS <- RAD-1/18/5051C/54B; FANCF <- RAD-1/18/50/51C/54B; FANCG <- RAD-1/50/51/51AP1/51C/54B; FANCI <- RAD-1/18/50/51/51AP1/51C/54B/54L;

2.5 Telomerase related synergies

2.5.1 TERT - ABC transporters cross family analysis

TERT and ABC family members found to be down regulated after ETC-1922159 treatment in CRC cells. Not much is known about the TERT and ABC transporters and research is still ongoing regarding the synergy of TERT and ABC transporters. The most recent work on telomerase and drug resistance in cancer by Lipinska *et al.* [154] talks on a range of theories about the mechanism of inactivation of telomerase in cancer cells that is accompanied by relatively increased sensitivity to some drugs. These mechanism has not been fully understood. Some association with the telomerase expression and drug resistance has been shown by Wang *et al.* [155] while no correlation between the two has been indicated by Sakin *et al.* [156]. However Keshet *et al.* [157], show a deep correlation in melanoma cells revealing co-expression of ABC transporters, ABCB5 and ABCC2 and hTERT. Based on these little known associations the search engine was able to rank the combinations of some of the members of ABC with TERT. Table 68 shows the rankings of TERT and ABC members w.r.t to each other. On the left half, we find ABC family to be down regulated w.r.t TERT. These are reflected in rankings of 381 (laplace), 1047 (linear) and 316 (rbf) for ABCF2 - TERT; 1201 (laplace), 49 (lin-

Ranking TRET vs ABC family

Ranking of ABC family w.r.t TRET				Ranking of TRET w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
ABCF2 - TERT	381	1047	316	ABCF2 - TERT	2069	238	2712
ABCA2 - TERT	1201	49	317	ABCA2 - TERT	1693	2739	1997
ABCE1 - TERT	1613	499	1217	ABCE1 - TERT	120	2736	294

Table 68 2^{nd} order interaction ranking between TRET vs ABC.

Unexplored combinatorial hypotheses	
ABC family w.r.t TRET	
TERT	ABCF2
TERT	ABCA2
TERT	ABCE1
TRET w.r.t ABC family	
ABCE1	TERT

Table 69 2^{nd} order combinatorial hypotheses between TRET and ABC family.

ear) and 317 (rbf) for ABCA2 - TERT; and 1613 (laplace), 499 (linear) and 1217 (rbf) for ABCE1 - TERT. On the right side we find TERT to be down regulated w.r.t ABCE1. These are reflected in 120 (laplace), 2736 (linear) and 294 (rbf) for ABCE1 - TERT.

So if we look at the above rankings, what we find is that the ABC family is down regulated along with TERT, synergistically (directly or indirectly) with moderate and high promise (rankings nearing to 1) in the top table. Vice versa, the same affect is not shown in table 69 for ABC-F2/A2 with TERT. If we look at the 2 way cross analysis what we find is the following combinatorial hypotheses in table 69 which is graphicaly reflected as - • ABC family w.r.t TRET with TERT -> ABCF2; TERT -> ABCA2; and TERT -> ABCE1 and • TRET w.r.t ABC family with ABCE1 -> TERT. Consequently, it is possible that the TERT does have influence over ABC-F2/A2 but with ABCE1, directionality could not be established. Further more, these low rankings point to high promise of down regulation that is observed in CRC treated with ETC-1922159. Which might mean that in CRC cells which have not been treated with ETC-1922159, it is highly possible that TERT is highly up regulated and also bolsters/influences the functioning of ABC transporters. Wet lab study and further experiments will be needed to establish the dual role of TERT and ABC transporters.

2.6 ABC transporter related synergies

2.6.1 ABC transporters - UBE2 cross family analysis

Not much is known about the interaction or any possible direct/indirect synergy of ABC transporters and the Ubiquitin-

Ranking ABC family w.r.t UBE2 family

Ranking of ABC family w.r.t UBE2-A				Ranking of ABC family w.r.t UBE2-B			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - UBE2-A	2101	185	382	ABC-A5 - UBE2-B	1223	1193	194
ABC-B11 - UBE2-A	129	2487	304	ABC-B11 - UBE2-B	125	103	571
ABC-C3 - UBE2-A	2137	2491	1023	ABC-C3 - UBE2-B	606	791	1411
ABC-C5 - UBE2-A	1630	490	2408	ABC-C5 - UBE2-B	1515	2317	2266
ABC-C13 - UBE2-A	742	1604	475	ABC-C13 - UBE2-B	2199	2254	2362
ABC-D1 - UBE2-A	316	620	596	ABC-D1 - UBE2-B	1082	374	1057
ABC-G1 - UBE2-A	46	819	533	ABC-G1 - UBE2-B	48	843	551
ABC-G2 - UBE2-A	398	259	261	ABC-G2 - UBE2-B	189	189	41
Ranking of ABC family w.r.t UBE2-F				Ranking of ABC family w.r.t UBE2-H			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - UBE2-F	997	2408	1784	ABC-A5 - UBE2-H	1247	2068	2438
ABC-B11 - UBE2-F	141	1122	578	ABC-B11 - UBE2-H	932	429	409
ABC-C3 - UBE2-F	931	2420	681	ABC-C3 - UBE2-H	540	1962	563
ABC-C5 - UBE2-F	628	1373	217	ABC-C5 - UBE2-H	1551	865	1450
ABC-C13 - UBE2-F	403	2464	1307	ABC-C13 - UBE2-H	1192	2492	2051
ABC-D1 - UBE2-F	2069	1959	1235	ABC-D1 - UBE2-H	1094	1016	1474
ABC-G1 - UBE2-F	209	1216	1450	ABC-G1 - UBE2-H	683	173	18
ABC-G2 - UBE2-F	690	1995	2120	ABC-G2 - UBE2-H	1328	1374	78
Ranking of ABC family w.r.t UBE2-J1				Ranking of ABC family w.r.t UBE2-Z			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - UBE2-J1	634	222	711	ABC-A5 - UBE2-Z	454	1059	1287
ABC-B11 - UBE2-J1	1182	1075	403	ABC-B11 - UBE2-Z	134	503	436
ABC-C3 - UBE2-J1	1232	719	1285	ABC-C3 - UBE2-Z	975	1722	2095
ABC-C5 - UBE2-J1	964	1342	2373	ABC-C5 - UBE2-Z	2348	845	1859
ABC-C13 - UBE2-J1	2095	2412	2360	ABC-C13 - UBE2-Z	1157	651	1335
ABC-D1 - UBE2-J1	542	1198	704	ABC-D1 - UBE2-Z	392	1660	943
ABC-G1 - UBE2-J1	306	97	122	ABC-G1 - UBE2-Z	545	142	354
ABC-G2 - UBE2-J1	335	668	591	ABC-G2 - UBE2-Z	747	285	530

Table 70 2^{nd} order interaction ranking between ABC w.r.t UBE2 family members.

conjugating enzyme E2 family. In CRC cells treated with ETC-1922159, family members of both were found to be up regulated. The search engine also assigned numerically high valued ranks to a few of 2^{nd} order synergies between the the two. We document here these synergies and show the possible unexplored combinations between the two familes. Tables 70 and 71 show the rankings of ABC w.r.t UBE2 and vice versa, respectively.

In table 70 we found **ABC-C3** up regulated w.r.t UBE2-A. This is reflected in the rankings of 2137 (laplace) and 2491 (linear) for ABC-C3 - UBE2-A. **ABC-C5** was up regulated w.r.t UBE2-B. This is reflected in the rankings of 2317 (laplace) and 2266 (rbf) for ABC-C5 - UBE2-B. **ABC-A5/D1/G2** were up regulated w.r.t UBE2-F. These are reflected in the rankings of 2408 (linear) and 1784 (rbf) for ABC-A5 - UBE2-F, 2069 (linear) and 1959 (rbf) for ABC-D1 - UBE2-F and 1995 (linear) and 2120 (rbf) for ABC-G2 - UBE2-F. **ABC-A5/C13** were up regulated w.r.t UBE2-H. These are reflected in 2068 (linear) and 2438 (rbf) for ABC-A5 - UBE2-H and 2492 (linear) and 2051 (rbf) for ABC-C13 - UBE2-H. **ABC-C13** was up regulated w.r.t UBE2-J1. This is reflected in the rankings of 2095 (laplace), 2412 (linear) and 2360 (rbf). **ABC-C5** was up regulated w.r.t UBE2-Z. This is reflected in rankings of 2348 (laplace) and 1859 (rbf) for ABC-C5 - UBE2-Z.

In table 71 we found **UBE2-A** up regulated w.r.t ABC-C5/G2. This is reflected in the rankings of 2122 (linear) and 2297 (rbf) for ABC-C5 - UBE2-A; and 2048 (laplace) and 1829 (linear) for ABC-G2 - UBE2-A. **UBE2-B** up regulated w.r.t ABC-

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Ranking UBE2 family w.r.t ABC family							
Ranking of UBE2-A w.r.t ABC				Ranking of UBE2-B w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - UBE2-A	1037	253	2091	ABC-A5 - UBE2-B	1846	2038	936
ABC-B11 - UBE2-A	1491	1269	2179	ABC-B11 - UBE2-B	1623	1304	1995
ABC-C3 - UBE2-A	1726	1906	1390	ABC-C3 - UBE2-B	1999	832	2050
ABC-C5 - UBE2-A	880	2122	2297	ABC-C5 - UBE2-B	612	2276	1681
ABC-C13 - UBE2-A	412	234	670	ABC-C13 - UBE2-B	467	1863	2496
ABC-D1 - UBE2-A	2507	237	1319	ABC-D1 - UBE2-B	2322	1917	2426
ABC-G1 - UBE2-A	907	2291	1573	ABC-G1 - UBE2-B	1194	1592	1239
ABC-G2 - UBE2-A	2048	1829	1376	ABC-G2 - UBE2-B	1833	2445	2506
Ranking of UNE2-F w.r.t ABC family				Ranking of UBE2-H w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - UBE2-F	2485	406	66	ABC-A5 - UBE2-H	508	2339	1110
ABC-B11 - UBE2-F	2003	1203	2422	ABC-B11 - UBE2-H	1950	1770	2461
ABC-C3 - UBE2-F	2132	2163	861	ABC-C3 - UBE2-H	2439	1972	2305
ABC-C5 - UBE2-F	406	1651	1838	ABC-C5 - UBE2-H	398	2473	2355
ABC-C13 - UBE2-F	821	959	1196	ABC-C13 - UBE2-H	2004	2317	1847
ABC-D1 - UBE2-F	2421	686	2176	ABC-D1 - UBE2-H	164	1641	648
ABC-G1 - UBE2-F	115	2202	1953	ABC-G1 - UBE2-H	201	1921	2288
ABC-G2 - UBE2-F	983	883	1012	ABC-G2 - UBE2-H	2063	1631	1354
Ranking of UBE2-J1 w.r.t ABC family				Ranking of UBE2-Z w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - UBE2-J1	1740	1467	1244	ABC-A5 - UBE2-Z	2336	1710	35
ABC-B11 - UBE2-J1	1806	991	1935	ABC-B11 - UBE2-Z	521	645	2168
ABC-C3 - UBE2-J1	2073	2291	631	ABC-C3 - UBE2-Z	1978	1823	1859
ABC-C5 - UBE2-J1	126	525	1409	ABC-C5 - UBE2-Z	1237	148	1928
ABC-C13 - UBE2-J1	2329	2153	1951	ABC-C13 - UBE2-Z	1185	137	2475
ABC-D1 - UBE2-J1	2263	1886	2249	ABC-D1 - UBE2-Z	2292	21	2381
ABC-G1 - UBE2-J1	1262	2418	2277	ABC-G1 - UBE2-Z	426	2515	1858
ABC-G2 - UBE2-J1	1558	2408	1304	ABC-G2 - UBE2-Z	2270	2080	2448

Table 71 2^{nd} order interaction ranking between UBE2 w.r.t ABC family members.

Unexplored combinatorial hypotheses	
ABC w.r.t UBE2	
ABC-C3	UBE2-A
ABC-C5	UBE2-B
ABC-A5/D1/G2	UBE2-F
ABC-A5/C13	UBE2-H
ABC-C13	UBE2-J1
ABC-C5	UBE2-Z
UBE2 w.r.t ABC	
UBEA-2	ABC-C5/G2
UBE2-B	ABC-A5/C3/C13/D1/G2
UBE2-F	ABC-B11/C3/D1/G1
UBE2-H	ABC-B11/C3/C5/C13/G1
UBE2-J1	ABC-B11/C3/C13/D1/G1/G2
UBE2-Z	ABC-C3/D1/G1/G2

Table 72 2^{nd} order combinatorial hypotheses between ABC and UBE2.

A5/C3/C13/D1/G2. This is reflected in the rankings of 1846 (laplace) and 2038 (linear) for ABC-A5 - UBE2-B; 1999 (laplace) and 2050 (rbf) for ABC-C3 - UBE2-B; 1863 (linear) and 2496 (rbf) for ABC-C13 - UBE2-B; 2322 (laplace), 1917 (linear) and 2426 (rbf) for ABC-D1 - UBE2-B and 1833 (laplace), 2445 (linear) and 2506 (rbf) for ABC-G2 - UBE2-B. **UBE2-F** was found up regulated w.r.t ABC-B11/C3/D1/G1. These were reflected in 2003 (laplace) and 2422 (rbf) for ABC-B11 - UBE2-F; 2132 (laplace) and 2163 (linear) for ABC-C3 - UBE2-F; 2421 (laplace) and 2176 (rbf) for ABC-D1 - UBE2-F; and 2202 (laplace) and 1953 (rbf) for ABC-G1 - UBE2-F. **UBE2-H** was found to be up regulated w.r.t ABC-B11/C3/C5/C13/G1. These are reflected in rankings of 1950 (laplace), 1770 (linear) and 2461 (rbf) for ABC-B11 - UBE2-H; 2439 (laplace), 1972 (linear) and 2305 (rbf) for ABC-C3 - UBE2-H; 2473 (linear) and 2355 (rbf) for ABC-C5 - UBE2-H; 2004 (laplace), 2317 (linear) and 1847 (rbf) for ABC-C13 - UBE2-H; and 1921 (linear) and 2288 (rbf) for ABC-G1 - UBE2-H; **UBE2-J1** was found to be up regulated w.r.t ABC-B11/C3/C13/D1/G1/G2; 1806 (laplace) and 1935 (rbf) for ABC-B11 - UBE2-J1; 2073 (laplace) and 2291 (linear) for ABC-C3 - UBE2-J1; 2329 (laplace), 2153 (linear) and 1951 (rbf) ABC-C13 - UBE2-J1; 2263 (laplace), 1886 (linear) and 2249 (rbf) for ABC-D1 - UBE2-J1; and 2418 (linear) and 2277 (rbf) for ABC-G1 - UBE2-J1; Finally, **UBE2-Z** was found up regulated w.r.t ABC-C3/D1/G1/G2. These are reflected in rankings of 1978 (laplace), 1823 (linear) and 1859 (rbf) for ABC-C3 - UBE2-Z; 2292 (laplace) and 2381 (linear) for ABC-D1 - UBE2-Z; 2515 (linear) and 1858 (rbf) for ABC-G1 - UBE2-Z; 2270 (laplace), 2080 (linear) and 2448 (rbf) for ABC-G2 - UBE2-Z.

Table 72 shows the derived influences which can be represented graphically, with the following influences - • ABC w.r.t UBE2 with ABC-C3 <- UBE2-A; ABC-C5 <- UBE2-B; ABC-A5/D1/G2 <- UBE2-F; ABC-A5/C13 <- UBE2-H; ABC-C13 <- UBE2-J1; ABC-C5 <- UBE2-Z; and • UBE2 w.r.t ABC with UBEA-2 <- ABC-C5/G2; UBE2-B <- ABC-A5/C3/C13/D1/G2; UBE2-F <- ABC-B11/C3/D1/G1; UBE2-H <- ABC-B11/C3/C5/C13/G1; UBE2-J1 <- ABC-B11/C3/C13/D1/G1/G2; UBE2-Z <- ABC-C3/D1/G1/G2.

2.6.2 ABC transporters intra cross family analysis

A range of ABC transporters were found to be up regulated in CRC cells after ETC-1922159 treatment. We checked the rankings of the ABC transporters within the ABC family and found multiple synergistic upregulation at 2nd order level that were ranked appropriately. Table 73 shows intra family rankings of ABC members among themselves. We found **ABC-C13** upregulated w.r.t ABC-A5. These were reflected in rankings of 1943 (linear) and 2151 (rbf); **ABC-C5/C13/G1** were up regulated w.r.t ABC-B11. These are reflected in rankings of 2226 (laplace) and 2241 (rbf) for ABC-C5 - ABC-B11; 1971 (laplace) and 2150 (rbf) for ABC-C13 - ABC-B11 and 1957 (laplace) and 1920 (linear) for ABC-G1 - ABC-B11; **ABC-C3/C13** were found to be up regulated w.r.t ABC-C5. These are reflected in 2084 (laplace), 2274 (linear) and 1758 (rbf) for ABC-C3 - ABC-C5 and 2476 (linear) and 2446 (rbf)

Ranking ABC family w.r.t ABC family							
Ranking of ABC family w.r.t ABC-A5				Ranking of ABC family w.r.t ABC-B11			
	laplace	linear	rbf		laplace	linear	rbf
ABC-B11 - ABC-A5	733	471	26	ABC-A5 - ABC-B11	1148	1443	1782
ABC-C3 - ABC-A5	111	493	2264	ABC-C3 - ABC-B11	845	527	1257
ABC-C5 - ABC-A5	1717	519	1921	ABC-C5 - ABC-B11	2226	1644	2241
ABC-C13 - ABC-A5	1243	1943	2151	ABC-C13 - ABC-B11	1971	609	2150
ABC-D1 - ABC-A5	1262	2387	1573	ABC-D1 - ABC-B11	891	217	854
ABC-G1 - ABC-A5	657	991	533	ABC-G1 - ABC-B11	1957	1920	669
ABC-G2 - ABC-A5	587	397	104	ABC-G2 - ABC-B11	685	1978	226
Ranking of ABC family w.r.t ABC-C3				Ranking of ABC family w.r.t ABC-C5			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - ABC-C3	163	861	1672	ABC-A5 - ABC-C5	2086	411	1243
ABC-B11 - ABC-C3	410	613	1501	ABC-B11 - ABC-C5	2398	272	464
ABC-C5 - ABC-C3	1591	2435	927	ABC-C3 - ABC-C5	2084	2274	1758
ABC-C13 - ABC-C3	405	880	1282	ABC-C13 - ABC-C5	226	2476	2446
ABC-D1 - ABC-C3	18	1145	2187	ABC-D1 - ABC-C5	2010	891	1257
ABC-G1 - ABC-C3	1858	173	842	ABC-G1 - ABC-C5	2402	894	741
ABC-G2 - ABC-C3	1462	275	1373	ABC-G2 - ABC-C5	2463	736	661
Ranking of ABC family w.r.t ABC-C13				Ranking of ABC family w.r.t ABC-D1			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - ABC-C13	2251	1219	1614	ABC-A5 - ABC-D1	163	1068	291
ABC-B11 - ABC-C13	1106	56	1171	ABC-B11 - ABC-D1	1273	130	1655
ABC-C3 - ABC-C13	2279	1431	365	ABC-C3 - ABC-D1	568	251	149
ABC-C5 - ABC-C13	1537	2178	690	ABC-C5 - ABC-D1	2423	538	2388
ABC-D1 - ABC-C13	2370	171	362	ABC-C13 - ABC-D1	2383	2029	425
ABC-G1 - ABC-C13	833	1544	1343	ABC-G1 - ABC-D1	1462	1175	827
ABC-G2 - ABC-C13	329	1323	1755	ABC-G2 - ABC-D1	467	670	2491
Ranking of ABC family w.r.t ABC-G1				Ranking of ABC family w.r.t ABC-G2			
	laplace	linear	rbf		laplace	linear	rbf
ABC-A5 - ABC-G1	2488	1776	1078	ABC-A5 - ABC-G2	1011	1640	1705
ABC-B11 - ABC-G1	2312	253	52	ABC-B11 - ABC-G2	988	481	1849
ABC-C3 - ABC-G1	273	1415	1139	ABC-C3 - ABC-G2	1102	1082	1563
ABC-C5 - ABC-G1	220	1988	437	ABC-C5 - ABC-G2	2284	1904	1829
ABC-C13 - ABC-G1	2389	427	1125	ABC-C13 - ABC-G2	929	1238	222
ABC-D1 - ABC-G1	1836	485	597	ABC-D1 - ABC-G2	814	995	1152
ABC-G2 - ABC-G1	2506	692	1143	ABC-G1 - ABC-G2	596	460	848

Table 73 2^{nd} order interaction ranking between ABC family members.

Unexplored combinatorial hypotheses	
ABC intra family	
ABC-C13	ABC-A5
ABC-C5/C13/G1	ABC-B11
ABC-C3/C13	ABC-C5
ABC-C5/C13	ABC-D1
ABC-A5	ABC-G1
ABC-C5	ABC-G2

Table 74 2^{nd} order combinatorial hypotheses between ABC family members.

for ABC-C13 - ABC-C5. **ABC-C5/C13** were found to be up regulated w.r.t ABC-D1. 2423 (laplace) and 2388 (rbf) for ABC-C5 - ABC-D1 and 2383 (laplace) and 2029 (linear) for ABC-C13 - ABC-D1. **ABC-A5** was found to be up regulated w.r.t ABC-G1. This is reflected in rankings of 2488 (laplace) and 1776 (linear) for ABC-A5 - ABC-G1. **ABC-A5** was found to be up regulated w.r.t ABC-G2 also. This is reflected in rankings of 2284 (laplace), 1904 (linear) and 1829 (rbf) for ABC-A5 - ABC-G2.

Table 74 shows the derived influences which can be represented graphically, with the following influences - • ABC intra family with ABC-C13 <- ABC-A5; ABC-C5/C13/G1 <- ABC-B11; ABC-C3/C13 <- ABC-C5; ABC-C5/C13 <- ABC-D1; ABC-A5 <- ABC-G1; ABC-C5 <- ABC-G2.

2.6.3 Interleukin - ABC transporters cross family analysis

Zhou *et al.*[158] have observed that the ABCA1 contributes to the secretion of interleukin 1β from macrophages. Haskó *et al.*[159] show that inhibitors of ABC transporters suppress interleukin-12 p40 production and major histocompatibility complex II up-regulation in macrophages. Park *et al.*[160] conclude that anti-cancer drug-induced IL-8 secretion increased the expression of ABC transporters and SP cells, promoting the growth of HCC in vitro. Marty *et al.*[161] show that ABC1 is required for the release of interleukin-1β by P2X7-stimulated and lipopolysaccharide-primed mouse Schwann cells. Lottaz *et al.*[162] observe that inhibition of ABC transporter downregulates interleukin-1β-mediated autocrine activation of human dermal fibroblasts. These findings and many more indicate the synergy between IL family and ABC transporters. In colorectal cancer cells treated with ETC-1922159, some of the members of both families were up regulated. Given the studied synergies, our search engine found multiple combinations which were ranked with high numerical values, thus indicating possible dual combinatorial role. Tables 75 and 76, each show rankings of ABC transporters w.r.t IL family on the left half and vice versa on the right half.

On the left half we found **IL-17REL** up regulated w.r.t ABCA5. This is reflected in the rankings of 2405 (linear) and 2202 (rbf) for IL17REL - ABCA5. **IL-2RG/6ST/15/15RA** up regulated w.r.t ABCB11. This is reflected in the rankings of 2182 (laplace), 2102 (linear) and 550 (rbf) for IL2RG - ABCB11; 1793 (laplace), 2140 (linear) and 1938 (rbf) for IL6ST - ABCB11; 2438 (laplace) and 2512 (linear) for IL15 - ABCB11; and 2271 (laplace) and 1784 (rbf) for IL15RA - ABCB11. **IL-8/15RA** up regulated w.r.t ABCC3. This is reflected in the rankings of 1767 (laplace) and 2419 (rbf) for IL8 - ABCC3 and 2403 (linear) and 1795 (rbf) for IL15RA - ABCC3. **IL-15RA/17REL** up regulated w.r.t ABCC5. These are reflected in rankings of 2255 (linear) and 1861 (rbf) for IL15RA - ABCC5 and 2462 (linear) and 2509 (rbf) for IL17REL - ABCC5. **IL-15RA/17REL** were up regulated w.r.t ABCC13. These are reflected in 2248 (laplace), 1955 (linear) and 2456 (rbf) for IL15RA - ABCC13 and 2339 (laplace) and 2137 (linear) for IL17REL - ABCC13. **IL-1A/1RAP/8/15RA** were up regulated w.r.t ABCD1. These are reflected in rankings of 1932 (laplace) and 2203 (rbf) for IL1A - ABCD1; 2508 (laplace), 2006 (linear) and 1907 (rbf) for IL1RAP - ABCD1; 2010 (laplace), 2315 (linear) and 1814 (rbf) for IL8 - ABCD1; and 2097 (laplace) and 1765 (linear) for IL15RA - ABCD1. **IL-1RAP** was up regulated w.r.t ABCG1. This was reflected in rankings of 2205 (linear) and 2339 (rbf) for IL1RAP - ABCG1. **IL-1RAP/15RA** were up regulated w.r.t ABCG2. These

Ranking ABC family VS IL family

Ranking of IL family w.r.t ABCA5				Ranking of ABCA5 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCA5	705	95	11	IL1A - ABCA5	677	2069	871
IL1B - ABCA5	240	35	353	IL1B - ABCA5	2069	790	2301
IL1RAP - ABCA5	1515	2354	514	IL1RAP - ABCA5	1763	335	2345
IL1RN - ABCA5	771	1093	1417	IL1RN - ABCA5	892	2252	1482
IL2RG - ABCA5	500	246	173	IL2RG - ABCA5	993	750	1745
IL6ST - ABCA5	2464	1564	1365	IL6ST - ABCA5	155	266	1386
IL8 - ABCA5	1676	1568	1111	IL8 - ABCA5	104	1261	946
IL10RB - ABCA5	492	146	643	IL10RB - ABCA5	2230	2184	2240
IL15 - ABCA5	638	1169	65	IL15 - ABCA5	661	169	711
IL15RA - ABCA5	2151	1672	740	IL15RA - ABCA5	706	1300	2031
IL17C - ABCA5	680	197	164	IL17C - ABCA5	615	575	1518
IL17REL - ABCA5	1014	2405	2202	IL17REL - ABCA5	212	1024	146
Ranking of IL family w.r.t ABCB11				Ranking of ABCB11 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCB11	1962	465	648	IL1A - ABCB11	551	140	385
IL1B - ABCB11	1778	851	438	IL1B - ABCB11	255	428	208
IL1RAP - ABCB11	1427	1704	1318	IL1RAP - ABCB11	1681	878	1709
IL1RN - ABCB11	1832	539	297	IL1RN - ABCB11	342	1912	779
IL2RG - ABCB11	2182	2102	550	IL2RG - ABCB11	814	67	584
IL6ST - ABCB11	1793	2140	1938	IL6ST - ABCB11	1347	1504	385
IL8 - ABCB11	1607	2441	1028	IL8 - ABCB11	349	846	1786
IL10RB - ABCB11	341	1119	449	IL10RB - ABCB11	2101	2419	1352
IL15 - ABCB11	2438	2512	576	IL15 - ABCB11	344	224	256
IL15RA - ABCB11	2271	1288	1784	IL15RA - ABCB11	1052	48	719
IL17C - ABCB11	1262	69	706	IL17C - ABCB11	653	316	437
IL17REL - ABCB11	50	305	783	IL17REL - ABCB11	1004	736	896
Ranking of IL family w.r.t ABCC3				Ranking of ABCC3 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCC3	1860	758	1538	IL1A - ABCC3	1343	1798	2459
IL1B - ABCC3	1764	749	896	IL1B - ABCC3	1647	1369	569
IL1RAP - ABCC3	1514	2294	1989	IL1RAP - ABCC3	2074	1377	303
IL1RN - ABCC3	647	607	1252	IL1RN - ABCC3	1366	975	1354
IL2RG - ABCC3	990	444	40	IL2RG - ABCC3	1229	379	844
IL6ST - ABCC3	98	1589	339	IL6ST - ABCC3	970	712	1342
IL8 - ABCC3	1767	1046	2419	IL8 - ABCC3	937	1033	430
IL10RB - ABCC3	1354	78	359	IL10RB - ABCC3	1609	29	1830
IL15 - ABCC3	1580	602	1560	IL15 - ABCC3	1087	1191	1084
IL15RA - ABCC3	189	2403	1795	IL15RA - ABCC3	2153	163	1324
IL17C - ABCC3	1587	778	2425	IL17C - ABCC3	466	631	2237
IL17REL - ABCC3	1135	403	54	IL17REL - ABCC3	2089	2388	1618
Ranking of IL family w.r.t ABCC5				Ranking of ABCC5 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCC5	2004	681	60	IL1A - ABCC5	2217	2022	1512
IL1B - ABCC5	1948	112	251	IL1B - ABCC5	1223	2137	942
IL1RAP - ABCC5	1038	355	2023	IL1RAP - ABCC5	1982	1892	2296
IL1RN - ABCC5	709	430	1087	IL1RN - ABCC5	1668	816	2142
IL2RG - ABCC5	1421	264	601	IL2RG - ABCC5	500	2018	1691
IL6ST - ABCC5	1569	2010	845	IL6ST - ABCC5	754	2326	874
IL8 - ABCC5	1869	143	1589	IL8 - ABCC5	855	1211	2434
IL10RB - ABCC5	1162	70	434	IL10RB - ABCC5	1337	736	958
IL15 - ABCC5	1262	147	389	IL15 - ABCC5	1947	1991	1584
IL15RA - ABCC5	1083	2255	1861	IL15RA - ABCC5	2457	1444	534
IL17C - ABCC5	2447	96	116	IL17C - ABCC5	1836	845	1802
IL17REL - ABCC5	54	2462	2509	IL17REL - ABCC5	1247	2149	1031

Table 75 2^{nd} order interaction ranking between ABC and IL family members.

were reflected in rankings of 2184 (laplace) and 2167 (linear) for IL1RAP - ABCG2 and 1910 (laplace), 2428 (linear) and 1921 (rbf) for IL15RA - ABCG2.

On the right half we found **ABCA5** up regulated w.r.t IL-1B/1RAP/10RB. These are reflected in the rankings of 2069 (laplace) and 2301 (rbf) for IL1B - ABCA5; 1763 (laplace) and 2345 (rbf) for IL1RAP - ABCA5; and 2230 (laplace), 2184 (linear) and 2240 (rbf) for IL10RB - ABCA5; **ABCB11** was up regulated w.r.t IL-10RB. This is reflected in the rankings of 2101 (laplace) and 2419 (linear) for IL10RB - ABCB11. **ABCC3** was up regulated w.r.t IL-1A/17REL. This is reflected in the rankings of 1798 (linear) and 2459 (rbf) for IL1A - ABCC3 and 2089 (laplace) and 2388 (linear) for IL17REL - ABCC3. **ABCC5** was up regulated w.r.t IL-1A/1RAP/15/17C. This are reflected in the rankings of 2217 (laplace) and 2022 (linear) for IL1A - ABCC5; 1982 (laplace), 1892 (linear) and 2296 (rbf) for IL1RAP - ABCC5; 1947 (laplace) and 1991 (linear) for IL15 - ABCC5 and 1836 (laplace) and 1802 (rbf) for IL17C - ABCC5. **ABCC13** was up regulated w.r.t IL-1RAP/15RA. This are reflected in the rankings of 2136 (laplace) and 2392 (linear) for IL1RAP - ABCC13 and 2397 (laplace) and 2485 (linear) for IL15RA - ABCC13; **ABCD1** was up regulated w.r.t IL-8/10RB. This are reflected in the rankings of 2501 (laplace) and 2154 (linear) for IL8 - ABCD1 and 1795 (laplace) and 2325 (rbf) for IL10RB - ABCD1. **ABCG2** was up regulated w.r.t IL-10RB. This is reflected in the rankings of 2144 (laplace), 2335 (linear) and 2434 (rbf) for IL10RB - ABCG2.

Table 77 shows the derived influences which can be represented graphically, with the following influences - • ABC w.r.t IL with IL-1B/1RAP/10RB -> ABCA5; IL-10RB -> ABCB11; IL-1A/17REL -> ABCC3; IL-1A/1RAP/15/17C -> ABCC5; IL-1RAP/15RA -> ABCC13; IL-8/10RB -> ABCD1 and IL-10RB -> ABCG2; • IL w.r.t ABC with IL-17REL <- ABCA5; IL-2RG/6ST/15/15RA <- ABCB11; IL-8/15RA <- ABCC3; IL-15RA/17REL <- ABCC5; IL-15RA/17REL <- ABCC13; IL-1A/1RAP/8/15RA <- ABCD1; IL-1RAP <- ABCG1 and IL-1RAP/15RA <- ABCG2;

2.6.4 BCL - ABC transporters cross family analysis

Ruzickova *et al.*[163] show clinically relevant interactions of anti-apoptotic Bcl-2 protein inhibitors with ABC transporters. Alla *et al.*[164] observe that E2F1 confers anticancer drug resistance by targeting ABC transporter family members and Bcl-2 via the p73/DNp73-miR-205 circuitry. Yasui *et al.*[165] show a range of ABC family members along with BCL member to be overexpressed while studying the alteration in copy numbers of genes as a mechanism for acquired drug resistance. These point to the possible synergistic workings of BCL with ABC. In colorectal cancer cells treated with ETC-1922159, these were found to be up regulated. The search engine pointed to some of these 2nd order combinations and alloted rankings of high numerical value, thus indicating possible synergy. Table 78 and 79 show rankings of BCL family w.r.t ABC members on the left half and vice versa on the right half.

On the left half we found **BCL2L1** up regulated w.r.t ABCC5. This is reflected in the rankings of 2239 (laplace) and 1845 (linear). **BCL2L2** was up regulated w.r.t ABC-B11/C5/C13/D1. These are reflected in the rankings of 2097 (laplace) and 2311 (rbf) for ABCB11 - BCL2L2; 2195 (laplace), 2359 (linear) and 2322 (rbf) for ABCC5 - BCL2L2; 2438 (laplace) and 2494 (linear) for ABCC13 - BCL2L2 and 2477 (laplace) and 2156 (rbf)

Ranking ABC family VS IL family							
Ranking of IL family w.r.t ABCC13				Ranking of ABCC13 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCC13	512	135	1207	IL1A - ABCC13	464	352	201
IL1B - ABCC13	152	103	1553	IL1B - ABCC13	635	974	60
IL1RAP - ABCC13	1092	502	2442	IL1RAP - ABCC13	2136	2392	33
IL1RN - ABCC13	1753	559	323	IL1RN - ABCC13	114	1016	1839
IL2RG - ABCC13	2064	674	1076	IL2RG - ABCC13	807	1079	938
IL6ST - ABCC13	332	1416	2112	IL6ST - ABCC13	119	1098	2323
IL8 - ABCC13	551	1200	1680	IL8 - ABCC13	592	984	907
IL10RB - ABCC13	631	621	561	IL10RB - ABCC13	2011	1272	1297
IL15 - ABCC13	502	296	373	IL15 - ABCC13	612	968	170
IL15RA - ABCC13	2248	1955	2456	IL15RA - ABCC13	2397	2485	790
IL17C - ABCC13	25	140	123	IL17C - ABCC13	924	308	711
IL17REL - ABCC13	2339	2137	1497	IL17REL - ABCC13	462	376	461
Ranking of IL family w.r.t ABCC5				Ranking of ABCC5 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCD1	1932	30	2203	IL1A - ABCD1	530	2046	1196
IL1B - ABCD1	569	109	1778	IL1B - ABCD1	1400	605	453
IL1RAP - ABCD1	2508	2006	1907	IL1RAP - ABCD1	399	840	1548
IL1RN - ABCD1	606	2003	789	IL1RN - ABCD1	551	2025	60
IL2RG - ABCD1	1064	284	2374	IL2RG - ABCD1	311	1233	1322
IL6ST - ABCD1	1347	1237	1220	IL6ST - ABCD1	1581	507	612
IL8 - ABCD1	2010	2315	1814	IL8 - ABCD1	2501	2154	539
IL10RB - ABCD1	631	825	85	IL10RB - ABCD1	1795	1028	2325
IL15 - ABCD1	890	325	1578	IL15 - ABCD1	1795	302	1258
IL15RA - ABCD1	2097	1765	1629	IL15RA - ABCD1	580	1240	2342
IL17C - ABCD1	1372	56	2509	IL17C - ABCD1	687	1753	851
IL17REL - ABCD1	5	2388	237	IL17REL - ABCD1	1423	642	2164
Ranking of IL family w.r.t ABCG1				Ranking of ABCG1 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCG1	724	67	80	IL1A - ABCG1	699	824	600
IL1B - ABCG1	938	178	533	IL1B - ABCG1	70	783	81
IL1RAP - ABCG1	1263	2205	2339	IL1RAP - ABCG1	2298	394	612
IL1RN - ABCG1	1240	688	1396	IL1RN - ABCG1	2465	834	1051
IL2RG - ABCG1	1396	7	112	IL2RG - ABCG1	587	24	21
IL6ST - ABCG1	357	845	520	IL6ST - ABCG1	1723	1345	177
IL8 - ABCG1	977	1835	1099	IL8 - ABCG1	1730	1748	382
IL10RB - ABCG1	2244	349	840	IL10RB - ABCG1	167	1315	61
IL15 - ABCG1	1960	613	1279	IL15 - ABCG1	2212	734	326
IL15RA - ABCG1	785	651	2191	IL15RA - ABCG1	1195	862	1876
IL17C - ABCG1	2516	486	51	IL17C - ABCG1	80	95	177
IL17REL - ABCG1	2229	732	150	IL17REL - ABCG1	1579	1025	452
Ranking of IL family w.r.t ABCG2				Ranking of ABCG2 family w.r.t IL			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - ABCG2	745	716	1299	IL1A - ABCG2	238	89	659
IL1B - ABCG2	354	232	668	IL1B - ABCG2	31	197	439
IL1RAP - ABCG2	2184	2167	1384	IL1RAP - ABCG2	1314	253	2434
IL1RN - ABCG2	783	228	11	IL1RN - ABCG2	552	1692	827
IL2RG - ABCG2	444	463	1024	IL2RG - ABCG2	261	87	1275
IL6ST - ABCG2	1647	1827	55	IL6ST - ABCG2	1792	1477	1222
IL8 - ABCG2	2212	1362	563	IL8 - ABCG2	448	441	1423
IL10RB - ABCG2	31	80	667	IL10RB - ABCG2	2144	2335	2434
IL15 - ABCG2	76	312	187	IL15 - ABCG2	247	590	832
IL15RA - ABCG2	1910	2428	1921	IL15RA - ABCG2	1116	1005	1059
IL17C - ABCG2	649	692	61	IL17C - ABCG2	784	462	775
IL17REL - ABCG2	883	1435	35	IL17REL - ABCG2	852	1606	1597

Table 76 2^{nd} order interaction ranking between ABC and IL family members.

Unexplored combinatorial hypotheses	
ABC w.r.t IL	
IL-1B/1RAP/10RB	ABCA5
IL-10RB	ABCB11
IL-1A/17REL	ABCC3
IL-1A/1RAP/15/17C	ABCC5
IL-1RAP/15RA	ABCC13
IL-8/10RB	ABCD1
IL-10RB	ABCG2
IL w.r.t ABC	
IL-17REL	ABCA5
IL-2RG/6ST/15/15RA	ABCB11
IL-8/15RA	ABCC3
IL-15RA/17REL	ABCC5
IL-15RA/17REL	ABCC13
IL-1A/1RAP/8/15RA	ABCD1
IL-1RAP	ABCG1
IL-1RAP/15RA	ABCG2

Table 77 2^{nd} order combinatorial hypotheses between ABC and IL family members.

for ABCD1 - BCL2L2. **BCL2L13** was up regulated w.r.t ABC-B11/C5/C13/D1/G1. These are reflected in the rankings of 2505 (laplace) and 1855 (rbf) for ABCB11 - BCL2L13; 1835 (linear) and 2178 (rbf) for ABCC5 - BCL2L13; 2484 (laplace), 2184 (linear) and 2410 (rbf) for ABCC13 - BCL2L13; 2472 (laplace) and 2201 (rbf) for ABCD1 - BCL2L13 and 2276 (linear) and 2095 (rbf) for ABCG1 - BCL2L13. **BCL3** was up regulated w.r.t ABC-D1/G1. These are reflected in the rankings of 2194 (linear) and 2106 (rbf) for ABCD1 - BCL3 and 2014 (laplace) and 2253 (rbf) for ABCG1 - BCL3. **BCL6** was up regulated w.r.t ABC-B11. These are reflected in the rankings of 2010 (linear) and 2350 (rbf) for ABC-B11 - BCL6. **BCL10** was up regulated w.r.t ABC-B11. These are reflected in the rankings of 2234 (laplace) and 2382 (rbf) for ABC-B11 - BCL10.

On the right half we found **ABCC3** up regulated w.r.t BCL2L1. This is reflected in the rankings of 2085 (laplace) and 2309 (linear) for ABCC3 - BCL2L1. **ABC-C5/C13** were up regulated w.r.t BCL2L13. These was reflected in the rankings of 1975 (laplace) and 2421 (linear) for ABCC5 - BCL2L13; and 1894 (laplace), 2335 (linear) and 2475 (rbf) for ABCC13 - BCL2L13. **ABC-C3** was up regulated w.r.t BCL3. This is reflected in the rankings of 1782 (linear) and 2186 (rbf) for ABCC3 - BCL3. **ABC-C5/C13** were up regulated w.r.t BCL6. This is reflected in the rankings of 1841 (linear) and 2389 (rbf) for ABCC5 - BCL6 and 2172 (laplace) and 2456 (linear) for ABCC13 - BCL6. **ABC-C5/C13/D1** were up regulated w.r.t BCL9L. This is reflected in the rankings of 1775 (laplace) and 2073 (rbf) for ABCC5 - BCL9L; 2475 (linear) and 2325 (rbf) for ABCC13 - BCL9L and 2440 (linear) and 2411 (rbf) for ABCD1 - BCL9L; **ABC-A5/C5/C13/D1** were up regulated w.r.t BCL10. These were reflected in the rankings of 1753 (laplace) and 2312 (rbf) for ABCA5 - BCL10; 1775 (laplace) and 2073 (rbf) for ABCC5 - BCL10; 2475 (linear) and 2325 (rbf) for ABCC13 -

Ranking BCL family VS ABC family

Ranking of BCL2L1 w.r.t ABC family				Ranking of ABC family w.r.t BCL2L1			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL2L1	18	560	1715	ABCA5 - BCL2L1	1522	220	1818
ABCB11 - BCL2L1	1124	2418	552	ABCB11 - BCL2L1	2002	234	10
ABCC3 - BCL2L1	564	394	64	ABCC3 - BCL2L1	2085	2309	929
ABCC5 - BCL2L1	2239	1845	823	ABCC5 - BCL2L1	599	847	1282
ABCC13 - BCL2L1	805	1590	2407	ABCC13 - BCL2L1	744	616	614
ABCD1 - BCL2L1	356	202	930	ABCD1 - BCL2L1	839	352	195
ABCG1 - BCL2L1	793	2005	885	ABCG1 - BCL2L1	1249	265	1165
ABCG2 - BCL2L1	199	99	906	ABCG2 - BCL2L1	401	620	277
Ranking of BCL2L2 w.r.t ABC family				Ranking of ABC family w.r.t BCL2L2			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL2L2	1476	324	1792	ABCA5 - BCL2L2	174	482	501
ABCB11 - BCL2L2	2097	1311	2311	ABCB11 - BCL2L2	148	380	1204
ABCC3 - BCL2L2	1091	1569	259	ABCC3 - BCL2L2	890	949	1398
ABCC5 - BCL2L2	2195	2359	2322	ABCC5 - BCL2L2	765	1875	736
ABCC13 - BCL2L2	2438	2494	898	ABCC13 - BCL2L2	2271	1436	1665
ABCD1 - BCL2L2	2477	831	2156	ABCD1 - BCL2L2	1432	1291	64
ABCG1 - BCL2L2	352	1653	2234	ABCG1 - BCL2L2	406	1206	966
ABCG2 - BCL2L2	1515	2409	1496	ABCG2 - BCL2L2	404	314	55
Ranking of BCL2L13 w.r.t ABC family				Ranking of ABC family w.r.t BCL2L13			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL2L13	1398	202	2292	ABCA5 - BCL2L13	655	951	1380
ABCB11 - BCL2L13	2505	261	1855	ABCB11 - BCL2L13	1579	53	224
ABCC3 - BCL2L13	1642	1769	1334	ABCC3 - BCL2L13	265	588	459
ABCC5 - BCL2L13	1427	1835	2178	ABCC5 - BCL2L13	1975	2421	927
ABCC13 - BCL2L13	2484	2184	2410	ABCC13 - BCL2L13	1894	2335	2475
ABCD1 - BCL2L13	2472	1579	2201	ABCD1 - BCL2L13	912	511	1041
ABCG1 - BCL2L13	3	2276	2095	ABCG1 - BCL2L13	957	649	488
ABCG2 - BCL2L13	2172	1723	1502	ABCG2 - BCL2L13	2142	392	1206
Ranking of BCL3 w.r.t ABC family				Ranking of ABC family w.r.t BCL3			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL3	940	45	777	ABCA5 - BCL3	960	1354	2477
ABCB11 - BCL3	260	1002	483	ABCB11 - BCL3	731	1483	2028
ABCC3 - BCL3	2101	214	304	ABCC3 - BCL3	1782	2186	1251
ABCC5 - BCL3	1155	775	1176	ABCC5 - BCL3	2192	957	280
ABCC13 - BCL3	270	1116	1619	ABCC13 - BCL3	1725	1407	1747
ABCD1 - BCL3	759	2194	2106	ABCD1 - BCL3	836	811	1359
ABCG1 - BCL3	2014	1559	2253	ABCG1 - BCL3	550	247	247
ABCG2 - BCL3	480	465	1949	ABCG2 - BCL3	792	798	1418

Table 78 2^{nd} order interaction ranking between BCL and ABC family members.

Ranking BCL family VS ABC family

Ranking of BCL6 w.r.t ABC family				Ranking of ABC family w.r.t BCL6			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL6	2045	557	1384	ABCA5 - BCL6	211	283	1615
ABCB11 - BCL6	1611	2010	2350	ABCB11 - BCL6	841	427	2320
ABCC3 - BCL6	1895	983	958	ABCC3 - BCL6	1084	570	594
ABCC5 - BCL6	615	597	567	ABCC5 - BCL6	1370	1841	2389
ABCC13 - BCL6	1097	2431	1731	ABCC13 - BCL6	2172	2456	1063
ABCD1 - BCL6	1446	1139	1953	ABCD1 - BCL6	1097	1297	827
ABCG1 - BCL6	1462	1688	1918	ABCG1 - BCL6	192	27	1111
ABCG2 - BCL6	947	1503	978	ABCG2 - BCL6	129	745	719
Ranking of BCL9L w.r.t ABC family				Ranking of ABC family w.r.t BCL9L			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL9L	67	1008	94	ABCA5 - BCL9L	1753	1167	2312
ABCB11 - BCL9L	1989	158	1705	ABCB11 - BCL9L	1033	494	48
ABCC3 - BCL9L	1307	2249	1357	ABCC3 - BCL9L	457	2296	971
ABCC5 - BCL9L	1694	432	477	ABCC5 - BCL9L	1775	1551	2073
ABCC13 - BCL9L	1724	1410	862	ABCC13 - BCL9L	110	2475	2325
ABCD1 - BCL9L	1366	2344	1666	ABCD1 - BCL9L	1016	2440	2411
ABCG1 - BCL9L	1248	1680	536	ABCG1 - BCL9L	1146	676	16
ABCG2 - BCL9L	2451	1119	224	ABCG2 - BCL9L	1263	1421	218
Ranking of BCL10 w.r.t ABC family				Ranking of ABC family w.r.t BCL10			
	laplace	linear	rbf		laplace	linear	rbf
ABCA5 - BCL10	687	176	808	ABCA5 - BCL10	1753	1167	2312
ABCB11 - BCL10	2234	2382	322	ABCB11 - BCL10	1033	494	48
ABCC3 - BCL10	589	379	492	ABCC3 - BCL10	457	2296	971
ABCC5 - BCL10	1489	397	1643	ABCC5 - BCL10	1775	1551	2073
ABCC13 - BCL10	956	538	1491	ABCC13 - BCL10	110	2475	2325
ABCD1 - BCL10	1009	470	1597	ABCD1 - BCL10	1016	2440	2411
ABCG1 - BCL10	1613	310	1115	ABCG1 - BCL10	1146	676	16
ABCG2 - BCL10	361	676	2020	ABCG2 - BCL10	1263	1421	218

Table 79 2^{nd} order interaction ranking between ABC and BCL family members.

Unexplored combinatorial hypotheses	
BCL w.r.t ABC	
ABC-C5	BCL2L1
ABC-B11/C5/C13/D1	BCL2L2
ABC-B11/C5/C13/D1/G1	BCL2L13
ABC-D1/G1	BCL3
ABC-B11	BCL6
ABC-B11	BCL10
ABC w.r.t BCL	
ABC-C3	BCL2L1
ABC-C5/C13	BCL2L13
ABC-C3	BCL3
ABC-C5/C13	BCL6
ABC-C5/C13/D1	BCL9L
ABC-A5/C5/C13/D1	BCL10

Table 80 2^{nd} order combinatorial hypotheses between BCL and ABC family members.

BCL10 and 2440 (linear) and 2411 (rbf) for ABCD1 - BCL10.

Table 80 shows the derived influences which can be represented graphically, with the following influences - • BCL w.r.t ABC with ABC-C5 -> BCL2L1; ABC-B11/C5/C13/D1 -> BCL2L2; ABC-B11/C5/C13/D1/G1 -> BCL2L13; ABC-D1/G1 -> BCL3; ABC-B11 -> BCL6; ABC-B11 -> BCL10; and • ABC w.r.t BCL with ABC-C3 <- BCL2L1; ABC-C5/C13 <- BCL2L13; ABC-C3 <- BCL3; ABC-C5/C13 <- BCL6; ABC-C5/C13/D1 <- BCL9L; ABC-A5/C5/C13/D1 <- BCL10.

2.6.5 CASPASE - ABC transporters cross family analysis

Hu *et al.*[166] observe that the loss of ABCB4 attenuates the caspase-dependent apoptosis regulating resistance to 5-Fu in colorectal cancer. Ihlefeld *et al.*[167] analyze whether the observed upregulation of the multidrug transporters contributed to the resistance of Sgpl1/-MEFs against chemotherapy-induced apoptosis by measuring the influence of ABC transporter inhibitors on cell viability and caspase-3 cleavage. Though recent developements, they point to the synergy between the transporters and the CASP family. In CRC cells, treated with ETC-1922159, these were found to be UP regulated. The engine alotted high numerical valued ranks to some of the 2^{nd} order combinations between the members of the two families. Tables 81 and 82 show the rankings of

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ABC transporters w.r.t CASP and vice versa.

In table 81, we found **ABC-C5** to be up regulated w.r.t CASP4. These are reflected in rankings of 2495 (laplace) and 2257 (rbf) for CASP4 - ABC-C5. **ABC-C5** was up regulated w.r.t CASP5. These are reflected in rankings of 2475 (laplace) and 2234 (rbf) for CASP5 - ABC-C5. **ABC-A5/C13/D1** were up regulated w.r.t CASP7. These are reflected in rankings of 2515 (laplace) and 1742 (linear) for CASP7 - ABC-C5; 2489 (laplace) and 2418 (linear) for CASP7 - ABC-C13; and 2323 (laplace) and 2004 (linear) for CASP7 - ABC-D1. **ABC-B11/C5/D1/G1** were up regulated w.r.t CASP9. These are reflected in rankings of 2001 (linear) and 2051 (rbf) for CASP9 - ABC-B11; 2180 (laplace) and 2343 (linear) for CASP9 - ABC-C5; 2267 (laplace) and 2382 (rbf) for CASP9 - ABC-C13; 1890 (linear) and 2286 (rbf) for CASP9 - ABC-G1; **ABC-A5/C13** were up regulated w.r.t CASP10. These are reflected in rankings of 2292 (laplace), 2311 (linear) and 1108 (rbf) for CASP10 - ABC-A5; 2139 (laplace) and 2203 (linear) for CASP10 - ABC-C13;

In table 82, we found **ABC-C5** to be up regulated w.r.t CASP4. These are reflected in rankings of 2495 (laplace) and 2257 (rbf) for CASP4 - ABC-C5. **ABC-C5** was up regulated w.r.t CASP5. These are reflected in rankings of 2475 (laplace) and 2234 (rbf) for CASP5 - ABC-C5. **ABC-A5/C13/D1** were up regulated w.r.t CASP7. These are reflected in rankings of 2515 (laplace) and 1742 (linear) for CASP7 - ABC-C5; 2489 (laplace) and 2418 (linear) for CASP7 - ABC-C13; and 2323 (laplace) and 2004 (linear) for CASP7 - ABC-D1. **ABC-B11/C5/D1/G1** were up regulated w.r.t CASP9. These are reflected in rankings of 2001 (linear) and 2051 (rbf) for CASP9 - ABC-B11; 2180 (laplace) and 2343 (linear) for CASP9 - ABC-C5; 2267 (laplace) and 2382 (rbf) for CASP9 - ABC-C13; 1890 (linear) and 2286 (rbf) for CASP9 - ABC-G1; **ABC-A5/C13** were up regulated w.r.t CASP10. These are reflected in rankings of 2292 (laplace), 2311 (linear) and 1108 (rbf) for CASP10 - ABC-A5; 2139 (laplace) and 2203 (linear) for CASP10 - ABC-C13;

In table 82, we found **CASP4** to be up regulated w.r.t ABC-D1. These are reflected in rankings of 1791 (laplace) and 1954 (rbf) for CASP4 - ABC-D1. **CASP5** was up regulated w.r.t ABC-C13. These are reflected in rankings of 2286 (laplace) and 1905 (rbf) for CASP5 - ABC-C13. **CASP7** was up regulated w.r.t ABC-C5. This is reflected in rankings of 2168 (laplace), 1881 (linear) and 2016 (rbf) for CASP7 - ABC-C5. **CASP9** were up regulated w.r.t ABC-C5/C13/D1/G1. These are reflected in rankings of 2404 (laplace) and 2374 (linear) for CASP9 - ABC-A5; 2449 (laplace) and 2506 (rbf) for CASP9 - ABC-C13; 1858 (laplace) and 2430 (rbf) for CASP9 - ABC-D1; and 2342 (linear) and 2468 (rbf) for CASP9 - ABC-G1; **CASP16** were up regulated w.r.t ABC-A5. This is reflected in rankings of 2477 (linear) and 2315 (rbf) for CASP16 - ABC-A5.

Table 83 shows the derived influences which can be represented graphically, with the following influences - • ABC w.r.t CASP with CASP-4 -> ABC-C5; CASP-5 -> ABC-C5; CASP-7 -> ABC-A5/C13/D1; CASP-9 -> ABC-B11/C5/D1/G1; CASP-10 -> ABC-A5/C13; and • CASP w.r.t ABC with CASP-4 <- ABC-D1; CASP-5 <- ABC-C13; CASP-7 <- ABC-C5; CASP-9 <- ABC-C5/C13/D1/G1; CASP-16 <- ABC-A5;

Ranking ABC family w.r.t CASP family

Ranking of ABC family w.r.t CASP4				Ranking of ABC family w.r.t CASP5			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - ABC-A5	957	682	991	CASP5 - ABC-A5	733	1986	421
CASP4 - ABC-B11	19	727	158	CASP5 - ABC-B11	513	406	355
CASP4 - ABC-C3	1242	857	1848	CASP5 - ABC-C3	685	1694	1558
CASP4 - ABC-C5	2495	1316	2257	CASP5 - ABC-C5	2475	1038	2234
CASP4 - ABC-C13	154	1537	1206	CASP5 - ABC-C13	1660	1581	853
CASP4 - ABC-D1	1494	964	999	CASP5 - ABC-D1	354	725	1304
CASP4 - ABC-G1	1405	70	326	CASP5 - ABC-G1	298	485	382
CASP4 - ABC-G2	157	176	523	CASP5 - ABC-G2	706	846	1598
Ranking of ABC family w.r.t CASP7				Ranking of ABC family w.r.t CASP9			
	laplace	linear	rbf		laplace	linear	rbf
CASP7 - ABC-A5	2515	1742	25	CASP9 - ABC-A5	1125	1863	694
CASP7 - ABC-B11	1299	207	348	CASP9 - ABC-B11	729	2001	2051
CASP7 - ABC-C3	992	511	2222	CASP9 - ABC-C3	1108	1470	1465
CASP7 - ABC-C5	1232	1449	2154	CASP9 - ABC-C5	2180	2343	1732
CASP7 - ABC-C13	2489	2418	1623	CASP9 - ABC-C13	2267	1472	2382
CASP7 - ABC-D1	1544	2323	2004	CASP9 - ABC-D1	1011	1086	174
CASP7 - ABC-G1	665	382	670	CASP9 - ABC-G1	580	1890	2286
CASP7 - ABC-G2	1930	23	963	CASP9 - ABC-G2	647	2374	310
Ranking of ABC family w.r.t CASP10				Ranking of ABC family w.r.t CASP16			
	laplace	linear	rbf		laplace	linear	rbf
CASP10 - ABC-A5	2292	2311	1108	CASP16 - ABC-A5	165	408	113
CASP10 - ABC-B11	2245	1467	1182	CASP16 - ABC-B11	495	949	1417
CASP10 - ABC-C3	760	2479	923	CASP16 - ABC-C3	50	4	556
CASP10 - ABC-C5	326	485	1429	CASP16 - ABC-C5	1635	2487	1309
CASP10 - ABC-C13	2139	2203	1524	CASP16 - ABC-C13	1517	936	1236
CASP10 - ABC-D1	2210	475	1655	CASP16 - ABC-D1	1029	1210	1285
CASP10 - ABC-G1	2337	128	71	CASP16 - ABC-G1	350	756	109
CASP10 - ABC-G2	2075	1693	1306	CASP16 - ABC-G2	318	476	515

Table 81 2^{nd} order interaction ranking between ABC and CASP family members.

2.7 Interleukin related synergies

2.7.1 NFkB-2/I - Interleukin cross family analysis

Hörber *et al.* [168] show that the atypical inhibitor of NF-κB, IκBζ, controls macrophage interleukin-10 expression. Yamazaki *et al.* [169] observe that stimulus-specific induction of a novel nuclear factor-κB regulator, IκB-ζ, via Toll/Interleukin-1 receptor is mediated by mRNA stabilization. Kurzrock *et al.* [170] show that Interleukin-1 increases expression of the LYT-10 (NFκB2) proto-oncogene/transcription factor in renal cell carcinoma lines. These studies and many others not indicated here, show the connection between Interleukin and NFkB-2 and NFkBI family. In CRC cells treated with ETC-1922159, members of these families were UP regulated. Table 84 shows the rankings of each family with the other.

On the left side, rankings of IL w.r.t NFkB-2/I has been indicated. We found **IL-15RA/17C** to be up regulated w.r.t NFkB2. These are reflected in rankings of 1787 (rbf) and 1957 (rbf) IL15RA - NFkB2 and 2288 (linear) and 2018 (rbf) IL17C - NFkB2. **IL-1RN/6ST/15RA** to be up regulated w.r.t NFkB2. These are

Ranking CASP family w.r.t ABC family

Ranking of CASP4 w.r.t ABC family				Ranking of CASP5 w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - ABC-A5	791	586	753	CASP5 - ABC-A5	696	427	48
CASP4 - ABC-B11	462	263	427	CASP5 - ABC-B11	1470	1300	242
CASP4 - ABC-C3	1013	54	1140	CASP5 - ABC-C3	821	286	459
CASP4 - ABC-C5	2396	26	209	CASP5 - ABC-C5	2368	665	171
CASP4 - ABC-C13	1305	775	2193	CASP5 - ABC-C13	2286	739	1905
CASP4 - ABC-D1	1791	591	1954	CASP5 - ABC-D1	653	440	972
CASP4 - ABC-G1	593	99	173	CASP5 - ABC-G1	2176	446	317
CASP4 - ABC-G2	423	109	1364	CASP5 - ABC-G2	332	122	533
Ranking of CASP7 w.r.t ABC family				Ranking of CASP9 w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
CASP7 - ABC-A5	1726	697	1874	CASP9 - ABC-A5	2404	2374	1265
CASP7 - ABC-B11	1549	189	1692	CASP9 - ABC-B11	998	1258	2046
CASP7 - ABC-C3	2331	1572	69	CASP9 - ABC-C3	1398	2358	1445
CASP7 - ABC-C5	2168	1881	2016	CASP9 - ABC-C5	1023	965	1080
CASP7 - ABC-C13	1822	865	1239	CASP9 - ABC-C13	2449	1545	2506
CASP7 - ABC-D1	111	813	2230	CASP9 - ABC-D1	1858	2430	412
CASP7 - ABC-G1	1609	983	1994	CASP9 - ABC-G1	305	2342	2468
CASP7 - ABC-G2	1094	952	102	CASP9 - ABC-G2	1868	1621	1154
Ranking of CASP10 w.r.t ABC family				Ranking of CASP16 w.r.t ABC family			
	laplace	linear	rbf		laplace	linear	rbf
CASP10 - ABC-A5	683	1453	1437	CASP16 - ABC-A5	960	2477	2315
CASP10 - ABC-B11	1301	774	558	CASP16 - ABC-B11	402	1860	794
CASP10 - ABC-C3	369	683	1453	CASP16 - ABC-C3	171	825	23
CASP10 - ABC-C5	1823	346	761	CASP16 - ABC-C5	2467	585	258
CASP10 - ABC-C13	1320	832	868	CASP16 - ABC-C13	428	177	64
CASP10 - ABC-D1	249	1440	387	CASP16 - ABC-D1	651	153	2010
CASP10 - ABC-G1	1687	1232	156	CASP16 - ABC-G1	2398	421	1120
CASP10 - ABC-G2	1151	651	464	CASP16 - ABC-G2	1193	734	479

Table 82 2^{nd} order interaction ranking between CASP and ABC family members.

Unexplored combinatorial hypotheses

ABC w.r.t CASP	
CASP-4	ABC-C5
CASP-5	ABC-C5
CASP-7	ABC-A5/C13/D1
CASP-9	ABC-B11/C5/D1/G1
CASP-10	ABC-A5/C13
CASP w.r.t ABC	
CASP-4	ABC-D1
CASP-5	ABC-C13
CASP-7	ABC-C5
CASP-9	ABC-C5/C13/D1/G1
CASP-16	ABC-A5

Table 83 2^{nd} order combinatorial hypotheses between BCL and ABC family members.

reflected in rankings of 1753 (laplace) and 1906 (linear) for IL1RN - NFkBIA; 2400 (linear) and 2094 (rbf) for IL6ST - NFkBIA and 2251 (laplace) and 2390 (linear) for IL15RA - NFkBIA. **IL-1RAP/6ST/8/17REL** to be up regulated w.r.t NFkB2. These are reflected in rankings of 2221 (linear) and 1807 (rbf) IL1RAP - NFkBIE; 2381 (linear) and 2277 (rbf) for IL6ST - NFkBIE; 2198 (linear) and 2133 (rbf) for IL8 - NFkBIE and 2216 (linear) and 2168 (rbf) for IL17REL - NFkBIE. **IL-1A/6ST/15** to be up regulated w.r.t NFkB2. These are reflected in rankings of 2381 (laplace) and 2049 (linear) for IL1A - NFkBIZ; 2279 (laplace) and 2431 (linear) for IL6ST - NFkBIZ and 1780 (laplace) and 2098 (linear) for IL15 - NFkBIZ;

On the right side, rankings of NFkB-2/I w.r.t IL has been indicated. We found **NFkB-2** to be up regulated w.r.t IL10RB. This is reflected in rankings of 2282 (laplace), 2381 (linear) and 1897 (rbf) for NFkB2 - IL10RB. **NFkBIZ** to be up regulated w.r.t IL-10RB/17REL. These were reflected in rankings of 2271 (laplace) and 2082 (rbf) for IL10RB - NFkBIZ and 1883 (linear) and 1830 (rbf) for IL17REL - NFkBIZ.

Table 85 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t NFkB with IL w.r.t NFkB-2/I with IL15RA <- NFkB2; IL17C <- NFkB2; IL1RN <- NFkBIA; IL6ST <- NFkBIA; IL15RA <- NFkBIA; IL1RAP <- NFkBIE; IL6ST <- NFkBIE; IL8 <- NFkBIE; IL17REL <- NFkBIE; IL1A <- NFkBIZ; IL6ST <- NFkBIZ; IL15 <- NFkBIZ; and • NFkB-2/I w.r.t IL with IL10RB -> NFkB2; IL10RB -> NFKBIZ; IL17REL -> NFkBIZ;

2.7.2 Potassium channel - Interleukin cross family analysis

In 1986, Lee *et al.* [171] showed that increased voltage-gated potassium conductance during interleukin 2-stimulated proliferation of a mouse helper T lymphocyte clone. Martin *et al.* [172] show that interleukin-4 activates large-conductance, calcium-activated potassium (BKCa) channels in human airway smooth muscle cells. However, the author is not aware of deep studies between the Potassium ion channel subfamily members (KCN) and interleukin. In CRC cells treated with ETC-1922159, these were found to be UP regulated. The search engine found alotted multiple combinations between the members of these two families. These were reflected in ranking of the each with the other in the following table 86 and 87. On the left is rankings of IL family with respect to the KCN family member and on the right, vice versa.

Beginning on the left side we found **IL-1A/1B/15RA/17C** to be up regulated w.r.t KCND3. These are reflected in rankings of 1995 (laplace) and 2255 (linear) for IL1A - KCND3; 2083 (laplace) and 1897 (linear) for IL1B - KCND3; 2074 (laplace) and 2495 (rbf) for IL15RA - KCND3; and 1881 (laplace) and 2139 (linear) for IL17C - KCND3. **IL-1A/1B** to be up regulated w.r.t KCNH2. These are reflected in rankings of 2103 (laplace) and 1832 (linear) for IL1A - KCNH2 and 2447 (laplace) and 2068 (linear) for IL1B - KCNH2; **IL-1A/1B/17C** to be up regulated w.r.t KCNH8. These are reflected in rankings of 2268 (laplace), 2507 (linear) and 1877 (rbf) for IL1A - KCNH8; 2223 (laplace), 2013 (linear) and 2204 (rbf) for IL1B - KCNH8; and 1847 (laplace), and 2354 (rbf) for IL17C - KCNH8. **IL-1A/1B/1RN/15** to be up regulated

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Ranking Interleukin family vs NFkB-2 family

Ranking of IL family w.r.t NFkB-2				Ranking of NFkB-2/I w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - NFkB2	1485	6	2494	IL1A - NFkB2	616	276	1358
IL1B - NFkB2	1852	638	1587	IL1B - NFkB2	283	284	1088
IL1RAP - NFkB2	1369	1849	1463	IL1RAP - NFkB2	967	377	161
IL1RN - NFkB2	1285	1963	1604	IL1RN - NFkB2	1386	2086	52
IL2RG - NFkB2	486	1077	1300	IL2RG - NFkB2	1436	1123	2163
IL6ST - NFkB2	493	814	283	IL6ST - NFkB2	2177	343	2255
IL8 - NFkB2	1907	865	335	IL8 - NFkB2	303	2355	1152
IL10RB - NFkB2	707	1607	595	IL10RB - NFkB2	2282	2381	1897
IL15 - NFkB2	792	1113	1434	IL15 - NFkB2	2112	1214	1217
IL15RA - NFkB2	1787	233	1957	IL15RA - NFkB2	1289	1235	1913
IL17C - NFkB2	2288	305	2018	IL17C - NFkB2	380	529	1492
IL17REL - NFkB2	9	2464	167	IL17REL - NFkB2	115	1540	308
Ranking of IL family w.r.t NFkBI-A				Ranking of NFkB-2/I w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - NFkBIA	116	46	1885	IL1A - NFkBIA	989	1179	705
IL1B - NFkBIA	328	56	1228	IL1B - NFkBIA	611	397	1378
IL1RAP - NFkBIA	1376	778	359	IL1RAP - NFkBIA	1131	515	1887
IL1RN - NFkBIA	1753	1906	267	IL1RN - NFkBIA	2357	578	382
IL2RG - NFkBIA	32	6	898	IL2RG - NFkBIA	132	684	784
IL6ST - NFkBIA	1011	2400	2094	IL6ST - NFkBIA	2008	533	90
IL8 - NFkBIA	1988	1234	1232	IL8 - NFkBIA	183	993	1109
IL10RB - NFkBIA	864	2239	8	IL10RB - NFkBIA	616	1251	107
IL15 - NFkBIA	1181	453	462	IL15 - NFkBIA	2227	958	165
IL15RA - NFkBIA	2251	2390	1652	IL15RA - NFkBIA	765	291	2301
IL17C - NFkBIA	538	229	330	IL17C - NFkBIA	450	178	19
IL17REL - NFkBIA	643	16	4	IL17REL - NFkBIA	1275	403	2190
Ranking of IL family w.r.t NFkBI-E				Ranking of NFkBI-E w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - NFkBIE	2486	27	76	IL1A - NFkBIE	433	1574	953
IL1B - NFkBIE	2089	39	311	IL1B - NFkBIE	1103	507	1931
IL1RAP - NFkBIE	201	2221	1807	IL1RAP - NFkBIE	474	1404	875
IL1RN - NFkBIE	2025	610	1153	IL1RN - NFkBIE	2051	381	468
IL2RG - NFkBIE	1141	986	654	IL2RG - NFkBIE	1327	1464	983
IL6ST - NFkBIE	1155	2381	2277	IL6ST - NFkBIE	309	143	939
IL8 - NFkBIE	259	2198	2133	IL8 - NFkBIE	1507	911	67
IL10RB - NFkBIE	1730	191	310	IL10RB - NFkBIE	305	478	1960
IL15 - NFkBIE	1922	365	117	IL15 - NFkBIE	2476	783	1302
IL15RA - NFkBIE	1912	839	1385	IL15RA - NFkBIE	424	526	1423
IL17C - NFkBIE	2179	105	404	IL17C - NFkBIE	2231	1205	321
IL17REL - NFkBIE	13	2216	2168	IL17REL - NFkBIE	333	831	949
Ranking of IL family w.r.t NFkBI-Z				Ranking of NFkBI-Z w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - NFkBIZ	2381	2049	1578	IL1A - NFkBIZ	157	792	1460
IL1B - NFkBIZ	1241	2210	463	IL1B - NFkBIZ	586	217	1617
IL1RAP - NFkBIZ	694	1077	936	IL1RAP - NFkBIZ	1326	240	1080
IL1RN - NFkBIZ	860	2151	231	IL1RN - NFkBIZ	2463	739	579
IL2RG - NFkBIZ	1362	2054	68	IL2RG - NFkBIZ	68	829	1212
IL6ST - NFkBIZ	2279	980	2431	IL6ST - NFkBIZ	996	1223	140
IL8 - NFkBIZ	992	1732	966	IL8 - NFkBIZ	816	1510	119
IL10RB - NFkBIZ	717	2275	571	IL10RB - NFkBIZ	2271	42	2082
IL15 - NFkBIZ	1780	2098	626	IL15 - NFkBIZ	2155	200	245
IL15RA - NFkBIZ	633	1726	2422	IL15RA - NFkBIZ	834	1284	1785
IL17C - NFkBIZ	1716	2430	1098	IL17C - NFkBIZ	848	1282	1391
IL17REL - NFkBIZ	14	75	314	IL17REL - NFkBIZ	289	1883	1830

Table 84 2^{nd} order combinatorial hypotheses between NFkB-2/I and IL

w.r.t KCNK1. These are reflected in rankings of 2290 (laplace) and 2066 (linear) for IL1A - KCNK1; 1941 (laplace) and 2452 (linear) and 1905 (rbf) for IL1B - KCNK1; 2468 (laplace) and 1897 (linear) for IL1RN - KCNK1; 2280 (laplace) and 2009 (rbf) for IL15 - KCNK1. **IL-1RN/10RB/17REL** to be up regulated w.r.t KCNK5. These are reflected in rankings of 1930 (linear) and 2136 (rbf) for IL1RN-KCNK5; 1879 (laplace), 2298 (linear) and 1903 (rbf) for IL10RB-KCKK5; and 2118 (laplace) and 1873 (rbf) for IL17REL - KCNK5; **IL-8/17REL** to be up regulated w.r.t KCNK5. These are reflected in rankings of 2168 (laplace) and 2442 (linear) for IL8 - KCNK6; and 2066 (laplace) and 2159 (linear) for

Unexplored combinatorial hypotheses

IL w.r.t NFkB-2/I	
IL15RA	NFkB2
IL17C	NFkB2
IL1RN	NFkBIA
IL6ST	NFkBIA
IL15RA	NFkBIA
IL1RAP	NFkBIE
IL6ST	NFkBIE
IL8	NFkBIE
IL17REL	NFkBIE
IL1A	NFkBIZ
IL6ST	NFkBIZ
IL15	NFkBIZ
NFkB-2/I w.r.t IL	
IL10RB	NFkB2
IL10RB	NFKBIZ
IL17REL	NFkBIZ

Table 85 2^{nd} order combinatorial hypotheses between IL and NFkB-2/I family.

IL17REL - KCNK6.

Beginning on the right side we found **KCND3** to be up regulated w.r.t IL-1A/1B/15RA/17C. These are reflected in rankings of 2495 (laplace), 2390 (linear) for IL1RAP - KCND3; 2048 (laplace), 2306 (linear) and 2197 (rbf) for IL10RB - KCND3 and 2511 (laplace) and 2517 (linear) for IL15RA - KCND3; **KCNH2** to be up regulated w.r.t IL-1A/1RAP. These are reflected in rankings of 1897 (laplace), 2152 (linear) and 2179 (rbf) for IL1A - KCNH2; and 2451 (laplace), 1805 (linear) and 2002 (rbf) for IL1RAP - KCNH2; **KCNH8** to be up regulated w.r.t IL-1B/10RB. These are reflected in rankings of 2060 (laplace) and 2177 (rbf) for IL1B - KCNH8; and 2381 (laplace) and 2008 (linear) for IL10RB - KCNH8; **KCNK1** to be up regulated w.r.t IL-1A/6ST/8. These are reflected in rankings of 1818 (linear) and 2362 (rbf) for IL1A - KCNK1; 2226 (laplace) and 2283 (rbf) for IL6ST - KCNK1; and 1872 (laplace) and 1978 (linear) for IL8 - KCNK1; **KCNK5** to be up regulated w.r.t IL-10RB. This is reflected in rankings of 1769 (linear) and 2206 (rbf) for IL10RB - KCNK5; **KCNK6** to be up regulated w.r.t IL-1RAP/10RB/15. These are reflected in rankings of 2386 (laplace) and 2053 (rbf) for IL1RAP - KCNK6; 1903 (linear) and 2156 (rbf) for IL10RB - KCNK6; and 1944 (laplace) and 2047 (rbf) for IL15 - KCNK6;

Ranking Interleukin family vs KCN family

Ranking of IL family w.r.t KCND3	laplace	linear	rbf	Ranking of KCND3 w.r.t IL family	laplace	linear	rbf
IL1A - KCND3	1995	2255	718	IL1A - KCND3	707	118	11
IL1B - KCND3	2083	1897	691	IL1B - KCND3	1064	411	133
IL1RAP - KCND3	212	1086	1690	IL1RAP - KCND3	2495	2390	114
IL1RN - KCND3	1091	1875	1551	IL1RN - KCND3	459	743	300
IL2RG - KCND3	2027	1557	403	IL2RG - KCND3	588	248	58
IL6ST - KCND3	28	24	2501	IL6ST - KCND3	1	1127	2482
IL8 - KCND3	46	1098	1426	IL8 - KCND3	1134	1639	890
IL10RB - KCND3	1573	2172	1302	IL10RB - KCND3	2048	2306	2197
IL15 - KCND3	1905	1606	716	IL15 - KCND3	296	68	240
IL15RA - KCND3	2074	483	2495	IL15RA - KCND3	2511	2517	1606
IL17C - KCND3	1881	2139	368	IL17C - KCND3	588	1383	277
IL17REL - KCND3	1715	2242	359	IL17REL - KCND3	1361	748	1905

Ranking of IL family w.r.t KCNH2	laplace	linear	rbf	Ranking of KCNH2 w.r.t IL family	laplace	linear	rbf
IL1A - KCNH2	2103	1832	356	IL1A - KCNH2	1897	2152	2179
IL1B - KCNH2	2447	2068	930	IL1B - KCNH2	1599	2025	653
IL1RAP - KCNH2	423	1275	2487	IL1RAP - KCNH2	2451	1805	2002
IL1RN - KCNH2	1600	828	779	IL1RN - KCNH2	233	2304	305
IL2RG - KCNH2	1501	903	929	IL2RG - KCNH2	823	701	1820
IL6ST - KCNH2	1016	1565	1929	IL6ST - KCNH2	435	1665	2142
IL8 - KCNH2	863	258	1395	IL8 - KCNH2	1103	1062	2255
IL10RB - KCNH2	1238	1335	1441	IL10RB - KCNH2	648	1445	1684
IL15 - KCNH2	2295	1419	1038	IL15 - KCNH2	389	1247	1033
IL15RA - KCNH2	1738	2263	296	IL15RA - KCNH2	515	1572	2265
IL17C - KCNH2	2084	1399	49	IL17C - KCNH2	1388	1021	1079
IL17REL - KCNH2	90	1956	1491	IL17REL - KCNH2	727	2338	524

Ranking of IL family w.r.t KCNH8	laplace	linear	rbf	Ranking of KCNH8 w.r.t IL family	laplace	linear	rbf
IL1A - KCNH8	2268	2507	1877	IL1A - KCNH8	29	1939	1438
IL1B - KCNH8	2223	2013	2204	IL1B - KCNH8	2060	472	2177
IL1RAP - KCNH8	1238	479	1717	IL1RAP - KCNH8	1950	651	150
IL1RN - KCNH8	1653	819	2040	IL1RN - KCNH8	1094	329	988
IL2RG - KCNH8	57	1530	651	IL2RG - KCNH8	1853	1224	390
IL6ST - KCNH8	2067	979	1640	IL6ST - KCNH8	607	368	800
IL8 - KCNH8	1558	439	1250	IL8 - KCNH8	2484	269	1048
IL10RB - KCNH8	937	448	416	IL10RB - KCNH8	2381	2008	726
IL15 - KCNH8	1575	1789	580	IL15 - KCNH8	1365	1649	2187
IL15RA - KCNH8	2082	1524	1550	IL15RA - KCNH8	1667	638	1648
IL17C - KCNH8	1847	1700	2354	IL17C - KCNH8	1232	1825	1519
IL17REL - KCNH8	1542	2	1803	IL17REL - KCNH8	1120	681	2060

Table 86 2^{nd} order combinatorial hypotheses between KCN and IL

Ranking Interleukin family vs KCN family

Ranking of IL family w.r.t KCNK1	laplace	linear	rbf	Ranking of KCNK1 w.r.t IL family	laplace	linear	rbf
IL1A - KCNK1	2290	2066	1071	IL1A - KCNK1	1644	1818	2362
IL1B - KCNK1	1941	2452	1905	IL1B - KCNK1	813	966	1554
IL1RAP - KCNK1	171	595	2490	IL1RAP - KCNK1	1103	1318	1803
IL1RN - KCNK1	2468	1897	391	IL1RN - KCNK1	2130	73	1326
IL2RG - KCNK1	2384	1028	755	IL2RG - KCNK1	650	2324	1413
IL6ST - KCNK1	862	131	807	IL6ST - KCNK1	2226	688	2283
IL8 - KCNK1	722	22	2147	IL8 - KCNK1	1872	1978	1201
IL10RB - KCNK1	1965	125	1204	IL10RB - KCNK1	1087	1633	1021
IL15 - KCNK1	2280	2009	502	IL15 - KCNK1	1639	506	2369
IL15RA - KCNK1	1567	1546	895	IL15RA - KCNK1	1126	1499	784
IL17C - KCNK1	2451	122	931	IL17C - KCNK1	1331	2472	611
IL17REL - KCNK1	1515	659	2391	IL17REL - KCNK1	979	2329	329

Ranking of IL family w.r.t KCNK5	laplace	linear	rbf	Ranking of KCNK5 w.r.t IL family	laplace	linear	rbf
IL1A - KCNK5	609	608	796	IL1A - KCNK5	1840	1512	576
IL1B - KCNK5	1297	110	543	IL1B - KCNK5	510	1379	347
IL1RAP - KCNK5	1137	2237	1314	IL1RAP - KCNK5	730	911	1003
IL1RN - KCNK5	1583	1930	2136	IL1RN - KCNK5	815	405	1431
IL2RG - KCNK5	223	601	14	IL2RG - KCNK5	1841	782	806
IL6ST - KCNK5	1038	867	295	IL6ST - KCNK5	455	848	1275
IL8 - KCNK5	819	1737	105	IL8 - KCNK5	272	479	1215
IL10RB - KCNK5	1879	2298	1903	IL10RB - KCNK5	457	1769	2206
IL15 - KCNK5	981	1630	1669	IL15 - KCNK5	1060	244	580
IL15RA - KCNK5	791	124	555	IL15RA - KCNK5	361	332	1662
IL17C - KCNK5	2345	449	919	IL17C - KCNK5	388	713	509
IL17REL - KCNK5	18	2118	1873	IL17REL - KCNK5	1377	2108	1634

Ranking of IL family w.r.t KCNK6	laplace	linear	rbf	Ranking of KCNK6 w.r.t IL family	laplace	linear	rbf
IL1A - KCNK6	140	180	615	IL1A - KCNK6	1683	944	860
IL1B - KCNK6	525	57	369	IL1B - KCNK6	620	1047	903
IL1RAP - KCNK6	1878	830	902	IL1RAP - KCNK6	2386	1248	2053
IL1RN - KCNK6	1834	1564	90	IL1RN - KCNK6	2047	970	1311
IL2RG - KCNK6	2181	974	7	IL2RG - KCNK6	691	2454	1443
IL6ST - KCNK6	728	1895	1270	IL6ST - KCNK6	440	125	1682
IL8 - KCNK6	2168	2442	869	IL8 - KCNK6	774	98	654
IL10RB - KCNK6	1821	560	85	IL10RB - KCNK6	802	1903	2156
IL15 - KCNK6	1589	304	2447	IL15 - KCNK6	1944	130	2047
IL15RA - KCNK6	87	436	2447	IL15RA - KCNK6	1835	1531	1529
IL17C - KCNK6	103	200	538	IL17C - KCNK6	1056	1350	1408
IL17REL - KCNK6	2066	2159	1735	IL17REL - KCNK6	1044	1263	947

Table 87 2^{nd} order combinatorial hypotheses between KCN and IL

Finally, table 88shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t KCN with IL-1A/1B/15RA/17C <- KCND3; IL-1A/1B <- KCNH2; IL-1A/1B/17C <- KCNH8; IL-1A/1B/1RN/15 <- KCNK1; IL-1RN/10RB/17REL <- KCNK5; IL-8/17REL <- KCNK6; and • KCN w.r.t IL family with IL-1A/1B/15RA/17C -> KCND3; IL-1A/1RAP -> KCNH2; IL-1B/10RB -> KCNH8; IL-1A/6ST/8 -> KCNK1; IL-10RB -> KCNK5; and IL-1RAP/10RB/15 -> KCNK6;

2.7.3 Mucin - Interleukin cross family analysis

Kerschner *et al.* [173] have observed that middle ear epithelial mucin production in response to interleukin-6 exposure in vitro. Chen *et al.* [174] observe that stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. Suppression of mucin 2 promotes interleukin-6 secretion and tumor growth in an orthotopic immune-competent colon cancer animal model was observed by Shan *et al.* [175]. Yokoigawa *et al.* [176] show enhanced production of interleukin 6 in peripheral blood monocytes stimulated with mucins secreted into the bloodstream. Gray *et al.* [177] show that interleukin-1β-induced mucin production in human airway epithelium is mediated by cyclooxygenase-2, prostaglandin E2 receptors, and cyclic AMP-protein kinase A signaling. Finally, in colorectal cancer, Hsu *et al.* [178] mucin 2 silencing promotes metastasis through interleukin-6 signaling. In CRC cells treated with ETC-1922159, both were found to be up regulated. Tables 89 and 90 show the rankings of IL family w.r.t MUC family on the left side and vice versa on the right side.

On the left side, we found **IL-1B/17C** to be up regulated with respect to MUC1. These are reflected in rankings of 2218 (laplace) 1757 (linear) for IL1B - MUC1; and 1841 (linear) and 2003 (rbf) for IL17C - MUC1; **IL-1A/1B/1RN/2RG/15/17C** were up regulated with respect to MUC3A. These are reflected in rankings of 2513 (laplace) and 2480 (linear) for IL1A - MUC3A; 1820 (laplace) and 2308 (linear) for IL1B - MUC3A; 2138 (laplace) and 2270 (linear) for IL1RN - MUC3A; 1816 (laplace), 2115 (linear) and 1900 (rbf) for IL2RG - MUC3A; 2391 (laplace) and 2288 (linear) for IL15 - MUC3A; and 2443 (laplace) and 2512 (linear) for IL17C - MUC3A; **IL-1RN/6ST/15RA** were up regulated with re-

Unexplored combinatorial hypotheses	
IL w.r.t KCN	
IL-1A/1B/15RA/17C	KCND3
IL-1A/1B	KCNH2
IL-1A/1B/17C	KCNH8
IL-1A/1B/1RN/15	KCNK1
IL-1RN/10RB/17REL	KCNK5
IL-8/17REL	KCNK6
KCN w.r.t IL family	
IL-1A/1B/15RA/17C	KCND3
IL-1A/1RAP	KCNH2
IL-1B/10RB	KCNH8
IL-1A/6ST/8	KCNK1
IL-10RB	KCNK5
IL-1RAP/10RB/15	KCNK6

Table 88 2^{nd} order combinatorial hypotheses between IL family w.r.t KCN family.

spect to MUC4. These are reflected in rankings of 2010 (laplace) and 1960 (rbf) for IL1RN - MUC4; 2204 (laplace) and 1765 (rbf) for IL6ST - MUC4; and 2190 (laplace), 1814 (linear) and 2061 (rbf) for IL15RA - MUC4; **IL-1A/2RG/8/15/17C** were up regulated with respect to MUC12. These are reflected in rankings of 1806 (laplace) and 2396 (rbf) for IL1A - MUC12; 2195 (laplace) and 2089 (rbf) for IL2RG - MUC12; 1814 (laplace) and 2497 (rbf) for IL8 - MUC12; 2408 (laplace) and 2340 (rbf) for IL15 - MUC12; and 2436 (laplace) and 2416 (rbf) for IL17C - MUC12; **IL-15RA** were up regulated with respect to MUC17. These are reflected in rankings of 2265 (laplace) and 2064 (linear) for IL15RA - MUC17. **IL-1RAP/8/17REL** were up regulated with respect to MUC20. These are reflected in rankings of 2025 (linear) and 2251 (rbf) for IL1RAP - MUC20; 1820 (laplace) and 2303 (rbf) for IL8 - MUC20; and 2121 (laplace) and 2267 (rbf) for IL17REL - MUC20.

On the left side, we found **MUC1** to be up regulated with respect to IL-1B. These are reflected in rankings of 1847 (laplace) and 2049 (rbf) for IL1B - MUC1. **MUC12** to be up regulated with respect to IL-1RN/2RG/6ST. These are reflected in rankings of 2505 (laplace) and 1891 (linear) for IL1RN - MUC12; 1913 (laplace) and 1833 (linear) for IL2RG - MUC12; and 2100 (laplace) and 1759 (linear) for IL6ST - MUC12. **MUC13** to be up regulated with respect to IL-1RAP/15RA. These are reflected in rankings of 1887 (laplace) and 2263 (rbf) for IL1RAP - MUC13; and 2109 (laplace) and 2402 (rbf) for IL15RA - MUC13; **MUC20** to be up regulated with respect to IL-1A/10RB/17C. These are reflected in rankings of 2218 (laplace) and 2260 (rbf) for IL1A - MUC20; 1883 (linear) and 1947 (rbf) for IL10RB - MUC20; and 2212 (laplace) and 1843 (linear) for IL17C - MUC20.

Finally, table 91 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t MUC with IL-1B/17C <- MUC1; IL-1A/1B/1RN/2RG/15/17C and MUC3A; IL-1RN/6ST/15RA <- MUC4; IL-1A/2RG/8/15/17C <- MUC12; IL-15RA <- MUC17; and IL-1RAP/8/17REL <- MUC20; and • MUC w.r.t IL with IL-1B <- MUC1; IL-1RN/2RG/6ST <- MUC12; IL-1RAP/15RA <- MUC13; and IL-1A/10RB/17C <- MUC20;

2.7.4 Interleukin - TP53 cross family analysis

In a new pathway connecting inflammation to cancer, Brighenti *et al.*[179] show that interleukin 6 downregulates p53 expression and activity by stimulating ribosome biogenesis. Tan *et al.*[180] show that loss of p53 attenuates the contribution of IL-6 deletion on suppressed tumor progression and extended survival in Kras-driven murine lung cancer. Pützer *et al.*[181] show that combination therapy with interleukin-2 and wild-type p53 expressed by adenoviral vectors potentiates tumor regression in a murine model of breast cancer. A critical role for p53 in the control of NF-κB-dependent gene expression in TLR4-stimulated dendritic cells exposed to genistein has been shown by Dijsselbloem *et al.*[182]. The authors previously demonstrated that genistein suppresses TNF-α induced NF-κB-dependent IL-6 gene expression in cancer cells by interfering with the mitogen- and stress-activated protein kinase 1 activation pathway. Schauer *et al.*[183] show that interleukin-1β promotes ovarian tumorigenesis through a p53/NF-κB-mediated inflammatory response in stromal fibroblasts. These findings indicate connection between IL and TP53 family. Table 92 shows the rankings of IL family w.r.t TP53 family on the left and vice versa on the right.

On the left side, we found **IL-17REL** to be up regulated with respect to TP53BP2. These are reflected in rankings of 1873 (linear) and 2403 (rbf). **IL-15RA** was up regulated with respect to TP53I3. These are reflected in rankings of 2069 (laplace), 2079 (linear) and 2228 (rbf) for IL15RA - TP53I3. **IL-1RN/2RG/8/10RB/17REL** was up regulated with respect to TP53INP1. These are reflected in rankings of 2482 (laplace) and 1911 (linear) for IL1RN - TP53INP1; 2152 (laplace) and 1798 (linear) for IL2RG - TP53INP1; 2388 (linear) and 2343 (rbf) for IL8 - TP53INP1; 2510 (laplace), 2293 (linear) for IL10RB - TP53INP1; and 2505 (linear) and 2509 (rbf) for IL17REL - TP53INP1.

On the right side, we found **TP53BP2** to be up regulated with respect to IL-1A/1B/2RG/6ST/8/15/15RA. These are reflected in rankings of 2306 (linear) and 2483 (rbf) for IL1A - TP53BP2; 2003 (laplace) and 2317 (rbf) for IL1B - TP53BP2;

Ranking Interleukin family vs MUC family

Ranking of IL family w.r.t MUC1	laplace	linear	rbf	Ranking of MUC1 w.r.t IL family	laplace	linear	rbf
IL1A - MUC1	1961	1711	107	IL1A - MUC1	111	879	535
IL1B - MUC1	2218	1757	228	IL1B - MUC1	1847	520	2049
IL1RAP - MUC1	837	604	146	IL1RAP - MUC1	1968	589	439
IL1RN - MUC1	1084	918	1859	IL1RN - MUC1	1752	353	507
IL2RG - MUC1	1872	272	1281	IL2RG - MUC1	1769	1009	285
IL6ST - MUC1	2415	1115	1633	IL6ST - MUC1	296	801	245
IL8 - MUC1	1276	544	1055	IL8 - MUC1	2079	1320	82
IL10RB - MUC1	291	1638	1710	IL10RB - MUC1	973	1691	924
IL15 - MUC1	212	1003	1060	IL15 - MUC1	160	205	942
IL15RA - MUC1	213	1346	1067	IL15RA - MUC1	1127	1057	1521
IL17C - MUC1	1215	1841	2003	IL17C - MUC1	3	236	7
IL17REL - MUC1	19	44	2069	IL17REL - MUC1	1142	541	1464

Ranking of IL family w.r.t MUC3A	laplace	linear	rbf	Ranking of MUC3A w.r.t IL family	laplace	linear	rbf
IL1A - MUC3A	2513	2480	194	IL1A - MUC3A	1426	1017	1484
IL1B - MUC3A	1820	2308	1086	IL1B - MUC3A	816	1157	908
IL1RAP - MUC3A	753	1270	526	IL1RAP - MUC3A	1403	1402	102
IL1RN - MUC3A	2138	2270	313	IL1RN - MUC3A	1123	360	1333
IL2RG - MUC3A	1816	2115	1900	IL2RG - MUC3A	480	1560	514
IL6ST - MUC3A	283	1126	1229	IL6ST - MUC3A	1601	908	889
IL8 - MUC3A	356	760	1517	IL8 - MUC3A	2350	587	80
IL10RB - MUC3A	1401	729	157	IL10RB - MUC3A	520	458	2324
IL15 - MUC3A	850	2391	2288	IL15 - MUC3A	1385	1351	959
IL15RA - MUC3A	1304	1949	959	IL15RA - MUC3A	1538	1685	584
IL17C - MUC3A	2443	2512	647	IL17C - MUC3A	2153	623	1349
IL17REL - MUC3A	200	243	2048	IL17REL - MUC3A	1274	1250	1387

Ranking of IL family w.r.t MUC4	laplace	linear	rbf	Ranking of MUC4 w.r.t IL family	laplace	linear	rbf
IL1A - MUC4	1268	489	112	IL1A - MUC4	42	1449	331
IL1B - MUC4	779	1142	393	IL1B - MUC4	780	301	393
IL1RAP - MUC4	1672	1203	926	IL1RAP - MUC4	460	358	883
IL1RN - MUC4	2010	438	1960	IL1RN - MUC4	1681	1164	51
IL2RG - MUC4	161	292	36	IL2RG - MUC4	581	659	1056
IL6ST - MUC4	2204	1116	1765	IL6ST - MUC4	977	1555	873
IL8 - MUC4	619	741	1030	IL8 - MUC4	222	1341	1552
IL10RB - MUC4	1818	1343	599	IL10RB - MUC4	87	1511	95
IL15 - MUC4	434	1268	602	IL15 - MUC4	440	806	276
IL15RA - MUC4	2190	1814	2061	IL15RA - MUC4	427	1145	305
IL17C - MUC4	255	60	558	IL17C - MUC4	167	152	159
IL17REL - MUC4	222	482	52	IL17REL - MUC4	2266	419	160

Ranking of IL family w.r.t MUC12	laplace	linear	rbf	Ranking of MUC12 w.r.t IL family	laplace	linear	rbf
IL1A - MUC12	1806	166	2396	IL1A - MUC12	706	84	570
IL1B - MUC12	1004	113	2086	IL1B - MUC12	1352	167	445
IL1RAP - MUC12	1906	1588	517	IL1RAP - MUC12	52	272	1955
IL1RN - MUC12	2209	669	235	IL1RN - MUC12	2505	1891	567
IL2RG - MUC12	2195	751	2089	IL2RG - MUC12	1913	1833	939
IL6ST - MUC12	1115	1522	1031	IL6ST - MUC12	2100	1759	1508
IL8 - MUC12	1814	1554	2497	IL8 - MUC12	439	121	1635
IL10RB - MUC12	2467	1114	1044	IL10RB - MUC12	381	1863	12
IL15 - MUC12	2408	192	2340	IL15 - MUC12	2400	1307	1408
IL15RA - MUC12	612	1636	203	IL15RA - MUC12	137	127	468
IL17C - MUC12	2436	484	2416	IL17C - MUC12	411	182	283
IL17REL - MUC12	2421	331	611	IL17REL - MUC12	1452	678	651

Table 89 2^{nd} order combinatorial hypotheses between MUC and IL

1842 (laplace), 1888 (linear) and 1791 (rbf) for IL2RG - TP53BP2; 1862 (laplace) and 2234 (rbf) for IL6ST - TP53BP2; 2356 (laplace), 2336 (linear) for IL8 - TP53BP2; 2029 (linear) and 1896 (rbf) for IL15 - TP53BP2; 2086 (laplace), 2287 (linear) and 2198 (rbf) for IL15RA - TP53BP2; **TP53I3** was up regulated with respect to IL-17REL. This is reflected in rankings of 2268 (laplace) and 2220 (rbf) for IL17REL - TP53I3. **TP53INP1** was up regulated with respect to IL2RG. This is reflected in rankings of 2063 (laplace) and 1864 (linear) and 1956 (rbf) IL2RG - TP53INP1. **TP53INP2** was up regulated with respect to IL6ST. This is reflected in rankings of 2512 (laplace) and 1952 (linear).

Ranking Interleukin family vs MUC family contd.

Ranking of IL family w.r.t MUC13	laplace	linear	rbf	Ranking of MUC13 w.r.t IL family	laplace	linear	rbf
IL1A - MUC13	655	2323	826	IL1A - MUC13	1176	148	803
IL1B - MUC13	2250	298	185	IL1B - MUC13	833	30	8
IL1RAP - MUC13	386	490	360	IL1RAP - MUC13	1887	1142	2263
IL1RN - MUC13	904	1614	698	IL1RN - MUC13	1749	1607	313
IL2RG - MUC13	1043	59	27	IL2RG - MUC13	434	852	1140
IL6ST - MUC13	635	1774	730	IL6ST - MUC13	1901	535	163
IL8 - MUC13	225	510	1130	IL8 - MUC13	2328	722	555
IL10RB - MUC13	944	491	1631	IL10RB - MUC13	1459	1841	342
IL15 - MUC13	1773	609	1047	IL15 - MUC13	315	465	302
IL15RA - MUC13	1884	1360	1067	IL15RA - MUC13	2109	158	2402
IL17C - MUC13	562	106	149	IL17C - MUC13	73	4	84
IL17REL - MUC13	1808	83	59	IL17REL - MUC13	694	676	586

Ranking of IL family w.r.t MUC17	laplace	linear	rbf	Ranking of MUC17 w.r.t IL family	laplace	linear	rbf
IL1A - MUC17	1573	2431	1622	IL1A - MUC17	881	311	254
IL1B - MUC17	1122	514	1035	IL1B - MUC17	676	1243	174
IL1RAP - MUC17	1634	1148	1469	IL1RAP - MUC17	136	369	2512
IL1RN - MUC17	38	260	911	IL1RN - MUC17	361	22	690
IL2RG - MUC17	754	218	403	IL2RG - MUC17	1379	530	177
IL6ST - MUC17	1616	554	1381	IL6ST - MUC17	1782	668	270
IL8 - MUC17	241	583	402	IL8 - MUC17	1612	436	1984
IL10RB - MUC17	401	464	51	IL10RB - MUC17	1707	1305	1857
IL15 - MUC17	307	438	878	IL15 - MUC17	466	366	596
IL15RA - MUC17	2265	2064	1458	IL15RA - MUC17	63	376	849
IL17C - MUC17	1045	581	2291	IL17C - MUC17	1530	285	1449
IL17REL - MUC17	656	657	456	IL17REL - MUC17	380	580	1306

Ranking of IL family w.r.t MUC20	laplace	linear	rbf	Ranking of MUC20 w.r.t IL family	laplace	linear	rbf
IL1A - MUC20	103	1729	18	IL1A - MUC20	2218	1499	2260
IL1B - MUC20	85	1810	30	IL1B - MUC20	1313	1719	735
IL1RAP - MUC20	974	2025	2251	IL1RAP - MUC20	1784	859	1705
IL1RN - MUC20	1176	2264	246	IL1RN - MUC20	1265	726	823
IL2RG - MUC20	405	2168	335	IL2RG - MUC20	2152	165	1400
IL6ST - MUC20	1475	1093	2233	IL6ST - MUC20	1743	203	1643
IL8 - MUC20	1820	538	2303	IL8 - MUC20	1875	883	488
IL10RB - MUC20	394	1884	312	IL10RB - MUC20	889	1883	1947
IL15 - MUC20	244	2241	166	IL15 - MUC20	1412	2057	1669
IL15RA - MUC20	589	1406	1406	IL15RA - MUC20	1450	1902	1570
IL17C - MUC20	228	2278	46	IL17C - MUC20	2212	1843	255
IL17REL - MUC20	2121	962	2267	IL17REL - MUC20	1130	1000	1868

Table 90 2^{nd} order combinatorial hypotheses between MUC and IL

Finally, table 93 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t TP53 with IL17REL <- TP53BP2; IL15RA <- TP53I3; IL-1RN/2RG/8/10RB/17REL <- TP53INP1; and • TP53 w.r.t IL with IL-1A/1B/2RG/6ST/8/15/15RA -> TP53BP2; IL17REL -> TP53I3; IL2RG -> TP53INP1; and IL6ST -> TP53INP2.

2.7.5 Interleukin - STAT cross family analysis

Jones *et al.* [184] study the roles of interleukin-6 in activation of STAT proteins and recruitment of neutrophils during Escherichia coli pneumonia. Characterization of the interleukin-4 nuclear activated factor/STAT and its activation independent of the insulin receptor substrate proteins have been studied by Kotanides *et al.* [185]. Adam *et al.* [186] have unraveled viral interleukin-6 binding to gp130 and activation of STAT-signaling pathways independently of the interleukin-6 receptor. Frank *et al.* [187] report the involvement of interleukin 2 signaling in phosphorylation of Stat proteins. Boyd *et al.* [188] show that interleukin-10 receptor signaling through STAT-3 regulates the apoptosis of retinal ganglion cells in response to stress. Essential role of endo-

Unexplored combinatorial hypotheses	
IL w.r.t MUC	
IL-1B/17C	MUC1
IL-1A/1B/1RN/2RG/15/17C	MUC3A
IL-1RN/6ST/15RA	MUC4
IL-1A/2RG/8/15/17C	MUC12
IL-15RA	MUC17
IL-1RAP/8/17REL	MUC20
MUC w.r.t IL	
IL-1B	MUC1
IL-1RN/2RG/6ST	MUC12
IL-1RAP/15RA	MUC13
IL-1A/10RB/17C	MUC20

Table 91 2^{nd} order combinatorial hypotheses between IL and NFkB-2/I family.

cytosis for interleukin-4-receptor-mediated JAK/STAT signalling has been studied in Kurgonaite *et al.*[189]. Contribution of the interleukin-6/STAT-3 signaling pathway to chondrogenic differentiation of human mesenchymal stem cells has been studied in Kondo *et al.*[190]. Tanaka *et al.*[191] show interleukin-10 induces inhibitory C/EBPβ through STAT-3 and represses HIV-1 transcription in macrophages. Jobst *et al.*[192] show that inhibition of interleukin-3-and interferon-α-induced JAK/STAT signaling by the synthetic α-X-2', 3, 4, 4'-tetramethoxychalcones α-Br-TMC and α-CF3-TMC. These indicate significant interaction between interleukin family and the STAT family. In CRC cells, treated with ETC-1922159 both were found to be up regulated. The search engine alotted high numerical ranked values to some of the 2^{nd} order combinations between the two. Table 94 indicates the rankings of IL family w.r.t STAT2 family on the left and vice versa on the right.

On the left side, we found **IL-1RAP/6ST/17REL** to be up regulated with respect to STAT2. These are reflected in rankings of 2111 (laplace), 2258 (linear) and 2012 (rbf) for IL1RAP - STAT2; 2167 (laplace) and 2313 (linear) for IL6ST - STAT2; and 2508 (laplace), 2488 (linear) and 2172 (rbf) for IL17REL - STAT2. **IL-1RAP/17REL** were up regulated with respect to STAT3. These are reflected in rankings of 2252 (linear) and 2211 (rbf) for IL1RAP - STAT3; and 2282 (linear) and 2517 (rbf) for IL17REL - STAT3; **IL-1RAP/15RA** were up regulated with respect to STAT5A. These are reflected in rankings of 1768 (laplace) and 2149 (linear) for IL1RAP - STAT5A; and 2342 (laplace) and 2350 (linear) for IL15RA - STAT5A.

On the right side, we found **STAT2** to be up regulated with

Ranking Interleukin family vs TP53 family

Ranking of IL family w.r.t TP53BP2	laplace	linear	rbf	Ranking of TP53BP2 w.r.t IL family	laplace	linear	rbf
IL1A - TP53BP2	2396	1377	302	IL1A - TP53BP2	390	2306	2483
IL1B - TP53BP2	1868	1606	16	IL1B - TP53BP2	2003	1319	2317
IL1RAP - TP53BP2	154	1863	1166	IL1RAP - TP53BP2	1565	1196	133
IL1RN - TP53BP2	320	1676	1920	IL1RN - TP53BP2	1559	1149	2489
IL2RG - TP53BP2	755	377	644	IL2RG - TP53BP2	1842	1888	1791
IL6ST - TP53BP2	2237	581	1526	IL6ST - TP53BP2	1862	1530	2234
IL8 - TP53BP2	1135	1279	2250	IL8 - TP53BP2	2356	2336	325
IL10RB - TP53BP2	645	977	289	IL10RB - TP53BP2	420	705	2040
IL15 - TP53BP2	1715	281	973	IL15 - TP53BP2	879	2029	1896
IL15RA - TP53BP2	1225	727	567	IL15RA - TP53BP2	2086	2287	2198
IL17C - TP53BP2	2286	1214	617	IL17C - TP53BP2	1158	1243	2313
IL17REL - TP53BP2	76	1873	2403	IL17REL - TP53BP2	1526	1463	1600
Ranking of IL family w.r.t TP53I3	laplace	linear	rbf	Ranking of TP53I3 w.r.t IL family	laplace	linear	rbf
IL1A - TP53I3	1140	1547	1558	IL1A - TP53I3	283	157	341
IL1B - TP53I3	759	333	1392	IL1B - TP53I3	156	164	463
IL1RAP - TP53I3	1521	885	1978	IL1RAP - TP53I3	432	605	818
IL1RN - TP53I3	737	340	1797	IL1RN - TP53I3	1504	1674	16
IL2RG - TP53I3	7	3	328	IL2RG - TP53I3	836	637	134
IL6ST - TP53I3	524	363	981	IL6ST - TP53I3	2157	897	778
IL8 - TP53I3	579	485	697	IL8 - TP53I3	1921	290	1265
IL10RB - TP53I3	185	137	758	IL10RB - TP53I3	345	1080	326
IL15 - TP53I3	240	244	428	IL15 - TP53I3	353	1153	456
IL15RA - TP53I3	2069	2079	2228	IL15RA - TP53I3	106	644	1794
IL17C - TP53I3	74	114	647	IL17C - TP53I3	49	75	37
IL17REL - TP53I3	597	326	1290	IL17REL - TP53I3	2268	429	2220
Ranking of IL family w.r.t TP53INP1	laplace	linear	rbf	Ranking of TP53INP1 w.r.t IL family	laplace	linear	rbf
IL1A - TP53INP1	2309	746	7	IL1A - TP53INP1	1049	1135	1138
IL1B - TP53INP1	2281	21	461	IL1B - TP53INP1	1395	1370	1684
IL1RAP - TP53INP1	531	1274	2407	IL1RAP - TP53INP1	2223	1460	680
IL1RN - TP53INP1	2482	1911	891	IL1RN - TP53INP1	1473	1252	2399
IL2RG - TP53INP1	2152	1798	932	IL2RG - TP53INP1	2063	1864	1956
IL6ST - TP53INP1	591	790	1740	IL6ST - TP53INP1	537	404	2042
IL8 - TP53INP1	573	2388	2343	IL8 - TP53INP1	1671	1787	1014
IL10RB - TP53INP1	2510	2293	1664	IL10RB - TP53INP1	1000	2339	218
IL15 - TP53INP1	663	878	1116	IL15 - TP53INP1	2147	588	429
IL15RA - TP53INP1	663	149	169	IL15RA - TP53INP1	1266	2264	1636
IL17C - TP53INP1	2455	220	435	IL17C - TP53INP1	823	523	438
IL17REL - TP53INP1	83	2505	2509	IL17REL - TP53INP1	1085	1476	1393
Ranking of IL family w.r.t TP53INP2	laplace	linear	rbf	Ranking of TP53INP2 w.r.t IL family	laplace	linear	rbf
IL1A - TP53INP2	1481	41	2490	IL1A - TP53INP2	952	505	487
IL1B - TP53INP2	489	310	267	IL1B - TP53INP2	200	26	146
IL1RAP - TP53INP2	1159	684	1263	IL1RAP - TP53INP2	1168	757	1827
IL1RN - TP53INP2	2374	779	110	IL1RN - TP53INP2	1735	1927	264
IL2RG - TP53INP2	2118	103	995	IL2RG - TP53INP2	1151	539	380
IL6ST - TP53INP2	261	1459	333	IL6ST - TP53INP2	2512	1952	113
IL8 - TP53INP2	82	679	779	IL8 - TP53INP2	2349	85	1561
IL10RB - TP53INP2	865	1991	67	IL10RB - TP53INP2	653	2479	236
IL15 - TP53INP2	1354	989	161	IL15 - TP53INP2	1105	449	1506
IL15RA - TP53INP2	1574	1545	2295	IL15RA - TP53INP2	345	488	825
IL17C - TP53INP2	449	56	221	IL17C - TP53INP2	1065	260	116
IL17REL - TP53INP2	1325	93	593	IL17REL - TP53INP2	1251	643	1832

Table 92 2^{nd} order combinatorial hypotheses between TP53 and IL

respect to IL-1RAP/1RN/2RG/15RA/17C/17REL. These are reflected in rankings of 1826 (laplace) and 2005 (linear) for IL1RAP - STAT2; 2050 (laplace) 2082 (linear) for IL1RN - STAT2; 1986 (laplace) 2021 (linear) and 2031 (rbf) for IL2RG - STAT2; 1988 (linear) and 1863 (rbf) for IL15RA - STAT2; 2473 (linear) and 1883 (rbf) for IL17C - STAT2; 1890 (linear) and 1885 (rbf) for IL17REL - STAT2. **STAT3** was up regulated with respect to IL-1RN/2RG. These are reflected in rankings of 2090 (laplace) and 2312 (linear) for IL1RN - STAT3; and 2233 (laplace) and 2146 (linear) IL2RG - STAT3. **STAT5A** was up regulated with respect to IL-2RG/8/17C. These are reflected in rankings of 1832 (linear) and 2149 (rbf) for IL2RG - STAT5A; 2000 (laplace) and 2386

Unexplored combinatorial hypotheses	
IL w.r.t TP53	
IL17REL	TP53BP2
IL15RA	TP53I3
IL-1RN/2RG/8/10RB/17REL	TP53INP1
TP53 w.r.t IL	
IL-1A/1B/2RG/6ST/8/15/15RA	TP53BP2
IL17REL	TP53I3
IL2RG	TP53INP1
IL6ST	TP53INP2

Table 93 2^{nd} order combinatorial hypotheses between IL and NFkB-2/I family.

(linear) for IL8 - STAT5A; and 1760 (laplace), 2060 (linear) and 2201 (rbf) for IL17C - STAT5A.

Finally, table 95 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t STAT with IL-1RAP/6ST/17REL <- STAT2; IL-1RAP/17REL <- STAT3 and IL-1RAP/15RA <- STAT5A; and • STAT w.r.t IL with IL-1RN/2RG -> STAT2; IL-1A/1RN/2RG/6ST/15 -> STAT3 and IL-2RG/8/17C -> STAT5A;

2.7.6 Interleukin - TRAF cross family analysis

Greene and O'Neill[193] show that interleukin-1 receptor-associated kinase and TRAF-6 mediate the transcriptional regulation of interleukin-2 by interleukin-1 via NFκB but unlike interleukin-1 are unable to stabilise interleukin-2 mRNA. Cao *et al.*[194] observe that TRAF6 is a signal transducer for interleukin-1. Schwandner *et al.*[195] show the requirement of tumor necrosis factor receptor-associated factor (TRAF) 6 in interleukin 17 signal transduction. Lomaga *et al.*[196] show that TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling. Jefferies *et al.*[197] observe that transactivation by the p65 subunit of NF-κB in response to interleukin-1 (IL-1) involves MyD88, IL-1 receptor-associated kinase 1, TRAF-6, and Rac1. Wu and Arron[198] study the role of TRAF6 as a molecular bridge spanning adaptive immunity, innate immunity and osteoimmunology and find relation with the interleukin-1 receptor family. These findings indicate the range of interaction between IL family and TRAF family. In CRC cells treated with ETC-1922159, these were found to be UP regulated. Table 96 show the rankings of IL family w.r.t TRAF family on the left side and vice versa on the right side.

On the left we found, we found **IL-1RAP/15RA/17REL** to be up regulated with respect to TRAF3IP2. These are reflected in rankings of 2482 (linear) and 2385 (rbf) for IL1RAP - TRAF3IP2; 2024 (laplace), 2162 (linear) and 1800 (rbf) for IL15RA - TRAF3IP2; and 2515 (linear) and 2057 (rbf) for IL17REL - TRAF3IP2. **IL-6ST/17REL** were up regulated with respect to TRAF4. These are reflected in rankings of 2333 (laplace) and 1914 (rbf) for IL6ST - TRAF4; and (laplace) and 2487 (rbf) for

Ranking Interleukin family vs STAT family							
Ranking of IL family w.r.t STAT2				Ranking of STAT2 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - STAT2	171	207	709	IL1A - STAT2	1000	687	1941
IL1B - STAT2	347	559	188	IL1B - STAT2	1629	1019	2351
IL1RAP - STAT2	2111	2258	2012	IL1RAP - STAT2	1826	2005	70
IL1RN - STAT2	828	1942	1226	IL1RN - STAT2	2050	2082	1030
IL2RG - STAT2	939	1424	272	IL2RG - STAT2	1986	2021	2031
IL6ST - STAT2	2167	2313	1042	IL6ST - STAT2	1532	1766	696
IL8 - STAT2	806	1012	69	IL8 - STAT2	397	1015	2349
IL10RB - STAT2	1093	2401	1260	IL10RB - STAT2	1566	1241	467
IL15 - STAT2	929	197	446	IL15 - STAT2	1875	1724	940
IL15RA - STAT2	537	415	1916	IL15RA - STAT2	1406	1988	1863
IL17C - STAT2	175	78	514	IL17C - STAT2	1199	2473	1883
IL17REL - STAT2	2508	2488	2172	IL17REL - STAT2	244	1890	1885
Ranking of IL family w.r.t STAT3				Ranking of STAT3 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - STAT3	2516	173	7	IL1A - STAT3	1872	1289	2350
IL1B - STAT3	1628	127	613	IL1B - STAT3	1367	2391	901
IL1RAP - STAT3	23	2252	2211	IL1RAP - STAT3	2169	1483	179
IL1RN - STAT3	2309	300	488	IL1RN - STAT3	2090	2312	1440
IL2RG - STAT3	1168	397	611	IL2RG - STAT3	2233	2146	1387
IL6ST - STAT3	1355	1217	381	IL6ST - STAT3	2400	2491	1953
IL8 - STAT3	2353	740	1176	IL8 - STAT3	1371	942	2018
IL10RB - STAT3	2494	1257	1320	IL10RB - STAT3	1118	406	1299
IL15 - STAT3	2164	903	62	IL15 - STAT3	2015	2412	1356
IL15RA - STAT3	1140	1572	1618	IL15RA - STAT3	1724	1638	1963
IL17C - STAT3	2437	30	20	IL17C - STAT3	554	1446	1428
IL17REL - STAT3	339	2282	2517	IL17REL - STAT3	573	2181	521
Ranking of IL family w.r.t STAT5A				Ranking of STAT5A w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - STAT5A	1631	1110	2210	IL1A - STAT5A	275	464	1645
IL1B - STAT5A	1194	1561	2223	IL1B - STAT5A	416	240	1659
IL1RAP - STAT5A	1768	1680	2149	IL1RAP - STAT5A	1852	391	432
IL1RN - STAT5A	119	285	908	IL1RN - STAT5A	86	2026	960
IL2RG - STAT5A	1136	1088	1435	IL2RG - STAT5A	1367	1832	2149
IL6ST - STAT5A	1441	2022	1697	IL6ST - STAT5A	1903	436	317
IL8 - STAT5A	1932	1543	1069	IL8 - STAT5A	2000	2386	4
IL10RB - STAT5A	897	87	2033	IL10RB - STAT5A	2103	1292	1326
IL15 - STAT5A	1116	801	1653	IL15 - STAT5A	436	2139	1041
IL15RA - STAT5A	2342	2350	788	IL15RA - STAT5A	621	1185	1537
IL17C - STAT5A	984	1386	2045	IL17C - STAT5A	1760	2060	2201
IL17REL - STAT5A	1308	755	3	IL17REL - STAT5A	477	369	992

Table 94 2^{nd} order combinatorial hypotheses between STAT and IL

Unexplored combinatorial hypotheses	
IL w.r.t STAT	
IL-1RAP/6ST/17REL	STAT2
IL-1RAP/17REL	STAT3
IL-1RAP/15RA	STAT5A
STAT w.r.t IL	
IL-1RN/2RG	STAT2
IL-1A/1RN/2RG/6ST/15	STAT3
IL-2RG/8/17C	STAT5A

Table 95 2^{nd} order combinatorial hypotheses between IL and STAT family.

Ranking Interleukin family vs TRAF family							
Ranking of IL family w.r.t TRAF3IP2				Ranking of TRAF3IP2 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TRAF3IP2	2142	100	666	IL1A - TRAF3IP2	1518	2265	1107
IL1B - TRAF3IP2	1155	110	1193	IL1B - TRAF3IP2	1953	1294	2359
IL1RAP - TRAF3IP2	704	2482	2385	IL1RAP - TRAF3IP2	913	2034	38
IL1RN - TRAF3IP2	272	497	133	IL1RN - TRAF3IP2	1044	538	1173
IL2RG - TRAF3IP2	1948	1043	942	IL2RG - TRAF3IP2	1767	2385	2059
IL6ST - TRAF3IP2	49	1244	1098	IL6ST - TRAF3IP2	257	1991	1871
IL8 - TRAF3IP2	1165	598	344	IL8 - TRAF3IP2	796	2192	2289
IL10RB - TRAF3IP2	1252	1426	552	IL10RB - TRAF3IP2	840	237	2096
IL15 - TRAF3IP2	1550	433	163	IL15 - TRAF3IP2	1428	1183	2219
IL15RA - TRAF3IP2	2024	2162	1800	IL15RA - TRAF3IP2	906	1995	1717
IL17C - TRAF3IP2	2253	61	98	IL17C - TRAF3IP2	1290	1587	1839
IL17REL - TRAF3IP2	18	2515	2057	IL17REL - TRAF3IP2	1836	2042	1568
Ranking of IL family w.r.t TRAF4				Ranking of TRAF4 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TRAF4	26	2316	707	IL1A - TRAF4	1806	439	1465
IL1B - TRAF4	582	2136	175	IL1B - TRAF4	1026	746	378
IL1RAP - TRAF4	1180	1714	961	IL1RAP - TRAF4	909	2225	1546
IL1RN - TRAF4	494	2347	590	IL1RN - TRAF4	625	1031	1939
IL2RG - TRAF4	1092	1860	275	IL2RG - TRAF4	1130	339	826
IL6ST - TRAF4	2333	344	1914	IL6ST - TRAF4	676	1966	1556
IL8 - TRAF4	749	604	950	IL8 - TRAF4	406	450	1531
IL10RB - TRAF4	580	2512	424	IL10RB - TRAF4	2407	1781	1136
IL15 - TRAF4	1131	2078	227	IL15 - TRAF4	905	2408	1759
IL15RA - TRAF4	551	1628	2237	IL15RA - TRAF4	1197	2125	2073
IL17C - TRAF4	236	2464	19	IL17C - TRAF4	1538	914	1515
IL17REL - TRAF4	2422	381	2487	IL17REL - TRAF4	575	1394	320
Ranking of IL family w.r.t TRAF6				Ranking of TRAF6 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TRAF6	1	343	2237	IL1A - TRAF6	1637	455	2334
IL1B - TRAF6	224	143	2107	IL1B - TRAF6	861	1386	1342
IL1RAP - TRAF6	1875	1483	1433	IL1RAP - TRAF6	2219	1984	1766
IL1RN - TRAF6	107	706	988	IL1RN - TRAF6	1334	1067	1301
IL2RG - TRAF6	790	1706	1028	IL2RG - TRAF6	695	1717	1986
IL6ST - TRAF6	1508	928	930	IL6ST - TRAF6	54	762	1130
IL8 - TRAF6	2088	1883	2089	IL8 - TRAF6	2457	2139	1218
IL10RB - TRAF6	17	786	1211	IL10RB - TRAF6	303	1825	1709
IL15 - TRAF6	320	1692	2045	IL15 - TRAF6	2071	2475	1500
IL15RA - TRAF6	1560	303	2392	IL15RA - TRAF6	1688	1189	1344
IL17C - TRAF6	42	227	1457	IL17C - TRAF6	2469	2309	1503
IL17REL - TRAF6	2454	2517	412	IL17REL - TRAF6	124	2067	823
Ranking of IL family w.r.t TRAFD1				Ranking of TRAFD1 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TRAFD1	2408	1040	1579	IL1A - TRAFD1	2121	699	1587
IL1B - TRAFD1	1478	2046	1321	IL1B - TRAFD1	756	2435	571
IL1RAP - TRAFD1	491	1639	447	IL1RAP - TRAFD1	528	857	2043
IL1RN - TRAFD1	895	1149	266	IL1RN - TRAFD1	1033	848	1374
IL2RG - TRAFD1	1025	1948	43	IL2RG - TRAFD1	1243	492	1579
IL6ST - TRAFD1	1835	1824	809	IL6ST - TRAFD1	1064	868	699
IL8 - TRAFD1	1318	896	663	IL8 - TRAFD1	650	671	1088
IL10RB - TRAFD1	329	2371	355	IL10RB - TRAFD1	2403	556	800
IL15 - TRAFD1	1165	1934	769	IL15 - TRAFD1	339	623	634
IL15RA - TRAFD1	351	260	2385	IL15RA - TRAFD1	265	1369	386
IL17C - TRAFD1	1191	1389	1486	IL17C - TRAFD1	756	1068	1390
IL17REL - TRAFD1	704	2222	788	IL17REL - TRAFD1	370	640	137

Table 96 2^{nd} order combinatorial hypotheses between TRAF and IL

IL17REL - TRAF4 2422; **IL-8/17REL** were up regulated with respect to TRAF6. These are reflected in rankings of 2088 (laplace), 1883 (linear) and 2089 (rbf) for IL8 - TRAF6; and 2454 (laplace) and 2517 (linear) for IL17REL - TRAF6; **IL-6ST** were up regulated with respect to TRAFD1. These are reflected in rankings of 1835 (laplace) and 1824 (linear) for IL6ST - TRAFD1.

On the right we found, we found **TRAF3IP2** was up regulated with respect to IL-1B/2RG/6ST/8/17REL. These are reflected in rankings of 1953 (laplace) and 2359 (rbf) for IL1B - TRAF3IP2; 1767 (laplace), 2385 (linear) and 2059 (rbf) for IL2RG - TRAF3IP2; 1991 (linear) and 1871 (rbf) for IL6ST - TRAF3IP2; 2192 (linear) and 2289 (rbf) for IL8 - TRAF3IP2; and

Unexplored combinatorial hypotheses	
IL w.r.t TRAF	
IL-1RAP/15RA/17REL	TRAF3IP2
IL-6ST/17REL	TRAF4
IL-8/17REL	TRAF6
IL-6ST	TRAFD1
TRAF w.r.t IL	
IL-1B/2RG/6ST/8/17REL	TRAF3IP2
IL-10RB/15/15RA	TRAF4
IL-1RAP/8/15/17C	TRAF6

Table 97 2^{nd} order combinatorial hypotheses between IL and TRAF family.

1836 (laplace) and 2042 (linear) for IL17REL - TRAF3IP2. **TRAF4** was up regulated with respect to IL-10RB/15/15RA. These are reflected in rankings of 2407 (laplace) and 1781 (linear) for IL10RB - TRAF4; 2408 (linear) and 1759 (rbf) for IL15 - TRAF4; and 2408 (linear) and 1759 (rbf) for IL15RA - TRAF4; **TRAF6** was up regulated with respect to IL-1RAP/8/15/17C. These are reflected in rankings of 2219 (laplace), 1984 (linear) and 1766 (rbf) for IL1RAP - TRAF6; 2457 (laplace) and 2139 (linear) for IL8 - TRAF6; 2071 (lapalce) and 2475 (linear) for IL15 - TRAF6; and 2469 (laplace) and 2309 (linear) for IL17C - TRAF6;

Finally, table 97 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t TRAF with IL-1RAP/15RA/17REL <- TRAF3IP2; IL-6ST/17REL <- TRAF4; IL-8/17REL <- TRAF6; and IL-6ST <- TRAFD1; and • TRAF w.r.t IL with IL-1B/2RG/6ST/8/17REL -> TRAF3IP2; IL-10RB/15/15RA -> TRAF4 and IL-1RAP/8/15/17C -> TRAF6.

2.7.7 Interleukin - metalloreductase STEAP4 cross family analysis

Ramadoss *et al.* [199] show that C/EBPα also regulates hepatic expression of STEAP4 during feeding, whereas both C/EBPα and STAT3 regulate expression of steap4 in the presence of high levels of IL-6. Also, Tanaka *et al.* [120] show STEAP4 is a tumor necrosis factor alpha-induced protein that regulates IL-6, IL-8, and cell proliferation in synovium from patients with rheumatoid arthritis. Gauss *et al.* [121] observe that the STEAP4 expression in adipocytes is normally induced by nutritional stress, leptin, and proinflammatory cytokines, including TNF-α, interleukin-1β, and interleukin-6. These were found to be up regulated in CRC cells treated with ETC-1922159. Table 98 shows the interaction between the IL family and STEAP4. We found that **IL-8/10RB/17C/17REL** was up regulated w.r.t STEAP4. These are reflected in rankings of 2204 (laplace) and 1987 (linear) for IL8 -

Ranking Interleukin family vs STEAP4 family							
Ranking of IL family w.r.t STEAP4				Ranking of STEAP4 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - STEAP4	422	482	992	IL1A - STEAP4	71	2358	2223
IL1B - STEAP4	423	814	982	IL1B - STEAP4	240	1570	1863
IL1RAP - STEAP4	2092	262	661	IL1RAP - STEAP4	1871	1898	2077
IL1RN - STEAP4	404	1602	370	IL1RN - STEAP4	195	2043	1763
IL2RG - STEAP4	1293	1458	1323	IL2RG - STEAP4	299	1562	1284
IL6ST - STEAP4	920	1641	2424	IL6ST - STEAP4	1374	504	1628
IL8 - STEAP4	2204	1987	1558	IL8 - STEAP4	794	1049	1615
IL10RB - STEAP4	2422	2310	1179	IL10RB - STEAP4	476	254	906
IL15 - STEAP4	700	1154	2320	IL15 - STEAP4	288	1965	2283
IL15RA - STEAP4	2277	1114	1528	IL15RA - STEAP4	1170	1334	1347
IL17C - STEAP4	433	2103	1889	IL17C - STEAP4	17	2426	1108
IL17REL - STEAP4	33	1965	2297	IL17REL - STEAP4	2439	715	100

Table 98 2^{nd} order combinatorial hypotheses between STEAP4 and IL

Unexplored combinatorial hypotheses	
IL w.r.t STEAP4	
IL-8/10RB/17C/17REL	STEAP4
STEAP4 w.r.t IL	
IL-1A/1RAP/1RN/15	STEAP4

Table 99 2^{nd} order combinatorial hypotheses between IL and STEAP4 family.

STEAP4; 2422 (laplace) and 2310 (linear) for IL10RB - STEAP4; 2103 (linear) and 1889 (rbf) for IL17C - STEAP4; and 1965 (linear) and 2297 (rbf) for IL17REL - STEAP4; Also **STEAP4** was up regulated w.r.t IL-1A/1RAP/1RN/15. These are reflected in rankings of 2358 (linear) and 2223 (rbf) for IL1A - STEAP4; 1871 (laplace), 1898 (linear) and 2077 (rbf) for IL1RAP - STEAP4; 2043 (linear) and 1763 (rbf) for IL1RN - STEAP4; and 1965 (linear) and 2283 (rbf) for IL15 - STEAP4;

Finally, table 99 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t STEAP4 with IL-8/10RB/17C/17REL <- STEAP4 • STEAP4 w.r.t IL with IL-1A/1RAP/1RN/15 -> STEAP4.

2.7.8 Interleukin - metalloreductase STEAP3 cross family analysis

Based on the interactions of STEAP4 and interleukin, we also generated rankings for STEAP3 and interleukin family. It was found that STEAP3 and interleukin family were down regulated. Table 100 shows the rankings of IL family w.r.t STEAP3 and vice versa. We found **IL-1RL2/17D/17RB/17RD/33/F2/F3.AS1** to be down regulated w.r.t STEAP3. These are reflected in rankings of 619 (laplace) and 1471 (linear) for IL1RL2 - STEAP3; 1338 (laplace), 1275 (linear) and 458 (rbf) for IL17D - STEAP3; 1101 (laplace) and 239 (rbf) for IL17RB - STEAP3; 1323 (laplace) and 810 (linear) for IL17RD - STEAP3; 1589 (laplace) and 781 (linear) and 1210 (rbf) for IL33 - STEAP3; 1571 (laplace) and 811 (linear)

Ranking Interleukin family vs STEAP3 family							
Ranking of IL family w.r.t STEAP3				Ranking of STEAP3 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1RL2 - STEAP3	619	1471	2246	IL1RL2 - STEAP3	835	2234	1733
IL17D - STEAP3	1338	1275	458	IL17D - STEAP3	596	705	2273
IL17RB - STEAP3	1101	2302	239	IL17RB - STEAP3	208	2462	404
IL17RD - STEAP3	1323	810	1834	IL17RD - STEAP3	2352	589	2233
IL33 - STEAP3	1589	781	1210	IL33 - STEAP3	1070	57	2098
ILF2 - STEAP3	1571	811	579	ILF2 - STEAP3	1986	1029	2474
ILF3 - STEAP3	261	1866	1953	ILF3 - STEAP3	121	2314	926
ILF3.AS1 - STEAP3	947	2255	926	ILF3.AS1 - STEAP3	1592	678	1094

Table 100 2^{nd} order combinatorial hypotheses between STEAP3 and IL

Unexplored combinatorial hypotheses
IL w.r.t STEAP3
IL-1RL2/17D/17RB/17RD/33/F2/F3.AS1 - STEAP3
STEAP3 w.r.t IL
IL-1RL2/17D/17RB/33/F3/F3.AS1 - STEAP3

Table 101 2^{nd} order combinatorial hypotheses between IL and STEAP3 family.

and 579 (rbf) for ILF2 - STEAP3; and 947 (laplace) and 926 (rbf) for ILF3.AS1 - STEAP3. **STEAP3** to be down regulated w.r.t IL-1RL2/17D/17RB/33/F3/F3.AS1. These are reflected in rankings of 835 (laplace) and 1733 (rbf) for IL1RL2 - STEAP3; 596 (laplace) and 705 (linear) for IL17D - STEAP3; 208 (laplace) and 404 (rbf) for IL17RB - STEAP3; 1070 (laplace) and 57 (linear) for IL33 - STEAP3; 121 (laplace) and 926 (rbf) for ILF3 - STEAP3 and 1592 (laplace), 678 (linear) and 1094 (rbf) for ILF3.AS1 - STEAP3.

Finally, table 101 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t STEAP3 with IL-1RL2/17D/17RB/17RD/33/F2/F3.AS1 <- STEAP3; and • STEAP3 w.r.t IL with IL-1RL2/17D/17RB/33/F3/F3.AS1 -> STEAP3.

2.7.9 Interleukin - ATP-binding cassette transporters

Haskó *et al.* [159] show that the inhibitors of ATP-binding cassette transporters suppress interleukin-12 p40 production and major histocompatibility complex II up-regulation in macrophages. Marty *et al.* [161] observe that ATP binding cassette transporter ABC1 is required for the release of interleukin-1β by P2X7-stimulated and lipopolysaccharide-primed mouse Schwann cells. Hamon *et al.* [200] observe that interleukin-1β secretion is impaired by inhibitors of the ATP binding cassette transporter, ABC1. Lottaz *et al.* [162] show that inhibition of ATP-binding cassette transporter downregulates interleukin-1β-mediated autocrine activation of human dermal fibroblasts. These findings indicate the interaction of ABC transporters with Interleukin family. In CRC cells, treated with ETC-1922159 these were found to be down

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Ranking Interleukin family vs ABC family							
Ranking of IL family w.r.t ABCA2				Ranking of ABCA2 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1RL2 - ABCA2	2055	2097	405	IL1RL2 - ABCA2	2022	2490	1234
IL17D - ABCA2	1778	2160	1120	IL17D - ABCA2	540	227	1006
IL17RB - ABCA2	2419	1404	1727	IL17RB - ABCA2	2146	1543	1991
IL17RD - ABCA2	2202	1799	358	IL17RD - ABCA2	1717	1671	517
IL33 - ABCA2	1076	1707	1854	IL33 - ABCA2	1507	497	743
ILF2 - ABCA2	944	1054	2607	ILF2 - ABCA2	831	822	752
ILF3 - ABCA2	1380	1369	1702	ILF3 - ABCA2	1691	2094	2275
ILF3.AS1 - ABCA2	2243	1006	1924	ILF3.AS1 - ABCA2	2058	1664	2165
Ranking of IL family w.r.t ABCE1				Ranking of ABCE1 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1RL2 - ABCE1	906	1403	2365	IL1RL2 - ABCE1	525	2034	723
IL17D - ABCE1	1531	636	753	IL17D - ABCE1	1432	2146	1401
IL17RB - ABCE1	459	2056	1993	IL17RB - ABCE1	1090	2618	263
IL17RD - ABCE1	1030	1332	1565	IL17RD - ABCE1	1523	727	2185
IL33 - ABCE1	1649	719	937	IL33 - ABCE1	2619	808	2025
ILF2 - ABCE1	20	310	560	ILF2 - ABCE1	2650	331	2103
ILF3 - ABCE1	2410	2409	1826	ILF3 - ABCE1	1767	2674	19
ILF3.AS1 - ABCE1	1154	2222	786	ILF3.AS1 - ABCE1	1788	1948	820
Ranking of IL family w.r.t ABCF2				Ranking of ABCF2 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1RL2 - ABCF2	1031	1806	2002	IL1RL2 - ABCF2	2257	818	1274
IL17D - ABCF2	2481	2016	1006	IL17D - ABCF2	796	2104	568
IL17RB - ABCF2	509	1294	2302	IL17RB - ABCF2	1271	621	1631
IL17RD - ABCF2	610	1935	1084	IL17RD - ABCF2	957	2276	1431
IL33 - ABCF2	735	2050	1855	IL33 - ABCF2	421	1781	252
ILF2 - ABCF2	2093	1104	2073	ILF2 - ABCF2	683	2304	529
ILF3 - ABCF2	812	1686	1080	ILF3 - ABCF2	1243	585	1452
ILF3.AS1 - ABCF2	430	2416	1983	ILF3.AS1 - ABCF2	2272	1169	862

Table 102 2^{nd} order combinatorial hypotheses between ABC and IL

Unexplored combinatorial hypotheses	
IL w.r.t ABC	
IL-1RB/33/F2/F3	ABCA2
IL-1RL2/17D/17RD/33/F2/F3.AS1	ABCE1
IL-17RB/17RD/F3	ABCF2
ABC w.r.t IL	
IL-17D/17RD/33/F2	ABCA2
IL-1RL2/17D/17RB/17RD	ABCE1
IL-1RL2/17D/17RB/17RD/33/F2/F3/F3.AS1	ABCF2

Table 103 2^{nd} order combinatorial hypotheses between IL and ABC family.

regulated. Table 102 shows rankings of IL family with respect to a few ABC members on the left and vice versa on the right.

On the left we found **IL-1RB/33/F2/F3** were down regulated w.r.t ABCA2. These are reflected in rankings of 1404 (linear) and 1727 (rbf) for IL17RB - ABCA2; 1076 (laplace), 1707 (linear) for IL33 - ABCA2; 944 (laplace) and 1054 (linear) for ILF2 - ABCA2; 1380 (laplace), 1369 (linear) and 1702 (rbf) for ILF3 - ABCA2; **IL-1RL2/17D/17RD/33/F2/F3.AS1** were up regulated w.r.t ABCE1. These are reflected in rankings of 906 (laplace) and 1403 (linear) for IL1RL2 - ABCE1; 1531 (laplace), 636 (linear) and 753 (rbf) for IL17D - ABCE1; 1030 (laplace), 1332 (linear) and 1565 (rbf) for IL17RD - ABCE1; 1649 (laplace), 719 (linear) and 937 (rbf) for IL33 - ABCE1; 20 (laplace), 310 (linear) and 560 (rbf) for ILF2 - ABCE1; and 1154 (laplace) and 786 (rbf) for ILF3.AS1 - ABCE1. **IL-17RB/17RD/F3** were up regulated w.r.t ABCF2. These are reflected in rankings of 509 (laplace) and 1294 (laplace) for IL17RB - ABCF2; 610 (laplace) and 1084 (rbf) for IL17RD - ABCF2; and 812 (laplace), 1686 (laplace) and 1080 (rbf) for ILF3 - ABCF2.

On the right, we found **ABCA2** were up regulated w.r.t IL-17D/17RD/33/F2. These are reflected in rankings of 540 (laplace), 227 (linear) and 1006 (rbf) for IL17D - ABCA2; 1717 (laplace), 1671 (linear) and 517 (rbf) for IL17RD - ABCA2; 1507 (laplace), 497 (linear) and 743 (rbf) for IL33 - ABCA2; and 831 (laplace), 822 (linear) and 752 (rbf) for ILF2 - ABCA2; **ABCE1** were up regulated w.r.t IL-1RL2/17D/17RB/17RD. These are reflected in rankings of 525 (laplace) and 723 (rbf) for IL1RL2 - ABCE1; 1432 (laplace) and 1401 (rbf) for IL17D - ABCE1; 1090 (laplace) and 263 (rbf) for IL17RB - ABCE1; and 1523 (laplace) and 727 (linear) for IL17RD - ABCE1; **ABCF2** were up regulated w.r.t IL-1RL2/17D/17RB/17RD/33/F2/F3/F3.AS1. These are reflected in rankings of 818 (rbf) and 1274 (rbf) for IL1RL2 - ABCF2; 796 (laplace) and 568 (rbf) for IL17D - ABCF2; 1271 (laplace), 621 (linear) and 1631 (rbf) for IL17RB - ABCF2; 957 (laplace) and 1431 (rbf) for IL17RD - ABCF2; 421 (laplace) and 252 (rbf) for IL33 - ABCF2; 683 (laplace) and 529 (rbf) for ILF2 - ABCF2; 1243 (laplace), 585 (linear) and 1452 (rbf) for ILF3 - ABCF2 and 1169 (linear) and 862 (rbf) for ILF3.AS1 - ABCF2.

Finally, table 103 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t ABC with IL-1RB/33/F2/F3 <- ABCA2; IL-1RL2/17D/17RD/33/F2/F3.AS1 <- ABCE1 and IL-17RB/17RD/F3 <- ABCF2. • ABC w.r.t IL with IL-17D/17RD/33/F2 -> ABCA2; IL-1RL2/17D/17RB/17RD -> ABCE1 and IL-1RL2/17D/17RB/17RD/33/F2/F3/F3.AS1 -> ABCF2.

2.7.10 Interleukin - TNF cross family analysis

Neta *et al.*[201] study the relationship of TNF to interleukins way back in 1992. The review by Rieckmann *et al.*[202] studies role of TNF-α and IL-6 in normal and pathophysiological conditions of B-cell function. Bethea *et al.*[203] demonstrate that IL-1β induces TNF-α gene expression in CH235-MG cells in a protein kinase C-dependent manner. Tumor necrosis factor (TNF)-α and interleukin (IL)-1β down-regulate intercellular adhesion molecule (ICAM)-2 expression on the endothelium as shown by McLaughlin *et al.*[204]. Zhai *et al.*[205] suggest that serum levels of tumor necrosis factor-α receptors and interleukin 6 (IL-6) are associated with the fibrotic process of coal workers' pneumoconiosis (CWP) and serum cytokine levels may be correlated with the severity of CWP. However, in arthritic conditions, Koenders:2006interleukin show that Interleukin-17 acts independently of TNF-α. Serum interleukin-6 (IL-6), IL-10, tumor necrosis factor (TNF) alpha, soluble type II TNF receptor, and transforming growth factor beta levels in human immunodeficiency virus type 1-infected individuals with Mycobacterium avium complex disease have been studied by Havlir *et al.*[206]. Tissi *et al.*[207] study the role of tumor necrosis factor alpha, interleukin-1β, and interleukin-6 in a mouse model of group B streptococcal arthritis. They conclude that their results account for a strong involvement of IL-1β and IL-6, but not of TNF-α, in the pathogenesis of GBS arthritis. Ismail *et al.*[208] study the role of tumor necrosis factor alpha (TNF-α) and interleukin-10 in the pathogenesis of severe murine monocytotropic ehrlichiosis. Their data suggest that the balance between TNF-α and IL-10 produced by either macrophages or T cells in response to infection with Ehrlichia may modulate the induction of apoptosis during the infection. Yap *et al.*[209] observe that Tumor necrosis factor (TNF) inhibits interleukin (IL)-1 and/or IL-6 stimulated synthesis of C-reactive protein (CRP) and serum amyloid A (SAA) in primary cultures of human hepatocytes. These findings suggest interactive role of IL and TNF family in a synergistic way. In CRC cells treated with ETC-1922159, both were found to be up regulated. The search engine assigned high valued numerical ranks to 2^{nd} order combinations of IL and TNF family members. These are tabulated in tables 104, 105, 106 and 107. The left side contains rankings of IL w.r.t TNF family and the right side contains rankings of TNF family w.r.t IL.

On the left side, we found **IL-1RAP/6ST/15RA** to be up regulated w.r.t TNF. These are reflected in the rankings of 1995 (linear) and 2255 (rbf) for IL1RAP - TNF; 2374 (laplace), 2037 (linear) and 2003 (rbf) for IL6ST - TNF; 2341 (laplace), 1843 (linear) and 2195 (rbf) for IL15RA - TNF; **IL-1B/2RG/15RA/17C** were up regulated w.r.t TNFAIP1. These are reflected in the rankings of 2398 (laplace) and 2449 (rbf) for IL1B - TNFAIP1; 1791 (laplace) and 2482 (rbf) for IL2RG - TNFAIP1; 1860 (laplace) and 1979 (linear) for IL15RA - TNFAIP1; 2382 (laplace) and 2446 (rbf) for IL17C - TNFAIP1. **IL-1RN/10RB** were up regulated w.r.t TNFAIP2. These are reflected in the rankings of 1769 (laplace) and 2475 (rbf) for IL1RN - TNFAIP2; and 2319 (laplace) and 2497 (rbf) for IL10RB - TNFAIP2; **IL-6ST/8/17REL** were up regulated w.r.t TNFAIP3. These are reflected in the rankings of 2068 (laplace), 2432 (linear) and 2282 (rbf) for IL6ST - TNFAIP3; 1918 (laplace) and 2255 (linear) for IL8 - TNFAIP3; and 2364 (laplace), 2503 (linear) and 2283 (rbf) for IL17REL - TNFAIP3; **IL-1RAP** was up regulated w.r.t TNFRSF1A. This is reflected in the rankings of 2500 (linear) and 2293 (rbf) for IL1RAP - TNFRSF1A; **IL-1RAP/15RA/17REL** were up regulated w.r.t TNFRSF10A. These are reflected in the rankings of 2104 (laplace) and 2027 (rbf) for IL1RAP - TNFRSF10A; 2126 (laplace), 2342 (linear) for IL15RA - TNFRSF10A; 2497 (laplace), 2470 (linear) and 2109 (rbf) for IL17REL - TNFRSF10A; **IL-15RA** was up regulated w.r.t TNFRSF10B. This is reflected in the rankings of 2330 (laplace) and 1932 (rbf) for IL15RA - TNFRSF10B; **IL-15RA** was

Ranking Interleukin family vs TNF family

Ranking of IL family w.r.t TNF	laplace	linear	rbf	Ranking of TNF w.r.t IL family	laplace	linear	rbf
IL1A - TNF	1382	727	725	IL1A - TNF	172	660	230
IL1B - TNF	519	539	187	IL1B - TNF	443	458	244
IL1RAP - TNF	1475	1995	2255	IL1RAP - TNF	564	550	1500
IL1RN - TNF	163	106	609	IL1RN - TNF	292	462	276
IL2RG - TNF	276	820	340	IL2RG - TNF	419	708	1035
IL6ST - TNF	2374	2037	2003	IL6ST - TNF	2410	1901	666
IL8 - TNF	921	1325	1148	IL8 - TNF	1072	206	118
IL10RB - TNF	346	595	339	IL10RB - TNF	2065	2120	2296
IL15 - TNF	242	944	616	IL15 - TNF	265	828	279
IL15RA - TNF	2341	1843	2195	IL15RA - TNF	131	914	1488
IL17C - TNF	906	1573	776	IL17C - TNF	2148	568	280
IL17REL - TNF	296	804	677	IL17REL - TNF	1223	1901	11
Ranking of IL family w.r.t TNFAIP1	laplace	linear	rbf	Ranking of TNFAIP1 w.r.t IL family	laplace	linear	rbf
IL1A - TNFAIP1	2515	549	1534	IL1A - TNFAIP1	533	1901	1548
IL1B - TNFAIP1	2398	440	2449	IL1B - TNFAIP1	1324	756	1062
IL1RAP - TNFAIP1	326	866	2226	IL1RAP - TNFAIP1	1555	1284	1291
IL1RN - TNFAIP1	1952	649	1453	IL1RN - TNFAIP1	1567	307	979
IL2RG - TNFAIP1	1791	104	2482	IL2RG - TNFAIP1	421	973	1169
IL6ST - TNFAIP1	156	1415	1062	IL6ST - TNFAIP1	1281	104	2086
IL8 - TNFAIP1	456	682	1389	IL8 - TNFAIP1	2293	2126	752
IL10RB - TNFAIP1	97	425	2020	IL10RB - TNFAIP1	716	2092	569
IL15 - TNFAIP1	367	1392	159	IL15 - TNFAIP1	24	436	324
IL15RA - TNFAIP1	1860	1979	611	IL15RA - TNFAIP1	873	2141	1853
IL17C - TNFAIP1	2382	1072	2446	IL17C - TNFAIP1	961	2143	791
IL17REL - TNFAIP1	307	79	161	IL17REL - TNFAIP1	1603	1462	1764
Ranking of IL family w.r.t TNFAIP2	laplace	linear	rbf	Ranking of TNFAIP2 w.r.t IL family	laplace	linear	rbf
IL1A - TNFAIP2	219	1815	790	IL1A - TNFAIP2	450	1041	465
IL1B - TNFAIP2	210	1123	538	IL1B - TNFAIP2	1923	557	944
IL1RAP - TNFAIP2	1535	660	1525	IL1RAP - TNFAIP2	105	229	845
IL1RN - TNFAIP2	1769	2475	683	IL1RN - TNFAIP2	957	868	839
IL2RG - TNFAIP2	1358	576	188	IL2RG - TNFAIP2	415	1132	613
IL6ST - TNFAIP2	2007	633	1704	IL6ST - TNFAIP2	1649	929	1558
IL8 - TNFAIP2	769	331	368	IL8 - TNFAIP2	1262	1412	1595
IL10RB - TNFAIP2	2319	2497	719	IL10RB - TNFAIP2	93	1583	204
IL15 - TNFAIP2	1362	2383	795	IL15 - TNFAIP2	537	749	120
IL15RA - TNFAIP2	2032	821	1502	IL15RA - TNFAIP2	519	737	1146
IL17C - TNFAIP2	868	1684	1770	IL17C - TNFAIP2	199	424	687
IL17REL - TNFAIP2	279	563	299	IL17REL - TNFAIP2	2057	437	2008

Table 104 2^{nd} order combinatorial hypotheses between TNF and IL

up regulated w.r.t TNFRSF10D. This is reflected in the rankings of 2197 (laplace) and 2126 (rbf) for IL-15RA - TNFRSF10D; **IL-8/15RA/17REL** were up regulated w.r.t TNFRSF12A. These are reflected in the rankings of 1827 (linear) and 2355 (rbf) for IL8 - TNFRSF12A; 2138 (laplace), 2090 (linear) and 1981 (rbf) for IL15RA - TNFRSF12A; 2475 (laplace) and 2496 (rbf) for IL17REL - TNFRSF12A. **IL-15RA** was up regulated w.r.t TNFRSF14. This is reflected in the rankings of 2378 (laplace) and 1929 (rbf) for IL-15RA - TNFRSF14; **IL-1B/1RAP/2RG** were up regulated w.r.t TNFRSF21. These are reflected in the rankings of 1862 (laplace), 2164 (linear), 2305 (rbf) for IL1B - TNFRSF21; 1762 (linear) and 2163 (rbf) for IL1RAP - TNFRSF21; and 2297 (linear) and 2351 (rbf) for IL2RG - TNFRSF21; **IL-1B/15RA/17C** were up regulated w.r.t TNFRSF10. These are reflected in the rankings of 2448 (linear) and 1993 (rbf) for IL1B - TNFSF10; 2163 (linear) and 2059 (rbf) for IL15RA - TNFSF10; and 2337 (linear) and 2431 (rbf) for IL17C - TNFSF10. **IL-15RA/17C** to be up regulated w.r.t TNFSF15. This is reflected in the rankings of 2222 (laplace) and 2328 (linear) for IL-17C - TNFSF15; and 2124 (laplace) and 2365 (rbf) for IL15RA - TNFSF15;

Ranking Interleukin family vs TNF family

Ranking of IL family w.r.t TNFAIP3	laplace	linear	rbf	Ranking of TNFAIP3 w.r.t IL family	laplace	linear	rbf
IL1A - TNFAIP3	2307	319	108	IL1A - TNFAIP3	78	51	2058
IL1B - TNFAIP3	495	98	339	IL1B - TNFAIP3	140	146	520
IL1RAP - TNFAIP3	30	2428	1376	IL1RAP - TNFAIP3	1802	1610	903
IL1RN - TNFAIP3	579	277	299	IL1RN - TNFAIP3	60	1610	1320
IL2RG - TNFAIP3	1705	330	125	IL2RG - TNFAIP3	1056	1608	2333
IL6ST - TNFAIP3	2068	2432	2282	IL6ST - TNFAIP3	1652	1470	1507
IL8 - TNFAIP3	1918	2255	1587	IL8 - TNFAIP3	2224	1717	118
IL10RB - TNFAIP3	1576	666	1377	IL10RB - TNFAIP3	1073	417	943
IL15 - TNFAIP3	732	254	273	IL15 - TNFAIP3	907	628	684
IL15RA - TNFAIP3	727	1547	1476	IL15RA - TNFAIP3	1340	445	1031
IL17C - TNFAIP3	1675	222	138	IL17C - TNFAIP3	1105	1887	866
IL17REL - TNFAIP3	2364	2503	2283	IL17REL - TNFAIP3	2040	1143	1486
Ranking of IL family w.r.t TNFRSF1A	laplace	linear	rbf	**Ranking of TNFRSF1A w.r.t IL family**	laplace	linear	rbf
IL1A - TNFRSF1A	1556	2184	1375	IL1A - TNFRSF1A	2028	113	226
IL1B - TNFRSF1A	1621	1917	446	IL1B - TNFRSF1A	147	2027	2247
IL1RAP - TNFRSF1A	1236	2500	2293	IL1RAP - TNFRSF1A	1339	1003	2062
IL1RN - TNFRSF1A	411	1571	755	IL1RN - TNFRSF1A	1713	387	102
IL2RG - TNFRSF1A	565	2350	574	IL2RG - TNFRSF1A	1191	597	1479
IL6ST - TNFRSF1A	2221	1465	561	IL6ST - TNFRSF1A	1143	291	225
IL8 - TNFRSF1A	1536	750	304	IL8 - TNFRSF1A	1483	669	673
IL10RB - TNFRSF1A	620	35	1791	IL10RB - TNFRSF1A	230	1510	385
IL15 - TNFRSF1A	345	489	384	IL15 - TNFRSF1A	157	838	425
IL15RA - TNFRSF1A	442	1155	697	IL15RA - TNFRSF1A	682	322	1575
IL17C - TNFRSF1A	1113	284	149	IL17C - TNFRSF1A	5	169	122
IL17REL - TNFRSF1A	766	336	249	IL17REL - TNFRSF1A	1547	452	22
Ranking of IL family w.r.t TNFRSF10A	laplace	linear	rbf	**Ranking of TNFRSF10A w.r.t IL family**	laplace	linear	rbf
IL1A - TNFRSF10A	366	73	48	IL1A - TNFRSF10A	1972	1805	2504
IL1B - TNFRSF10A	317	45	367	IL1B - TNFRSF10A	2375	2373	2320
IL1RAP - TNFRSF10A	2104	1342	2027	IL1RAP - TNFRSF10A	981	1665	2504
IL1RN - TNFRSF10A	1739	346	173	IL1RN - TNFRSF10A	1261	2287	2469
IL2RG - TNFRSF10A	645	1448	1009	IL2RG - TNFRSF10A	1244	2246	2467
IL6ST - TNFRSF10A	1307	823	1778	IL6ST - TNFRSF10A	2128	2320	1738
IL8 - TNFRSF10A	402	1615	1908	IL8 - TNFRSF10A	566	733	2117
IL10RB - TNFRSF10A	1243	689	2119	IL10RB - TNFRSF10A	389	532	723
IL15 - TNFRSF10A	321	1602	358	IL15 - TNFRSF10A	2414	2260	1705
IL15RA - TNFRSF10A	2126	2342	148	IL15RA - TNFRSF10A	2398	1970	2088
IL17C - TNFRSF10A	981	269	1027	IL17C - TNFRSF10A	1831	2025	1718
IL17REL - TNFRSF10A	2497	2470	2109	IL17REL - TNFRSF10A	1034	1482	2068

Table 105 2^{nd} order combinatorial hypotheses between TNF and IL

On the right side, we found **TNF** was up regulated w.r.t IL-6ST/10RB. These are reflected in the rankings of 2410 (laplace) and 1901 (linear) for IL6ST - TNF; and 2065 (laplace), 2120 (linear) and 2296 (rbf) for IL10RB - TNF; **TNFAIP1** was up regulated w.r.t IL-8/15RA. These are reflected in the rankings of 2293 (laplace) and 2126 (linear) for IL8 - TNFAIP1; and 2141 (linear) and 1853 (rbf) for IL15RA - TNFAIP1; **TNFRSF1A** was up regulated w.r.t IL-1B. This is reflected in the rankings of 2027 (linear) and 2247 (rbf) for IL1B - TNFRSF1A; **TNFRSF10A** was up regulated w.r.t IL-1A/1B/1RN/2RG/6ST/15/15RA/17C. These are reflected in the rankings of 1972 (laplace), 1805 (linear) and 2504 (rbf) for IL1A - TNFRSF10A; 2375 (laplace), 2373 (linear) and 2320 (rbf) for IL1B - TNFRSF10A; 2287 (linear) and 2469 (rbf) for IL1RN - TNFRSF10A; 2246 (linear) and 2467 (rbf) for IL2RG - TNFRSF10A; 2128 (laplace) and 2320 (linear) for IL6ST - TNFRSF10A; 2414 (laplace) and 2260 (linear) for IL15 - TNFRSF10A; 2398 (laplace) and 1970 (linear) and 2088 (rbf) for IL15RA - TNFRSF10A; and 1831 (laplace) and 2025 (linear) for IL17C - TNFRSF10A; **TNFRSF10B** was up regulated w.r.t IL-1RN. This is reflected in the rankings of 2087 (laplace) and 1966 (rbf) for IL1RN - TNFRSF10B; **TNFRSF10D** was up regulated w.r.t IL-1A/1B/2RG/6ST/10RB/15/17C/17REL. These are reflected in

Ranking Interleukin family vs TNF family

Ranking of IL family w.r.t TNFRSF10B	laplace	linear	rbf	Ranking of TNFRSF10B w.r.t IL family	laplace	linear	rbf
IL1A - TNFRSF10B	771	190	110	IL1A - TNFRSF10B	294	1870	1471
IL1B - TNFRSF10B	2301	109	19	IL1B - TNFRSF10B	829	626	1465
IL1RAP - TNFRSF10B	752	2148	1579	IL1RAP - TNFRSF10B	2102	1685	405
IL1RN - TNFRSF10B	840	2005	443	IL1RN - TNFRSF10B	2087	1403	1966
IL2RG - TNFRSF10B	1868	1485	57	IL2RG - TNFRSF10B	1616	2134	1376
IL6ST - TNFRSF10B	788	1851	1038	IL6ST - TNFRSF10B	1149	510	1603
IL8 - TNFRSF10B	1494	1467	2312	IL8 - TNFRSF10B	1769	1763	196
IL10RB - TNFRSF10B	461	1770	1497	IL10RB - TNFRSF10B	1212	994	1542
IL15 - TNFRSF10B	360	1028	620	IL15 - TNFRSF10B	1712	815	2039
IL15RA - TNFRSF10B	2330	932	1932	IL15RA - TNFRSF10B	1640	1375	2210
IL17C - TNFRSF10B	557	1911	91	IL17C - TNFRSF10B	1594	969	1624
IL17REL - TNFRSF10B	457	1701	2422	IL17REL - TNFRSF10B	1074	2117	347
Ranking of IL family w.r.t TNFRSF10D	laplace	linear	rbf	**Ranking of TNFRSF10D w.r.t IL family**	laplace	linear	rbf
IL1A - TNFRSF10D	143	625	21	IL1A - TNFRSF10D	2415	2517	1894
IL1B - TNFRSF10D	185	142	191	IL1B - TNFRSF10D	2513	2300	2430
IL1RAP - TNFRSF10D	1106	1750	1376	IL1RAP - TNFRSF10D	811	1241	1946
IL1RN - TNFRSF10D	881	520	337	IL1RN - TNFRSF10D	2512	1658	857
IL2RG - TNFRSF10D	713	413	905	IL2RG - TNFRSF10D	2514	2419	2043
IL6ST - TNFRSF10D	752	2009	1617	IL6ST - TNFRSF10D	2324	2515	460
IL8 - TNFRSF10D	1267	903	629	IL8 - TNFRSF10D	463	446	2468
IL10RB - TNFRSF10D	1072	1050	1031	IL10RB - TNFRSF10D	1822	1959	982
IL15 - TNFRSF10D	108	842	333	IL15 - TNFRSF10D	2490	2234	2019
IL15RA - TNFRSF10D	2197	943	2126	IL15RA - TNFRSF10D	1895	1048	24
IL17C - TNFRSF10D	11	268	7	IL17C - TNFRSF10D	2493	2062	2488
IL17REL - TNFRSF10D	54	638	278	IL17REL - TNFRSF10D	2514	100	2452
Ranking of IL family w.r.t TNFRSF12A	laplace	linear	rbf	**Ranking of TNFRSF12A w.r.t IL family**	laplace	linear	rbf
IL1A - TNFRSF12A	52	2189	374	IL1A - TNFRSF12A	239	2080	1330
IL1B - TNFRSF12A	709	1592	1066	IL1B - TNFRSF12A	1422	516	1025
IL1RAP - TNFRSF12A	606	1030	1639	IL1RAP - TNFRSF12A	165	1595	1273
IL1RN - TNFRSF12A	122	1173	1182	IL1RN - TNFRSF12A	2176	529	1135
IL2RG - TNFRSF12A	206	1875	756	IL2RG - TNFRSF12A	1705	1060	2416
IL6ST - TNFRSF12A	2128	898	1092	IL6ST - TNFRSF12A	707	2213	2187
IL8 - TNFRSF12A	1132	1827	2355	IL8 - TNFRSF12A	461	1199	1587
IL10RB - TNFRSF12A	51	37	238	IL10RB - TNFRSF12A	852	781	910
IL15 - TNFRSF12A	281	1535	686	IL15 - TNFRSF12A	1984	1469	530
IL15RA - TNFRSF12A	2138	2090	1981	IL15RA - TNFRSF12A	1065	576	1568
IL17C - TNFRSF12A	326	2512	52	IL17C - TNFRSF12A	1497	1898	2209
IL17REL - TNFRSF12A	2475	587	2496	IL17REL - TNFRSF12A	148	1299	410
Ranking of IL family w.r.t TNFRSF14	laplace	linear	rbf	**Ranking of TNFRSF14 w.r.t IL family**	laplace	linear	rbf
IL1A - TNFRSF14	208	29	683	IL1A - TNFRSF14	2061	1969	693
IL1B - TNFRSF14	70	664	924	IL1B - TNFRSF14	592	1647	1743
IL1RAP - TNFRSF14	1356	2249	756	IL1RAP - TNFRSF14	2103	1414	1691
IL1RN - TNFRSF14	1001	794	745	IL1RN - TNFRSF14	1898	2414	975
IL2RG - TNFRSF14	1619	1780	1158	IL2RG - TNFRSF14	2009	1949	1367
IL6ST - TNFRSF14	2248	221	619	IL6ST - TNFRSF14	1033	1923	2175
IL8 - TNFRSF14	517	299	1301	IL8 - TNFRSF14	1776	578	2205
IL10RB - TNFRSF14	1595	156	943	IL10RB - TNFRSF14	763	1457	834
IL15 - TNFRSF14	1265	550	1692	IL15 - TNFRSF14	2039	954	1230
IL15RA - TNFRSF14	2378	1929	1577	IL15RA - TNFRSF14	2440	2031	253
IL17C - TNFRSF14	11	40	605	IL17C - TNFRSF14	1856	1836	671
IL17REL - TNFRSF14	46	306	293	IL17REL - TNFRSF14	2312	72	1623

Table 106 2^{nd} order combinatorial hypotheses between IL and TNF

the rankings of 2415 (laplace), 2517 (linear) and 1894 (rbf) for IL1A - TNFRSF10D; 2513 (laplace), 2300 (linear) and 2430 (rbf) for IL1B - TNFRSF10D; 2514 (laplace), 2419 (linear) and 2043 (rbf) for IL2RG - TNFRSF10D; 2324 (laplace), 2515 (linear) for IL6ST - TNFRSF10D; 1822 (laplace), 1959 (linear) for IL10RB - TNFRSF10D; 2490 (laplace), 2234 (linear) and 2019(rbf) for IL15 - TNFRSF10D; 2493 (laplace), 2062 (linear) and 2488 (rbf) for IL17C - TNFRSF10D; and 2514 (laplace) and 2452 (rbf) for IL17REL - TNFRSF10D. **TNFRSF12A** was up regulated w.r.t IL-16ST/17C. These are reflected in the rankings of 2213 (linear) and 2187 (rbf) for IL6ST - TNFRSF12A; and 1898 (linear) and 2209 (rbf) for IL17C - TNFRSF12A; **TNFRSF14** was up regulated w.r.t IL-1A/1RN/2RG/6ST/8/15RA/17C. These are reflected in the rankings of 2061 (laplace) and 1969 (linear) for IL1A - TN-

Ranking Interleukin family vs TNF family

Ranking of IL family w.r.t TNFRSF21				Ranking of TNFRSF21 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TNFRSF21	904	2313	1127	IL1A - TNFRSF21	322	1745	688
IL1B - TNFRSF21	1862	2164	2305	IL1B - TNFRSF21	1336	157	829
IL1RAP - TNFRSF21	1446	1762	2163	IL1RAP - TNFRSF21	563	22	497
IL1RN - TNFRSF21	1593	2373	627	IL1RN - TNFRSF21	1626	1341	320
IL2RG - TNFRSF21	403	2297	2351	IL2RG - TNFRSF21	618	719	981
IL6ST - TNFRSF21	1372	1894	753	IL6ST - TNFRSF21	2019	1123	1143
IL8 - TNFRSF21	1204	1944	1585	IL8 - TNFRSF21	2493	999	1513
IL10RB - TNFRSF21	238	845	1081	IL10RB - TNFRSF21	2502	842	1641
IL15 - TNFRSF21	1591	1905	1740	IL15 - TNFRSF21	65	1459	96
IL15RA - TNFRSF21	421	1934	1269	IL15RA - TNFRSF21	98	1109	1259
IL17C - TNFRSF21	2130	1039	1676	IL17C - TNFRSF21	2272	1163	266
IL17REL - TNFRSF21	557	765	61	IL17REL - TNFRSF21	1846	704	2381
Ranking of IL family w.r.t TNFRS10				Ranking of TNFRS10 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TNFSF10	120	1575	2499	IL1A - TNFSF10	2369	1086	1034
IL1B - TNFSF10	972	2448	1993	IL1B - TNFSF10	2348	1544	1076
IL1RAP - TNFSF10	754	1045	2015	IL1RAP - TNFSF10	1613	2470	966
IL1RN - TNFSF10	740	1535	570	IL1RN - TNFSF10	1035	75	1074
IL2RG - TNFSF10	2272	1447	1285	IL2RG - TNFSF10	1032	882	1271
IL6ST - TNFSF10	1978	227	778	IL6ST - TNFSF10	1647	1602	2369
IL8 - TNFSF10	818	1702	791	IL8 - TNFSF10	1161	790	2265
IL10RB - TNFSF10	744	1146	2257	IL10RB - TNFSF10	1496	2252	1864
IL15 - TNFSF10	967	1382	1910	IL15 - TNFSF10	1400	1383	486
IL15RA - TNFSF10	346	2163	2059	IL15RA - TNFSF10	1458	790	1428
IL17C - TNFSF10	460	2337	2431	IL17C - TNFSF10	558	1004	942
IL17REL - TNFSF10	1728	145	989	IL17REL - TNFSF10	1664	718	250
Ranking of IL family w.r.t TNFRS15				Ranking of TNFRS15 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - TNFSF15	1177	2494	979	IL1A - TNFSF15	1014	613	1449
IL1B - TNFSF15	1435	1529	1571	IL1B - TNFSF15	1898	1032	767
IL1RAP - TNFSF15	271	1665	2368	IL1RAP - TNFSF15	890	843	793
IL1RN - TNFSF15	2319	377	566	IL1RN - TNFSF15	414	1457	1704
IL2RG - TNFSF15	316	874	487	IL2RG - TNFSF15	2332	1362	1632
IL6ST - TNFSF15	1834	1004	1471	IL6ST - TNFSF15	771	1171	1445
IL8 - TNFSF15	1266	1571	1141	IL8 - TNFSF15	2422	515	966
IL10RB - TNFSF15	1488	326	1367	IL10RB - TNFSF15	1611	2041	1635
IL15 - TNFSF15	1356	1508	737	IL15 - TNFSF15	201	1922	1756
IL15RA - TNFSF15	2124	956	2365	IL15RA - TNFSF15	1551	668	864
IL17C - TNFSF15	2222	2328	954	IL17C - TNFSF15	2403	1049	1338
IL17REL - TNFSF15	1214	177	208	IL17REL - TNFSF15	513	1515	1943

Table 107 2^{nd} order combinatorial hypotheses between IL and TNF

FRSF14; 1898 (laplace) and 2414 (linear) for IL1RN - TNFRSF14; 2009 (laplace) and 1949 (linear) for IL2RG - TNFRSF14; 1923 (linear) and 2175 (rbf) for IL6ST - TNFRSF14; 1776 (laplace) and 2205 (rbf) for IL8 - TNFRSF14; 2440 (laplace) and 2031 (linear) for IL15RA - TNFRSF14; and 1856 (laplace) and 1836 (linear) for IL17C - TNFRSF14. **TNFRSF21** was up regulated w.r.t IL-17REL. This is reflected in the rankings of 1846 (laplace) and 2381 (rbf) for IL17REL - TNFRSF21; **TNFRSF10** was up regulated w.r.t IL-10RB. This is reflected in the rankings 2252 (linear) and 1864 (rbf) of IL10RB - TNFSF10; **TNFRSF15** was up regulated w.r.t IL-15. This is reflected in the rankings of 1922 (linear) and 1756 (rbf) for IL15 - TNFSF15.

Finally, table 108 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t TNF with IL-1RAP/6ST/15RA <- TNF; IL-1B/2RG/15RA/17C <- TNFAIP1; IL-1RN/10RB <- TNFAIP2; IL-6ST/8/17REL <- TNFAIP3; IL-1RAP <- TNFRSF1A; IL-1RAP/15RA/17REL <- TNFRSF10A; IL-15RA <- TNFRSF10B; IL-15RA <- TNFRSF10D; IL-8/15RA/17REL <- TNFRSF12A; IL-15RA <- TNFRSF14; IL-1B/1RAP/2RG <- TNFRSF21; IL-1B/15RA/17C <- TNFSF10 andIL-17C <- TNFSF15;and • TNF w.r.t IL with IL-6ST/10RB

Unexplored combinatorial hypotheses

IL w.r.t TNF	
IL-1RAP/6ST/15RA	TNF
IL-1B/2RG/15RA/17C	TNFAIP1
IL-1RN/10RB	TNFAIP2
IL-6ST/8/17REL	TNFAIP3
IL-1RAP	TNFRSF1A
IL-1RAP/15RA/17REL	TNFRSF10A
IL-15RA	TNFRSF10B
IL-15RA	TNFRSF10D
IL-8/15RA/17REL	TNFRSF12A
IL-15RA	TNFRSF14
IL-1B/1RAP/2RG	TNFRSF21
IL-1B/15RA/17C	TNFSF10
IL-17C	TNFSF15
TNF w.r.t IL	
IL-6ST/10RB	TNF
IL-8/15RA	TNFAIP1
IL-1B	TNFRSF1A
IL-1A/1B/1RN/2RG/6ST/15/15RA/17C	TNFRSF10A
IL-1RN	TNFRSF10B
IL-1A/1B/2RG/6ST/10RB/15/17C/17REL	TNFRSF10D
IL-6ST/17C	TNFRSF12A
IL-1A/1RN/2RG/6ST/8/15RA/17C/17REL	TNFRSF14
IL-17REL	TNFRSF14
IL10RB	TNFSF10
IL15	TNFSF15

Table 108 2^{nd} order combinatorial hypotheses between IL and TNF family.

-> TNF; IL-8/15RA -> TNFAIP1; IL-1B -> TNFRSF1A; IL-1A/1B/1RN/2RG/6ST/15/15RA/17C -> TNFRSF10A; IL-1RN -> TNFRSF10B; IL-1A/1B/2RG/6ST/10RB/15/17C/17REL -> TNFRSF10D; IL-6ST/17C -> TNFRSF12A; IL-1A/1RN/2RG/6ST/8/15RA/17C/17REL -> TNFRSF14; IL-17REL -> TNFRSF14; IL10RB -> TNFSF10; and IL15 -> TNFSF15;

2.8 BCL related synergies

2.8.1 Interleukin - BCL cross family analysis

Qin *et al.*[210] observe that IL-6 inhibits starvation-induced autophagy via the STAT3/Bcl-2 signaling pathway. Gabellini *et al.*[211] observed that interleukin 8 mediates bcl-xL-induced enhancement of human melanoma cell dissemination and angiogenesis in a zebrafish xenograft model. Guruprasath *et al.*[212] show taht interleukin-4 receptor-targeted delivery of Bcl-xL siRNA sensitizes tumors to chemotherapy and inhibits tumor growth. Maraskovsky *et al.*[213] indicate that Bcl-2 can rescue T lymphocyte development in interleukin-7 receptor-deficient mice but not in mutant rag-$1^{-/-}$ mice. Akashi *et al.*[214] show that Bcl-2 rescues T lymphopoiesis in interleukin-7 receptor-deficient mice. Interleukin-10 increases Bcl-2 expression and survival in primary human CD34+ hematopoietic progenitor cells as shown by Weber-Nordt *et al.*[215]. Interleukin-7 and interleukin-15 regulate the expression of thebcl-2 and c-myb genes in cutaneous T-cell lymphoma cells as shown by Qin *et al.*[216]. Bcl-2 is a negative regulator of interleukin-1β secretion in murine macrophages in pharmacological-induced apoptosis as shown by Escandell *et al.*[217]. Alas *et al.*[218] observe that inhibition of interleukin 10 by rituximab results in down-regulation of bcl-2 and sensitization of B-cell non-HodgkinâĂŹs lymphoma to apoptosis. These findings indicate the synergy between BCL and Interleukin in different pathological cases. In CRC cells treated with ETC-1922159, these were found to be up regulated. Tables 109 and 110 indicate the rankings of the IL and BCL family.

On the left side is the rankings of IL w.r.t BCL family and the right side, the vice versa. We found **IL-1A/1B/17C** up regulated w.r.t BCL2L1. These are reflected in rankings of 2482 (laplace) and 1834 (rbf) for IL1A - BCL2L1; 2252 (laplace), 1920 (linear) for IL1B - BCL2L1; and 2481 (laplace), 2410 (linear) and 2512 (rbf) for IL17C - BCL2L1; **IL-6ST/17REL** were up regulated w.r.t BCL2L2. These are reflected in rankings of 2239 (laplace), 1927 (linear) and 2085 (rbf) for IL6ST - BCL2L2; and 2454 (laplace), 2510 (linear) and 2482 (rbf) for IL17REL - BCL2L2. **IL-17REL** were up regulated w.r.t BCL2L13. These are reflected in rankings of 2420 (laplace), 2419 (linear) and 2464 (rbf) for IL17REL - BCL2L13; **IL-6ST/15RA** were up regulated w.r.t BCL3. These are reflected in rankings of 1928 (laplace) and 2344 (rbf) for IL6ST - BCL3; and 2478 (laplace), 1820 (linear) and 2500 (rbf) for IL15RA - BCL3; **IL-1RAP/6ST/8/17REL** were up regulated w.r.t BCL6. These are reflected in rankings of 2360 (linear) and 1813 (rbf) for IL1RAP - BCL6; 2419 (laplace) and 1962 (rbf) for IL6ST - BCL6; 2363 (laplace) and 2233 (linear) for IL8 - BCL6; and 2253 (laplace) and 2396 (linear) for IL17REL - BCL6; **IL-1A/6ST/8/17REL** were up regulated w.r.t BCL9L. These are reflected in rankings of 1932 (laplace) and 1942 (linear) for IL1A - BCL9L; 2249 (laplace) and 1960 (linear) for IL6ST - BCL9L; 2197 (linear) and 2162 (rbf) for IL8 - BCL9L; and 2308 (linear) and 1926 (rbf) for IL17REL - BCL9L; **IL-6ST/15RA** were up regulated w.r.t BCL10. These are reflected in rankings of 2008 (laplace) and 1816 (rbf) for IL6ST - BCL10; and 2064 (linear) and 1789 (rbf) for IL15RA - BCL10;

On the right side is the rankings of BCL w.r.t IL family. We found **BCL2L1** up regulated IL-1B/2RG/10RB. These are reflected in rankings of 1838 (laplace) and 2132 (rbf) for IL1B - BCL2L1; 2048 (laplace) and 1949 (rbf) for IL2RG - BCL2L1; and 1965 (linear) and 2024 (rbf) for IL10RB - BCL2L1; **BCL2L2** was up regulated IL-1A/1B/1RN/6ST/8/15/17C. These are reflected in

Ranking IL family vs BCL family

Ranking of IL family w.r.t BCL2L1	laplace	linear	rbf	Ranking of BCL2L1 w.r.t IL family	laplace	linear	rbf
IL1A - BCL2L1	2482	859	1834	IL1A - BCL2L1	780	1156	1712
IL1B - BCL2L1	2252	1920	1482	IL1B - BCL2L1	1838	954	2132
IL1RAP - BCL2L1	1128	815	1935	IL1RAP - BCL2L1	870	1777	1262
IL1RN - BCL2L1	648	2504	650	IL1RN - BCL2L1	973	385	1297
IL2RG - BCL2L1	1542	1439	700	IL2RG - BCL2L1	2048	486	1949
IL6ST - BCL2L1	663	553	1432	IL6ST - BCL2L1	284	674	468
IL8 - BCL2L1	260	202	2070	IL8 - BCL2L1	1430	1343	1417
IL10RB - BCL2L1	1867	347	17	IL10RB - BCL2L1	1659	1965	2024
IL15 - BCL2L1	1558	775	381	IL15 - BCL2L1	690	542	1277
IL15RA - BCL2L1	2136	1177	1533	IL15RA - BCL2L1	581	1107	972
IL17C - BCL2L1	2481	2410	2512	IL17C - BCL2L1	695	1739	1775
IL17REL - BCL2L1	815	657	374	IL17REL - BCL2L1	981	1225	509
Ranking of IL family w.r.t BCL2L2	laplace	linear	rbf	Ranking of BCL2L2 w.r.t IL family	laplace	linear	rbf
IL1A - BCL2L2	138	361	86	IL1A - BCL2L2	2407	2362	2464
IL1B - BCL2L2	165	389	108	IL1B - BCL2L2	1807	2462	2344
IL1RAP - BCL2L2	623	1523	861	IL1RAP - BCL2L2	77	1897	1711
IL1RN - BCL2L2	2324	530	984	IL1RN - BCL2L2	2298	1620	2092
IL2RG - BCL2L2	2137	285	347	IL2RG - BCL2L2	2429	850	1744
IL6ST - BCL2L2	2239	1927	2085	IL6ST - BCL2L2	477	2046	1859
IL8 - BCL2L2	894	1418	1346	IL8 - BCL2L2	1803	1072	2024
IL10RB - BCL2L2	2243	738	1020	IL10RB - BCL2L2	1041	145	843
IL15 - BCL2L2	110	650	1347	IL15 - BCL2L2	2474	2142	2416
IL15RA - BCL2L2	258	1715	361	IL15RA - BCL2L2	1377	1211	2298
IL17C - BCL2L2	554	12	147	IL17C - BCL2L2	1168	2512	2447
IL17REL - BCL2L2	2454	2510	2482	IL17REL - BCL2L2	539	1875	1442
Ranking of IL family w.r.t BCL2L13	laplace	linear	rbf	Ranking of BCL2L13 w.r.t IL family	laplace	linear	rbf
IL1A - BCL2L13	1572	458	174	IL1A - BCL2L13	1456	811	2403
IL1B - BCL2L13	927	227	424	IL1B - BCL2L13	1286	1446	2348
IL1RAP - BCL2L13	278	718	1941	IL1RAP - BCL2L13	823	2450	2510
IL1RN - BCL2L13	608	1277	881	IL1RN - BCL2L13	2503	623	2378
IL2RG - BCL2L13	507	1182	5	IL2RG - BCL2L13	2483	1648	2248
IL6ST - BCL2L13	1778	1403	246	IL6ST - BCL2L13	1899	2473	2046
IL8 - BCL2L13	178	468	1606	IL8 - BCL2L13	2099	910	2294
IL10RB - BCL2L13	991	1211	804	IL10RB - BCL2L13	2120	1895	194
IL15 - BCL2L13	1868	432	15	IL15 - BCL2L13	2515	2160	2420
IL15RA - BCL2L13	1629	2134	685	IL15RA - BCL2L13	933	1844	2318
IL17C - BCL2L13	995	84	20	IL17C - BCL2L13	2004	2434	2500
IL17REL - BCL2L13	2420	2419	2464	IL17REL - BCL2L13	1490	760	442
Ranking of IL family w.r.t BCL3	laplace	linear	rbf	Ranking of BCL3 w.r.t IL family	laplace	linear	rbf
IL1A - BCL3	880	2462	396	IL1A - BCL3	474	436	1045
IL1B - BCL3	975	1507	40	IL1B - BCL3	799	303	926
IL1RAP - BCL3	1425	821	1129	IL1RAP - BCL3	44	164	1115
IL1RN - BCL3	149	471	311	IL1RN - BCL3	37	1784	477
IL2RG - BCL3	454	365	505	IL2RG - BCL3	524	2060	335
IL6ST - BCL3	1928	755	2344	IL6ST - BCL3	316	1457	607
IL8 - BCL3	1052	743	2044	IL8 - BCL3	2266	1236	1983
IL10RB - BCL3	95	800	1625	IL10RB - BCL3	2187	1600	2170
IL15 - BCL3	1041	820	214	IL15 - BCL3	17	966	182
IL15RA - BCL3	2478	1820	2500	IL15RA - BCL3	462	1476	1100
IL17C - BCL3	737	1682	8	IL17C - BCL3	1069	923	1926
IL17REL - BCL3	218	424	2019	IL17REL - BCL3	692	1897	1274

Table 109 2^{nd} order combinatorial hypotheses between BCL and IL

rankings of 2407 (laplace), 2362 (linear) and 2464 (rbf) for IL1A - BCL2L2; 1807 (laplace), 2462 (linear) and 2344 (rbf) for IL1B - BCL2L2; 2298 (laplace) and 2092 (rbf) for IL1RN - BCL2L2; 2046 (linear) and 1859 (rbf) for IL6ST - BCL2L2; 1803 (laplace) and 2024 (rbf) for IL8 - BCL2L2; 2474 (laplace), 2142 (linear) and 2416 (rbf) for IL15 - BCL2L2; and 2512 (linear) and 2447 (rbf) for IL17C - BCL2L2; **BCL2L13** was up regulated IL-1RAP/1RN/2RG/6ST/8/10RB/15/15RA/17C. These are reflected in rankings of 2450 (linear) and 2510 (rbf) for IL1RAP - BCL2L13; 2503 (laplace) and 2378 (rbf) for IL1RN - BCL2L13; 2483 (laplace) and 2248 (rbf) for IL2RG - BCL2L13; 1899 (laplace), 2473 (linear) and 2046 (rbf) for IL6ST - BCL2L13;

Ranking IL family vs BCL family

Ranking of IL family w.r.t BCL6				Ranking of BCL6 w.r.t IL family			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL6	157	5	1029	IL1A - BCL6	1034	2503	1669
IL1B - BCL6	274	767	1904	IL1B - BCL6	2298	2423	2294
IL1RAP - BCL6	1021	2360	1813	IL1RAP - BCL6	2403	1289	777
IL1RN - BCL6	2015	366	506	IL1RN - BCL6	1919	2301	1680
IL2RG - BCL6	425	553	480	IL2RG - BCL6	1389	2106	2478
IL6ST - BCL6	2419	1589	1962	IL6ST - BCL6	92	184	1752
IL8 - BCL6	2363	2233	1343	IL8 - BCL6	2123	2068	181
IL10RB - BCL6	853	383	1983	IL10RB - BCL6	847	1980	1186
IL15 - BCL6	500	397	1767	IL15 - BCL6	1297	1925	1014
IL15RA - BCL6	1686	1432	2269	IL15RA - BCL6	2084	1791	2203
IL17C - BCL6	227	255	2412	IL17C - BCL6	1349	1499	1321
IL17REL - BCL6	2253	2396	63	IL17REL - BCL6	38	1949	1930
Ranking of IL family w.r.t BCL9L				**Ranking of BCL9L w.r.t IL family**			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL9L	1932	1942	210	IL1A - BCL9L	1620	1559	986
IL1B - BCL9L	1966	88	79	IL1B - BCL9L	361	1449	2484
IL1RAP - BCL9L	218	957	881	IL1RAP - BCL9L	984	623	1689
IL1RN - BCL9L	1629	937	132	IL1RN - BCL9L	689	55	1593
IL2RG - BCL9L	415	104	92	IL2RG - BCL9L	2113	892	567
IL6ST - BCL9L	2249	1960	1142	IL6ST - BCL9L	1718	1210	737
IL8 - BCL9L	814	2197	2162	IL8 - BCL9L	1679	1920	933
IL10RB - BCL9L	743	632	660	IL10RB - BCL9L	1631	717	1236
IL15 - BCL9L	1343	279	280	IL15 - BCL9L	568	1068	1794
IL15RA - BCL9L	1714	111	1279	IL15RA - BCL9L	206	951	251
IL17C - BCL9L	2029	196	94	IL17C - BCL9L	1031	573	1870
IL17REL - BCL9L	128	2308	1926	IL17REL - BCL9L	1214	1341	839
Ranking of IL family w.r.t BCL10				**Ranking of BCL10 w.r.t IL family**			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL10	5	1720	506	IL1A - BCL10	513	2405	1889
IL1B - BCL10	201	2404	803	IL1B - BCL10	2100	432	1251
IL1RAP - BCL10	1597	598	1869	IL1RAP - BCL10	1929	499	2112
IL1RN - BCL10	107	724	126	IL1RN - BCL10	1846	1823	209
IL2RG - BCL10	232	665	650	IL2RG - BCL10	1885	1803	1577
IL6ST - BCL10	2008	1698	1816	IL6ST - BCL10	451	71	337
IL8 - BCL10	1614	719	1555	IL8 - BCL10	204	1653	544
IL10RB - BCL10	2009	466	1053	IL10RB - BCL10	2244	2150	1578
IL15 - BCL10	35	2072	580	IL15 - BCL10	2174	1618	1375
IL15RA - BCL10	1477	2064	1789	IL15RA - BCL10	1810	1656	1835
IL17C - BCL10	8	2009	1232	IL17C - BCL10	705	1777	207
IL17REL - BCL10	2397	89	550	IL17REL - BCL10	839	1214	377

Table 110 2^{nd} order combinatorial hypotheses between BCL and IL

2099 (laplace) and 2294 (rbf) for IL8 - BCL2L13; 2120 (laplace) and 1895 (linear) for IL10RB - BCL2L13; 2515 (laplace), 2160 (linear) and 2420 (rbf) for IL15 - BCL2L13; 1844 (linear) and 2318 (rbf) for IL15RA - BCL2L13; and 2004 (laplace), 2434 (linear) and 2500 (rbf) for IL17C - BCL2L13; **BCL3** was up regulated IL-8/10RB. These are reflected in rankings of 2266 (laplace) and 1983 (rbf) for IL8 - BCL3; and 2187 (laplace) and 2170 (rbf) for IL10RB - BCL3; 2298 (laplace); 2423 (linear) and 2294 (rbf) for IL1B - BCL6; 1919 (laplace) and 2301 (linear) for IL1RN - BCL6; 2106 (linear) and 2478 (rbf) for IL2RG - BCL6; 2123 (laplace), 2068 (linear) for IL8 - BCL6; 2084 (laplace), 1791 (linear) and 2203 (rbf) for IL15RA - BCL6; and for 1949 (linear) and 1930 (rbf) for IL17REL - BCL6; **BCL10** was up regulated IL-1A/1RAP/1RN/2RG/10RB/15RA. These are reflected in rankings of 2405 (linear) and 1889 (rbf) for IL1A - BCL10; 1929 (laplace) and 2112 (rbf) for IL1RAP - BCL10; 1846 (laplace) and 1823 (linear) for IL1RN - BCL10; 1885 (laplace) and 1803 (linear) for IL2RG - BCL10; 2244 (laplace) and 2150 (linear) for IL10RB - BCL10; and 1810 (laplace) and 1835 (rbf) for IL15RA - BCL10;

Unexplored combinatorial hypotheses

IL w.r.t BCL	
IL-1A/1B/17C	BCL2L1
IL-6ST/17REL	BCL2L2
IL-17REL	BCL2L13
IL-6ST/15RA	BCL3
IL-1RAP/6ST/8/17REL	BCL6
IL-1A/6ST/8/17REL	BCL9L
IL-6ST/15RA	BCL10
BCL w.r.t IL	
IL-1B/2RG/10RB	BCL2L1
IL-1A/1B/1RN/6ST/8/15/17C	BCL2L2
IL-1RAP/1RN/2RG/6ST/8/10RB/15/15RA/17C	BCL2L13
IL-8/10RB	BCL3
IL-1B/1RN/2RG/8/15RA/17REL	BCL6
IL-1A/1RAP/1RN/2RG/10RB/15RA	BCL10

Table 111 2^{nd} order combinatorial hypotheses between IL and BCL family.

Finally, table 111 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t BCL with IL-1A/1B/17C <- BCL2L1; IL-6ST/17REL <- BCL2L2; IL-17REL <- BCL2L13; IL-6ST/15RA <- BCL3; IL-1RAP/6ST/8/17REL <- BCL6; IL-1A/6ST/8/17REL <- BCL9L; and IL-6ST/15RA <- BCL10; • BCL w.r.t IL with IL-1B/2RG/10RB -> BCL2L1; IL-1A/1B/1RN/6ST/8/15/17C -> BCL2L2; IL-1RAP/1RN/2RG/6ST/8/10RB/15/15RA/17C -> BCL2L13; IL-8/10RB -> BCL3; IL-1B/1RN/2RG/8/15RA/17REL -> BCL6; and IL-1A/1RAP/1RN/2RG/10RB/15RA -> BCL10;

2.8.2 Selenbp1 - BCL cross family analysis

Deng *et al.*[219] study the effects of selenium on lead-induced alterations in Aβ production and Bcl-2 family proteins. Yaming *et al.*[220] studied the effects of selenium dioxide on apoptosis, Bcl-2 and p53 expression, intracellular reactive oxygen species and calcium level in three human lung cancer cell lines. Activity of selenium on cell proliferation, cytotoxicity, and apoptosis and on the expression of CASP9, BCL-XL and APC in intestinal adenocarcinoma cells has been studied by Mauro *et al.*[221]. These studies suggest the synergy between BCL and Selenium based genes. In CRC cells treated with ETC-1922159, these were found to be down regulated. Table 112 shows the rankings of BCL family w.r.t to SELENBP1 and vice versa.

On the right side, we found **BCL-6B/11A** to be up regulated with respect to SELENBP1. These were reflected in the rankings of 182 (laplace), 110 (linear) and 494 (rbf) for SELENBP1 - BCL6B; and 905 (laplace), 931 (linear) and 401 (rbf) for SELENBP1 - BCL11A. On the left side **SELENBP1** was up regulated w.r.t BCL-9/11B. These are reflected in rankings of 1568 (linear)

Ranking SELENBP1 vs BCL family							
Ranking of BCL family w.r.t SELENBP1				Ranking of SELENBP1 w.r.t BCL			
	laplace	linear	rbf		laplace	linear	rbf
SELENBP1 - BCL2L12	2426	2033	2629	SELENBP1 - BCL2L12	2589	2195	2082
SELENBP1 - BCL6B	2446	2575	1956	SELENBP1 - BCL6B	182	110	494
SELENBP1 - BCL7A	2620	1326	2006	SELENBP1 - BCL7A	2015	1799	767
SELENBP1 - BCL9	2453	1568	1738	SELENBP1 - BCL9	2538	1916	1793
SELENBP1 - BCL11A	1921	2463	1566	SELENBP1 - BCL11A	905	931	401
SELENBP1 - BCL11B	1896	299	1385	SELENBP1 - BCL11B	2496	2636	2510

Table 112 2^{nd} order combinatorial hypotheses between BCL and SELENBP1

Unexplored combinatorial hypotheses	
SELENBP1 w.r.t BCL	
SELENBP1	BCL-9/11B
BCL w.r.t SELENBP1	
SELENBP1	BCL-6B/11A

Table 113 2^{nd} order combinatorial hypotheses between SELENBP1 and BCL family.

and 1738 (rbf) for SELENBP1 - BCL9; and 299 (linear) and 1385 (rbf) for SELENBP1 - BCL11B; Finally, table 113 shows the derived influences which can be represented graphically, with the following influences - • SELENBP1 w.r.t BCL with SELENBP1 <- BCL-9/11B; and • BCL w.r.t SELENBP1 with SELENBP1 -> BCL-6B/11A;

2.8.3 TP53 - BCL cross family analysis

The p53-Bcl-2 connection has been studied by Hemann and Lowe[222]. Tomita *et al.*[223] show wild type p53, but not tumor-derived mutants, bind to Bcl2 via the DNA binding domain and induce mitochondrial permeabilization. Bcl-2 constitutively suppresses p53-dependent apoptosis in colorectal cancer cells as shown by Jiang and Milner[224]. The tissue dependent interactions between p53 and Bcl-2 in vivo has been studied by Li *et al.*[225]. Synthetic lethality of combined Bcl-2 inhibition and p53 activation in AML has been studied by Pan *et al.*[226]. Zaidi *et al.*[227] observe that the chloroquine-induced neuronal cell death is p53 and Bcl-2 family-dependent but caspase-independent. Relationship of p53, bcl-2, and tumor proliferation to clinical drug resistance in non-Hodgkin's lymphomas has been studied in Wilson *et al.*[228]. TP53 and BCL family members were found to be up regulated in CRC cells treated with ETC-1922159. Table 114 show rankings of BCL and TP53 family w.r.t to each other.

On the left side, we found **BCL2L2** to be up regulated w.r.t TP53-I3/INP2. These are reflected in the rankings of 2423 (laplace), 2377 (linear) and 2452 (rbf) for TP53I3 - BCL2L2; 1827 (linear) and 2035 (rbf) for TP53INP2 - BCL2L2. **BCL2L13** to be up regulated w.r.t TP53-INP2. These are reflected in the rankings of 2427 (linear) and 2008 (rbf) for TP53INP2 - BCL2L13; **BCL6** to be up regulated w.r.t TP53-I3/INP2. These are reflected in the rankings of 2275 (laplace), 2312 (linear) and 2146 (rbf) for TP53I3 - BCL6; and 2329 (linear) and 2352 (rbf) for TP53INP2 - BCL6; **BCL9L** to be up regulated w.r.t TP53-BP2. These are reflected in the rankings of 2320 (linear) and 2197 (rbf) for TP53BP2 - BCL9L; **BCL10** to be up regulated w.r.t TP53-BP2/INP2. These are reflected in the rankings of 2230 (laplace) and 2418 (linear) for TP53BP2 - BCL10 and 1910 (linear) and 2087 (rbf) for TP53INP2 - BCL10;

On the right side, we found **TP53-BP2/I3** to be up regulated w.r.t BCL2L1. These are reflected in the rankings of 1786 (laplace) and 1961 (linear) for TP53BP2 - BCL2L1; 1980 (laplace) and 1752 (linear) for TP53I3 - BCL2L1; **TP53-INP1** were up regulated w.r.t BCL3. These are reflected in the rankings for 2259 (linear) and 2043 (rbf) for TP53INP1 - BCL3; **TP53-BP2/INP2** were up regulated w.r.t BCL9L. These are reflected in the rankings for 2093 (laplace) and 2217 (linear) for TP53BP2 - BCL9L; and 2222 (laplace) and 1900 (linear) for TP53INP2 - BCL9L;

Finally, table 115 shows the derived influences which can be represented graphically, with the following influences - • BCL w.r.t TP53 with TP53-I3/INP2 <- BCL2L2; TP53-INP2 <- BCL2L13; TP53-I3/INP2 <- BCL6; TP53-BP2 <- BCL9L; and TP53-BP2/INP2 <- BCL10; • TP53 w.r.t BCL with TP53-BP2/I3 <- BCL2L1; TP53-INP1 <- BCL3 and TP53-BP2/INP2 <- BCL9L.

2.8.4 CASP - BCL cross family analysis

Expression of caspase and BCL-2 apoptotic family members in mouse preimplantation embryos have been studied by Exley *et al.*[229]. Swanton *et al.*[230] observed that Bcl-2 regulates a caspase-3/caspase-2 apoptotic cascade in cytosolic extracts. Their role in the regulation of the immune response of Caspases, Bcl-2 family proteins and other components of the death machinery has been observed in Pellegrini and Strasser[231]. Moriishi *et al.*[232] show that Bcl-2 family members do not inhibit apoptosis by binding the caspase activator Apaf-1. In CRC cells treated with ETC-1922159, these families were found to be UP regulated. Table 116 shows rankings of CASP and BCL family.

On the left side, we found **BCL2L2** to be up regulated w.r.t CASP-10/16. These are reflected in the rankings of 2043 (linear) and 1809 (rbf) for CASP10 - BCL2L2; and 2263 (laplace) and 1863 (rbf) for CASP16 - BCL2L2; **BCL2L13** to be up regulated w.r.t CASP-4/5/16. These are reflected in the rankings of 1873 (laplace) and 2415 (rbf) for CASP4 - BCL2L13; 1962 (laplace), 2514 (linear) and 2493 (rbf) for CASP5 - BCL2L13; and 1762 (laplace), 2492 (linear) and 2166 (rbf) for CASP16 - BCL2L13; **BCL3** to be up regulated w.r.t CASP-10. These are reflected in the rankings of 2409 (laplace) and 2011 (linear) for CASP10 - BCL3; **BCL6** to be up regulated w.r.t CASP-5/16. These are reflected in

Ranking TP53 family vs BCL family

Ranking of BCL2L1 w.r.t TP53 family				Ranking of TP53 family w.r.t BCL2L1			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL2L1	2431	1529	1728	TP53BP2 - BCL2L1	1786	1961	1225
TP53I3 - BCL2L1	799	554	728	TP53I3 - BCL2L1	1980	1752	756
TP53INP1 - BCL2L1	1064	1154	1414	TP53INP1 - BCL2L1	1193	258	1850
TP53INP2 - BCL2L1	282	2371	851	TP53INP2 - BCL2L1	830	1477	1512
Ranking of BCL2L2 w.r.t TP53 family				Ranking of TP53 family w.r.t BCL2L2			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL2L2	1471	34	1367	TP53BP2 - BCL2L2	1076	2168	1658
TP53I3 - BCL2L2	2423	2377	2452	TP53I3 - BCL2L2	1911	245	378
TP53INP1 - BCL2L2	1693	180	987	TP53INP1 - BCL2L2	482	1653	1130
TP53INP2 - BCL2L2	1688	1827	2035	TP53INP2 - BCL2L2	85	376	1146
Ranking of BCL2L13 w.r.t TP53 family				Ranking of TP53 family w.r.t BCL2L13			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL2L13	1515	1261	1842	TP53BP2 - BCL2L13	1128	1827	1613
TP53I3 - BCL2L13	1264	1501	1963	TP53I3 - BCL2L13	419	1088	959
TP53INP1 - BCL2L13	759	387	205	TP53INP1 - BCL2L13	1550	1616	1245
TP53INP2 - BCL2L13	507	2427	2008	TP53INP2 - BCL2L13	1190	573	513
Ranking of BCL3 w.r.t TP53 family				Ranking of TP53 family w.r.t BCL3			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL3	1754	335	226	TP53BP2 - BCL3	1177	1625	423
TP53I3 - BCL3	388	392	25	TP53I3 - BCL3	921	1151	233
TP53INP1 - BCL3	2350	766	472	TP53INP1 - BCL3	1126	2259	2043
TP53INP2 - BCL3	266	1184	379	TP53INP2 - BCL3	325	609	726
Ranking of BCL6 w.r.t TP53 family				Ranking of TP53 family w.r.t BCL6			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL6	1172	1783	1120	TP53BP2 - BCL6	1667	1140	185
TP53I3 - BCL6	2275	2312	2146	TP53I3 - BCL6	979	71	859
TP53INP1 - BCL6	201	1818	1572	TP53INP1 - BCL6	1458	1200	2503
TP53INP2 - BCL6	1681	2329	2352	TP53INP2 - BCL6	346	833	1557
Ranking of BCL9L w.r.t TP53 family				Ranking of TP53 family w.r.t BCL9L			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL9L	263	2320	2197	TP53BP2 - BCL9L	2093	2217	1010
TP53I3 - BCL9L	819	635	789	TP53I3 - BCL9L	1249	927	107
TP53INP1 - BCL9L	2090	1740	1179	TP53INP1 - BCL9L	2113	854	1711
TP53INP2 - BCL9L	640	951	316	TP53INP2 - BCL9L	2222	1900	151
Ranking of BCL10 w.r.t TP53 family				Ranking of TP53 family w.r.t BCL10			
	laplace	linear	rbf		laplace	linear	rbf
TP53BP2 - BCL10	2230	2418	73	TP53BP2 - BCL10	493	1999	351
TP53I3 - BCL10	727	1159	1301	TP53I3 - BCL10	519	1572	446
TP53INP1 - BCL10	543	1223	1275	TP53INP1 - BCL10	1094	1120	1848
TP53INP2 - BCL10	632	1910	2087	TP53INP2 - BCL10	789	1566	848

Table 114 2^{nd} order combinatorial hypotheses between BCL and SELENBP1

Unexplored combinatorial hypotheses

BCL w.r.t TP53	
TP53-I3/INP2	BCL2L2
TP53-INP2	BCL2L13
TP53-I3/INP2	BCL6
TP53-BP2	BCL9L
TP53-BP2/INP2	BCL10
TP53 w.r.t BCL	
TP53-BP2/I3	BCL2L1
TP53-INP1	BCL3
TP53-BP2/INP2	BCL9L

Table 115 2^{nd} order combinatorial hypotheses between SELENBP1 and BCL family.

the rankings of 1787 (laplace), 2124 (linear) and 2309 (rbf) for CASP5 - BCL6; and 2397 (laplace), 2166 (linear) and 2387 (rbf) for CASP16 - BCL6.

On the right side, we found **CASP-5/7** to be up regulated w.r.t BCL2L1. These are reflected in the rankings of 1992 (laplace) and 2053 (linear) for CASP5 - BCL2L1; and 2203 (linear) and 1750 (rbf) for CASP7 - BCL2L1. **CASP-4/7** to be up regulated w.r.t BCL2L1. These are reflected in the rankings of 1902 (linear) and 1979 (rbf) for CASP4 - BCL2L13 and 1877 (laplace) and 2216 (rbf) for CASP7 - BCL2L13; **CASP-7/16** to be up regulated w.r.t BCL9L. These are reflected in the rankings of 1813 (laplace) and 1980 (rbf) for CASP7 - BCL9L; and 2499 (linear) and 2027 (rbf) for CASP16 - BCL9L; **CASP-7** to be up regulated w.r.t BCL10. These are reflected in the rankings of 2489 (laplace) and 1945 (rbf) for CASP7 - BCL10.

2.8.5 MUC - BCL cross family analysis

MUC1 and bcl-2 expression in preinvasive lesions and adenosquamous carcinoma of the lung have been studied by Demirag *et al.*[233]. Sheng *et al.*[234] report that MUC13 prevents colorectal cancer cell death by promoting two distinct pathways of NF-kB activation, consequently upregulating BCL-X_L. In CRC cells treated with ETC-1922159, family members of BCL and MUC were found up regulated. The search engine assigned high valued numerical ranks to some of the 2^{nd} order combinations of BCL-MUC family members. Table 118 show the rankings of the members with respect to each other.

On the left side, we found **BCL2L1** to be up regulated w.r.t MUC-1/13. These are reflected in the rankings of 2055 (laplace), 2297 (linear) and 1854 (rbf) for MUC1 - BCL2L1; and 1927 (laplace) and 2108 (rbf) for MUC13 - BCL2L1; **BCL2L2** was up regulated w.r.t MUC-4/13/17. These are reflected in the rankings of 2506 (linear) and 1988 (rbf) for MUC4 - BCL2L2; 2084 (laplace) and 2402 (linear) for MUC13 - BCL2L2; and 2283 (laplace) and 2212 (linear) for MUC17 - BCL2L2; **BCL2L13** was up regulated w.r.t MUC-1/12. These are reflected in the rankings of 2029 (laplace) and 2347 (linear) for MUC1 - BCL2L13; and 2353 (linear) and 1997 (rbf) for MUC12 - BCL2L13; **BCL3** was up regulated w.r.t MUC-20. These are reflected in the rankings of 2512 (laplace) and 2440 (rbf) for MUC20 - BCL3; **BCL6** was up regulated w.r.t MUC-17. These are reflected in the rankings of 2411(laplace), 2153 (linear) and 1808 (rbf) for MUC17 - BCL6; **BCL9L** was up regulated w.r.t MUC-17. These are reflected in the rankings of 2101 (laplace) and 2408 (rbf) for MUC20 - BCL9L.

On the right side, we found **MUC3A** to be up regulated w.r.t BCL2L2. These are reflected in the rankings of 2099 (laplace) and 2397 (rbf) for MUC3A - BCL2L2; **MUC3A** to be up regulated w.r.t BCL9L. These are reflected in the rankings of 2180 (linear) and 2106 (rbf) for MUC3A - BCL9L;

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Ranking CASP family vs BCL family

Ranking of BCL2L1 w.r.t CASP family	laplace	linear	rbf	Ranking of CASP family w.r.t BCL2L1	laplace	linear	rbf
CASP4 - BCL2L1	170	1441	1555	CASP4 - BCL2L1	355	1603	202
CASP5 - BCL2L1	1236	766	1261	CASP5 - BCL2L1	1992	2053	291
CASP7 - BCL2L1	2235	1161	1252	CASP7 - BCL2L1	657	2203	1750
CASP9 - BCL2L1	291	984	692	CASP9 - BCL2L1	833	1386	1855
CASP10 - BCL2L1	1162	2043	218	CASP10 - BCL2L1	721	2088	101
CASP16 - BCL2L1	239	34	305	CASP16 - BCL2L1	43	489	351
Ranking of BCL2L2 w.r.t CASP family				Ranking of CASP family w.r.t BCL2L2			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - BCL2L2	1144	1441	2348	CASP4 - BCL2L2	988	966	1400
CASP5 - BCL2L2	1896	766	914	CASP5 - BCL2L2	401	174	1136
CASP7 - BCL2L2	895	1161	1604	CASP7 - BCL2L2	2371	1352	1312
CASP9 - BCL2L2	1414	984	1933	CASP9 - BCL2L2	863	720	102
CASP10 - BCL2L2	1335	2043	1809	CASP10 - BCL2L2	1630	1912	884
CASP16 - BCL2L2	2263	34	1863	CASP16 - BCL2L2	2	151	114
Ranking of BCL2L13 w.r.t CASP family				Ranking of CASP family w.r.t BCL2L13			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - BCL2L13	1873	1096	2415	CASP4 - BCL2L13	1257	1902	1979
CASP5 - BCL2L13	1962	2514	2493	CASP5 - BCL2L13	1438	1376	664
CASP7 - BCL2L13	601	1195	756	CASP7 - BCL2L13	1877	1646	2216
CASP9 - BCL2L13	1592	2371	1376	CASP9 - BCL2L13	447	1618	844
CASP10 - BCL2L13	489	384	987	CASP10 - BCL2L13	1403	1048	354
CASP16 - BCL2L13	1762	2492	2166	CASP16 - BCL2L13	1927	376	510
Ranking of BCL3 w.r.t CASP family				Ranking of CASP family w.r.t BCL3			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - BCL3	18	844	1229	CASP4 - BCL3	335	172	1629
CASP5 - BCL3	728	953	1616	CASP5 - BCL3	343	498	628
CASP7 - BCL3	737	574	580	CASP7 - BCL3	1313	1804	1556
CASP9 - BCL3	1478	284	242	CASP9 - BCL3	2392	1123	1394
CASP10 - BCL3	2409	2011	1425	CASP10 - BCL3	156	838	1678
CASP16 - BCL3	868	103	715	CASP16 - BCL3	361	162	2505
Ranking of BCL6 w.r.t CASP family				Ranking of CASP family w.r.t BCL6			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - BCL6	1311	2266	1297	CASP4 - BCL6	27	507	944
CASP5 - BCL6	1787	2124	2309	CASP5 - BCL6	760	10	770
CASP7 - BCL6	996	1314	2322	CASP7 - BCL6	1478	1230	2366
CASP9 - BCL6	1022	824	2021	CASP9 - BCL6	1855	903	1296
CASP10 - BCL6	469	1559	1085	CASP10 - BCL6	591	787	1410
CASP16 - BCL6	2397	2166	2387	CASP16 - BCL6	1514	54	1881
Ranking of BCL9L w.r.t CASP family				Ranking of CASP family w.r.t BCL9L			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - BCL9L	578	897	325	CASP4 - BCL9L	1758	1346	1584
CASP5 - BCL9L	1075	791	1134	CASP5 - BCL9L	363	1731	632
CASP7 - BCL9L	2279	1347	632	CASP7 - BCL9L	1813	853	1980
CASP9 - BCL9L	98	1126	455	CASP9 - BCL9L	1472	717	940
CASP10 - BCL9L	24	841	2358	CASP10 - BCL9L	675	1449	699
CASP16 - BCL9L	591	666	233	CASP16 - BCL9L	12	2499	2027
Ranking of BCL10 w.r.t CASP family				Ranking of CASP family w.r.t BCL10			
	laplace	linear	rbf		laplace	linear	rbf
CASP4 - BCL10	1272	1457	619	CASP4 - BCL10	244	1637	426
CASP5 - BCL10	1732	1092	1293	CASP5 - BCL10	667	2488	522
CASP7 - BCL10	1448	1028	681	CASP7 - BCL10	2489	1516	1945
CASP9 - BCL10	612	553	205	CASP9 - BCL10	1644	1117	956
CASP10 - BCL10	2289	1694	1401	CASP10 - BCL10	664	917	84
CASP16 - BCL10	27	102	301	CASP16 - BCL10	2192	3	387

Table 116 2^{nd} order combinatorial hypotheses between BCL and SELENBP1

Unexplored combinatorial hypotheses

BCL w.r.t CASP	
CASP-10/16	BCL2L2
CASP-4/5/16	BCL2L13
CASP-10	BCL3
CASP-5/16	BCL6
CASP w.r.t BCL	
CASP-5/7	BCL2L1
CASP-4/7	BCL2L13
CASP-7/16	BCL9L
CASP-7	BCL10

Table 117 2^{nd} order combinatorial hypotheses between CASP and BCL family.

2.8.6 EXOSC - BCL cross family analysis

The exosome complex is involved in the degradation of various kinds of RNA. Recently, Deng *et al.*[235] observe that Exosome-transmitted LINC00461 promotes multiple myeloma cell proliferation and suppresses apoptosis by modulating microRNA/BCL-2 expression. Xu *et al.*[236] show that Exosome-derived microRNA-29c induces apoptosis of BIU-87 cells by down regulating BCL-2 and MCL-1. Exosomes were demonstrated to upregulate the expression of Bcl-2 and Cyclin D1 proteins, but reduce the levels of Bax and caspase-3 proteins in these cells in work of Yang *et al.*[237]. In western blot analysis results showed that exosomes can block the significant reduction of BCL-2, full-length caspase-3 and full-length PARP, while preventing the increase of BAX, cleaved caspase-3 and cleaved PARP induced by VP16, as studied by Wang *et al.*[238]. These findings point to the definite synergistic role of exosome with BCL family. In CRC cells, both exosome components EXOSC and BCL family members were found to be down regulated, after ETC-1922159 drug treatment. The search engine allocated low numerical valued ranks for many of the EXOSC and BCL combinations which might suggest greater role of EXOSC along with BCL. However, the nature of the mechanism between the two families yet needs to be explored, despite the generated hypothesis of possible synergy.

Table 120 shows rankings of EXOSC and BCL family with respect to each other. Left half of the table shows rankings of EXOSC w.r.t BCL and right half shows the vice versa. On the left, we find **EXOSC2** to be down regulated w.r.t BCL-2L12/6B/7A/9/11A/11B. These are shown in the rankings of 723 (laplace), 355 (linear) and 1211 (rbf) for EXOSC2 - BCL2L12; 1092 (laplace), 1033 (linear) and 638 (rbf) for EXOSC2 - BCL6; 1633 (laplace), 1047 (linear) and 317 (rbf) for EXOSC2 - BCL7A; 699 (laplace), 559 (linear) and 425 (rbf) for EXOSC2 - BCL9; 338 (laplace), 319 (linear) and 1598 (rbf) for EXOSC2 - BCL11A; and 1285 (laplace), 1440 (linear) and 812 (rbf) for EXOSC2 - BCL11B; **EXOSC3** was found to down regulated w.r.t BCL11B. This is reflected in rankigns of 1677 (laplace), 199 (linear) and 267 (rbf) for EXOSC3 - BCL11B. **EXOSC5** was found to be down regulated w.r.t BCL family. These are reflected in the rankings of 498 (laplace), 1342 (linear) and 436 (rbf) for EXOSC5 - BCL2L12; 786 (laplace), 1272 (linear) and 1194 (rbf) for EXOSC5 - BCL6B; 374 (laplace), 1338 (linear) and 874 (rbf) for

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Ranking MUC family vs BCL family							
Ranking of BCL2L1 w.r.t MUC family				Ranking of MUC family w.r.t BCL2L1			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL2L1	2055	2297	1854	MUC1 - BCL2L1	1226	1681	986
MUC3A - BCL2L1	603	2089	1637	MUC3A - BCL2L1	759	1107	678
MUC4 - BCL2L1	531	1137	711	MUC4 - BCL2L1	1758	999	487
MUC12 - BCL2L1	882	810	1305	MUC12 - BCL2L1	1591	900	272
MUC13 - BCL2L1	1927	1201	2108	MUC13 - BCL2L1	98	2160	1099
MUC17 - BCL2L1	1170	917	743	MUC17 - BCL2L1	2500	93	148
MUC20 - BCL2L1	1810	700	1627	MUC20 - BCL2L1	270	343	423
Ranking of BCL2L2 w.r.t MUC family				Ranking of MUC family w.r.t BCL2L2			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL2L2	1578	1425	1826	MUC1 - BCL2L2	2476	903	739
MUC3A - BCL2L2	1542	370	159	MUC3A - BCL2L2	2099	241	2397
MUC4 - BCL2L2	1323	2506	1988	MUC4 - BCL2L2	797	727	851
MUC12 - BCL2L2	602	2504	815	MUC12 - BCL2L2	516	38	1688
MUC13 - BCL2L2	2084	2402	1200	MUC13 - BCL2L2	2201	717	233
MUC17 - BCL2L2	2283	2212	1279	MUC17 - BCL2L2	903	295	913
MUC20 - BCL2L2	890	1886	480	MUC20 - BCL2L2	1892	569	1040
Ranking of BCL2L13 w.r.t MUC family				Ranking of MUC family w.r.t BCL2L13			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL2L13	2029	2347	550	MUC1 - BCL2L13	1838	903	739
MUC3A - BCL2L13	2140	1123	1100	MUC3A - BCL2L13	173	241	2397
MUC4 - BCL2L13	1497	1918	1579	MUC4 - BCL2L13	1906	727	851
MUC12 - BCL2L13	581	2353	1997	MUC12 - BCL2L13	2096	38	1688
MUC13 - BCL2L13	1210	2185	1658	MUC13 - BCL2L13	1688	717	233
MUC17 - BCL2L13	1079	1270	1254	MUC17 - BCL2L13	1167	295	913
MUC20 - BCL2L13	187	2081	535	MUC20 - BCL2L13	1653	569	1040
Ranking of BCL3 w.r.t MUC family				Ranking of MUC family w.r.t BCL3			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL3	458	1016	1881	MUC1 - BCL3	273	360	1683
MUC3A - BCL3	1642	668	588	MUC3A - BCL3	1044	860	1452
MUC4 - BCL3	427	321	457	MUC4 - BCL3	624	1360	585
MUC12 - BCL3	1813	311	1623	MUC12 - BCL3	1193	1092	132
MUC13 - BCL3	2151	641	1407	MUC13 - BCL3	279	65	603
MUC17 - BCL3	1106	531	2310	MUC17 - BCL3	305	1285	257
MUC20 - BCL3	2512	63	2440	MUC20 - BCL3	16	539	2198
Ranking of BCL6 w.r.t MUC family				Ranking of MUC family w.r.t BCL6			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL6	1652	2294	173	MUC1 - BCL6	1550	595	788
MUC3A - BCL6	2323	1435	187	MUC3A - BCL6	407	809	318
MUC4 - BCL6	723	711	1403	MUC4 - BCL6	176	203	1963
MUC12 - BCL6	184	1024	1267	MUC12 - BCL6	1126	26	229
MUC13 - BCL6	158	1083	2198	MUC13 - BCL6	1633	1052	603
MUC17 - BCL6	2411	2153	1808	MUC17 - BCL6	242	719	1026
MUC20 - BCL6	925	840	2153	MUC20 - BCL6	1132	1669	652
Ranking of BCL9L w.r.t MUC family				Ranking of MUC family w.r.t BCL9L			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL9L	2194	744	1112	MUC1 - BCL9L	1144	1999	896
MUC3A - BCL9L	2114	1441	1359	MUC3A - BCL9L	901	2180	2106
MUC4 - BCL9L	882	466	1526	MUC4 - BCL9L	658	1152	781
MUC12 - BCL9L	1547	526	2391	MUC12 - BCL9L	1733	1510	366
MUC13 - BCL9L	1545	1891	796	MUC13 - BCL9L	1529	502	602
MUC17 - BCL9L	1282	1160	1362	MUC17 - BCL9L	955	1788	99
MUC20 - BCL9L	2101	116	2408	MUC20 - BCL9L	307	1516	1042
Ranking of BCL10 w.r.t MUC family				Ranking of MUC family w.r.t BCL10			
	laplace	linear	rbf		laplace	linear	rbf
MUC1 - BCL10	1325	1524	1900	MUC1 - BCL10	547	1319	284
MUC3A - BCL10	1298	1004	1509	MUC3A - BCL10	1681	751	2250
MUC4 - BCL10	304	1632	1050	MUC4 - BCL10	591	570	151
MUC12 - BCL10	1019	1093	2239	MUC12 - BCL10	38	1155	817
MUC13 - BCL10	358	1687	2004	MUC13 - BCL10	517	2229	455
MUC17 - BCL10	524	2038	1579	MUC17 - BCL10	216	803	132
MUC20 - BCL10	1380	619	2081	MUC20 - BCL10	97	465	239

Table 118 2^{nd} order combinatorial hypotheses between BCL and SELENBP1

Unexplored combinatorial hypotheses	
MUC w.r.t BCL	
MUC-3A	BCL2L2
MUC-3A	BCL9L
BCL w.r.t MUC	
MUC-1/13	BCL2L1
MUC-4/13/17	BCL2L2
MUC-1/12	BCL2L13
MUC-20	BCL3
MUC-17	BCL6
MUC-20	BCL9L

Table 119 2^{nd} order combinatorial hypotheses between MUC and BCL family.

EXOSC5 - BCL7A; 613 (laplace), 946 (linear) and 772 (rbf) for EXOSC5 - BCL9; 459 (laplace), 90 (linear) and 1034 (rbf) for EXOSC5 - BCL11A; and 1404 (laplace) and 1558 (linear) for EXOSC5 - BCL11B; **EXOSC6** was found to be down regulated w.r.t BCL family. These are reflected in rankings of 1676 (laplace), 787 (linear) and 944 (rbf) for EXOSC6 - BCL7A; 1059 (linear) and 1091 (rbf) for EXOSC6 - BCL9; 1677 (laplace) and 1573 (linear) for EXOSC6 - BCL11A; **EXOSC7** was found to be down regulated w.r.t BCL family. These are reflected in rankings of 666 (laplace); 98 (linear) and 743 (rbf) EXOSC7 - BCL6B; 1501 (linear) and 1513 (rbf) for EXOSC7 - BCL7A; and 1477 (laplace) and 1217 (rbf) for EXOSC7 - BCL11A; **EXOSC8** was found to be down regulated w.r.t BCL family. Thesea reflected in 1175 (laplace), 1504 (linear) and 1743 (rbf) for EXOSC8 - BCL7A; 906 (linear) and 1130 (rbf) EXOSC8 - BCL11A; and 605 (linear) and 374 (rbf) for EXOSC8 - BCL11B; **EXOSC9** found to be down regulate w.r.t BCL family. These are reflected in rankings of 1179 (laplace); 1018 (linear) and 687 (rbf) for EXOSC9 - BCL2L12; 437 (laplace), 852 (linear) and 1358 (rbf) EXOSC9 - BCL6B; 821 (laplace), 346 (linear) and 727 (rbf) for EXOSC9 - BCL7A; 1305 (laplace) and 299 (rbf) EXOSC9 - BCL9; 1569 (laplace), 549 (linear) and 1456 (rbf) for EXOSC9 - BCL11B.

On the right, we find **BCL-6B/11A/11B** to be down regulated w.r.t EXOSC2. These are reflected in the rankings of 202 (laplace), 81 (linear) and 194 (rbf) for EXOSC2 - BCL6B; 574 (laplace), 834 (linear) and 1055 (rbf) for EXOSC2 - BCL11A; and 1368 (laplace), 1353 (linear) and 1455 (rbf) for EXOSC2 - BCL11B. **BCL-6B/7A/11A** was found to be down regulated w.r.t EXOSC3. These are reflected in rankings of 571 (laplace), 335 (linear) and 307 (rbf) for EXOSC3 - BCL6B; 1739 (laplace) and 1700 (rbf) for EXOSC3 - BCL7A; and 1018 (laplace), 1345 (linear) and 483 (rbf) for EXOSC3 - BCL11A; **BCL-6B/11A/11B** was found to be down regulated w.r.t EXOSC5. These were reflected in rankings of 571 (laplace), 335 (linear) and 307 (rbf) for EXOSC5 - BCL6B; 756 (laplace), 389 (linear) and 1183 (rbf) for EXOSC5 - BCL11A; and 1368 (laplace), 1353 (linear) and 1455 (rbf) for EXOSC5 - BCL11B. **BCL-9** was found to be down regulated w.r.t EXOSC6.

Ranking EXOSC family vs BCL family

Ranking of EXOSC2 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC2			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC2 - BCL2L12	723	355	1211	EXOSC2 - BCL2L12	1498	1889	1856
EXOSC2 - BCL6B	1092	1033	638	EXOSC2 - BCL6B	202	81	194
EXOSC2 - BCL7A	1633	1047	317	EXOSC2 - BCL7A	2403	2531	2405
EXOSC2 - BCL9	699	559	425	EXOSC2 - BCL9	2552	2230	1755
EXOSC2 - BCL11A	338	319	1598	EXOSC2 - BCL11A	574	834	1055
EXOSC2 - BCL11B	1285	1440	812	EXOSC2 - BCL11B	1067	1574	730
Ranking of EXOSC3 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC3			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC3 - BCL2L12	2280	1640	1955	EXOSC3 - BCL2L12	1976	1482	2399
EXOSC3 - BCL6B	2429	2273	2407	EXOSC3 - BCL6B	571	335	307
EXOSC3 - BCL7A	2100	1374	2674	EXOSC3 - BCL7A	1739	1882	1700
EXOSC3 - BCL9	2437	2223	2245	EXOSC3 - BCL9	2380	1912	2321
EXOSC3 - BCL11A	2212	2090	116	EXOSC3 - BCL11A	1018	1345	483
EXOSC3 - BCL11B	1677	199	267	EXOSC3 - BCL11B	2572	1876	2395
Ranking of EXOSC5 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC5			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC5 - BCL2L12	498	1342	436	EXOSC5 - BCL2L12	2174	1635	1824
EXOSC5 - BCL6B	786	1272	1194	EXOSC5 - BCL6B	330	193	107
EXOSC5 - BCL7A	374	1338	874	EXOSC5 - BCL7A	2582	2701	2415
EXOSC5 - BCL9	613	946	772	EXOSC5 - BCL9	1777	1511	2011
EXOSC5 - BCL11A	459	90	1034	EXOSC5 - BCL11A	756	389	1183
EXOSC5 - BCL11B	1404	2520	1558	EXOSC5 - BCL11B	1368	1353	1455
Ranking of EXOSC6 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC6			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC6 - BCL2L12	1327	1857	2063	EXOSC6 - BCL2L12	2268	1527	478
EXOSC6 - BCL6B	1965	2525	1825	EXOSC6 - BCL6B	18	2334	2512
EXOSC6 - BCL7A	1676	787	944	EXOSC6 - BCL7A	593	2653	2037
EXOSC6 - BCL9	1838	1059	1091	EXOSC6 - BCL9	1846	851	1564
EXOSC6 - BCL11A	1677	1573	2217	EXOSC6 - BCL11A	596	2307	2547
EXOSC6 - BCL11B	1897	1736	1126	EXOSC6 - BCL11B	2094	2223	81
Ranking of EXOSC7 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC7			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC7 - BCL2L12	1899	1755	974	EXOSC7 - BCL2L12	1721	1551	1099
EXOSC7 - BCL6B	666	98	743	EXOSC7 - BCL6B	2730	2690	2689
EXOSC7 - BCL7A	2290	1501	1513	EXOSC7 - BCL7A	1282	831	1218
EXOSC7 - BCL9	2363	1134	2219	EXOSC7 - BCL9	1845	1234	328
EXOSC7 - BCL11A	1477	2239	1217	EXOSC7 - BCL11A	520	117	686
EXOSC7 - BCL11B	2396	1524	2037	EXOSC7 - BCL11B	1529	2720	1418
Ranking of EXOSC8 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC8			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC8 - BCL2L12	2042	2152	506	EXOSC8 - BCL2L12	1967	1525	2275
EXOSC8 - BCL6B	2469	2134	2224	EXOSC8 - BCL6B	190	1630	472
EXOSC8 - BCL7A	1175	1504	1743	EXOSC8 - BCL7A	2065	2351	1069
EXOSC8 - BCL9	1733	2452	1164	EXOSC8 - BCL9	2640	1895	1747
EXOSC8 - BCL11A	1864	906	1130	EXOSC8 - BCL11A	944	2303	532
EXOSC8 - BCL11B	1547	605	374	EXOSC8 - BCL11B	2581	2728	2359
Ranking of EXOSC9 w.r.t BCL family				Ranking of BCL family w.r.t EXOSC9			
	laplace	linear	rbf		laplace	linear	rbf
EXOSC9 - BCL2L12	1179	1018	687	EXOSC9 - BCL2L12	2105	1762	1453
EXOSC9 - BCL6B	437	852	1358	EXOSC9 - BCL6B	634	304	146
EXOSC9 - BCL7A	821	346	727	EXOSC9 - BCL7A	985	2017	2207
EXOSC9 - BCL9	1305	1849	299	EXOSC9 - BCL9	1197	1279	2154
EXOSC9 - BCL11A	892	2426	2011	EXOSC9 - BCL11A	481	441	1372
EXOSC9 - BCL11B	1569	549	1456	EXOSC9 - BCL11B	2606	1454	133

Table 120 2^{nd} order combinatorial hypotheses between BCL and EXOSC

These are reflected in rankigns of 851 (linear) and 1564 (rbf) for EXOSC6 - BCL9. **BCL-2L12/7A/9/11A/11B** was found to be down regulated w.r.t EXOSC7. These are reflected in rankings of 1551 (linear) and 1099 (rbf) for EXOSC7 - BCL2L12; 1282 (laplace), 831 (linear) and 1218 (rbf) for EXOSC7 - BCL7A; 1234 (linear) and 328 (rbf) for EXOSC7 - BCL9; 520 (laplace), 117 (linear) and 686 (rbf) for EXOSC7 - BCL11A; and 1529 (laplace) and 1418 (rbf) for EXOSC7 - BCL11B; **BCL-6B/11A** was found to be down regulated with EXOSC8. These are reflected in rankings of 190 (laplace), 1630 (linear) and 472 (rbf) for EXOSC8 - BCL6B; and 944 (laplace) and 532 (rbf) for EXOSC8 - BCL11A. Finally,

Unexplored combinatorial hypotheses

EXOSC w.r.t BCL	
EXOSC2	BCL-2L12/6B/7A/9/11A/11B
EXOSC3	BCL-11B
EXOSC5	BCL-2L12/6B/7A/9/11A/11B
EXOSC6	BCL-7A/9/11A
EXOSC7	BCL-6B/7A/11A
EXOSC8	BCL-7A/11A/11B
EXOSC9	BCL-2L12/6B/7A/9/11B
BCL w.r.t EXOSC	
EXOSC2	BCL-6B/11A/11B
EXOSC3	BCL-6B/7A/11A
EXOSC5	BCL-6B/11A/11B
EXOSC6	BCL-2L12/9
EXOSC7	BCL-2L12/7A/9/11A/11B
EXOSC8	BCL-6B/11A
EXOSC9	BCL-6B/9/11A/11B

Table 121 2^{nd} order combinatorial hypotheses between EXOSC and BCL family.

BCL-6B/9/11A/11B was found to be down regulated with EXOSC9. These are reflected in rankings of 634 (laplace), 304 (linear) and 146 (rbf) for EXOSC9 - BCL6B; 1197 (laplace) and 1279 (rbf) for EXOSC9 - BCL9; 481 (laplace), 441 (linear) and 1372 (rbf) for EXOSC9 - BCL11A; and 1454 (linear) and 133 (rbf) for EXOSC9 - BCL11B.

Table 121 shows the derived influences which can be represented graphically, with the following influences - • EXOSC w.r.t BCL with EXOSC2 <- BCL-2L12/6B/7A/9/11A/11B; EXOSC3 <- BCL-11B; EXOSC5 <- BCL-2L12/6B/7A/9/11A/11B; EXOSC6 <- BCL-7A/9/11A; EXOSC7 <- BCL-6B/7A/11A; EXOSC8 <- BCL-7A/11A/11B and EXOSC9 <- BCL-2L12/6B/7A/9/11B; and • BCL w.r.t EXOSC with EXOSC2 -> BCL-6B/11A/11B; EXOSC3 -> BCL-6B/7A/11A; EXOSC5 -> BCL-6B/11A/11B; EXOSC6 -> BCL-2L12/9; EXOSC7 -> BCL-2L12/7A/9/11A/11B; EXOSC8 -> BCL-6B/11A and EXOSC9 -> BCL-6B/9/11A/11B.

2.9 Poliovirus-receptor related synergies

2.9.1 PVR - Interferon cross family analysis

Brown *et al.*[239] show that cancer immunotherapy with recombinant poliovirus induces IFN-dominant activation of dendritic cells and tumor antigen-specific CTLs. Stamm *et al.*[240] show that immune checkpoints PVR and PVRL2 are prognostic markers in AML and their blockade represents a new therapeutic option. Stamm *et al.*[241] observe that expression of novel immune checkpoint molecules PVR and PVRL2 confers a negative prognosis to patients with acute myeloid leukemia and their blockade augments T-Cell mediated lysis of AML cells alone or in combination with the BiTE® antibody construct AMG 330. In a latest development, Whelan *et al.*[242] observe that poliovirus receptor related immunoglobulin domain containing (PVRIG) and poliovirus receptor-related 2 (PVRL2) are induced in cancer and inhibit CD8+ T-cell function. For colorectal cancer, the were highest percentage of $PVR^{+}PVRL2^{-}$ cells. In CRC cells treated with ETC-1922159, it was found that PVR, PVRL2 and PVRL4 were up regulated. Whelan *et al.*[242] report that when they compared the combination of receptor blockade (i.e., anti-PVRIG and anti-TIGIT) with the combination of ligand blockade (i.e., anti-PVR and anti-PVRL2), similar increases in IFN-γ were observed, suggesting no additional functional interactions are present among these proteins. This might also suggest that expression of PVRL2 blocks the production of IFN-γ. Using the search engine, rankings at 2^{nd} order indicate similar patterns of combinatorial synergy. These ranks are tabulated in table 122. Note that high numerical valued ranks indicate a synergy between PVR and IFN family. However, low numercial valued ranks possibly indicate the negative role, i.e PVR family up regulation leads to blocking of IFN family production.

Here we depict the possible synergy of up regulation of PVR family with IFN family in CRC cells treated with ETC-1922159. However, of low numerical valued ranks might indicate the similar behaviour as found by Whelan *et al.*[242]. On the left we find PVR ranks w.r.t IFN and on the right vice versa. We found **PVR** to be up regulated w.r.t IFN-E/GR2/LR1. These are reflected in rankings of 2044 (linear) and 1975 (rbf) for PVR - IFNE; 1911 (laplace) and 1871 (linear) for PVR - IFNGR2; and 2212 (linear) and 1884 (rbf) for PVR - IFNLR1; **PVRL2** was up regulated w.r.t IFN-E. This was reflected in rankings of 1851 (laplace) and 2120 (rbf) for PVRL2 - IFNE; Reversibly, in context of findings by Whelan *et al.*[242] all low numerical valued ranks point to the fact that PVR/PVRL2/PVRL4 up regulation might be blocking the production of IFN family members. On the right side, we found **IFN-GR1/LR1** to be up regulated w.r.t PVR. These are reflected in rankings of 2268 (laplace), 2040 (linear) and 2235 (rbf) for PVR - IFNGR1 and 2119 (laplace) and 1918 (linear) for PVR - IFNLR1; **IFN-GR2** was up regulated w.r.t PVRL2. These are reflected in rankings of 2049 (laplace) and 2056 (rbf) for PVRL2 - IFNGR2; **IFN-E** was up regulated w.r.t PVRL4. These are reflected in rankings of 2026 (laplace) and 1908 (linear). Again, reversibly, in context of findings by Whelan *et al.*[242] all low numerical valued ranks point to the fact that IFN family up regulation might indicate bloackage of PVR family members.

Table 123 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t IFN with PVR <- IFN-E/GR2/LR1; PVRL2 <- IFN-E; and • IFN w.r.t PVR with IFN-GR1/LR1 -> PVR; IFN-GR2 -> PVRL2; IFN-E -> PVRL4;

RANKING PVR FAMILY VS IFN FAMILY							
RANKING OF PVR W.R.T IFN FAMILY				RANKING OF IFN FAMILY W.R.T PVR			
	laplace	linear	rbf		laplace	linear	rbf
PVR - IFNAR2	1378	1651	1539	PVR - IFNAR2	1630	161	930
PVR - IFNE	1305	2044	1975	PVR - IFNE	1071	1486	362
PVR - IFNGR1	1331	268	1000	PVR - IFNGR1	2268	2040	2235
PVR - IFNGR2	1911	1871	1426	PVR - IFNGR2	598	1059	832
PVR - IFNLR1	717	2212	1884	PVR - IFNLR1	2119	1918	1499
PVR - IFNWP19	1648	1438	1547	PVR - IFNWP19	1699	168	2218
RANKING OF PVRL2 W.R.T IFN FAMILY				RANKING OF IFN FAMILY W.R.T PVRL2			
	laplace	linear	rbf		laplace	linear	rbf
PVRL2 - IFNAR2	1877	1085	492	PVRL2 - IFNAR2	623	1259	2073
PVRL2 - IFNE	1851	990	2120	PVRL2 - IFNE	683	328	1416
PVRL2 - IFNGR1	1174	510	526	PVRL2 - IFNGR1	1352	1885	1433
PVRL2 - IFNGR2	1608	173	1036	PVRL2 - IFNGR2	2049	490	2056
PVRL2 - IFNLR1	1577	701	1333	PVRL2 - IFNLR1	535	1258	295
PVRL2 - IFNWP19	1455	954	182	PVRL2 - IFNWP19	870	1803	1394
RANKING OF PVRL4 W.R.T IFN FAMILY				RANKING OF IFN FAMILY W.R.T PVRL4			
	laplace	linear	rbf		laplace	linear	rbf
PVRL4 - IFNAR2	1555	227	2433	PVRL4 - IFNAR2	490	2303	1701
PVRL4 - IFNE	64	781	1466	PVRL4 - IFNE	2026	1908	465
PVRL4 - IFNGR1	2218	651	188	PVRL4 - IFNGR1	560	793	889
PVRL4 - IFNGR2	220	31	873	PVRL4 - IFNGR2	213	2079	31
PVRL4 - IFNLR1	284	958	683	PVRL4 - IFNLR1	766	1432	2153
PVRL4 - IFNWP19	138	2271	384	PVRL4 - IFNWP19	788	1046	921

Table 122 2^{nd} order combinatorial hypotheses between IFN and PVR family

UNEXPLORED COMBINATORIAL HYPOTHESES	
PVR w.r.t IFN	
PVR	IFN-E/GR2/LR1
PVRL2	IFN-E
IFN w.r.t PVR	
IFN-GR1/LR1	PVR
IFN-GR2	PVRL2
IFN-E	PVRL4

Table 123 2^{nd} order combinatorial hypotheses between PVR and IFN family.

2.9.2 Interferon - Wnt cross family analysis

The crosstalk between β-catenin signaling and type I, type II and type III interferons in lung cancer cells has been observed by Bai *et al.*[243]. Hillesheim *et al.*[244] show that β-catenin promotes the type I IFN synthesis and the IFN-dependent signaling response but is suppressed by influenza A virus-induced RIG-I/NF-κB signaling. Ohsugi *et al.*[245] show that decreased expression of interferon-induced protein 2 (IFIT2) by Wnt/β-catenin signaling confers anti-apoptotic properties to colorectal cancer cells. In CRC cells treated with ETC-1922159, members of Wnt and IFN family were up regulated. The search engine assigned high numerical valued ranks to a few of the 2^{nd} order combinations. These are depicted

Ranking IFN family vs WNT family

Ranking of IFNAR2 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t IFNAR2	laplace	linear	rbf
IFNAR2 - WNT2B	826	829	1463	IFNAR2 - WNT2B	785	1146	1642
IFNAR2 - WNT4	680	658	802	IFNAR2 - WNT4	1969	130	126
IFNAR2 - WNT7B	1009	1252	581	IFNAR2 - WNT7B	2208	1635	1647
IFNAR2 - WNT9A	532	180	1737	IFNAR2 - WNT9A	1223	1422	1632
Ranking of IFNE w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t IFNE	laplace	linear	rbf
IFNE - WNT2B	1612	1973	519	IFNE - WNT2B	1057	1146	239
IFNE - WNT4	1609	2262	1320	IFNE - WNT4	585	440	6
IFNE - WNT7B	1872	1240	2341	IFNE - WNT7B	2055	941	936
IFNE - WNT9A	2114	1029	267	IFNE - WNT9A	124	458	708
Ranking of IFNGR1 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t IFNGR1	laplace	linear	rbf
IFNGR1 - WNT2B	1623	144	361	IFNGR1 - WNT2B	1057	1849	2282
IFNGR1 - WNT4	225	455	1773	IFNGR1 - WNT4	2428	1226	2479
IFNGR1 - WNT7B	1004	1259	1135	IFNGR1 - WNT7B	710	2278	2164
IFNGR1 - WNT9A	601	958	1864	IFNGR1 - WNT9A	1668	1725	1462
Ranking of IFNGR2 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t IFNGR2	laplace	linear	rbf
IFNGR2 - WNT2B	1224	1322	2156	IFNGR2 - WNT2B	828	1599	400
IFNGR2 - WNT4	584	1117	59	IFNGR2 - WNT4	498	33	168
IFNGR2 - WNT7B	1185	745	242	IFNGR2 - WNT7B	1964	1020	638
IFNGR2 - WNT9A	754	501	676	IFNGR2 - WNT9A	261	1711	654
Ranking of IFNLR1 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t IFNLR1	laplace	linear	rbf
IFNLR1 - WNT2B	1621	851	510	IFNLR1 - WNT2B	2263	1683	2216
IFNLR1 - WNT4	1538	250	220	IFNLR1 - WNT4	2364	231	503
IFNLR1 - WNT7B	1012	173	506	IFNLR1 - WNT7B	406	573	446
IFNLR1 - WNT9A	347	134	2160	IFNLR1 - WNT9A	1815	1709	106
Ranking of IFNWP19 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t IFNWP19	laplace	linear	rbf
IFNWP19 - WNT2B	826	176	787	IFNWP19 - WNT2B	1600	2096	1650
IFNWP19 - WNT4	680	1507	391	IFNWP19 - WNT4	1441	2423	2330
IFNWP19 - WNT7B	1009	1101	1327	IFNWP19 - WNT7B	1838	966	1478
IFNWP19 - WNT9A	532	1404	431	IFNWP19 - WNT9A	1354	1968	703

Table 124 2^{nd} order combinatorial hypotheses between WNT and IFN family

in table 124.

On the left, is the rankings of IFN family w.r.t Wnt family. On the right are the rankings of Wnt family w.r.t IFN family. On the left we found **IFNE** to be up regulated w.r.t WNT7B. These are depicted in rankings of 1872 (laplace) and 2341 (rbf) for IFNE - WNT7B. On the right, we found **WNT-2B/4/7B** to be up regulated w.r.t IFNGR1. These are reflected in ranking of 1849 (linear) and 2282 (rbf) for IFNGR1 - WNT2B; 2428 (laplace) and 2479 (rbf) for IFNGR1 - WNT4 and 2278 (linear) and 2164 (rbf) for IFNGR1 - WNT7B. **WNT-2B** was up regulated w.r.t IFNLR1. This is reflected in ranking of 2263(laplace) and 2216 (rbf) for IFNLR1 - WNT2B; Finally, **WNT4** was up regulated w.r.t IFNWP19. This is reflected in ranking of 2423 (linear) and 2330 (rbf) for IFNWP19 - WNT4. Table 125 shows the derived influences which can be represented graphically, with the following influences - • IFN w.r.t WNT with IFNE <- WNT7B; • WNT w.r.t IFN with IFNGR1 -> WNT2B; IFNGR1 -> WNT-2B/4/7B; IFNLR1 -> WNT2B; and IFNWP19 -> WNT4.

2.9.3 PVR - WNT cross family analysis

Mutations in PVRL4, encoding cell adhesion molecule nectin-4, causes Ectodermal dysplasia-syndactyly syndrome, Brancati *et al.* [1]. Interaction with cadherins also implies an influence of nectin-4 on Wnt signaling, which plays a relevant role in limb development (Brancati *et al.* [1]). However, not much work has been done to explore the relation of Wnts and PVR family. In CRC cells treated with ETC-1922159, both were found up regulated. The search engine alloted high numerical valued rankings to some combinations thus indicating a possibility of high combinatorial synergy also. Table 126 shows the rankings of PVR family w.r.t to Wnts on the left and vice versa on the right. We found, **PVR** up regulated w.r.t WNT9A and this is reflected in rankings of 2322 (laplace) and 2202 (rbf). On the right, we found **WNT-7B/9A** to be up regulated w.r.t PVR. These are reflected in rankings of 2216 (laplace), 1844 (linear) and 2096 (rbf) for PVR - WNT7B; and 2152 (laplace) and 2120 (rbf) for PVR - WNT9A. Also, **WNT-4** was up regulated w.r.t PVRL2. This is reflected in rankings of 2324 (laplace) and 2462 (linear) for PVRL2 - WNT4.

Table 127 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t WNT with PVR <- WNT9A; and • WNT w.r.t PVR with WNT-7B/9A <- PVR and WNT4 <- PVRL2; In the light of the recent findings of PVR with IFN and the known interactions between IFN and Wnts, there might be a possibilty to explore the bridge of PVR, IFN and WNTs. The above 3 fold (PVR - IFN; IFN - WNT; WNT - PVR), 2 way cross family analysis might shed light on the possible combinations that might be of import.

2.9.4 PVR - Integrin cross family analysis

PVRL4 promotes anchorage-independence by driving cell-to-cell attachment and matrix-independent integrin β4/SHP-2/c-Src activation, as observed by Pavlova *et al.* [246]. Integrins are the major metazoan receptors for cell adhesion to extracellular matrix proteins and, in vertebrates, also play important roles in certain cell-cell adhesions Hynes [247]. It has been recently shown that human NK cells recognize PVR through the receptor DNAM-1, which triggers NK cell stimulation in association with *beta*2 integrin. Fuchs *et al.* [248] additionally show that NK cells recognize PVR through

Unexplored combinatorial hypotheses

IFN w.r.t WNT	
IFNE	WNT7B
WNT w.r.t IFN	
IFNGR1	WNT2B
IFNGR1	WNT4/WNT7B
IFNLR1	WNT2B
IFNWP19	WNT4

Table 125 2^{nd} order combinatorial hypotheses between IFN and WNT family.

Ranking PVR family vs WNT family

Ranking of PVR w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t PVR	laplace	linear	rbf
PVR - WNT2B	2204	733	1	PVR - WNT2B	1205	2257	607
PVR - WNT4	1295	970	878	PVR - WNT4	38	2470	1094
PVR - WNT7B	1237	770	1887	PVR - WNT7B	2216	1844	2096
PVR - WNT9A	2322	649	2202	PVR - WNT9A	2152	2120	1131
Ranking of PVRL2 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t PVRL2	laplace	linear	rbf
PVRL2 - WNT2B	616	375	2381	PVRL2 - WNT2B	1901	1044	621
PVRL2 - WNT4	1110	1584	1391	PVRL2 - WNT4	2324	216	2462
PVRL2 - WNT7B	2186	1122	349	PVRL2 - WNT7B	560	560	953
PVRL2 - WNT9A	110	1367	1858	PVRL2 - WNT9A	1044	1502	794
Ranking of PVRL4 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t PVRL4	laplace	linear	rbf
PVRL4 - WNT2B	949	565	95	PVRL4 - WNT2B	78	966	1938
PVRL4 - WNT4	885	1672	2149	PVRL4 - WNT4	611	1922	1488
PVRL4 - WNT7B	299	241	798	PVRL4 - WNT7B	1192	1159	2505
PVRL4 - WNT9A	1375	1306	492	PVRL4 - WNT9A	1383	634	224

Table 126 2^{nd} order combinatorial hypotheses between WNT and PVR family

Unexplored combinatorial hypotheses

PVR w.r.t WNT	
PVR	WNT9A
WNT w.r.t PVR	
WNT-7B/9A	PVR
WNT4	PVRL2

Table 127 2^{nd} order combinatorial hypotheses between PVR and WNT family.

an additional receptor, CD96, or T cell-activated increased late expression (Tactile). Ferroptosis is a type of programmed cell death dependent on iron and characterized by the accumulation of lipid peroxides, and is genetically and biochemically distinct from other forms of regulated cell death such as apoptosis (Wikipedia contributors[249]). Cell clustering mediated by the adhesion protein PVRL4 is necessary for $\alpha 6 \beta 4$ integrinâĂŞpromoted ferroptosis resistance in matrix-detached cells, as observed by Brown *et al.*[250]. These findings suggest the possibility to synergy between PVR and Integrin family. In CRC cells treated with ETC-1922159, PVR and integrin families were up regulated. The search engine alloted high numerical valued ranks to some of the 2^{nd} order combinations of PVR and integrin family members thus pointing to possible synergy in CRC cells. Table 128 shows the rankings of PVR along with integrin family members.

On the left side, we found **PVRL2** to be up regulated w.r.t ITG-B4. This is reflected in the rankings of 1857 (laplace) and 1750 (rbf) for ITGB4-PVRL2. **PVRL4** was up regulated w.r.t ITGB5. This is reflected in rankings of 2418 (linear) and 1802 (rbf) for ITGB5-PVRL4. On the right side, **ITG-A2/B8** were found up regulated w.r.t PVR. These are reflected in rankings of 2062 (linear)

Ranking PVR family vs ITG family

Ranking of PVR w.r.t ITG family	laplace	linear	rbf	Ranking of ITG family w.r.t PVR	laplace	linear	rbf
ITGA2-PVR	294	564	1996	ITGA2-PVR	627	2062	2106
ITGA3-PVR	1739	117	1420	ITGA3-PVR	2172	99	827
ITGA6-PVR	214	1328	435	ITGA6-PVR	576	2199	817
ITGB1-PVR	1896	136	1121	ITGB1-PVR	1506	1093	2203
ITGB1BP1-PVR	1876	1724	1505	ITGB1BP1-PVR	1241	1108	535
ITGB4-PVR	783	1495	1044	ITGB4-PVR	1499	120	873
ITGB5-PVR	1719	981	490	ITGB5-PVR	1269	1433	914
ITGB6-PVR	1457	664	1744	ITGB6-PVR	1686	988	879
ITGB8-PVR	283	290	334	ITGB8-PVR	1407	2498	2366
Ranking of PVRL2 w.r.t ITG family	laplace	linear	rbf	Ranking of ITG family w.r.t PVRL2	laplace	linear	rbf
ITGA2-PVRL2	1072	501	851	ITGA2-PVRL2	1883	327	1141
ITGA3-PVRL2	960	1905	1160	ITGA3-PVRL2	1199	1937	39
ITGA6-PVRL2	352	993	212	ITGA6-PVRL2	2102	709	1337
ITGB1-PVRL2	720	1751	836	ITGB1-PVRL2	922	568	1546
ITGB1BP1-PVRL2	1436	1313	88	ITGB1BP1-PVRL2	168	2470	2408
ITGB4-PVRL2	1857	1269	1750	ITGB4-PVRL2	565	440	1197
ITGB5-PVRL2	238	100	1314	ITGB5-PVRL2	543	1738	1605
ITGB6-PVRL2	1873	582	1492	ITGB6-PVRL2	1052	2428	2364
ITGB8-PVRL2	695	612	1500	ITGB8-PVRL2	2046	2385	2110
Ranking of PVRL4 w.r.t ITG family	laplace	linear	rbf	Ranking of ITG family w.r.t PVRL4	laplace	linear	rbf
ITGA2-PVRL4	69	951	917	ITGA2-PVRL4	2154	666	1266
ITGA3-PVRL4	66	1648	825	ITGA3-PVRL4	2355	357	801
ITGA6-PVRL4	994	528	109	ITGA6-PVRL4	2359	299	157
ITGB1-PVRL4	1631	1724	917	ITGB1-PVRL4	2100	1282	526
ITGB1BP1-PVRL4	1369	90	462	ITGB1BP1-PVRL4	1815	1287	2362
ITGB4-PVRL4	743	1602	2443	ITGB4-PVRL4	126	1844	703
ITGB5-PVRL4	2418	1802	119	ITGB5-PVRL4	1818	834	2256
ITGB6-PVRL4	500	1187	122	ITGB6-PVRL4	1618	2425	402
ITGB8-PVRL4	861	699	780	ITGB8-PVRL4	1641	394	1282

Table 128 2^{nd} order combinatorial hypotheses between ITG and PVR family

and 2106 (rbf) for ITGA2-PVR; and 2498 (linear) and 2366 (rbf) for ITGB8-PVR. **ITG-B1BP1/B6/B8** were found up regulated w.r.t PVRL2. These are reflected in rankings of 2470 (linear) and 2408 (rbf) for ITGB1BP1-PVRL2; 2428 (linear) and 2364 (rbf) for ITGB6-PVRL2; and 2046 (laplace), 2385 (linear) and 2110 (rbf) for ITGB8-PVRL2. **ITG-B1BP1/B5** were found up regulated w.r.t PVRL4. These are reflected in rankings of 1815 (laplace) and 2362 (rbf) for ITGB1BP1-PVRL4; and 1818 (laplace) and 2256 (rbf) for ITGB5-PVRL4.

Table 129 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t ITG with PVRL2 <- ITGB4; and PVRL4 <- ITGB5 and • ITG w.r.t PVR with ITG-A2/B8 <- PVR; ITG-B1BP1/B6/B8 <- PVRL2; and ITG-B1BP1/B5 <- PVRL4.

2.9.5 PVR - TNF cross family analysis

Abdullah *et al.*[251] show that wild-type measles virus infection upregulates poliovirus receptor-related 4 and causes apoptosis in brain endothelial cells by induction of Tumor Necrosis Factor-related apoptosis-inducing ligand. Fabre-Lafay *et al.*[252] show that Nectin-4 (PVRL4), a new serological breast cancer marker, is a substrate for tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17. These and other findings indicate the role of poliovirus receptor along with TNF family members. In CRC cells

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Unexplored combinatorial hypotheses	
PVR w.r.t ITG	
PVRL2	ITGB4
PVRL4	ITGB5
ITG w.r.t PVR	
ITG-A2/B8	PVR
ITG-B1BP1/B6/B8	PVRL2
ITG-B1BP1/B5	PVRL4

Table 129 2^{nd} order combinatorial hypotheses between PVR and ITG family.

treated with ETC-1922159, PVR and TNF families were up regulated. The search engine alloted high numerical valued ranks to some of the 2^{nd} order combinations of PVR and TNF family members thus pointing to possible synergy in CRC cells. Table 130 shows the rankings of PVR along with TNF family members.

On the left side, we found **PVR** to be up regulated w.r.t TNF and TNF-AIP1/AIP2/RSF1A/RSF10A. This is reflected in the rankings of 1963 (laplace), 2422 (linear) and 1822 (rbf) for TNF-PVR; 2210 (linear) and 2243 (rbf) for TNFAIP1-PVR; 2028 (laplace) and 2451 (rbf) for TNFAIP2-PVR; 2029 (laplace) and 2078 (rbf) for TNFRSF1A-PVR and 1978 (linear) and 1942 (rbf) for TNFRSF10A-PVR. **PVRL2** to be up regulated w.r.t TNF-AIP2. This is reflected in the rankings of 2515 (laplace) and 2423 (linear) for TNFAIP2-PVRL2. On the right side, **TNFRSF14** to be up regulated w.r.t PVR. This is reflected in rankigns of 2351 (laplace) and 2289 (linear) for TNFRSF14-PVR. **TNF-AIP1/AIP2/RSF1A/RSF10B/RSF21** to be up regulated w.r.t PVRL2. These are reflected in rankings of 2244 (laplace) and 1932 (rbf) for TNFAIP1-PVRL2; 2337 (laplace), 2483 (linear) and 2401 (rbf) for TNFAIP2-PVRL2; 2355 (laplace) and 1810 (rbf) for TNFRSF1A-PVRL2; and 2120 (laplace) and 1782 (rbf) for TNFRSF21-PVRL2. **TNF-AIP2/RSF10D/RSF12A/RSF21** to be up regulated w.r.t PVRL4. These are reflected in rankings of 2270 (laplace) and 2429 (linear) for TNFAIP2-PVRL4; 1799 (laplace) and 2430 (rbf) for TNFRSF10D-PVRL4; 2386 (laplace) and 2064 (rbf) for TNFRSF12A-PVRL4; and 2441 (laplace) and 1917 (linear) for TNFRSF21-PVRL4.

Table 131 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t TNF with PVR <- TNF, TNF-AIP1/AIP2/RSF1A/RSF10A; and PVRL2 <- TNF-AIP2; and • TNF w.r.t PVR with TNFRSF14 <- PVR; TNF-AIP1/AIP2/RSF1A/RSF10B/RSF21 <- PVRL2; and TNF-AIP2/RSF10D/RSF12A/RSF21 <- PVRL4.

Ranking PVR vs TNF family

Ranking of PVR w.r.t TNF family				Ranking of TNF family w.r.t PVR			
	laplace	linear	rbf		laplace	linear	rbf
TNF-PVR	1963	2422	1822	TNF-PVR	451	54	209
TNFAIP1-PVR	88	2210	2243	TNFAIP1-PVR	527	474	743
TNFAIP2-PVR	2028	300	2451	TNFAIP2-PVR	1422	632	1486
TNFAIP3-PVR	2454	1065	1293	TNFAIP3-PVR	517	1476	1611
TNFRSF1A-PVR	2029	500	2078	TNFRSF1A-PVR	1530	778	1865
TNFRSF10A-PVR	1140	1978	1942	TNFRSF10A-PVR	2124	1648	1420
TNFRSF10B-PVR	1529	1608	463	TNFRSF10B-PVR	151	1266	649
TNFRSF10D-PVR	1321	2136	1561	TNFRSF10D-PVR	1997	732	1614
TNFRSF12A-PVR	507	93	1816	TNFRSF12A-PVR	1149	1358	2417
TNFRSF14-PVR	983	1419	409	TNFRSF14-PVR	2351	2289	1577
TNFRSF21-PVR	485	541	1910	TNFRSF21-PVR	1414	969	1247
TNFSF10-PVR	1482	317	297	TNFSF10-PVR	681	1150	1983
TNFSF15-PVR	210	194	56	TNFSF15-PVR	635	2086	1054
Ranking of PVRL2 w.r.t TNF family				Ranking of TNF family w.r.t PVRL2			
	laplace	linear	rbf		laplace	linear	rbf
TNF-PVRL2	831	367	526	TNF-PVRL2	2494	652	966
TNFAIP1-PVRL2	867	1568	1962	TNFAIP1-PVRL2	2244	27	1932
TNFAIP2-PVRL2	2515	2423	1062	TNFAIP2-PVRL2	2337	2483	2401
TNFAIP3-PVRL2	973	595	988	TNFAIP3-PVRL2	1334	777	896
TNFRSF1A-PVRL2	742	1326	1798	TNFRSF1A-PVRL2	1741	2355	1810
TNFRSF10A-PVRL2	830	1008	478	TNFRSF10A-PVRL2	1027	1672	3
TNFRSF10B-PVRL2	27	2160	1210	TNFRSF10B-PVRL2	253	1794	168
TNFRSF10D-PVRL2	312	1154	1229	TNFRSF10D-PVRL2	564	1719	170
TNFRSF12A-PVRL2	1282	382	1056	TNFRSF12A-PVRL2	594	1870	1376
TNFRSF14-PVRL2	288	922	264	TNFRSF14-PVRL2	2148	1496	232
TNFRSF21-PVRL2	1590	771	1034	TNFRSF21-PVRL2	2120	734	1782
TNFSF10-PVRL2	472	1160	1056	TNFSF10-PVRL2	98	695	714
TNFSF15-PVRL2	373	2154	420	TNFSF15-PVRL2	768	296	2448
Ranking of PVRL4 w.r.t TNF family				Ranking of TNF family w.r.t PVRL4			
	laplace	linear	rbf		laplace	linear	rbf
TNF-PVRL4	540	680	284	TNF-PVRL4	983	2010	1345
TNFAIP1-PVRL4	1885	5	131	TNFAIP1-PVRL4	965	1896	1196
TNFAIP2-PVRL4	72	2496	120	TNFAIP2-PVRL4	2270	2429	239
TNFAIP3-PVRL4	1926	599	794	TNFAIP3-PVRL4	1442	1809	1269
TNFRSF1A-PVRL4	615	1904	641	TNFRSF1A-PVRL4	1328	2481	1316
TNFRSF10A-PVRL4	337	974	1802	TNFRSF10A-PVRL4	1375	324	1822
TNFRSF10B-PVRL4	1762	1126	483	TNFRSF10B-PVRL4	76	40	1225
TNFRSF10D-PVRL4	2232	1056	92	TNFRSF10D-PVRL4	1799	1327	2430
TNFRSF12A-PVRL4	601	1722	1566	TNFRSF12A-PVRL4	2386	1670	2064
TNFRSF14-PVRL4	444	1007	193	TNFRSF14-PVRL4	1514	402	447
TNFRSF21-PVRL4	12	552	1875	TNFRSF21-PVRL4	2441	1917	1689
TNFSF10-PVRL4	1149	1554	341	TNFSF10-PVRL4	150	1907	743
TNFSF15-PVRL4	936	1057	1160	TNFSF15-PVRL4	2019	1452	760

Table 130 2^{nd} order combinatorial hypotheses between PVR and TNF family

Unexplored combinatorial hypotheses	
PVR w.r.t TNF	
PVR	TNF, TNF-AIP1/AIP2/RSF1A/RSF10A
PVRL2	TNF-AIP2
TNF w.r.t PVR	
TNFRSF14	PVR
TNF-AIP1/AIP2/RSF1A/RSF10B/RSF21	PVRL2
TNF-AIP2/RSF10D/RSF12A/RSF21	PVRL4

Table 131 2^{nd} order combinatorial hypotheses between PVR and TNF family.

2.9.6 PVR - IL cross family analysis

Fabre-Lafay *et al.*[252] show that Nectin-4 (PVRL4), is a new serological breast cancer marker and a substrate for tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17. Among the 24 ADAMs, tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17 is involved in various biological processes and cleaves numerous substrates including tumor necrosis factor (TNF)-α, TNF receptor, epidermal growth factor receptor L, c-fms, c-kit, p75NTR, growth hormone receptor, interleukin-6 receptor, interleukin-1 receptor, vascular cell adhesion molecule-1, L-selectin, collagen VII, MUC1, Notch, CX3CL-1, CD40, β-amyloid precursor, and prion protein. Thus there exists an indirect synergy between PVRL4 and interleukin. In CRC cells treated with ETC-1922159, members of PVR family and interleukin family were found up regulated. Our search engine alloted high numerical valued ranks to some of the combinations of both families, thereby indicating possible synergy.

Table 132, shows the rankings of PVR and IL family with respect to each other. On the left we found, **PVR** to be up regulated w.r.t IL-2RG/8/10RB/15/17C/17REL. These are reflected in rankings of 2007 (laplace) and 2476 (rbf) for IL2RG-PVR, 2429 (laplace) and 2507 (linear) for IL8-PVR, 2310 (laplace) and 2190 (linear) for IL10RB-PVR, 2065 (laplace), 2008 (linear) and 2385 (rbf) for IL15-PVR, 2114 (laplace) and 2301 (linear) for IL17C-PVR and 2317 (linear) and 1971 (rbf) for IL17REL-PVR. On the right side we found, **IL-1RAP/6ST/15RA/17REL** to be up regulated w.r.t PVR. These are reflected in the rankings of 2194 (linear) and 2026 (rbf), for IL1RAP-PVR; 2434 (linear) and 1767 (rbf) for IL6ST-PVR; 1865 (linear) and 2405 (rbf) for IL15RA-PVR; and 2408 (linear) and 2028 (rbf) for IL17REL-PVR. **IL-1A/1B/2RG/6ST** was up regulated w.r.t PVRL2. These are reflected in rankings of 2168 (laplace) and 2431 (linear) for IL1A-PVRL2; 2390 (linear) and 2067 (rbf) for IL1B-PVRL2; 1908 (laplace) and 1959 (rbf) for IL2RG-PVRL2; 2349 (laplace) and 2158 (rbf) for IL6ST-PVRL2; 1968 (laplace) and 2084 (rbf) for IL10RB-PVRL2; and 2137 (laplace) and 2004 (rbf) for IL17REL-PVRL2. **IL-15RA/17C/17REL** was up regulated w.r.t PVRL4. These are reflected in rankings of 2429 (laplace) and 1758 (rbf) for IL15RA-PVRL4; 1782 (laplace) and 2245 (linear) for IL17C-PVRL4 and 1934 (laplace) and 2140 (linear) for IL17REL-PVRL4.

Table 133 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t IL with PVR <- IL-2RG/8/10RB/15/17C/17REL; and *bullet* IL w.r.t PVR with IL-1RAP/6ST/15RA/17REL <- PVR; IL-1A/1B/2RG/6ST <- PVRL2; and IL-15RA/17C/17REL <- PVRL4.

2.9.7 PVR - Collagen cross family analysis

Fabre-Lafay *et al.*[252] show that Nectin-4 (PVRL4), is a new serological breast cancer marker and a substrate for tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17. Among the 24 ADAMs, tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17 is involved in various biological processes and cleaves numerous substrates including tumor necrosis factor (TNF)-α, TNF receptor, epidermal growth factor receptor L, c-fms, c-kit, p75NTR, growth hormone receptor, interleukin-6 receptor, interleukin-1 receptor, vascular cell adhesion molecule-1, L-selectin, collagen VII, MUC1, Notch, CX3CL-1, CD40, β-amyloid

RANKING PVR VS IL FAMILY

RANKING OF PVR W.R.T IL FAMILY	laplace	linear	rbf	RANKING OF IL FAMILY W.R.T PVR	laplace	linear	rbf
IL1A-PVR	295	854	2060	IL1A-PVR	2419	822	1099
IL1B-PVR	708	1282	1092	IL1B-PVR	1739	405	155
IL1RAP-PVR	980	714	197	IL1RAP-PVR	370	2194	2026
IL1RN-PVR	1273	25	2065	IL1RN-PVR	2025	266	796
IL2RG-PVR	2007	704	2476	IL2RG-PVR	250	740	988
IL6ST-PVR	1125	356	1368	IL6ST-PVR	706	2434	1767
IL8-PVR	2429	2507	257	IL8-PVR	92	1468	812
IL10RB-PVR	2310	2190	1140	IL10RB-PVR	1362	798	881
IL15-PVR	2065	2008	2385	IL15-PVR	1612	134	658
IL15RA-PVR	376	1621	1736	IL15RA-PVR	752	1865	2405
IL17C-PVR	2114	2301	1160	IL17C-PVR	894	26	350
IL17REL-PVR	482	2317	1971	IL17REL-PVR	1010	2408	2028
RANKING OF PVRL2 W.R.T IL FAMILY	laplace	linear	rbf	RANKING OF IL FAMILY W.R.T PVRL2	laplace	linear	rbf
IL1A-PVRL2	493	849	1517	IL1A-PVRL2	2168	2431	774
IL1B-PVRL2	1234	180	1177	IL1B-PVRL2	1425	2390	2067
IL1RAP-PVRL2	2029	1039	943	IL1RAP-PVRL2	1393	1104	670
IL1RN-PVRL2	1168	295	347	IL1RN-PVRL2	959	2382	481
IL2RG-PVRL2	356	1752	1964	IL2RG-PVRL2	1908	990	1959
IL6ST-PVRL2	243	770	513	IL6ST-PVRL2	2349	384	2158
IL8-PVRL2	1138	641	532	IL8-PVRL2	612	489	1686
IL10RB-PVRL2	1746	639	2502	IL10RB-PVRL2	1968	839	2084
IL15-PVRL2	1107	1263	759	IL15-PVRL2	1841	1579	399
IL15RA-PVRL2	1216	1194	330	IL15RA-PVRL2	473	811	1472
IL17C-PVRL2	507	920	402	IL17C-PVRL2	1167	1469	43
IL17REL-PVRL2	79	1306	2210	IL17REL-PVRL2	2137	962	2004
RANKING OF PVRL4 W.R.T IL FAMILY	laplace	linear	rbf	RANKING OF IL FAMILY W.R.T PVRL4	laplace	linear	rbf
IL1A-PVRL4	338	1487	666	IL1A-PVRL4	1409	1219	2410
IL1B-PVRL4	1713	110	481	IL1B-PVRL4	908	305	399
IL1RAP-PVRL4	864	269	523	IL1RAP-PVRL4	1704	2070	309
IL1RN-PVRL4	2496	643	144	IL1RN-PVRL4	964	1264	697
IL2RG-PVRL4	858	1229	2101	IL2RG-PVRL4	18	1504	727
IL6ST-PVRL4	117	605	744	IL6ST-PVRL4	1954	976	204
IL8-PVRL4	1041	1291	975	IL8-PVRL4	1441	234	1826
IL10RB-PVRL4	73	523	278	IL10RB-PVRL4	2137	1296	506
IL15-PVRL4	2062	549	556	IL15-PVRL4	1029	1377	281
IL15RA-PVRL4	302	1519	2186	IL15RA-PVRL4	2429	1246	1758
IL17C-PVRL4	25	110	14	IL17C-PVRL4	1782	2245	54
IL17REL-PVRL4	1487	1107	1148	IL17REL-PVRL4	1934	2140	107

Table 132 2^{nd} order combinatorial hypotheses between IL and PVR family

UNEXPLORED COMBINATORIAL HYPOTHESES

PVR w.r.t IL	
PVR	IL-2RG/8/10RB/15/17C/17REL
IL w.r.t PVR	
IL-1RAP/6ST/15RA/17REL	PVR
IL-1A/1B/2RG/6ST	PVRL2
IL-15RA/17C/17REL	PVRL4

Table 133 2^{nd} order combinatorial hypotheses between PVR and IL family.

precursor, and prion protein. Thus there exists an indirect synergy between PVRL4 and collagen. In CRC cells treated with ETC-1922159, members of PVR family and collagen family were found up regulated. Our search engine alloted high numerical valued ranks to some of the combinations of both families, thereby indicating possible synergy.

Table 134, shows the rankings of PVR and COL family with respect to each other. On the left we found, **PVR** to be up regulated w.r.t COL6A1. This is reflected in rankings of 2259 (laplace) and 2385 (rbf) for COL6A1-PVR. On the right side, we found **COL5A3** up regulated w.r.t PVR. This is reflected in rankings of 2341 (laplace) and 2472 (rbf) for COL5A3-PVR. **COL9A2** was up regulated w.r.t PVRL2. This is reflected in rankings of 2483 (laplace) and 2363 (rbf) for COL9A2-PVRL2.

Table 135 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t COL with PVR <- COL6A1; and • COL w.r.t PVR with COL5A3 <- PVR; and COL9A2 <- PVRL2.

Ranking PVR vs COL family

Ranking of PVR w.r.t COL family	laplace	linear	rbf	Ranking of COL family w.r.t PVR	laplace	linear	rbf
COL5A3-PVR	193	790	616	COL5A3-PVR	2341	1172	2472
COL6A1-PVR	2259	1740	2385	COL6A1-PVR	2213	70	1280
COL7A1-PVR	1448	1166	424	COL7A1-PVR	144	1008	1701
COL9A2-PVR	218	166	1375	COL9A2-PVR	244	2501	351
COL17A1-PVR	1800	1167	1528	COL17A1-PVR	1145	559	685
COL28A1-PVR	263	1273	177	COL28A1-PVR	1255	2266	1034
Ranking of PVRL2 w.r.t COL family	laplace	linear	rbf	**Ranking of COL family w.r.t PVRL2**	laplace	linear	rbf
COL5A3-PVRL2	1275	1132	515	COL5A3-PVRL2	962	1588	640
COL6A1-PVRL2	533	1954	826	COL6A1-PVRL2	2372	850	1193
COL7A1-PVRL2	594	2111	1299	COL7A1-PVRL2	22	662	2168
COL9A2-PVRL2	1336	939	970	COL9A2-PVRL2	2483	1548	2363
COL17A1-PVRL2	1157	1080	1232	COL17A1-PVRL2	173	1103	728
COL28A1-PVRL2	991	348	1618	COL28A1-PVRL2	955	864	1981
Ranking of PVRL4 w.r.t COL family	laplace	linear	rbf	**Ranking of COL family w.r.t PVRL4**	laplace	linear	rbf
COL5A3-PVRL4	692	1155	1446	COL5A3-PVRL4	499	405	331
COL6A1-PVRL4	221	1906	571	COL6A1-PVRL4	1701	2059	1315
COL7A1-PVRL4	859	1320	1088	COL7A1-PVRL4	1364	2205	65
COL9A2-PVRL4	1893	754	1155	COL9A2-PVRL4	1397	1797	1053
COL17A1-PVRL4	1124	1647	431	COL17A1-PVRL4	1401	1174	596
COL28A1-PVRL4	417	1536	433	COL28A1-PVRL4	642	2446	1540

Table 134 2^{nd} order combinatorial hypotheses between COL and PVR family

2.9.8 PVR - MUCIN cross family analysis

[252] show that Nectin-4 (PVRL4), is a new serological breast cancer marker and a substrate for tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17. Among the 24 ADAMs, tumor necrosis factor-α-converting enzyme (TACE)/ADAM-17 is involved in various biological processes and cleaves numerous substrates including tumor necrosis factor (TNF)-α, TNF receptor, epidermal growth factor receptor L, c-fms, c-kit, p75NTR, growth hormone receptor, interleukin-6 receptor, interleukin-1 receptor, vascular cell adhesion molecule-1, L-selectin, collagen VII, MUC1, Notch, CX3CL-1, CD40, β-amyloid precursor, and prion protein. Thus there exists an indirect synergy between PVRL4 and Mucin. In CRC cells treated with ETC-1922159, members of PVR family and Mucin family were found up regulated. Our search engine alloted high numerical valued ranks to some of the combinations of both families, thereby indicating possible synergy.

Unexplored combinatorial hypotheses	
PVR w.r.t COL	
PVR	COL6A1
COL w.r.t PVR	
COL5A3	PVR
COL9A2	PVRL2

Table 135 2^{nd} order combinatorial hypotheses between PVR and MUC family.

Table 136, shows the rankings of PVR and MUC family with respect to each other. On the left we found, **PVR** to be up regulated w.r.t 1772 (laplace) and 2085 (rbf) for MUC20-PVR. **PVRL2** was up regulated w.r.t MUC17. This is reflected in rankings of 2098 (linear) and 1869 (rbf) for MUC17-PVRL2. **PVRL4** was up regulated w.r.t MUC13. This is reflected in rankings of 2160 (laplace) and 1937 (rbf) for MUC13-PVRL4. On the right side, **MUC-1/3A** were found up regulated w.r.t PVRL4. These are reflected in rankings of 2272 (laplace) and 1827 (linear) for MUC1-PVRL4; and 2103 (linear) and 1835 (rbf) for MUC3A-PVRL4.

Table 137 shows the derived influences which can be represented graphically, with the following influences - • PVR w.r.t MUC with PVR <- MUC20; PVRL2 <- MUC17 and PVRL4 <- MUC13 • MUC w.r.t PVR with MUC1 <- PVRL4; and MUC3A <- PVRL4.

2.10 Anthrax toxin receptor related synergies

2.10.1 ANTXR2 - Collagen cross family analysis

Anthrax toxin receptor ANTRX is known to capture the Bacillus anthracis toxin and form the cause of the anthrax disease. Regulatory mechanism of the ANTXR1 has been demostrated essential component in the fibrosis processes in fibroproliferative diseases. Loss of ANTXR1 (a.k.a TEM8) in fibroblasts leads to increased rates of synthesis of fiber-forming collagens, resulting in progressive fibrosis in skin and other organs Besschetnova *et al.*[253]. TEM8 interacts with the cleaved C5 domain of collagen 3(VI) Nanda *et al.*[254]. Hotchkiss *et al.*[255] also indicate the interaction of TEM8 and collagens. Bell *et al.*[256] indicate that a recombinant portion of ANTXR2 (a.k.a CMG2) was found to bind collagen type IV and laminin, suggesting a potential role in basement membrane matrix synthesis and assembly. Bürgi *et al.*[257] show that CMG2/ANTXR2 regulates extracellular collagen VI which accumulates in hyaline fibromatosis syndrome. A distinctive early childhood-onset disorder, systemic hyalinosis, is characterized by mutations in the anthrax toxin receptor 2 gene (ANTRX2) as shown by Shieh *et al.*[258]. Not much is known about the behaviour of ANTRX2 with collagens in colorectal cancer. In

Ranking PVR vs MUC family

Ranking of PVR w.r.t MUC family	laplace	linear	rbf	Ranking of MUC family w.r.t PVR	laplace	linear	rbf
MUC1-PVR	2173	1184	1021	MUC1-PVR	2106	377	426
MUC3A-PVR	64	130	1828	MUC3A-PVR	136	1217	1004
MUC4-PVR	2000	804	1026	MUC4-PVR	2494	366	586
MUC12-PVR	1449	1589	1899	MUC12-PVR	2370	224	18
MUC13-PVR	1701	1292	1226	MUC13-PVR	1230	144	59
MUC17-PVR	209	684	881	MUC17-PVR	2388	320	1048
MUC20-PVR	1772	1242	2085	MUC20-PVR	1380	188	1039
Ranking of PVRL2 w.r.t MUC family	laplace	linear	rbf	Ranking of MUC family w.r.t PVRL2	laplace	linear	rbf
MUC1-PVRL2	828	454	2362	MUC1-PVRL2	1690	923	1060
MUC3A-PVRL2	584	708	2332	MUC3A-PVRL2	2031	164	546
MUC4-PVRL2	91	1214	478	MUC4-PVRL2	1315	1150	230
MUC12-PVRL2	1129	1655	1439	MUC12-PVRL2	1820	1417	94
MUC13-PVRL2	1052	179	329	MUC13-PVRL2	471	1760	240
MUC17-PVRL2	328	2098	1869	MUC17-PVRL2	873	2111	1462
MUC20-PVRL2	1407	1350	1612	MUC20-PVRL2	1348	325	133
Ranking of PVRL4 w.r.t MUC family	laplace	linear	rbf	Ranking of MUC family w.r.t PVRL4	laplace	linear	rbf
MUC1-PVRL4	569	99	155	MUC1-PVRL4	2272	1827	1457
MUC3A-PVRL4	1088	1214	2498	MUC3A-PVRL4	1698	2103	1835
MUC4-PVRL4	18	13	714	MUC4-PVRL4	1518	1251	789
MUC12-PVRL4	526	449	1420	MUC12-PVRL4	311	1059	2065
MUC13-PVRL4	2160	1404	1937	MUC13-PVRL4	1540	45	1570
MUC17-PVRL4	731	221	234	MUC17-PVRL4	1736	2206	219
MUC20-PVRL4	22	1820	361	MUC20-PVRL4	626	722	2232

Table 136 2^{nd} order combinatorial hypotheses between MUC and PVR family

Unexplored combinatorial hypotheses

PVR w.r.t MUC	
PVR	MUC20
PVRL2	MUC17
PVRL4	MUC13
MUC w.r.t PVR	
MUC1	PVRL4
MUC3A	PVRL4

Table 137 2^{nd} order combinatorial hypotheses between PVR and MUC family.

Ranking ANTRX2 vs COL family

Ranking of ANTRX2 w.r.t COL family	laplace	linear	rbf	Ranking of COL family w.r.t ANTXR2	laplace	linear	rbf
COL5A3-ANTXR2	2006	1473	2217	COL5A3-ANTXR2	984	1782	933
COL6A1-ANTXR2	1935	1061	1366	COL6A1-ANTXR2	324	2211	398
COL7A1-ANTXR2	1002	2119	1690	COL7A1-ANTXR2	1722	956	2121
COL9A2-ANTXR2	1498	552	1361	COL9A2-ANTXR2	2391	80	135
COL17A1-ANTXR2	1906	1086	780	COL17A1-ANTXR2	576	2504	229
COL28A1-ANTXR2	1409	2259	2296	COL28A1-ANTXR2	478	1731	2362

Table 138 2^{nd} order combinatorial hypotheses between ANTRX2 and COL family

Unexplored combinatorial hypotheses

ANTXR2 w.r.t COL	
COL5A3	ANTXR2
COL28A1	ANTXR2
COL w.r.t ANTXR2	
COL7A1	ANTXR2
COL28A1	ANTXR2

Table 139 2^{nd} order combinatorial hypotheses between ANTRX2 and COL family.

CRC cells treated with ETC-1922159 these were up regulated. Our search engine was able to rank the 2nd order combinations between these two to see if there is a possible existing synergy based on the already explored pathological functionality in the above works. At in silico level we found possible high numerical valued ranks pointed to some of the combinations of ANTXR2 and collagen family.

On the left side of table 138 we found **ANTXR2** to be up regulated w.r.t COL-5A3/28A1 (probably COL-7A1 also). These are reflected in rankings of 2006 (laplace) and 2217 (rbf) for COL5A3-ANTXR2; 2259 (linear) and 2296 (rbf) for COL28A1-ANTXR2 and probably 2119 (linear) and 1690 (rbf) for COL7A1-ANTXR2. On the right side, we found, **COL-7A1/28A1** up regulated w.r.t ANTXR2. These are reflected in rankings of 1722 (laplace) and 2121 (rbf) for COL7A1-ANTXR2 and 1731 (linear) and 2362 (rbf) for COL28A1-ANTXR2. Table 139 shows the derived influences which can be represented graphically, with the following influences - • ANTXR2 w.r.t COL with COL5A3 -> ANTXR2 and COL28A1 -> ANTXR2; and • COL w.r.t ANTXR2 with COL7A1 <- ANTXR2 and COL28A1 <- ANTXR2.

2.10.2 ANTXR2 - Integrin cross family analysis

To define whether there is a possible functional cooperation between TEM8/ANTXR1 and integrins to accomplish cell spreading, Werner *et al.*[259] sought to disrupt the function of collagen binding integrins, which mostly belong to $\beta1$ family of integrins, with $\beta1$ integrin-blocking antibodies. Their experiments suggest that the participation of $\beta1$ integrins can be excluded in TEM8-mediated cell spreading on collagen in primary fibroblasts. However, collectively, they indicate that the participation of these integrins in TEM8 spreading on collagen vary with cell type. The cytoplasmic domain of ANTXR1 affects binding of the protective antigen which is similar to integrin I domains that convert between open and closed conformations that bind ligand with high and low affinities, respectively. These findings are observed by Go *et al.*[260]. Scobie *et al.*[261] observe similar behaviour. Abnormal clustering of TEM8/ANTXR1 with integrin $\beta1$ and vascular endothelial growth factor receptor 2 (VEGFR2) occurs in endothelial cells within cutaneous infantile hemangiomas, the most com-

RANKING ANTRX2 VS ITG FAMILY

Ranking of ANTXR2 w.r.t ITG family				Ranking of ITG family w.r.t ANTXR2			
	laplace	linear	rbf		laplace	linear	rbf
ITGA2-ANTXR2	2261	1129	2444	ITGA2-ANTXR2	657	1662	215
ITGA3-ANTXR2	2027	2134	179	ITGA3-ANTXR2	305	1402	278
ITGA6-ANTXR2	1065	1850	1660	ITGA6-ANTXR2	352	2029	583
ITGB1-ANTXR2	2192	1273	1431	ITGB1-ANTXR2	1538	987	1593
ITGB1BP1-ANTXR2	2444	498	2128	ITGB1BP1-ANTXR2	1743	152	534
ITGB4-ANTXR2	1484	699	249	ITGB4-ANTXR2	123	1420	2116
ITGB5-ANTXR2	1318	1860	2315	ITGB5-ANTXR2	2216	718	1182
ITGB6-ANTXR2	1205	1262	1244	ITGB6-ANTXR2	1200	2000	1896
ITGB8-ANTXR2	1710	2354	2136	ITGB8-ANTXR2	296	1724	1485

Table 140 2^{nd} order combinatorial hypotheses between ANTRX2 and ITG family

UNEXPLORED COMBINATORIAL HYPOTHESES

ANTXR2 w.r.t ITG	
ANTXR2	ITG-A2/A3
ANTXR2	ITG-B1BP1/B5/B8
ITG w.r.t ANTXR2	
ITGB6	ANTXR2

Table 141 2^{nd} order combinatorial hypotheses between ANTRX2 and ITG family.

RANKING ANTRX2 VS MMP FAMILY

Ranking of ANTXR2 w.r.t MMP family				Ranking of MMP family w.r.t ANTXR2			
	laplace	linear	rbf		laplace	linear	rbf
MMP1-ANTXR2	1428	1407	1620	MMP1-ANTXR2	244	2009	2142
MMP14-ANTXR2	1067	1141	900	MMP14-ANTXR2	866	971	443
MMP15-ANTXR2	1457	740	1881	MMP15-ANTXR2	121	2219	1926
MMP28-ANTXR2	2468	1765	1202	MMP28-ANTXR2	11	1857	2092

Table 142 2^{nd} order combinatorial hypotheses between ANTRX2 and MMP family

UNEXPLORED COMBINATORIAL HYPOTHESES

ANTXR2 w.r.t MMP	
ANTXR2	MMP28
MMP w.r.t ANTXR2	
MMP-1/15/28	ANTXR2

Table 143 2^{nd} order combinatorial hypotheses between ANTRX2 and MMP family.

mon vascular anomaly in childhood Besschetnova *et al.*[253]. These findings suggest the possibility to synergy between ANTXR2 and Integrin family. In CRC cells treated with ETC-1922159, ANTXR2 and integrin families were up regulated. The search engine alloted high numerical valued ranks to some of the 2^{nd} order combinations of ANTXR2 and integrin family members thus pointing to possible synergy in CRC cells. Table 140 shows the rankings of ANTRX2 along with integrin family members.

On the left side, we found **ANTRX2** to be up regulated w.r.t ITG-A2/A3/B1BP1/B5/B8. These are reflected in the rankings of 2261 (laplace) and 2444 (rbf) for ITGA2-ANTXR2; 2027 (laplace) and 2134 (linear) for ITGA3-ANTXR2; 2444 (laplace) and 2128 (rbf) for ITGB1BP1-ANTXR2; 1860 (linear)and 2315 (rbf) for ITGB5-ANTXR2; and 2354 (linear)and 2136 (rbf) for ITGB8-ANTXR2. On the right side, we found **ITGB6** to be up regulated w.r.t ANTRX2. These are reflected in the rankings of 2000 (linear) and 1896 (rbf) for ITGB6-ANTXR2; Table 141 shows the derived influences which can be represented graphically, with the following influences - • ANTXR2 w.r.t ITG with ITG-A2/A3 -> ANTXR2 and ITG-B1BP1/B5/B8 -> ANTXR2; and • ITG w.r.t ANTXR2 with ITGB6 <- ANTXR2.

2.10.3 ANTXR2 - MMP cross family analysis

Compromised interactions between TEM8/ANTXR1-deficient endothelial and fibroblastic cells cause dramatic reduction in the activity of the matrix-degrading enzyme MMP2 Besschetnova *et al.*[253]. They observe experimentally that loss of MMP2 activity requires loss of TEM8/ANTXR1 function in both endothelial and fibroblastic cells. Matrix metalloproteinases (MMP) are members of the metzincin group of proteases which share the conserved zinc-binding motif in their catalytic active site Löffek *et al.*[262]. these enzymes are capable of degrading all kinds of extracellular matrix proteins, but also can process a number of bioactive molecules as well as play a major role in cell behaviors such as proliferation, migration, differention, apoptosis and host defense, Wikipedia contributors[263]. In CRC cells treated with ETC-1922159, ANTXR2 and integrin families were up regulated. The search engine alloted high numerical valued ranks to some of the 2^{nd} order combinations of ANTXR2 and integrin family members thus pointing to possible synergy in CRC cells. Table 142 shows the rankings of ANTRX2 along with MMP family members.

On the left side, we found **ANTXR2** to be upregulated w.r.t MMP28. This is reflected in rankings of 2468 (laplace) and 1765 (linear) for MMP28-ANTXR2. On the right side we found **MMP-1/15/28** up regulated w.r.t ANTXR2. These are reflected in rankings of 2009 (linear) and 2142 (rbf) for MMP1-ANTXR2; 2219 (linear) and 1926 (rbf) for MMP15-ANTXR2; and 1857 (linear) and 2092 (rbf) for MMP28-ANTXR2. Table 143 shows the derived influences which can be represented graphically, with the following influences - • ANTXR2 w.r.t MMP with ANTXR2 <- MMP28 and • MMP w.r.t ANTXR2 with MMP-1/15/28 <- ANTXR2.

2.10.4 ANTXR2 - WNT cross family analysis

Abrami *et al.*[264] show that LRP6 can indeed form a complex with ATRs (anthrax toxin receptors), and that this interaction plays a role both in Wnt signalling and in anthrax toxin endocyto-

Ranking ANTRX2 vs WNT family

Ranking of ANTRX2 w.r.t WNT family	laplace	linear	rbf	Ranking of WNT family w.r.t ANTXR2	laplace	linear	rbf
WNT2B-ANTXR2	1160	1013	2286	WNT2B-ANTXR2	1577	1367	944
WNT4-ANTXR2	1735	1833	2341	WNT4-ANTXR2	175	1643	97
WNT7B-ANTXR2	2453	304	1196	WNT7B-ANTXR2	2106	242	1144
WNT9A-ANTXR2	1618	487	1766	WNT9A-ANTXR2	2317	162	845

Table 144 2^{nd} order combinatorial hypotheses between ANTRX2 and WNT family

Unexplored combinatorial hypotheses	
ANTXR2 w.r.t WNT	
ANTXR2	WNT4

Table 145 2^{nd} order combinatorial hypotheses between ANTRX2 and WNT family.

sis. Through the ATR-LRP6 interaction, adhesion to the extracellular matrix could locally control Wnt signalling. The authors demonstrated that physical and functional interaction between CMG2/ANTXR2 and LRP6 also raised the possibility that the complex clinical manifestation of Systemic Hyalinosis might be due in part to defects in Wnt signalling. Fluorescence microscopy and biochemical analyses showed that LRP6 enables toxin internalization by interacting at the cell surface with PA receptors TEM8/ATR and/or CMG2/ANTXR2 to form a multi-component complex that enters cells upon PA binding (Wei *et al.*[265]). Verma *et al.*[266] postulate that the developmentally controlled expression of TEM8 modulates endothelial cell response to canonical Wnt signaling to regulate vessel patterning and density. These findings definitely indicate the synergy of ANTRX with Wnts. In CRC cells treated with ETC-1922159, ANTXR2 and WNT families were up regulated. The search engine alloted high numerical valued ranks to some of the 2^{nd} order combinations of ANTXR2 and WNT family members thus pointing to possible synergy in CRC cells. Table 144 shows the rankings of ANTRX2 along with WNT family members.

On the left side, we found **ANTXR2** to be upregulated w.r.t WNT4. This is reflected in rankings of 1833 (linear) and 2341 (rbf) for WNT4-ANTXR2. Table 145 shows the derived influences which can be represented graphically, with the following influences - • ANTXR2 w.r.t WNT with ANTXR2 <- WNT4. This synergistic upregulation of the WNT4 with ANTXR2 might indicate possible control over the signalling in CRC cells treated with ETC-1922159.

2.10.5 ANTXR2 - TNF cross family analysis

The author could not find much about TNF-ANTXR2 combinations in pathological cases in existing literature, however, Lee *et al.*[267] report the "both LeTx and EdTx markedly inhibited LPS-

Ranking ANTRX2 vs TNF family

Ranking of ANTRX2 w.r.t TNF family	laplace	linear	rbf	Ranking of TNF family w.r.t ANTXR2	laplace	linear	rbf
TNF-ANTXR2	1439	1568	1285	TNF-ANTXR2	709	1758	1479
TNFAIP1-ANTXR2	1552	1769	1946	TNFAIP1-ANTXR2	1252	2177	218
TNFAIP2-ANTXR2	125	962	2134	TNFAIP2-ANTXR2	659	1156	2109
TNFAIP3-ANTXR2	1184	1253	1558	TNFAIP3-ANTXR2	1429	2485	1731
TNFRSF1A-ANTXR2	1063	310	2145	TNFRSF1A-ANTXR2	1557	2471	935
TNFRSF10A-ANTXR2	351	1358	1280	TNFRSF10A-ANTXR2	2260	32	2377
TNFRSF10B-ANTXR2	2278	2218	982	TNFRSF10B-ANTXR2	852	715	216
TNFRSF10D-ANTXR2	1352	891	1685	TNFRSF10D-ANTXR2	2258	454	2363
TNFRSF12A-ANTXR2	551	1283	1794	TNFRSF12A-ANTXR2	2190	1150	2061
TNFRSF14-ANTXR2	999	442	498	TNFRSF14-ANTXR2	2370	1777	1014
TNFRSF21-ANTXR2	897	997	298	TNFRSF21-ANTXR2	1474	343	510
TNFRSF10-ANTXR2	2151	966	324	TNFRSF10-ANTXR2	2065	112	339
TNFRSF15-ANTXR2	868	967	1590	TNFRSF15-ANTXR2	664	1211	1669

Table 146 2^{nd} order combinatorial hypotheses between ANTRX2 and TNF family

induced transcription of tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 in J774A.1 cells. In contrast, EdTx synergised with LPS to increase the transcription of IL-6 and IL-8 in HAECs. We showed that HAECs are suitable for anthrax toxin research and express higher levels of the two anthrax toxin receptors - tumour endothelial marker 8 (TEM8/ANTXR1) and capillary morphogenesis protein 2 (CMG2/ANTXR2) - than do J774A.1 cells". The high expression of the ANTXR-1/2 is shown, however, the possible synergy between ANTXR and TNFs in not shown. Our search engine pointed to some of the combinations in CRC cells treated with ETC-1922159 treatment. In table 146, on the left we found **ANTXR2** to be up regulated w.r.t TNF-AIP1/RSF10B. These are reflected in rankings of 1769 (linear) and 1946 (rbf) for TNFAIP1-ANTXR2 and 2278 (linear) and 2218 (rbf) for TNFRSF10B-ANTXR2. On the right we found, **TNFRSF10A/RSF10D/RSF12A/RSF14** was up regulated w.r.t ANTXR2. These are reflected in rankings of 2260 (laplace) and 2377 (rbf) for TNFRSF10A-ANTXR2, 2258 (laplace) and 2363 (rbf) for TNFRSF10D-ANTXR2, 2190 (laplace) and 2061 (rbf) for TNFRSF12A-ANTXR2 and 2370(laplace) and 1777 (linear) for TNFRSF14-ANTXR2.

Table 147 shows the derived influences which can be represented graphically, with the following influences - • ANTXR2 w.r.t TNF with ANTXR2 <- TNFAIP1 and ANTXR2 <- TNFRSF10B and • TNF w.r.t ANTXR2 with TNFRSF10A <- ANTXR2; TNFRSF10D <- ANTXR2; TNFRSF12A <- ANTXR2 and TNFRSF14 <- ANTXR2. This synergistic upregulation of the TNF with ANTXR2 might indicate possible control over the signalling in CRC cells treated with ETC-1922159.

2.10.6 ANTXR2 - IL cross family analysis

The author could not find much about TNF-ANTXR2 combinations in pathological cases in existing literature, however, Lee *et al.*[267] report the "both LeTx and EdTx markedly inhibited LPS-induced transcription of tumour necrosis factor alpha (TNF-α), interleukin (IL)-1β, and IL-6 in J774A.1 cells. In contrast,

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UNEXPLORED COMBINATORIAL HYPOTHESES

ANTXR2 w.r.t TNF	
ANTXR2	TNFAIP1
ANTXR2	TNFRSF10B
TNF w.r.t ANTXR2	
TNFRSF10A	ANTXR2
TNFRSF10D	ANTXR2
TNFRSF12A	ANTXR2
TNFRSF14	ANTXR2

Table 147 2^{nd} order combinatorial hypotheses between ANTRX2 and TNF family.

EdTx synergised with LPS to increase the transcription of IL-6 and IL-8 in HAECs. We showed that HAECs are suitable for anthrax toxin research and express higher levels of the two anthrax toxin receptors - tumour endothelial marker 8 (TEM8/ANTXR1) and capillary morphogenesis protein 2 (CMG2/ANTXR2) âĂŞ than do J774A.1 cells". The high expression of the ANTXR-1/2 is shown, however, the possible synergy between ANTXR and IL in not shown. Our search engine pointed to some of the combinations in CRC cells treated with ETC-1922159 treatment. In table 148, on the left we found **ANTXR2** to be up regulated w.r.t IL-1RN/6ST/17C/17REL. These are reflected in rankings of 1914 (linear) and 1894 (rbf) for IL1RN-ANTXR2; 1944 (laplace), 2219 (linear) and 1914 (rbf) for IL6ST-ANTXR2; 1832 (laplace) and 2334 (linear) for IL17C-ANTXR2 and 1889 (linear) and 2303 (rbf) for IL17REL-ANTXR2. On the right we found, **IL-1A/1B/6ST/17C** was up regulated w.r.t ANTXR2. These are reflected in rankings of 2356 (linear) and 1859 (rbf) for IL1A-ANTXR2; 1780 (linear) and 1865 (rbf) for IL6ST-ANTXR2; 1924 (laplace) and 1901 (rbf) for IL15RA-ANTXR2; and 2121 (linear) and 2437 (rbf) for IL17C-ANTXR2.

Table 149 shows the derived influences which can be represented graphically, with the following influences - • ANTXR2 w.r.t IL with ANTXR2 <- IL1RN; ANTXR2 <- IL6ST; ANTXR2 <- IL17C and ANTXR2 <- IL17REL; and • IL w.r.t ANTXR2 with IL1A <- ANTXR2; IL1B <- ANTXR2; IL6ST <- ANTXR2; and IL17C <- ANTXR2.

RANKING ANTRX2 VS IL FAMILY

RANKING OF ANTRX2 W.R.T IL FAMILY				RANKING OF IL FAMILY W.R.T ANTXR2			
	laplace	linear	rbf		laplace	linear	rbf
IL1A-ANTXR2	1733	454	2253	IL1A-ANTXR2	275	2356	1859
IL1B-ANTXR2	1222	1302	714	IL1B-ANTXR2	330	2011	1762
IL1RAP-ANTXR2	1288	367	80	IL1RAP-ANTXR2	2339	442	747
IL1RN-ANTXR2	1389	1914	1894	IL1RN-ANTXR2	349	1031	1919
IL2RG-ANTXR2	1897	25	432	IL2RG-ANTXR2	368	1867	450
IL6ST-ANTXR2	1944	2219	1914	IL6ST-ANTXR2	46	1780	1865
IL8-ANTXR2	1169	1281	1398	IL8-ANTXR2	1343	2002	434
IL10RB-ANTXR2	1737	496	1545	IL10RB-ANTXR2	1403	800	754
IL15-ANTXR2	787	1812	927	IL15-ANTXR2	1002	1340	481
IL15RA-ANTXR2	840	800	1695	IL15RA-ANTXR2	1924	636	1901
IL17C-ANTXR2	1832	2334	1191	IL17C-ANTXR2	339	2121	2437
IL17REL-ANTXR2	29	1889	2303	IL17REL-ANTXR2	2406	111	960

Table 148 2^{nd} order combinatorial hypotheses between ANTRX2 and IL family

UNEXPLORED COMBINATORIAL HYPOTHESES

ANTXR2 w.r.t IL	
ANTXR2	IL1RN
ANTXR2	IL6ST
ANTXR2	IL17C
ANTXR2	IL17REL
IL w.r.t ANTXR2	
IL1A	ANTXR2
IL1B	ANTXR2
IL6ST	ANTXR2
IL17C	ANTXR2

Table 149 2^{nd} order combinatorial hypotheses between ANTRX2 and IL family.

2.11 Matrix metalloproteinases related synergies

2.11.1 MMP - WNT cross family analysis

2.11.2 MMP - TNF cross family analysis

2.11.3 MMP - IL cross family analysis

2.11.4 MMP - ABC transporter cross family analysis

Conclusion

We present here a range of multiple synergistic 2^{nd} combinations that were ranked via a search engine and later conduct two-cross family analysis between components of these combinations. Via majority voting across the ranking methods, we were able to find plausible unexplored synergistic combinations that might be prevalent in CRC cells after treatment with ETC-1922159 drug. The two-way cross family analysis also assists in deriving influences between components which serve as hypotheses for further tests. In short, we are now able to locate possible synergies via this ranking search engine and two-way cross family analysis for 2^{nd} order combinations in CRC cells treated with ETC-1922159. Further wet lab tests on these combinations for verification is needed. Also, if found true, it paves way for biologists/oncologists to further investigate and understand the mechanism behind the synergy through wet experiments.

Conflict of interest

There are no conflicts to declare.

Author's contributions

Concept, design, in silico implementation - SS. Analysis and interpretation of results - SS. Manuscript writing - SS. Manuscript revision - SS. Approval of manuscript - SS

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Source of Data

Data used in this research work was released in a publication in Madan *et al.*[268]. The ETC-1922159 was released in Singapore in July 2015 under the flagship of the Agency for Science, Technology and Research (A*STAR) and Duke-National University of Singapore Graduate Medical School (Duke-NUS).

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Appendix

Choice of sensitivity indices

The SENSITIVITY PACKAGE (Faivre *et al.*[269] and Iooss and Lemaître[270]) in R langauge provides a range of functions to compute the indices and the following indices will be taken into account for addressing the posed questions in this manuscript.

1. sensiFdiv - conducts a density-based sensitivity analysis where the impact of an input variable is defined in terms of dissimilarity between the original output density function and the output density function when the input variable is fixed. The dissimilarity between density functions is measured with Csiszar f-divergences. Estimation is performed through kernel density estimation and the function kde of the package ks. Borgonovo[271] and Da Veiga[272]

2. sensiHSIC - conducts a sensitivity analysis where the impact of an input variable is defined in terms of the distance between the input/output joint probability distribution and the product of their marginals when they are embedded in a Reproducing Kernel Hilbert Space (RKHS). This distance corresponds to HSIC proposed by Gretton *et al.*[273] and serves as a dependence measure between random variables.

3. soboljansen - implements the Monte Carlo estimation of the Sobol indices for both first-order and total indices at the same time (all together 2p indices), at a total cost of (p+2) × n model evaluations. These are called the Jansen estimators. Jansen[274] and Saltelli *et al.*[275]

4. sobol2002 - implements the Monte Carlo estimation of the Sobol indices for both first-order and total indices at the same time (all together 2p indices), at a total cost of (p+2) ×n model evaluations. These are called the Saltelli estimators. This estimator suffers from a conditioning problem when estimating the variances behind the indices computations. This can seriously affect the Sobol indices estimates in case of largely non-centered output. To avoid this effect, you have to center the model output before applying "sobol2002". Functions ”soboljansen" and "sobolmartinez" do not suffer from this problem. Saltelli[276]

5. sobol2007 - implements the Monte Carlo estimation of the Sobol indices for both first-order and total indices at the same time (all together 2p indices), at a total cost of (p+2) × n model evaluations. These are called the Mauntz estimators. Saltelli and Annoni[277]

6. sobolmartinez - implements the Monte Carlo estimation of the Sobol indices for both first-order and total indices using correlation coefficients-based formulas, at a total cost of (p + 2) × n model evaluations. These are called the Martinez estimators.

7. sobol - implements the Monte Carlo estimation of the Sobol sensitivity indices. Allows the estimation of the indices of the variance decomposition up to a given order, at a total cost of (N + 1) × n where N is the number of indices to estimate. Sobol'[278]