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Machine Learning Discoveries of Interleukin-X Synergy in ETC-1922159 Treated Colorectal Cancer Cells †

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‡   ML dicoveries of Interleukin-X synergy in ETC-1922159 treated CRC cells.

Abstract: Often, in biology, we are faced with the problem of exploring relevant unknown biological hypotheses in the form of myriads of combinations of factors/genes/proteins that might be affecting the pathway under certain conditions. In colorectal cancer (CRC) cells treated with ETC-1922159, many genes were found up and down regulated, individually. A recently developed search engine ranked combinations of Interleukin (IL)-X (X, a particular gene/protein) at 2nd order level after drug administration. These rankings reveal which IL-X combinations might be working synergistically in CRC. If found true, oncologists can further test the combination of interest in wet lab and determine the mechanism of functioning between the IL and X. In this research work, we cover combinations of IL with nuclear factor κ B (NFκB), Potassium ion channel sub- family members (KCN), mucin (MUC), TP53, STAT, TNF receptor associated factor (TRAF), STEAP4 metalloreductase, STEAP3 metalloreductase, ATP-binding cassette (ABC) transporters and tumor necrosis factor (TNF).

Keywords: interleukin (IL); porcupine inhibitor ETC-1922159; sensitivity analysis; colorectal cancer

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1. Introduction

In the unpublished preprint Sinha [1], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway.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 direct or indirect manner. Interested readers are advised to go through unpublished preprints Sinha [1] and Sinha [2] for details regarding the search engine and the discoveries mentioned in there.

2. Materials and Methods

2.1. Combinatorial Search Problem and a Possible Solution

The issue of combinatorial search problem and a possible solution has been addressed in Sinha [3] and Sinha [2]. The details of the methodology of this manuscript have been explained in great detail in Sinha [3] & its application 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.

Briefly, from Sinha [2], the pipleline works by computing sensitivity indicies for each of these unique combinations and then vectorising these indices to connote and form discriminative feature vector for each combination. Since each combination is unique, the training and the test data are same. In the training data, the combinations are arranged and ranks from 1 to n are assigned. The ranking algorithm then learns the patterns from these combinations/sensitivity index vectors. Next the learned model is used to rank the test data by generating the ranking score for each of the unique

combination. Sorting these shuffled scores of test data leads to prioritization of the combinations. Joachims [4] show an example of applying learned model to training data (same as the test data) in https://www.cs.cornell.edu/people/tj/svm_light/svm_rank.html. Note that these combinations are now ranked and give the biologists a chance to narrow down their focus on crucial biological hypotheses in the form of combinations which the biologists might want to test. Analogous to the webpage search engine, where the click of a button for a few key-words leads to a ranked list of web links, the pipeline uses sensitivity indices as an indicator of the strength of the influence of factors or their combinations, as a criteria to rank the combinations.

3. Results & Discussion

3.1. Interleukin Related Synergies

3.1.1. NFκB-2/I - Interleukin Cross Family Analysis

Hörber *et al.* [5] show that the atypical inhibitor of NF-κB, IκBζ, controls macrophage interleukin-10 expression. Yamazaki *et al.* [6] 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.* [7] 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 1 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 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 2 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;

Table 1. 2nd order combinatorial hypotheses between NFkB-2/I and IL.

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 2. 2nd order combinatorial hypotheses between IL and NFkB-2/I family.

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

3.1.2. Potassium Channel - Interleukin Cross Family Analysis

In 1986, Lee *et al.* [8] showed that increased voltage-gated potassium conductance during interleukin 2-stimulated proliferation of a mouse helper T lymphocyte clone. Martin *et al.* [9] 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 Tables 3 and 4. 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 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 IL17REL - KCNK6.

Table 3. 2nd order combinatorial hypotheses between KCN and IL.

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

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;

Table 4. 2nd order combinatorial hypotheses between KCN and IL.

RANKING INTERLEUKIN FAMILY VS KCN FAMILY							
RANKING OF IL FAMILY W.R.T KCNK1				RANKING OF KCNK1 W.R.T IL FAMILY			
	laplace	linear	rbf		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				RANKING OF KCNK5 W.R.T IL FAMILY			
	laplace	linear	rbf		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				RANKING OF KCNK6 W.R.T IL FAMILY			
	laplace	linear	rbf		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

Finally, Table 5 shows 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;

Table 5. 2nd order combinatorial hypotheses between IL family w.r.t KCN family.

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

3.1.3. Mucin - Interleukin Cross Family Analysis

Kerschner *et al.* [10] have observed that middle ear epithelial mucin production in response to interleukin-6 exposure in vitro. Chen *et al.* [11] 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.* [12]. Yokoigawa *et al.* [13] show enhanced production of interleukin 6 in peripheral blood monocytes stimulated with mucins secreted into the bloodstream. Gray *et al.* [14] 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.* [15] mucin 2 silencing promotes metastasis through interleukin-6 signaling. In CRC cells treated with ETC-1922159, both were found to be up regulated. Tables 6 and 7 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 respect 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.

Table 6. 2nd order combinatorial hypotheses between MUC and IL.

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 7. 2nd order combinatorial hypotheses between MUC and IL.

RANKING INTERLEUKIN FAMILY VS MUC FAMILY CONTD.

RANKING OF IL FAMILY W.R.T MUC13				RANKING OF MUC13 W.R.T IL FAMILY		
	laplace	linear	rbf		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				RANKING OF MUC17 W.R.T IL FAMILY		
	laplace	linear	rbf		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				RANKING OF MUC20 W.R.T IL FAMILY		
	laplace	linear	rbf		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

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 8 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;

Table 8. 2nd order combinatorial hypotheses between IL and NFkB-2/I family.

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

3.1.4. Interleukin - TP53 Cross Family Analysis

In a new pathway connecting inflammation to cancer, Brighenti *et al.* [16] show that interleukin 6 downregulates p53 expression and activity by stimulating ribosome biogenesis. Tan *et al.* [17] 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.* [18] 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.* [19]. 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.* [20] 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 9 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; 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).

Finally, Table 10 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.

Table 9. 2nd order combinatorial hypotheses between TP53 and IL.

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 10. 2nd order combinatorial hypotheses between IL and NFkB-2/I family.

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

3.1.5. Interleukin - STAT Cross Family Analysis

Jones *et al.* [21] 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.* [22]. Adam *et al.* [23] have unraveled viral interleukin-6 binding to gp130 and activation of STAT-signaling pathways independently of the interleukin-6 receptor. Frank *et al.* [24] report the involvement of interleukin 2 signaling in phosphorylation of Stat proteins. Boyd *et al.* [25] show that interleukin-10 receptor signaling through STAT-3 regulates the apoptosis of retinal ganglion cells in response to stress. Essential role of endocytosis for interleukin-4-receptor-mediated JAK/STAT signalling has been studied in Kurgonaite *et al.* [26]. Contribution of the interleukin-6/STAT-3 signaling pathway to chondrogenic differentiation of human mesenchymal stem cells has been studied in Kondo *et al.* [27]. Tanaka *et al.* [28] show interleukin-10 induces inhibitory C/EBPβ through STAT-3 and represses HIV-1 transcription in macrophages. Jobst *et al.* [29] 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 2nd order combinations between the two. Table 11 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 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 (linear) for IL8 - STAT5A; and 1760 (laplace), 2060 (linear) and 2201 (rbf) for IL17C - STAT5A.

Finally, Table 12 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;

Table 11. 2nd order combinatorial hypotheses between STAT and IL.

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 12. 2nd order combinatorial hypotheses between IL and STAT family.

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

3.1.6. Interleukin - TRAF Cross Family Analysis

Greene and O'Neill [30] 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.* [31] observe that TRAF6 is a signal transducer for interleukin-1. Schwandner *et al.* [32] show the requirement of tumor necrosis factor receptor-associated factor (TRAF) 6 in interleukin 17 signal transduction. Lomaga *et al.* [33] show that TRAF6 deficiency results in osteopetrosis and defective interleukin-1, CD40, and LPS signaling. Jefferies *et al.* [34] 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 [35] 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 13 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 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 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 14 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.

Table 13. 2nd order combinatorial hypotheses between TRAF and IL.

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 14. 2nd order combinatorial hypotheses between IL and TRAF family.

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

3.1.7. Interleukin - Metalloreductase STEAP4 Cross Family Analysis

Ramadoss *et al.* [36] 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.* [37] 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. These were found to be up regulated in CRC cells treated with ETC-1922159. Table 15 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 - 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 16 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.

Table 15. 2nd order combinatorial hypotheses between STEAP4 and IL.

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 16. 2nd order combinatorial hypotheses between IL and STEAP4 family.

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

3.1.8. 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 17 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) 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 18 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.

Table 17. 2nd order combinatorial hypotheses between STEAP3 and IL.

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 18. 2nd order combinatorial hypotheses between IL and STEAP3 family.

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

3.1.9. Interleukin - ATP-Binding Cassette Transporters

Haskó *et al.* [38] 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.* [39] 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.* [40] observe that interleukin-1β secretion is impaired by inhibitors of the ATP binding cassette transporter, ABC1. Lottaz *et al.* [41] 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 regulated. Table 19 shows rankings of IL family with respect to a few ABC members on the left and vice versa on the right.

Table 19. 2nd order combinatorial hypotheses between ABC and IL.

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

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 20 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.

Table 20. 2nd order combinatorial hypotheses between IL and ABC family.

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

3.1.10. Interleukin - TNF Cross Family Analysis

Neta *et al.* [42] study the relationship of TNF to interleukins way back in 1992. The review by Rieckmann *et al.* [43] studies role of TNF-α and IL-6 in normal and pathophysiological conditions of B-cell function. Bethea *et al.* [44] 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.* [45]. Zhai *et al.* [46] 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 *et al.* [47] 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.* [48]. Tissi *et al.* [49] 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.* [50] 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.* [51] 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 2nd order combinations of IL and TNF family members. These are tabulated in Tables 21–24. 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 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;

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 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 - TNFRSF14; 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.

Table 21. 2nd order combinatorial hypotheses between TNF and IL.

RANKING INTERLEUKIN FAMILY VS TNF FAMILY

RANKING OF IL FAMILY W.R.T TNF				RANKING OF TNF W.R.T IL FAMILY			
	laplace	linear	rbf		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				RANKING OF TNFAIP1 W.R.T IL FAMILY			
	laplace	linear	rbf		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				RANKING OF TNFAIP2 W.R.T IL FAMILY			
	laplace	linear	rbf		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 22. 2nd order combinatorial hypotheses between TNF and IL.

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 23. 2nd order combinatorial hypotheses between IL and TNF.

RANKING INTERLEUKIN FAMILY VS TNF FAMILY							
RANKING OF IL FAMILY W.R.T TNFRSF10B				**RANKING OF TNFRSF10B W.R.T IL FAMILY**			
	laplace	linear	rbf		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				**RANKING OF TNFRSF10D W.R.T IL FAMILY**			
	laplace	linear	rbf		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				**RANKING OF TNFRSF12A W.R.T IL FAMILY**			
	laplace	linear	rbf		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				**RANKING OF TNFRSF14 W.R.T IL FAMILY**			
	laplace	linear	rbf		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 24. 2nd order combinatorial hypotheses between IL and TNF.

RANKING INTERLEUKIN FAMILY VS TNF FAMILY

RANKING OF IL FAMILY W.R.T TNFRSF21	laplace	linear	rbf	RANKING OF TNFRSF21 W.R.T IL FAMILY	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	laplace	linear	rbf	RANKING OF TNFRS10 W.R.T IL FAMILY	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	laplace	linear	rbf	RANKING OF TNFRS15 W.R.T IL FAMILY	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

Finally, Table 25 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 $- >$ 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;

Table 25. 2nd order combinatorial hypotheses between IL and TNF family.

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

Conclusion

Presented here are a range of multiple synergistic Interleukin 2nd order combinations that were ranked via a search engine. Later, two way cross family analysis between components of these combinations were conducted. Via majority voting across the ranking methods, it was possible 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. If found true, it paves way for biologists/oncologists to further investigate and understand the mechanism behind the synergy through wet experiments.

Source of Data

Data used in this research work was released in a publication in Madan *et al.* [52]. 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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