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Machine Learning Discoveries of DNA Repair-X Synergy in ETC-1922159 Treated Colorectal Cancer Cells

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Machine Learning Discoveries of DNA Repair-X Synergy in ETC-1922159 Treated Colorectal Cancer 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 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 DNA repair gene-X (X, a particular gene/protein) at 2^{nd} order level after drug administration. These rankings reveal which Wnt-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 Wnt and X. In this research work, we cover combinations of RAD with X-ray repair cross complementing (XRCC) family, 5'-3' exoribonuclease 2 (XRN2), NFKB repressing factor (NKRF), B cell CLL/lymphoma (BCL) family, exosome component (EXOSC) family, FA complementation group (FANC) family and XRCC with EXOSC.

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In the unpublished preprint Sinha [1], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway.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 Interested readers are advised to go through unpublished preprints Sinha [1] and Sinha [2] for details regarding the search engine and the discoveries mentioned in there.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

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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. DNA Repair Related Synergies

3.1.1. 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 [5] and Thacker and Zdzienicka [6]. Sultana et al. [7] 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. [8] 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 indicate 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 1 shows the rankings of RAD family w.r.t XRCC family and 2 shows the rankings of the XRCC family w.r.t RAD family. In table 1 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;

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

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

In Table 2 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;

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

Ranking XRCC family w.r.t RAD family							
Ranking of XRCC w.r.t RAD1				Ranking of XRCC w.r.t RAD18			
	laplace	linear	rbf		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				Ranking of XRCC w.r.t RAD51			
	laplace	linear	rbf		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				Ranking of XRCC w.r.t RAD51C			
	laplace	linear	rbf		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				Ranking of XRCC w.r.t RAD54L			
	laplace	linear	rbf		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 3 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;

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Table 3. 2^{nd} order combinatorial hypotheses between RAD and XRCC.

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

3.1.2. XRN2 - RAD Cross Family Analysis

XRN2 (5'-3' exoribonuclease 2) is involved in RNA synthesis/trafficking and termination. Morales et al. [9] 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 engine gave rankings to the combinations of the XRN2 and RAD family members with low numerical valued in silico ranks. Table 4 shows the rankings of XRN2 w.r.t RAD family and vice versa. Following this is the derived influences in table 5. 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 4. 2^{nd} order interaction ranking between RAD family vs XRN2.

Ranking XRN2 w.r.t RAD family							
Ranking of RAD family w.r.t XRN2				Ranking of XRN2 w.r.t RAD family			
	laplace	linear	rbf		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 5 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.

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Table 5. 2^{nd} order combinatorial hypotheses between RAD and 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

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3.1.3. 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 6 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 6. 2^{nd} order interaction ranking between RAD family vs NKRF.

Ranking NKRF w.r.t RAD family							
Ranking of NFRK w.r.t RAD family				Ranking of RAD family w.r.t NKRF			
	laplace	linear	rbf		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 7 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.

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Table 7. 2^{nd} order combinatorial hypotheses between RAD and XRN2.

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

3.1.4. RAD - BCL Cross Family Analysis

Saintigny et al. [10] 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-kB following cytosolic DNA sensing, Meng et al. [11] demonstrated that BCL10 was recruited to the dsDNA–RAD50 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 8 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** 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.

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Table 8. 2^{nd} order interaction ranking between RAD and BCL family members.

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

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)

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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 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**, 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 9 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.

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Table 9. 2^{nd} order combinatorial hypotheses between RAD and BCL members.

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

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3.1.5. RAD - EXOSC Cross Family Analysis

Marin-Vicente et al. [12] 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. [13]). 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 10 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;

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Table 10. 2^{nd} order interaction ranking between RAD and EXOSC family members.

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

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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 - 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 11 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.

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Table 11. 2^{nd} order combinatorial hypotheses between RAD and EXOSC members.

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

3.1.6. 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 12 shows the rankings of XRCC vs EXOSC family members.

Table 12. 2^{nd} order interaction ranking between RAD and EXOSC family members.

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 13. 2^{nd} order combinatorial hypotheses between XRCC and EXOSC members.

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

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.

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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 (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;

Table 13 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.

3.1.7. 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 [14]). Cohn and D'Andrea [15] 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. [16] 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. [17]. Liang et al. [18] observe the role of trimeric RAD51 and RAD51AP1-UAF1 complex in FANCD2. Taniguchi et al. [19] observe S-phase-specific interaction of the Fanconi anemia protein, FANCD2, with BRCA1 and RAD51. Zadorozhny et al. [20] show Fanconi anemia associated mutations destabilize RAD51 filaments and impair replication fork protection. Geng et al. [21] 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 [22]. García-Luis and Machín [23] 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 15 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 -

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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.

Table 14. 2^{nd} order combinatorial hypotheses between RAD and FANC members.

Ranking RAD family VS FANC family							
Ranking of RAD family w.r.t FANCB				Ranking of FANCB w.r.t RAD family			
	laplace	linear	rbf		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				Ranking of FANCD2 w.r.t RAD family			
	laplace	linear	rbf		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				Ranking of FANCD2OS w.r.t RAD family			
	laplace	linear	rbf		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				Ranking of FANCF w.r.t RAD family			
	laplace	linear	rbf		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				Ranking of FANCG w.r.t RAD family			
	laplace	linear	rbf		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				Ranking of FANCI w.r.t RAD family			
	laplace	linear	rbf		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

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 -

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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 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 15. 2^{nd} order combinatorial hypotheses between RAD and FANC family.

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 15 shows the derived influences which can be represented graphically, with the following influences - • 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;

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Conclusions

Presented here are a range of multiple synergistic DNA repair gene 2^{nd} 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. [24]. 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).

Author 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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