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Article

# Machine Learning Discoveries of BCL-X Synergy in ETC-1922159 Treated Colorectal Cancer Cells ‡

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† ML discoveries of BCL-X synergy in ETC-1922159 treated CRC cells.

‡ Aspects of unpublished work were presented in a poster session at (1) the recently concluded first ever Wnt Gordon Conference, from 6-11 August 2017, held in Stowe, VT 05672, USA.

**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 BCL-X (X, a particular gene/protein) at 2<sup>nd</sup> order level after drug administration. These rankings reveal which BCL-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 BCL and X. In this research work, we cover combinations of BCL with Interleukin (IL), Selenbp1, TP53, caspase (CASP), mucin (MUC) and exosome (EXOSC).

**Keywords:** BCL; porcupine inhibitor ETC-1922159; sensitivity analysis; colorectal cancer

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In the unpublished preprint Sinha [1], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway.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 Interested readers are advised to go through unpublished preprints Sinha [1] and Sinha [2] for details regarding the search engine and the discoveries mentioned in there.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

##### 3.1.1. Interleukin - BCL cross Family Analysis

Qin et al. [5] observe that IL-6 inhibits starvation-induced autophagy via the STAT3/Bcl-2 signaling pathway. Gabellini et al. [6] observed that interleukin 8 mediates bcl-xL-induced enhancement of human melanoma cell dissemination and angiogenesis in a zebrafish xenograft model. Guruprasath et al. [7] show that interleukin-4 receptor-targeted delivery of Bcl-xL siRNA sensitizes tumors to chemotherapy and inhibits tumor growth. Maraskovsky et al. [8] indicate that Bcl-2 can rescue T lymphocyte development in interleukin-7 receptor-deficient mice but not in mutant rag-1<sup>-/-</sup> mice. Akashi et al. [9] show that Bcl-2 rescues T lymphopoiesis in interleukin-7 receptor-deficient mice. Interleukin-10 increases Bcl-2 expression and survival in primary human CD34+ hematopoietic progenitor cells as shown by Weber-Nordt et al. [10]. Interleukin-7 and interleukin-15 regulate the expression of the bcl-2 and c-myc genes in cutaneous T-cell lymphoma cells as shown by Qin et al. [11]. Bcl-2 is a negative regulator of interleukin-1 $\beta$  secretion in murine macrophages in pharmacological-induced apoptosis as shown by Escandell et al. [12]. Alas et al. [13] observe that inhibition of interleukin 10 by rituximab results in down-regulation of bcl-2 and sensitization of B-cell non-Hodgkin's lymphoma to apoptosis. These findings indicate the synergy between BCL and Interleukin in different pathological cases. In CRC cells treated with ETC-1922159, these were found to be up regulated. Tables 1 and 2 indicate the rankings of the IL and BCL family.

**Table 1.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and IL

RANKING IL FAMILY VS BCL FAMILY							
RANKING OF IL FAMILY W.R.T BCL2L1				RANKING OF BCL2L1 W.R.T IL FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL2L1	2482	859	1834	IL1A - BCL2L1	780	1156	1712
IL1B - BCL2L1	2252	1920	1482	IL1B - BCL2L1	1838	954	2132
IL1RAP - BCL2L1	1128	815	1935	IL1RAP - BCL2L1	870	1777	1262
IL1RN - BCL2L1	648	2504	650	IL1RN - BCL2L1	973	385	1297
IL2RG - BCL2L1	1542	1439	700	IL2RG - BCL2L1	2048	486	1949
IL6ST - BCL2L1	663	553	1432	IL6ST - BCL2L1	284	674	468
IL8 - BCL2L1	260	202	2070	IL8 - BCL2L1	1430	1343	1417
IL10RB - BCL2L1	1867	347	17	IL10RB - BCL2L1	1659	1965	2024
IL15 - BCL2L1	1558	775	381	IL15 - BCL2L1	690	542	1277
IL15RA - BCL2L1	2136	1177	1533	IL15RA - BCL2L1	581	1107	972
IL17C - BCL2L1	2481	2410	2512	IL17C - BCL2L1	695	1739	1775
IL17REL - BCL2L1	815	657	374	IL17REL - BCL2L1	981	1225	509

Table 1. Cont.

RANKING IL FAMILY VS BCL FAMILY							
RANKING OF IL FAMILY W.R.T BCL2L2				RANKING OF BCL2L2 W.R.T IL FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL2L2	138	361	86	IL1A - BCL2L2	2407	2362	2464
IL1B - BCL2L2	165	389	108	IL1B - BCL2L2	1807	2462	2344
IL1RAP - BCL2L2	623	1523	861	IL1RAP - BCL2L2	77	1897	1711
IL1RN - BCL2L2	2324	530	984	IL1RN - BCL2L2	2298	1620	2092
IL2RG - BCL2L2	2137	285	347	IL2RG - BCL2L2	2429	850	1744
IL6ST - BCL2L2	2239	1927	2085	IL6ST - BCL2L2	477	2046	1859
IL8 - BCL2L2	894	1418	1346	IL8 - BCL2L2	1803	1072	2024
IL10RB - BCL2L2	2243	738	1020	IL10RB - BCL2L2	1041	145	843
IL15 - BCL2L2	110	650	1347	IL15 - BCL2L2	2474	2142	2416
IL15RA - BCL2L2	258	1715	361	IL15RA - BCL2L2	1377	1211	2298
IL17C - BCL2L2	554	12	147	IL17C - BCL2L2	1168	2512	2447
IL17REL - BCL2L2	2454	2510	2482	IL17REL - BCL2L2	539	1875	1442
RANKING OF IL FAMILY W.R.T BCL2L13				RANKING OF BCL2L13 W.R.T IL FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL2L13	1572	458	174	IL1A - BCL2L13	1456	811	2403
IL1B - BCL2L13	927	227	424	IL1B - BCL2L13	1286	1446	2348
IL1RAP - BCL2L13	278	718	1941	IL1RAP - BCL2L13	823	2450	2510
IL1RN - BCL2L13	608	1277	881	IL1RN - BCL2L13	2503	623	2378
IL2RG - BCL2L13	507	1182	5	IL2RG - BCL2L13	2483	1648	2248
IL6ST - BCL2L13	1778	1403	246	IL6ST - BCL2L13	1899	2473	2046
IL8 - BCL2L13	178	468	1606	IL8 - BCL2L13	2099	910	2294
IL10RB - BCL2L13	991	1211	804	IL10RB - BCL2L13	2120	1895	194
IL15 - BCL2L13	1868	432	15	IL15 - BCL2L13	2515	2160	2420
IL15RA - BCL2L13	1629	2134	685	IL15RA - BCL2L13	933	1844	2318
IL17C - BCL2L13	995	84	20	IL17C - BCL2L13	2004	2434	2500
IL17REL - BCL2L13	2420	2419	2464	IL17REL - BCL2L13	1490	760	442
RANKING OF IL FAMILY W.R.T BCL3				RANKING OF BCL3 W.R.T IL FAMILY			
	laplace	linear	rbf		laplace	linear	rbf
IL1A - BCL3	880	2462	396	IL1A - BCL3	474	436	1045
IL1B - BCL3	975	1507	40	IL1B - BCL3	799	303	926
IL1RAP - BCL3	1425	821	1129	IL1RAP - BCL3	44	164	1115
IL1RN - BCL3	149	471	311	IL1RN - BCL3	37	1784	477
IL2RG - BCL3	454	365	505	IL2RG - BCL3	524	2060	335
IL6ST - BCL3	1928	755	2344	IL6ST - BCL3	316	1457	607
IL8 - BCL3	1052	743	2044	IL8 - BCL3	2266	1236	1983
IL10RB - BCL3	95	800	1625	IL10RB - BCL3	2187	1600	2170
IL15 - BCL3	1041	820	214	IL15 - BCL3	17	966	182
IL15RA - BCL3	2478	1820	2500	IL15RA - BCL3	462	1476	1100
IL17C - BCL3	737	1682	8	IL17C - BCL3	1069	923	1926
IL17REL - BCL3	218	424	2019	IL17REL - BCL3	692	1897	1274

**Table 2.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and IL

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

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

(laplace) and 1960 (linear) for IL6ST - BCL9L; 2197 (linear) and 2162 (rbf) for IL8 - BCL9L; and 2308 (linear) and 1926 (rbf) for IL17REL - BCL9L; **IL-6ST/15RA** were up regulated w.r.t BCL10. These are reflected in rankings of 2008 (laplace) and 1816 (rbf) for IL6ST - BCL10; and 2064 (linear) and 1789 (rbf) for IL15RA - BCL10;

On the right side is the rankings of BCL w.r.t IL family. We found **BCL2L1** up regulated IL-1B/2RG/10RB. These are reflected in rankings of 1838 (laplace) and 2132 (rbf) for IL1B - BCL2L1; 2048 (laplace) and 1949 (rbf) for IL2RG - BCL2L1; and 1965 (linear) and 2024 (rbf) for IL10RB - BCL2L1; **BCL2L2** was up regulated IL-1A/1B/1RN/6ST/8/15/17C. These are reflected in rankings of 2407 (laplace), 2362 (linear) and 2464 (rbf) for IL1A - BCL2L2; 1807 (laplace), 2462 (linear) and 2344 (rbf) for IL1B - BCL2L2; 2298 (laplace) and 2092 (rbf) for IL1RN - BCL2L2; 2046 (linear) and 1859 (rbf) for IL6ST - BCL2L2; 1803 (laplace) and 2024 (rbf) for IL8 - BCL2L2; 2474 (laplace), 2142 (linear) and 2416 (rbf) for IL15 - BCL2L2; and 2512 (linear) and 2447 (rbf) for IL17C - BCL2L2; **BCL2L13** was up regulated IL-1RAP/1RN/2RG/6ST/8/10RB/15/15RA/17C. These are reflected in rankings of 2450 (linear) and 2510 (rbf) for IL1RAP - BCL2L13; 2503 (laplace) and 2378 (rbf) for IL1RN - BCL2L13; 2483 (laplace) and 2248 (rbf) for IL2RG - BCL2L13; 1899 (laplace), 2473 (linear) and 2046 (rbf) for IL6ST - BCL2L13; 2099 (laplace) and 2294 (rbf) for IL8 - BCL2L13; 2120 (laplace) and 1895 (linear) for IL10RB - BCL2L13; 2515 (laplace), 2160 (linear) and 2420 (rbf) for IL15 - BCL2L13; 1844 (linear) and 2318 (rbf) for IL15RA - BCL2L13; and 2004 (laplace), 2434 (linear) and 2500 (rbf) for IL17C - BCL2L13; **BCL3** was up regulated IL-8/10RB. These are reflected in rankings of 2266 (laplace) and 1983 (rbf) for IL8 - BCL3; and 2187 (laplace) and 2170 (rbf) for IL10RB - BCL3; 2298 (laplace); 2423 (linear) and 2294 (rbf) for IL1B - BCL6; 1919 (laplace) and 2301 (linear) for IL1RN - BCL6; 2106 (linear) and 2478 (rbf) for IL2RG - BCL6; 2123 (laplace), 2068 (linear) for IL8 - BCL6; 2084 (laplace), 1791 (linear) and 2203 (rbf) for IL15RA - BCL6; and for 1949 (linear) and 1930 (rbf) for IL17REL - BCL6; **BCL10** was up regulated IL-1A/1RAP/1RN/2RG/10RB/15RA. These are reflected in rankings of 2405 (linear) and 1889 (rbf) for IL1A - BCL10; 1929 (laplace) and 2112 (rbf) for IL1RAP - BCL10; 1846 (laplace) and 1823 (linear) for IL1RN - BCL10; 1885 (laplace) and 1803 (linear) for IL2RG - BCL10; 2244 (laplace) and 2150 (linear) for IL10RB - BCL10; and 1810 (laplace) and 1835 (rbf) for IL15RA - BCL10;

Finally, Table 3 shows the derived influences which can be represented graphically, with the following influences - • IL w.r.t BCL with IL-1A/1B/17C < - BCL2L1; IL-6ST/17REL < - BCL2L2; IL-17REL < - BCL2L13; IL-6ST/15RA < - BCL3; IL-1RAP/6ST/8/17REL < - BCL6; IL-1A/6ST/8/17REL < - BCL9L; and IL-6ST/15RA < - BCL10; • BCL w.r.t IL with IL-1B/2RG/10RB - > BCL2L1; IL-1A/1B/1RN/6ST/8/15/17C - > BCL2L2; IL-1RAP/1RN/2RG/6ST/8/10RB/15/15RA/17C - > BCL2L13; IL-8/10RB - > BCL3; IL-1B/1RN/2RG/8/15RA/17REL - > BCL6; and IL-1A/1RAP/1RN/2RG/10RB/15RA - > BCL10;

**Table 3.** 2<sup>nd</sup> order combinatorial hypotheses between IL and BCL family.

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

### 3.1.2. Selenbp1 - BCL cross Family Analysis

Deng et al. [14] study the effects of selenium on lead-induced alterations in  $A\beta$  production and Bcl-2 family proteins. Yaming et al. [15] studied the effects of selenium dioxide on apoptosis, Bcl-2 and p53 expression, intracellular reactive oxygen species and calcium level in three human lung cancer cell lines. Activity of selenium on cell proliferation, cytotoxicity, and apoptosis and on the expression of CASP9, BCL-XL and APC in intestinal adenocarcinoma cells has been studied by Mauro et al. [16]. These studies suggest the synergy between BCL and Selenium based genes. In CRC cells treated with ETC-1922159, these were found to be down regulated. Table 4 shows the rankings of BCL family w.r.t to SELENBP1 and vice versa.

On the right side, we found **BCL-6B/11A** to be up regulated with respect to SELENBP1. These were reflected in the rankings of 182 (laplace), 110 (linear) and 494 (rbf) for SELENBP1 - BCL6B; and 905 (laplace), 931 (linear) and 401 (rbf) for SELENBP1 - BCL11A. On the left side **SELENBP1** was up regulated w.r.t BCL-9/11B. These are reflected in rankings of 1568 (linear) and 1738 (rbf) for SELENBP1 - BCL9; and 299 (linear) and 1385 (rbf) for SELENBP1 - BCL11B; Finally, Table 5 shows the derived influences which can be represented graphically, with the following influences - • SELENBP1 w.r.t BCL with SELENBP1 < - BCL-9/11B; and • BCL w.r.t SELENBP1 with SELENBP1 - > BCL-6B/11A;

**Table 4.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and SELENBP1

RANKING SELENBP1 VS BCL FAMILY							
RANKING OF BCL FAMILY W.R.T SELENBP1	RANKING OF SELENBP1 W.R.T BCL						
	laplace	linear	rbf				
SELENBP1 - BCL2L12	2426	2033	2629	SELENBP1 - BCL2L12	2589	2195	2082
SELENBP1 - BCL6B	2446	2575	1956	SELENBP1 - BCL6B	182	110	494
SELENBP1 - BCL7A	2620	1326	2006	SELENBP1 - BCL7A	2015	1799	767
SELENBP1 - BCL9	2453	1568	1738	SELENBP1 - BCL9	2538	1916	1793
SELENBP1 - BCL11A	1921	2463	1566	SELENBP1 - BCL11A	905	931	401
SELENBP1 - BCL11B	1896	299	1385	SELENBP1 - BCL11B	2496	2636	2510

**Table 5.** 2<sup>nd</sup> order combinatorial hypotheses between SELENBP1 and BCL family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
SELENBP1 w.r.t BCL	
SELENBP1	BCL-9/11B
BCL w.r.t SELENBP1	
SELENBP1	BCL-6B/11A

### 3.1.3. TP53 - BCL cross Family Analysis

The p53-Bcl-2 connection has been studied by Hemann and Lowe [17]. Tomita et al. [18] show wild type p53, but not tumor-derived mutants, bind to Bcl2 via the DNA binding domain and induce mitochondrial permeabilization. Bcl-2 constitutively suppresses p53-dependent apoptosis in colorectal cancer cells as shown by Jiang and Milner [19]. The tissue dependent interactions between p53 and Bcl-2 in vivo has been studied by Li et al. [20]. Synthetic lethality of combined Bcl-2 inhibition and p53 activation in AML has been studied by Pan et al. [21]. Zaidi et al. [22] observe that the chloroquine-induced neuronal cell death is p53 and Bcl-2 family-dependent but caspase-independent. Relationship of p53, bcl-2, and tumor proliferation to clinical drug resistance in non-Hodgkin's lymphomas has been studied in Wilson et al. [23]. TP53 and BCL family members were found to be up regulated in CRC cells treated with ETC-1922159. Table 6 show rankings of BCL and TP53 family w.r.t to each other.

**Table 6.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and SELENBP1.

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

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

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

for 2259 (linear) and 2043 (rbf) for TP53INP1 - BCL3; **TP53-BP2/INP2** were up regulated w.r.t BCL9L. These are reflected in the rankings for 2093 (laplace) and 2217 (linear) for TP53BP2 - BCL9L; and 2222 (laplace) and 1900 (linear) for TP53INP2 - BCL9L;

Finally, Table 7 shows the derived influences which can be represented graphically, with the following influences - • BCL w.r.t TP53 with TP53-I3/INP2 < - BCL2L2; TP53-INP2 < - BCL2L13; TP53-I3/INP2 < - BCL6; TP53-BP2 < - BCL9L; and TP53-BP2/INP2 < - BCL10; • TP53 w.r.t BCL with TP53-BP2/I3 < - BCL2L1; TP53-INP1 < - BCL3 and TP53-BP2/INP2 < - BCL9L.

**Table 7.** 2<sup>nd</sup> order combinatorial hypotheses between SELENBP1 and BCL family.

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

### 3.1.4. CASP - BCL cross Family Analysis

Expression of caspase and BCL-2 apoptotic family members in mouse preimplantation embryos have been studied by Exley et al. [24]. Swanton et al. [25] observed that Bcl-2 regulates a caspase-3/caspase-2 apoptotic cascade in cytosolic extracts. Their role in the regulation of the immune response of Caspases, Bcl-2 family proteins and other components of the death machinery has been observed in Pellegrini and Strasser [26]. Moriishi et al. [27] show that Bcl-2 family members do not inhibit apoptosis by binding the caspase activator Apaf-1. In CRC cells treated with ETC-1922159, these families were found to be UP regulated. Table 8 shows rankings of CASP and BCL family.

On the left side, we found **BCL2L2** to be up regulated w.r.t CASP-10/16. These are reflected in the rankings of 2043 (linear) and 1809 (rbf) for CASP10 - BCL2L2; and 2263 (laplace) and 1863 (rbf) for CASP16 - BCL2L2; **BCL2L13** to be up regulated w.r.t CASP-4/5/16. These are reflected in the rankings of 1873 (laplace) and 2415 (rbf) for CASP4 - BCL2L13; 1962 (laplace), 2514 (linear) and 2493 (rbf) for CASP5 - BCL2L13; and 1762 (laplace), 2492 (linear) and 2166 (rbf) for CASP16 - BCL2L13; **BCL3** to be up regulated w.r.t CASP-10. These are reflected in the rankings of 2409 (laplace) and 2011 (linear) for CASP10 - BCL3; **BCL6** to be up regulated w.r.t CASP-5/16. These are reflected in the rankings of 1787 (laplace), 2124 (linear) and 2309 (rbf) for CASP5 - BCL6; and 2397 (laplace), 2166 (linear) and 2387 (rbf) for CASP16 - BCL6.

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

**Table 8.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and SELENBP1.

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

**Table 9.** 2<sup>nd</sup> order combinatorial hypotheses between CASP and BCL family.

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

### 3.1.5. MUC - BCL cross Family Analysis

MUC1 and bcl-2 expression in preinvasive lesions and adenosquamous carcinoma of the lung have been studied by Demirag et al. [28]. Sheng et al. [29] report that MUC13 prevents colorectal cancer cell death by promoting two distinct pathways of NF- $\kappa$ B activation, consequently upregulating BCL-X<sub>L</sub>. In CRC cells treated with ETC-1922159, family members of BCL and MUC were found up regulated. The search engine assigned high valued numerical ranks to some of the 2<sup>nd</sup> order combinations of BCL-MUC family members. Table 10 show the rankings of the members with respect to each other.

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

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

**Table 10.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and SELENBP1.

RANKING MUC FAMILY VS BCL FAMILY							
RANKING OF BCL2L1 W.R.T MUC FAMILY	RANKING OF MUC FAMILY W.R.T BCL2L1						
	laplace	linear	rbf	laplace	linear	rbf	
MUC1 - BCL2L1	2055	2297	1854	MUC1 - BCL2L1	1226	1681	986
MUC3A - BCL2L1	603	2089	1637	MUC3A - BCL2L1	759	1107	678
MUC4 - BCL2L1	531	1137	711	MUC4 - BCL2L1	1758	999	487
MUC12 - BCL2L1	882	810	1305	MUC12 - BCL2L1	1591	900	272
MUC13 - BCL2L1	1927	1201	2108	MUC13 - BCL2L1	98	2160	1099
MUC17 - BCL2L1	1170	917	743	MUC17 - BCL2L1	2500	93	148
MUC20 - BCL2L1	1810	700	1627	MUC20 - BCL2L1	270	343	423

Table 10. Cont.

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

**Table 11.** 2<sup>nd</sup> order combinatorial hypotheses between MUC and BCL family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
MUC w.r.t BCL	
MUC-3A	BCL2L2
MUC-3A	BCL9L
BCL w.r.t MUC	
MUC-1/13	BCL2L1
MUC-4/13/17	BCL2L2
MUC-1/12	BCL2L13
MUC-20	BCL3
MUC-17	BCL6
MUC-20	BCL9L

### 3.1.6. EXOSC - BCL cross Family Analysis

The exosome complex is involved in the degradation of various kinds of RNA. Recently, Deng et al. [30] observe that Exosome-transmitted LINC00461 promotes multiple myeloma cell proliferation and suppresses apoptosis by modulating microRNA/BCL-2 expression. Xu et al. [31] show that Exosome-derived microRNA-29c induces apoptosis of BIU-87 cells by down regulating BCL-2 and MCL-1. Exosomes were demonstrated to upregulate the expression of Bcl-2 and Cyclin D1 proteins, but reduce the levels of Bax and caspase-3 proteins in these cells in work of Yang et al. [32]. In western blot analysis results showed that exosomes can block the significant reduction of BCL-2, full-length caspase-3 and full-length PARP, while preventing the increase of BAX, cleaved caspase-3 and cleaved PARP induced by VP16, as studied by Wang et al. [33]. These findings point to the definite synergistic role of exosome with BCL family. In CRC cells, both exosome components EXOSC and BCL family members were found to be down regulated, after ETC-1922159 drug treatment. The search engine allocated low numerical valued ranks for many of the EXOSC and BCL combinations which might suggest greater role of EXOSC along with BCL. However, the nature of the mechanism between the two families yet needs to be explored, despite the generated hypothesis of possible synergy.

Table 12 shows rankings of EXOSC and BCL family with respect to each other. Left half of the table shows rankings of EXOSC w.r.t BCL and right half shows the vice versa. On the left, we find **EXOSC2** to be down regulated w.r.t BCL-2L12/6B/7A/9/11A/11B. These are shown in the rankings of 723 (laplace), 355 (linear) and 1211 (rbf) for EXOSC2 - BCL2L12; 1092 (laplace), 1033 (linear) and 638 (rbf) for EXOSC2 - BCL6; 1633 (laplace), 1047 (linear) and 317 (rbf) for EXOSC2 - BCL7A; 699 (laplace), 559 (linear) and 425 (rbf) for EXOSC2 - BCL9; 338 (laplace), 319 (linear) and 1598 (rbf) for EXOSC2 - BCL11A; and 1285 (laplace), 1440 (linear) and 812 (rbf) for EXOSC2 - BCL11B; **EXOSC3** was found to down regulated w.r.t BCL11B. This is reflected in rankings of 1677 (laplace), 199 (linear) and 267 (rbf) for EXOSC3 - BCL11B. **EXOSC5** was found to be down regulated w.r.t BCL family. These are reflected in the rankings of 498 (laplace), 1342 (linear) and 436 (rbf) for EXOSC5 - BCL2L12; 786 (laplace), 1272 (linear) and 1194 (rbf) for EXOSC5 - BCL6B; 374 (laplace), 1338 (linear) and 874 (rbf) for EXOSC5 - BCL7A; 613 (laplace), 946 (linear) and 772 (rbf) for EXOSC5 - BCL9; 459 (laplace), 90 (linear) and 1034 (rbf) for EXOSC5 - BCL11A; and 1404 (laplace) and 1558 (linear) for EXOSC5 - BCL11B; **EXOSC6** was found to be down regulated w.r.t BCL family. These are reflected in rankings of 1676 (laplace), 787 (linear) and 944 (rbf) for EXOSC6 - BCL7A; 1059 (linear) and 1091 (rbf) for EXOSC6 - BCL9; 1677 (laplace) and 1573 (linear) for EXOSC6 - BCL11A; **EXOSC7** was found to be down regulated w.r.t BCL family. These are reflected in rankings of 666 (laplace); 98 (linear) and 743 (rbf) EXOSC7 - BCL6B; 1501 (linear) and 1513 (rbf) for EXOSC7 - BCL7A; and 1477 (laplace) and 1217 (rbf) for EXOSC7 - BCL11A; **EXOSC8** was found to be down regulated w.r.t BCL family. These reflected in 1175 (laplace), 1504 (linear) and 1743 (rbf) for EXOSC8 - BCL7A; 906 (linear) and 1130 (rbf) EXOSC8 - BCL11A; and 605 (linear) and 374 (rbf) for EXOSC8 - BCL11B; **EXOSC9** found to be down regulate w.r.t BCL family. These are reflected in rankings of 1179 (laplace); 1018 (linear) and 687 (rbf) for EXOSC9 - BCL2L12; 437 (laplace), 852 (linear) and 1358 (rbf) EXOSC9 - BCL6B; 821 (laplace), 346 (linear)

and 727 (rbf) for EXOSC9 - BCL7A; 1305 (laplace) and 299 (rbf) EXOSC9 - BCL9; 1569 (laplace), 549 (linear) and 1456 (rbf) for EXOSC9 - BCL11B.

**Table 12.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and EXOSC.

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

On the right, we find **BCL-6B/11A/11B** to be down regulated w.r.t EXOSC2. These are reflected in the rankings of 202 (laplace), 81 (linear) and 194 (rbf) for EXOSC2 - BCL6B; 574 (laplace), 834 (linear) and 1055 (rbf) for EXOSC2 - BCL11A; and 1368 (laplace), 1353 (linear) and 1455 (rbf) for EXOSC2 - BCL11B. **BCL-6B/7A/11A** was found to be down regulated w.r.t EXOSC3. These are reflected in rankings of 571 (laplace), 335 (linear) and 307 (rbf) for EXOSC3 - BCL6B; 1739 (laplace) and 1700 (rbf) for EXOSC3 - BCL7A; and 1018 (laplace), 1345 (linear) and 483 (rbf) for EXOSC3 - BCL11A; **BCL-6B/11A/11B** was found to be down regulated w.r.t EXOSC5. These were reflected in rankings of 571 (laplace), 335 (linear) and 307 (rbf) for EXOSC5 - BCL6B; 756 (laplace), 389 (linear) and 1183 (rbf) for EXOSC5 - BCL11A; and 1368 (laplace), 1353 (linear) and 1455 (rbf) for EXOSC5 - BCL11B. **BCL-9** was found to be down regulated w.r.t EXOSC6. These are reflected in rankings of 851 (linear) and 1564 (rbf) for EXOSC6 - BCL9. **BCL-2L12/7A/9/11A/11B** was found to be down regulated w.r.t EXOSC7. These are reflected in rankings of 1551 (linear) and 1099 (rbf) for EXOSC7 - BCL2L12; 1282 (laplace), 831 (linear) and 1218 (rbf) for EXOSC7 - BCL7A; 1234 (linear) and 328 (rbf) for EXOSC7 - BCL9; 520 (laplace), 117 (linear) and 686 (rbf) for EXOSC7 - BCL11A; and 1529 (laplace) and 1418 (rbf) for EXOSC7 - BCL11B; **BCL-6B/11A** was found to be down regulated with EXOSC8. These are reflected in rankings of 190 (laplace), 1630 (linear) and 472 (rbf) for EXOSC8 - BCL6B; and 944 (laplace) and 532 (rbf) for EXOSC8 - BCL11A. Finally, **BCL-6B/9/11A/11B** was found to be down regulated with EXOSC9. These are reflected in rankings of 634 (laplace), 304 (linear) and 146 (rbf) for EXOSC9 - BCL6B; 1197 (laplace) and 1279 (rbf) for EXOSC9 - BCL9; 481 (laplace), 441 (linear) and 1372 (rbf) for EXOSC9 - BCL11A; and 1454 (linear) and 133 (rbf) for EXOSC9 - BCL11B.

Table 13 shows the derived influences which can be represented graphically, with the following influences - • EXOSC w.r.t BCL with EXOSC2 < - BCL-2L12/6B/7A/9/11A/11B; EXOSC3 < - BCL-11B; EXOSC5 < - BCL-2L12/6B/7A/9/11A/11B; EXOSC6 < - BCL-7A/9/11A; EXOSC7 < - BCL-6B/7A/11A; EXOSC8 < - BCL-7A/11A/11B and EXOSC9 < - BCL-2L12/6B/7A/9/11B; and • BCL w.r.t EXOSC with EXOSC2 - > BCL-6B/11A/11B; EXOSC3 - > BCL-6B/7A/11A; EXOSC5 - > BCL-6B/11A/11B; EXOSC6 - > BCL-2L12/9; EXOSC7 - > BCL-2L12/7A/9/11A/11B; EXOSC8 - > BCL-6B/11A and EXOSC9 - > BCL-6B/9/11A/11B.

**Table 13.** 2<sup>nd</sup> order combinatorial hypotheses between EXOSC and BCL family.

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

## Conclusion

Presented here are a range of multiple synergistic BCL 2<sup>nd</sup> 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.

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