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Posted Date: 11 September 2024

doi: 10.20944/preprints202409.0908.v1

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Article

# Machine Learning Discoveries of ABC Transporter-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 ATP-binding cassette (ABC) transporters-X (X, a particular gene/protein) at 2<sup>nd</sup> order level after drug administration. These rankings reveal which ABC-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 ABC and X. In this research work, we cover combinations of ABC with ubiquitin-conjugating enzymes (UBE2), Interleukin (IL), BCL and Caspase (CASP).

**Keywords:** ATP-binding cassette (ABC) transporters; 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In the unpublished preprint Sinha [1], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway.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 Interested readers are advised to go through unpublished preprints Sinha [1] and Sinha [2] for details regarding the search engine and the discoveries mentioned in there.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 indicies for each of these unique combinations and then vectorising these indices to connote and form discriminative feature vector for each combination. Since each combination is unique, the training and the test data are same. In the training data, the combinations are arranged and ranks from 1 to n are assigned. The ranking algorithm then learns the patterns from these combinations/sensitivity

index vectors. Next the learned model is used to rank the test data by generating the ranking score for each of the unique combination. Sorting these shuffled scores of test data leads to prioritization of the combinations. Joachims [4] show an example of applying learned model to training data (same as the test data) in [https://www.cs.cornell.edu/people/tj/svm\\_light/svm\\_rank.html](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. ABC Transporter Related Synergies

##### 3.1.1. ABC Transporters - UBE2 Cross Family Analysis

Not much is known about the interaction or any possible direct/indirect synergy of ABC transporters and the Ubiquitin-conjugating enzyme E2 family. In CRC cells treated with ETC-1922159, family members of both were found to be up regulated. The search engine also assigned numerically high valued ranks to a few of 2<sup>nd</sup> order synergies between the the two. We document here these synergies and show the possible unexplored combinations between the two families. Tables 1 and 2 show the rankings of ABC w.r.t UBE2 and vice versa, respectively.

**Table 1.** 2<sup>nd</sup> order interaction ranking between ABC w.r.t UBE2 family members.

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

**Table 2.** 2<sup>nd</sup> order interaction ranking between UBE2 w.r.t ABC family members.

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

In Table 1 we found **ABC-C3** up regulated w.r.t UBE2-A. This is reflected in the rankings of 2137 (laplace) and 2491 (linear) for ABC-C3 - UBE2-A. **ABC-C5** was up regulated w.r.t UBE2-B. This is reflected in the rankings of 2317 (laplace) and 2266 (rbf) for ABC-C5 - UBE2-B. **ABC-A5/D1/G2** were up regulated w.r.t UBE2-F. These are reflected in the rankings of 2408 (linear) and 1784 (rbf) for ABC-A5 - UBE2-F, 2069 (linear) and 1959 (rbf) for ABC-D1 - UBE2-F and 1995 (linear) and 2120 (rbf) for ABC-G2 - UBE2-F. **ABC-A5/C13** were up regulated w.r.t UBE2-H. These are reflected in 2068 (linear) and 2438 (rbf) for ABC-A5 - UBE2-H and 2492 (linear) and 2051 (rbf) for ABC-C13 - UBE2-H. **ABC-C13** was up regulated w.r.t UBE2-J1. This is reflected in the rankings of 2095 (laplace), 2412 (linear) and 2360 (rbf). **ABC-C5** was up regulated w.r.t UBE2-Z. This is reflected in rankings of 2348 (laplace) and 1859 (rbf) for ABC-C5 - UBE2-Z. In Table 2 we found **UBE2-A** up regulated w.r.t ABC-C5/G2. This is reflected in the rankings of 2122 (linear) and 2297 (rbf) for ABC-C5 - UBE2-A; and 2048 (laplace) and 1829 (linear) for ABC-G2 - UBE2-A. **UBE2-B** up regulated w.r.t ABC-A5/C3/C13/D1/G2. This is reflected in the rankings of 1846 (laplace) and 2038 (linear) for ABC-A5 - UBE2-B; 1999 (laplace) and 2050 (rbf) for ABC-C3 - UBE2-B; 1863 (linear) and 2496 (rbf) for ABC-C13 - UBE2-B; 2322 (laplace), 1917 (linear) and 2426 (rbf) for ABC-D1 - UBE2-B and 1833 (laplace), 2445 (linear) and 2506 (rbf) for ABC-G2 - UBE2-B. **UBE2-F** was found up regulated w.r.t ABC-B11/C3/D1/G1. These were reflected in 2003 (laplace) and 2422 (rbf) for ABC-B11 - UBE2-F; 2132 (laplace) and 2163 (linear) for ABC-C3 - UBE2-F; 2421 (laplace) and 2176 (rbf) for ABC-D1 - UBE2-F; and 2202 (laplace) and 1953 (rbf) for ABC-G1 - UBE2-F. **UBE2-H** was found to be up regulated w.r.t ABC-B11/C3/C5/C13/G1. These are reflected in rankings of 1950 (laplace), 1770 (linear) and 2461 (rbf) for ABC-B11 - UBE2-H; 2439 (laplace), 1972 (linear) and 2305 (rbf) for ABC-C3 - UBE2-H; 2473 (linear) and 2355 (rbf) for ABC-C5 - UBE2-H; 2004 (laplace), 2317 (linear)

and 1847 (rbf) for ABC-C13 - UBE2-H; and 1921 (linear) and 2288 (rbf) for ABC-G1 - UBE2-H; **UBE2-J1** was found to be up regulated w.r.t ABC-B11/C3/C13/D1/G1/G2; 1806 (laplace) and 1935 (rbf) for ABC-B11 - UBE2-J1; 2073 (laplace) and 2291 (linear) for ABC-C3 - UBE2-J1; 2329 (laplace), 2153 (linear) and 1951 (rbf) ABC-C13 - UBE2-J1; 2263 (laplace), 1886 (linear) and 2249 (rbf) for ABC-D1 - UBE2-J1; and 2418 (linear) and 2277 (rbf) for ABC-G1 - UBE2-J1; Finally, **UBE2-Z** was found up regulated w.r.t ABC-C3/D1/G1/G2. These are reflected in rankings of 1978 (laplace), 1823 (linear) and 1859 (rbf) for ABC-C3 - UBE2-Z; 2292 (laplace) and 2381 (linear) for ABC-D1 - UBE2-Z; 2515 (linear) and 1858 (rbf) for ABC-G1 - UBE2-Z; 2270 (laplace), 2080 (linear) and 2448 (rbf) for ABC-G2 - UBE2-Z. Table 3 shows the derived influences which can be represented graphically, with the following influences - • ABC w.r.t UBE2 with ABC-C3 < - UBE2-A; ABC-C5 < - UBE2-B; ABC-A5/D1/G2 < - UBE2-F; ABC-A5/C13 < - UBE2-H; ABC-C13 < - UBE2-J1; ABC-C5 < - UBE2-Z; and • UBE2 w.r.t ABC with UBEA-2 < - ABC-C5/G2; UBE2-B < - ABC-A5/C3/C13/D1/G2; UBE2-F < - ABC-B11/C3/D1/G1; UBE2-H < - ABC-B11/C3/C5/C13/G1; UBE2-J1 < - ABC-B11/C3/C13/D1/G1/G2; UBE2-Z < - ABC-C3/D1/G1/G2.

**Table 3.** 2<sup>nd</sup> order combinatorial hypotheses between ABC and UBE2.

| UNEXPLORED COMBINATORIAL HYPOTHESES |                         |
|-------------------------------------|-------------------------|
| ABC w.r.t UBE2                      |                         |
| ABC-C3                              | UBE2-A                  |
| ABC-C5                              | UBE2-B                  |
| ABC-A5/D1/G2                        | UBE2-F                  |
| ABC-A5/C13                          | UBE2-H                  |
| ABC-C13                             | UBE2-J1                 |
| ABC-C5                              | UBE2-Z                  |
| UBE2 w.r.t ABC                      |                         |
| UBE2-A                              | ABC-C5/G2               |
| UBE2-B                              | ABC-A5/C3/C13/D1/G2     |
| UBE2-F                              | ABC-B11/C3/D1/G1        |
| UBE2-H                              | ABC-B11/C3/C5/C13/G1    |
| UBE2-J1                             | ABC-B11/C3/C13/D1/G1/G2 |
| UBE2-Z                              | ABC-C3/D1/G1/G2         |

### 3.1.2. ABC Transporters Intra Cross Family Analysis

A range of ABC transporters were found to be up regulated in CRC cells after ETC-1922159 treatment. We checked the rankings of the ABC transporters within the ABC family and found multiple synergistic upregulation at 2nd order level that were ranked appropriately. Table 4 shows intra family rankings of ABC members among themselves. We found **ABC-C13** upregulated w.r.t ABC-A5. These were reflected in rankings of 1943 (linear) and 2151 (rbf); **ABC-C5/C13/G1** were up regulated w.r.t ABC-B11. These are reflected in rankings of 2226 (laplace) and 2241 (rbf) for ABC-C5 - ABC-B11; 1971 (laplace) and 2150 (rbf) for ABC-C13 - ABC-B11 and 1957 (laplace) and 1920 (linear) for ABC-G1 - ABC-B11; **ABC-C3/C13** were found to be up regulated w.r.t ABC-C5. These are reflected in 2084 (laplace), 2274 (linear) and 1758 (rbf) for ABC-C3 - ABC-C5 and 2476 (linear) and 2446 (rbf) for ABC-C13 - ABC-C5. **ABC-C5/C13** were found to be up regulated w.r.t ABC-D1. 2423 (laplace) and 2388 (rbf) for ABC-C5 - ABC-D1 and 2383 (laplace) and 2029 (linear) for ABC-C13 - ABC-D1. **ABC-A5** was found to be up regulated w.r.t ABC-G1. This is reflected in rankings of 2488 (laplace) and 1776 (linear) for ABC-A5 - ABC-G1. **ABC-A5** was found to be up regulated w.r.t ABC-G2 also. This is reflected in rankings of 2284 (laplace), 1904 (linear) and 1829 (rbf) for ABC-A5 - ABC-G2.

**Table 4.** 2<sup>nd</sup> order interaction ranking between ABC family members.

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

Table 5 shows the derived influences which can be represented graphically, with the following influences - • ABC intra family with ABC-C13 < - ABC-A5; ABC-C5/C13/G1 < - ABC-B11; ABC-C3/C13 < - ABC-C5; ABC-C5/C13 < - ABC-D1; ABC-A5 < - ABC-G1; ABC-C5 < - ABC-G2.

**Table 5.** 2<sup>nd</sup> order combinatorial hypotheses between ABC family members.

| UNEXPLORED COMBINATORIAL HYPOTHESES |         |
|-------------------------------------|---------|
| ABC intra family                    |         |
| ABC-C13                             | ABC-A5  |
| ABC-C5/C13/G1                       | ABC-B11 |
| ABC-C3/C13                          | ABC-C5  |
| ABC-C5/C13                          | ABC-D1  |
| ABC-A5                              | ABC-G1  |
| ABC-C5                              | ABC-G2  |

### 3.1.3. Interleukin - ABC Transporters Cross Family Analysis

Zhou *et al.* [5] have observed that the ABCA1 contributes to the secretion of interleukin 1 $\beta$  from macrophages. Haskó *et al.* [6] show that inhibitors of ABC transporters suppress interleukin-12 p40 production and major histocompatibility complex II up-regulation in macrophages. Park *et al.* [7] conclude that anti-cancer drug-induced IL-8 secretion increased the expression of ABC transporters and SP cells, promoting the growth of HCC in vitro. Marty *et al.* [8] show that ABC1 is required for the release of interleukin-1 $\beta$  by P2X7-stimulated and lipopolysaccharide-primed mouse Schwann cells. Lottaz *et al.* [9] observe that inhibition of ABC transporter downregulates interleukin-1 $\beta$ -mediated autocrine activation of human dermal fibroblasts. These findings and many more indicate the synergy between IL family and ABC transporters. In colorectal cancer cells treated with ETC-1922159, some of the members of both families were up regulated. Given the studied synergies, our search engine found multiple combinations which were ranked with high numerical values, thus indicating possible dual combinatorial role. Tables 6 and 7, each show rankings of ABC transporters w.r.t IL family on the left half and vice versa on the right half. On the left half we found **IL-17REL** up regulated w.r.t ABCA5. This is reflected in the rankings of 2405 (linear) and 2202 (rbf) for IL17REL - ABCA5. **IL-2RG/6ST/15/15RA** up regulated w.r.t ABCB11. This is reflected in the rankings of 2182 (laplace), 2102 (linear) and 550 (rbf) for IL2RG - ABCB11; 1793 (laplace), 2140 (linear) and 1938 (rbf) for IL6ST - ABCB11; 2438 (laplace) and 2512 (linear) for IL15 - ABCB11; and 2271 (laplace) and 1784 (rbf) for IL15RA - ABCB11. **IL-8/15RA** up regulated w.r.t ABCC3. This is reflected in the rankings of 1767 (laplace) and 2419 (rbf) for IL8 - ABCC3 and 2403 (linear) and 1795 (rbf) for IL15RA - ABCC3. **IL-15RA/17REL** up regulated w.r.t ABCC5. These are reflected in rankings of 2255 (linear) and 1861 (rbf) for IL15RA - ABCC5 and 2462 (linear) and 2509 (rbf) for IL17REL - ABCC5. **IL-15RA/17REL** were up regulated w.r.t ABCC13. These are reflected in 2248 (laplace), 1955 (linear) and 2456 (rbf) for IL15RA - ABCC13 and 2339 (laplace) and 2137 (linear) for IL17REL - ABCC13. **IL-1A/1RAP/8/15RA** were up regulated w.r.t ABCD1. These are reflected in rankings of 1932 (laplace) and 2203 (rbf) for IL1A - ABCD1; 2508 (laplace), 2006 (linear) and 1907 (rbf) for IL1RAP - ABCD1; 2010 (laplace), 2315 (linear) and 1814 (rbf) for IL8 - ABCD1; and 2097 (laplace) and 1765 (linear) for IL15RA - ABCD1. **IL-1RAP** was up regulated w.r.t ABCG1. This was reflected in rankings of 2205 (linear) and 2339 (rbf) for IL1RAP - ABCG1. **IL-1RAP/15RA** were up regulated w.r.t ABCG2. These were reflected in rankings of 2184 (laplace) and 2167 (linear) for IL1RAP - ABCG2 and 1910 (laplace), 2428 (linear) and 1921 (rbf) for IL15RA - ABCG2.

**Table 6.** 2<sup>nd</sup> order interaction ranking between ABC and IL family members.

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

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

**Table 7.** 2<sup>nd</sup> order interaction ranking between ABC and IL family members.

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

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

**Table 8.** 2<sup>nd</sup> order combinatorial hypotheses between ABC and IL family members.

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

### 3.1.4. BCL - ABC Transporters Cross Family Analysis

Ruzickova *et al.* [10] show clinically relevant interactions of anti-apoptotic Bcl-2 protein inhibitors with ABC transporters. Alla *et al.* [11] observe that E2F1 confers anticancer drug resistance by targeting ABC transporter family members and Bcl-2 via the p73/DNp73-miR-205 circuitry. Yasui *et al.* [12] show a range of ABC family members along with BCL member to be overexpressed while studying the alteration in copy numbers of genes as a mechanism for acquired drug resistance. These point to the possible synergistic workings of BCL with ABC. In colorectal cancer cells treated with ETC-1922159, these were found to be up regulated. The search engine pointed to some of these 2nd order combinations and allotted rankings of high numerical value, thus indicating possible synergy. Table 9 and 10 show rankings of BCL family w.r.t ABC members on the left half and vice versa on the right half.

**Table 9.** 2<sup>nd</sup> order interaction ranking between BCL and ABC family members.

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

On the left half we found **BCL2L1** up regulated w.r.t ABCC5. This is reflected in the rankings of 2239 (laplace) and 1845 (linear). **BCL2L2** was up regulated w.r.t ABC-B11/C5/C13/D1. These are reflected in the rankings of 2097 (laplace) and 2311 (rbf) for ABCB11 - BCL2L2; 2195 (laplace), 2359 (linear) and 2322 (rbf) for ABCC5 - BCL2L2; 2438 (laplace) and 2494 (linear) for ABCC13 - BCL2L2 and 2477 (laplace) and 2156 (rbf) for ABCD1 - BCL2L2. **BCL2L13** was up regulated w.r.t ABC-B11/C5/C13/D1/G1. These are reflected in the rankings of 2505 (laplace) and 1855 (rbf) for ABCB11 - BCL2L13; 1835 (linear) and 2178 (rbf) for ABCC5 - BCL2L13; 2484 (laplace), 2184 (linear) and 2410 (rbf) for ABCC13 - BCL2L13; 2472 (laplace) and 2201 (rbf) for ABCD1 - BCL2L13 and 2276 (linear) and 2095 (rbf) for ABCG1 - BCL2L13. **BCL3** was up regulated w.r.t ABC-D1/G1. These are reflected in the rankings of 2194 (linear) and 2106 (rbf) for ABCD1 - BCL3 and 2014 (laplace) and 2253 (rbf) for ABCG1 - BCL3. **BCL6** was up regulated w.r.t ABC-B11. These are reflected in the rankings of 2010 (linear) and 2350 (rbf) for ABC-B11 - BCL6. **BCL10** was up regulated w.r.t ABC-B11. These are reflected in the rankings of 2234 (laplace) and 2382 (rbf) for ABC-B11 - BCL10.

**Table 10.** 2<sup>nd</sup> order interaction ranking between ABC and BCL family members.

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

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

Table 11 shows the derived influences which can be represented graphically, with the following influences - • BCL w.r.t ABC with ABC-C5 - > BCL2L1; ABC-B11/C5/C13/D1 - > BCL2L2; ABC-B11/C5/C13/D1/G1 - > BCL2L13; ABC-D1/G1 - > BCL3; ABC-B11 - > BCL6; ABC-B11 - > BCL10; and • ABC w.r.t BCL with ABC-C3 < - BCL2L1; ABC-C5/C13 < - BCL2L13; ABC-C3 < - BCL3; ABC-C5/C13 < - BCL6; ABC-C5/C13/D1 < - BCL9L; ABC-A5/C5/C13/D1 < - BCL10.

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

| UNEXPLORED COMBINATORIAL HYPOTHESES |         |
|-------------------------------------|---------|
| BCL w.r.t ABC                       |         |
| ABC-C5                              | BCL2L1  |
| ABC-B11/C5/C13/D1                   | BCL2L2  |
| ABC-B11/C5/C13/D1/G1                | BCL2L13 |
| ABC-D1/G1                           | BCL3    |
| ABC-B11                             | BCL6    |
| ABC-B11                             | BCL10   |
| ABC w.r.t BCL                       |         |
| ABC-C3                              | BCL2L1  |
| ABC-C5/C13                          | BCL2L13 |
| ABC-C3                              | BCL3    |
| ABC-C5/C13                          | BCL6    |
| ABC-C5/C13/D1                       | BCL9L   |
| ABC-A5/C5/C13/D1                    | BCL10   |

### 3.1.5. CASPASE - ABC transporters cross family analysis

Hu *et al.* [13] observe that the loss of ABCB4 attenuates the caspase-dependent apoptosis regulating resistance to 5-Fu in colorectal cancer. Ihlefeld *et al.* [14] analyze whether the observed upregulation of the multidrug transporters contributed to the resistance of Sgpl1/-MEFs against chemotherapy-induced apoptosis by measuring the influence of ABC transporter inhibitors on cell viability and caspase-3 cleavage. Though recent developments, they point to the synergy between the transporters and the CASP family. In CRC cells, treated with ETC-1922159, these were found to be UP regulated. The engine allotted high numerical valued ranks to some of the 2<sup>nd</sup> order combinations between the members of the two families. Tables 12 and 13 show the rankings of ABC transporters w.r.t CASP and vice versa. In Table 12, we found **ABC-C5** to be up regulated w.r.t CASP4. These are reflected in rankings of 2495 (laplace) and 2257 (rbf) for CASP4 - ABC-C5. **ABC-C5** was up regulated w.r.t CASP5. These are reflected in rankings of 2475 (laplace) and 2234 (rbf) for CASP5 - ABC-C5. **ABC-A5/C13/D1** were up regulated w.r.t CASP7. These are reflected in rankings of 2515 (laplace) and 1742 (linear) for CASP7 - ABC-C5; 2489 (laplace) and 2418 (linear) for CASP7 - ABC-C13; and 2323 (laplace) and 2004 (linear) for CASP7 - ABC-D1. **ABC-B11/C5/D1/G1** were up regulated w.r.t CASP9. These are reflected in rankings of 2001 (linear) and 2051 (rbf) for CASP9 - ABC-B11; 2180 (laplace) and 2343 (linear) for CASP9 - ABC-C5; 2267 (laplace) and 2382 (rbf) for CASP9 - ABC-C13; 1890 (linear) and 2286 (rbf) for CASP9 - ABC-G1; **ABC-A5/C13** were up regulated w.r.t CASP10. These are reflected in rankings of 2292 (laplace), 2311 (linear) and 1108 (rbf) for CASP10 - ABC-A5; 2139 (laplace) and 2203 (linear) for CASP10 - ABC-C13; In Table 13, we found **ABC-C5** to be up regulated w.r.t CASP4. These are reflected in rankings of 2495 (laplace) and 2257 (rbf) for CASP4 - ABC-C5. **ABC-C5** was up regulated w.r.t CASP5. These are reflected in rankings of 2475 (laplace) and 2234 (rbf) for CASP5 - ABC-C5. **ABC-A5/C13/D1** were up regulated w.r.t CASP7. These are reflected in rankings of 2515 (laplace) and 1742 (linear) for CASP7 - ABC-C5; 2489 (laplace) and 2418 (linear) for CASP7 - ABC-C13; and 2323 (laplace) and 2004 (linear) for CASP7 - ABC-D1. **ABC-B11/C5/D1/G1** were up regulated w.r.t CASP9. These are reflected in rankings of 2001 (linear) and 2051 (rbf) for CASP9 - ABC-B11; 2180 (laplace) and 2343 (linear) for CASP9 - ABC-C5; 2267 (laplace) and 2382 (rbf) for CASP9 - ABC-C13; 1890 (linear) and 2286 (rbf) for CASP9 - ABC-G1; **ABC-A5/C13** were up regulated w.r.t CASP10. These are reflected in rankings of 2292 (laplace), 2311 (linear) and 1108 (rbf) for CASP10 - ABC-A5; 2139 (laplace) and 2203 (linear) for CASP10 - ABC-C13; In Table 13, we found **CASP4** to be up regulated w.r.t ABC-D1. These are reflected in rankings of 1791 (laplace) and 1954 (rbf) for CASP4 - ABC-D1. **CASP5** was up regulated w.r.t ABC-C13. These are reflected in rankings of 2286 (laplace) and 1905 (rbf) for CASP5 - ABC-C13. **CASP7** was up regulated w.r.t ABC-C5. This is reflected in rankings of 2168 (laplace), 1881 (linear) and 2016 (rbf) for CASP7 - ABC-C5. **CASP9** were up regulated w.r.t

ABC-C5/C13/D1/G1. These are reflected in rankings of 2404 (laplace) and 2374 (linear) for CASP9 - ABC-A5; 2449 (laplace) and 2506 (rbf) for CASP9 - ABC-C13; 1858 (laplace) and 2430 (rbf) for CASP9 - ABC-D1; and 2342 (linear) and 2468 (rbf) for CASP9 - ABC-G1; **CASP16** were up regulated w.r.t ABC-A5. This is reflected in rankings of 2477 (linear) and 2315 (rbf) for CASP16 - ABC-A5. Table 14 shows the derived influences which can be represented graphically, with the following influences - • ABC w.r.t CASP with CASP-4 – > ABC-C5; CASP-5 – > ABC-C5; CASP-7 – > ABC-A5/C13/D1; CASP-9 – > ABC-B11/C5/D1/G1; CASP-10 – > ABC-A5/C13; and • CASP w.r.t ABC with CASP-4 < – ABC-D1; CASP-5 < – ABC-C13; CASP-7 < – ABC-C5; CASP-9 < – ABC-C5/C13/D1/G1; CASP-16 < – ABC-A5;

**Table 12.** 2<sup>nd</sup> order interaction ranking between ABC and CASP family members.

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

**Table 13.** 2<sup>nd</sup> order interaction ranking between CASP and ABC family members.

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

**Table 14.** 2<sup>nd</sup> order combinatorial hypotheses between BCL and ABC family members.

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

## Conclusion

Presented here are a range of multiple synergistic ABC transporter 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.

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

**Data Availability Statement:** Data used in this research work was released in a publication in Madan *et al.* [15]. 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).

**Acknowledgments:** Special thanks to Mrs. Rita Sinha and Mr. Prabhat Sinha for supporting the author financially, without which this work could not have been made possible.

**Conflicts of Interest:** There are no conflicts to declare.

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