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

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Abstract: Aurora kinase B (AURKB) is one of the components that make up a complex called the chromosome passenger complex (CPC). The major functions of AURKB are to regulate kinetochore-microtubule attachments as well as cytokinesis. In colorectal cancer (CRC) cells treated with ETC-1922159, AURKB was found to be down regulated along with other genes. A recently developed search engine ranked combinations of AURKB-X (X, a particular gene/protein) at 2^{nd} order level after drug administration. Some of these combinations have been tested in wet lab, however many have been pointed out by the search engine that are yet to be explored/tested. These rankings reveal which AURKB-X combinations might be working synergistically in CRC. In this research work, I cover combinations of AURKB with ZW10 interacting kinetochore protein (ZWINT/ZWINT-1), inner centromere protein (INCENP), targeting protein for xenopus kinesin-like protein 2 (TPX2), WNT pathway components, chromatin licensing and DNA replication factor 1 (CDT1), G2 and S-phase expressed 1 (GTSE1), vaccinia related kinase 1 (VRK1), RecQ like helicase 4 (RECQL4), histone H3 associated protein kinase (HASPIN/GSG2), centromere protein (CENP), E2F transcription factor (E2F), cell division cycle (CDC), ubiquitin specific peptidase (USP), Nucleoporin (NUP), gem nuclear organelle associated protein (GEMIN), mitotic arrest deficient 2 like (MAD2L), homeobox (HOX), DExH-box helicase (DHX), polo like kinase (PLK), budding uninhibited by benzimidazoles (BUB), DNA topoisomerase (TOP), cyclin dependent kinase (CDK), alkB homolog lysine demethylase (ALKBH), protein arginine methyltransferase (PRMT), shugoshin (SGO), spindle and kinetochore associated complex subunit (SKA), growth arrest specific (GAS) and kinesin family member (KIF) family.

Keywords: AURKB; Porcupine inhibitor ETC-1922159; sensitivity analysis; colorectal cancer

1. Introduction

1.1. Aurora Kinase

Aurora kinases (AURKs) regulate chromosome-microtubule attachments, centrosome duplication and separation, chromosome condensation, bipolar spindle assembly, the spindle checkpoint and cytokinesis (Zhang [1]). Drosophila aurora was first identified by Glover et al. [2] where mutations in aurora prevented centrosome separation. Comprehensive review on AURKs can be found in Carmena and Earnshaw [3] and Willems et al. [4]. Bischoff et al. [5] identified human homologue of drosophila aurora kinase which was amplified in human colorectal cancers. Further, Ota et al. [6] found increased phosphorylation of histone H3 for maintenance of proper chromosome dynamics during mitosis, due to AIM-1/AURKB overexpression, thus leading to chromosome instability. They also observe that there was increased expression of the AIM-1 gene in human colorectal tumors. Recently, the findings of overexpression of AURKB in colorectal cancer has been confirmed in Shah et al. [7] and Li et al. [8]. In this research, I focus on Aurora kinase B (AURKB). AURKB works in tandem with multiple components and some combinations of AURKB have been confrimed in wet lab. However, many of the combinations have not been explored/tested or are known. To reveal these combinations, I use a

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modification of a recently published machine learning based search engine, details of which are given in the next section.

1.2. Combinatorial Search Problem and a Possible Solution

In a recently published work Sinha [9], a frame work of a search engine was developed which can rank combinations of factors (genes/proteins) in a signaling pathway. Readers are requested to go through the adaptation of the above mentioned work for gaining deeper insight into the working of the pipeline and its use of published data set generated after administration of ETC-1922159, Sinha [10]. The work uses SVM package by Joachims [11] in https://www.cs.cornell.edu/people/tj/svm_light/svm_rank.html. I use the adaptation to rank 2^{nd} order gene combinations.

2. Results & Discussion

2.1. AURKB Related Synergies

2.1.1. AURKB - ZWINT / INCENP / TPX2 / WNT Pathway Components / CDT1 / GTSE1 / VRK1 / RECQL4 / GSG2

Kasuboski et al. [12] identified Zwint-1 (ZWITN) as a novel Aurora B substrate required for regulation of the spindle assembly checkpoint. Abdul Azeez et al. [13] studied the structural mechanism of AURKB activation that binds to the C-terminal domain of INCENP (full activation of which requires phosphorylation of two serine residues of INCENP). TPX2 is a co-activator protein of AURKB which forms the core of the chromosomal passenger complex, as shown by Iyer and Tsai [14]. Luo et al. [15] demonstrate an atypical function of a centrosomal module in WNT signalling as WNT-PCP protein DVL2 (as studied in Luga et al. [16]) associated with CEP192-PLK4/AURKB complex. Agarwal et al. [17] provides mechanistic insight into how CDT1 stabilizes kinetochore–microtubule attachments via an AURKB phosphorylation. GTSE1 regulates AURKB activity via spindle microtubule dynamics, as shown by Tipton et al. [18]. Moura et al. [19] propose formation of a complex between VRK1 and AURKB in the phosphorylation of Histone H3 and progression of mitosis. Fang et al. [20] demonstrate that RECQL4 interacts with AURKB, thus forming an axis which is essential for cell cycle progression, cellular proliferation and mitotic integrity. Zhang and Huang [21] found that one of the factors for promotion of thyroid cancer was stabilization of AURKB by GSG2. All these combinations have been established in wet lab experiments and in colorectal cancer cells treated with ETC-1922159, these components taken individually and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these INDIVIDUAL member along with AURKB.

Table 1 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 2 generated from analysis of the ranks in Table 1. The Table 1 shows rankings of individual members w.r.t AURKB. ZWINT - AURKB shows low ranking of 1 (laplace) , 38 (linear) and 18 (rbf). INCENP - AURKB shows low ranking of 678 (laplace) , 941 (linear) and 571 (rbf). TPX2 - AURKB shows low ranking of 10 (laplace) , 10 (linear) , and (rbf). WNT10B - AURKB shows low ranking of 583 (laplace) , 491 (linear) and 578 (rbf). CDT1 - AURKB shows low ranking of 318 (laplace) , 135 (linear) and 290 (rbf). GTSE1 - AURKB shows low ranking of 537 (laplace) , 283 (linear) and 137 (rbf). VRK1 - AURKB shows low ranking of 181 (laplace) , 848 (linear) and 229 (rbf). RECQL4 - AURKB shows low ranking of 897 (laplace) , 439 (linear) and 508 (rbf). GSG2 - AURKB shows low ranking of 74 (laplace) , 189 (linear) and 375 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

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Table 1. 2^{nd} order interaction ranking between AURKB VS INDIVIDUAL family members.

RANKING INDIVIDUAL FAMILY VS AURKB			
RANKING OF INDIVIDUAL FAMILY W.R.T AURKB			
	laplace	linear	rbf
ZWINT - AURKB	1	38	18
INCENP - AURKB	678	941	571
TPX2 - AURKB	10	10	7
WNT10B - AURKB	583	491	578
CDT1 - AURKB	318	135	290
GTSE1 - AURKB	537	283	137
VRK1 - AURKB	181	848	229
RECQL4 - AURKB	897	439	508
GSG2 - AURKB	74	189	375

One can also interpret the results of the Table 1 graphically, with the following influences - • INDIVIDUAL family w.r.t AURKB with AURKB $->$ ZWINT / INCENP / TPX2 / WNT10B / CDT1 / GTSE1 / VRK1 / RECQL4 / GSG2 .

Table 2. 2^{nd} order combinatorial hypotheses between AURKB and Individual members.

UNEXPLORED COMBINATORIAL HYPOTHESES	
Individual members w.r.t AURKB	
ZWINT / INCENP / TPX2 / WNT10B	AURKB
CDT1 / GTSE1 / VRK1 / RECQL4 / GSG2	AURKB

2.1.2. AURKB - CENP

Kong et al. [22] demonstrate that CENPC-MIS12C interaction helps in recruiting AURKB, thus forming a regulatory loop which is important for chromosome segregation. Further, Liu et al. [23] show that AURKB phosphorylates CENPW thus enhancing the interaction between CENPW and CENPT to ensure chromosome segregation. In colorectal cancer cells treated with ETC-1922159, CENP family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these CENP member along with AURKB.

Table 3 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 4 generated from analysis of the ranks in Table 3. The Table 3 shows rankings of individual members w.r.t AURKB. CENPU - AURKB shows low ranking of 38 (laplace), 35 (linear) and 11 (rbf). CENPF - AURKB shows low ranking of 39 (laplace), 58 (linear) and 136 (rbf). CENPH - AURKB shows low ranking of 83 (laplace), 22 (linear) and 88 (rbf). CENPA - AURKB shows low ranking of 122 (laplace), 49 (linear) and 38 (rbf). CENPE - AURKB shows low ranking of 143 (laplace), 27 (linear) and 829 (rbf). CENPJ - AURKB shows low ranking of 164 (laplace), 113 (linear) and 592 (rbf). CENPW - AURKB shows low ranking of 217 (laplace), 241 (linear) and 512 (rbf). CENPK - AURKB shows low ranking of 232 (laplace), 276 (linear) and 49 (rbf). CENPI - AURKB shows low ranking of 368 (laplace), 521 (linear) and 65 (rbf). CENPN - AURKB shows low ranking of 546 (laplace), 906 (linear) and 366 (rbf). CENPM - AURKB shows low ranking of 713 (laplace), 414 (linear) and 858 (rbf). CENPL - AURKB shows low ranking of 748 (laplace), 1117 (linear) and 695 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, CENPO and CENPV showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

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Table 3. 2^{nd} order interaction ranking between AURKB VS CENP family.

RANKING CENP FAMILY VS AURKB			
RANKING OF CENP FAMILY W.R.T AURKB			
	laplace	linear	rbf
CENPU - AURKB	38	35	11
CENPF - AURKB	39	58	136
CENPH - AURKB	83	22	88
CENPA - AURKB	122	49	38
CENPE - AURKB	143	27	829
CENPJ - AURKB	164	113	592
CENPW - AURKB	217	241	512
CENPK - AURKB	232	276	49
CENPI - AURKB	368	521	65
CENPN - AURKB	546	906	366
CENPM - AURKB	713	414	858
CENPL - AURKB	748	1117	695
CENPO - AURKB	1962	2075	2344
CENPV - AURKB	2609	2669	2611

One can also interpret the results of the Table 3 graphically, with the following influences - • CENP family w.r.t AURKB with AURKB $-$ > CENP-U/F/H/A/E/J/W/K/I/N/M/L.

Table 4. 2^{nd} order combinatorial hypotheses between AURKB and CENP family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
CENP family w.r.t AURKB	
CENP-U/F/H/A/E/J/W/K/I/N/M/L	AURKB

2.1.3. AURKB - E2F

In clear cell renal cell carcinoma (ccRCC), Li et al. [8] showed that AURKB/CDC37 complex promotes E2F1 release as one of the activity, which in turn activates AURKB transcription and forms a positive feedforward loop in ccRCC. In colorectal cancer cells treated with ETC-1922159, E2F family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these E2F member along with AURKB.

Table 5 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 6 generated from analysis of the ranks in Table 5. The Table 5 shows rankings of individual members w.r.t AURKB. E2F8 - AURKB shows low ranking of 95 (laplace), 252 (linear) and 125 (rbf). E2F1 - AURKB shows low ranking of 499 (laplace), 243 (linear) and 1086 (rbf). E2F7 - AURKB shows low ranking of 1034 (laplace), 777 (linear) and 313 (rbf). E2F2 - AURKB shows low ranking of 1057 (laplace), 1498 (linear) and 839 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, E2F5 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 5. 2^{nd} order interaction ranking between AURKB VS E2F family.

RANKING E2F FAMILY VS AURKB			
RANKING OF E2F FAMILY W.R.T AURKB			
	laplace	linear	rbf
E2F8 - AURKB	95	252	125
E2F1 - AURKB	499	243	1086
E2F7 - AURKB	1034	777	313
E2F2 - AURKB	1057	1498	839
E2F5 - AURKB	2615	1462	2727

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One can also interpret the results of the Table 5 graphically, with the following influences - • E2F family w.r.t AURKB with AURKB $->$ E2F-8/1/7/2.

Table 6. 2^{nd} order combinatorial hypotheses between AURKB and E2F family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
E2F family w.r.t AURKB	
E2F-8/1/7/2	AURKB

2.1.4. AURKB - CDC

As mentioned in the preceding section, Li et al. [8] identifified of CDC37 as a molecular chaperone for AURKB ehich is effective in formation of AURKB/E2F1-positive feedforward loop in ccRCC. In colorectal cancer cells treated with ETC-1922159, CDC family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these CDC member along with AURKB.

Table 7 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 8 generated from analysis of the ranks in Table 7. The Table 7 shows rankings of individual members w.r.t AURKB. CDC20 - AURKB shows low ranking of 60 (laplace), 48 (linear) and 260 (rbf). CDC7 - AURKB shows low ranking of 116 (laplace), 52 (linear) and 20 (rbf). CDC45 - AURKB shows low ranking of 157 (laplace), 50 (linear) and 111 (rbf). CDC25C - AURKB shows low ranking of 235 (laplace), 153 (linear) and 282 (rbf). CDC25A - AURKB shows low ranking of 340 (laplace), 364 (linear) and 798 (rbf). CDC6 - AURKB shows low ranking of 1080 (laplace), 708 (linear) and 1075 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, CDC23 and CDC123 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 7. 2^{nd} order interaction ranking between AURKB VS CDC family.

RANKING CDC FAMILY VS AURKB			
RANKING OF CDC FAMILY W.R.T AURKB			
	laplace	linear	rbf
CDC20 - AURKB	60	48	260
CDC7 - AURKB	116	52	20
CDC45 - AURKB	157	50	111
CDC25C - AURKB	235	153	282
CDC25A - AURKB	340	364	798
CDC6 - AURKB	1080	708	1075
CDC23 - AURKB	1852	1250	2441
CDC123 - AURKB	2437	1646	2207

One can also interpret the results of the Table 7 graphically, with the following influences - • CDC family w.r.t AURKB with AURKB $->$ CDC-20/7/45/25C/25A/6.

Table 8. 2^{nd} order combinatorial hypotheses between AURKB and CDC family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
CDC family w.r.t AURKB	
CDC-20/7/45/25C/25A/6	AURKB

2.1.5. AURKB - USP

In gastric cancer, Tu et al. [24] showed that transcription factor FUBP1 activates USP29 gene transcription leading to stabilization of AURKB. In colorectal cancer cells treated with ETC-1922159,

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USP family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these USP member along with AURKB.

Table 9 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 10 generated from analysis of the ranks in Table 9. The Table 9 shows rankings of individual members w.r.t AURKB. USP13 - AURKB shows low ranking of 129 (laplace), 240 (linear) and 862 (rbf). USP28 - AURKB shows low ranking of 1082 (laplace), 798 (linear) and 935 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, USP10, USP1, USP36 and USP39 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 9. 2^{nd} order interaction ranking between AURKB VS USP family.

RANKING USP FAMILY VS AURKB			
RANKING OF USP FAMILY W.R.T AURKB			
	laplace	linear	rbf
USP13 - AURKB	129	240	862
USP10 - AURKB	1038	1852	2502
USP28 - AURKB	1082	798	935
USP1 - AURKB	2170	2306	1900
USP36 - AURKB	2647	1986	1449
USP39 - AURKB	2729	2633	2242

One can also interpret the results of the Table 9 graphically, with the following influences - • USP family w.r.t AURKB with AURKB $->$ USP-13/28.

Table 10. 2^{nd} order combinatorial hypotheses between AURKB and USP family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
USP family w.r.t AURKB	
USP-13/28	AURKB

2.1.6. AURKB - RANBP/NUP

Di Cesare et al. [25] found that RANBP2/NUP358 controlled the SUMOylation of AURKB in early mitosis. In colorectal cancer cells treated with ETC-1922159, RANBP/NUP family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these RANBP/NUP member along with AURKB.

Table 11 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 12 generated from analysis of the ranks in Table 11. The Table 11 shows rankings of individual members w.r.t AURKB. RANBP1 - AURKB shows low ranking of 448 (laplace), 1179 (linear) and 638 (rbf). NUP35 - AURKB shows low ranking of 761 (laplace), 421 (linear) and 34 (rbf). NUP155 - AURKB shows low ranking of 886 (laplace) and 1471 (linear). NUP210 - AURKB shows low ranking of 937 (laplace) and 520 (linear). NUP43 - AURKB shows low ranking of 1033 (laplace), 405 (linear) and 959 (rbf). NUP37 - AURKB shows low ranking of 1160 (laplace), 863 (linear) and 1346 (rbf). NUP160 - AURKB shows low ranking of 1181 (laplace), 742 (linear) and 1412 (rbf). NUP107 - AURKB shows low ranking of 1194 (laplace), 1527 (linear) and 883 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, RANBP17, NUP93, NUP133, NUP85, NUP88, NUP205, NUP54, NUP188 and NUP62 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

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Table 11. 2^{nd} order interaction ranking between AURKB VS NUP family.

RANKING RANBP/NUP FAMILY VS AURKB			
RANKING OF RANBP/NUP FAMILY W.R.T AURKB			
	laplace	linear	rbf
RANBP1 - AURKB	448	1179	638
RANBP17 - AURKB	2185	2291	925
NUP35 - AURKB	761	421	34
NUP155 - AURKB	886	1471	1554
NUP210 - AURKB	937	520	1725
NUP43 - AURKB	1033	405	959
NUP37 - AURKB	1160	863	1346
NUP160 - AURKB	1181	742	1412
NUP107 - AURKB	1194	1527	883
NUP93 - AURKB	1319	1943	1959
NUP133 - AURKB	2195	2049	1324
NUP85 - AURKB	2272	2534	2674
NUP88 - AURKB	2343	2449	1742
NUP205 - AURKB	2456	1676	2234
NUP54 - AURKB	2586	2617	2735
NUP188 - AURKB	2652	1224	2442
NUP62 - AURKB	2682	2742	2712

One can also interpret the results of the Table 11 graphically, with the following influences - • NUP family w.r.t AURKB with AURKB $->$ RANBP1 and AURKB $->$ NUP-35/155/210/43/37/160/107.

Table 12. 2^{nd} order combinatorial hypotheses between AURKB and NUP family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
NUP family w.r.t AURKB	
RANBP1	AURKB
NUP-35/155/210/43/37/160/107	AURKB

2.1.7. AURKB - GEMIN

Non small cell lung cancer progression occurs as GEMIN6 expression positively correlates with AURKB, as has been shown by Lin et al. [26]. In colorectal cancer cells treated with ETC-1922159, GEMIN family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these GEMIN member along with AURKB.

Table 13 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 14 generated from analysis of the ranks in Table 13. The Table 13 shows rankings of individual members w.r.t AURKB. GEMIN6 - AURKB shows low ranking of 367 (laplace), 971 (linear) and 523 (rbf). GEMIN5 - AURKB shows low ranking of 595 (laplace), 841 (linear) and 345 (rbf). GEMIN2 - AURKB shows low ranking of 954 (laplace) and 687 (linear). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, GEMIN4 and GEMIN7 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

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Table 13. 2^{nd} order interaction ranking between AURKB VS GEMIN family.

RANKING GEMIN FAMILY VS AURKB			
RANKING OF GEMIN FAMILY W.R.T AURKB			
	laplace	linear	rbf
GEMIN6 - AURKB	367	971	523
GEMIN5 - AURKB	595	841	345
GEMIN2 - AURKB	954	687	2150
GEMIN4 - AURKB	1556	659	2082
GEMIN7 - AURKB	2447	1968	2434

One can also interpret the results of the Table 13 graphically, with the following influences - • GEMIN family w.r.t AURKB with AURKB $->$ GEMIN-6/5/2.

Table 14. 2^{nd} order combinatorial hypotheses between AURKB and GEMIN family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
GEMIN family w.r.t AURKB	
GEMIN-6/5/2	AURKB

2.1.8. AURKB - MAD2L

Marima et al. [27] show that overexpression of AURKB augments the expression of MAD2L2 and both work synergistically in tumorigenesis and DNA damage response. In colorectal cancer cells treated with ETC-1922159, MAD2L family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these MAD2L member along with AURKB.

Table 15 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 16 generated from analysis of the ranks in Table 15. The Table 15 shows rankings of individual members w.r.t AURKB. MAD2L1 - AURKB shows low ranking of 114 (laplace), 109 (linear) and 477 (rbf). MAD2L2 - AURKB shows low ranking of 852 (laplace) and 678 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Table 15. 2^{nd} order interaction ranking between AURKB VS MAD2L family.

RANKING MAD2L FAMILY VS AURKB			
RANKING OF MAD2L FAMILY W.R.T AURKB			
	laplace	linear	rbf
MAD2L1 - AURKB	114	109	477
MAD2L2 - AURKB	852	1872	678

One can also interpret the results of the Table 15 graphically, with the following influences - • MAD2L family w.r.t AURKB with AURKB $->$ MAD2L-1/2.

Table 16. 2^{nd} order combinatorial hypotheses between AURKB and MAD2L family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
MAD2L family w.r.t AURKB	
MAD2L-1/2	AURKB

2.1.9. AURKB - HOX

Kim et al. [28] observe that castration-resistant prostate cancer deploy the bromodomain and BRD4 to epigenetically regulate HOXB13 gene expression which activates AURKA/AURKB. In colorectal cancer cells treated with ETC-1922159, HOX family members and AURKB, were found to be down

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regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these HOX member along with AURKB.

Table 17 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 18 generated from analysis of the ranks in Table 17. The Table 17 shows rankings of individual members w.r.t AURKB. HOXB9 - AURKB shows low ranking of 447 (laplace), 1286 (linear) and 1240 (rbf). HOXB8 - AURKB shows low ranking of 689 (laplace), 236 (linear) and 128 (rbf). HOXB5 - AURKB shows low ranking of 1297 (laplace), 1415 (linear) and 1006 (rbf). HOXA9 - AURKB shows low ranking of 1430 (linear) and 1415 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, HOXB4, HOXA11, HOXB13, HOXB3 and HOXB7 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 17. 2^{nd} order interaction ranking between AURKB VS HOX family.

RANKING HOX FAMILY VS AURKB			
RANKING OF HOX FAMILY W.R.T AURKB			
	laplace	linear	rbf
HOXB9 - AURKB	447	1286	1240
HOXB8 - AURKB	689	236	128
HOXB4 - AURKB	1101	1939	1711
HOXB5 - AURKB	1297	1415	1006
HOXA11 - AURKB	1505	2329	1721
HOXB13 - AURKB	2314	2670	2228
HOXB3 - AURKB	2380	2593	2026
HOXB7 - AURKB	2435	2518	2668
HOXA9 - AURKB	2643	1430	1415

One can also interpret the results of the Table 17 graphically, with the following influences - • HOX family w.r.t AURKB with AURKB $->$ HOX-B9/B8/B5/A9.

Table 18. 2^{nd} order combinatorial hypotheses between AURKB and HOX family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
HOX family w.r.t AURKB	
HOX-B9/B8/B5/A9	AURKB

2.1.10. AURKB - DHX

Zhu et al. [29] show that AURKB targets DHX9 to promote hepatocellular carcinoma progression. In colorectal cancer cells treated with ETC-1922159, DHX family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these DHX member along with AURKB.

Table 19 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 20 generated from analysis of the ranks in Table 19. The Table 19 shows rankings of individual members w.r.t AURKB. DHX33 - AURKB shows low ranking of 606 (laplace), 947 (linear) and 1374 (rbf). DHX57 - AURKB shows low ranking of 1113 (laplace), 754 (linear) and 642 (rbf). DHX37 - AURKB shows low ranking of 1432 (linear) and 1430 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, DHX40, DHX35, DHX30 and DHX9 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

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Table 19. 2^{nd} order interaction ranking between AURKB VS DHX family.

RANKING DHX FAMILY VS AURKB			
RANKING OF DHX FAMILY W.R.T AURKB			
	laplace	linear	rbf
DHX33 - AURKB	606	947	1374
DHX57 - AURKB	1113	754	642
DHX40 - AURKB	1316	1679	1595
DHX35 - AURKB	1448	2012	2312
DHX30 - AURKB	1658	2235	2205
DHX37 - AURKB	1715	1432	1430
DHX9 - AURKB	2560	2434	2065

One can also interpret the results of the Table 19 graphically, with the following influences - • DHX family w.r.t AURKB with AURKB $->$ DHX-33/57/37.

Table 20. 2^{nd} order combinatorial hypotheses between AURKB and DHX family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
DHX family w.r.t AURKB	
DHX-33/57/37	AURKB

2.1.11. AURKB - PLK

Chu et al. [30] show that AURKB activation requires Survivin priming phosphorylation, which is catalyzed by PLK1. Inhibition of PLK1 prevents AURKB activation and correct spindle microtubule attachment. In colorectal cancer cells treated with ETC-1922159, PLK family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these PLK member along with AURKB.

Table 21 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 22 generated from analysis of the ranks in Table 21. The Table 21 shows rankings of individual members w.r.t AURKB. PLK1 - AURKB shows low ranking of 732 (laplace), 755 (linear) and 522 (rbf). PLK4 - AURKB shows low ranking of 958 (laplace), 454 (linear) and 37 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Table 21. 2^{nd} order interaction ranking between AURKB VS PLK family.

RANKING PLK FAMILY VS AURKB			
RANKING OF PLK FAMILY W.R.T AURKB			
	laplace	linear	rbf
PLK1 - AURKB	732	755	522
PLK4 - AURKB	958	454	37

One can also interpret the results of the Table 21 graphically, with the following influences - • PLK family w.r.t AURKB with AURKB $->$ PLK-1/4.

Table 22. 2^{nd} order combinatorial hypotheses between AURKB and PLK family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
PLK family w.r.t AURKB	
PLK-1/4	AURKB

2.1.12. AURKB - BUB

Roy et al. [31] show evidence that AURKB phosphorylates BUB1 which maintains spindle assembly checkpoint signaling. In colorectal cancer cells treated with ETC-1922159, BUB family members

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and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these BUB member along with AURKB.

Table 23 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 24 generated from analysis of the ranks in Table 23. The Table 23 shows rankings of individual members w.r.t AURKB. BUB1 - AURKB shows low ranking of 58 (laplace), 239 (linear) and 476 (rbf). BUB1B - AURKB shows low ranking of 100 (laplace), 103 (linear) and 537 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, BUB3 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 23. 2^{nd} order interaction ranking between AURKB VS BUB family.

RANKING BUB FAMILY VS AURKB			
RANKING OF BUB FAMILY W.R.T AURKB			
	laplace	linear	rbf
BUB1 - AURKB	58	239	476
BUB1B - AURKB	100	103	537
BUB3 - AURKB	1773	1836	747

One can also interpret the results of the Table 23 graphically, with the following influences - • BUB family w.r.t AURKB with AURKB $-$ > BUB-1/1B.

Table 24. 2^{nd} order combinatorial hypotheses between AURKB and BUB family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
BUB family w.r.t AURKB	
BUB-1/1B	AURKB

2.1.13. AURKB - TOP

Via proteomic analysis Morrison et al. [32] identified phosphorylated TOP2A as a potential AURKB substrate. In colorectal cancer cells treated with ETC-1922159, TOP family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these TOP member along with AURKB.

Table 25 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 26 generated from analysis of the ranks in Table 25. The Table 25 shows rankings of individual members w.r.t AURKB. TOP2A - AURKB shows low ranking of 23 (laplace), 19 (linear) and 36 (rbf). TOP1MT - AURKB shows low ranking of 563 (laplace), 618 (linear) and 418 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, TOPBP1 and TOP2B showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 25. 2^{nd} order interaction ranking between AURKB VS TOP family.

RANKING TOP FAMILY VS AURKB			
RANKING OF TOP FAMILY W.R.T AURKB			
	laplace	linear	rbf
TOP2A - AURKB	23	19	36
TOP1MT - AURKB	563	618	418
TOPBP1 - AURKB	1950	1973	2279
TOP2B - AURKB	2322	1739	2033

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One can also interpret the results of the Table 25 graphically, with the following influences - • TOP family w.r.t AURKB with AURKB $-$ > TOP-2A/1MT.

Table 26. 2^{nd} order combinatorial hypotheses between AURKB and TOP family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
TOP family w.r.t AURKB	
TOP-2A/1MT	AURKB

2.1.14. AURKB - CDK

Lee et al. [33] demonstrate that CDK4 could occupy the promoter region of genes like AURKB and CENPP. Further, gain- and loss- of function experiments showed that CDK4 regulated expressiong of AURKB and CENPP. In colorectal cancer cells treated with ETC-1922159, CDK family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these CDK member along with AURKB.

Table 27 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 28 generated from analysis of the ranks in Table 27. The Table 27 shows rankings of individual members w.r.t AURKB. CDK1 - AURKB shows low ranking of 30 (laplace), 4 (linear) and 206 (rbf). CDK20 - AURKB shows low ranking of 653 (laplace), 832 (linear) and 1002 (rbf). CDK4 - AURKB shows low ranking of 1453 (laplace) and 1338 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, CDK6 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 27. 2^{nd} order interaction ranking between AURKB VS CDK family.

RANKING CDK FAMILY VS AURKB			
RANKING OF CDK FAMILY W.R.T AURKB			
	laplace	linear	rbf
CDK1 - AURKB	30	4	206
CDK20 - AURKB	653	832	1002
CDK4 - AURKB	1453	2213	1338
CDK6 - AURKB	2263	2388	2424

One can also interpret the results of the Table 27 graphically, with the following influences - • CDK family w.r.t AURKB with AURKB $-$ > CDK-1/20/4.

Table 28. 2^{nd} order combinatorial hypotheses between AURKB and CDK family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
CDK family w.r.t AURKB	
CDK-1/20/4	AURKB

2.1.15. AURKB - ALKBH

Zhang et al. [34] suggest that ALKBH5 may proliferate renal cell carcinoma by stabilizing AURKB. In colorectal cancer cells treated with ETC-1922159, ALKBH family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these ALKBH member along with AURKB.

Table 29 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 30 generated from analysis of the ranks in Table 29. The Table 29 shows rankings of individual members w.r.t AURKB. ALKBH2 - AURKB shows low ranking of 494 (laplace), 758 (linear) and 438 (rbf). ALKBH8 - AURKB shows low ranking of 1013 (laplace), 942 (linear) and 632 (rbf). These

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rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, ALKBH4 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 29. 2^{nd} order interaction ranking between AURKB VS ALKBH family.

RANKING ALKBH FAMILY VS AURKB			
RANKING OF ALKBH FAMILY W.R.T AURKB			
	laplace	linear	rbf
ALKBH2 - AURKB	494	758	438
ALKBH8 - AURKB	1013	942	632
ALKBH4 - AURKB	1599	2324	2640

One can also interpret the results of the Table 29 graphically, with the following influences - • ALKBH family w.r.t AURKB with AURKB $->$ ALKBH-2/8.

Table 30. 2^{nd} order combinatorial hypotheses between AURKB and ALKBH family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
ALKBH family w.r.t AURKB	
ALKBH-2/8	AURKB

2.1.16. AURKB - PRMT

Kim et al. [35] show that asymmetric dimethylation on histone H3 by PRMT6 recruits the chromosomal passenger complex to chromosome arms and facilitates histone H3S10 phosphorylation by AURKB. In colorectal cancer cells treated with ETC-1922159, PRMT family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these PRMT member along with AURKB.

Table 31 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 32 generated from analysis of the ranks in Table 31. The Table 31 shows rankings of individual members w.r.t AURKB. PRMT6 - AURKB shows low ranking of 769 (laplace), 418 (linear) and 626 (rbf). PRMT1 - AURKB shows low ranking of 1388 (laplace) and 686 (linear). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Table 31. 2^{nd} order interaction ranking between AURKB VS PRMT family.

RANKING PRMT FAMILY VS AURKB			
RANKING OF PRMT FAMILY W.R.T AURKB			
	laplace	linear	rbf
PRMT6 - AURKB	769	418	626
PRMT1 - AURKB	1388	686	1818

One can also interpret the results of the Table 31 graphically, with the following influences - • PRMT family w.r.t AURKB with AURKB $->$ PRMT-6/1.

Table 32. 2^{nd} order combinatorial hypotheses between AURKB and PRMT family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
PRMT family w.r.t AURKB	
PRMT-6/1	AURKB

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2.1.17. AURKB - SGO

Asai et al. [36] show that SET is recruited through interaction with SGO2 (also known as SGOL2), and maintains AURKB activity by counteracting PP2A in mitotic cells, at the inner centromere. In colorectal cancer cells treated with ETC-1922159, SGO family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these SGO member along with AURKB.

Table 33 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 34 generated from analysis of the ranks in Table 33. The Table 33 shows rankings of individual members w.r.t AURKB. SGOL1 - AURKB shows low ranking of 225 (laplace), 146 (linear) and 122 (rbf). SGOL2 - AURKB shows low ranking of 534 (laplace), 473 (linear) and 284 (rbf). SGOL1-AS1 - AURKB shows low ranking of 239 (laplace), 174 (linear) and 100 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Table 33. 2^{nd} order interaction ranking between AURKB VS SGO family.

RANKING SGO FAMILY VS AURKB			
RANKING OF SGO FAMILY W.R.T AURKB			
	laplace	linear	rbf
SGOL1 - AURKB	225	146	122
SGOL2 - AURKB	534	473	284
SGOL1-AS1 - AURKB	239	174	100

One can also interpret the results of the Table 33 graphically, with the following influences - • SGO family w.r.t AURKB with AURKB $-$ > SGO-L1/L2/L1-AS1.

Table 34. 2^{nd} order combinatorial hypotheses between AURKB and SGO family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
SGO family w.r.t AURKB	
SGO-L1/L2/L1-AS1	AURKB

2.1.18. AURKB - SKA

The spindle and kinetochore-associated (SKA) complex is required for chromosome segregation and consists of two copies each of SKA1, SKA2, and SKA3 proteins. SKA complex regulates, and is regulated by AURKB as shown by Redli et al. [37]. Also, Chan et al. [38] show that AURKB phosphorylates both SKA1 and SKA3 to inhibit the kinetochore localization of the SKA complex. Finally, Zhang et al. [39] show that CDK1 phosphorylates SKA3 which occurs during mitosis and is required for the kinetochore localization of the SKA complex. In colorectal cancer cells treated with ETC-1922159, SKA family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these SKA member along with AURKB.

Table 35 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 36 generated from analysis of the ranks in Table 35. The Table 35 shows rankings of individual members w.r.t AURKB. SKA1 - AURKB shows low ranking of 56 (laplace), 75 (linear) and 324 (rbf). SKA3 - AURKB shows low ranking of 128 (laplace), 140 (linear) and 160 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, SKA2 showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

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Table 35. 2^{nd} order interaction ranking between AURKB VS SKA family.

RANKING SKA FAMILY VS AURKB			
RANKING OF SKA FAMILY W.R.T AURKB			
	laplace	linear	rbf
SKA1 - AURKB	56	75	324
SKA2 - AURKB	1328	2317	2609
SKA3 - AURKB	128	140	160

One can also interpret the results of the Table 35 graphically, with the following influences - • SKA family w.r.t AURKB with AURKB $->$ SKA-1/3.

Table 36. 2^{nd} order combinatorial hypotheses between AURKB and SKA family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
SKA family w.r.t AURKB	
SKA-1/3	AURKB

2.1.19. AURKB - GAS

Fackler et al. [40] show that GAS2L3 associates with AURKB and survivin. In colorectal cancer cells treated with ETC-1922159, GAS family members and AURKB, were found to be down regulated and their regulation was recorded independently. I was able to rank 2^{nd} order combination of these GAS member along with AURKB.

Table 37 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 38 generated from analysis of the ranks in Table 37. The Table 37 shows rankings of individual members w.r.t AURKB. GAS5 - AURKB shows low ranking of 1100 (laplace) and 1482 (rbf). GAS2L3 - AURKB shows low ranking of 1577 (laplace) and 1329 (rbf). GAS6 - AURKB shows low ranking of 1362 (linear) and 1122 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Table 37. 2^{nd} order interaction ranking between AURKB VS GAS family.

RANKING GAS FAMILY VS AURKB			
RANKING OF GAS FAMILY W.R.T AURKB			
	laplace	linear	rbf
GAS5 - AURKB	1100	1772	1482
GAS2L3 - AURKB	1577	1871	1329
GAS6 - AURKB	1637	1362	1122

One can also interpret the results of the Table 37 graphically, with the following influences - • GAS family w.r.t AURKB with AURKB $->$ GAS-5/2L3/6.

Table 38. 2^{nd} order combinatorial hypotheses between AURKB and GAS family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
GAS family w.r.t AURKB	
GAS-5/2L3/6	AURKB

2.1.20. AURKB - KIF

Via experiments and mathematical modeling, Uehara et al. [41] demonstrate that AURKB activity gradient determines the spatial distribution of KIF2A and limits KIF2A mediated depolymerization in an interchromosomal microtubule length dependent fashion. In colorectal cancer cells treated with ETC-1922159, KIF family members and AURKB, were found to be down regulated and their regulation

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was recorded independently. I was able to rank 2^{nd} order combination of these KIF member along with AURKB.

Table 39 shows rankings of these combinations. Followed by this is the unexplored combinatorial hypotheses in Table 40 generated from analysis of the ranks in Table 39. The Table 39 shows rankings of individual members w.r.t AURKB. KIF4A - AURKB shows low ranking of 24 (laplace), 13 (linear) and 21 (rbf). KIF11 - AURKB shows low ranking of 40 (laplace), 29 (linear) and 139 (rbf). KIF2C - AURKB shows low ranking of 42 (laplace), 67 (linear) and 41 (rbf). KIF20A - AURKB shows low ranking of 61 (laplace), 40 (linear) and 445 (rbf). KIF23 - AURKB shows low ranking of 70 (laplace), 69 (linear) and 281 (rbf). KIF15 - AURKB shows low ranking of 92 (laplace), 57 (linear) and 94 (rbf). KIF14 - AURKB shows low ranking of 110 (laplace), 190 (linear) and 161 (rbf). KIFC1 - AURKB shows low ranking of 139 (laplace), 452 (linear) and 367 (rbf). KIF20B - AURKB shows low ranking of 155 (laplace), 253 (linear) and 896 (rbf). KIF22 - AURKB shows low ranking of 184 (laplace), 192 (linear) and 300 (rbf). KIF18A - AURKB shows low ranking of 213 (laplace), 129 (linear) and 649 (rbf). KIF18B - AURKB shows low ranking of 229 (laplace), 249 (linear) and 19 (rbf). KIF9 - AURKB shows low ranking of 1167 (laplace), 776 (linear) and 1111 (rbf). KIF7 - AURKB shows low ranking of 1380 (laplace), 697 (linear) and 1147 (rbf). These rankings point to the synergy existing between the two components, which have been down regulated after the drug treatment.

Further, KIF27 and KIF13A showed high ranking with AURKB, thus indicating that they might not be working synergistically with AURKB, before the drug treatment.

Table 39. 2^{nd} order interaction ranking between AURKB VS KIF family.

RANKING KIF FAMILY VS AURKB							
	RANKING OF KIF FAMILY W.R.T AURKB						
	laplace	linear	rbf		laplace	linear	rbf
KIF4A - AURKB	24	13	21	KIF11 - AURKB	40	29	139
KIF2C - AURKB	42	67	41	KIF20A - AURKB	61	40	445
KIF23 - AURKB	70	69	281	KIF15 - AURKB	92	57	94
KIF14 - AURKB	110	190	161	KIFC1 - AURKB	139	452	367
KIF20B - AURKB	155	253	896	KIF22 - AURKB	184	192	300
KIF18A - AURKB	213	129	649	KIF18B - AURKB	229	249	19
KIF9 - AURKB	1167	776	1111	KIF7 - AURKB	1380	697	1147
KIF27 - AURKB	1581	1833	1081	KIF13A - AURKB	2740	1774	2350

One can also interpret the results of the Table 39 graphically, with the following influences - • KIF family w.r.t AURKB with AURKB $->$ KIF-4A / 11 / 2C / 20A / 23 / 15 / 14 / C1 / 20B / 22 / 18A / 18B / 9 / 7.

Table 40. 2^{nd} order combinatorial hypotheses between AURKB and KIF family.

UNEXPLORED COMBINATORIAL HYPOTHESES	
KIF family w.r.t AURKB	
KIF-4A/11/2C/20A/23/15/14/C1/20B/22/18A/18B/9/7	AURKB

3. Conclusion

Presented here are a range of multiple synergistic AURKB 2^{nd} order combinations that were ranked via a machine learning based search engine. Via majority voting across the ranking methods, it was possible to find plausible unexplored synergistic combinations of AURKB-X that might be prevalent in CRC cells after treatment with ETC-1922159 drug.

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

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References

1. Zhang, X. Aurora kinases. *Current Biology* **2008**, *18*, R146–R148.
2. Glover, D.M.; Leibowitz, M.H.; McLean, D.A.; Parry, H. Mutations in aurora prevent centrosome separation leading to the formation of monopolar spindles. *Cell* **1995**, *81*, 95–105.
3. Carmena, M.; Earnshaw, W.C. The cellular geography of aurora kinases. *Nature reviews Molecular cell biology* **2003**, *4*, 842–854.
4. Willems, E.; Dedobbeleer, M.; Digregorio, M.; Lombard, A.; Lumapat, P.N.; Rogister, B. The functional diversity of Aurora kinases: a comprehensive review. *Cell division* **2018**, *13*, 1–17.
5. Bischoff, J.R.; Anderson, L.; Zhu, Y.; Mossie, K.; Ng, L.; Souza, B.; Schryver, B.; Flanagan, P.; Clairvoyant, F.; Ginther, C.; et al. A homologue of Drosophila aurora kinase is oncogenic and amplified in human colorectal cancers. *The EMBO journal* **1998**.
6. Ota, T.; Suto, S.; Katayama, H.; Han, Z.B.; Suzuki, F.; Maeda, M.; Tanino, M.; Terada, Y.; Tatsuka, M. Increased mitotic phosphorylation of histone H3 attributable to AIM-1/Aurora-B overexpression contributes to chromosome number instability. *Cancer research* **2002**, *62*, 5168–5177.
7. Shah, E.T.; Molloy, C.; Gough, M.; Kryza, T.; Samuel, S.G.; Tucker, A.; Bhatia, M.; Ferguson, G.; Heyman, R.; Vora, S.; et al. Inhibition of Aurora B kinase (AURKB) enhances the effectiveness of 5-fluorouracil chemotherapy against colorectal cancer cells. *British Journal of Cancer* **2024**, *130*, 1196–1205.
8. Li, L.; Xie, K.; Xie, H.; Wang, L.; Li, Z.; Lu, Q.; Feng, J. AURKB promotes colorectal cancer progression by triggering the phosphorylation of histone H3 at serine 10 to activate CCNE1 expression. *Aging (Albany NY)* **2024**, *16*, 8019.
9. Sinha, S. Machine learning ranking of plausible (un) explored synergistic gene combinations using sensitivity indices of time series measurements of Wnt signaling pathway. *Integrative Biology* **2024**, *16*, zyae020.
10. Sinha, S. Sensitivity analysis based ranking reveals unknown biological hypotheses for down regulated genes in time buffer during administration of PORCN-WNT inhibitor ETC-1922159 in CRC. *bioRxiv* **2017**, p. 180927.
11. Joachims, T. Training linear SVMs in linear time. In Proceedings of the Proceedings of the 12th ACM SIGKDD international conference on Knowledge discovery and data mining. ACM, 2006, pp. 217–226.
12. Kasuboski, J.M.; Bader, J.R.; Vaughan, P.S.; Tauhata, S.B.; Winding, M.; Morrissey, M.A.; Joyce, M.V.; Boggess, W.; Vos, L.; Chan, G.K.; et al. Zwint-1 is a novel Aurora B substrate required for the assembly of a dynein-binding platform on kinetochores. *Molecular biology of the cell* **2011**, *22*, 3318–3330.
13. Abdul Azeez, K.R.; Chatterjee, S.; Yu, C.; Golub, T.R.; Sobott, F.; Elkins, J.M. Structural mechanism of synergistic activation of Aurora kinase B/C by phosphorylated INCENP. *Nature communications* **2019**, *10*, 3166.
14. Iyer, J.; Tsai, M.Y. A novel role for TPX2 as a scaffold and co-activator protein of the Chromosomal Passenger Complex. *Cellular signalling* **2012**, *24*, 1677–1689.
15. Luo, Y.; Barrios-Rodiles, M.; Gupta, G.D.; Zhang, Y.Y.; Ogunjimi, A.A.; Bashkurov, M.; Tkach, J.M.; Underhill, A.Q.; Zhang, L.; Bourmoum, M.; et al. Atypical function of a centrosomal module in WNT signalling drives contextual cancer cell motility. *Nature communications* **2019**, *10*, 2356.
16. Luga, V.; Zhang, L.; Viloria-Petit, A.M.; Ogunjimi, A.A.; Inanlou, M.R.; Chiu, E.; Buchanan, M.; Hosein, A.N.; Basik, M.; Wrana, J.L. Exosomes mediate stromal mobilization of autocrine Wnt-PCP signaling in breast cancer cell migration. *Cell* **2012**, *151*, 1542–1556.
17. Agarwal, S.; Smith, K.P.; Zhou, Y.; Suzuki, A.; McKenney, R.J.; Varma, D. Cdt1 stabilizes kinetochore–microtubule attachments via an Aurora B kinase–dependent mechanism. *Journal of Cell Biology* **2018**, *217*, 3446–3463.
18. Tipton, A.R.; Wren, J.D.; Daum, J.R.; Siefert, J.C.; Gorbsky, G.J. GTSE1 regulates spindle microtubule dynamics to control Aurora B kinase and Kif4A chromokinesin on chromosome arms. *Journal of Cell Biology* **2017**, *216*, 3117–3132.

 doi:10.20944/preprints202412.2470.v1

19. Moura, D.S.; Campillo-Marcos, I.; Vázquez-Cedeira, M.; Lazo, P.A. VRK1 and AURKB form a complex that cross inhibit their kinase activity and the phosphorylation of histone H3 in the progression of mitosis. *Cellular and Molecular Life Sciences* **2018**, *75*, 2591–2611.
20. Fang, H.; Niu, K.; Mo, D.; Zhu, Y.; Tan, Q.; Wei, D.; Li, Y.; Chen, Z.; Yang, S.; Balajee, A.S.; et al. RecQL4-Aurora B kinase axis is essential for cellular proliferation, cell cycle progression, and mitotic integrity. *Oncogenesis* **2018**, *7*, 68.
21. Zhang, F.; Huang, C. GSG2 promotes thyroid cancer via stabilizing AURKB and activating AKT pathway. *Aging (Albany NY)* **2024**, *16*, 5091.
22. Kong, W.; Hara, M.; Tokunaga, Y.; Okumura, K.; Hirano, Y.; Miao, J.; Takenoshita, Y.; Hashimoto, M.; Sasaki, H.; Fujimori, T.; et al. CENP-C-Mis12 complex establishes a regulatory loop through Aurora B for chromosome segregation. *Life Science Alliance* **2025**, *8*.
23. Liu, W.; Dou, Z.; Wang, C.; Zhao, G.; Wu, F.; Wang, C.; Aikhionbare, F.; Ye, M.; Sedzro, D.M.; Yang, Z.; et al. Aurora B promotes the CENP-T–CENP-W interaction to guide accurate chromosome segregation in mitosis. *Journal of Molecular Cell Biology* **2024**, p. mjae001.
24. Tu, R.; Kang, Y.; Pan, Y.; Da, Y.; Ren, D.; Zhang, R.; Cai, Z.; Liu, Y.; Xu, J.; Ma, J.; et al. USP29 activation mediated by FUBP1 promotes AURKB stability and oncogenic functions in gastric cancer. *Cancer Cell International* **2024**, *24*, 33.
25. Di Cesare, E.; Moroni, S.; Bartoli, J.; Damizia, M.; Giubettini, M.; Koerner, C.; Krenn, V.; Musacchio, A.; Lavia, P. Aurora B SUMOylation is restricted to centromeres in early mitosis and requires RANBP2. *Cells* **2023**, *12*, 372.
26. Lin, J.; Liu, B.; Zhang, Y.; Lv, L.; Cheng, D.; Zhang, W.; Shi, Y.; Jiang, X.; Tang, L.; Yuan, Y.; et al. Gemin6 promotes c-Myc stabilisation and non-small cell lung cancer progression via accelerating AURKB mRNA maturation. *Clinical and Translational Medicine* **2022**, *12*.
27. Marima, R.; Hull, R.; Penny, C.; Dlamini, Z. Mitotic syndicates Aurora Kinase B (AURKB) and mitotic arrest deficient 2 like 2 (MAD2L2) in cohorts of DNA damage response (DDR) and tumorigenesis. *Mutation Research/Reviews in Mutation Research* **2021**, *787*, 108376.
28. Kim, E.H.; Cao, D.; Mahajan, N.P.; Andriole, G.L.; Mahajan, K. ACK1–AR and AR–HOXB13 signaling axes: Epigenetic regulation of lethal prostate cancers. *Nar Cancer* **2020**, *2*, zcaa018.
29. Zhu, G.; Luo, L.; He, Y.; Xiao, Y.; Cai, Z.; Tong, W.; Deng, W.; Xie, J.; Zhong, Y.; Hu, Z.; et al. AURKB targets DHX9 to promote hepatocellular carcinoma progression via PI3K/AKT/mTOR pathway. *Molecular Carcinogenesis* **2024**.
30. Chu, Y.; Yao, P.Y.; Wang, W.; Wang, D.; Wang, Z.; Zhang, L.; Huang, Y.; Ke, Y.; Ding, X.; Yao, X. Aurora B kinase activation requires survivin priming phosphorylation by PLK1. *Journal of molecular cell biology* **2011**, *3*, 260–267.
31. Roy, B.; Han, S.J.; Fontan, A.N.; Jema, S.; Joglekar, A.P. Aurora B phosphorylates Bub1 to promote spindle assembly checkpoint signaling. *Current Biology* **2022**, *32*, 237–247.
32. Morrison, C.; Henzing, A.J.; Jensen, O.N.; Osheroff, N.; Dodson, H.; Kandels-Lewis, S.E.; Adams, R.R.; Earnshaw, W.C. Proteomic analysis of human metaphase chromosomes reveals topoisomerase II alpha as an Aurora B substrate. *Nucleic acids research* **2002**, *30*, 5318–5327.
33. Lee, S.H.; Rodriguez, L.R.; Majumdar, R.; De Marval, P.L.M.; Rodriguez-Puebla, M.L. CDK4 has the ability to regulate Aurora B and Cenpp expression in mouse keratinocytes. *Oncology Letters* **2021**, *22*, 732.
34. Zhang, X.; Wang, F.; Wang, Z.; Yang, X.; Yu, H.; Si, S.; Lu, J.; Zhou, Z.; Lu, Q.; Wang, Z.; et al. ALKBH5 promotes the proliferation of renal cell carcinoma by regulating AURKB expression in an m6A-dependent manner. *Annals of translational medicine* **2020**, *8*.
35. Kim, S.; Kim, N.H.; Park, J.E.; Hwang, J.W.; Myung, N.; Hwang, K.T.; Kim, Y.A.; Jang, C.Y.; Kim, Y.K. PRMT6-mediated H3R2me2a guides Aurora B to chromosome arms for proper chromosome segregation. *Nature communications* **2020**, *11*, 612.
36. Asai, Y.; Fukuchi, K.; Tanno, Y.; Koitabashi-Kiyozuka, S.; Kiyozuka, T.; Noda, Y.; Matsumura, R.; Koizumi, T.; Watanabe, A.; Nagata, K.; et al. Aurora B kinase activity is regulated by SET/TAF1 on Sgo2 at the inner centromere. *Journal of Cell Biology* **2019**, *218*, 3223–3236.
37. Redli, P.M.; Gasic, I.; Meraldi, P.; Nigg, E.A.; Santamaria, A. The Ska complex promotes Aurora B activity to ensure chromosome biorientation. *Journal of Cell Biology* **2016**, *215*, 77–93.

 doi:10.20944/preprints202412.2470.v1

38. Chan, Y.W.; Jeyaprakash, A.A.; Nigg, E.A.; Santamaria, A. Aurora B controls kinetochore–microtubule attachments by inhibiting Ska complex–KMN network interaction. *Journal of Cell Biology* **2012**, *196*, 563–571.
39. Zhang, Q.; Sivakumar, S.; Chen, Y.; Gao, H.; Yang, L.; Yuan, Z.; Yu, H.; Liu, H. Ska3 phosphorylated by Cdk1 binds Ndc80 and recruits Ska to kinetochores to promote mitotic progression. *Current Biology* **2017**, *27*, 1477–1484.
40. Fackler, M.; Wolter, P.; Gaubatz, S. The GAR domain of GAS 2L3 mediates binding to the chromosomal passenger complex and is required for localization of GAS2L3 to the constriction zone during abscission. *The FEBS Journal* **2014**, *281*, 2123–2135.
41. Uehara, R.; Tsukada, Y.; Kamasaki, T.; Poser, I.; Yoda, K.; Gerlich, D.W.; Goshima, G. Aurora B and Kif2A control microtubule length for assembly of a functional central spindle during anaphase. *Journal of Cell Biology* **2013**, *202*, 623–636.
42. Madan, B.; Ke, Z.; Harmston, N.; Ho, S.Y.; Frois, A.; Alam, J.; Jeyaraj, D.A.; Pendharkar, V.; Ghosh, K.; Virshup, I.H.; et al. Wnt addiction of genetically defined cancers reversed by PORCN inhibition. *Oncogene* **2016**, *35*, 2197.