## **BRAF mutant colorectal cancer:** A different entity

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ESMO 16th World Congress on Gastrointestinal Cancer 25 June, 2014 - 28 June, 2014





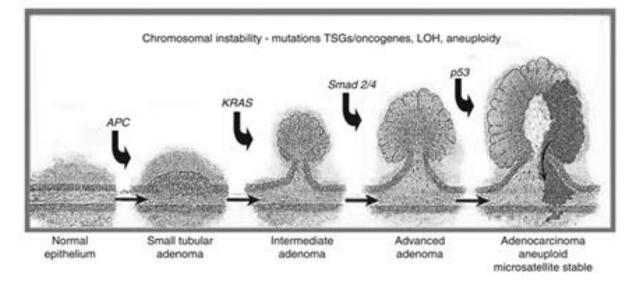
### **Colorectal cancer (CRC) is a heterogeneous disease but patients are not yet selected for individualized treatments**



- Colorectal cancer is the second leading cause of cancer death
- Although several treatments exist, we do not have a good way to select patients for individualized treatments
- Only *RAS* status has been established as a predictor of anti-EGFR treatment activity
- New technologies that allow genetic definition of different types of colon cancer based on the expression, methylation, mutation rate of the genes might help in better understanding CRC biology
- The better understanding of CRC biology might drive personalized treatments

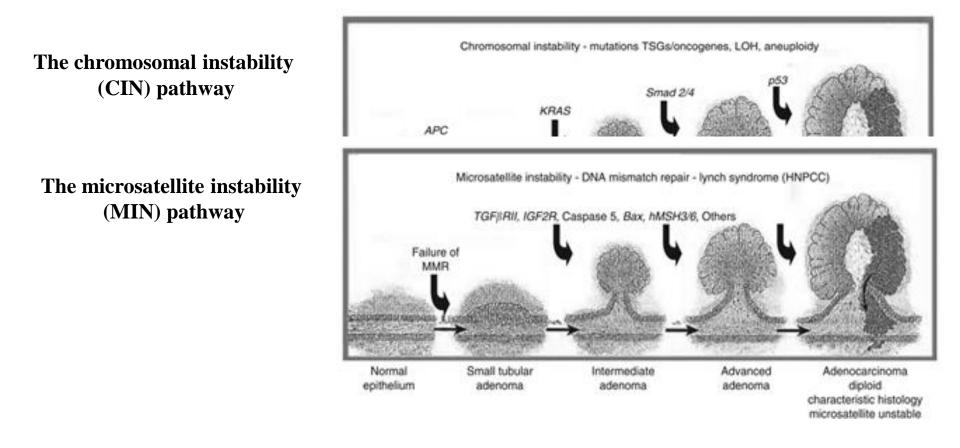
### **Colon carcinogenesis is a multi step process**

The chromosomal instability (CIN) pathway



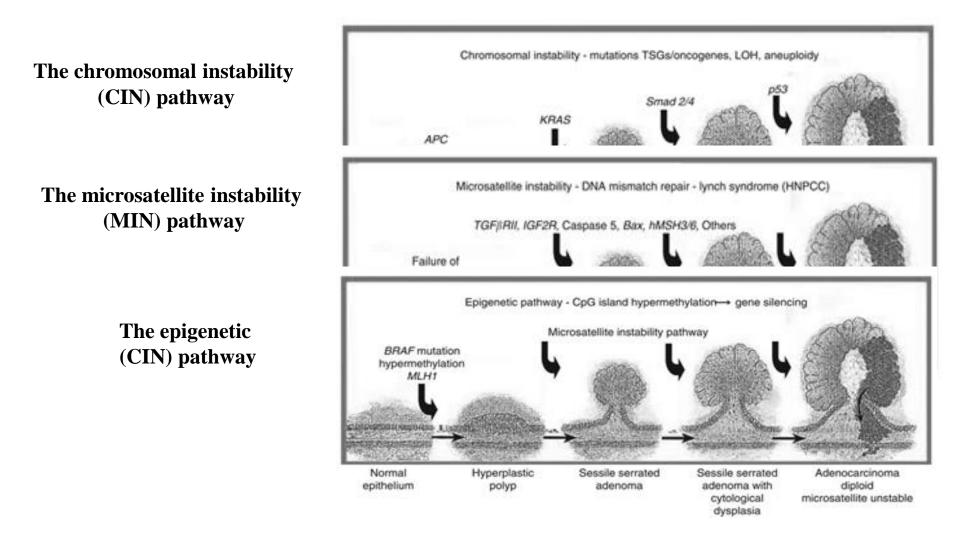
Adapted from Ahnen DJ: The American College of Gastroenterology Emily Couric Lecture— The Adenoma–Carcinoma Sequence Revisited: Has the Era of Genetic Tailoring Finally Arrived? *The American Journal of Gastroenterology* 106, 190-198 (February 2011)

### Colon carcinogenesis is a multi step process



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### Colon carcinogenesis is a multi step process



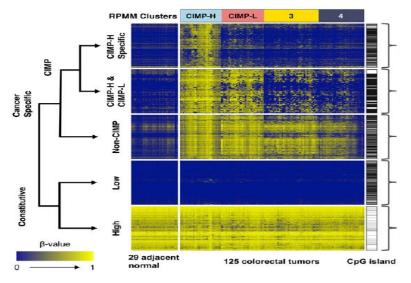
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### CRC is a heterogeneous disease at ...

...gene expression level

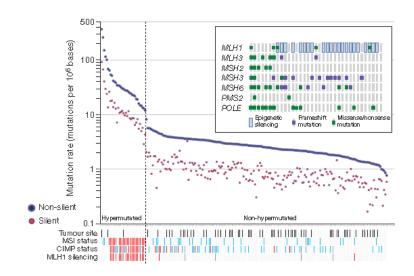
Adapted from Tejpar et al, PETACC 3 trial, ASCO 2010

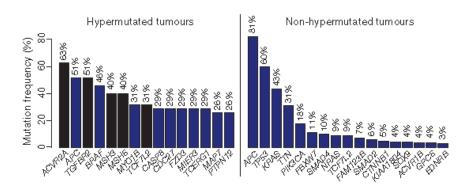
### ...methylation level



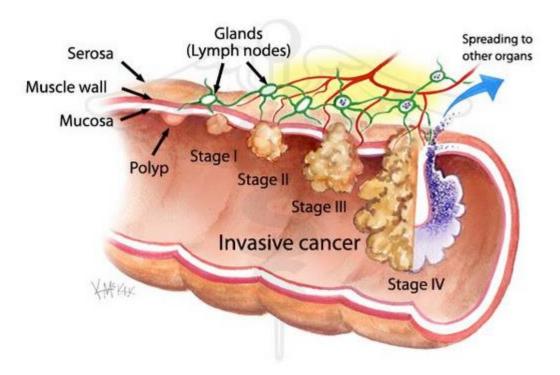
Adapted from Hinoue T et al: Genome-scale analysis of aberrant DNA methylation in colorectal cancer. Genome Res. 2011 Jun 9

### **CRC** is a heterogeneous disease at mutational rate level





Adapted from "Comprehensive molecular characterization of human colon and rectal cancer" The cancer genome atlas Network Nature, 2012 Jul 18;487(7407):330-7 The biology of CRC tells us that CRC is a heterogeneous disease at different levels but we still treat our patients by only considering the TNM classification



VOLUME 30 · NUMBER 12 · APRIL 20 2012

JOURNAL OF CLINICAL ONCOLOGY

Identification of a Poor-Prognosis *BRAF*-Mutant–Like Population of Patients With Colon Cancer

Vlad Popovici, Eva Budinska, Sabine Tejpar, Scott Weinrich, Heather Estrella, Graeme Hodgson, Eric Van Cutsem, Tao Xie, Fred T. Bosman, Arnaud D. Roth, and Mauro Delorenzi

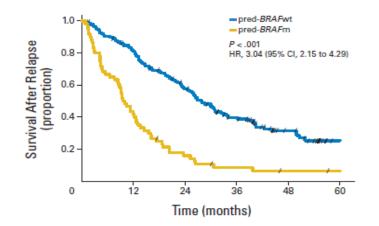
A combined oncogenic pathway signature of *BRAF*, *KRAS* and *PI3KCA* mutation improves colorectal cancer classification and cetuximab treatment prediction

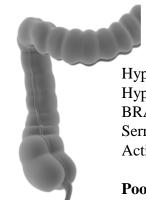
Sun Tian,<sup>1</sup> Iris Simon,<sup>1</sup> Victor Moreno,<sup>2,3</sup> Paul Roepman,<sup>1</sup> Josep Tabernero,<sup>4</sup> Mireille Snel,<sup>1</sup> Laura van't Veer,<sup>1</sup> Ramon Salazar,<sup>2</sup> Rene Bernards,<sup>1,5</sup> Gabriel Capella<sup>2</sup>

The BRAF - signature identifies:

- 1) Tumors that carry the BRAF V600E gene mutation with 96% sensitivity and 86% specificity
- 2) 30% of KRAS mutant CC
  13% of double wild type CC
  which carry the same gene expression profile as BRAF V600E

### **BRAF V600E and BRAF like CC tumors have poor outcome as compared to non BRAF like tumours**





Hypermutation (MSI) Hypermethylation (CIMP) BRAF status (BRAF –like) Serrated pathway Activation of MAPK pathway

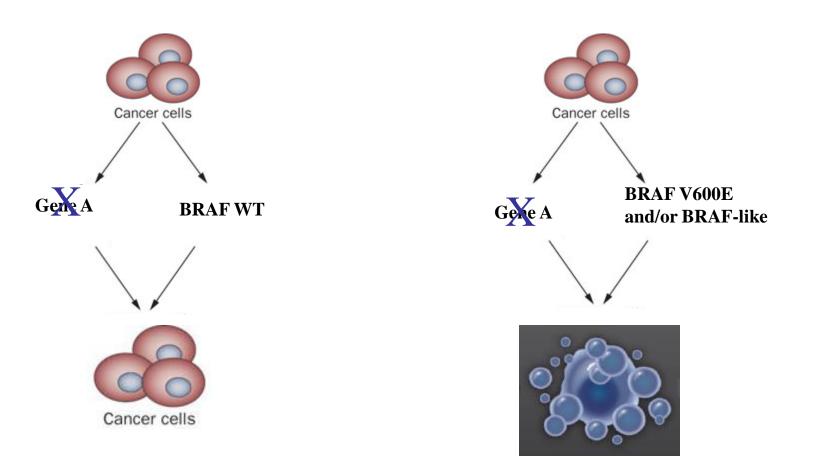
Poor SAR Non responsive to chemotherapy

### Identification of synthetic lethal interactions with the BRAF oncogene in CC

• to provide additional drug targets for therapeutic exploration

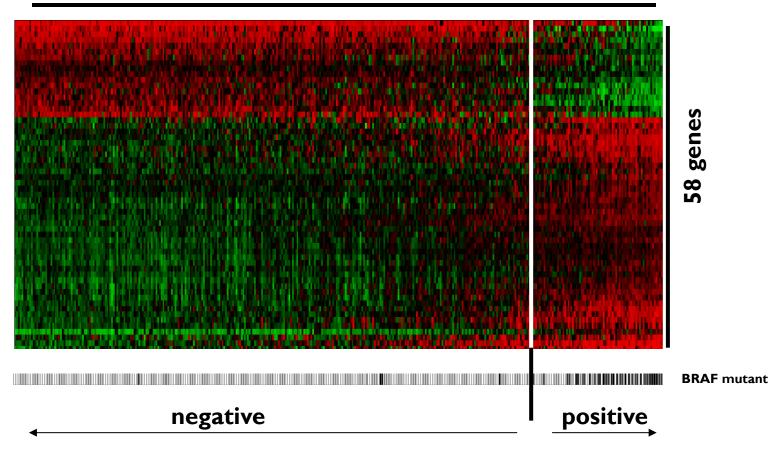
• to shed new light on BRAF mechanisms of action

# Which are the genes synthetically lethal with BRAF V600E in CC?

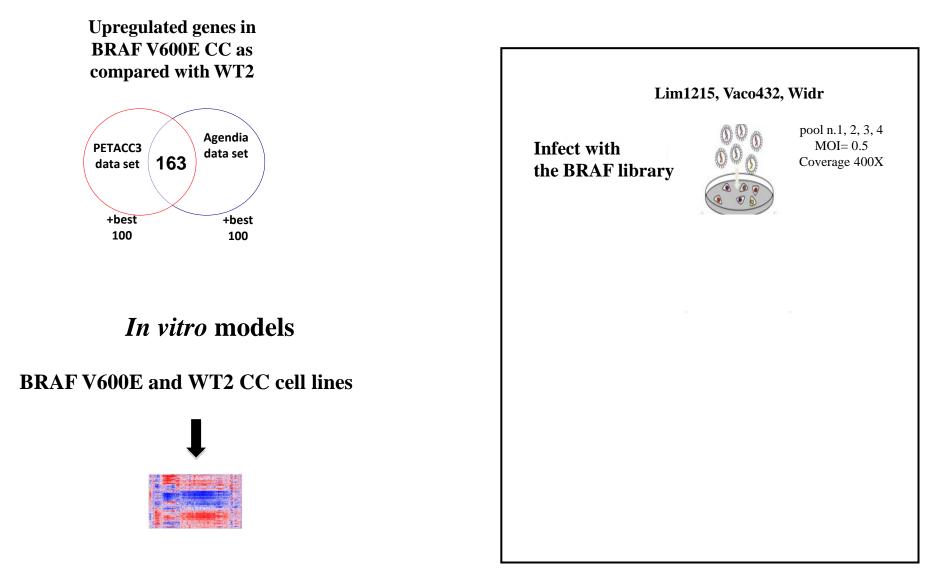


BRAF signature <u>up-regulated genes</u> are most likely to be candidates for synthetic lethality with BRAFV600E in CC

N=399 patients



### Set up experiment



### Negative selected genes in BRAF V600E vs WT2 CC cell lines

#### **Criteria for selecting hits:**

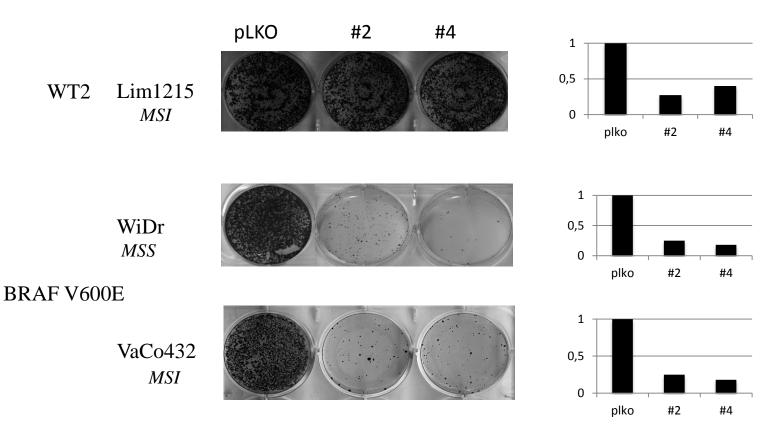
Depletion of BRAF mut cells over time must be at least 50% as compared to Time 0  $log2 (Mut T13/T0) \le -1$ 

Depletion of BRAF mut cells must be at least 1.5 fold higher than LIM1215 (LIM1215 T13/T0 fold change)/(BRAF Mut T13/T0 fold change) ≥ 1,5

*multiple hairpins* 

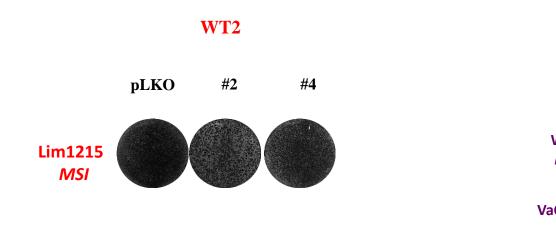
TRCN0000063415         ANTXR2         0.54127007         -0.885579478         0.05597073         0.31181298         -1.681247088         0.00027389         1.735880472           TRCN000007430         ANXA2,NHP2L1         0.05369382         -1.03272356         0.2257721         -1.91174931         3.3465.65         7         2.72184.248           TRCN000074798         ANXA2,NHP2L1QPRS1         0.03341995         -4.00346666         11005.F11         0.0331731         -8.29342605         6.47595.28         10.52265798           TRCN0000074091         ANXA2,NHP2L1QPRS1         0.04223476         -1.13150346         0.02267198         -0.1235796         -3.016740192         1.9426E-09         2.15046565           TRCN0000074051         ANXA2,NHP2L1QPRS1         0.4223476         -1.13150346         0.02267198         -0.1235796         -3.016740192         1.9426E-09         2.15046565           TRCN000007305         APOL2         0.3959597         -3.154166656         0.00312733         -5.98252681         7.0819-22         4.00305051           TRCN000077655         Conf32         0.47956559         -1.06139956         0.38674566         0.03127433         -4.99877312         5.0675.45         2.10973212         5.0675.45         2.10973212         5.0675.45         2.0566730         2.6457E-08         <	Тад	GeneSymbol	Lim1215	foldChange	log2FoldChange	pval	BRAF V600E foldChange	log2FoldChange	pval	Lim1215/BRAF V600E
TRCN0000063417         ANTXR2         0.51748765         0.990403671         0.03729236         0.26577127         1.911742931         3.3463E-05         1.947116572           TRCN0000074800         ANAXA,NHP2L1,OPRS1         0.03341935         4.09046601         1.005E-11         0.00317431         8.29934206         6.7958-83         0.522826599           TRCN000007499         ANXA2,NHP2L1,OPRS1         0.2657725         -1.91209049         0.02567955         0.1235796         -3.016740192         1.9426E-09         2.15046565           TRCN000003107         APOL2         0.94928776         -5.542605         0.02317433         4.9987712         0.64757E9         -1.61043942         -2.6485643         4.1618-08         2.10047515           TRCN000003107         APOL2         0.9395975         -3.38126864         7.5822605         0.02317433         4.9987712         0.67757E9         -0.67757E9         -0.75757E9         -0.676576E9         1.73723298188         -0.75775F9	TRCN0000059338	ABCA3		0.53608408	-0.899468812	0.0547169	0.1450598	-2.785280313	1.4972E-08	3.695607399
TRCN000074800         AVXA2;NHP211         0.05869392         4.090645015         3.6048-07         0.02583538         5.274507823         5.1352E-07         2.27184288           TRCN000074789         AVXA2;NHP21LOPR51         0.03581939         4.9034666         1.1005-11         0.00174331         8.299342065         6.4759E-38         1.05286679           TRCN0000074801         AVXA2;NHP21LOPR51         0.46228346         -1.13150346         0.02567793         0.27722097         -1.85081678         0.00072522         1.65763070           TRCN0000038107         APOL2         0.34527875         -1.534166555         0.0130239         0.143842         2.604856433         4.1013E-08         2.000305001           TRCN0000035107         APOL2         0.03999757         -3.58216-05         0.03127433         4.998877312         5.067321         0.5078519         -1.60139956         0.0387444         0.24180128         -2.04810527         1.3181-65         2.0686134           TRCN0000057807         Conf32         0.59676456         0.0387444         0.24180128         -2.04810527         -2.79667305         2.4657648         1.78732381         0.12061773         -3.0868204         2.2692-09         2.169322162           TRCN0000057807         Conf32         0.256686         -1.94137644         0.6801713	TRCN000063415	ANTXR2		0.54127007	-0.885579478	0.05597073	0.31181298	-1.681247088	0.00027389	1.735880472
TRCN0000074798         ANXA2, NHF2L1, OPRS1         0.03314199         4.903146666         1.1005E-11         0.00317431         8.299342605         6.4759E-38         10.5282599           TRCN0000074799         ANXA2, NHF2L1, OPRS1         0.26570725         -1.31209049         002156795         0.1235796         -3.015740152         1.94266-09         2.150466563           TRCN0000083105         APOL2         0.4523847         -1.33150466         7.5822-05         0.0231763         -3.8256681         7.0819F-22         4.0030501           TRCN000007952         Sch732         0.2409377         -2.19666504         0.3376456         0.03127431         -5.82526681         7.0819F-22         4.0030501           TRCN000007765         Csorf32         0.24690577         -2.19666503         0.0327433         -0.9987444         0.00127438         -0.9987444         0.00025262         1.5475477819           TRCN000007575         Csorf32         0.2460316         0.9877456         0.03874444         0.2101781         -2.3566730         2.068871344           TRCN000007585         Coll9         0.3854264         -1.37472333         0.0496915         0.102277         -2.4545776         1.738354813           TRCN0000005755         Coll9         0.38542654         -1.374773333         0.04969159	TRCN000063417	ANTXR2		0.51748765	-0.950403671	0.03729236	0.26577127	-1.911742931	3.3463E-05	1.947116572
TRCN00007479         ANXA2,NHP2L1,OPRS1         0.26570725         -1.91209049         0.02156795         0.12355796         -3.016740192         1.9426E-09         2.150465583           TRCN0000037401         ANXA2,NHP2L1,OPRS1         0.46228346         -1.13150346         0.02156798         0.27722087         -1.85881678         0.00072582         1.667563076           TRCN0000083107         APOL2         0.9395975         -1.38146564         7.5823E.05         0.02397165         5.38252681         7.0819E-22         4.00305501           TRCN0000031252         TINI9         0.21809577         -1.9120966304         8.3777E-05         0.03192743         4.99887312         5.067351-19         6.97365541           TRCN000007767         Csrf32         0.50460816         0.986764566         0.0387444         0.24180128         -0.7661702         2.2698671344           TRCN0000073651         CL142         0.26579807         -1.961293759         0.99472819         0.1485215        75667307         2.445876-08         1.12832848           TRCN0000073652         CL19         0.38544264         -1.37472933         0.00496915         0.2167873        2389716         3.238584204         1.937579617         1.932227         -2.18911306         7.8848E-10         1.666631999           TRCN000001	TRCN0000074800	ANXA2;NHP2L1		0.05869392	-4.090645015	3.6043E-07	0.02583538	-5.274507823	5.1352E-07	2.27184248
TRCN0000074801         ANXA2,NHP2L1,OPRS1         0.46228346         -1.113150346         0.02261798         0.27722097         -1.850891678         0.0072582         1.667563076           TRCN000003105         APOL2         0.34527875         -1.53416656         0.0013029         0.1643842         -2.604856433         4.16134.08         2.100437515           TRCN000003765         C56732         0.47956559         -1.06019995         0.30884837         0.03098741         -1.69018394         0.0022628         1.54756719           TRCN000005767         C56732         0.59469610         0.98674566         0.0347484         0.2418027         1.31356.02         2.068671344           TRCN000075767         C56732         0.59469610         0.98674844         0.2418027         2.30816027         1.3156.02         2.06867134           TRCN000007381         CL4,CCL41,CCL412         0.2605566         -1.941437684         0.6601713         0.1201761         -3.05862004         2.2591-09         2.16932216           TRCN0000073652         CD109         0.3842634         -1.375472933         0.0496915         0.2167873         -2.458788         3.24846-07         2.18368297           TRCN0000059752         CD11         0.37448565         -1.415631422         0.00357448         0.145139456435	TRCN0000074798	ANXA2;NHP2L1;OPRS1		0.03341995	-4.903146666	1.1005E-11	0.00317431	-8.299342605	6.4759E-38	10.52826599
IRCN000008105         APOL2         0.34527875         -1.534166565         0.00130329         0.1643842         -2.604856433         4.1613E-08         2.100437515           TRCN000000000000000000000000000000000000	TRCN0000074799	ANXA2;NHP2L1;OPRS1		0.26570725	-1.91209049	0.02156795	0.12355796	-3.016740192	1.9426E-09	2.150466568
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TRCN0000153292         BTNL9         0.21809577         -2.196966304         8.3777E-05         0.03127433         -4.998877312         5.0673E-19         6.973655741           TRCN0000077965         CSorf32         0.47955559         1.060199956         0.03684837         0.30988741         1.690183940         0.0002768         1.547587819           TRCN0000077967         CSorf32         0.50460816         0.986764566         0.03874484         0.24180128         -2.048106227         1.3136E-05         2.08871344           TRCN0000057891         CCL4;CCL4L1;CCL4L2         0.26035686         -1.941437684         0.06801713         0.12001761         -3.05868204         2.2629E-09         2.169322162           TRCN0000057851         CCL4;CCL4L1;CCL4L2         0.26035686         -1.941437684         0.06801713         0.12001761         -3.05868204         2.2629E-09         2.169322162           TRCN000005755         FC011         0.37484565         -1.41561422         0.00374873         0.1818931         -2.458788         4.3248E-07         2.18368299           TRCN0000016120         GBP1         0.55539951         -0.848402187         0.0994408         0.2297247         -1.738156435         0.0002566         1.852560477         1.78156435         0.0002566         1.852560477         TCNE <td< td=""><td>TRCN0000083105</td><td>APOL2</td><td></td><td>0.34527875</td><td>-1.534166565</td><td>0.00130329</td><td>0.1643842</td><td>-2.604856433</td><td>4.1613E-08</td><td>2.100437515</td></td<>	TRCN0000083105	APOL2		0.34527875	-1.534166565	0.00130329	0.1643842	-2.604856433	4.1613E-08	2.100437515
TRCN000007965         CSorf32         0.47956559         -1.060199956         0.30988741         -1.690183944         0.0002628         1.547547819           TRCN000007597         CSorf32         0.50460816         -0.986764566         0.03874484         0.24180128         -2.048106227         1.3136-05         2.086871344           TRCN0000057891         CL4/CCL41/CCL41/2         0.26579807         -1.961293759         0.09472819         0.14858215         -2.750667305         2.6457E-08         1.728323818           TRCN0000057891         CL4/CCL41/CCL41/2         0.205666         -1.94147564         0.06801713         0.1201761         -3.05682004         2.216932162           TRCN00000037167         CD55         0.21244013         -2.24487179         0.00217426         0.132227         -2.918911306         7.8848E-10         1.60661999           TRCN0000009755         ER01L         0.3784455         -1.415631422         0.00357843         0.18189931         -2.445788         4.3248E-07         2.183688299           TRCN0000016119         GBP1         0.35539951         -0.84402187         0.0994408         0.2975247         -1.738156435         0.002266         1.852860477           TRCN0000016120         GBP1         0.16610092         -2.589868061         0.00357134         0.2174514	TRCN0000083107	APOL2		0.09595975	-3.381426864	7.5823E-05	0.02397165	-5.382526681	7.0819E-22	4.003050501
TRCN0000079767         CSorf32         0.50460816         -0.986764566         0.03874484         0.24180128         -2.048106227         1.3136E-05         2.086871344           TRCN00000037317         CLLB2         0.25679807         1.961293759         0.09472819         0.14858215         -2.750667305         2.6437E-08         1.783323818           TRCN0000057891         CLL4,CLLL1,CLL12         0.26035686         1.941437684         0.06801713         0.12001761         -3.058682004         2.2692E-09         2.169322162           TRCN0000057555         CD12144013         -2.23487179         0.00217426         0.132227         -2.918911306         7.8848E-10         1.606631999           TRCN0000059755         FRO1L         0.37484565         1.415631422         0.00357468         0.16037071         -2.458788         4.3248E-07         2.138568259           TRCN0000161151         GBP1         0.1561092         -2.58968061         0.0095408         0.2975247         1.738156435         0.0002266         1.852864077           TRCN000016110         GBP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.271723922         4.1751609         1.06420205           TRCN000016120         GBP1         0.16610929         -2.58968061         0.0095798	TRCN0000153292	BTNL9		0.21809577	-2.196966304	8.3777E-05	0.03127433	-4.998877312	5.0673E-19	6.973635741
TRCN000003717         CALB2         0.25679807         -1.961293759         0.09472819         0.14858215         -2.750667305         2.6457E-08         1.72832818           TRCN00000037891         CCL4,CCL4L1,CCL4L2         0.26035686         -1.94143768         0.06801713         0.12001761         -3.058682004         2.2639E-09         2.169322162           TRCN0000037652         CD109         0.38542634         -1.375472933         0.00496915         0.20167873         -2.39869122         1.1945E-06         1.100806199           TRCN000000392         DAPK1         0.397214         -1.33202106         0.00577843         0.18189931         -2.458788         4.3248E-07         2.183688299           TRCN0000016119         GP1         0.55539951         -0.844402187         0.0994408         0.2997547         -1.78156435         0.0002266         1.852864077           TRCN0000116119         GP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.27172922         1.7076E-05         1.723368339           TRCN0000036226         GLRX         0.36613834         -1.499539237         0.0421693         0.2355764         -2.324770322         1.7076E-05         1.723368339           TRCN0000161511         MAPRE2         0.51596158         -0.54664442	TRCN0000077965	C5orf32		0.47956559	-1.060199956	0.03684837	0.30988741	-1.690183944	0.00022628	1.547547819
TRCN0000057891         CL4;CC14L1;CC14L2         0.26035686         -1.91437684         0.06801713         0.12001761         -3.058682004         2.2629E-09         2.169322162           TRCN0000073652         CD109         0.38542634         -1.375472933         0.0046915         0.20167873         -2.309869122         1.1945E-06         1.911090619           TRCN00000082         DAPK1         0.372114         -1.33202106         0.00577843         0.1812927         -2.918911306         7.8484E-107         2.18688299           TRCN000000982         DAPK1         0.37484565         -1.415631422         0.00577843         0.18189931         -2.649517434         3.1731E-08         2.337369813           TRCN00000116119         GBP1         0.55539951         0.848402187         0.0994408         0.29975247         -1.738155435         0.0002266         1.852860477           TRCN0000016120         GBP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.21723922         4.751E-09         1.60402025           TRCN0000036226         GLRX         0.3661384         -1.40953237         0.6217314         0.21245507         -2.234770322         1.7076E-05         1.72368339           TRCN0000063243         KINE         0.24553147         0.01905082         <	TRCN0000077967	C5orf32		0.50460816	-0.986764566	0.03874484	0.24180128	-2.048106227	1.3136E-05	2.086871344
TRCN0000073652         CD109         0.38542634         -1.375472933         0.00496915         0.20167873         -2.309869122         1.1945E-06         1.911090619           TRCN000000382         DAPK1         0.3972114         -1.33202106         0.00577483         0.132227         -2.918911306         7.8484E-10         1.606631999           TRCN000005975         ERO1L         0.37484565         -1.415631422         0.00354685         0.16037071         -2.45878         4.3248E-07         2.138368229           TRCN0000116119         GBP1         0.5539951         0.048402187         0.0994408         0.29975247         -1.738156435         0.0002266         1.852860477           TRCN0000116120         GBP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.271723922         4.1751E-09         1.60420205           TRCN0000016120         GBP1         0.1661092         -2.589868061         0.0195082         0.2355526         -2.085877218         1.8116E-05         1.967003933           TRCN000004724         KCNK1         0.46243259         -1.1268501         0.01905082         0.2356518         -1.950693731         2.6255E-05         T.787581131           TRCN000005231         KITLG         0.2757196         -1.1268501         0.0190503	TRCN0000053717	CALB2		0.25679807	-1.961293759	0.09472819	0.14858215	-2.750667305	2.6457E-08	1.728323818
TRCN0000057167         CD55         0.21244013         -2.23487179         0.00217426         0.132227         -2.918911306         7.8848E-10         1.606631999           TRCN000000982         DAPK1         0.3972114         -1.33202106         0.00577843         0.18189931         -2.458788         4.3248E-07         2.183688299           TRCN0000016119         GBP1         0.55539951         -0.848402187         0.0935485         0.16037071         -2.4651734         3.1731E-08         2.337369813           TRCN0000116119         GBP1         0.6610092         -2.589868061         0.00856215         0.1035414         -3.27173922         4.1751E-09         1.604202053           TRCN0000161618         GBP2         0.46333341         -1.109877375         0.04201693         0.2355286         -2.08587718         8.1816E-05         1.967003933           TRCN0000036226         GLRX         0.36613834         -1.449539237         0.05217314         0.21245507         -2.234770322         1.7076E-05         1.723368339           TRCN000003626         GLX         0.3651384         -1.4999002         0.0085798         0.04318121         -4.51232745         4.5229E-18         6.288983029           TRCN0000036369         MSAA8B         0.47784747         -1.8594999002         0.00825369 <td>TRCN0000057891</td> <td>CCL4;CCL4L1;CCL4L2</td> <td></td> <td>0.26035686</td> <td>-1.941437684</td> <td>0.06801713</td> <td>0.12001761</td> <td>-3.058682004</td> <td>2.2629E-09</td> <td>2.169322162</td>	TRCN0000057891	CCL4;CCL4L1;CCL4L2		0.26035686	-1.941437684	0.06801713	0.12001761	-3.058682004	2.2629E-09	2.169322162
TRCN000000982         DAPK1         0.3972114         -1.33202106         0.00577843         0.18189931         -2.458788         4.3248E-07         2.183688299           TRCN000016119         GBP1         0.5553951         0.48402187         0.09975247         -1.738156435         0.0002266         1.852860477           TRCN0000116119         GBP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.271723922         4.1751E-09         1.60402025           TRCN0000036226         GLRX         0.36613834         -1.449539237         0.05217314         0.212557         -2.234770322         1.707E-05         1.72368339           TRCN0000036226         GLRX         0.36613834         -1.449539237         0.05217314         0.21245507         -2.234770322         1.707E-05         1.72368339           TRCN0000036226         GLRX         0.36613834         -1.449539237         0.05217314         0.21245507         -2.234770322         1.707E-05         1.73365843999           TRCN000005231         KITLG         0.27557196         -1.89499002         0.00859798         0.04381821         -4.512325745         4.6229E-18         6.288983029           TRCN0000016511         MAPRE2         0.5156158         -0.59464442         0.0825669         0.24758314<	TRCN0000073652	CD109		0.38542634	-1.375472933	0.00496915	0.20167873	-2.309869122	1.1945E-06	1.911090619
TRCN0000059755         ERO1L         0.37484565         -1.415631422         0.00354685         0.16037071         -2.640517434         3.1731E-08         2.337369813           TRCN0000116119         GBP1         0.55539951         -0.848402187         0.0994408         0.29975247         -1.738156435         0.0002266         1.852860477           TRCN0000116120         GBP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.271723922         4.1751E-09         1.60402020           TRCN0000036226         GLX         0.36613834         -1.449539237         0.05217314         0.21245507         -2.234770322         1.7076E-05         1.723368393           TRCN000004724         KCNK1         0.46243259         -1.11268501         0.0190502         0.2355286         -2.0857718         1.8116E-05         1.72736883920           TRCN0000059231         KTLG         0.27557196         -1.859499002         0.00059798         0.04381821         -4.512325745         4.6229E-18         6.288893029           TRCN0000063649         MS4A8B         0.49784442         -1.06233147         0.042953         0.27770401         -1.8483008         4.5971E-05         1.792715971           TRCN0000063649         MS4A8B         0.47784757         -1.847634448	TRCN0000057167	CD55		0.21244013	-2.23487179	0.00217426	0.132227	-2.918911306	7.8848E-10	1.606631999
TRCN000016119         GBP1         0.55539951         -0.848402187         0.0994408         0.29975247         -1.738156435         0.0002266         1.852860477           TRCN000016120         GBP1         0.16610092         -2.589868061         0.00856215         0.10354114         -3.271723922         4.1751E-09         1.60420205           TRCN000006226         GLRX         0.46333341         -1.109877375         0.04201693         0.23555286         -2.085877218         1.8116E-05         1.967003933           TRCN0000064262         GLRX         0.36613834         -1.449539237         0.05217314         0.21245507         -2.234770322         1.7076E-05         1.723368339           TRCN0000059231         KTLG         0.27557196         -1.859499002         0.00059788         0.44381821         -4.51235745         4.6229E-18         6.288983029           TRCN0000059231         KTLG         0.27757496         -1.85499002         0.00659788         0.4348121         -4.51235745         4.6229E-18         6.288983029           TRCN0000063649         MS4A8B         0.49784442         -1.006233147         0.0429053         0.27770401         -1.84838008         4.5971E-05         1.792715971           TRCN000003451         RANBP2         0.16630518         -2.58809519         4.9	TRCN000000982	DAPK1		0.3972114	-1.33202106	0.00577843	0.18189931	-2.458788	4.3248E-07	2.183688299
TRCN000016120GBP10.16610092-2.5898680610.008562150.10354114-3.2717239224.1751E-091.60420205TRCN000016184GBP20.46333341-1.1098773750.042016930.23555286-2.0858772181.8116E-051.967003933TRCN0000036226GLRX0.36613834-1.4495392370.052173140.21245507-2.2347703221.7076E-051.723368339TRCN000004724KCNK10.46243259-1.112685010.019050820.25869181-1.9506937312.6255E-051.787581131TRCN000059231KTLG0.27557196-1.8594990020.00059780.04318214.5123257454.6229E-186.288983029TRCN000016511MAPRE20.515961580.9546644420.086253690.29458316-1.7632531420.000117751.772179712TRCN000003649MS4A8B0.49784442-1.0062331470.04290530.27770401-1.84838084.5971E-051.792715971TRCN000003451RANBP20.16630518-2.880950194.9878E-060.08120005-3.622375595.7674E-132.048092024TRCN000003453RANBP20.14259261-1.1759487190.021413940.13208078-2.9205075875.0253E-093.350923772TRCN000003454SAMD90.43103282-1.2141303780.0279780.1764814-2.550934283.4886E-072.52587149TRCN000003455SLCAA410.2406411-2.0550450.007959110.21278578-2.2922484582.3546E-061.864251545TRCN00000356708SFRED1 <td>TRCN0000059755</td> <td>ERO1L</td> <td></td> <td>0.37484565</td> <td>-1.415631422</td> <td>0.00354685</td> <td>0.16037071</td> <td>-2.640517434</td> <td>3.1731E-08</td> <td>2.337369813</td>	TRCN0000059755	ERO1L		0.37484565	-1.415631422	0.00354685	0.16037071	-2.640517434	3.1731E-08	2.337369813
TRCN000016184       GBP2       0.46333341       -1.109877375       0.04201693       0.23555286       -2.085877218       1.8116E-05       1.967003933         TRCN0000036226       GLX       0.36613834       -1.449539237       0.05217314       0.21245507       -2.234770322       1.7076E-05       1.723368339         TRCN0000044724       KCNK1       0.46243259       -1.11268501       0.01905082       0.25869181       -1.950693731       2.6255E-05       1.787581131         TRCN000016511       MAPRE2       0.51596158       -0.954664442       0.06825369       0.24958316       -1.763253142       0.00011775       1.77179172         TRCN000003649       MS4A8B       0.49784442       -1.00623147       0.0429053       0.27770401       -1.84838008       4.5971E-05       1.792715971         TRCN000003451       RABRP2       0.16630518       -2.88095019       4.9878E-06       0.08120005       -3.62237559       5.7674E-13       2.048092027         TRCN000003453       RANBP2       0.44259261       -1.175948719       0.02141394       0.13208078       -2.920507587       5.0253E-09       3.350923772         TRCN000003454       SAMD9       0.43103282       -1.24130378       0.027978       0.1278578       -2.23256356       5.0956E-06       1.846215365     <	TRCN0000116119	GBP1		0.55539951	-0.848402187	0.0994408	0.29975247	-1.738156435	0.0002266	1.852860477
TRCN000036226GLRX0.36613834-1.4495392370.052173140.21245507-2.2347703221.7076E-051.723368339TRCN0000044724KCNK10.46243259-1.112685010.019050820.25869181-1.9506937312.6255E-051.787581131TRCN0000059231KITLG0.27557196-1.8594990020.000597980.04381821-4.5123257454.6229E-186.288983029TRCN000003649MS4A8B0.4978442-0.05231470.04290530.27770401-1.484380084.5971E-051.79217971TRCN000003649MS4A8B0.4978442-1.006231470.04290530.27770401-1.484380084.5971E-051.79217971TRCN000003451RANBP20.16630518-2.5880950194.9878E-060.08120005-3.6223755595.7674E-132.048092025TRCN000003453RANBP20.16630518-2.5880950194.9878E-060.08120005-3.622375595.7674E-132.048092025TRCN000003454SAMBP20.44259261-1.179487190.021413940.13208078-2.920575875.0258E-091.8369237715TRCN0000134554SAMD90.43103282-1.2141303780.0279780.17064814-2.5509034283.4886E-072.52585749TRCN0000034595SLC4A410.1356074-2.002094420.1458716-2.7772275170.00171291.649675786TRCN0000034575SLC4A40.2406411-2.0550450.02794180.0972762-3.3550897917.1644E-084.46605211TRCN0000035708SRED10.35876794	TRCN0000116120	GBP1		0.16610092	-2.589868061	0.00856215	0.10354114	-3.271723922	4.1751E-09	1.60420205
TRCN000044724KCNK10.46243259-1.112685010.019050820.25869181-1.9506937312.6255E-051.787581131TRCN000059231KITLG0.27557196-1.8594990020.000597980.04381821-4.5123257454.6229E-186.288983029TRCN0000036364MS4A8B0.49784442-1.0062331470.04290530.27770401-1.848380084.5971E-051.792715971TRCN0000047691RAB2780.27784757-1.8476344480.014613850.1804369-2.4671848096.1348E-071.53696264TRCN000003451RANBP20.16630518-2.58905194.9878E-060.08120005-3.622375595.7674E-132.048092025TRCN000003451RANBP20.16630518-2.58905194.9878E-060.08120005-3.622375595.7674E-132.048092025TRCN00003453RANBP20.16630518-2.58050194.9878E-060.081200078-2.920575875.0253E-093.350923772TRCN00003453RANBP20.44259261-1.1759487190.021413940.13208078-2.920575875.0253E-093.3509237715TRCN00003453RANBP20.44259261-1.1759487190.0279780.17064814-2.5509034283.4886E-072.525857149TRCN000003453RANBP30.430282-1.2141303780.0279780.17064814-2.5509034283.4886E-072.525857149TRCN0000038265SLC4A110.1535094-2.7036011370.027451810.0225547-3.6037445994.4076-061.86625154TRCN0000038265SLC4A11	TRCN0000116184	GBP2		0.46333341	-1.109877375	0.04201693	0.23555286	-2.085877218	1.8116E-05	1.967003933
TRCN0000059231 KITLG         0.27557196         -1.859499002         0.00059798         0.04381821         -4.512325745         4.6229E-18         6.288983029           TRCN000016511         MAPRE2         0.51596158         -0.954664442         0.08625369         0.29458316         -1.763253142         0.00011775         1.751497222           TRCN0000063649         MS4A88         0.49784442         -1.006233147         0.0429053         0.27770401         -1.84838008         4.5971E-05         1.792715971           TRCN000003451         RABZ78         0.27784757         -1.847634448         0.1461385         0.18084369         -2.467184809         6.1348E-07         1.536396264           TRCN000003451         RANBP2         0.16630518         -2.588095019         4.9878E-06         0.08120005         -3.62237559         5.7674E-13         2.048092025           TRCN000003451         RANBP2         0.44259261         -1.175948719         0.02141394         0.13208078         -2.29256356         5.0956E-06         1.846215365           TRCN000003453         RANBP2         0.44259261         -1.175948719         0.21278778         -2.23256356         5.0956E-06         1.846215365           TRCN0000015554         SAMD9         0.43103282         -1.214130378         0.027778         0.1706481	TRCN000036226	GLRX		0.36613834	-1.449539237	0.05217314	0.21245507	-2.234770322	1.7076E-05	1.723368339
TRCN0000116511         MAPRE2         0.51596158         -0.954664442         0.08625369         0.29458316         -1.763253142         0.00011775         1.751497222           TRCN0000063649         MS4A8B         0.49784442         -1.006233147         0.0429053         0.27770401         -1.84838008         4.5971E-05         1.792715971           JRCN000003451         RAB278         0.27784757         -1.847634448         0.01461385         0.18084369         -2.467184809         6.1348E-07         1.536396264           TRCN000003451         RANBP2         0.16630518         -2.58809519         4.9878E-06         0.08120005         -3.62237559         5.7674E-13         2.048092025           TRCN000003453         RANBP2         0.44259261         -1.175948719         0.02141394         0.13208078         -2.920507587         5.0258E-09         3.350923772           TRCN000014554         SAMD9         0.43103282         -1.214130378         0.027978         0.17064814         -2.550903428         3.4886E-07         2.525857149           TRCN0000038265         SLC3A44         0.2406411         -2.055045         0.0029442         0.14587176         -2.777227517         0.00017129         1.649675786           TRCN0000038265         SLC4A11         0.13535049         -2.703601137	TRCN0000044724	KCNK1		0.46243259	-1.11268501	0.01905082	0.25869181	-1.950693731	2.6255E-05	1.787581131
TRCN000063649         MS4A8B         0.4978442         -1.006233147         0.0429053         0.27770401         -1.84838008         4.5971E-05         1.792715971           TRCN0000047691         RAB278         0.27784757         -1.847634448         0.01461385         0.18084369         -2.467184809         6.1348E-07         1.536396264           TRCN000003451         RANBP2         0.16630518         -2.588095019         4.9878E-06         0.08120005         -3.62237559         5.7674E-13         2.048092025           TRCN000003453         RANBP2         0.44259261         -1.175948719         0.02141394         0.13208078         -2.920507587         5.0253E-09         3.350923772           TRCN000014554         SAMD9         0.43103282         -1.214130378         0.02778         0.110764814         -2.55003428         3.4886E-07         2.525857149           TRCN0000043987         SLC36A4         0.2406411         -2.055045         0.020778         0.17064814         -2.55003428         3.4886E-06         1.864215365           TRCN0000043987         SLC36A4         0.2406411         -2.055045         0.00209442         0.14587176         -2.777227517         0.00017129         1.649675786           TRCN0000035575         SPCC11         0.1356094         -2.07601137	TRCN0000059231	KITLG		0.27557196	-1.859499002	0.00059798	0.04381821	-4.512325745	4.6229E-18	6.288983029
DRENDO00047691         RAB278         0.27784757         -1.847634448         0.01461385         0.18084369         -2.467184809         6.1348E-07         1.536396264           TRCN000003451         RANBP2         0.16630518         -2.588095019         4.9878E-06         0.08120005         -3.62237559         5.7674E-13         2.048092025           TRCN000003453         RANBP2         0.44259261         -1.175948719         0.02141394         0.13208078         -2.920507587         5.0253E-09         3.350923772           TRCN000014554         SAMD9         0.43103282         -1.214130378         0.027978         0.21278578         -2.29248436         3.4886E-07         2.52585149           TRCN0000014554         SAMD9         0.43103282         -1.214130378         0.027978         0.10764814         -2.550093428         3.4886E-07         2.525857149           TRCN0000014554         SAMD9         0.43103282         -1.214130378         0.027978         0.107064814         -2.550093428         3.4886E-07         2.525857149           TRCN0000014554         SAMD9         0.43103282         -1.214130378         0.027978         0.10764814         -2.550093428         3.4886E-07         1.56675765           TRCN0000043987         SLC36A4         0.2406411         -2.055045 <t< td=""><td>TRCN0000116511</td><td>MAPRE2</td><td></td><td>0.51596158</td><td>-0.954664442</td><td>0.08625369</td><td>0.29458316</td><td>-1.763253142</td><td>0.00011775</td><td>1.751497222</td></t<>	TRCN0000116511	MAPRE2		0.51596158	-0.954664442	0.08625369	0.29458316	-1.763253142	0.00011775	1.751497222
TRCN000003451         RANBP2         0.16630518         -2.588095019         4.9878E-06         0.08120005         -3.622375559         5.7674E-13         2.048092025           TRCN000003453         RANBP2         0.44259261         -1.175948719         0.02141394         0.13208078         -2.920507587         5.0253E-09         3.350923772           TRCN000003453         RANBP2         0.39284838         -1.3479555         0.09463595         0.21278578         -2.232526356         5.0956E-06         1.846215365           TRCN000014554         SAMD9         0.43103282         -1.214130378         0.027978         0.17064814         -2.59093428         3.4886E-07         2.525857149           TRCN0000014554         SAMD9         0.43103282         -1.214130378         0.00795911         0.2016891         -2.99248436         2.3546E-06         1.854977715           TRCN0000014554         SAMD9         0.43064511         -2.055045         0.00209442         0.14587176         -2.777227517         0.00017129         1.649675786           TRCN0000034265         SLC4A11         0.1353094         -2.03601137         0.02745181         0.08225547         -3.63744599         4.4074E-06         1.866251554           TRCN0000015575         SPOCD1         0.43645696         -1.196088705	TRCN000063649	MS4A8B		0.49784442	-1.006233147	0.0429053	0.27770401	-1.84838008	4.5971E-05	1.792715971
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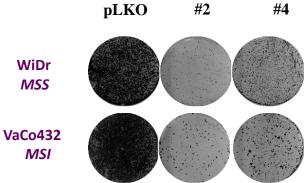
### **RANBP2** is selectively synthetic lethal with **BRAF V600E** in CC



#### **RANBP2 mRNA relative expression**

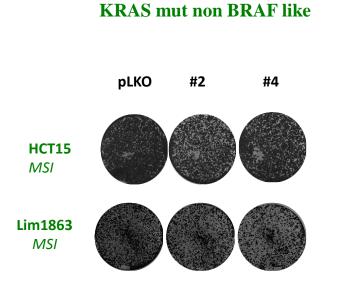
### **RANBP2** is selectively synthetic lethal with **BRAF V600E** in **CRC**



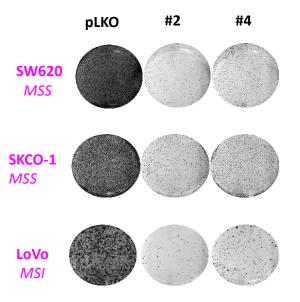


**BRAF V600E** 

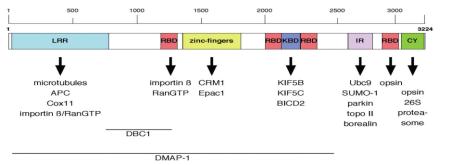
### **RANBP2** is also synthetic lethal with **BRAF** likeness in **CRC**



**KRAS mut BRAF like** 



### RANBP2 (Nup358)



## Schematic representation of RANBP2 domain organization and binding partners

Nucleus 3:2, 162–171; March/April 2012; G 2012 Landes Bioscience

J Biol Chem. 2012 Jan 6;287(2):819-31. Epub 2011 Nov 21.

### Specific armadillo repeat sequences facilitate β-catenin nuclear transport in live cells via direct binding to nucleoporins Nup62, Nup153, and RanBP2/Nup358.

Sharma M, Jamieson C, Johnson M, Molloy MP, Henderson BR.

Westmead Institute for Cancer Research, The University of Sydney, Westmead, New South Wales 2145, Australia. manisha.sharma@sydney.edu.au

Gastroenterology, 2008 Jun;134(7):1961-71, 1971.e1-4. Epub 2008 Mar 10.

#### Regulation of Wnt signaling by the nuclear pore complex.

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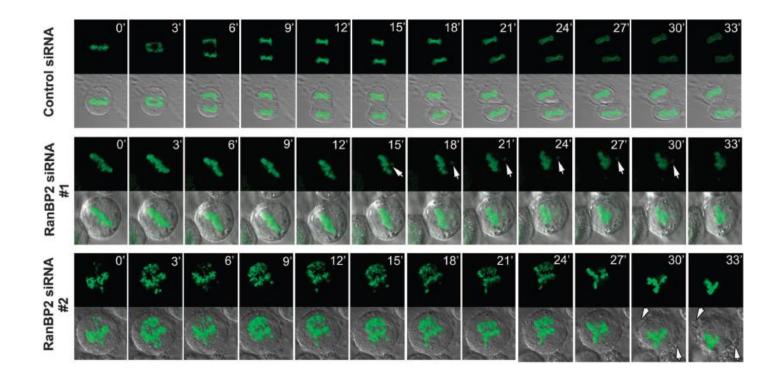
Chemotherapy Division and Cancer Proteomics Project, National Cancer Center Research Institute, Tokyo, Japan.

The Journal of Biological Chemistry @ 2002 by The American Society for Biochemistry and Molecular Biology, Inc.

Vol. 277, No. 51, Issue of December 20, pp. 50131-50136, 2002 Printed in U.S.A.

Sumoylation of Mdm2 by Protein Inhibitor of Activated STAT (PIAS) and RanBP2 Enzymes\*

### **RANBP2** depletion induces abnormal chromosomal segregation



### Conclusions

- The BRAF-like signature identifies BRAF V600E tumors with 96% sensitivity and 86% specificity and also a group of BRAF wild type tumors which share the same gene expression profile
- The BRAF-like tumors share a common poor prognosis
- The BRAF-like tumors belong to a specific CC subtype: hypermutated (MSI), hypermethylated, right sided location, serrated and MAPK pathway activated tumors.
- <u>RANBP2 is selectively synthetic lethal with BRAF V600E and BRAF</u> <u>likeness in CC</u>
- Ongoing research is focused on better defining the role of RANBP2 and its depletion in BRAF V600E tumors and on identifing treatments which could mimic RANBP2 KD

### **Acknowledgments**



NKI/AvL <u>Valentina Gambino</u> Andreas Schlicker René Bernards Lodewyk Wessels

Bernards' group Beijersbergen's group

### Agendia

Iris Simon Sun Tian Paul Roepman



**SIB** Giovanni d' ario Mauro Delorenzi

*Clinical Pharmacology* Jan Schellens



**KUL** Sabine Tejpar



European Society for Medical Oncology

The work has been granted by ESMO (fellowship for translational research) and FP7 - Coltheres