

Supplemental Materials and Methods:

Chemical agent and antibodies

B-Raf inhibitor RAF265 [5-(2-(5-(trifluoromethyl)-1H-imidazol-2-yl)pyridin-4-yloxy)-N-(4-trifluoromethyl)phenyl-1-methyl-1H-benzp{D, }imidazol-2-amine] was kindly provided by Novartis Pharma AG and dissolved in solvent ethanol:propylene glycol:2.5% tween-80 (percentage 6:23:71) for oral delivery to mice by gavage. Antibodies to phospho-ERK1/2 Thr²⁰²/Tyr²⁰⁴(4370), phosphoMEK1/2(2338 and 9121), phospho-cyclin D1(3300), cyclin D1 (2978), PLK1 (4513) BIM (2933), BAX (2772), BCL2 (2876) were from Cell Signaling Technology. Additional antibodies for phospho-ERK1,2 detection for western blot were from Promega (V803A), and Santa Cruz (E-Y, SC7383). Total ERK antibody for western blot analysis was K-23 from Santa Cruz (SC-94). Ki67 antibody (ab833) was from ABCAM, Mcl1 antibody (559027) was from BD Biosciences, Factor VIII antibody was from Dako (A082), CD31 antibody was from Dianova, (DIA310), and Cot antibody was from Santa Cruz Biotechnology (sc-373677). For the cyclin D1 second antibody staining was with an Alexa Fluor 568 donkey anti-rabbit IgG (Invitrogen, A10042) (1:200 dilution). The pMEK1 fluorescence was developed using the Alexa Fluor 488 chicken anti-rabbit IgG second antibody (1:200 dilution). TUNEL staining kits were from Promega (G2350).

Mouse Implant Studies:

Biopsy tissues were delivered to research laboratory in ice-cold Dulbecco's Modified Eagle Medium (DMEM) buffer solution. As the tissue mass available from each biopsy was limited, we first passaged the biopsy tissue in Balb/c nu/Foxn1 athymic nude mice (6-8 weeks of age and weighing 22-25g, purchased from Harlan Sprague Dawley, USA) to increase the volume of tumor for further implantation. Briefly, after eliminating necrotic or non-tumor tissue, the biopsy tissue was dissected into 3×3×3 mm pieces in a tissue culture dish and the tissue pieces were kept in ice-cold DMEM solution. Mice (5-10) were anesthetized by inhalation of 2.5% isoflurane (Baxter Healthcare Corporation, USA) through a nose cone. Mouse skin was sterilized with 7.5% Povidone-iodine (Betadine, Purdue Products L.P., USA) and a 6 mm incision was made in mouse flank skin followed by preparing a small pocket between the dermis and the underlying fascia. One or two tumor pieces were inserted into the subcutaneous pocket and the skin wound was closed by surgical clips. The analgesic, Burprenex (Reckitt & Colman Pharmaceuticals), was given once, intraperitoneally (i.p.) at 4.5 µg/kg body weight, after implantation. Antibiotic cream was applied daily to skin wounds for 5 days and the general health conditions were monitored regularly. Tumor size was measured by microcalipers weekly and when tumor size reached ~600 mm³ (usually in 10-14 days), mice were euthanized by over-dose inhalation of isoflurane, tumors were collected and pooled in a cold DMEM solution and dissected into 3×3×3 mm tissue pieces. After washing in DMEM solution twice, each tumor piece was inserted into a surgically made pocket of subcutaneous tissue of a recipient nude mouse (passage 2) and wounds were closed. When tumor size reached ~100 mm³, the passage 2 nude mice were divided into 2 groups (minimum of 5 mice per group) and given RAF265, 40 mg/kg, or an equivalent volume of vehicle solvent, by oral gavage, once daily(QD). (Preliminary experiments using 10, 30 and 60 mg/Kg doses of RAF265 QD revealed significant weight loss at 60 mg/Kg and Phase I trials with humans with regionally advanced or metastatic cutaneous melanoma determined that a dose of 48mg/Kg QD was the MTD continuous dose of RAF265 (17). The tumor growth and mouse body weight were monitored once a week. After ~30 days of treatment (or less if tumors reached a diameter of 1.5cm, mice were sacrificed, tumors were collected for volume determination by fluid displacement, and divided for further studies. Response to therapy with RAF265 was defined as >50% reduction of tumor volume relative to vehicle-treated mice. All animal experiments were performed under guidelines of the Institutional Animal Care and Use Committee.

Preparation and Staining of Tissue Microarrays:

Tissue sections of 6-µm thickness were cut for H&E staining. After the H&E stained slides were evaluated by the dermatopathologist, four tissue cores of 1 mm diameter from each paraffin block were punched and transferred manually to an assigned location in a Tissue Micro-Array (TMA) paraffin block module by using a TMA assembly instrument (Beecher Instruments Micro-Array Technology, USA). Punches from a set of control

paraffin blocks of human liver, kidney, lung, skin, and mouse liver, spleen, kidney, skin tissue were assembled into each TMA block. After heating to 37°C for 15 min, TMA blocks were cut into 6 µm sections which were then subjected to routine processing for immunohistochemical (IHC) staining. IHC staining with antibody against human phospho-ERK1/2 (Thr²⁰²/Tyr²⁰⁴) Ki67, Factor VIII, and CD31 was performed on TMA using the Vector ABC kit and NovaRED substrate kit. Immunofluorescence was used to examine pMEK1/2 (and cyclin D1 in TMAs. For the cyclin D1 second antibody staining was with Alexa Fluor 568 donkey anti-rabbit IgG (1:200 dilution). The pMEK1 fluorescence was developed using Alexa Fluor 488 chicken anti-rabbit IgG second antibody (1:200 dilution) TUNEL staining for apoptosis was also performed on TMAs.

Quantification of Vascularity within Tumors:

Immunohistochemistry for CD31 and Factor VIII was performed on all TMA's. Microvessel density in tumor cores was analyzed by an experienced veterinary pathologist blind to the TMA composition. Vessels were counted in each tissue core. For partial cores or cores with areas of tumor necrosis, counts were normalized based on the percentage of viable tumor tissue present in the core. The mean number of vessels for control and RAF265 treated cores was calculated for each patient TMA and comparisons were made between tumors from vehicle control treated and RAF265 treated mice. The mean vessel densities for control and RAF265 treatments were also compared between all responding tumors and all non-responding tumors.

Genome-wide expression profiling of melanoma

Briefly, RNA quality was first checked for chemical purity using a NanoDrop spectrophotometer (NanoDrop Technologies, Wilmington, DE, USA) and then assessed for RNA integrity by the Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). 100 ng of total RNA were amplified and labeled using the Affymetrix Whole-Transcript (WT) Sense Target Labeling Protocol and Affymetrix GeneChip Human Gene ST 1.0 arrays were hybridized with labeled sense DNA, washed, stained, and scanned according to manufacturer's instruction. Raw gene expression data (.cel files, Affymetrix human gene ST 1.0 platform) were pre-processed and normalized using the robust multi-array average (RMA) expression measure. Pre-processing was performed using the justRMA function of the bioconductor package affy (<http://www.bioconductor.org/packages/release/bioc/html/affy.html>). Expression values were in log₂ format after RMA. The R package limma of R2.10.0 statistics software was used to analyze differential expressions between drug-responding and non-responding tumors. Since there were multiple arrays (technical replicates) for a single sample, we estimated the correlation between technical replicates from a series of arrays, and applied the correlation information for linear modeling, and moderated paired t-statistics were computed by empirical Bayes shrinkage of the standard errors towards a common value. Winner probes were selected based on the following cutoffs: (1) fold change >2; (2) false discovery rate based on the moderated *t*-test followed by Benjamini and Hochberg's multiple-test adjustment <0.1; and (3) log odds ratio of differential expression (B statistic) >1. Pearson correlation coefficient was used to perform two-way unsupervised gene expression hierarchical cluster analysis on both samples. Results were shown in a heatmap by bioconductor R package Heatplus. In some analyses of differential gene expression among RAF265 responders versus non-responders the Hochberg's step-up method was used.

Western Blot:

Tumors from Raf265 and Vehicle-treated mice were excised and stabilized in RNA_{later} (Ambion) according to the manufacturer's recommendations. To prepare protein lysates approximately 0.01g of each tumor tissue sample was homogenized in RIPA buffer containing protease and phosphatase inhibitors (Sigma). 15 µg of each protein lysate were loaded onto 10, 12 or 15% polyacrylamide gels, separated by SDS-PAGE and transferred onto nitrocellulose membranes. Membranes were blocked in 5% non-fat milk solution (Bio-Rad). Alternatively, 5% BSA (Sigma) was used as a blocking solution when phosphorylated proteins were analyzed. Membranes were incubated with appropriate

primary antibodies overnight and then with secondary antibodies for additional 2-24 hrs. HRP-conjugated goat anti-mouse and goat anti-rabbit secondary antibodies were obtained from Jackson ImmunoResearch. Light Chain specific HRP-conjugated goat anti-mouse IgG (Jackson ImmunoResearch) was used as a secondary antibody for detection of Cot. The levels of target proteins were examined by chemiluminescence (Cell Signaling Technology).

Legends for Supplemental Figures:

Supplemental Table S1. Patient clinical characteristics. The data shown were collected in December 2010 for each of the patients that provided melanoma tumor tissue for this study.

Supplemental Table S2. Mutational profile of human melanomas. Mutational profile of 17 human melanoma tissues was performed by SNaPshot assay, which is designed to survey 43 common somatic point mutations in six genes (*BRAF*, *NRAS*, *KIT*, *GNAQ*, *GNA11*, and *CTNNB1*) potentially relevant to existing and emerging targeted therapies in melanoma.

Supplemental Table S3. Gene expression profiling differences between BRAF mutant versus BRAF WT melanoma tumors in this study.

Supplemental Table 4. Results from GSEA Analysis of gene expression data. Genes identified to exhibit enriched expression ($p < 0.05$) in A. Genes with enriched expression in RAF265 responsive BRAF WT tumors compared to non-responsive tumors; B. Genes with enriched expression in RAF265 non-responsive BRAF WT tumors compared to responsive tumors; C. Genes with enriched expression in RAF265 responsive tumors compared to non-responsive tumors regardless of BRAF mutation status; D. Genes with enriched expression in RAF265 non-responsive tumors compared to responsive tumors regardless of BRAF mutation status;

Supplemental Figure S1A. Phospho-ERK expression analyzed by immunohistochemistry of tissue microarrays in human melanoma lesions taken directly from patients. The mean \pm SD of four biological repeats is shown. **Figure S1B.** Comparison of phospho-ERK staining on tissue microarrays from orthotopic implants of human melanoma lesions onto athymic nude mice. IHC staining of human phospho-ERK1/2 in implanted tissues treated with RAF265 or vehicle control as described in Methods. The mean \pm SD of four biological repeats is shown. No statistically significant difference in phospho-ERK staining was observed between control and RAF265 treatment implants for each melanoma biopsy tissue derived transplant tumors based upon the Student's t test. **Figure 1C.** Representative pERK staining of TMAs from tumor implants of mice treated with RAF265 or control diluent. The upper panel shows pERK for control treated (A), RAF 265 treated (B) tumor implants from responding patient V05 and the internal control skin (right upper panel). The lower panel shows pERK for control treated tumor implant (D), RAF265 treated tumor implant (E) from patient V12, with the right lower panel (F) showing the internal control pERK staining of skin.

Supplemental Figure S2A. Quantitative analysis of Ki67 staining of TMAs of melanoma tumor implants in mice treated or not treated with RAF265. **Figure S2B.** Quantitation of TUNEL staining of TMAs prepared from melanoma tumor implants growing in mice treated or not treated with RAF265. * indicate values that are statistically different based upon a p value of ≤ 0.05 . **Figure S2C** Representative TUNEL staining. Green staining is indicative of apoptosis based upon the TUNEL assay. TMA cores from tumor implants of patient V19 treated with RAF265 (A-D), or

treated with vehicle control buffer (E-G), or normal skin control (H); TMA cores from tumor implants of patient V18 treated with RAF265 (I-L), or treated with vehicle control buffer (M-O), or normal skin control (P).

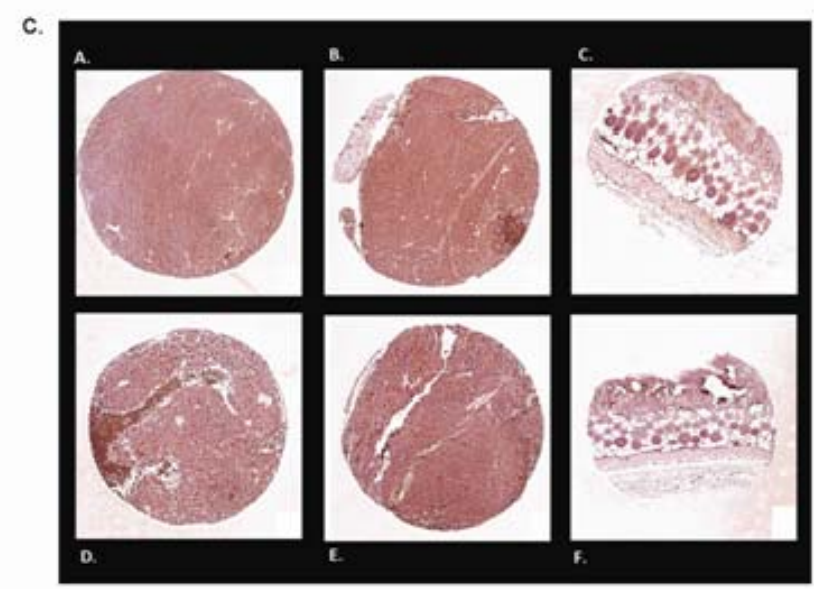
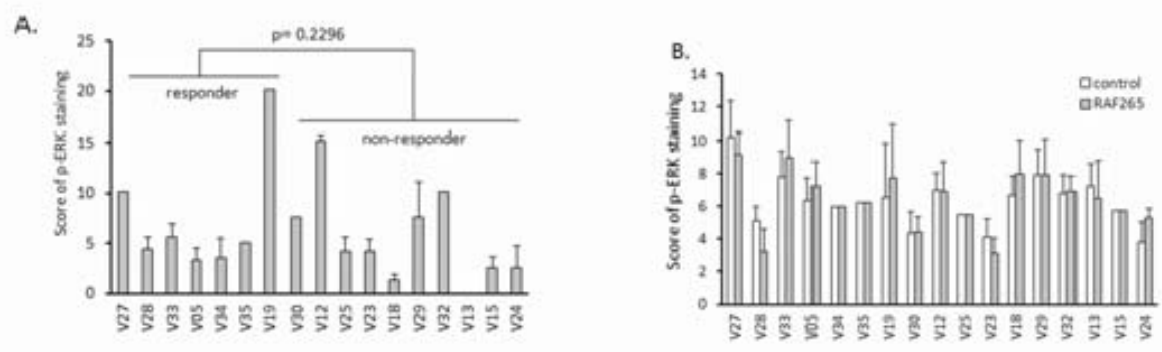
Supplemental Figure S3: Graphical depiction of growth curves of melanoma tumor implants in mice treated with RAF265 or Vehicle control. Tumors size was measured at least weekly as described in methods. Note: For V15, the control and RAF265 treated lines on the graph are superimposed.

Supplemental Figure S4: A. Ingenuity Pathway analysis of genes involved in cell development and cell growth in RAF265 responsive versus non-responsive tumors, irrespective of BRAF mutation status, B. Ingenuity Pathway analysis of genes involved in cancer in RAF265 responsive versus non-responsive tumors, irrespective of BRAF mutation status. C. Ingenuity Pathway analysis of genes involved in gene expression, connective tissue development and tissue morphology in RAF265 responsive versus non-responsive tumors, irrespective of BRAF mutation status. For A-C, Red indicates genes with enhanced expression in RAF265 responders and Green indicates genes with reduced expression in RAF265 responders.

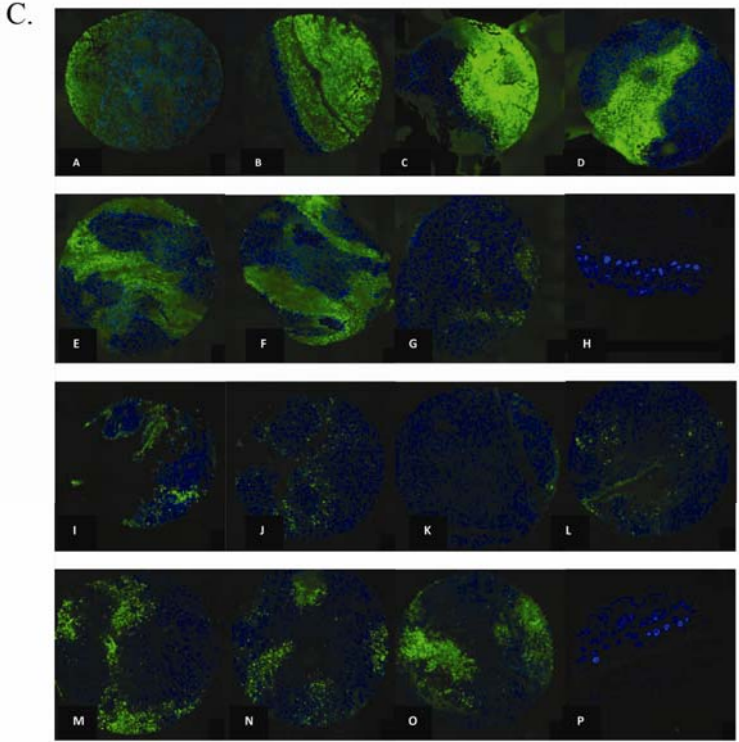
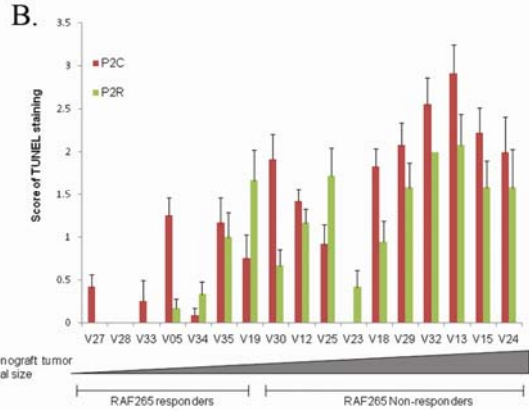
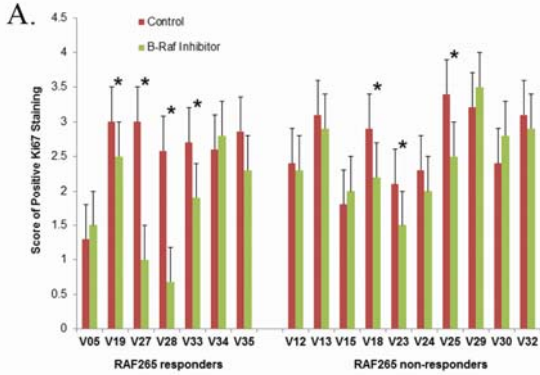
Supplemental Figure S5. Representative IHC of TMAs showing Factor VIII staining in V28 vehicle control treated tumors (A, 20X; B, 40X) and V28 RAF265 treated tumors (C, 20X, D, 40X, E, 40X from another field). Staining was developed with DAB and Factor VIII positive staining is brown. No significant differences were observed in the vasculature based upon the staining pattern, though the RAF265 tumors frequently showed areas of reduced cellularity as noted in C and D. The insert at the bottom shows the quantitation of vessels within each core, citing the mean number of vessels per core based upon CD31 and Factor VIII staining. For responders the number of cores evaluated for control=38 and for RAF265 treated is=35 ; For non-responders the n for control =55 and for Raf265 treated =70. Data are recorded as mean \pm STDEV.

Supplemental Figure S6: A. Pathway analysis of genes involved in cancer, cell death, cell growth and proliferation shown by GSEA analysis to be enriched in BRAFWT tumors that were non-responders to RAF265. B. Pathway analysis of genes involved in cellular movement, cancer and cell cycle shown by GSEA analysis to be enriched in tumors (both BRAF mutant and WT) that were non-responders to RAF265, C. Pathway analysis of genes involved in cell cycle, cell growth and proliferation, DNA replication, recombination and repair shown by GSEA analysis to be enriched in tumors (both BRAF mutant and WT) that were non-responders to RAF265.

Supplemental Figure S1

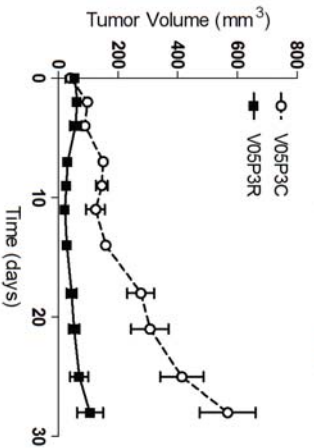


Supplemental Figure S2

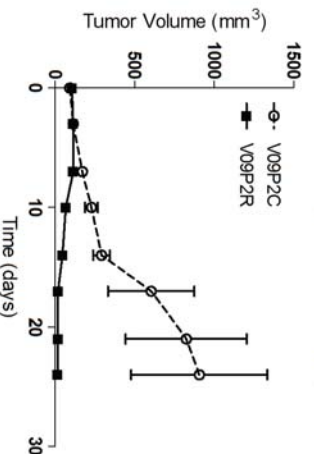


Supplemental Figure S3

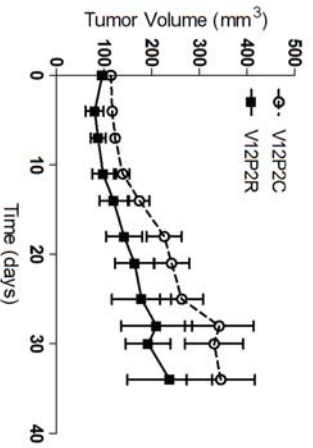
V05P3 (RAF265 vs. Control)



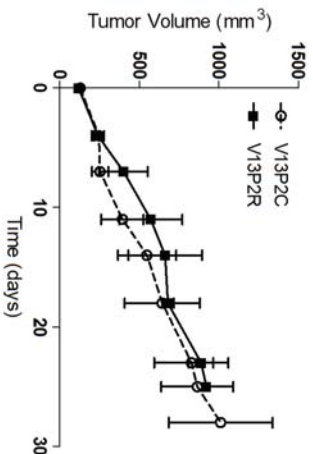
V09P2 (RAF265 vs. Control)



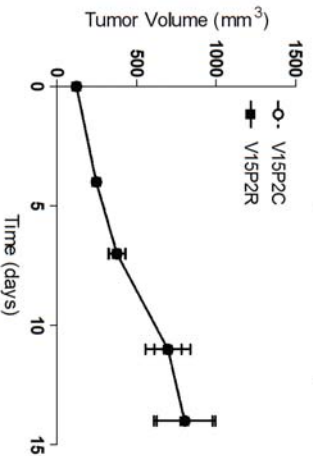
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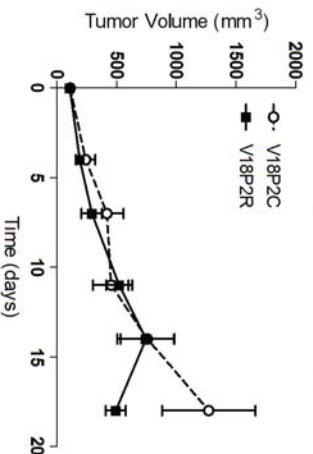
V13P2 (RAF265 vs. Control)



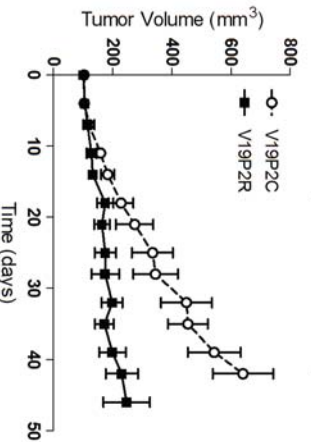
V15P2 (RAF265 vs. Control)



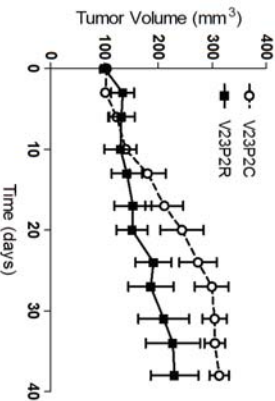
V18P2 (RAF265 vs. Control)



V19P2 (RAF265 vs. Control)

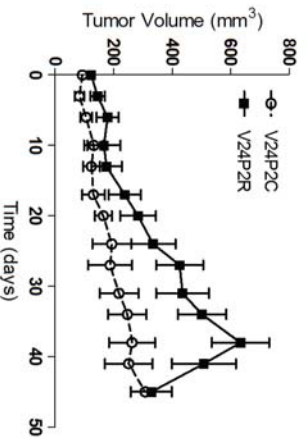


V23P2 (RAF265 vs. Control)

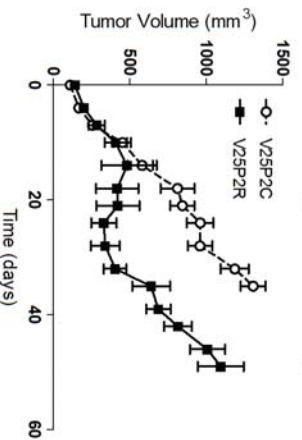


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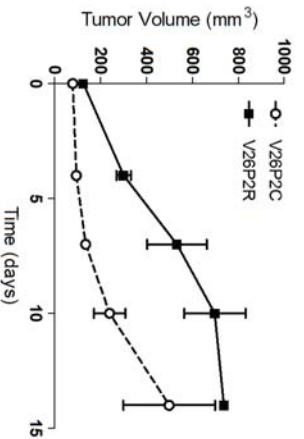
V24P2 (RAF265 vs. Control)



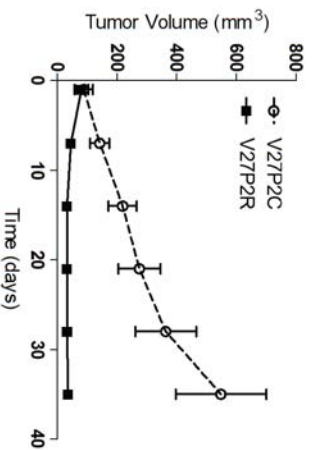
V25P2 (RAF265 vs. Control)



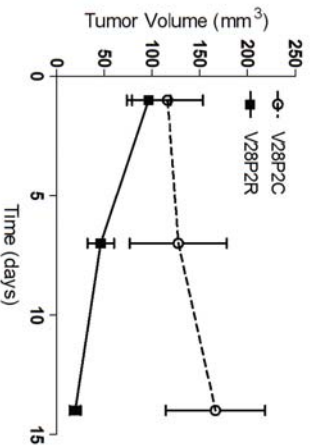
V26P2 (RAF265 vs. Control)



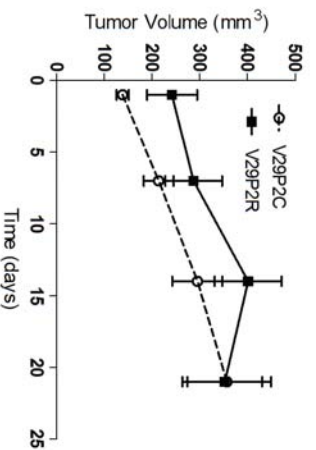
V27P2 (RAF265 vs. Control)



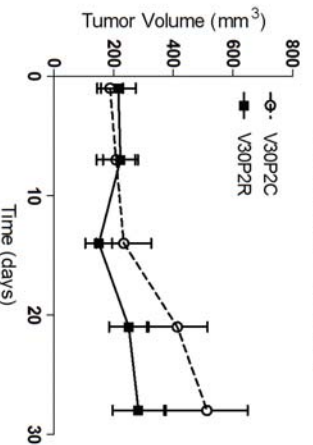
V28P2 (RAF265 vs. Control)



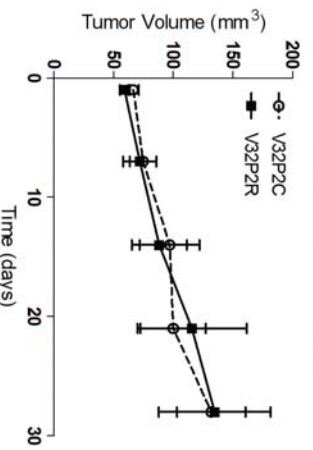
V29P2 (RAF265 vs. Control)



V30P2 (RAF265 vs. Control)

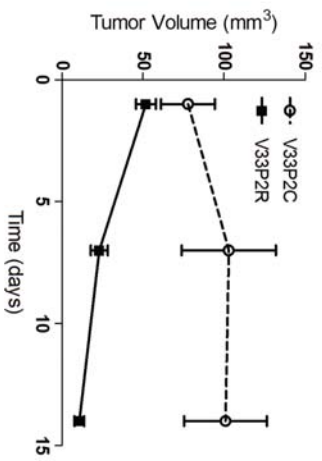


V32P2 (RAF265 vs. Control)

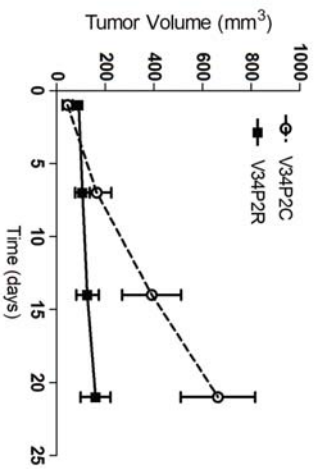


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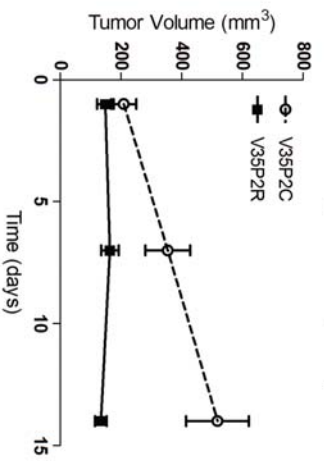
V33P2 (RAF265 vs. Control)

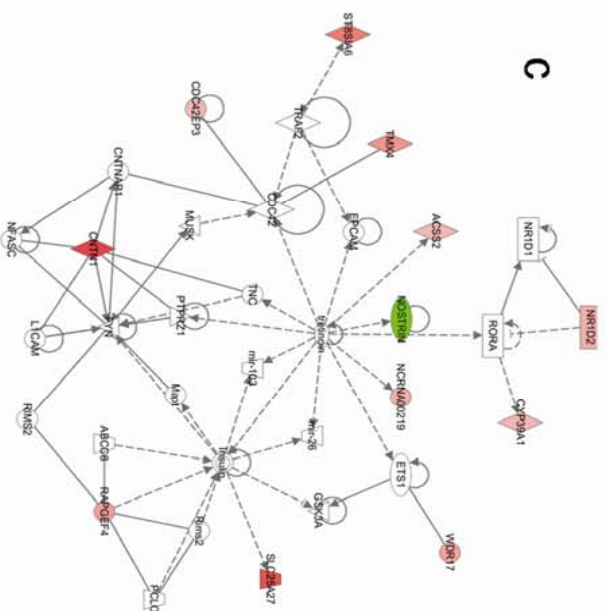
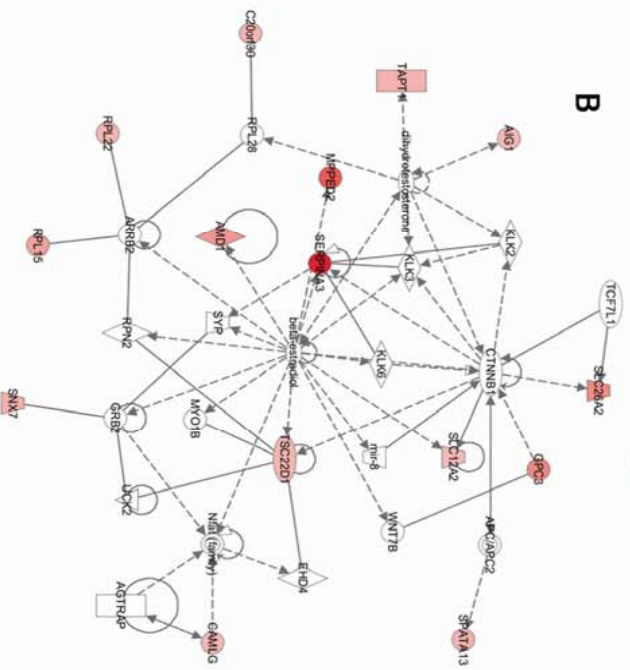
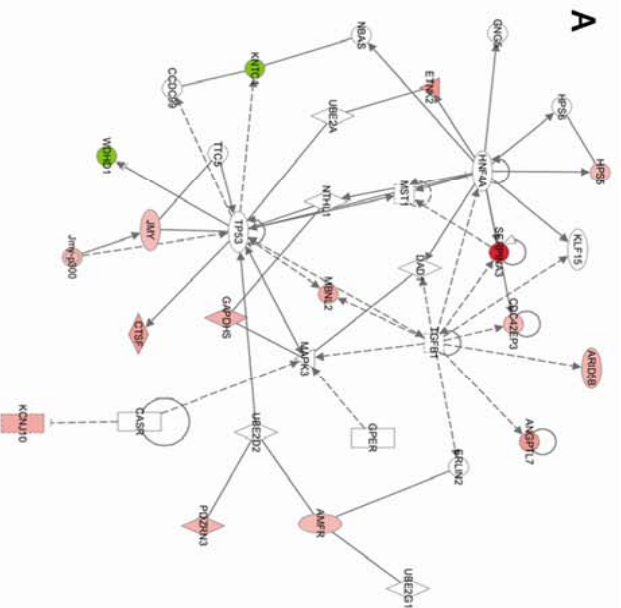


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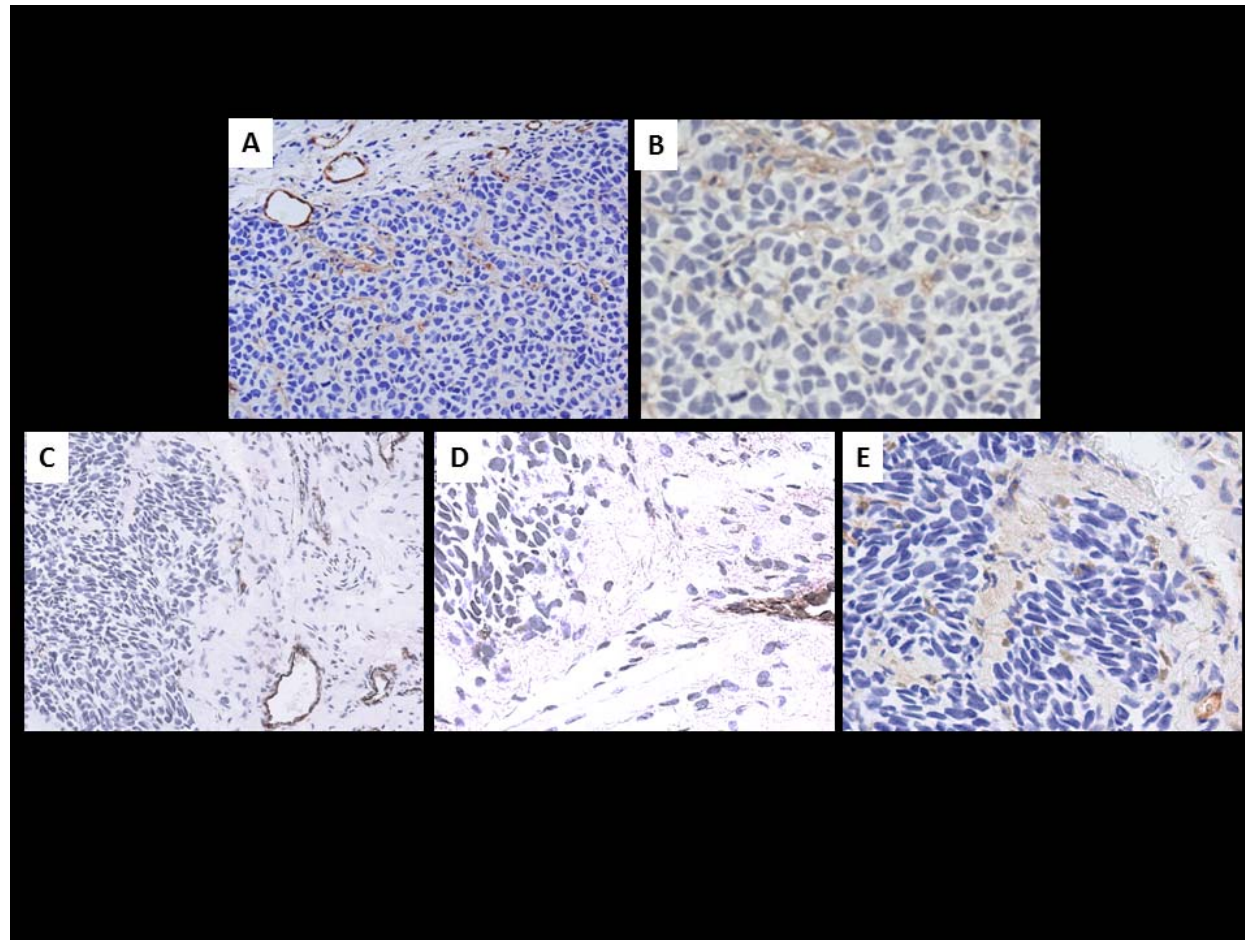


V35P2 (RAF265 vs. Control)



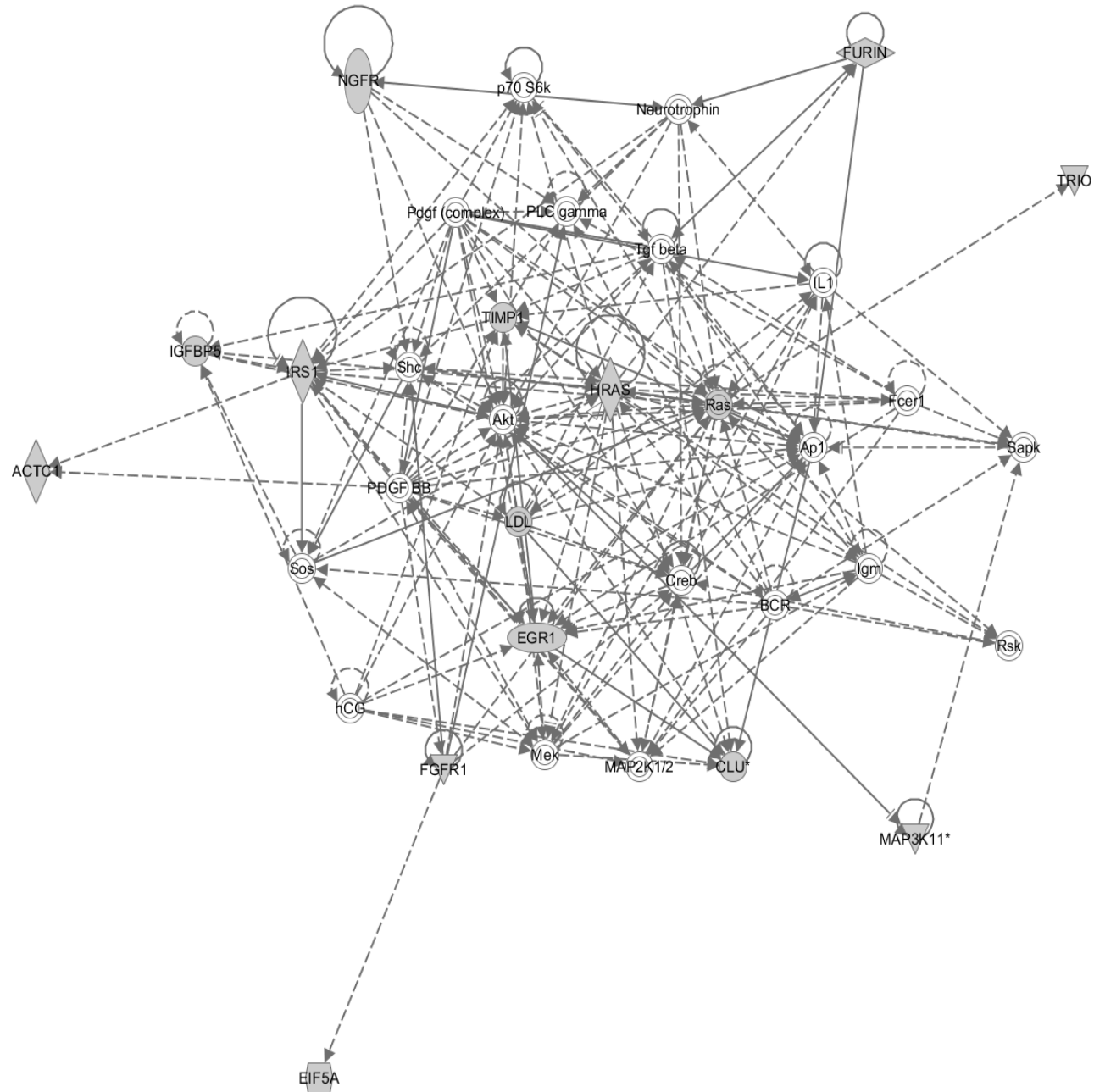


Supplemental Figure S5:

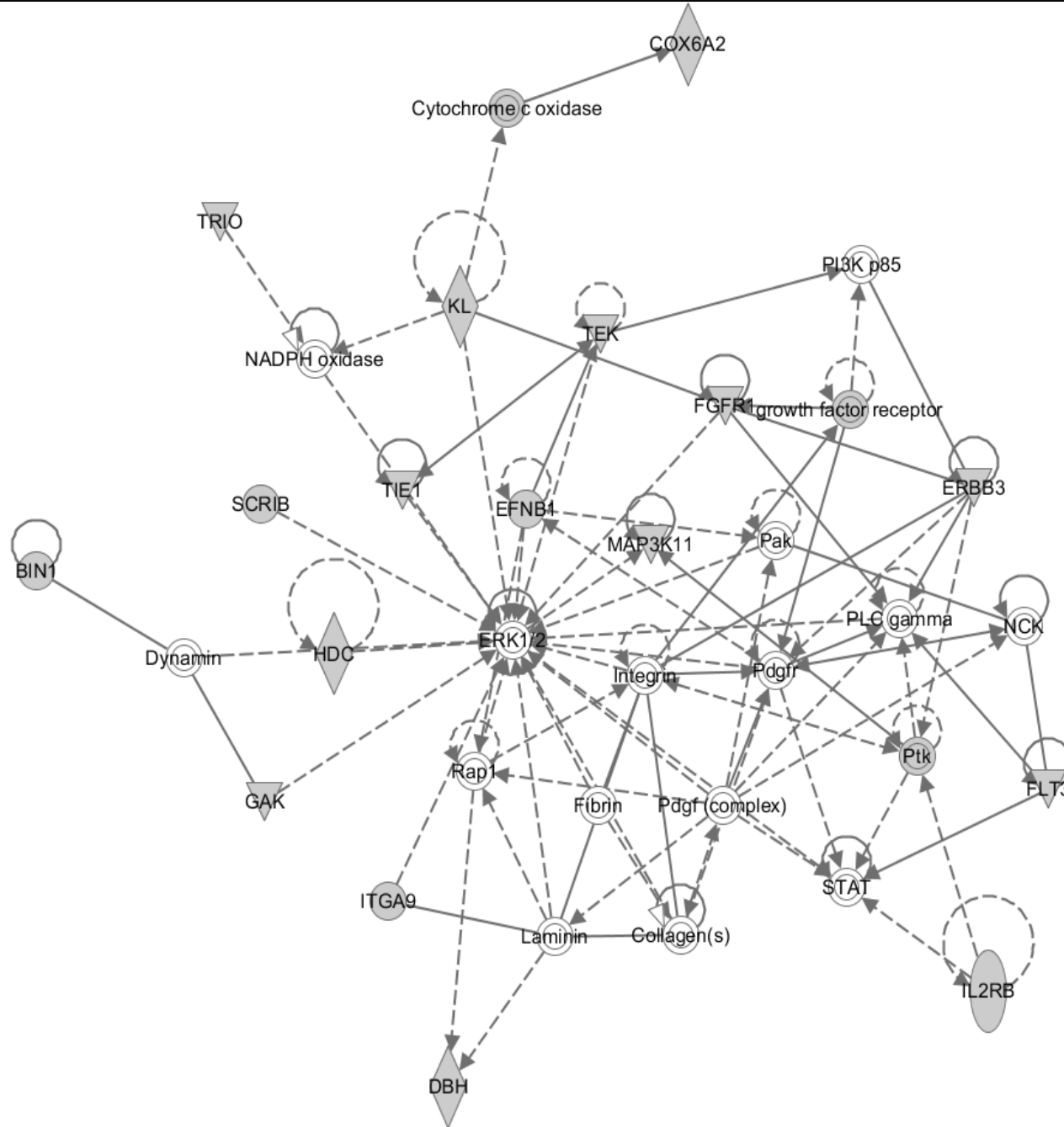


RAF-265 Responders		RAF-265 Non-Responders	
Mean Vessel Number/Core		Mean Vessel Number/Core	
Vehicle Control	RAF265 Treated	Vehicle Control	RAF-265 Treated
22	27	26	25

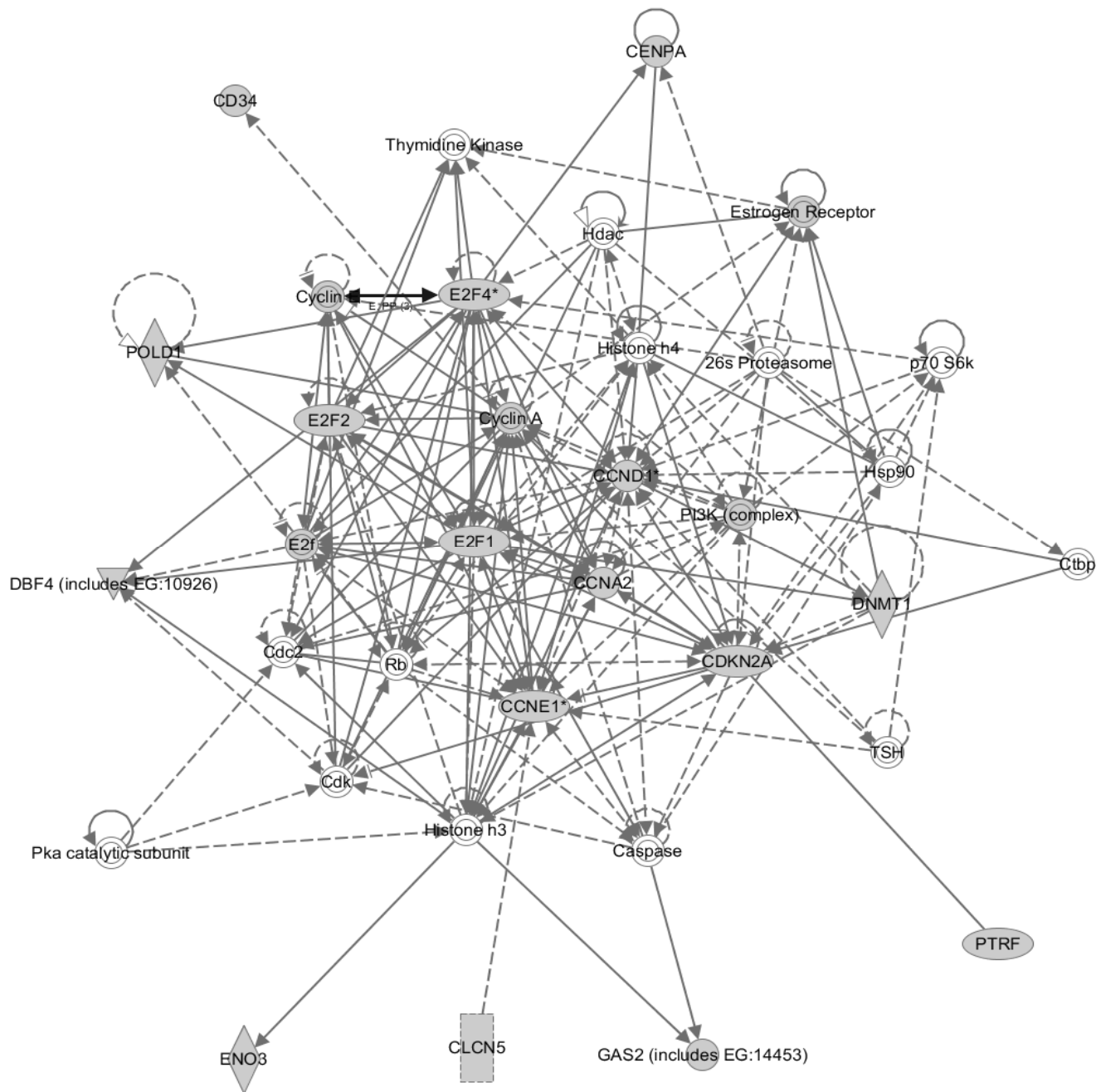
Supplemental Figure 6A. Genes Identified by GSEA Analysis as Enriched in RAF265 Non-Responding BRAF^{WT} Tumors: Pathways Related to Cancer, Cell Death, Cell Growth and Proliferation



Supplemental Figure 6B. Genes Identified by GSEA Analysis as Enriched in RAF265 Non-Responding Tumors Regardless of BRAF Mutation Status: Pathways Associated with Cell Movement, Cancer and Cell Cycle



Supplemental Figure 6C. Genes Identified by GSEA Analysis as Enriched in RAF265 Non-Responding Tumors Regardless of BRAF Mutation Status: Pathways Associated with Cell Cycle, Cell Growth/Proliferation, DNA Replication, Recombination and Repair



Supplemental Table 1: Patient Characteristics

PatientStudy#	Gender	RAF265 Response	Mutation	Survival from DX	Survival fromBX	Status	Location of Primary	Subtype Of Primary Lesion	Breslo mm	Clark's Level	Ulceration	Treatment Prior to Surgery		
												Immuno	Radiation	Chemo
V05	M	Yes	V600E	8 mo	7 mo	DOD	Ankle	Nodular	6.5	V	Yes	N	Y	N
V09	M	N/A	V600E	24 mo		DOD	unknown	Unknown				Y	Y	N
V12	M	No	V600E	18 mo	12 mo	DOD	leg	Superficial Spreading	3.2	IV	Yes	Y	Y	Y
V13,15	M	No	V600K	85+ mo	42+ mo	Alive	Back	Melanoma Not Specified	2.1	II	No	N	Y	Y
V18	M	No	V600E	62 mo	6-7 mo	DOD	Back	Nodular	3.4	IV	Yes	Y	Y	N
V19	M	Yes	WT	36+ mo	33+ mo	Alive	Scalp	Nodular	7	V	Yes	Y	Y	Y
V23	M	No	V600E	15 mo	6 mo	DOD	Abdomen	Nodular	6.7	IV	Yes	N	Y	N
V24	F	No	WT	6 mo	3 mo	DOD	Leg	Superficial Spreading	2.2	III	Yes	Y	N	N
V25	M	No	WT	12 mo	9 mo	DOD	Shoulder	Lentigo Malignant	0.2	II	No	N	Y	N
V26	F	N/A	V600E	16 mo	3 mo	DOD	Unknown	Unknown				N	Y	N
V27	M	Yes	V600E	26+ mo	25+ mo	Alive	Unknown	Unknown				N	Y	N
V28	F	Yes	cKit	37 mo	27 mo	DOD	Unknown	Melanoma Not Specified	0.4	II			N	
V29	M	No	V600E	41 mo	18 mo	DOD	Unknown	Unknown				Y	Y	Y
V30	F	No	V600E	13 mo	11 mo	DOD	Heel	Melanoma Not Specified	10	V	Yes	N	N	Y
V32	M	No	WT	9 mo	3 mo	DOD	Toe	Nodular	3.4	IV	No	Y	N	N
V33	F	Yes	WT	14 mo	11 mo	Alive		Unknown						
V34	M	Yes	NRasQ61R	66+ mo	20+ mo	Alive		Unknown				Y		
V35	M	Yes	WT	19+ mo	19+ mo	Alive		Unknown				N		

Supplemental Table 2: Mutational Profile of Human Melanoma Tumors

Sample	BRAF	CTNNB1	GNAQ	GNA11	KIT	NRAS
V05	V600E; c1799T>A	WT	WT	WT	WT	WT
V12	V600E; c1799T>A	WT	WT	WT	WT	WT
V13	V600K; c1798_1799GT>AA	WT	WT	WT	WT	WT
V15	V600K; c1798_1799GT>AA	WT	WT	WT	WT	WT
V18	V600E; c1799T>A	WT	WT	WT	WT	WT
V19	WT	WT	WT	WT	WT	WT
V23	V600E; c1799T>A	WT	WT	WT	WT	WT
V24	WT	WT	WT	WT	WT	WT
V25	WT	WT	WT	WT	WT	WT
V27	V600E; c1799T>A	WT	WT	WT	WT	WT
V28	WT	WT	WT	WT	pL576P;c1727T>C	WT
V29	V600E; c1799T>A	WT	WT	WT	WT	WT
V30	V600E; c1799T>A	WT	WT	WT	WT	WT
V32	WT	WT	WT	WT	WT	WT
V33	WT	WT	WT	WT	WT	WT
V34	WT	WT	WT	WT	WT	p.Q61R;c18
V35	WT	WT	WT	WT	WT	WT

Supplementary Table S3: Genes Differentially Expressed in BRAF Mutant Melanoma Tumors Compared to BRAF WT Tumors

<u>Gene.Symbol</u>	<u>Description</u>	<u>Log FC</u>	<u>Adjusted P value</u>	<u>Biological.Process</u>	GO.Cellular Component.Term	GO.Molecular Function.ID	GO.Molecular.Function.Term
APBA2	amyloid beta (A4) precursor protein-binding, family A, member 2 (X11-like) (APBA2), mRNA.	1.19	0.001	nervous system development // protein transport	---	GO:0005515 // GO:0005515	protein binding // protein binding
IGFBP2	insulin-like growth factor binding protein 2, 36kDa (IGFBP2), mRNA.	1.41	0.002	regulation of cell growth // signal transduction	extracellular region // extracellular space	GO:0005520 // GO:0031994 // GO:0031995	insulin-like growth factor binding // insulin-like growth factor I binding // insulin-like growth factor II binding
PTPRG	protein tyrosine phosphatase, receptor type, G (PTPRG), mRNA.	1.10	0.002	protein amino acid dephosphorylation // one-carbon compound metabolic process // transmembrane receptor protein tyrosine kinase signaling pathway	integral to plasma membrane // membrane	GO:0004089 // GO:0005001 // GO:0008270 // GO:0016787	carbonate dehydratase activity // transmembrane receptor protein tyrosine phosphatase activity // zinc ion binding // hydrolase activity
DZIP1	DAZ interacting protein 1 (DZIP1), transcript variant 2, mRNA.	1.34	0.002	multicellular organismal development // germ cell development // spermatogenesis // cell differentiation	intracellular // nucleus // cytoplasm // protein complex	GO:0005515 // GO:0008270 // GO:0046872	protein binding // zinc ion binding // metal ion binding
FADS2	fatty acid desaturase 2 (FADS2), mRNA.	1.27	0.003	lipid metabolic process // unsaturated fatty acid biosynthetic process // transport // oxidation reduction	membrane fraction // endoplasmic reticulum // endoplasmic reticulum membrane // integral to plasma membrane // membrane plasma membrane // membrane	GO:0005506 // GO:0016491 // GO:0016717 // GO:0020037	iron ion binding // oxidoreductase activity // oxidoreductase activity, acting on paired donors, with oxidation of a pair of donors resulting in the reduction of molecular oxygen to two molecules of water // heme binding
FRAS1	Fraser syndrome 1 (FRAS1), mRNA.	1.30	0.005	cell communication	plasma membrane // integral to membrane	GO:0005509	calcium ion binding
SRGAP1	SLIT-ROBO Rho GTPase activating protein 1 (SRGAP1), mRNA.	1.01	0.018	signal transduction	intracellular	GO:0005096	GTPase activator activity
CYP7B1	cytochrome P450, family 7, subfamily B, polypeptide 1 (CYP7B1), mRNA.	1.29	0.020	lipid metabolic process // bile acid biosynthetic process // steroid metabolic process // cholesterol metabolic process // oxidation reduction	endoplasmic reticulum // endoplasmic reticulum membrane //	GO:0004497 // GO:0005506 // GO:0008396 // GO:0008396 // GO:0009055 //	monooxygenase activity // iron ion binding // oxysterol 7-alpha-hydroxylase activity // oxysterol 7-alpha-hydroxylase activity // electron carrier activity // heme

					endoplasmic reticulum membrane // microsome // membrane	GO:0020037 // GO:0033783 // GO:0046872	binding // 25-hydroxycholesterol 7alpha-hydroxylase activity // metal ion binding
COL11A1	collagen, type XI, alpha 1 (COL11A1), transcript variant A, mRNA.	1.51	0.03	cartilage condensation // phosphate transport // visual perception // sensory perception of sound // extracellular matrix organization and biogenesis	extracellular region // collagen // collagen type XI // cytoplasm	GO:0005201 // GO:0005201 // GO:0030674	extracellular matrix structural constituent // extracellular matrix structural constituent // protein binding, bridging
IFIT1	interferon-induced protein with tetratricopeptide repeats 1 (IFIT1), transcript variant 2, mRNA.	-1.43	0.02	biological_process	cytoplasm	GO:0005488	binding
CPEB2	cytoplasmic polyadenylation element binding protein 2 (CPEB2), transcript variant B, mRNA.	-1.05	0.02	regulation of translation	cytoplasm	GO:0000166 // GO:0003723	nucleotide binding // RNA binding
NEDD4L	neural precursor cell expressed, developmentally down-regulated 4-like (NEDD4L), mRNA.	-1,16	0.02	protein modification process // sodium ion transport // cellular sodium ion homeostasis // excretion // response to metal ion // protein ubiquitination // water homeostasis // regulation of protein catabolic process // interspecies interaction between organisms // positive regulation of endocytosis	intracellular // cytoplasm	GO:0004842 // GO:0005515 // GO:0005515 // GO:0016874 // GO:0017080	ubiquitin-protein ligase activity // protein binding // protein binding // ligase activity // sodium channel regulator activity
PRUNE2	prune homolog 2 (Drosophila) (PRUNE2), transcript variant 1, mRNA.	-1.29	0.02	apoptosis // induction of apoptosis // G1 phase	cytoplasm	GO:0016491 // GO:0030145 // GO:0046872 // GO:0046914	oxidoreductase activity // manganese ion binding // metal ion binding // transition metal ion binding
PPM2C	protein phosphatase 2C, magnesium-dependent, catalytic subunit (PPM2C), nuclear gene encoding mitochondrial protein, mRNA.	-1.00	0.01	protein amino acid dephosphorylation	mitochondrion // mitochondrial matrix // protein serine/threonine phosphatase complex	GO:0000287 // GO:0003824 // GO:0004722 // GO:0004741 // GO:0005509 // GO:0005509 // GO:0016787	magnesium ion binding // catalytic activity // protein serine/threonine phosphatase activity // [pyruvate dehydrogenase (lipoamide)] phosphatase activity // calcium ion binding // calcium ion binding // hydrolase activity
SYT11	synaptotagmin XI (SYT11), mRNA.	-1.10	0.01	transport	synaptic vesicle // membrane // integral to	GO:0005215 // GO:0005509 // GO:0005544	transporter activity // calcium ion binding // calcium-dependent phospholipid binding

					membrane // cell junction // cytoplasmic vesicle // synapse		
MINPP1	multiple inositol polyphosphate histidine phosphatase, 1 (MINPP1), mRNA.	-1.30	0.01	polyphosphate metabolic process // bone mineralization	endoplasmic reticulum // endoplasmic reticulum lumen	GO:0003993 // GO:0004446 // GO:0008969 // GO:0016787 // GO:0034417	acid phosphatase activity // multiple inositol-polyphosphate phosphatase activity // phosphohistidine phosphatase activity // hydrolase activity // bisphosphoglycerate 3-phosphatase activity
NR4A3	nuclear receptor subfamily 4, group A, member 3 (NR4A3), transcript variant 2, mRNA.	-1.06	0.01	transcription // regulation of transcription, DNA-dependent // biological_process	nucleus // nucleus	GO:0003700 // GO:0003707 // GO:0004879 // GO:0004887 // GO:0005488 // GO:0008270 // GO:0043565 // GO:0046872	transcription factor activity // steroid hormone receptor activity // ligand-dependent nuclear receptor activity // thyroid hormone receptor activity // binding // zinc ion binding // sequence-specific DNA binding // metal ion binding
ITGB8	integrin, beta 8 (ITGB8), mRNA.	-2.22	0.01	ganglioside metabolic process // cell adhesion // cell adhesion // cell-matrix adhesion // integrin-mediated signaling pathway	integrin complex // integrin complex // membrane // integral to membrane	GO:0004872 // GO:0005488 // GO:0005515	receptor activity // binding // protein binding
OAS1	2',5'-oligoadenylate synthetase 1, 40/46kDa (OAS1), transcript variant 1, mRNA.	-1.31	0.01	nucleobase, nucleoside, nucleotide and nucleic acid metabolic process // immune response	nucleus // cytoplasm // mitochondrion // endoplasmic reticulum // microsome	GO:0003723 // GO:0005524 // GO:0016740 // GO:0016779	RNA binding // ATP binding // transferase activity // nucleotidyltransferase activity
LYPD1	LY6/PLAUR domain containing 1 (LYPD1), transcript variant 1, mRNA.	-1.43	0.01	---	plasma membrane // anchored to membrane	---	---
SFT2D2	SFT2 domain containing 2 (SFT2D2), mRNA.	-1.06	0.01	protein transport	membrane // integral to membrane	---	---
NR4A1	nuclear receptor subfamily 4, group A, member 1 (NR4A1), transcript variant 1, mRNA.	-1.11	0.01	transcription // regulation of transcription, DNA-dependent // signal transduction	nucleus // nucleoplasm	GO:0003700 // GO:0003707 // GO:0004879 // GO:0008270 // GO:0043565 // GO:0046872	transcription factor activity // steroid hormone receptor activity // ligand-dependent nuclear receptor activity // zinc ion binding // sequence-specific DNA binding // metal ion binding
AGPAT9	1-acylglycerol-3-phosphate O-acyltransferase 9	-1.83	0.01	metabolic process // phospholipid biosynthetic process	endoplasmic reticulum // endoplasmic reticulum	GO:0003841 // GO:0008415 // GO:0016740	1-acylglycerol-3-phosphate O-acyltransferase activity // acyltransferase activity // transferase activity

	(AGPAT9), mRNA.				membrane // membrane // integral to membrane		
DKK1	dickkopf homolog 1 (<i>Xenopus laevis</i>) (DKK1), mRNA.	-1.73	0.006	multicellular organismal development // negative regulation of Wnt receptor signaling pathway // embryonic limb morphogenesis	extracellular region // plasma membrane	GO:0004871 // GO:0005515 // GO:0008083 // GO:0050750	signal transducer activity // protein binding // growth factor activity // low-density lipoprotein receptor binding
PFKFB4	6-phosphofructo- 2-kinase/fructose- 2,6-biphosphatase 4 (PFKFB4), mRNA.	-1.13	0.006	fructose 2,6-bisphosphate metabolic process // fructose 2,6-bisphosphate metabolic process // metabolic process	cellular compone nt // cytosol	GO:0000166 // GO:0003873 // GO:0003873 // GO:0003873 // GO:0004331 // GO:0005524 // GO:0016301 // GO:0016740 // GO:0016787	nucleotide binding // 6- phosphofructo-2-kinase activity // 6-phosphofructo-2-kinase activity // 6-phosphofructo-2-kinase activity // fructose-2,6-bisphosphate 2- phosphatase activity // ATP binding // kinase activity // transferase activity // hydrolase activity
QDPR	quinoid dihydropteridine reductase (QDPR), mRNA.	-1.21	0.005	amino acid metabolic process // L-phenylalanine catabolic process // tetrahydrobiopterin biosynthetic process // dihydrobiopterin metabolic process // oxidation reduction	cytoplasm	GO:0004155 // GO:0005488 // GO:0009055 // GO:0016491	6,7-dihydropteridine reductase activity // binding // electron carrier activity // oxidoreductase activity
GPRC5A	G protein-coupled receptor, family C, group 5, member A (GPRC5A), mRNA.	-1.07	0.005	signal transduction // G- protein coupled receptor protein signaling pathway	plasma membrane // integral to plasma membrane // cytoplasmic vesicle membrane // cytoplasmic vesicle	GO:0004872 // GO:0004930	receptor activity // G-protein coupled receptor activity
SLC17A5	solute carrier family 17 (anion/sugar transporter), member 5 (SLC17A5), mRNA.	-1.09	0.005	transport // anion transport	membrane fraction // lysosomal membrane // integral to plasma membrane // membrane	GO:0005215 // GO:0005351 // GO:0015293	transporter activity // sugar:hydrogen symporter activity // symporter activity
IFI6	interferon, alpha- inducible protein 6 (IFI6), transcript variant 1, mRNA.	-1.58	0.005	release of cytochrome c from mitochondria // anti-apoptosis // immune response // negative regulation of caspase activity // negative regulation of mitochondrial depolarization	mitochondrion // membrane // integral to membrane	GO:0005515	protein binding
WIPI1	WD repeat domain, phosphoinositide interacting 1 (WIPI1), mRNA.	1.18	0.002	autophagy // vesicle targeting, trans-Golgi to endosome	autophagic vacuole membrane // cytoplasm // endosome // Golgi apparatus	GO:0005102 // GO:0030331 // GO:0032266 // GO:0050681	receptor binding // estrogen receptor binding // phosphatidylinositol 3-phosphate binding // androgen receptor binding

					// trans-Golgi network // endosome membrane // cytoplasmic vesicle // pre-autophagosomal structure membrane		
L1CAM	L1 cell adhesion molecule (L1CAM), transcript variant 1, mRNA.	-1.74	0.002	cell adhesion // multicellular organismal development // nervous system development // cell differentiation	plasma membrane // integral to membrane	GO:0005515	protein binding
SLC16A6	solute carrier family 16, member 6 (monocarboxylic acid transporter 7) (SLC16A6), mRNA.	-2.76	0.002	transport // monocarboxylic acid transport	membrane fraction // plasma membrane // integral to plasma membrane // integral to membrane	GO:0005215 // GO:0008028 // GO:0015293	transporter activity // monocarboxylic acid transmembrane transporter activity // symporter activity
SLC6A15	solute carrier family 6, member 15 (SLC6A15), transcript variant 1, mRNA.	-1.91	0.002	neurotransmitter transport // neurotransmitter transport	integral to plasma membrane // membrane	GO:0005328 // GO:0015293	neurotransmitter:sodium symporter activity // symporter activity
ATP6V0D2	ATPase, H+ transporting, lysosomal 38kDa, V0 subunit d2 (ATP6V0D2), mRNA.	-1.20	0.002	ion transport // proton transport	proton-transporting two-sector ATPase complex	GO:0016787 // GO:0046961	hydrolase activity // hydrogen ion transporting ATPase activity, rotational mechanism
CAPG	capping protein (actin filament), gelsolin-like (CAPG), mRNA.	-1.39	0.002	protein complex assembly // cell projection biogenesis // barbed-end actin filament capping	nucleus // cytoplasm // F-actin capping protein complex // melanosome ruffle // cytoplasm // cytosol // cytoskeleton // actin filament // microvillus // membrane // apical plasma membrane // extrinsic to membrane // extrinsic to membrane // filopodium // cortical	GO:0003779	actin binding
EZR	ezrin (EZR), transcript variant 1, mRNA.	-1.30	0.001	cytoskeletal anchoring at plasma membrane // leukocyte adhesion // regulation of cell shape // membrane to membrane docking // actin filament bundle formation		GO:0005198 // GO:0008092 // GO:0043621 // GO:0050839 // GO:0051015	structural molecule activity // cytoskeletal protein binding // protein self-association // cell adhesion molecule binding // actin filament binding

IFI27	interferon, alpha-inducible protein 27 (IFI27), mRNA.	-1.68	0.001	biological_process	cytoskeleton membrane // integral to membrane	GO:0003674	molecular_function
LONRF3	LON peptidase N-terminal domain and ring finger 3 (LONRF3), transcript variant 1, mRNA.	-1.21	0.001	ATP-dependent proteolysis	---	GO:0004176 // GO:0005515 // GO:0008270 // GO:0046872	ATP-dependent peptidase activity // protein binding // zinc ion binding // metal ion binding
CD109	CD109 molecule (CD109), mRNA.	-1.92	3.7E-04	---	extracellular region // plasma membrane // anchored to membrane	GO:0004867 // GO:0005515 // GO:0017114	serine-type endopeptidase inhibitor activity // protein binding // wide-spectrum protease inhibitor activity
CXorf57	chromosome X open reading frame 57 (CXorf57), mRNA.	-1.32	2.4E-04	---	---	---	---
AVPI1	arginine vasopressin-induced 1 (AVPI1), mRNA.	-1.48	2.4E-04	activation of MAPK activity // cell cycle	---	---	---
ENTHD1	ENTH domain containing 1 (ENTHD1), mRNA.	-2.34	1.5E-04	---	---	---	---
DUSP10	dual specificity phosphatase 10 (DUSP10), transcript variant 1, mRNA.	-1.98	6.2E-05	protein amino acid dephosphorylation // protein amino acid dephosphorylation // response to stress // JNK cascade	nucleus // cytoplasm	GO:0004725 // GO:0016787 // GO:0016791 // GO:0017017	protein tyrosine phosphatase activity // hydrolase activity // phosphatase activity // MAP kinase tyrosine/serine/threonine phosphatase activity

SUPPLEMENTAL TABLE S4: GSEA ANALYSIS

The * indicates those genes also identified in the Dry study showing resistance or sensitivity to MAPK inhibitors

	Genes Enriched in BRAF^{WT} RAF-265 Responsive Tumors
	Gene Title
ACADM	acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain
ACAT1	acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase)
ADRBK2	adrenergic, beta, receptor kinase 2
AHR	aryl hydrocarbon receptor
ALDOC	aldolase C, fructose-bisphosphate
ANKMY2	ankyrin repeat and MYND domain containing 2
APAF1	apoptotic peptidase activating factor
BAAT	bile acid Coenzyme A: amino acid N-acyltransferase (glycine N-choloyltransferase)
BIRC2	baculoviral IAP repeat-containing 2
*BNIP3	BCL2/adenovirus E1B 19kDa interacting protein 3
C11ORF54	chromosome 11 open reading frame 54
CALB2	calbindin 2, 29kDa (calretinin)
CASD1	CAS1 domain containing 1
CASP1	caspase 1, apoptosis-related cysteine peptidase (interleukin 1, beta, convertase)
CD36	CD36 molecule (thrombospondin receptor)
CDH2	cadherin 2, type 1, N-cadherin (neuronal)
CEPT1	choline/ethanolamine phosphotransferase 1
CNBP	CCHC-type zinc finger, nucleic acid binding protein
CPB2	carboxypeptidase B2 (plasma, carboxypeptidase U)
CREB1	cAMP responsive element binding protein 1
CYCS	cytochrome c, somatic
DDX10	DEAD (Asp-Glu-Ala-Asp) box polypeptide 10
DHCR24	24-dehydrocholesterol reductase

DLEU2	deleted in lymphocytic leukemia, 2
DMD	dystrophin (muscular dystrophy, Duchenne and Becker types)
DNMBP	dynamain binding protein
FAS	Fas (TNF receptor superfamily, member 6)
FBP1	fructose-1,6-bisphosphatase 1
FGFR1OP2	FGFR1 oncogene partner 2
FN1	fibronectin 1
GLRA2	glycine receptor, alpha 2
HMGCL	3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria)
HMGCS1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1 (soluble)
HMOX1	heme oxygenase (decycling) 1
HSPB1	heat shock 27kDa protein 1
IL1A	interleukin 1, alpha
JRKL	jerky homolog-like (mouse)
KIF11	kinesin family member 11
KLHL9	kelch-like 9 (Drosophila)
LPHN3	latrophilin 3
LPL	lipoprotein lipase
MEI	malic enzyme 1, NADP(+)-dependent, cytosolic
NAPIL-1	nucleosome assembly protein 1-like 1
NEB	nebulin
NEK7	NIMA (never in mitosis gene a)-related kinase 7
PAH	phenylalanine hydroxylase
PICALM	phosphatidylinositol binding clathrin assembly protein
PLCB1	phospholipase C, beta 1 (phosphoinositide-specific)
PPMIA (PP2c)	protein phosphatase 1A (formerly 2C), magnesium-dependent, alpha isoform
PPP3CA	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform (calcineurin A alpha)
PPP3CA	protein phosphatase 3 (formerly 2B), catalytic subunit, alpha isoform (calcineurin A alpha)
PRKACB	protein kinase, cAMP-dependent, catalytic, beta
PRKAR2B	protein kinase, cAMP-dependent, regulatory, type II, beta
RAF1	v-raf-1 murine leukemia viral oncogene homolog 1
RAP2A	RAP2A, member of RAS oncogene family

RMD5A	required for meiotic nuclear division 5 homolog A (S. cerevisiae)
S100A2	S100 calcium binding protein A2
SCD	stearoyl-CoA desaturase (delta-9-desaturase)
SCL38A2	solute carrier family 38, member 2
SCML2	sex comb on midleg-like 2 (Drosophila)
SDHD	succinate dehydrogenase complex, subunit D, integral membrane protein
SEPP1	selenoprotein P, plasma, 1
SFRS11	splicing factor, arginine/serine-rich 11
SLC4A7	solute carrier family 4, sodium bicarbonate cotransporter, member 7
SNX13	sorting nexin 13
TIMM17A	translocase of inner mitochondrial membrane 17 homolog A (yeast)
TLE4	transducin-like enhancer of split 4 (E(sp1) homolog, Drosophila)
TUBB2B	tubulin, beta 2B
UBE3A	ubiquitin protein ligase E3A (human papilloma virus E6-associated protein, Angelman syndrome)
VLDLR	very low density lipoprotein receptor
YTHDC1	YTH domain containing 1
ZNF337	zinc finger protein 337
	Genes Enriched in BRAF^{WT} RAF265 Non-responsive Tumors
*CLU	clusterin
*ETV4	ets variant gene 4 (E1A enhancer binding protein, E1AF)
*FGFR1	fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)
*TRIO	triple functional domain (PTPRF interacting)
*TYR	tyrosinase (oculocutaneous albinism IA)
ACTC1	actin, alpha, cardiac muscle 1
ACTN1	actinin, alpha 1
ACVRL1	activin A receptor type II-like 1
ADA	adenosine deaminase
ADAMTSL2	ADAMTS-like 2
ADRA1B	adrenergic, alpha-1B-, receptor

AES	amino-terminal enhancer of split
AGRN	NO INFORMATION
ALDH4A1	aldehyde dehydrogenase 4 family, member A1
AMH	anti-Mullerian hormone
AP3B2	adaptor-related protein complex 3, beta 2 subunit
APOD	apolipoprotein D
ARHGDI1A	Rho GDP dissociation inhibitor (GDI) alpha
ARHGEF15	Rho guanine nucleotide exchange factor (GEF) 15
ATP1A3	ATPase, Na⁺/K⁺ transporting, alpha 3 polypeptide
ATP5D	ATP synthase, H⁺ transporting, mitochondrial F1 complex, delta subunit
B3GAT3	beta-1,3-glucuronyltransferase 3 (glucuronosyltransferase I)
B4GALT7	xylosylprotein beta 1,4-galactosyltransferase, polypeptide 7 (galactosyltransferase I)
BCAP31	B-cell receptor-associated protein 31
CAPN1	calpain 1, (mu/l) large subunit
CCDC69	coiled-coil domain containing 69
CCND1	cyclin D1
CD34	CD34 molecule
CDA	cytidine deaminase
CDK5	cyclin-dependent kinase 5
CLEC3B	C-type lectin domain family 3, member B
COL6A2	collagen, type VI, alpha 2
CRHBP	corticotropin releasing hormone binding protein
CRIP1	cysteine-rich protein 1 (intestinal)
CRMP1	collapsin response mediator protein 1
CTSH	cathepsin H
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2
DAG1	dystroglycan 1 (dystrophin-associated glycoprotein 1)
DPM2	dolichyl-phosphate mannosyltransferase polypeptide 2, regulatory subunit
DTYMK	deoxythymidylate kinase (thymidylate kinase)
DYNLT1	dynein, light chain, Tctex-type 1
EFNA2	ephrin-A2
EGR1	early growth response 1
EIF5A	eukaryotic translation initiation factor 5A

ENG	endoglin (Osler-Rendu-Weber syndrome 1)
EPHX1	epoxide hydrolase 1, microsomal (xenobiotic)
FBN1	fibrillin 1
FOLR1	folate receptor 1 (adult)
FURIN	furin (paired basic amino acid cleaving enzyme)
FYN	FYN oncogene related to SRC, FGR, YES
GAK	cyclin G associated kinase
GAS2L1	growth arrest-specific 2 like 1
GAS6	growth arrest-specific 6
GDPD5	glycerophosphodiester phosphodiesterase domain containing 5
GJB1	gap junction protein, beta 1, 32kDa (connexin 32, Charcot-Marie-Tooth neuropathy, X-linked)
GPR56	G protein-coupled receptor 56
GPRC5A	G protein-coupled receptor, family C, group 5, member A
GSTP1	glutathione S-transferase pi
HES2	hairy and enhancer of split 2 (Drosophila)
HPRT1	hypoxanthine phosphoribosyltransferase 1 (Lesch-Nyhan syndrome)
HRAS	v-Ha-ras Harvey rat sarcoma viral oncogene homolog
HS3ST3A1	heparan sulfate (glucosamine) 3-O-sulfotransferase 3A1
HS3ST3B1	heparan sulfate (glucosamine) 3-O-sulfotransferase 3B1
HYAL2	hyaluronoglucosaminidase 2
IGFBP5	insulin-like growth factor binding protein 5
INPPL1	inositol polyphosphate phosphatase-like 1
IRS1	insulin receptor substrate 1
ITGA3	integrin, alpha 3 (antigen CD49C, alpha 3 subunit of VLA-3 receptor)
ITPKA	inositol 1,4,5-trisphosphate 3-kinase A
ITPKB	inositol 1,4,5-trisphosphate 3-kinase B
KRT17	keratin 17
KRT5	keratin 5 (epidermolysis bullosa simplex, Dowling-Meara/Kobner/Weber-Cockayne types)
KRT7	keratin 7
LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4
LMNA	lamin A/C

LOXL1	lysyl oxidase-like 1
LY6E	lymphocyte antigen 6 complex, locus E
MAP3K11	mitogen-activated protein kinase kinase kinase 11
MAP4K2	mitogen-activated protein kinase kinase kinase kinase 2
MDK	midkine (neurite growth-promoting factor 2)
MMP14	matrix metalloproteinase 14 (membrane-inserted)
MMP15	matrix metalloproteinase 15 (membrane-inserted)
MTA1	metastasis associated 1
MTHFD1	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1, methenyltetrahydrofolate cyclohydrolase, formyltetrahydrofolate synthetase
NCDN	neurochondrin
NGFR	nerve growth factor receptor (TNFR superfamily, member 16)
NR4A1	nuclear receptor subfamily 4, group A, member 1
NRTN	neurturin
PCMT1	protein-L-isoaspartate (D-aspartate) O-methyltransferase
PECAM1	platelet/endothelial cell adhesion molecule (CD31 antigen)
POLR2E	polymerase (RNA) II (DNA directed) polypeptide E, 25kDa
POLR2L	polymerase (RNA) II (DNA directed) polypeptide L, 7.6kDa
PPAP2B	phosphatidic acid phosphatase type 2B
PPM1G	protein phosphatase 1G (formerly 2C), magnesium-dependent, gamma isoform
PPP3CC	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)
PTPRB	protein tyrosine phosphatase, receptor type, B
PTRF	polymerase I and transcript release factor
RAMP2	receptor (calcitonin) activity modifying protein 2
RPL39L	ribosomal protein L39-like
SEMA6A	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A
SHOX	short stature homeobox
SLC02A1	solute carrier organic anion transporter family, member 2A1
SLC6A7	solute carrier family 6 (neurotransmitter transporter, L-proline), member 7

SPIB	Spi-B transcription factor (Spi-1/PU.1 related)
TEK	TEK tyrosine kinase, endothelial (venous malformations, multiple cutaneous and mucosal)
TGM2	transglutaminase 2 (C polypeptide, protein-glutamine-gamma-glutamyltransferase)
TIE1	tyrosine kinase with immunoglobulin-like and EGF-like domains 1
TIMP1	TIMP metalloproteinase inhibitor 1
TK1	thymidine kinase 1, soluble
TLE2	transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila)
TYMS	thymidylate synthetase
XYLT1	xylosyltransferase I
XYLT2	xylosyltransferase II
ZBTB7A	zinc finger and BTB domain containing 7A
	Genes Enriched in RAF265 Responsive Tumors
	Regardless of BRAF Mutation Status
*SERPINB1	serpin peptidase inhibitor, clade B (ovalbumin), member 1
*TRIB1	tribbles homolog 1 (Drosophila)
AARDC3	arrestin domain containing 3
ABCF2	ATP-binding cassette, sub-family F (GCN20), member 2
ACTG1	actin, gamma 1
ACTR1A	ARP1 actin-related protein 1 homolog A, cencentractin alpha (yeast)
AHR	aryl hydrocarbon receptor
ALDOC	aldolase C, fructose-bisphosphate
ANXA2	annexin A2
AP2M1	adaptor-related protein complex 2, mu 1 subunit
AP3S1	adaptor-related protein complex 3, sigma 1 subunit
API5	apoptosis inhibitor 5
ASNS	asparagine synthetase
BET1	BET1 homolog (S. cerevisiae)
C11ORF54	chromosome 11 open reading frame 54
CAV2	caveolin 2
CD36	CD36 molecule (thrombospondin receptor)
CD55	CD55 molecule, decay accelerating factor for complement (Cromer blood group)
CDC37L1	CDC37 cell division cycle 37 homolog (S. cerevisiae)-like 1

CDH1	cadherin 1, type 1, E-cadherin (epithelial)
CEBPZ	CCAAT/enhancer binding protein zeta
CSAD	cysteine sulfinic acid decarboxylase
CYB5B	cytochrome b5 type B (outer mitochondrial membrane)
CYCS	cytochrome c, somatic
CYP2B6	cytochrome P450, family 2, subfamily B, polypeptide 6
CYP2C9	cytochrome P450, family 2, subfamily C, polypeptide 9
CYP51A1	cytochrome P450, family 51, subfamily A, polypeptide 1
DHCR24	24-dehydrocholesterol reductase
DLD	dihydrolipoamide dehydrogenase
EIF2S2	eukaryotic translation initiation factor 2, subunit 2 beta, 38kDa
ELOVL1	elongation of very long chain fatty acids (FEN1/Elo2, SUR4/Elo3, yeast)-like 1
ENO2	enolase 2 (gamma, neuronal)
ETHE1	ethylmalonic encephalopathy 1
FBP1	fructose-1,6-bisphosphatase 1
FBP1	fructose-1,6-bisphosphatase 1
GABRA2	gamma-aminobutyric acid (GABA) A receptor, alpha 2
GFPT1	glutamine-fructose-6-phosphate transaminase 1
GOT1	glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)
GPT2	glutamic pyruvate transaminase (alanine aminotransferase) 2
HECTD2	HECT domain containing 2
HK2	hexokinase 2
HMGCS1	3-hydroxy-3-methylglutaryl-Coenzyme A synthase 1 (soluble)
HMOX1	heme oxygenase (decycling) 1
HSP90AA1	heat shock protein 90kDa alpha (cytosolic), class A member 1
HSPC159	NO INFORMATION
IGBP1	immunoglobulin (CD79A) binding protein 1
IGFBP3	insulin-like growth factor binding protein 3
ITGA2	integrin, alpha 2 (CD49B, alpha 2 subunit of VLA-2 receptor)
KTN1	kinectin 1 (kinesin receptor)

LARP4	La ribonucleoprotein domain family, member 4
LGALS1	lectin, galactoside-binding, soluble, 1 (galectin 1)
LPL	lipoprotein lipase
MDH1	malate dehydrogenase 1, NAD (soluble)
MDH1	malate dehydrogenase 1, NAD (soluble)
ME1	malic enzyme 1, NADP(+)-dependent, cytosolic
NFIL3	nuclear factor, interleukin 3 regulated
P2RX7	purinergic receptor P2X, ligand-gated ion channel, 7
PAN3	PAN3 polyA specific ribonuclease subunit homolog (S. cerevisiae)
PDHX	pyruvate dehydrogenase complex, component X
PFKM	phosphofructokinase, muscle
PGK1	phosphoglycerate kinase 1
PHKA1	phosphorylase kinase, alpha 1 (muscle)
PIK3C3	phosphoinositide-3-kinase, class 3
PIK3CA	phosphoinositide-3-kinase, catalytic, alpha polypeptide
PK1	phosphoglycerate kinase 1
PLAG1	pleiomorphic adenoma gene 1
PLD3	phospholipase D family, member 3
PRDX1	peroxiredoxin 1
PSMD8	proteasome (prosome, macropain) 26S subunit, non-ATPase, 8
PTCH1	patched homolog 1 (Drosophila)
RAB10	RAB10, member RAS oncogene family
RAB11A	RAB11A, member RAS oncogene family
RAB1A	RAB1A, member RAS oncogene family
RAB27A	RAB27A, member RAS oncogene family
RAB5A	RAB5A, member RAS oncogene family
RAB6A	RAB6A, member RAS oncogene family
RAB9A	NO INFORMATION
REEP5	receptor accessory protein 5
RHEB	Ras homolog enriched in brain
SACMIL	SAC1 suppressor of actin mutations 1-like (yeast)
SARS	seryl-tRNA synthetase
SC4MOL	sterol-C4-methyl oxidase-like
SCD	stearoyl-CoA desaturase (delta-9-desaturase)

SDHB	succinate dehydrogenase complex, subunit B, iron sulfur (lp)
SLCOA1	solute carrier family 20 (phosphate transporter), member 1
SNAI2	snail homolog 2 (Drosophila)
SQLE	squalene epoxidase
UBT2B10	UDP glucuronosyltransferase 2 family, polypeptide B10
UGDH	UDP-glucose dehydrogenase
VLDLR	very low density lipoprotein receptor
XBP1	X-box binding protein 1
XPOT	exportin, tRNA (nuclear export receptor for tRNAs)
	Genes Enriched in RAF-265 Non-responsive Tumors
	Regardless of BRAF Mutation Status
*CLU	clusterin
*COL5A1	collagen, type V, alpha 1
*ERBB3	v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)
*FGFR1	fibroblast growth factor receptor 1 (fms-related tyrosine kinase 2, Pfeiffer syndrome)
*FZD2	frizzled homolog 2 (Drosophila)
*TRIO	triple functional domain (PTPRF interacting)
*TYR	tyrosinase (oculocutaneous albinism IA)
ACTA1	actin, alpha 1, skeletal muscle
ACTC1	actin, alpha, cardiac muscle 1
ACTN3	actinin, alpha 3
ADAMTSL2	ADAMTS-like 2
ARHGEF15	Rho guanine nucleotide exchange factor (GEF) 15
ARID1A	AT rich interactive domain 1A (SWI- like)
ASS1	argininosuccinate synthetase 1
ATP2A1	ATPase, Ca ⁺⁺ transporting, cardiac muscle, fast twitch 1
BIN1	bridging integrator 1
BRD3	bromodomain containing 3
CASZ1	castor homolog 1, zinc finger (Drosophila)
CCDC69	coiled-coil domain containing 69
CCNA2	cyclin A2
CCND1	cyclin D1

CCNE1	cyclin E1
CD34	CD34 molecule
CDKN2A	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4)
CENPA	centromere protein A
CENPE	centromere protein E, 312kDa
CKM	creatine kinase, muscle
CLCN5	chloride channel 5 (nephrolithiasis 2, X-linked, Dent disease)
CLEC3B	C-type lectin domain family 3, member B
COL11A1	collagen, type XI, alpha 1
COL6A1	collagen, type VI, alpha 1
COL6A2	collagen, type VI, alpha 2
COX6A2	cytochrome c oxidase subunit VIa polypeptide 2
CRIP1	cysteine-rich protein 1 (intestinal)
CYP4F2	cytochrome P450, family 4, subfamily F, polypeptide 2
DAAM2	dishevelled associated activator of morphogenesis 2
DBF4	DBF4 homolog (<i>S. cerevisiae</i>)
DBH	dopamine beta-hydroxylase (dopamine beta-monoxygenase)
DNMT1	DNA (cytosine-5-)-methyltransferase 1
DUSP27	dual specificity phosphatase 27 (putative)
E2F1	E2F transcription factor 1
E2F2	E2F transcription factor 2
E2F4	E2F transcription factor 4, p107/p130-binding
E2F4	E2F transcription factor 2
EFNA2	ephrin-A2
EFNB1	ephrin-B1
EGFR	epidermal growth factor receptor (erythroblastic leukemia viral (v-erb-b) oncogene homolog, avian)
ENG	endoglin (Osler-Rendu-Weber syndrome 1)
ENO3	enolase 3 (beta, muscle)
ENO3	enolase 3 (beta, muscle)
ENPEP	glutamyl aminopeptidase (aminopeptidase A)
EPHA5	EPH receptor A5
ESR2	estrogen receptor 2 (ER beta)
FANCG	Fanconi anemia, complementation group G

FBLN1	fibulin 1
FBXL22	F-box and leucine-rich repeat protein 22
FLT3	fms-related tyrosine kinase 3
GAD1	glutamate decarboxylase 1 (brain, 67kDa)
GAK	cyclin G associated kinase
GAS2	growth arrest-specific 2
GAS2L1	growth arrest-specific 2 like 1
GAS6	growth arrest-specific 6
GDPD5	glycerophosphodiester phosphodiesterase domain containing 5
H1C1	hypermethylated in cancer 1
HDC	histidine decarboxylase
HES2	hairy and enhancer of split 2 (Drosophila)
HFE2	hemochromatosis type 2 (juvenile)
HYAL1	hyaluronoglucosaminidase 1
HYAL2	hyaluronoglucosaminidase 2
ICAM2	intercellular adhesion molecule 2
IGFBP5	insulin-like growth factor binding protein 5
IL1RL1	interleukin 1 receptor-like 1
IL2RB	interleukin 2 receptor, beta
ITGA9	integrin, alpha 9
ITPKA	inositol 1,4,5-trisphosphate 3-kinase A
JUP	junction plakoglobin
KBTBD5	kelch repeat and BTB (POZ) domain containing 5
KL	klotho
LDB3	LIM domain binding 3
LILRA4	leukocyte immunoglobulin-like receptor, subfamily A (with TM domain), member 4
LRP6	low density lipoprotein receptor-related protein 6
LTK	leukocyte tyrosine kinase
MAP3K11	mitogen-activated protein kinase kinase kinase 11
MAPKBIP2 (mapkb INTERACTI NG PROTIEN 2)	mitogen-activated protein kinase 8 interacting protein 2

MDF1	MyoD family inhibitor
MMP15	matrix metalloproteinase 15 (membrane-inserted)
MMP9	matrix metalloproteinase 9 (gelatinase B, 92kDa gelatinase, 92kDa type IV collagenase)
MYF6	myogenic factor 6 (herculin)
MYH3	myosin, heavy chain 3, skeletal muscle, embryonic
MYH3	myosin, heavy chain 3, skeletal muscle, embryonic
MYLPF	NO INFORMATION
MYOM2	myomesin (M-protein) 2, 165kDa
NCDN	neurochondrin
NEIL1	nei endonuclease VIII-like 1 (E. coli)
PDE1A	phosphodiesterase 1A, calmodulin-dependent
PGAM2	phosphoglycerate mutase 2 (muscle)
PIK3CD	phosphoinositide-3-kinase, catalytic, delta polypeptide
PLCB1	phospholipase C, beta 1 (phosphoinositide-specific)
PLCB2	phospholipase C, beta 2
PNMT	phenylethanolamine N-methyltransferase
POLD1	polymerase (DNA directed), delta 1, catalytic subunit 125kDa
POU3F4	POU domain, class 3, transcription factor 4
PPP3CC	protein phosphatase 3 (formerly 2B), catalytic subunit, gamma isoform (calcineurin A gamma)
PRKAG3	protein kinase, AMP-activated, gamma 3 non-catalytic subunit
PRL	prolactin
PTPRM	protein tyrosine phosphatase, receptor type, M
PTRF	polymerase I and transcript release factor
PYGM	phosphorylase, glycogen; muscle (McArdle syndrome, glycogen storage disease type V)
RAMP2	receptor (calcitonin) activity modifying protein 2
SCRIB	scribbled homolog (Drosophila)
SEMA6A	sema domain, transmembrane domain (TM), and cytoplasmic domain, (semaphorin) 6A
SERPINB5	serpin peptidase inhibitor, clade B (ovalbumin), member 5
SGCA	sarcoglycan, alpha (50kDa dystrophin-associated glycoprotein)

SLC6A7	solute carrier family 6 (neurotransmitter transporter, L-proline), member 7
SOX8	SRY (sex determining region Y)-box 8
SPIB	Spi-B transcription factor (Spi-1/PU.1 related)
SRL	sarcalumenin
TEK	TEK tyrosine kinase, endothelial (venous malformations, multiple cutaneous and mucosal)
TH	tyrosine hydroxylase
TIE1	tyrosine kinase with immunoglobulin-like and EGF-like domains 1
TLE2	transducin-like enhancer of split 2 (E(sp1) homolog, Drosophila)
TMEM38A	transmembrane protein 38A
TNNC2	troponin C type 2 (fast)
TNNI2	troponin I type 2 (skeletal, fast)
TNNT2	troponin T type 2 (cardiac)
TNNT3	troponin T type 3 (skeletal, fast)
TPH1	tryptophan hydroxylase 1 (tryptophan 5-monooxygenase)
TPM1	tropomyosin 1 (alpha)
TPM2	tropomyosin 2 (beta)
TTN	titin
UNC45B	unc-45 homolog B (C. elegans)
USP2	ubiquitin specific peptidase 2
VIP	vasoactive intestinal peptide