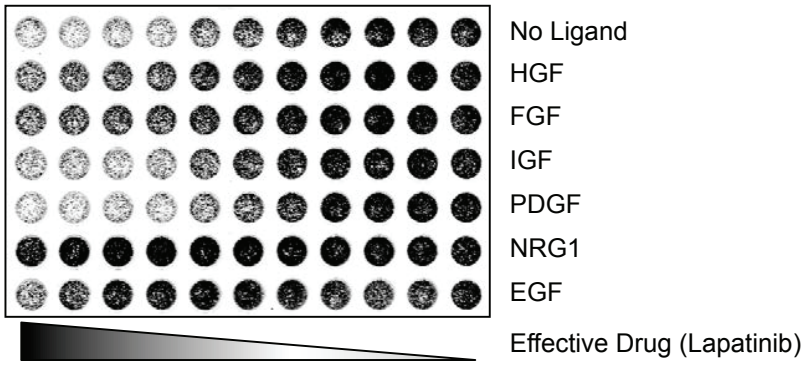
doi:10.1038/nature11249

a

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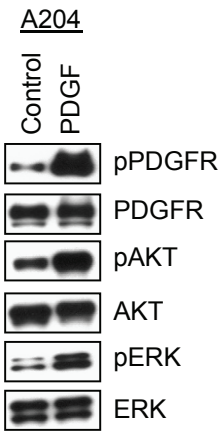
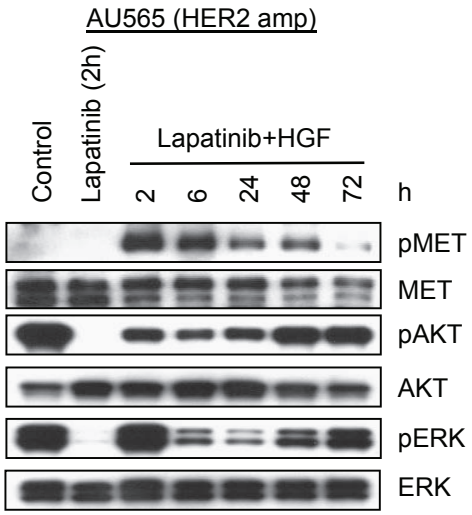



c

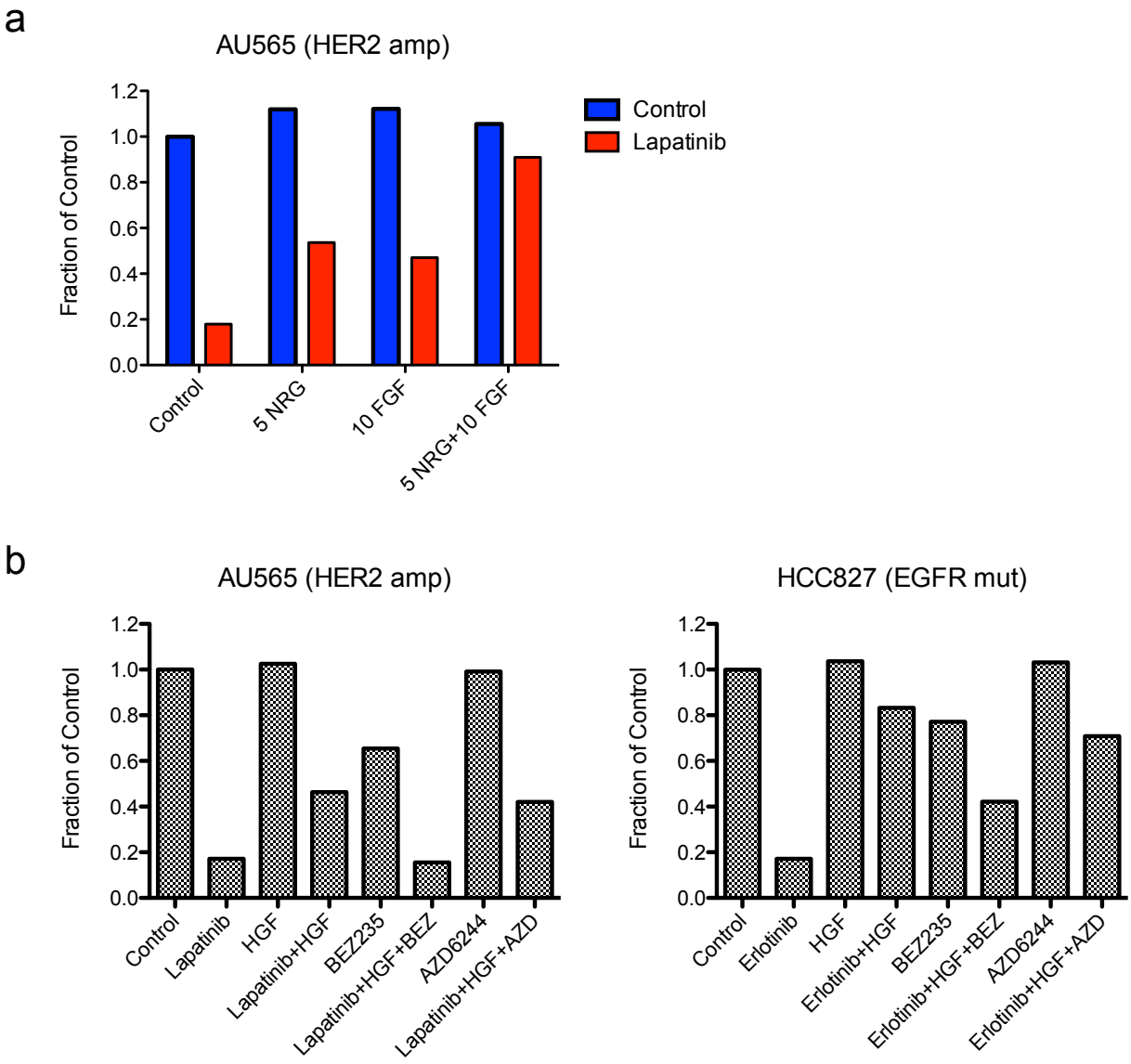
Cisplatin

| Kinase Addiction | Cell Line | HGF | FGF | IGF | PDGF | NRG1 | EGF |
|---|---|---|---|---|---|---|---|
| | | | | | | | |
| **HER2 amplified** | AU565 | NR | NR | NR | NR | NR | NR |
| **MET amplified** | GTL16 | NR | NR | NR | NR | NR | NR |
| **ALK mutation** | SHSY5Y | NR | NR | NR | NR | NR | NR |
| **NRG1 driven** | CHL-1 | NR | NR | NR | NR | NR | NR |
| **EGF-like ligand driven** | H1648 | NR | NR | NR | NR | NR | NR |
| **BRAF mutation** | SK MEL 28 | NR | NR | NR | NR | NR | NR |

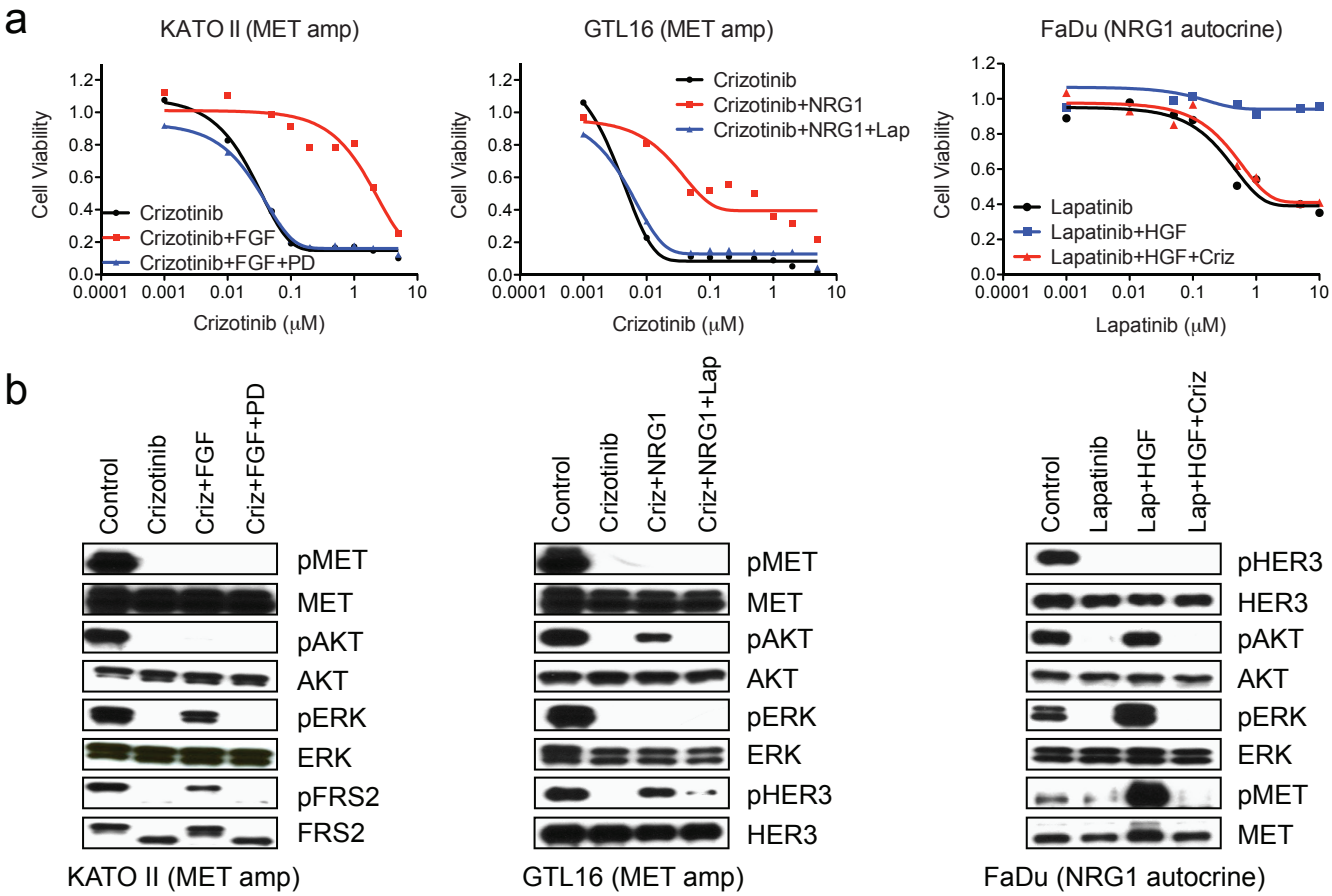
d




**Supplemental Figure 1.**
**a,** Illustration depicting an example of results from the matrix screen. Kinase-addicted cancer cell lines were treated with an appropriate kinase inhibitor +/- indicated RTK ligands (50ng/mL). **b,** Immunoblots showing activation of PDGFR following stimulation with PDGF (50ng/mL, 30mins). **c,** Summary of screen results from six kinase addicted cancer cell lines co-treated with cisplatin and six individual RTK ligands. NR denotes no rescue. **d,** Time course showing the sustained survival signals (pAKT and pERK) following HGF (50ng/mL) stimulation in lapatinib (1μM) treated AU565 *HER2* amplified breast cancer cells.



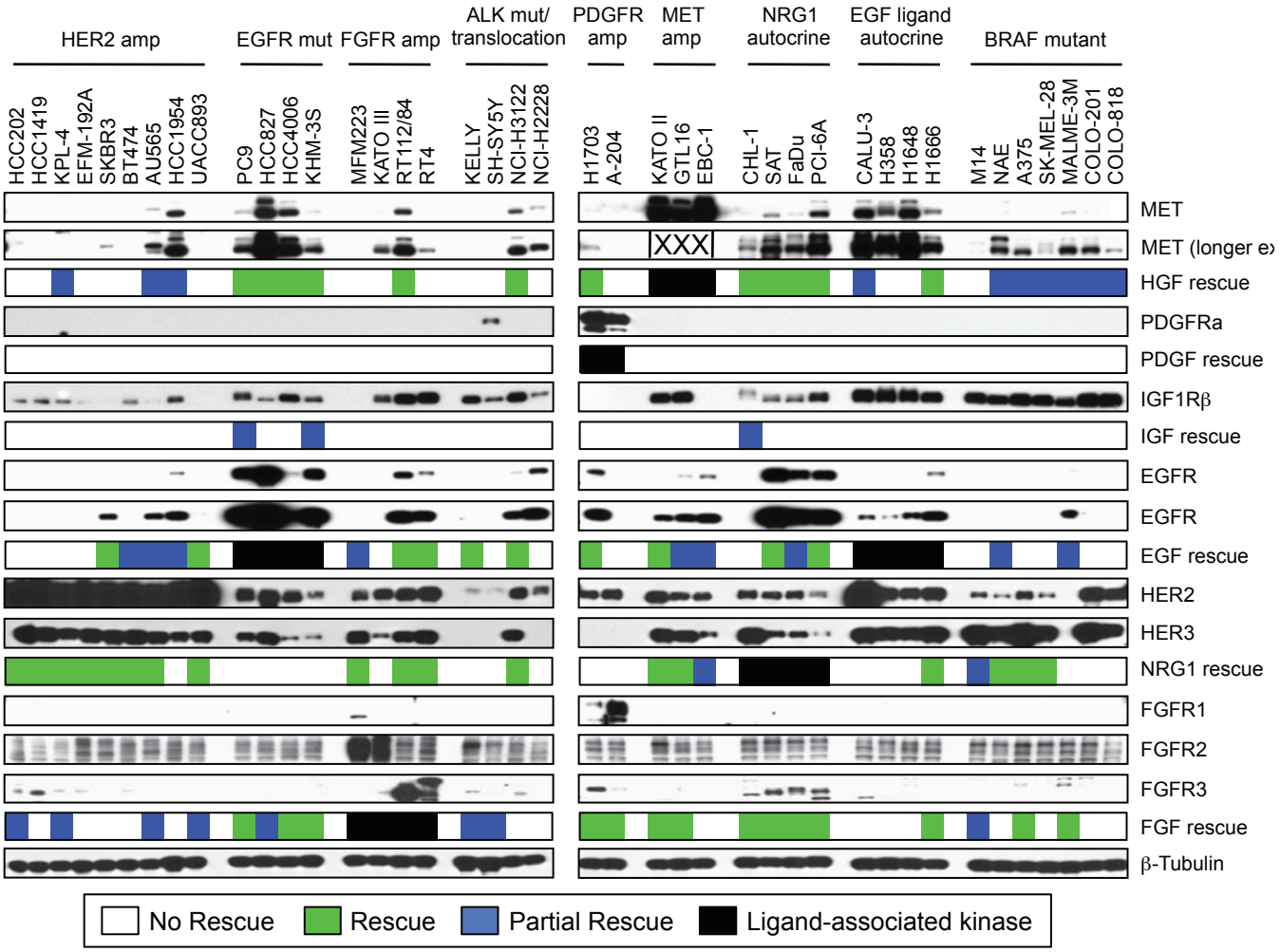

**Supplemental Figure 2.**
**a,** Cell viability assay demonstrating the additive rescue from kinase inhibition by activating both the PI3K and MAPK pathways (72h). AU565 sells were co-treated with lapatinib (1μM) in combination with 10ng/mL NRG1 or FGF. **b,** Cell viability assay demonstrating inhibition of the PI3K pathway is more potent at reversing ligand–induced rescue than the MAPK pathway. Cells were treated with the appropriate kinase inhibitors in the presence of HGF (50ng/mL). Cells were then treated with either 100nM PI3K inhibitor (BEZ235) or MAPK inhibitor (AZD6244). Graphs show average values of technical duplicates from one representative experiment out of two independent experiments.




**Supplemental Figure 3.**

**a,** Cell viability assay demonstrating suppression of cell proliferation in three kinase addicted cancer cell lines following drug treatment (72h). Cells were co-treated with 50ng/mL RTK ligand in the presence of the appropriate secondary kinase inhibitor (0.5μM) as indicated. PD: PD173074, Lap: lapatinib, Criz: crizotinib. Graphs show average values of technical duplicates from one representative experiment out of two independent experiments. **b,** Immunoblots showing the effect of acute kinase inhibition (1μM) in the presence and absence of RTK ligands (50ng/mL, 2h) on AKT and ERK phosphorylation. Cells were co-treated with secondary kinase inhibitor (0.5μM) as appropriate. Criz: crizotinib, PD: PD173074, Lap: lapatinib.

a

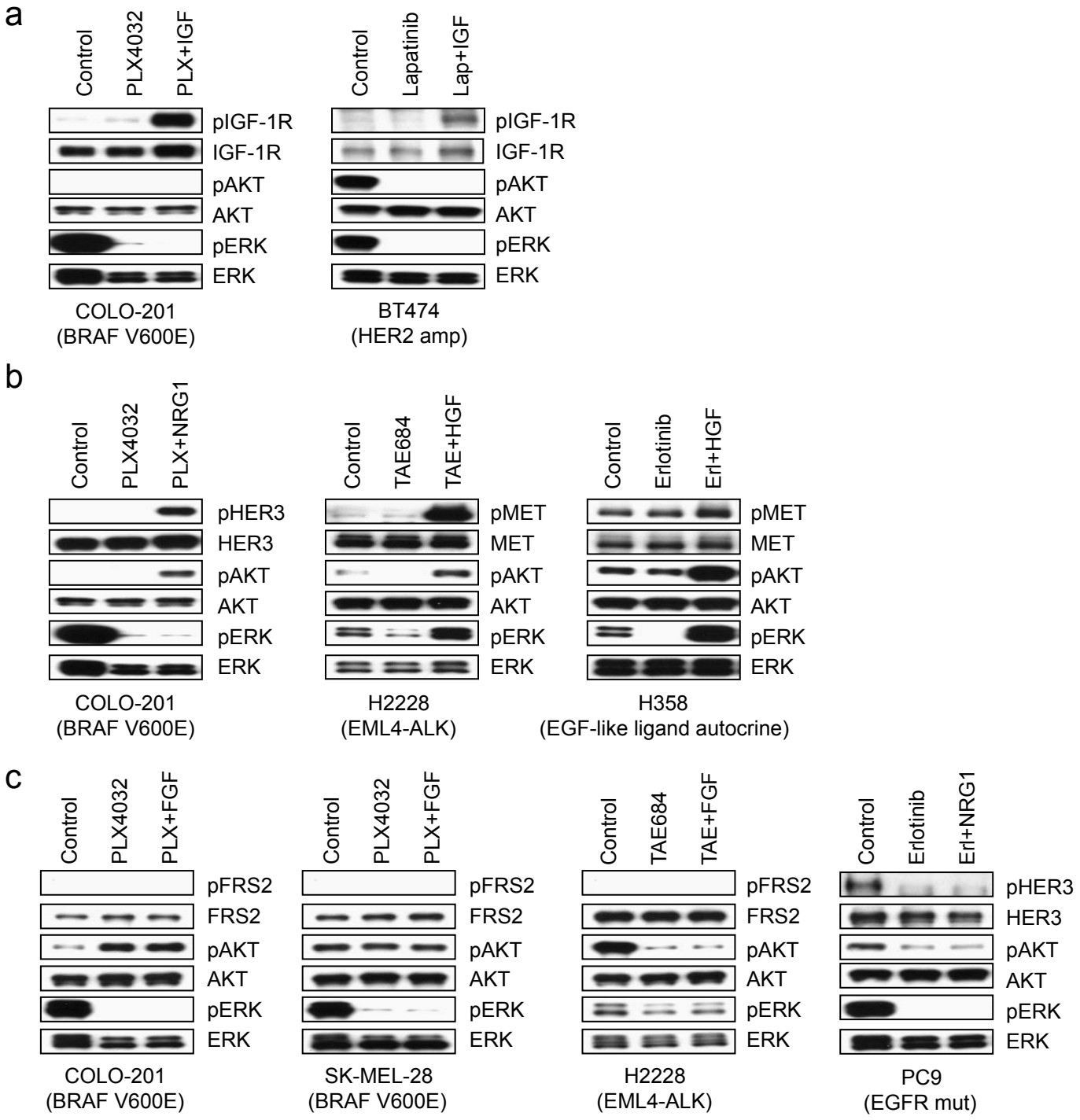



b

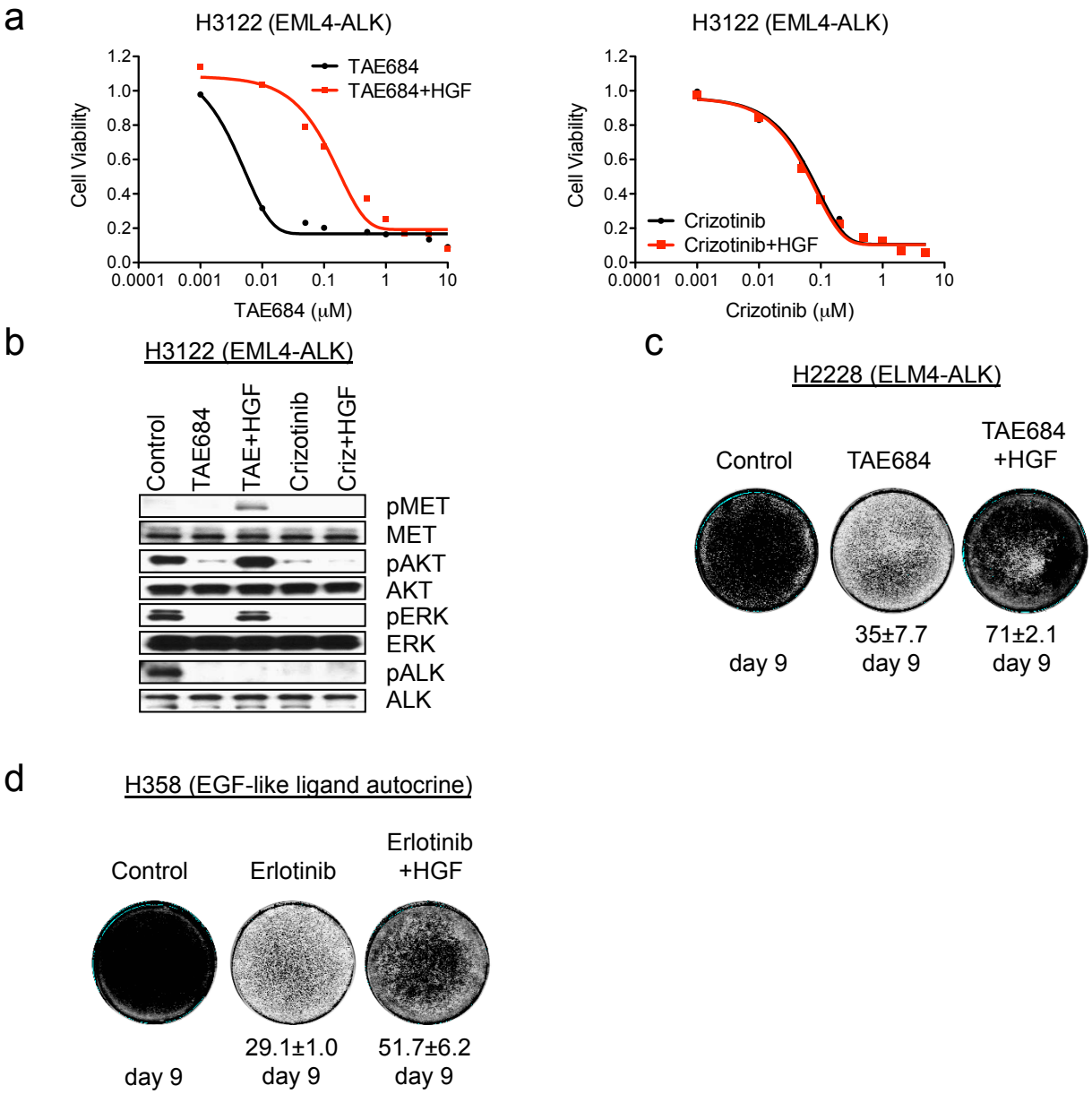
| RTK\Ligand | p-value |
|---|---|
| MET\HGF | p<0.001 |
| PDGFR\PDGF | p=1 |
| IGF-1R\IGF | p=1 |
| EGFR\EGF | p<0.001 |
| HER3\NRG1 | p=0.005 |
| FGFR\FGF | p=1 |

**Supplemental Figure 4.**

**a,** Immunoblots showing expression of MET, PDGFRα, IGF1Rβ, EGFR, HER2, HER3, FGFR1, FGFR2 and FGFR3 in the panel of 41 kinase addicted cancer cell lines from the matrix screen. RTK ligand rescue is indicated; green squares denotes complete rescue, blue squares denotes partial rescue, white squares denotes no rescue and black squares denotes ligand-associated kinase. X denotes removed sample, amp denotes amplified and mut denotes mutated. Equal loading was determined using β-tubulin. **b,** Table associating RTK expression with the ability of RTK ligands to rescue kinase-addicted cells from kinase inhibition. Statistical significance was determined using 2x2 contingency table. p values are given.

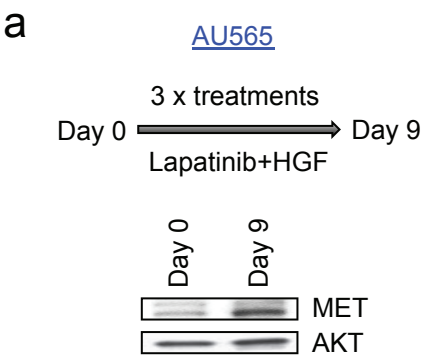


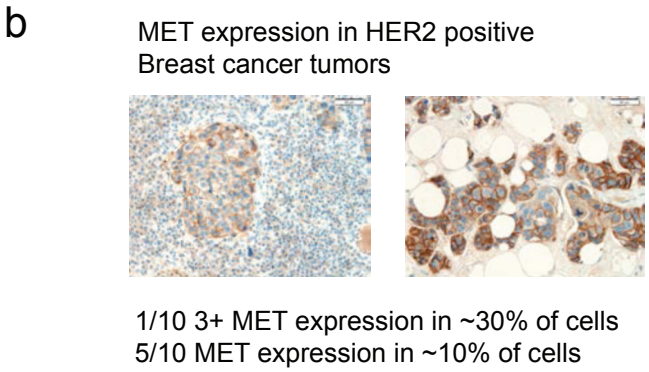

**Supplemental Figure 5.**
**a,** Immunoblots demonstrating activation of receptor without coupling to downstream survival signals in receptor expressing non-RTK ligand rescued cells. PLX: PLX4032, Lap: lapatinib. **b,** Immunoblots demonstrating activation of receptor with coupling to at least one downstream survival signal in receptor expressing non-RTK ligand rescued cells. PLX: PLX4032, TAE: TAE684, Erl: erlotinib. **c,** Immunoblots demonstrating the failure of RTK ligands to activate the cognate receptor and corresponding downstream survival signals in receptor expressing non-RTK ligand rescued cells. PLX: PLX4032, TAE: TAE684, Erl: erlotinib.

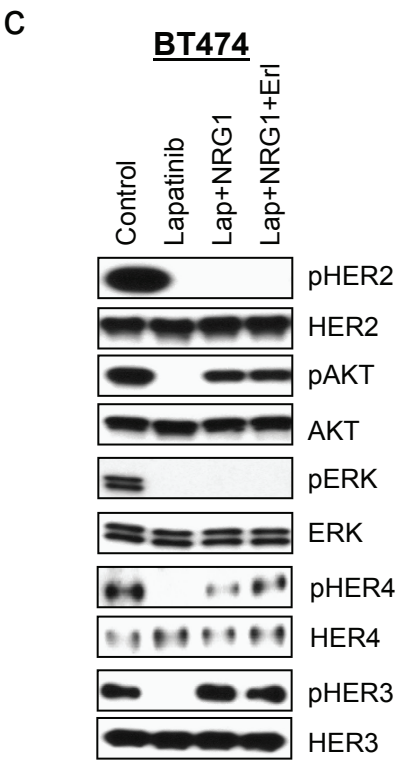



**Supplemental Figure 6.**

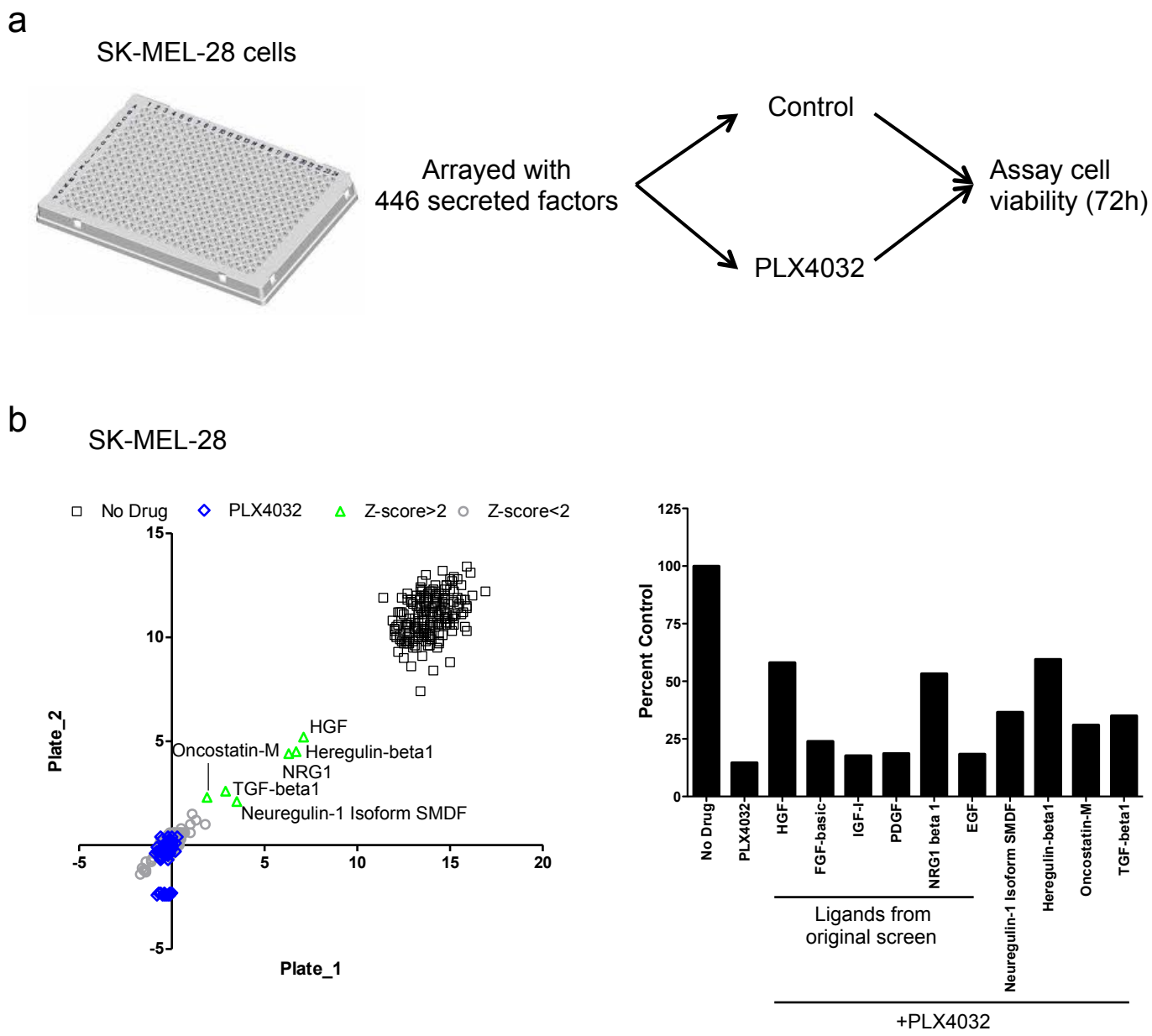
**a,** Cell viability assay demonstrating suppression of cell proliferation in H3122 EML4-ALK translocated NSCLC cancer cell line following treatment with TAE684 or crizotinib (72h). Cells were co-treated with 50ng/mL HGF. Graphs show average values of technical duplicates from one representative experiment out of two independent experiments. **b,** Immunoblots showing the effect of acute TAE684 or crizotinib (1μM) treatment in the presence and absence of HGF (50ng/mL, 2h) on AKT and ERK phosphorylation. **c**, Syto 60 staining of H2228 EML4-ALK translocated NSCLC cells treated with TAE684 (2μM) in the presence and absence of HGF (50ng/mL) as indicated. Cells were treated every 3 days for 9 days. Images are representative of three biological replicates and values indicate mean +/- s.d. **d**, Syto 60 staining of H358 EGF-like ligand-driven NSCLC cells treated with Erlotinib (5μM) in the presence and absence of HGF (50ng/mL) as indicated. Cells were treated every 3 days for 9 days. Images are representative of three biological replicates and values indicate mean +/- s.d.



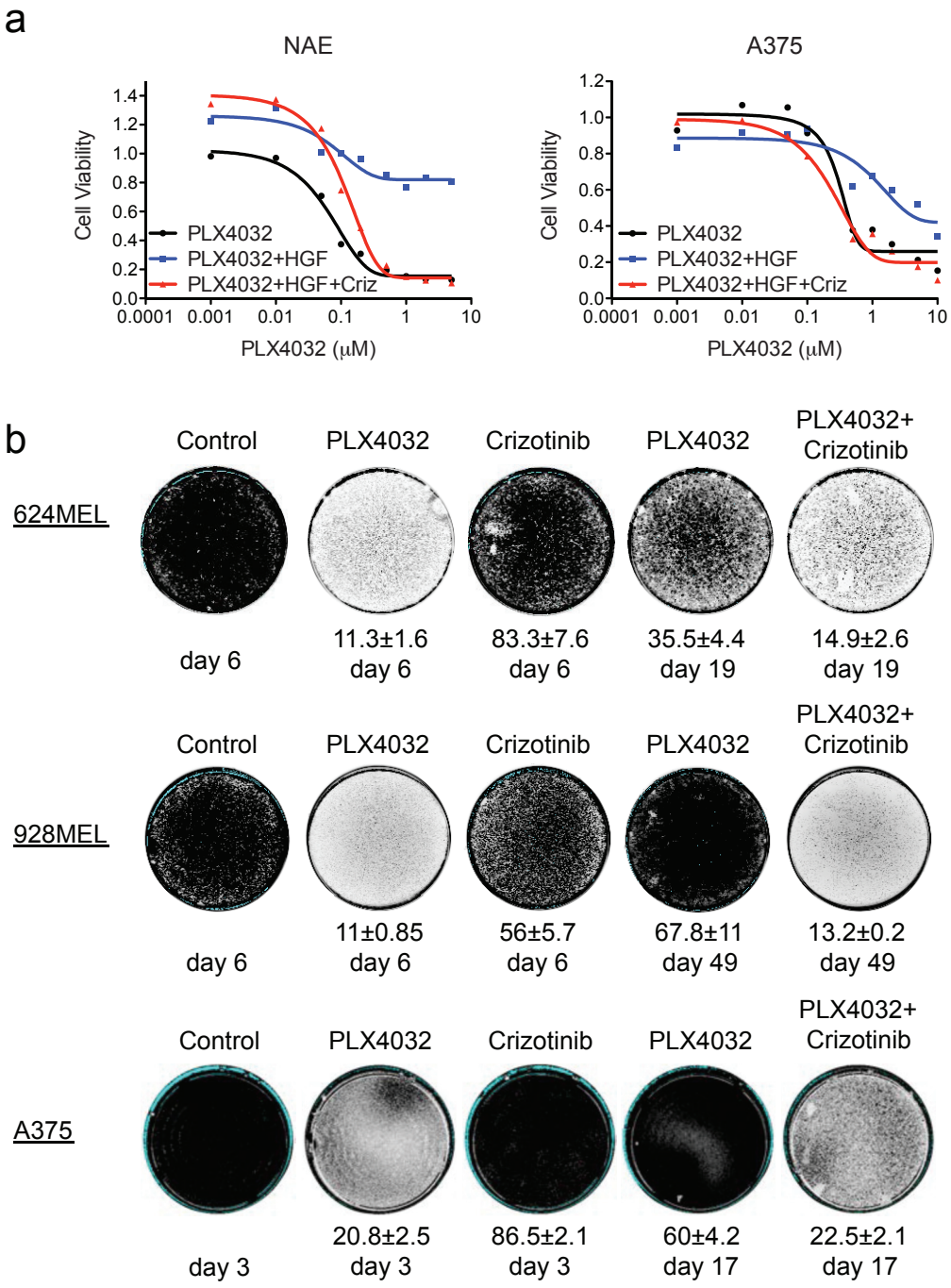




**Supplemental Figure 7.**
**a,** Selection of AU565 cells expressing elevated MET following 3x treatments with lapatinib (1μM) and HGF. **b,** Representative IHC showing MET expression in HER2 3+ breast cancer tissues. **c,** Immunoblots showing the effect of lapatinib (1μM) in the presence and absence of NRG1 (50ng/mL, 2h) on AKT and ERK phosphorylation. Cells were co-treated with erlotinib (0.5μM) as indicated. Lap: lapatinib, Erl: erlotinib.




**Supplemental Figure 8.**
**a,** Illustration depicting the analysis of 446 tested secreted factors on PLX4032 sensitivity in SK-MEL-28 cells. **b,** Summary of the results from the analysis of 446 tested secreted factors on 5μM PLX4032 treated SK-MEL-28 cells in the presence of 50ng/mL ligand (72h). Graph represents the ligands form the original analysis and newly identified soluble factors that rescued SK-MEL-28 cells from PLX4032 sensitivity. Graph shows the average value of two biological replicates.




**Supplemental Figure 9.**

**a,** Cell viability assay demonstrating suppression of cell proliferation in two *BRAF* mutant cell lines following treatment with PLX4032 (72h). Cells were co-treated with 50ng/mL RTK ligand and crizotinib (Criz, 0.5μM) as indicated. Graphs show average values of technical duplicates from one representative experiment out of two independent experiments. **b,** Syto 60 cell staining of A375, 624MEL and 928MEL *BRAF* mutant melanoma cell lines treated with either PLX4032 (5μM) and/or crizotinib (1μM) as indicated. Cells were treated twice weekly for the indicated times. Images are representative of three biological replicates and values indicate mean +/- s.d.

## 928MEL

### Study data with Control Antibody

| Group # | Antibody Treatment | SMI Treatment | Dose (mg/kg) | Regimen | %TGI days | %TGI (AUC/Day) | lower CI | upper CI | PR | CR | Max %BW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | - | 10 | QW | 28 | 0 | 0 | 0 | 0 | 0 | -13.2 |
| 2 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) | 10 + 50 | QW, BID | 28 | 131 | 103 | 172 | 1 | 0 | -5.48 |
| 3 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | GDC-0712 (100 mg/kg, PO, QD) | 10 + 100 | QW, QD | 28 | 53 | -3 | 92 | 0 | 0 | -8.36 |
| 4 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD) | 10 + 50 + 100 | QW, BID, QD | 28 | 164 | 132 | 216 | 8 | 0 | -5.36 |

### Study data with Anti-MET agonist Antibody

| Group # | Antibody Treatment | SMI Treatment | Dose (mg/kg) | Regimen | %TGI days | %TGI (AUC/Day) | lower CI | upper CI | PR | CR | Max %BW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | - | 10 + 50 | QD | 28 | 0 | 0 | 0 | 0 | 0 | -16 |
| 6 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) | 10 + 100 | QD | 28 | 39 | -14 | 70 | 0 | 0 | -14.9 |
| 7 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | GDC-0712 (100 mg/kg, PO, QD) | 10 + 50 + 100 | BID, QD | 28 | 56 | 13 | 82 | 0 | 0 | -12.5 |
| 8 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD) | 10 + 50 | BID, QD | 28 | 147 | 129 | 178 | 10 | 0 | -10.6 |

## 624MEL

### Study data with Control Antibody

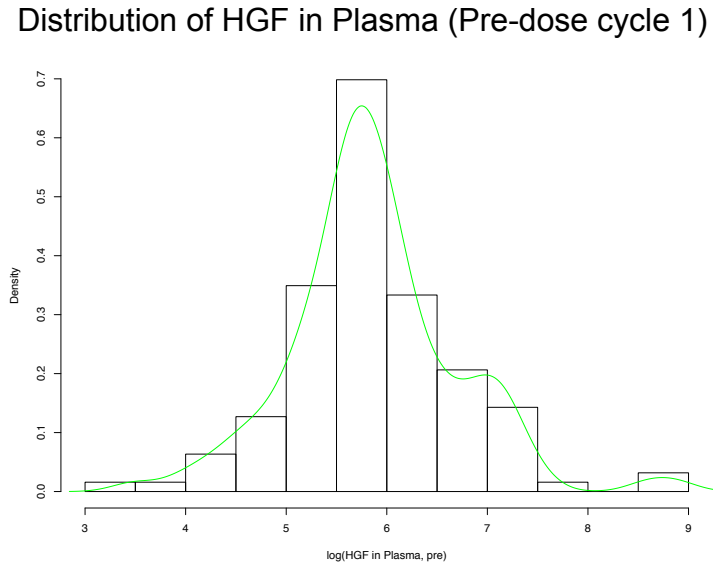
| Group # | Antibody Treatment | SMI Treatment | Dose (mg/kg) | Regimen | %TGI days | %TGI (AUC/Day) | lower CI | upper CI | PR | CR | Max %BW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | - | 10 | QW | 29 | 0 | 0 | 0 | 0 | 0 | -12.4 |
| 2 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) | 10 + 50 | QW, BID | 29 | 51 | 29 | 67 | 0 | 0 | -4.05 |
| 3 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | GDC-0712 (100 mg/kg, PO, QD) | 10 + 100 | QW, QD | 29 | 37 | 10 | 57 | 0 | 0 | -11.6 |
| 4 | Anti-gp120 isotype control Ab (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD) | 10 + 50 + 100 | QW, BID, QD | 29 | 81 | 72 | 89 | 0 | 0 | -3.34 |

### Study data with Anti-MET agonist Antibody

| Group # | Antibody Treatment | SMI Treatment | Dose (mg/kg) | Regimen | %TGI days | %TGI (AUC/Day) | lower CI | upper CI | PR | CR | Max %BW |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | - | 10 + 50 | QD | 29 | 0 | 0 | 0 | 0 | 0 | -9.14 |
| 6 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) | 10 + 100 | QD | 29 | 27 | -7 | 50 | 0 | 0 | -8.99 |
| 7 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | GDC-0712 (100 mg/kg, PO, QD) | 10 + 50 + 100 | BID, QD | 29 | 38 | 10 | 56 | 0 | 0 | -10.4 |
| 8 | 3D6.16.6 (MET:1580) (10 mg/kg, IP, QW) | PLX4032 (50 mg/kg, PO, BID) + GDC-0712 (100 mg/kg, PO, QD) | 10 + 50 | BID, QD | 29 | 73 | 58 | 83 | 0 | 0 | -5.5 |

**Supplemental Figure 10.**
Tables summarizing results from the 928MEL and 624MEL xenograft studies.

a

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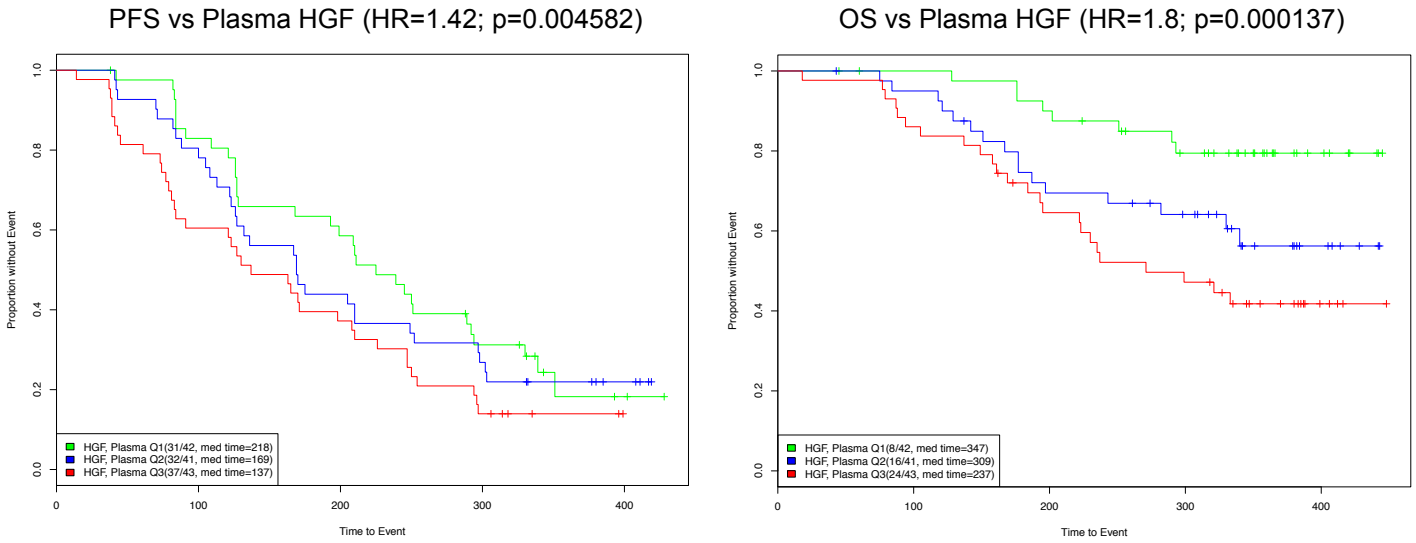
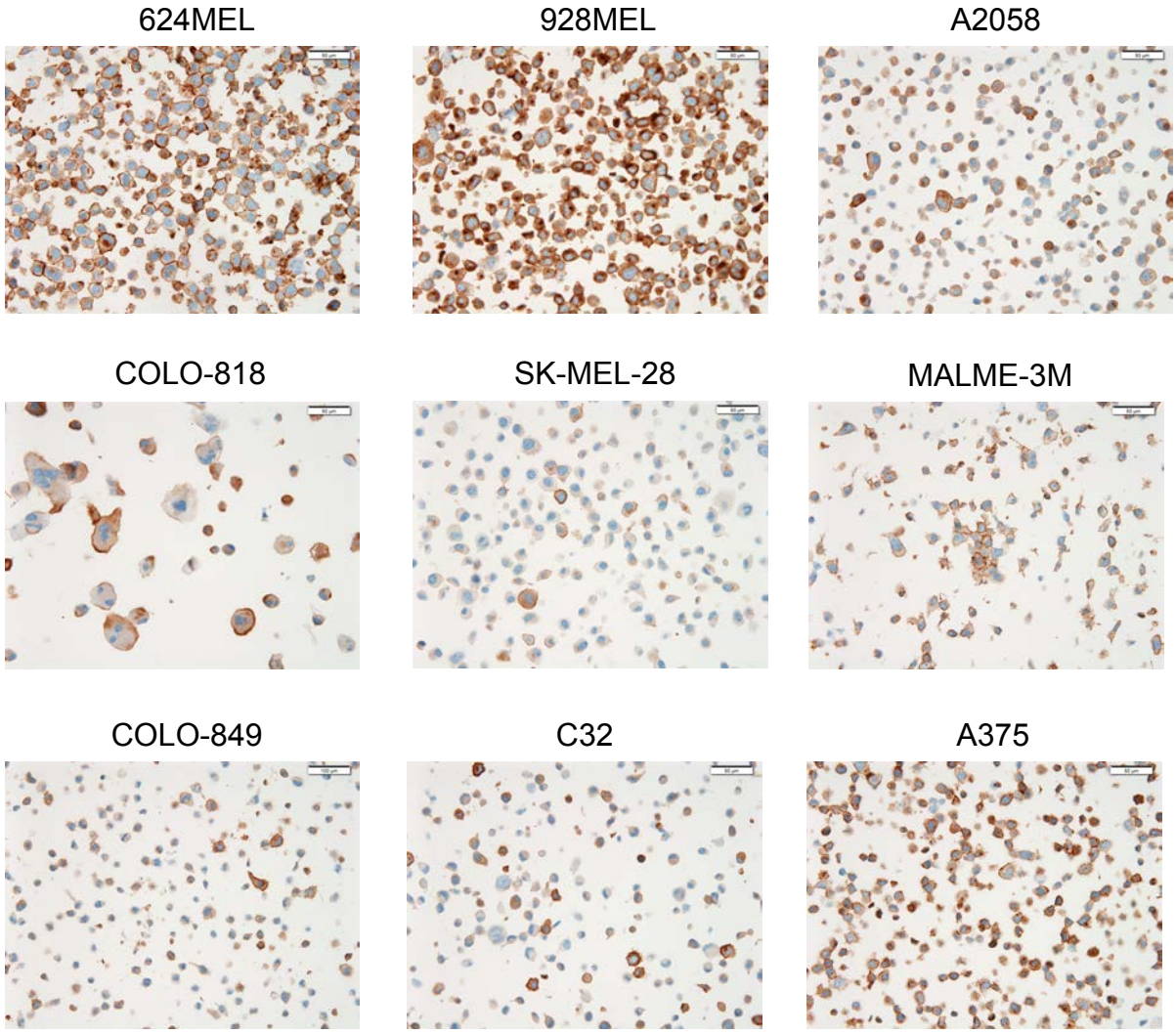


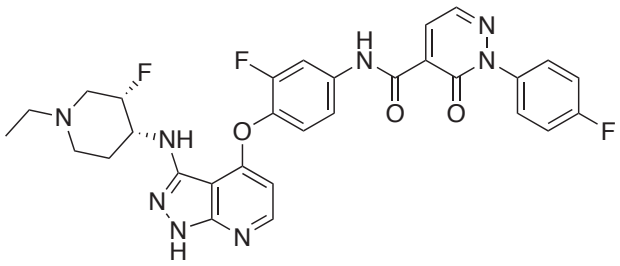

**Supplemental Figure 11.**

**a,** Histogram (black) showing the frequency distribution of the log (HGF) levels, with empirical density (green) superimposed, from 126 metastatic melanoma patients enrolled on the BRIM2 trial, pre-dose cycle 1 (Kolmogorov-Smirnoff p-value for departures from normality is 0.18). **b,** Progression free survival (PFS) and overall survival (OS) in metastatic melanoma patients treated with PLX4032. Patients were stratified into three groups based on their plasma HGF level (green is low (Q1), blue is intermediate (Q2), and red is high (Q3). Number of events/patients and medium time to event is shown for each group. The cox-proportional model of the outcome on the continuous outcome was used to calculate the hazard ratio and corresponding p-value.




**Supplemental Figure 12.**
"IHC" staining of MET protein in *BRAF* mutant melanoma cancer cells grown in culture.

a



b

| Enzyme Assay | |
|---|---|
| Kinase | $IC_{50}$ (μM) |
| cMet | 0.005 |
| Mer | 0.004 |
| HIPK4 | 0.005 |
| Rse | 0.017 |
| MuSK | 0.036 |

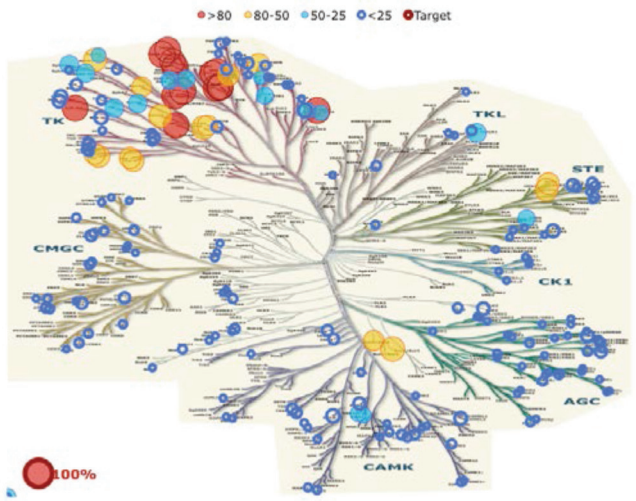
c

| Cell Assay | | |
|---|---|---|
| Kinase | Assay (Cell Line) | $IC_{50}$ (μM) |
| cMet | Autophos ELISA (MKN45) | 0.014 |
| KDR | Autophos ELISA (CHO-KDR) | 0.43 |
| Axl | Autophos MSD (A172) | 0.0017 |
| TrkA | Autophos MSD (CHO-TrkA) | 0.034 |
| TrkB | AutophosELISA (CHO-TrkB) | 0.07 |

d

| Selectivity Profiling | |
|---|---|
| Kinase | Percent Inhibition @ 0.1 μM |
| Mer | 96 |
| HIPK4 | 93 |
| Met | 92.75 |
| Axl | 90 |
| Flt3 | 88 |
| Ros | 82 |
| TrkC | 80 |
| TrkA | 71.5 |
| Rse | 70 |
| Lck | 66 |
| Met(1250T) | 66 |
| MuSK | 65 |
| TrkB | 64 |
| Ron | 56 |
| B-Raf | 52.5 |

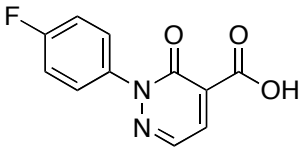
e



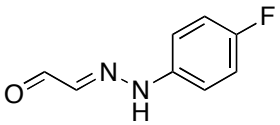

**Supplemental Figure 13.**
**a,** Structure of GDC-0712. **b,** Enzyme IC50s for cMet and selected kinases. cMet potency was determined using phosphorylation of poly(Glu,Tyr) by activated cMet kinase domain, with detection by ELISA. Data is geometric mean of multiple determinations (n=5). Other kinase assays were carried out using Invitrogen SelectScreen service according to Invitrogen standard protocols. All IC50s were determined with [ATP] at approximate values for Km. **c,** Potency and selectivity of GDC-0712 against selected RTKs in cell-based assays. All assays measured RTK autophosphorylation in the cell lines specified in the table, following 2-hour incubation with compound in the presence of 10% FBS. **d,** Kinase selectivity profiling data. GDC-0712 was assayed at 0.1 μM against a panel of 210 kinases using Invitrogen SelectScreen service. All kinases with >50% inhibition are listed. **e,** Graphic representation of GDC-0712 kinase selectivity. Percent inhibition of specific kinases at 0.1 μM compound is represented by size and color of circles overlaid on the human kinome.

**Supplemental Methods: GDC-0712 synthesis and physical characterisation.**

GDC-0712 (N-(4-(3-((3S,4R)-1-ethyl-3-fluoropiperidin-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide) (according to the procedures described in international patent application WO2007103308 A2):

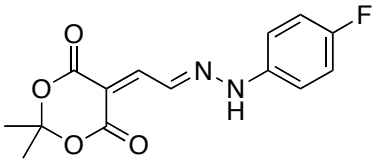


Preparation of **2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-carboxylic acid**.



Step A: Preparation of **(E)-2-(2-(4-fluorophenyl)hydrazono)acetaldehyde**:

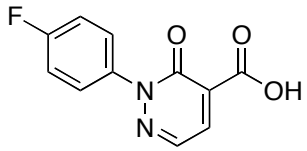
A mixture of 1-(4-fluorophenyl)hydrazine hydrochloride (5.0 g, 30.75 mmol), water (20 mL), and acetic acid (20 mL) was added with stirring to a 40% aqueous solution of glyoxal (17.6 mL, 153.8 mmol) over 20 minutes. Stirring was continued for 2 hours and the mixture was then filtered. The precipitate was washed with water and dried to afford 5.0 g (98%) of the desired product. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, 1H), 8.63 (br s, 1H), 7.24 (m, 1H), 7.16 (m, 2H), 7.06 (m, 2H); $^{19}$F NMR (376 MHz, CDCh) δ-120.3. LRMS (ESI pos) m/e 151.1 (M-16).



Step B: Preparation of **(E)-5-(2-(2-(4-fluorophenyl)hydrazono)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione**:

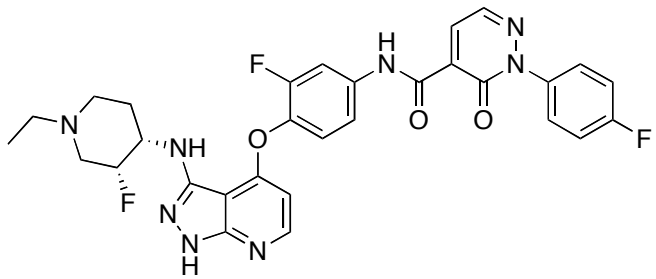
A suspension of dioxan-dione (1.44 g, 10.0 mmol) and (E)-2-(2-(4-fluorophenyl)hydrazono)acetaldehyde (1.66 g, 10.0 mmol) in toluene (15 mL) was treated with acetic acid (5 drops) and piperidine (5 drops). The reaction mixture was then stirred at room temp for 17 hours. The precipitated condensation product was filtered and thoroughly washed with light petroleum to afford 2.87 g (98%) of the desired product. $^{1}$H

NMR (400 MHz, $CD_3OD/CDCl_3$) δ 8.72 (d, 1H), 8.24 (d, 1H), 7.32 (m, 2H), 7.08 (t, 2H), 1.76 (s, 6H); $^{19}$FNMR (376 MHz, $CDCl_3$) δ -119.1.

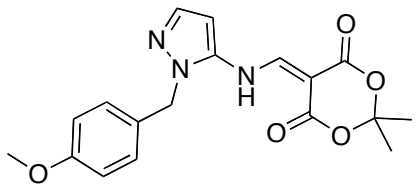


Step C: Preparation of **2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazin-4-carboxylic acid**:

A mixture of (E)-5-(2-(2-(4-fluorophenyl)hydrazono)ethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (0.60 g, 2.05 mmol) and NaOMe (0.133 g, 2.46 mmol) in MeOH (10 mL) was heated under reflux for 15 hours. The salt was treated with cold 1N HCl solution, extracted with DCM, dried over $MgSO_4$, and concentrated to afford 0.42 g (87%) of the desired product. $^1$H NMR (400 MHz, $CDCl_3$) δ 13.57 (br s, 1H), 8.29 (m,2H), 7.63 (m, 2H), 7.24 (m, 2H); $^{19}$F NMR (376 MHz, $CDCl_3$) δ-110.7. LRMS (ESI pos) m/e 235.1 (M+1).



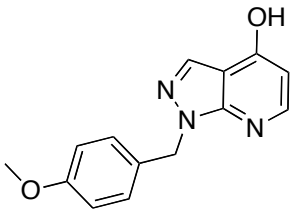
Preparation of **±N-(4-(3-((3R,4S)-1-ethyl-3-fluoropiperidin-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide**.



Step A: Preparation of **5-((1-(4-methoxybenzyl)-1H-pyrazol-5-ylamino)methylene)-2,2- dimethyl-1,3-dioxane-4,6-dione**:

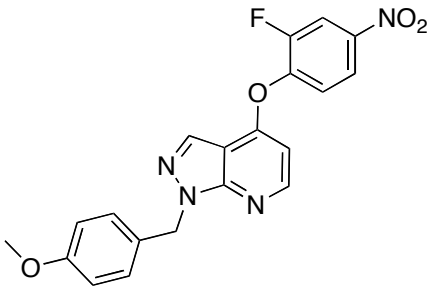
A stirred mixture of triethoxymethane (339 mL, 2037 mmol), and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (35.2 g, 244 mmol) was heated to 80°C for 1 hour. A suspension of 1-(4-methoxybenzyl)-1H-pyrazol-5-amine [41.4 g, 204 mmol; prepared

according to the procedure described previously[29], except desalting was performed as follows: 1-(4-methoxybenzyl)-lH-pyrazol-5-amine hydrochloride (44 g) was partitioned between MTBE (300 mL) and 1N aqueous NaOH (300 mL), after separating the phases, the aqueous suspension was re-extracted with MTBE (8 x 100 mL), followed by drying ($Na_2SO_4$) the combined organic phases, and concentration in vacuo to obtain the free-based 1-(4-methoxybenzyl)-lH-pyrazol-5-amine (30 g)] in triethoxymethane (339 mL, 2037 mmol) was added at once and heating at 80°C was continued for 18 hours under $N_2$. After cooling to room temperature, toluene azeotrope (2 x 200 mL) was utilized to remove EtOH. The resulting suspension was diluted with diethyl ether (500 mL) and filtered to obtain a yellow solid (33.5 g, 46%). $^1$H NMR (400 MHz, $CDCl_3$) δ 11.13 (d, *J*=13 Hz, 1H), 8.26 (d, *J*=13 Hz, 1H), 7.50 (d, *J*=2 Hz, 1H), 7.25 (d, *J*=9 Hz, 2H), 6.88 (d, *J*=9 Hz, 2H), 6.21 (d, *J*=2 Hz, 1H), 5.28 (s, 2H), 3.78 (s, 3H), 1.74 (s, 6H).



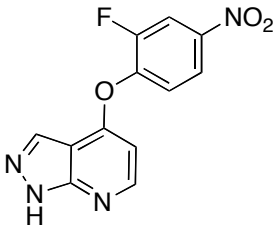

Step B: Preparation of **l-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridin-4-ol**:

To a stirred biphenyl-diphenyl ether eutectic (also called Dowtherm) (100 mL) at 240°C under $N_2$ was added 5-((1-(4-methoxybenzyl)-1H-pyrazol-5-ylamino)methylene)-2,2-dimethyl-1,3-dioxane-4,6-dione (33.5 g, 93.7 mmol) in portions as a solid over a 10 minute period. After addition was complete, the mixture was heated at 240°C for 10 minutes. After cooling to room temperature, the mixture was diluted with hexanes (300 mL), and the hexanes were decanted along with the majority of the Dowtherm. The remaining residue was diluted with diethyl ether (200 mL), and the ether was decanted from the residue and discarded. Lastly the residue was suspended in DCM (100 mL). The stirred suspension was diluted with diethyl ether (300 mL) and filtered. The resulting off-white solid (22.7 g, 91%) was dried under high vacuum. $^1$H NMR (400 MHz, DMSO-d6) δ 11.7 (br s, 1H), 8.17 (br s, 1H), 8.08 (s, 1H), 7.20 (d, *J*=9 Hz, 2H), 6.86 (d, *J*=9 Hz, 2H), 6.45 (br s, lH), 5.50 (s, 2H), 3.70 (s, 3H).



Step C: Preparation of **4-(2-fluoro-4-nitrophenoxy)-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine**:

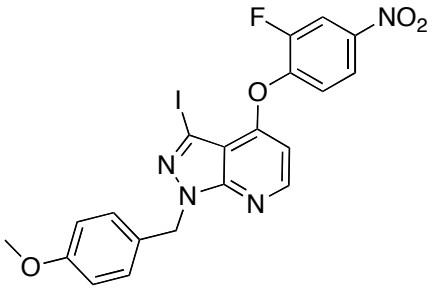
A stirred mixture of 1-(4-methoxybenzyl)-1H-pyrazolo[3,4-b]pyridin-4-ol (22.00 g, 86.18 mmol) cesium carbonate (28.08 g, 86.18 mmol), 1,2-difluoro-4-nitrobenzene (13.71 g, 86.18 mmol) and DMA (100 mL) was heated to 100°C for 1 hour. After cooling to room temperature, the mixture was partitioned between DCM (500 mL) and water (500 mL). The phases were separated, and the organic phase was washed with water (3 x 200 mL), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The resulting residue was triturated with diethyl ether (100 mL) and hexanes (200 mL) co-solvent, and the resulting beige powder was filtered. A second crop was obtained after cooling in a -10°C freezer overnight. The two crops were combined (28 g, 82%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, *J*=5.5 Hz, 1H), 8.16 (m, 2H), 7.86 (s, 1H), 7.39 (m, I H), 7.35 (d, *J*=8.6 Hz, 2H), 6.84 (d, *J*=8.2 Hz, 2H), 6.48 (d, *J*=5.5 Hz, lH), 5.65 (s, 2H), 3.76 (s, 3H). $^{19}$F NMR (376 MHz, $CDC1_3$) δ -124.2 (m).



Step D: Preparation of **4-(2-fluoro-4-nitrophenoxy)-1H-pyrazolo[3,4-b]pyridine**:

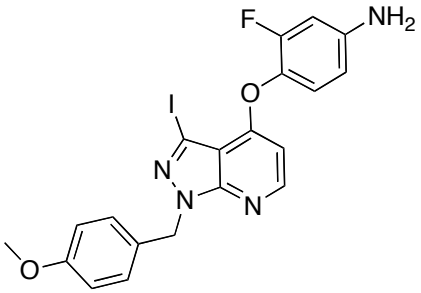
A stirred mixture of 4-(2-fluoro-4-nitrophenoxy)-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (27.6 g, 70.0 mmol) and TFA (53.9 mL, 700 mmol) was heated to reflux for 18 hours under $N_2$. The reaction was allowed to cool to room temperature, and then concentrated in vacuo using toluene (4 x 100 mL) to azeotrope residual TFA. The residue was diluted with EtOAc (200 mL) and carefully neutralized (pH = 8-9) with saturated aqueous $NaHCO_3$ (100 mL). The biphasic suspension was stirred at room temperature for

30 minutes. The suspension was filtered. The resulting solid was dried by toluene azeotrope (2 x 200 mL) to obtain the product (18.7 g, 97%). $^1$H NMR (DMSO-d6, 400 MHz) δ 13.85 (br s, 1H), 8.40 (m, 2H), 8.15 (m, 1H), 7.91 (s, 1H), 7.66 (m, 1H), 6.65 (m, 1H).

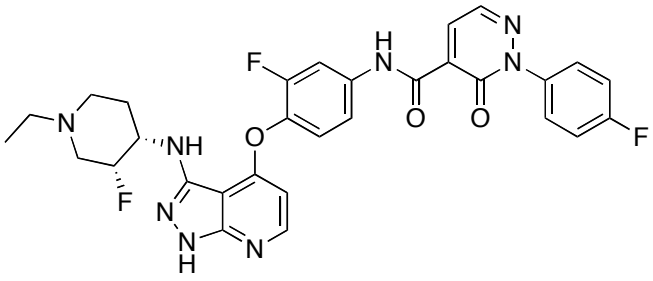



Step E: Preparation of **4-(2-fluoro-4-nitrophenoxy)-3-iodo-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine**:

To a stirred solution of 4-(2-fluoro-4-nitrophenoxy)-1H-pyrazolo[3,4-b]pyridine (16.7 g, 60.9 mmol) in DMF (250 mL) was added freshly ground potassium hydroxide (10.3 g, 183 mmol) followed by iodine (23.2 g, 91.4 mmol) under $N_2$ at room temperature. The dark reaction was stirred at room temperature for 18 hours, covered by a foil to minimize light exposure. The reaction was then heated to 50°C for 3 hours. The reaction was allowed to cool to room temperature. The crude reaction mixture was transferred via cannula into a stirred solution of 1-(chloromethyl)-4-methoxybenzene (11.1 g, 70.7 mmol) in DMF (100 mL) which was cooled in an ice bath under $N_2$. The reaction was allowed to stir for 18 hours under $N_2$ at room temperature. The mixture was then diluted with DCM (1L) and washed with 5% aqueous $Na_2S_2O_3$ (1L). The aqueous phase was back-extracted with DCM (2 x 200 mL). The combined organic phases were washed with water (4 x 500 mL), dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The resulting residue was triturated with DCM (100 mL), and the undissolved solid removed by filtration. The filtrate was purified by Biotage Flash 65, eluting with 10% EtOAc/hexanes, 20% EtOAclhexanes, then 30% EtOAc/hexanes to elute the desired product. The ·product was obtained as a pale yellow solid (16.6 g, 47%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.42 (d, *J*=6 Hz, lH), 8.16 (m, 2H), 7.38 (d, *J*=9 Hz, 2H), 7.3.4 (m, 1H), 6.84 (d, *J*=9 Hz, 2H), 6.36 (d, *J*=6 Hz, IH), 5.63 (s, 2H), 3.77 (s, 3H).



Step F: Preparation of 3-fluoro-4-(3-iodo-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yloxy)aniline: A stirred mixture of 4-(2-fluoro-4-nitrophenoxy)-3-iodo-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridine (10.4 g, 20.0 mmol), stannous chloride-dihydrate (22.6 g, 100.0 mmol), and absolute EtOH (200 mL) was heated to 65°C for 1.5 hours under $N_2$. After cooling to room temperature, the reaction was concentrated in vacuo, and then diluted with DCM (1.00 mL) and water (100 mL). Aqueous 2N NaOH was added until the pH of the aqueous phase was in the 11-12 range. The biphasic suspension was filtered through a pad of celite, rinsing with DCM (3 x 100 mL). The filtered biphase was separated, and the aqueous phase was re-extracted with DCM (3 x 75 mL). The combined organic phases were dried ($Na_2SO_4$), filtered, and concentrated. Yield: 7.90 g, 78%. The product was used in the next step without purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J*=6 Hz, 1H), 7.35 (d, *J*=9 Hz, 2H), 7.03 (t, *J*=9 Hz, lH), 6.83 (d, *J*=9 Hz, 2H), 6.53 (m, 2H), 6.24 (m, 1H), 5.61 (s, 2H), 3.81 (s, 2H), 3.76 (s, 3H).



Step G: Preparation of **±N-(4-(3-((3R,4S)-1-ethyl-3-fluoropiperidin-4-ylamino)-1H-pyrazolo[3,4-b]pyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide**:

A mixture of 3-fluoro-4-(3-iodo-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yloxy)aniline (0.123 g, 0.25 mmol), ±(3S,4R)-tert-butyl 4-amino-3-fluoropiperidine-1-carboxylate (0.164 g, 0.750 mmol, prepared according to WO 2006/087543), copper(I) iodide (0.00952 g, 0.0500 mmol), (S)-pyrrolidine-2-carboxylic acid (0.0115 g, 0.100

mmol), $K_2CO_3$ (0.173 g, 1.25 mmol), and DMSO (1 mL) was stirred at 100°C for 3 days. The reaction was partitioned between EtOAc and water. The phases were separated and the aqueous phase was re-extracted with EtOAc (5 mL). The combined organic phases were washed with water, dried ($Na_2SO_4$), filtered, and concentrated. The crude was purified by preparative TLC (1 mm thickness, Rf=0.56) eluting with 10% MeOH/$CHCl_3$ (LRMS (APCI+): m/z 581 (M+ 1) detected). The purified material ((3*R*,4*S*)-*tert*-butyl 4-(4-(4-amino-2-fluorophenoxy)-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-ylamino)-3-fluoropiperidine-1-carboxylate) was then added to a reaction mixture containing EDCI (43.6 mg, 0.227 mmol), 2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid (53.2 mg, 0.227 mmol), HOBt-hydrate (34.8 mg; 0.227 mmol) and DIEA (0.0792 ml, 0.455 mmol) in DCM (1 mL) at ambient temperature that had been stirring for 15 min. The resulting solution was stirred for 18 hours at ambient temperature. To a separate 1 dram vial was added an additional equivalent of the 2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxylic acid, HOBt, DIEA, and EDCI in DCM (0.5 mL). This mixture was stirred for 15 minutes, then added to the original reaction mixture, which was stirred for an additional day at ambient temperature. The crude reaction mixture was loaded directly on to a preparative TLC plate (2 mm thickness) and eluted with 10% MeOH/DCM (Rf.=0.70). A second preparative TLC plate (1 mm thickness, Rf=0.17) eluting with 1:1 EtOAc/hexanes was utilized to obtain pure product ((3*R*,4*S*)-*tert*-butyl 3-fluoro-4-(4-(2-fluoro-4-(2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamido)phenoxy)-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-ylamino)piperidine-1-carboxylate, 35 mg, 39%). Combined material (58 mg, 0.0728 mmol) from several reactions was then treated with 2,2,2-trifluoroacetic acid (0.280 ml, 3.64 mmol) and stirred for 5 minutes at room temperature under $N_2$. The mixture was concentrated in vacuo, using toluene to azeotrope (3 x 5 mL) residual TFA. The crude product was carried forward as a TFA salt without purification at this step and was combined with acetaldehyde (5 mg, 0.1 mmol), sodium triacetoxyborohydride (25 mg, 0.12 mmol), and DCM (0.5 mL) was stirred at room temperature for 18 hours. Water (5 mL) was added, and the aqueous layer was extracted with DCM (3 x 5 mL). The organic layers were combined and dried ($Na_2SO_4$). Concentrated and purified by preparative TLC, eluting with 5% MeOH (containing 7N $NH_3$) in $CHCl_3$ to give *N*-(4-(3-

((3*R*,4*S*)-1-ethyl-3-fluoropiperidin-4-ylamino)-1-(4-methoxybenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-4-yloxy)-3-fluorophenyl)-2-(4-fluorophenyl)-3-oxo-2,3-dihydropyridazine-4-carboxamide, Yield: 8 mg (14%). LRMS (APCI+): m/z 725 (M+1) detected. This material was combined with 2,2,2-trifluoroacetic acid (0.43 mL, 5.5 mmol) and heated to 80°C in a sealed vessel for 2 hours. The reaction was concentrated in vacuo, using toluene (2 x 5 mL) to azeotrope residual TFA. The resulting residue was dissolved in DCM, and purified by preparative TLC. The purified product was re-dissolved in DCM (1 mL) and acidified with 2N HCl in diethyl ether (0.5 mL). The solvent and excess HCl was removed in vacuo, using EtOH to azeotrope (3 x 5 mL). The product was obtained as a pale yellow powder (4 mg, 51%). HPLC: 95% purity (220 nm); LRMS (ESI+): 97% purity, 220 nm, m/z 605 (M+1) detected; $^{1}$H NMR (400 MHz, MeOD-d3) δ 11.98 (s, 1H), 8.35 (m, 3H), 8.09 (d, *J*=13 Hz, 1H), 7.67 (m, 2H), 7.53 (m, 2H), 7.29 (t, *J*=9 Hz, 2H), 6.42 (d, *J*=5 Hz, 1H), 5.37 (d, *J*=47 Hz, 1H), 4.26 (m, 1H), 3.97 (m, 1H), 3.66 (m, 1H), 3.52 (m, 1H), 3.28 (m, 2H), 2.34 (m, 2H), 1.39 (t, *J*=7 Hz, 3H).

## References

29 Misra, R. N. *et al.* 1H-Pyrazolo[3,4-b]pyridine inhibitors of cyclin-dependent kinases. *Bioorg Med Chem Lett* **13**, 1133-1136 (2003).

| Cat # | Product Name | Product Category | Manufacturer |
|---|---|---|---|
| 310-11 | 4-1BB Ligand | Human Growth Factors and Cytokines | Peprotech |
| 310-15 | 4-1BB Receptor | Human Growth Factors and Cytokines | Peprotech |
| 120-14 | Activin-A (Insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-15 | Activin-B (Insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-22 | AITRL | Human Growth Factors and Cytokines | Peprotech |
| 100-55B | Amphiregulin (98 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 130-06 | ANG-1 (HeLa cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 130-07 | ANG-2 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-10C | APRIL (insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 450-17 | Artemin | Human Neurotrophins | Peprotech |
| 310-13 | BAFF | Human Growth Factors and Cytokines | Peprotech |
| 310-13R | BAFF Receptor | Human Growth Factors and Cytokines | Peprotech |
| 300-47 | BCA-1/BLC (CXCL13) | Human Chemokines | Peprotech |
| 310-16 | BCMA | Human Growth Factors and Cytokines | Peprotech |
| 450-02 | BDNF | Human Neurotrophins | Peprotech |
| 450-01 | beta-NGF | Human Neurotrophins | Peprotech |
| 100-50 | Betacellulin | Human Growth Factors and Cytokines | Peprotech |
| 120-04 | BMP-13/CDMP-2 | Human Growth Factors and Cytokines | Peprotech |
| 120-02 | BMP-2 | Human Growth Factors and Cytokines | Peprotech |
| 120-24B | BMP-3 | Human Growth Factors and Cytokines | Peprotech |
| 120-05 | BMP-4 (HeLa cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-05ET | BMP-4 (truncated; E.coli derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-06 | BMP-6 (HEK 293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-03 | BMP-7 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
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| 300-55 | CXCL16 | Human Chemokines | Peprotech |
| 120-25 | CYR61 | Human Growth Factors and Cytokines | Peprotech |
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| 150-15 | E-Selectin (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-44 | EG-VEGF | Human Growth Factors and Cytokines | Peprotech |
| 100-15R | EGF Receptor (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
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| 300-22B | ENA-78/CXCL5 (8-78 a.a.) | Human Chemokines | Peprotech |
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| 100-18B | FGF-basic | Human Growth Factors and Cytokines | Peprotech |
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| 120-28 | GDF-15/MIC-1 (cell culture derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-07 | GDF-2 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
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| 450-37 | GMF-beta | Human Neurotrophins | Peprotech |
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| 300-40 | GRO-gamma (CXCL3) | Human Chemokines | Peprotech |
| 300-11 | GRO/MGSA (CXCL1) | Human Chemokines | Peprotech |
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| 100-39 | HGF (Insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
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| 300-46 | I-TAC (CXCL11) | Human Chemokines | Peprotech |
| 150-05 | ICAM-1 (CHO cell derived) | Human Growth Factors | Peprotech |

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|---|---|---|---|
| | | and Cytokines | |
| 300-02BC | IFN-beta (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 300-02 | IFN-gamma | Human Growth Factors and Cytokines | Peprotech |
| 300-02L | IFN-lambda 1 | Human Growth Factors and Cytokines | Peprotech |
| 300-02K | IFN-lambda 2 | Human Growth Factors and Cytokines | Peprotech |
| 300-02J | IFN-omega | Human Growth Factors and Cytokines | Peprotech |
| 350-10 | IGF-BP1 | Human Growth Factors and Cytokines | Peprotech |
| 350-06B | IGF-BP2 (insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-08 | IGF-BP3 | Human Growth Factors and Cytokines | Peprotech |
| 350-05B | IGF-BP4 (insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-05 | IGF-BP5 | Human Growth Factors and Cytokines | Peprotech |
| 350-07B | IGF-BP6 (insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 350-09 | IGF-BP7 | Human Growth Factors and Cytokines | Peprotech |
| 100-11 | IGF-I | Human Growth Factors and Cytokines | Peprotech |
| 100-12 | IGF-II | Human Growth Factors and Cytokines | Peprotech |
| 200-10 | IL-10 | Human Growth Factors and Cytokines | Peprotech |
| 200-11 | IL-11 | Human Growth Factors and Cytokines | Peprotech |
| 200-12 | IL-12p70 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 200-12p80H | IL-12p80 (insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 200-13 | IL-13 | Human Growth Factors and Cytokines | Peprotech |
| 200-13A | IL-13 Variant | Human Growth Factors and Cytokines | Peprotech |
| 200-15 | IL-15 | Human Growth Factors and Cytokines | Peprotech |
| 200-16A | IL-16 (121 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 200-16 | IL-16 (130 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 200-17 | IL-17A | Human Growth Factors and Cytokines | Peprotech |
| 200-28 | IL-17B | Human Growth Factors and Cytokines | Peprotech |
| 200-27 | IL-17D | Human Growth Factors and Cytokines | Peprotech |
| 200-24 | IL-17E | Human Growth Factors and Cytokines | Peprotech |

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| 200-25 | IL-17F | Human Growth Factors and Cytokines | Peprotech |
| 200-19 | IL-19 | Human Growth Factors and Cytokines | Peprotech |
| 200-01A | IL-1alpha | Human Growth Factors and Cytokines | Peprotech |
| 200-01B | IL-1beta | Human Growth Factors and Cytokines | Peprotech |
| 200-01RA | IL-1RA | Human Growth Factors and Cytokines | Peprotech |
| 200-02 | IL-2 | Human Growth Factors and Cytokines | Peprotech |
| 200-20 | IL-20 | Human Growth Factors and Cytokines | Peprotech |
| 200-21 | IL-21 | Human Growth Factors and Cytokines | Peprotech |
| 200-22 | IL-22 | Human Growth Factors and Cytokines | Peprotech |
| 200-23 | IL-23 (insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 200-03 | IL-3 | Human Growth Factors and Cytokines | Peprotech |
| 200-31 | IL-31 | Human Growth Factors and Cytokines | Peprotech |
| 200-33 | IL-33 | Human Growth Factors and Cytokines | Peprotech |
| 200-34 | IL-34 (HEK293 cells) | Human Growth Factors and Cytokines | Peprotech |
| 200-04 | IL-4 | Human Growth Factors and Cytokines | Peprotech |
| 200-05 | IL-5 | Human Growth Factors and Cytokines | Peprotech |
| 200-06 | IL-6 | Human Growth Factors and Cytokines | Peprotech |
| 200-07 | IL-7 | Human Growth Factors and Cytokines | Peprotech |
| 200-08M | IL-8 (72 a.a.) (CXCL8) | Human Chemokines | Peprotech |
| 200-08 | IL-8 (77 a.a.) (CXCL8) | Human Chemokines | Peprotech |
| 200-09 | IL-9 | Human Growth Factors and Cytokines | Peprotech |
| 300-12 | IP-10 (CXCL10) | Human Chemokines | Peprotech |
| 100-19 | KGF (FGF-7) | Human Growth Factors and Cytokines | Peprotech |
| 100-53 | KLOTHO (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 300-58 | LAG-1 (CCL4L1) | Human Chemokines | Peprotech |
| 300-56 | LD78-beta (CCL3L1) | Human Chemokines | Peprotech |
| 300-44 | LEC/NCC-4 (CCL-16) | Human Chemokines | Peprotech |
| 300-27 | Leptin | Human Growth Factors and Cytokines | Peprotech |
| 310-09B | LIGHT (Insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 300-20 | Lymphotactin (XCL1) | Human Chemokines | Peprotech |
| 300-25 | M-CSF | Human Growth Factors | Peprotech |

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| | | and Cytokines | |
| 450-06 | MANF | Human Neurotrophins | Peprotech |
| 130-12 | Maspin | Human Growth Factors and Cytokines | Peprotech |
| 300-04 | MCP-1/MCAF (CCL2) | Human Chemokines | Peprotech |
| 300-15 | MCP-2 (CCL8) | Human Chemokines | Peprotech |
| 300-17 | MCP-3 (CCL7) | Human Chemokines | Peprotech |
| 300-24 | MCP-4 (CCL13) | Human Chemokines | Peprotech |
| 300-36 | MDC (67 a.a.) (CCL22) | Human Chemokines | Peprotech |
| 300-36A | MDC (69 a.a.) (CCL22) | Human Chemokines | Peprotech |
| 300-57 | MEC (CCL28) | Human Chemokines | Peprotech |
| 130-01 | MIA | Human Growth Factors and Cytokines | Peprotech |
| 130-02 | MIA-2 | Human Growth Factors and Cytokines | Peprotech |
| 450-16 | Midkine | Human Neurotrophins | Peprotech |
| 300-26 | MIG (CXCL9) | Human Chemokines | Peprotech |
| 300-08 | MIP-1alpha (CCL3) | Human Chemokines | Peprotech |
| 300-09 | MIP-1beta (CCL4) | Human Chemokines | Peprotech |
| 300-29 | MIP-3 (CCL23) | Human Chemokines | Peprotech |
| 300-29A | MIP-3alpha (CCL20) | Human Chemokines | Peprotech |
| 300-29B | MIP-3beta (CCL19) | Human Chemokines | Peprotech |
| 300-34 | MIP-4 (CCL18) | Human Chemokines | Peprotech |
| 300-43 | MIP-5 (CCL15) | Human Chemokines | Peprotech |
| 120-00 | Myostatin | Human Growth Factors and Cytokines | Peprotech |
| 120-12 | Myostatin Propeptide | Human Growth Factors and Cytokines | Peprotech |
| 300-14 | NAP-2 (CXCL7) | Human Chemokines | Peprotech |
| 450-36D | Neuritin | Human Neurotrophins | Peprotech |
| 450-11 | Neurturin | Human Neurotrophins | Peprotech |
| 450-18 | NNT-1/BCSF-3 | Human Growth Factors and Cytokines | Peprotech |
| 120-10C | NOGGIN (293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-26 | NOV | Human Growth Factors and Cytokines | Peprotech |
| 450-03 | NT-3 | Human Neurotrophins | Peprotech |
| 450-04 | NT-4 | Human Neurotrophins | Peprotech |
| 300-10T | Oncostatin-M (209 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 300-10 | Oncostatin-M (227 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 450-14 | Osteoprotegerin | Human Growth Factors and Cytokines | Peprotech |
| 130-03 | OTOR | Human Growth Factors and Cytokines | Peprotech |
| 310-28 | OX40 Ligand (Insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-13A | PDGF-AA | Human Growth Factors and Cytokines | Peprotech |
| 100-00AB | PDGF-AB | Human Growth Factors and Cytokines | Peprotech |
| 100-14B | PDGF-BB | Human Growth Factors | Peprotech |

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| | | and Cytokines | |
| 100-00CC | PDGF-CC | Human Growth Factors and Cytokines | Peprotech |
| 150-06 | PECAM-1 (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 130-13 | PEDF | Human Growth Factors and Cytokines | Peprotech |
| 450-12 | Persephin | Human Neurotrophins | Peprotech |
| 300-16 | PF-4 (CXCL4) | Human Chemokines | Peprotech |
| 450-15 | Pleiotrophin | Human Neurotrophins | Peprotech |
| 100-06 | PlGF-1 | Human Growth Factors and Cytokines | Peprotech |
| 100-56 | PlGF-2 | Human Growth Factors and Cytokines | Peprotech |
| 100-57 | PlGF-3 | Human Growth Factors and Cytokines | Peprotech |
| 100-46 | Prokineticin-2 | Human Growth Factors and Cytokines | Peprotech |
| 100-07 | Prolactin | Human Growth Factors and Cytokines | Peprotech |
| 100-09 | PTHrP | Human Growth Factors and Cytokines | Peprotech |
| 300-06 | RANTES (CCL5) | Human Chemokines | Peprotech |
| 130-15 | Relaxin-2 | Human Growth Factors and Cytokines | Peprotech |
| 130-10 | Relaxin-3 | Human Growth Factors and Cytokines | Peprotech |
| 450-22 | RELM-beta | Human Growth Factors and Cytokines | Peprotech |
| 450-19 | Resistin | Human Growth Factors and Cytokines | Peprotech |
| 310-29 | sCD100 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 110-01 | sCD14 (293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-26 | sCD23 | Human Growth Factors and Cytokines | Peprotech |
| 310-30 | sCD27 Ligand (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 450-42 | sCD30 Ligand (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-31 | sCD34 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-02 | sCD40 Ligand | Human Growth Factors and Cytokines | Peprotech |
| 300-07 | SCF | Human Growth Factors and Cytokines | Peprotech |
| 100-22A | SCGF-alpha | Human Growth Factors and Cytokines | Peprotech |
| 100-22B | SCGF-beta | Human Growth Factors and Cytokines | Peprotech |
| 300-28A | SDF-1alpha (CXCL12) | Human Chemokines | Peprotech |
| 300-28B | SDF-1beta (CXCL12) | Human Chemokines | Peprotech |
| 140-08 | sDLL-1 (HEK293 cell derived) | Human Growth Factors | Peprotech |

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| | | and Cytokines | |
| 140-07 | sDLL-4 (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-03H | sFas Ligand (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-20 | sFas Receptor | Human Growth Factors and Cytokines | Peprotech |
| 120-29 | sFRP-1 (HeLa cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 200-02R | sIL-2Ralpha (Insect cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 200-04R | sIL-4Ralpha (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 200-06R | sIL-6Ralpha (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 150-11 | Slit2-N (HEK293 cell derived) | Human Neurotrophins | Peprotech |
| 100-45 | Sonic Hedgehog | Human Growth Factors and Cytokines | Peprotech |
| 120-36 | SPARC/Osteonectin (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 310-01 | sRANK Ligand | Human Growth Factors and Cytokines | Peprotech |
| 310-08 | sRANK Receptor | Human Growth Factors and Cytokines | Peprotech |
| 310-07 | sTNF-receptor Type I | Human Growth Factors and Cytokines | Peprotech |
| 310-12 | sTNF-receptor Type II | Human Growth Factors and Cytokines | Peprotech |
| 310-18 | sTRAIL receptor-1 | Human Growth Factors and Cytokines | Peprotech |
| 310-19 | sTRAIL receptor-2 | Human Growth Factors and Cytokines | Peprotech |
| 310-04 | sTRAIL/Apo2L | Human Growth Factors and Cytokines | Peprotech |
| 310-17 | TACI | Human Growth Factors and Cytokines | Peprotech |
| 300-63 | TAFA-2 | Human Growth Factors and Cytokines | Peprotech |
| 300-30 | TARC (CCL17) | Human Chemokines | Peprotech |
| 300-45 | TECK (CCL25) | Human Chemokines | Peprotech |
| 300-60 | TFF-1 | Human Growth Factors and Cytokines | Peprotech |
| 300-59 | TFF-2 | Human Growth Factors and Cytokines | Peprotech |
| 300-61 | TFF-3 | Human Growth Factors and Cytokines | Peprotech |
| 100-16A | TGF-alpha | Human Growth Factors and Cytokines | Peprotech |
| 100-21 | TGF-beta1 (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-35B | TGF-beta2 (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-36E | TGF-beta3 | Human Growth Factors and Cytokines | Peprotech |
| 310-23 | TL-1A | Human Growth Factors | Peprotech |

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| | | and Cytokines | |
| 160-01 | TLR-3 (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 300-01A | TNF-alpha | Human Growth Factors and Cytokines | Peprotech |
| 300-01B | TNF-beta | Human Growth Factors and Cytokines | Peprotech |
| 300-18 | TPO | Human Growth Factors and Cytokines | Peprotech |
| 120-09 | TSG | Human Growth Factors and Cytokines | Peprotech |
| 300-62 | TSLP | Human Growth Factors and Cytokines | Peprotech |
| 310-06 | TWEAK | Human Growth Factors and Cytokines | Peprotech |
| 310-21 | TWEAK Receptor | Human Growth Factors and Cytokines | Peprotech |
| 150-16 | VAP-1 (CHO cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 130-11 | Vaspin | Human Growth Factors and Cytokines | Peprotech |
| 150-04 | VCAM-1 (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-20A | VEGF-A (121 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 100-20 | VEGF-A (165 a.a.) | Human Growth Factors and Cytokines | Peprotech |
| 100-20B | VEGF-B | Human Growth Factors and Cytokines | Peprotech |
| 100-20C | VEGF-C (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 100-20D | VEGF-D (HEK293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 130-09 | Visfatin | Human Growth Factors and Cytokines | Peprotech |
| 120-18 | WISP-1 | Human Growth Factors and Cytokines | Peprotech |
| 120-20 | WISP-3 | Human Growth Factors and Cytokines | Peprotech |
| 120-17 | WNT-1 | Human Growth Factors and Cytokines | Peprotech |
| 120-31 | WNT-7A (HEK 293 cell derived) | Human Growth Factors and Cytokines | Peprotech |
| 120-HD-001 | PDGF | Growth Factors | R&D Systems |
| 236-EG-01M | EGF | Growth Factors | R&D Systems |
| 11350-1 | IFN | Cytokines & Receptors | R&D Systems |
| 1927-ZN-010 | BMP-1/PCP | Growth Factors | R&D Systems |
| 1073-BP-010 | BMP-8a | Growth Factors | R&D Systems |
| 3209-BP-010 | BMP-9 | Growth Factors | R&D Systems |
| 272-I-010 | CCL1/I-309/TCA-3 | Chemokines & Receptors | R&D Systems |
| 324-HC-010 | CCL14a/HCC-1 | Chemokines & Receptors | R&D Systems |
| 394-PA-010 | CCL18/PARC | Chemokines & Receptors | R&D Systems |
| 279-MC-010 | CCL2/JE/MCP-1 | Chemokines & Receptors | R&D Systems |
| 270-LD-010 | CCL3/MIP-1 alpha | Chemokines & Receptors | R&D Systems |

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| 271-BME-010 | CCL4/MIP-1 beta | Chemokines & Receptors | R&D Systems |
| 278-RN-010 | CCL5/RANTES | Chemokines & Receptors | R&D Systems |
| 282-P3-010 | CCL7/MCP-3/MARC | Chemokines & Receptors | R&D Systems |
| 281-CP-010 | CCL8/MCP-2 | Chemokines & Receptors | R&D Systems |
| 275-GR-010 | CXCL1/GRO alpha/KC/CINC-1 | Chemokines & Receptors | R&D Systems |
| 266-IP-010 | CXCL10/IP-10/CRG-2 | Chemokines & Receptors | R&D Systems |
| 350-NS-010 | CXCL12/SDF-1 alpha | Chemokines & Receptors | R&D Systems |
| 351-FS-010 | CXCL12/SDF-1 beta | Chemokines & Receptors | R&D Systems |
| 276-GB-010 | CXCL2/GRO beta/MIP-2/CINC-3 | Chemokines & Receptors | R&D Systems |
| 277-GG-010 | CXCL3/GRO gamma/CINC-2/DCIP-1 | Chemokines & Receptors | R&D Systems |
| 393-NP-010 | CXCL7/NAP-2 | Chemokines & Receptors | R&D Systems |
| 208-IL-010 | CXCL8/IL-8 | Chemokines & Receptors | R&D Systems |
| 618-IL-010 | CXCL8/IL-8 | Chemokines & Receptors | R&D Systems |
| 392-MG-010 | CXCL9/MIG | Chemokines & Receptors | R&D Systems |
| 6628-DK-010 | Dkk-2 | Growth Factors | R&D Systems |
| 1269-DK-010 | Dkk-4 | Growth Factors | R&D Systems |
| 126-FL-010 | Fas Ligand/TNFSF6 | Cytokines & Receptors | R&D Systems |
| 6937-GD-010 | GDF-1 | Growth Factors | R&D Systems |
| 788-G8-010 | GDF-8/Myostatin | Growth Factors | R&D Systems |
| 200-LA-010 | IL-1 alpha/IL-1F1 | Cytokines & Receptors | R&D Systems |
| 1870-IL-010 | IL-26/AK155 | Cytokines & Receptors | R&D Systems |
| 2526-IL-010 | IL-27 | Cytokines & Receptors | R&D Systems |
| 1737-MS-010 | MIS/AMH | Growth Factors | R&D Systems |
| 295-OM-010 | Oncostatin M/OSM | Cytokines & Receptors | R&D Systems |
| 192-SF-010 | sFRP-3 | Growth Factors | R&D Systems |
| 1319-TL-010 | TL1A/TNFSF15 | Cytokines & Receptors | R&D Systems |
| 375-TL-010 | TRAIL/TNFSF10 | Cytokines & Receptors | R&D Systems |
| 390-TN-010 | TRANCE/TNFSF11/RANK L | Cytokines & Receptors | R&D Systems |
| 6179-WN-010 | Wnt-11 | Growth Factors | R&D Systems |
| 5036-WN-010 | Wnt-3a | Growth Factors | R&D Systems |
| 645-WN-010 | Wnt-5a | Growth Factors | R&D Systems |
| 670-FR-100 | GFR alpha-3/GDNF R alpha-3 | Growth Factors | R&D Systems |
| 683-RK-100 | RANK/TNFRSF11A | Cytokines & Receptors | R&D Systems |
| 1548-TR-100 | TROY/TNFRSF19 | Cytokines & Receptors | R&D Systems |
| 11200-1 | IFN-alpha | Cytokines & Receptors | R&D Systems |
| 11175-1 | IFN-alpha 1 | Cytokines & Receptors | R&D Systems |
| 11105-1 | IFN-alpha 2 | Cytokines & Receptors | R&D Systems |
| 11177-1 | IFN-alpha 4 | Cytokines & Receptors | R&D Systems |
| 11180-1 | IFN-alpha 4 | Cytokines & Receptors | R&D Systems |
| 11115-1 | IFN-alpha B2 | Cytokines & Receptors | R&D Systems |
| 11120-1 | IFN-alpha C | Cytokines & Receptors | R&D Systems |
| 11125-1 | IFN-alpha D | Cytokines & Receptors | R&D Systems |
| 11130-1 | IFN-alpha F | Cytokines & Receptors | R&D Systems |
| 11135-1 | IFN-alpha G | Cytokines & Receptors | R&D Systems |
| 11145-1 | IFN-alpha H2 | Cytokines & Receptors | R&D Systems |
| 11150-1 | IFN-alpha I | Cytokines & Receptors | R&D Systems |
| 11160-1 | IFN-alpha J1 | Cytokines & Receptors | R&D Systems |
| 11165-1 | IFN-alpha K | Cytokines & Receptors | R&D Systems |
| 11190-1 | IFN-alpha WA | Cytokines & Receptors | R&D Systems |
| 240-B-002 | TGF-beta 1 | Growth Factors | R&D Systems |
| 302-B2-002 | TGF-beta 2 | Growth Factors | R&D Systems |
| 243-B3-002 | TGF-beta 3 | Growth Factors | R&D Systems |
| 615-BMC-020 | BMP-5 | Growth Factors | R&D Systems |

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| 320-EO-020 | CCL11/Eotaxin | Chemokines & Receptors | R&D Systems |
| 359-EA-200 | Ephrin-A3 | Growth Factors | R&D Systems |
| 369-EA-200 | Ephrin-A4 | Growth Factors | R&D Systems |
| 374-EA-200 | Ephrin-A5 | Growth Factors | R&D Systems |
| 395-EB-200 | Ephrin-B3 | Growth Factors | R&D Systems |
| 1234-IL-025 | IL-17C | Cytokines & Receptors | R&D Systems |
| B001-5 | IL-18/IL-1F4 | Cytokines & Receptors | R&D Systems |
| 1975-IL-025 | IL-1F7/FIL1 zeta | Cytokines & Receptors | R&D Systems |
| 2926-BP-025 | BMP-10 | Growth Factors | R&D Systems |
| 327-P4-025 | CCL13/MCP-4 | Chemokines & Receptors | R&D Systems |
| 363-MG-025 | CCL15/MIP-1 delta | Chemokines & Receptors | R&D Systems |
| 628-LK-025 | CCL15/MIP-1 delta | Chemokines & Receptors | R&D Systems |
| 802-HC-025 | CCL16/HCC-4 | Chemokines & Receptors | R&D Systems |
| 364-DN-025 | CCL17/TARC | Chemokines & Receptors | R&D Systems |
| 361-MI-025 | CCL19/MIP-3 beta | Chemokines & Receptors | R&D Systems |
| 360-MP-025 | CCL20/MIP-3 alpha | Chemokines & Receptors | R&D Systems |
| 366-6C-025 | CCL21/6Ckine | Chemokines & Receptors | R&D Systems |
| 336-MD-025 | CCL22/MDC | Chemokines & Receptors | R&D Systems |
| 508-CK-025 | CCL23/Ck beta 8-1 | Chemokines & Receptors | R&D Systems |
| 371-MP-025 | CCL23/MPIF-1 | Chemokines & Receptors | R&D Systems |
| 343-E2-025 | CCL24/Eotaxin-2/MPIF-2 | Chemokines & Receptors | R&D Systems |
| 334-TK-025 | CCL25/TECK | Chemokines & Receptors | R&D Systems |
| 653-E3-025 | CCL26/Eotaxin-3 | Chemokines & Receptors | R&D Systems |
| 376-CT-025 | CCL27/CTACK | Chemokines & Receptors | R&D Systems |
| 717-VC-025 | CCL28 | Chemokines & Receptors | R&D Systems |
| 509-MI-025 | CCL3L1/MIP-1 alpha Isoform LD78 beta | Chemokines & Receptors | R&D Systems |
| 3046-MB-025 | CCL4L1/LAG-1 | Chemokines & Receptors | R&D Systems |
| 6420-CL-025 | CD40 Ligand/TNFSF5 | Cytokines & Receptors | R&D Systems |
| 365-FR-025 | CX3CL1/Fractalkine | Chemokines & Receptors | R&D Systems |
| 672-IT-025 | CXCL11/I-TAC | Chemokines & Receptors | R&D Systems |
| 6448-SD-025 | CXCL12/SDF-1 | Chemokines & Receptors | R&D Systems |
| 801-CX-025 | CXCL13/BLC/BCA-1 | Chemokines & Receptors | R&D Systems |
| 866-CX-025 | CXCL14/BRAK | Chemokines & Receptors | R&D Systems |
| 4207-DM-025 | CXCL17/VCC-1 | Chemokines & Receptors | R&D Systems |
| 795-P4-025 | CXCL4/PF4 | Chemokines & Receptors | R&D Systems |
| 649-EN-025 | CXCL5/ENA-70 | Chemokines & Receptors | R&D Systems |
| 651-NA-025 | CXCL5/ENA-74 | Chemokines & Receptors | R&D Systems |
| 254-XB-025 | CXCL5/ENA-78 | Chemokines & Receptors | R&D Systems |
| 333-GC-025 | CXCL6/GCP-2 | Chemokines & Receptors | R&D Systems |
| 6148-DR-025 | Draxin | Growth Factors | R&D Systems |
| BT359 | Ephrin-A3 | Growth Factors | R&D Systems |
| BT369 | Ephrin-A4 | Growth Factors | R&D Systems |
| BT374 | Ephrin-A5 | Growth Factors | R&D Systems |
| BT395 | Ephrin-B3 | Growth Factors | R&D Systems |
| 231-BC-025 | FGF acidic | Growth Factors | R&D Systems |
| 234-FSE-025 | FGF basic | Growth Factors | R&D Systems |
| 2246-FG-025 | FGF-12 | Growth Factors | R&D Systems |
| 3867-FG-025 | FGF-22 | Growth Factors | R&D Systems |
| 1206-F3-025 | FGF-3 | Growth Factors | R&D Systems |
| 1593-FB-025 | FGF-BP | Growth Factors | R&D Systems |
| 3095-FB-025 | Fibulin 5/DANCE | Growth Factors | R&D Systems |
| 694-GL-025 | GITR Ligand/TNFSF18 | Cytokines & Receptors | R&D Systems |
| 1965-IL-025 | IL-24 | Cytokines & Receptors | R&D Systems |

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| 1375-IL-025 | IL-26/AK155 | Cytokines & Receptors | R&D Systems |
| 1587-IL-025 | IL-28A/IFN-lambda 2 | Cytokines & Receptors | R&D Systems |
| 5259-IL-025 | IL-28B/IFN-lambda 3 | Cytokines & Receptors | R&D Systems |
| 1598-IL-025 | IL-29/IFN-lambda 1 | Cytokines & Receptors | R&D Systems |
| 1078-IL-025 | IL-36 alpha/IL-1F6 | Cytokines & Receptors | R&D Systems |
| 1099-IL-025 | IL-36 beta/IL-1F8 | Cytokines & Receptors | R&D Systems |
| 2320-IL-025 | IL-36 gamma/IL-1F9 | Cytokines & Receptors | R&D Systems |
| 1705-HH-025 | Indian Hedgehog/Ihh | Growth Factors | R&D Systems |
| 746-LF-025 | Lefty-A | Growth Factors | R&D Systems |
| 378-SM-025 | Neuregulin-1 Isoform SMDF | Growth Factors | R&D Systems |
| 3870-N1-025 | Neuropilin-1 | Growth Factors | R&D Systems |
| 2215-N2-025 | Neuropilin-2 | Growth Factors | R&D Systems |
| 3218-ND-025 | Nodal | Growth Factors | R&D Systems |
| 185-OS-025 | Osteoprotegerin/TNFRSF11B | Cytokines & Receptors | R&D Systems |
| 1159-SB-025 | PDGF-DD | Growth Factors | R&D Systems |
| 1826-TS-025 | Pentraxin 3/TSG-14 | Growth Factors | R&D Systems |
| 4645-RS-025 | R-Spondin 1 | Growth Factors | R&D Systems |
| 3266-RS-025 | R-Spondin 2 | Growth Factors | R&D Systems |
| 3500-RS-025 | R-Spondin 3 | Growth Factors | R&D Systems |
| 4575-RS-025 | R-Spondin 4 | Growth Factors | R&D Systems |
| 1827-SF-025 | sFRP-4 | Growth Factors | R&D Systems |
| 1549-S1-025 | Soggy-1/DkkL1 | Growth Factors | R&D Systems |
| 1406-ST-025 | SOST/Sclerostin | Growth Factors | R&D Systems |
| 2347-VE-025 | VEGF | Growth Factors | R&D Systems |
| 695-LT-025 | XCL1/Lymphotactin | Chemokines & Receptors | R&D Systems |
| 308-FK-005 | Flt-3 Ligand | Growth Factors | R&D Systems |
| 201-LB-005 | IL-1 beta/IL-1F2 | Cytokines & Receptors | R&D Systems |
| 219-IL-005 | IL-12 | Cytokines & Receptors | R&D Systems |
| 288-TP-005 | Thrombopoietin/Tpo | Growth Factors | R&D Systems |
| 6076-WN-005 | Wnt-4 | Growth Factors | R&D Systems |
| 11100-1 | IFN-alpha A | Cytokines & Receptors | R&D Systems |
| 2036-BC-050 | BOC | Growth Factors | R&D Systems |
| 1028-CL-050 | CD30 Ligand/TNFSF8 | Cytokines & Receptors | R&D Systems |
| 4777-DH-050 | Desert Hedgehog/Dhh | Growth Factors | R&D Systems |
| 1118-DK-050 | Dkk-3 | Growth Factors | R&D Systems |
| 1810-EC-050 | Endocan/ESM-1 | Growth Factors | R&D Systems |
| 6417-A1-050 | Ephrin-A1 | Growth Factors | R&D Systems |
| 5988-FZ-050 | Frizzled-1 | Growth Factors | R&D Systems |
| 3459-FZ-050 | Frizzled-10 | Growth Factors | R&D Systems |
| 5847-FZ-050 | Frizzled-4 | Growth Factors | R&D Systems |
| 1617-FZ-050 | Frizzled-5 | Growth Factors | R&D Systems |
| 1617-FZC-050 | Frizzled-5 | Growth Factors | R&D Systems |
| 6178-FZ-050 | Frizzled-7 | Growth Factors | R&D Systems |
| 6129-FZ-050 | Frizzled-8 | Growth Factors | R&D Systems |
| 5190-GR-050 | Gremlin | Growth Factors | R&D Systems |
| 317-ILB-050 | IL-17/IL-17A | Cytokines & Receptors | R&D Systems |
| 3040-IL-050 | IL-32 alpha | Cytokines & Receptors | R&D Systems |
| 5889-KB-050 | Klotho beta | Growth Factors | R&D Systems |
| 3468-LE-050 | LEDGF | Growth Factors | R&D Systems |
| 296-HR-050 | Neuregulin-1 alpha/NRG1 alpha | Growth Factors | R&D Systems |
| 377-HB-050 | Neuregulin-1 beta 1/NRG1 beta 1 | Growth Factors | R&D Systems |
| 5898-NR-050 | Neuregulin-1/NRG1 | Growth Factors | R&D Systems |
| 2420-PG-050 | Progranulin/PGRN | Growth Factors | R&D Systems |

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| 6266-SF-050 | sFRP-5 | Growth Factors | R&D Systems |
| 5154-TA-050 | TAFA1/FAM19A1 | Chemokines & Receptors | R&D Systems |
| 4179-TA-050 | TAFA2/FAM19A2 | Chemokines & Receptors | R&D Systems |
| 5099-TA-050 | TAFA4/FAM19A4 | Chemokines & Receptors | R&D Systems |
| 5148-TA-050 | TAFA5/FAM19A5 | Chemokines & Receptors | R&D Systems |
| 1341-WF-050 | WIF-1 | Growth Factors | R&D Systems |

**Supplemental Table 1:** List of the 446 secreted factors used in the screen.