

## EXPERIMENTAL PROCEDURES

### Cell lines and culture

A549, Calu-1, H23, A427, H460, H727, SK-MES-1, EKVX, H2170, H322M, H520, H522, H226, LUDLU-1, HOP92 were obtained from the CRUK Central Cell Services facility; H358, H441, SK-LU-1, H1734, H1792, H2122 were obtained from ATCC and H1171, HCC78, HCC95, H510A, Type II cells were obtained from Olivier Pardo and Michael Seckl (Imperial College, London); NL-20 were obtained from Silvia Carvalho and Yosef Yarden (Weizmann Institute, Rehovot). All cell lines were maintained in either RPMI/10%FCS or DMEM/10%FCS as appropriate with the following exceptions: MCF10A cells were maintained in Ham's nutrient mixture F12/ DMEM (1:1) containing 5% horse serum and 10 µg/mL insulin, 20 ng/mL EGF, 5 µg/mL hydrocortisone, and 100 ng/mL cholera toxin. Minimal medium consisted of Ham's nutrient mixture F12/DMEM (1:1) containing 5% horse serum. NL-20 cells were maintained in Ham's nutrient mixture F12 containing 4%FCS and 5 µg/mL insulin, 10 ng/mL EGF, 500 ng/mL hydrocortisone, 1 µg/mL transferrin, 0.1x non-essential amino acids and 2.7g/L glucose. Minimal medium consisted of Ham's nutrient mixture F12 containing 0.4%FCS. Typell cells were maintained in DCCM-1 serum-free medium containing 10%FCS. Minimal medium consisted of DCCM-1 serum-free medium. 4-hydroxytamoxifen (4-OHT) was purchased from Sigma and dissolved in ethanol to obtain a 0.5 mM stock solution.

### Small molecule inhibitors

Selumetinib, PD-0325901, CI-1040, AZ628, GDC-0879, GDC0941, PIK-90, PIK-75, NVP-BEZ235, BX-795 and GDC-0449 were obtained from Axon Medchem. Trametinib, BMS-754807, OSI-906, PF-04691502 and MK-2206 were obtained from Active Biochem. L779450, PLX4720, ZM336372, Picropodophyllin, IGF1R Inhibitor II, Akti-1/2, SU11274, MG-132, PSI, Doxorubicin, MK2a Inhibitor and Deguelin were obtained from Calbiochem/Merck. GW5074, BMS-345541, Fasudil, Y-27632, PP242 and

10058-F4 were obtained from Sigma. Sorafenib, Dasatinib, Bortezomib, Docetaxel, Everolimus, Temsirolimus, Rapamycin, Erlotinib and Gefitinib were obtained from LC Laboratories. SC-514, 5Z-7-Oxozeaenol and PF-573,228 were obtained from Tocris. 17-AAG, 17-DMAG, BIIB021, NVP-AUY922 and PF-02341066 were obtained from Selleck. SB590885 was obtained from Caltag-MedSystems. AZD8055 was obtained from ChemieTek. Topotecan was obtained from TopoGEN. CAY10576 was obtained from Cayman. NVP-AEW541 was a generous gift from Novartis A.G.

### **Western blotting**

Antibodies directed against Phospho-ERK (Thr202/Tyr204), Phospho-AKT (Ser473 and Thr308), Phospho-S6 (Ser235/Ser236), Phospho-S6K (Thr389), Phospho-EGFR (Tyr1068), IRS1, IRS2, IGF1R, INSR, EGFR, Pan-ERK, Pan-AKT and Pan-S6 were obtained from Cell Signaling. Antibodies directed against Phospho-IRS1 (Tyr612) and Phospho-PRAS40 (Thr246) were obtained from Invitrogen. Antibody directed against KRAS was obtained from Santa Cruz. Antibody directed against p85 $\alpha$  was obtained from Millipore.