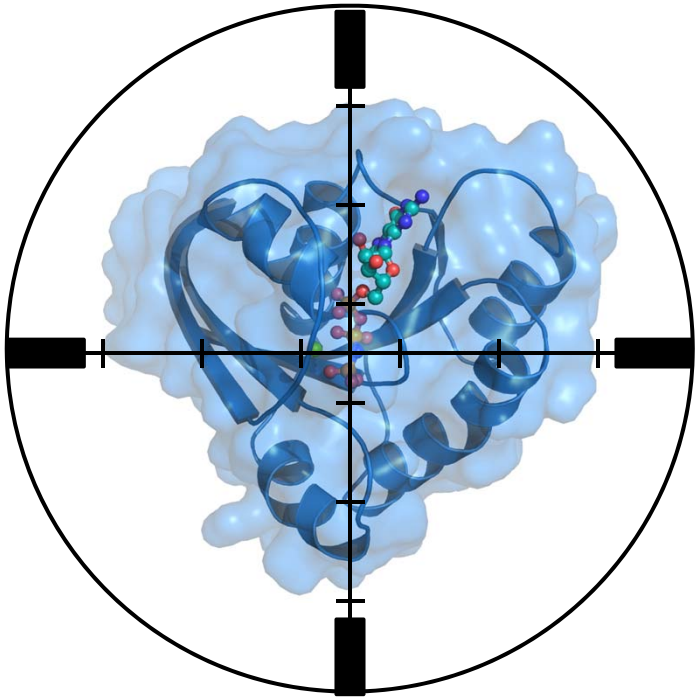
LifeSci Advisors
October 17, 2016



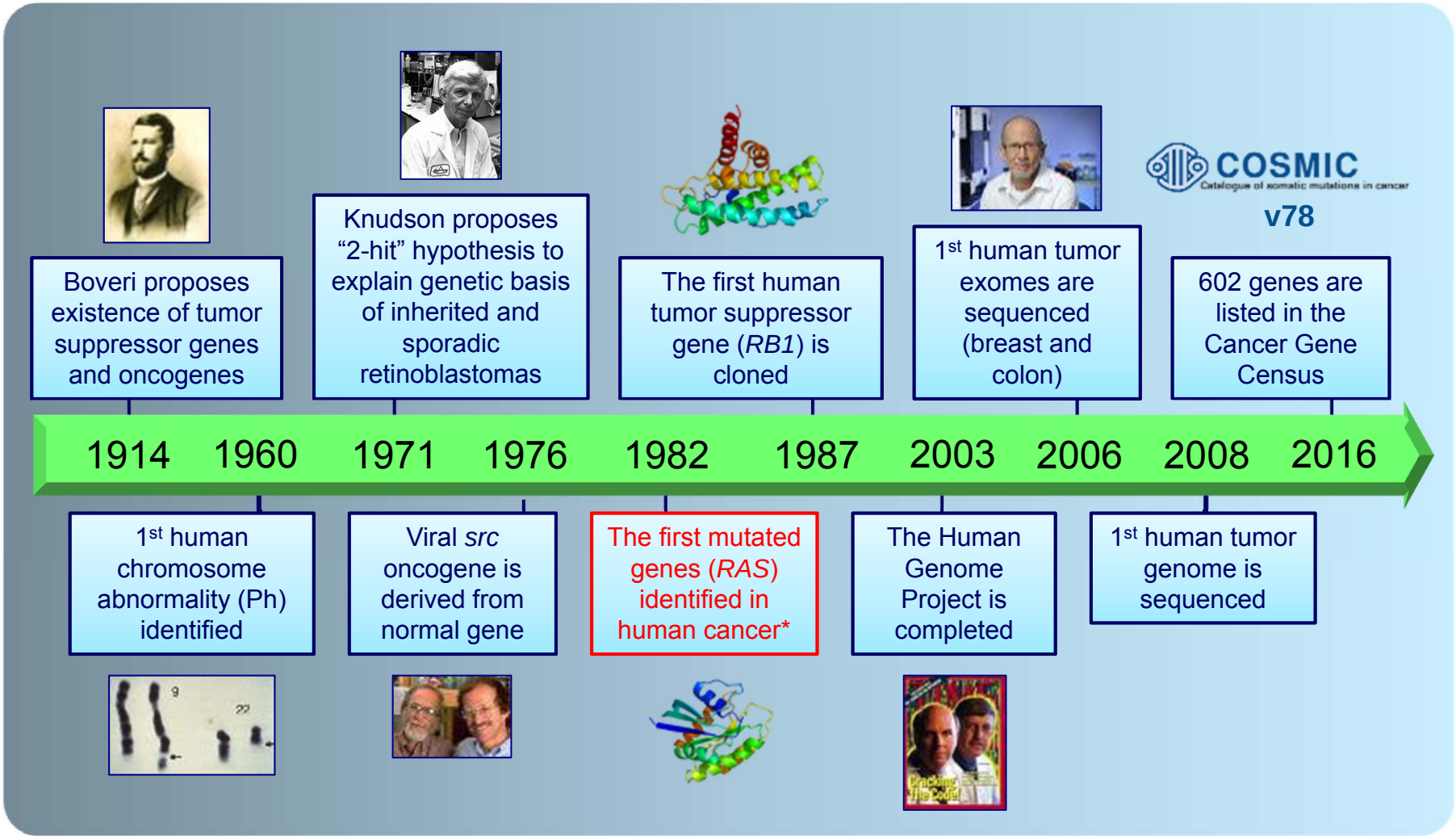
RAS – the beating heart of cancer

Drugging undruggable RAS:

State-of-the-art

Channing J. Der, PhD
Sarah Graham Kenan Professor of Pharmacology
University of North Carolina at Chapel Hill
Lineberger Comprehensive Cancer Center

Genetic basis of cancer



The three RAS genes (HRAS, KRAS and NRAS) comprise the most frequently mutated gene family in cancer (~25%)

RAS mutations are associated with the major causes of cancer deaths

RAS mutation frequency

%	Cancer
97	Pancreatic ductal adenocarcinoma
52	Colorectal adenocarcinoma
43	Multiple myeloma
32	Lung adenocarcinoma
28	Skin cutaneous melanoma
25	Uterine corpus endometrioid carcinoma
13	Thyroid carcinoma
13	Uterine carcinosarcoma
12	Stomach adenocarcinoma
11	Acute myeloid leukaemia
11	Bladder urothelial carcinoma
8	Cervical adenocarcinoma
6	Head & neck squamous cell carcinoma

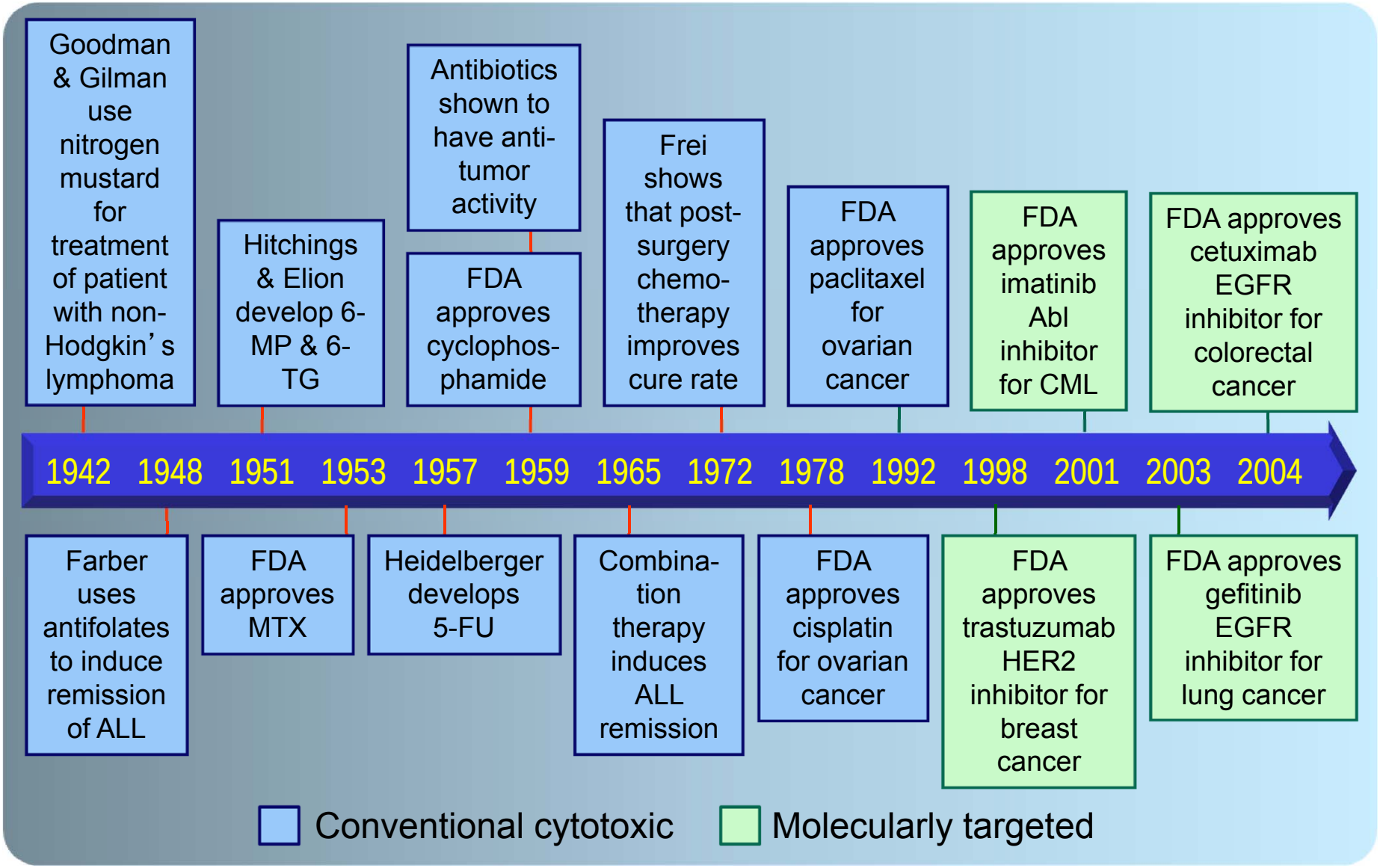
Cox et al (2014) Nat Rev Drug Discov 13:828

Estimated US cancer deaths

Site	Deaths	%
Lung & bronchus	158,080	26.5
Colon & rectum	49,190	8.3
Pancreas	41,780	7.0
Breast	40,890	6.9
Liver & intrahepatic bile duct	27,170	4.6
Prostate	26,120	4.4
Non-Hodgkin lymphoma	20,150	3.4
Urinary bladder	16,390	2.7
Brain & nervous system	16,050	2.7
Esophagus	15,690	2.6
Ovary	14,240	2.4
Kidney & renal pelvis	14,240	2.4
Myeloma	12,650	2.1

Siegel et al (2016) CA Cancer J Clin 66:7

History of cancer chemotherapy: the signaling targeted era begins in 1998



FDA approved signal transduction inhibitors I

1998	Trastuzumab (HER2) for HER2 metastatic breast cancer (1998) and gastric cancer (2010)
2001	Imatinib (BCR-Abl) for CML (2001) and GIST (2002)
	Gefitinib (EGFR) for NSCLC (2003)
2004	Cetuximab (EGFR) for metastatic CRC (2004) and SCCHN (2006)
	Bevacizumab (VEGF) for CRC (2004), NSCLC (2006), breast (2007), glioblastoma (2009) and RCC (2009)
	Erlotinib (EGFR) for NSCLC (2004) and PDAC (2005)
2005	Sorafenib (Raf, VEGFR, PDGFR) for RCC (2005)
2006	Sunitinib (Flt3, VEGFR, PDGFR) for GIST and RCC (2006), and pancreatic neuroendocrine tumors (2011)
	Dasatinib (BCR-Abl, Src, Lck, Yes, Fyn, Kit, EphA2 and PDGFR) for imatinib-resistant CML and Ph-positive ALL (2006) and Ph-positive CML (2010)
	Panitumumab (EGFR) for CRC (2006)
2007	Lapatinib (EGFR, HER2) for metastatic breast cancer (2007)
	Temsirolimus (mTOR) for RCC (2007)
	Nilotinib (BCR-Abl, Kit, PDGFR) for CML (2007)
2009	Everolimus (mTOR) for RCC (2009), pancreatic neuroendocrine tumors (2011), HER2-negative breast cancer (2012) and renal angiomyololipoma associated with TSC (2012)
	Pazopanib (VEGFR) for RCC (2009)
2011	Vemurafenib (B-Raf) for B-Raf(V600E) metastatic melanoma (2011)
	Vandetanib (VEGFR, EGFR, Ret) for thyroid cancer (2011)

Compiled from http://www.centerwatch.com

FDA approved signal transduction inhibitors II

2012

Crizotinib (Alk, Met) for *ALK* rearranged NSCLC (2011)
Axitinib (VEGFR, PDGFR, Kit) for RCC (2012)
Vismodegib (Smoothened) for metastatic basal cell carcinoma (2012) and basal cell carcinoma (2012)
Regorafenib (VEGFR1-3, TIE-2, PDGFRβ, FGFR1, RET, KIT, Raf) for metastatic CRC (2012) and GIST (2013)
Pertuzumab (HER2) for HER2 metastatic breast cancer (2012)
Axitinib (VEGFR1-3) for advanced RCC (2012)
Ponatinib (Abl, Src) for Ph positive CML (2012)
Cabozantinib (MET, VEGFR2) for metastatic medullary thyroid cancer (2012)
Bosutinib (Ab, Src) for Ph positive CML (2012)

2013

Dabrafenib (B-Raf) for B-Raf(V600E) metastatic melanoma (2013)
Regorafinib (VEGFR2, TIE2, etc) for GIST (2013)
Trametinib (MEK1/2) for B-Raf V600E/K metastatic melanoma (2013)
Afatinib (EGFR, HER2/4) for EGFR mutant NSCLC (2013)
Imbruvica (Btk) for mantle cell lymphoma (2013), CLL (2014) and Waldenström's macroglobulinemia (2015)

2014

Ramucirumab (VEGFR2) for gastric cancer (2014)
Idelalisib (p110 delta) for CLL, follicular B-cell NHL and small lymphocytic lymphoma (2014)
Ceritinib (ALK) for metastatic NSCLC (2014)

Compiled from http://www.centerwatch.com

FDA approved signal transduction inhibitors III

2015

Palbociclib (CDK4/6) for ER-positive, HER2-negative breast cancer (2015)
Lenvatinib (VEGFR1) for iodine-refractory thyroid cancer (2015) and RCC (2016)
Nivolumab (PD-1) for NSCLC (2015) and Hodgkin lymphoma (2016)
Cobimetinib (BRAF) for BRAF V600E/K mutant melanoma
Alectinib (Alk, Met) for *ALK* rearranged NSCLC
Osimertinib (EGFR) for EGFR T790M mutant NSCLC

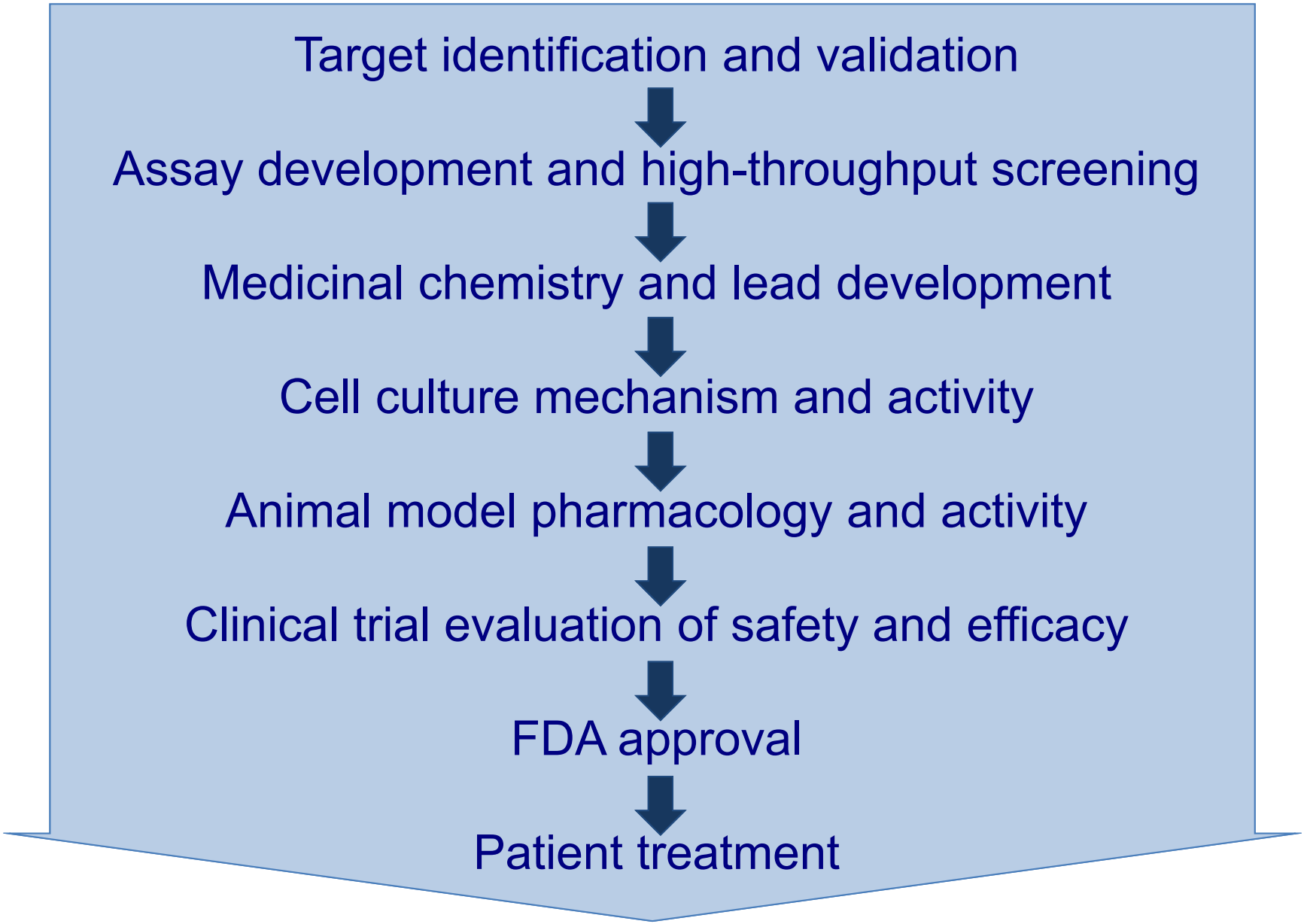
2016

Cabozantinib (MET, VEGFR2) for RCC
Venetoclax (BCL-2) for 17p deletion-positive CLL
Atezolizumab (PD-L1) for urothelial carcinoma

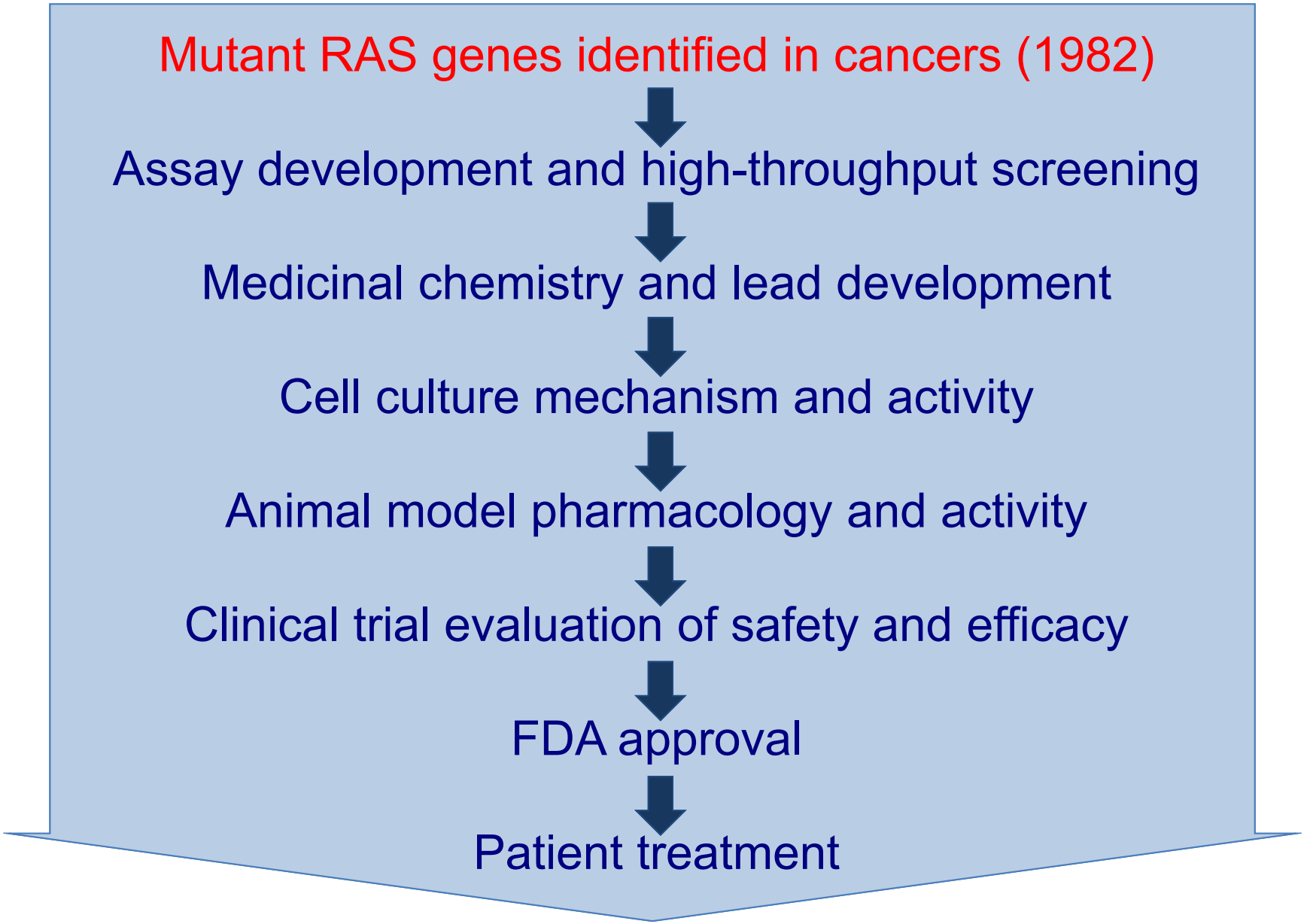
Despite more than three decades of intense effort, to date, no effective anti-RAS drug has reached the clinic

Compiled from http://www.centerwatch.com

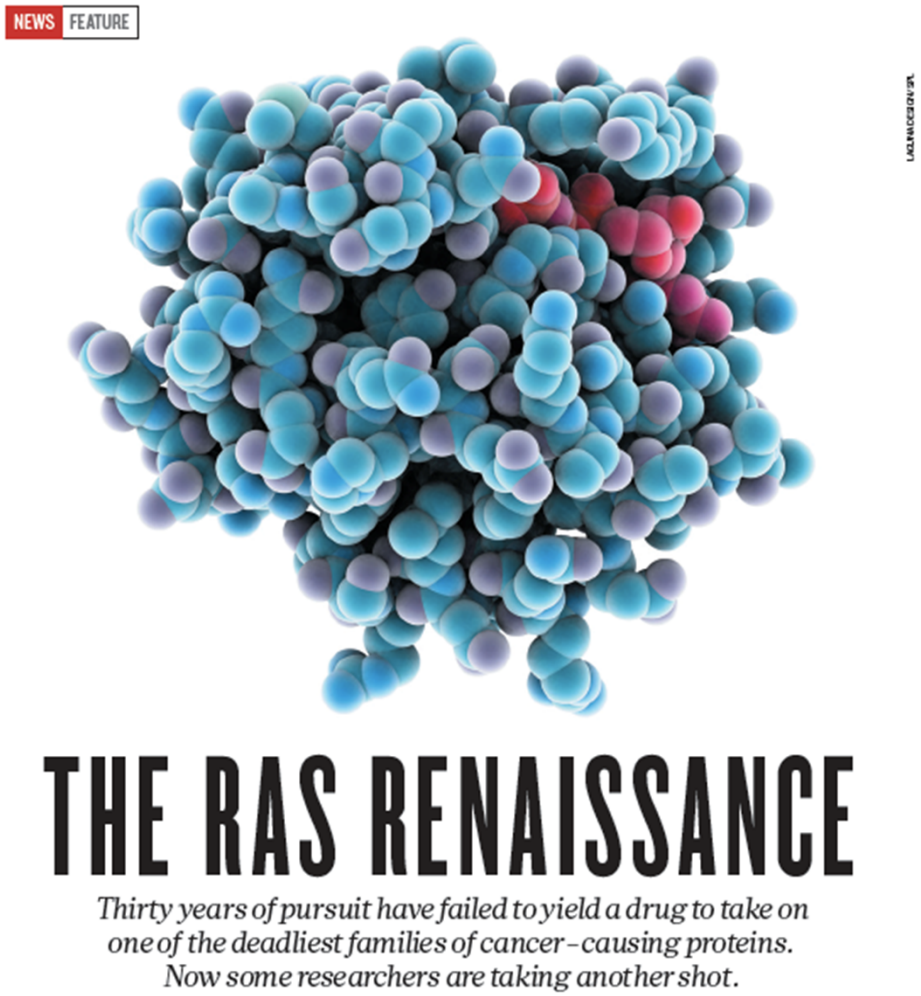
Drug discovery 101



34 years and counting…how far have we gotten?



A RAS research frenzy has begun, again

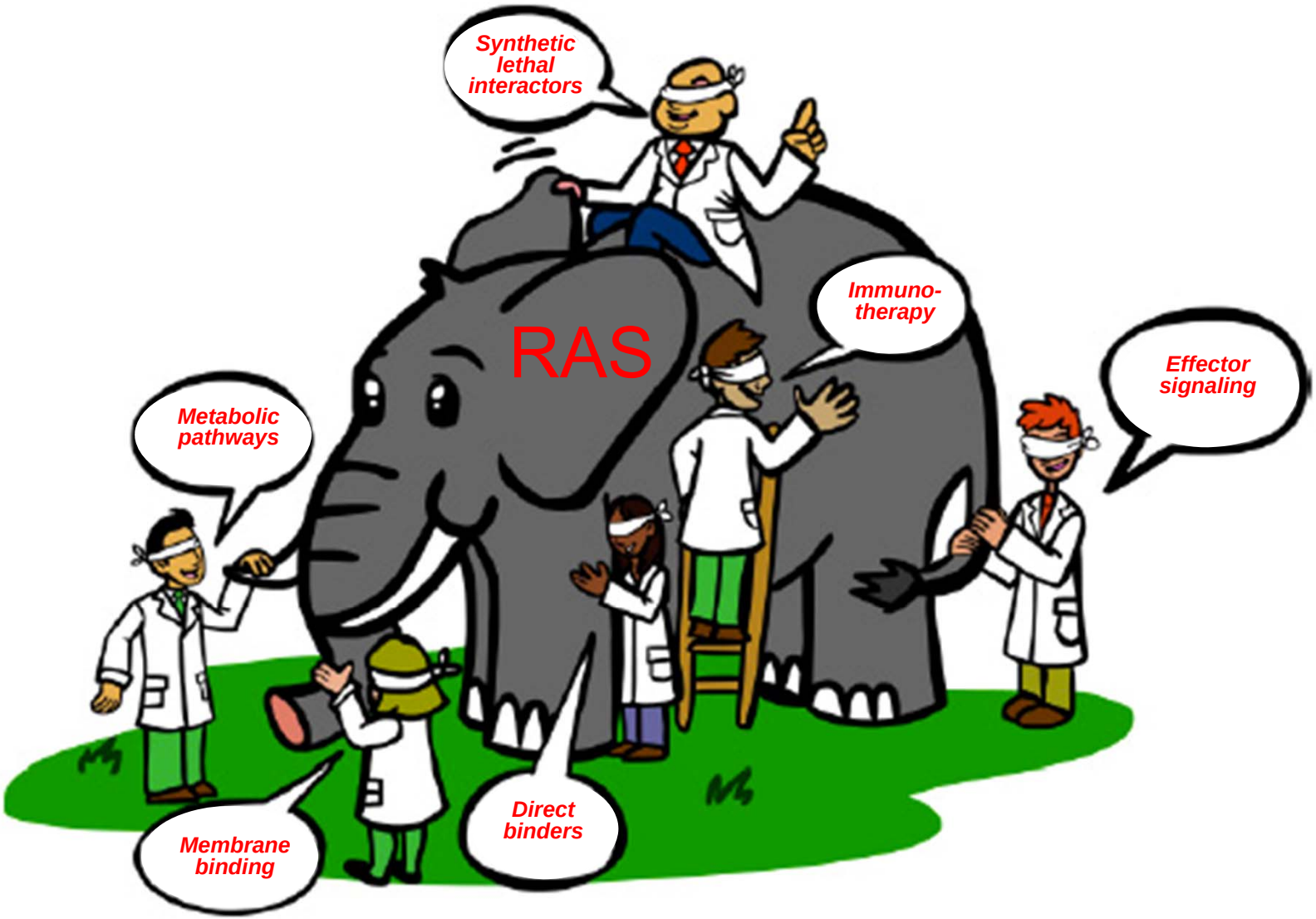


Ledford (2015) Cancer: The Ras renaissance. Nature 520:278

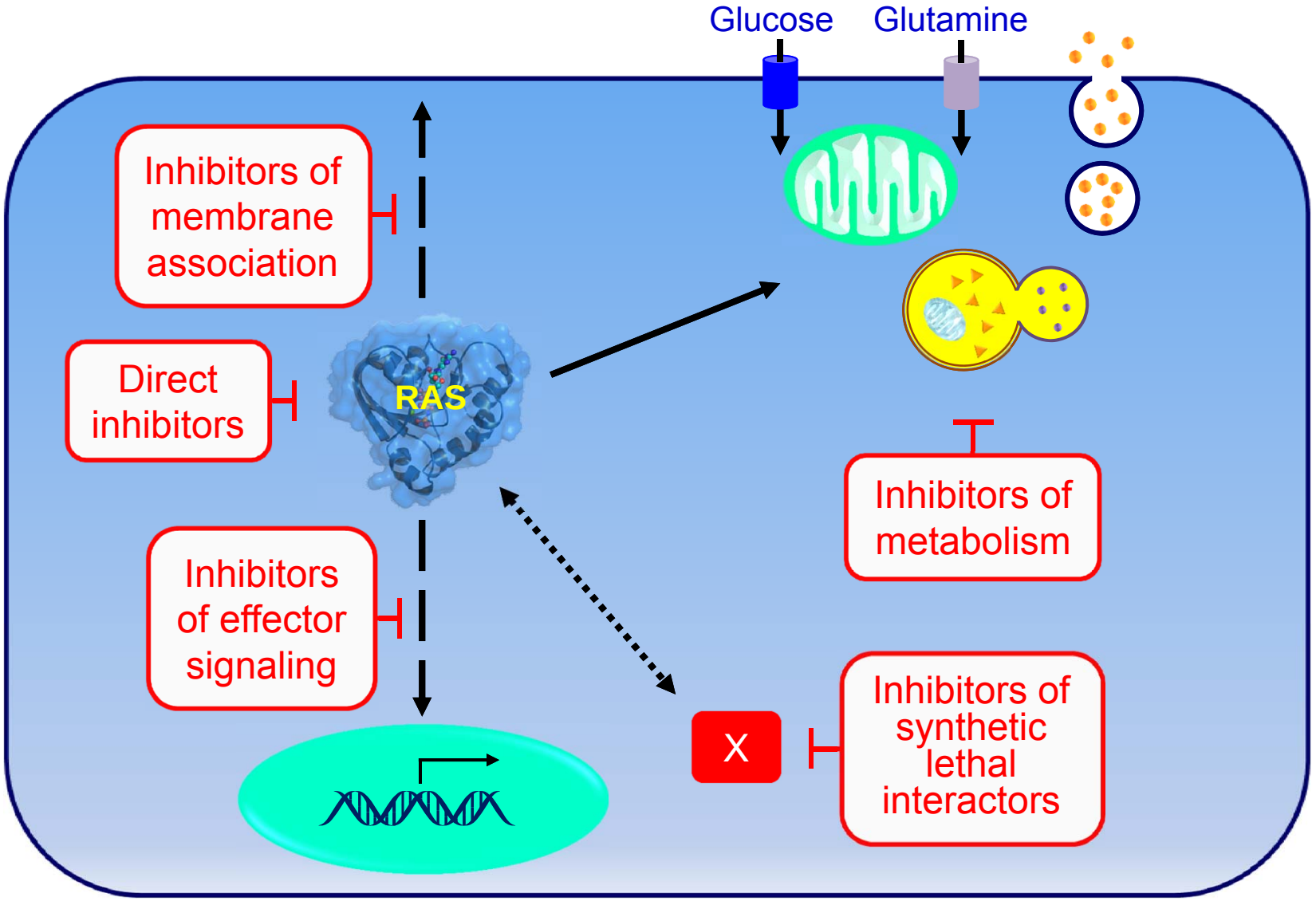
The NCI RAS Initiative is announced in 2013

http://news.sciencemag.org/scienceinsider/2013/06/us-cancer-institute-megaproject-.html

What is the “best” way to target RAS?

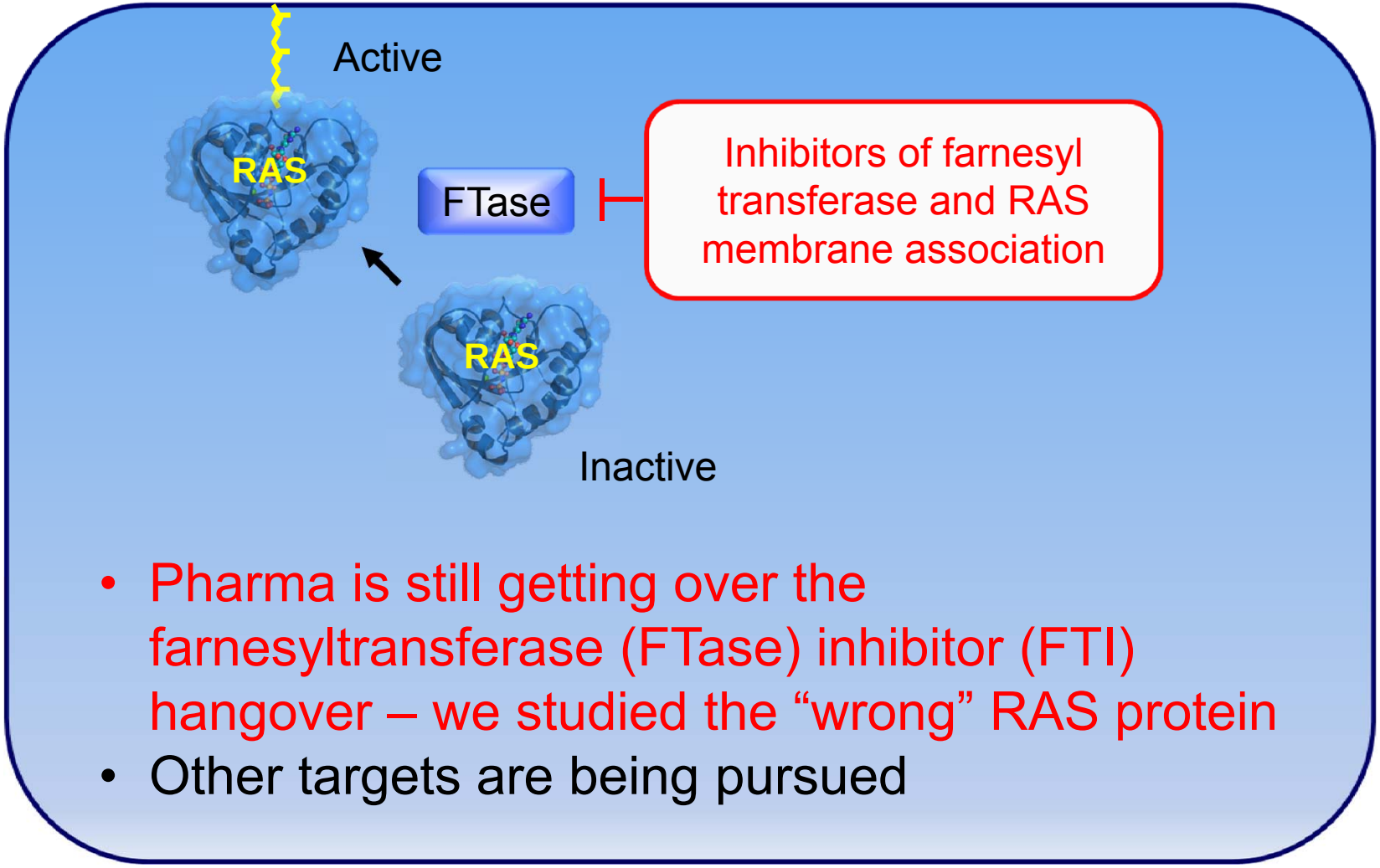


Approaches for targeting RAS



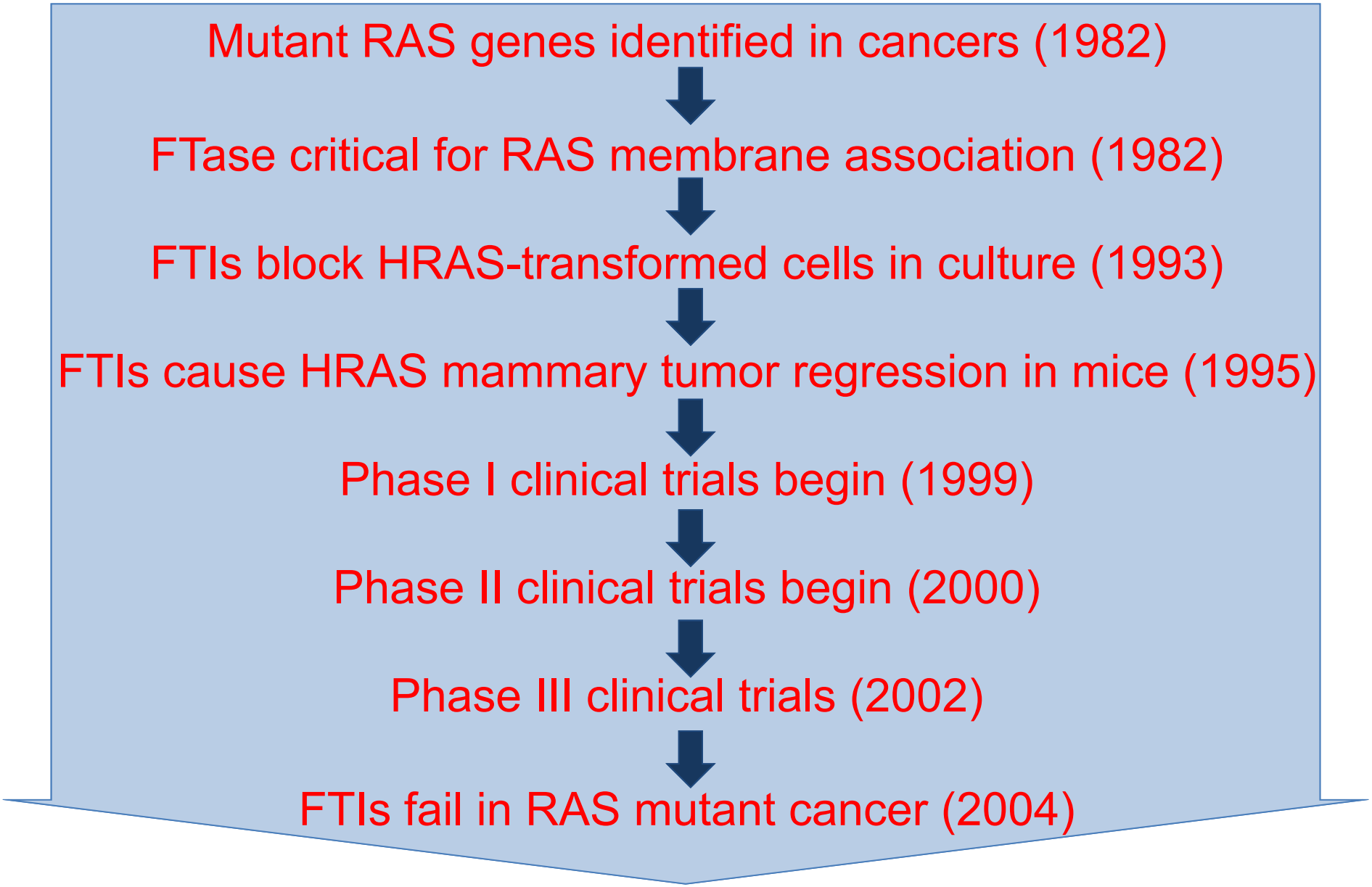
Cox et al (2014) Nat Rev Drug Discov 13:828

Targeting RAS membrane association: targeting the "wrong" RAS



- Pharma is still getting over the farnesyltransferase (FTase) inhibitor (FTI) hangover – we studied the "wrong" RAS protein
- Other targets are being pursued

Failure of FTIs: RAS is undruggable?



FTIs are not effective against *KRAS*-mutant pancreatic cancers

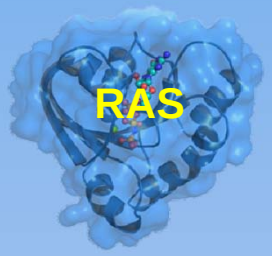
A phase II study of farnesyl transferase inhibitor R115777 in pancreatic cancer: a Southwest Oncology Group (SWOG 9924) study.
Macdonald et al (2005) Invest New Drugs 23:485

Phase III trial of gemcitabine plus tipifarnib compared with gemcitabine plus placebo in advanced pancreatic cancer.
Van Cutsem et al (2004) J Clin Oncol 22:1430

Phase II and pharmacodynamic study of the farnesyltransferase inhibitor R115777 as initial therapy in patients with metastatic pancreatic adenocarcinoma.
Cohen et al (2003) J Clin Oncol 21:1301

Targeting RAS membrane association

Inhibitors of membrane association

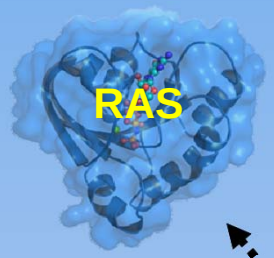


- FTase
- GGTase I
- PDEδ
- RCE1
- ICMT
- DHHC

- Pharma is still getting over the farnesyltransferase inhibitor hangover
- Other targets are being pursued – but these enzymes support the function of many other proteins – innocent bystanders?

RAS synthetic lethal interactors: another misstep

*STK33
*PLK1
*TBK1
GATA2
Survivin
*TAK1
WT1
ARHGEF2
SNAI2
RAN



Identification of genes whose functions are critical only in RAS-mutant cells

X

Inhibitors of synthetic lethal interactors

*Protein kinases identified – pharma jumps on the bandwagon

RNAi off-target activities are a concern

STK33 Kinase Activity Is Nonessential in KRAS-Dependent Cancer Cells

Carol Babij[1], Yihong Zhang[1], Robert J. Kurzeja[2], Anke Munzli[3], Amro Shehabeldin[2], Manory Fernando[1], Kim Quon[1], Paul D. Kassner[3], Astrid A. Ruefli-Brasse[1], Vivienne J. Watson[1], Flordeliza Fajardo[1], Angela Jackson[1], James Zondlo[2], Yu Sun[2], Aaron R. Ellison[2], Cherylene A. Plewa[2], Tisha San Miguel[3], John Robinson[2],

5818 Cancer Res; 71(17) September 1, 2011 AACR American Association for Cancer Research

"…our findings refute earlier proposals that STK33 inhibition may be a useful therapeutic approach to target human KRAS mutant tumors."

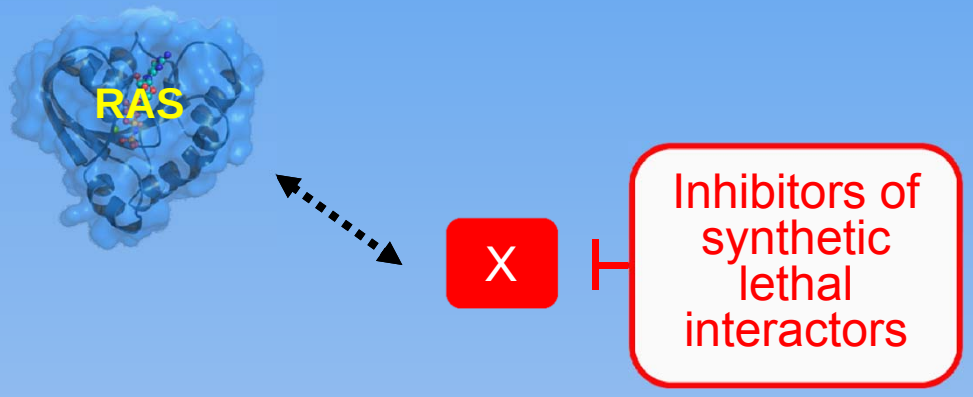
STK33 kinase inhibitor BRD-8899 has no effect on KRAS-dependent cancer cell viability

Tuoping Luo[a,b,1], Kristina Masson[a,1], Jacob D. Jaffe[a], Whitney Silkworth[a], Nathan T. Ross[a,2], Christina A. Scherer[a], Claudia Scholl[c], Stefan Fröhling[c], Steven A. Carr[a], Andrew M. Stern[a], Stuart L. Schreiber[a,b,d,3], and Todd R. Golub[a,d,e,3]

2860–2865 | PNAS | **February 21, 2012** | vol. 109 | no. 8

"…our data are most consistent with the view that inhibition of STK33's kinase activity does not represent a promising anti-KRAS therapeutic strategy."

RAS synthetic lethal interactors: another misstep



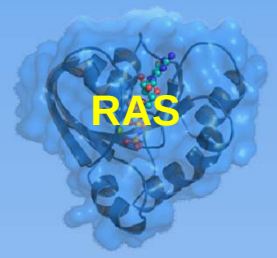
"On the basis of experience to date, *RAS* synthetic lethality has so far fallen way short of its original promise and remains unproven as an approach to finding effective new ways of tackling *RAS*-mutant cancers"

Downward (2015) Clin Cancer Res 21:1802

Is there still hope that this may work?

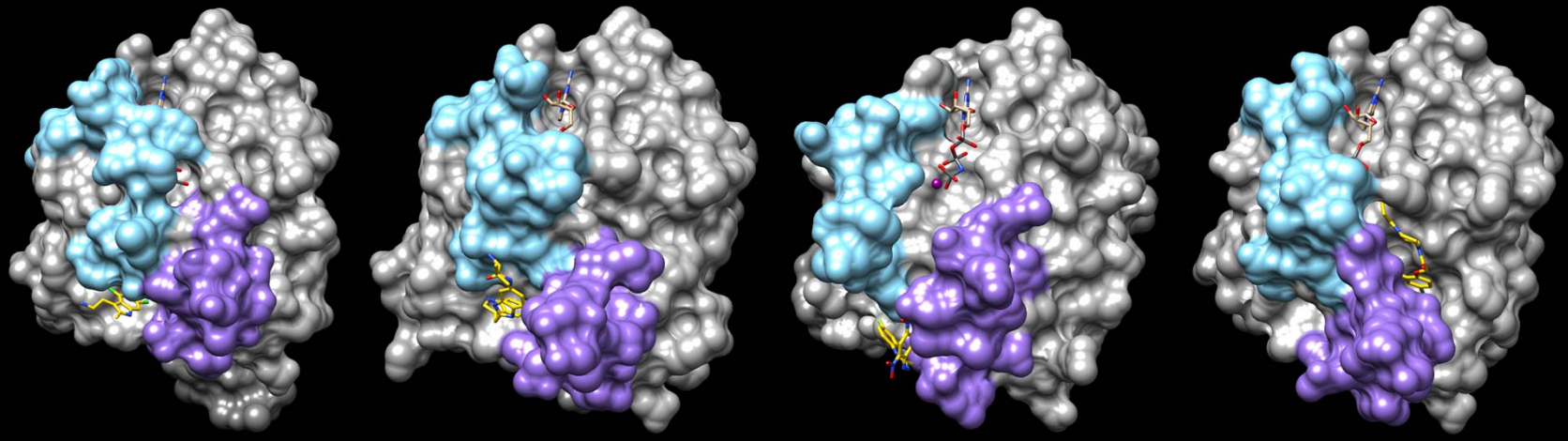
Direct RAS binders: undruggable?

Direct inhibitors



Druggability is a term used in drug discovery to describe a biological target such as a protein that is known or is predicted to bind with high affinity to a drug. Furthermore, by definition, the binding of the drug to a druggable target must alter the function of the target with a therapeutic benefit to the patient.

Cell-active direct RAS binding molecules have been identified



DCAI
2012

VU0460009
2012

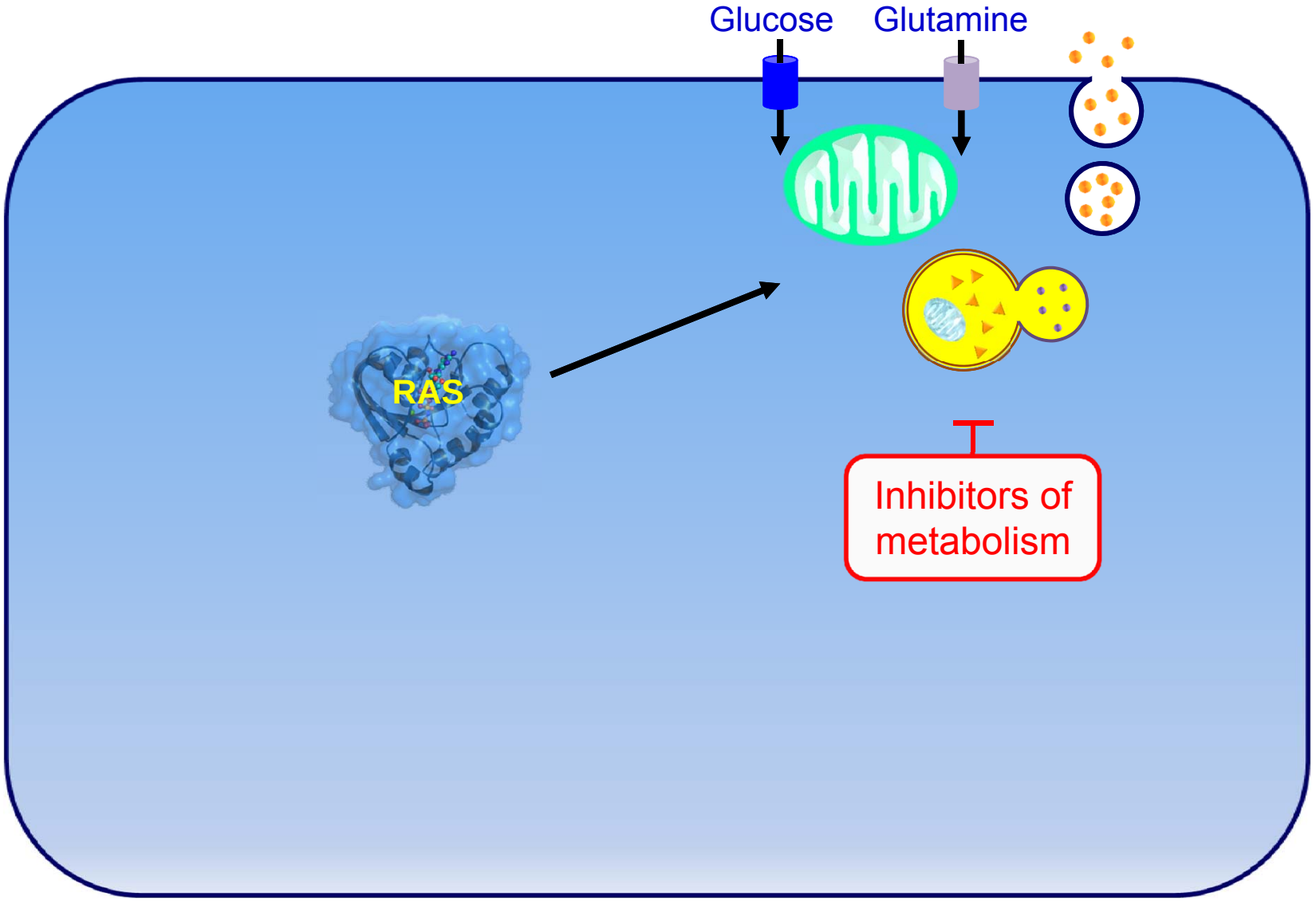
Kobe 2601
2013

Shokat
2013

Whether potent and selective inhibitors can be developed into clinically active and effective anti-RAS drugs remains unclear

Cox et al (2014) Nat Rev Drug Discov 13:828

Targeting metabolism: Warburg revisited



Cox et al (2014) Nat Rev Drug Discov 13:828

Warburg effect

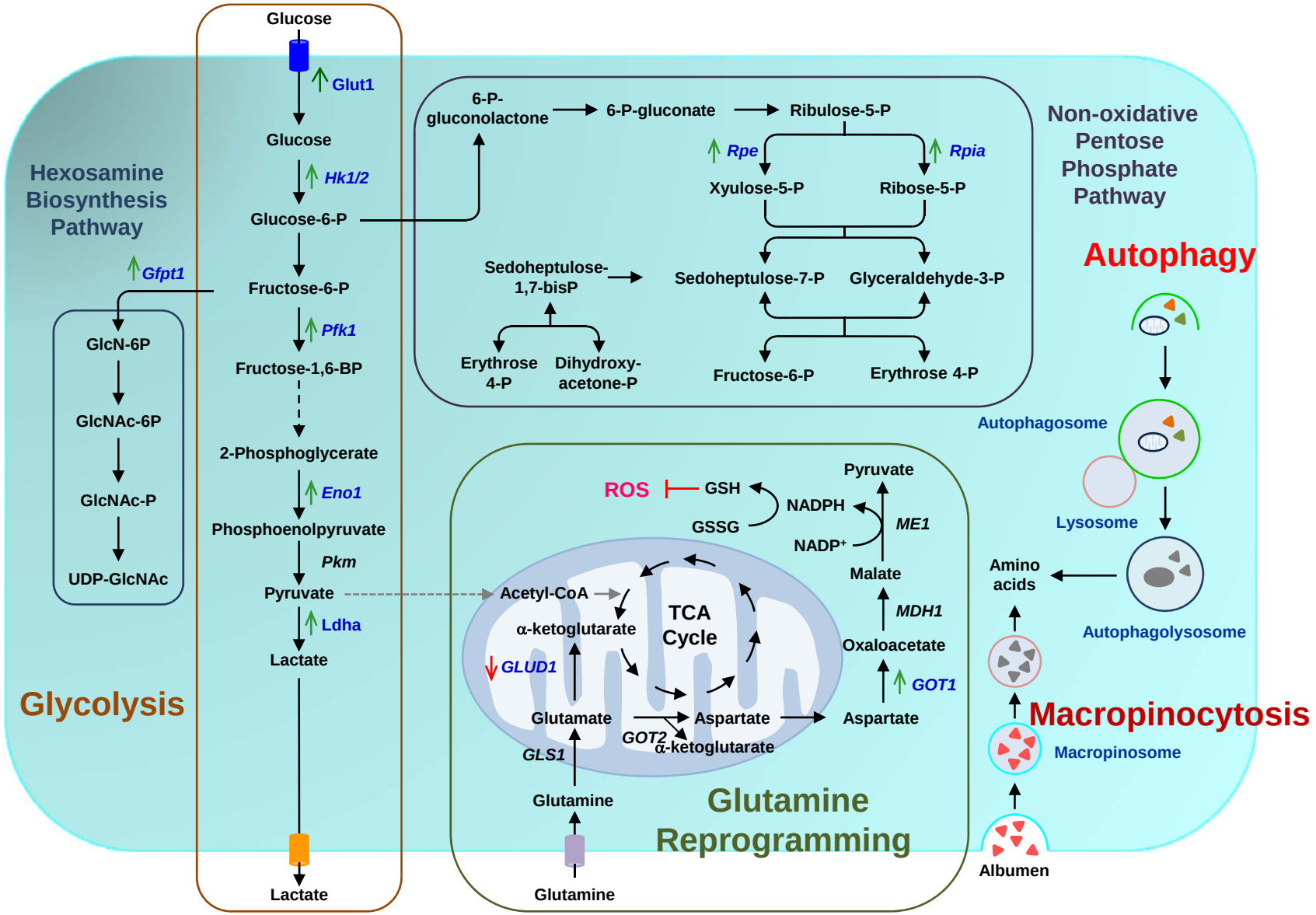
The Nobel Prize in Physiology or Medicine 1931

Otto Heinrich Warburg

"Cancer, above all other diseases, has countless secondary causes. But, even for cancer, there is only one prime cause. Summarized in a few words, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar."

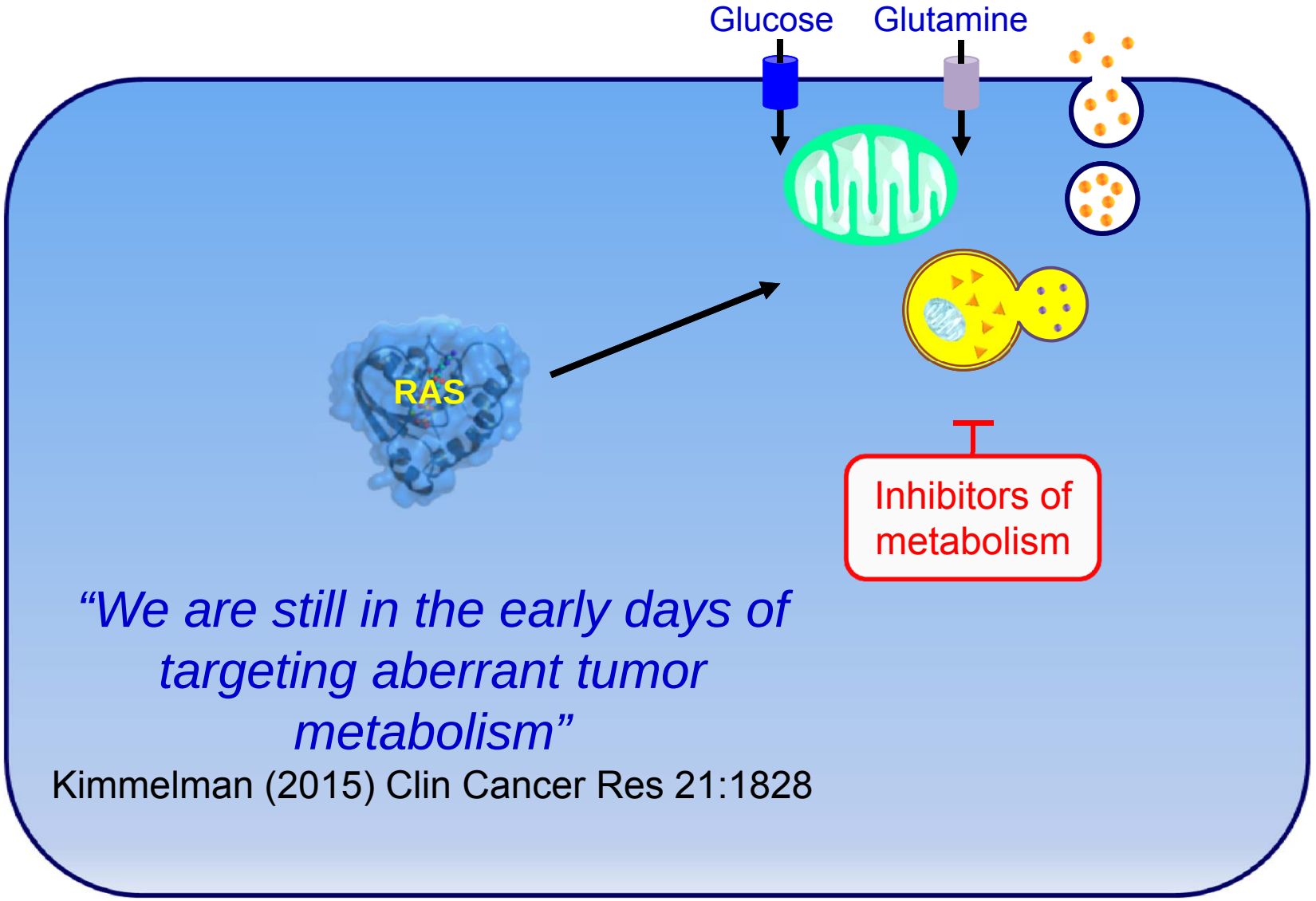
Warburg O, Posener K, Negelein E (1924) üeber den Stoffwechsel der Tumoren. Biochem Z 152: 319

RAS drives aberrant metabolism to feed the cancer cell



Cox et al (2014) Nat Rev Drug Discov 13:828

Targeting metabolism: early days

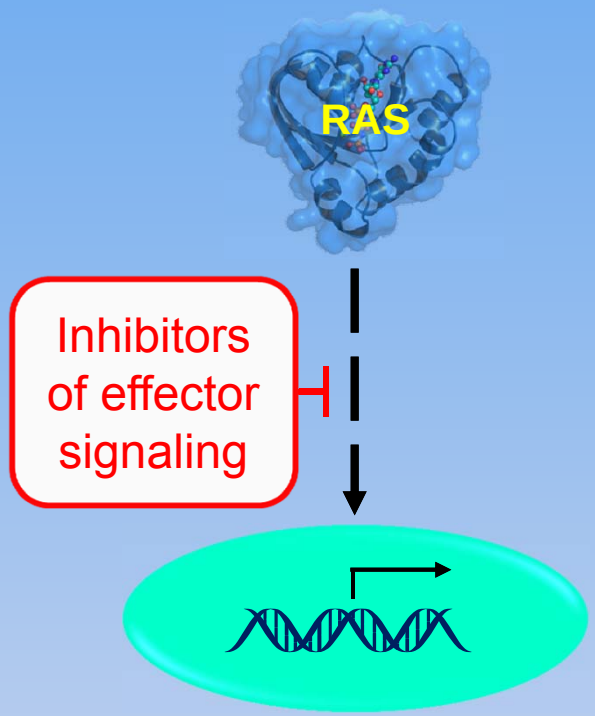


"We are still in the early days of targeting aberrant tumor metabolism"

Kimmelman (2015) Clin Cancer Res 21:1828

Cox et al (2014) Nat Rev Drug Discov 13:828

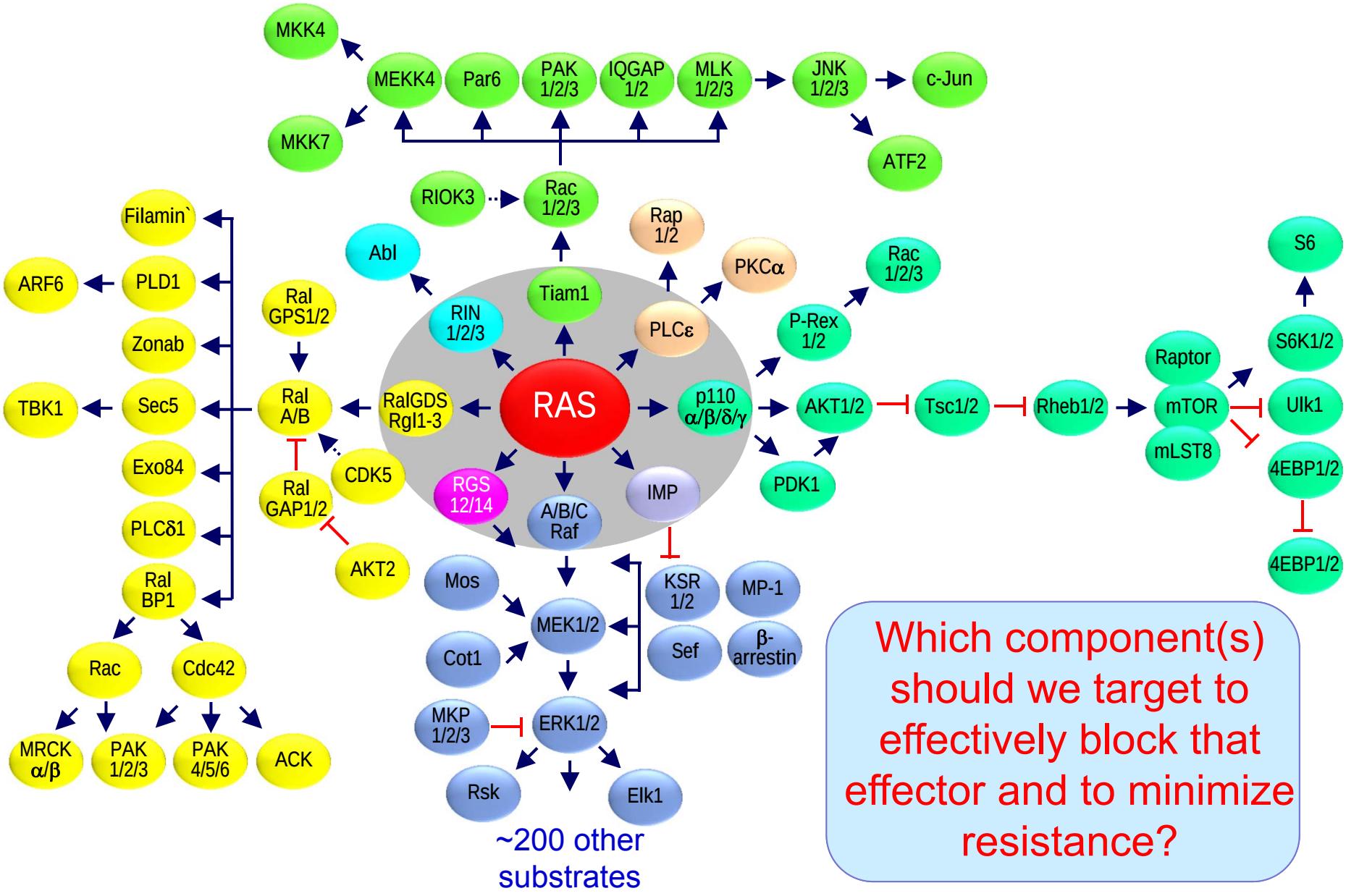
Targeting RAS effectors: our best bet?



- Protein kinase effectors – highly druggable targets
- Many RAS effector inhibitors are currently under clinical evaluation

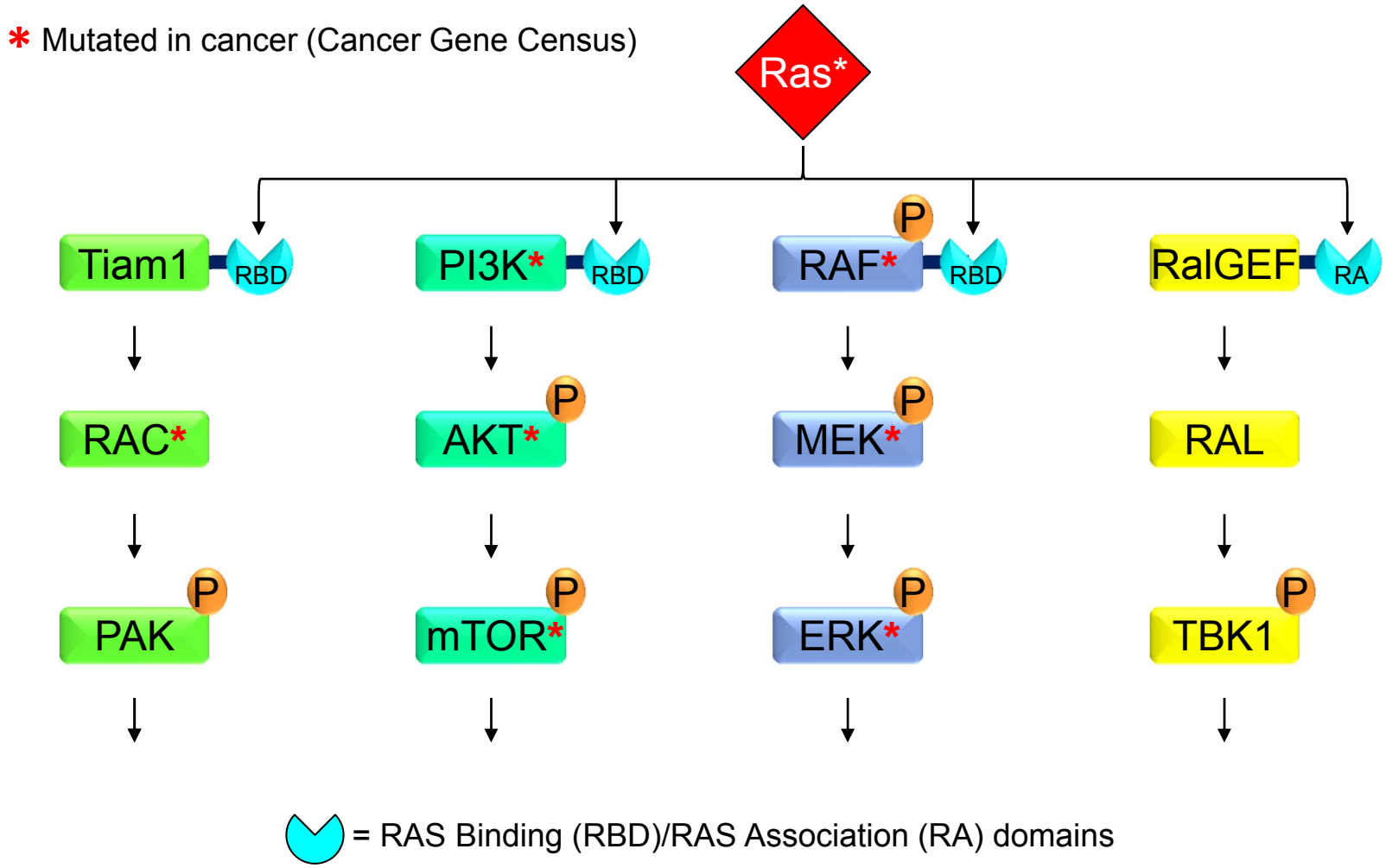
Cox et al (2014) Nat Rev Drug Discov 13:828
Ryan (2015) Trends Cancer 1:183

RAS effector signaling is complex

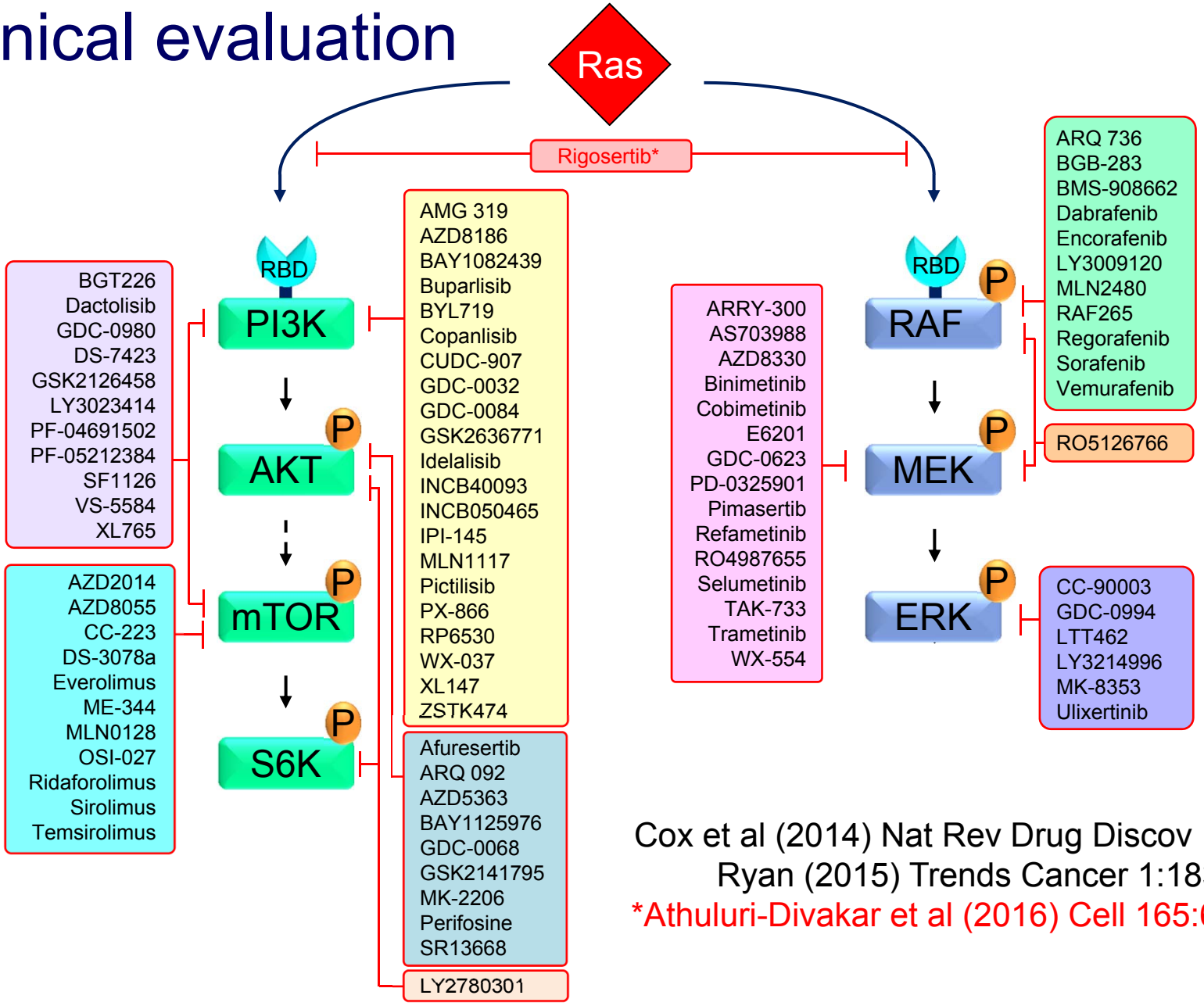


Which component(s) should we target to effectively block that effector and to minimize resistance?

Validated effectors of RAS-dependent cancer growth

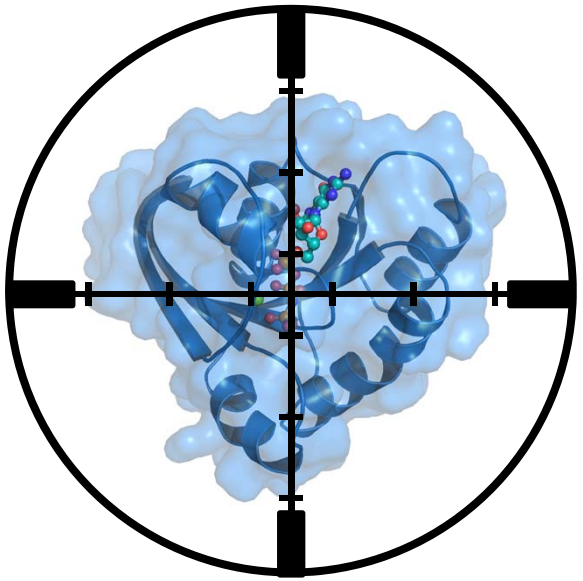


Inhibitors of RAS effector signaling under clinical evaluation



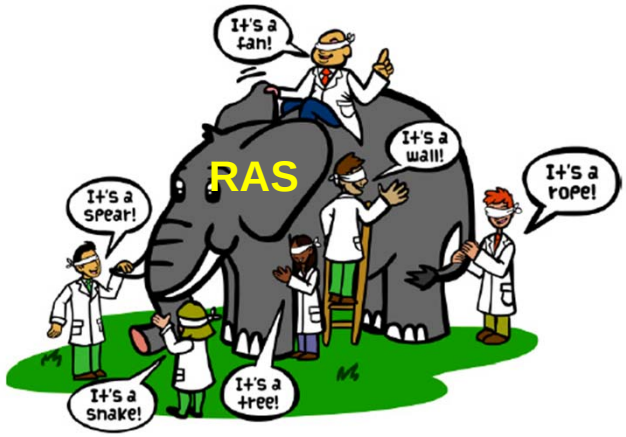
Cox et al (2014) Nat Rev Drug Discov 13:828
Ryan (2015) Trends Cancer 1:183
*Athuluri-Divakar et al (2016) Cell 165:643

Is RAS druggable?

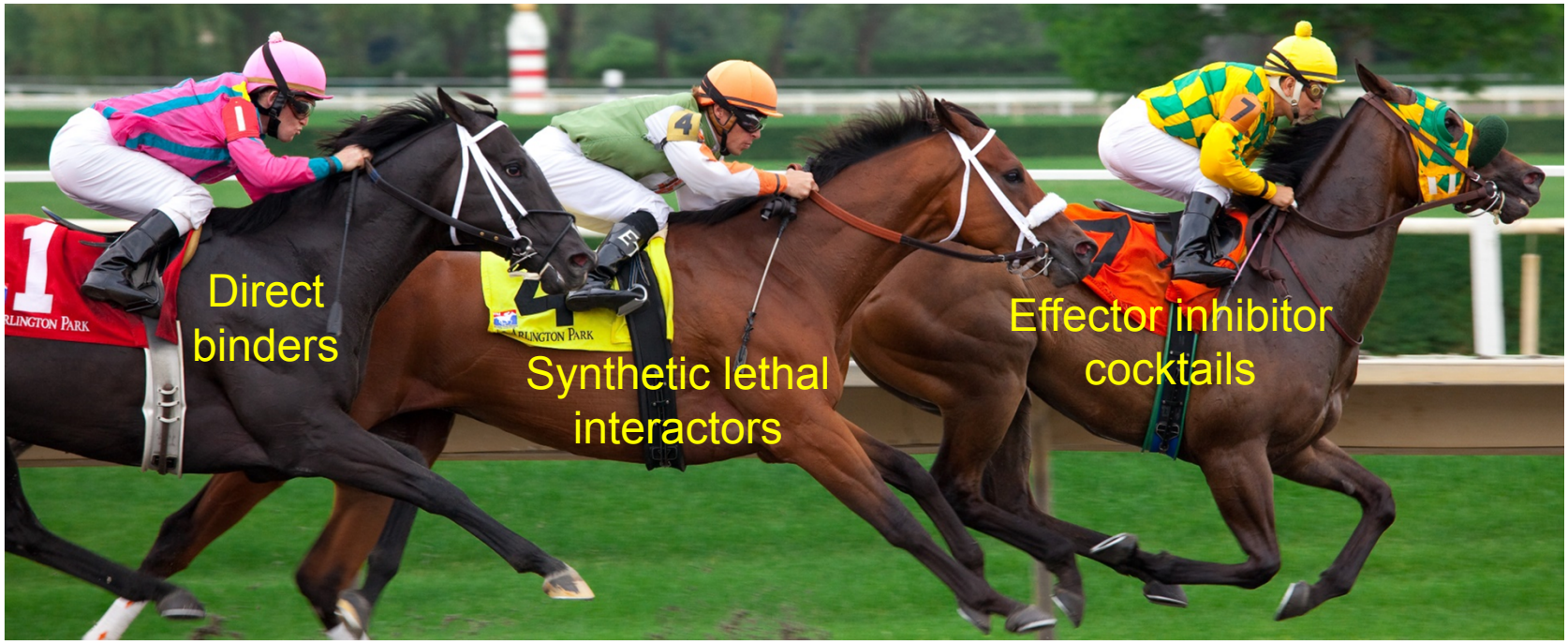


Can we kill RAS?

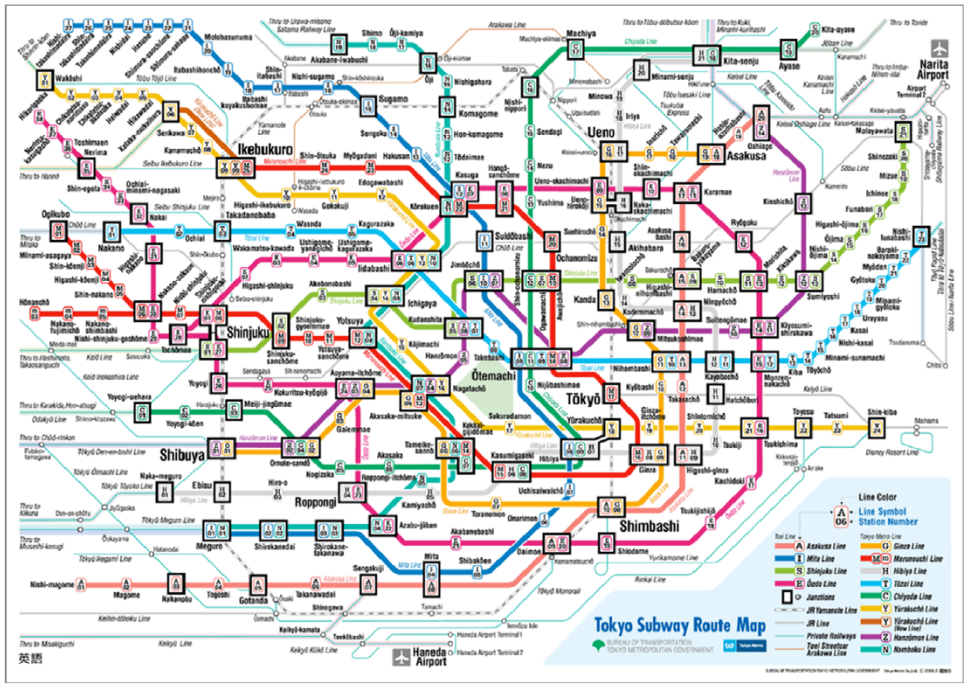
Best bet for the long elusive anti-RAS drug?

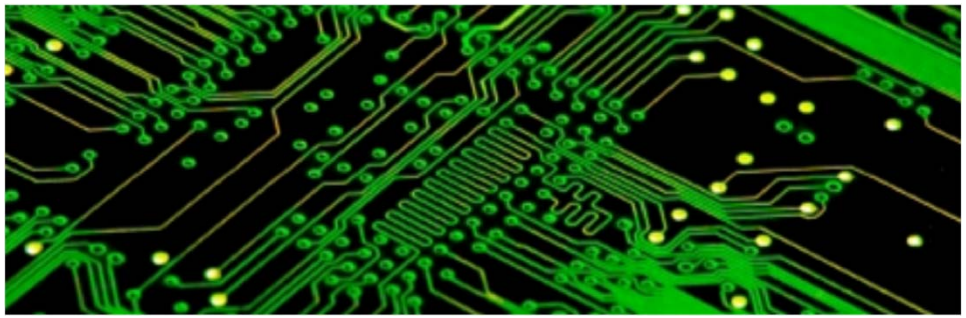


There will be multiple “anti-RAS” therapies, for different cancer subtypes



If a signaling pathway is critical, the cancer cell will have many ways to overcome the block and make the connection





Understanding RAS Signaling and Targeting the "Untargetable"

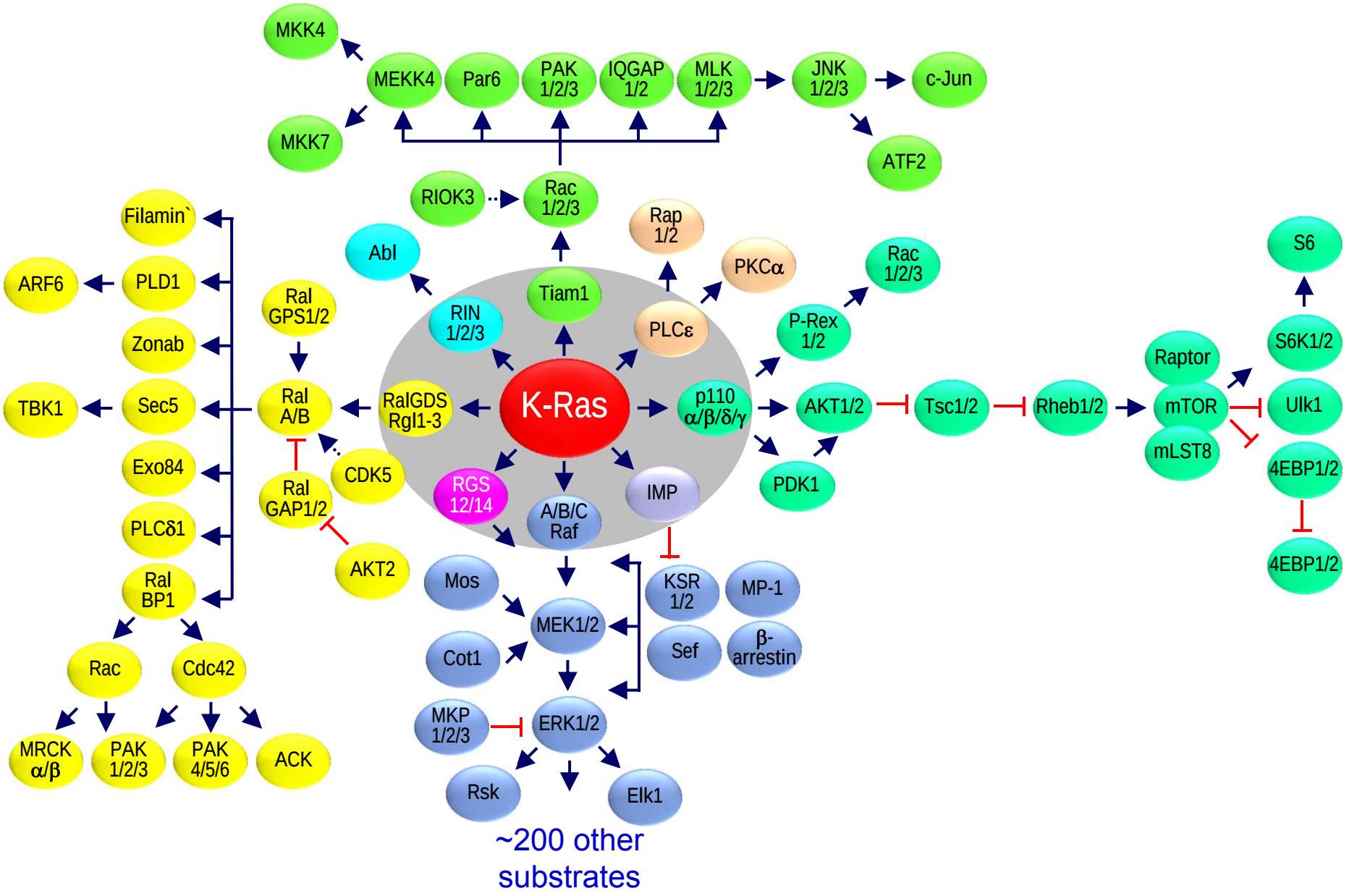
E. Premkumar Reddy, Ph.D.

Icahn School of Medicine at Mount Sinai
New York

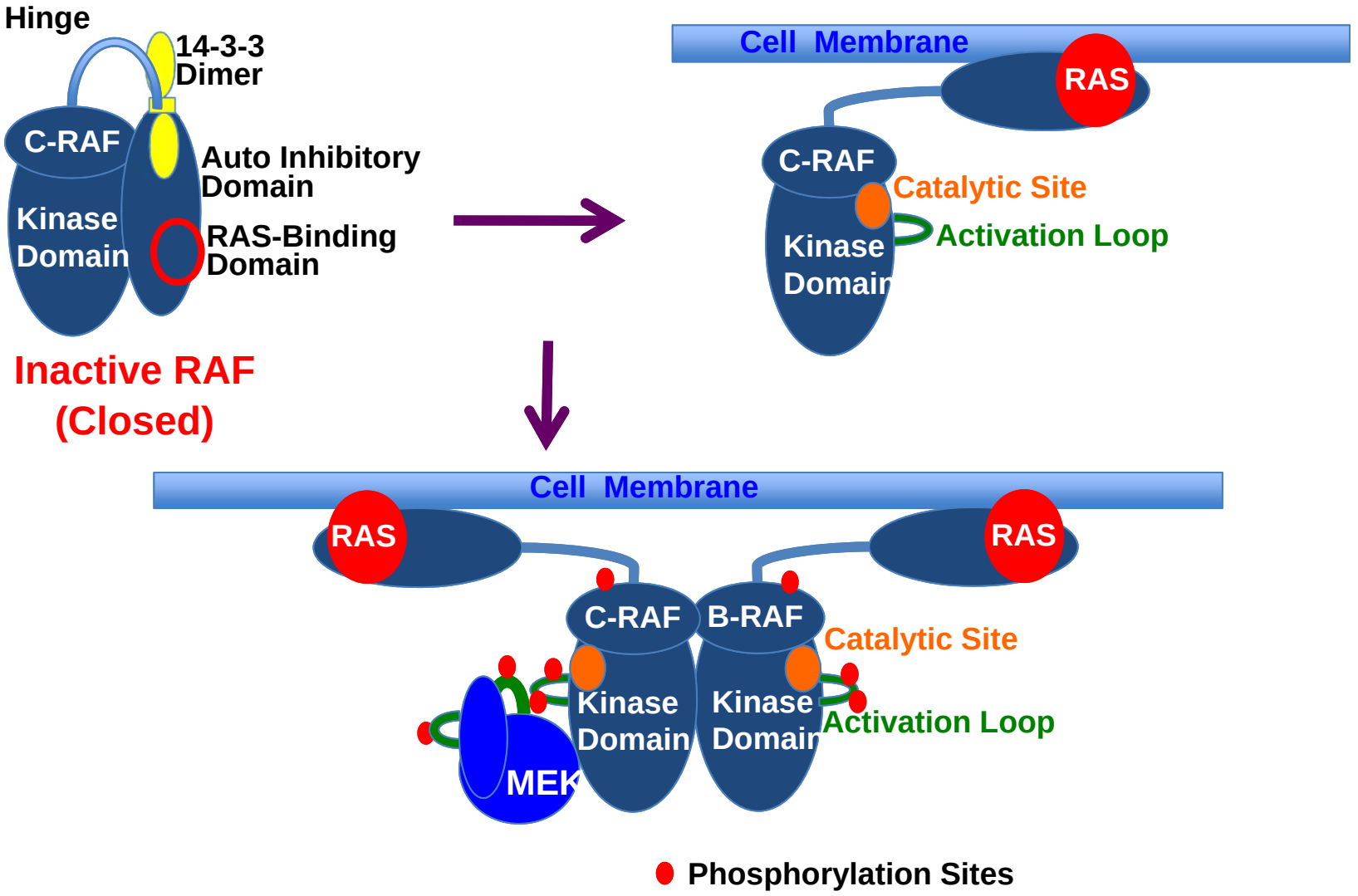
Rigosertib Background

- Rigosertib is a novel small molecule ras mimetic
  - Patent protected for composition and use
  - Entered clinical trials in 2005
  - More than 1,000 patients in trials
  - Well-tolerated; efficacy signal in MDS and solid tumors
- Mechanism of action studies over a decade
  - Key differentiation with chemotherapeutics, targeted kinases and epigenetic modulators
  - Molecular mechanism of action revealed in 2016
    - Cell publication in April 2016

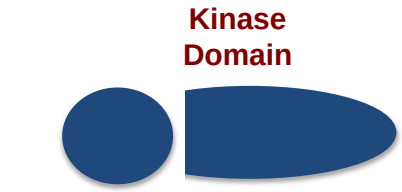
Ras effector signaling is complex

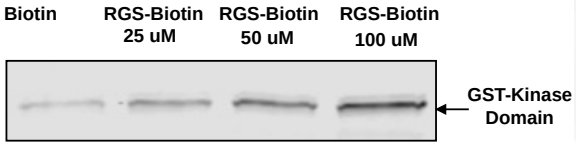


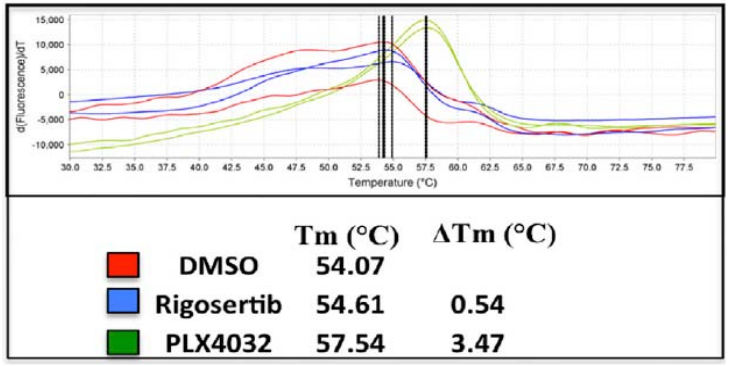
Ras-Raf Pathway

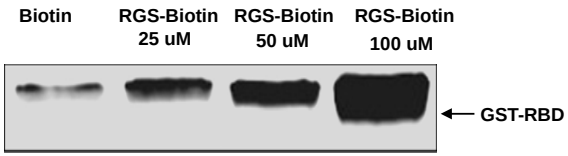


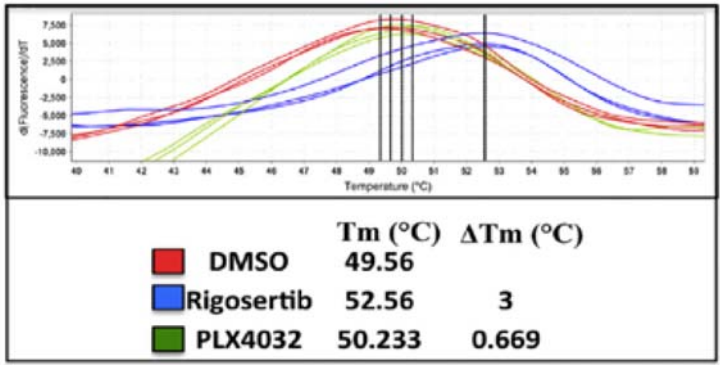
Rigosertib Binds to RBD Domain of RAF

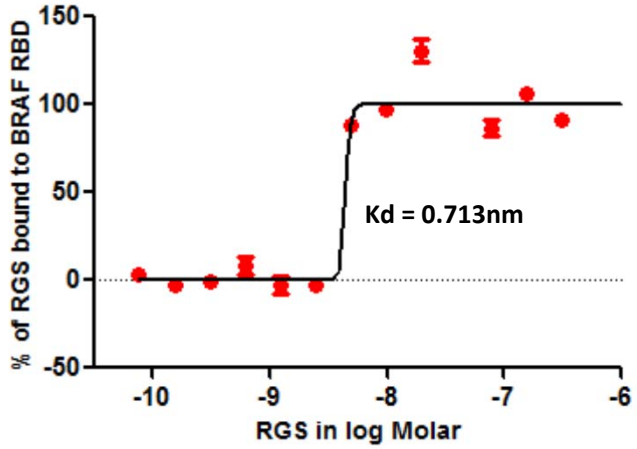












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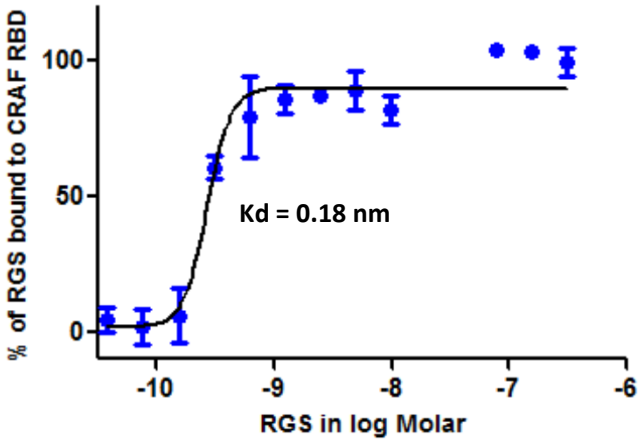
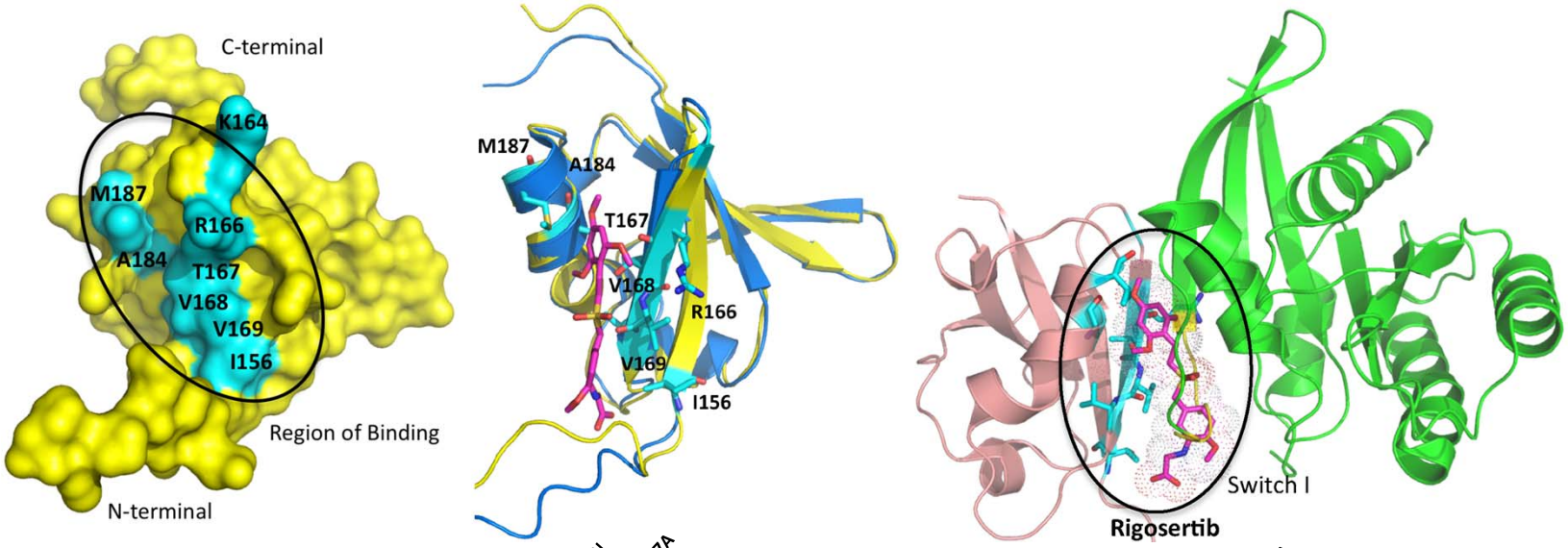
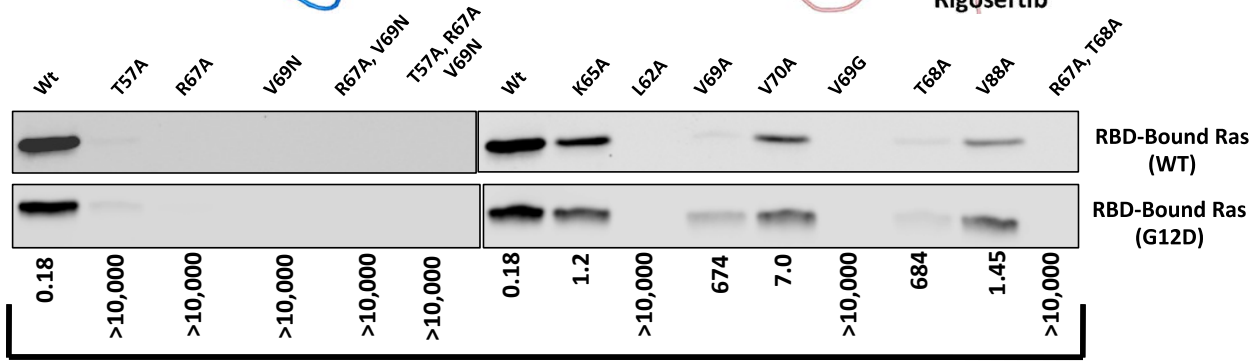
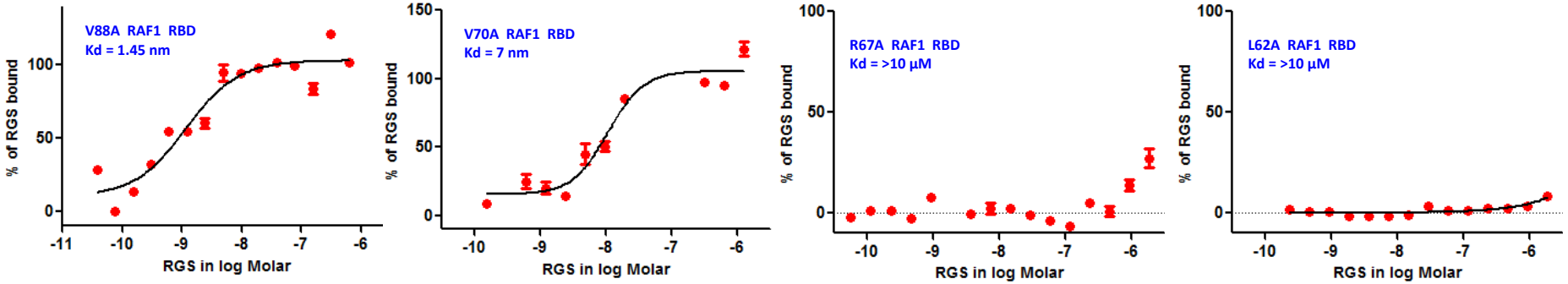


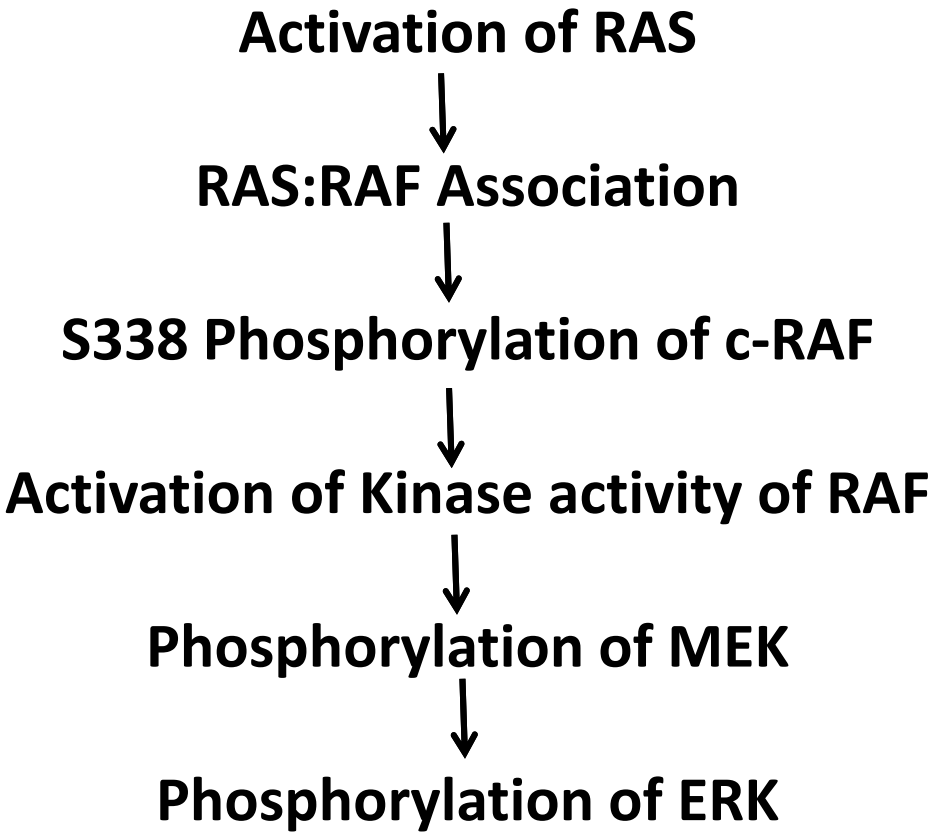
Structure of Rigosertib:Raf-RBD Complex



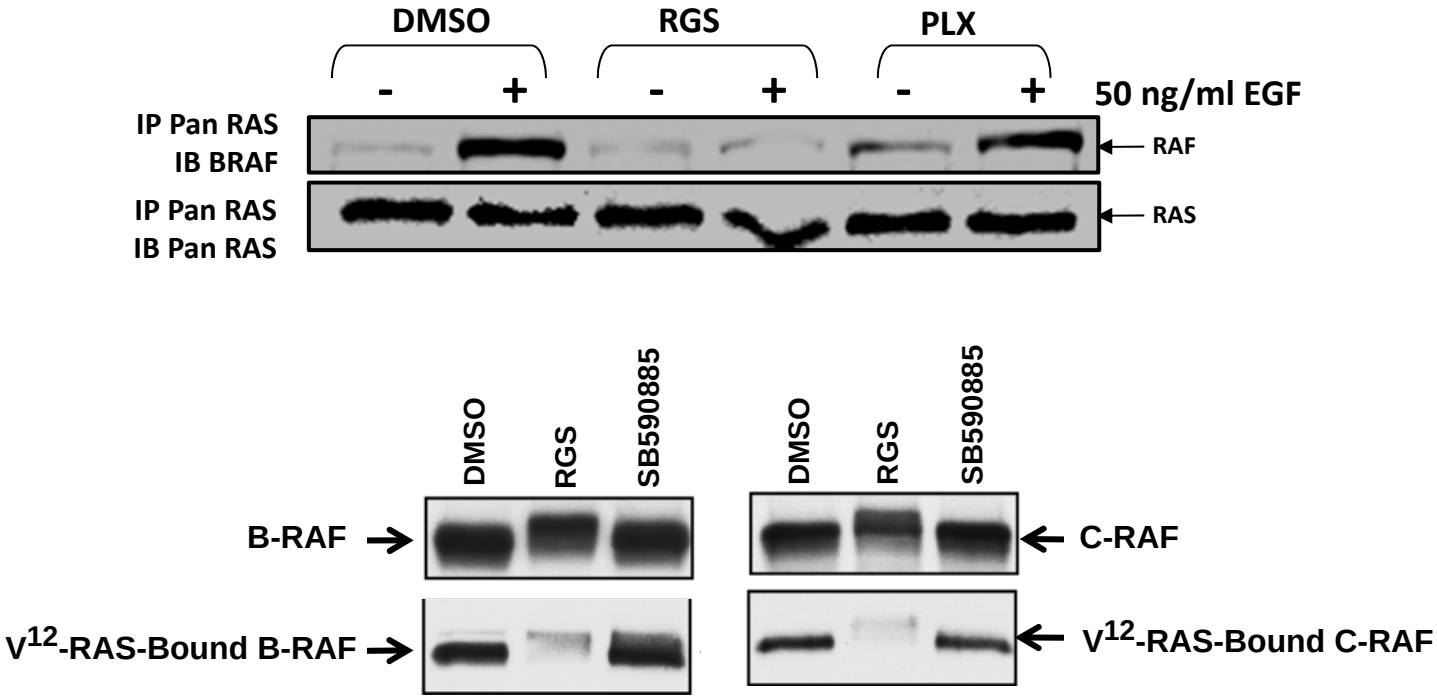




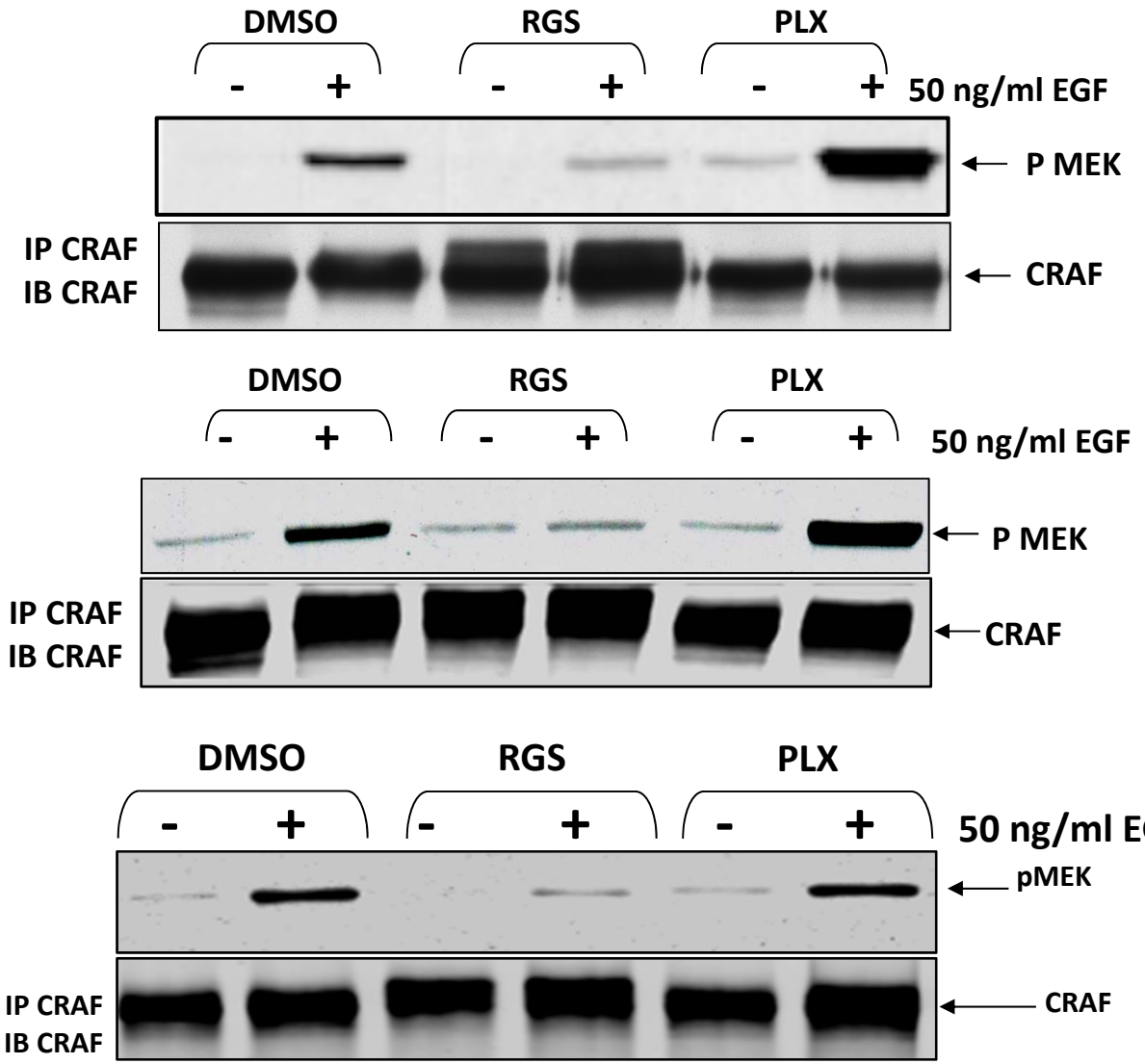
Events Associated with RAS activation



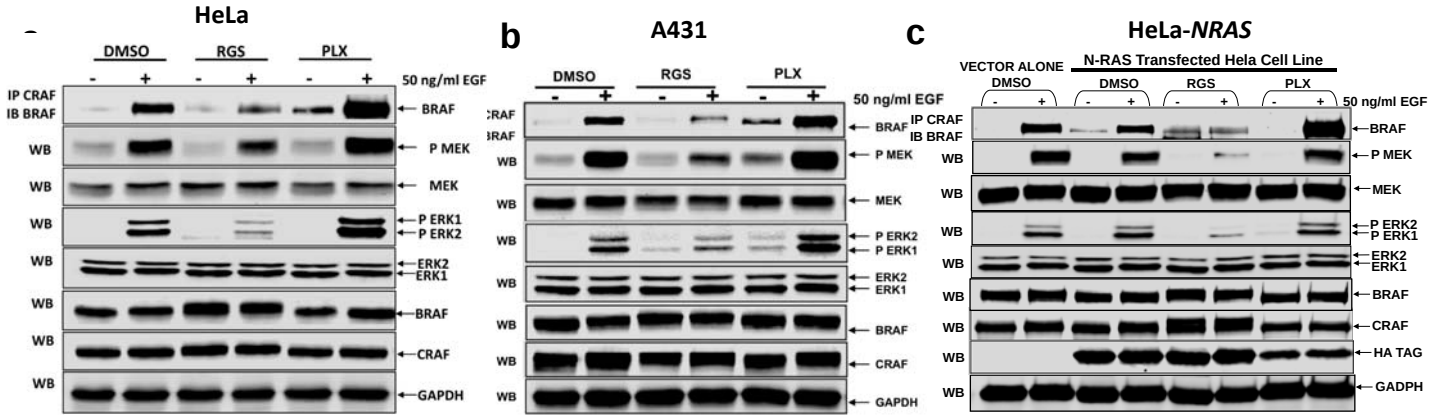
Inhibition of Ras-Raf interactions by Rigosertib

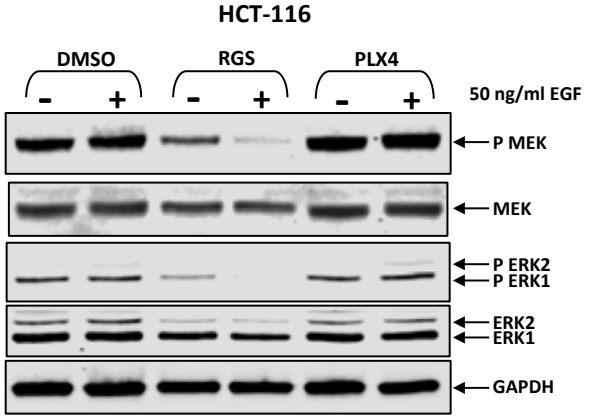


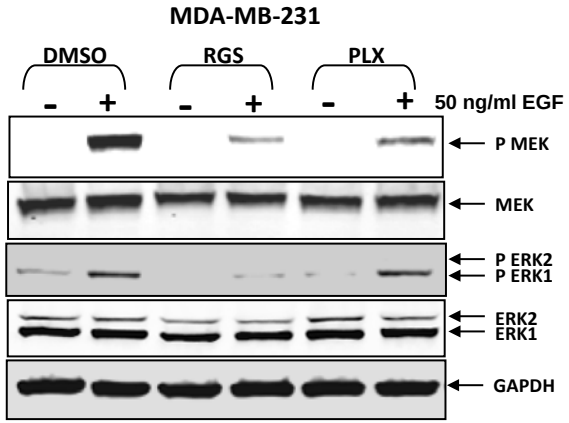
Rigosertib Blocks Growth Factor-Induced Raf Kinase Activity

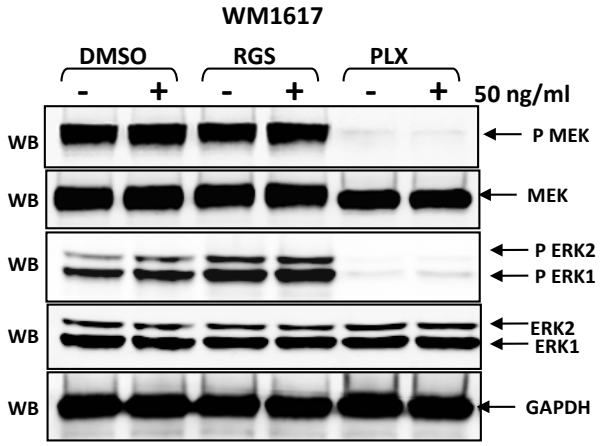


Rigosertib Inhibits Growth Factor-Induced ERK/MAPK Signaling

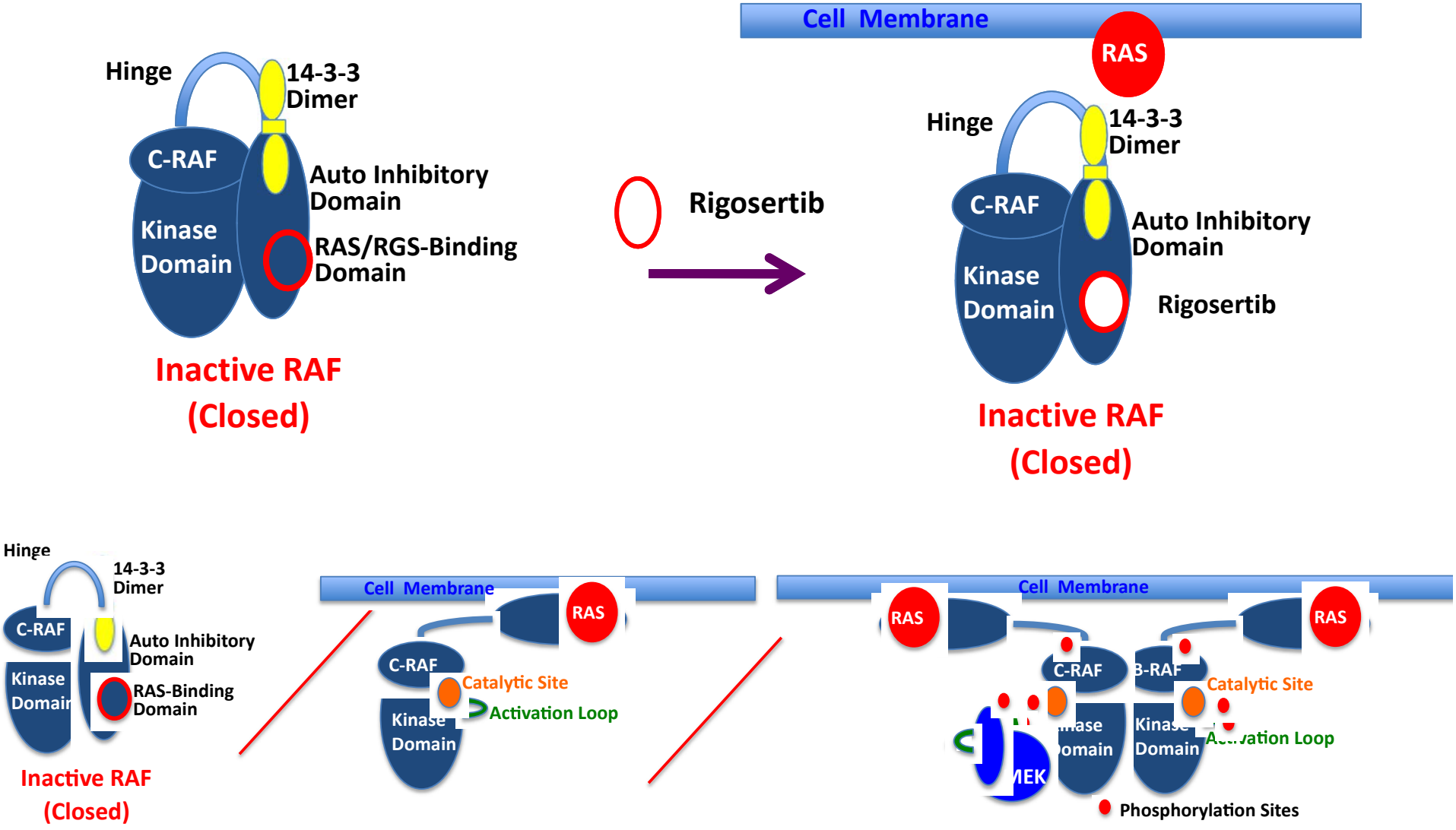




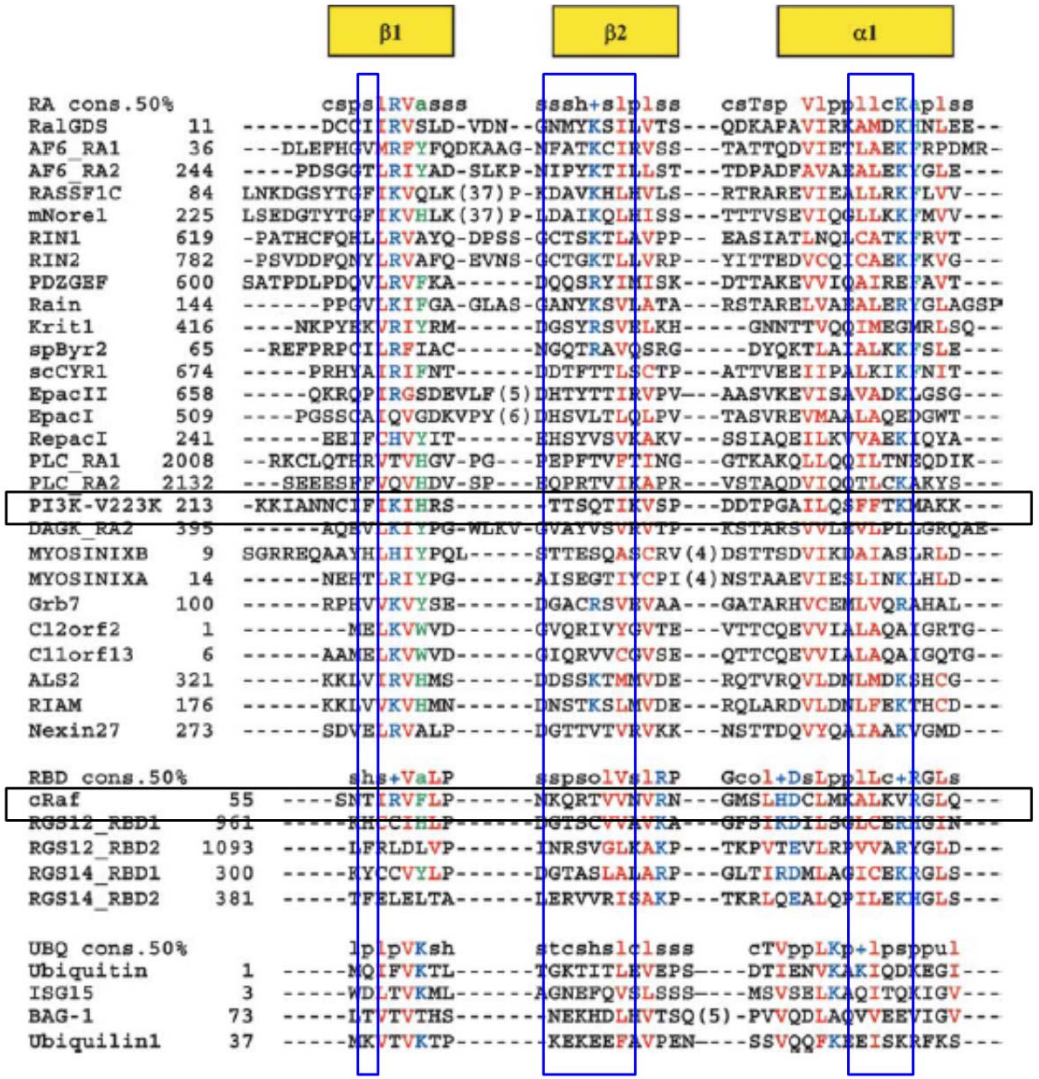




Binding of Rigosertib to RAF Disrupts RAS-RAF Interaction



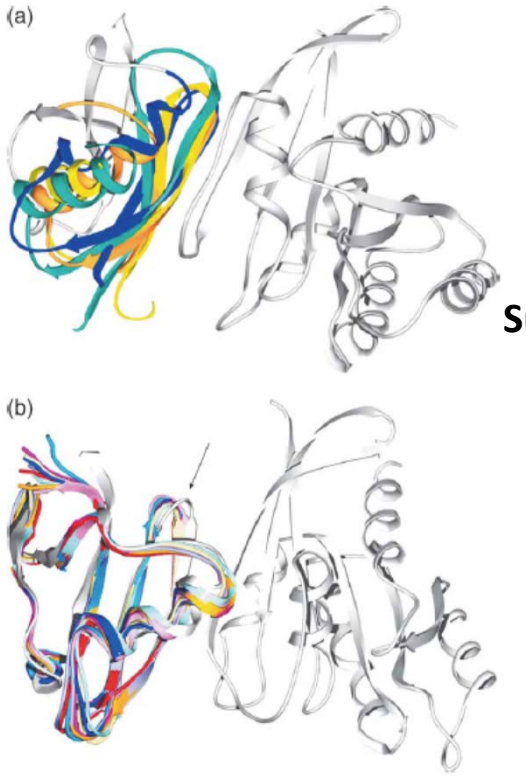
Ras-Binding Domains have nearly Identical Secondary & Tertiary Structure in spite of lack of Extensive Sequence Homology



Sequence Alignment of RA and RB Domains

Yellow: Hydrophobic Core; Cyan: Conserved Charged Amino Acids

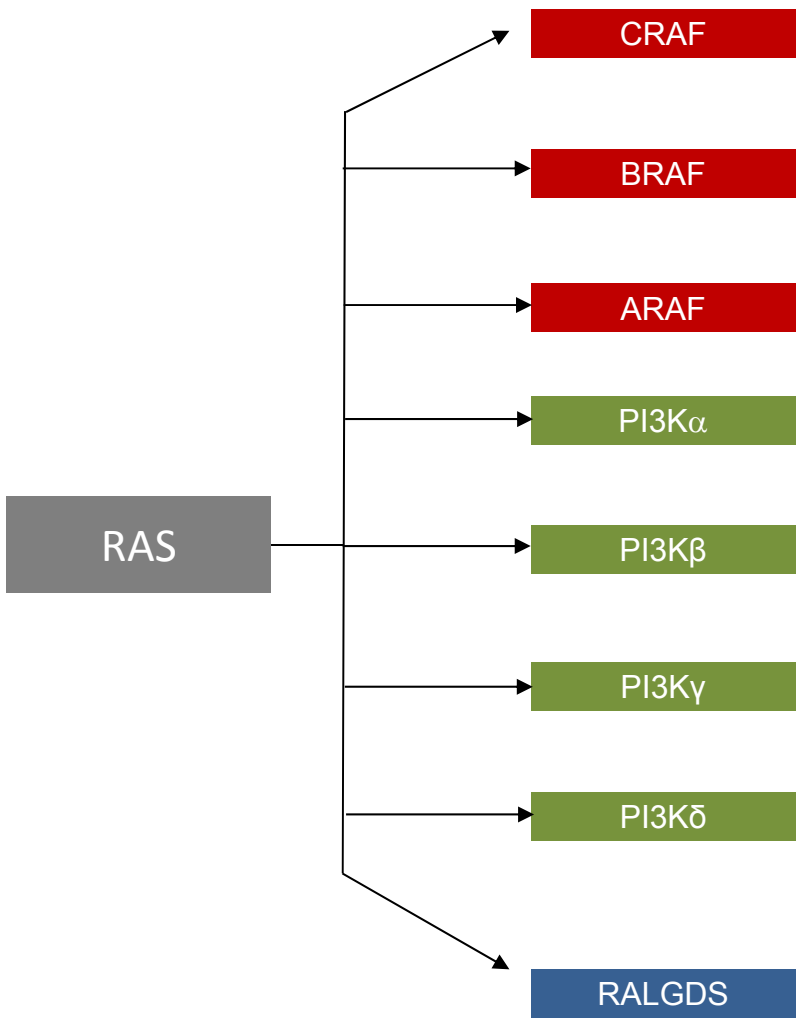
Red: Conserved Hydrophobic AA; Green: Conserved Aromatic AA

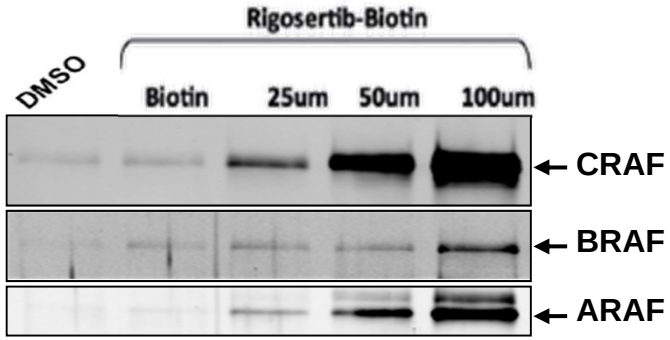


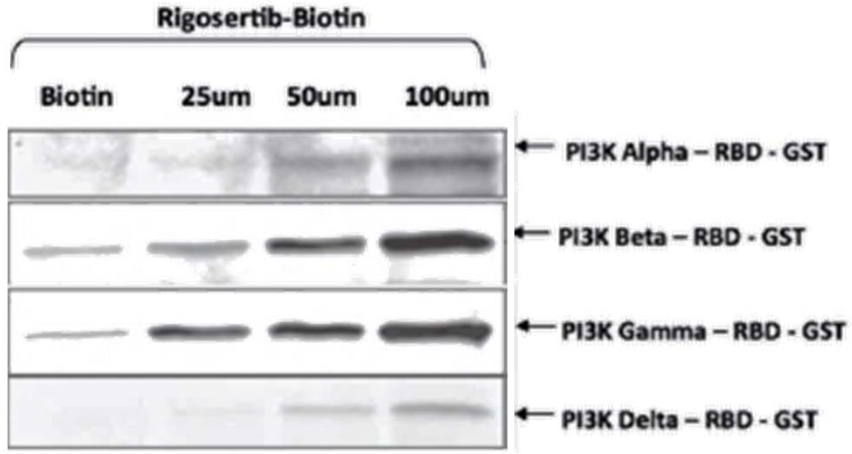
Raf
Ral-GDS
PI3K
Crystal
Structures
Superimposed

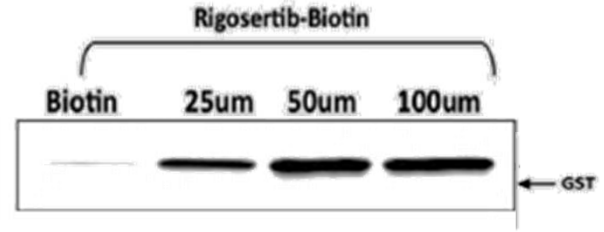
NMR
Structures
of 10 RBDs
Super-
Imposed

Rigosertib Binds to RBD Domains of RALGDS- and PI3Ks

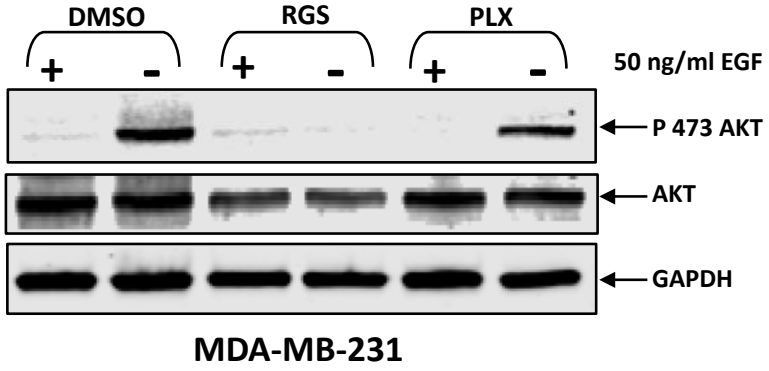




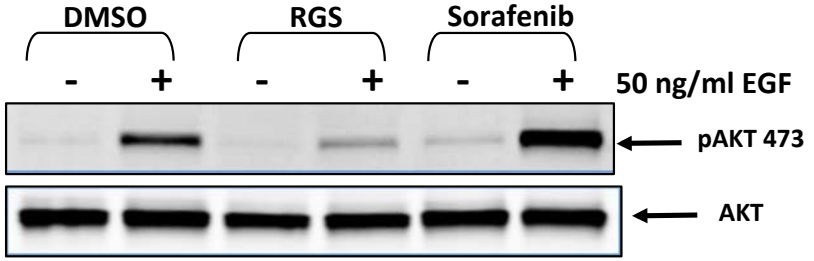




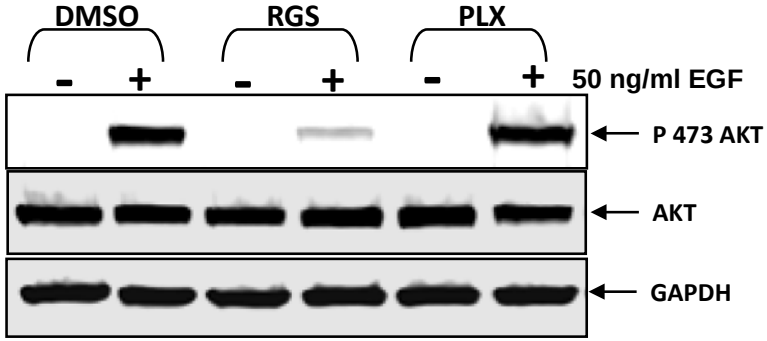
Rigosertib blocks AKT Activation



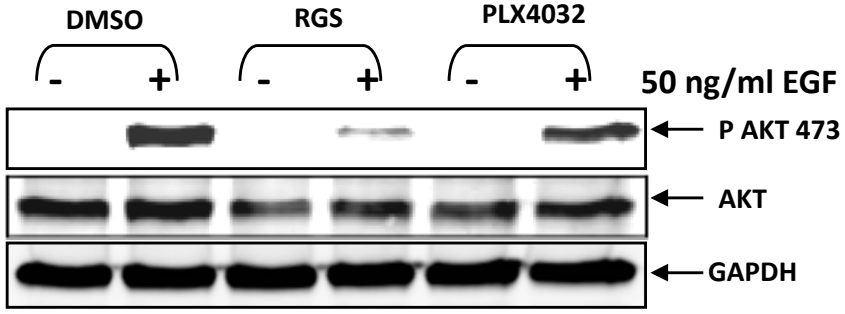
MDA-MB-231



MIA PaCa-2



HCT-116

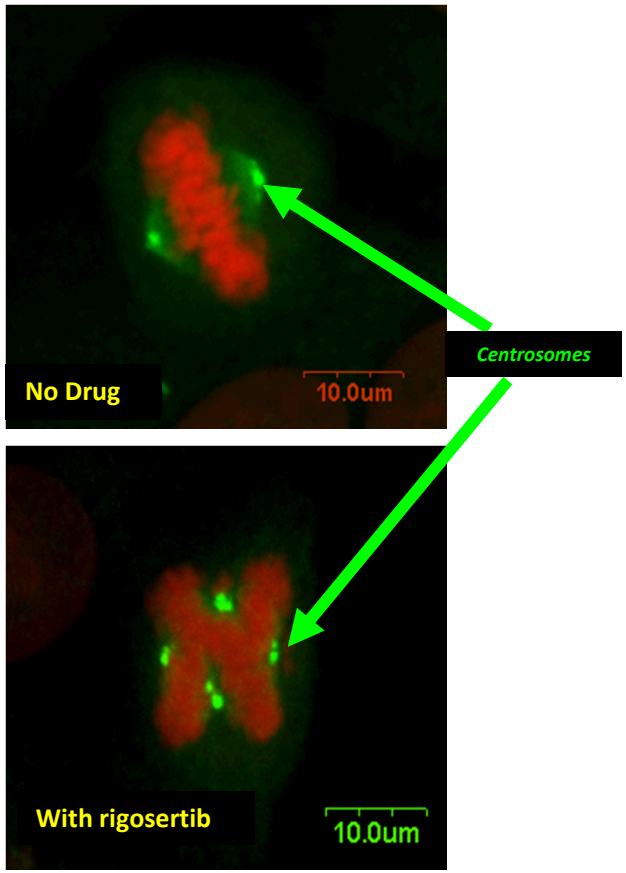


SNF96.2 (NF-1)

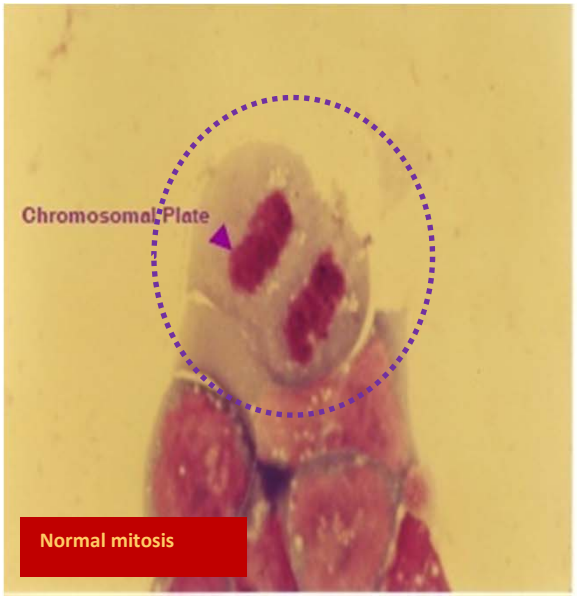
Rigosertib Causes Mitotic Catastrophe of Cancer Cells

Mitotic Catastrophe in Cancer Cells Treated with Rigosertib*

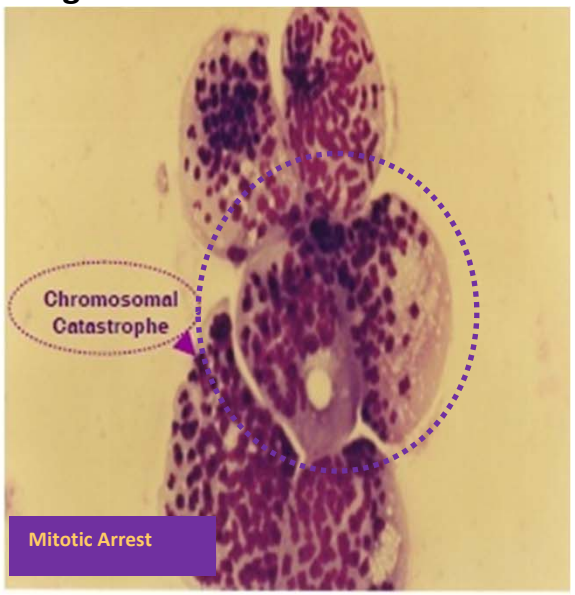
- In cancer cells Rigosertib causes chromosome "blow up" (below)
- Increased number of centrosomes (green, on right) cause this effect



Vehicle Treated Leukemic Cells



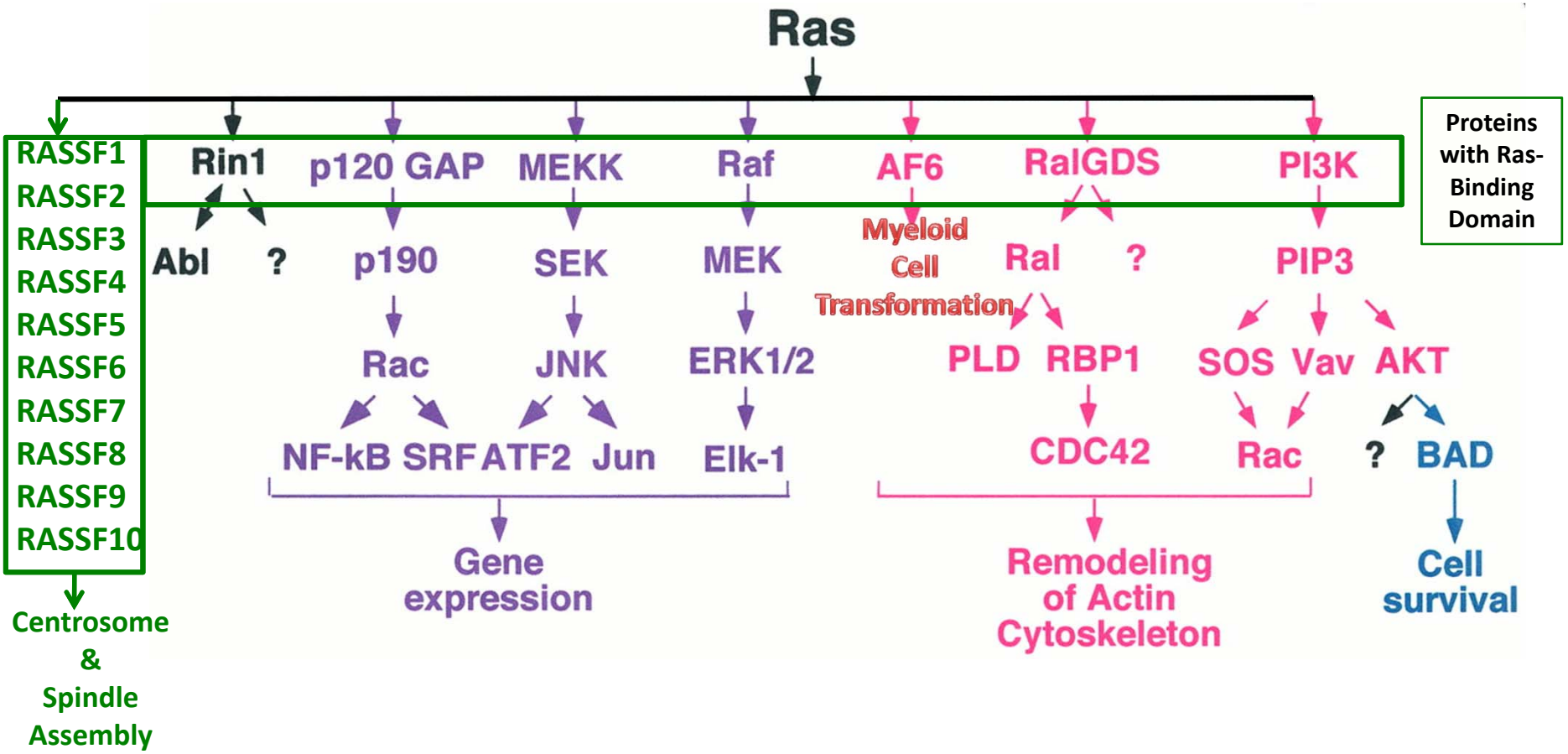
Rigosertib Treated Leukemic Cells



****Dr. Holland, Mt. Sinai***

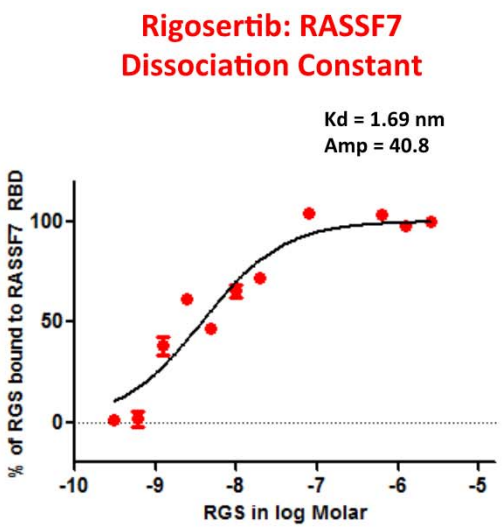
Ras Signals Thru Multiple Effectors

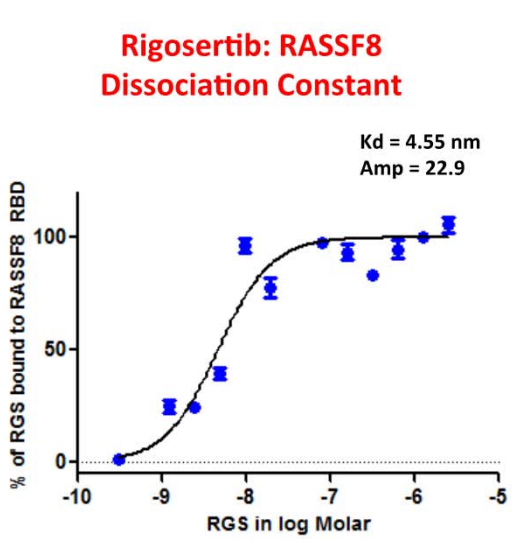
Vojtek A B , and Der C J J. Biol. Chem. 1998;273:19925-19928

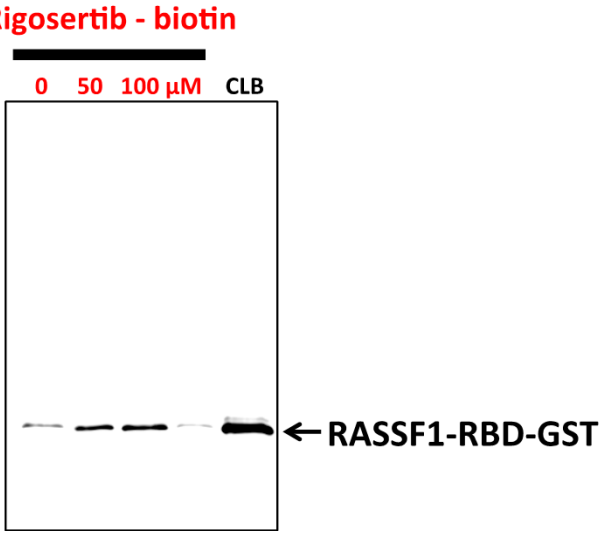


jbc

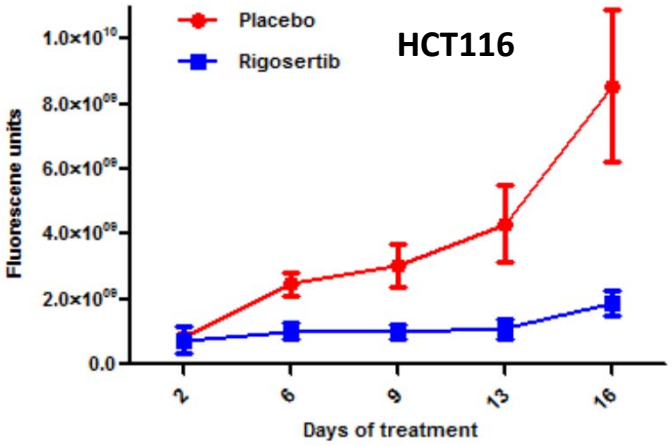
Rigosertib binds to the RA domains of RSSF Proteins

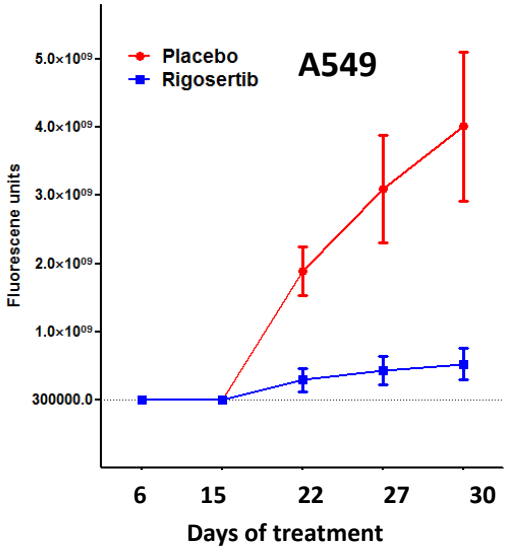


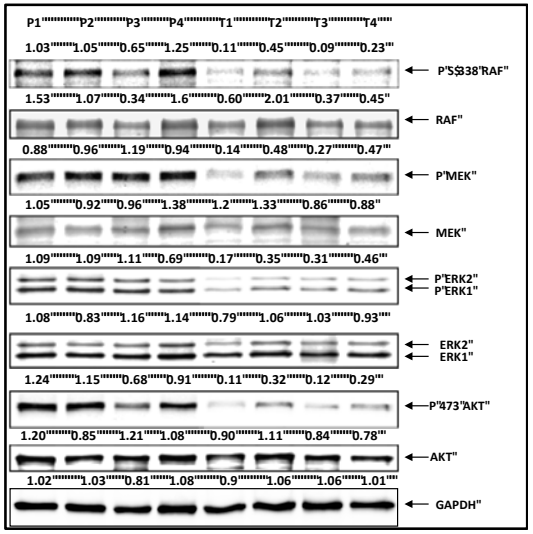




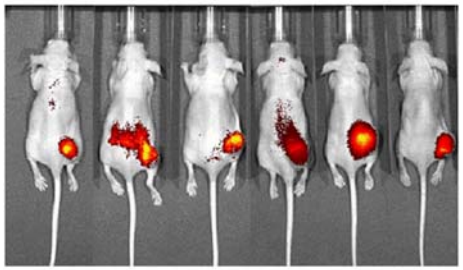
Inhibition of Tumor Growth by Rigosertib in Mouse Xenograft Assays



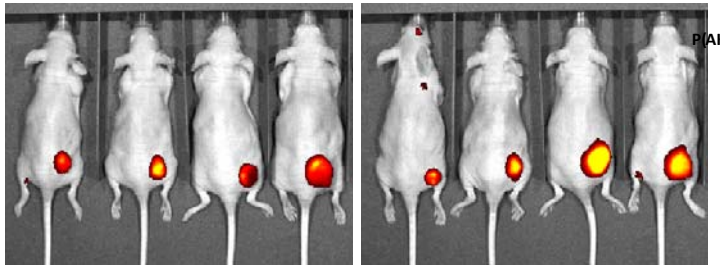




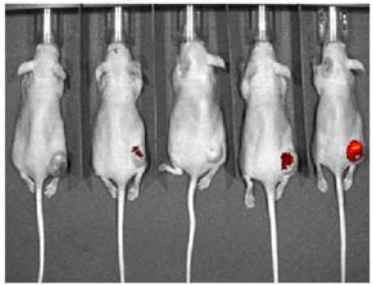
Control - untreated



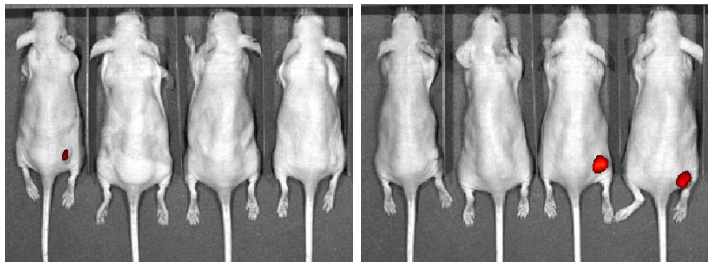
Placebo - treated

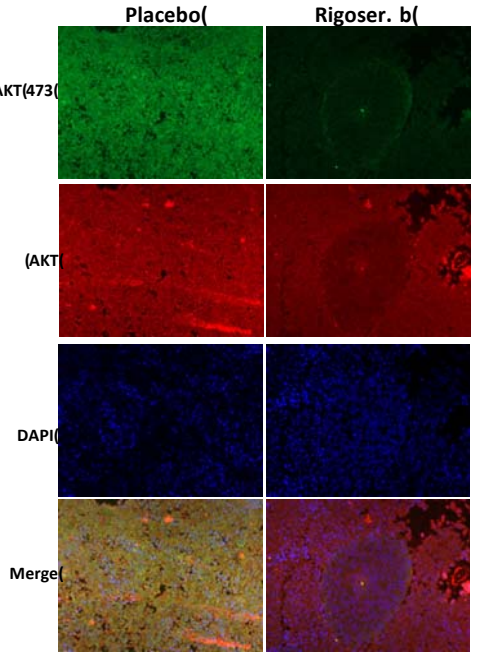


Rigosertib treated

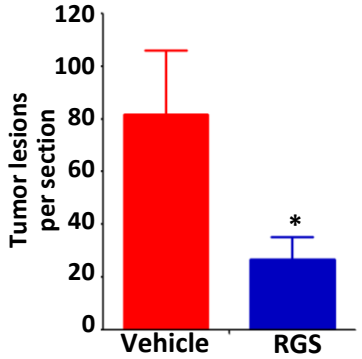


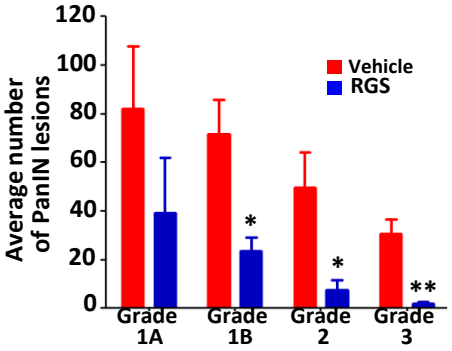
Rigosertib treated

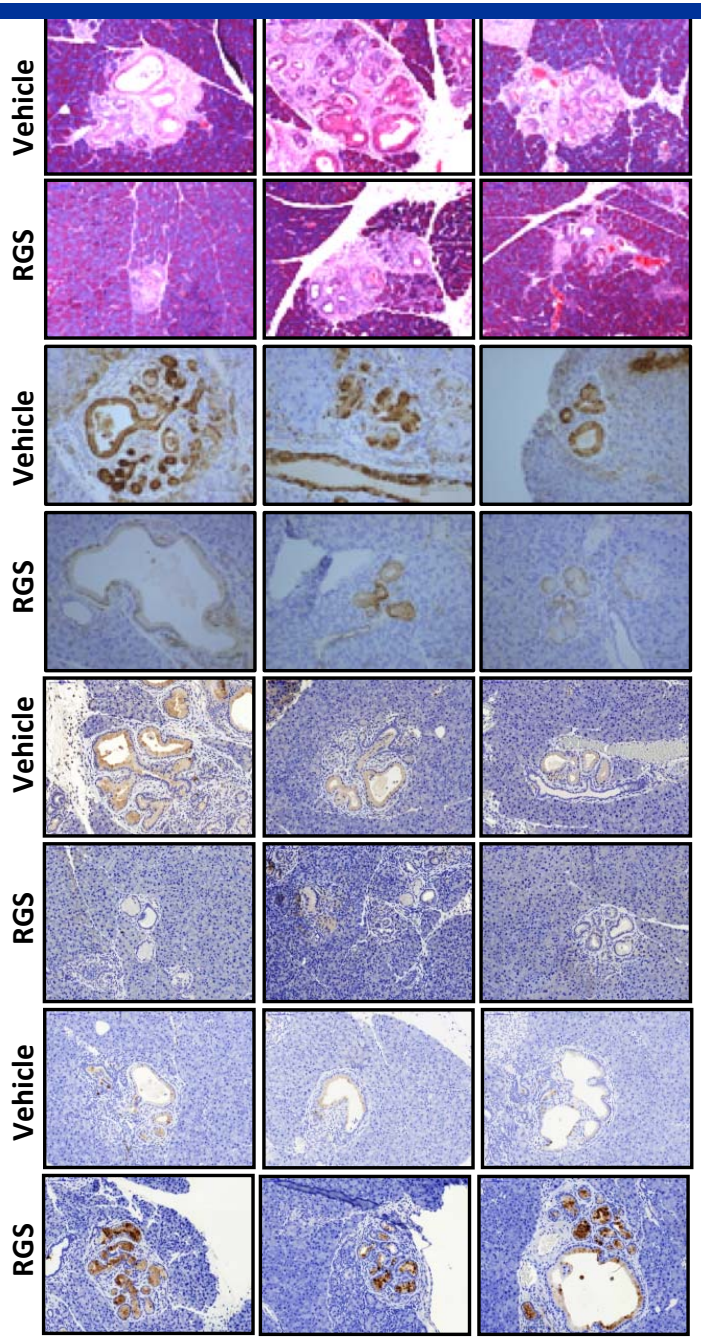


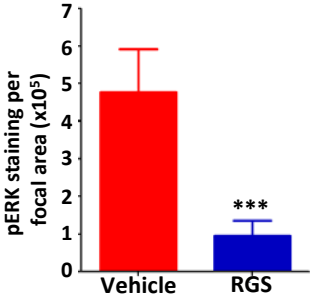


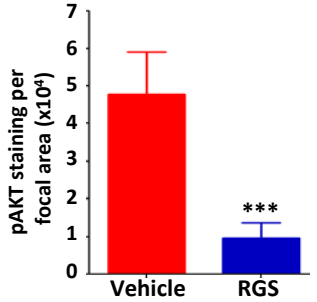
Rigosertib Suppresses Growth of RAS-driven Pancreatic Cancer.

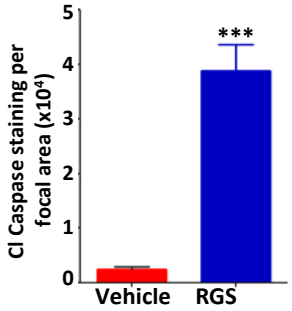








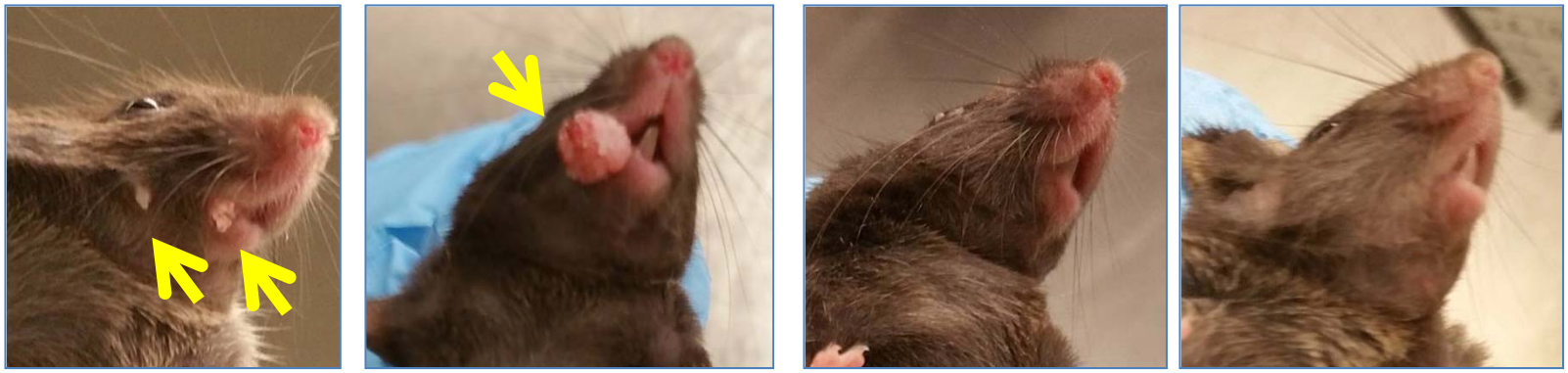




PDX-1-CRE; LSL-KRAS ^{G12D} - Rigosertib treatment

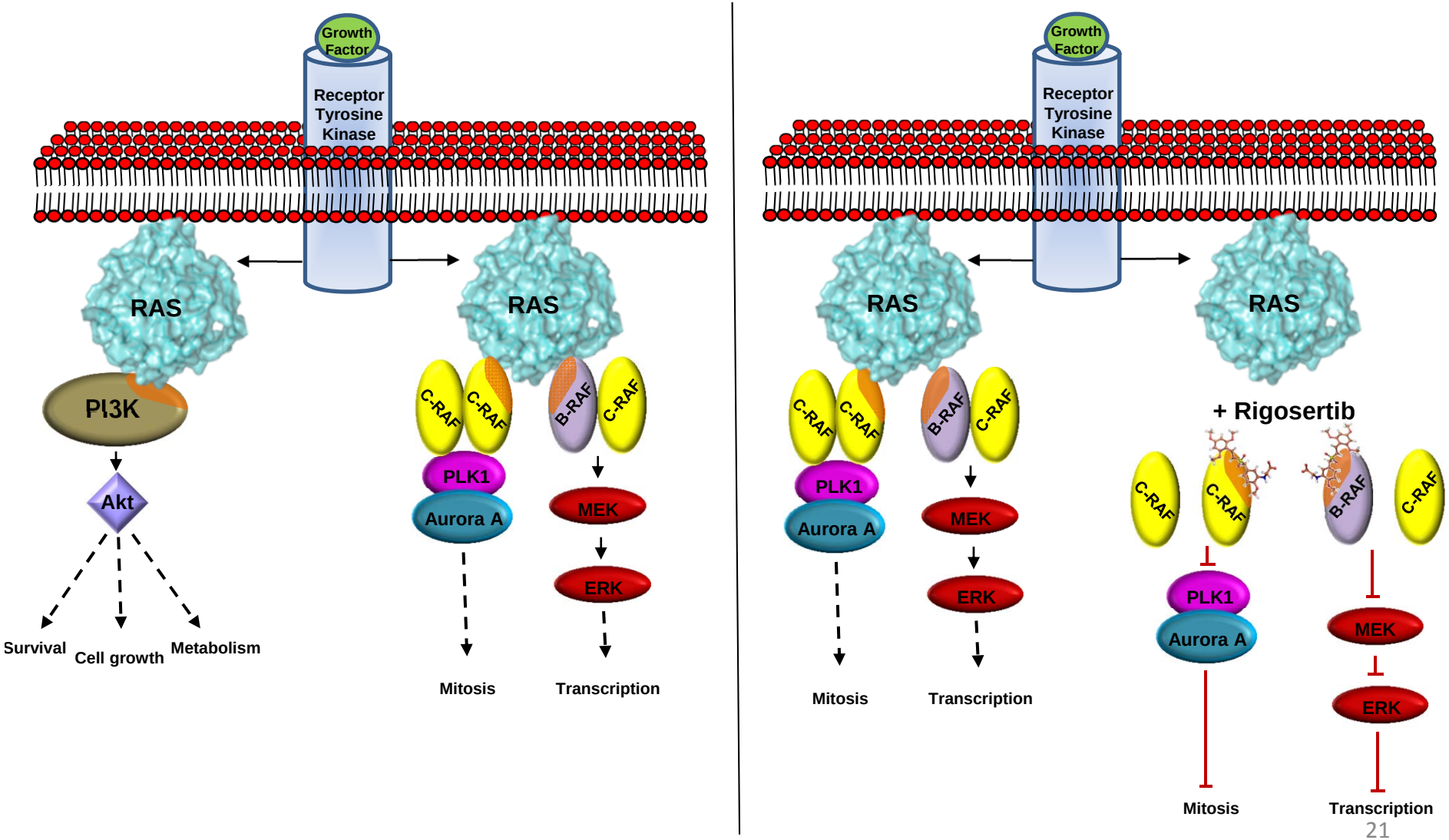
Vehicle treated

Rigosertib treated



Papillomas are highlighted in yellow

Rigosertib Mechanism of Action

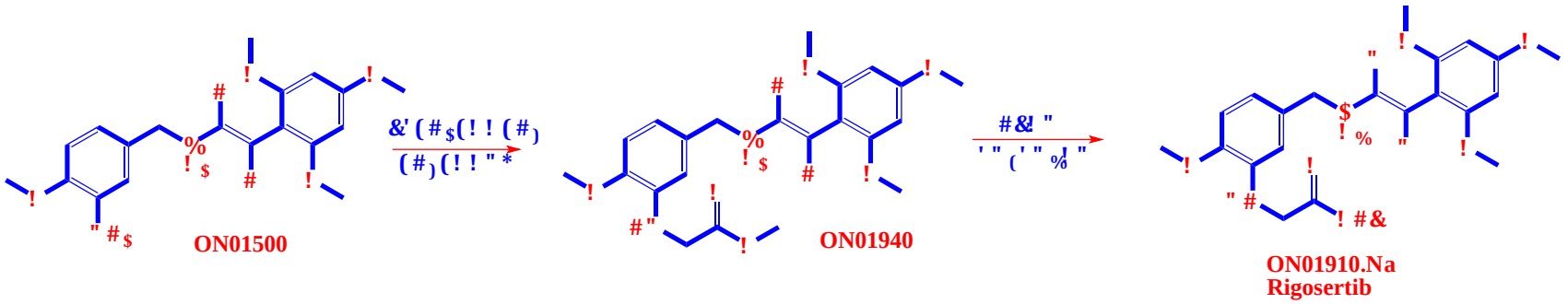


Conclusions

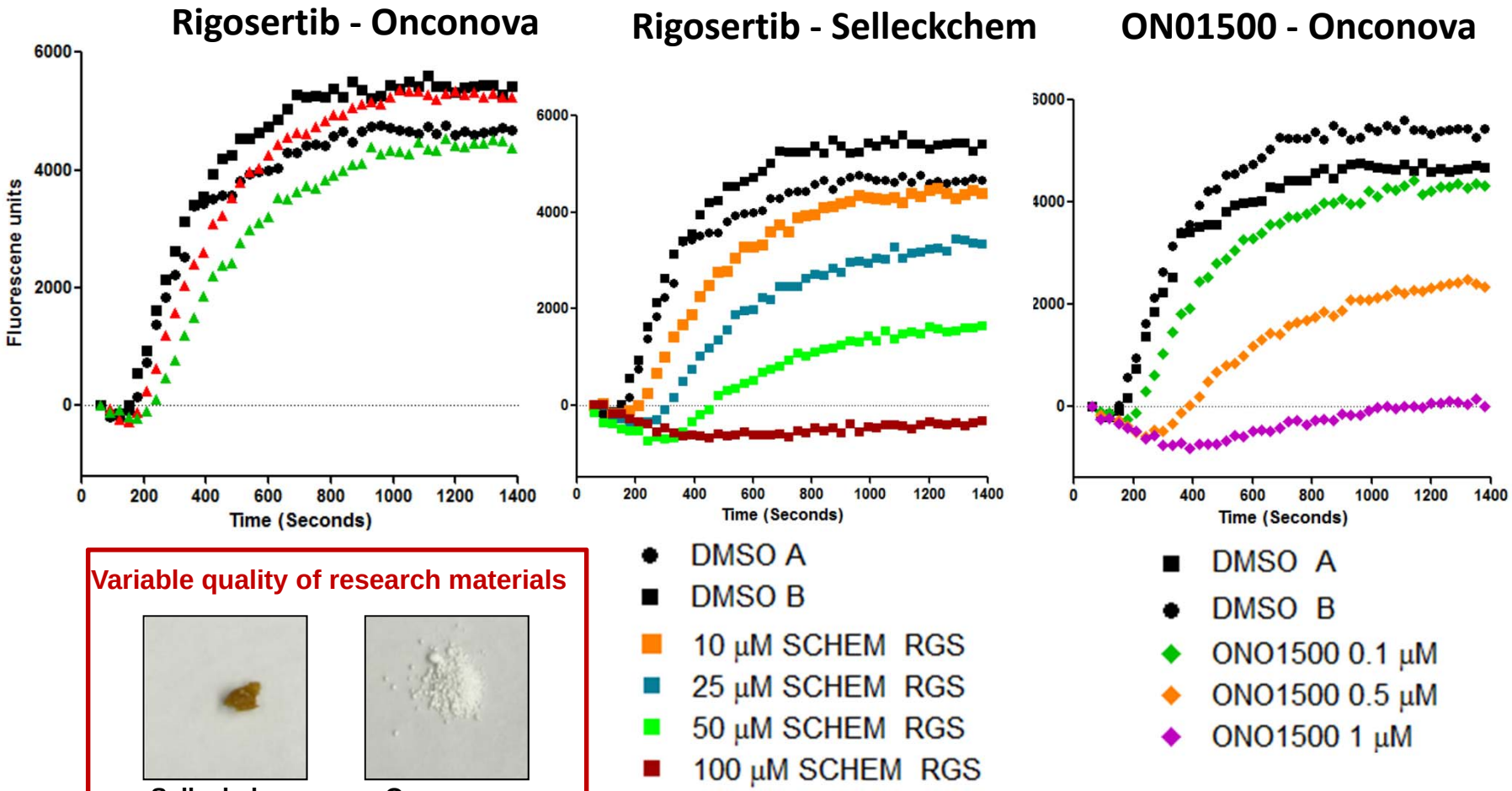
- Rigosertib binds to signaling proteins via RBD
  - Ras Binding Domains (RBD) conserved across pathways
  - Allows for blockade of multiple pathways
  - Specificity of binding being investigated
  - Second generation molecules in the works
- Novel mechanism conducive for many cancer types
  - Strong mechanistic rationale for MDS and AML
  - Single agent and combination approaches feasible for solid tumors

SUPPLEMENTAL SLIDES

Synthetic Protocol for Rigosertib



Tubulin Polymerization Assays

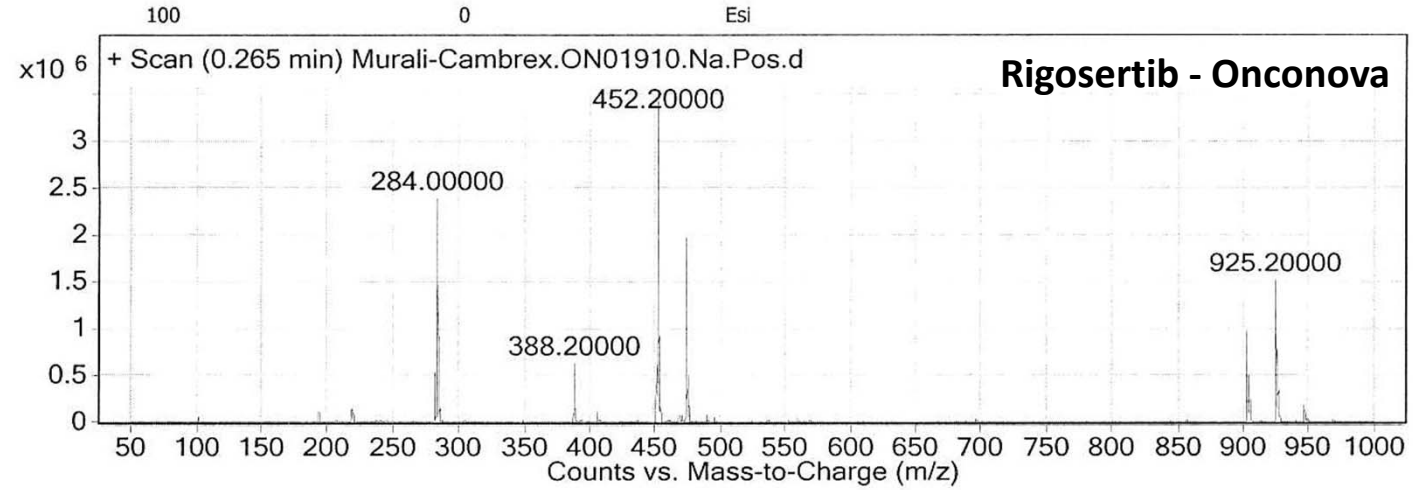


Variable quality of research materials

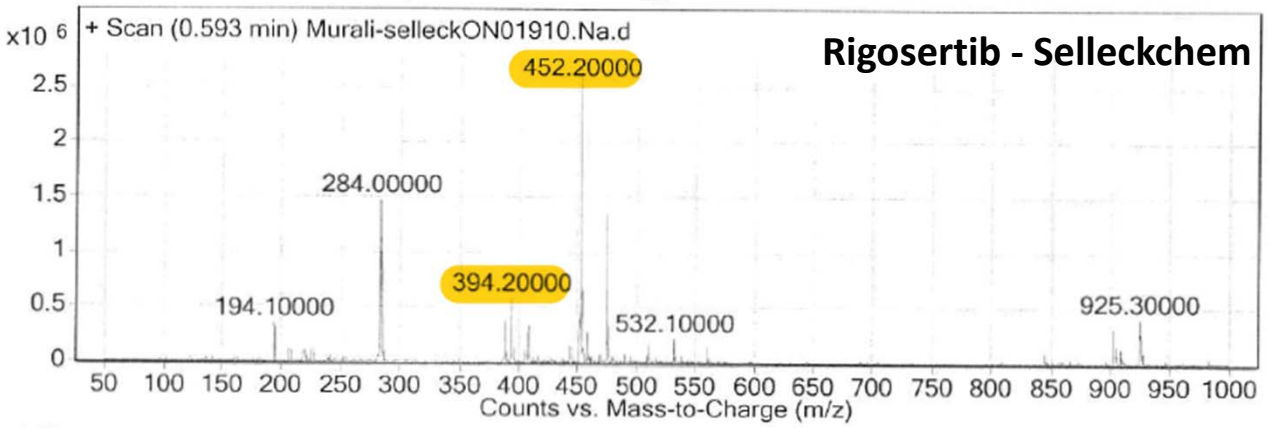
Sellechchem Onconova

Compound	Kd value
Onconova Rigosertib	>20 µM
Selleckchem Rigosertib	142 nM
ON01500	42 nM

LCMS Analysis of Rigosertib preparations



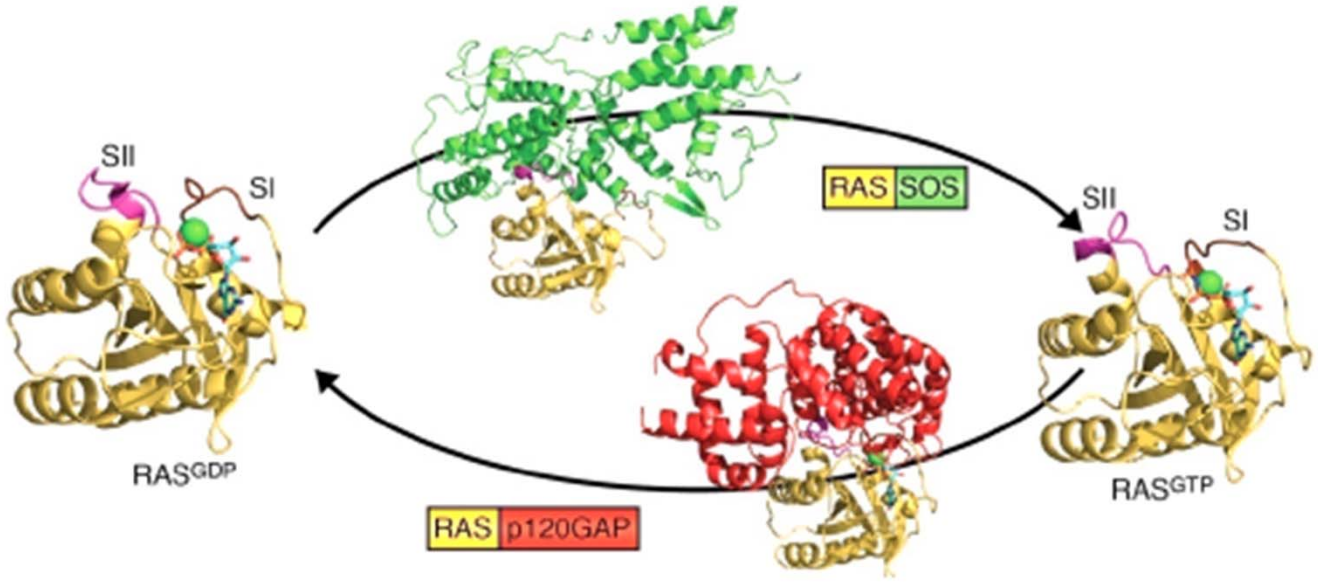
Peak List

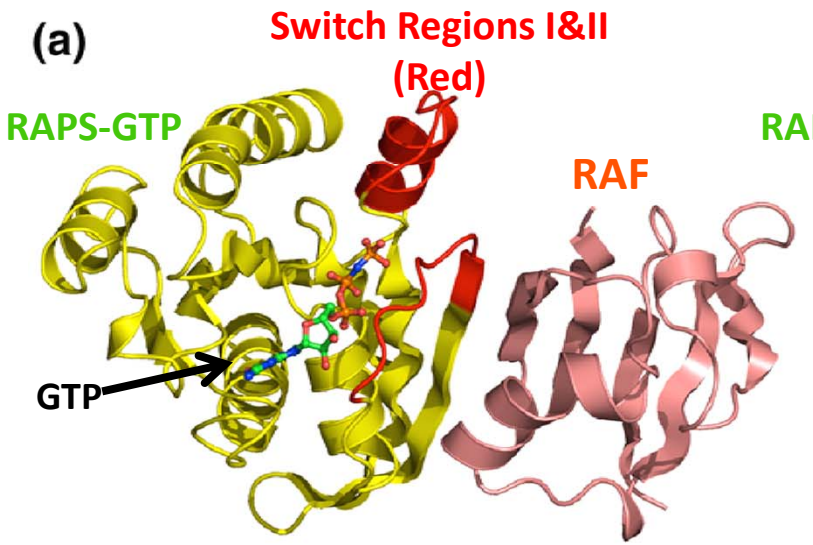


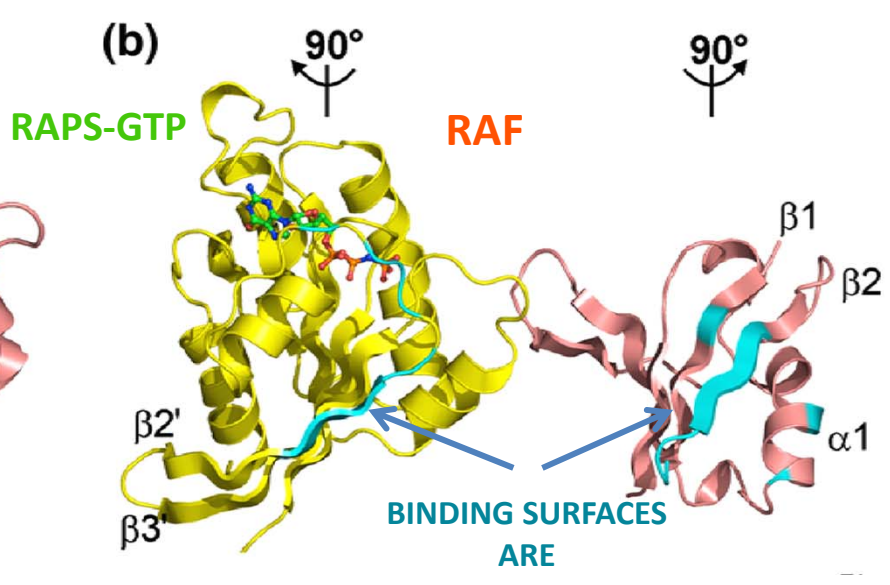
01910M+1 ion= 452.2
1910Na+1 ion= 474.1
1910 2M+1 ion= 903.3
1910Na 2M+1 ion= 925.2
1910-SO2 M+1 ion= 388
1910-2,4,6-Triphenyl (451-168)+1 ion= 284

01500 = 394.2

RAS GDP - GTP CYCLE

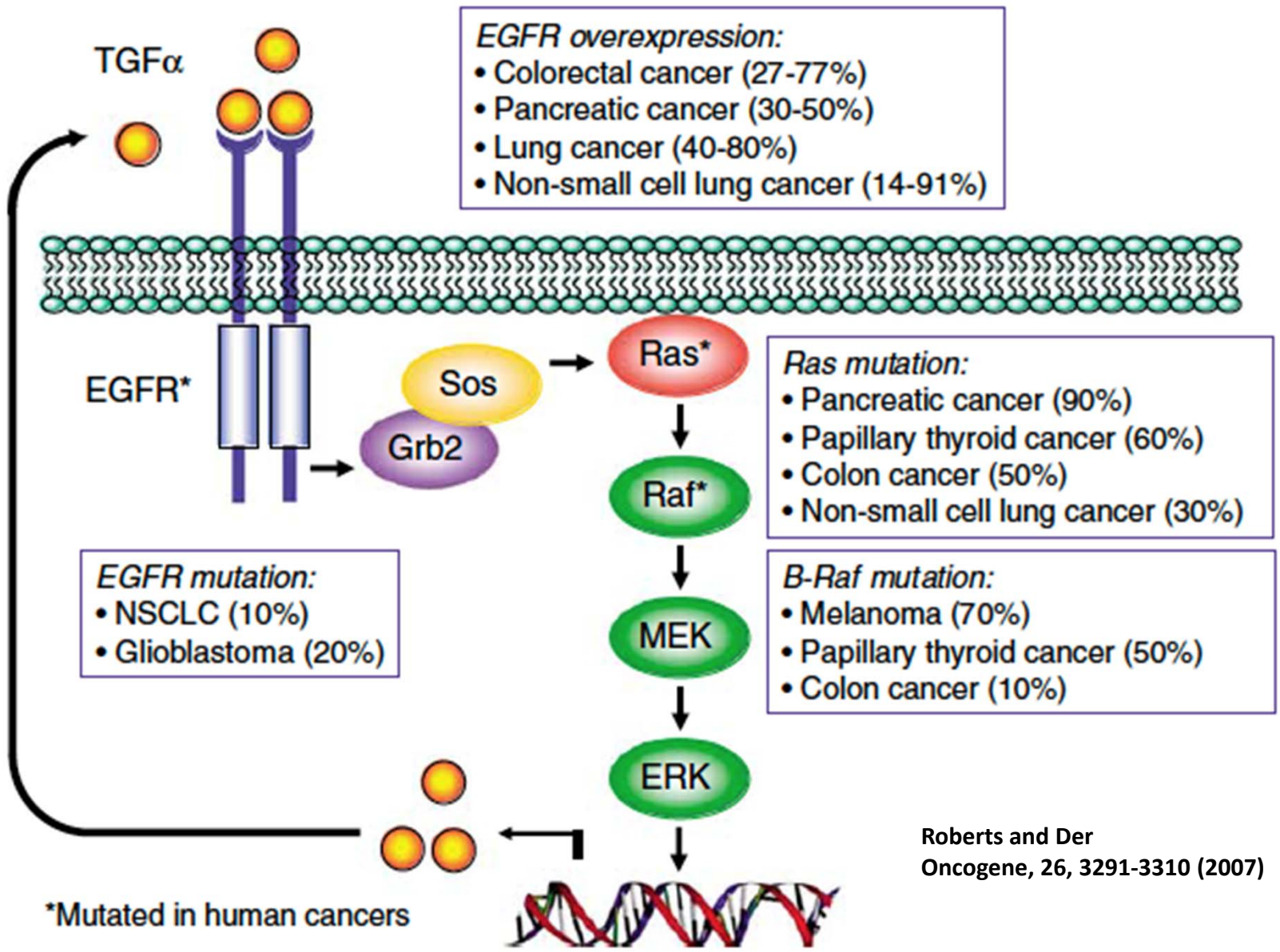






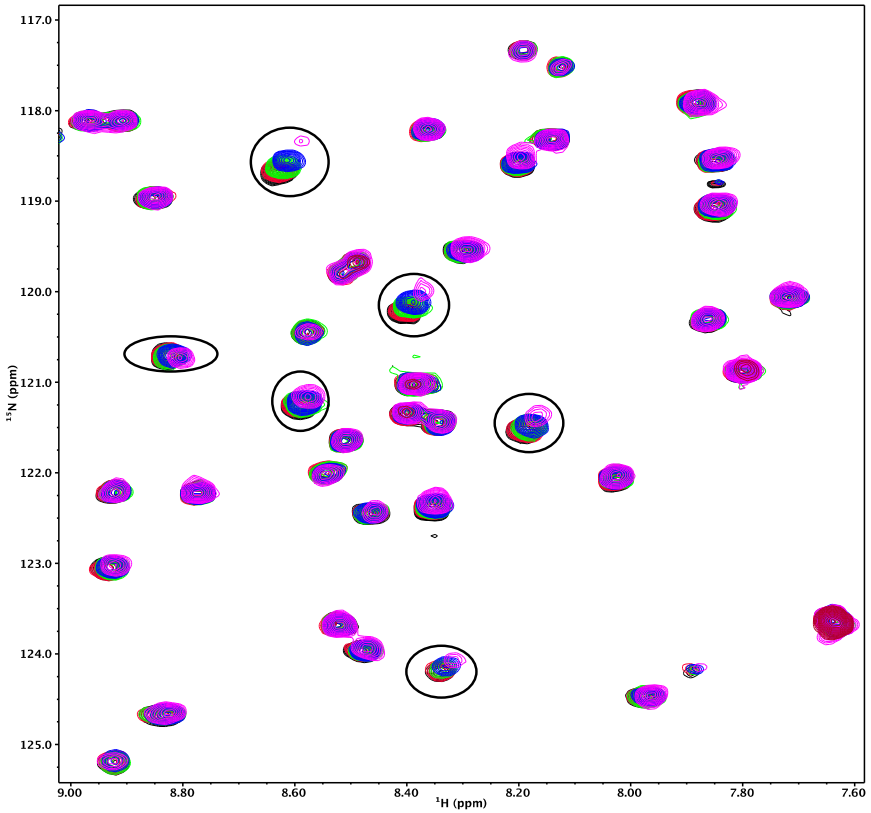
Filchtinski et al, JMB, 399:422-4352010.

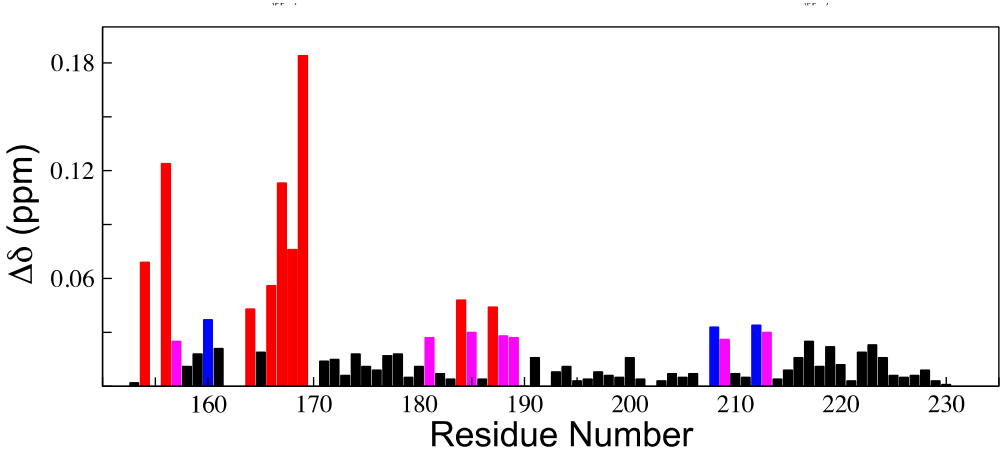
The Ras/Raf Pathway in Human Cancer



Roberts and Der
Oncogene, 26, 3291-3310 (2007)

NMR Spectrum of Raf-RBD bound to Rigosertib





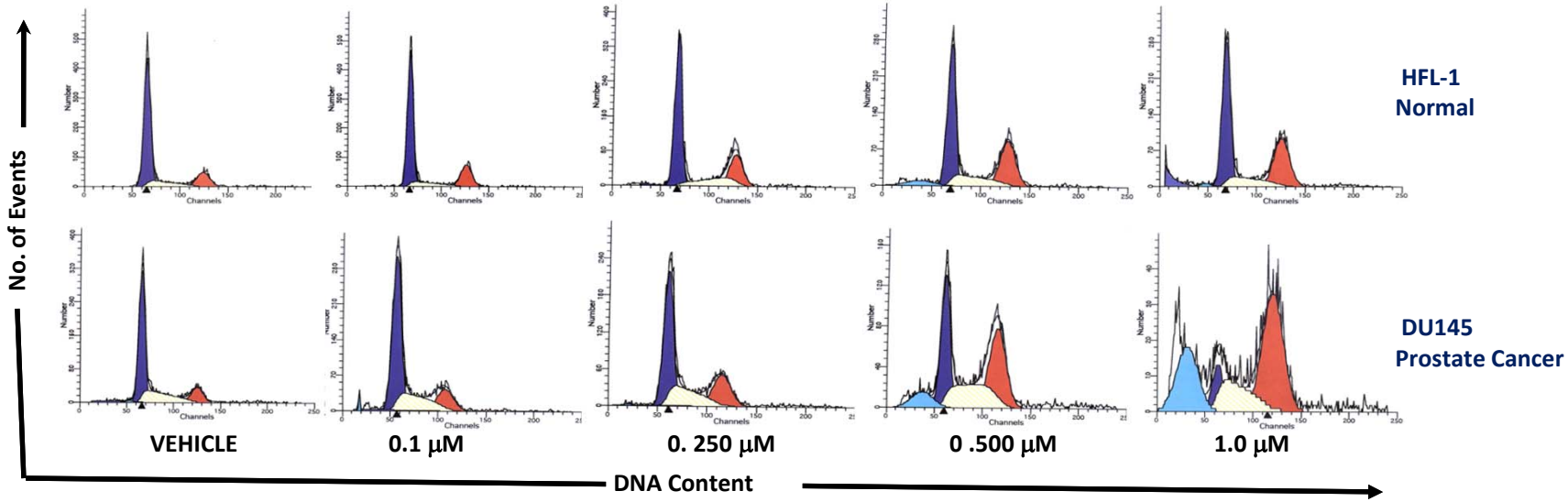
Titration of ^{15}N BRBD with rigosertib

50 μM ^{15}N BRBD; 200 mM NaCl; pH 7.4; 900 MHz

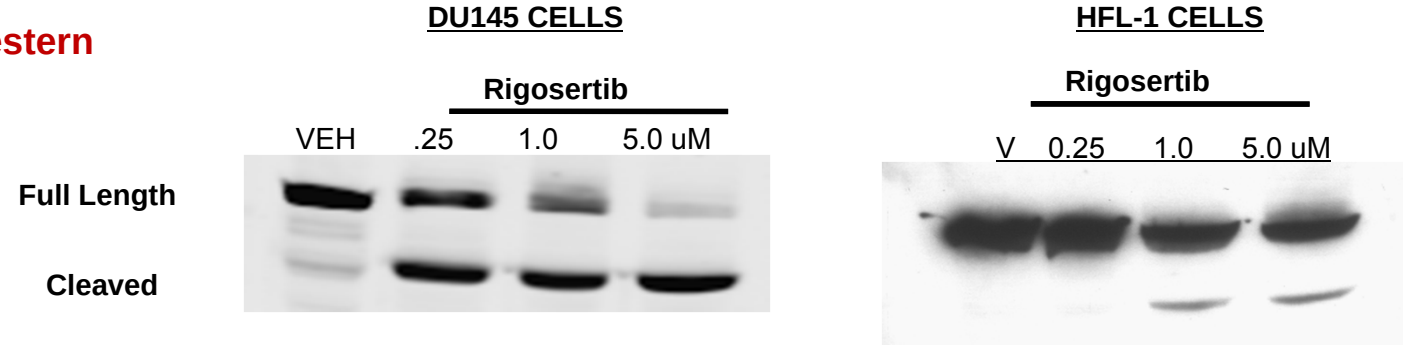
Circles show the amino acid residues of Raf-RBD that come in contact with Rigosertib

Rigosertib Induces Apoptosis Only in Cancer Cells

FACS Analysis: Rigosertib 24 HOUR TREATMENT



PARP Western



DU145 (human prostate carcinoma)and HFL-1 (normal human fibroblasts) cells were treated with increasing concentrations of Rigosertib or DMSO (Vehicle) for 48 hours. Cells were harvested and total protein was resolved by 10% SDS-PAGE, western blotted and hybridized to anti-PARP.

ONCONOVA THERAPEUTICS

Rigosertib Development

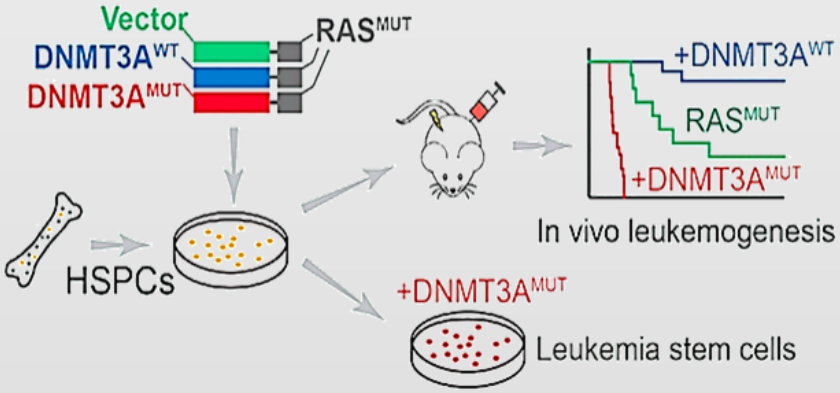
Steven M Fruchtman, M.D.

October 17, 2016

Oral Rigosertib in Combination with Azacitidine for MDS

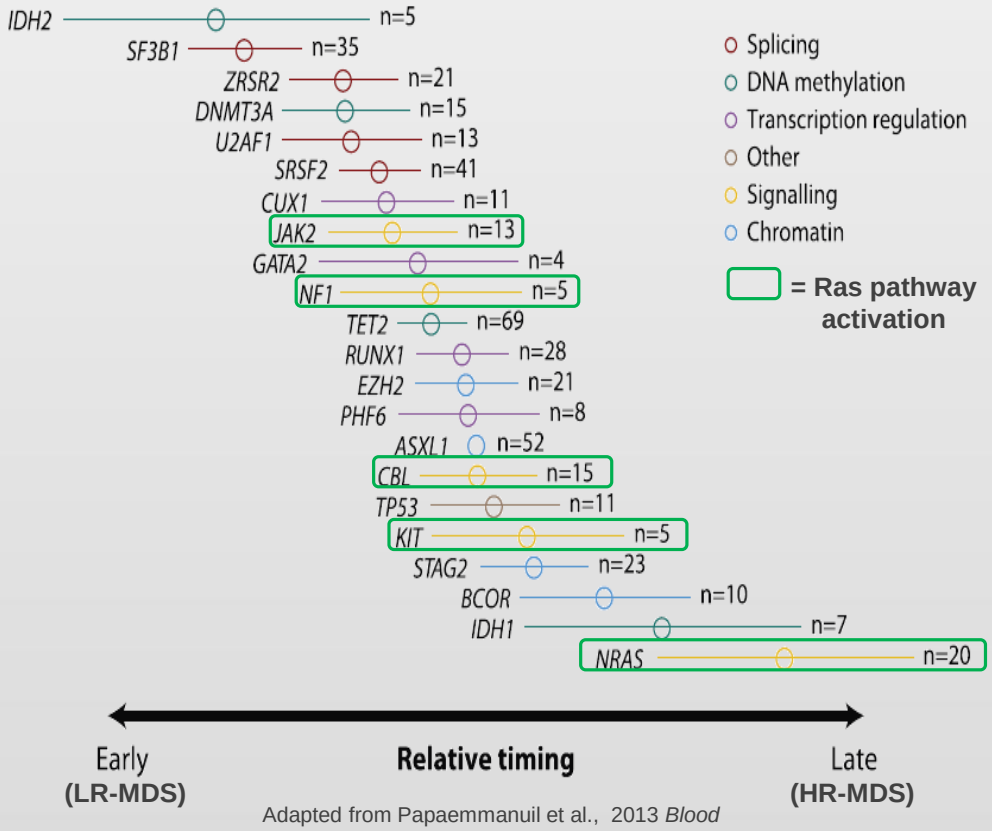
Epigenetic and Growth Factor Pathway Mutations Synergize Inducing Leukemic Transformation

AML Animal Model



Lu et al., 2016 *Cancer Cell*

Temporal Order of Gene Mutations in 107 MDS Patients



Adapted from Papaemmanuil et al., 2013 *Blood*

Pre-clinical/clinical evidence suggest combination of epigenetic therapy plus growth factor signaling inhibitor could be effective in curbing MDS pathogenesis

RIGOSERTIB AND AZACITIDINE ARE SYNERGISTIC AGAINST LEUKEMIA CELL LINES

- **Combination of rigosertib with AZA produced an increase of 1.7- to 2.9-fold in cytotoxicity ($p<0.05$) in HL-60 cells***
- **Interaction resulted in a synergistic effect with combination indexes between 0.3 and 0.75**
- **Sequence of administration influenced degree of cytotoxicity; rigosertib priming offered optimal results**
- **These preclinical results provided rationale for combining agents in a Phase 1/2 study in MDS and AML patients with optimal sequence**
- **U.S. patent issued for combination therapy**

*Skidan I, Zinzar S, Holland J, Silverman. Toxicology of a novel small molecule ON01910Na on human bone marrow and leukemic cells in vitro. *AACR Meeting Abstracts*, Apr 2006:309

Oral Rigosertib + Azacitidine for HMA Treatment Naive MDS

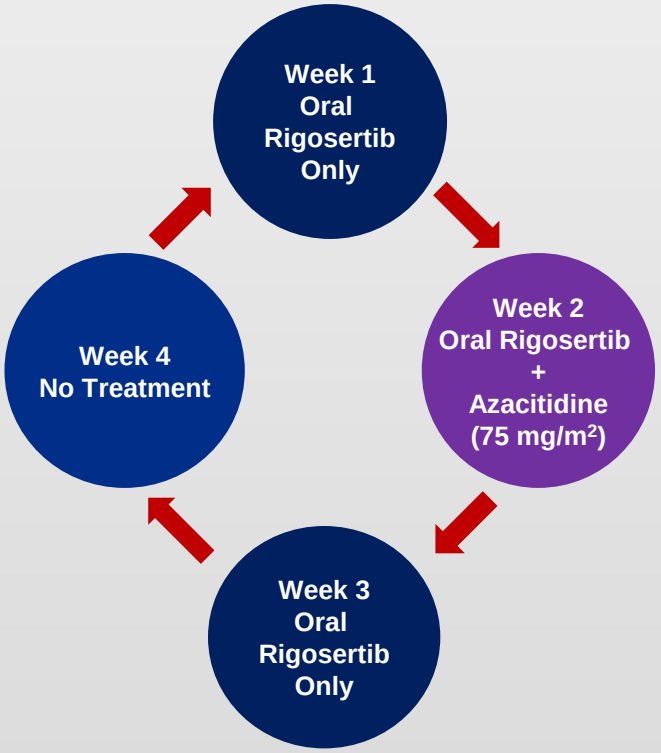
In Higher-risk MDS patients:

- Efficacy of single-agent DNMT* inhibitors (HMAs) is limited
  - Low CR and PR rates (7-20%)
  - Limited median duration of benefit of ~15 months
- Combination with other agents is warranted
  - Combinations should not add burdensome toxicities
- DNMT inhibition in combination with novel mechanisms may improve response rates and duration of benefit

**DNA Methyl Transferase inhibitors are also known as Hypomethylating Agents (HMAs)*

Rigosertib + Azacitidine Combination

- Phase 1 combination was well tolerated
  - Evidence of efficacy in patients with MDS*
- Azacitidine given one week per month
  - Full dose and administrative scheme per label
- Rigosertib given 3 of 4 weeks; and initially
  - Recommended Phase 2 dose of 560/280 mg BID
- Adverse event profile of combination similar to single-agent azacitidine (per label)



*Navada S, Garcia-Manero G, Wilhelm F, et al. A phase I/II study of the combination of oral rigosertib and azacitidine in patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). *ASH* 2014; Abstract 3252.

Phase 2 Rigosertib + Azacitidine

Interim Phase 2 data –ASH 2015 (Update ASH 2016)

- **Overall response rate of 84% in 19 patients who never received an HMA**
- Overall response rate of 64% in 11 patients who received prior HMA
- HMA naïve and HMA failure patients received same dose/schedule of treatment with combination

Response Assessment per 2006 IWG Criteria			
Patient Characteristics	Eval (n=30)	HMA Naïve/1st-line (n=19)	HMA Failure*/2nd-line (n=11)
Complete Remission (CR %)	6/30 (20)	5/19 (26)	1/11 (9)
Overall Response Rate (ORR %)	23/30 (77)	16/19 (84)	7/11 (64)

*8 patients received previous therapy with azacitidine, 2 with decitabine and 1 with both HMAs; prior HMA cycles ranged from 4-20

Navada S, et al. A phase 2 study of the combination of oral rigosertib and azacitidine in patients with myelodysplastic syndrome (MDS). *ASH* 2015; Abstract 910

Combination Program to Enter Pivotal Stage - 2017

- **Successful End-of-Phase 2 meeting with FDA in September 2016**
- **Agreement reached on patient population and primary approval endpoint**
  - **First-line Higher-risk MDS patients**
  - **Composite response endpoint of CR + PR**
- **Trial to be conducted with Corporate Partner SymBio in Japan**

Key Parameters and Milestones for Oral Rigosertib + Azacitidine Program		
Phase 3 Trial Design	Randomized Controlled	1:1 randomization between Aza + placebo and Aza + oral rigo
Primary Endpoint	Composite Response	Complete and Partial Response per IWG 2006 criteria
Regulatory Path	To be explored	Special Protocol Assessment (SPA), Fast-track and BTD*
Phase 2 Data	ASH 2016	Safety and efficacy, duration of response, subgroups
Final protocol	After FDA/EMA review	H1-2017
Trial start	Global trial	H2-2017

*Breakthrough Designation

INTRAVENOUS RIGOSERTIB
INSPIRE PIVOTAL TRIAL

Single-agent IV Rigosertib for 2nd-line HR-MDS

Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial

*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, Gianluca Gaidano, Bart L Scott, Peter Greenberg, Uwe Platzbecker, David P Steensma, Suman Kambhampati, Karl-Anton Kreuzer, Lucy A Godley, Ehab Atallah, Robert Collins Jr, Hagop Kantarjian, Elias Jabbour, Francois E Wilhelm, Nozar Azarnia, Lewis R Silverman, for the ONTIME study investigators**

Summary

Background Hypomethylating drugs are the standard treatment for patients with high-risk myelodysplastic syndromes. Survival is poor after failure of these drugs; there is no approved second-line therapy. We compared the overall survival of patients receiving rigosertib and best supportive care with that of patients receiving best supportive care only in patients with myelodysplastic syndromes with excess blasts after failure of azacitidine or decitabine treatment.

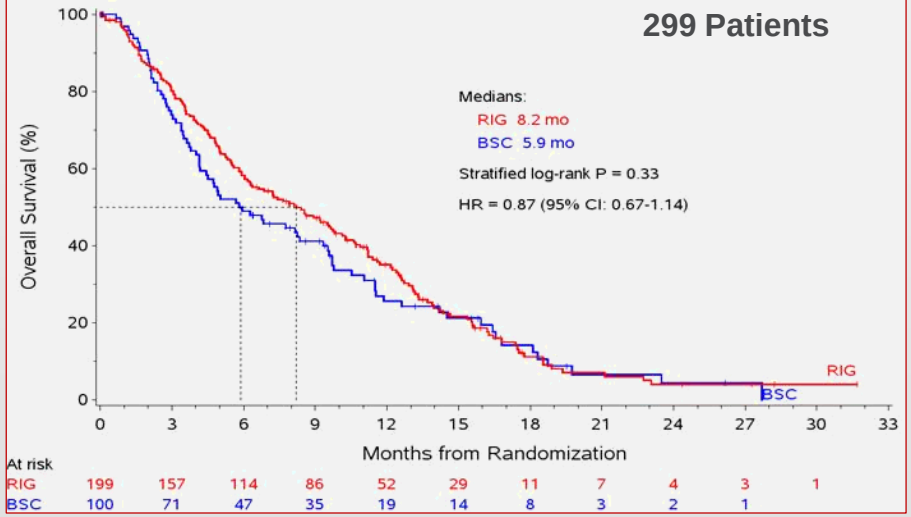
Lancet Oncol 2016

Published Online March 8, 2016 http://dx.doi.org/10.1016/S1470-2045(16)00009-7

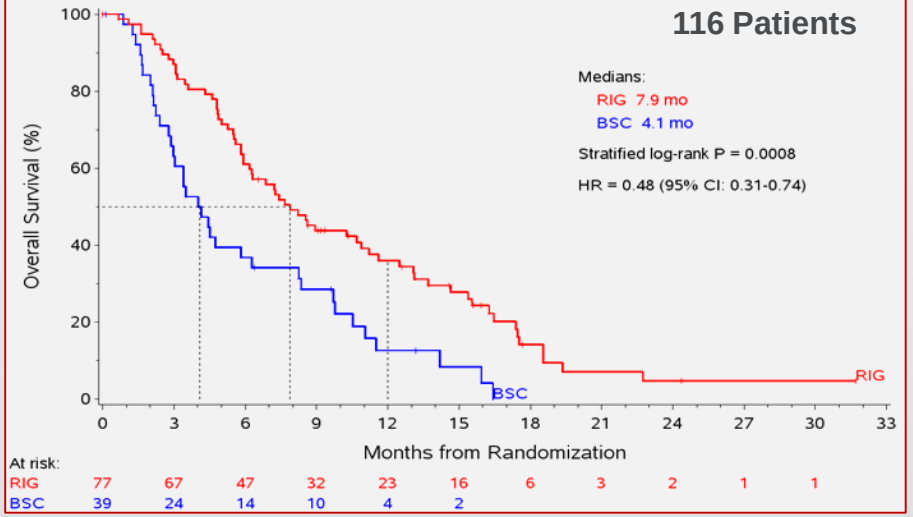
Patient Population for Phase 3 INSPIRE Trial

Data from ONTIME Paper* Recently Published in *Lancet Oncology*

ITT for ONTIME Trial



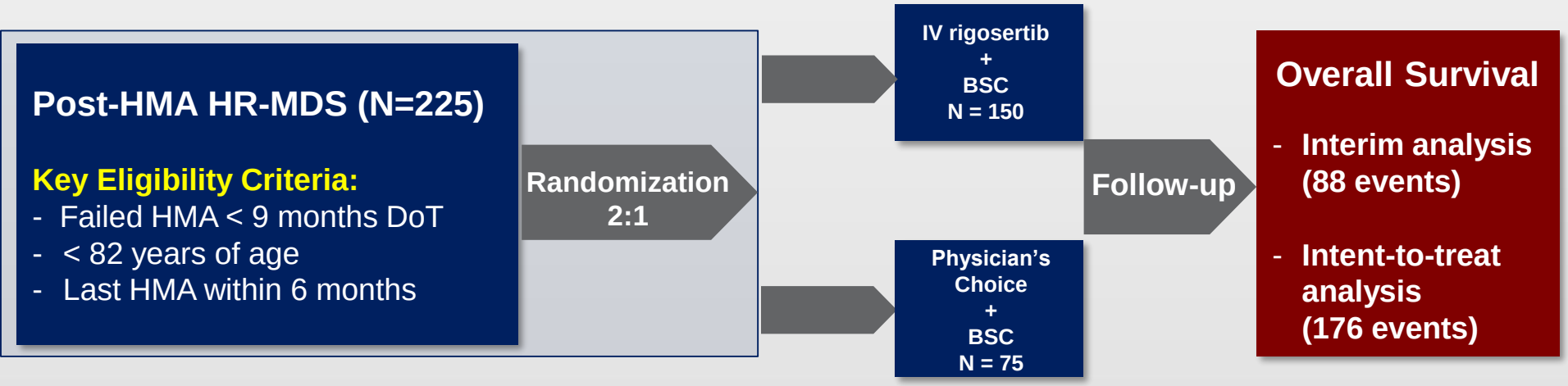
Subpopulation for INSPIRE Trial (ONTIME subset)



- ITT OS analysis of ONTIME – HR= 0.87; NS survival benefit
- ITT OS of proposed INSPIRE population – HR = 0.48; P = 0.0008

*Guillermo Garcia-Manero, Pierre Fenaux, Aref Al-Kali, Maria R Baer, Mikkael A Sekeres, Gail J Roboz, et al. Rigosertib versus best supportive care for patients with higher-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial; *The Lancet Oncology* 2016 (17): 496–508

INSPIRE: Rigosertib Phase 3 Trial



- Statistical analysis: two analysis planned

  1. Power 0.80; Target HR < 0.625; (reduce mortality by > 37.5%)
  2. α for ITT = 0.04; α for IPSS-R VHR = 0.01
  3. Trial can succeed in two ways: ITT population or IPSS-R Very High Risk

- Genomic sequencing of patient samples

Commentary on new trial in recent publication: Emilio P Alessandrino, Matteo G Della Porta. Novel trial designs for high-risk myelodysplastic syndromes;*The Lancet Oncology* 2016 (17): 410–412

INSPIRE Trial Progress

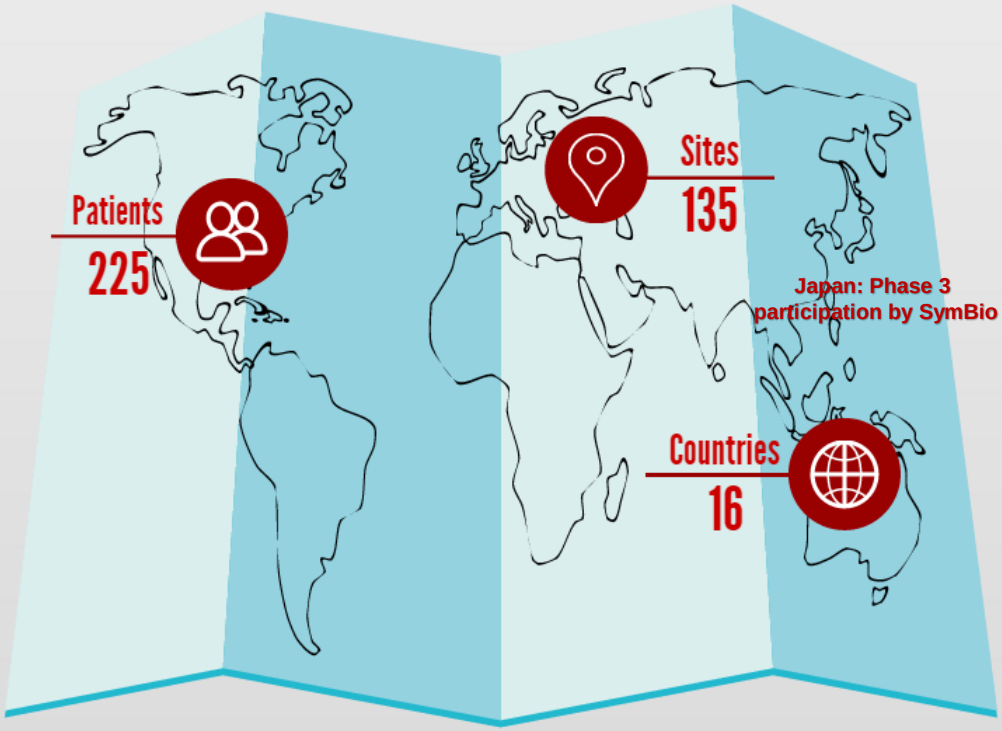
*The **IN**ternational **S**tudy of **P**hase III **I**V **R**igos**E**rtib, or INSPIRE, is based on guidance received from the U.S. Food and Drug Administration and European Medicines Agency and derives from the findings of the ONTIME Phase 3 trial. Our partner SymBio is enrolling patients in Japan after discussions with the PMDA.*

Goals:

- 16 countries
- 135 sites
- 225 randomized patients

Status:

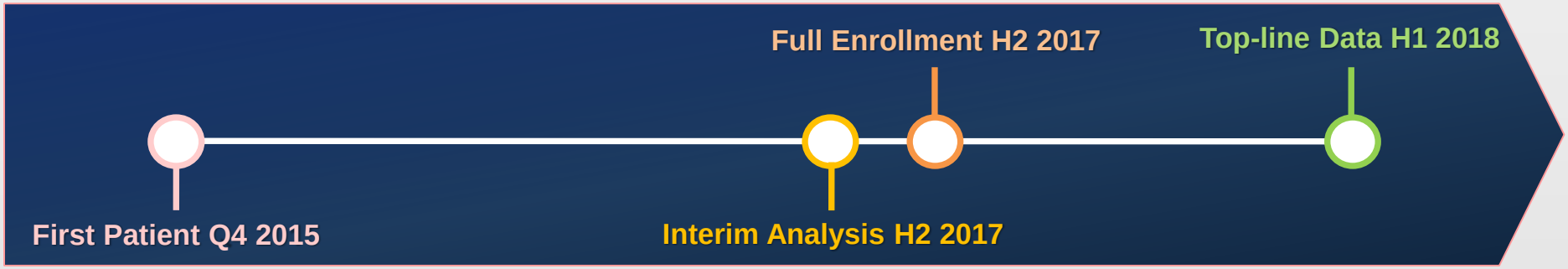
- 120+ sites activated
  - U.S., Europe, Japan, Australia, Israel



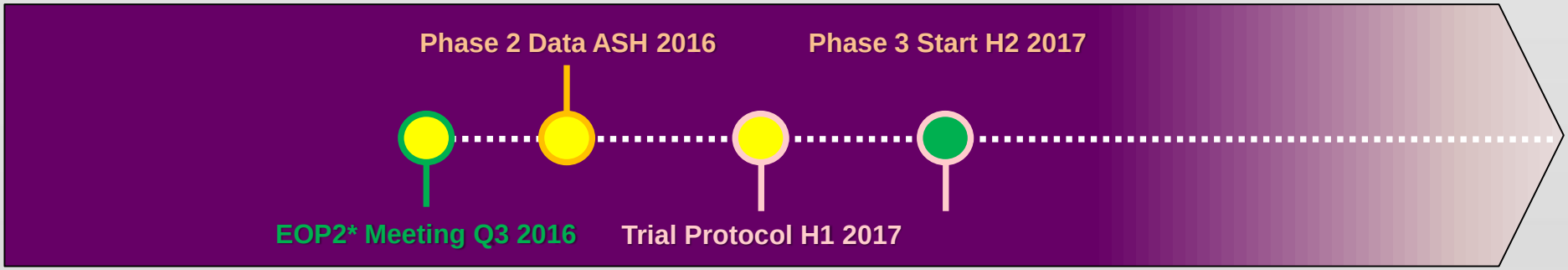
Interim analysis planned for H2-2017

Pivotal Trial Timelines

Timeline for INSPIRE Global Trial



Timeline for Pivotal trial of Oral Rigosertib + Azacitidine



*EOP2: End of Phase 2 meeting: completed in September 2016

Thank you