Frederick National Laboratory
for Cancer Research

NCI RAS Initiative Update

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February 3rd, 2015

Outline

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- **Introduction**
- **Structural Biology and Biophysics**
- **Targets and Assays**
  - Biochemical screens
  - Cell-based screens
  - Multimerization and localization
  - Cell surface
- **RAS Community**
- **Oversight and Feedback**

The NCI RAS Initiative

What is RAS, and why is it so important?

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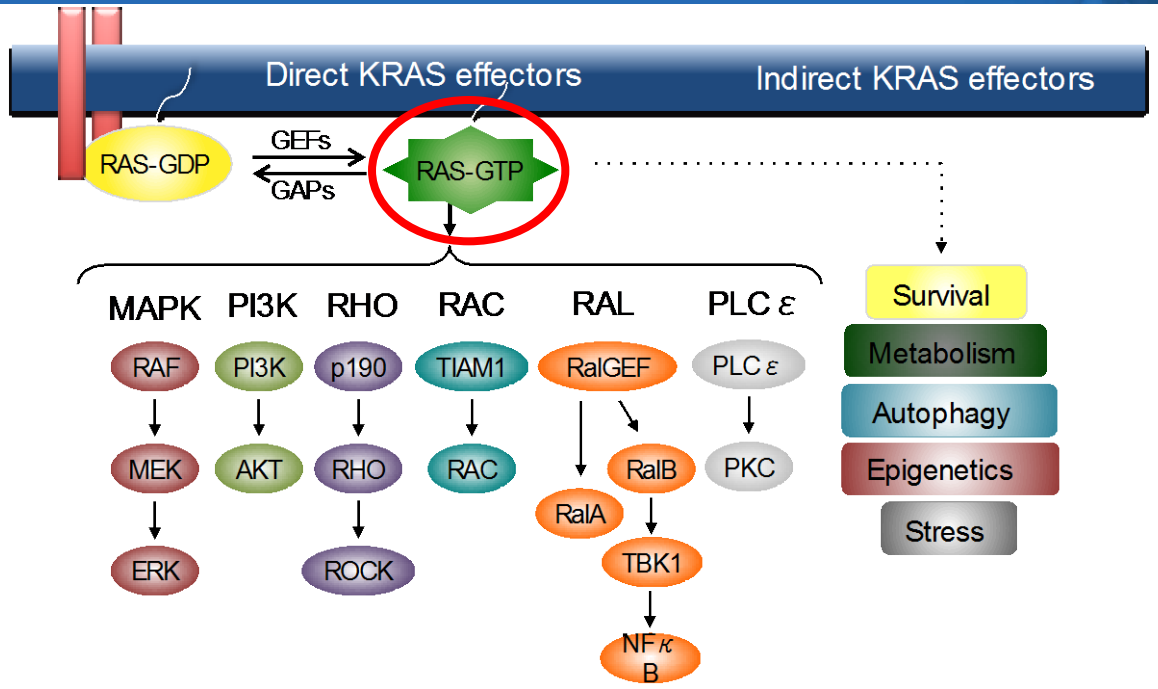
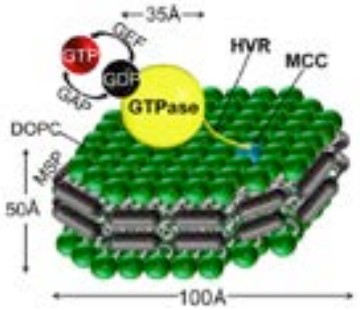


Cancer	KRAS Mutation	US - new KRAS cases/yr	5 yr survival
Colorectal	45 %	60,000	45 %
Lung	35 %	45,600	17 %
Pancreas	95 %	32,200	6 %
		137,800	

Protein Biology/Biophysical Characterization

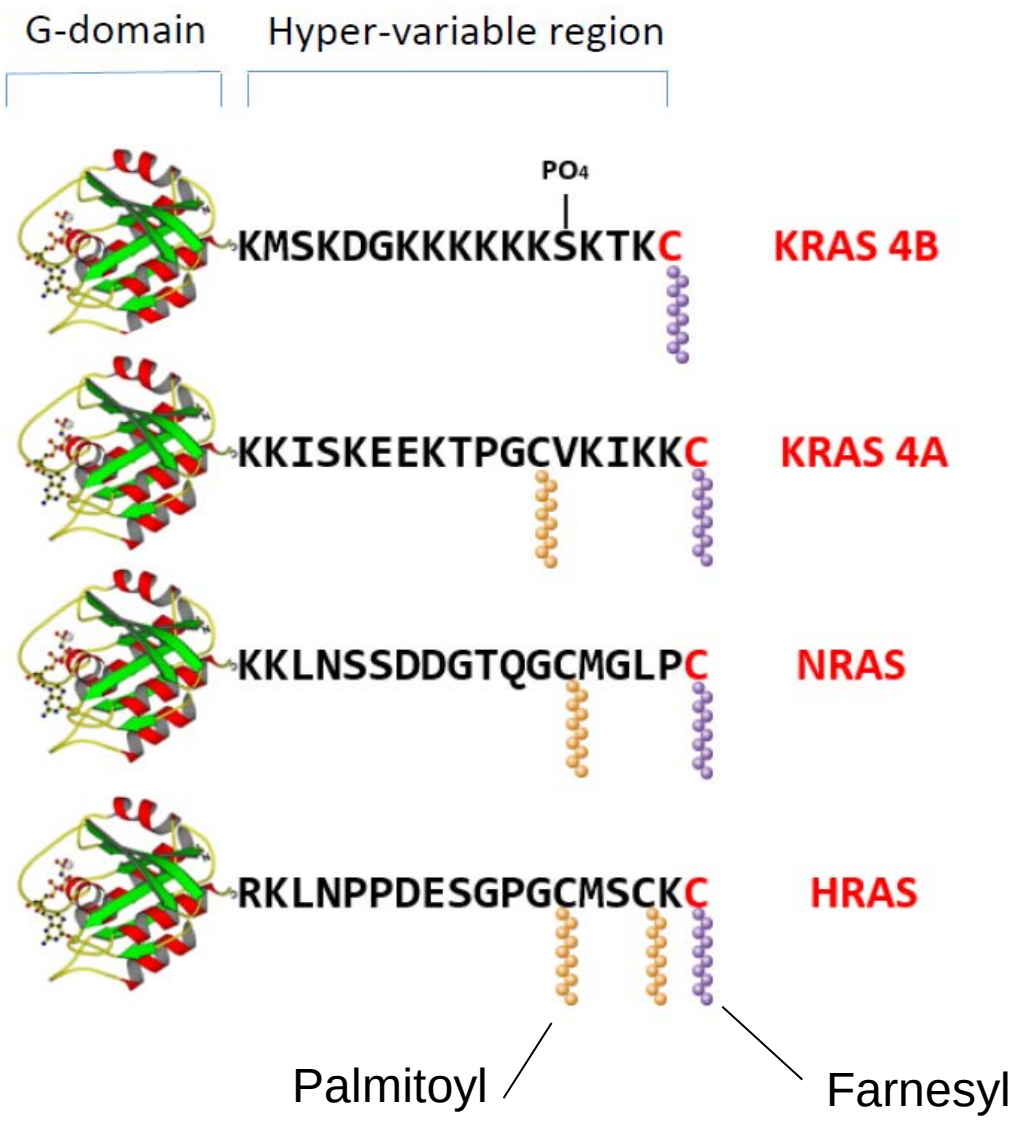


Andy Stephen

Dom Esposito

The RAS family of small GTPases

- 21 kDa small GTPases
- high homology in first 164 aa
- More than 100 members
- post-translational modifications
- membrane association



Characterization of WT KRAS and mutants –

Nucleotide binding kinetics determine KRAS signaling

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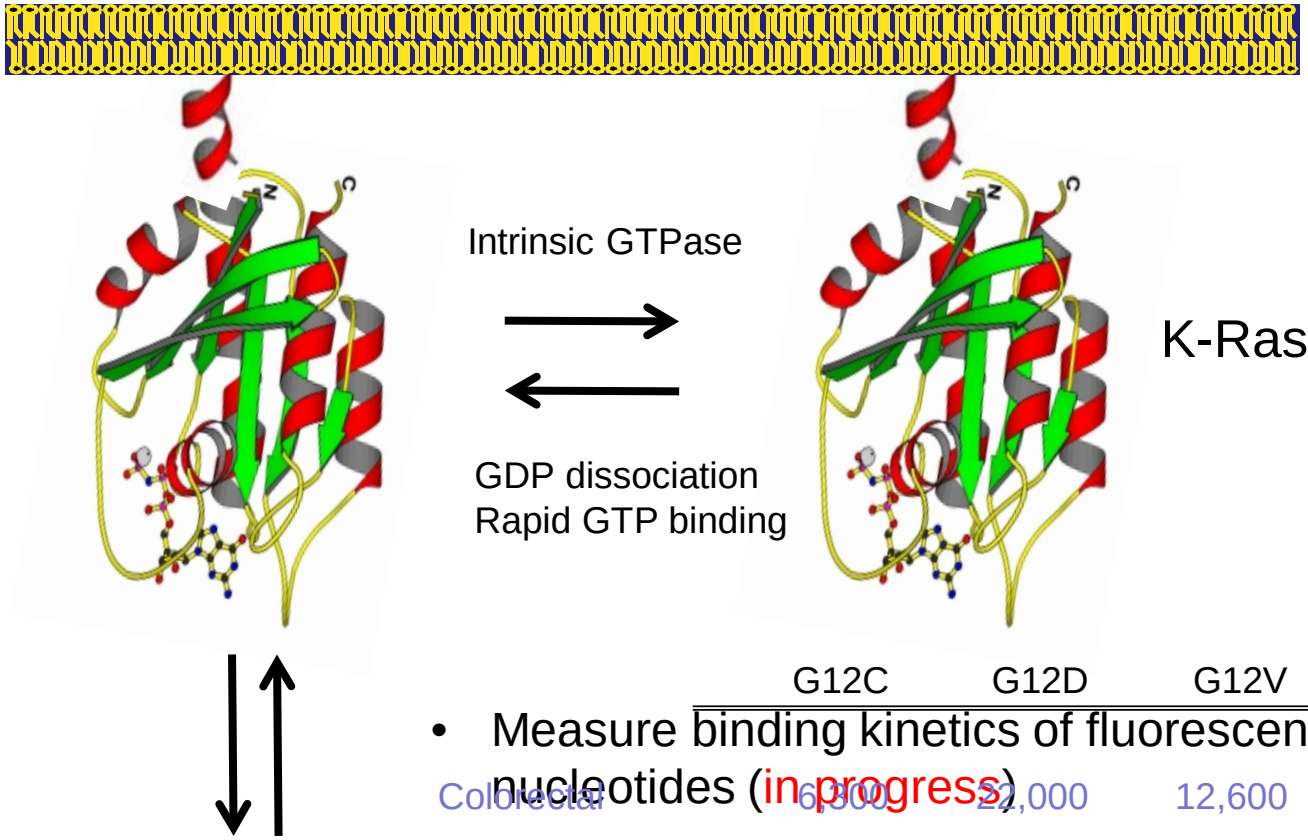
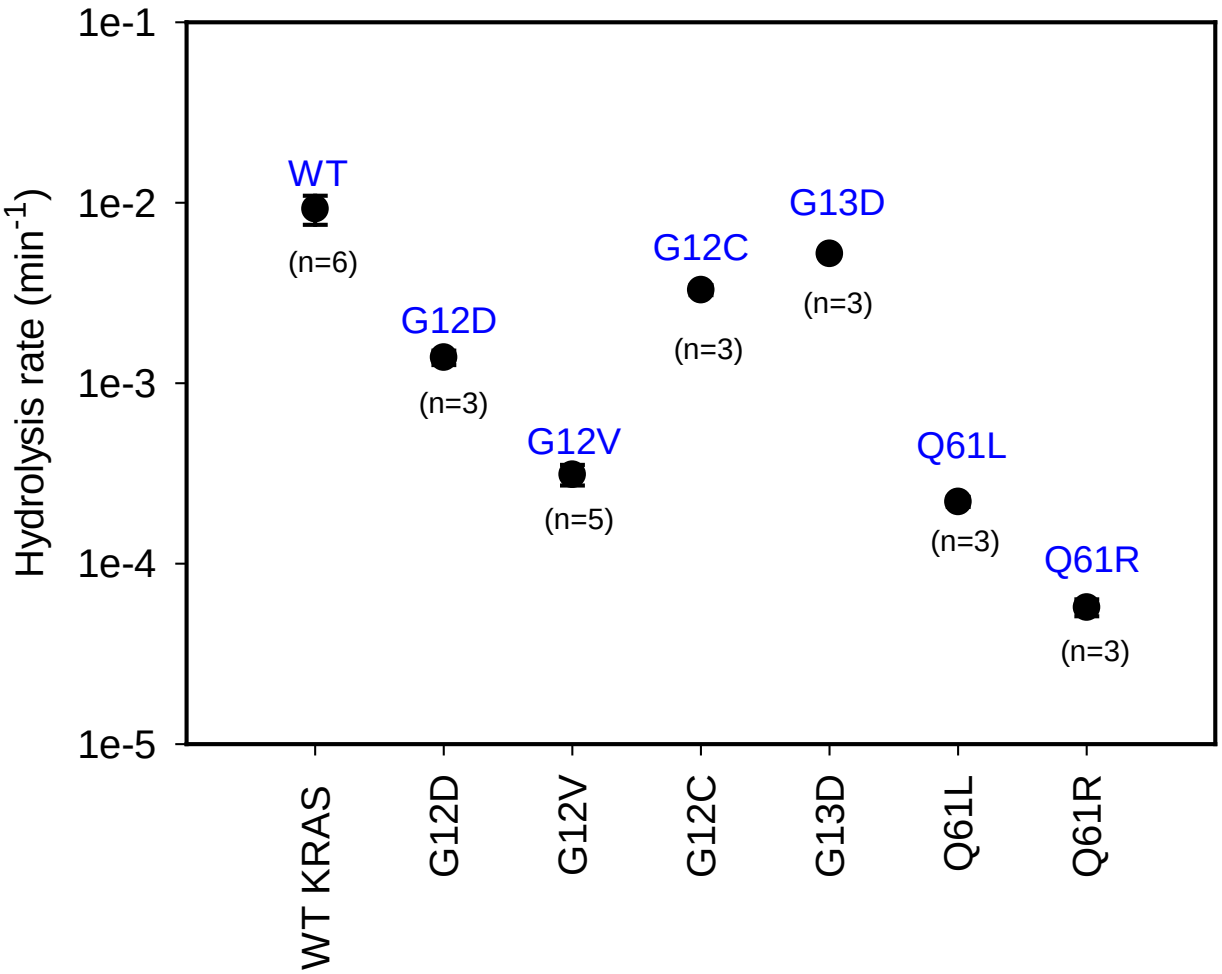


- Measure binding kinetics of fluorescent nucleotides (in progress)
- Measure binding affinity of CRAF (in progress)
- Measure intrinsic GTPase activity (complete)

	G12C	G12D	G12V	G13D
Colorectal	6,300	22,000	12,600	11,250
Lung	22,000	9,520	11,900	1,190
Pancreas	1,200	19,000	12,000	1,000
Total	29,500	50,520	36,500	13,440

KRAS characterization: Intrinsic GTPase activity



E. coli produced full-length KRAS 4b

MANT-GppNHpNon-hydrol dissociates 4 times faster from G13D compared with WT KRAS

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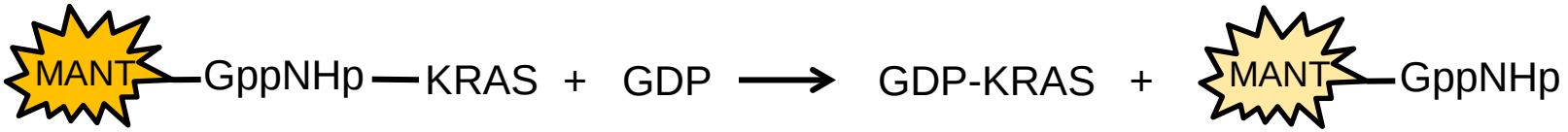

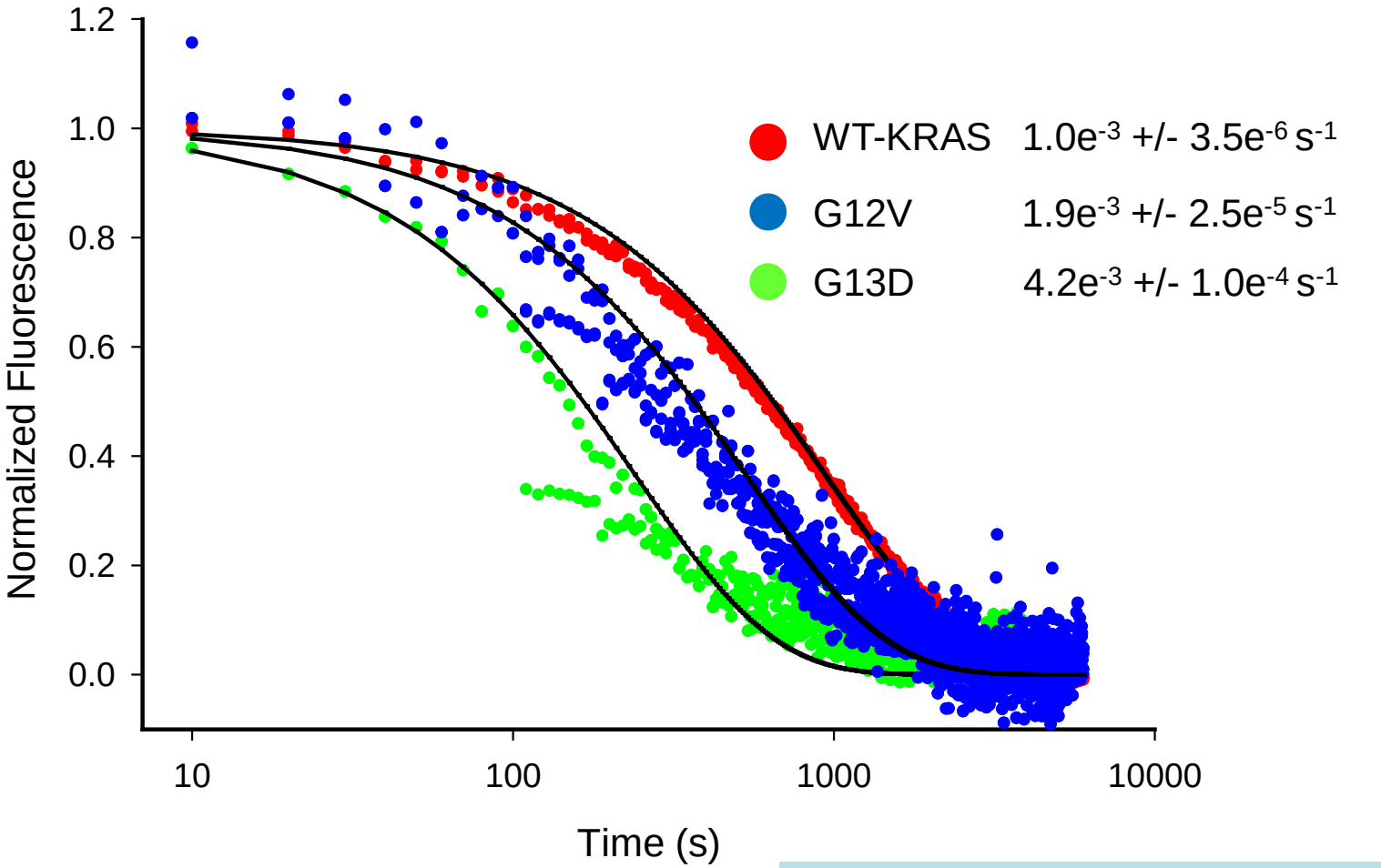

Pat Alexander/Matt Fivash

E. coli produced full-length KRAS 4b

Binding of RAF Ras Binding Domain $(RBD)_{1-149}$ to WT KRAS

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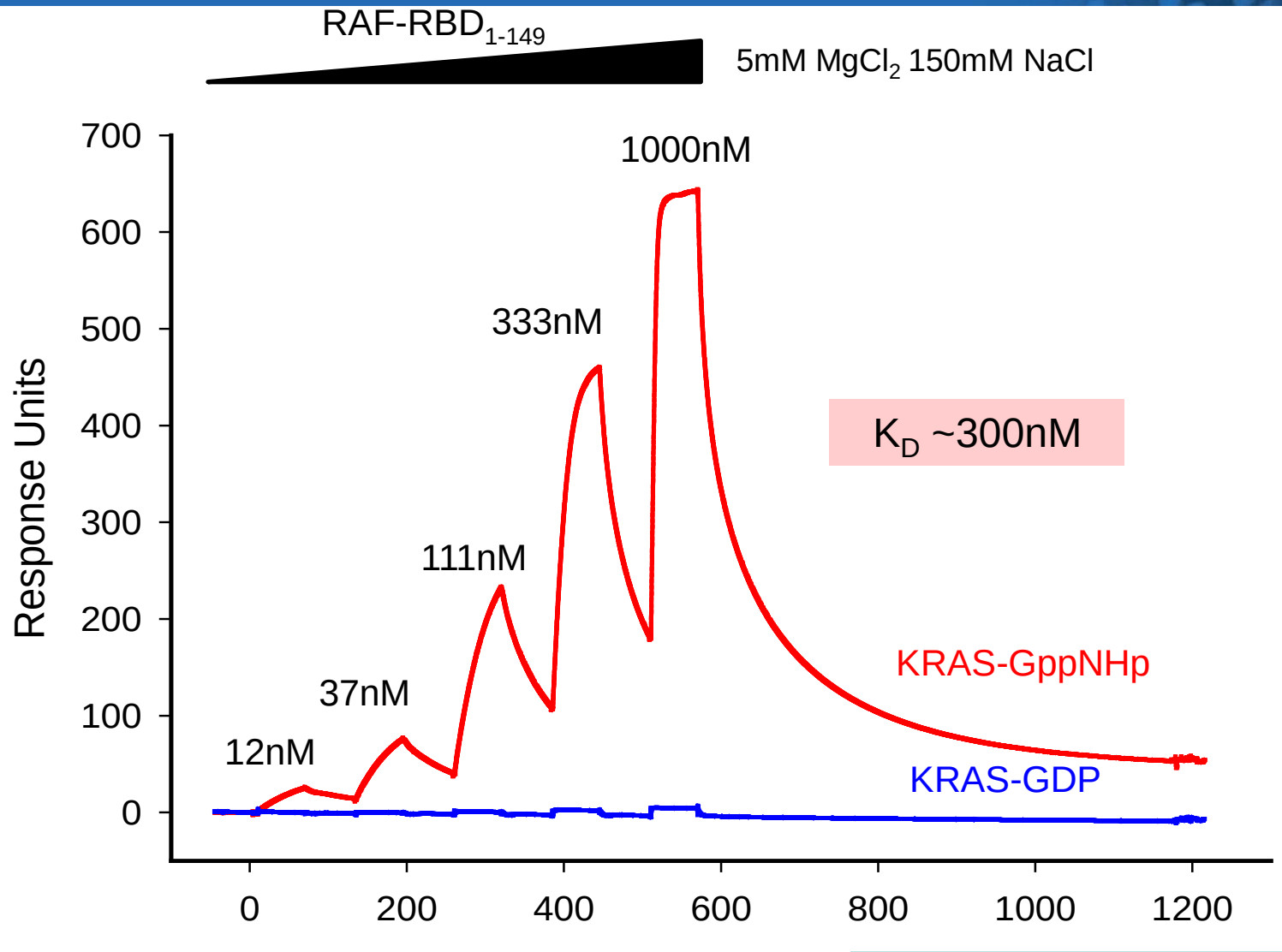

Lakshman Bindu/Karen Worthy

E. coli produced full-length KRAS 4b

Ongoing characterization

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- **Analysis of WT, G12C, G12D, G12V, G13D, Q61H, Q61L**
  - GTP hydrolysis rate of truncated protein
  - nucleotide off-rate
  - RAF-RBD binding

- **Limited analysis of "rare" KRAS oncogenic mutants:**

  G12A, G12H, G12S, G12R, G13C, Q61H, R68S, K117N, A146T, A146V
  - Intrinsic GTP hydrolysis
  - GppNHp off-rate for subset

Fully Processed Recombinant KRAS

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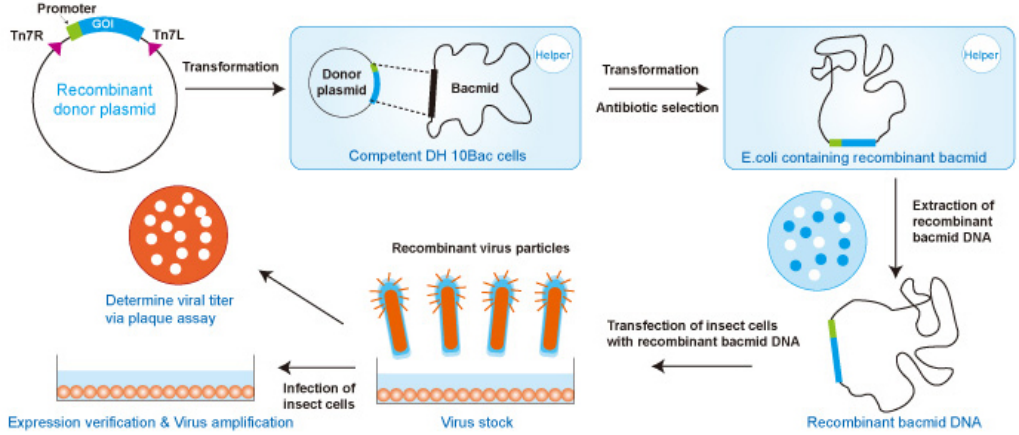
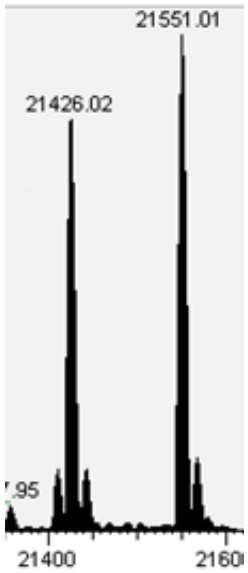
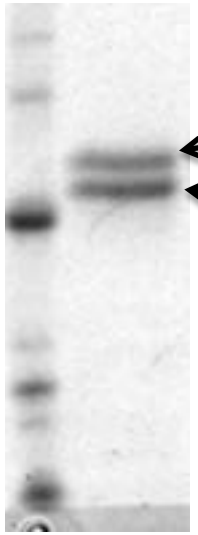
RAS only works when in the membrane
- Drugs that affect membrane dependent signaling?

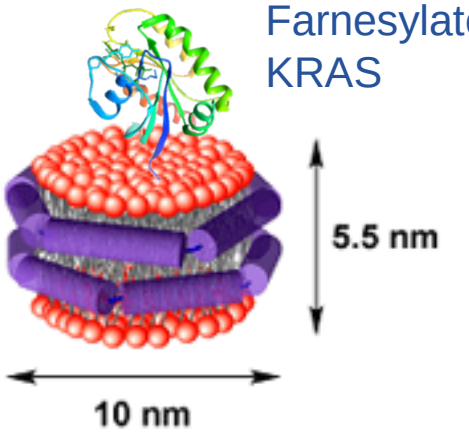


- KRAS expressed in insect cells
- Human farnesyltransferase (FNTA/FNTB), ICMT cloned
- Triple infection of FNTA/FNTB, KRAS, and ICMT





21,412 Da: farnesylated, -AAX
21,426 Da: farnesylated, -AAX, methylated
21,551 Da: unprocessed



Processed KRAS and lipid interactions – liposomes and nanodiscs

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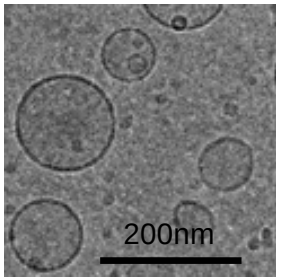
Literature suggests poly-basic region at KRAS C-terminus interact with negatively charged lipids in the plasma membrane.

Processed KRAS – lipid interactions

Liposomes

- SPR to evaluate optimal lipid composition

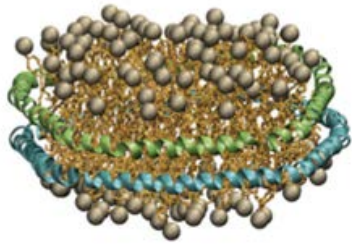


Tethered bilayers

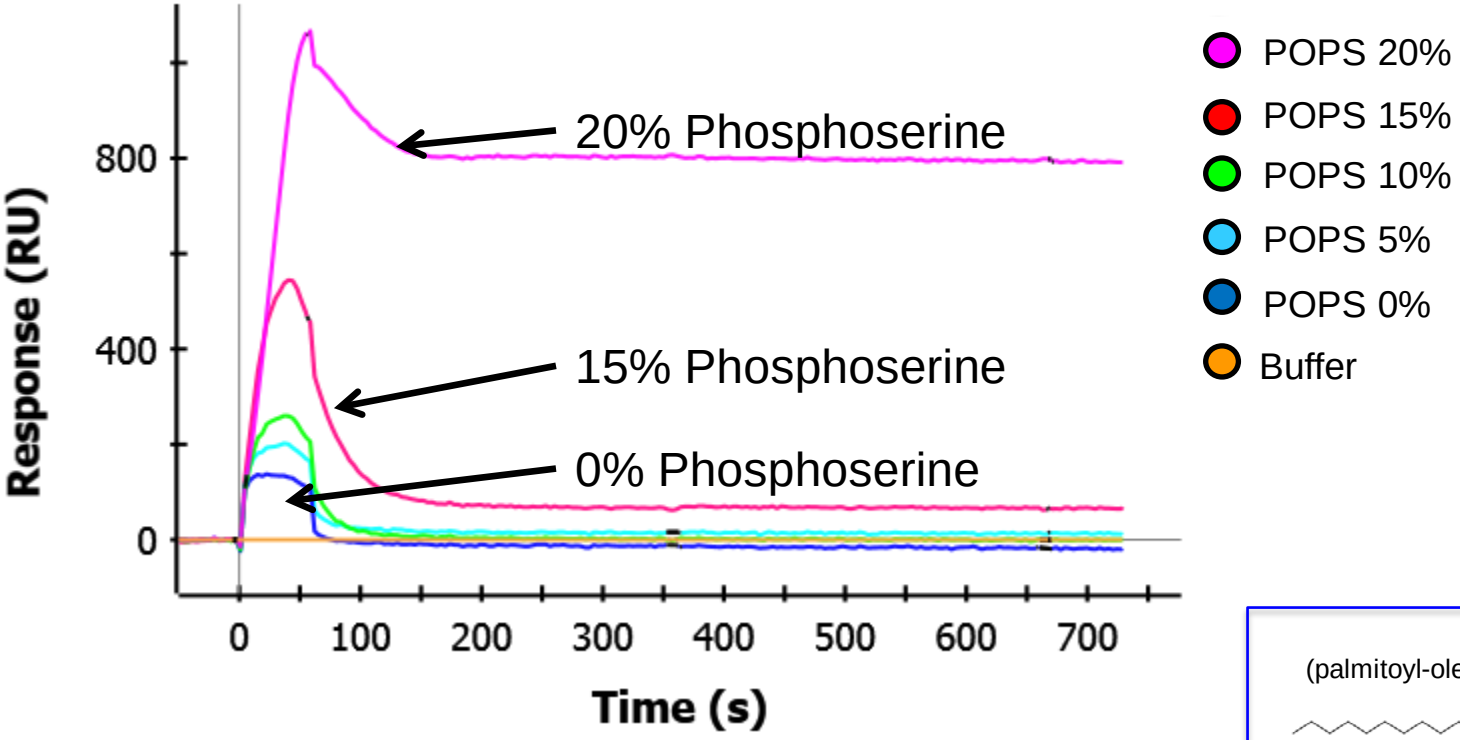
- Fluorescence fluctuation spectroscopy (Jay Groves, UC Berkeley)
- Neutron scattering (NIST)

Nanodiscs

- Collaboration with Steve Sligar (UI Champaign-Urbana)
- Structural biology by cryo-EM and NMR
- Next-generation HTS assays

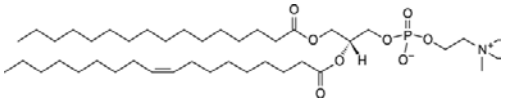


Binding of processed KRAS to liposomes is dependent on the phosphoserine content

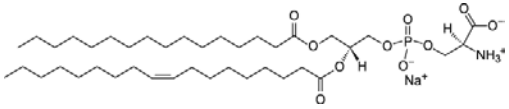


5μM processed KRAS binding to liposomes with variable phosphoserine content

POPC
(palmitoyl-oleoyl phosphatidylcholine)



POPS
(palmitoyl-oleoyl phosphatidylserine)



Lakshman Bindu

Plans for structural and biophysical analysis of fully processed KRAS

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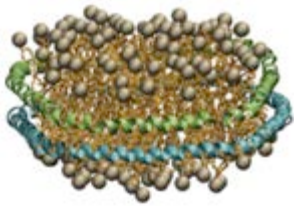
KRAS-lipid interactions

Prepare and QC nanodiscs

Prepare and QC liposomes



Crystallography

Hi-Res Cryo-EM structure (NCI)

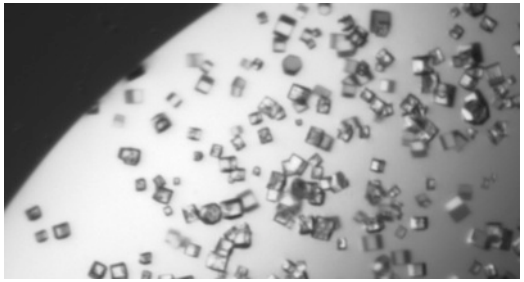
NMR structure KRAS-nanodisc (NMR-FAM)

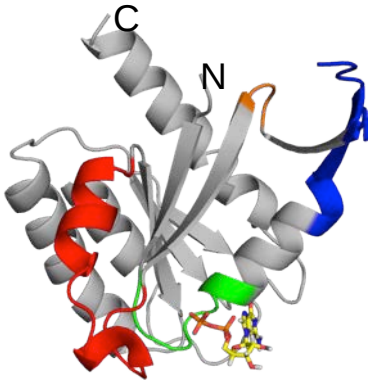
Quantitate KRAS-liposome interactions by SPR or FCS (Sligar/Groves)

KRAS-membrane orientation by neutron reflectivity (NIST)

Intrinsic/GAP GTP hydrolysis
RAF-RBD binding
Next generation screening assays

Structural Biology





Dhirendra Simanshu

RAS Structural Biology

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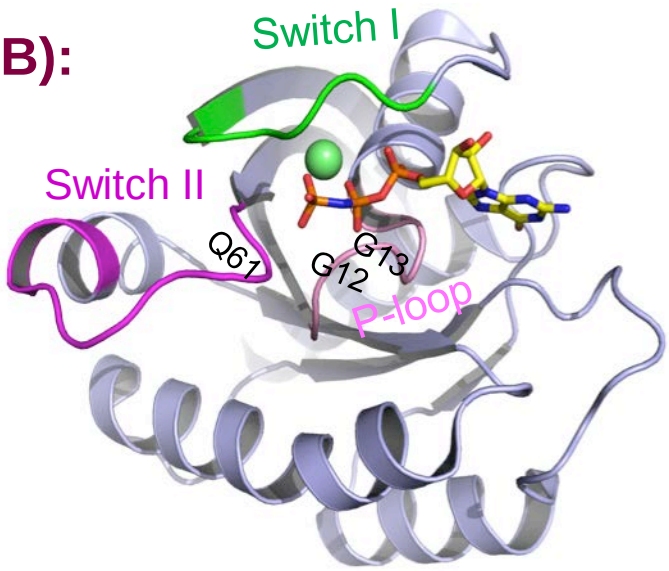
Structures available in Protein Data Bank (PDB):

- HRAS: 120 structures
- KRAS: 36 structures
- NRAS: 1 structure



KRAS bound to GTP analog

PDB code: 3GFT

Challenges to targeting RAS cancers

- No structure of KRAS mutants with any effector or regulator.
- No structural insights about how RAS activates Raf kinase.
- No structural information on full-length processed RAS.
- No structural information on full-length Raf – free or in complex with RAS.

Structural Biology Goals

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- **Determine structures of wild-type KRAS and oncogenic mutants in inactive (GDP-bound) and active (GTP/GMPPNP) states**

  G12C G12D G12V G13D Q61H Q61L

- **Determine structures of KRAS complexes with various effectors and regulatory proteins to aid structure-based drug design**
  - Calmodulin
  - GAPs : RASA1, NF1
  - Effectors : Raf (RBD and Kinase domain, full-length), PI3-Kinase
  - Farnesyl binding : PDE6δ, smgGDS

- **KRAS4a structure – Comparison with KRAS4b**

- **NMR efforts: processed full-length KRAS bound to nanodisc.**

  Que Van at FNLCR

Crystal structures of KRAS in complex with GDP and GMPPNP (non-hydrolysable GTP analog)

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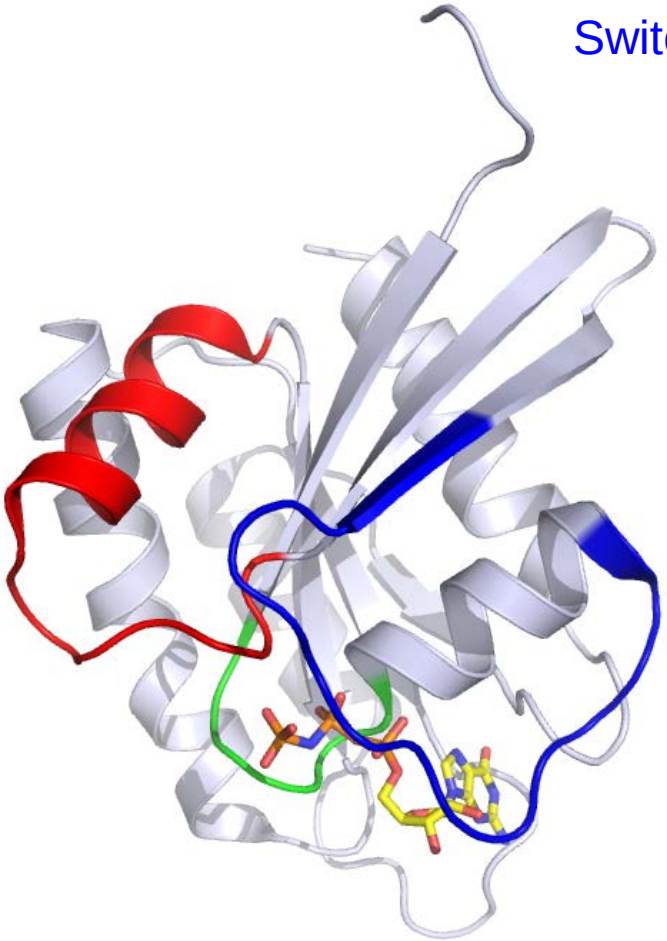
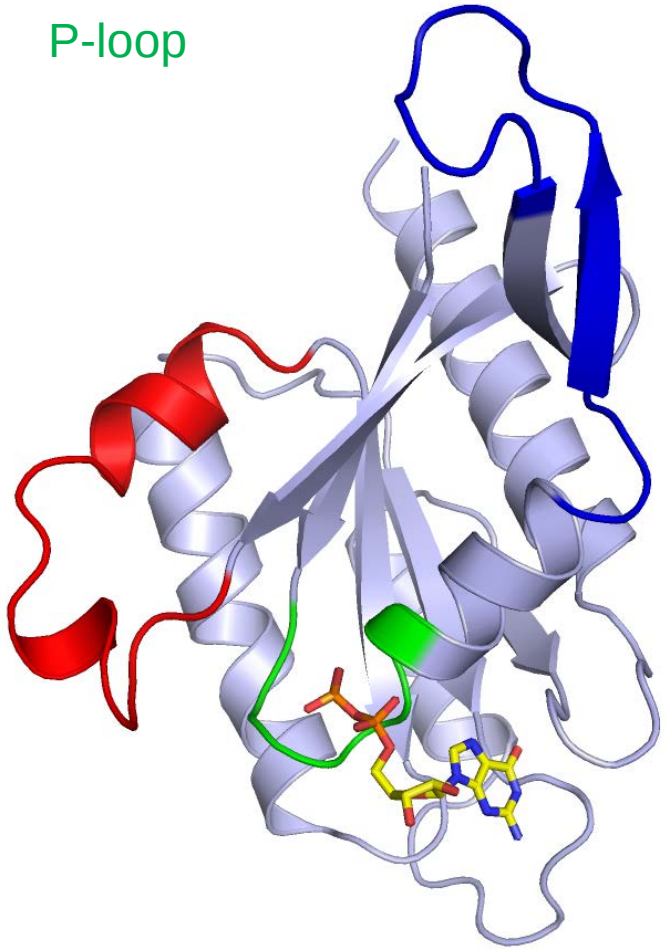
Switch-I Switch-II P-loop



KRAS(1-166)-GMPPNP complex at 1.35 Ang



Full-length-KRAS-GDP complex at 1.6 Ang

Beryllium CRO

Comparison of Switch-I conformations suggests large inherent flexibility

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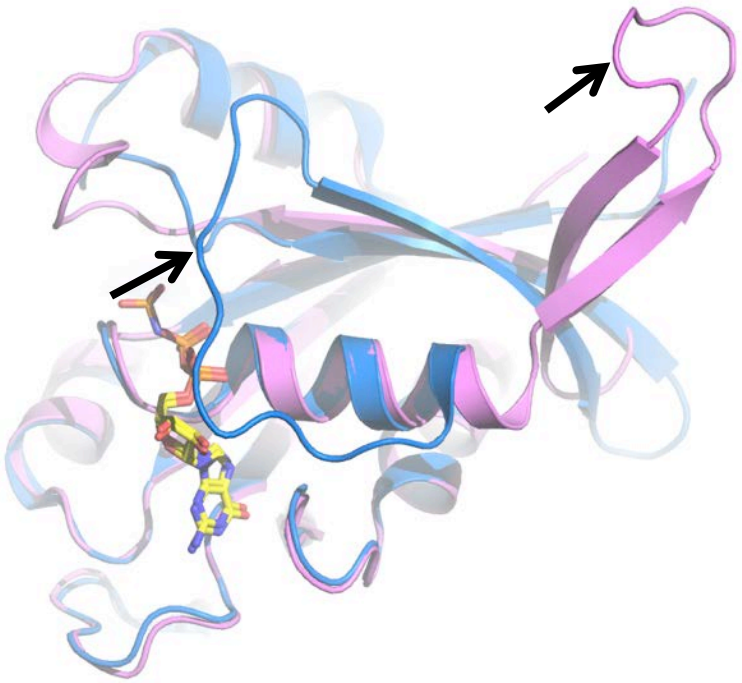
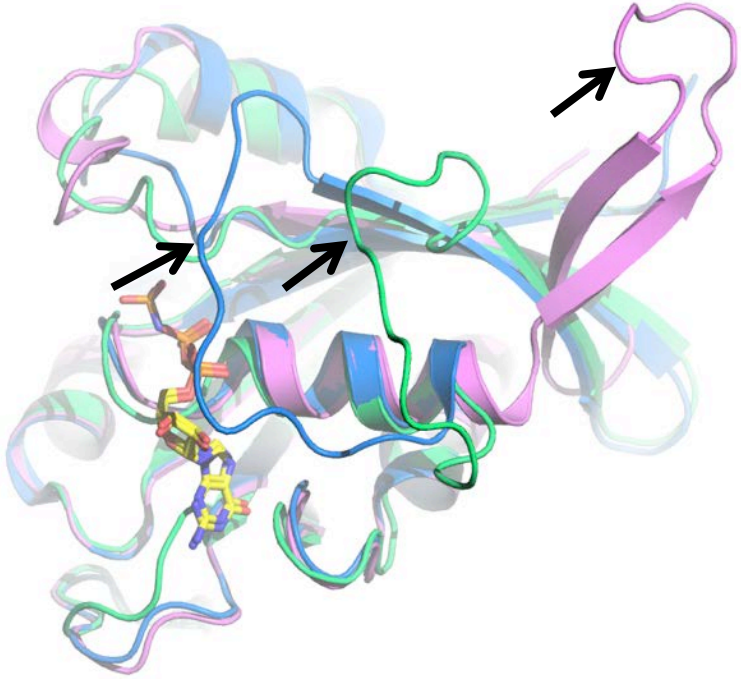


KRAS-GDP complex

KRAS-GMPPNP complex



KRAS-GDP complex

KRAS-GMPPNP complex

Allosteric HRAS-SOS complex

Structural analysis of KRAS-GDP complex

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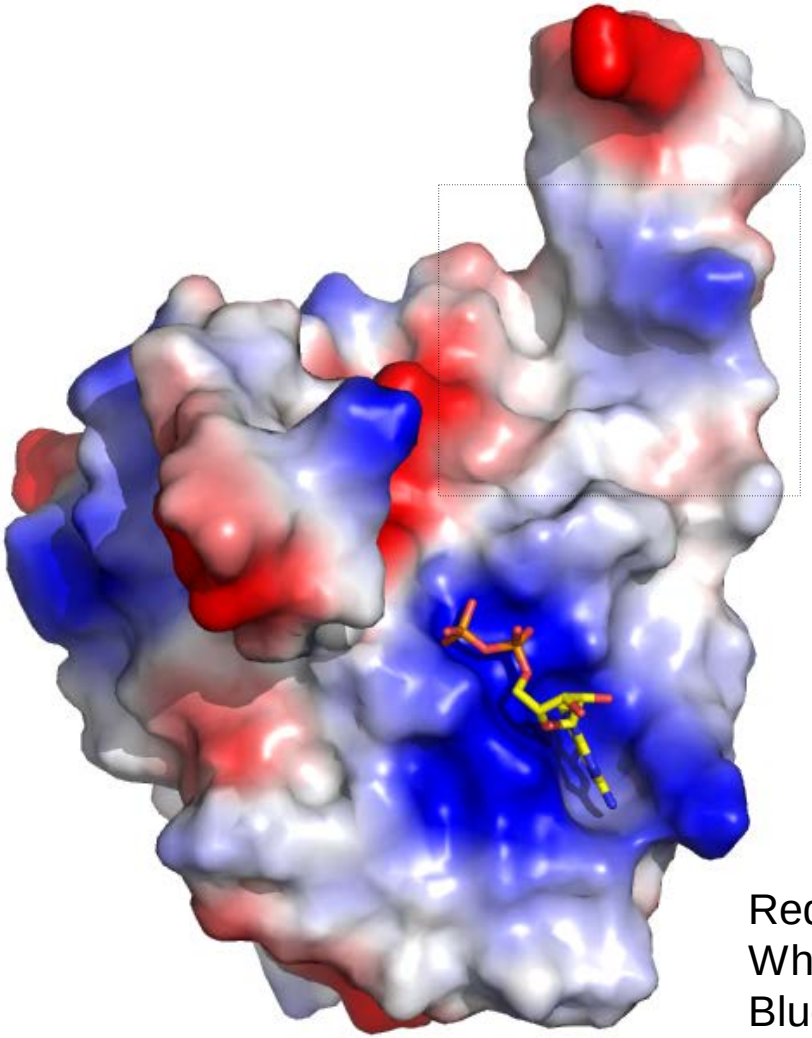
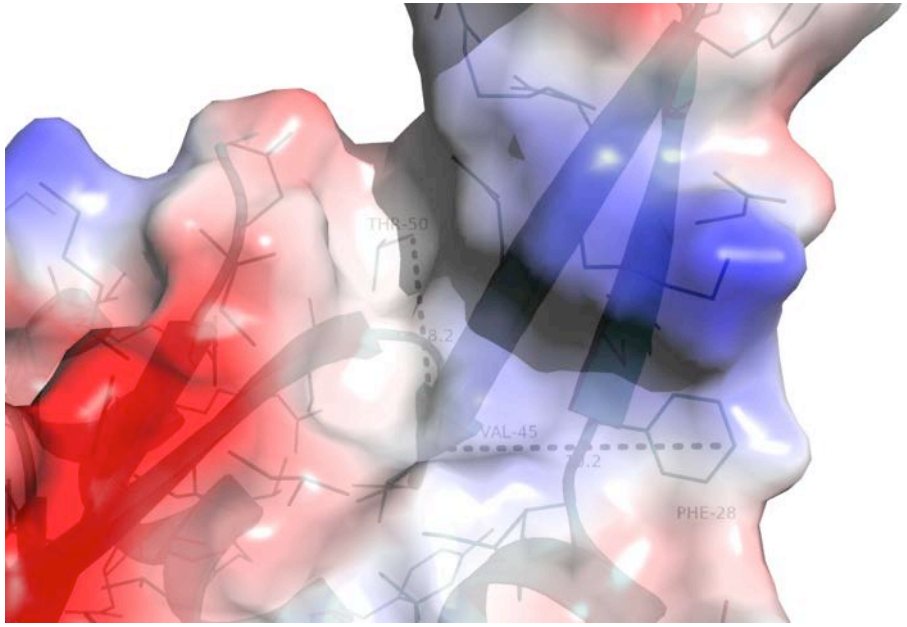
Electrostatic surface representation of KRAS-GDP complex





Enlarged view of the hinge region

Red - negative charge
White - neutral
Blue - positive charge

Collaborative efforts: RAS Structural Biology

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Agni Ghosh and Steve Almo (Albert Einstein College of Medicine)

- $KRAS^{G12D}$-GAP complex (RASA1 and NF1)

Carla Mattos (Northeastern University)

- Calmodulin-KRAS complex

Ken Westover (UT-Southwestern)

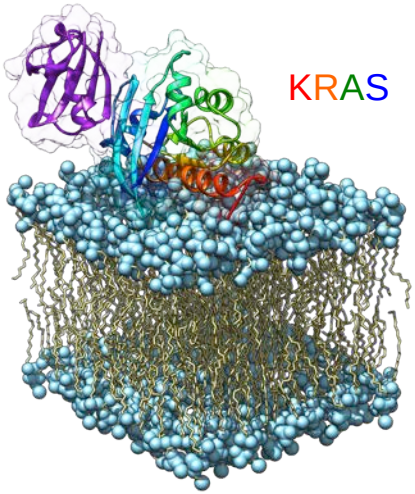
- GDP bound structures of KRAS oncogenic mutants

National Magnetic Resonance Facility at Madison (NMRFAM)

- NMR structure of processed full-length KRAS bound to nanodisc

Targets & Assays

CRAF-RBD



KRAS

Matt Holderfield

KRAS-effector binding AlphaScreen assay

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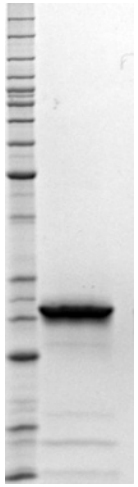
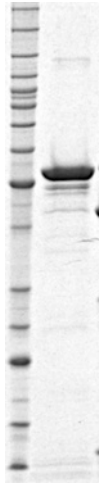
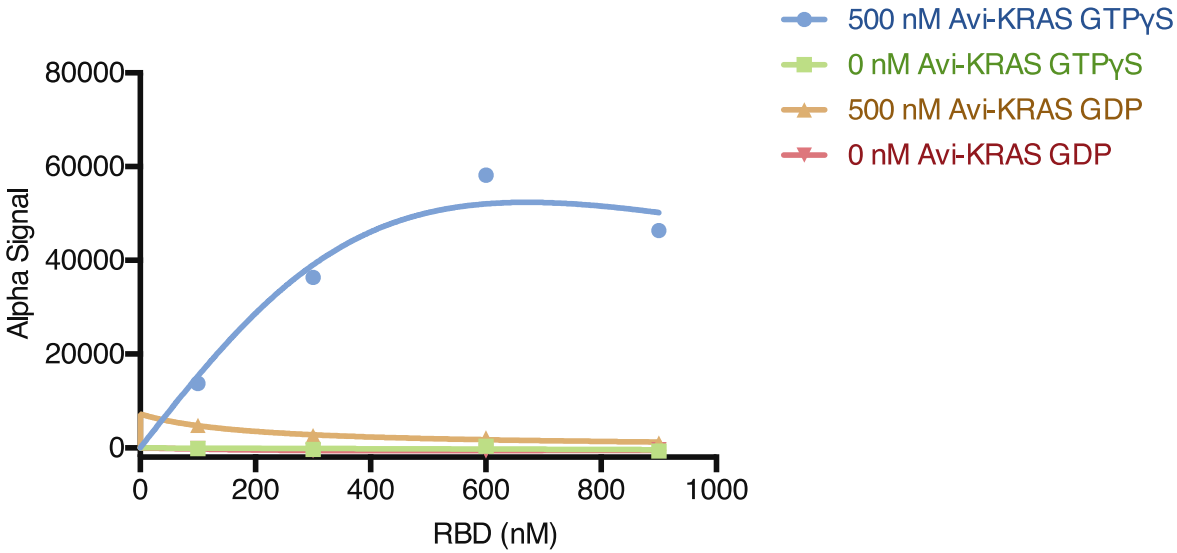
Avi-KRAS



GST-CRAF-RBD

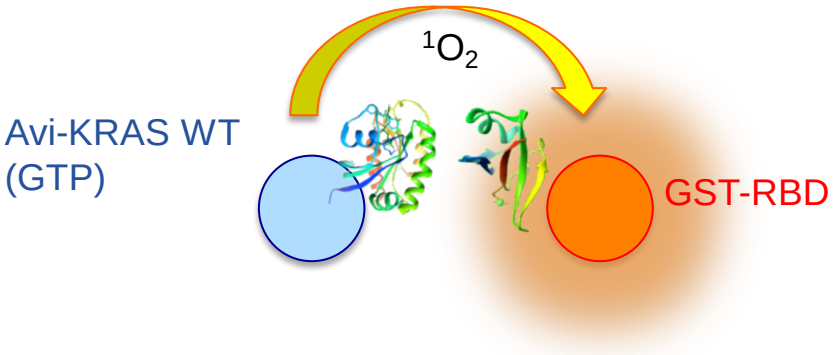




Purified, recombinant protein used for KRAS:CRAF-RBD binding assay in vitro using AlphaScreen technology

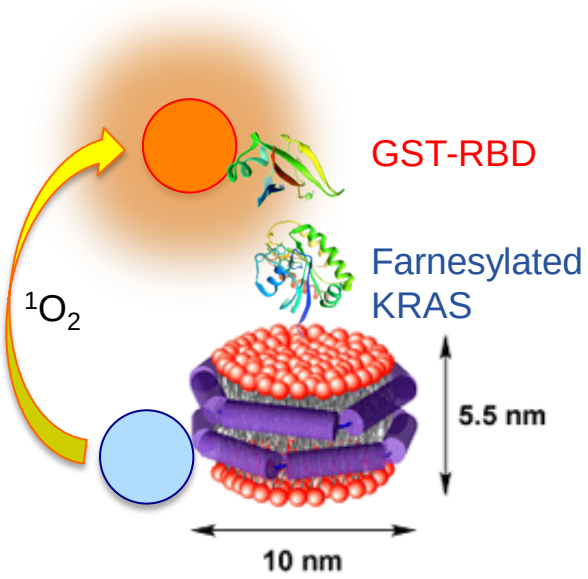
Binding is highly GTP dependent

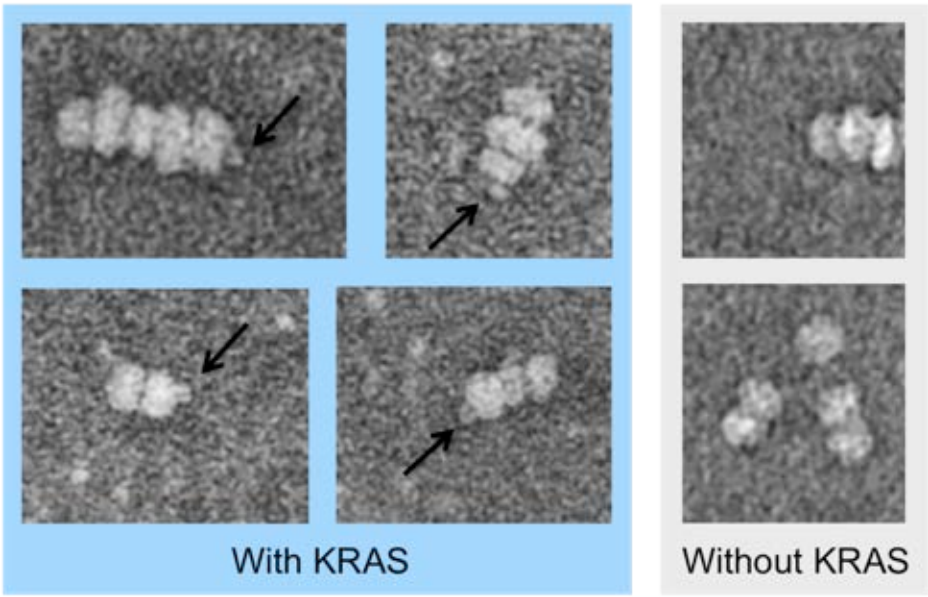
Assay is ready for pilot screening



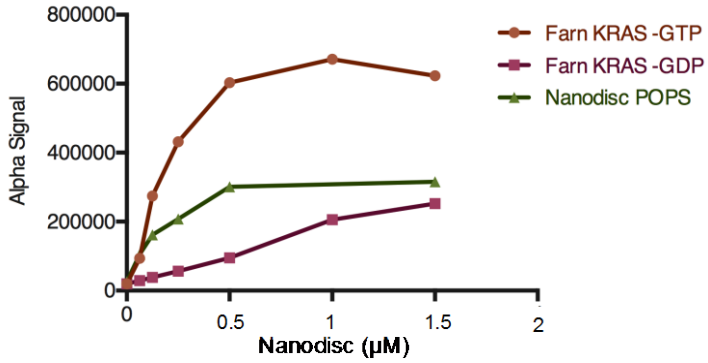
Pete Frank, John-Paul Denson, Maria Abreu-Blanco

KRAS Nanodisc complex





Ulrich Baxa and Que Van



Maria Abreu-Blanco

Belt protein and lipids self-assemble into bilayer disk structures

Farnesylated KRAS self-associates with the lipid surface of nanodiscs

His6 tag on the belt protein is available for tag-based binding assays such as AlphaScreen

RAS-Dependent MEFs

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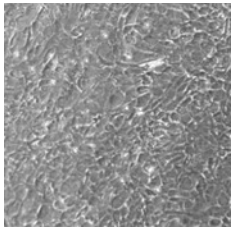
$HRAS^{-/-}$ $NRAS^{-/-}$ $KRAS^{lox/lox}$ MEFs

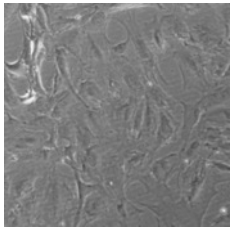
Drosten M, Dhawahir A, Sum EY, Urosevic J, Lechuga CG, Esteban LM, Castellano E, Guerra C, Santos E, **Barbacid M**. EMBO J. 2010

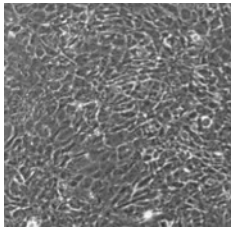
Untreated MEFs



+4-OHT

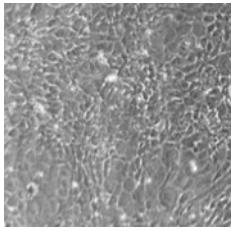
G1 arrest (day 19)





+KRAS G12D

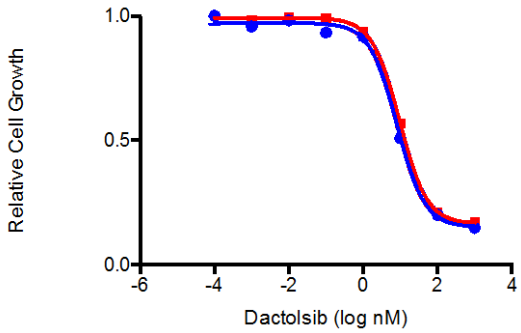
Re-enter cell cycle

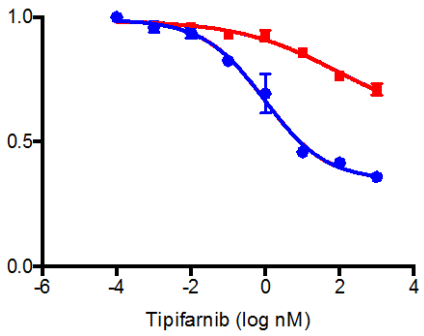


+HRAS

drug sensitivity

KRAS G12D
HRAS





In the queue:

KRAS G12V	KRAS G12A	KRAS Q61R	RB-/-
KRAS G12C	KRAS WT	BRAF V600E	P53-/-

Rachel Bagni, Katie Beam, Dan Soppet, Maria Abreu-Blanco, Kanika Sharma

RAS-dependent MEF Pilot screening results

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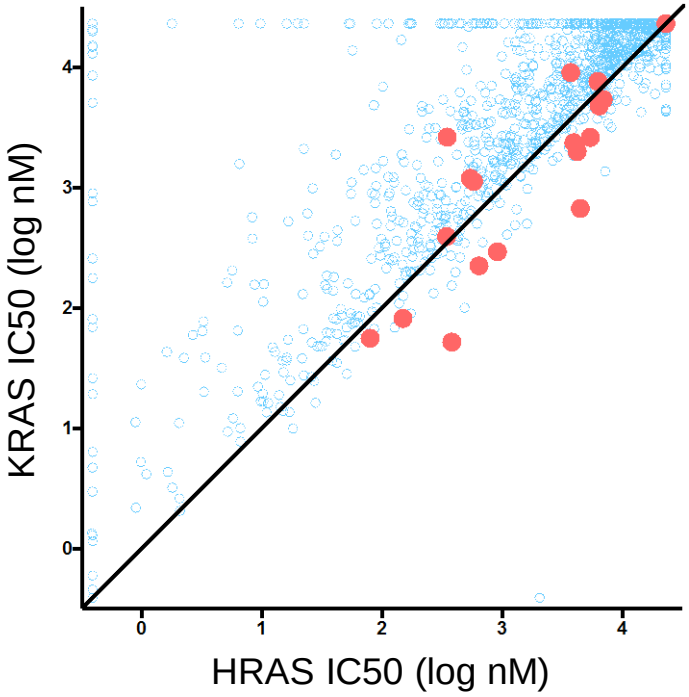
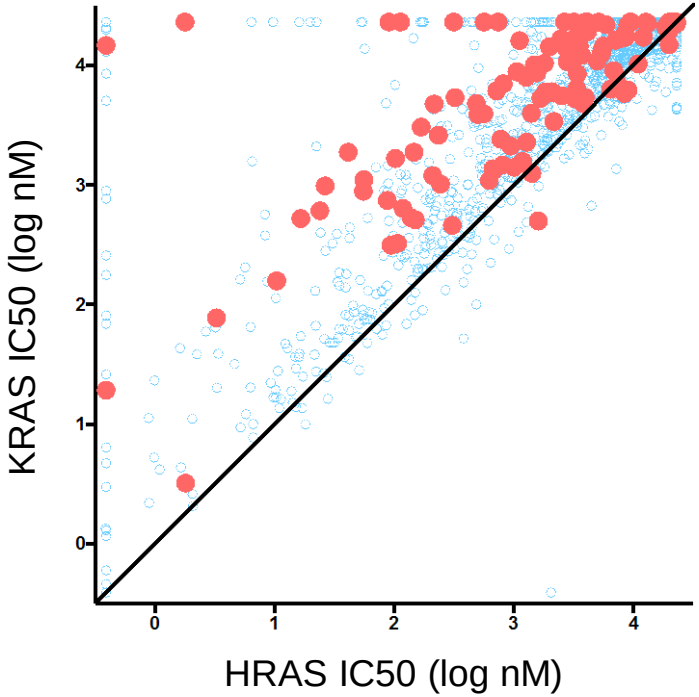
MEK and ERK inhibitors



RTK inhibitors

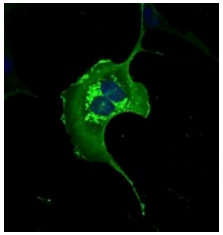


MEK/ERK inhibitors are equipotent in HRAS-WT and KRAS G12D

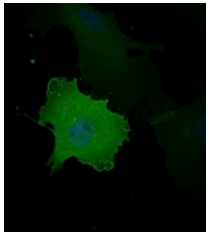
Receptor tyrosine kinase inhibitors preferentially inhibit HRAS-WT but not KRAS-G12D

With NCATS, Ajit Jadhav, Kyle Brimacombe and Anton Simeonov

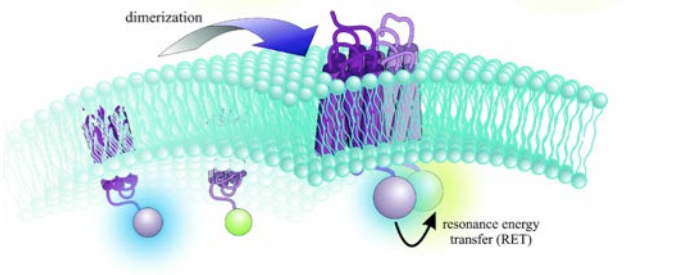
Multimerization and Localization Assays



Ras-GFP

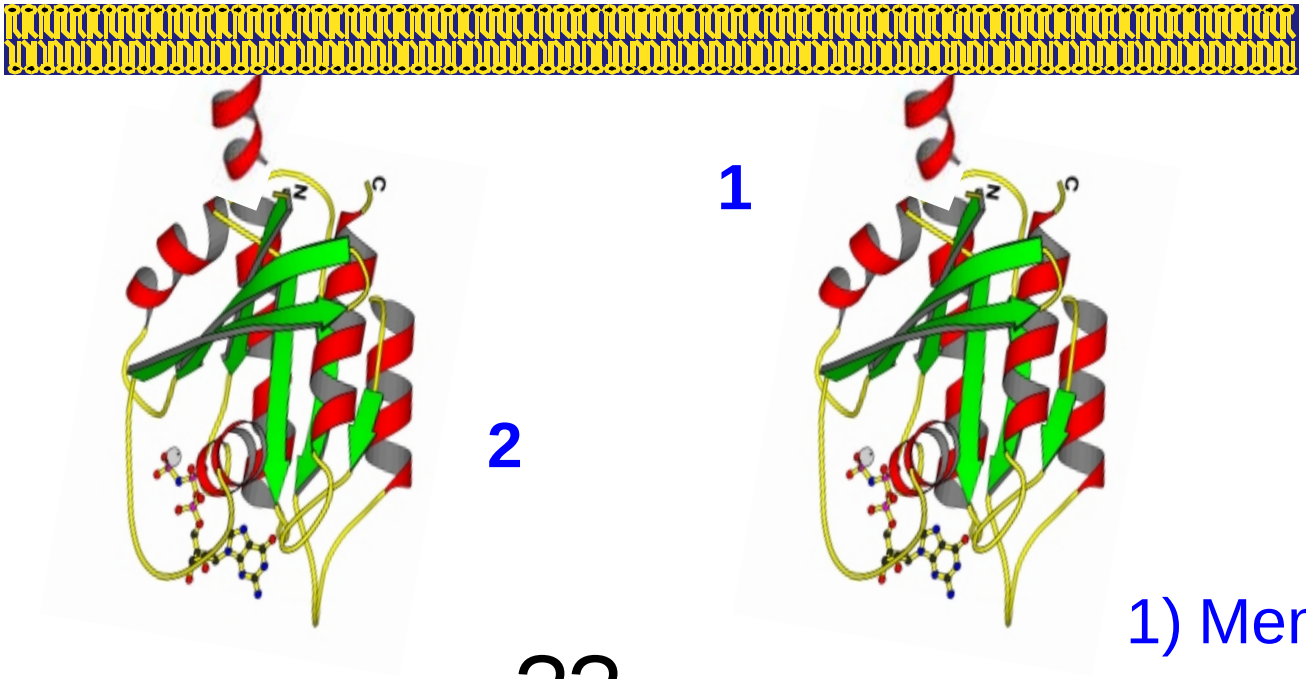


+ FTI



Tommy Turbyville

Assays for Compounds that Disrupt KRAS Signaling



1) Membrane localization

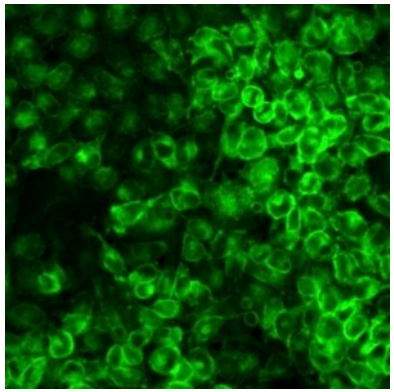
2) Multimerization assay

Signal

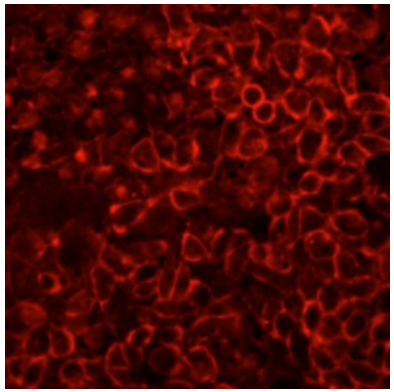
Localization Assay

Frederick National Laboratory for Cancer Research

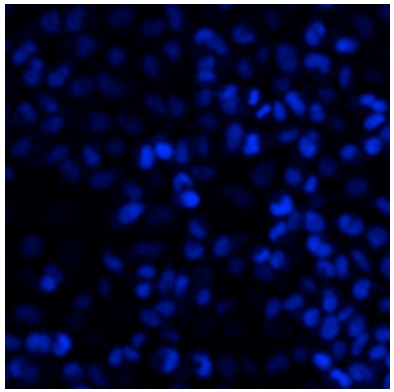
GFP-KRAS-G12V



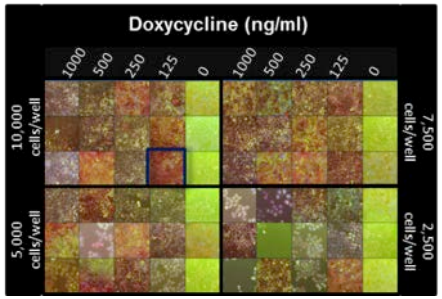
Membrane



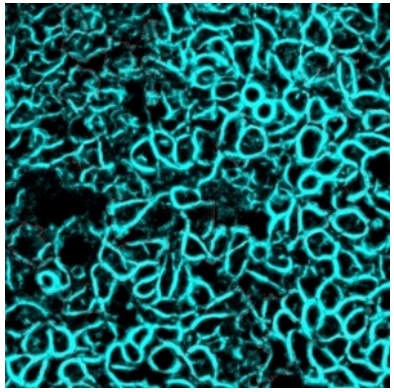
Nuclei



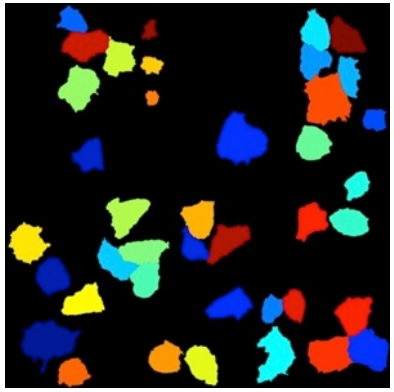
Multiwell confocal imaging



Segmentation and Data Analysis →



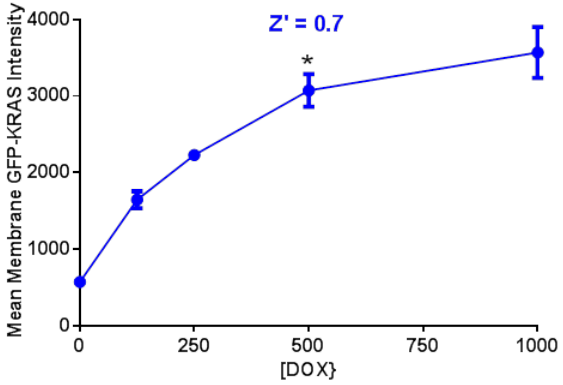
Probability Map



Mask

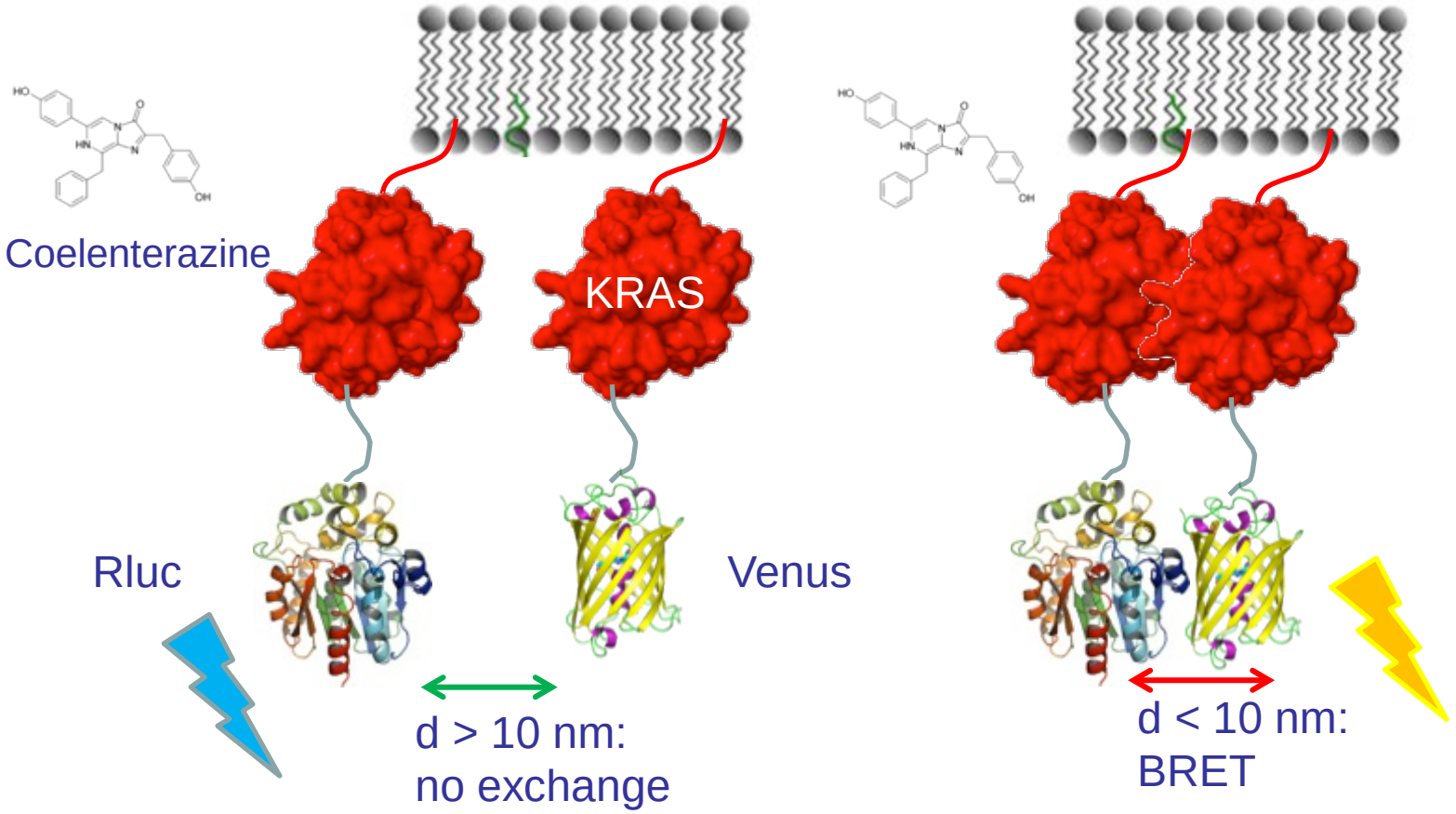
Segmented Boundary

Membrane Localized GFP Signal



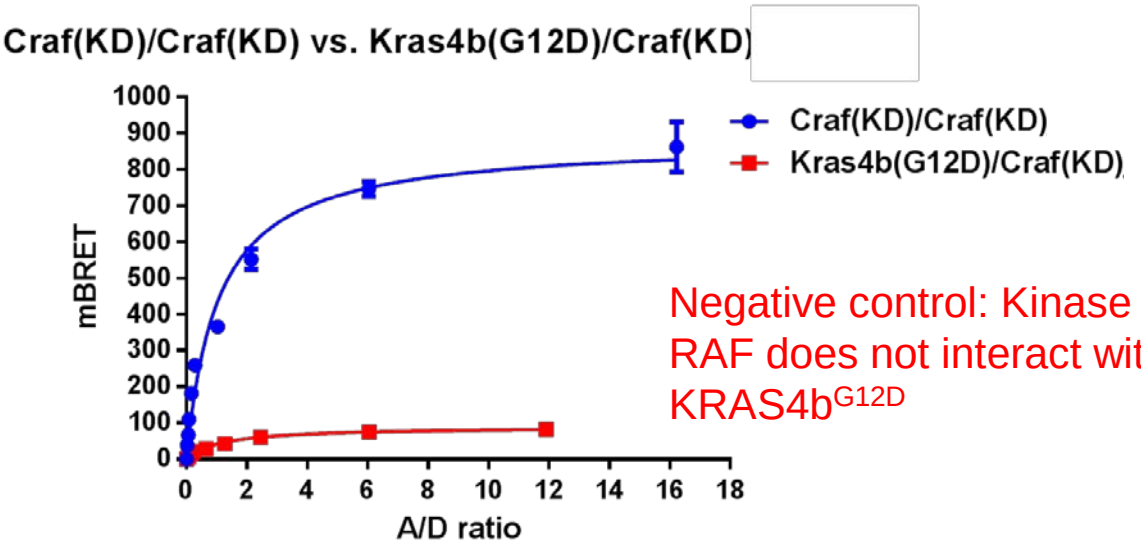
Bioluminescence resonance energy transfer (BRET)

Frederick National Laboratory for Cancer Research



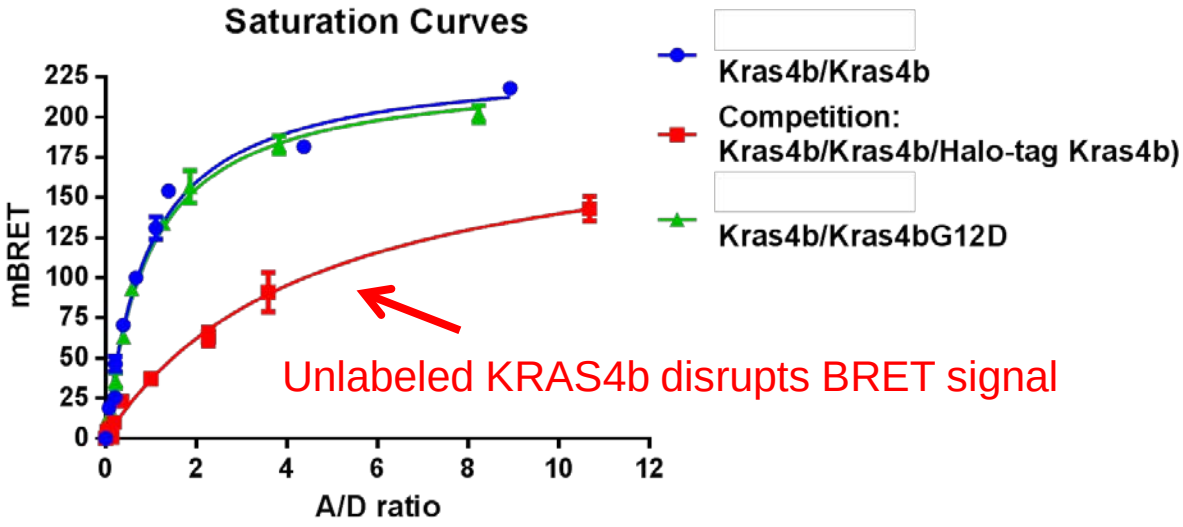
Goal is to develop a primary assay to screen for inhibitors of KRAS multimerization.

BRET Control Saturation Curves



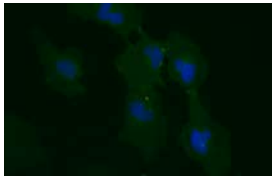
Kinase domain of RAF serves as a positive control

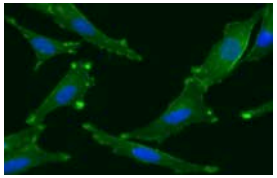
Negative control: Kinase domain of RAF does not interact with KRAS4b^{G12D}

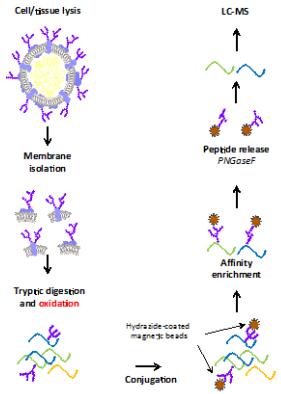


Unlabeled KRAS4b disrupts BRET signal

RAS Cell Surface



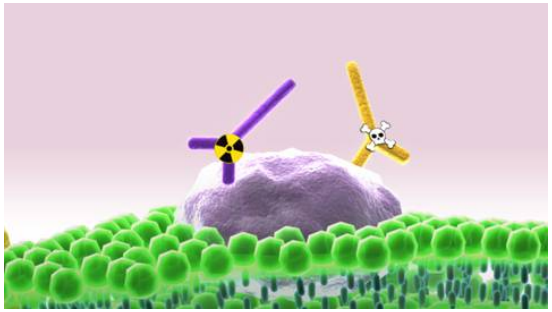


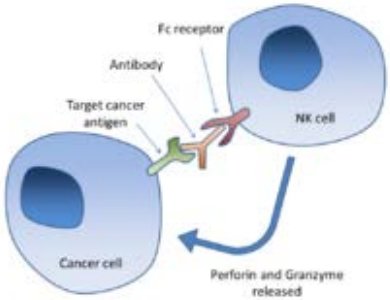


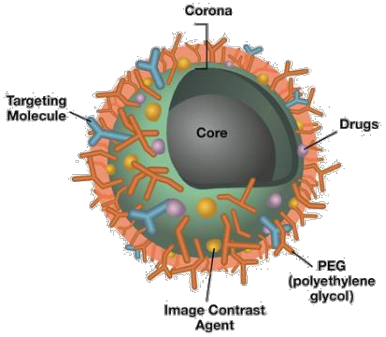
Gordon Whiteley

Mapping the surface of KRAS cancer cells

- **Objectives and rationale**
  - Survey the surface of KRAS-driven cells to generate a list of proteins differentially associated with KRAS phenotype
  - These KRAS associated cell surface determinants could represent new targets for
    - antibody-mediated attack
    - immune based therapy
    - nanoparticle delivery







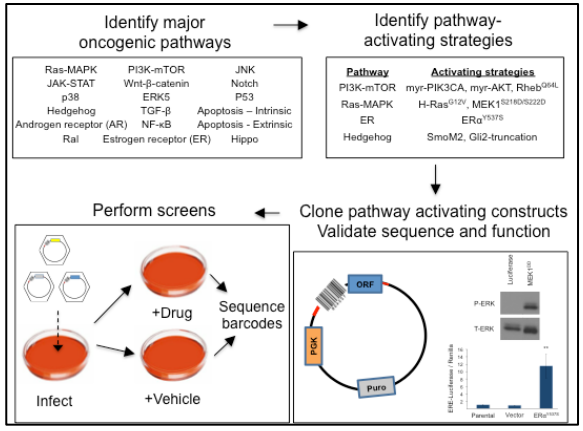
Cell Surface Strategy

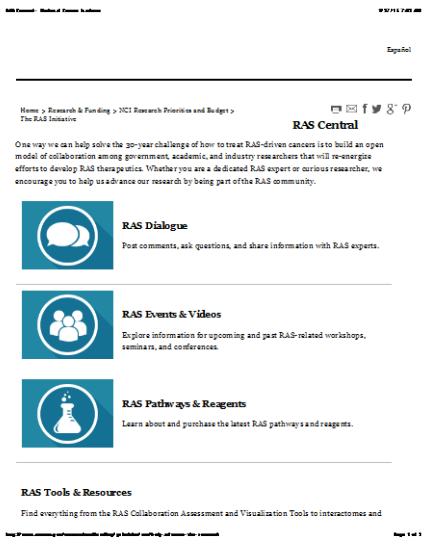
Frederick National Laboratory for Cancer Research

- **Adapt cell surface protein labeling for mass spec proteomic analysis of KRAS cells *in vitro* and *in vivo***
  - In house development of “tumor-surface proteomics”
- **Collaborate to use selective panning technologies (phage display) to survey the KRAS cell surface**
  - Robert Rottapel and Sachdev Sidhu, Univ Toronto
  - Renata Pasqualini, Univ New Mexico (December visit to FNL)
- **Use RNA seq and ER-polysome profiling to predict protein complement on KRAS cell surface**
  - Martin McIntosh, FHCRC
- **Bioinformatic Approaches**
  - Renata Grifantini, Externautics, Italy (December visit to FNL)
- **Immunotherapy Workshop**
  - Elizabeth Jaffe and Bob Schrieber to help organize (at 2015 AACR)

Enabling the Community:

RAS Reference Reagents and Cancer.gov/RAS





Español

Home > Research & Funding > NCI Research Priorities and Budget > The RAS Initiative

RAS Central

One way we can help solve the 30-year challenge of how to treat RAS-driven cancers is to build an open model of collaboration among government, academic, and industry researchers that will re-energize efforts to develop RAS therapeutics. Whether you are a dedicated RAS expert or curious researcher, we encourage you to help us advance our research by being part of the RAS community.

RAS Dialogue

Post comments, ask questions, and share information with RAS experts.

RAS Events & Videos

Explore information for upcoming and past RAS-related workshops, seminars, and conferences.

RAS Pathways & Reagents

Learn about and purchase the latest RAS pathways and reagents.

RAS Tools & Resources

Find everything from the RAS Collaboration Assessment and Visualization Tools to interactomes and

Dom Esposito

Jim Hartley

RAS Reference Reagents

Frederick National Laboratory for Cancer Research

External reagent requests (since July 2014)

- 15 requests for RRR reagents (clone sets and other items)
- 8 approved TSAs, 2 approved MTAs, 5 others in progress
- Fred Hutch, Baylor, Munich, Stanford, MIT, Broad, Northwestern, CRUK

RAS Initiative support—344 constructs generated since July 2014

- 212 constructs for protein expression (TBU-C/Project 1)
- 79 constructs for Project 3
- 53 constructs for TBU-Z

RAS Pathway clone set underway (181 clones)

Kris Wood collaboration underway (200+ cancer toolkit clones)

Cancer.Gov/RAS v2.1

Frederick National Laboratory for Cancer Research

In English | En español

National Cancer Institute
at the National Institutes of Health

We Can Answer Your Questions
1-800-4-CANCER

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The RAS Initiative

The RAS Initiative

- The Problem
- A Collaborative Solution
- RAS Projects at FNLCR
- RAS Laboratory Groups
- RAS Initiative Oversight
- RAS Spokes
- Join the RAS Initiative

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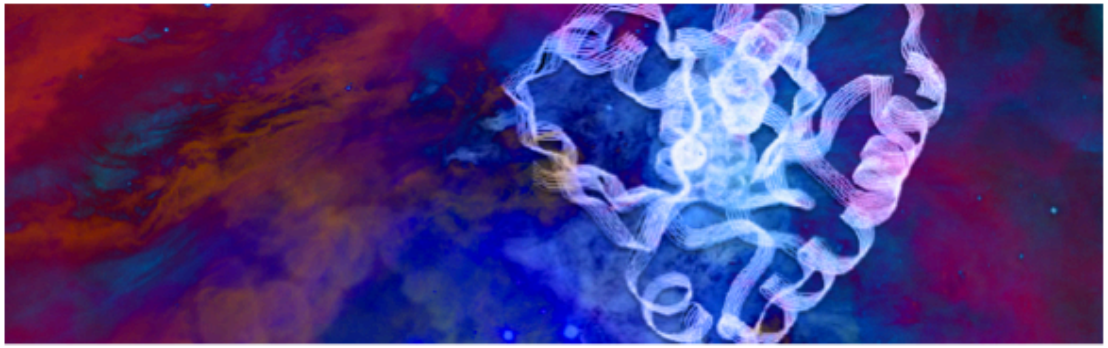


Development of the RAS Initiative at the Frederick National Laboratory for Cancer Research (FNLCR)

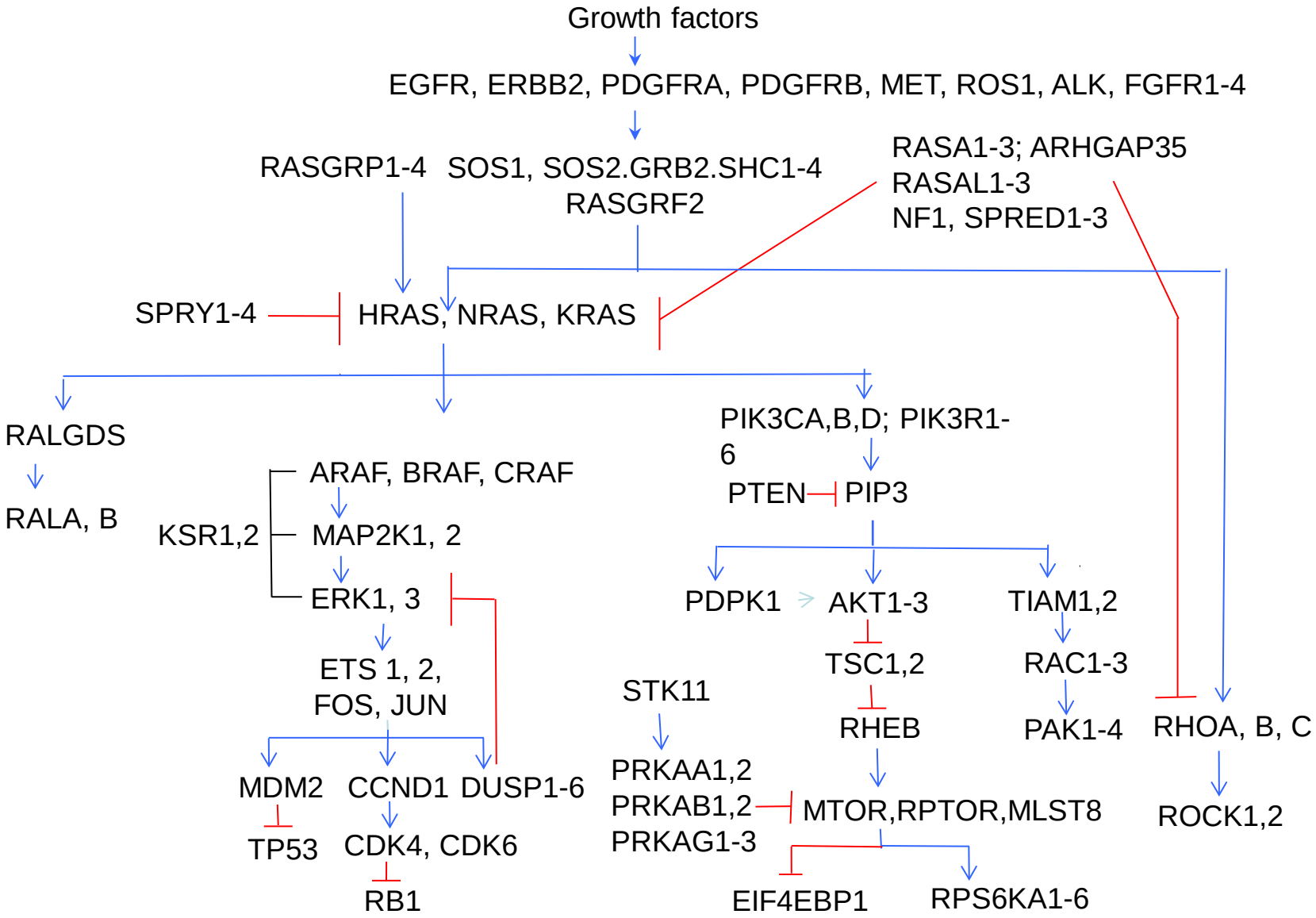
Since the early 1970s, the National Cancer Institute (NCI) has been responsible for a contract that supports the only Federally Funded Research and Development Center (FFRDC) devoted principally to biomedical research. Located on a government campus in Frederick, MD, the FFRDC has provided a variety of laboratory services to the scientific community, performed research in response to national needs, and supervised subcontracts for the NCI for over 40 years.

Message from NCI Director Harold Varmus

In 2011, following a suggestion by the NCI's National Cancer Advisory Board, NCI Director Harold Varmus named the operational laboratory arm of the FFRDC Frederick National Laboratory for Cancer Research (FNLCR) and established an advisory committee (now called the

A **RAS Initiative** view of RAS signaling:
*An invitation for discussion at **Cancer.gov/RAS***

Frederick National Laboratory for Cancer Research



RAS Community feedback on RAS signaling model:

Frederick National Laboratory for Cancer Research

RAS Pathway v2.0

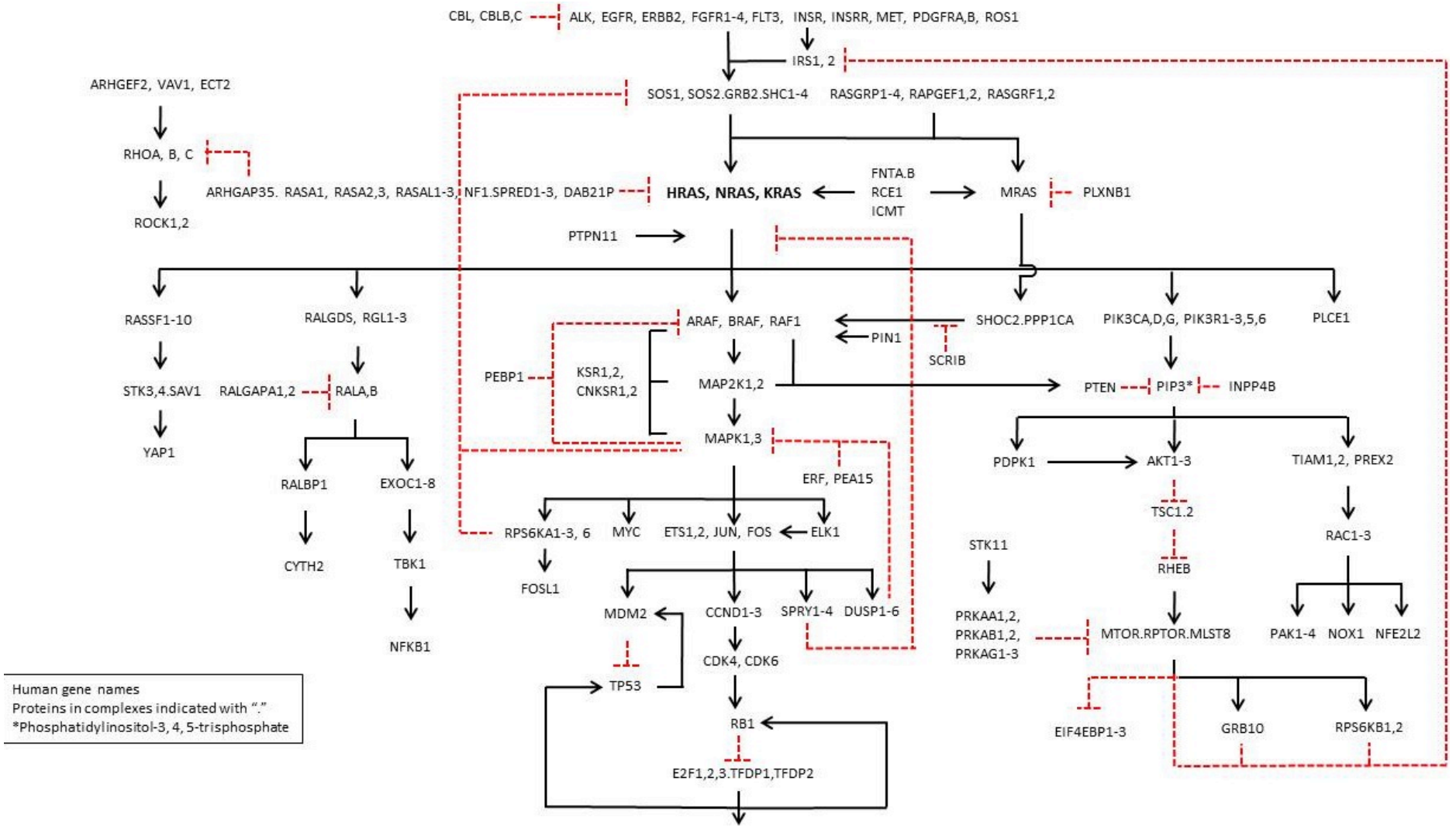
January 13, 2015 by Frank McCormick

Our original pathway diagram (posted on October 22, 2014) has been altered incorporating suggestions from the following investigators:

- Phil Stork (stork@ohsu.edu) suggested adding RASGRP1, but but we left out PDZGEF1 which (I think) is a RAP1 GEF, not a RAS GEF. Any input on this would be welcome.
- Julie Irving (julie.irving@ncl.ac.uk) suggested adding FLT3 (also suggested by Kevin Shannon shannonk@peds.ucsf.edu), PTPN11 (also suggested by Ben Braun, UC San Francisco) and CBL. On Ben's advice, PTPN11 was kept vague with a positive arrow to RAS activation of RAF, without a clear target.
- Manuela Baccarini (manuela.baccarini@univie.ac.at) noted that MAP2K1 activates PTEN by sending it to the plasma membrane. RAF1 inhibits ROCK2, but was not included in our updated diagram because the drawing was getting too complicated. This may be fixed in a subsequent version.
- Mike Nickerson (nickersonml@mail.nih.gov) included negative feedback to IRS1 and 2 from the PI3 kinase pathway.
- Anne Goriely (anne.goriely@imm.ox.ac.uk) suggested adding the MRAS (RRAS3) –SHOC2.PPP1CA pathways that activate RAF kinase and ERF, an ETS-family protein that inhibits ERK1 (aka MAPK3) and 2 (MAPK1).
- Eric Collisson (eric.collison@ucsf.edu) suggested adding the RHO GEF ARHGEF2, aka GEF-H1. Rob Rottopel has recently shown this also acts on the MAPK pathway via interaction with KSR1, but I couldn't find a way of representing that in this version.
- Jim DeCaprio (james_decaprio@dfci.harvard.edu) suggested adding cyclin D2 (CCND2) and 3 (CCND3) in addition to Cyclin D1 (CCND1) as MAPK targets. Ping Lu (klu@bidmc.harvard.edu) suggested adding PIN1 as an activator of RAF1 kinase (aka CRAF). It could have been added at many other sites (see Cell Res 24, 1033, 2014 for a review by Zhimin Lu and Tony Hunter).
- Michael Tainsky (mat@wayne.edu) noted that AP2 is essential for RAS transformation, but I couldn't find a direct link to the RAS pathway. Any suggestions are welcome.
- Maria Zajac-Kaye (mzajackaye@ufl.edu) suggested adding E2F target genes, including thymidilate synthase (TYMS). Target genes that appear on other parts of the pathway were not listed, to keep it simple.
- Ramon Parsons (ramon.parsons@mssm.edu) suggested adding the RAC GEF, PREX2.
- Shyam Biswal (sbiswal@jhu.edu) and Carola Neumann (neumannc@upmc.edu) suggested adding NFE2L2 (aka NRF2), and NOX1.
- Eric O'Neill (eric.oneill@oncology.ox.ac.uk) suggested adding a mini-version of the Hippo pathway (RASSF, MST [STK3 and 4], SAV1, YAP1).
- Joe Ramos (joeramos@hawaii.edu) and Naoto Ueno (nueno@mdanderson.org) suggested adding PEA15.
- Larry Feig (larry.feig@tufts.edu) suggested adding RASGRF1 and 2.
- Howard Crawford (crawford.howard@mayo.edu) proposed adding VAV1, ECT2 and TIAM1. Howard also suggested DOCK10, but I wasn't sure where to put it. Suggestions welcome!
- Mike White (michael.white@utsouthwestern.edu) suggested adding EXOC1-8 connected to the RALA, B node and CNKSR1, CNKSR2, SHOC2 connected to the RAF node.
- Karen Cichowski (kcichowski@rics.bwh.harvard.edu) suggested adding DAB21P and INPP4B.
- Andrew Sharrocks (a.d.sharrocks@manchester.ac.uk) suggested adding ELK1.
- Mark Philips (philim01@nyu.edu) suggested adding FNTA and B, RCE1 and ICMT1.
- Debbie Morrison (morrisod@mail.nih.gov) suggested adding a feedback arrow from MAPK1,3 to the RAFs.
- Channing Der (cjder@med.unc.edu) suggested adding MYC as a MAPK1/3 substrate. He also included RGL, RGL2 and RGL3 with RALGDS as another effector that links RAS with RAL. Additionally, the RALGAPs, RALGAPA1 and RALGAPA2, and PLCE1 are included as RAS effectors.
- Philippe Roux (philippe.roux@umontreal.ca) pointed out errors in the pathway as originally drawn: "The pathway should indicate that RPS6KB1 and RPS6KB2 are targets of mTOR (they are the p70 S6Ks). The related p90 S6Ks (RPS6KA1, RPS6KA2, RPS6KA3, RPS6KA6) are actually targets of MAPK1/3, and should be transferred to that branch of the pathway." Steen Hansen (steen.hansen@childrens.harvard.edu) also pointed out these errors and suggested we add FOSL1 downstream of RPS6KA1,2,3 and 6. Additionally, there are two more isoforms of EIF4EBPs, and thus the pathway should indicate EIF4EBP1-3.
- Julian Downward (julian.downward@cancer.org.uk) also noted some errors, "You should have PIK3CA, PIK3CD and PIK3CG here, but not PIK3CB as p110beta does not interact with RAS. Also, for regulatory subunits, there should be PIK3R 1, 2, 3, 5, and 6, but not 4 – this is VPS15, the regulatory partner of VPS34. PIK3R 5 and 6 are the regulatory subunits of p110gamma, so are fine to have here."

A **RAS Initiative** view of RAS signaling: *v 2.0 at **Cancer.gov/RAS***

Frederick National Laboratory for Cancer Research



Frederick National Laboratory for Cancer Research

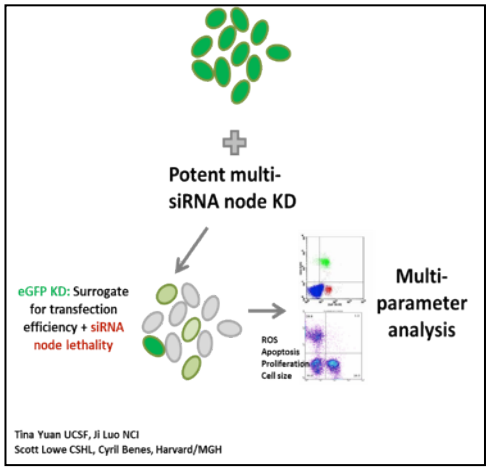
RAS Initiative Oversight Follow-up

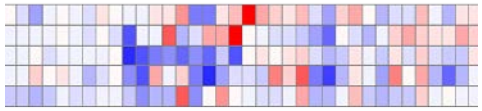
RAS *Ad Hoc* Working Group Meeting (October 31, 2014) – Action Items

Frederick National Laboratory for Cancer Research

- **Publish protocols for production of fully processed KRAS protein and associated structural studies and assays.**
  - Manuscript to be submitted by end of February 2015
- **Establish process for collaboration and providing reagents to community**
  - Processed KRAS will be provided to collaborators
  - Protocols and reagents provided to others
- **Optimize RAS-less MEF screen: understand and eliminate sources of variation**
  - Use validation inhibitor panels at NCATS
  - Evaluate conditional oncogenic KRAS MEFs (Tuveson)
- **Node-knockdown-based (SiREN) approach will produce a large data set that will be discussed at the next Working Group meeting.**
  - Experiments completed, data analysis ongoing

RAS *Ad Hoc* Working Group Meeting (October 31, 2014) – Action Items





Rachel Bagni

Bob Stephens

- **Node-knockdown-based (SiREN) approach will produce a large data set that will be discussed at the next Working Group meeting.**
  - Experiments completed, data analysis ongoing

RAS Initiative Postdoctoral Fellowships

Frederick National Laboratory for Cancer Research

- **Postdoc Program**
  - *Pancreatic Action Network/FNL Fellows*
    - ***Lynn McGregor*** *(Shokat lab)*
    - ***John Hunter*** *(Westover lab)*

THE PANCREATIC CANCER ACTION NETWORK AND THE NATIONAL CANCER INSTITUTE'S FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH COLLABORATE ON TWO 2015 FELLOWSHIPS TO ADVANCE KRAS RESEARCH

A critical area of continuing research aimed at better understanding pancreatic cancer and developing new, more effective ways to treat it is focused on a genetic mutation found in most pancreatic tumors: KRAS.

And now, the Pancreatic Cancer Action Network has formed a unique partnership with the National Cancer Institute's (NCI's) Frederick National Laboratory for Cancer Research (FNLCR) to advance KRAS research. FNLCR is a government-owned, contractor-operated facility devoted exclusively to biomedical research and development.

Our organization and FNLCR have awarded year-long Fellowships that commenced on January 1, 2015, to John Hunter, Ph.D., and Lynn McGregor, Ph.D. Dr. Hunter is working in the laboratory of Kenneth Westover, M.D., Ph.D., at the University of Texas Southwestern Medical Center. His Fellowship is being funded by Ambassador Cynthia Stroum, the Pancreatic Cancer Action Network's Founding Board Chair Emeritus, in memory of her father, Samuel Stroum. Dr. McGregor is conducting her postdoctoral work under the mentorship of Kevan Shokat, Ph.D., at the University of California, San Francisco (UCSF).

Interactions with the RAS Community

Frederick National Laboratory for Cancer Research

NCI RAS Initiative at FNL

Seminars at FNL
Channing Der, UNC
Ken Westover, UTSW
Carla Mattos, Northeastern
Mark Philips, NYU
Vadim Gaponenko, U Chicago
Josh Salafsky, Biodesy
Calvin Kuo, Stanford
Kris Wood, Duke
Mariano Barbacid, CNIO Madrid
Cyril Benes, MGH
Carolyn Buser, GSK
Stephen Sligar, U Illinois
Raffit Hassan, NCI
Renata Grifantini, Externautics Siena
Renata Pasqualini, U New Mexico
Andrew Bradbury, Los Alamos
Kent Rossman, U North Carolina

Recipients of RAS Reference Reagents
Chris Kemp, Fred Hutch
Eric Chang, Baylor
Silvia Thone, Munich
Peter Jackson, Stanford
Tyler Jacks, MIT
Calvin Kuo, Stanford
Bill Hahn, Broad/DFCI
Karla Satchell, Northwestern
Julian Downward, CRUK

Outside collaborators
Steve Almo, AECOM
Jim Wells, UCSF
Channing Der, UNC
Ken Westover, UT Southwestern
Carla Mattos, Northeastern
Steve Sligar, U Illinois
Jay Groves, UC Berkeley
Hirsch Nanda, Susan Kreuger, NIST
John Markley, National Magnetic Resonance Facility at Madison (NMRFAM)
Kris Wood, UNC
Immuno-MRM of RAS pathway
Mandy Paulovich, Fred Hutch
Steve Carr, Broad
John Koomen, Moffit
Tina Yuan, Cameron Pitt, UCSF
Dave Tuveson, CSH

NIH collaborators
Ji Luo, NCI
Anton Simeonov, NCATS
Debbie Morrison, NCI
Rajat Varma, NIAID

RAS workshops
Synthetic Lethality, January 6-7 2014
Pathways, June 11, 2014
Cell Surfaces, July 23, 2014
2015 AACR Annual Mtg, agenda pending

Information exchanges
David Weber, U Maryland
Hirsch Nanda, Susan Kreuger, NIST
Amanda Altieri, U Maryland
David Barford, ICR UK
Bill Sellers, Novartis
Kurt Auger, GSK
Paul Cohen, DARPA
Ian Prior, U Liverpool
Said Sebti, Moffitt