The Ras Project: Overview

The clinical need

- High incidence of RAS mutations in cancer
- No drugs that target RAS proteins directly or indirectly
- No therapies effective for RAS-driven cancers
- RAS cancers excluded from treatment with targeted therapies

The approach

- Focus on alleles of RAS that cause human cancer (G12D, G12C, G12V, G13D)
- Hub and Spoke model
- Solve critical structures, coordinate drug discovery efforts
- Optimize novel assays for disrupting RAS signaling
- Map surfaces of KRAS cancer cells to facilitate drug delivery, immune attack
- Optimize MABs, proteins, cell lines, mice, etc for research community

The opportunities

- New ways of targeting un-druggable proteins
- Better, faster ways of structural analysis
- New ways of interrogating signaling networks
- Power of RNAi for target identification and therapy
- Harnessing the immune system
- Better mouse models

RAS mutations in human cancer

Pancreatic	95%	KRAS
Colorectal	45%	KRAS
Lung adenoCA	35%	KRAS
AML	30%	NRAS
Melanoma	15%	NRAS
Bladder	5%	HRAS

Major knowledge gaps

- No structures of mutant KRAS proteins with regulators or effectors
- Different alleles have different clinical outcomes, don’t know why
- Don’t know which effectors are important in established cancers
- Don’t know which cancers remain RAS-dependent
- Signaling complexes un-characterized
- Don’t know how to target KRAS cancers for drug delivery or immune therapy

Project One: Allele specific compounds.

Focus on the alleles that are most prevalent in human cancer, G12D, G12C, G12V and G13D. G12V and G12C

- Determine which effectors each of these engages
- Solve structures of mutant protein complexed with relevant effectors and regulator
- Identify new opportunities for small molecule intervention

KRAS mutations in 3 diseases

	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

Distinct biological and clinical properties of KRAS alleles

KRAS G12V, G12C worse clinical outcome than G12D

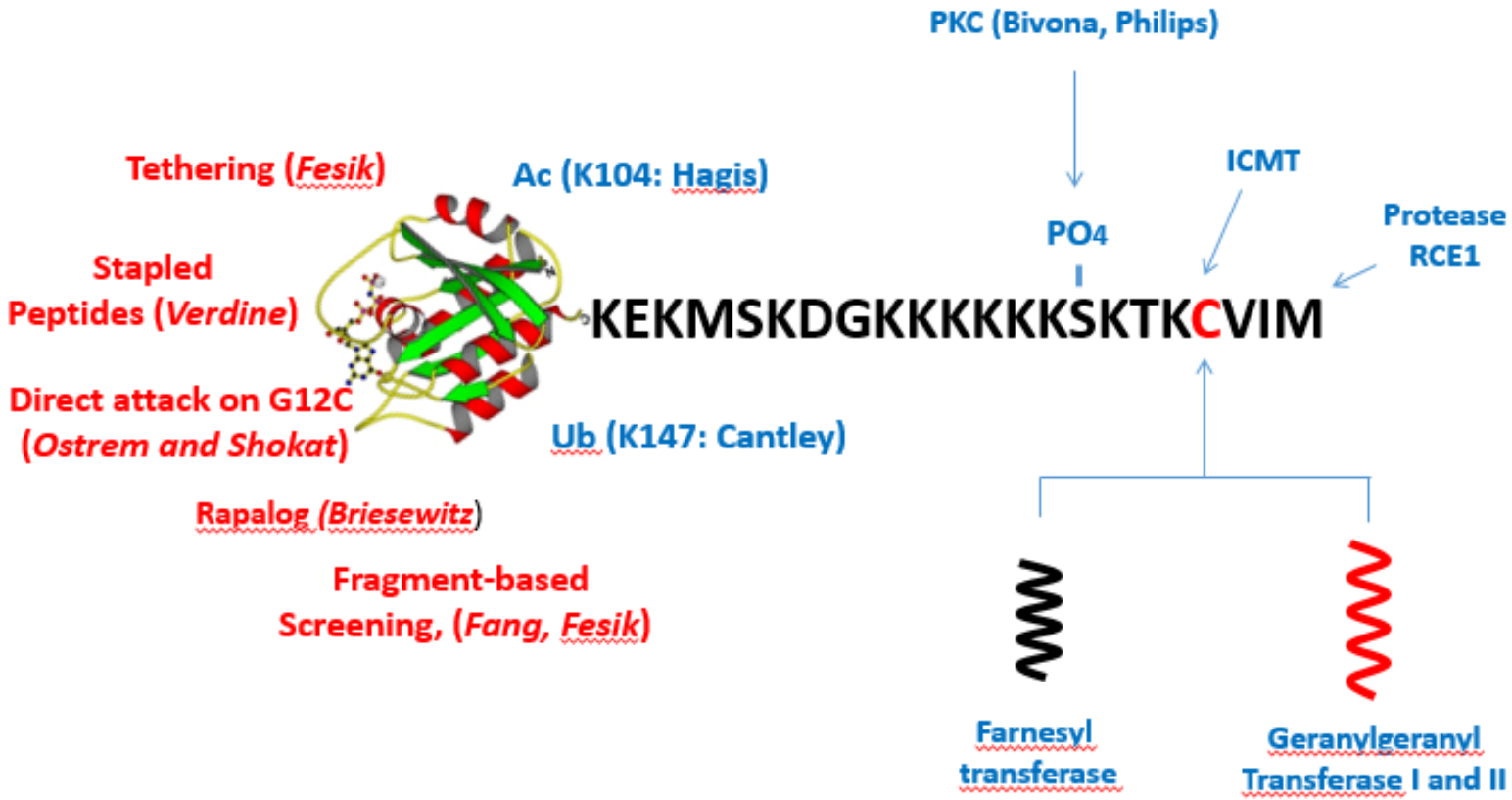
KRAS G12D: elevated PI 3’ kinase, MAPK signaling

KRAS G12C, G12V: elevated RalGDS signaling

KRAS G13D: responds to Cetuximab: G12 mutants do not….

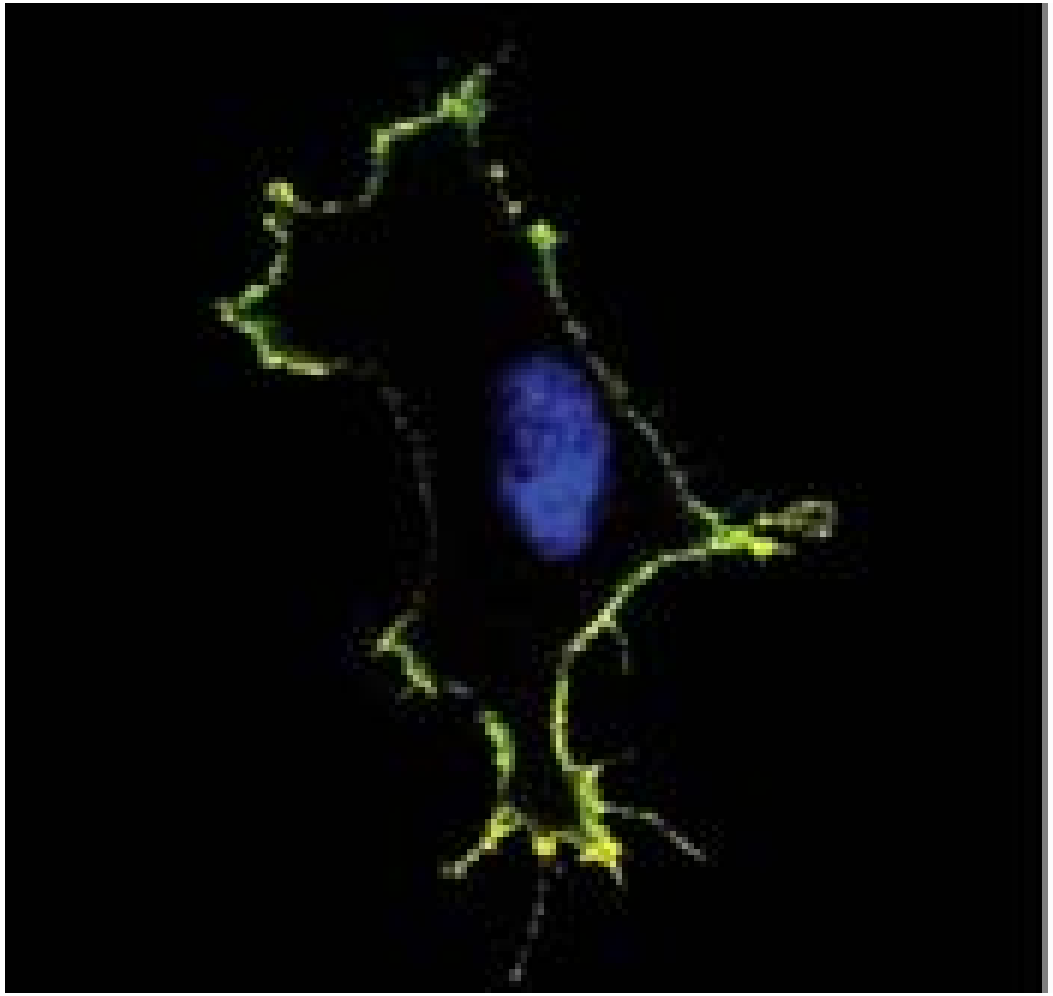
Project Two: KRAS selective compounds.

Ablation of KRAS may be effective, without being allele specific



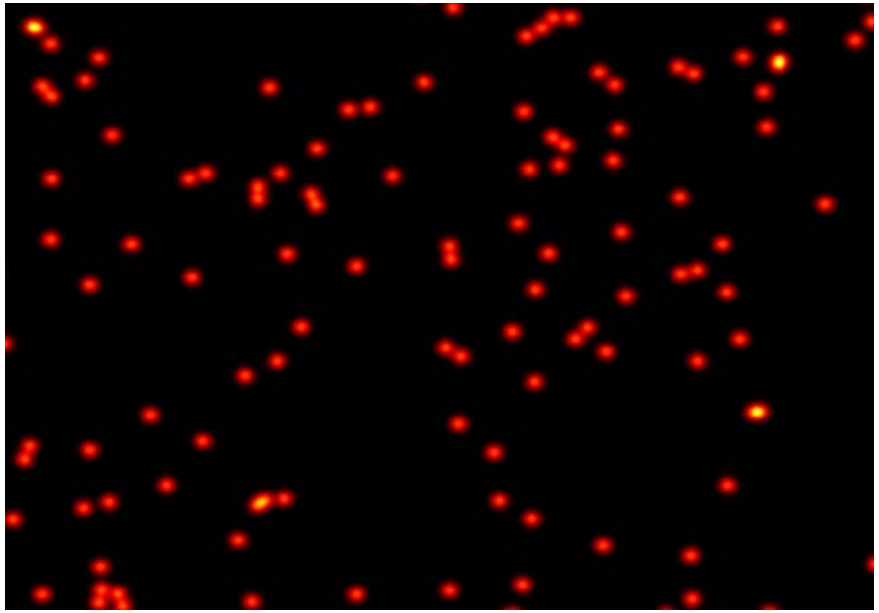
Project Two: KRAS selective compounds.

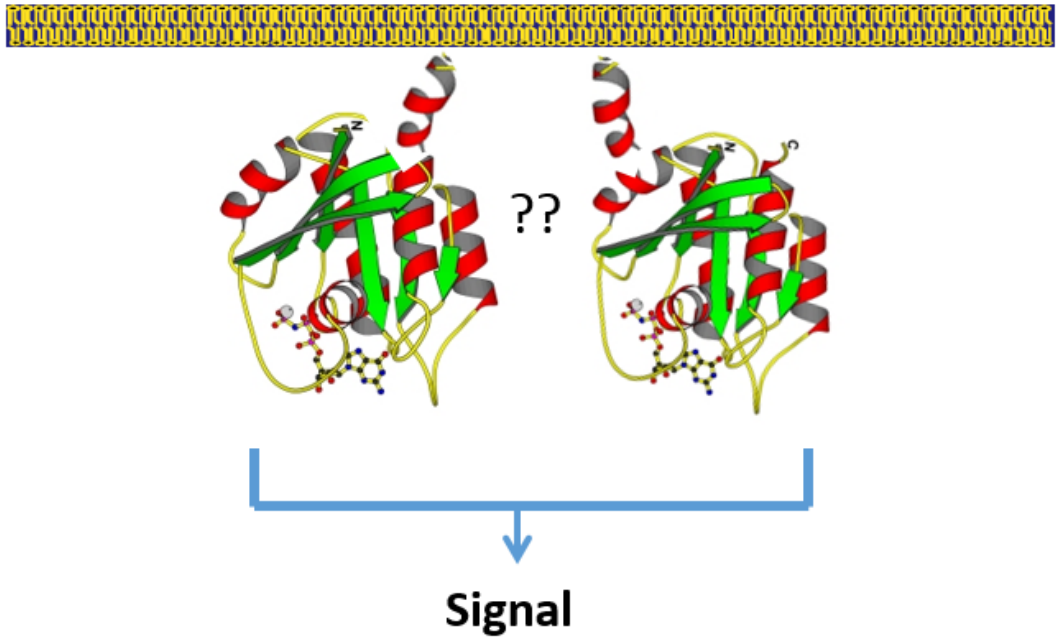
Preventing KRAS signaling from the plasma membrane (eg from Mark Philips)



Project Three: Disrupting KRAS complexes

- Develop imaging methods to identify KRAS complexes in cells
- Develop screens for disrupting complexes





Project Four: Mapping the surface of KRAS cancer cells

- analyze the protein composition of K-RAS cancer cell membranes
- identify peptides that could be targeted by immunotherapy
- Identify proteins that could target nanoparticles for drug delivery
- Use mass spec, phage display, bioinformatics, etc

Project Five: Next-generation synthetic lethal screens

- Develop synthetic lethal screens in 3D models, and in vivo
- Engineer mice to facilitate screens
- Test combinations of siRNAs, shRNAs and/or small molecules