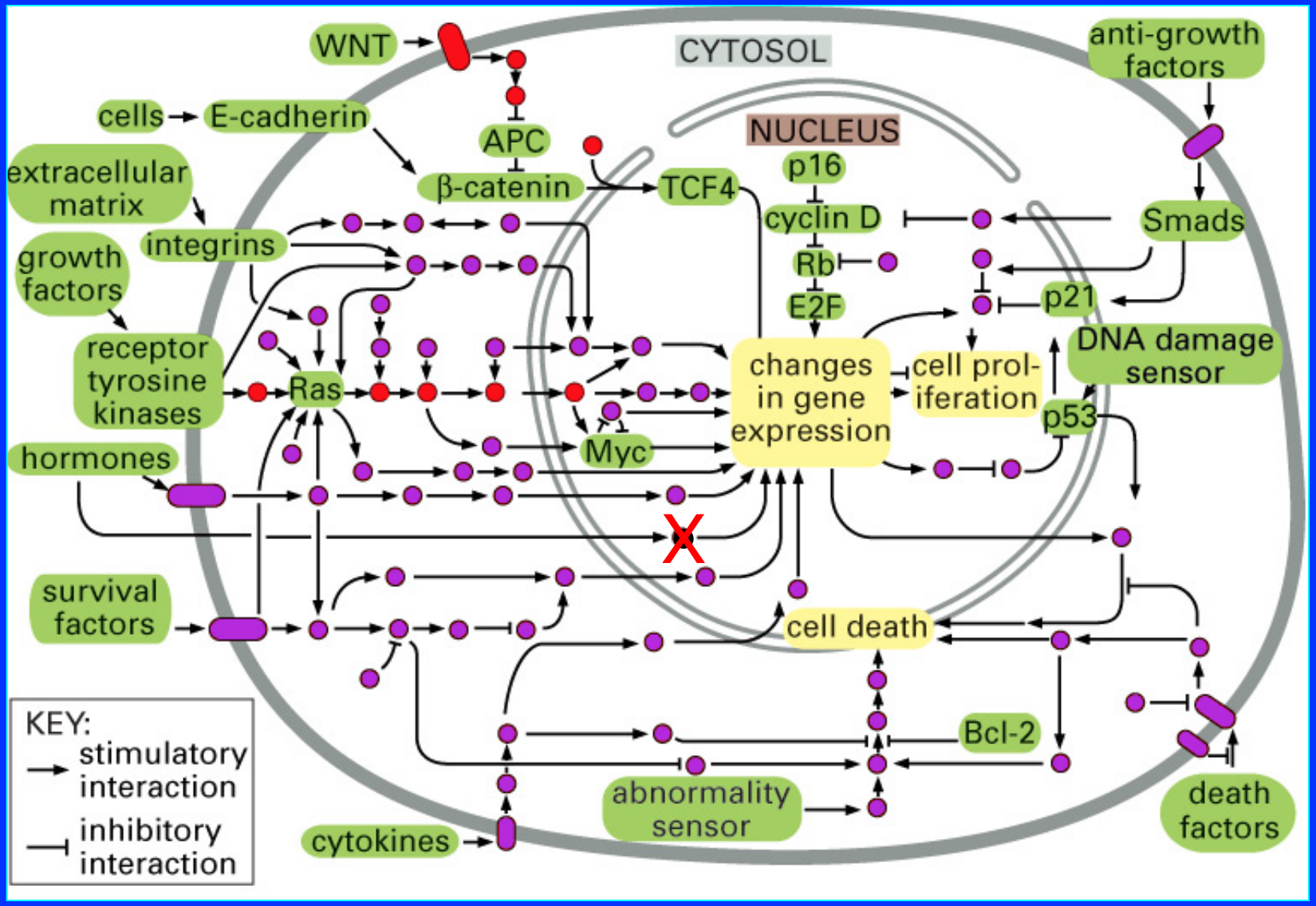


Hanahan, Weinberg

- signaling and other “targeted” drugs work

  Trastuzumab, Imatinib, Erlotinib, PLX4032, Olaparib…

- responses are not durable

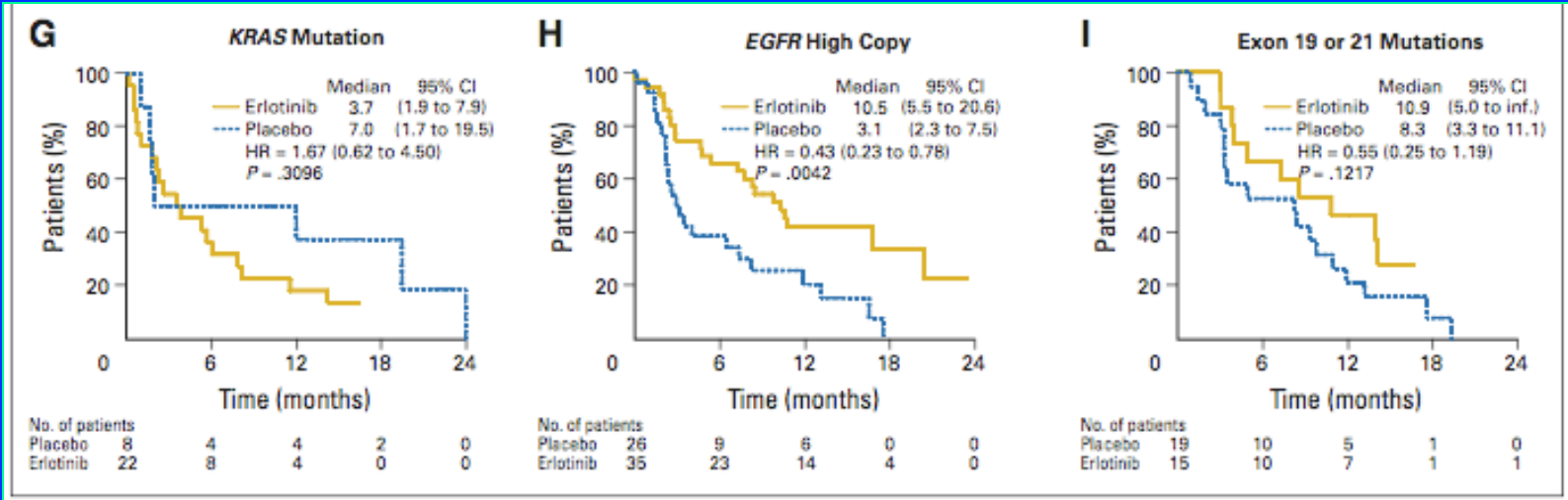
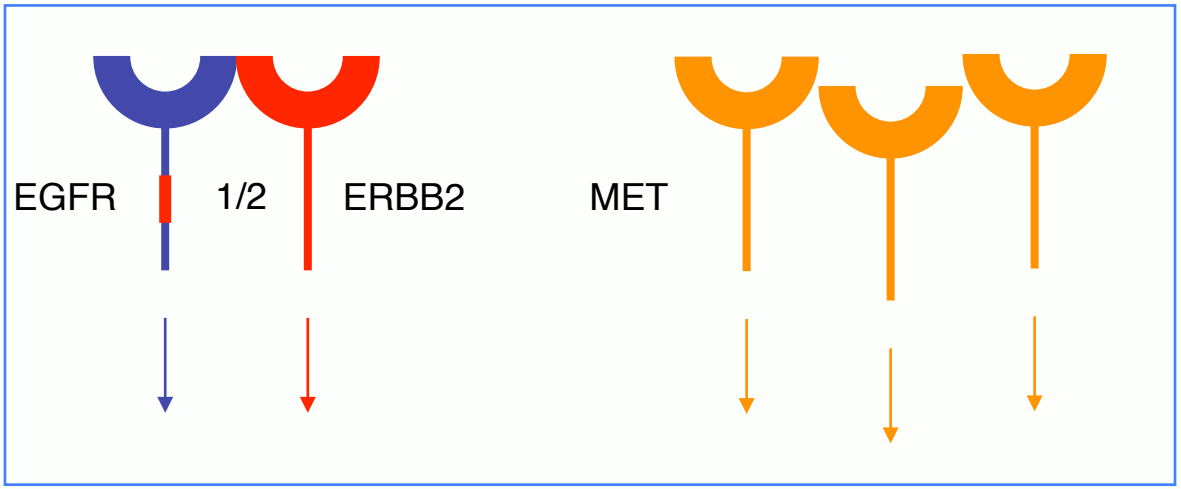


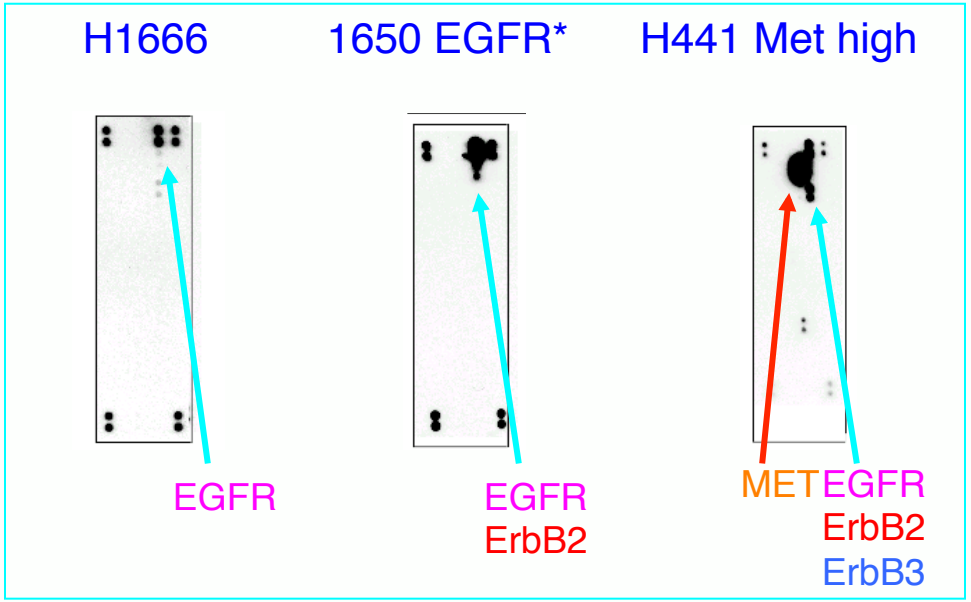
Fig 1. Kaplan-Meier survival curves of subgroup studied for various markers as well as impact of erlotinib according to marker status. HR, hazard ratio.

Erlotinib: NSCLC

1.What are the scientific challenges and opportunities in codevelopment?
Rationale

Multiple Drivers

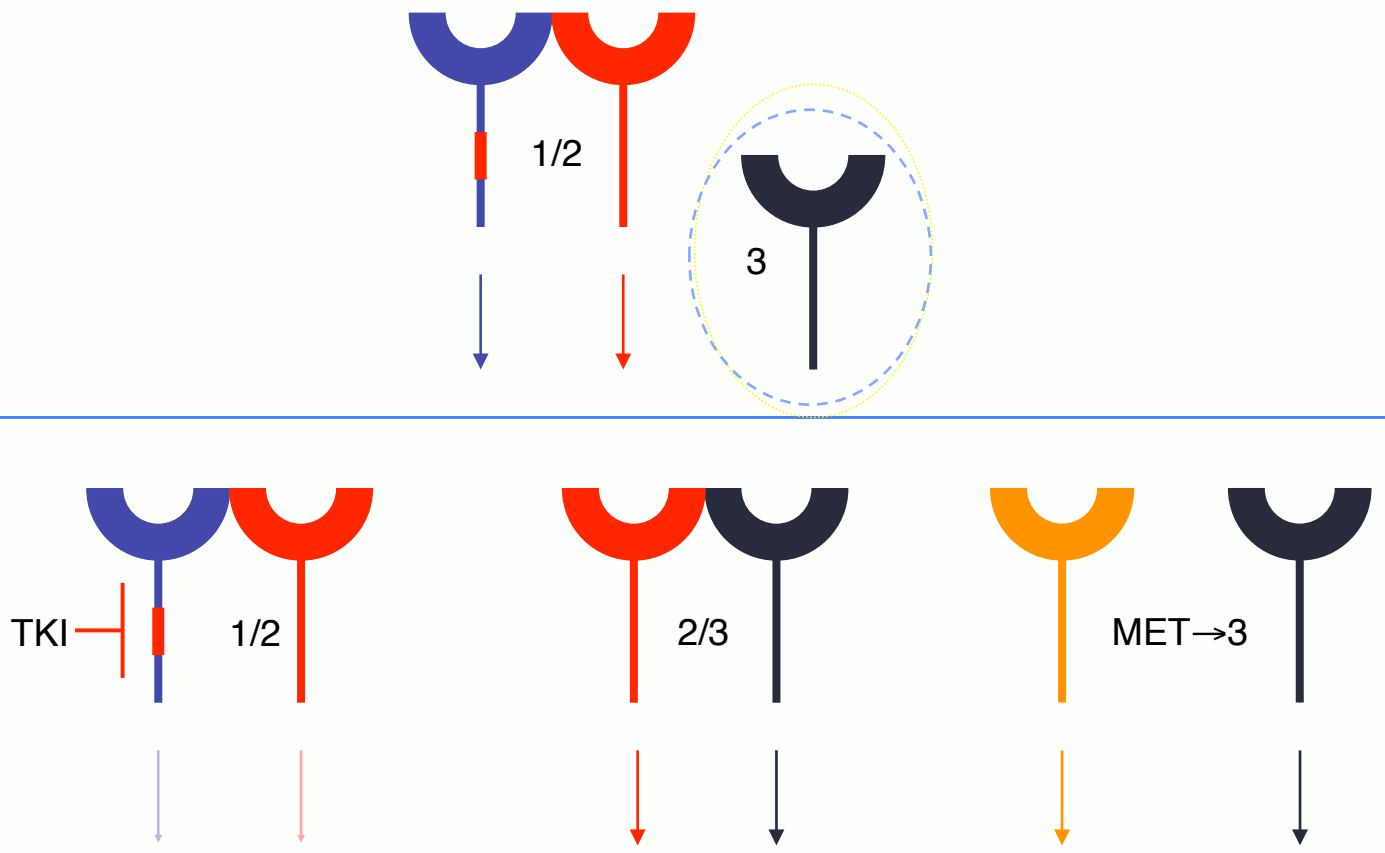




Agarwal …Stern Br.J.Cancer 100:941

1.What are the scientific challenges and opportunities in codevelopment?
Rationale

Receptor Bypass



Moasser , White, Engelmann

1. What are the scientific challenges and opportunities in codevelopment?
   Rationale

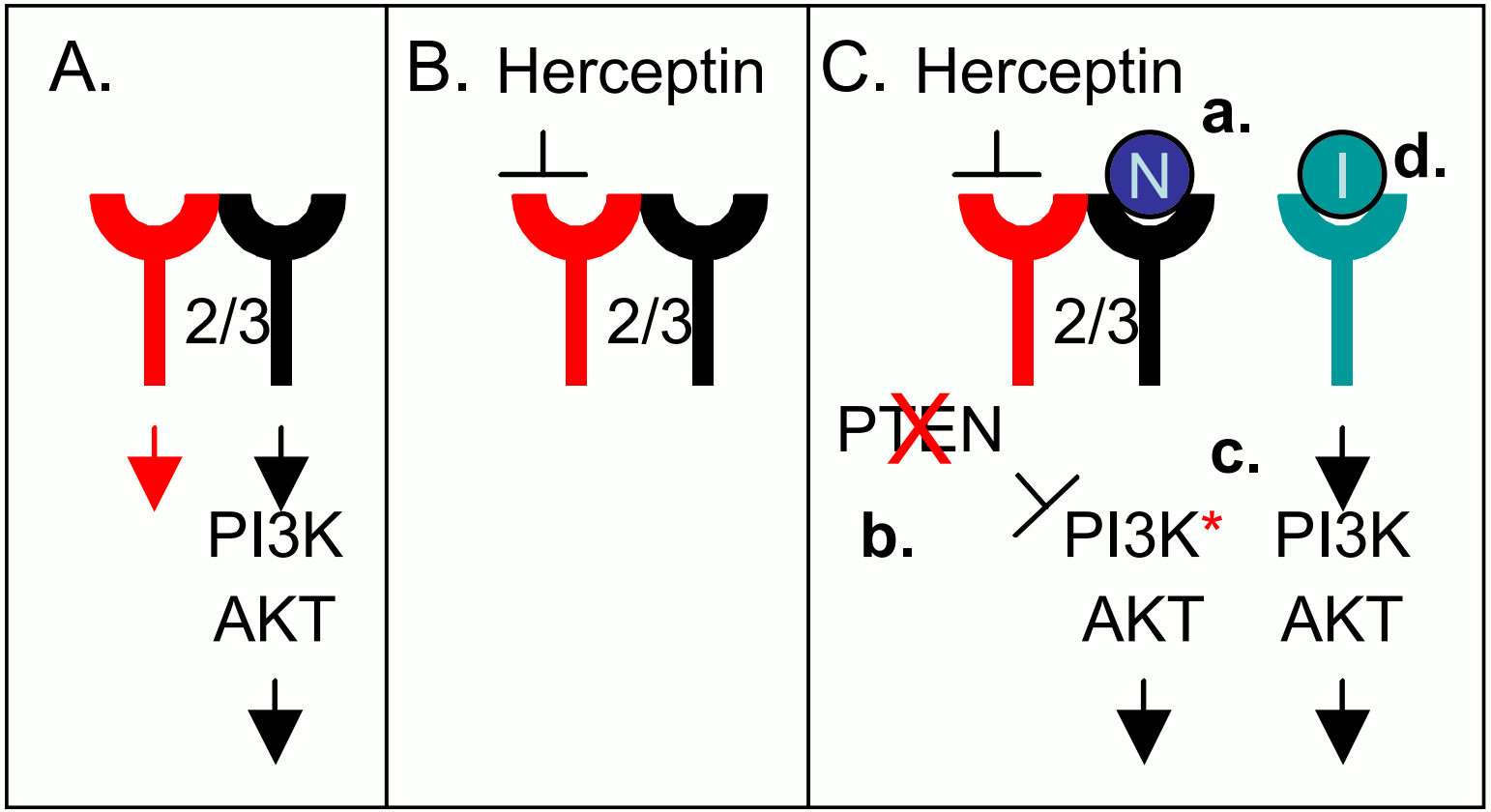
Ligand Bypass

Hynes, Esteva, Arteaga

1.What are the scientific challenges and opportunities in codevelopment?

Rationale

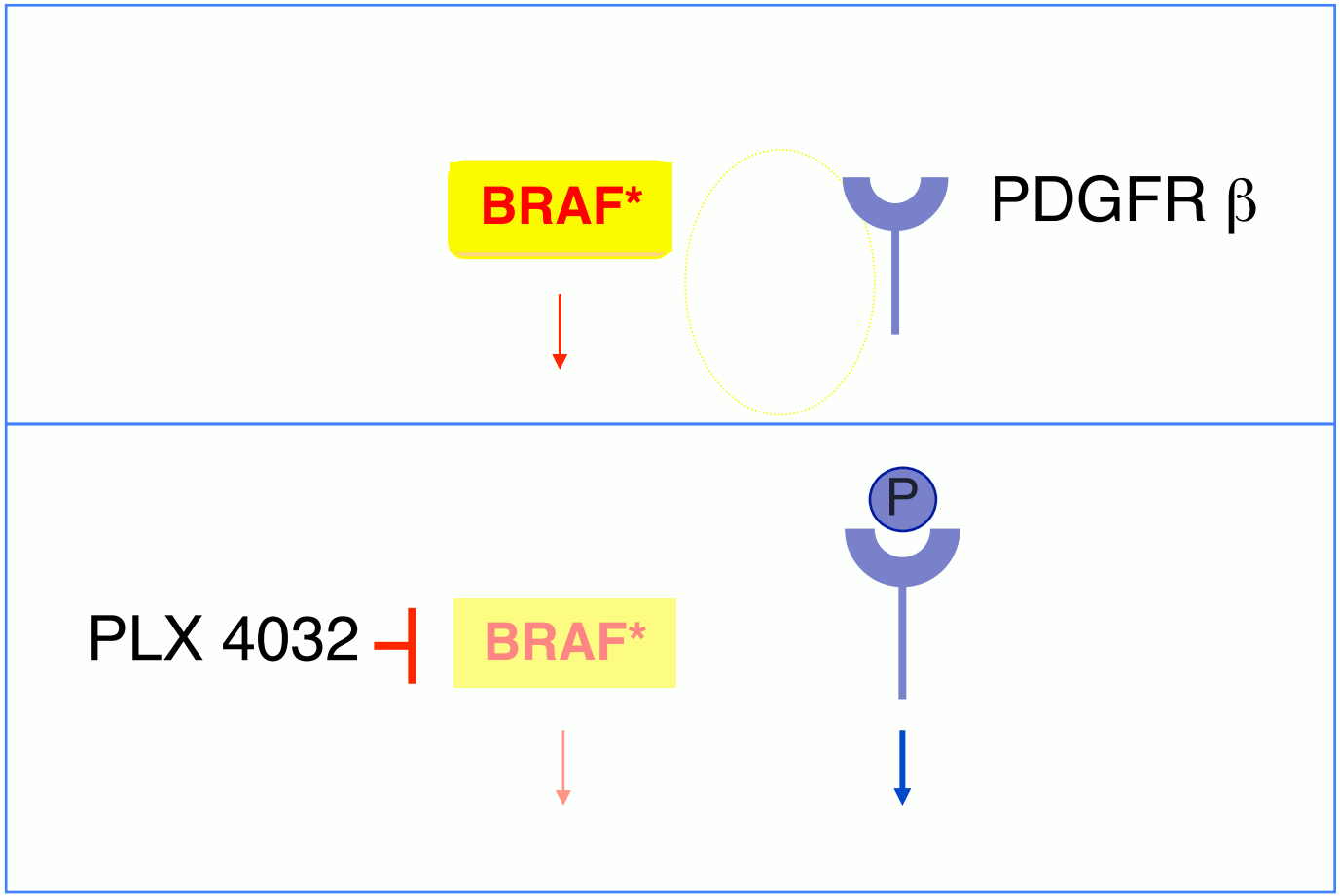
Pathway Resistance



Yu, Hung

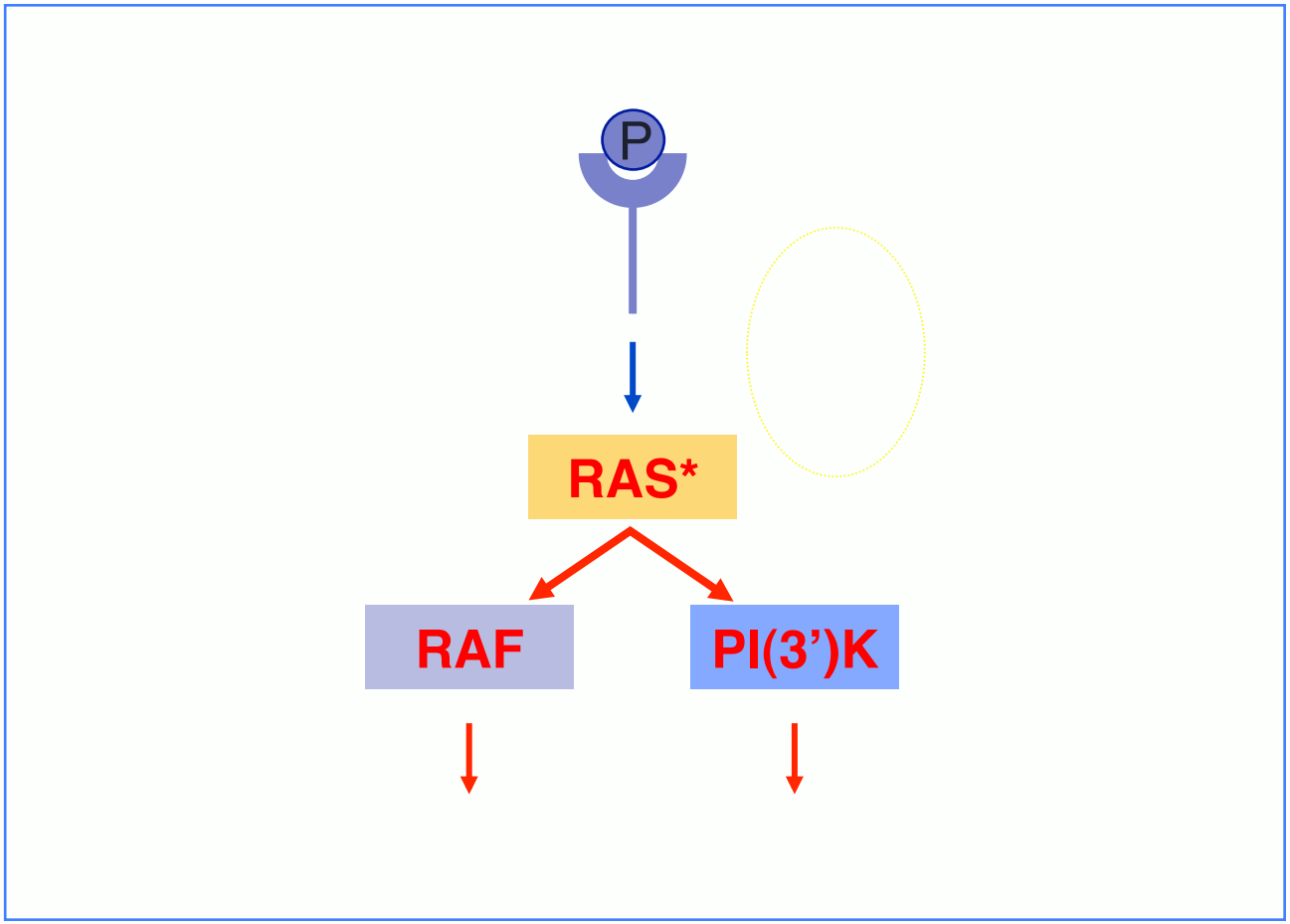
1. What are the scientific challenges and opportunities in codevelopment?
   Rationale

Autocrine Bypass



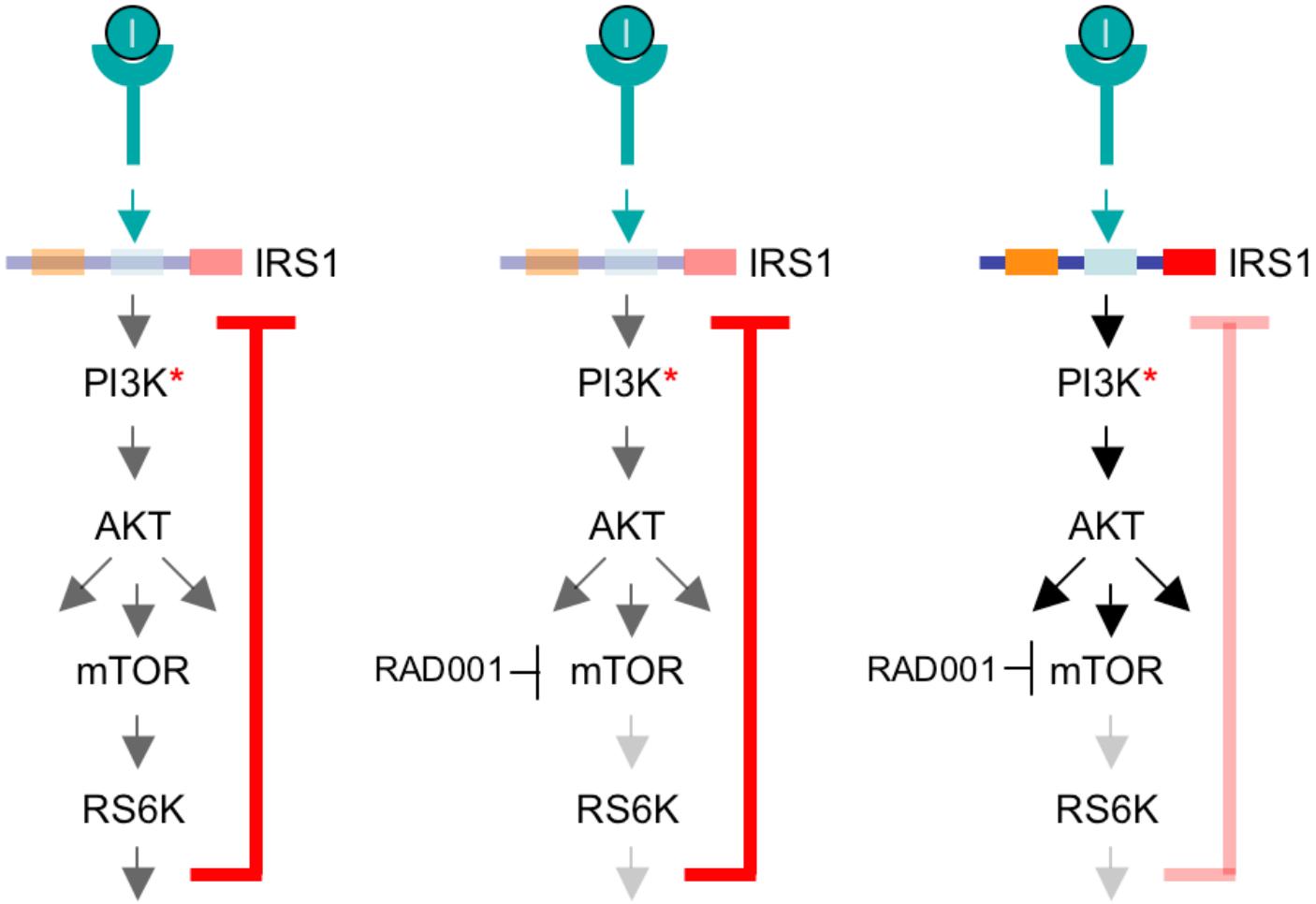
Lo

Pathway Bifurcation



1.What are the scientific challenges and opportunities in codevelopment?
Rationale

Homeostatic Feedback Mechanisms



Rosen

1. What are the scientific challenges and opportunities in codevelopment?
   Rationale

SURGERY

CHEMOTHERAPY

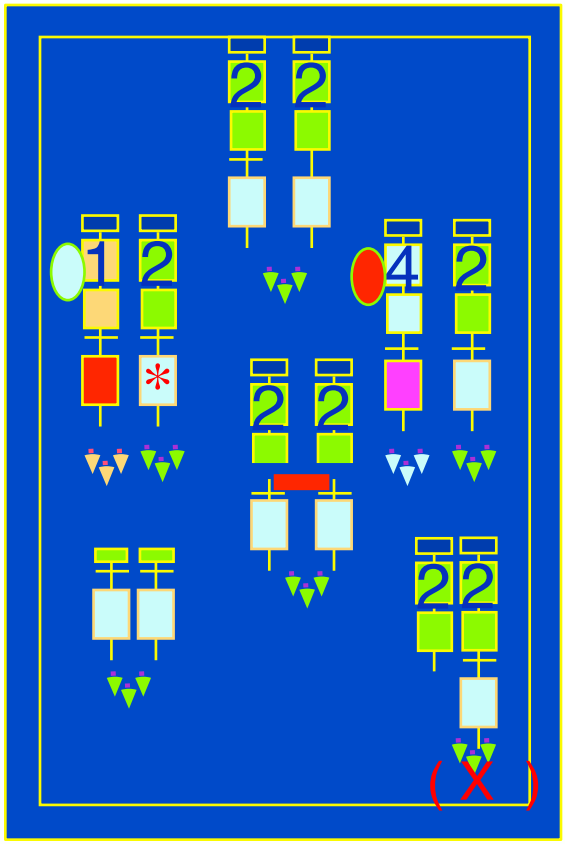
RADIOTHERAPY

SIGNALING

IMMUNOTHERAPY

DNA DAMAGE

IMMUNOMODULATION



DNA/cDNA sequencing
- Copy Number
- Transcription
- SNP
- Substitutions, InDels
- DNA Rearrangements
- microRNA
- Epigenetics

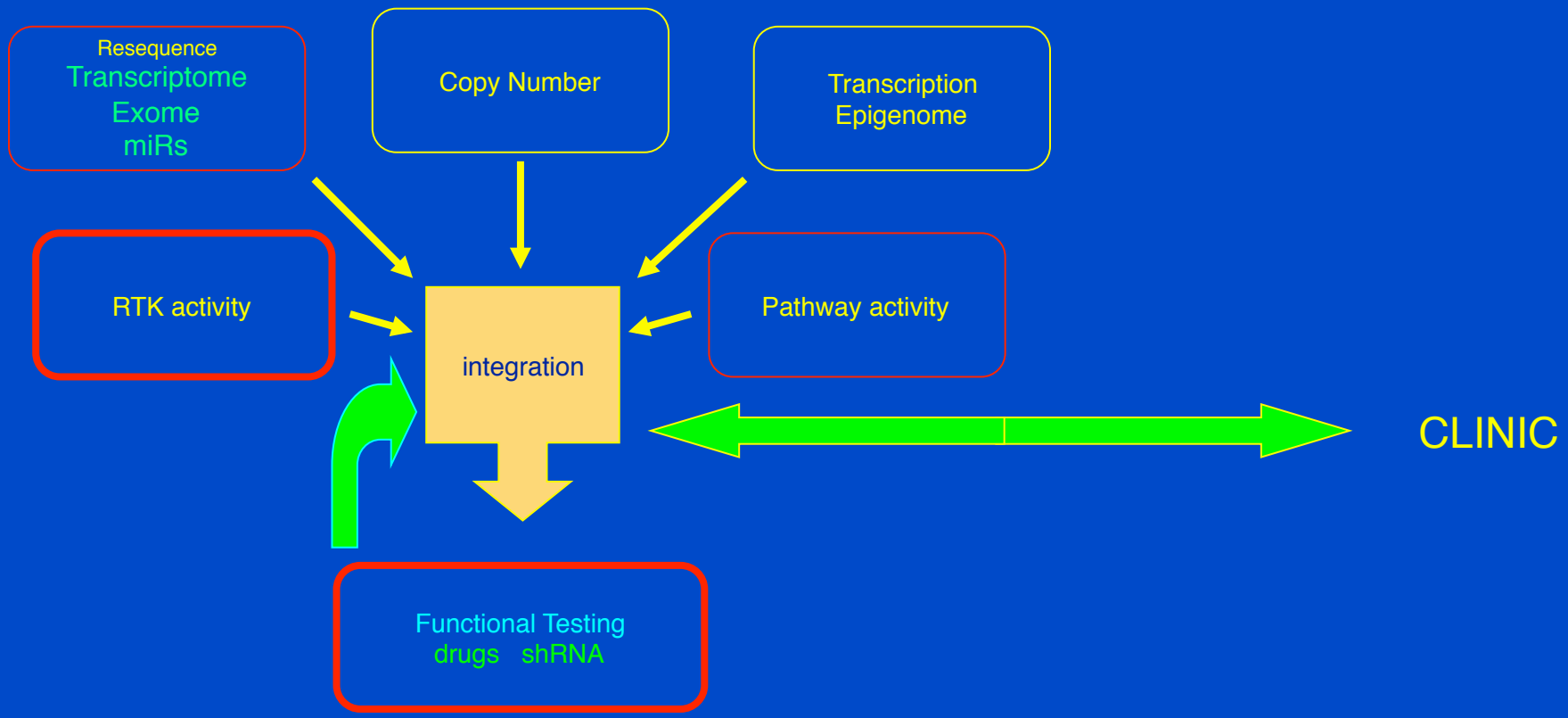
proteomics

identify driver(s)
identify patterns of sensitivity
identify drug sensitivity signatures
anticipate drug resistance
learn how to kill cancer cells
distill for clinical practice

Yale SPORE in Skin Cancer

Ruth Halaban, PI

- >>200 melanomas banked
- matched early passage cell cultures
- parallel analysis



Single agent screening

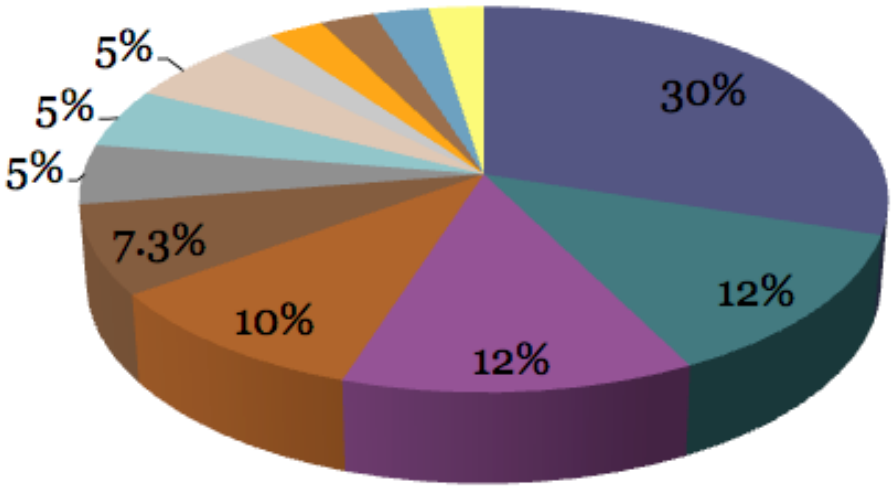
MARCUS BOSENBERG

- Single agent screening
  - 153 compounds
  - 16 point dose response curves
  - 26 human melanoma lines, two breast, mouse
- clustering for patterns of single agent dose responses
- integration with SPORE data to...
  - identify genotype-based sensitivity
  - identify biomarkers predictive of response or resistance

Single agent screening

Yale Center for Small Molecule Discovery

- 153 compounds
- 16 point dose response curves in triplicate
- 3 day assays: CellTiterGlo
- 26 human melanoma lines, two breast, mouse



RTK / MAPK pathway	30%
Conventional therapies	12%
PI3K pathway	12%
Kinases	10%
Apoptosis pathway	10%
Chromatin remodeling	7.3%...
HSP90	
NFkB	
Cell cycle	
Herbal	
Jak/Stat signaling	
Nucleotide metabolism	
Proteasome inhibitor	

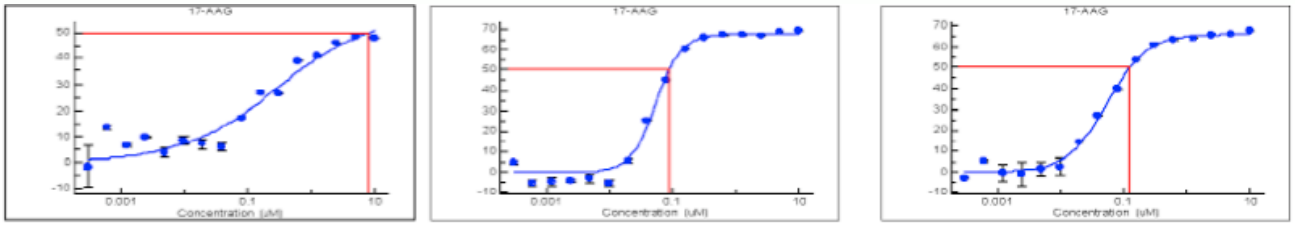
1 ALK
2 EGFR
2 EGFR
2 EGFR/HER2
3 FGFR
3 FGFR
3 IGF1R
3 IGF1R
3 IGF1R
4 MET
5 FGFR,VEGF, KIT
5 AXL, Src,JAK,...
5 Kit,P,Abl
5 VEGFR,PDGFR,
5 PDGFR/VEGFR
5 Abl/Src
5 Abl/Src
5 VEGFR/EGFR
5 VEGFR/PDGFR/K
5 VEGFR,Kit,PDGF
6 JAK2
6 Stat3
6 Stat3
7 Src
8 p38
9 Jnk
10 Raf
10 Raf
10 BRaf
10 MEK
10 MEK
10 MEK
12 Chk
11 Akt
11 PI3K
11 mTOR
11 PI3K
11 Akt
11 Akt
11 mTOR
11 mTOR
NFkb, mTOR
11 mTOR
11 PI3K,pentose
12 kinases
12 Rho kinase
13 HSP90
13 HSP90
12 Aurora
12 GSK3beta
12 CDK4
12 CDK
12 CDK
14 TLR
14 NOTCH
14 ER
14 RXR
14 RAR
14 HedgeHog
14 HedgeHog
14 Cox2
14 MIF
14 MIF
14 MIF
14 MIF
14 MIF
14 MIF
14 MIF
14.00
14 Bcl-2 inhibitor
14 Bcl-2 inhibitor
14 proteasome
14 MYC
21 microtubule
21 microtubule
21 microtubule
21 microtubule
22 HDAC
22 SAHA HDACi
22 5-AzaC
23 PARP
31 Pt drug
31 Pt drug
31 Pt drug
31 Pt drug

Single Agents

cell lines

drugs

1



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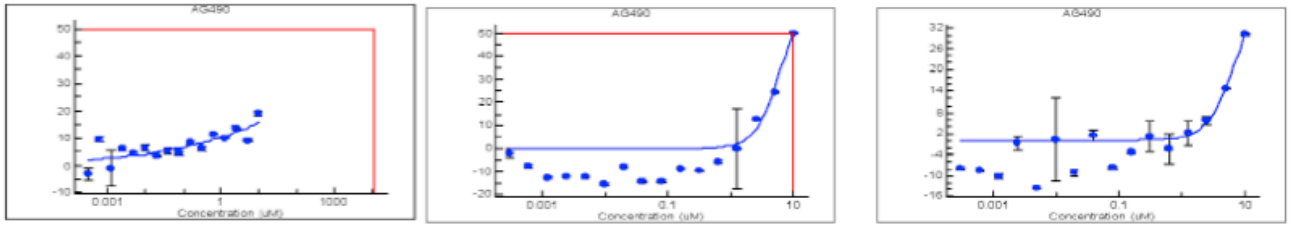

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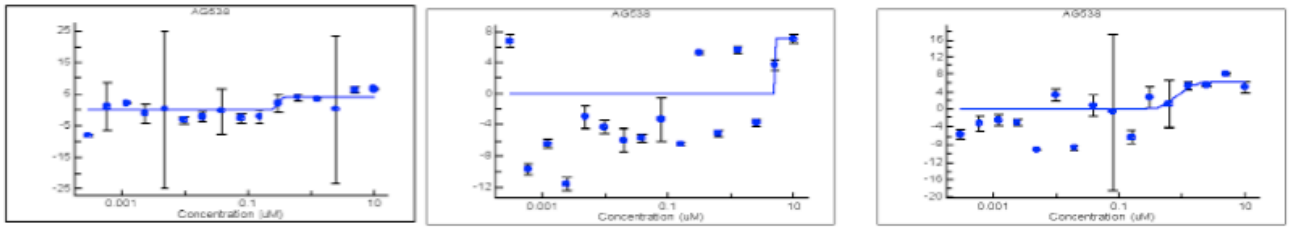

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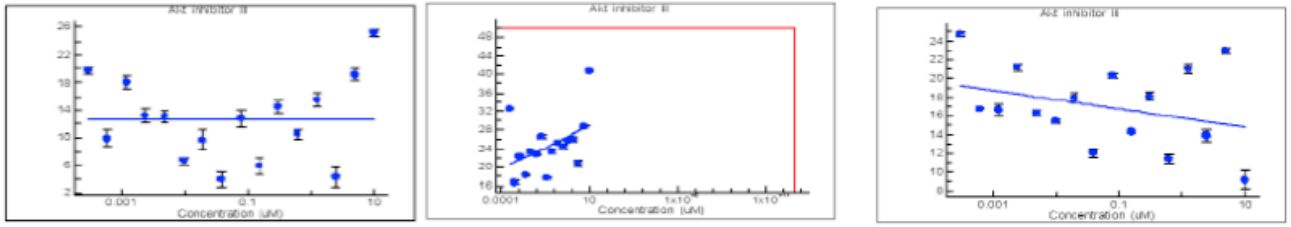

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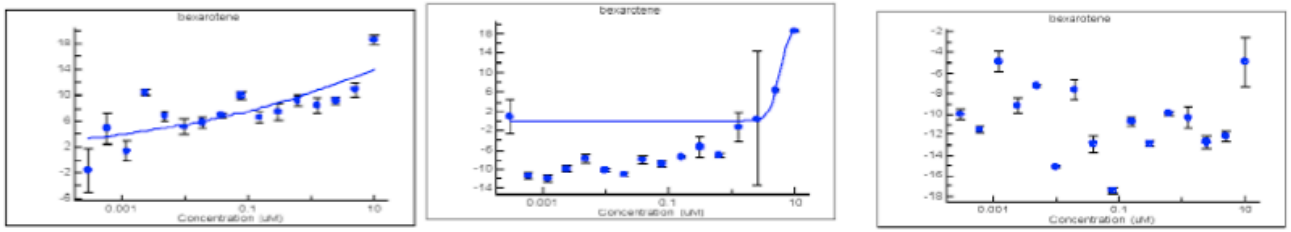
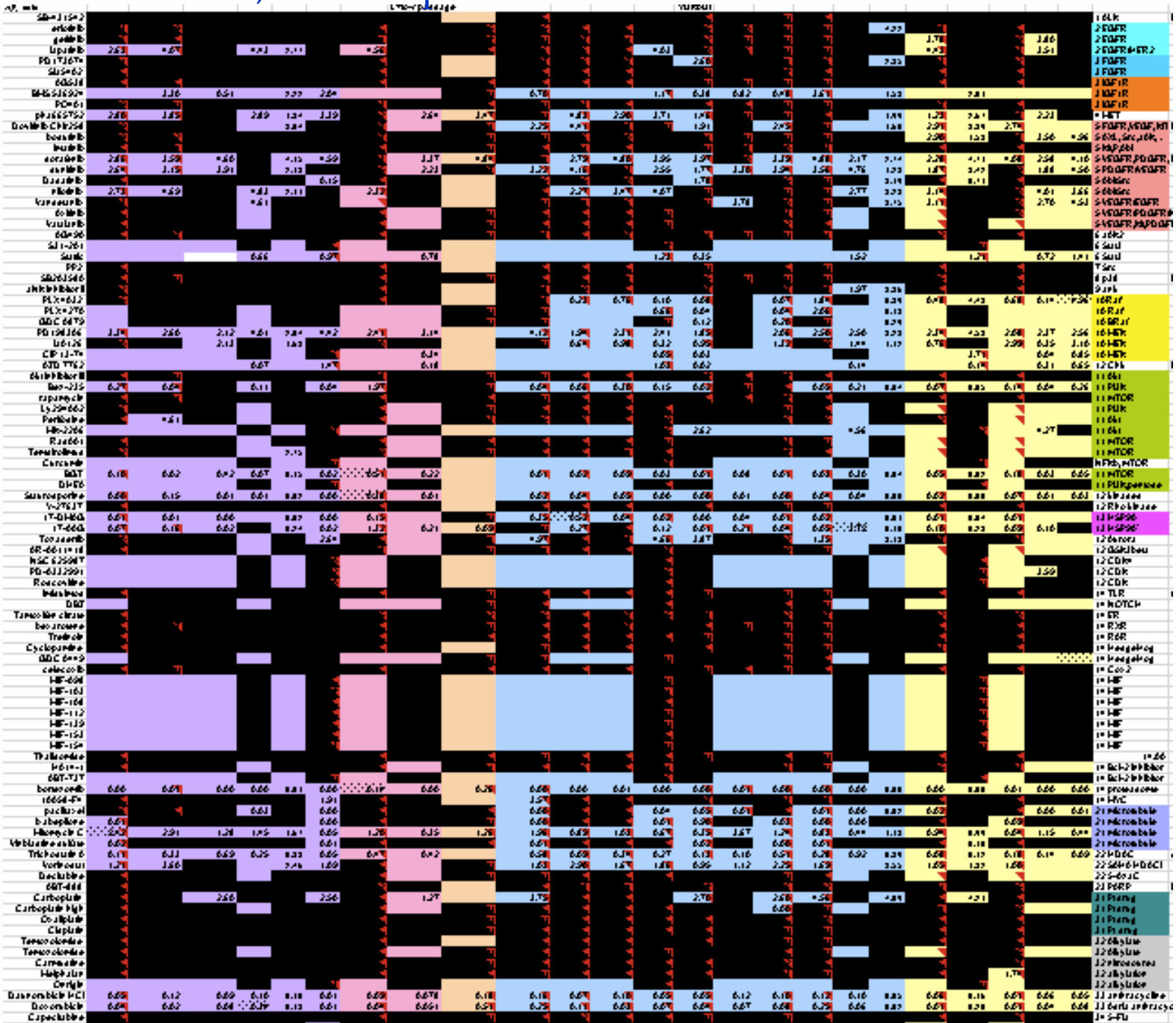
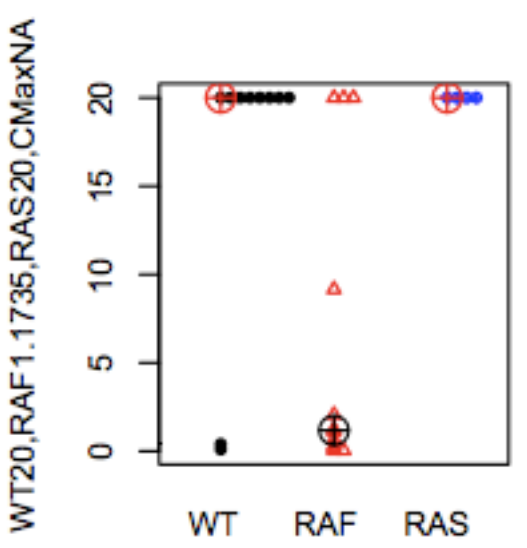


30 Cell Strains, 153 compounds

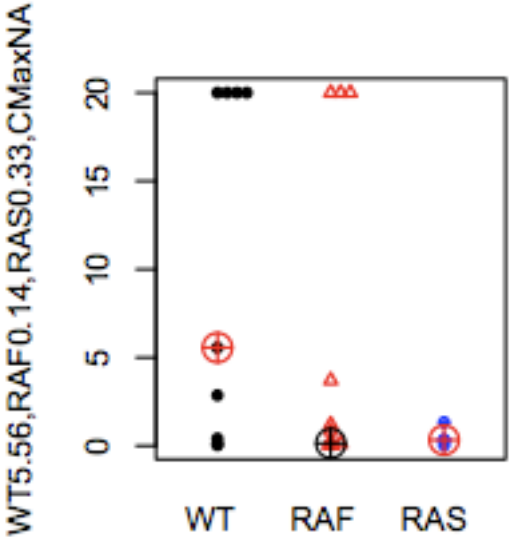


Does drug sensitivity assort with Genotype?

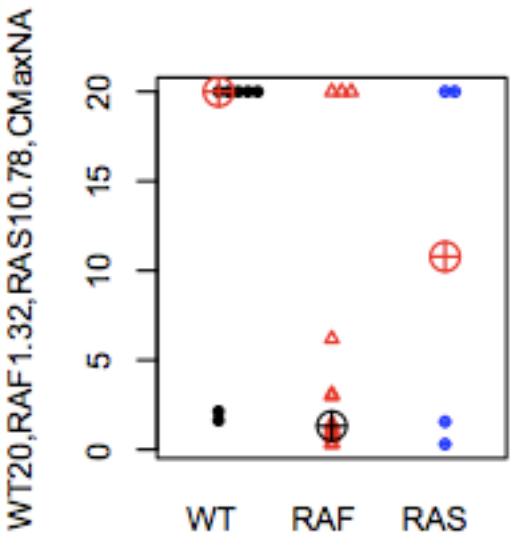
uM conc. 50% Growth Inhibition by Genotype



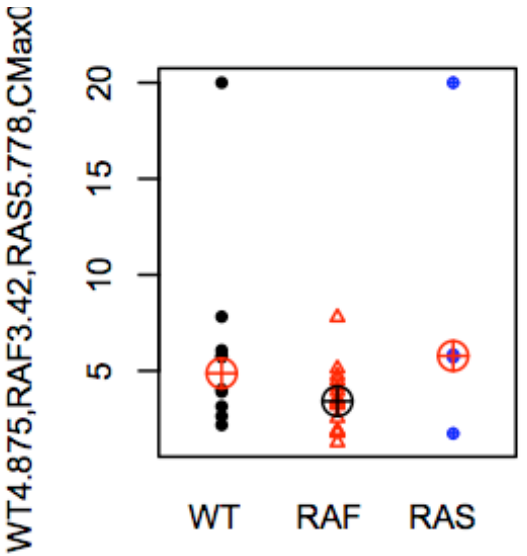
PLX 4720



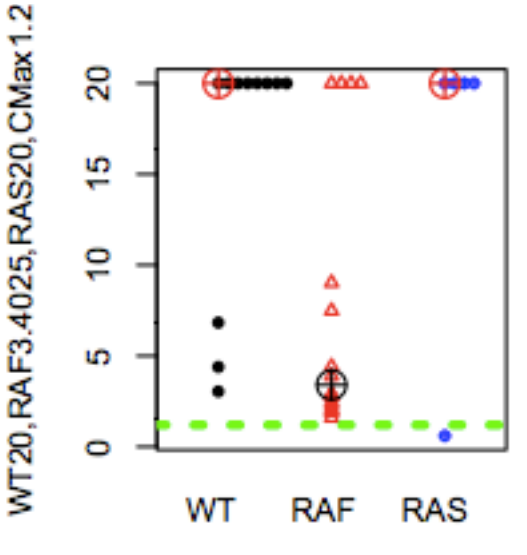
MEK inhibitor



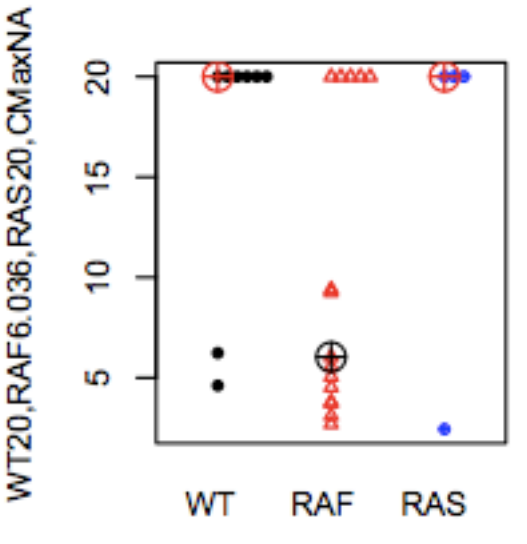
MEK inhibitor



TK inhibitor



TK inhibitor



TK inhibitor

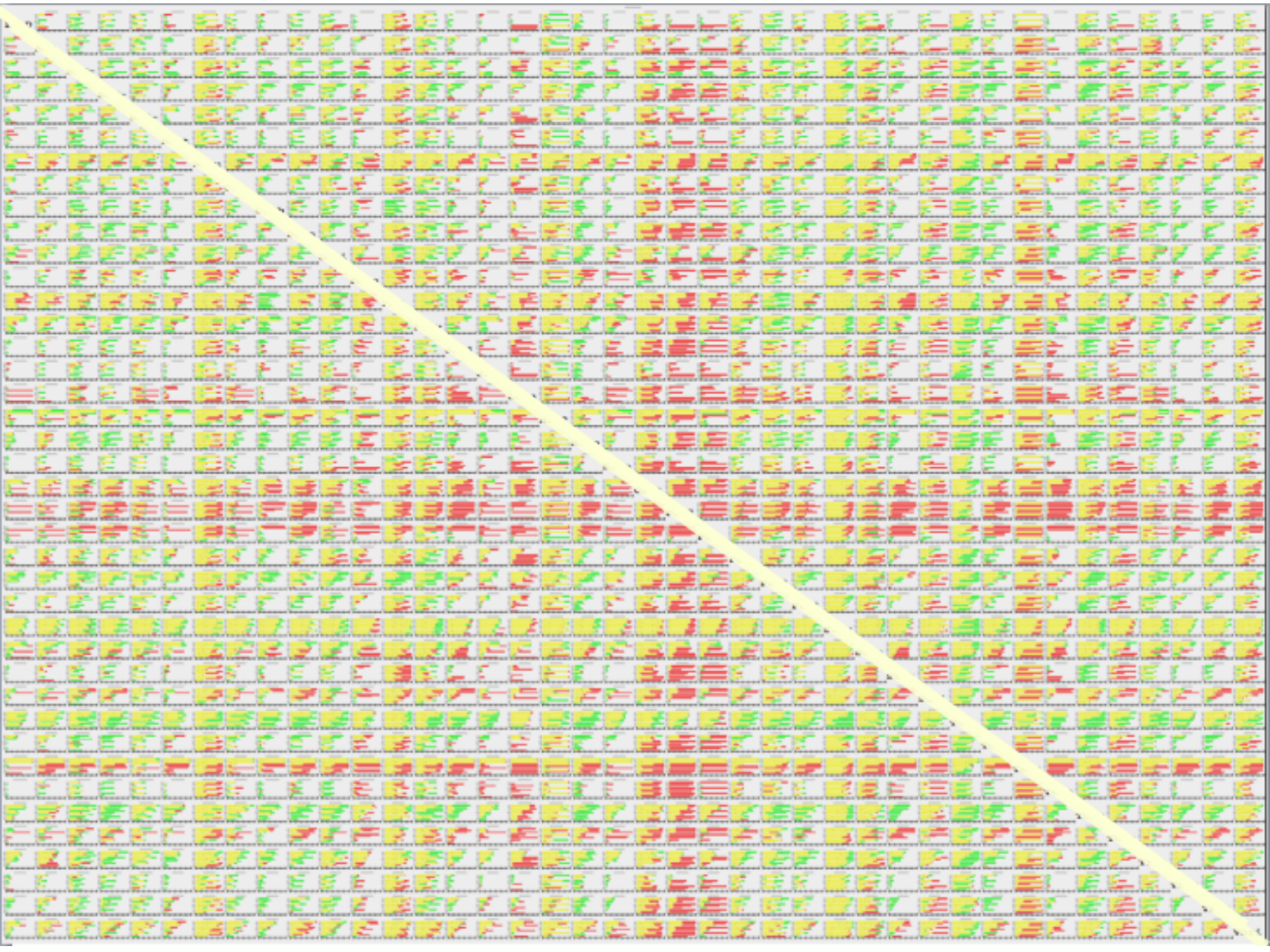
combination screening

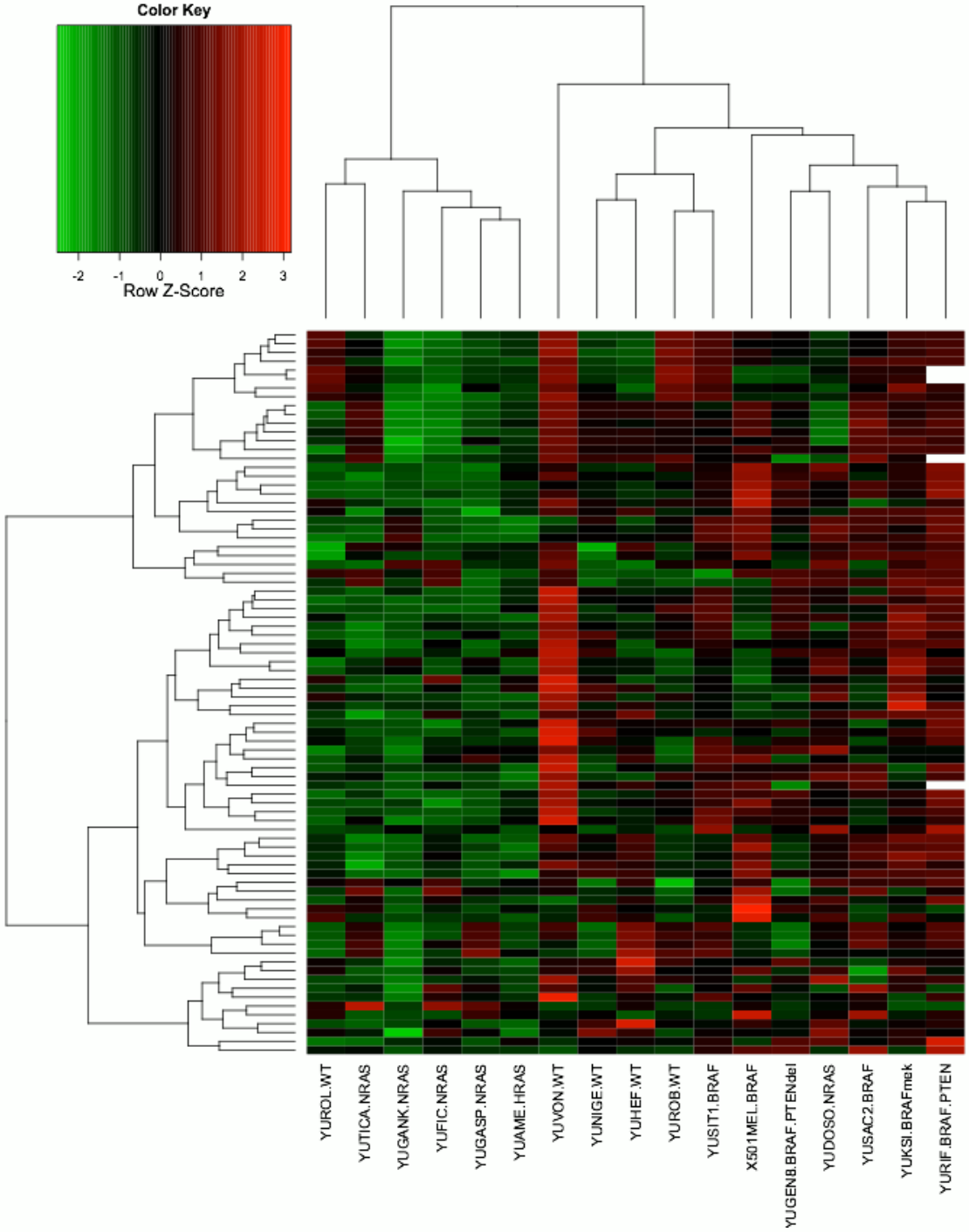
Yale Center for Small Molecule Discovery

- Identify potentiators of...
  - maximal effect
  - dose-dependence
  - cell killing
- drugs
- interacting pathways

Combination testing

- 40 compounds at 3 concentrations
- *BRAF, RAS, WT*
- filter data to detect:
  - Synergy
  - Selective effect (genotype based)
  - Completeness of effect
  - Antagonistic effects
  - Enrichment for one agent in combos



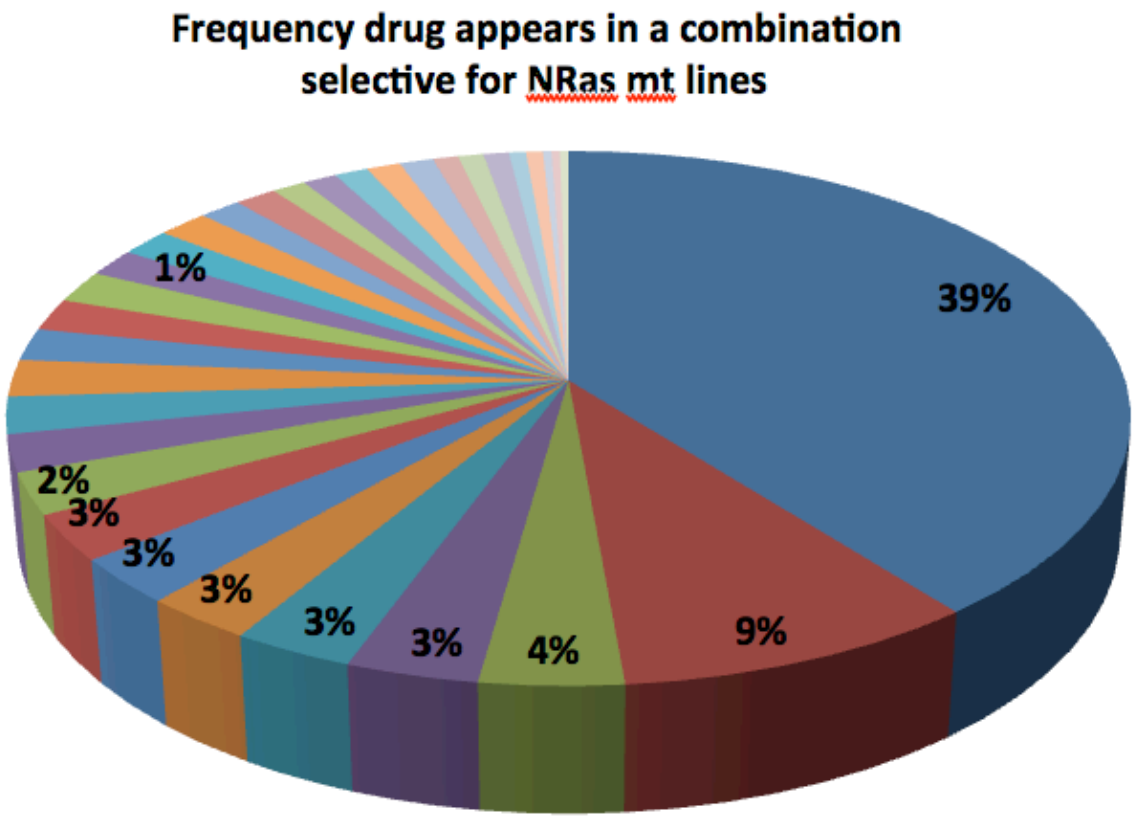


drug combinations

James Platt

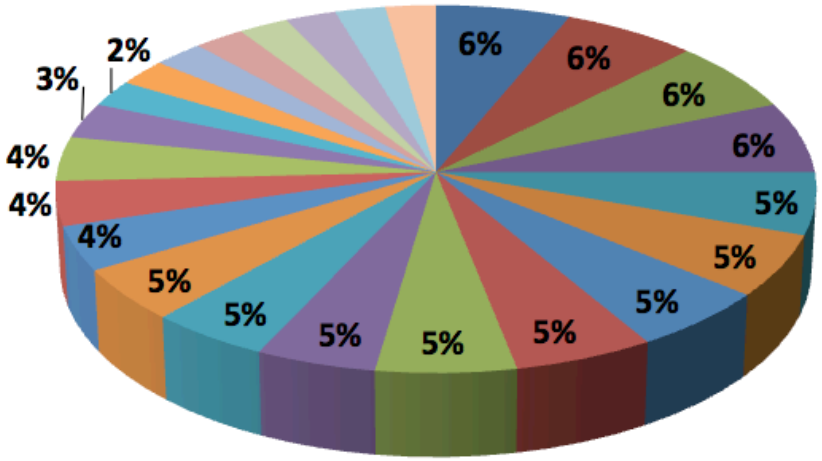
Drug	#times in a combo
A	141
B	33
C	13
D	12
E	11
F	10
G	10
H	10
I	9
J	8
K	8
L	8
M	7
N	7
O	7
P	6
Q	6
R	6
S	5
T	5
U	4
V	4
W	4
X	4
Y	4
Z	3
AA	3
BB	3
CC	2
DD	2
EE	1
FF	1
GG	1

filters for.. threshold combination effect
threshold maximum effect
internal consistency of combination data points
< CMax
…

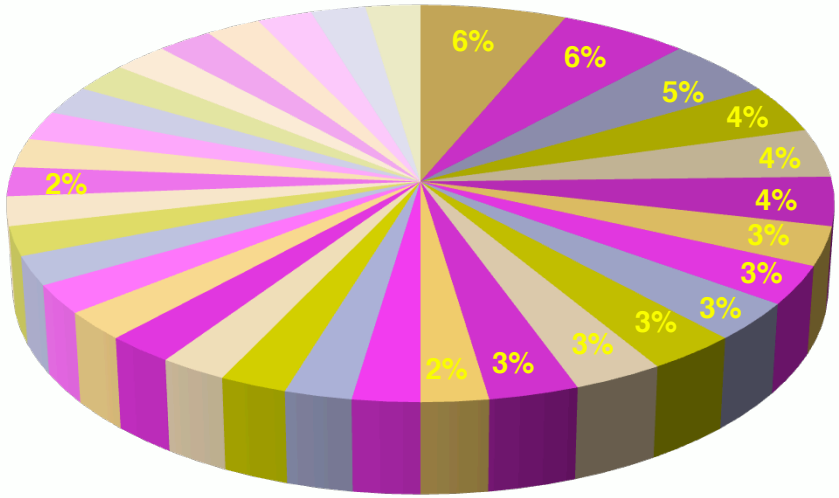


Matt Held
James Platt

Frequency of combinations selective for NRas mt lines
(at least 3 combinations as cutoff)

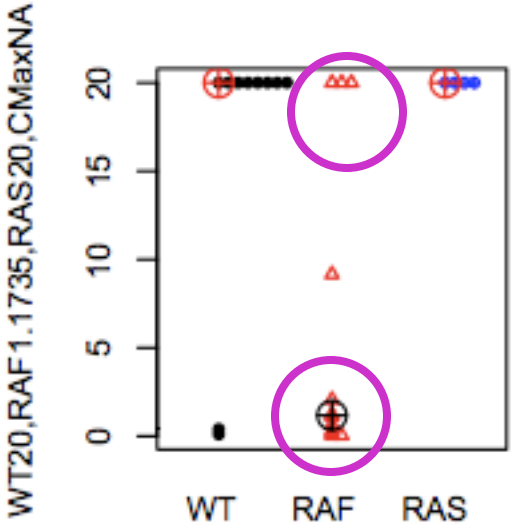


Frequency of combinations selective for BRaf mt lines
(at least 3 combinations as cutoff)



What accounts for variable sensitivity?

uM conc. 50% Growth Inhibition by Genotype



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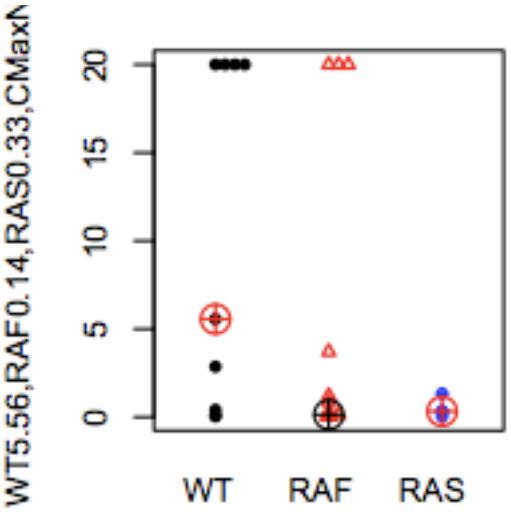
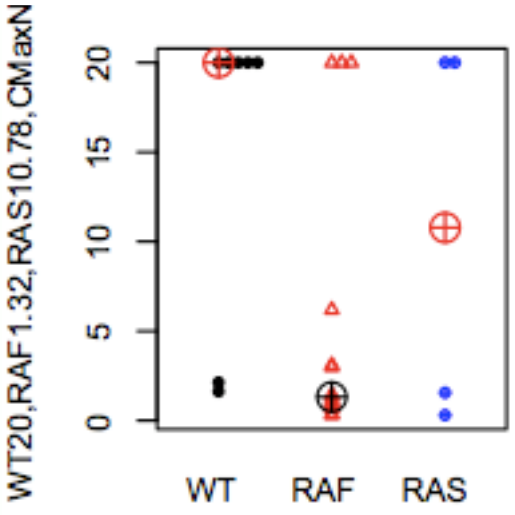
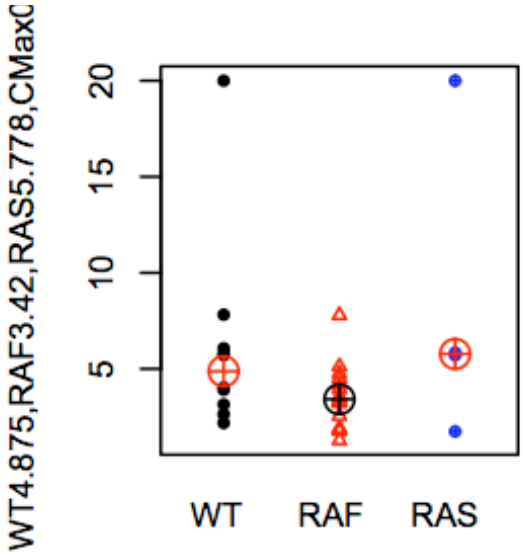


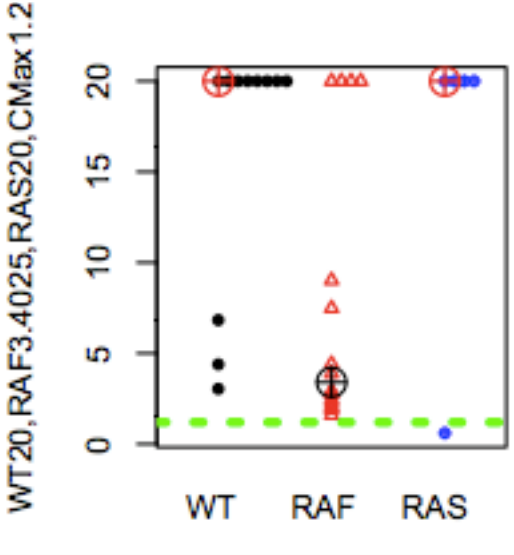
MEK inhibitor



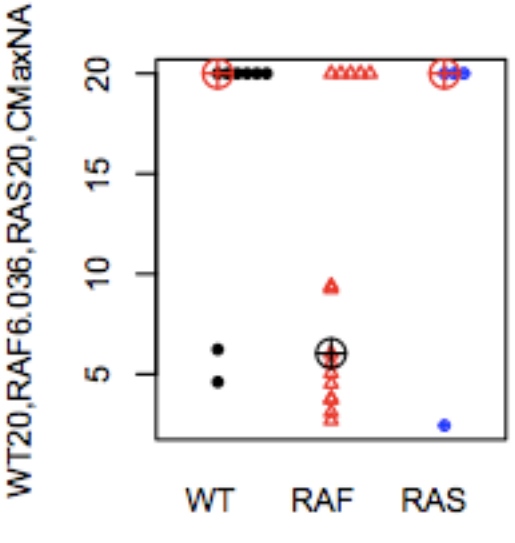
MEK inhibitor



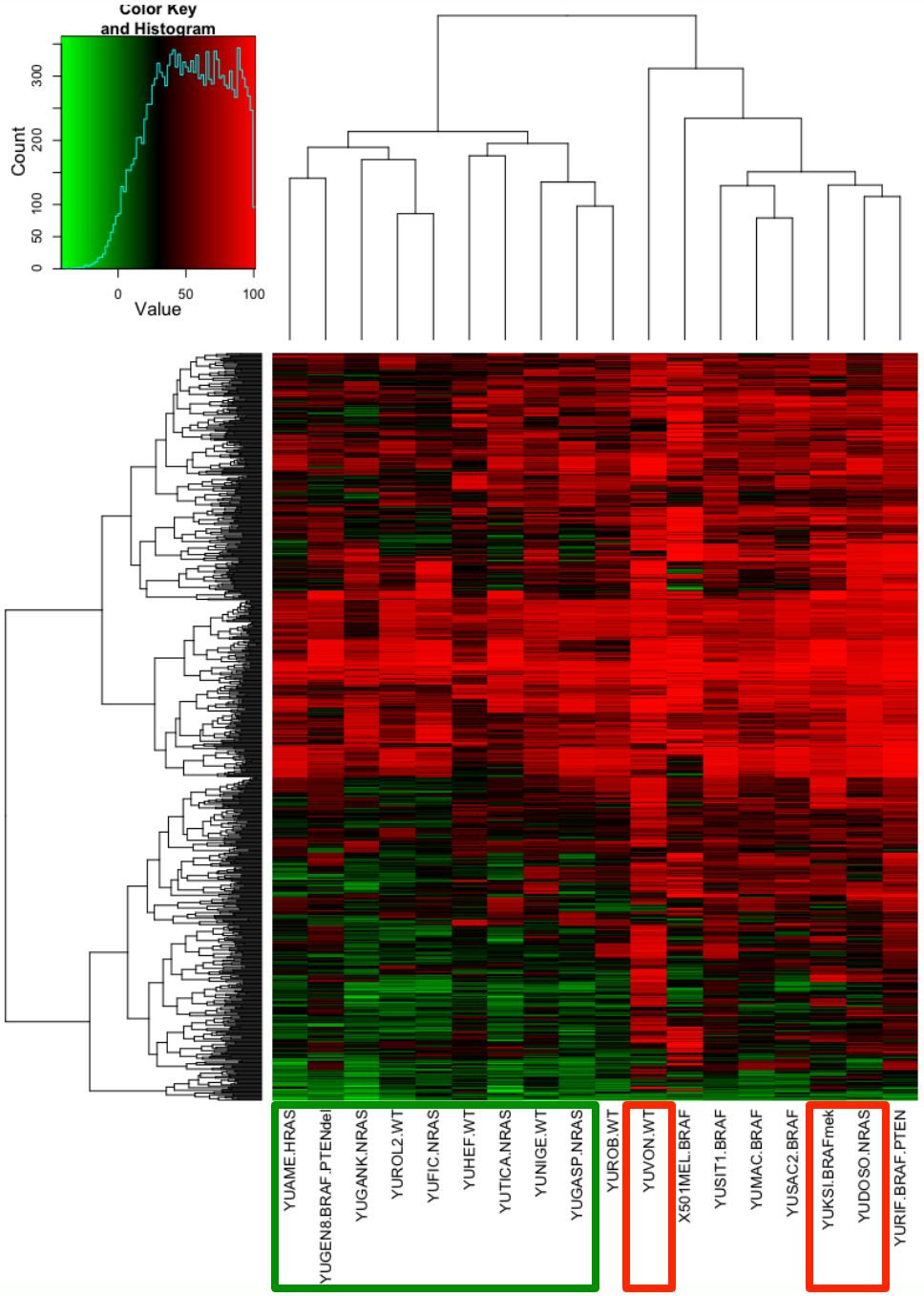
TK inhibitor



TK inhibitor



TK inhibitor



Resistance Signature:
Supervised clustering
transcription
profiles
resistant vs
Sensitive *WT/NRAS*

James Platt

Summary

ongoing:

- cells from defined mouse models (Marcus Bosenberg)
- connect to phosphoproteomic data
- link to exome sequencing, CN, ...
- animals

for...

- mechanism
- apoptosis
- pathway/target interactions
- predict sensitivity

1. What are the scientific challenges and opportunities in codevelopment?

Rationale:

Scientific challenges for single signaling therapies

- Resilience through transcriptional routes (autocrine circuits)
- Resilience through intra-pathway feedback and inter-pathway cross-talk
- Pathways have multiple efferents
- Redundant drivers (EGFR + MET amplification)
- Bypass mutations (PTEN)

Rapid routes to resistance

- Genetic and epigenetic plasticity
- On-target mutations
- Bypass mutations
- Tumor cell population heterogeneity

Ignorance about...

- Inducing tumor cell kill

1.What are the scientific challenges and opportunities in codevelopment?

Rationale:

Scientific **opportunities** for signaling therapies

- Feedback/network responses to signaling perturbations
- Crosstalk of signaling, DNA damage responses, cell cycle regulation
- Best combinations of pathway inhibition
- In vitro and in vivo assay development
- Epigenetic regulation, esp. for reactivation TS genes

Combinations with other modalities...

- DNA damage agents/Radiotherapy with repair inhibitors
- Immunomodulation to complement other approaches
- Immunomodulation in partnership with Ab therapies

1.What are the scientific challenges and opportunities in codevelopment?

Practical Challenges/opportunities for investigation

Academic role

- Cancer biology/genetics
- Target identification (molecules, pathways, interactions)
- Pharmacology, medicinal chemistry

Access to compounds

- IP
- Federal: NCI DTP, Experimental Therapeutics Program (NExT)
- Pharma: on-target but shelved compounds
- si/shRNA for target selection

1.What are the scientific challenges and opportunities in codevelopment?

Practical Challenges/opportunities for investigation

Scale: exponential nature of combination screens

- Focus on targets/pathways rather than drugs
- Hypothesis: know the target and relevant pathways
  - e.g. Trastuzumab to dual and pan-ErbB
  - e.g. immunomodulation
  - e.g. PARP inhibitors X BRCA1

- How do effective therapies work?
  - Trastuzumab, Lapatinib

- Sensitization screens vs. single challengers
- Genetic and functional information about co-activation

7. What lessons have been learned, and what would you recommend to improve?

- **Still much basic and applied science remains**
  interactions of target pathways
  apoptosis
  patterns of drug response
  patterns of drug resistance
  interpreting transcriptional phenotypes
  feedback pathways
  Toxicology

Patient selection

- Mapping t.c. and animal models onto clinical predictions
- Clinical: rebiopsies, neoadjuvant models
- Monitoring: biopsy, CTC for tumor burden

9. Is there a role for precompetitive collaboration for development of combination Cancer therapies?

- Overall alignment of Academic, Pharma, and NIH goals
- But...

  IP, proprietary information, credit, priorities

- Government: economy of scale, drug and shRNA libraries

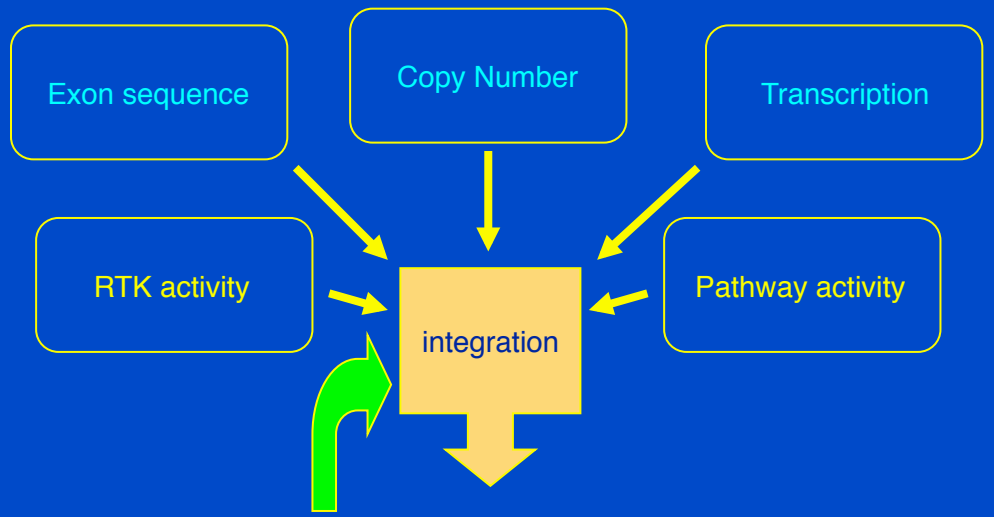
- Bidirectional interaction Pharma and Academia

Yale SPORE in Skin Cancer

Ruth Halaban, PI

M. Sznol, R.Tigelaar co-PI

Antonella Bachiocchi



Kat Tworkoski
Garima Singhal
Tina Zito

Rahul Dalal
Betsy Cowell

Michael Krauthammer
Sebastian Szpakowski

Cell Signaling Technology
Ting-Lei Gu
Meghan Tucker

Matthew Held
Casey Langdon
Sierra Colavito
Tisheeka Steed

Marcus Bosenberg
Ashok Chakraborty
James Platt

Harriet Kluger

Roslyn and Jeremy Meyer Fund
Harold J. Lloyd Trust
Anonymous

Yale Small Molecule Discovery Center
Janie Merkel
Michael Salcius
Mariya Kolesnikova