ModEncode and a Drosophila Search for Cancer Therapeutics

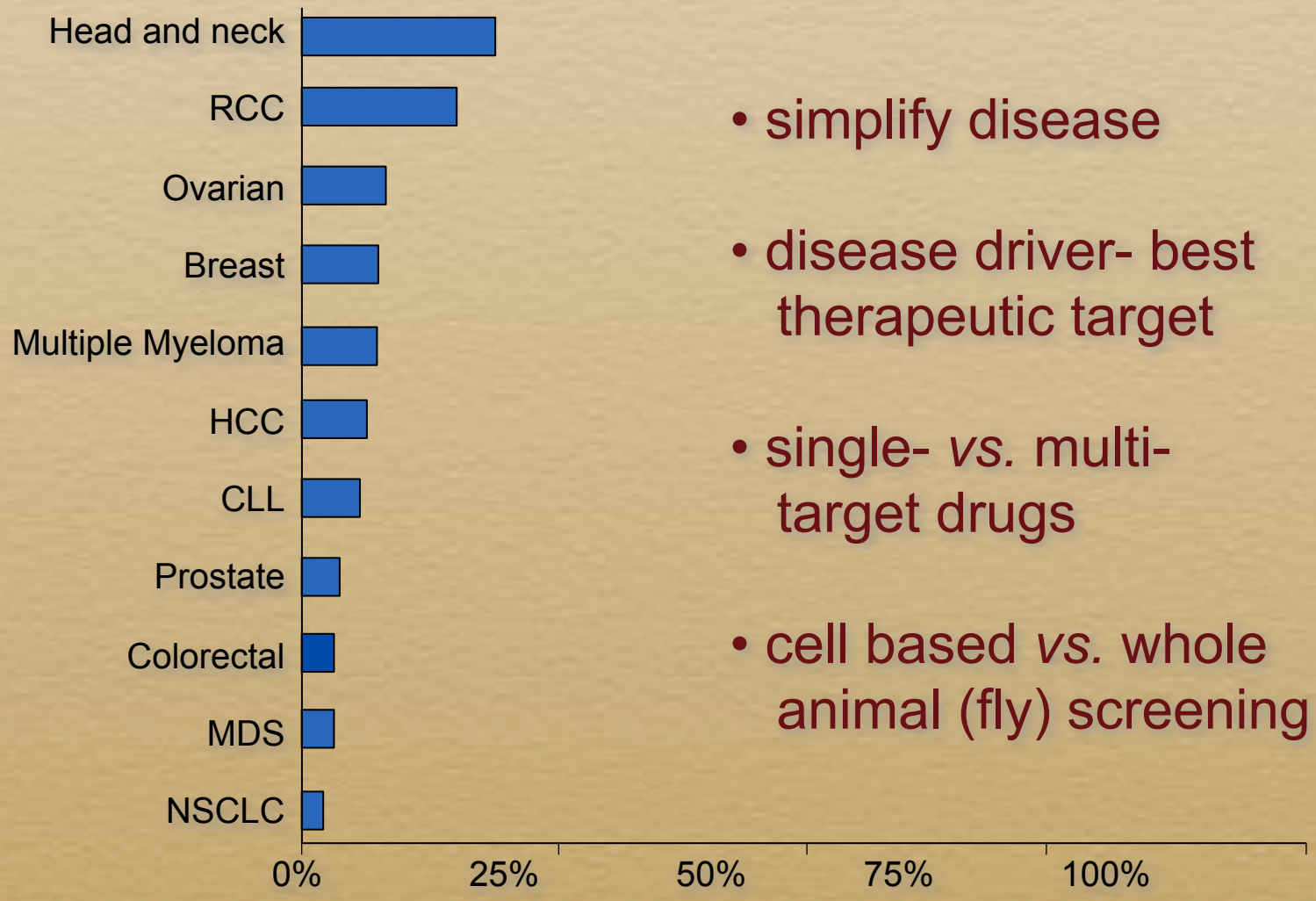
Ross L. Cagan

Mount Sinai School of Medicine

Medros, Inc

- co-founder
- stock, BOD

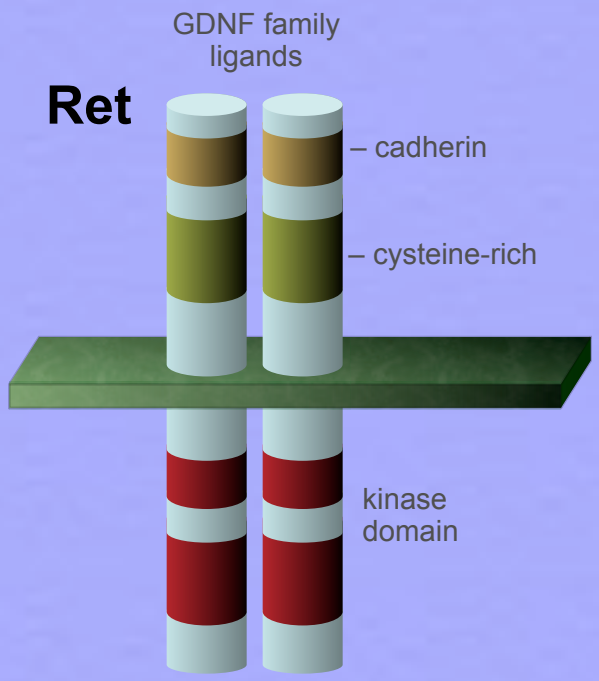
Clinical Trial Success Rates by Tumor Type

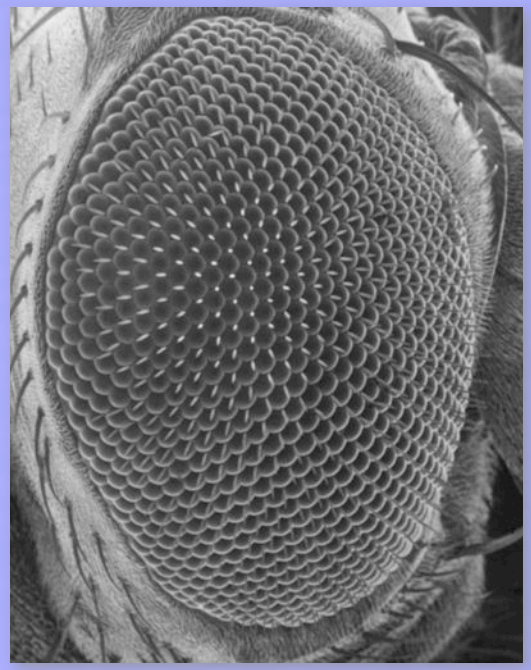


- simplify disease
- disease driver- best therapeutic target
- single- *vs.* multi-target drugs
- cell based *vs.* whole animal (fly) screening

American Cancer Society

Drosophila Model of Medullary Thyroid Carcinoma



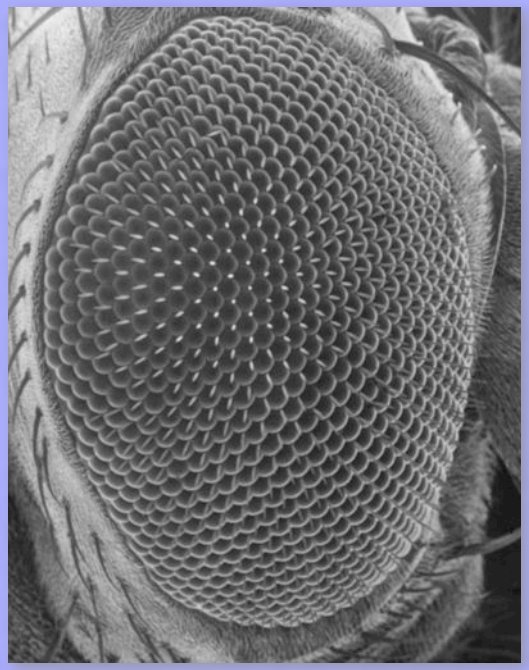


wild type

Ret(MEN2B)

Read, Genetics 2005

Fly Identification, Validation of Caprelsa



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Vidal, Can Res 2005

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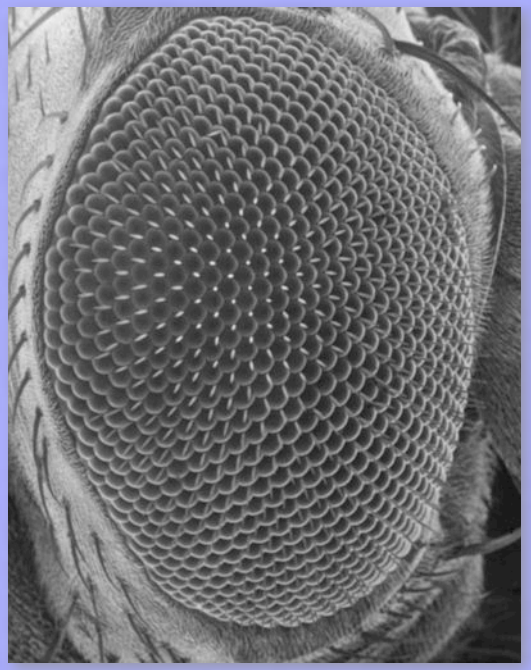

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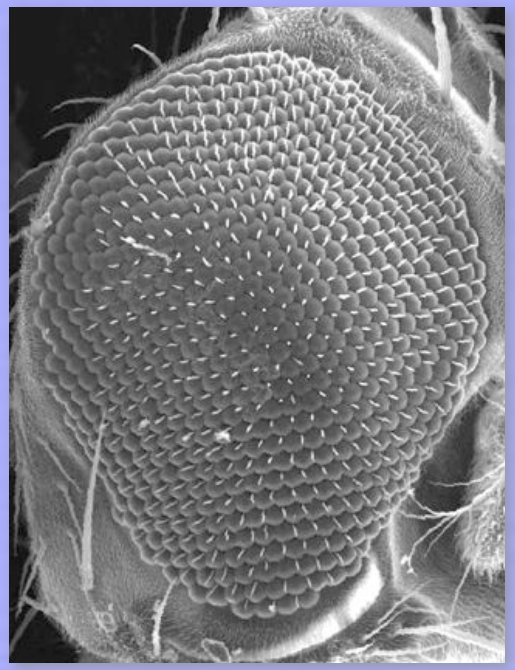

Ret(MEN2B)
+ ZD6474

Vidal, Can Res 2005

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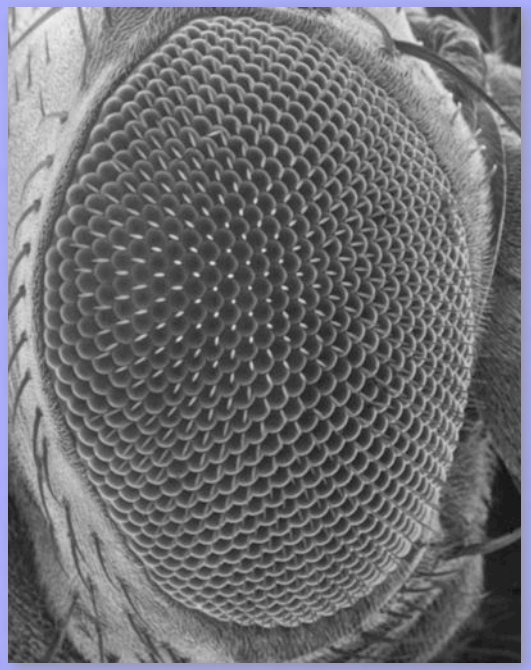

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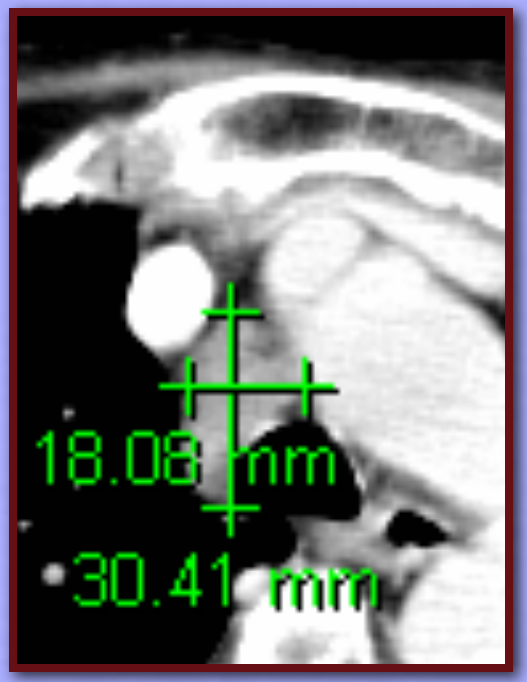
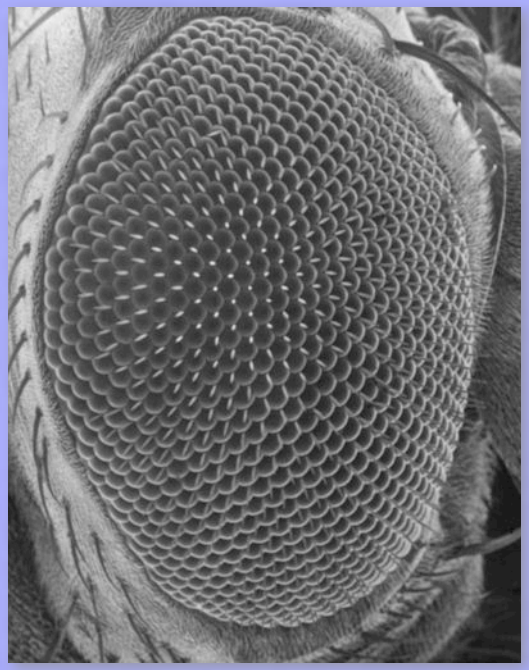


Massimo Santoro, Sam Wells
"Caprelsa"

Vidal, Can Res 2005

Epigenetic Regulation: Sin3a Opposes Transformation



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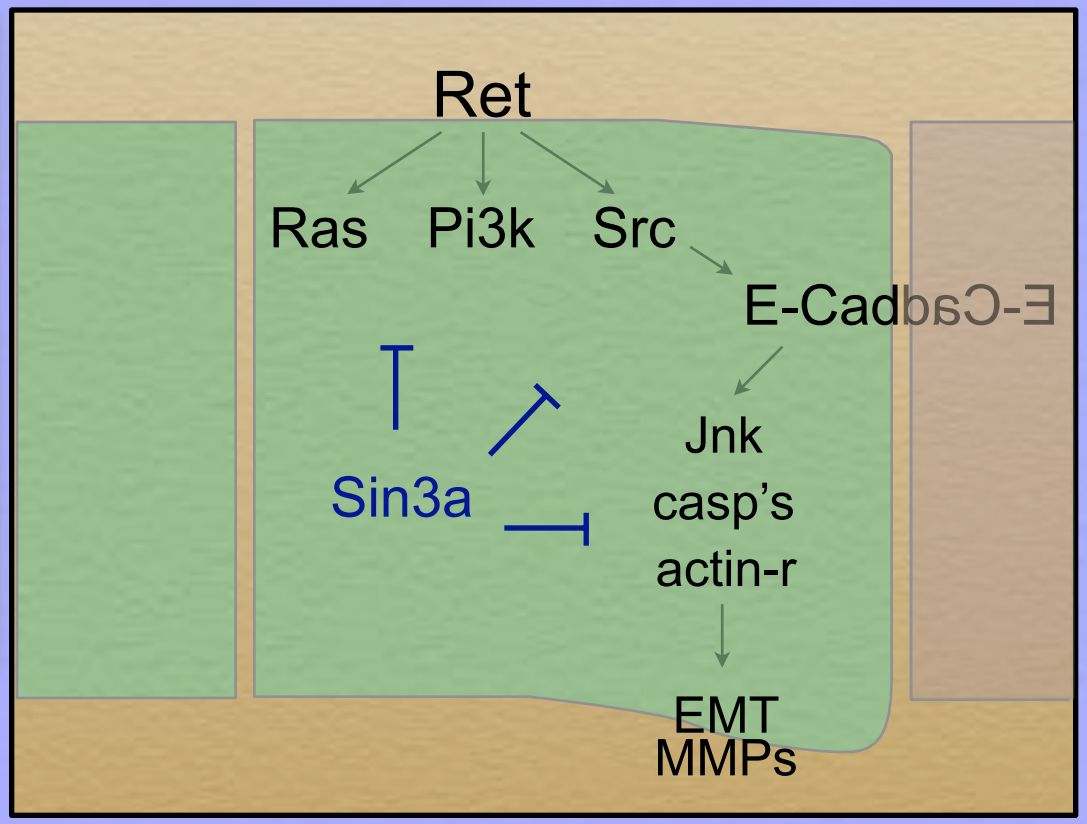
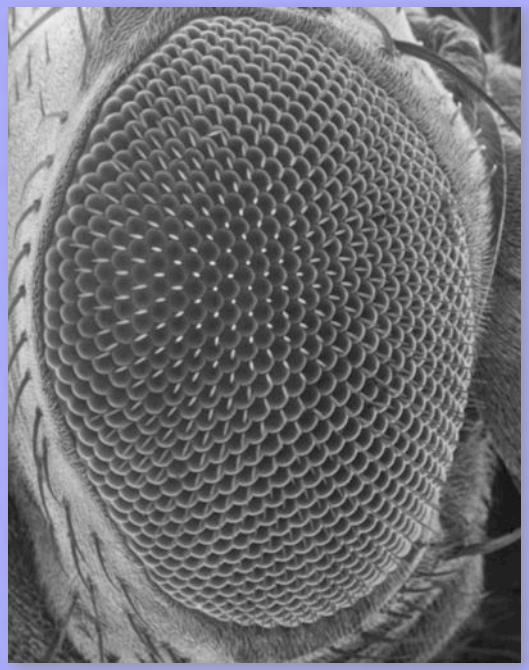


Read, MCB 2005
Vidal, Dev Cell 2006
Das, in press

Epigenetic Regulation: Sin3a Opposes Transformation



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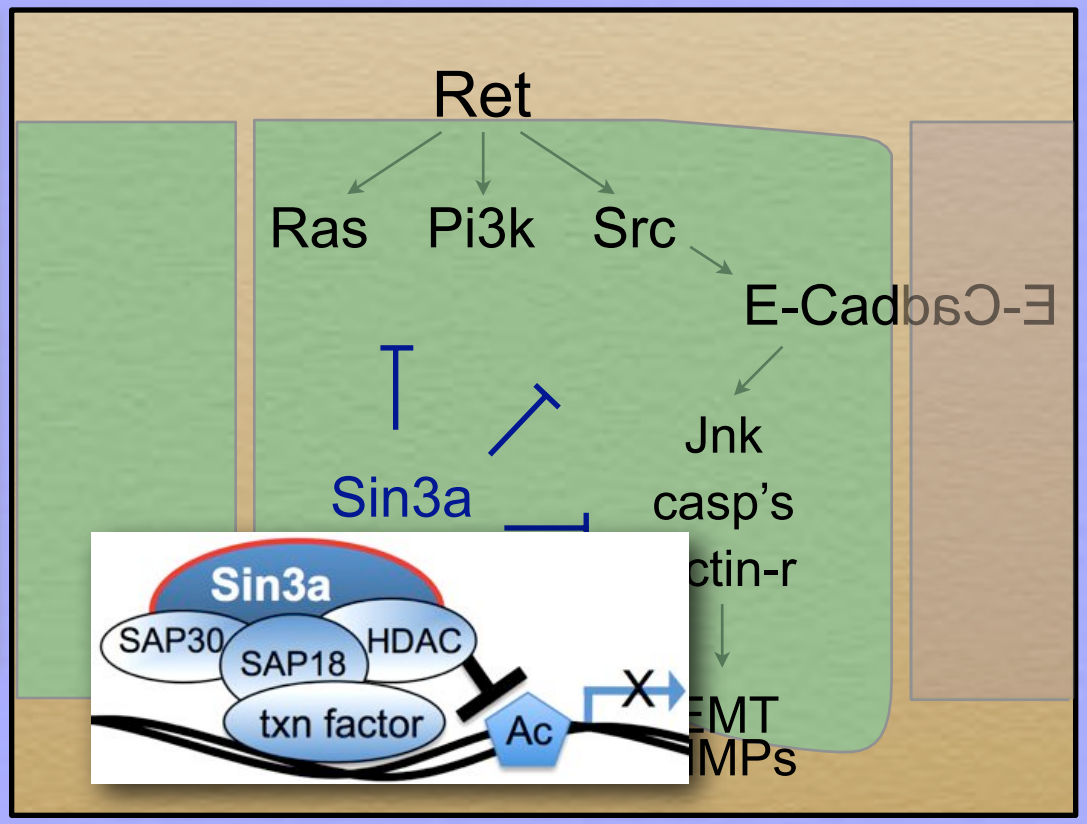

Tirtha Das

Read, MCB 2005
Vidal, Dev Cell 2006
Das, in press

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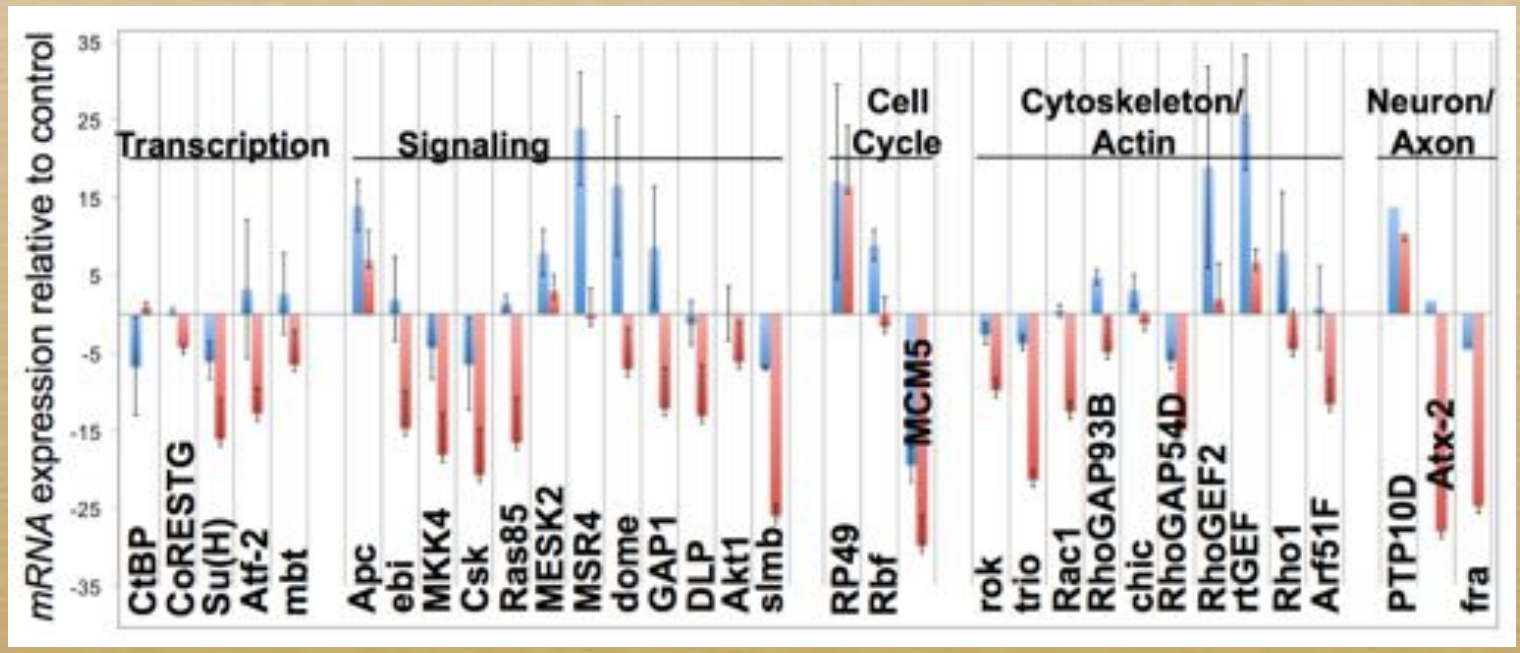

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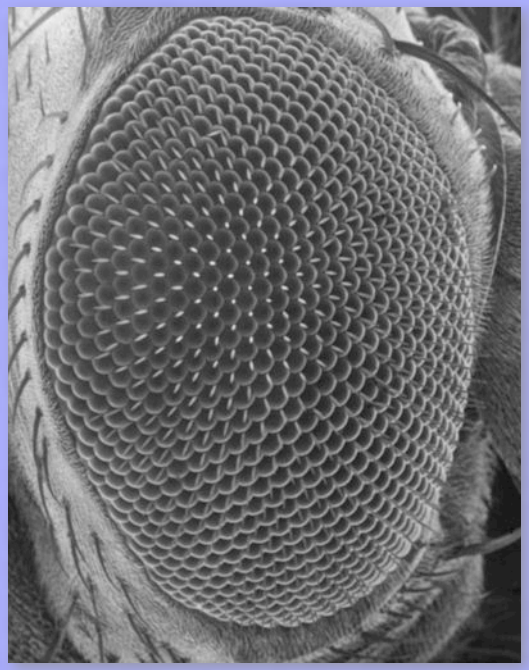

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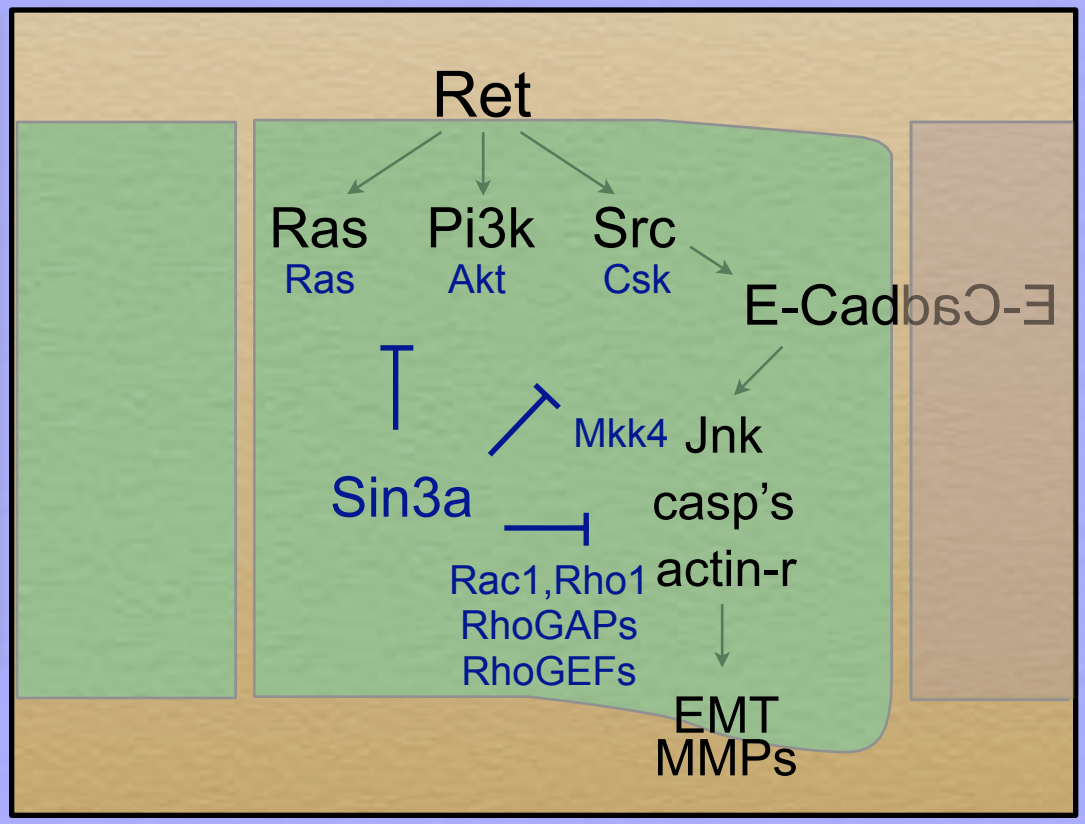

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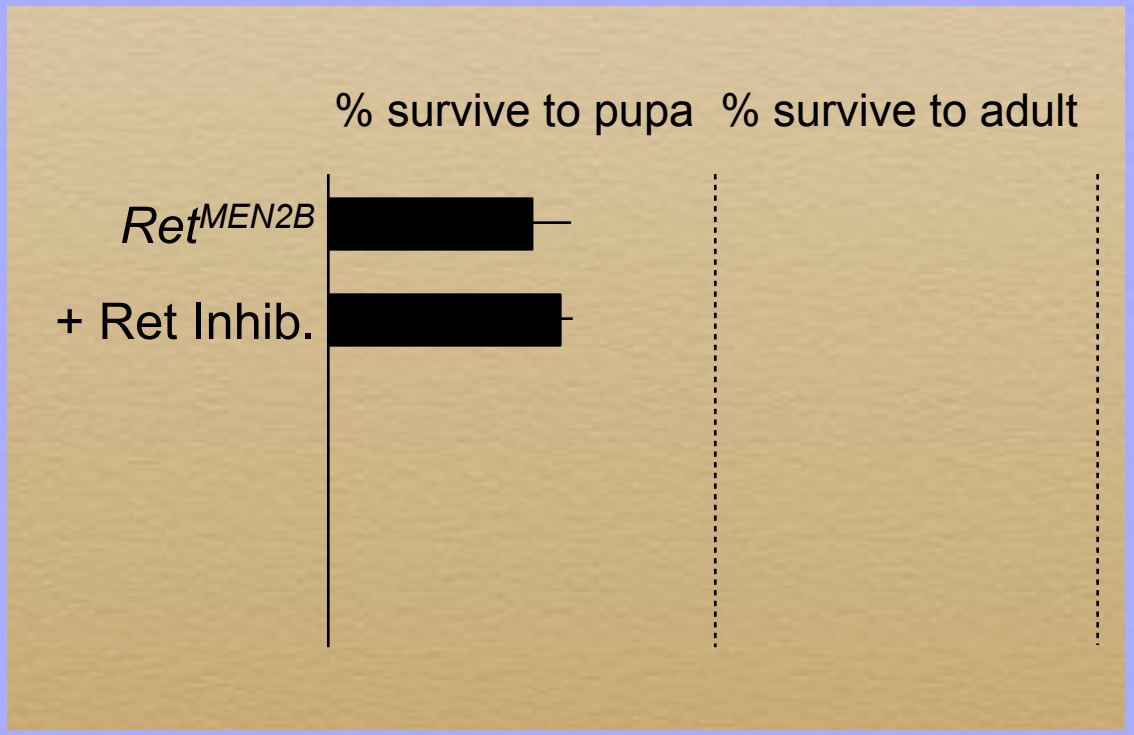
Fly Approach to Novel Kinase Inhibitors

Combined flies, in vitro data to 'predict' better drugs



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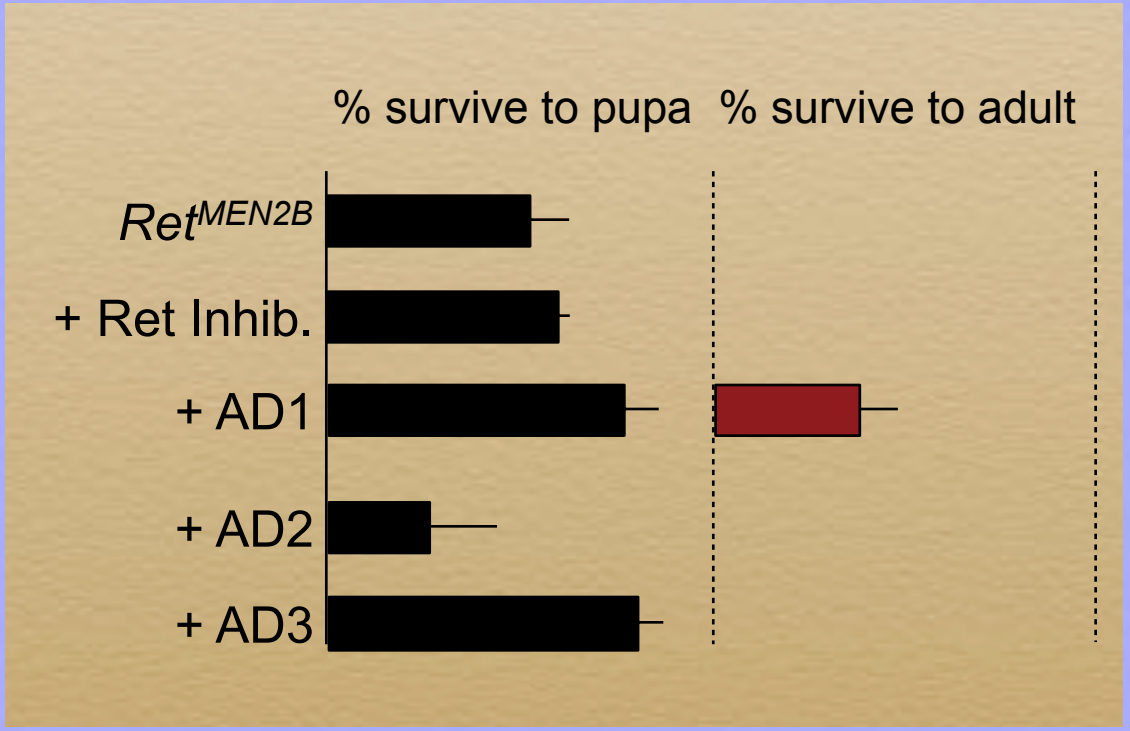

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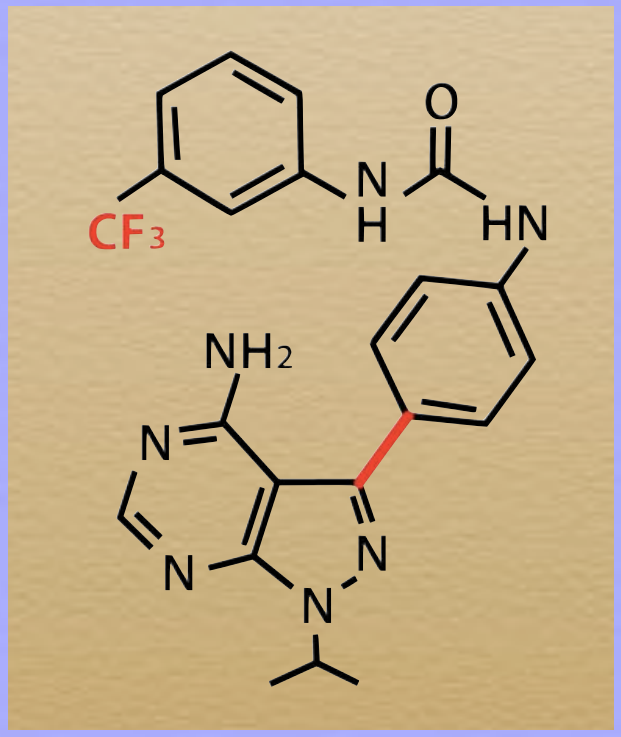

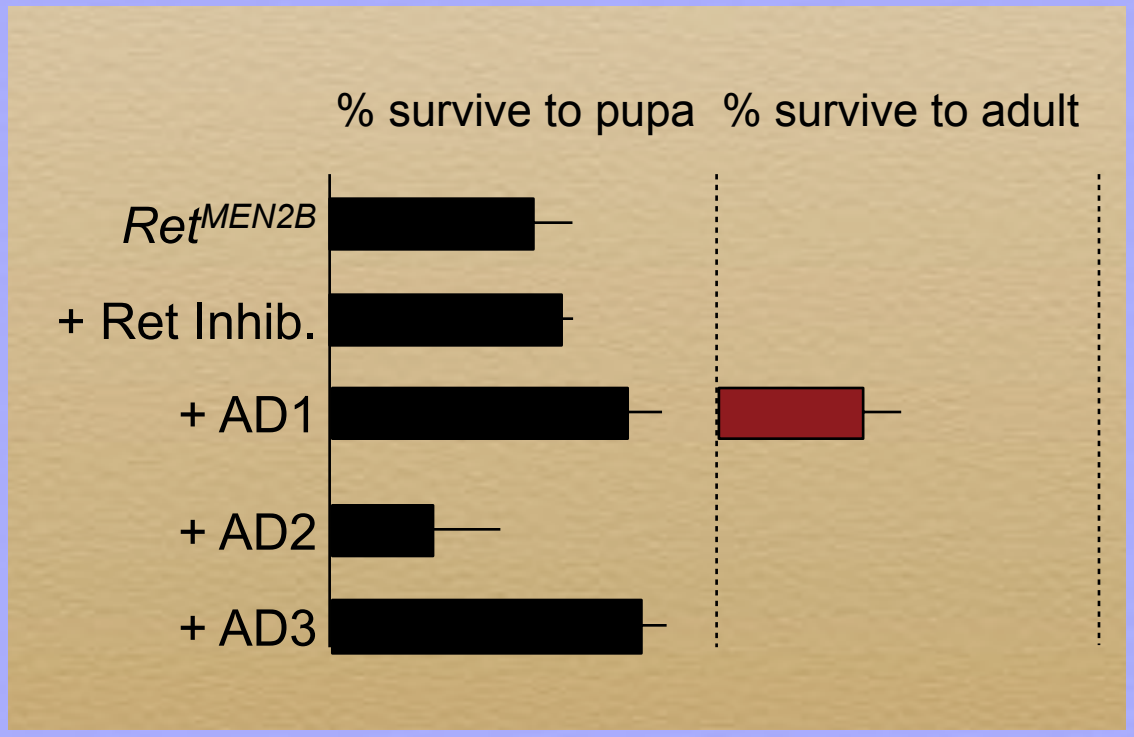

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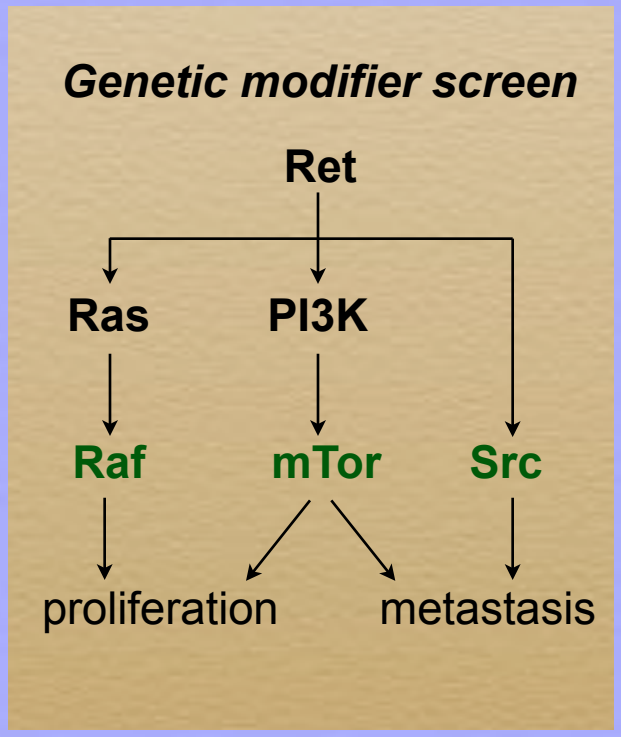

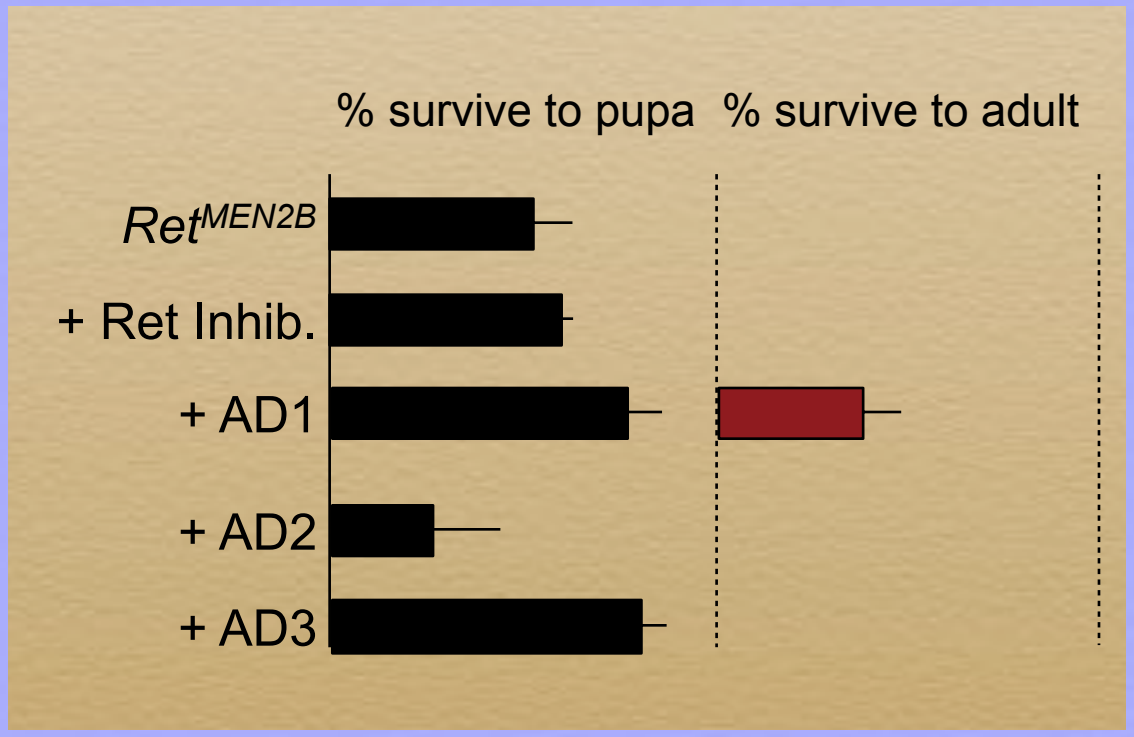

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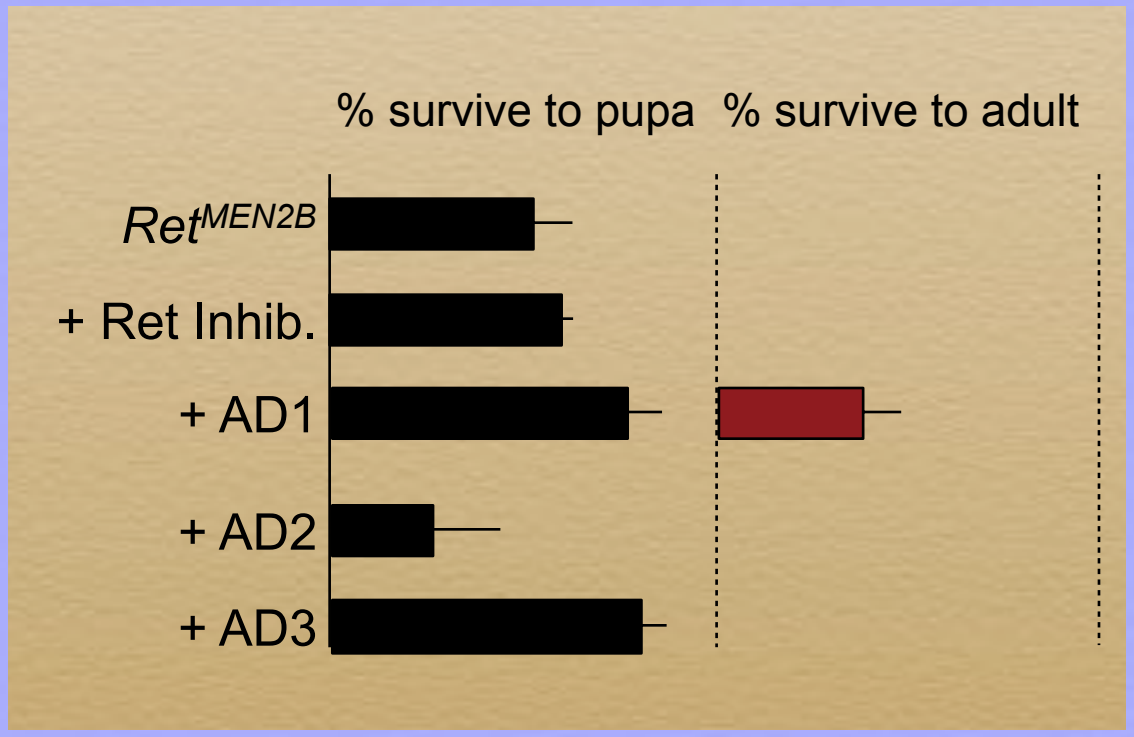
***in vitro* kinase assays**

comparing inhibitors

	AD1	AD2	AD3
Ret	+++	+++	+++
Src	+++	+++	+
BRAF	+++	+	+++
mTor	++	+++	+



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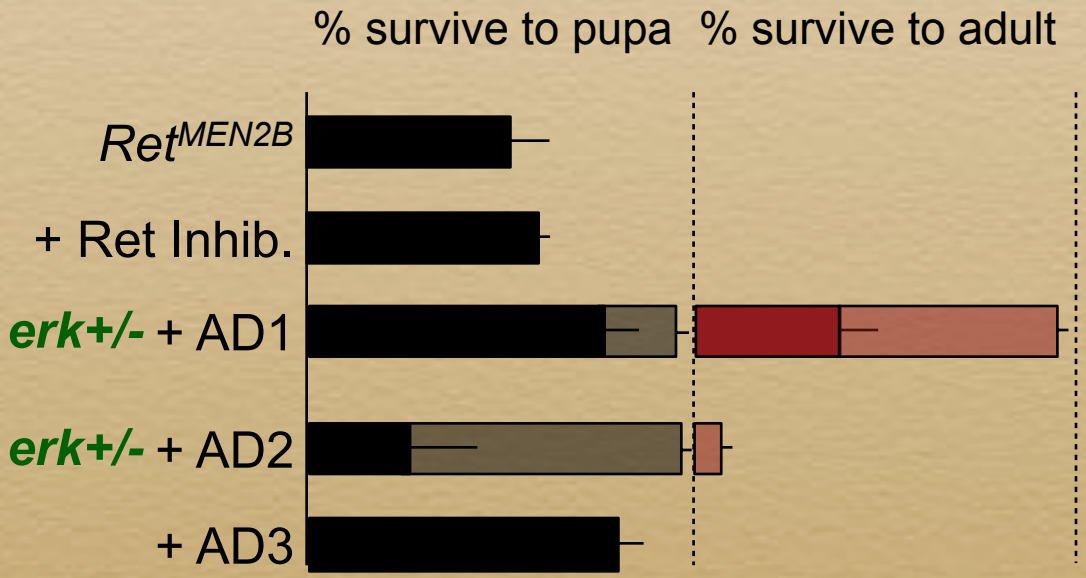

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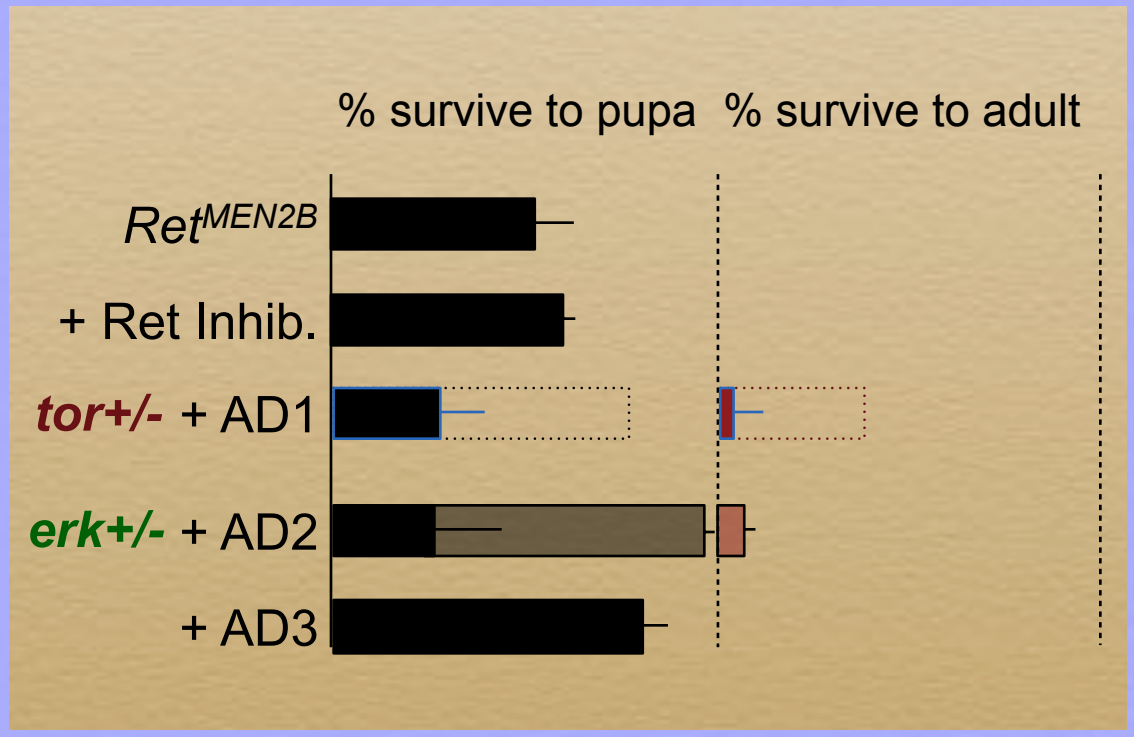

Fly Approach to Novel Kinase Inhibitors

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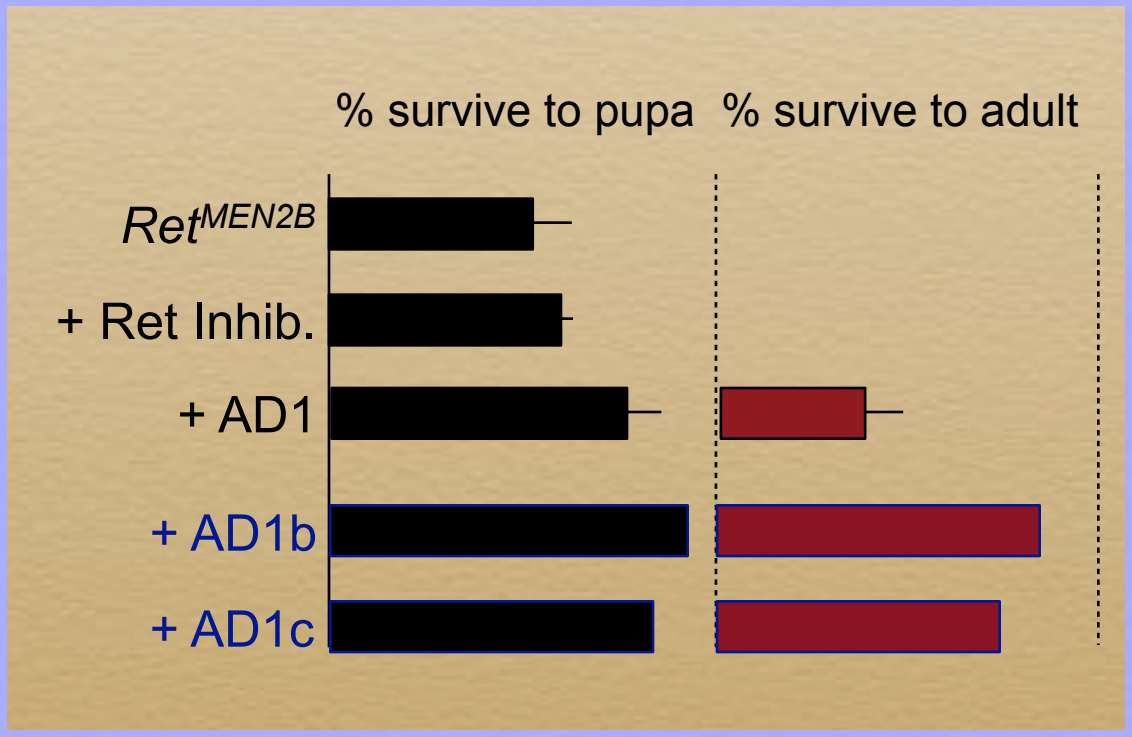
***in vitro* kinase assays**

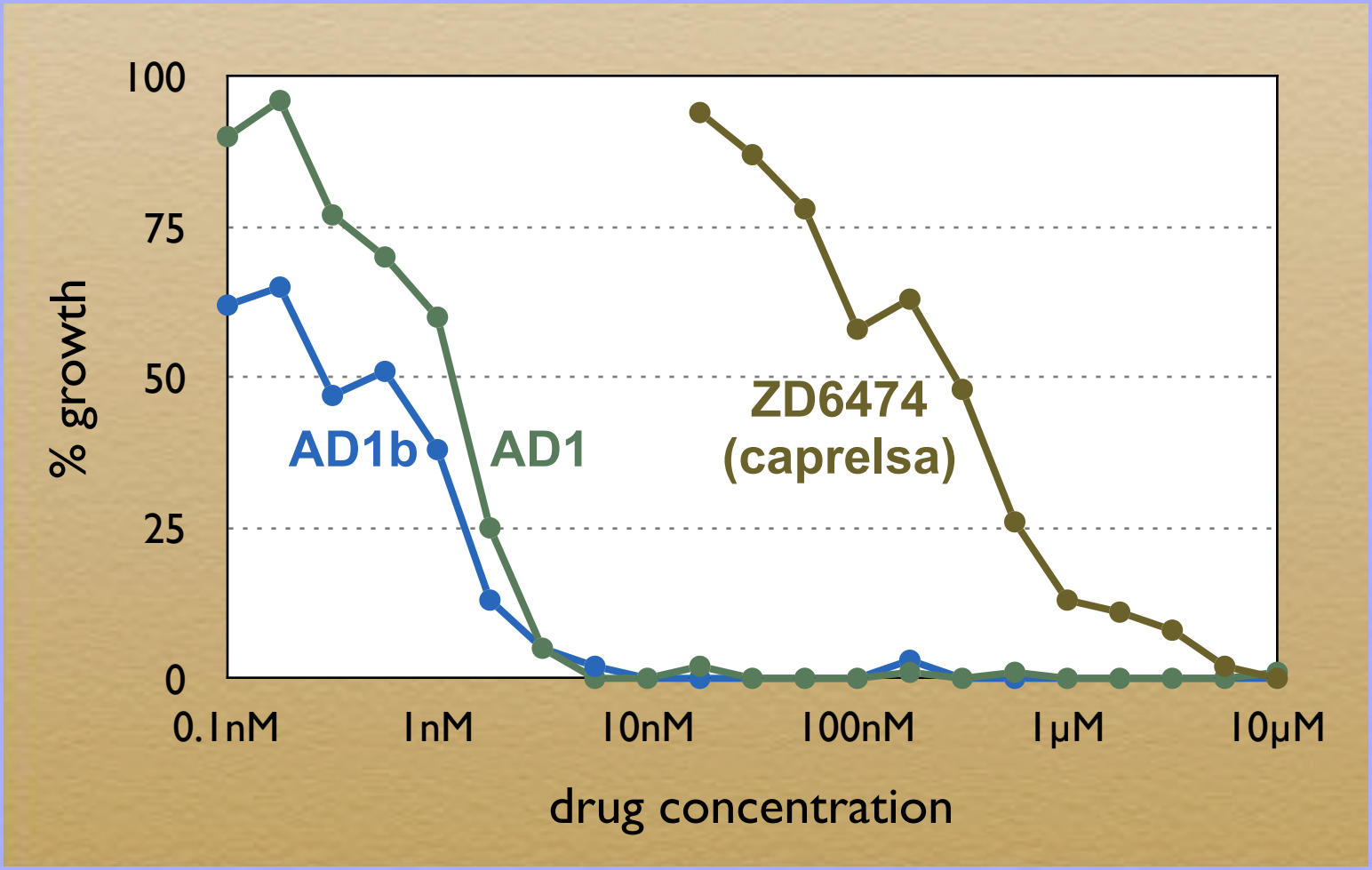
comparing inhibitors

	AD1	AD1b	AD1c
Ret	+++	+++	+++
Src	+++	++	+++
BRAF	+++	++	++
mTor	++	+	+
S6K	+++	+++	+++



AD1, AD1B show activity in mammalian MEN2 models

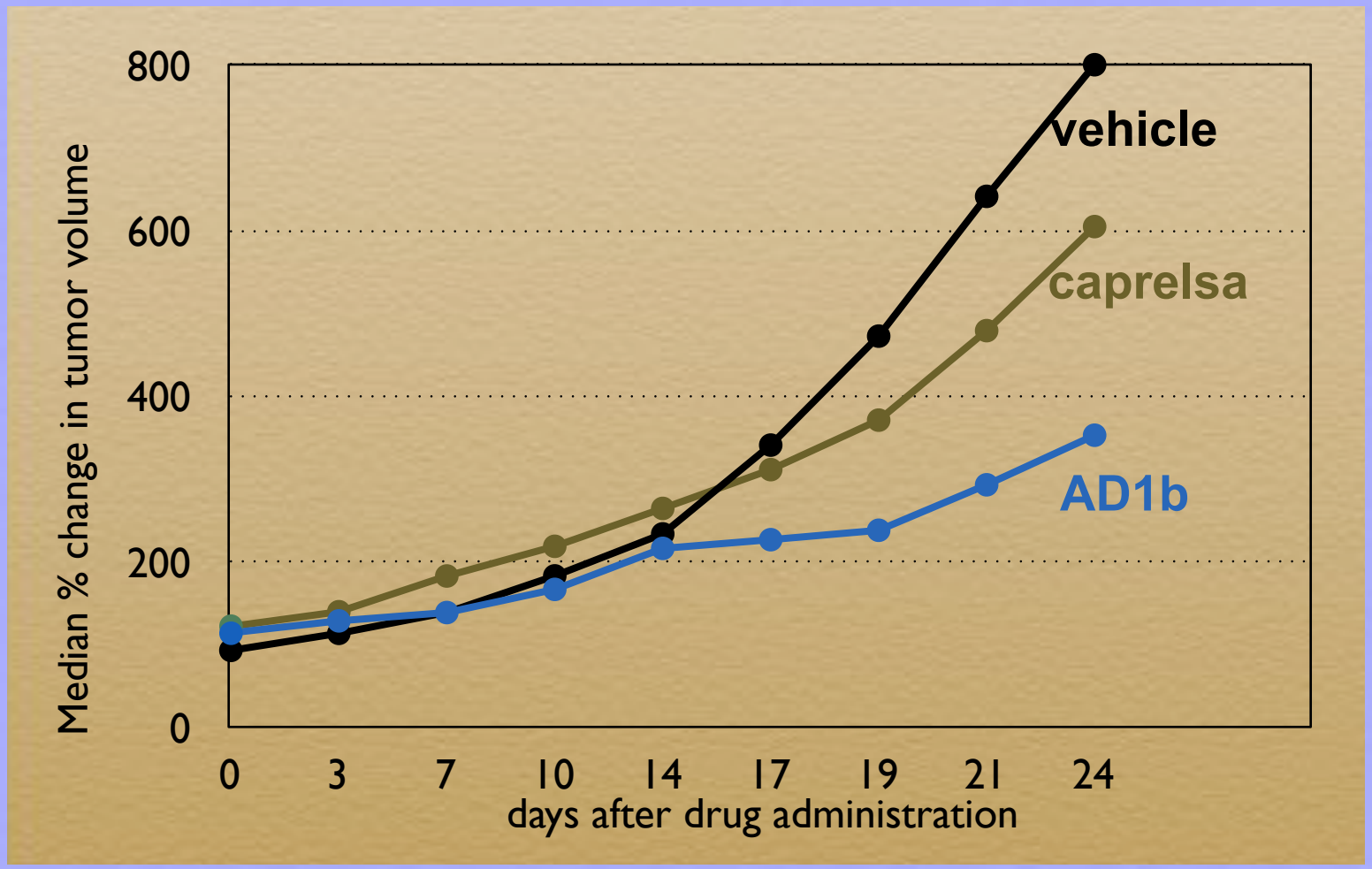
Validation of Fly Results on MZ-CRC-1 (MEN2B) Cell Line



Dar, Nature 2012

AD1, AD1B show activity in mammalian MEN2 models

TT cells grown in mouse for 46 days prior to oral drug administration



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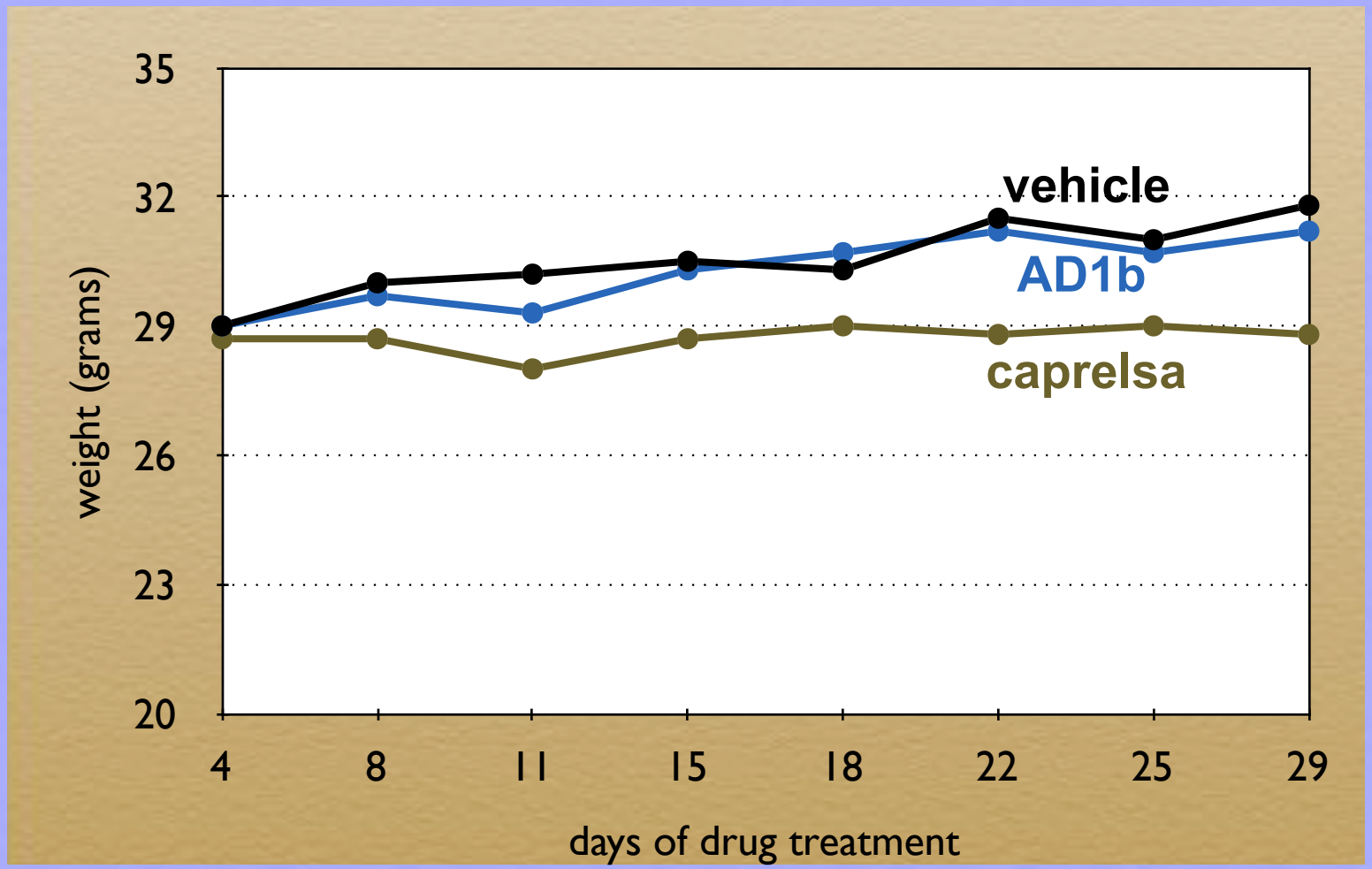
AD1, AD1b demonstrated low toxicity at therapeutic doses



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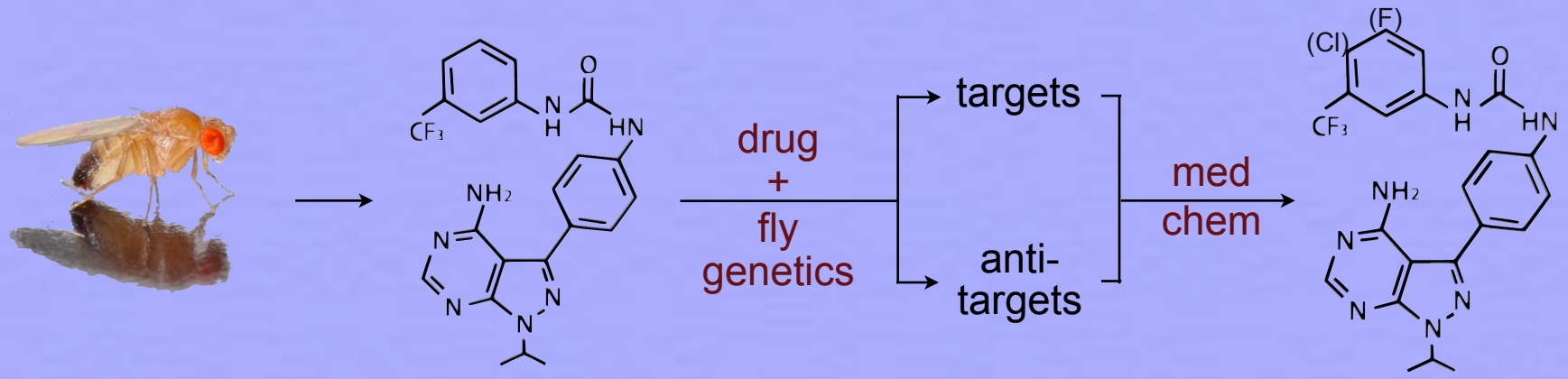

Multigenic adult models

four-hit colorectal model

Double combinations

PIK3CA *P53*^{RNAi}
P53^{RNAi} *Pten*^{RNAi}
Med^{RNAi} *Pten*^{RNAi}
Apc^{RNAi} *Pten*^{RNAi}

Triple combinations

Ras1^{V12} *Pten*^{RNAi} *Apc*^{RNAi}
Ras1^{V12} *P53*^{RNAi} *Pten*^{RNAi}
EGFR^{act} *P53*^{RNAi} *Pten*^{RNAi}
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EGFR^{act} *Med*^{RNAi} *Apc*^{RNAi} *P53*^{R}

Bangi, in revision

Multigenic adult models

four-hit

colorectal

model

hyperproliferation

multilayering

EMT

distant migration

~~senescence~~

~~apoptosis~~

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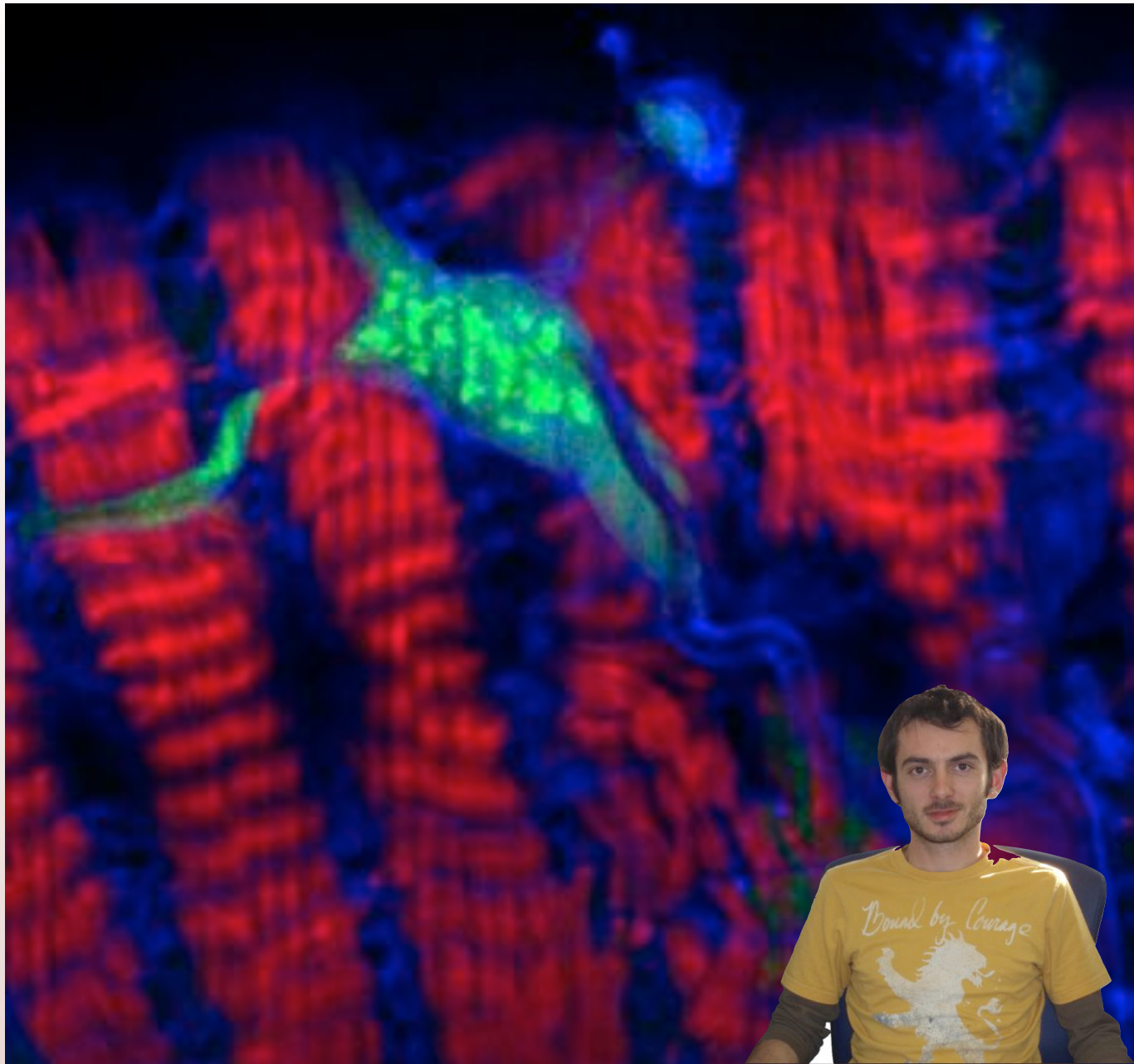

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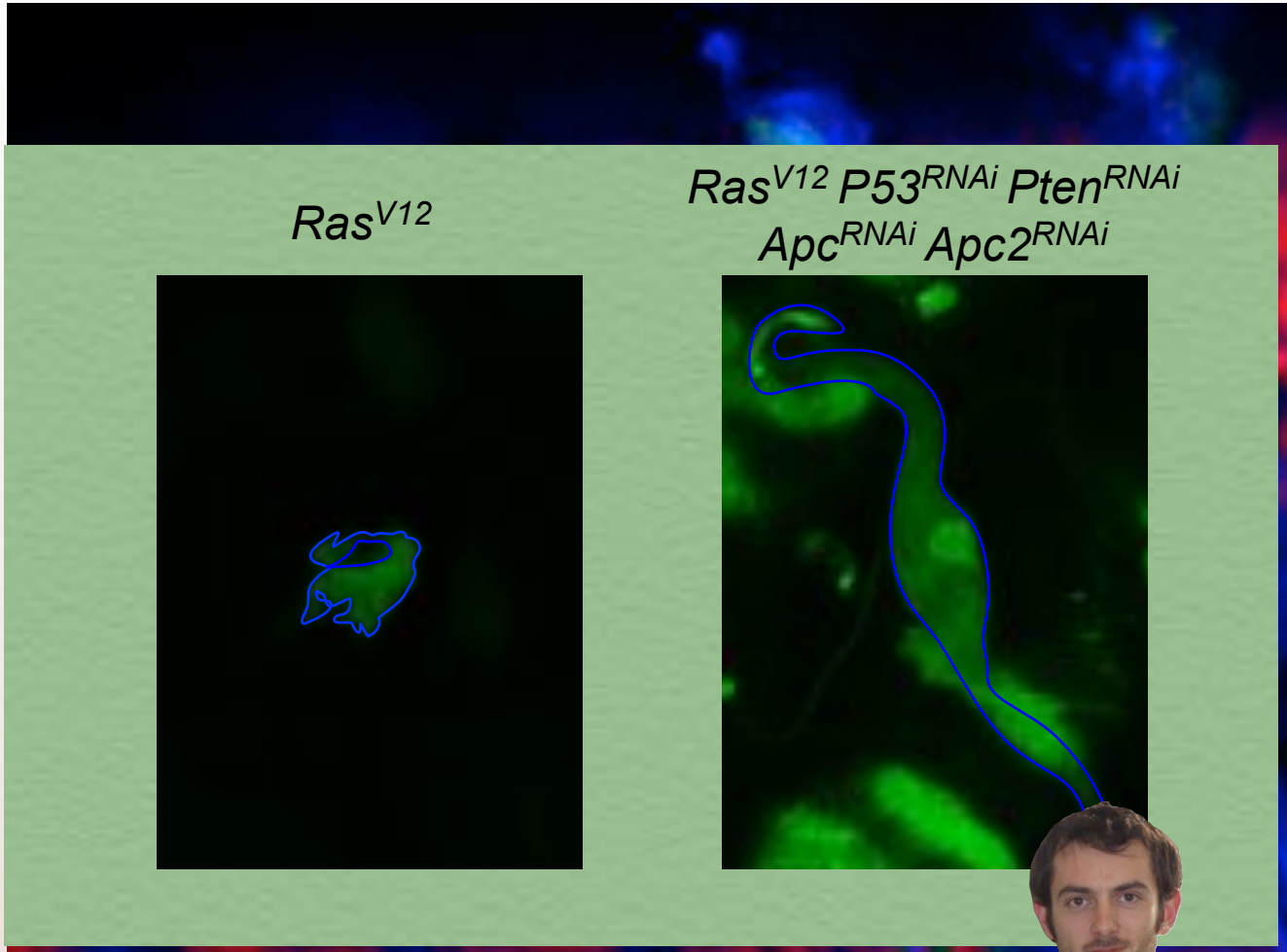

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ras^{V12}	*ras^{V12} $p53^{RNAi}$ $pten^{RNAi}$ apc^{RNAi}*
LY294002 (PI3K)	
Wortmannin (PI3K)	
SL327 (MEK)	
PI103 (MEK)	
AZD6244 (MEK)	
GW5074 (Raf)	
Dasatinib (Src/Abl)	
SP600125 (JNK)	
Rapamycin (mTor)	
BEZ235 (PI3K+mTor)	
Enzastaurin (PKCß)	
LBH589 (HDAC)	
Bortezomib (proteosome)	

Bangi, in revision

Summary

complex drugs

- whole animal screening
- target ID: epigenetics
- chemical genetics → polypharmacology

complex models

- 4-hit colorectal models
- drug sensitivity: 4 ≠ 1

Thanks to:
National Institutes of Health
ModEncode
American Cancer Society