Functional exploration of human cancer genomes using flies

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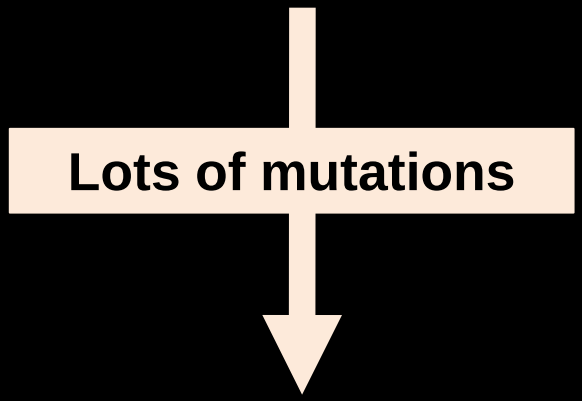
Cancer is a complex, multigenic disease

Normal epithelial cell



Metastatic tumor cell

Comprehensive catalogue of tumor genomes by the Cancer Genome Atlas (TCGA)

Genomic landscape of colorectal cancer

-- ~30 colorectal cancer drivers

-- recurrently mutated in colon tumors

-- backed by functional evidence

Genomic landscape of colorectal cancer

Genomic landscape of colorectal cancer

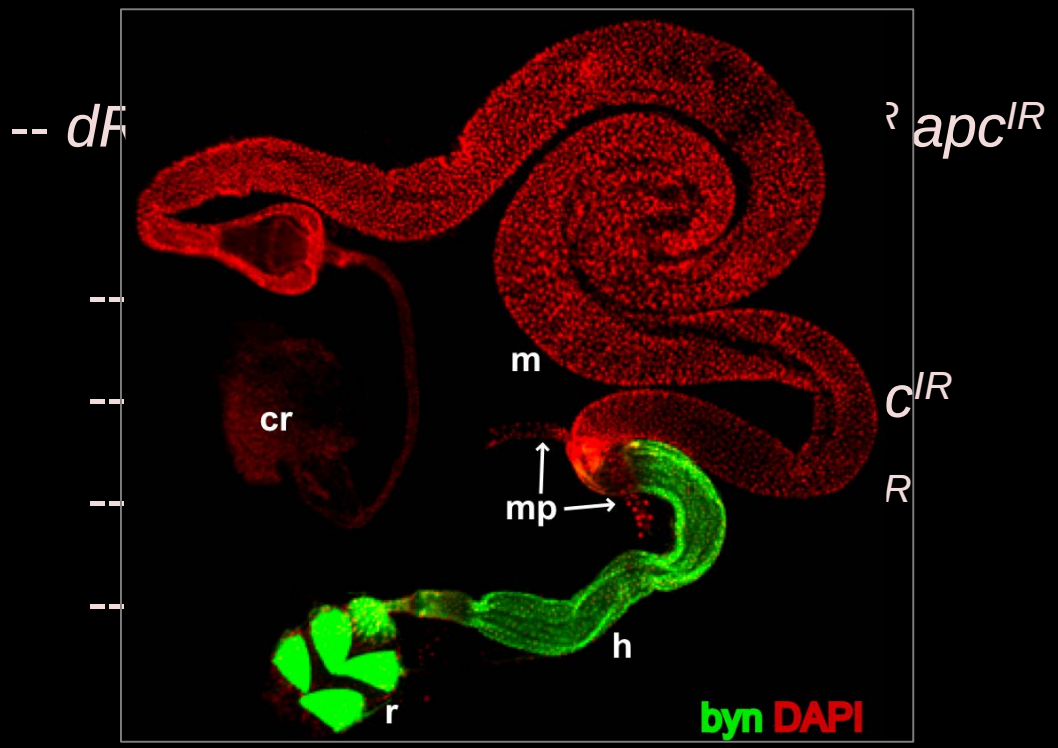
Recurrent mutations in 5 pathways		In flies:
-- Wnt	(92%)	*apc*^{IR}
-- Ras/MAPK	(63%)	*dRas*^{G12V} , *dEGFR*
-- PI3K	(57%)	*pten*^{IR}
-- TGF-β	(77%)	*dSmad4*^{IR}
-- TP53	(74%)	*p53*^{IR}

TCGA patients sorted by pathway deregulation status

Modeling the complexity of human colon tumors in Drosophila

195 colon tumor genomes from the TCGA → 33 multigenic fly models

Adult Drosophila gut (colon: green)



Tumor phenotypes observed in multigenic models

-- Proliferation

-- Multilayering

-- evasion of apoptosis

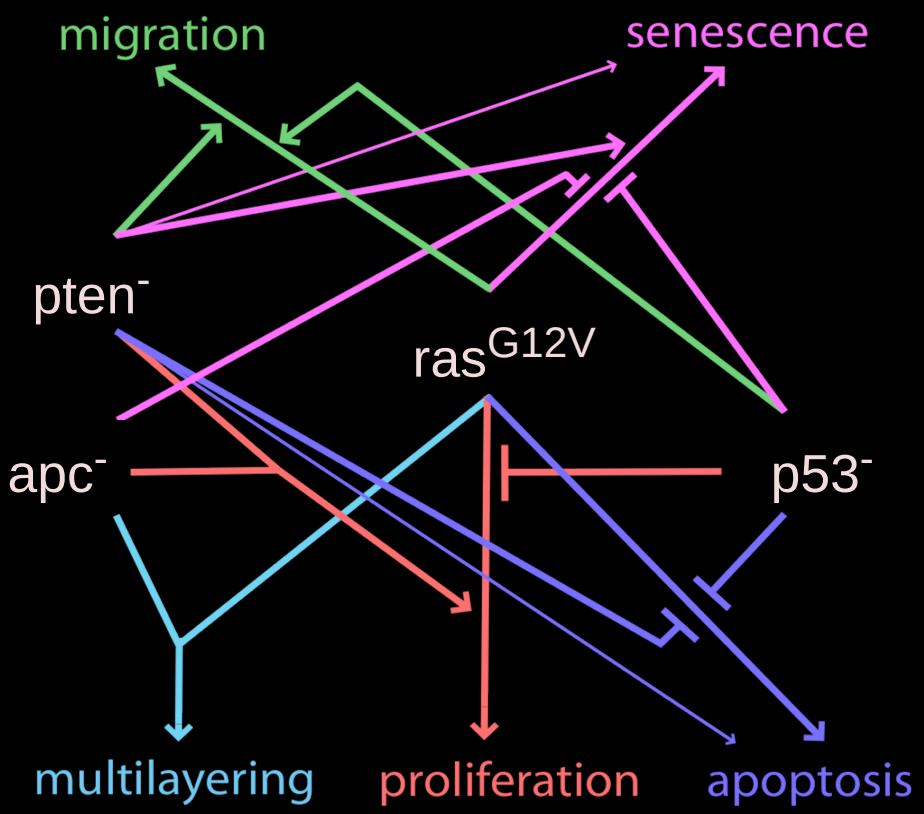
-- evasion of senescence

-- EMT/Migration

-- Dissemination to distant sites

Correlating tumor genotype with cancer phenotypes using a diverse set of models

Complex interactions between individual mutations

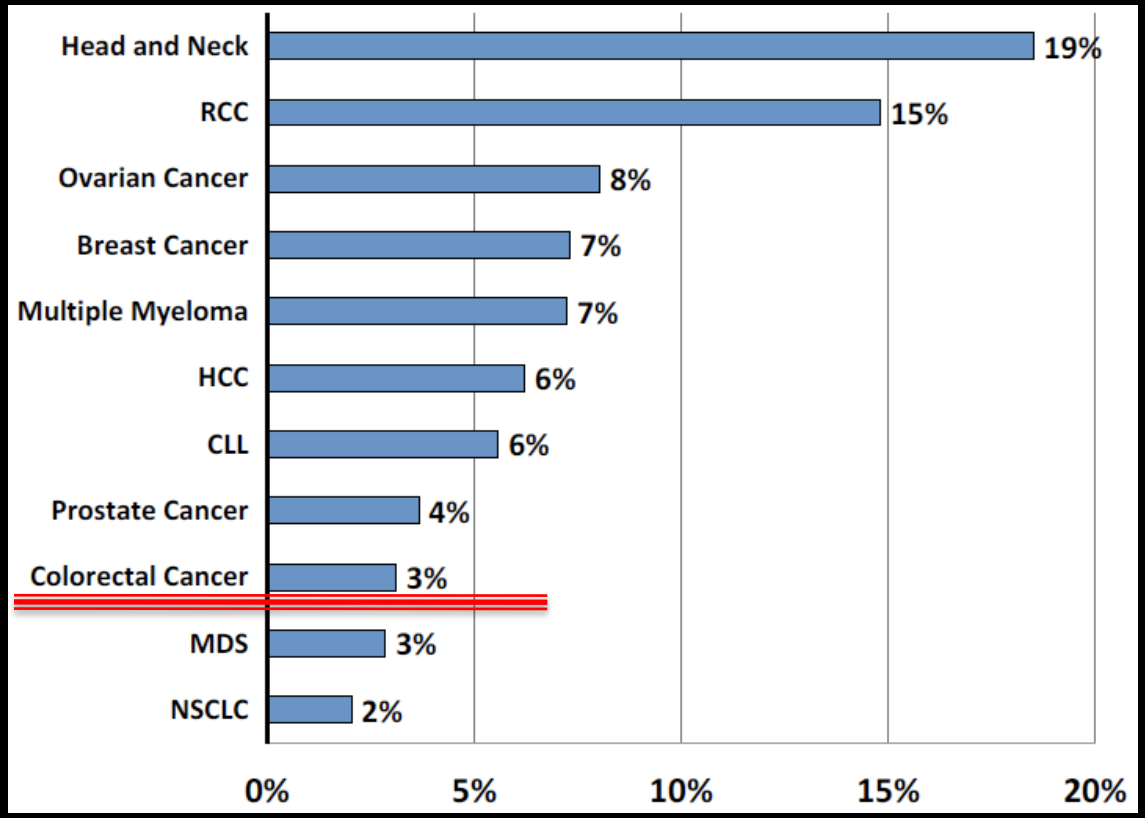


What about drug response?

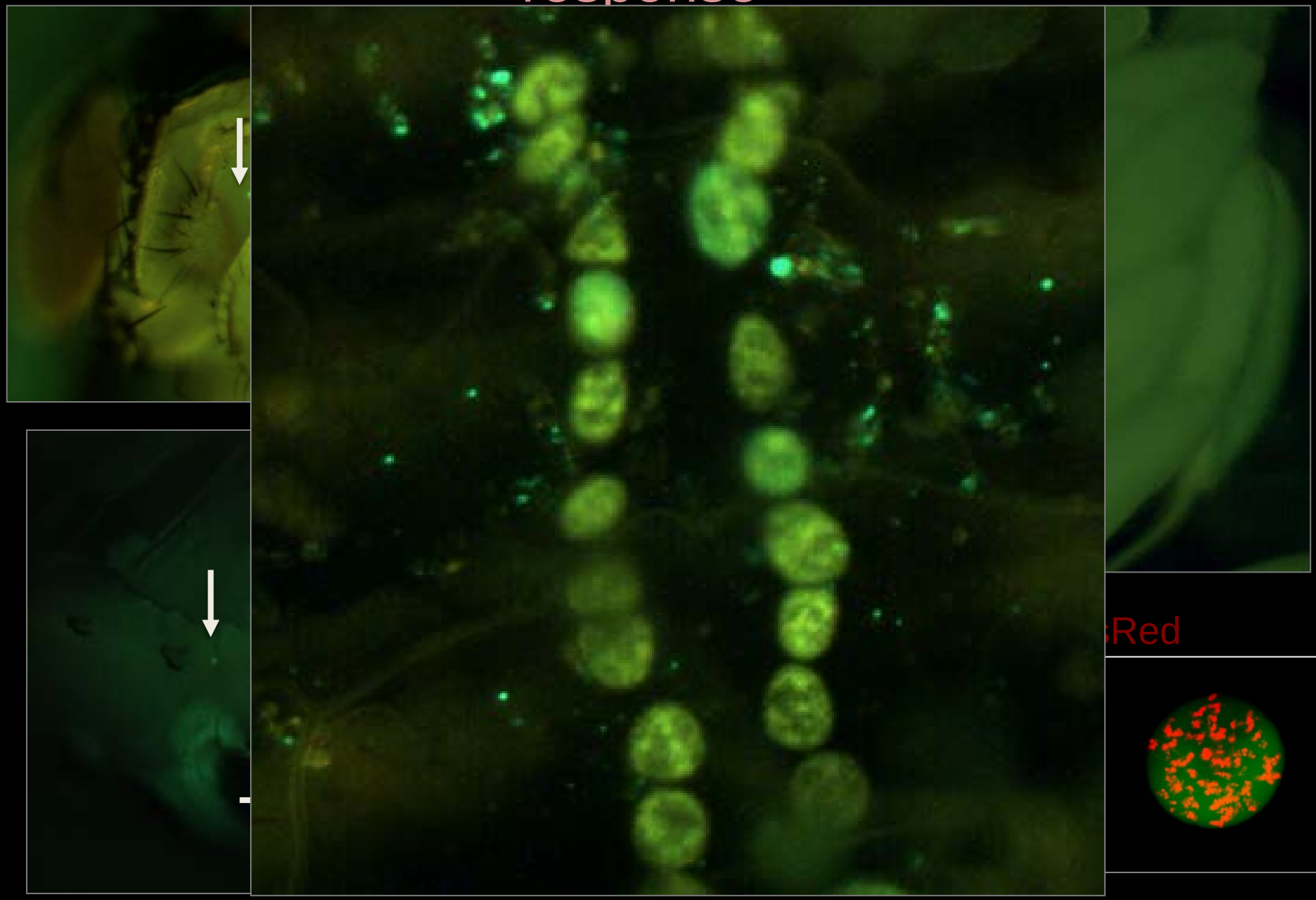
Testing drug response using genetically compex models

Most oncology drugs that enter clinical trials fail!

Oncology Clinical Trials Success Rates (Bio/Biomed Tracker)

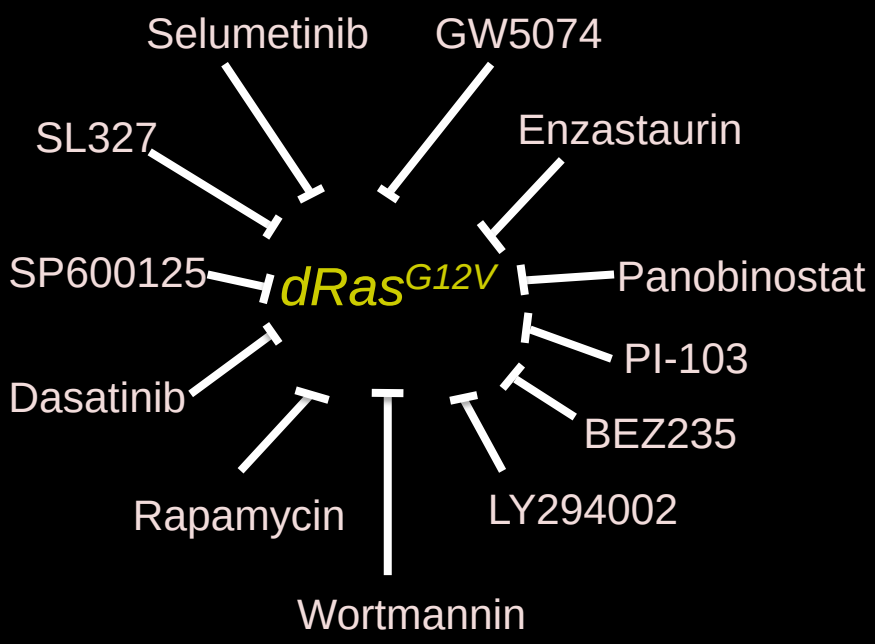


Dissemination to distant sites as a readout for drug response



Intrinsic drug resistance is an emergent property of genetically complex models

12/16 compounds



0/16 compounds

dRas^{G12V} p53^{IR}
ptenI^{R} apc^{IR}

No effect with Sorafenib, Everolimus, Cisplatin
No therapeutic window with bortezomib due to toxicity

Intrinsic drug resistance is another emergent property of multigenic models

PI3K pathway inhibitors

-- biomarkers of resistance

-- resistance mechanism

-- drug combination

-- mammalian validation

Key points

-- complexity matters

-- need a large number models

Next steps

Questions:

-- How much complexity is needed?

-- Fly models as personalized drug discovery tools?

Next generation models

Two upgrades:

-- genes instead of pathways

-- patient specific variants

CPCT Pipeline

Generate high quality tumor genomic profiles

(whole exome, targeted panels, copy number analysis)

Build patient specific fly models

base model
-- recurrent cancer drivers only
-- 3-5 genes/patient

personalized model
-- additional deleterious mutations
-- up to 10 genes/patient

Drug screening
(single agent & combination screens)

--FDA cancer set (62 drugs)

-- Full FDA set (1200 drugs)

Personalized treatment recommendations by the multidisciplinary tumor board

Why use flies?

-- sophisticated genetics

-- conserved epithelia

-- conserved pathways

-- conserved drug activity

-- speed, scale, low cost

-- *in vivo* drug screens

Thank you…

First generation models

Cagan Laboratory

Alex Teague
Jess Esernio

Xenografts:

Greg Carbonetti
Elisa de Stanchina, Ph.D.

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Mouse Models:

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