## Functional exploration of human cancer genomes using flies

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Center for Personalized Cancer Therapeutics (CPCT) Icahn School of Medicine at Mount Sinai, New York NY, USA Cancer is a complex, multigenic disease

Normal epithelial cell



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

Metastatic tumor cell

### Genomic landscape of colorectal cancer

--~30 colorectal cancer drivers

-- recurrently mutated in colon tumors

-- backed by functional evidence

## Genomic landscape of colorectal cancer

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### Genomic landscape of colorectal cancer

Recurrent mutations i	<u>n 5 pathways</u>	In flies:
Wnt	(92%)	apc <sup>IR</sup>
Ras/MAPK	(63%)	dRas <sup>G12V</sup> , dEGFR
PI3K	(57%)	pten <sup>IR</sup>
TGF-β	(77%)	dSmad4 <sup>IR</sup>
TP53	(74%)	p53 <sup>IR</sup>

#### TCGA patients sorted by pathway deregulation status



## Modeling the complexity of human colon tumors in Drosophila

195 colon tumor genomes from the TCGA







## 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!



# Dissemination to distant sites as a readout for drug response



# Intrinsic drug resistance is an emergent property of genetically complex models



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



- -- 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

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## **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.

Antitumor Assessment Core Facility Sloan Kettering Cancer Institute NY

#### Mouse Models:

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