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

- Head and neck
- RCC
- Ovarian
- Breast
- Multiple Myeloma
- HCC
- CLL
- Prostate
- Colorectal
- MDS
- NSCLC

- 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

Ret (MEN2B)
Fly Identification, Validation of Caprelsa

wild type

Vidal, Can Res 2005
Fly Identification, Validation of Caprelsa

wild type
Ret(MEN2B)
Ret(MEN2B) + ZD6474

Vidal, Can Res 2005
Fly Identification, Validation of Caprelsa

Massimo Santoro, Sam Wells

“Caprelsa”

Vidal, Can Res 2005
Epigenetic Regulation: Sin3a Opposes Transformation

Ret(MEN2B) wild type

Epigenetic Regulation: Sin3a Opposes Transformation

Read, MCB 2005
Vidal, Dev Cell 2006
Das, in press
Epigenetic Regulation: Sin3a Opposes Transformation

Wild type

Ret → Ras, Pi3k, Src → E-Cad, Jnk, casp’s, actin-r, EMMPs

Sin3a

Read, MCB 2005
Vidal, Dev Cell 2006
Das, in press
Epigenetic Regulation: Sin3a Opposes Transformation

Read, MCB 2005
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Epigenetic Regulation: Sin3a Opposes Transformation

- Ret
- Pi3k Ras Src
- E-Cad
- Jnk casp’s actin-r
- EMT MMPs
- Sin3a
- Ras Akt
- Csk
- Mkk4
- Rac1, Rho1 RhoGAPs RhoGEFs

Read, MCB 2005
Vidal, Dev Cell 2006
Das, in press
Fly Approach to Novel Kinase Inhibitors

Combined flies, *in vitro* data to ‘predict’ better drugs

% survive to pupa  % survive to adult

$Ret^{MEN2B}$

+ Ret Inhib.
Fly Approach to Novel Kinase Inhibitors

Combined flies, in vitro data to ‘predict’ better drugs

Ret^{MEN2B} + Ret Inhib. + AD1 + AD2 + AD3

% survive to pupa % survive to adult
Fly Approach to Novel Kinase Inhibitors

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% survive to pupa  % survive to adult

Ret<sup>MEN2B</sup> + Ret Inhib. + AD1 + AD2 + AD3

Chemical structures and graphs illustrating the survival rates of flies with and without inhibitors.
Fly Approach to Novel Kinase Inhibitors

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**Genetic modifier screen**

- Ret
- Ras → PI3K
- Raf → mTor → Src
- Proliferation → Metastasis

<table>
<thead>
<tr>
<th>Ret&lt;sup&gt;MEN2B&lt;/sup&gt;</th>
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- Ras, PI3K, Raf, mTor, Src

- Proliferation vs. Metastasis
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**In vitro kinase assays comparing inhibitors**

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Combined flies, *in vitro* data to ‘predict’ better drugs

**in vitro** kinase assays
comparing inhibitors

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% survive to pupa  % survive to adult

- \[\text{Ret}^{\text{MEN2B}}\] + Ret Inhib.
- \(\text{erk}^{+/-}\) + AD1
- \(\text{erk}^{+/-}\) + AD2
- + AD3
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Combined flies, in vitro data to ‘predict’ better drugs

*in vitro* kinase assays comparing inhibitors

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% survive to pupa % survive to adult

- Ret\textsuperscript{MEN2B}
- + Ret Inhib.
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Fly Approach to Novel Kinase Inhibitors

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**in vitro kinase assays**

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% survive to pupa  % survive to adult

**Ret**

- + Ret Inhib.
- + AD1
- + AD1b
- + AD1c
AD1, AD1B show activity in mammalian MEN2 models

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

![Graph showing the activity of AD1, AD1B, and ZD6474 (caprelsa) at different drug concentrations.](Dar, Nature 2012)
AD1, AD1B show activity in mammalian MEN2 models

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

Median % change in tumor volume

- vehicle
- caprelsa
- AD1b

Dar, Nature 2012
AD1, AD1B show activity in mammalian MEN2 models

AD1, AD1b demonstrated low toxicity at therapeutic doses

![Graph showing weight (grams) over days of drug treatment]

- **Vehicle**
- **AD1b**
- **Caprelsa**

*Dar, Nature 2012*
Fly Approach to Novel Kinase Inhibitors
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$^{RNAi}$
- Med$^{RNAi}$ P53$^{RNAi}$ Pten$^{RNAi}$
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Quadruple combinations
- $Ras1^{V12}$ Pten$^{RNAi}$ Apc$^{RNAi}$ P53$^{RNAi}$
- $Ras1^{V12}$ Med$^{RNAi}$ Apc$^{RNAi}$ P53$^{RNAi}$
- EGFR$^{act}$ Med$^{RNAi}$ Apc$^{RNAi}$ P53$^{RNAi}$
Multigenic adult models

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- hyperproliferation
- multilayering
- EMT
- distant migration
- senescence
- apoptosis

Bangi, in revision
Multigenic adult models

- four-hit colorectal model
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Bangi, in revision
Multigenic adult models

four-hit colorectal model

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Bangi, in revision
Multigenic adult models

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\( ras^V12 \)

LY294002 (PI3K)
Wortmannin (PI3K)
SL327 (MEK)
PI103 (MEK)
AZD6244 (MEK)
GW5074 (Raf)
Dasatinib (Src/Abl)
SP600125 (JNK)
Rapamycin (mTor)
BEZ235 (PI3K+mTor)
Enzastaurin (PKC\(\beta\))
LBH589 (HDAC)
Bortezomib (proteosome)

\( ras^V12 \ p53^{RNAi} \ pten^{RNAi} \ apc^{RNAi} \)
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