A Teaching Affiliate
of Harvard Medical School

Dissecting Cross-resistance in Small Cell Lung Cancer

Benjamin Drapkin

Chabner Colloquium

November 18th, 2019

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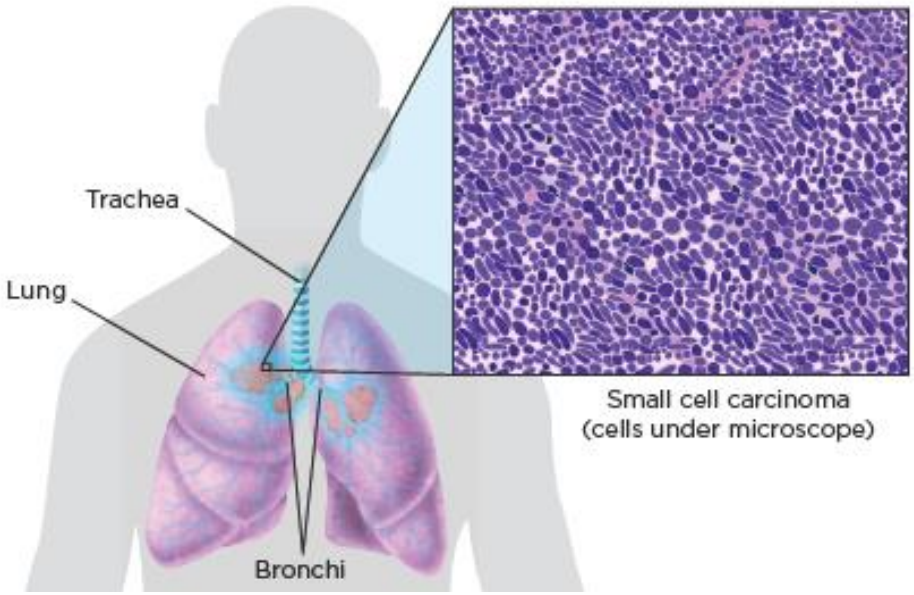
Systemic Therapy and Cross-Resistance in SCLC



- 240,000-300,000 cases annually world-wide.
- Usually metastatic at presentation.
- 9-11 month survival for metastatic disease.
- Only 1-2% resected (node-negative only).
- No clinical role for biopsy at relapse.

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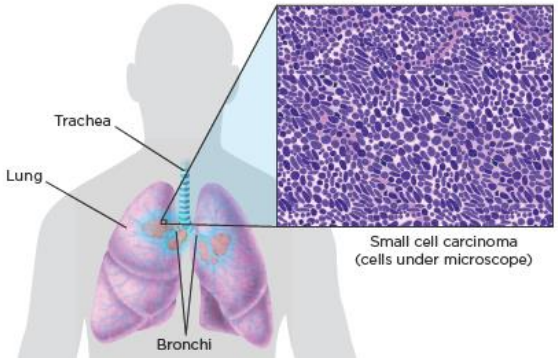
Systemic Therapy and Cross-Resistance in SCLC



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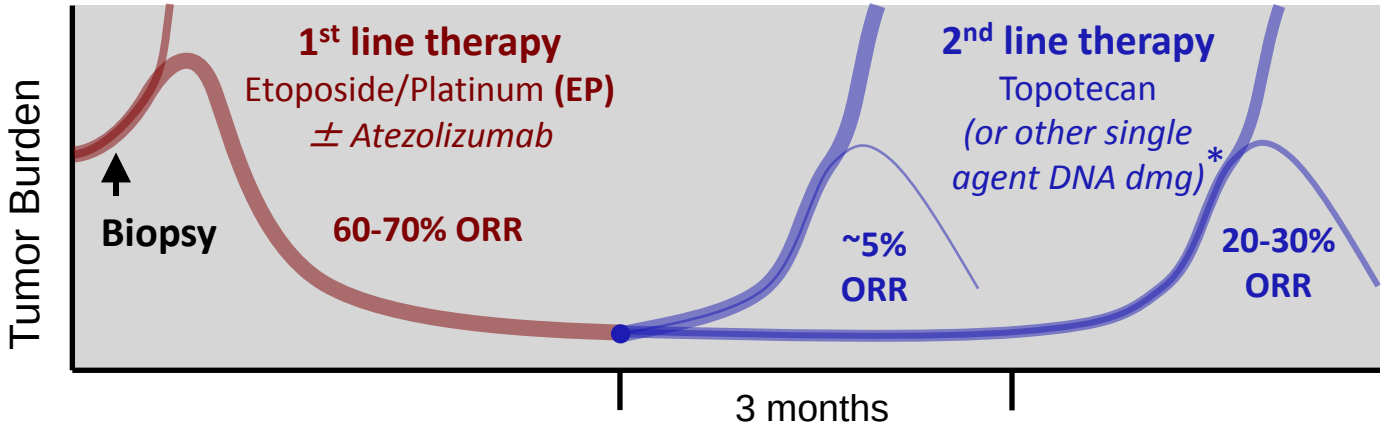

* **Other 2nd line:**
Irinotecan, TMZ, Gemcitabine, Ifosfamide, Vinorelbine, Taxanes

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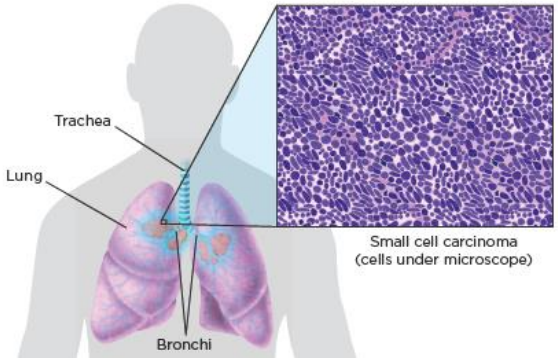
Systemic Therapy and Cross-Resistance in SCLC



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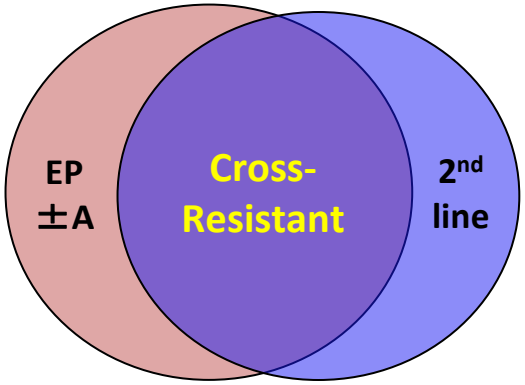
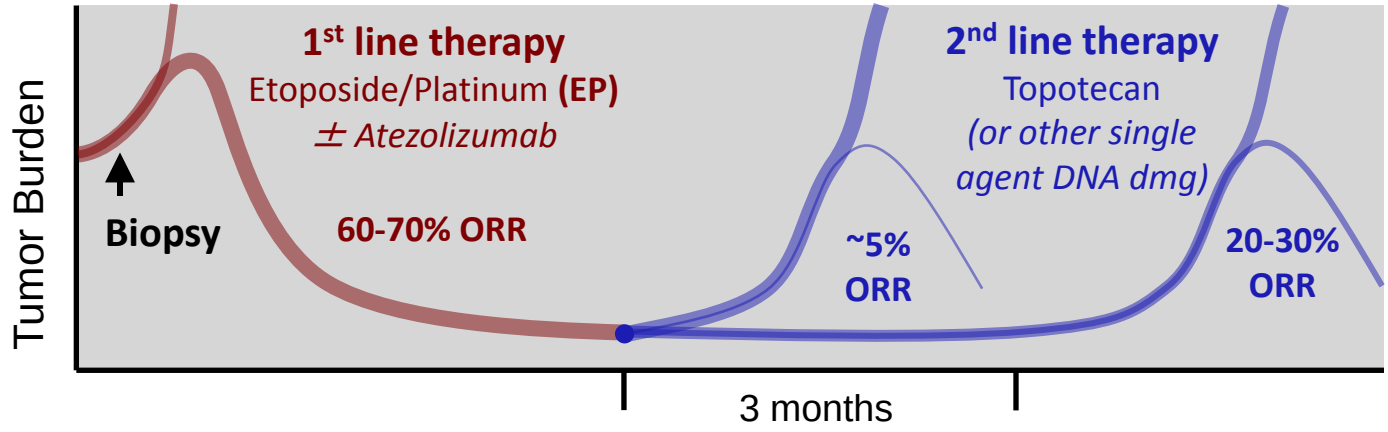


What makes SCLC tumors cross-resistant?

Model System Pre-Req's:

- Retain molecular features of SCLC in patients.
- Recapitulate clinical responses to DNA damaging regimens.
- Capture diversity of SCLC cases (inter-tumoral heterogeneity).



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SCLC patient-derived xenograft (PDX) project at MGH

MGH Main Campus

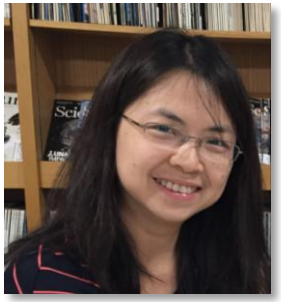
Anna Farago

Mustafa Sakhi,
Vashine Kamesan,
Nikita Thareja

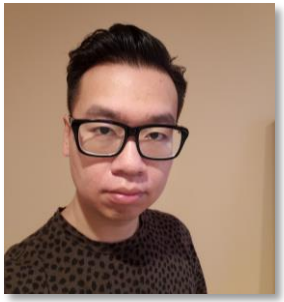
Charlestown Navy Yard

Nick Dyson

Marcello Stanzione

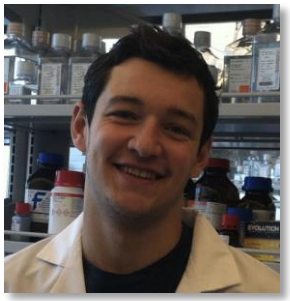


Jun Zhong



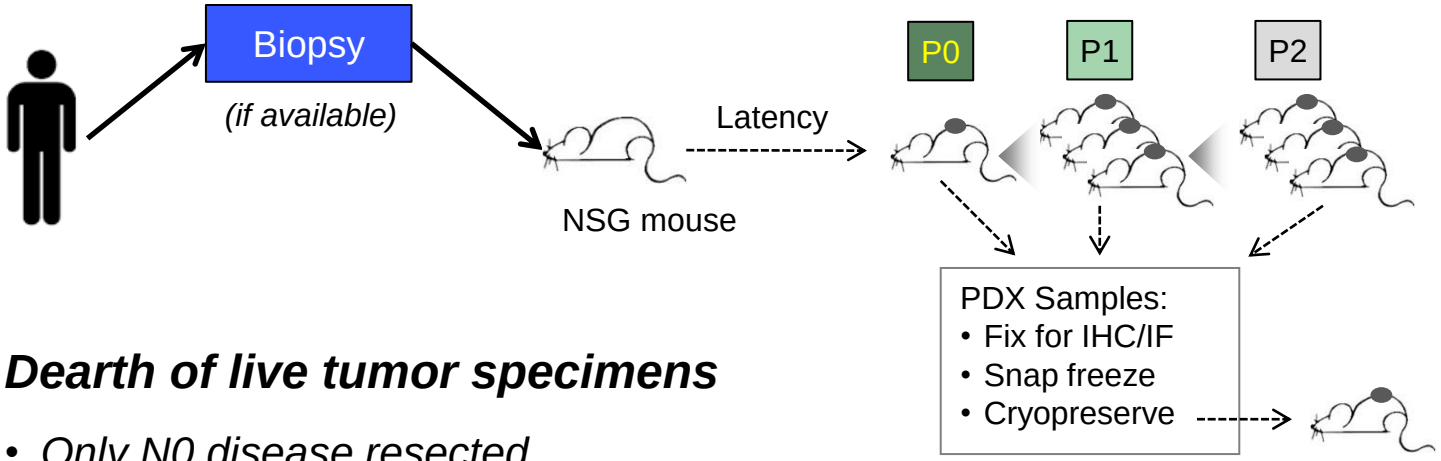
Edmond Wong

Sarah Phat



David Myers

Approach to SCLC PDX development



Dearth of live tumor specimens

- *Only N0 disease resected*
- *No clinical role for re-biopsy*

1. Hann et al., Cancer Res 2008

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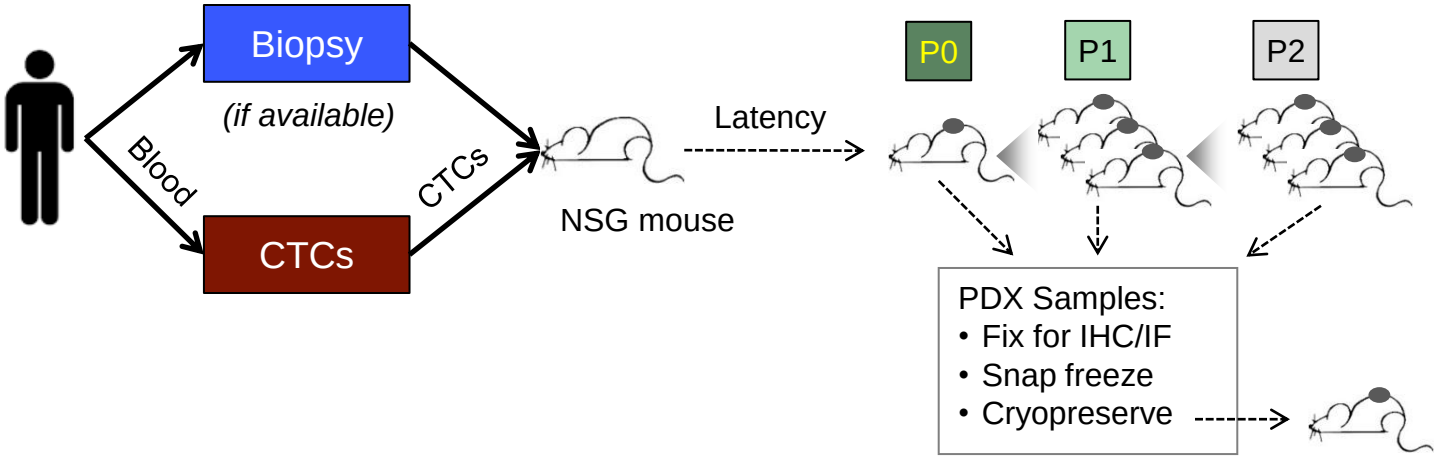
Approach to SCLC PDX development



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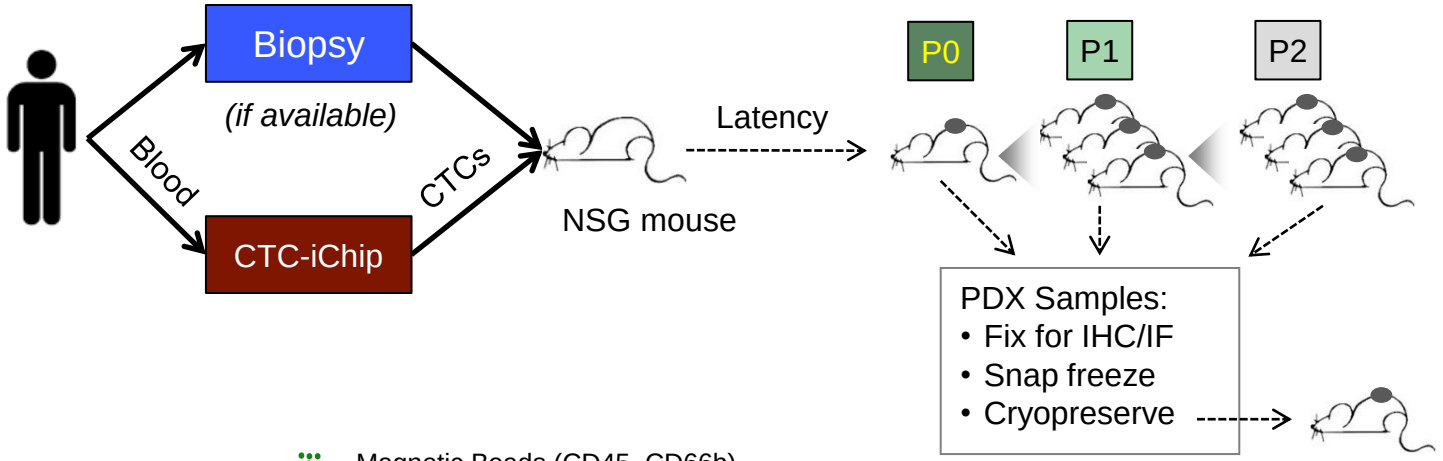

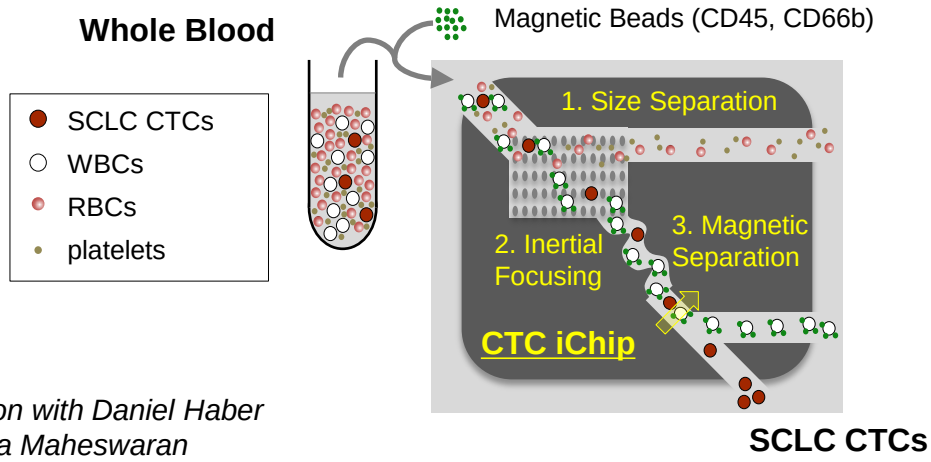

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In collaboration with Daniel Haber and Shyamala Maheswaran

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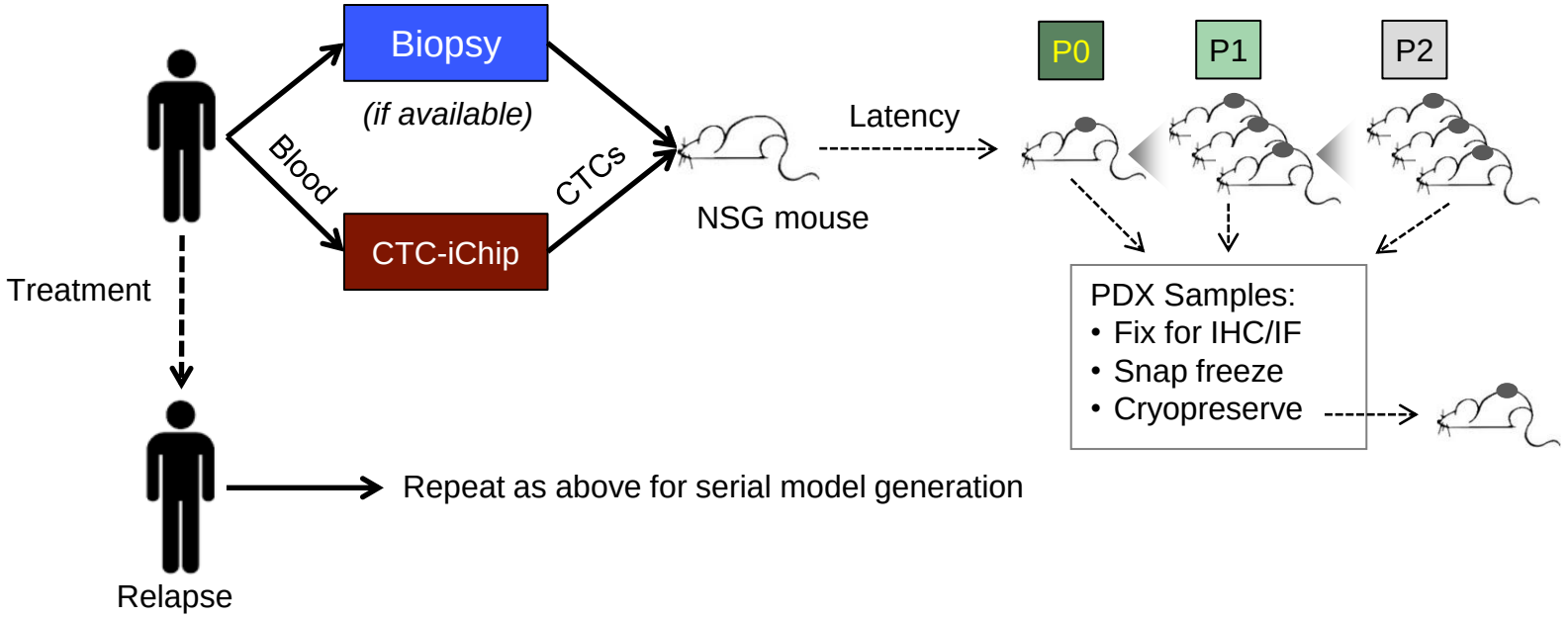

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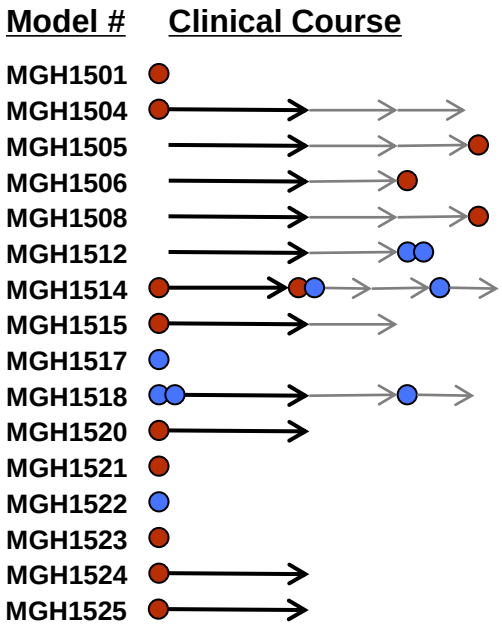
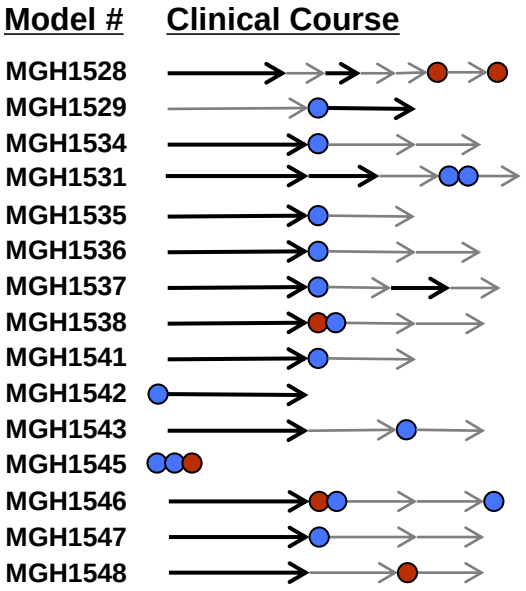
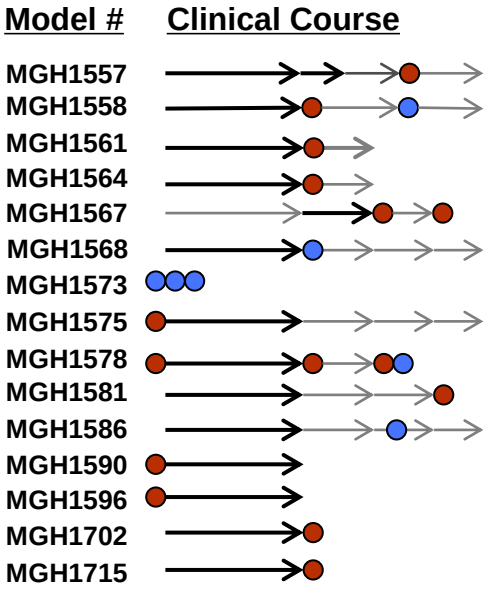
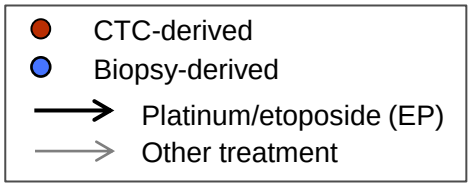
Library of SCLC PDX models









PDX Take Rate (per attempt, monitored 1 year)	
CTC (iChip)	**35%**
Biopsy or Effusion	**86%**

Intertumoral Heterogeneity

66 SCLC PDX models from 46 patients, initiated June 2014 – Dec. 2018

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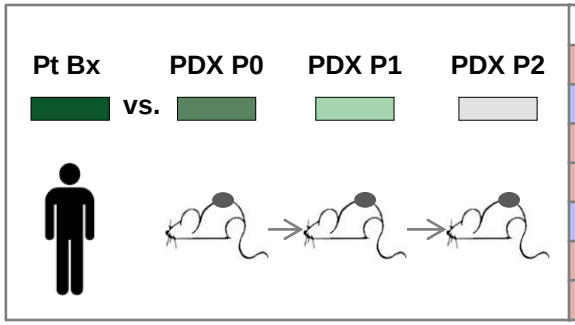
Genomic fidelity of PDX models



Model	Source
MGH1504-1	CTC
MGH1512-1	biopsy
MGH1514-1	CTC
MGH1515-1	CTC
MGH1518-1	biopsy
MGH1525-1	CTC
MGH1528-1	CTC

Whole exome sequencing comparison of patient vs. PDX

- 7 matched PDX models
  - 2 biopsy-derived
  - 5 CTC-derived
- 3 genomes per model
  - Patient tumor biopsy (**Pt Bx**)
  - Initial PDX (**PDX P0**)
  - PDX after two passages (**PDX P2**)

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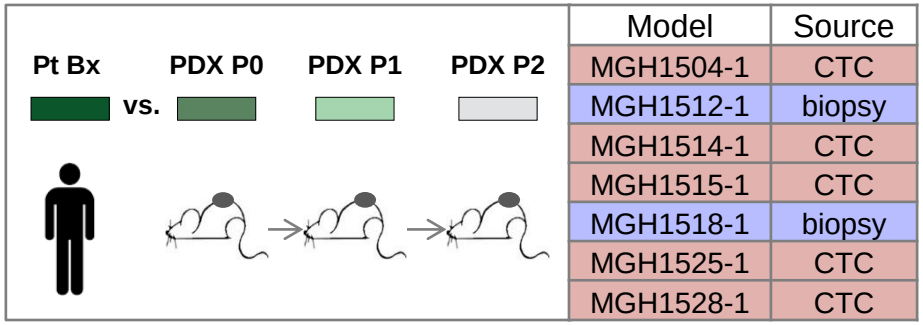

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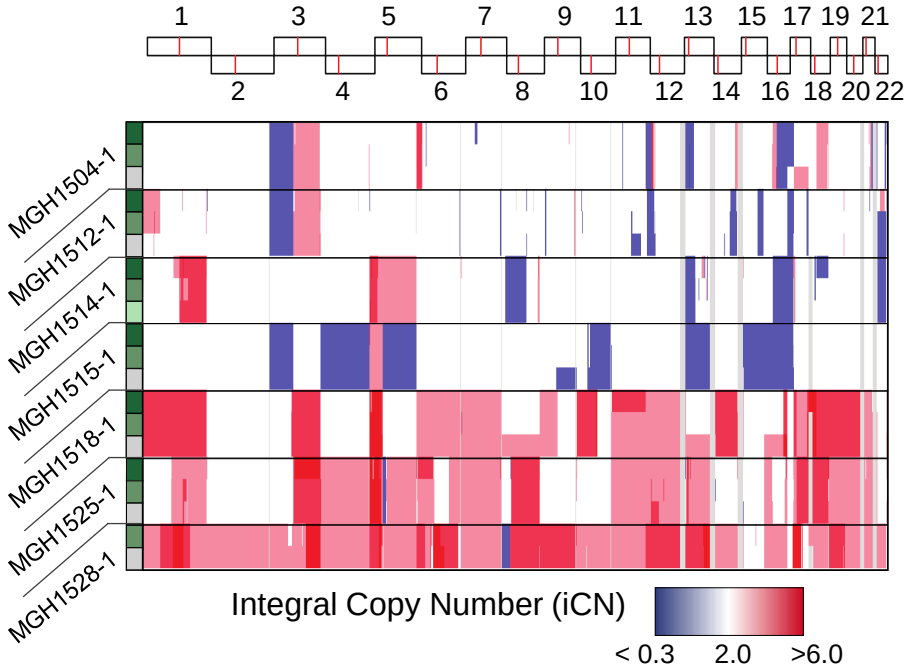

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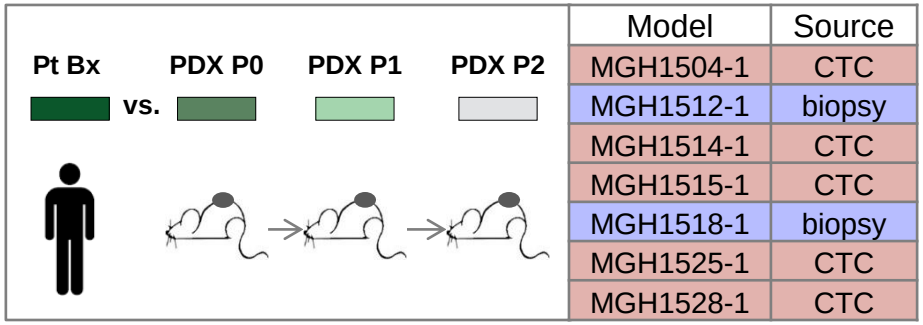

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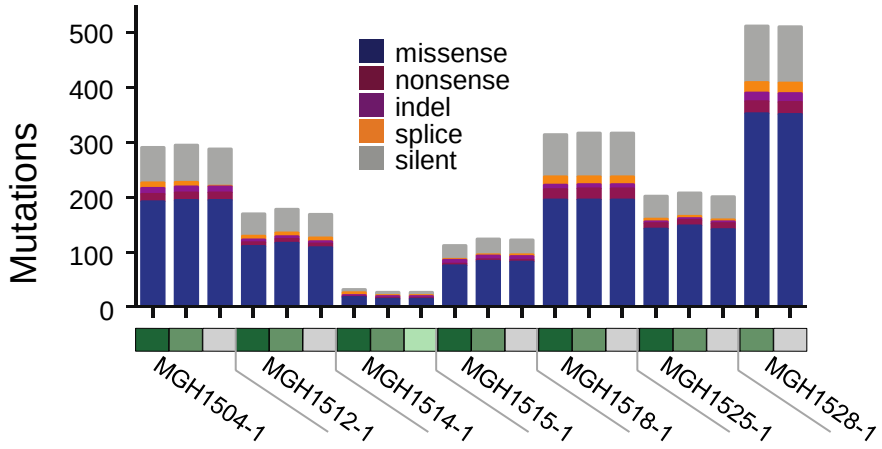

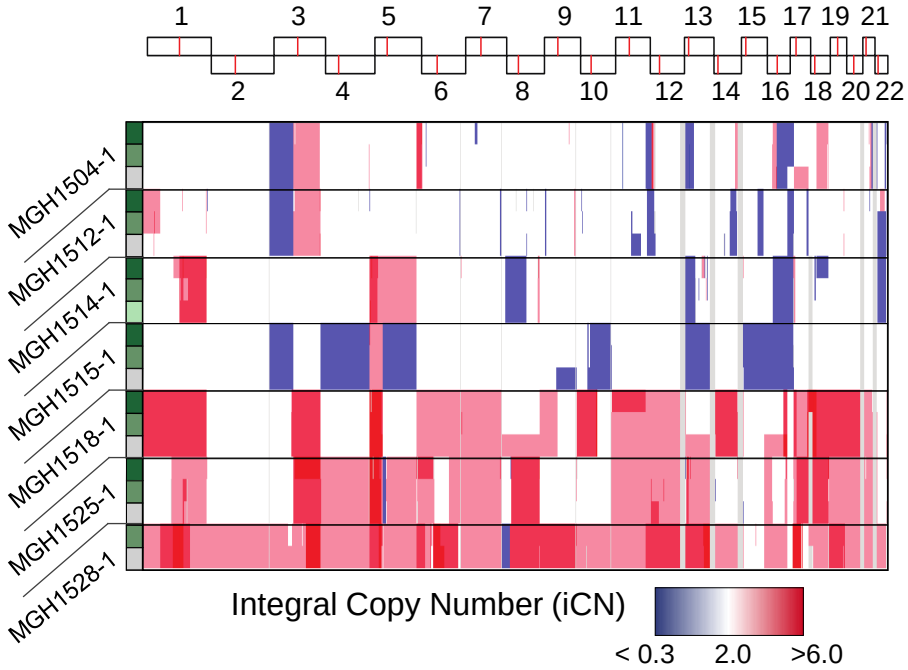

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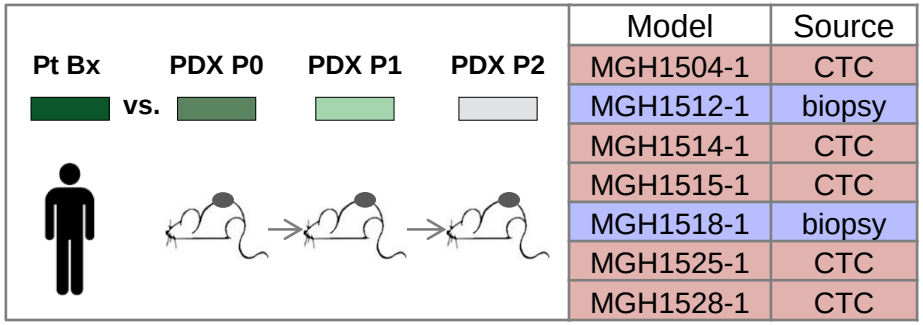

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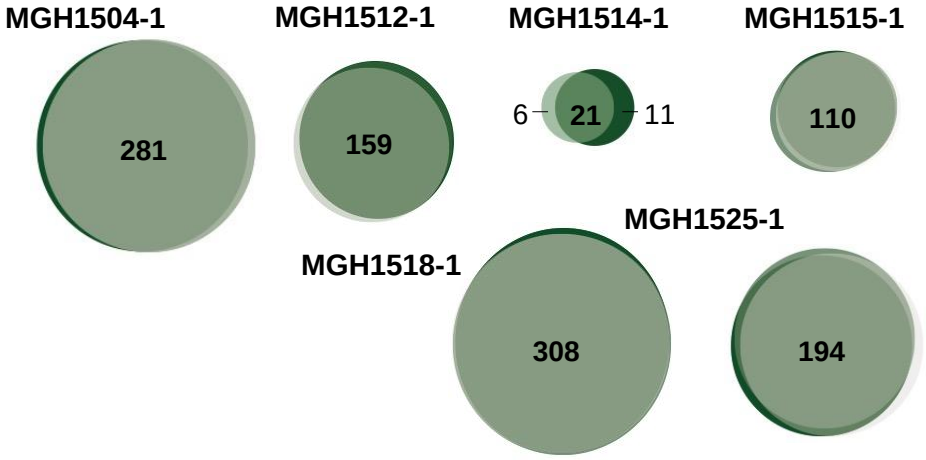

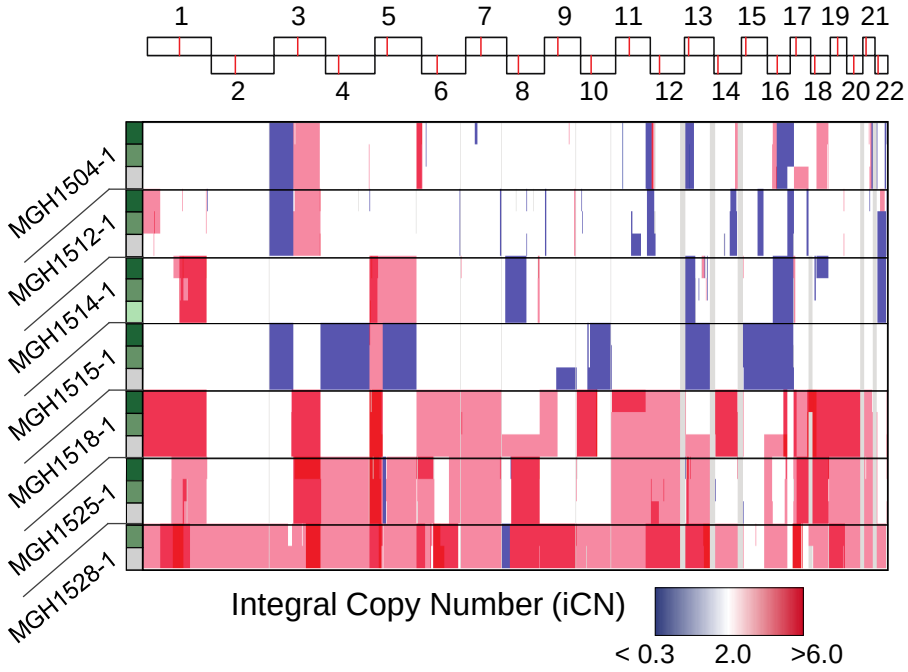

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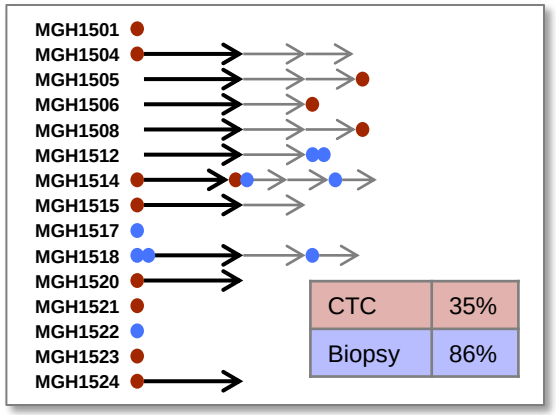
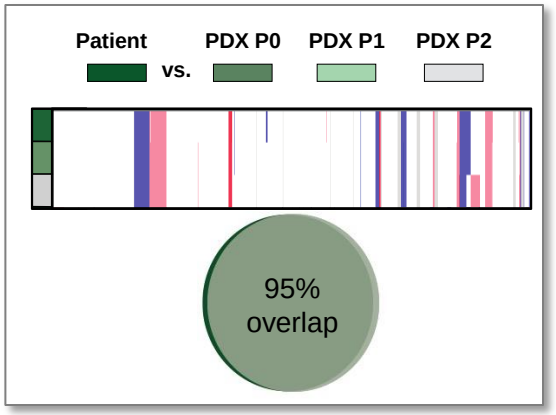
Summary of SCLC PDX system





1. Intertumoral Heterogeneity: 66 PDX models biopsies, effusions and CTCs
2. Genomic Fidelity: alterations retained, and few changes with passaging

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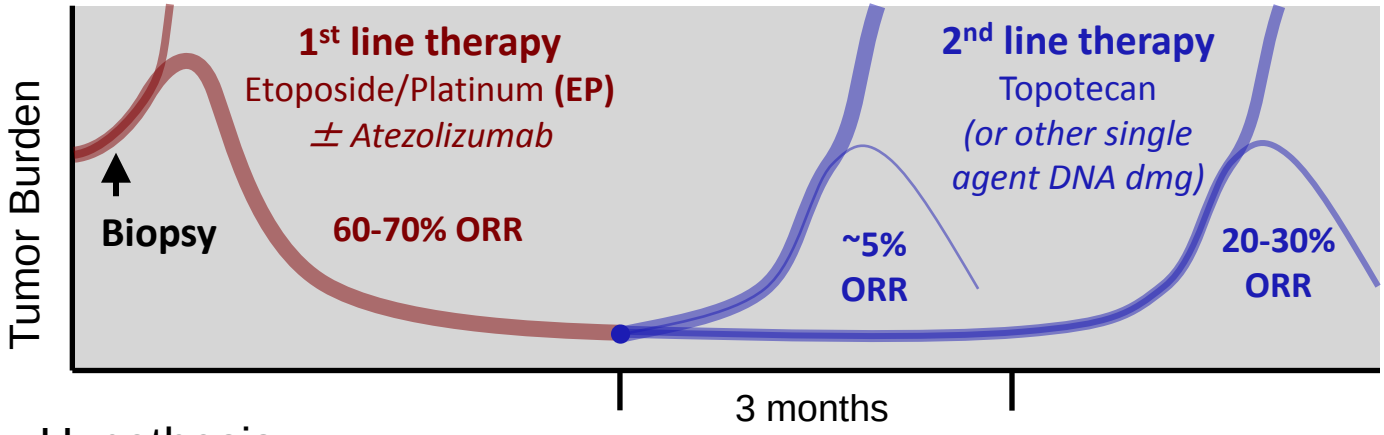
SCLC PDX Trial of Cisplatin/Etoposide (EP)



Hypothesis:

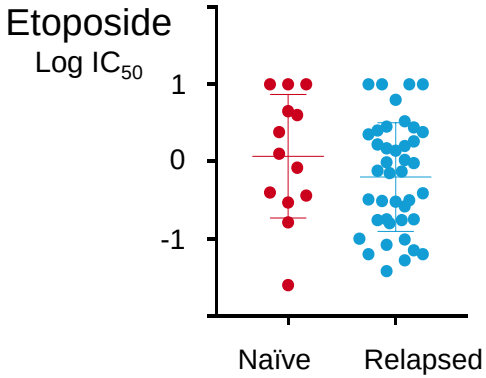
If PDX models of SCLC faithfully capture clinical response to EP,

then models derived before EP should be more sensitive than models derived after.

SCLC Cell Line Patient Treatment Hx.

- Chemo-naïve
- Post-relapse

Polley et al., JNCI 2016



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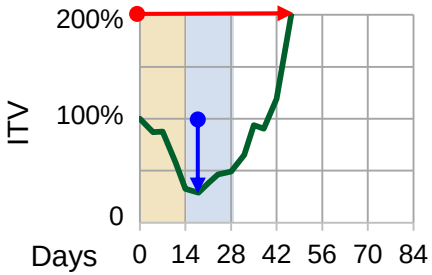
SCLC PDX Trial of Cisplatin/Etoposide (EP)

Tumor Metrics



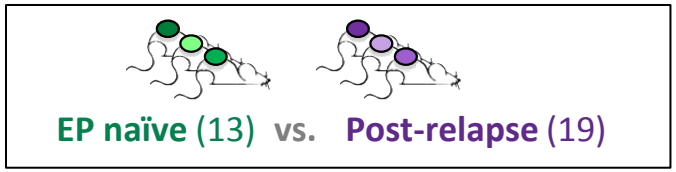
Treatment

Response

Best Response
(% initial tumor volume)

Time to Progression (TTP)
(2x ITV)

32 model panel
treated with EP:



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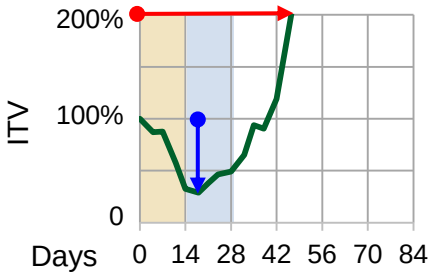
SCLC PDX sensitivity to Platinum + Etoposide (EP) reflects patient treatment history

Tumor Metrics



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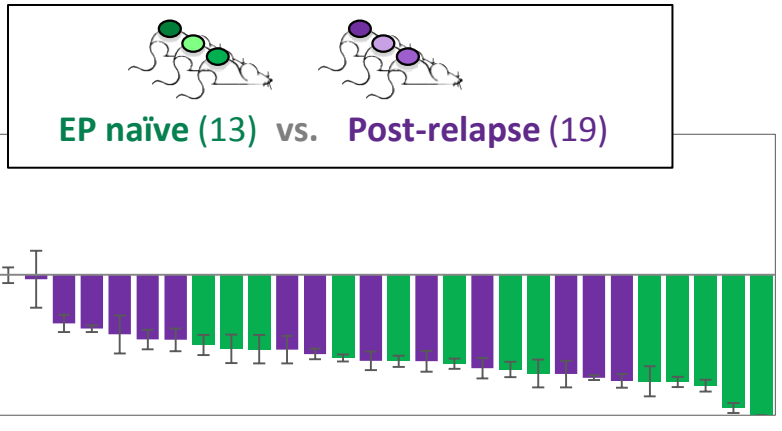

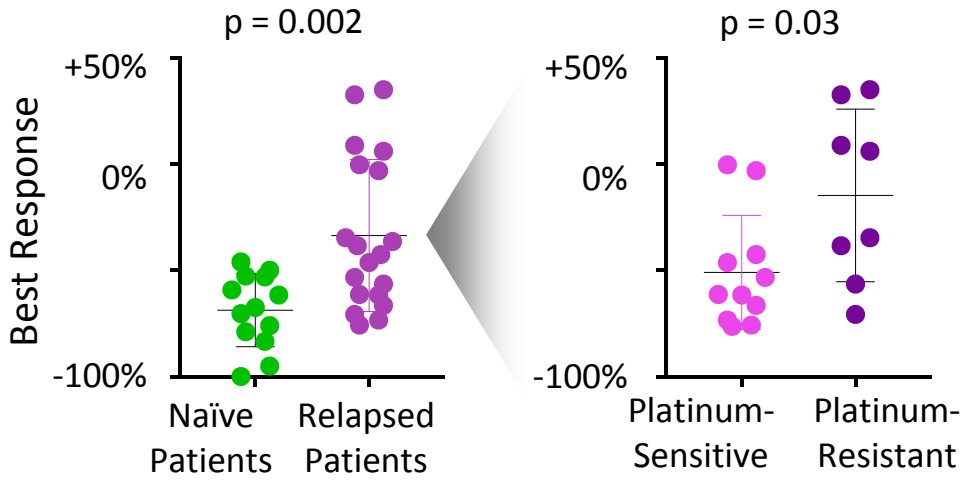

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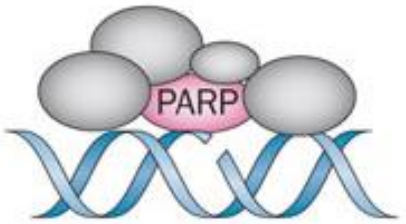
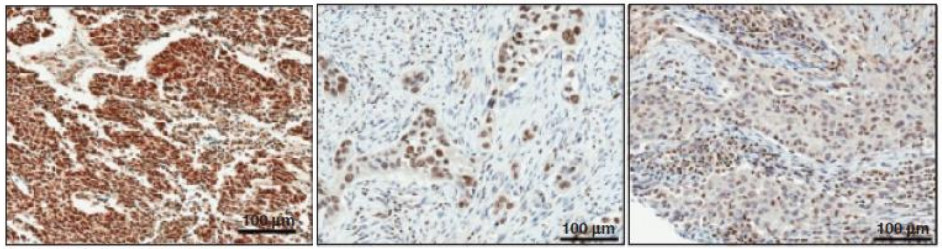
Olaparib + temozolomide (OT) in relapsed SCLC



PARP1 IHC



Byers et al., Cancer Discovery 2012

Rationale for combination

- High PARP1 expression in SCLC (see IHC figure)
- Sensitivity to PARP inhibitors *in vitro*
- Sensitivity to DNA alkylating agents
- OT synergy *in vitro* in multiple tumor models

Sonnenblick et al., 2015
Byers et al., 2012
Cardnell et al., 2013
Stewart et al., 2017
George et al., 2015
Lok et al., 2016
Hopkins et al., 2015
Murai et al., 2014
Pietanza et al., 2012

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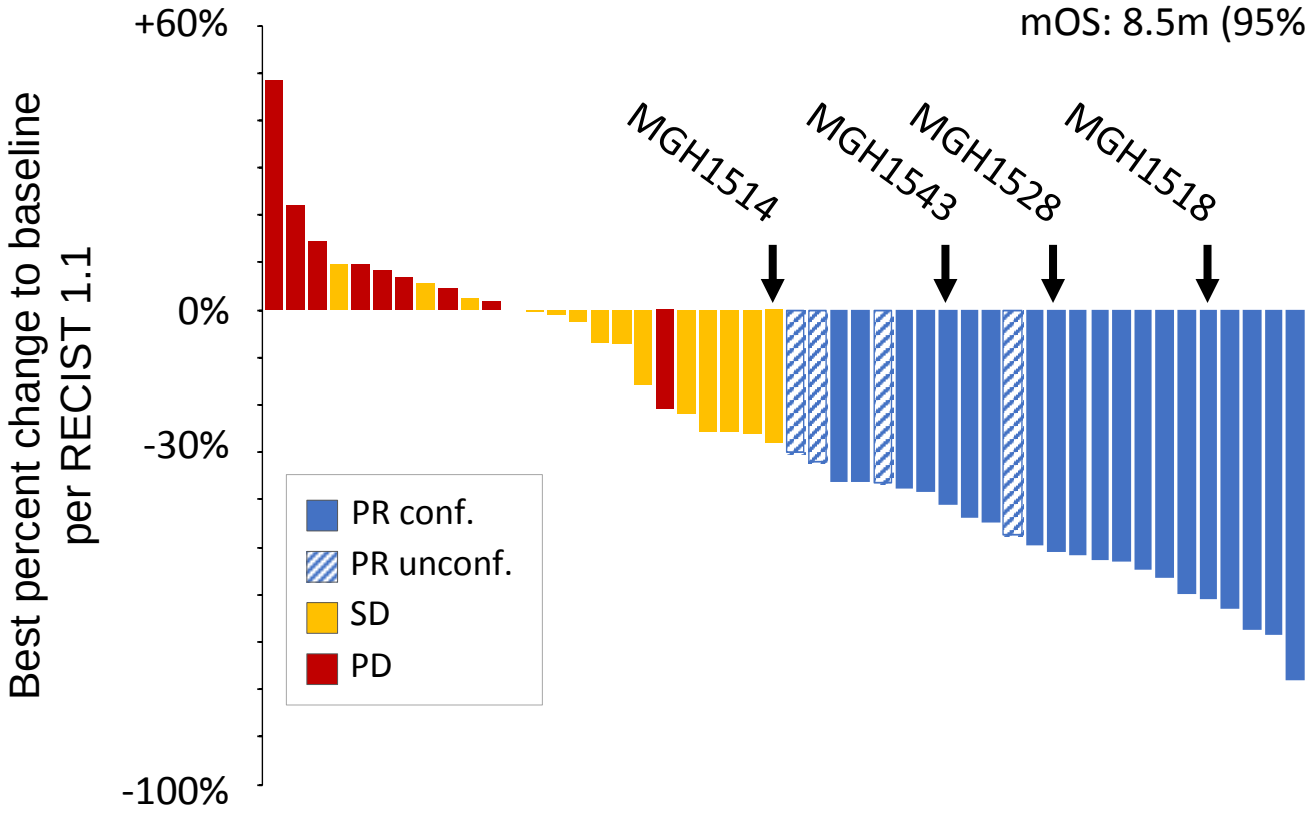
Phase I/II trial of Olaparib/Temozolomide in relapsed SCLC

48 patients with evaluable response
ORR: 41.7%
mPFS: 4.2 mo (95% CI 2.8-5.7)
mOS: 8.5m (95% CI 5.1-11.3)



Anna Farago

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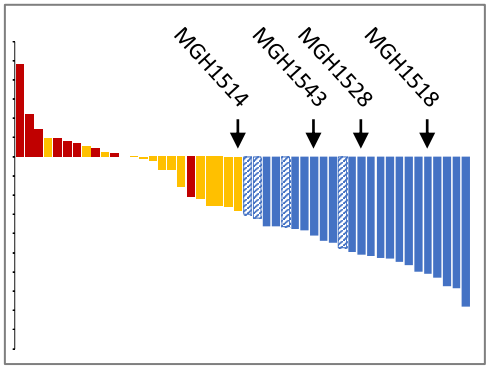
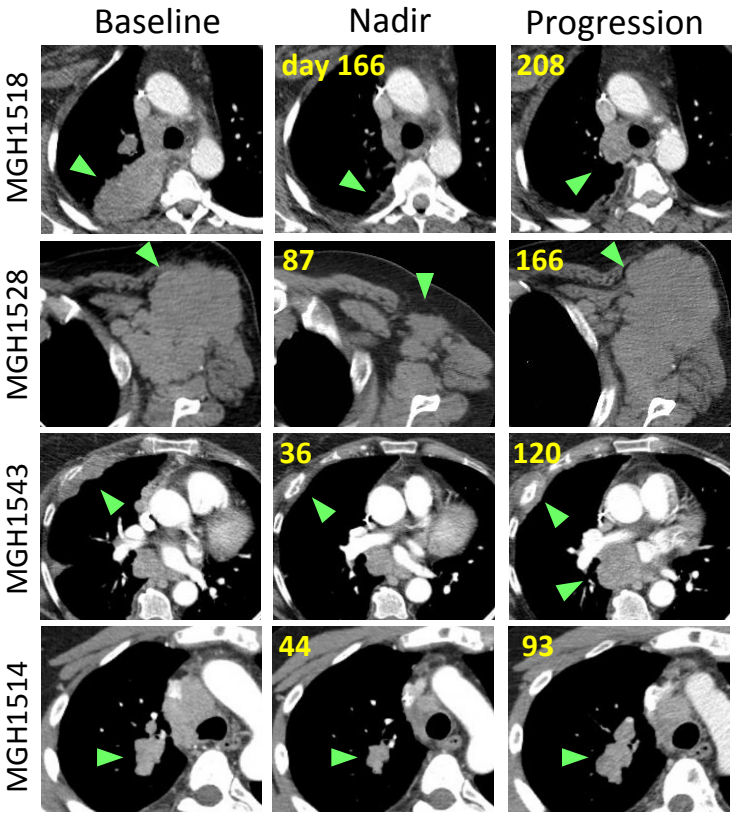
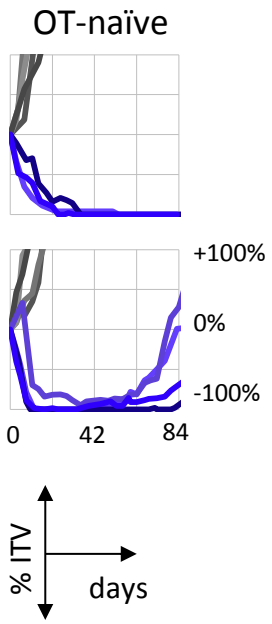
PDX models from OT trial patients recapitulate clinical response and resistance



2 OT-naïve PR models





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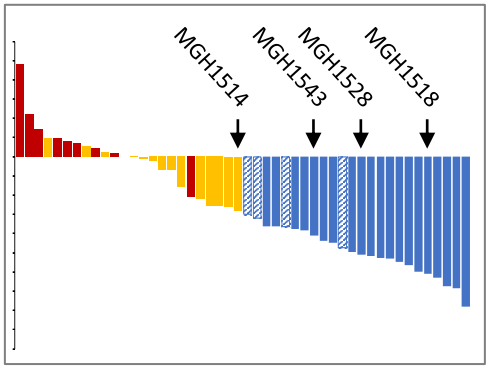
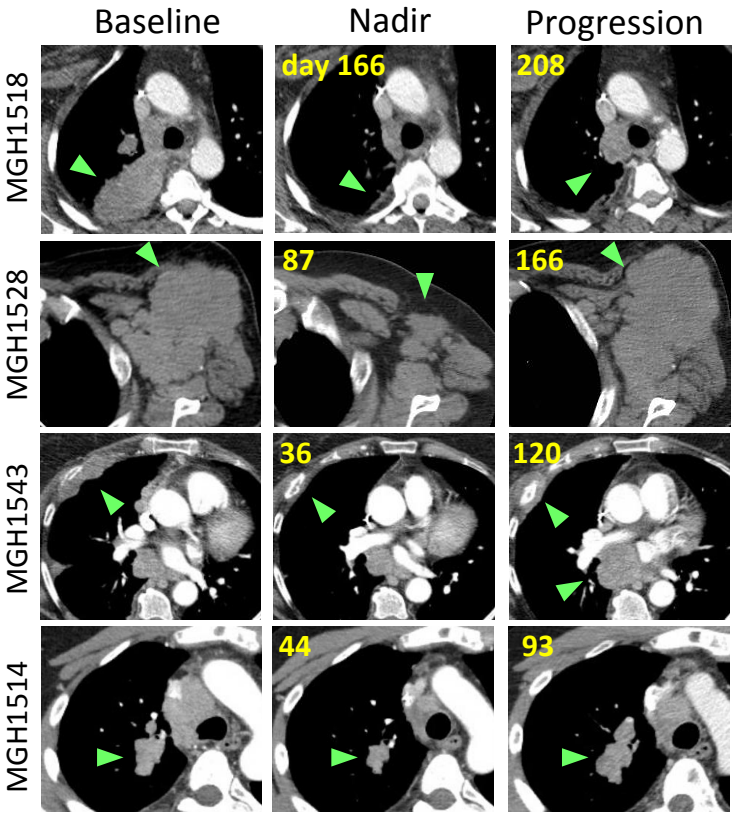
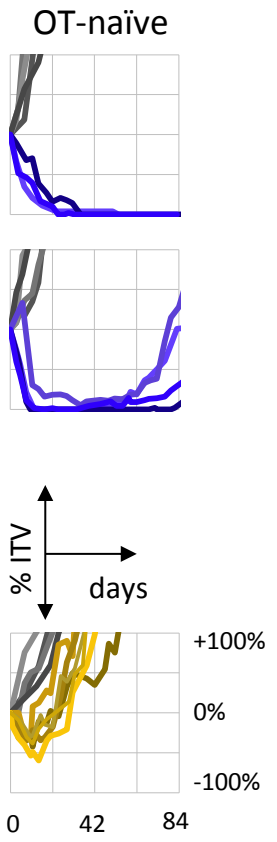
PDX models from OT trial patients recapitulate clinical response and resistance



2 OT-naïve PR models

1 OT-naïve SD model





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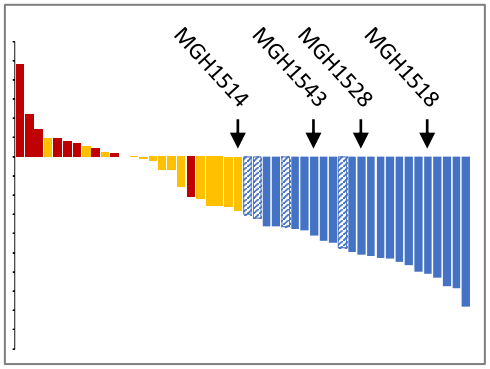
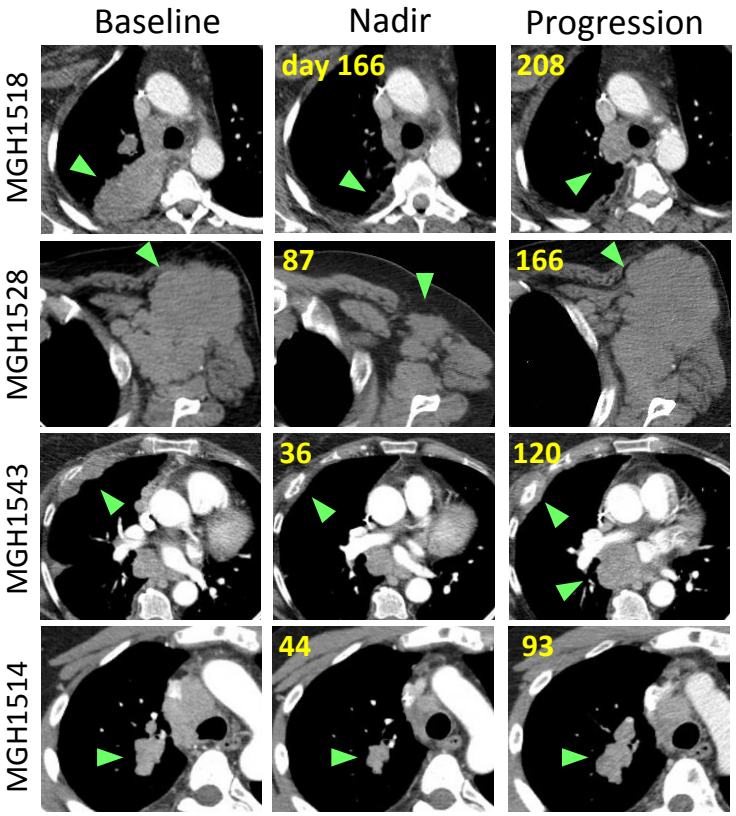
PDX models from OT trial patients recapitulate clinical response and resistance

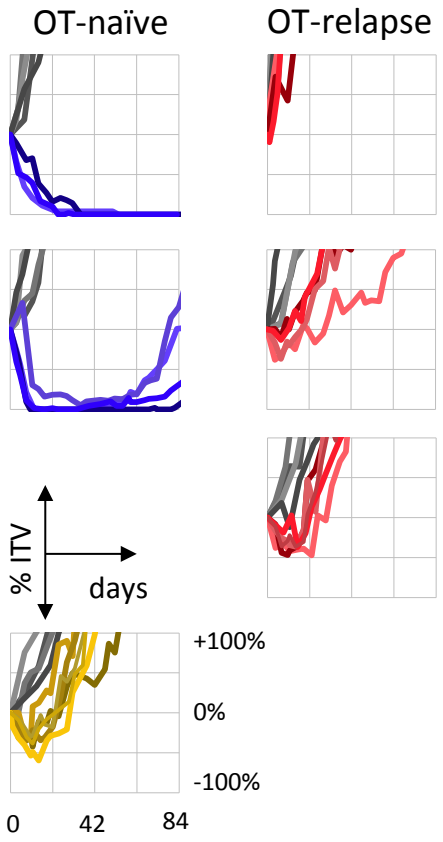


2 OT-naïve PR models

1 OT-naïve SD model

3 OT-relapse models
including 2 serial models





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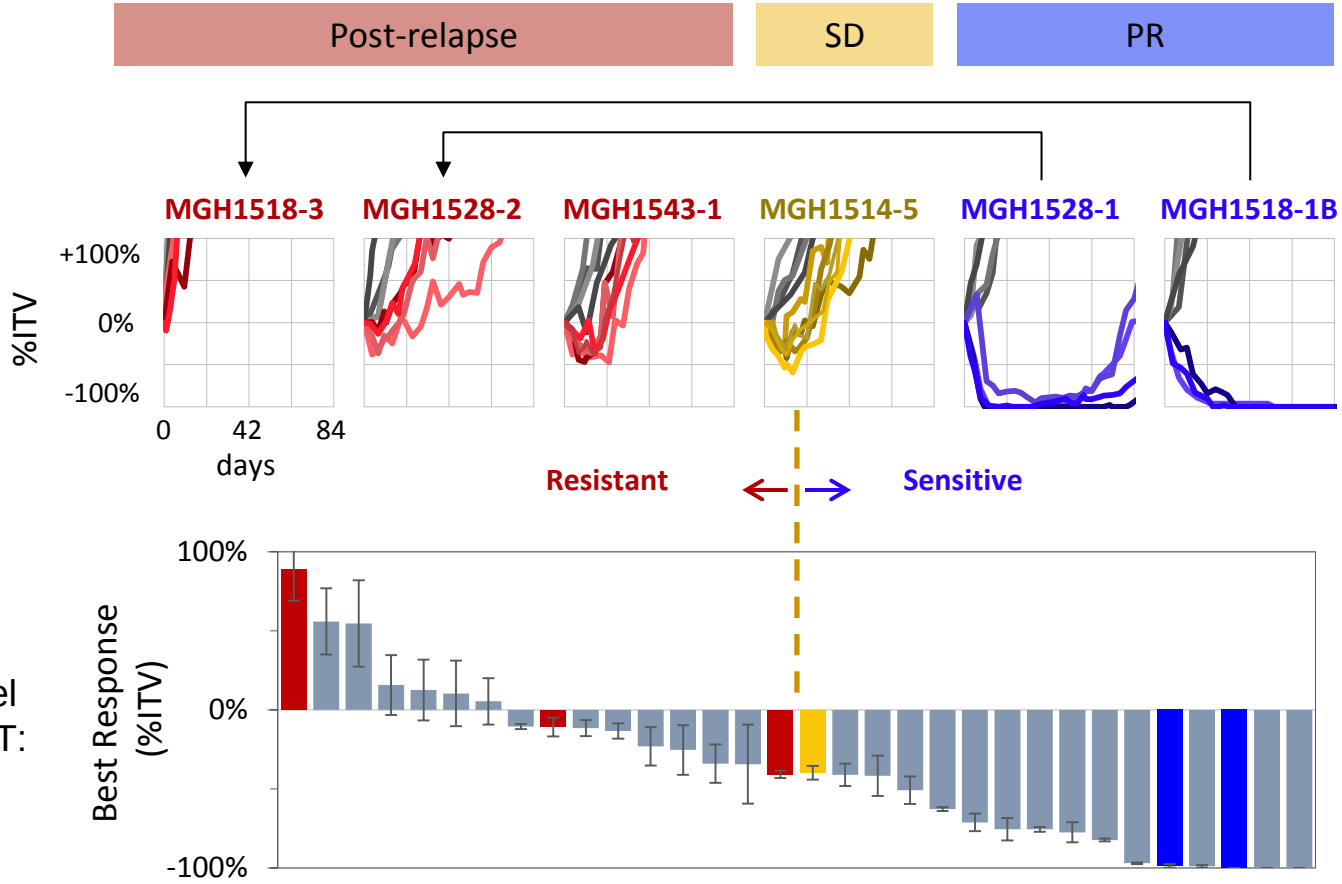
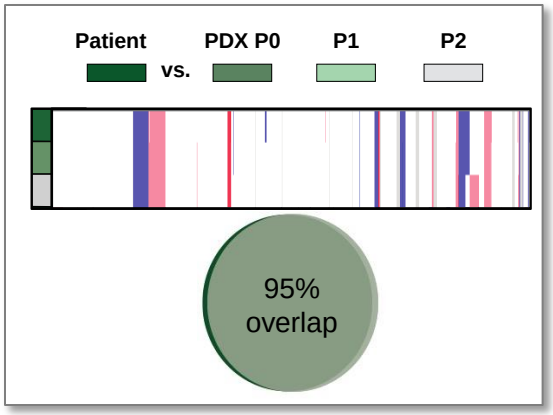
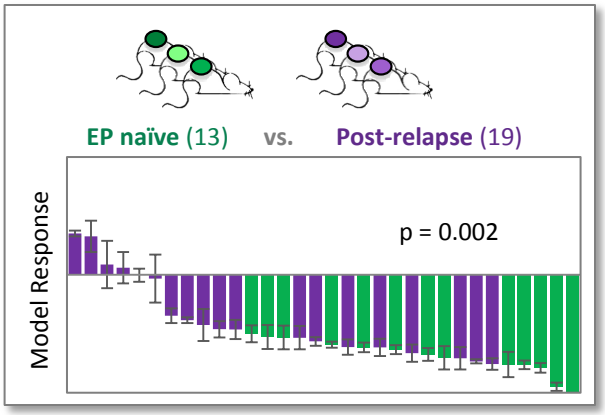
PDX models of OT trial patients define co-clinical trial response categories

32 model panel treated with OT:



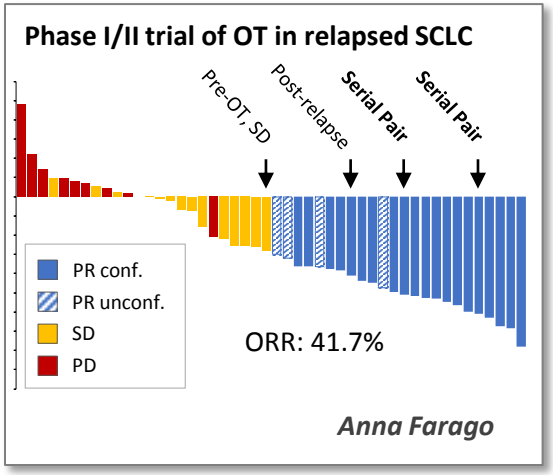
Molecular and functional fidelity of SCLC PDX models to their corresponding patients

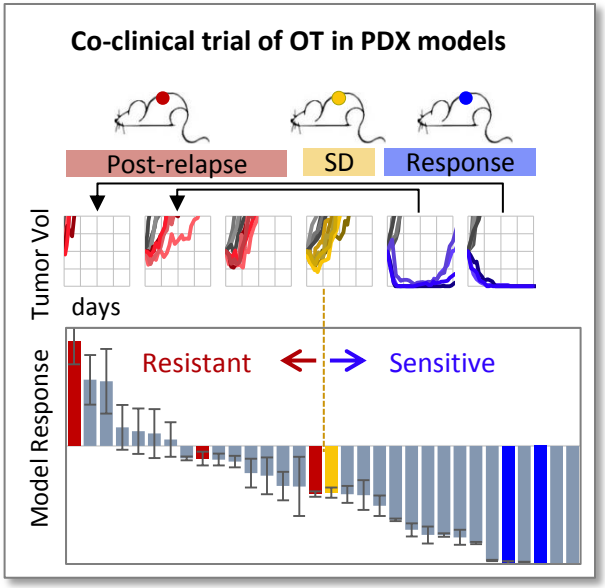




- Genomic alterations are retained from patients, and stable with passaging.
- PDX sensitivities to first-line cisplatin/etoposide (**EP**) reflect clinical history.

Drapkin et al., Cancer Disc. 2018





- Olaparib/Temozolomide (**OT**) is active in SCLC following relapse.
- PDX models derived from OT trial patients recapitulate OT sensitivity.
- These trial patient models can be used to divide panel into sensitive and resistant cohorts.

Farago et al., Cancer Disc. 2019

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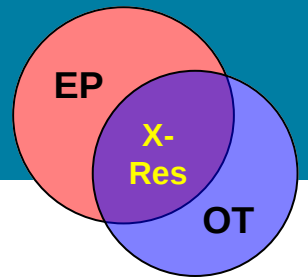
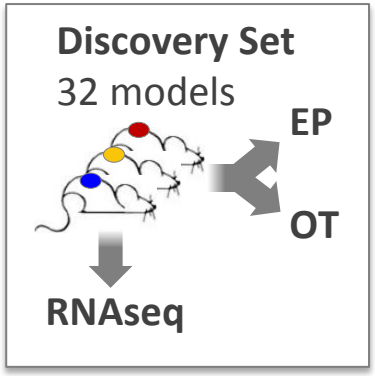
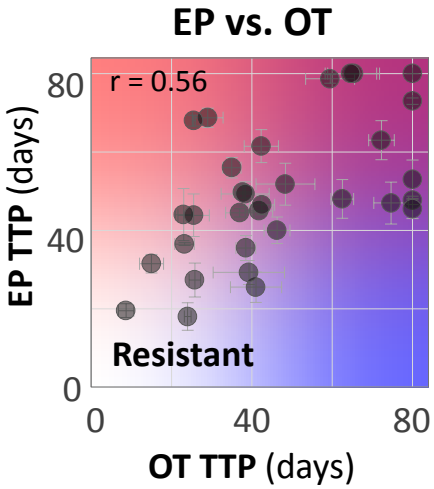
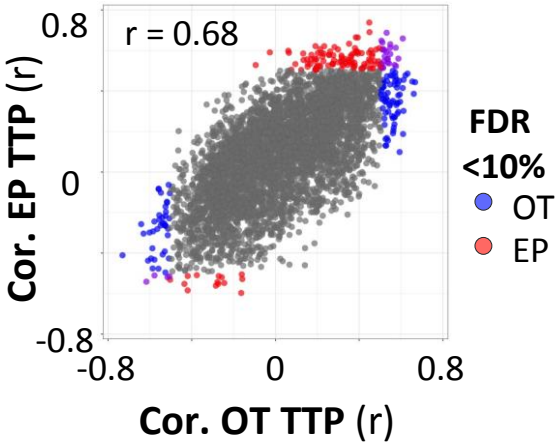
Transcriptional profiles of EP and OT sensitivity are highly correlated







Drug-gene expression: EP vs. OT



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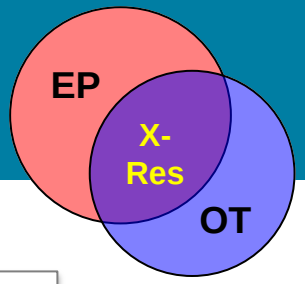
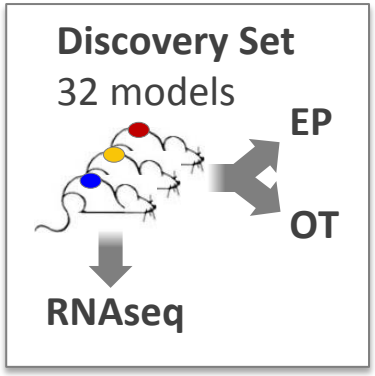
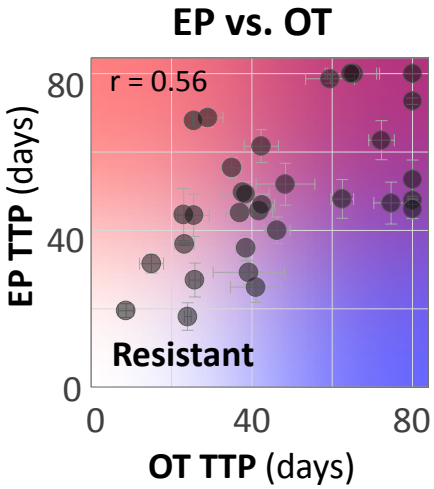
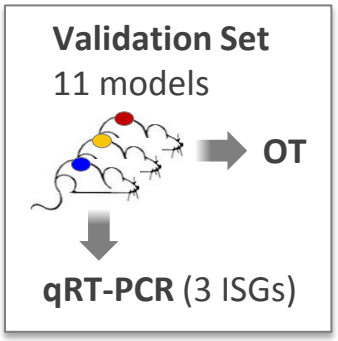
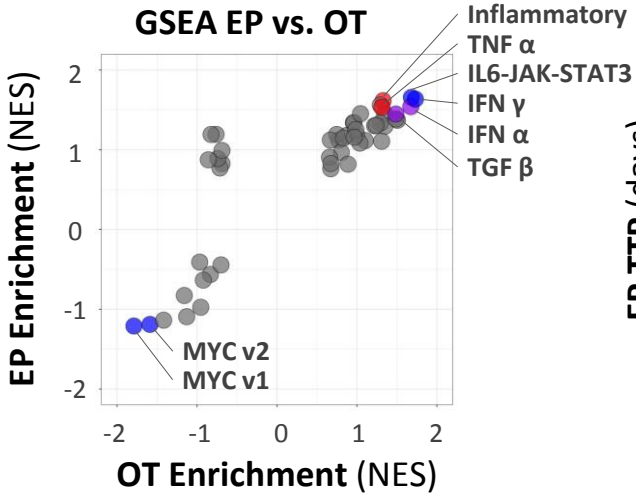
Low Basal Interferon-Stimulated Gene (ISG) expression marks EP/OT cross-resistance

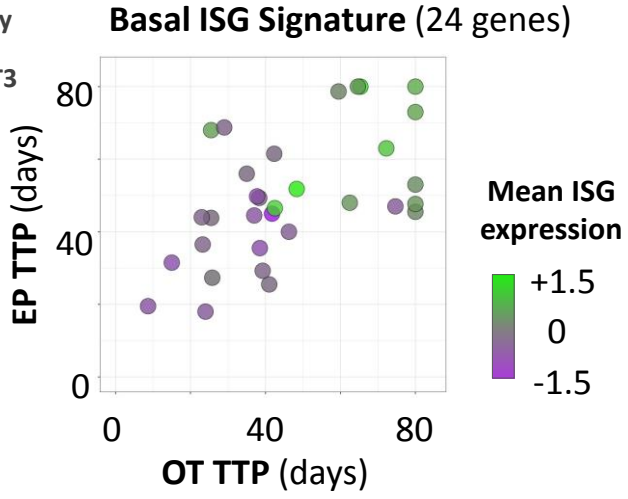


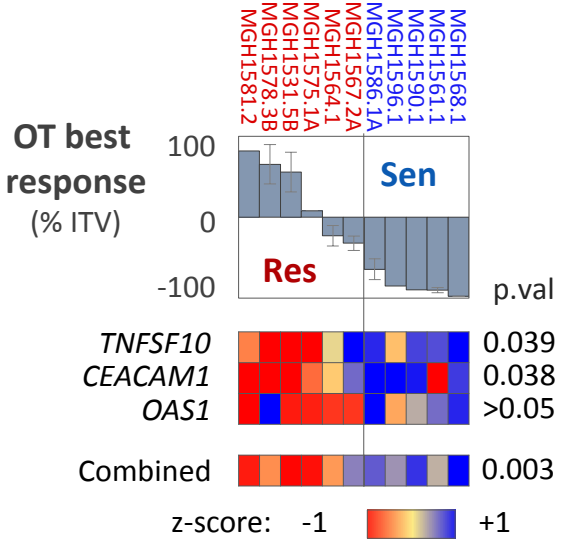












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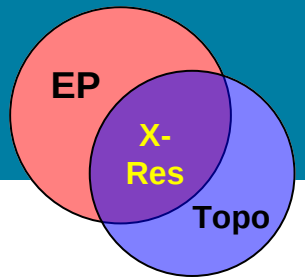
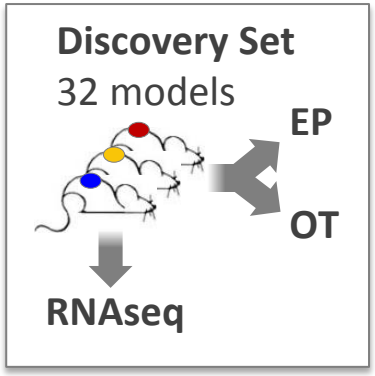
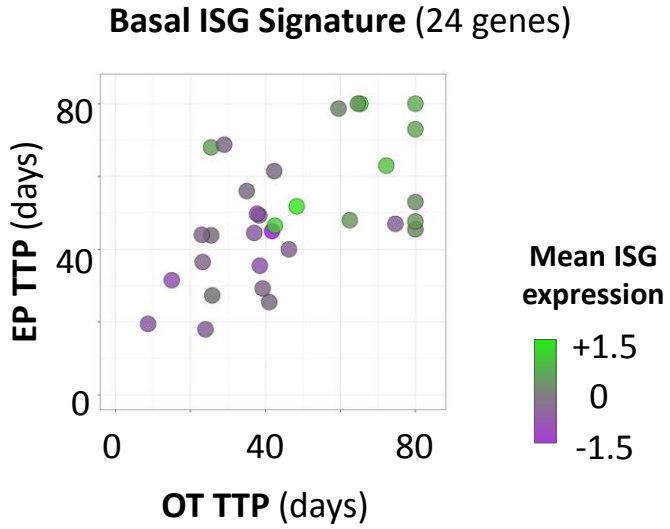
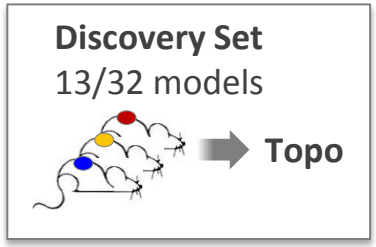
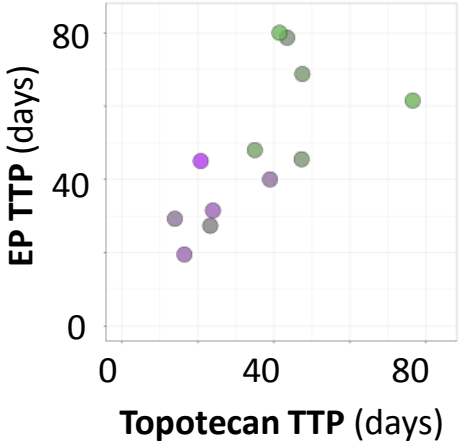
Low Basal Interferon-Stimulated Gene (ISG) expression marks EP/Topotecan cross-resistance











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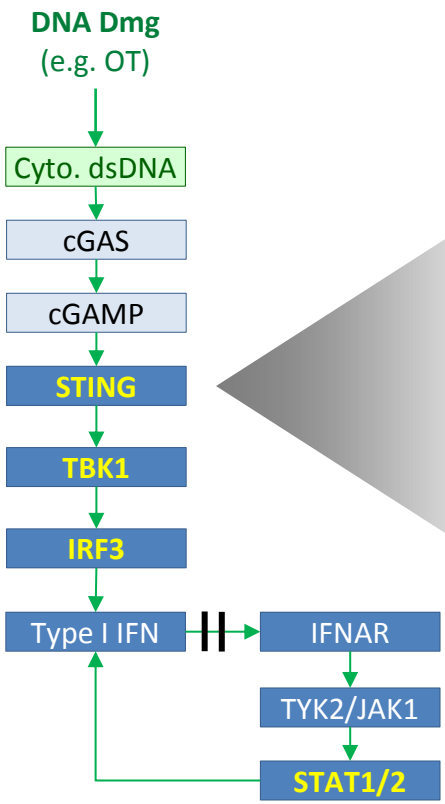
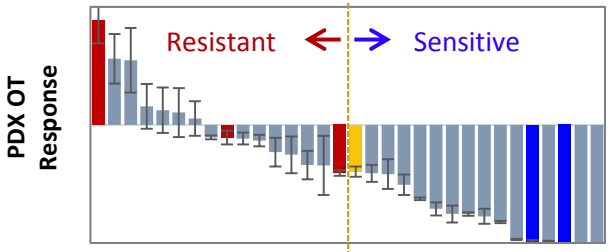
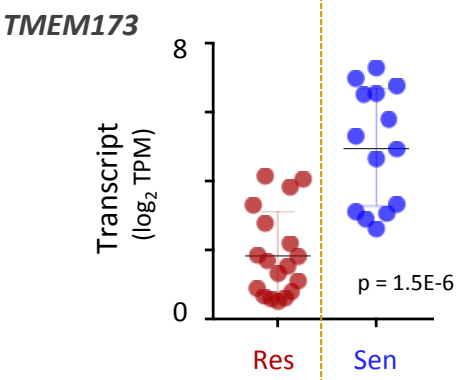
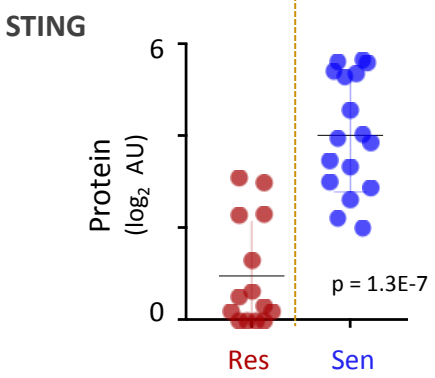
STING expression may underly the basal ISG signature









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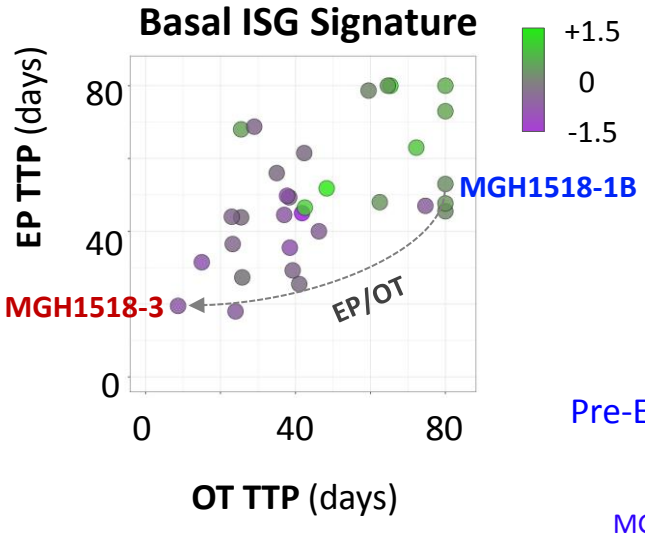
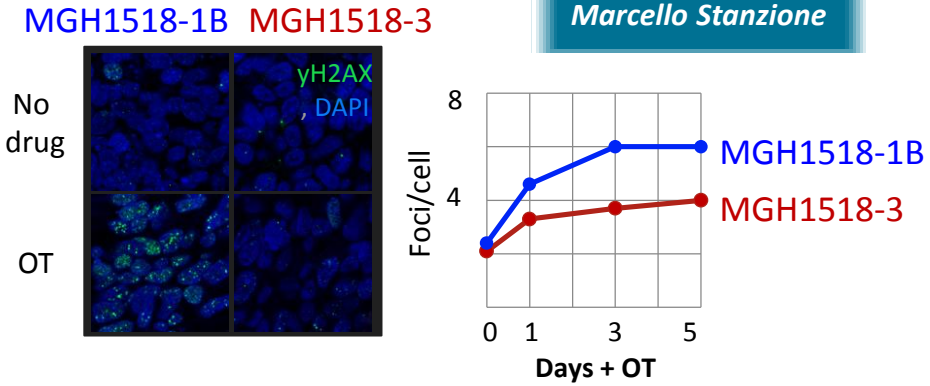
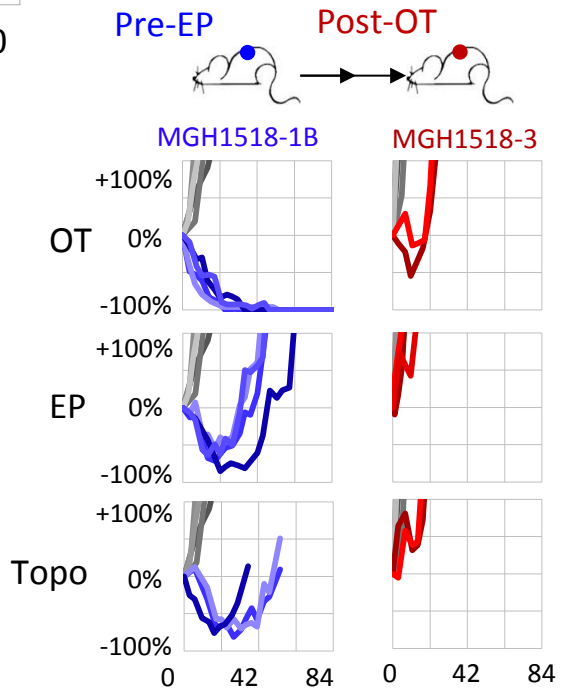
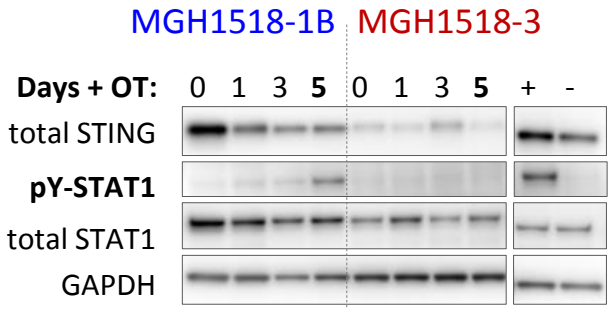
Basal ISG expression represents capacity for interferon induction with DNA damage





Marcello Stanzione





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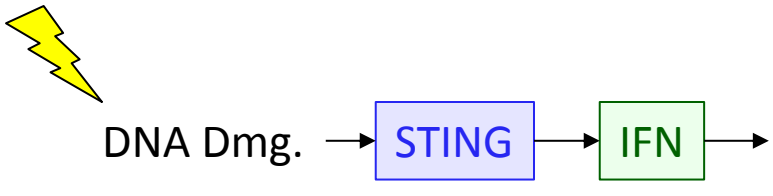
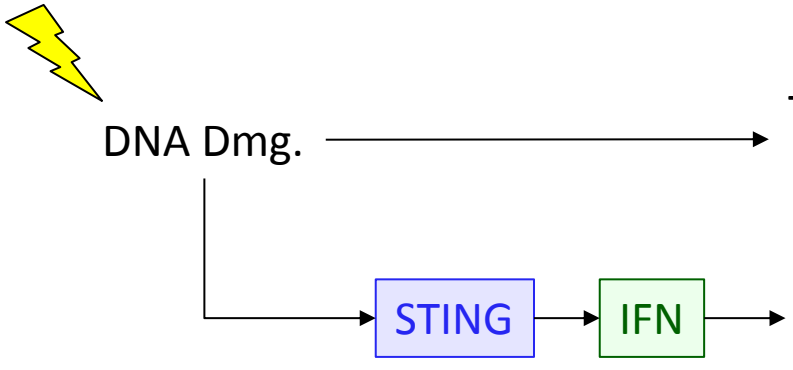
Marker vs. mediator of cross-resistance





Significance & Next Steps

- STING silencing is a cross-resistance mechanism
- ± STING/IFN in sensitive vs. resistant models

- Low STING/ISG expression are biomarkers for cross-resistance
- Assess in patient tumors

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Thank You!

Nick Dyson and **Anna Farago**

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