# Present and Future Prospects of PDX model in Lung Cancer

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# Outline

I. Introduction

II. Technical Optimization: Preclinical Models

III. Model Fidelity and Clinical Concordance

IV. Translational Applications: From Drugs to Mechanisms

V. Challenges and Future Prospects

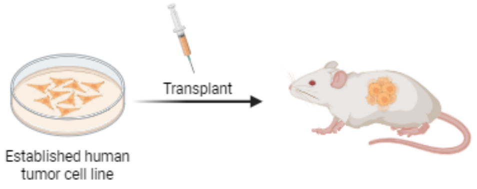
VI. Conclusion

# I. Introduction: Structural limitations of clinical studies

- Limited ability to establish **causality**
- Lack of **control over treatment conditions**
- Restricted evaluation of **direct biological drug effects**
- Difficulty defining the boundary between efficacy and toxicity

# II. Preclinical models: Cell line-derived xenograft (CDX)

| Feature | CDX (Cell-lines) |
|---|---|
| Heterogeneity | Low |
| TME Preservation | No |
| Take Rate | >90% |
| Establish Time | Days |
| Predictive Value | 30-40% |
| Cost | Low |
| Drug Screening | Fast |




Biorender; Rudin et al. Nat Commun 2020

**Metastasis Results from Preexisting Variant Cells Within a Malignant Tumor**

Abstract. *Clones derived in vitro from a parent culture of murine malignant melanoma cells varied greatly in their ability to produce metastatic colonies in the lungs upon intravenous inoculation into syngeneic mice. This suggests that the parent tumor is heterogeneous and that highly metastatic tumor cell variants preexist in the parental population.*

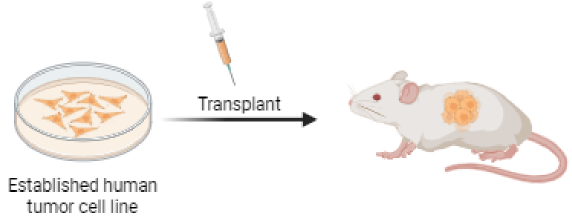
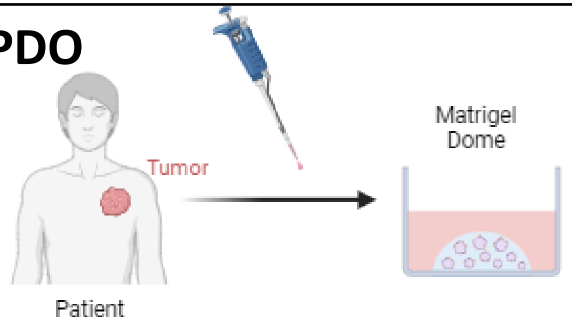
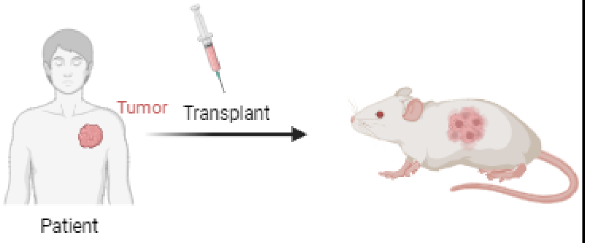
The question of why cancer cells metastasize is one of the most important issues in tumor biology. In human cancer it is the process of metastasis, the formation of secondary tumor foci at distant sites, that eventually defeats the efforts of both surgeon and clinical oncologist. In spite of the importance of this phenomenon, little is known about the pathogenesis of metastatic foci or their relationship to the primary tumor. Studies with transplantable tumors in rodents have shown that both host factors and properties of the tumor cells can contribute to the success or failure of the metastatic process (*1*).

Earlier studies with the B16 melanoma in syngeneic C57BL mice showed that the majority of tumor cells injected intravenously die very rapidly in the circulation, and only about 0.1 percent survive and yield metastases (*2*). Further experiments suggested that the survival of these few tumor cells was not a random occurrence, but was due to certain unique properties of the surviving cells (*3*). In this study, we wished to determine whether these unique metastatic cells preexisted in the tumor cell population, or whether they arose during metastasis by a process of adaptation to local environmental conditions. If highly metastatic variant cells could be shown to preexist in the parent population, this would support the suggestion by Nowell (*4*) that tumor cell variants arise within developing tumors, are subjected to host selection pressures, and are responsible for the emergence of new sublines with increased malignant potential.

To distinguish between these possibilities, we performed an experiment similar in design to the classical fluctuation test devised by Luria and Delbrück to distinguish between selection and adaptation in the origin of bacterial mutants (*5*). In our study a cell suspension of the B16 melanoma parent line was divided into two parts. One portion was used to inject syngeneic C57BL/6 mice intravenously. The other portion was used to produce clones, which were then also injected intravenously into groups of C57BL/6 mice (Fig. 1). Eighteen days af-

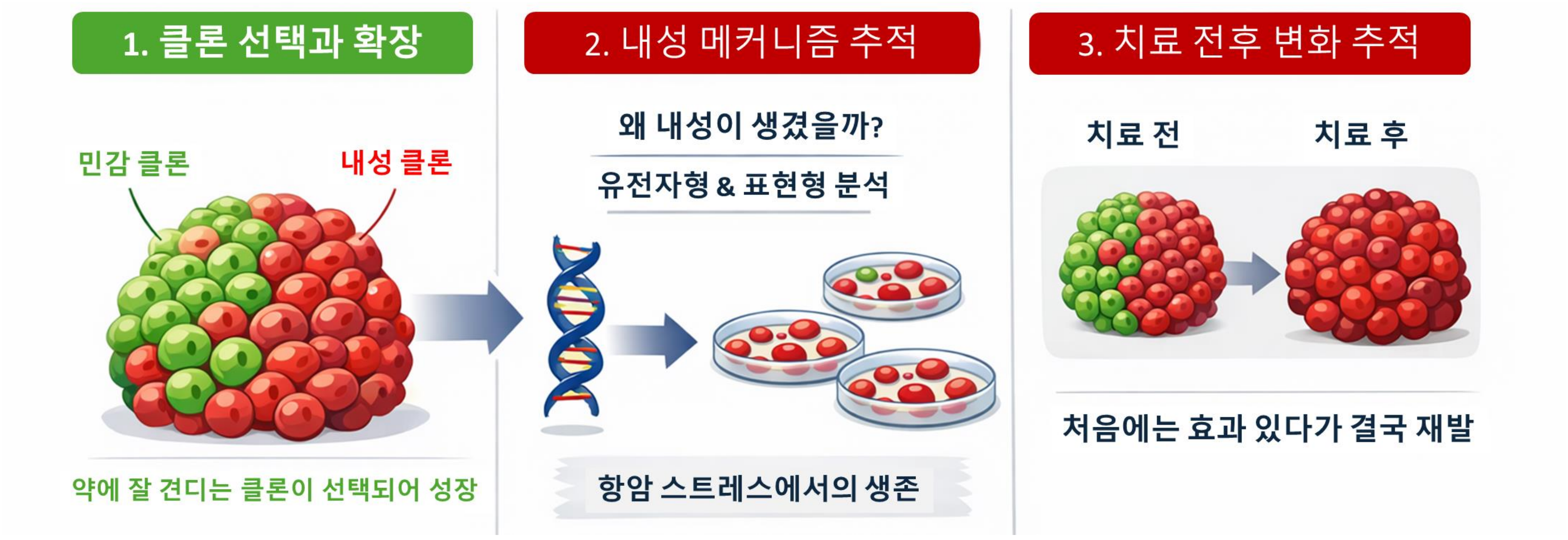
Fidler & Kripke, Science, 1977

# II. Preclinical models: CDX vs PDO vs PDX - Comparative Analysis

| **Feature** | **CDX (Cell-lines)**   | **PDO**   | **PDX**   |
|---|---|---|---|
| Heterogeneity | Low | High | High ✓ |
| TME Preservation | No | Limited | Yes ✓ |
| Take Rate | >90% | >85% | 40-80% |
| Establish Time | Days | 1-2 weeks | 3-6 months |
| Predictive Value | 30-40% | 70-80% | 87% ✓ |
| Cost | Low | Medium | High |
| Drug Screening | Fast | Fast | Slow |

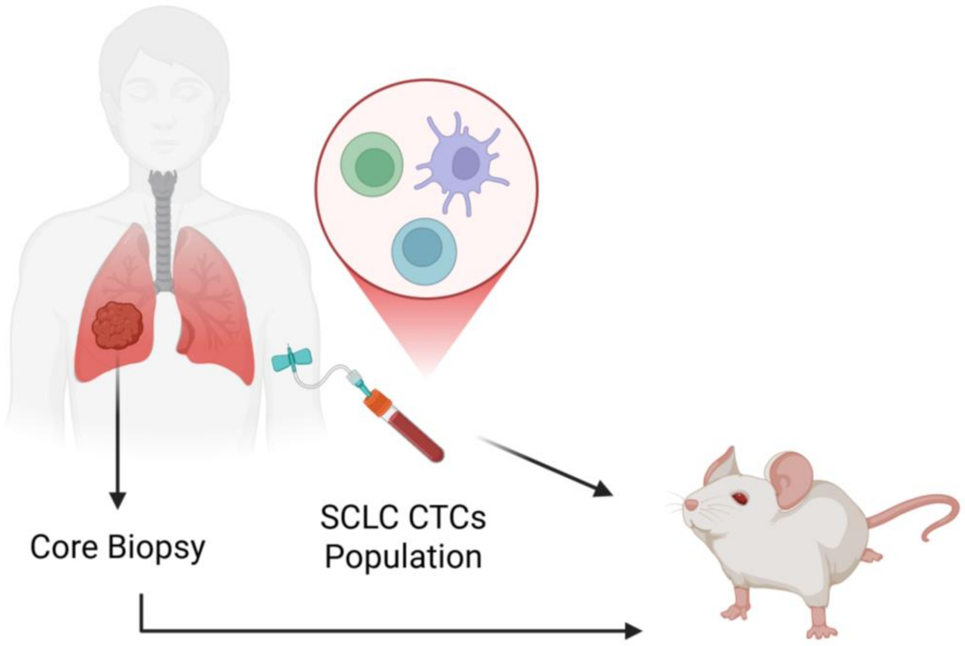
# II. Preclinical models: PDX enables evolutionary questions impossible with other models

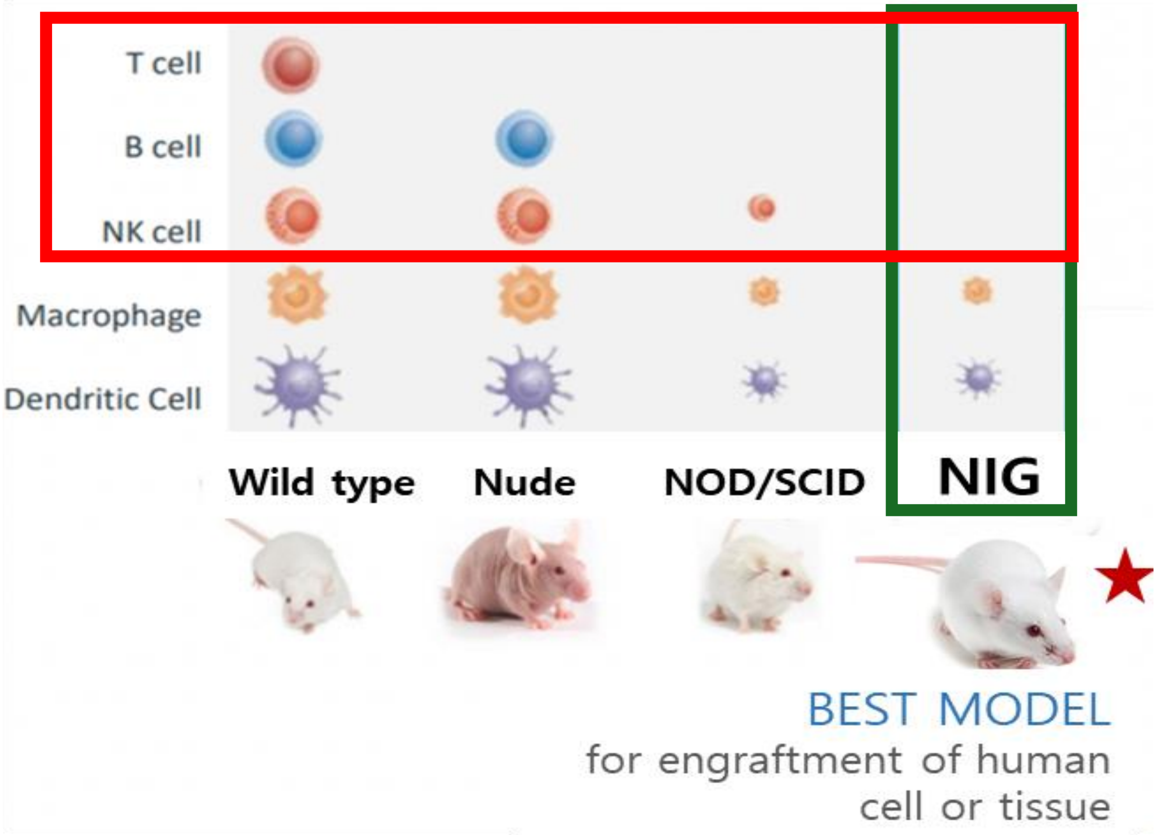
- Therapy-driven clonal selection
- Survival under genome-wide stress
- Temporal tracking of the same lineage




Illustrated by ChatGPT

# II. Preclinical models: What Is a Patient-Derived Xenograft (PDX) Model?

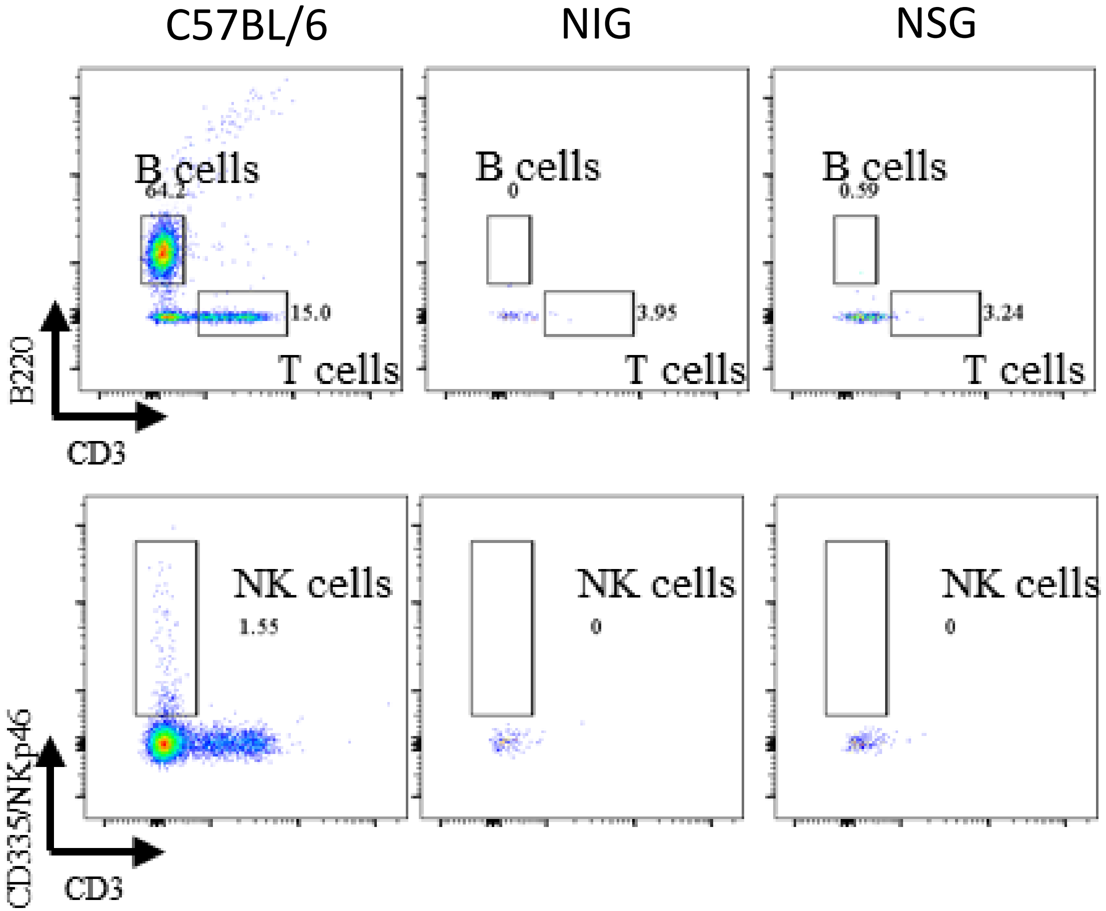


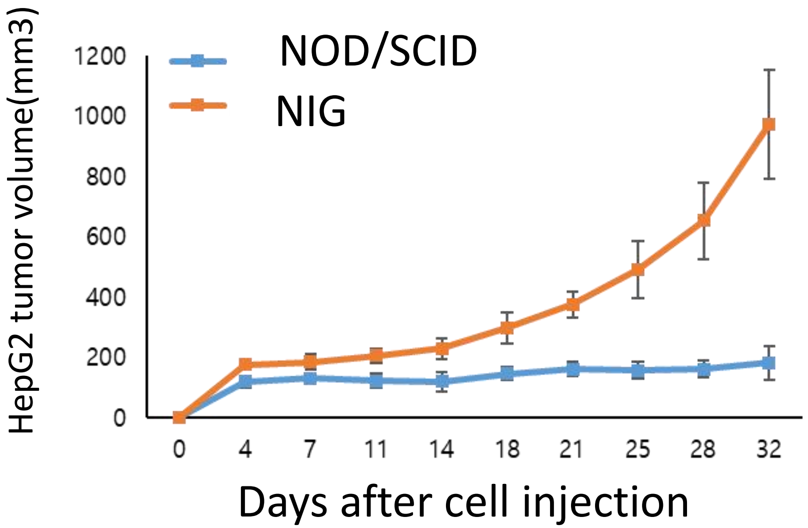



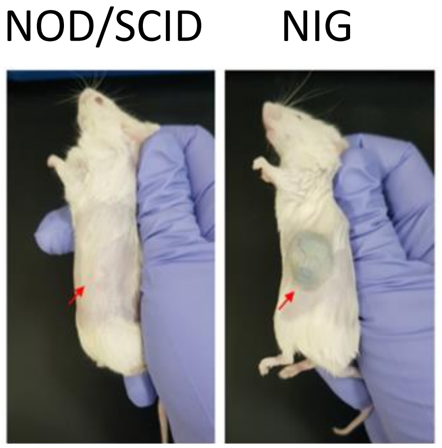

PDX directly transfers a patient's tumor into mice, preserving native tumor biology

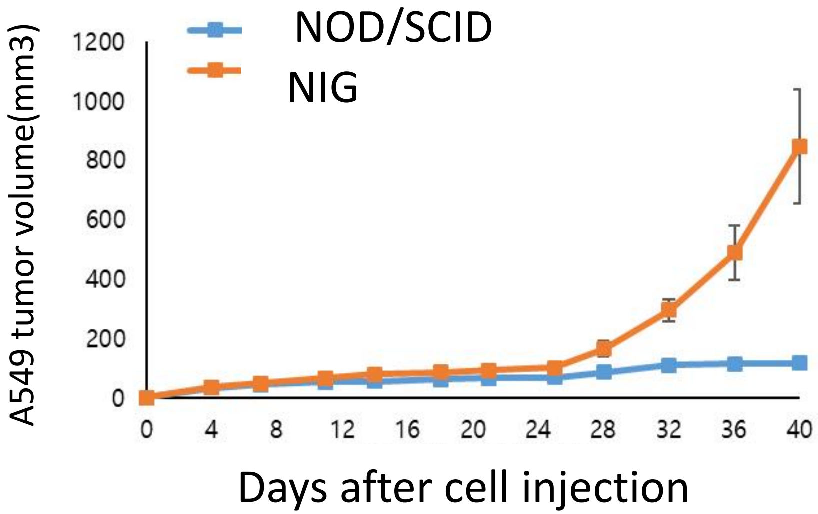
# II. Preclinical models: Immune Landscape and Tumor Engraftment in NIG Mice

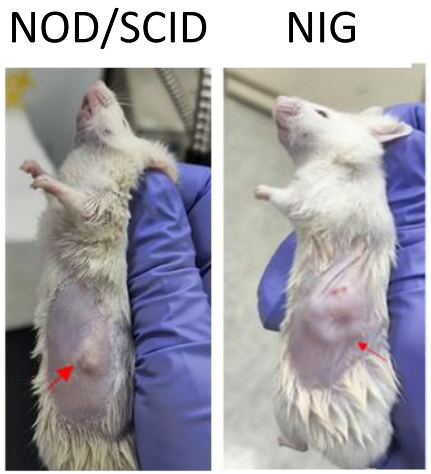
혈액 내 림프구 분석 결과(FACS)

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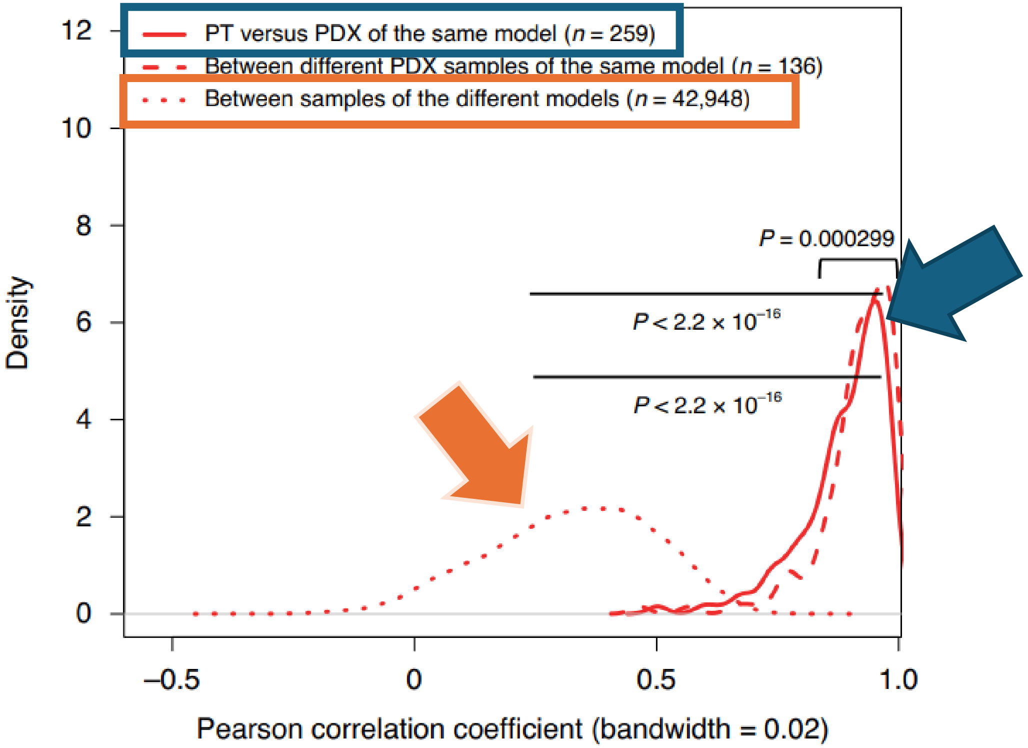
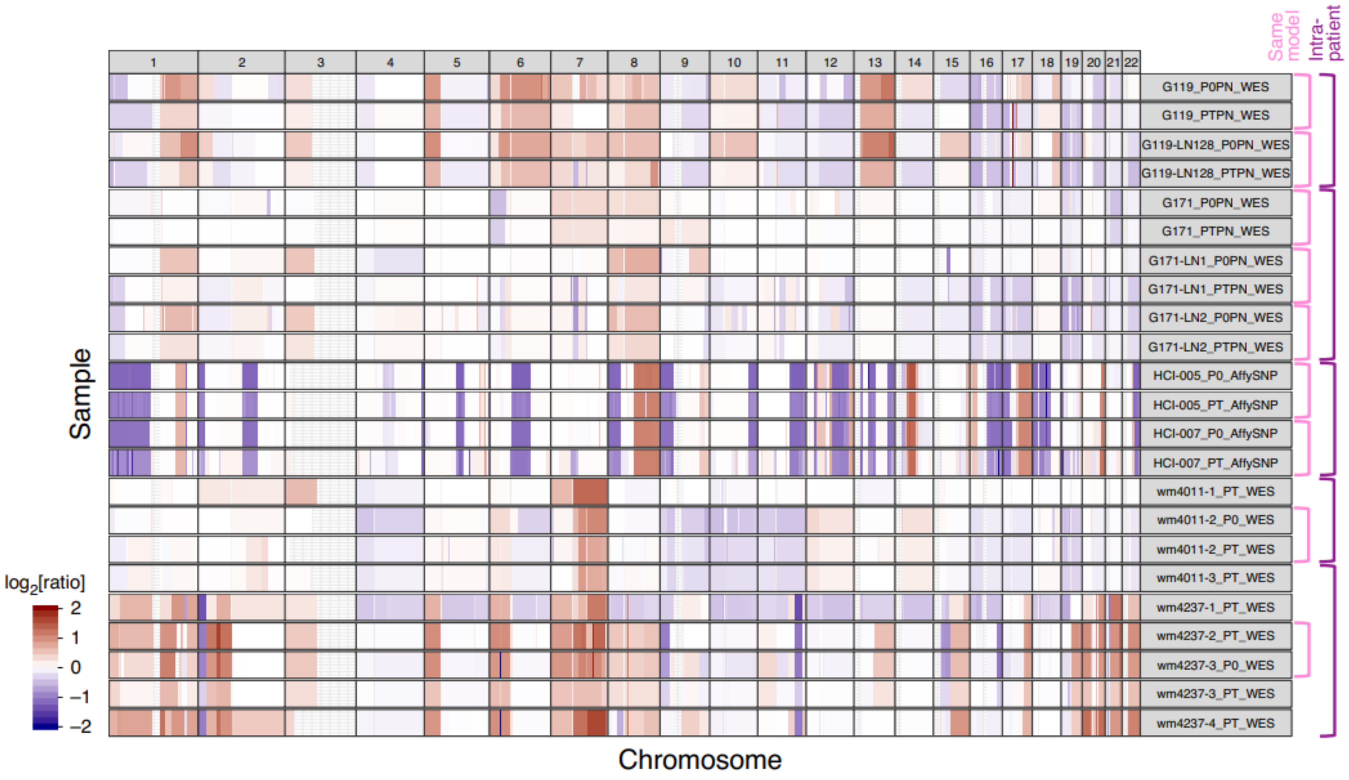
# III. Model Fidelity and Clinical Concordance: Patient-specific genetic patterns conserved in matched PDXs

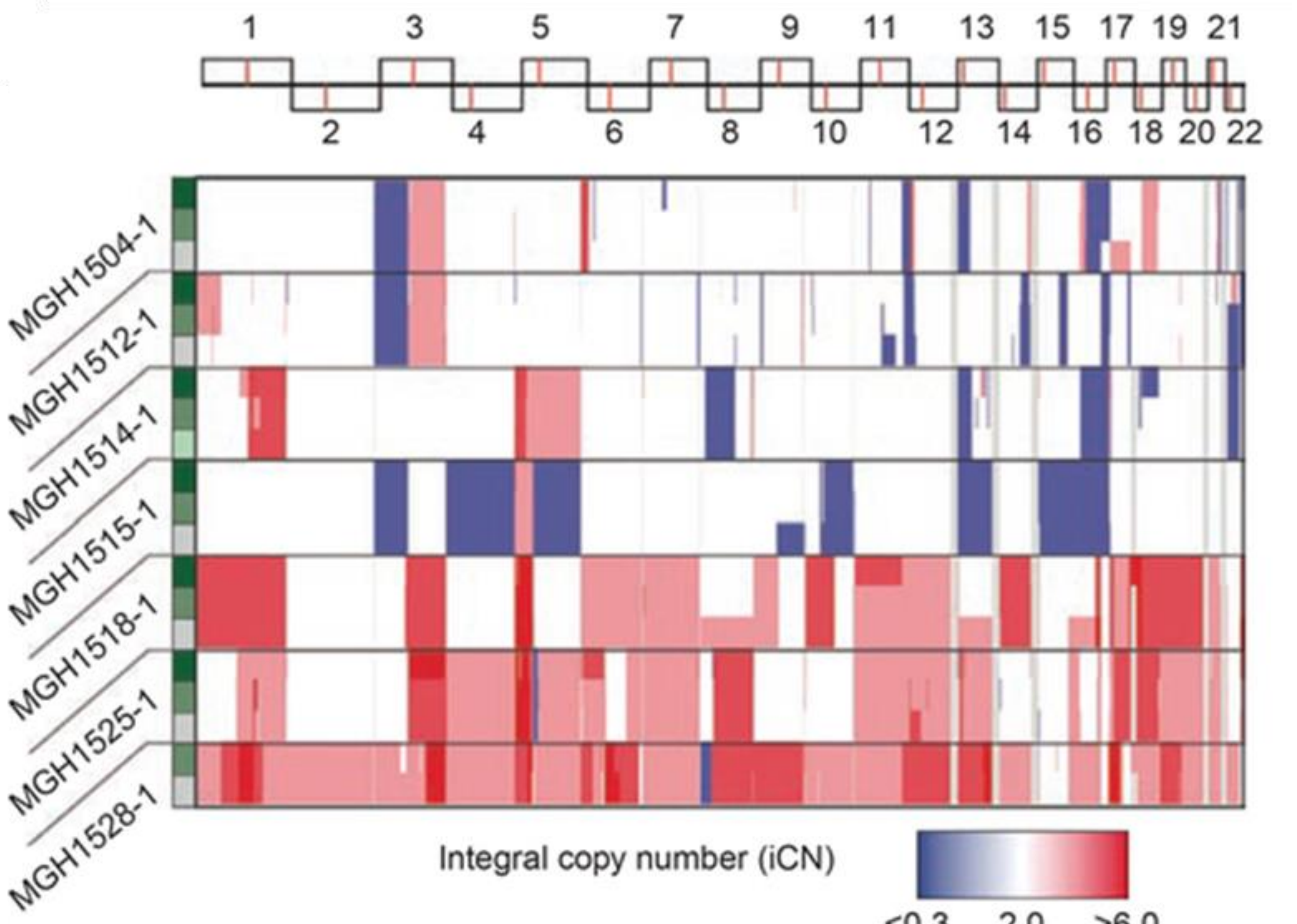


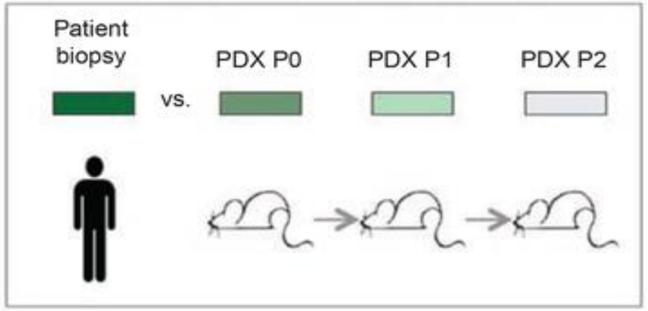




Strong CNA pattern conservation from patients through PDXs

Woo X, et al. Nature genetics, 2021

# III. Model Fidelity and Clinical Concordance:
# SCLC PDXs maintain patient tumor genomic landscape

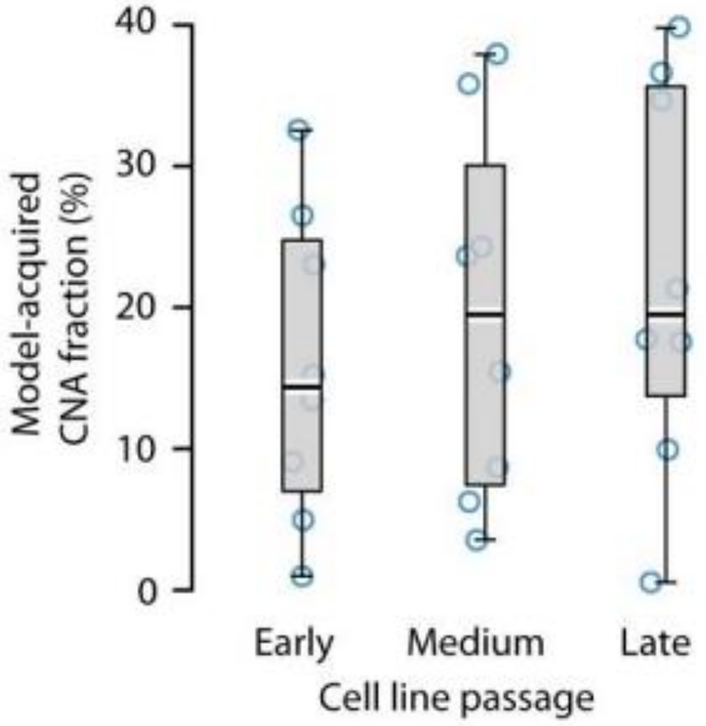


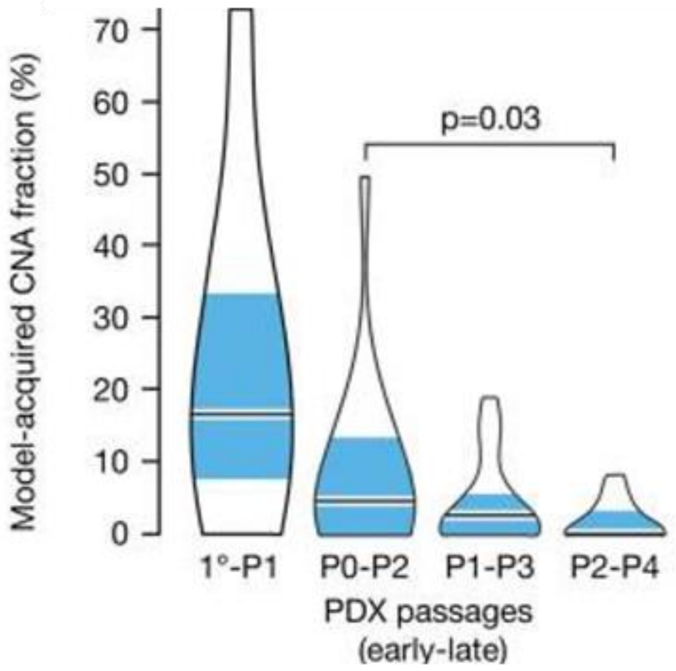

Drapkin et al., Cancer Discov, 2018

# III. Model Fidelity and Clinical Concordance: Preservation of CNA during serial passaging

## Lung Cancer Cell lines



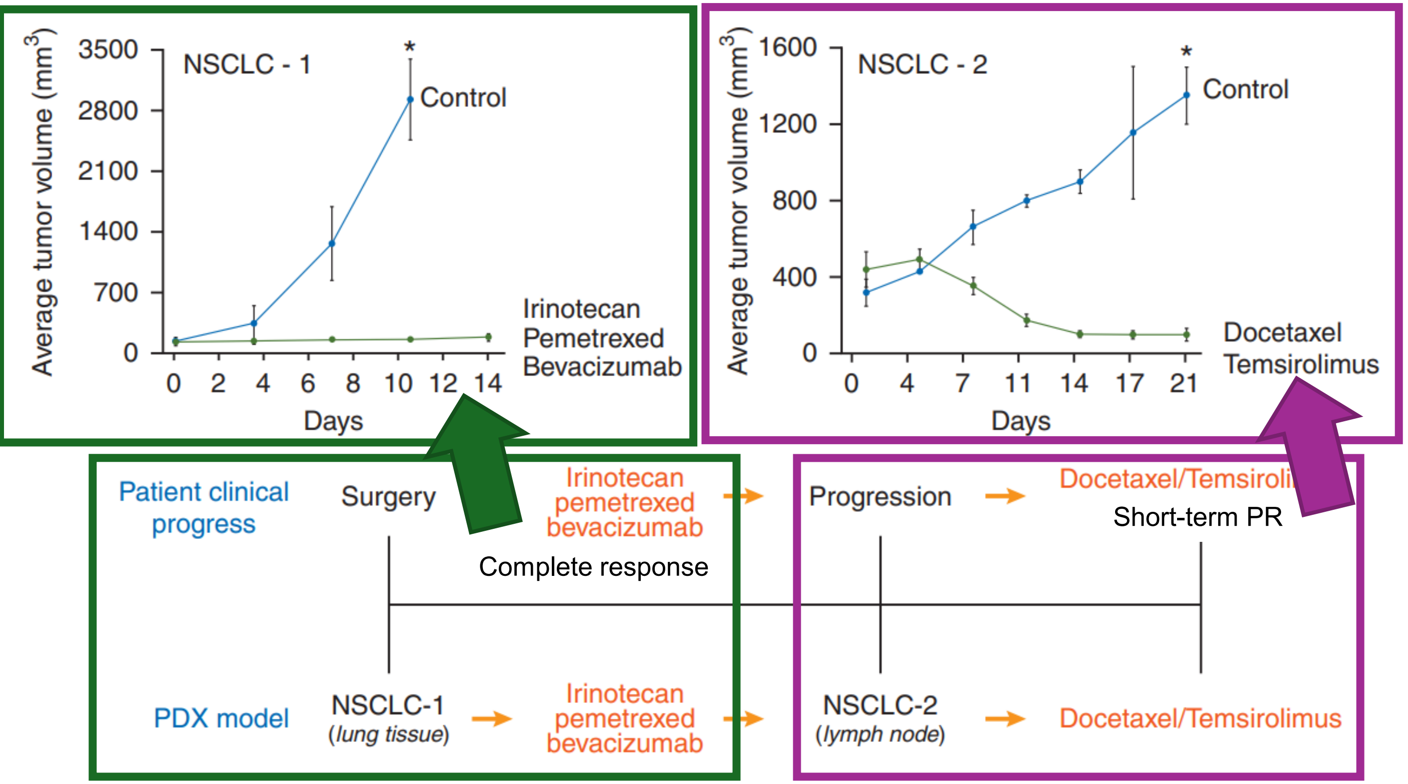

## PDX

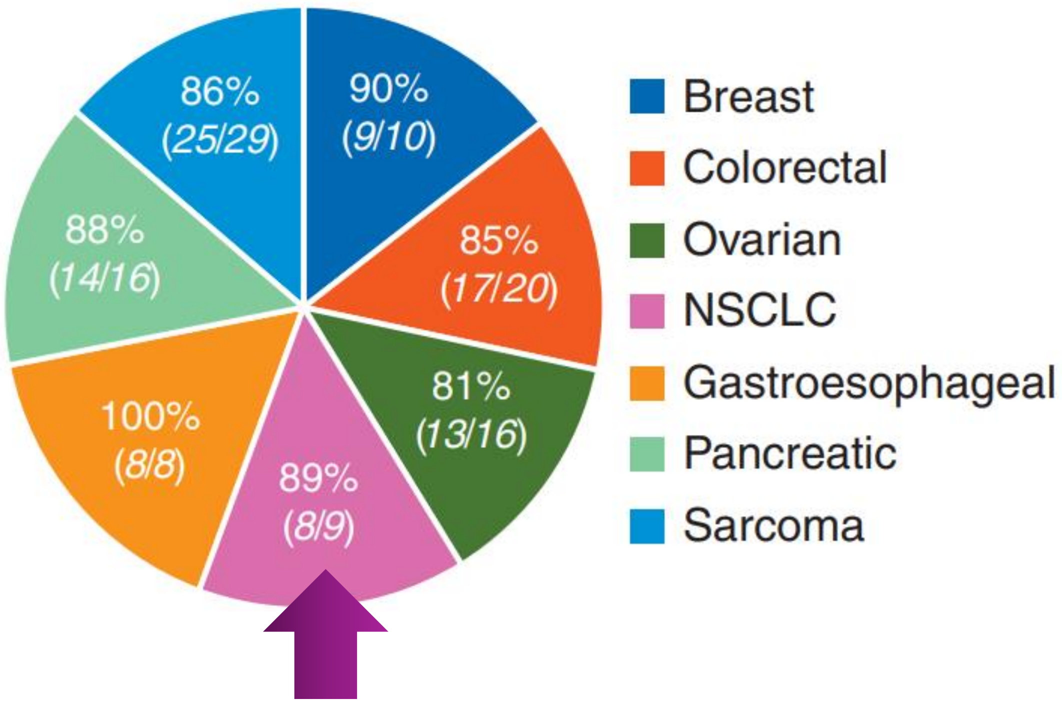



## PDX Models Preserve Stable Truncal and CNA Architecture

Ben-David et al, Nature Genetics , 2017

# III. Model Fidelity and Clinical Concordance: PDX effectively capture responses to oncology therapy

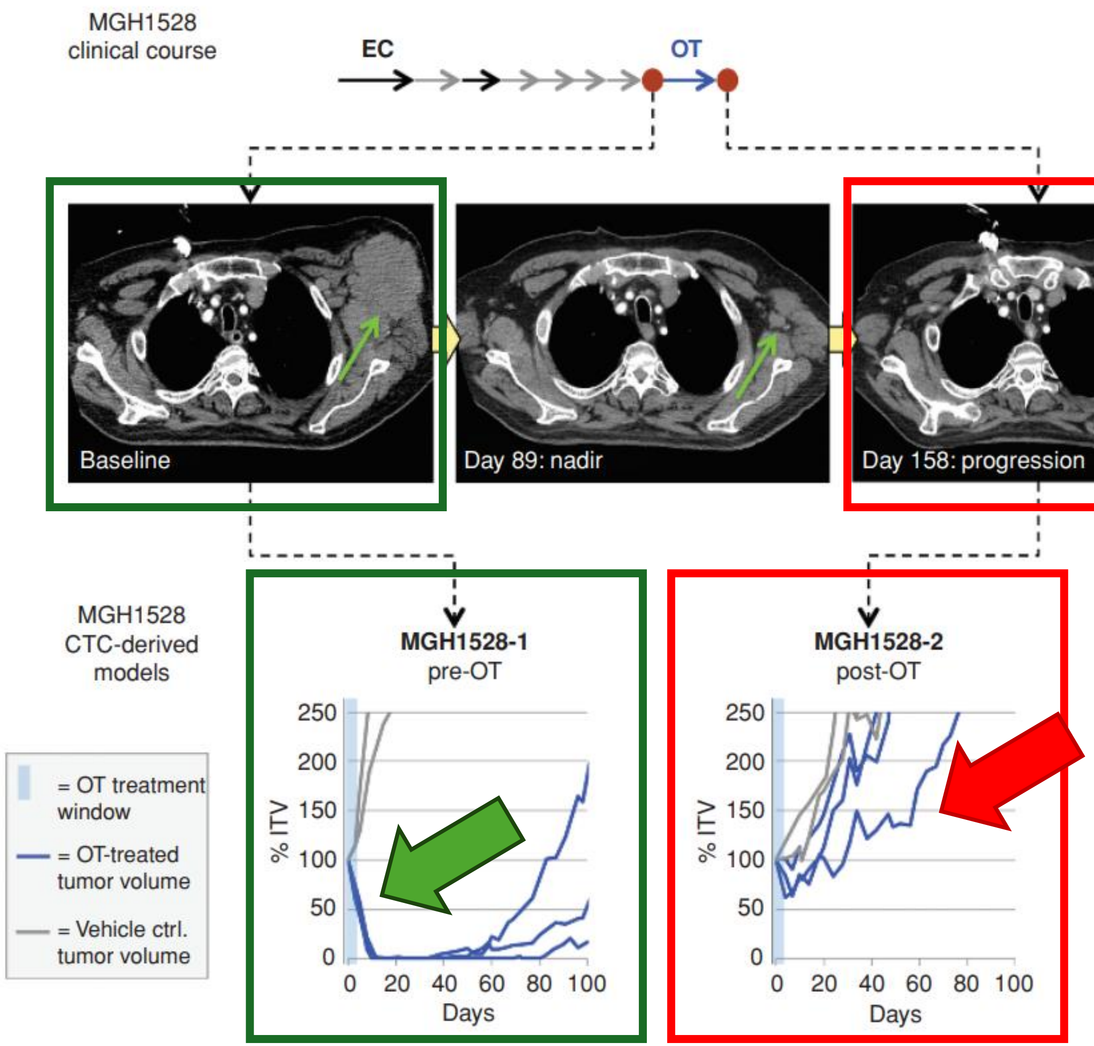



NSCLC patient–derived PDX models recapitulate clinical drug responses with **89% concordance**

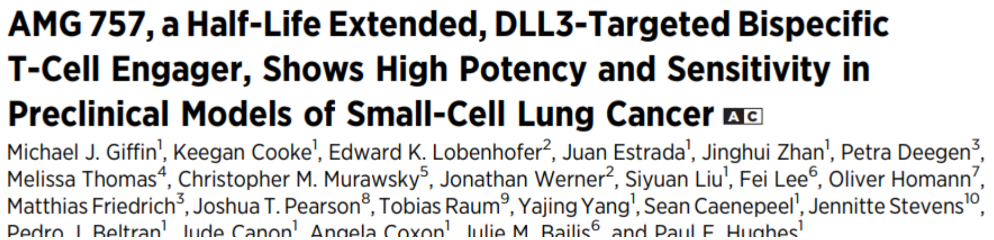
Izumchenko et al., Ann Oncol, 2017

# III. Model Fidelity and Clinical Concordance: PDX recapitulates clinical responses of patients with SCLC



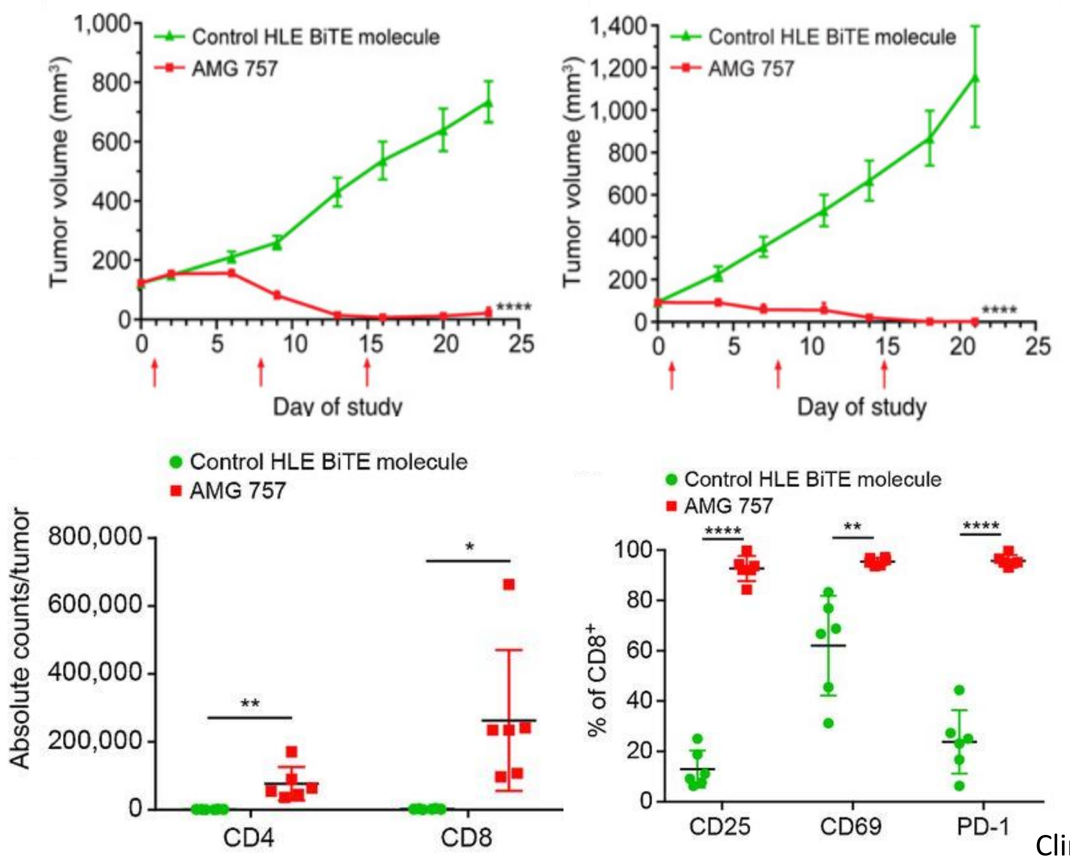

Drapkin et al Cancer Discovery 2018

# IV. Translational Applications: for approved / near-approved drugs

**AMG 757, a Half-Life Extended, DLL3-Targeted Bispecific T-Cell Engager, Shows High Potency and Sensitivity in Preclinical Models of Small-Cell Lung Cancer**

Michael J. Giffin[1], Keegan Cooke[1], Edward K. Lobenhofer[2], Juan Estrada[1], Jinghui Zhan[1], Petra Deegen[3], Melissa Thomas[4], Christopher M. Murawsky[5], Jonathan Werner[2], Siyuan Liu[1], Fei Lee[6], Oliver Homann[7], Matthias Friedrich[3], Joshua T. Pearson[8], Tobias Raum[9], Yajing Yang[1], Sean Caenepeel[1], Jennitte Stevens[10], Pedro J. Beltran[1], Jude Canon[1], Angela Coxon[1], Julie M. Bailis[6], and Paul E. Hughes[1]

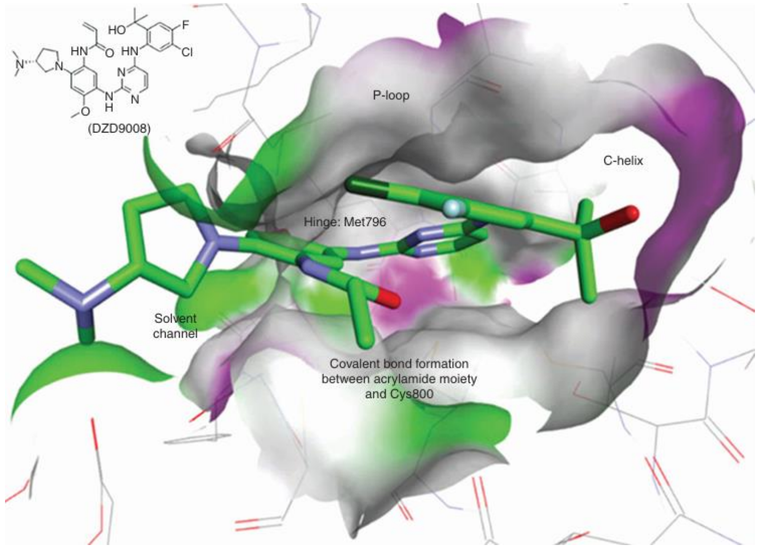



Clin Cancer Res 2021


RESEARCH ARTICLE

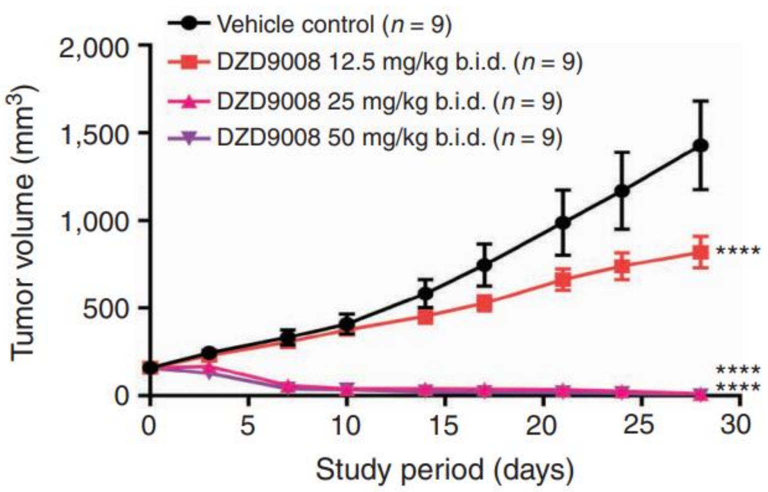
# Sunvozertinib, a Selective EGFR Inhibitor for Previously Treated Non–Small Cell Lung Cancer with *EGFR* Exon 20 Insertion Mutations

Mengzhao Wang[1], James Chih-Hsin Yang[2], Paul L. Mitchell[3], Jian Fang[4], D. Ross Camidge[5], Weiqi Nian[6], Chao-Hua Chiu[7], Jianying Zhou[8], Yanqiu Zhao[9], Wu-Chou Su[10], Tsung-Ying Yang[11], Viola W. Zhu[12], Michael Millward[13], Yun Fan[14], Wen-Tsung Huang[15], Ying Cheng[16], Liyan Jiang[17], Daniel Brungs[18], Lyudmila Bazhenova[19], Chee Khoon Lee[20], Bo Gao[21], Yan Xu[1], Wei-Hsun Hsu[22], Li Zheng[23], and Pasi A. Jänne[24]

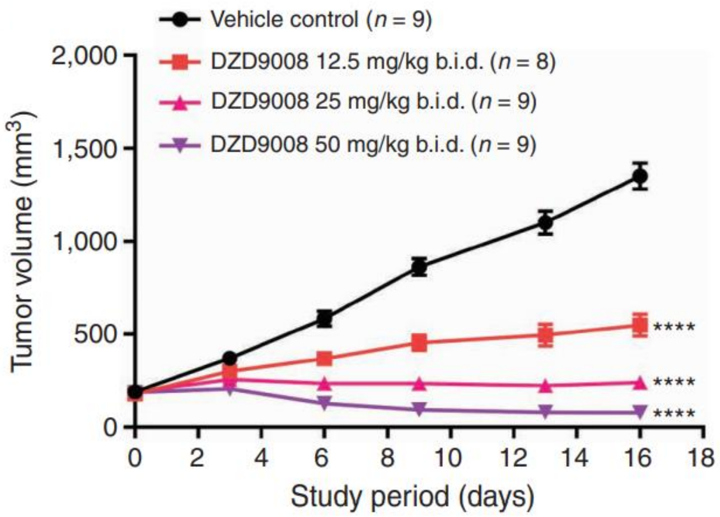


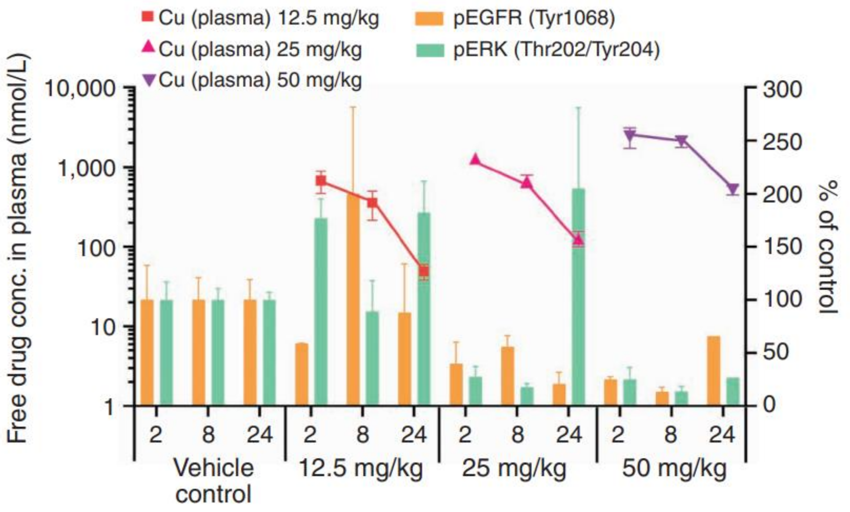

Cell discovery 2022

## EGFRexon20ins insNPH

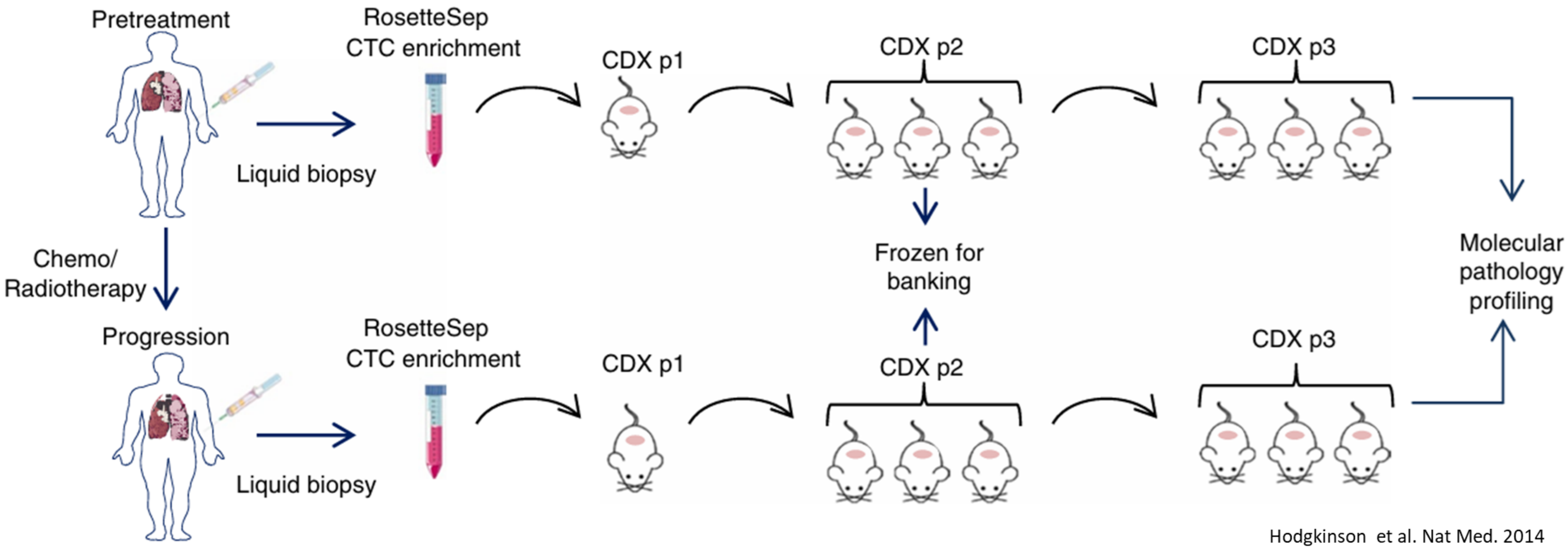



## EGFRwt



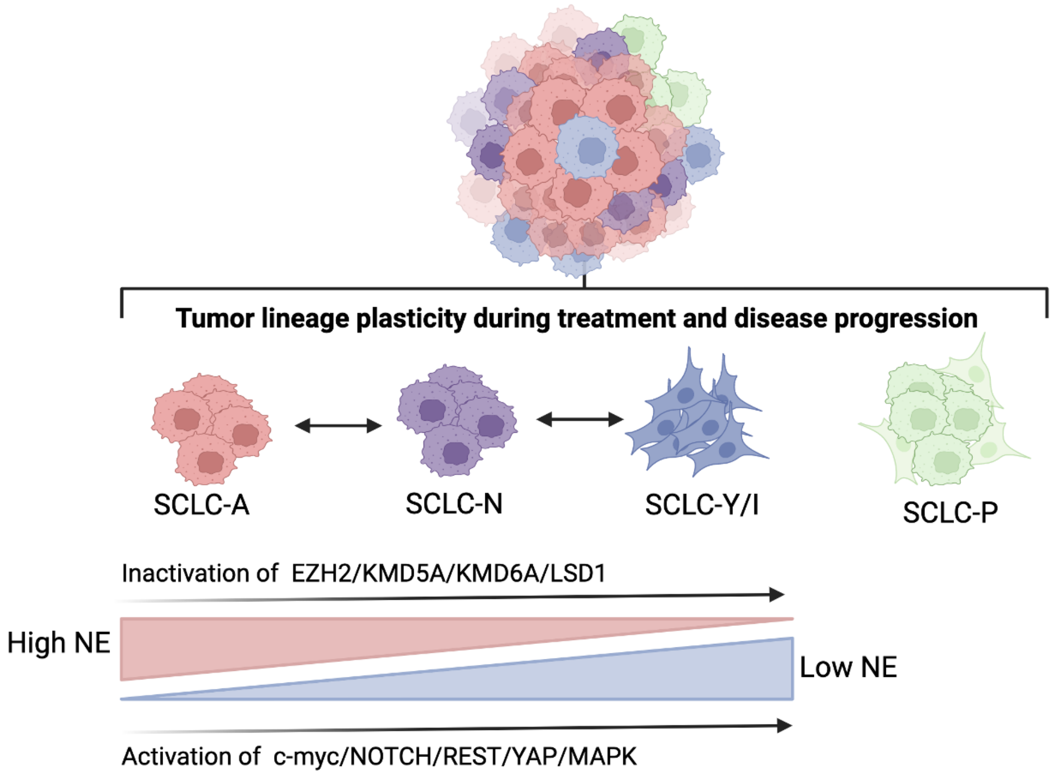



# IV. Translational Applications: Dissecting Chemoresistance Biology in SCLC

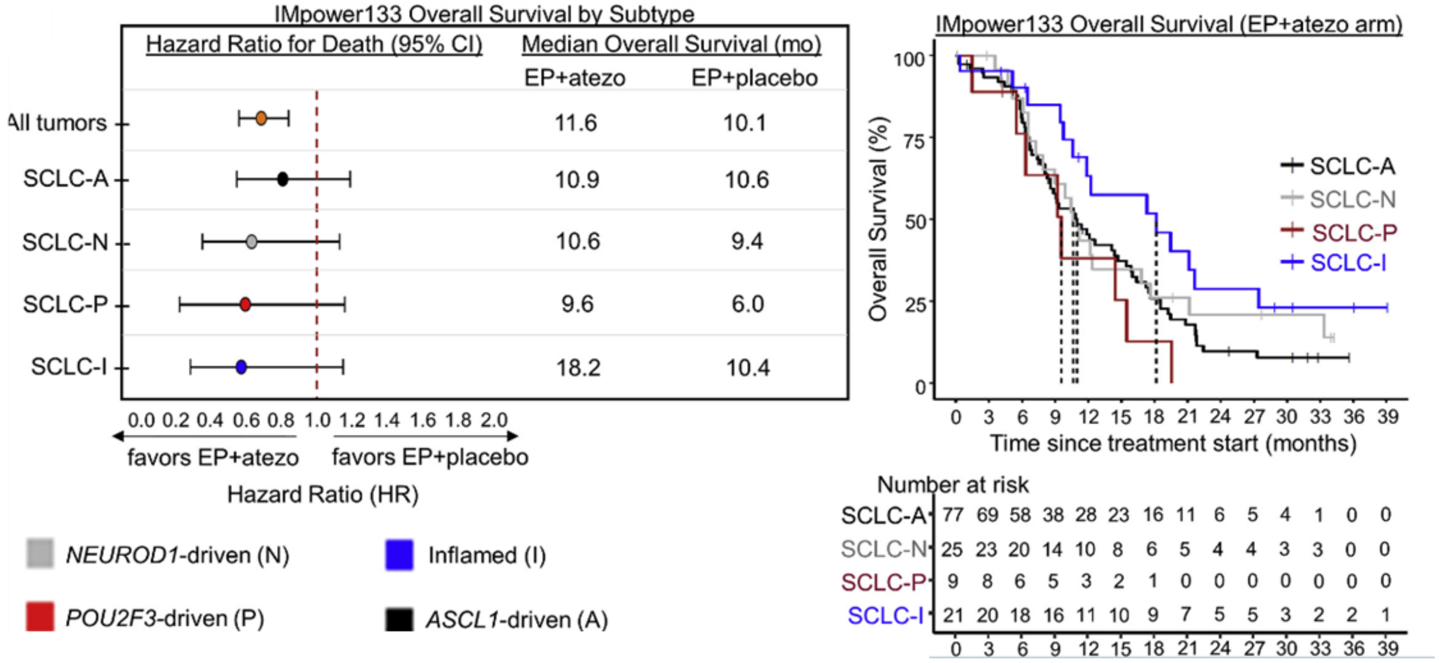



Hodgkinson et al. Nat Med. 2014

# Lineage Plasticity as a Central Driver of Chemoresistance in SCLC




Redin et al., Trends in Cancer 2024

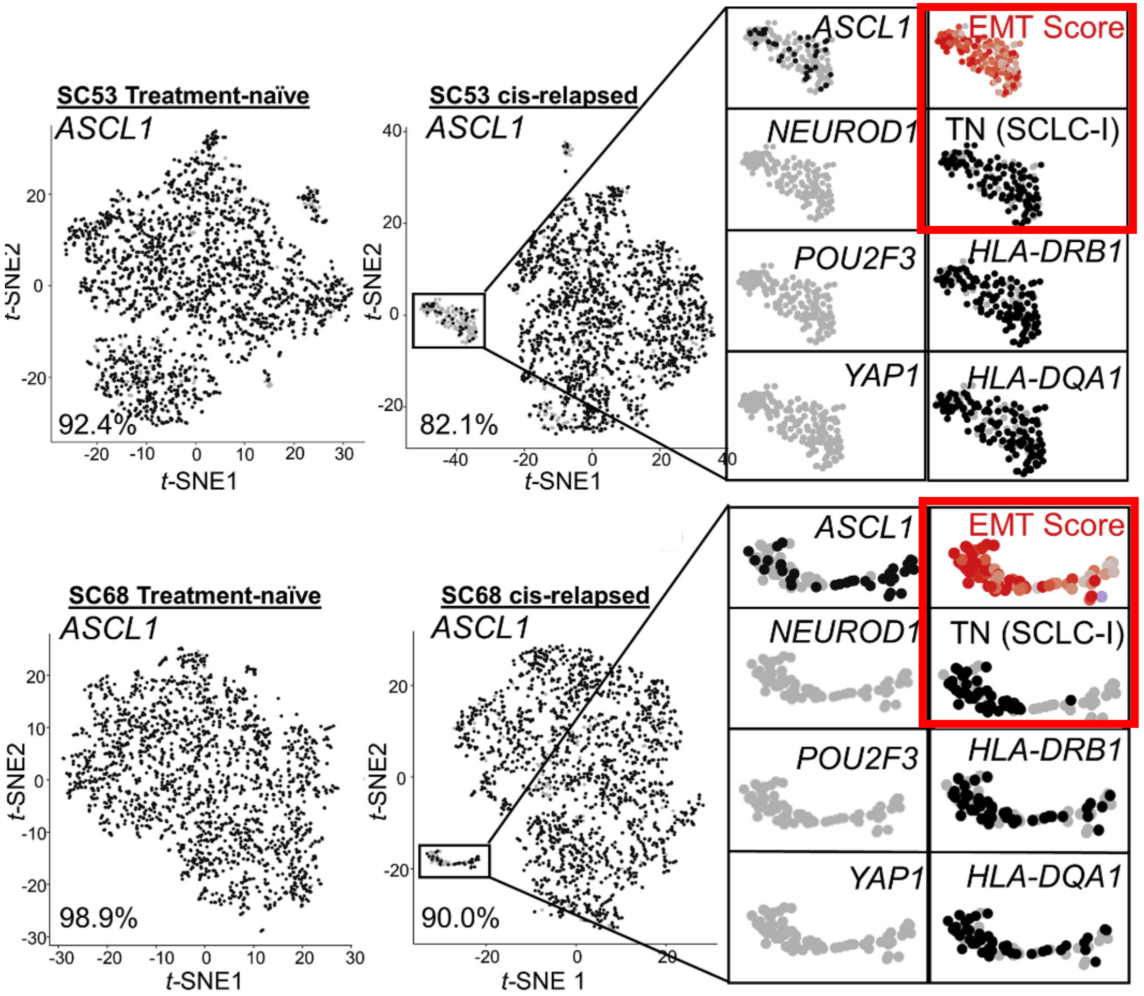



Gay CM et al., Cancer Cell 2021

# Cisplatin treatment of SCLC-A PDX induces intratumoral shifts toward SCLC-I

PDX1 – SC53

PDX2 – SC68

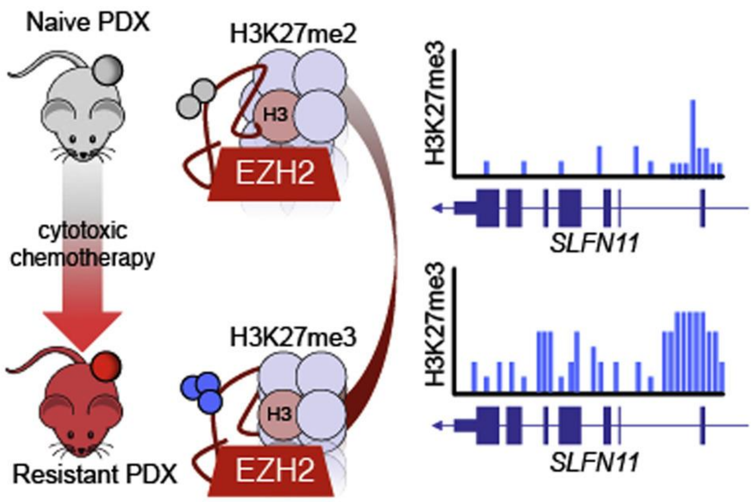


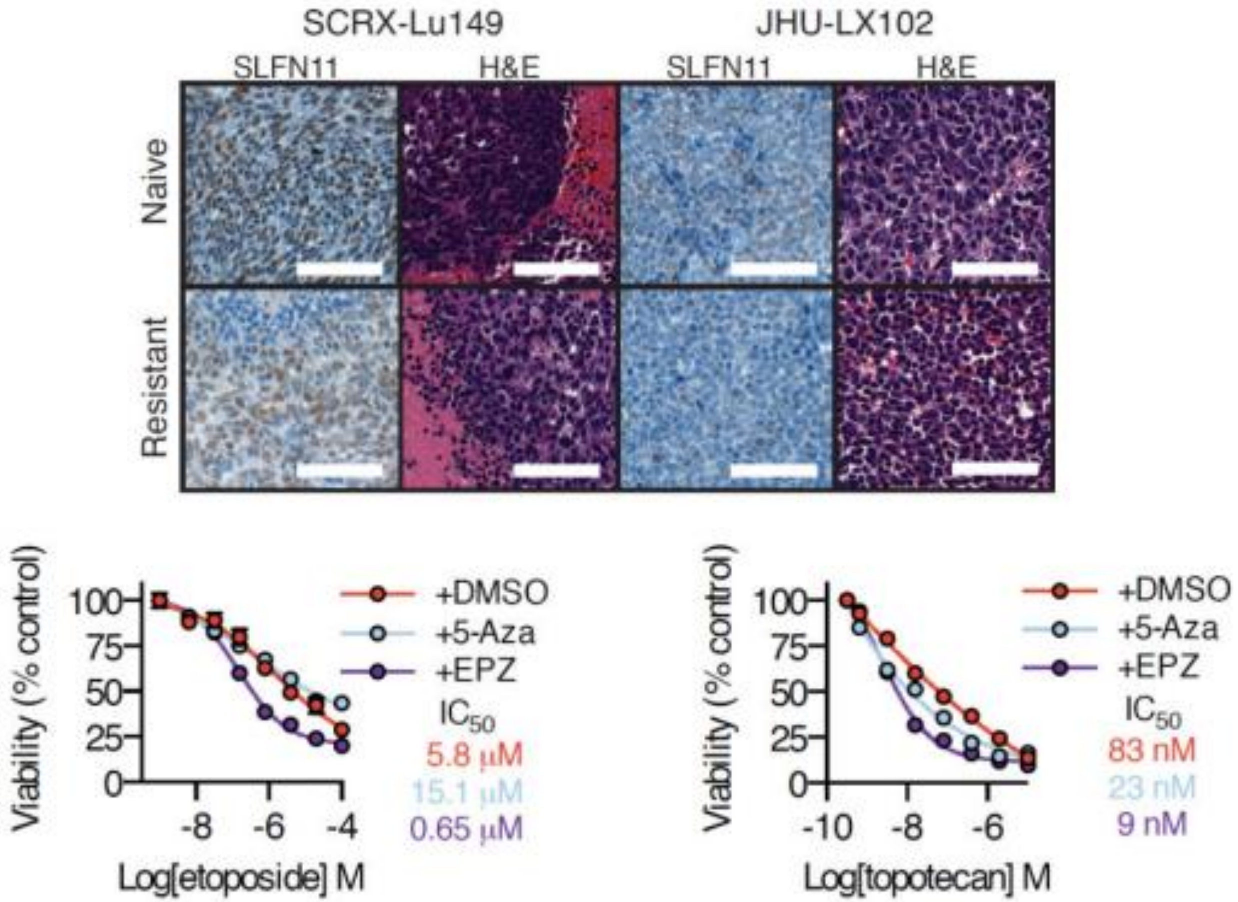

Gay CM et al., Cancer Cell 2021

# Chemosensitive Relapse in Small Cell Lung Cancer Proceeds through an EZH2-SLFN11 Axis

Eric E. Gardner,[1,2] Benjamin H. Lok,[2,3] Valentina E. Schneeberger,[2] Patrice Desmeules,[4] Linde A. Miles,[2] Paige K. Arnold,[5] Andy Ni,[6] Inna Khodos,[7] Elisa de Stanchina,[2,7] Thuyen Nguyen,[8] Julien Sage,[8] John E. Campbell,[9] Scott Ribich,[9] Natasha Rekhtman,[4] Afshin Dowlati,[10] Pierre P. Massion,[11] Charles M. Rudin,[2,12,13,*] and John T. Poirier[2,13,14,*]

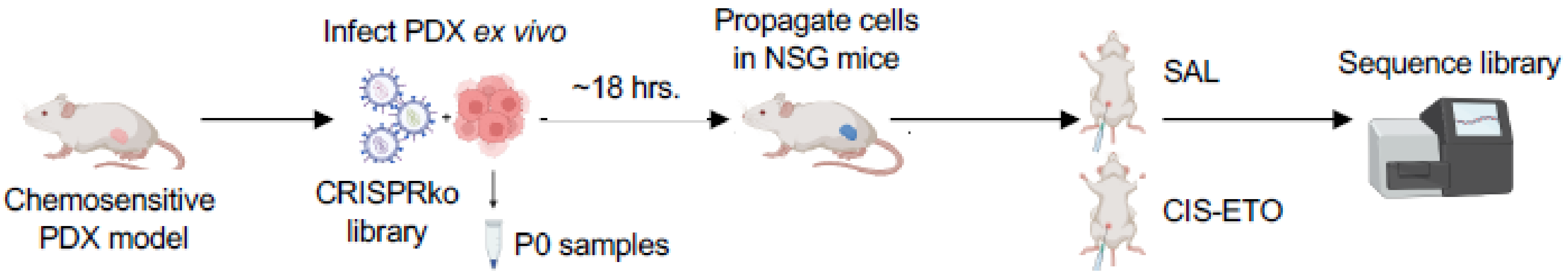
Cancer Cell, 2017

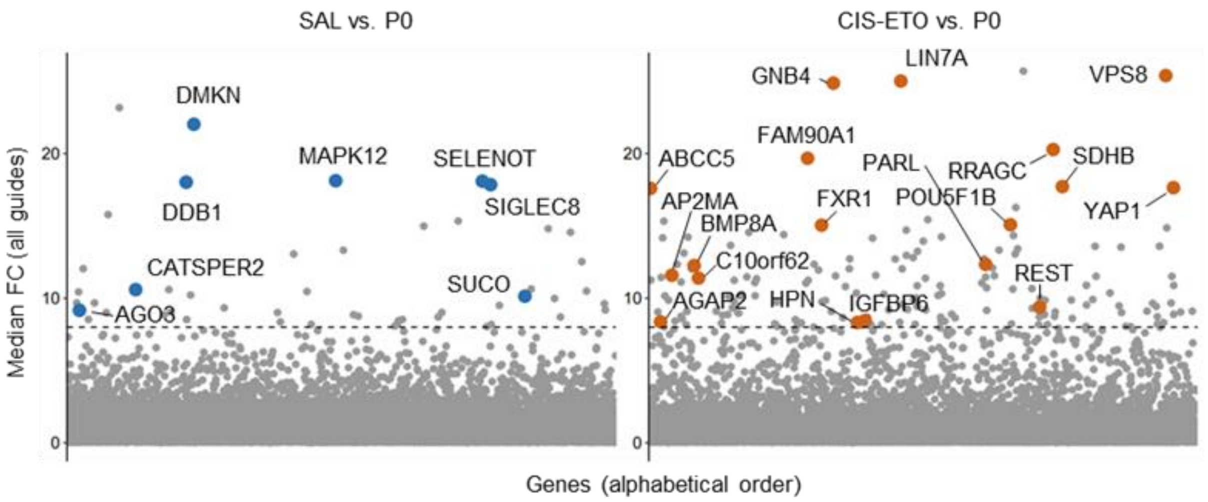


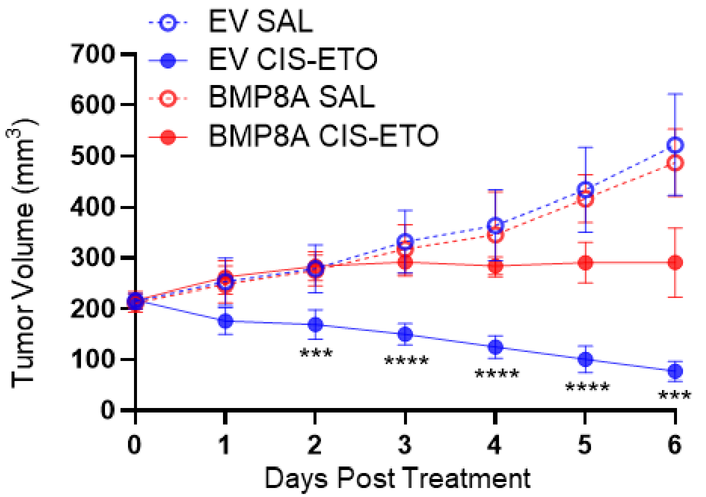



# IV. Translational Applications: Dissecting Chemoresistance Biology in SCLC

## Schematic of the *in vivo* CRISPR screens using PDX models

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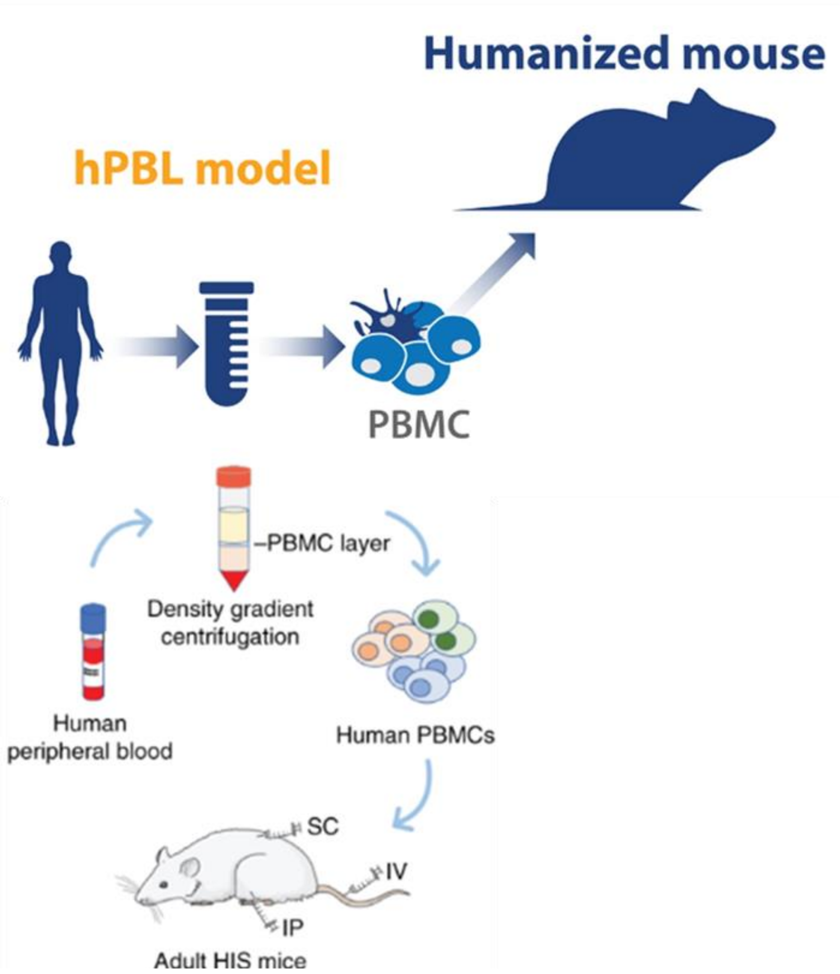
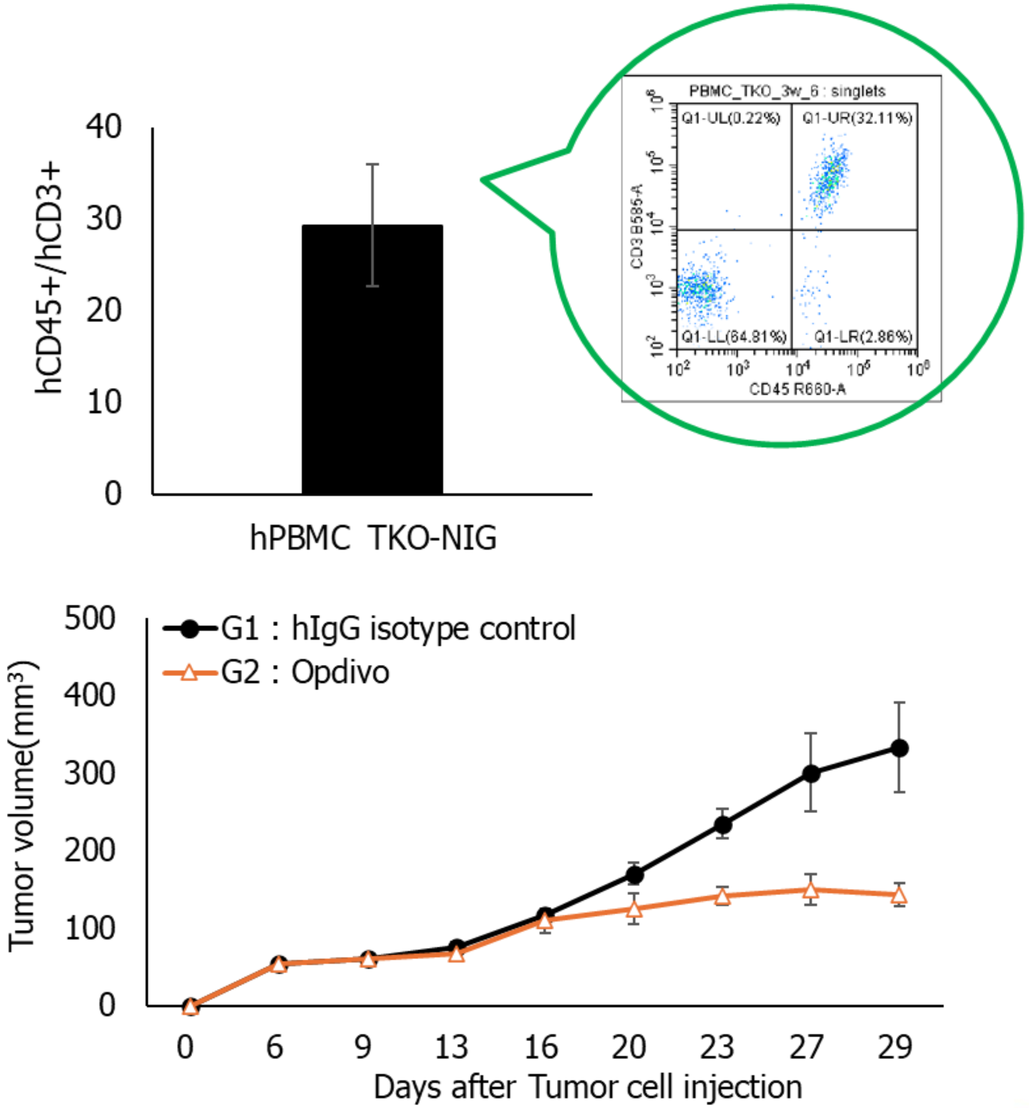
Unpublished data

# V. Challenges and Future Prospects : Limitations for studies using PDX models

| 항목 | PDX | PDO |
|---|---|---|
| 구축 시간 | 2-6개월 | 2-4주 |
| 비용 | 높음 (마우스·유지비) | 낮음 (배양액·배지) |
| 미세환경 | Human stromal→ mouse stromal | 스토로마 없음 (co-culture로 보완) |
| 면역환경 | 없음 (면역결핍 마우스) | 없음 (humanized 필요) |

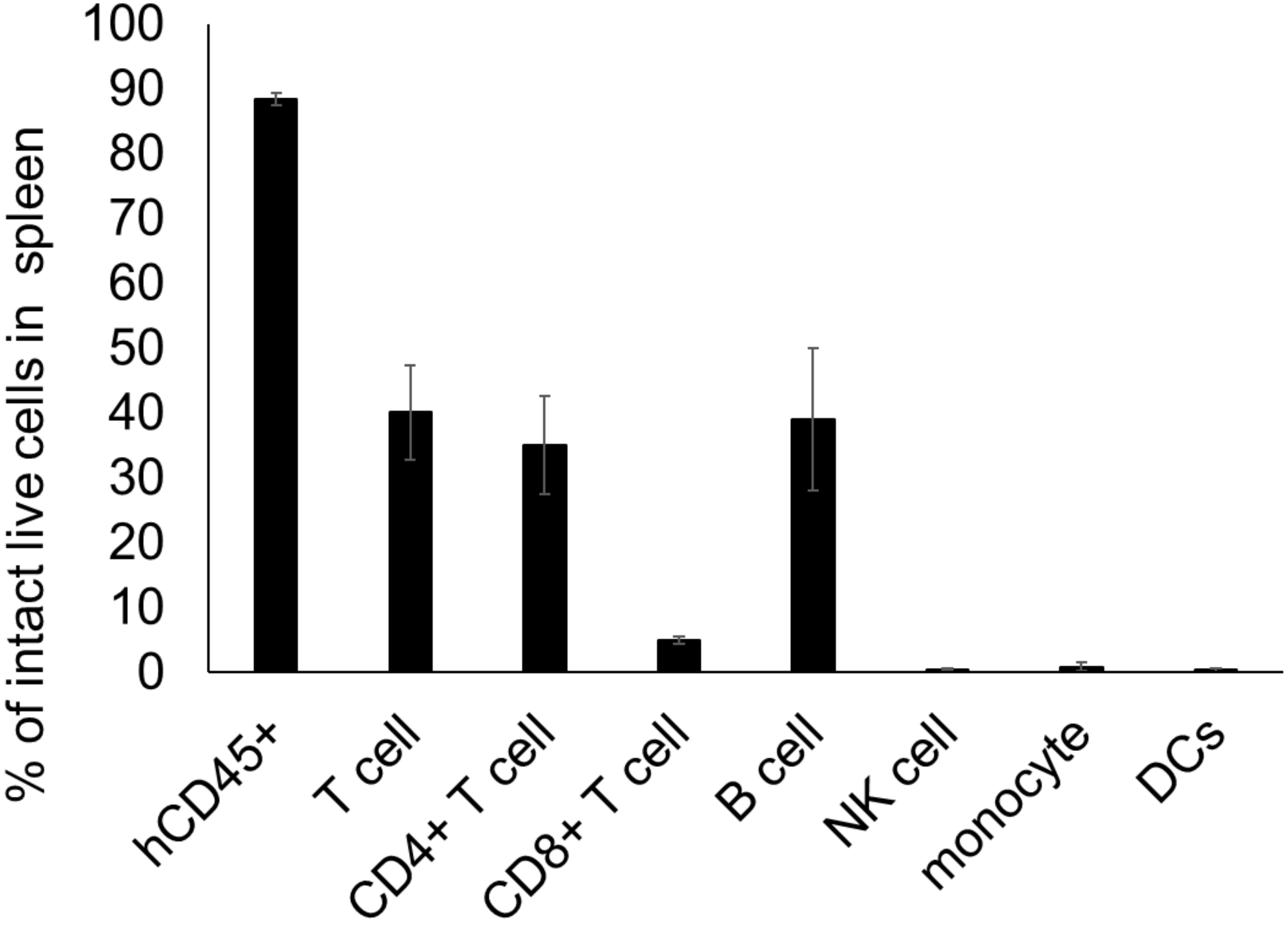
# V. Challenges and Future Prospects : Introducing immune pressure into PDX models




Park et al., Transplant Proc. 2024

# V. Challenges and Future Prospects : Human Immune Reconstitution in CD34⁺ Humanized Mice

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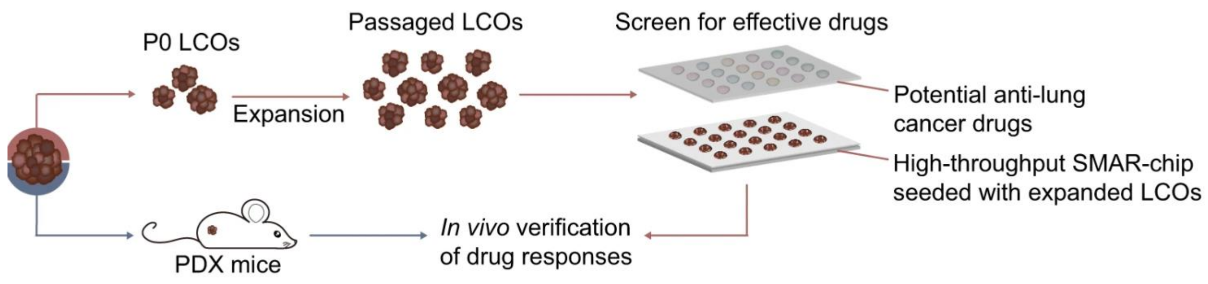
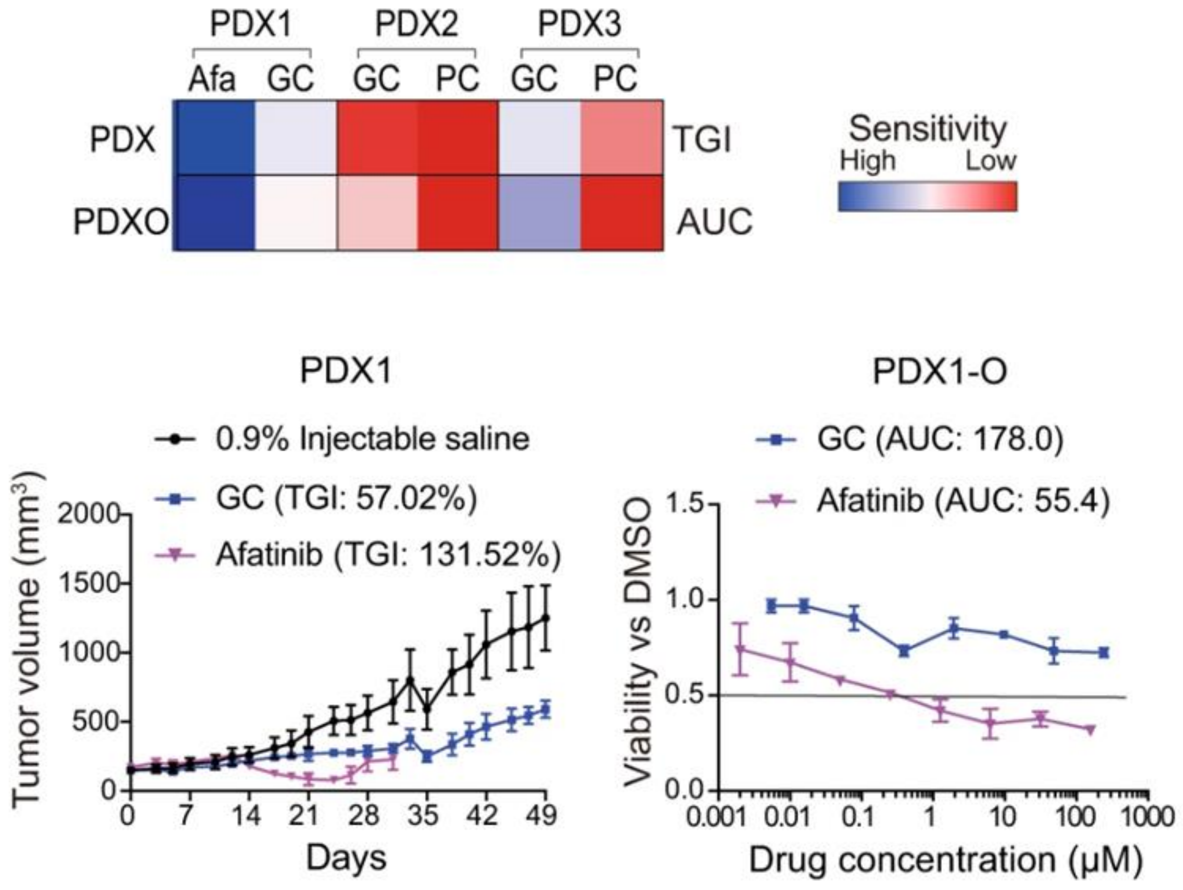
# V. Challenges and Future Prospects : Can we compress time without losing fidelity?




Two-step organoid → PDX validation workflow




Hu et al., Nature Comm, 2021

# VI. Conclusion

- **Why PDX matters**
  - PDX models overcomes the structural limitations of clinical studies
  - PDX models maintain the **patient's genomic and phenotypic landscape** through passages
  - PDX recapitulates **actual clinical drug responses** in patients with lung cancer

- **Where we are**
  - PDX has become a **critical translational platform supporting new therapies** by revealing tumor biology beyond efficacy endpoints
  - PDX allows **mechanistic dissection of complex resistance biology**, including lineage plasticity

- **Where we are going**
  - The field is moving toward **humanized PDX models** for immuno-oncology
  - Integrated **organoid–PDX workflows** will improve scalability and speed while preserving clinical relevance and biological fidelity.

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