Preclinical Models of Cancer

PATH4500: Cancer Biology I

October 27, 2025

Carla Concepcion-Crisol, PhD

Goal: To bridge basic discovery and clinical application

Challenge: How do we model the complexity of human cancer?

“All models are wrong, but some models are useful.”

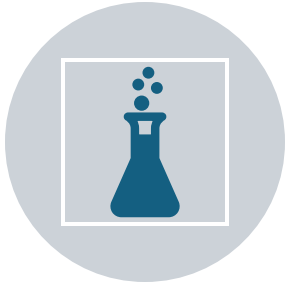
George E.P. Box

Key Learning Objectives

Understand various preclinical models of cancer

Assess the strengths and weaknesses of these models

Make informed decisions about which model is most suitable to use for what question



Design preclinical studies

Preclinical models of cancer

- *In vitro*
  - Cell lines
  - Spheroids
- *Ex vivo*
  - Organoids
  - Organ-on-a-chip
- *In vivo*
  - Genetically engineered mouse models (GEMMs)
  - Patient-derived xenografts (PDXs)
  - Syngeneic and transplant models
- (Deeper) dive into lung cancer models
- Research-in-progress examples

Some considerations

Fidelity to the biology

- Tumor initiation, progression, invasion, metastasis
- Therapeutic response
- Histopathology
- Tumor-stroma interactions
- Immunocompetence
- Secondary mutations
- How faithful to human biology?

What question are you asking?

Some considerations

Practical

- Speed
- Scale
- Cost
- Ease of genetic manipulation

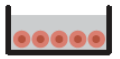
Is the model “good enough”?

Fidelity and practicality often compete

Table 1. Properties of cancer model systems.
GEMM, genetically engineered mouse model; MDO, murine-derived organoid; MDOX, murine-derived organoid transplantation; CLs, cell lines; PDX, patient-derived xenograft; iPS, inducible pluripotential stem cell; PDO, patient-derived organoid; PDOX, patient-derived organoid transplantation.





	GEMM	MDO	MDOX	CLs	PDX	iPS	PDO	PDOX
Wild-type cell culture	+	+	+	–	–	+	+	–
Preinvasive cancer models	+	+	+	–	–	+	+	+
Invasive cancer models	+	+	+	+	+	+	+	+
Metastatic cancer models	+	+	+	+	+	+	+	+
Cost	$$$$	$$	$$$	$	$$	$$	$$	$$$
Time	++++	+	++	+	++++	+++	++	+++
Success rate	high	med	med	med	med	low	med	med
Throughput therapies	low	med	low	high	low	high	med	low

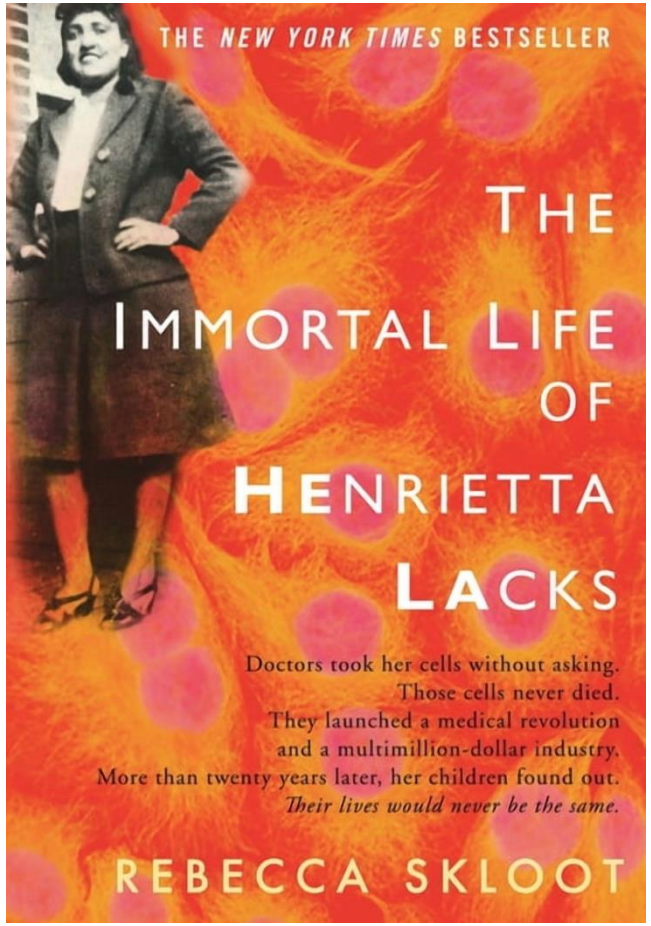
+ denotes 1 month or less; ++, 1–2 months; +++, 1–6 months; ++++, oftentimes more than several months.

PMID: 31171691

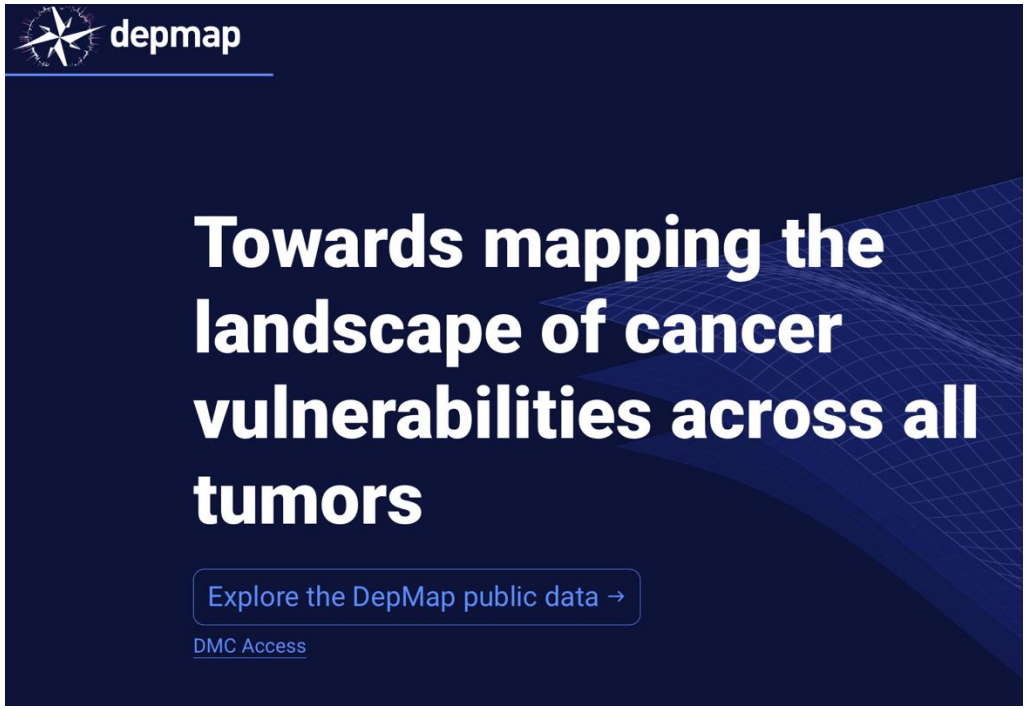
Cell lines

1951: The first human cancer cell line, HeLa, was established from cervical cancer cells of Henrietta Lacks without her knowledge or consent

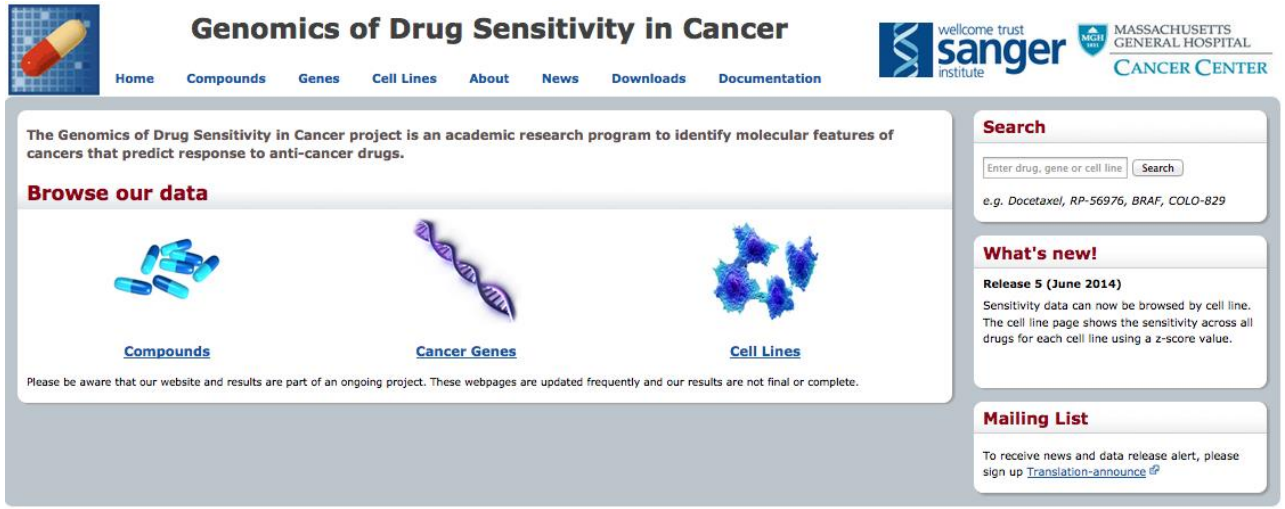
1990s: The National Cancer Institute launched the NCI-60 project, which led to a panel of 60 human cancer cell lines of various types



Cell lines



CCLE Cancer Cell Line Encyclopedia

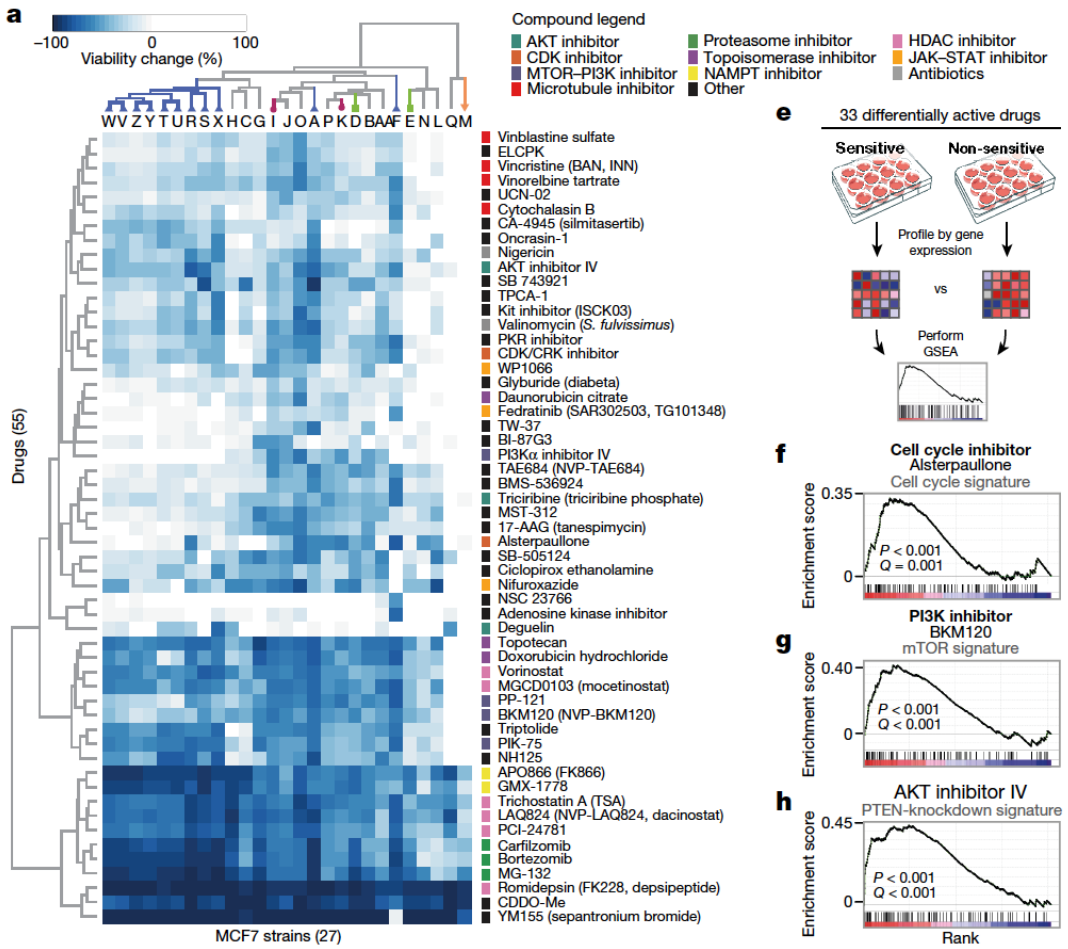


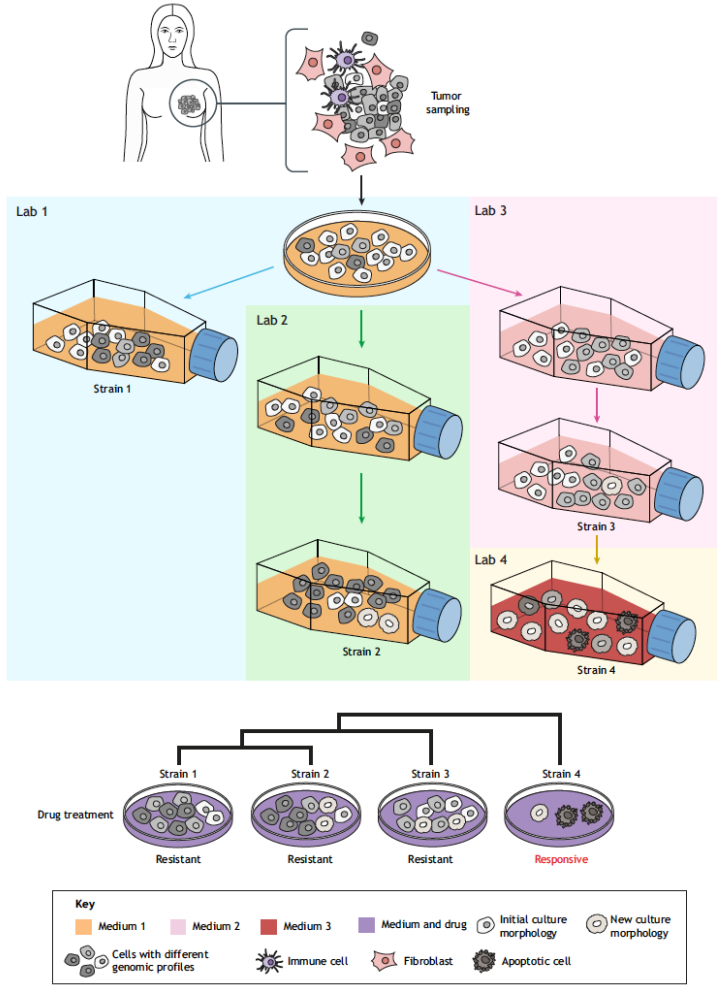
https://depmap.org/portal/home/#/

https://sites.broadinstitute.org/ccle/

https://www.cancerrxgene.org

Cell lines





PMID: 30459183, PMID: 30089904

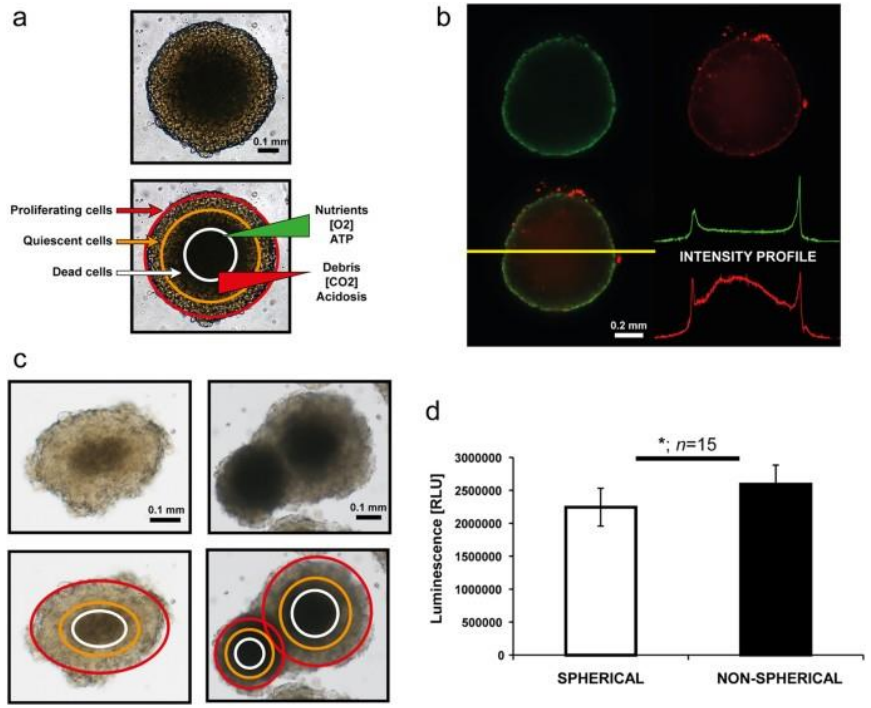
2D to 3D: cancer spheroids

3D aggregates of immortalized cancer cell lines

Often uses ultra-low adhesion dishes

Some form without addition of extracellular matrix (ECM) proteins; others require the addition of basement membrane extract (BME) or collagen for efficient formation

Mimic cell-cell interaction, hypoxia, drug penetration, response and resistance and production/deposition of extracellular matrix to an extent greater than 2D cultures



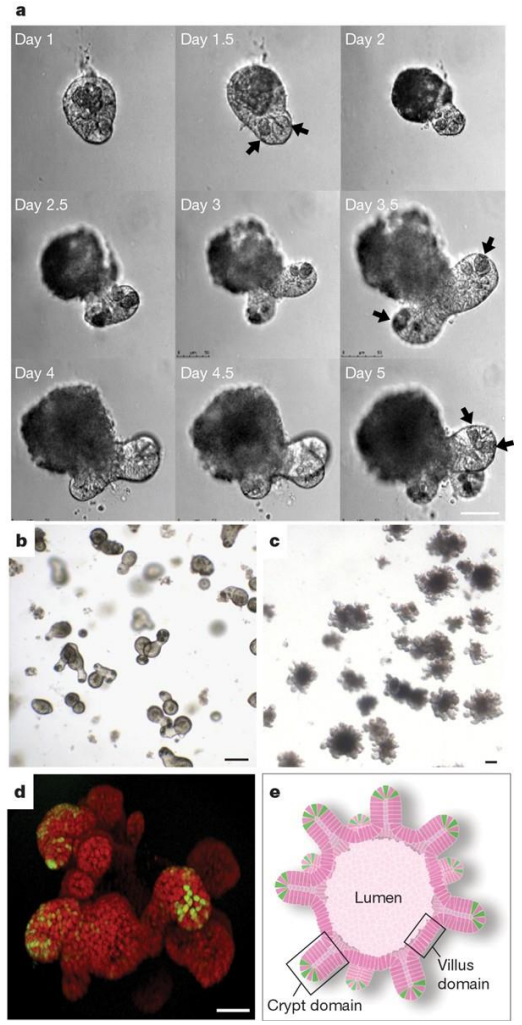
PMID: 26752500

Organoids represent a breakthrough in modeling normal tissues

Microscopic self-organizing, 3D structures that are grown from stem cells *in vitro*

Recapitulate many structural and functional aspects of *in vivo* counterpart organs

Adapted to culture tumor organoids of various cancer types



PMID: 19329995

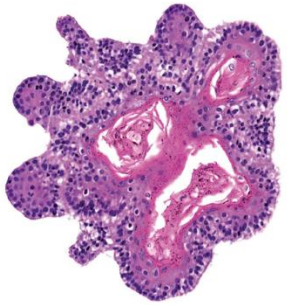
Patient-derived organoids (PDOs)

Mimic the 3D structure and function of human tissues

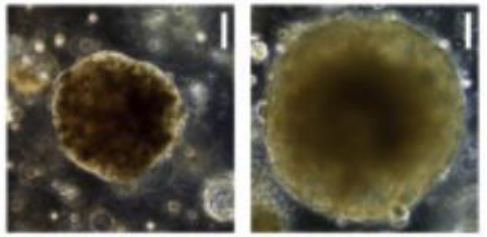
Capture the cellular heterogeneity and spatial organization found within tumors

Cultures with stromal cells enable studies of the tumor microenvironment (TME)

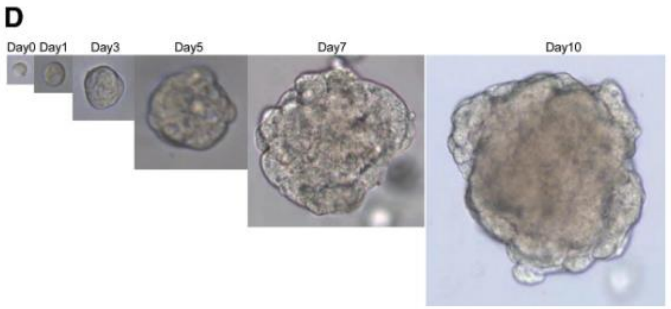
Uses extracellular matrices, air-liquid interface (ALI) cultures, chips, microfluidics



Squamous cell carcinoma (oral mucosa)



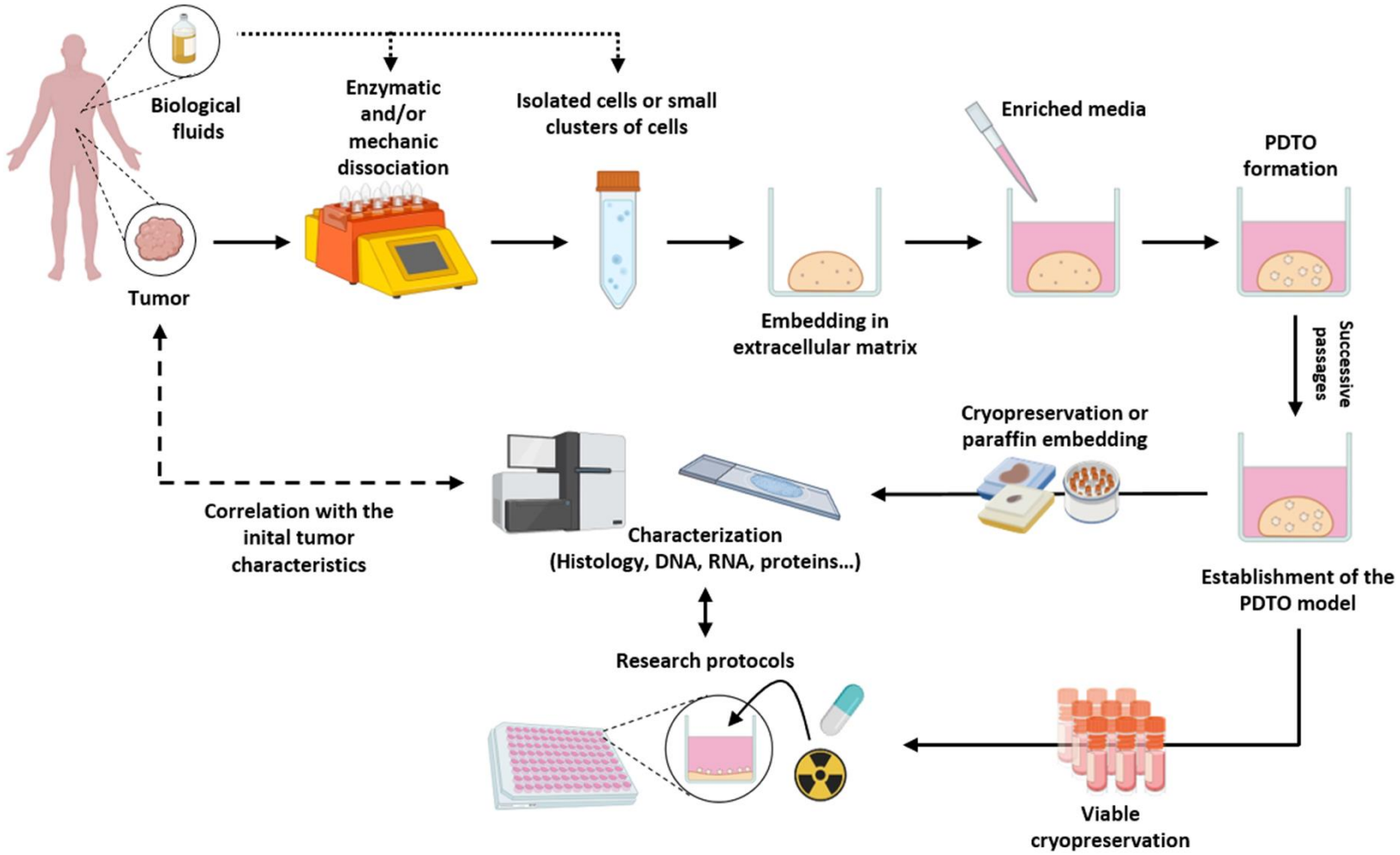
Bladder cancer



Human colon adenocarcinoma organoids

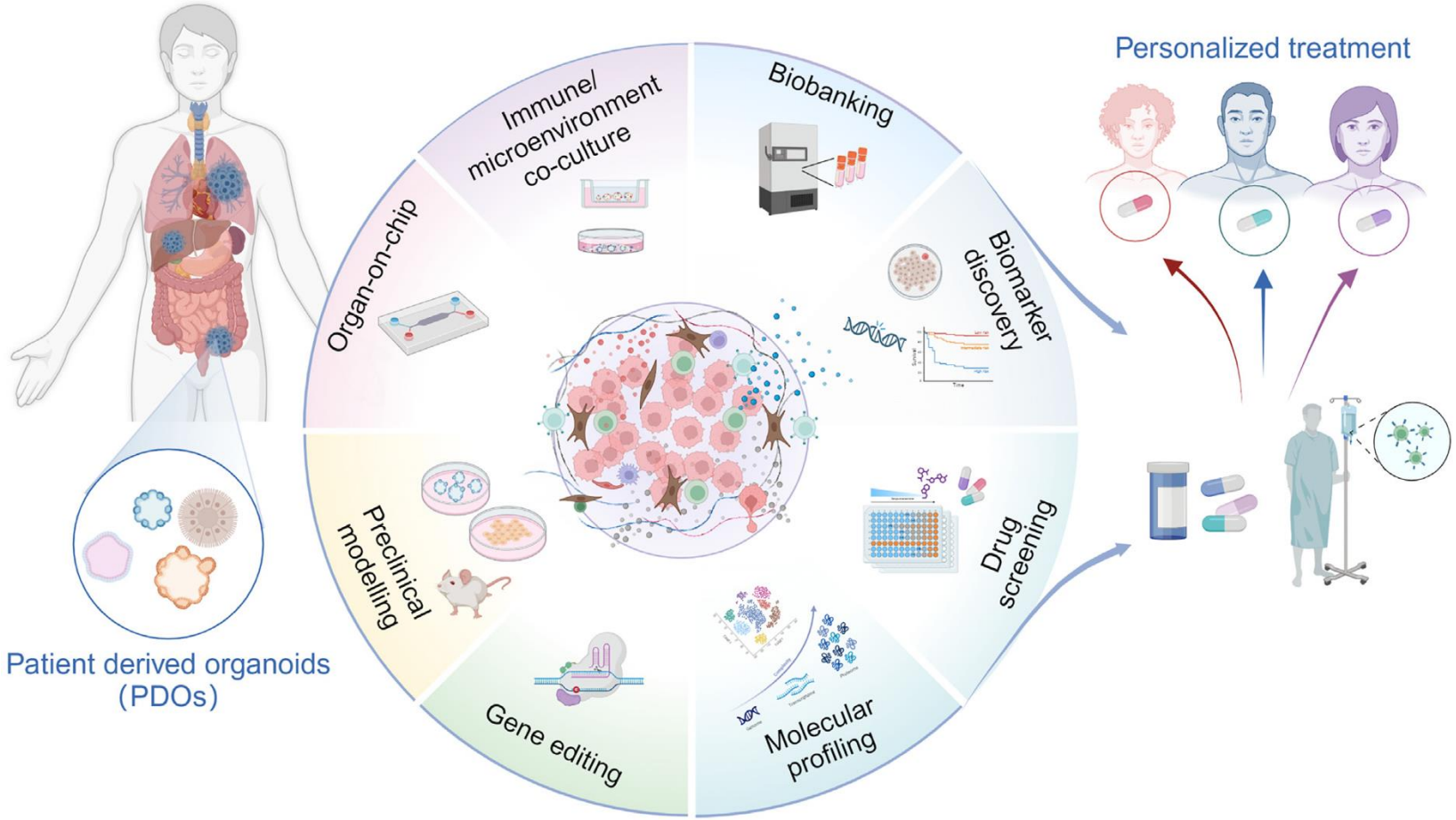
PMID: 29625057, PMID: 31171691, PMID: 21889923

Patient-derived organoids (PDOs)



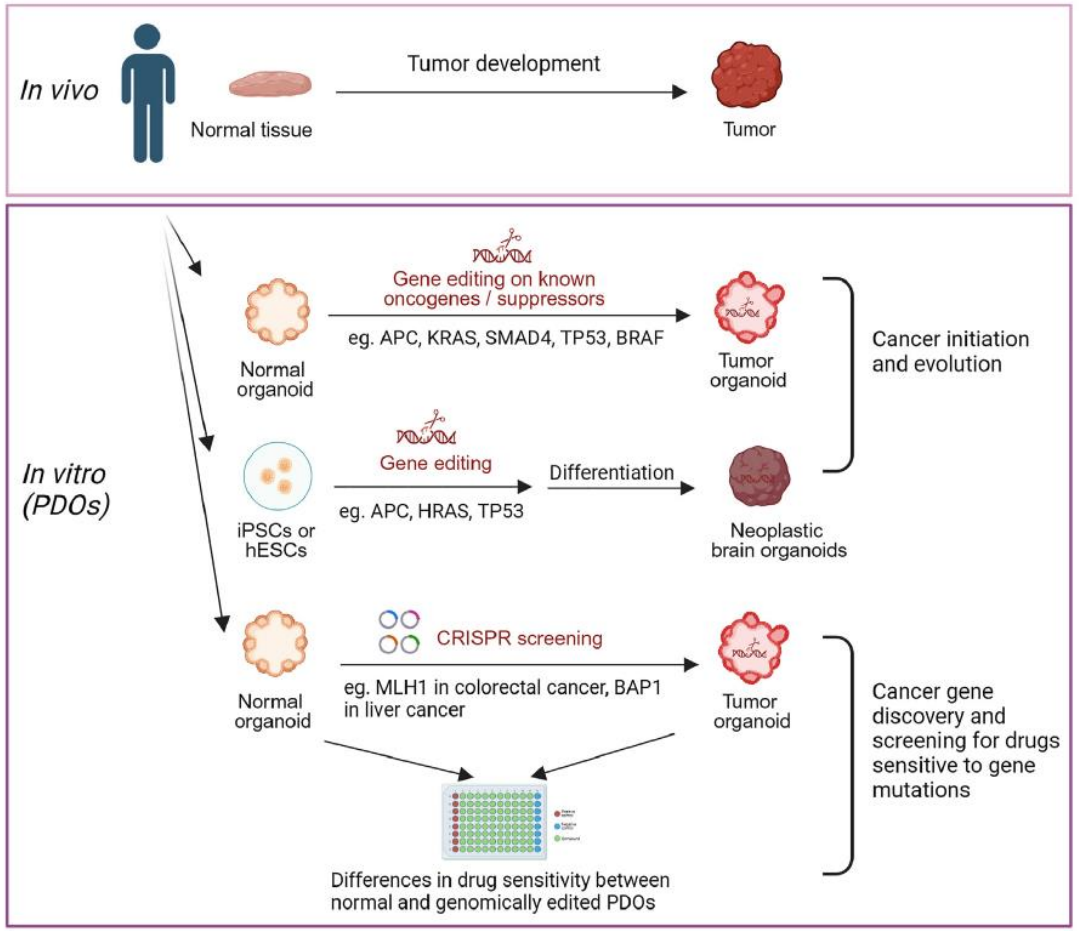
PMID: 38945959

Patient-derived organoids (PDOs)



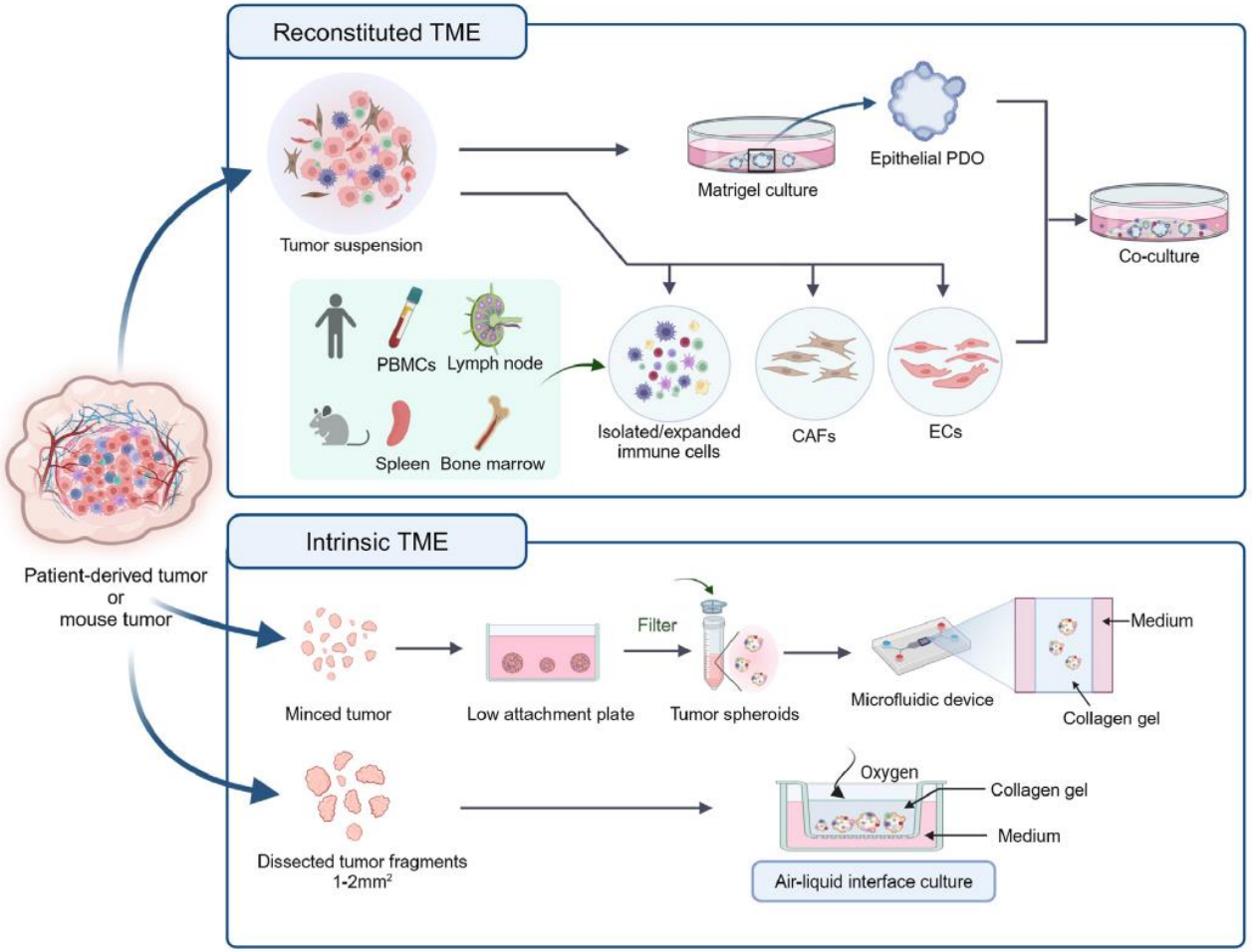
PMID: 39341206

Patient-derived organoids (PDOs)



PMID: 39341206

Patient-derived organoids (PDOs)

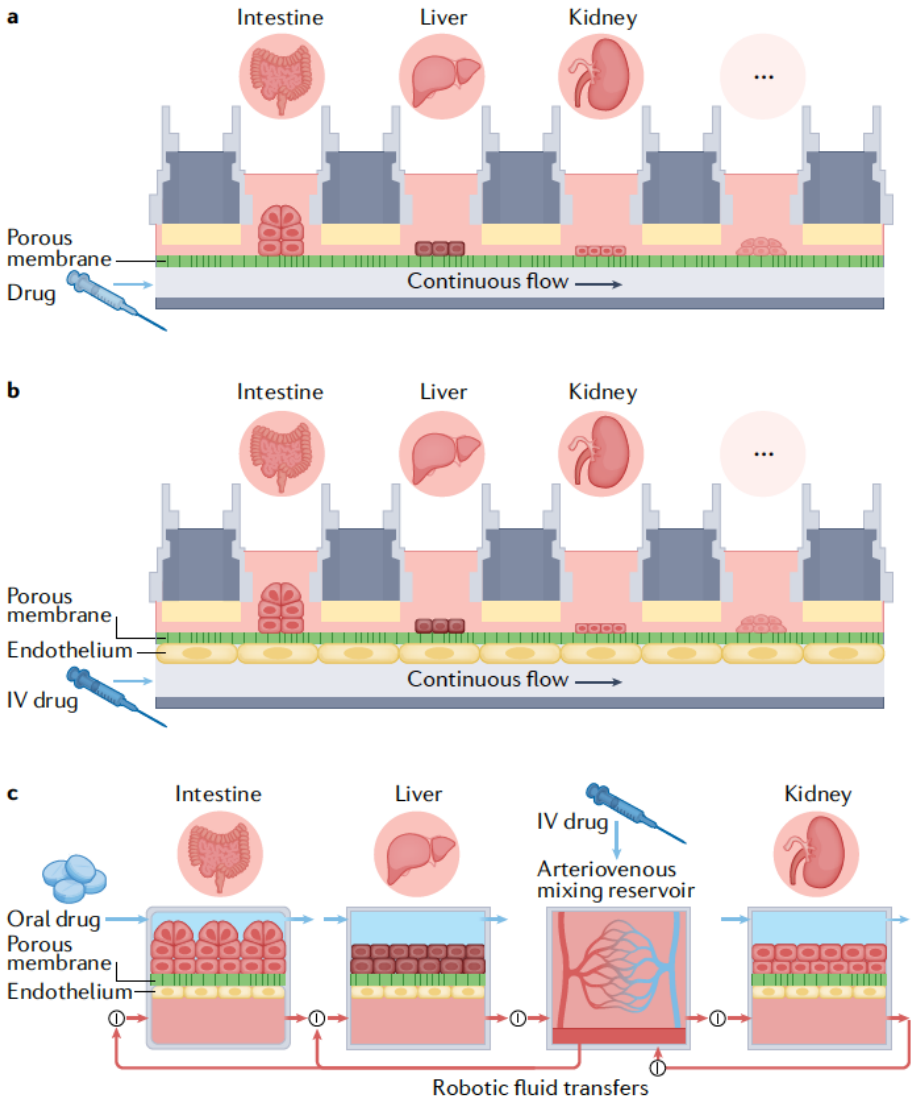


PMID: 39341206

Organ-on-a-chip

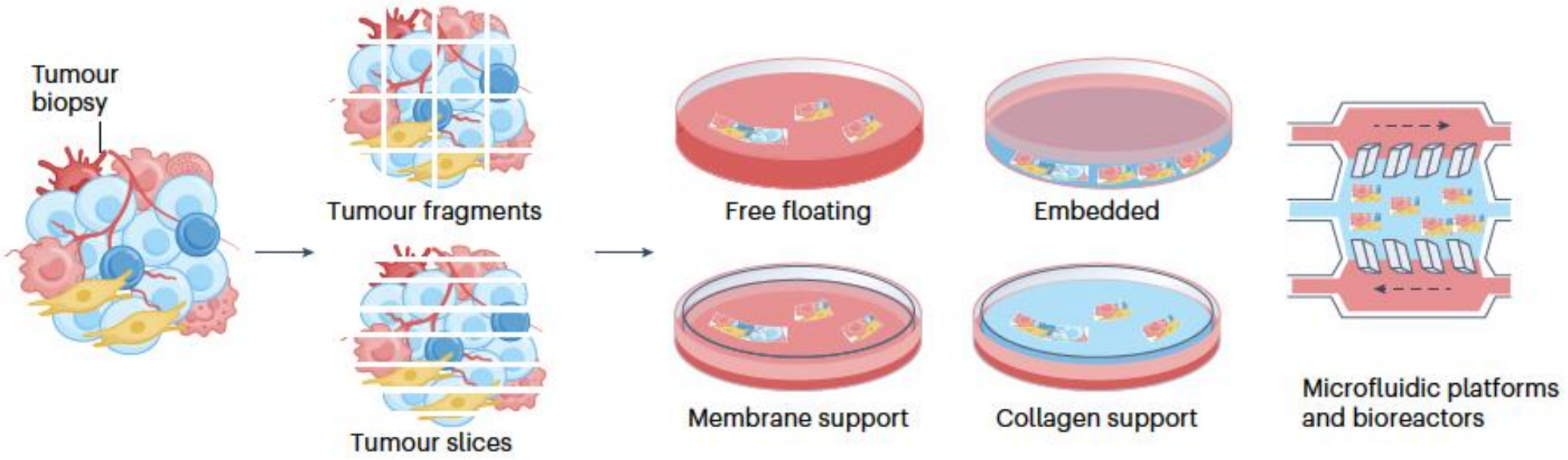
Microfluidic culture devices that contain hollow channels lined by living cells and tissues cultured under dynamic flow

Fluid flow, shear stress, nutrient supply can be controlled



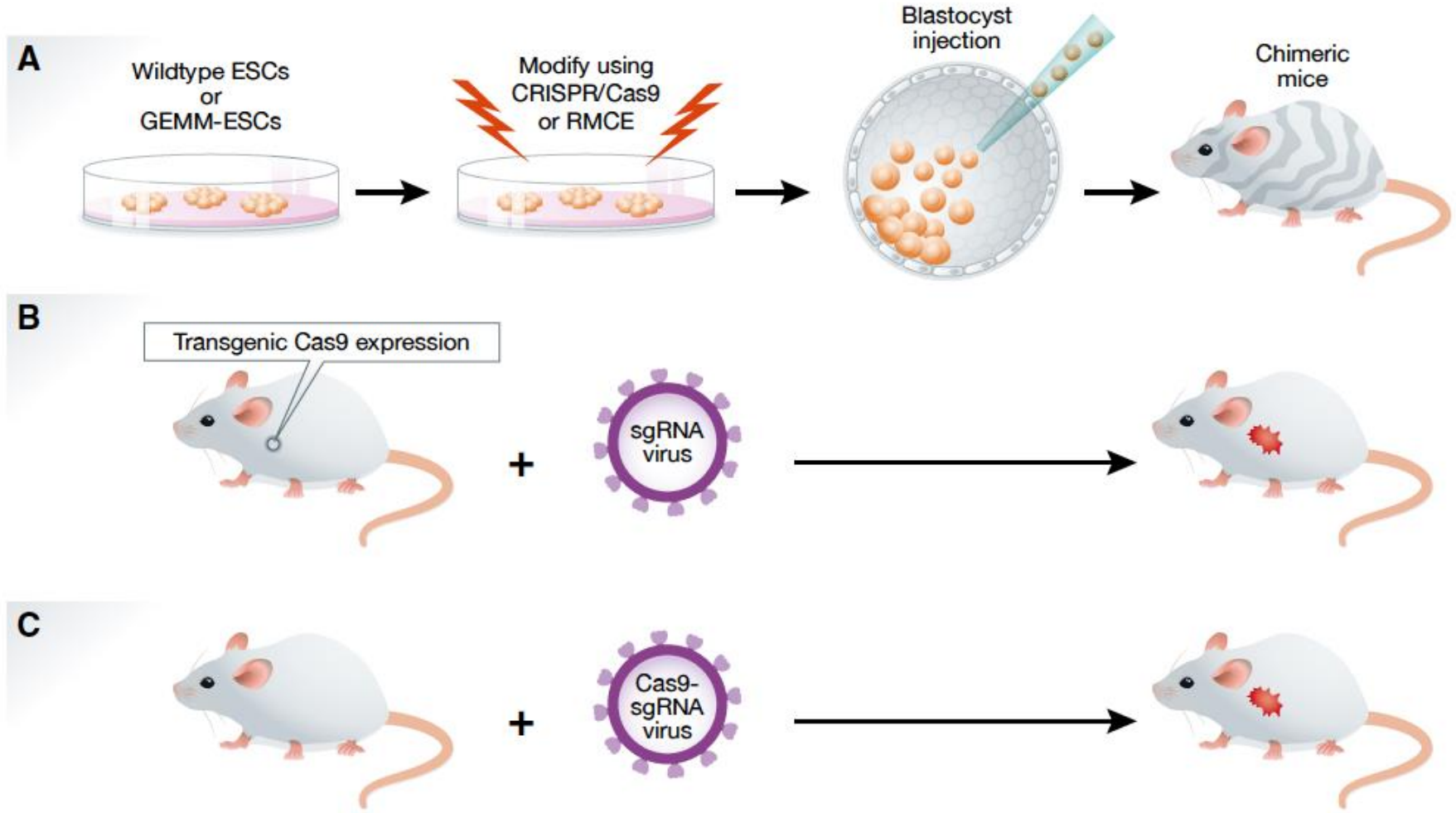
PMID: 35338360

Non-organoid tumor explant culture



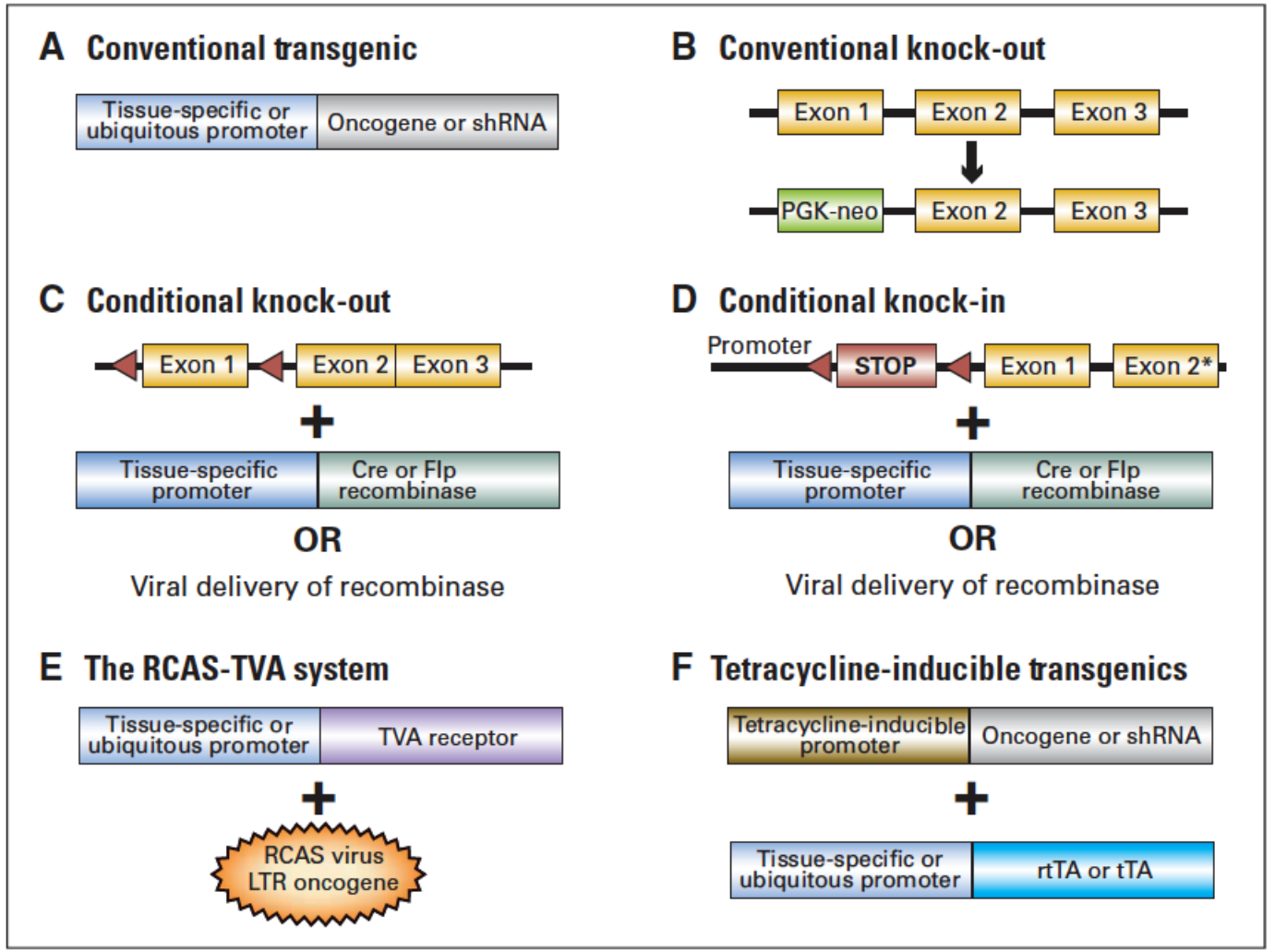
PMID: 38977835

Genetically engineered mouse models (GEMMs)



PMID: 28028012

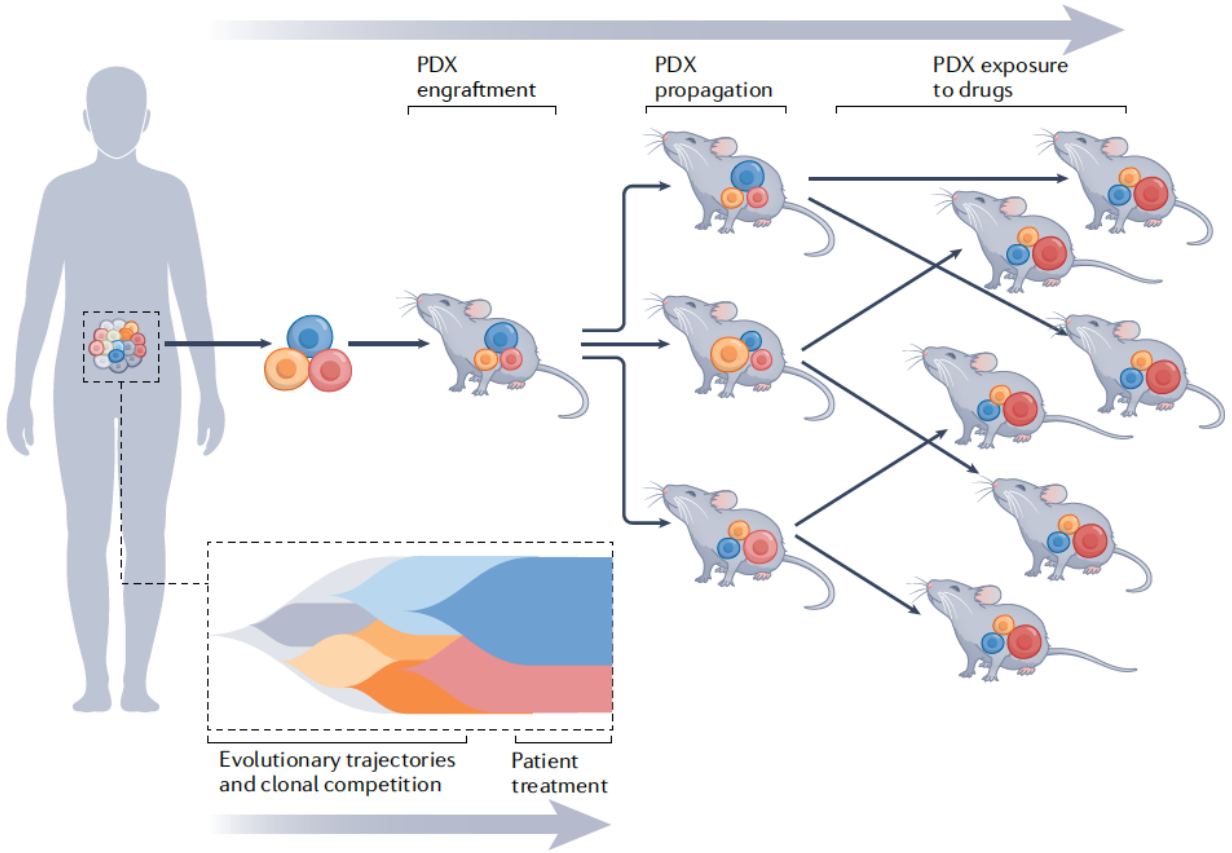
Genetically engineered mouse models (GEMMs)



PMID: 21263096

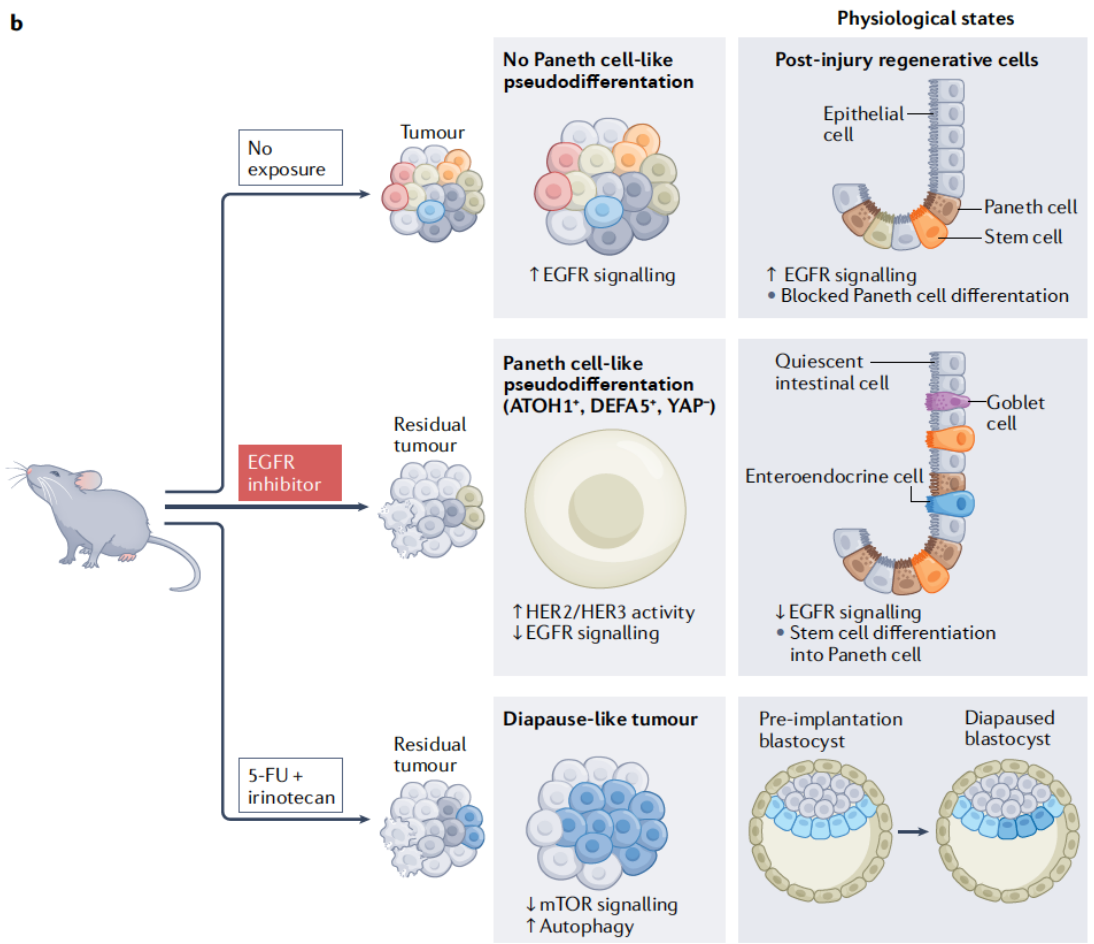
Patient-derived xenografts (PDXs)

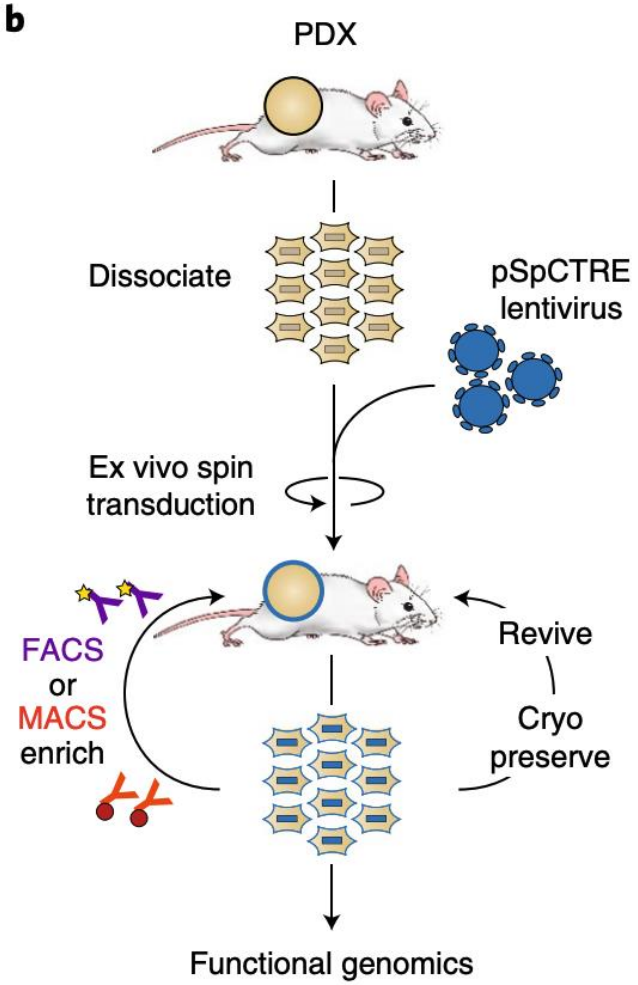
Tumor fragments from surgical resections or biopsies that are propagated in mice through a series of implants and explants in immunodeficient mice



PMID: 38977835

Patient-derived xenografts (PDXs)





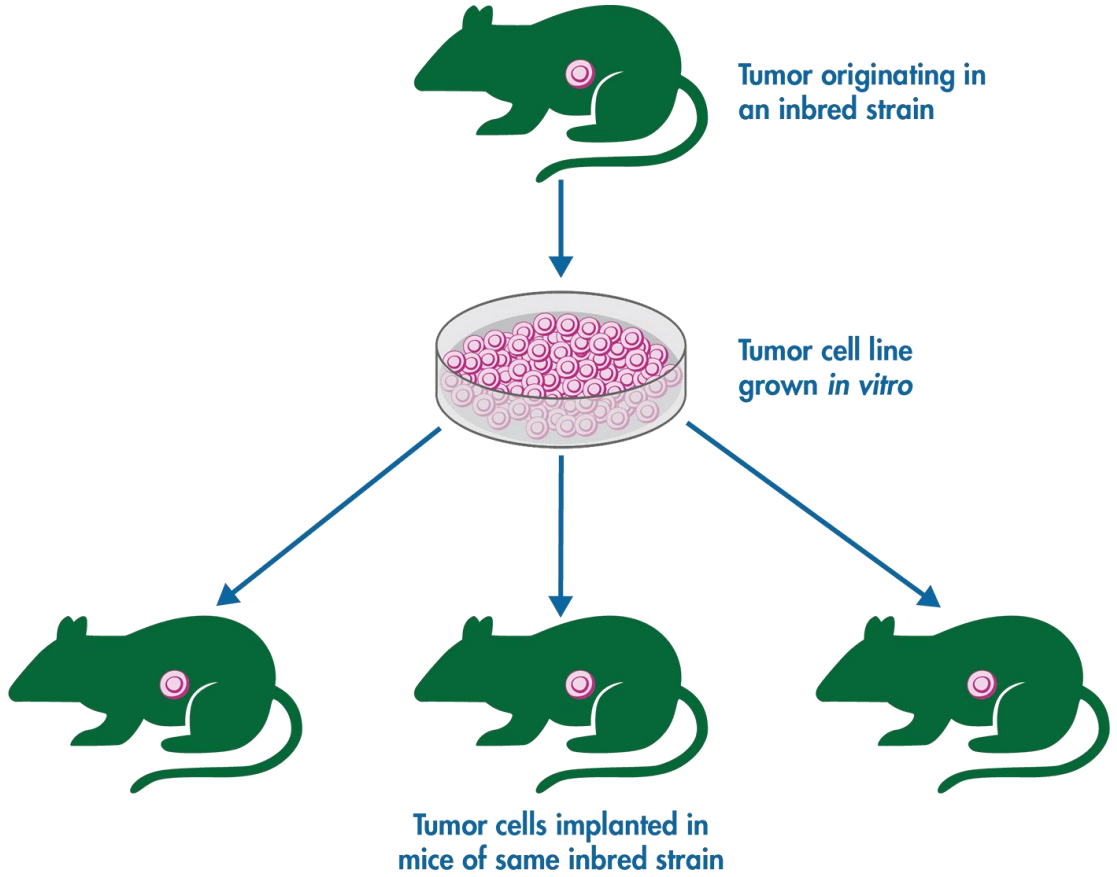
PMID: 36151307; PMID: 33345196

Syngeneic models

Models wherein cancer cells from one mouse are transplanted to another without the risk of rejection

Immunocompetent – enabling immuno-oncology studies

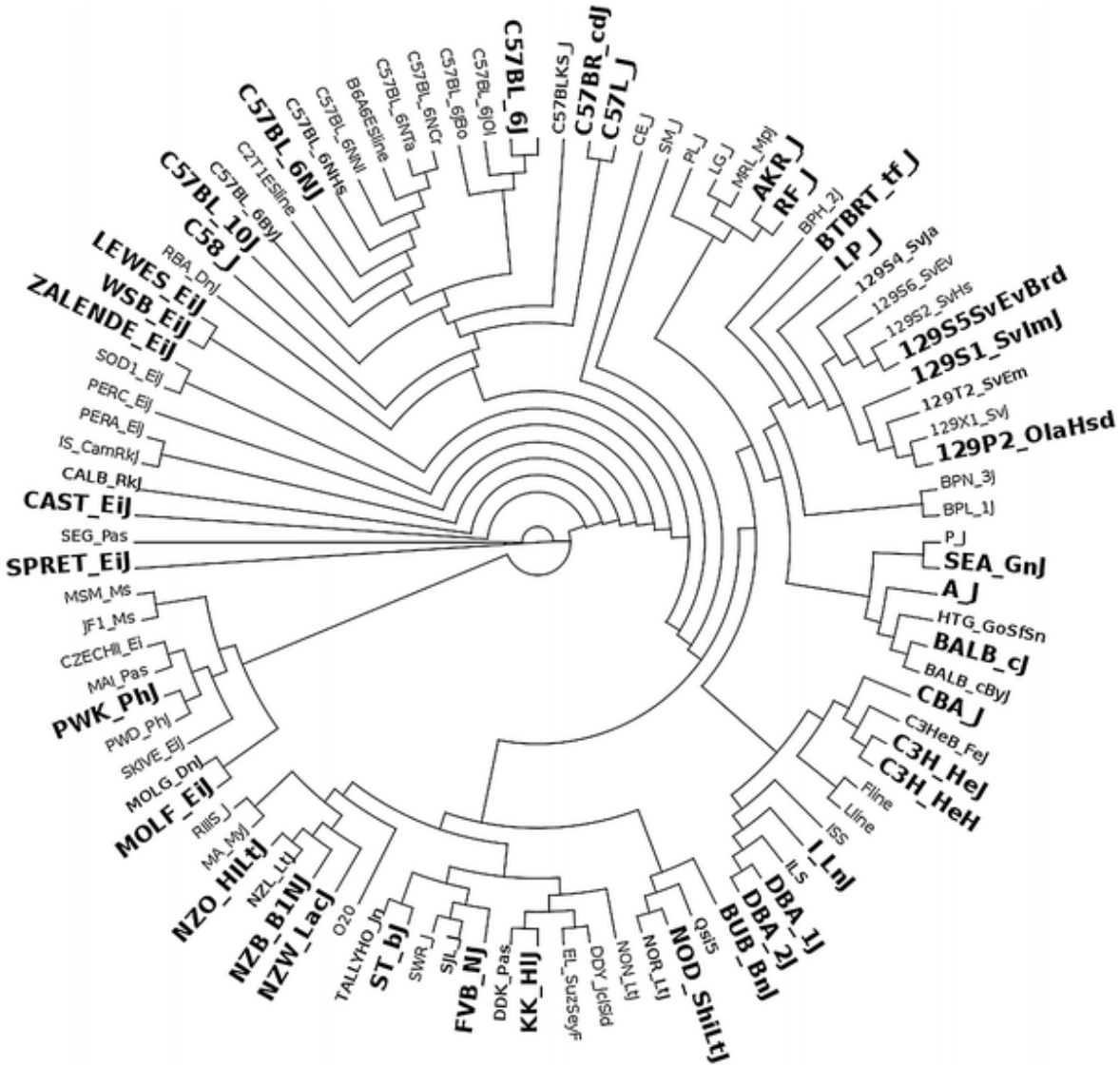
Transplantation site is determined by the route of delivery (e.g. orthotopic vs subcutaneous)



How important is the site of transplantation?

Image: Reaction Biology 2025

A phylogenetic tree of inbred laboratory strains



PMID: 26123534

Examples of immunodeficient transplant recipients

Strain Names	Mature B Cells	Mature T Cells	Dendritic Cells	Macrophages	Natural Killer Cells	Complement	Leakiness
NU/J (002019) **Inbred Nude**	Present	Absent	Present	Present	Present	Present	N/A
B6 Rag1 (002216) **Rag1 KO** B6.129S7-*Rag1*^{tm1Mom}/J	Absent	Absent	Present	Present	Present	Present	Absent
NOD *scid* gamma MHC Class I/II DKO (025216) **NSG-MHC I/II DKO** NOD.Cg-*Prkdc*^{scid} *H2-K1*$^{b-tm1Bpe}$ *H2-Ab1*$^{g7-em1Mvw}$ *H2-D1*$^{b-tm1Bpe}$ *Il2rg*^{tm1Wjl}/SzJ	Absent	Absent	Defective	Defective	Absent	Absent	Absent

Quick Poll

You need to rapidly screen 50 different compounds for basic cell death. Which model would you start with?

A) Cell line
B) PDX mouse
C) Tumor organoid

You are studying a very rare tumor. Which model would you start with?

A) Cell line
B) PDX mouse
C) Tumor organoid

Case Study

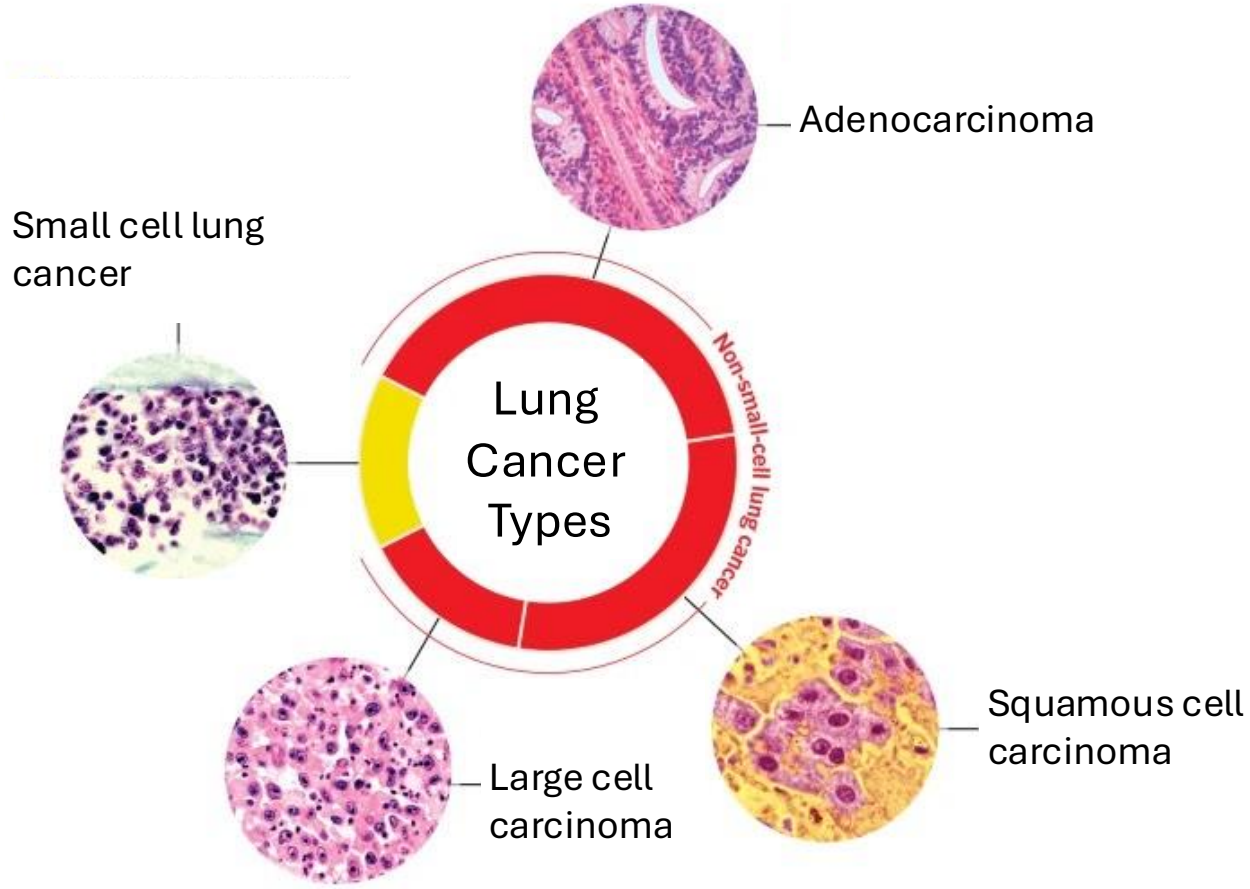
You discover a rare, aggressive form of lung cancer defined by a complex fusion event involving a chromatin regulator. You want to study if this specific genetic change drives resistance to standard chemotherapy and if so, its underlying mechanism.

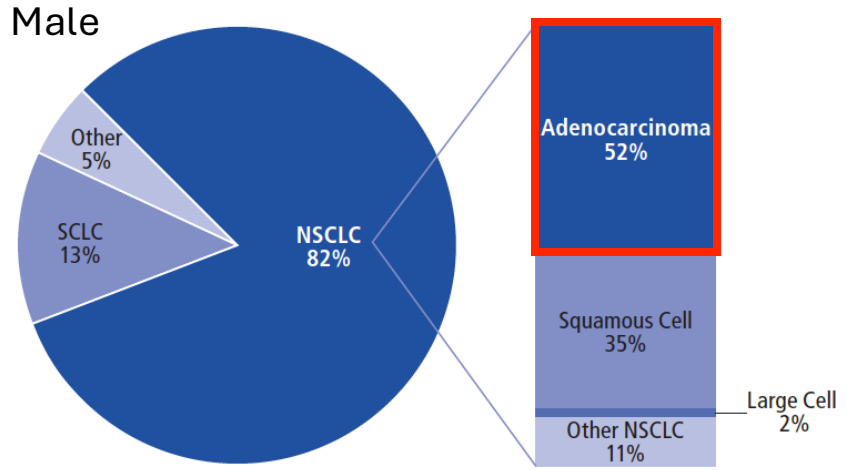
Cell Line Status: No commercial cell lines carry this specific fusion.
Patient Tissue: You have access to a fresh biopsy from one patient with this tumor.

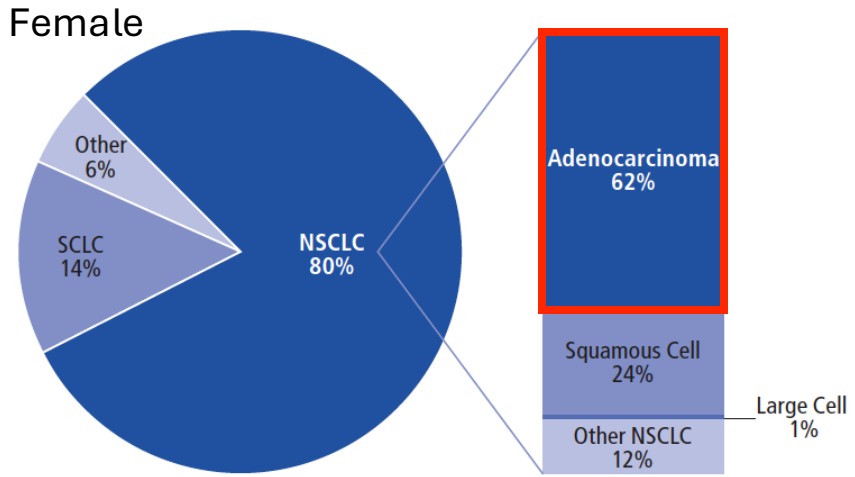
Which preclinical model will you choose to determine if (and how) this genetic change drives resistance?

A (deeper) dive into the evolution of various lung cancer models

Types and subtypes of lung cancer



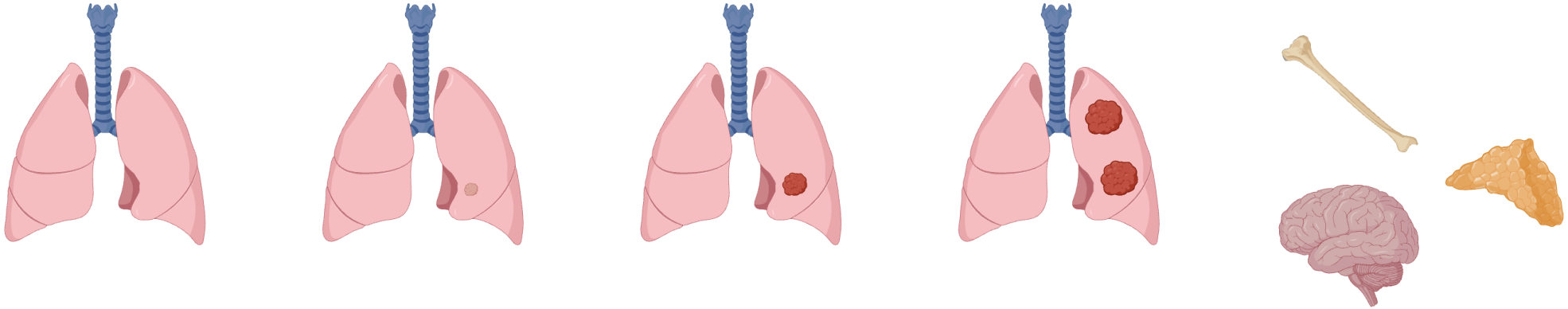




PMID: 25208070, PMID: 39817679

Lung cancer progression

Normal | Pre-cancer | Early | Advanced | Metastasis

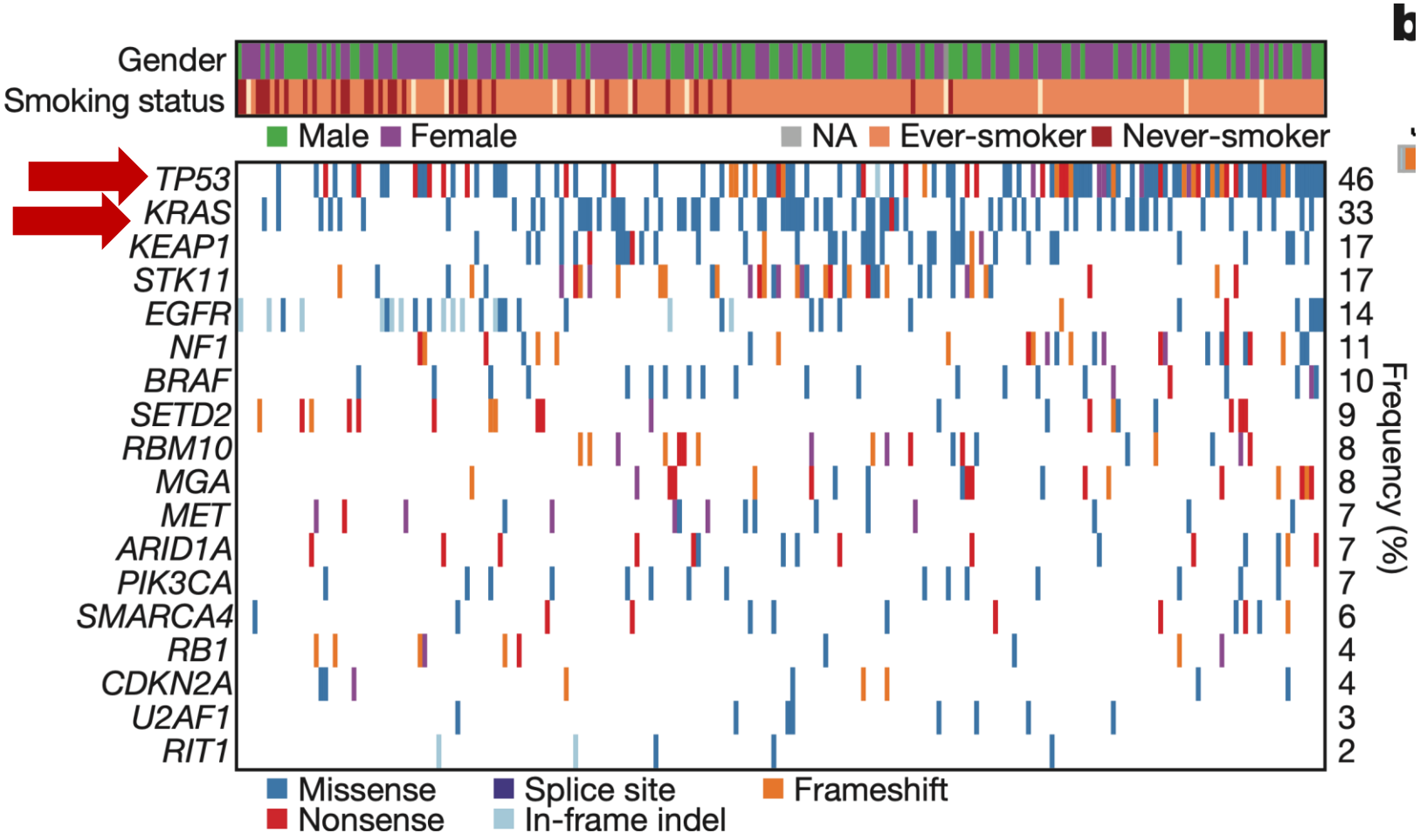


Smoking
Pollution
Occupational hazards
Other environmental factors

Tumor progression

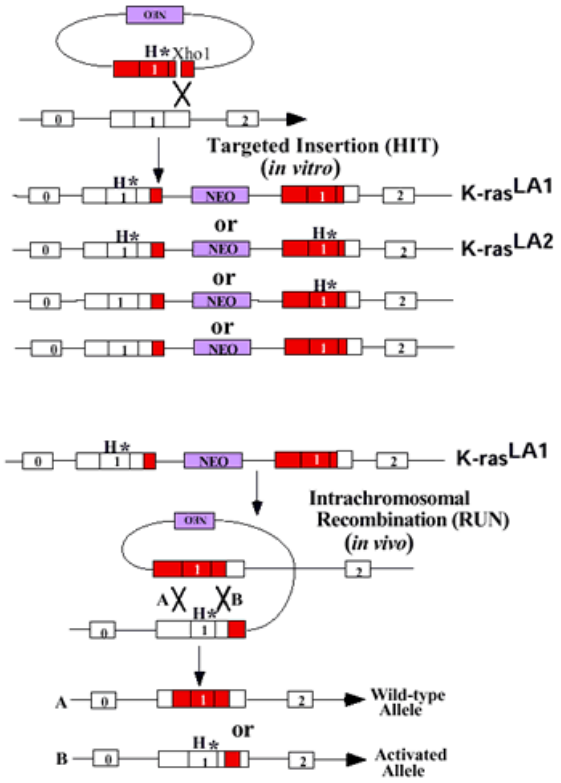
Lineage fidelity

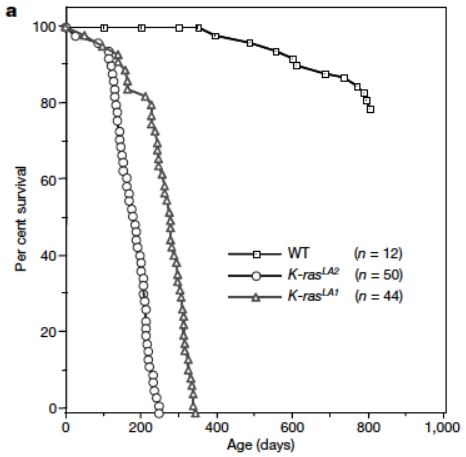
Somatic mutations in lung adenocarcinoma (LUAD)

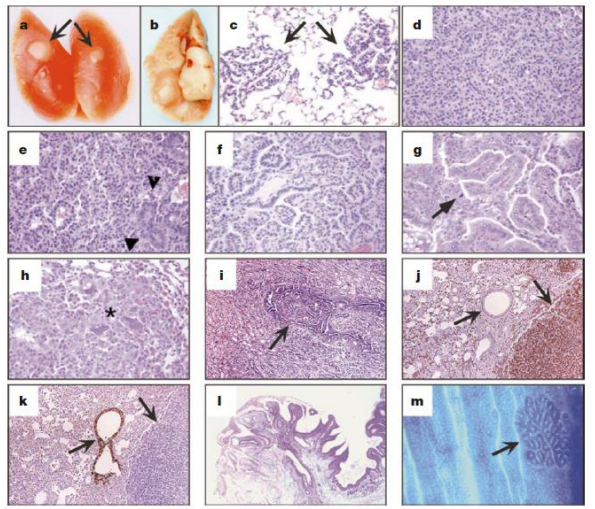


PMID: 25079552

The pioneer: the latent KRAS model (*Kras*^{LA1} & *Kras*^{LA2})







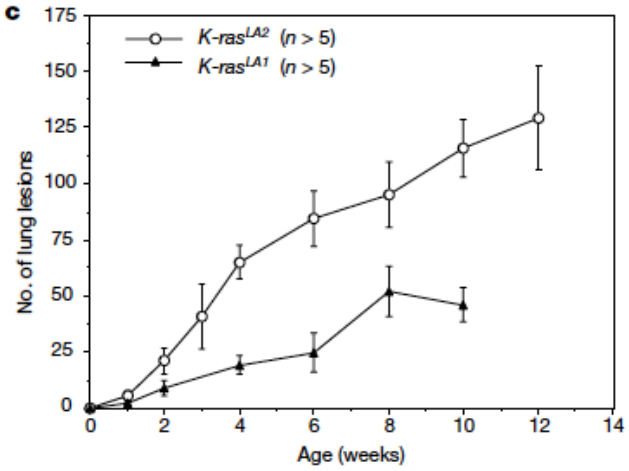


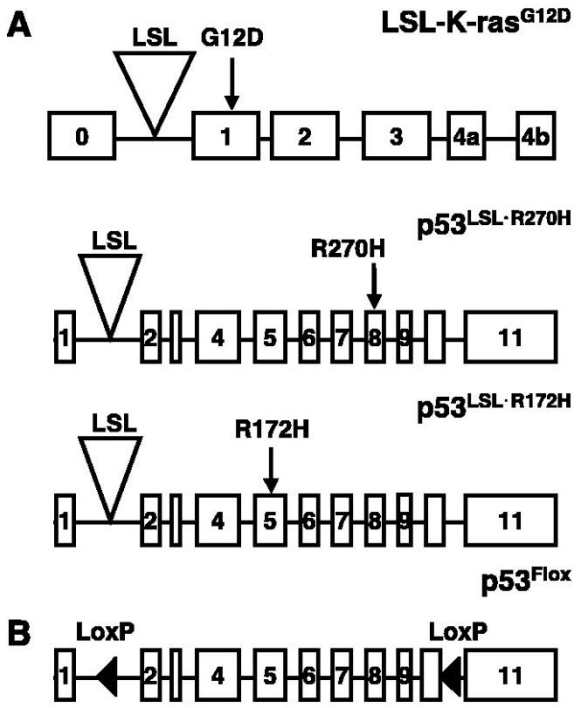
Table 1 Effect of *p53* status on the tumour spectrum in *K-ras*^{LA} mice

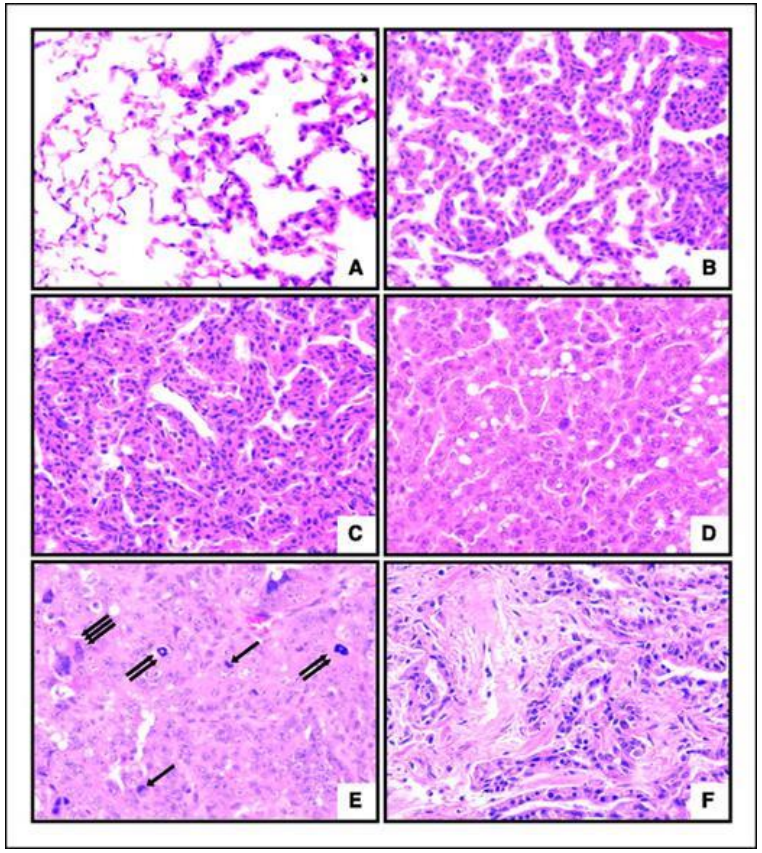
Tumour type	*K-ras*$^{LA1+/-}$; *p53*$^{+/-}$	*K-ras*$^{LA1+/-}$; *p53*$^{-/-}$
Lung adenocarcinoma	100	100
Thymic lymphoma	37	39
Papilloma	24	4
Fibrosarcoma	3	28
Haemangiosarcoma	2	33
Duodenal adenocarcinoma	0	2
Undifferentiated sarcoma	1	0
Histiocytic sarcoma	1	4
Medullablastoma	0	2
Osteosarcoma	0	2
Teratoma	0	2

Percentage of animals with a given tumour type. Numbers were combined for animals from both *K-ras*^{LA1} and *K-ras*^{LA2}. *K-ras*$^{LA1+/-}$; *p53*$^{+/-}$ (n = 54); *K-ras*$^{LA1+/-}$; *p53*$^{-/-}$ (n = 87).

PMID: 11323676

Temporal and spatial control: the conditional KP model





How to deliver Cre into lung cells?

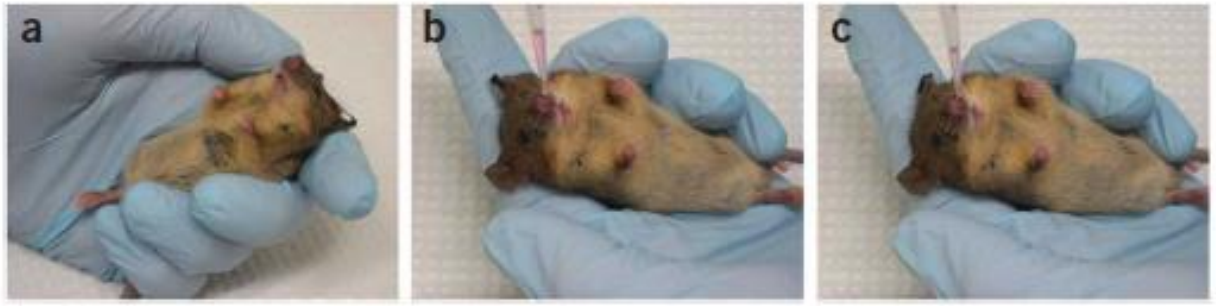
- Intratracheal or intranasal
  - Adenovirus-Cre
  - Lentivirus-Cre
- Germline
  - Cell-type specific CreER mouse lines (e.g. *Sftpc-CreER*, *Scgb1a1-CreER)*

PMID: 16288016

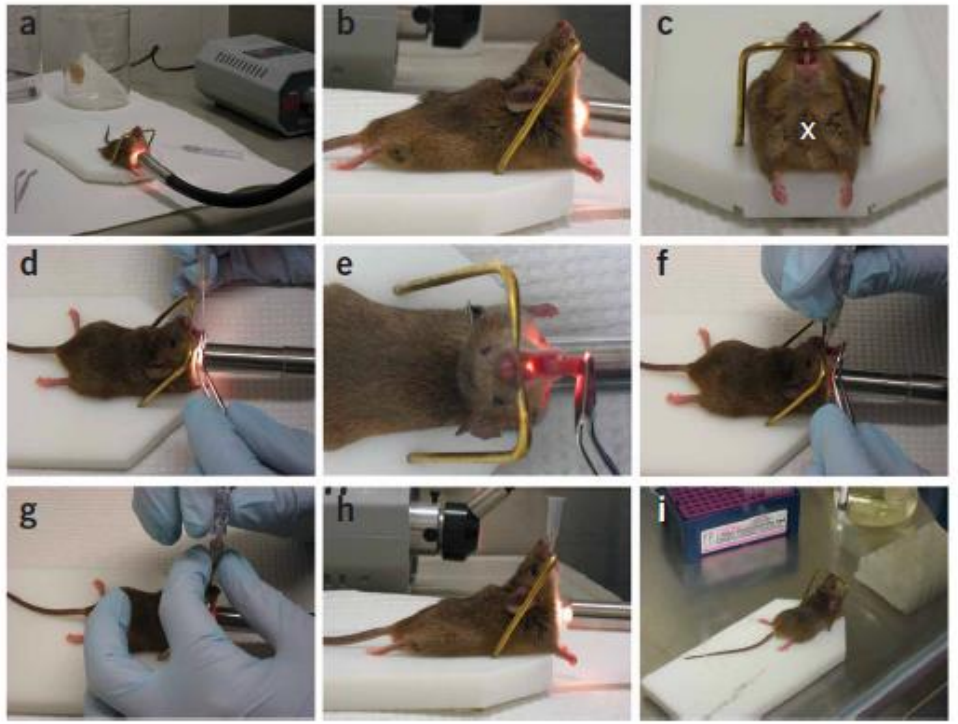
Temporal and spatial control: the conditional KP model

How to deliver Cre into lung cells?

Intranasal



Intratracheal



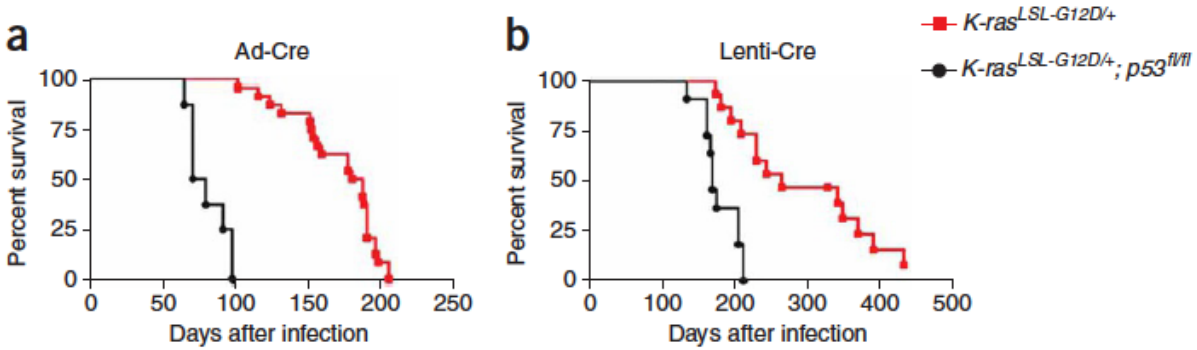
PMID: 19561589

Temporal and spatial control: the conditional KP model

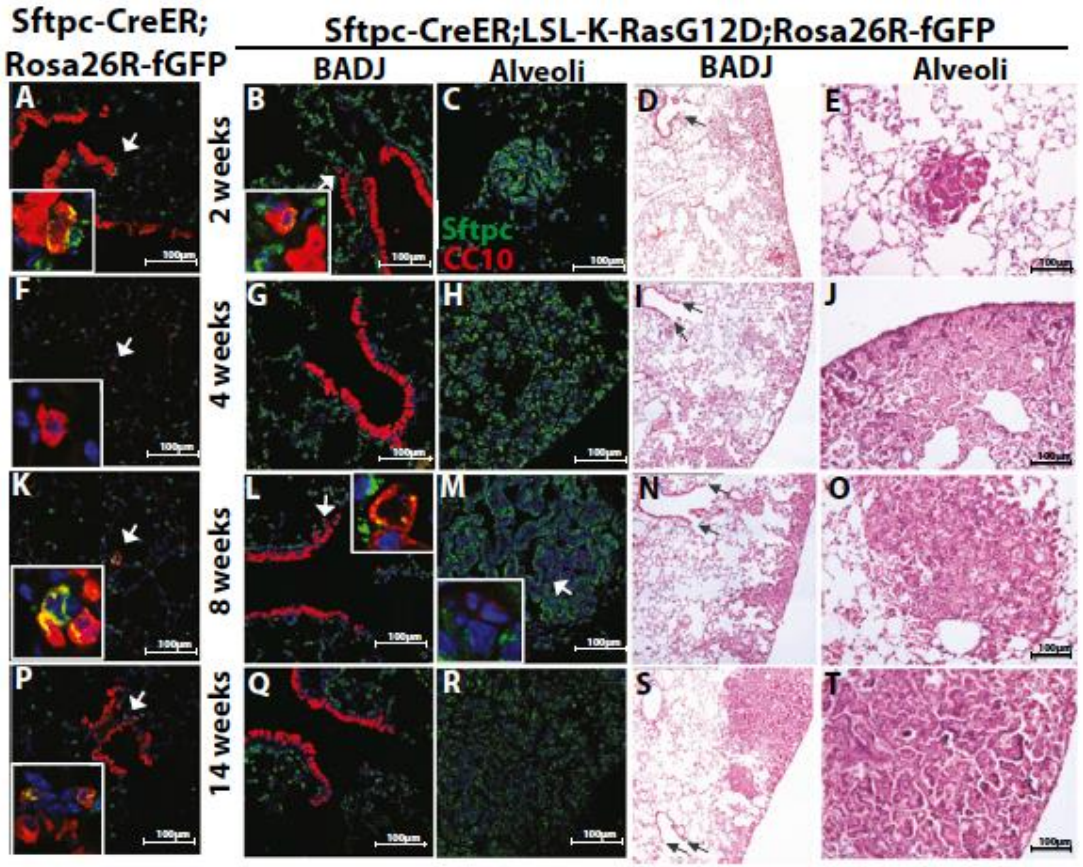
How to deliver Cre into lung cells?

Adenovirus

Lentivirus

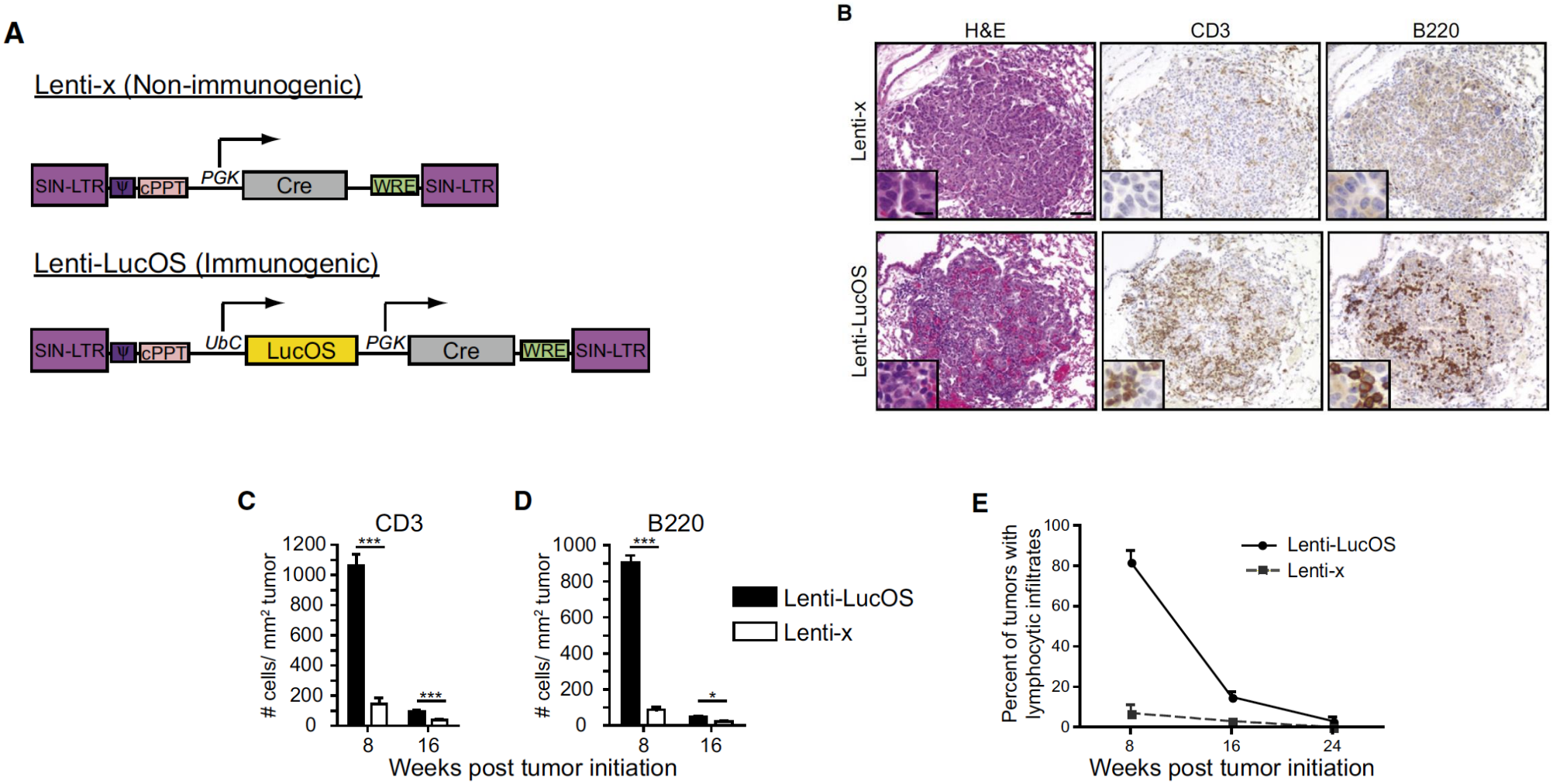


Germline



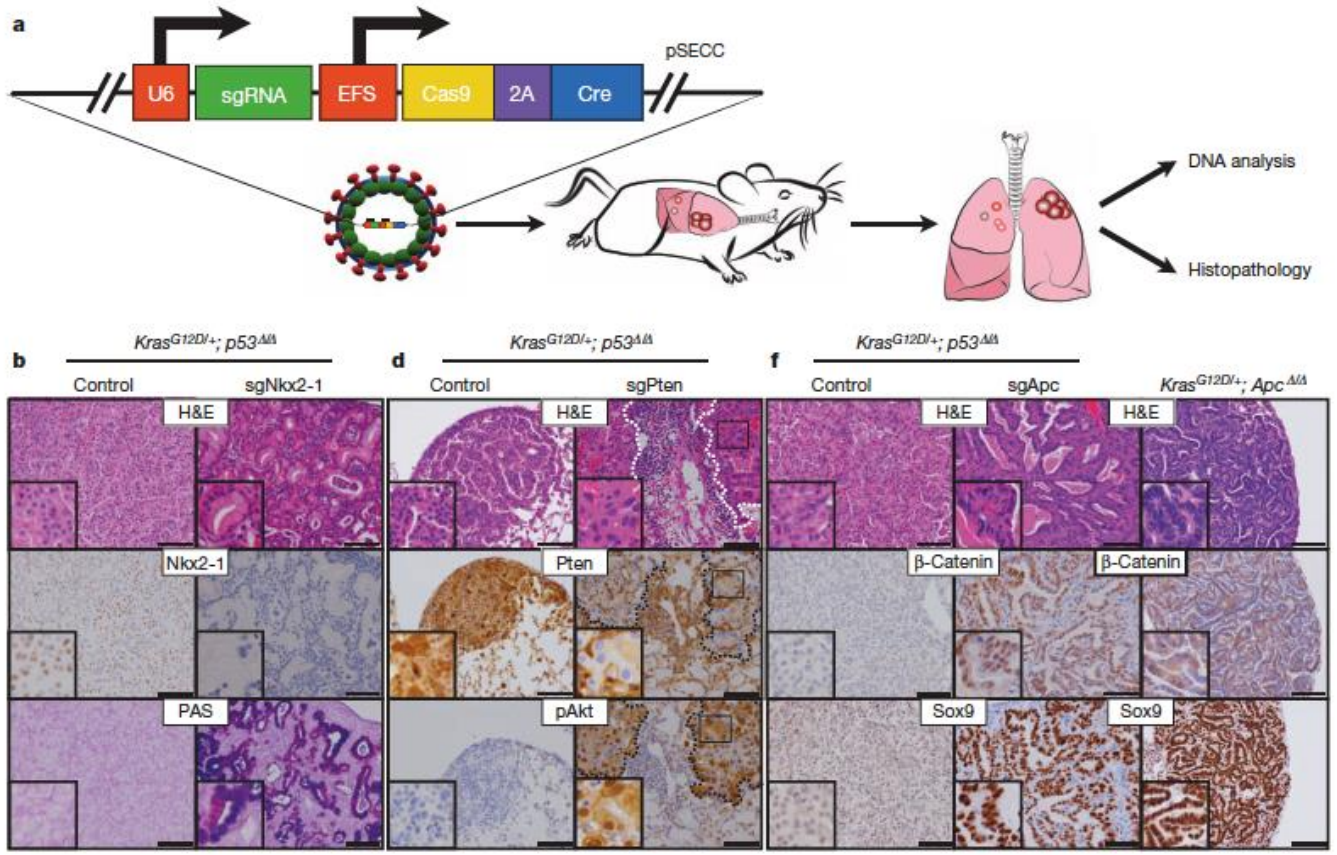
PMID: 19561589

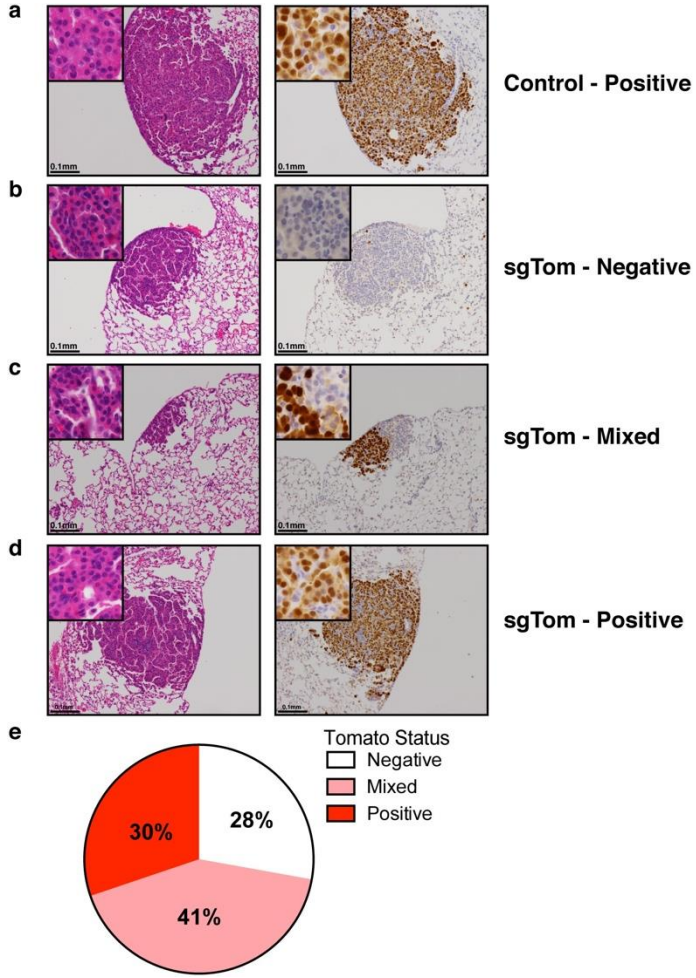
Immunogenic KP models



PMID: 21251614

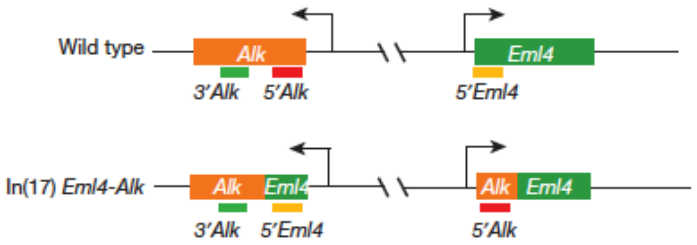
KP models in the CRISPR era

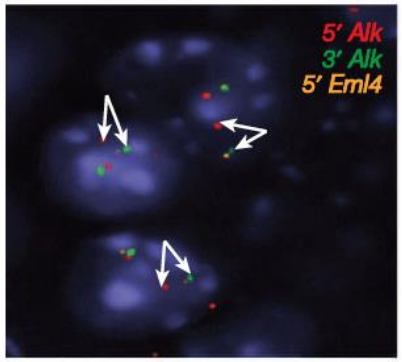


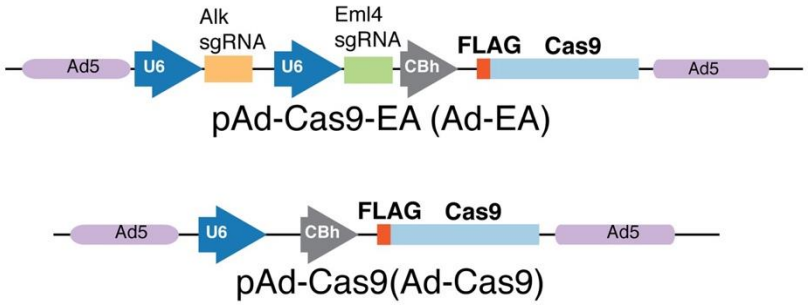


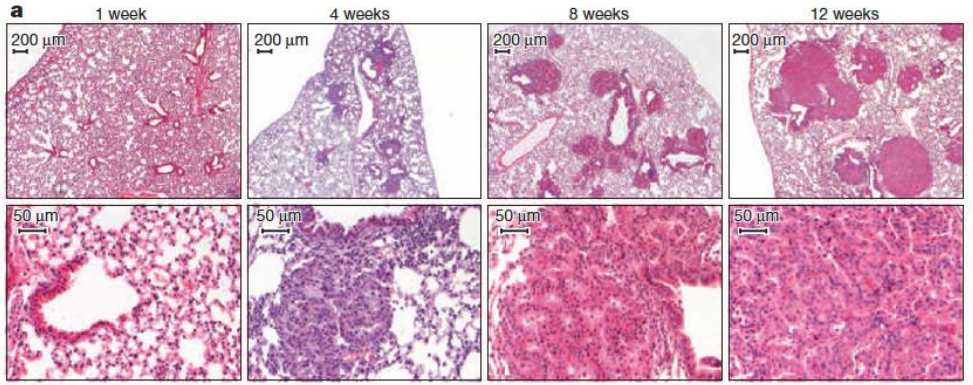
PMID: 25337879

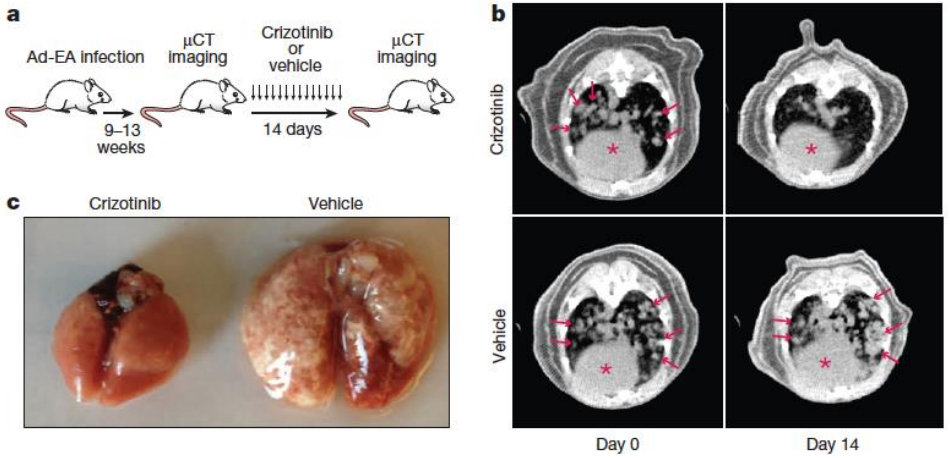
Lung models via CRISPR beyond KP





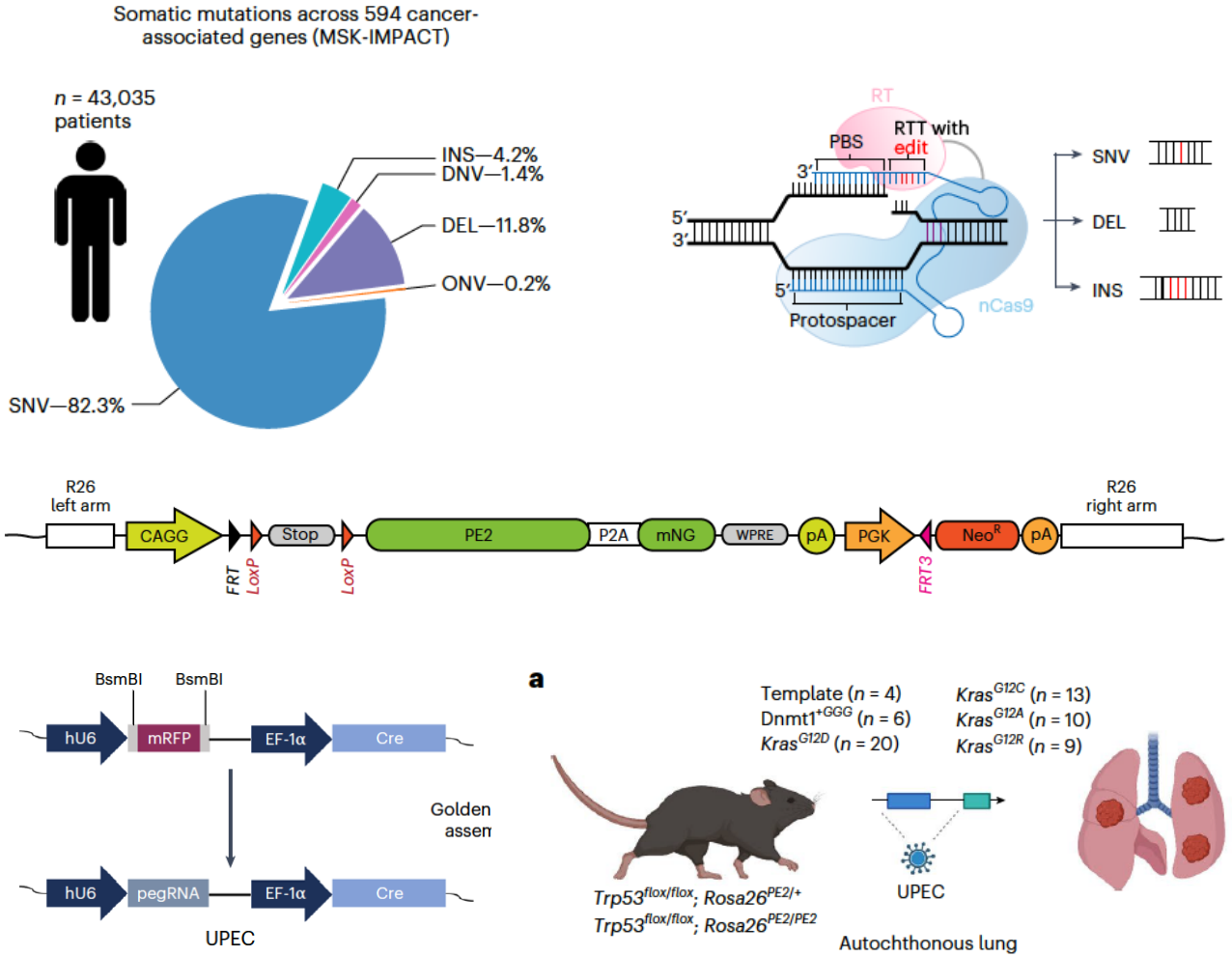


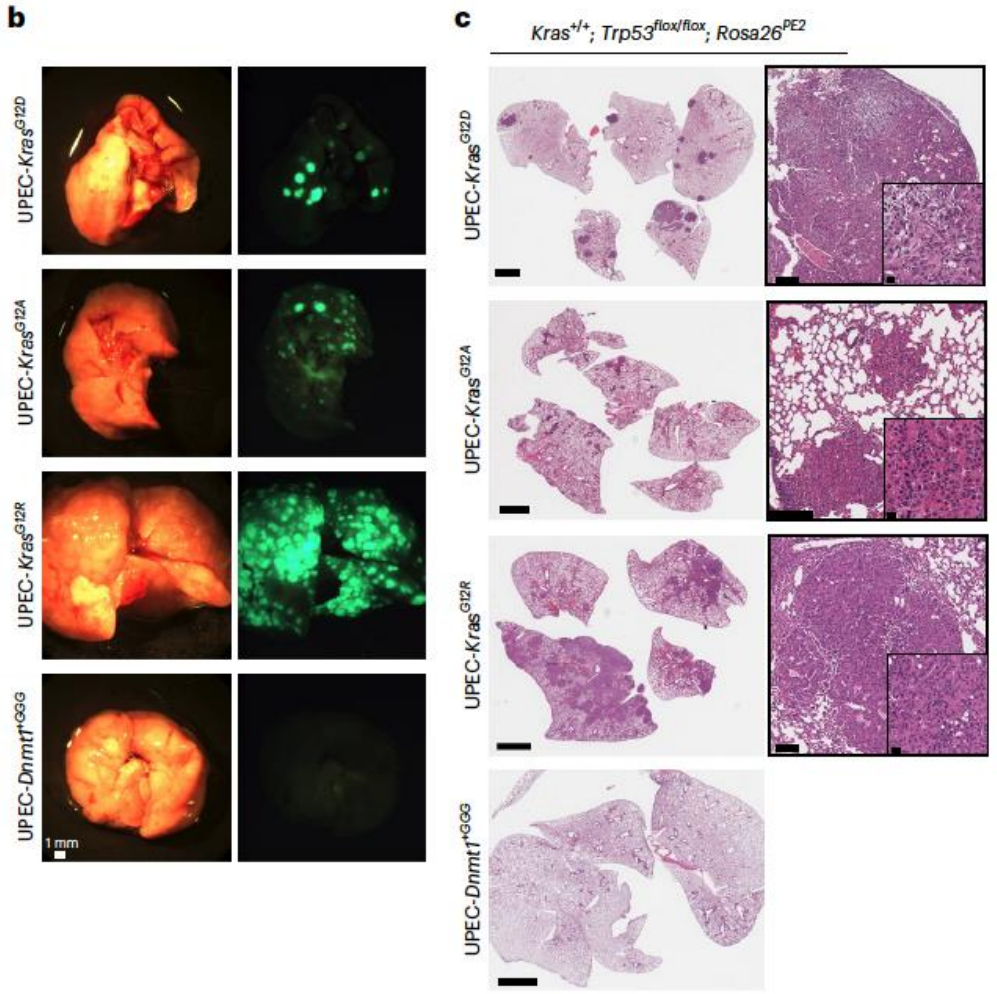




PMID: 25337876

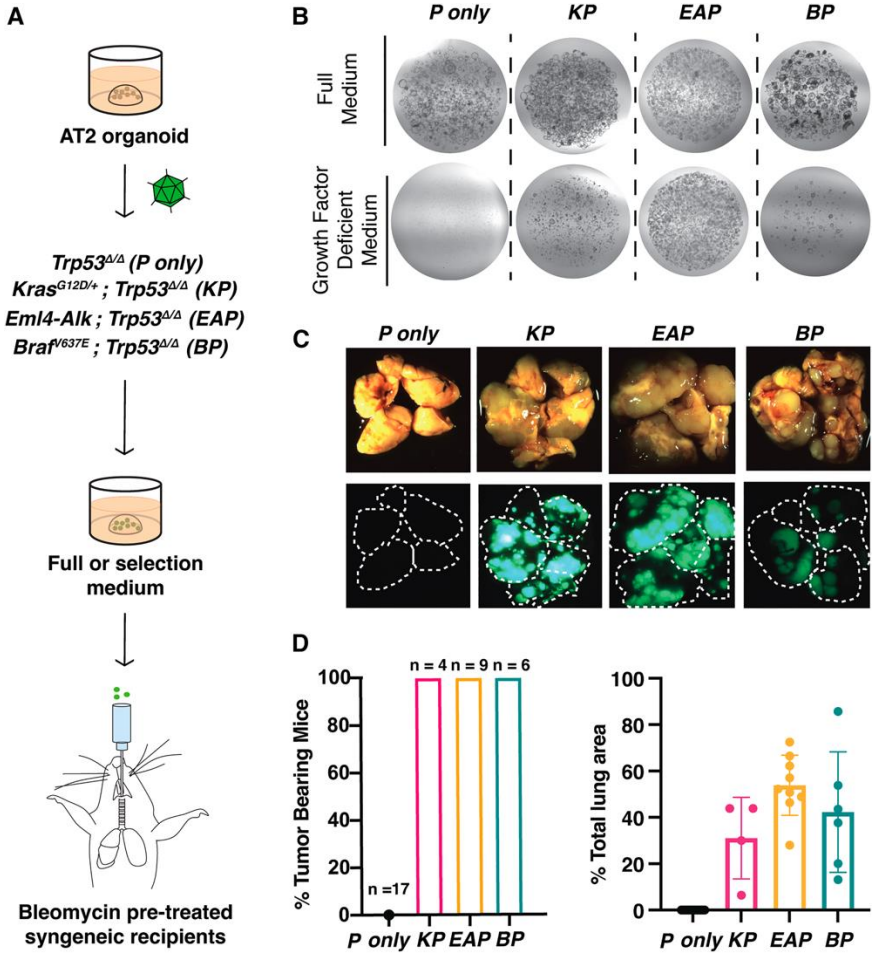
KP models in the precision genome editing era

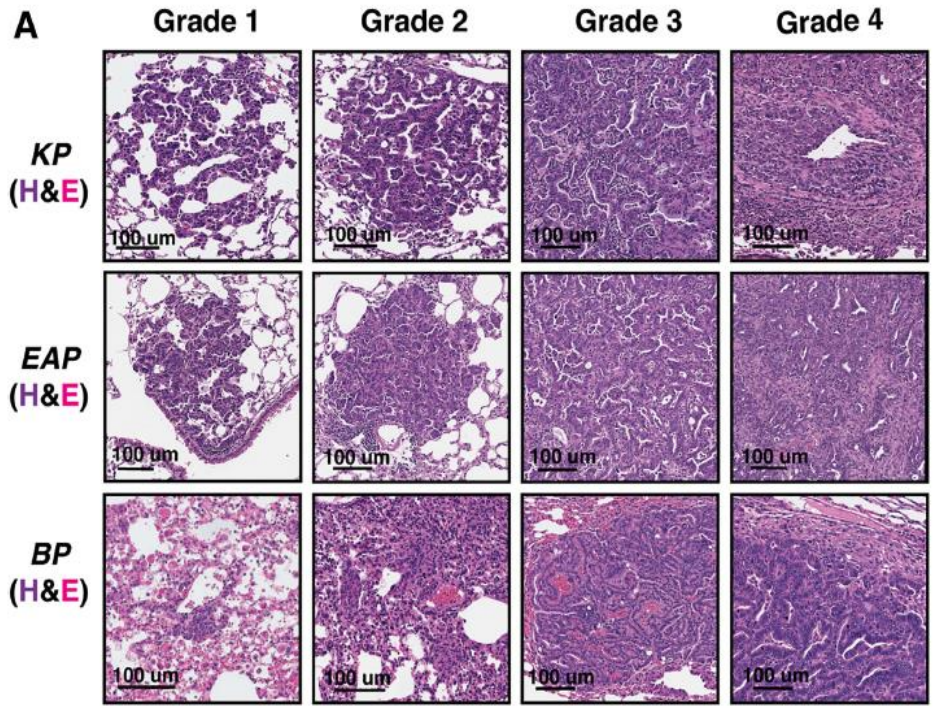


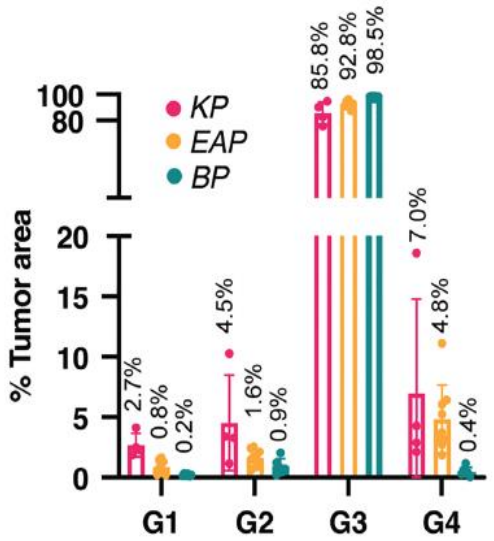


PMID: 37169967

Don’t forget about organoids!

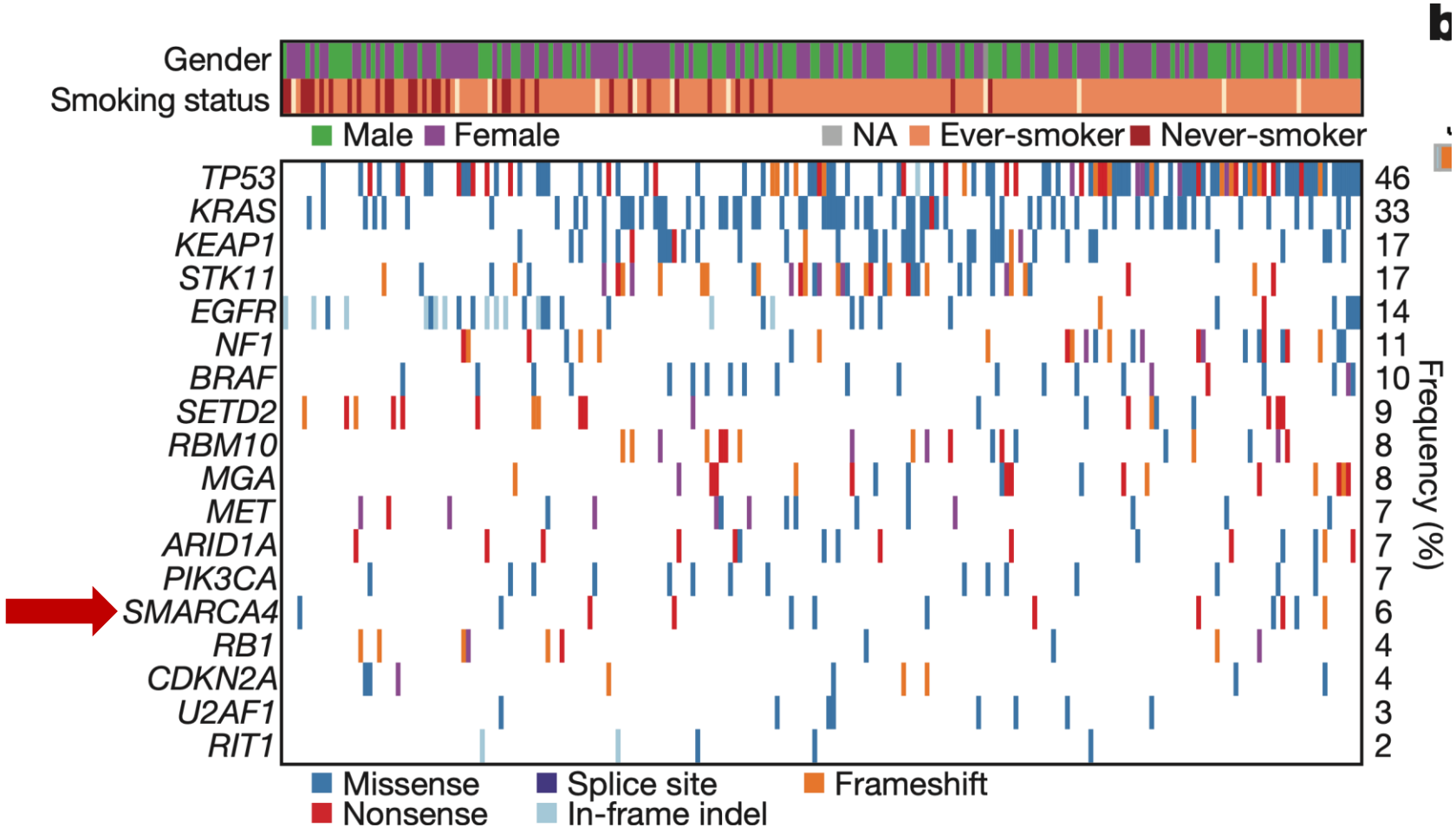






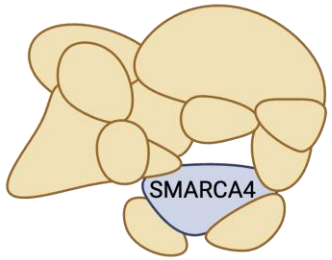
PMID: 36175034

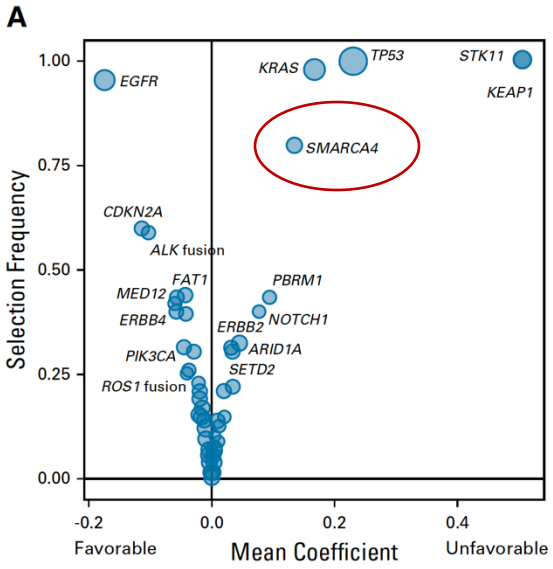
Somatic mutations in lung adenocarcinoma

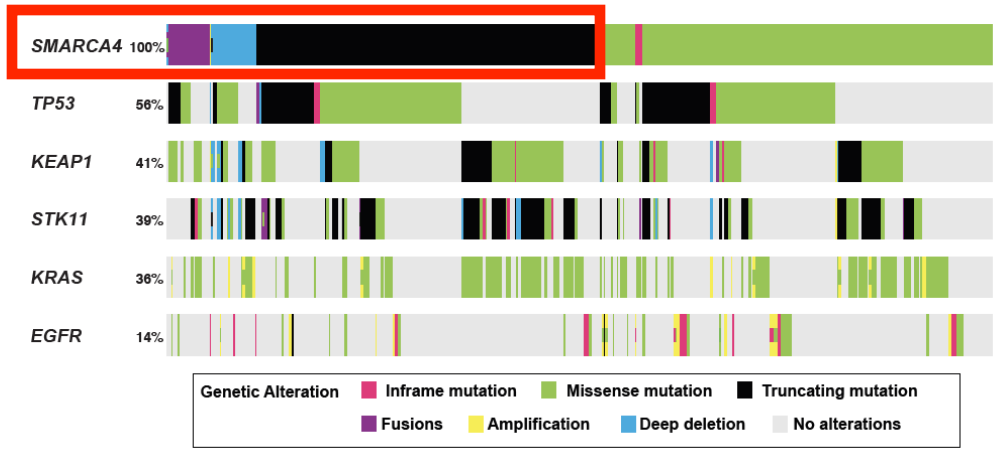


PMID: 25079552

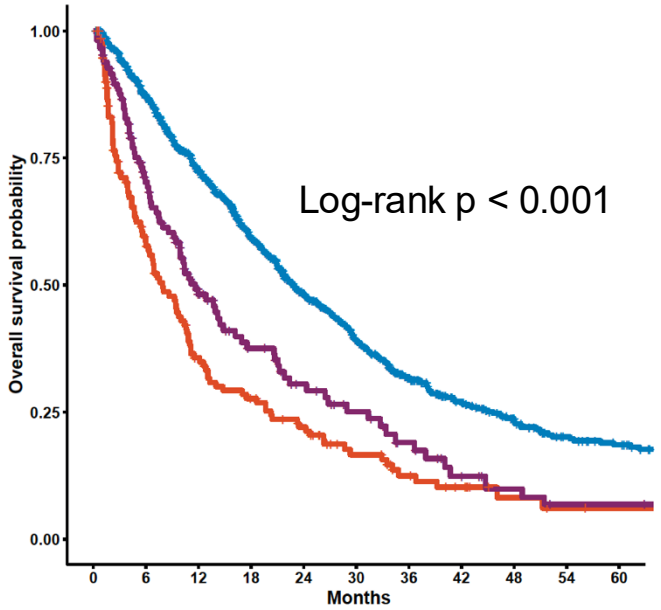
SMARCA4 alterations are associated with poor survival in non-small cell lung cancer





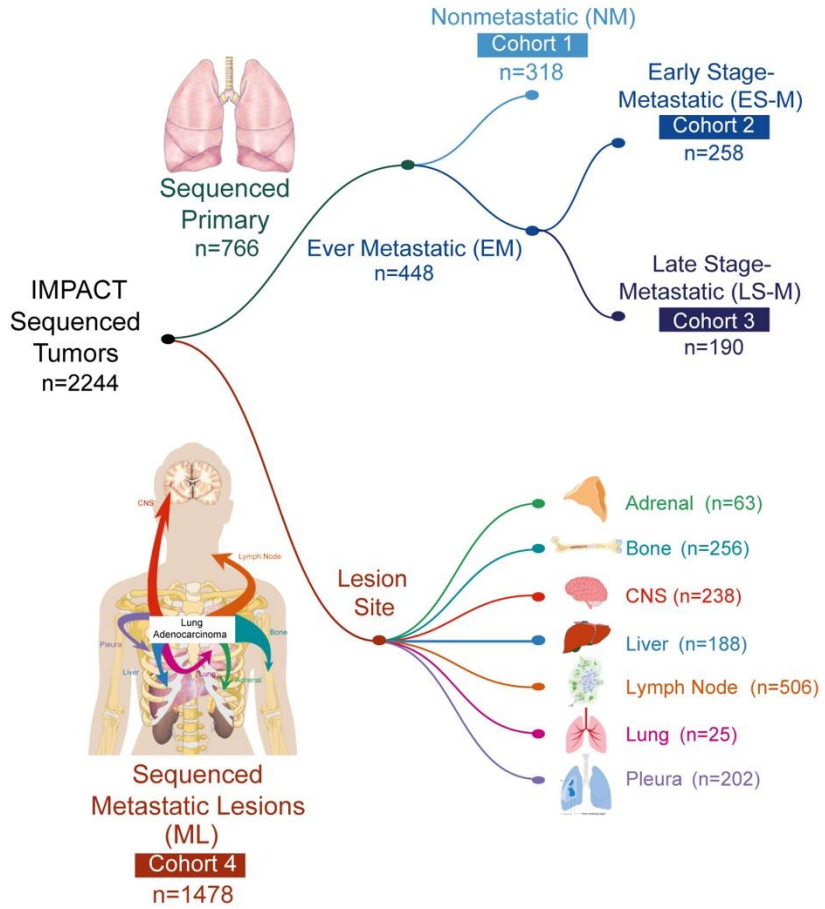


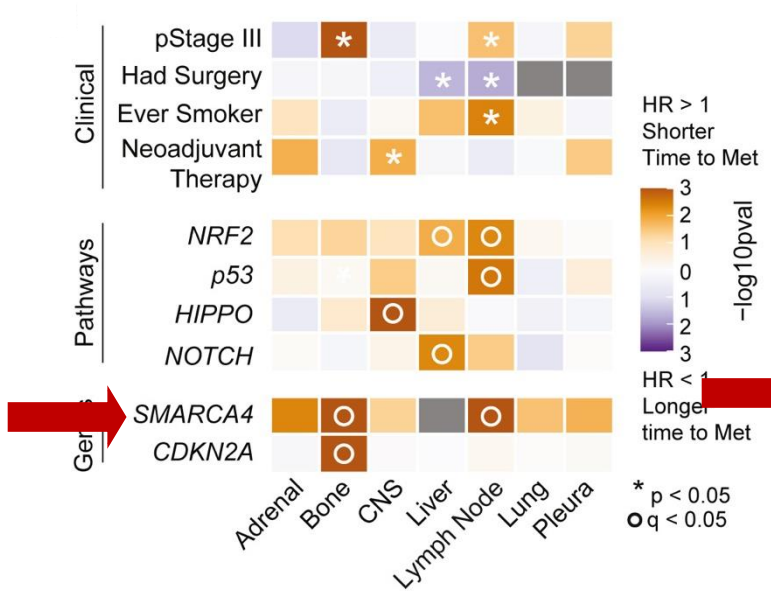
Patients with NSCLC grouped by *SMARCA4* status (n=1288)

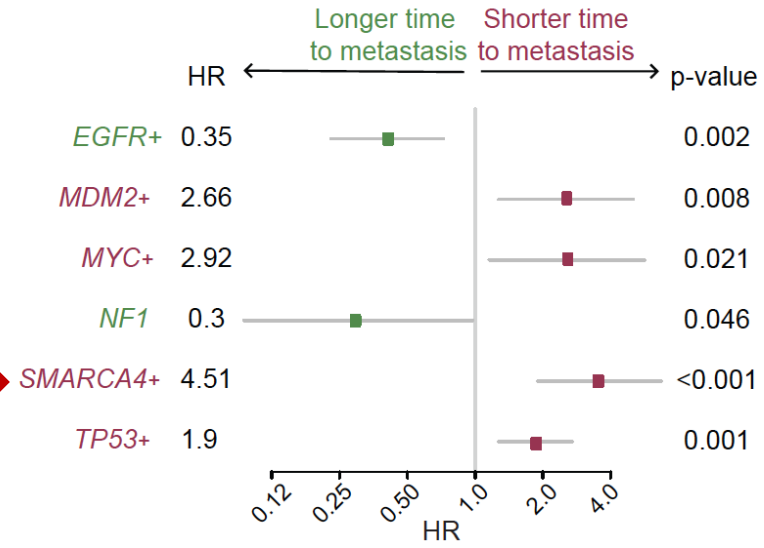


PMID: 32709715, PMID: 31008437

SMARCA4 alterations are associated with shorter time to metastasis



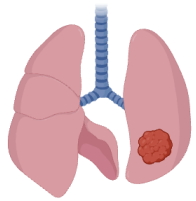




PMID: 37084736

Modeling SMARCA4 deficiency to determine the consequences of chromatin deregulation on tumor evolution

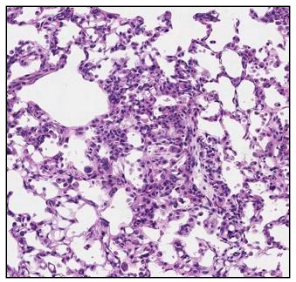
Ad-Cre



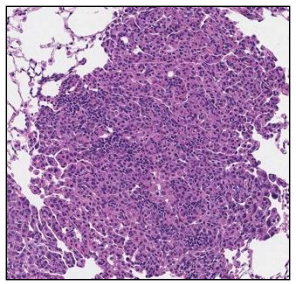
Kras$^{LSL\text{-}G12D/+}$; *Trp53*$^{fl/fl}$ (KP)
Kras$^{LSL\text{-}G12D/+}$; *Trp53*$^{fl/fl}$; *Smarca4*$^{fl/+}$ (KPS-HET)
Kras$^{LSL\text{-}G12D/+}$; *Trp53*$^{fl/fl}$; *Smarca4*$^{fl/fl}$ (KPS)

Kras$^{G12D/+}$; *Trp53*$^{-/-}$ (KP)
Kras$^{G12D/+}$; *Trp53*$^{-/-}$; *Smarca4*$^{-/+}$ (KPS-HET)
Kras$^{G12D/+}$; *Trp53*$^{-/-}$; *Smarca4*$^{-/-}$ (KPS)

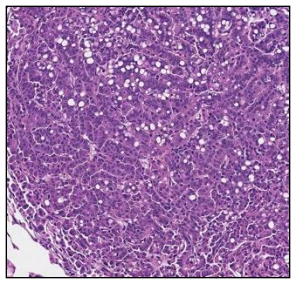
Tumor progression



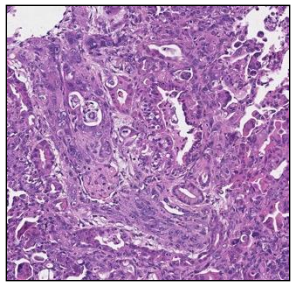
Grade 1



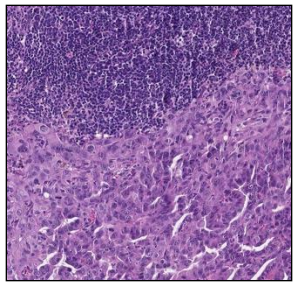
Grade 2



Grade 3



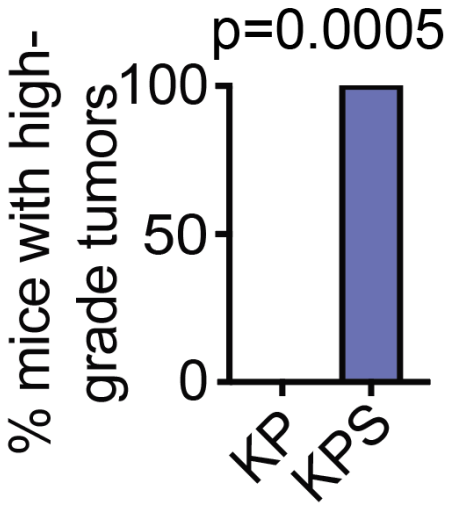
Grade 4

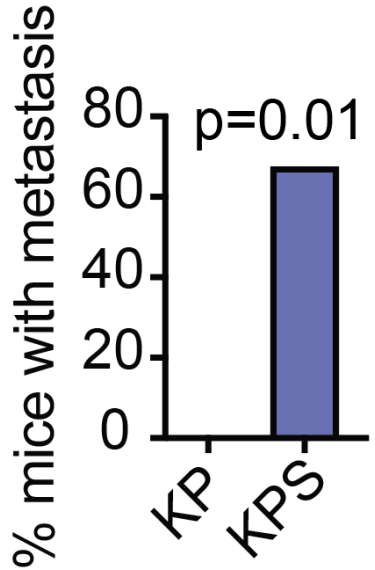


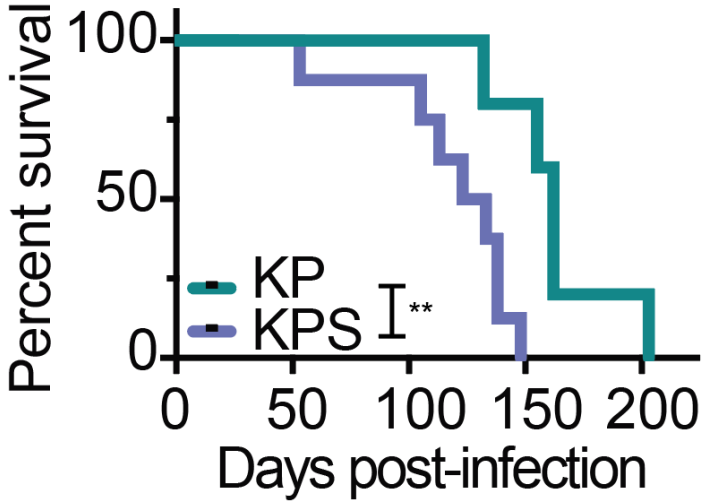
Metastasis

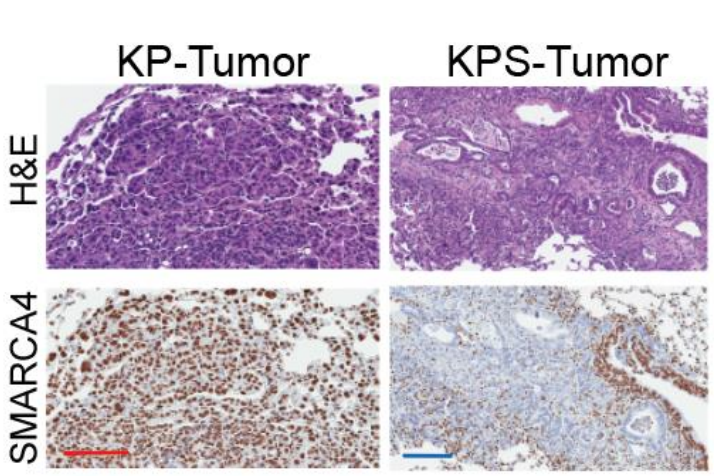
PMID: 34561242

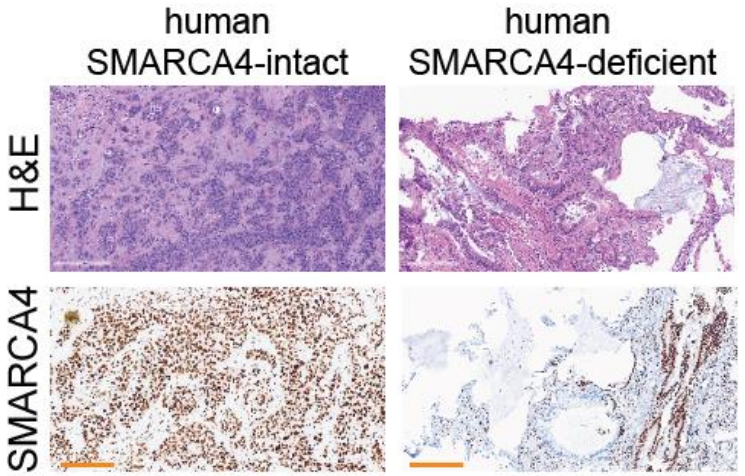
SMARCA4-deficient LUAD GEMMs phenocopy the human disease





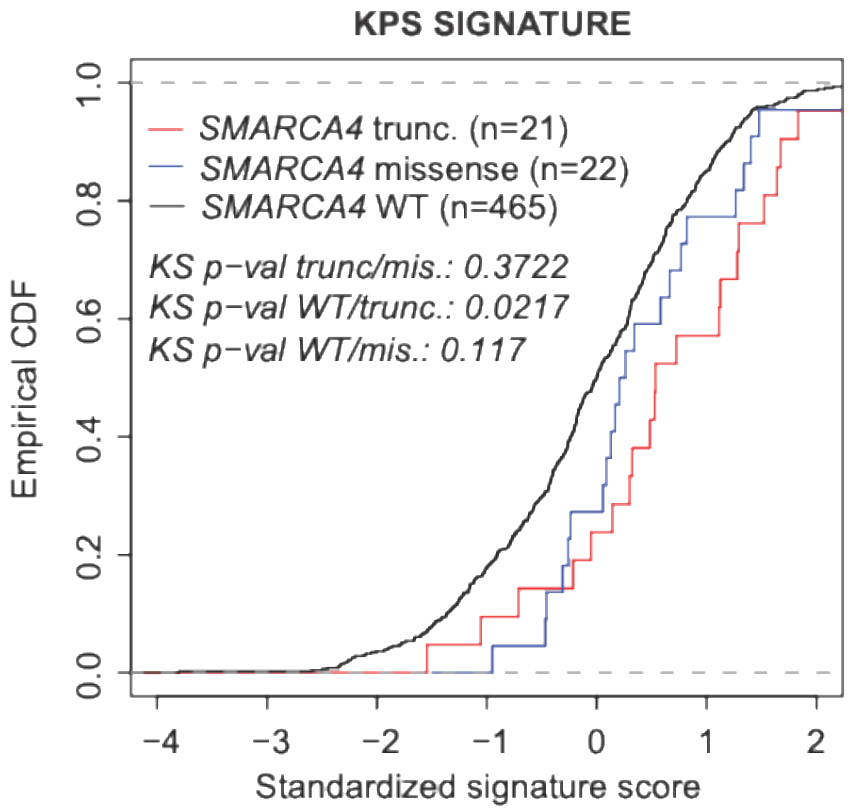


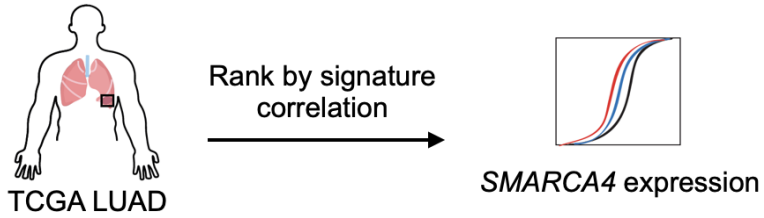


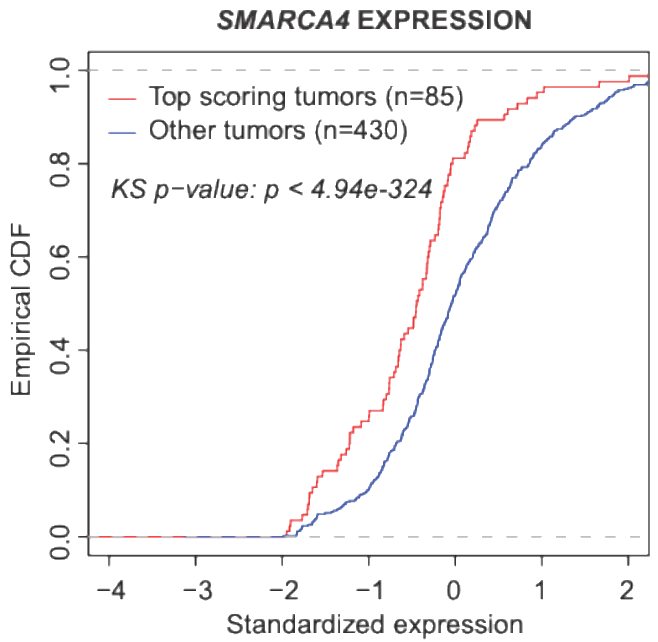


PMID: 34561242

SMARCA4-deficient LUAD GEMMs capture transcriptional states of the human disease



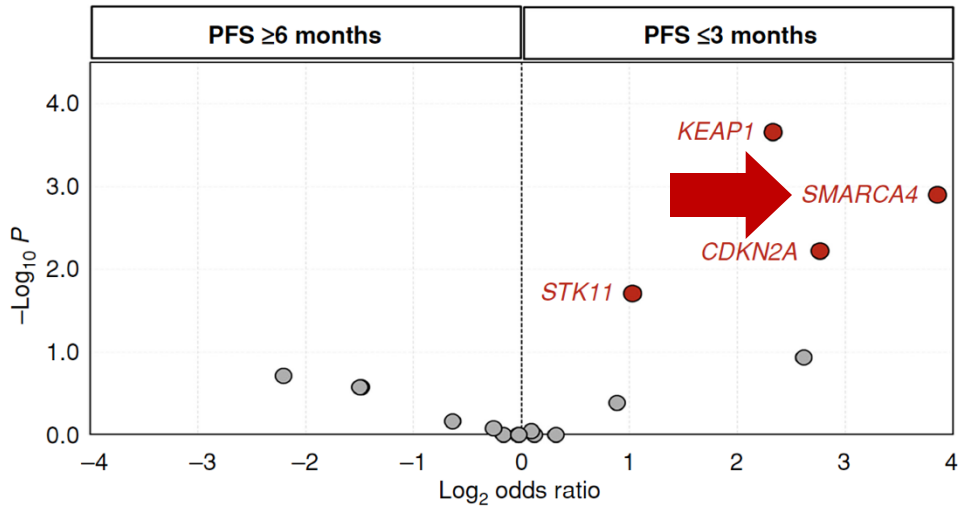


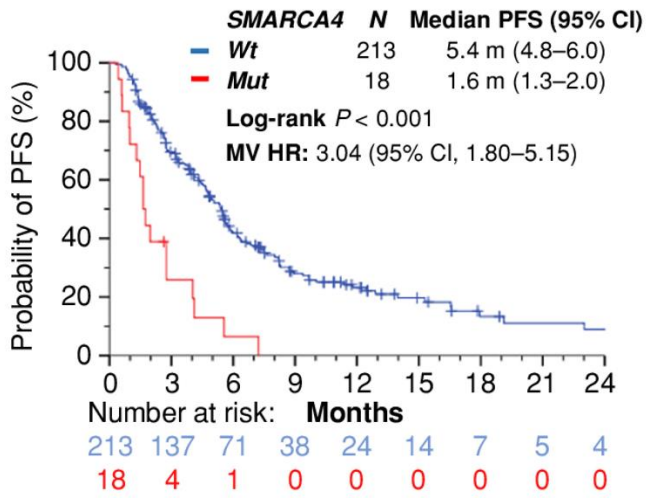


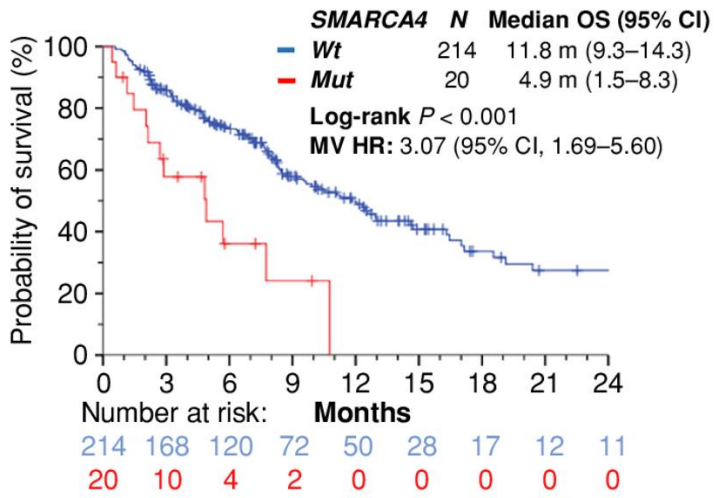
Top scoring tumors (z > 1) enriched for SMARCA4 truncating mutations (p = 3.18e-3)

PMID: 34561242

SMARCA4 alterations are associated with poor responses to KRAS-G12C inhibition in the clinic

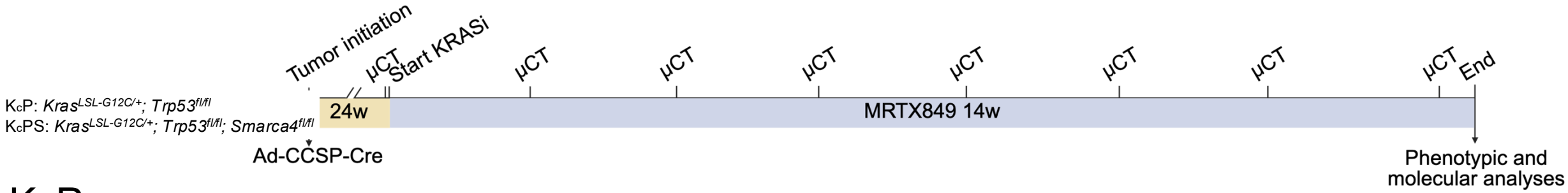




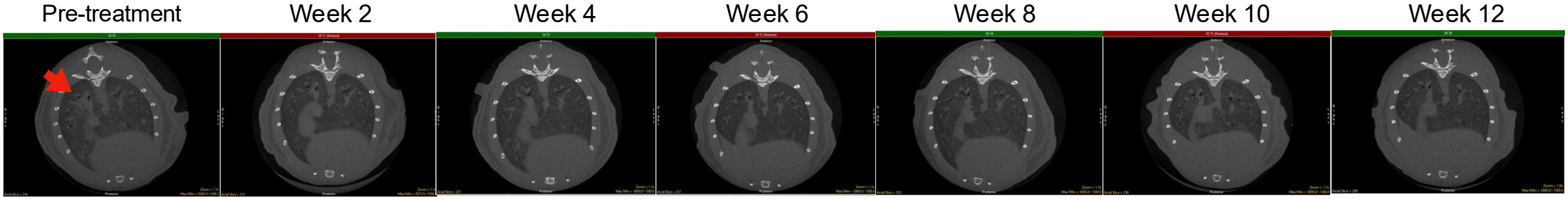


PMID: 37068173

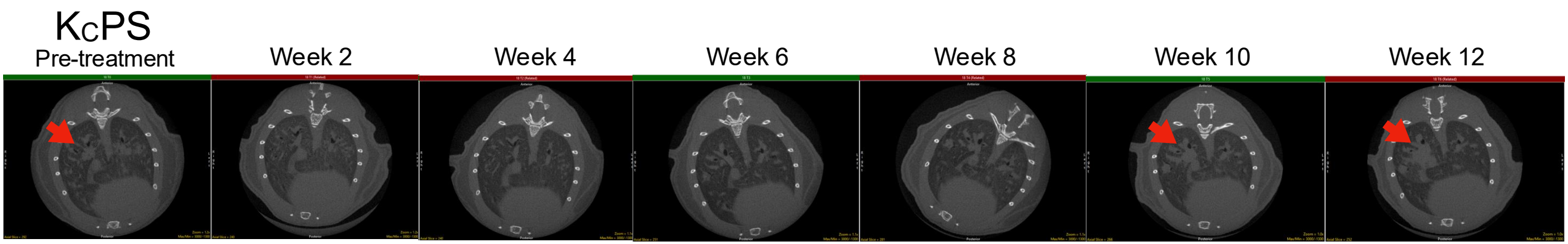
SMARCA4 deficiency accelerates the onset of acquired resistance



KcP

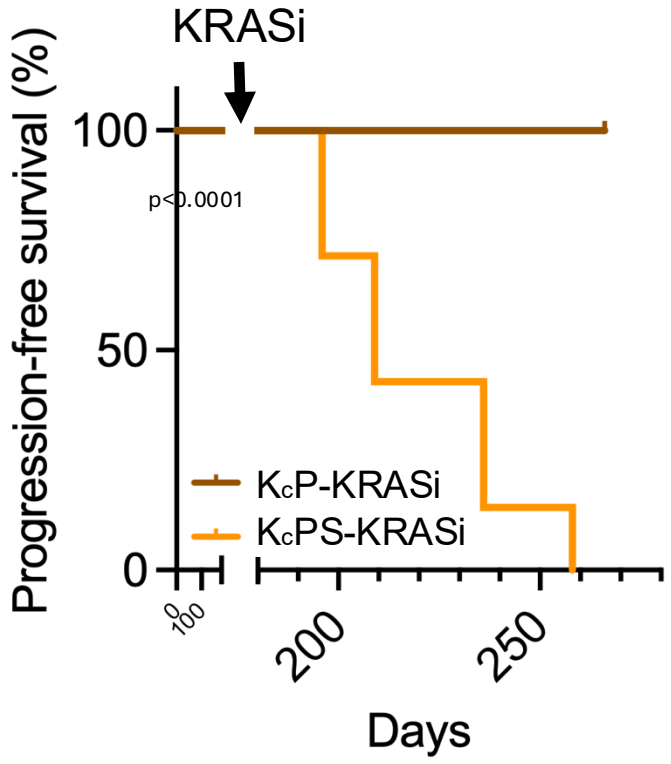


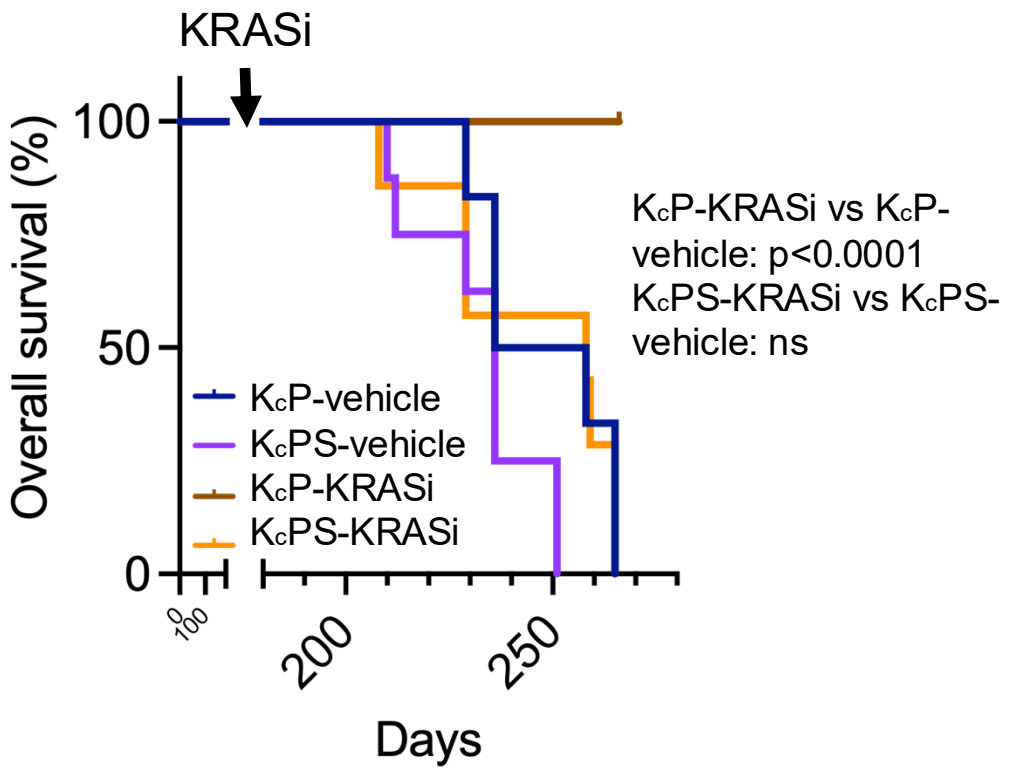
KcPS



Vicky Liu, unpublished data

SMARCA4 deficiency abrogates the survival benefit of KRASi

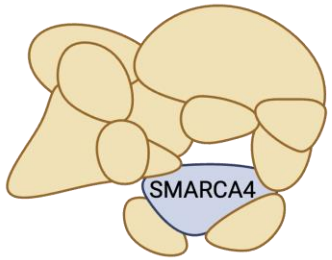


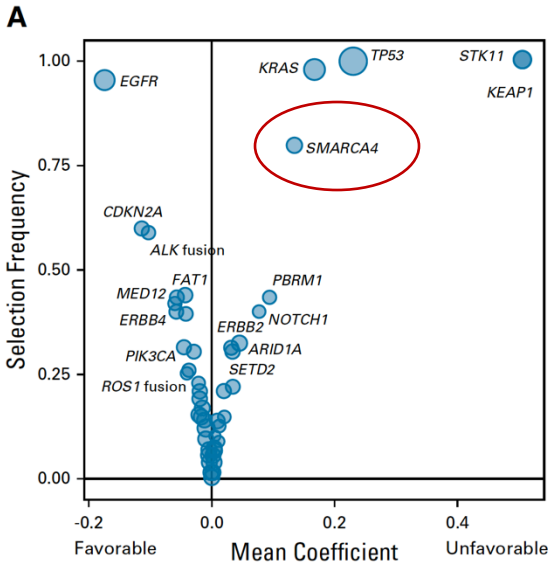


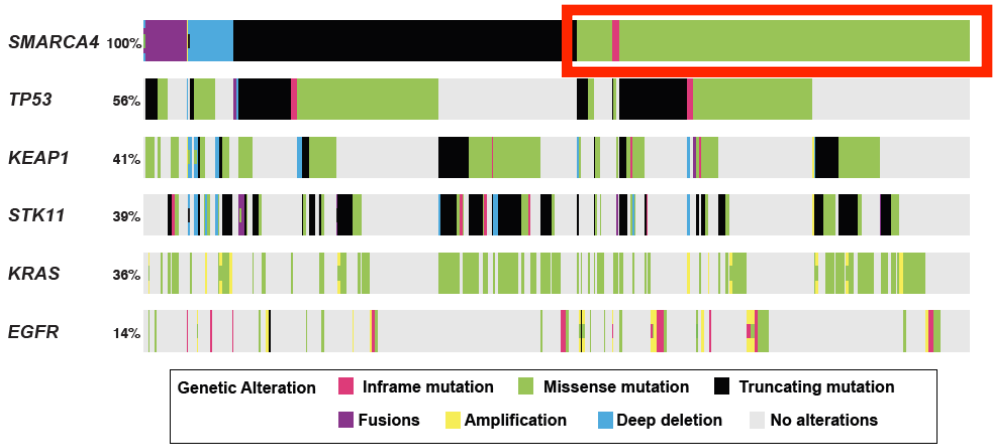
KcP: *Kras*$^{LSL\text{-}G12C/+}$; *Trp53*$^{fl/fl}$
KcPS: *Kras*$^{LSL\text{-}G12C/+}$; *Trp53*$^{fl/fl}$; *Smarca4*$^{fl/fl}$

Vicky Liu, unpublished data

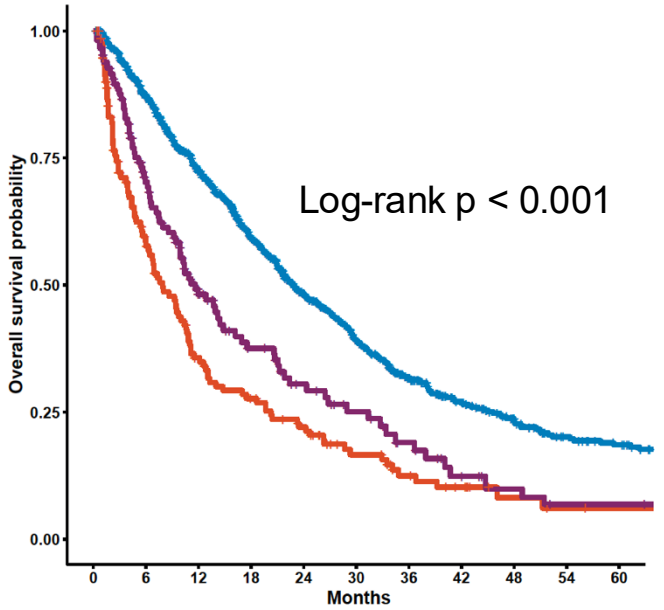
SMARCA4 alterations are associated with poor survival in non-small cell lung cancer





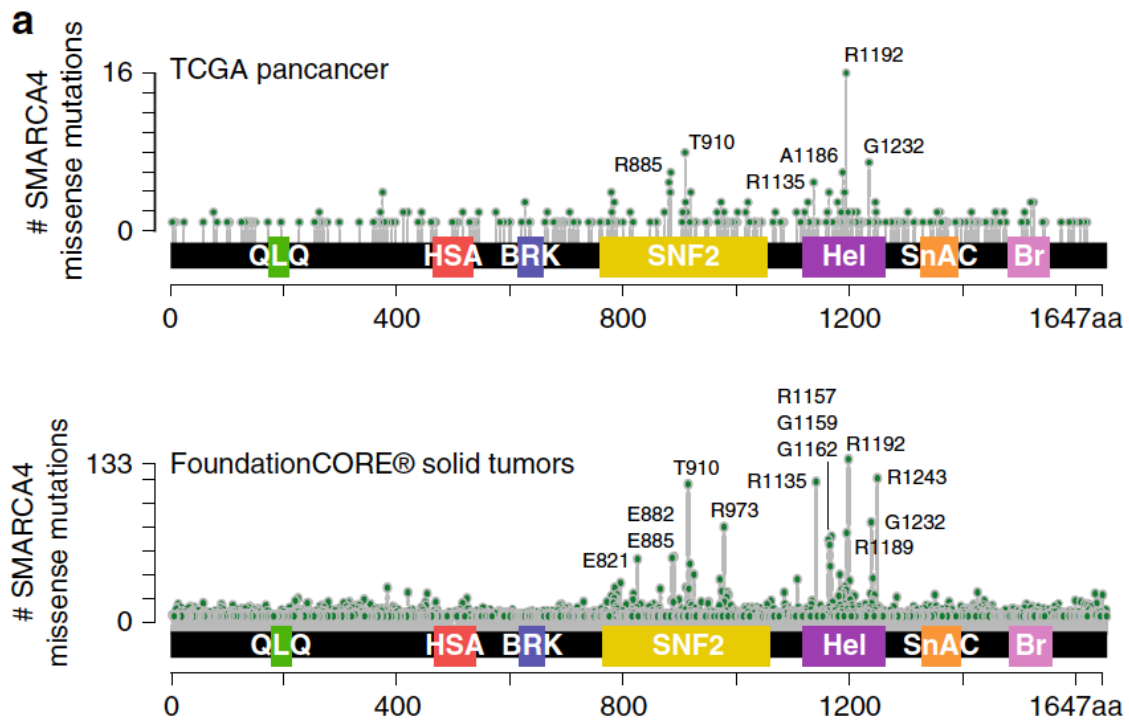


Patients with NSCLC grouped by *SMARCA4* status (n=1288)



PMID: 32709715, PMID: 31008437

Modeling *SMARCA4* cancer variants via prime editing *in vivo*



Lentivirus:

Germline: *Trp53*$^{fl/fl}$; *Rosa26*$^{LSL\text{-}PE2}$

PMID: 33144586, Zoe Cho

Choose your model **based on the question** you're asking!

Know the **caveats and nuances** of the model you're using or developing. Models are **powerful.** However, a model is "just" a model! **No model is perfect.**

It is critical to **use a variety** of models to fully test a hypothesis.