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Associate Program Director, Hematology/Oncology Fellowship Program
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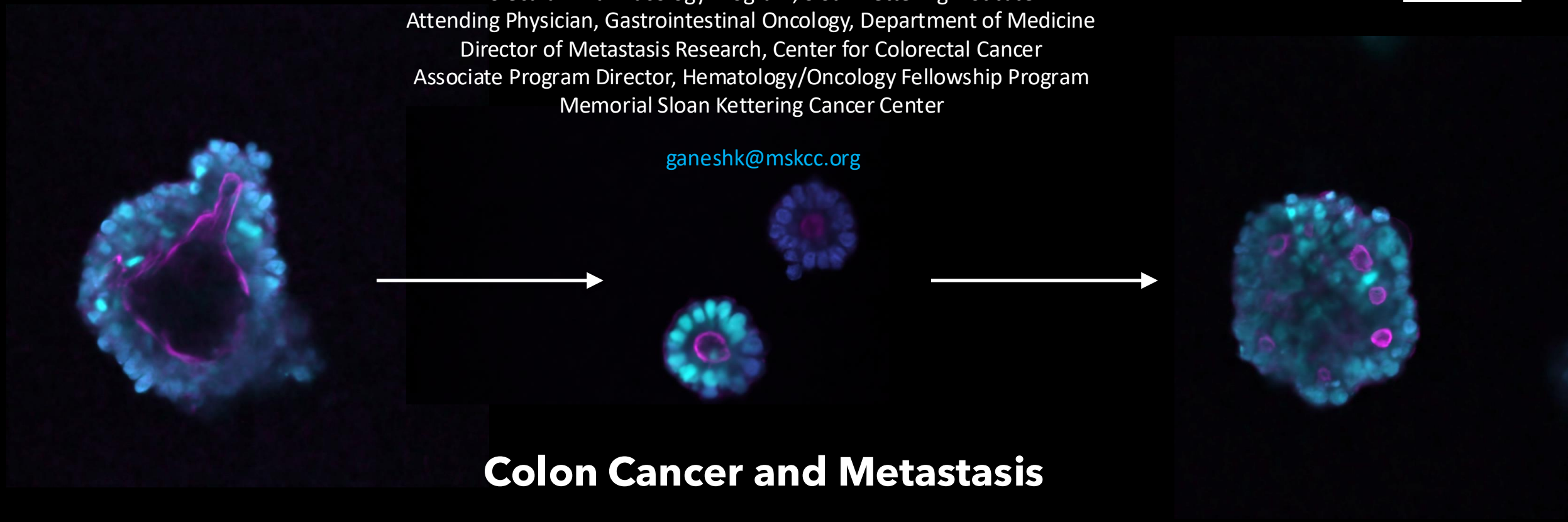


Colon Cancer and Metastasis

GSK Cancer Biology Course
Gerstner Sloan Kettering Graduate School
March 25, 2026

Disclosures

I have the following relevant financial relationships to disclose:

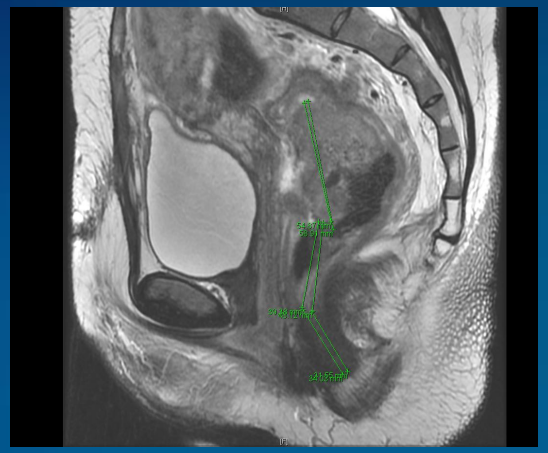
Employee of: Memorial Sloan Kettering Cancer Center

Consultant for: Seres Therapeutics

Grant/Research Support from: NIH/NCI, Stand Up to Cancer, AACR, Burroughs Wellcome Funds, Damon Runyon Cancer Research Foundation, Pershing Square Cancer Research Foundation, Dalton Family Foundation, Anna Fuller Fund, Society of Memorial Sloan Kettering, Gerry Metastasis and Tumor Ecosystems Center

Patents: Related to patient-derived ex vivo models and molecules for targeting tumor regenerative states

GH: 28 year old female with rectal cancer



Stage III rectal cancer
Diagnosed during labor
09/2012

Chemoradiation +

→

Curative Surgery

Disease-free
for >2 years

Rx: 01/2015-03/2016

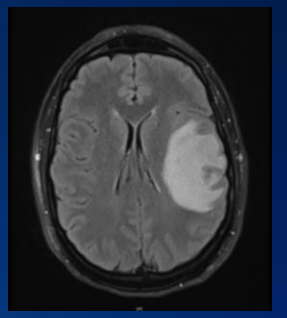
←→

Lung surgery
Brain surgery

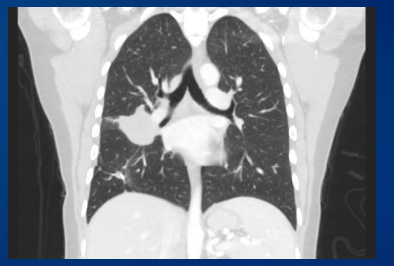
3xChemotherapy
2xTargeted
Therapy

Anti PD-1
Immunotherapy
Clinical Trial

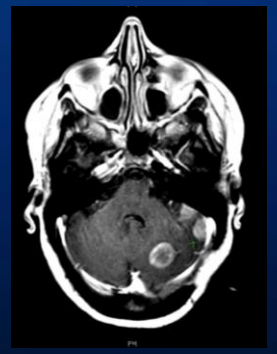
01/2015:
lung
metastasis



03/2015:
brain
metastasis

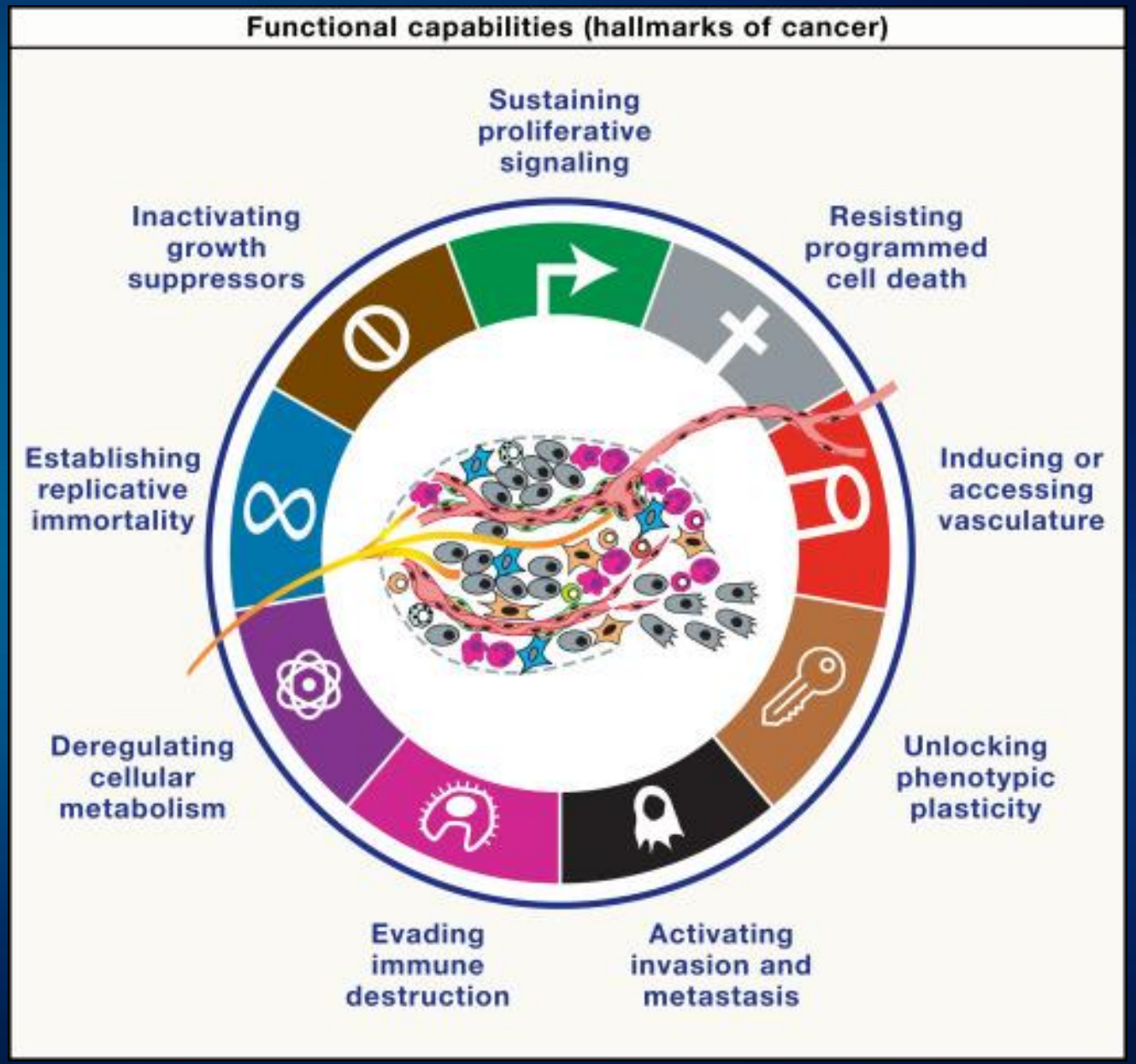


03/2016:
relapsed
lung
metastases



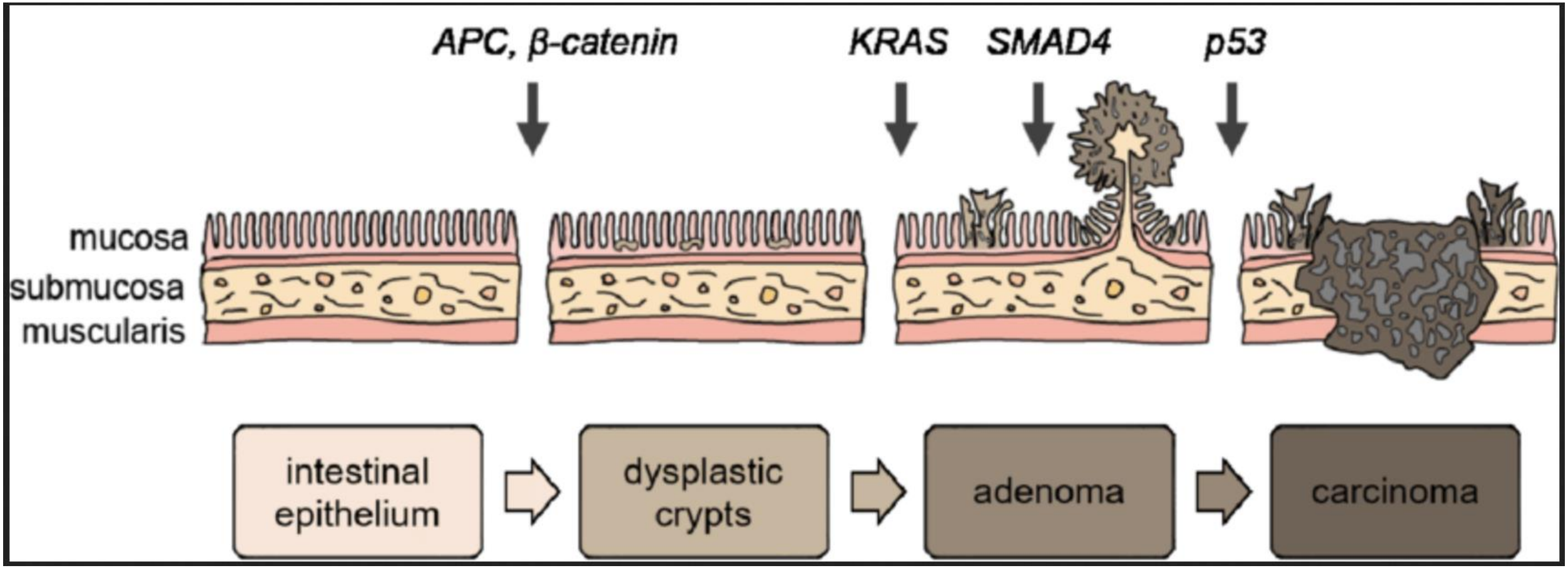
03/2016:
relapsed
brain
metastases

Hallmarks of Cancer

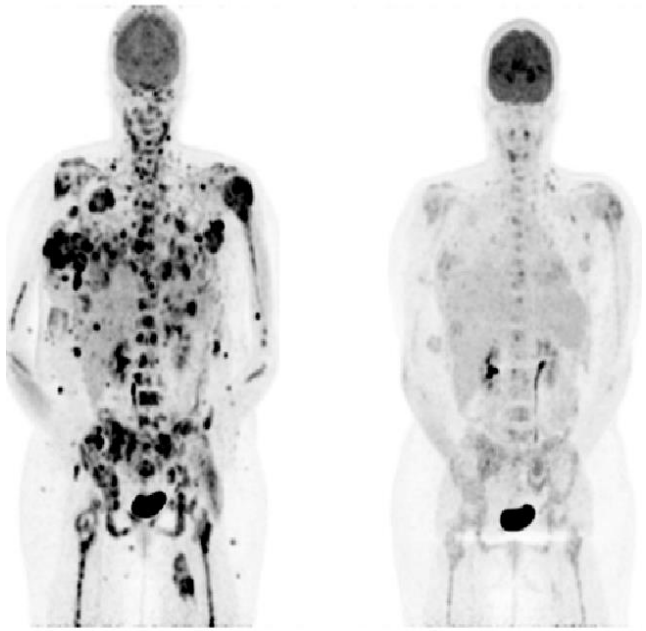


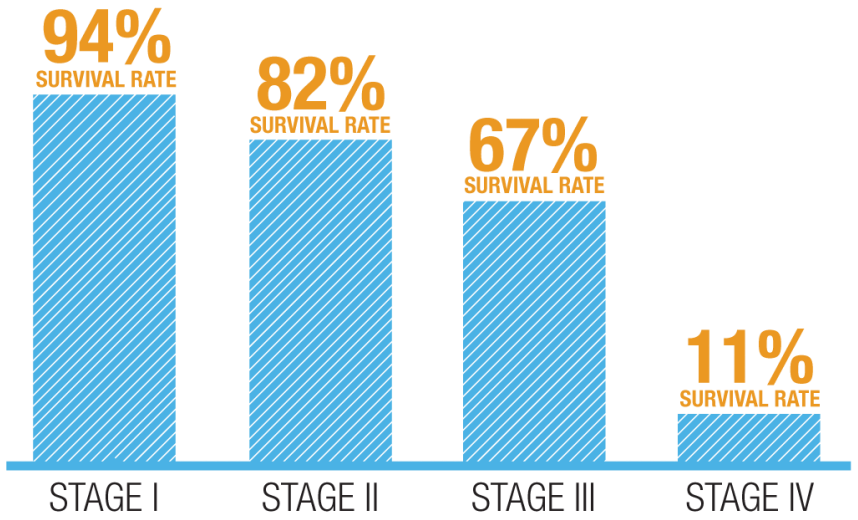
Hanahan, D. *Cell*, 2026

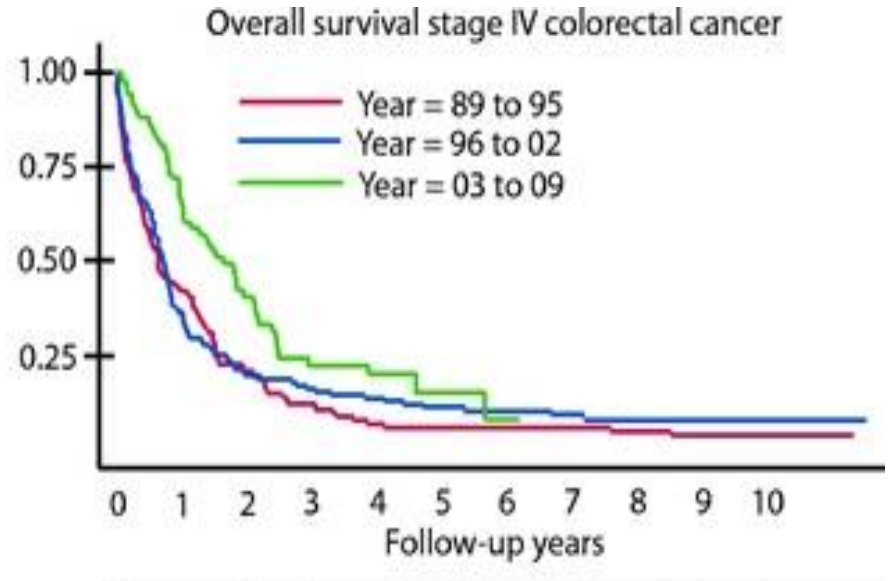
Vogelstein adenoma:carcinoma sequence



Metastasis causes >90% of cancer death







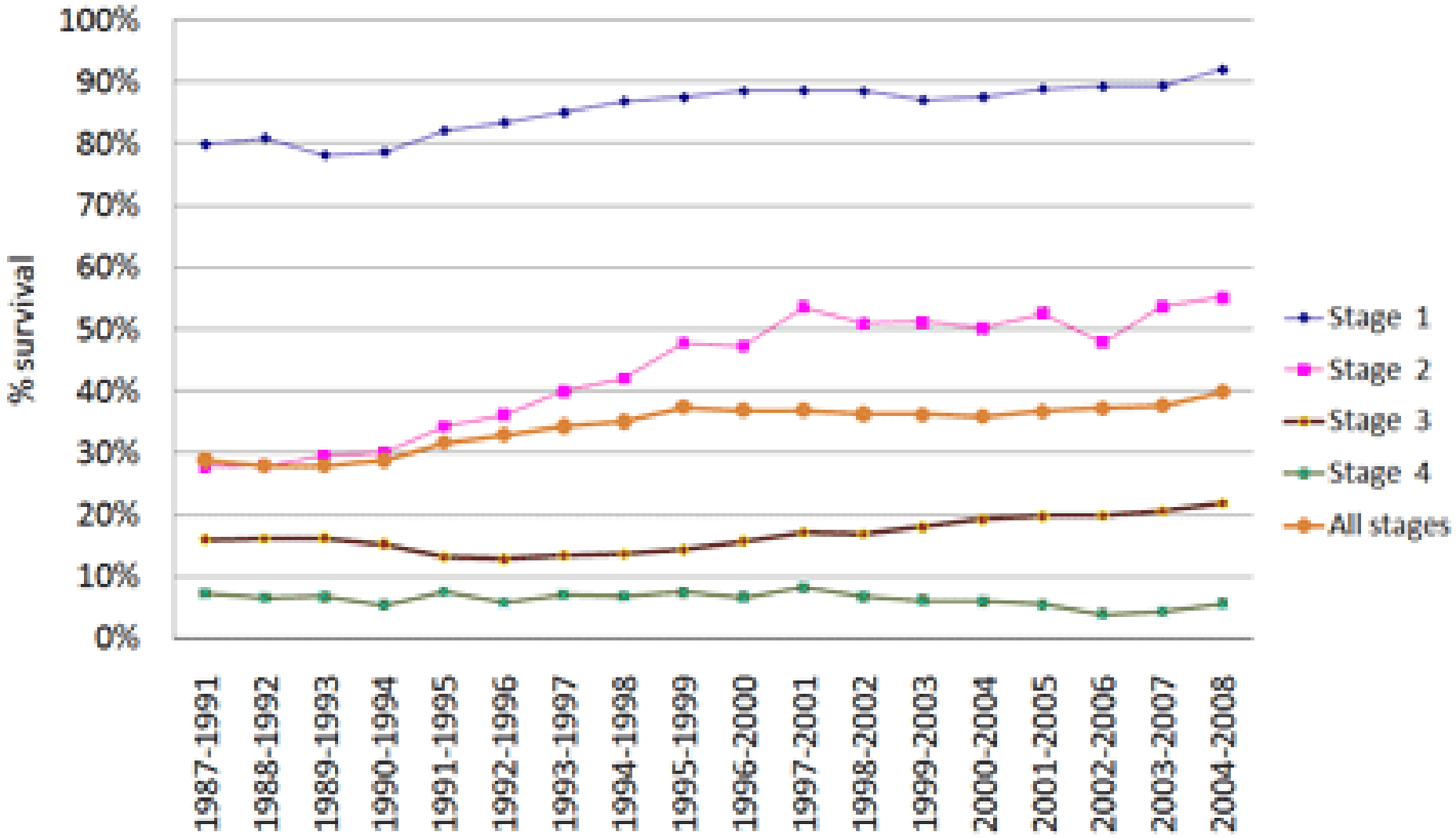
SEER-Medicare

Metastasis

- “Meta” = Other “Stasis” = Place

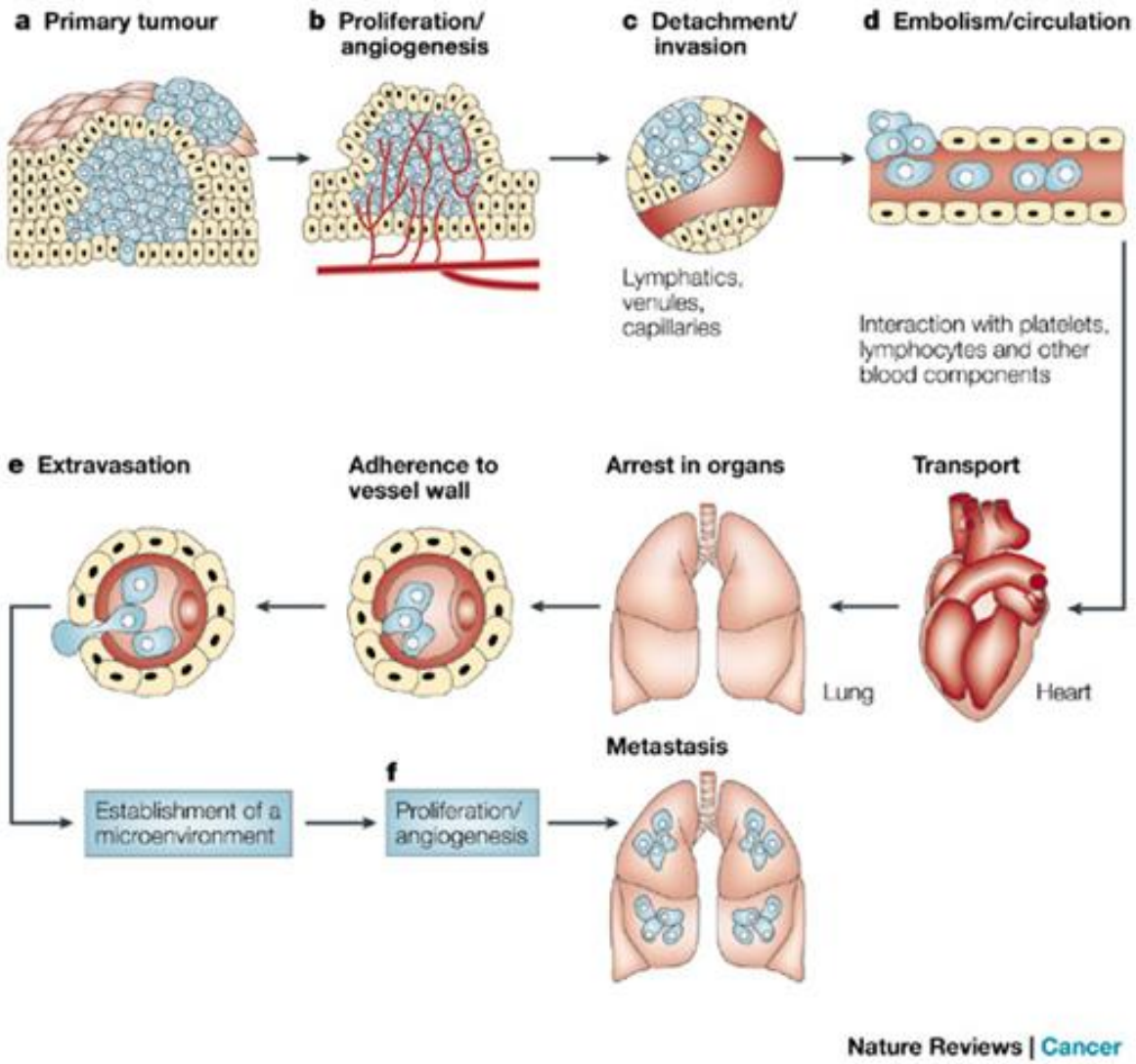
- The development of secondary malignant growths at a distance from a primary site of cancer.

So how do we pharmacologically target cancer: **Metastasis causes 90% of cancer death**

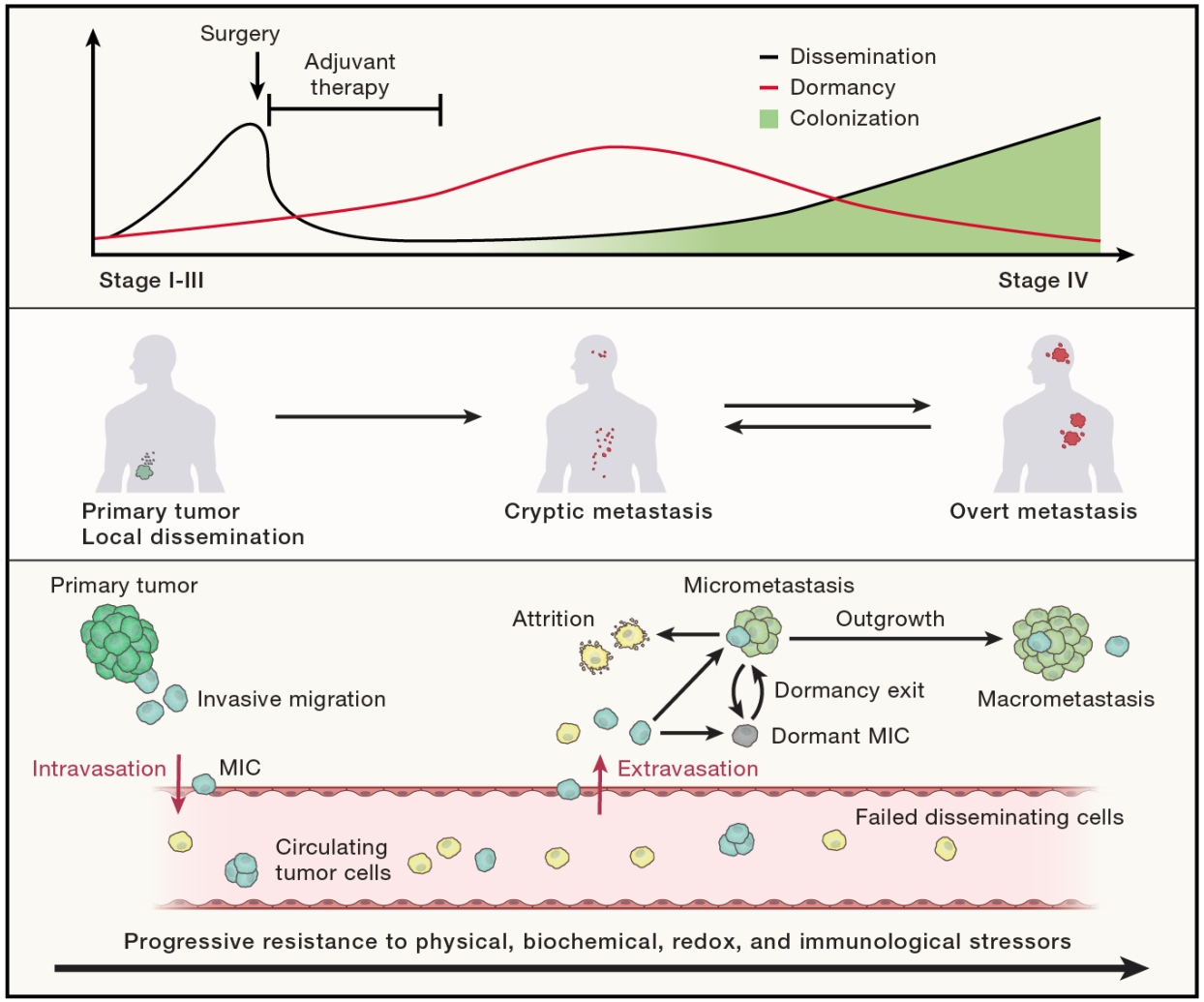


Source: SEER-Medicare

The metastatic cascade

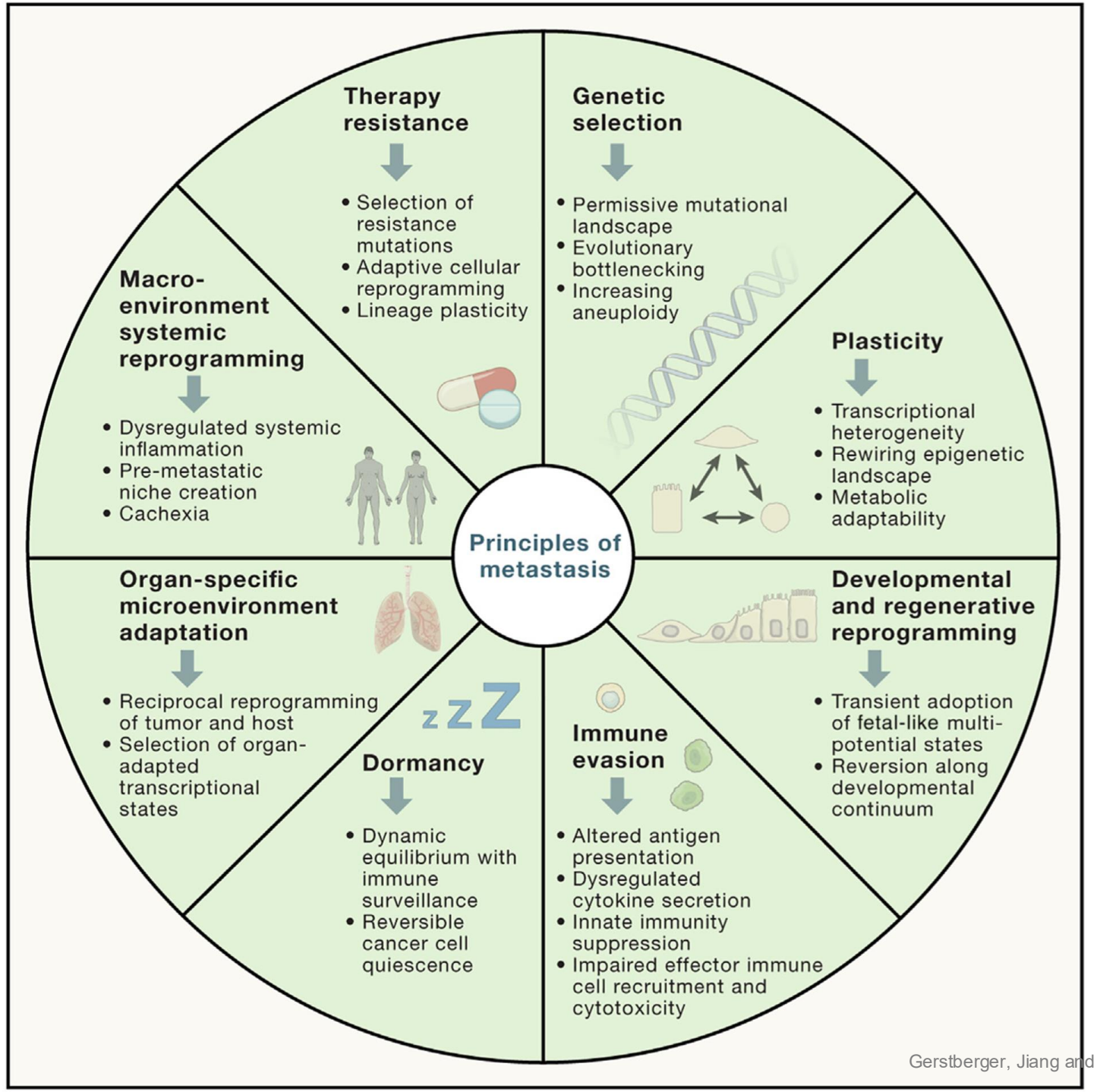


Metastasis involves co-evolution of the tumor and host



Gerstberger, Jiang and Ganesh, *Cell*, 2023

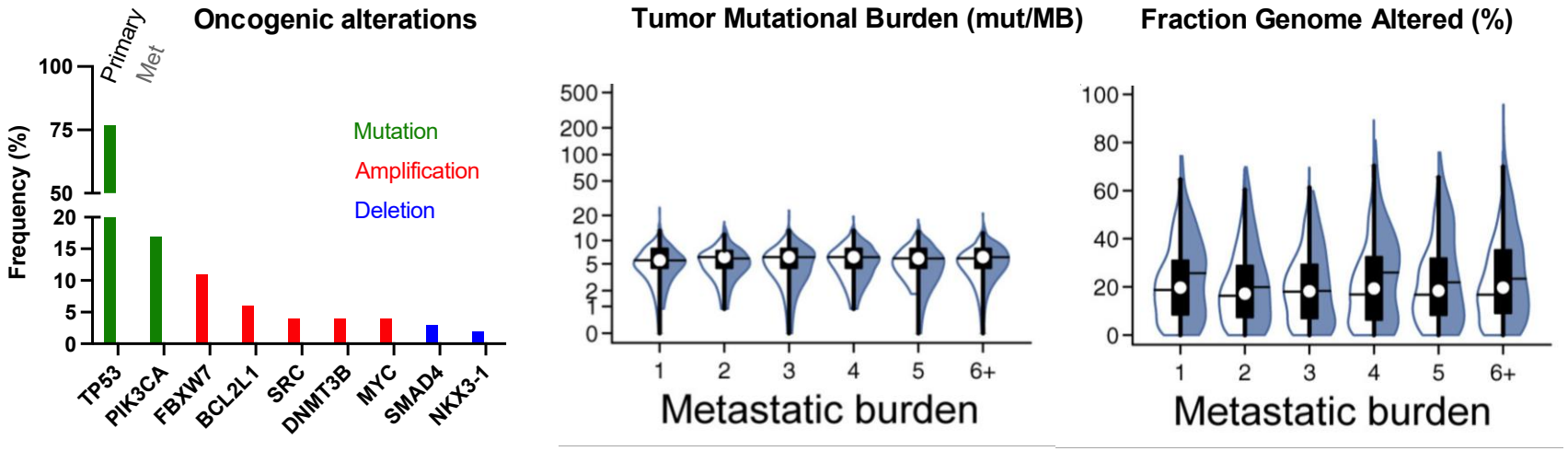
The goal of most cancer drugs is to target metastasis, not primary tumors



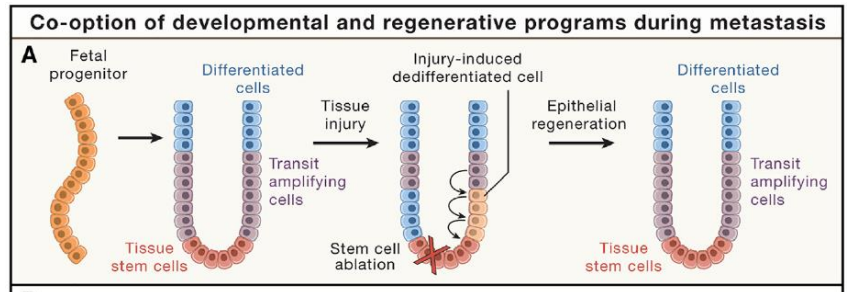
Gerstberger, Jiang and Ganesh, *Cell*, 2023

Genetic alterations do not explain the emergence of metastasis

Colorectal cancer

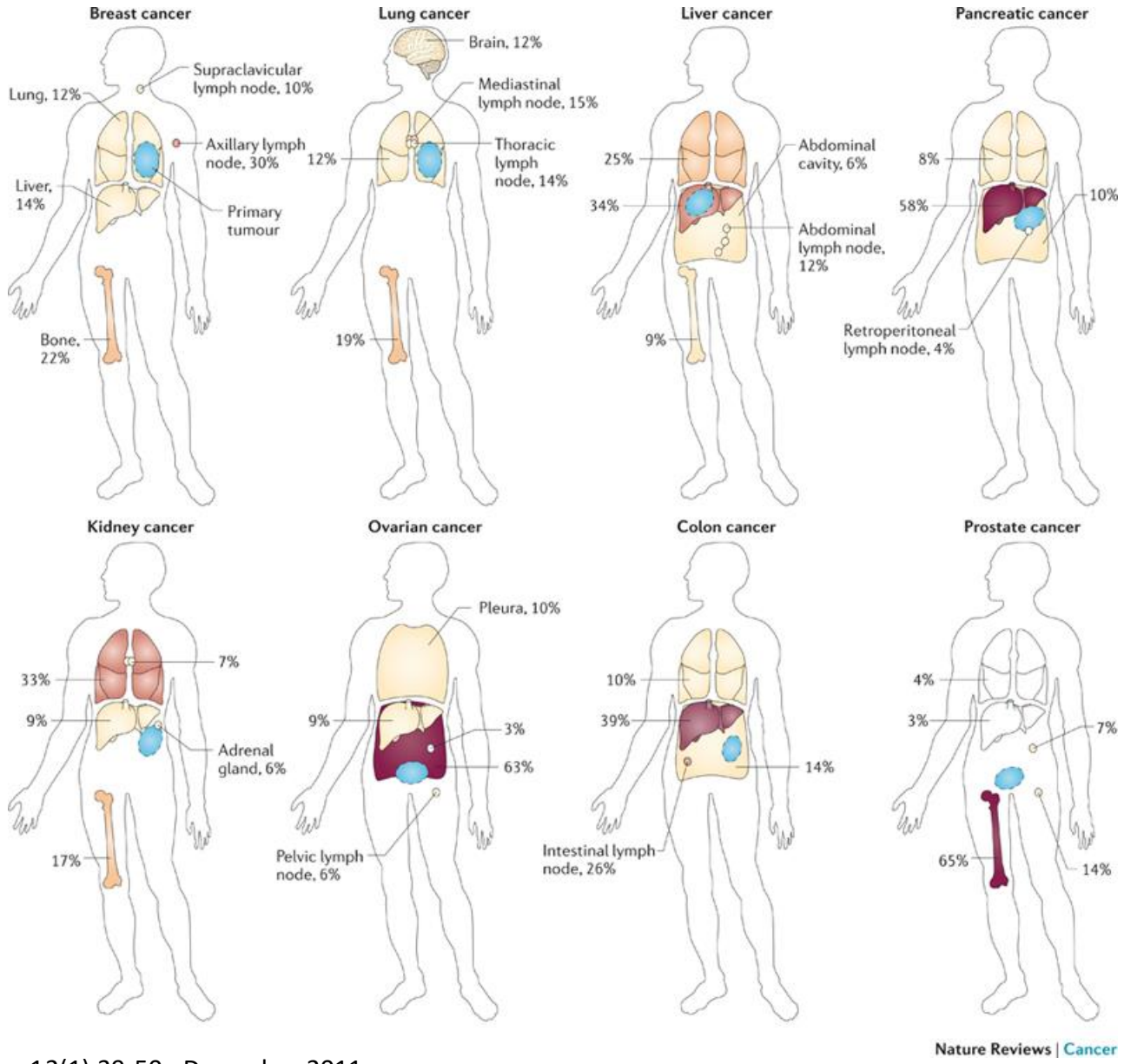


Yaeger R., *et al., Cancer Cell* 2018
Nguyen, Fong, *et al.*, *Cell* 2021



Gerstberger, Jiang and Ganesh, *Cell*, 2023

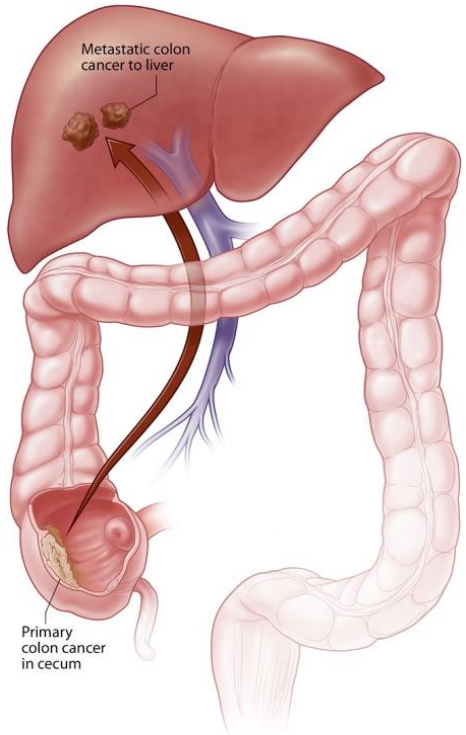
Patterns of metastatic dissemination



Nature Reviews Cancer 12(1):39-50 · December 2011

What determines organ-tropism of metastasis?

Mechanistic theory: determined by the pattern of blood flow. *James Ewing 1929*



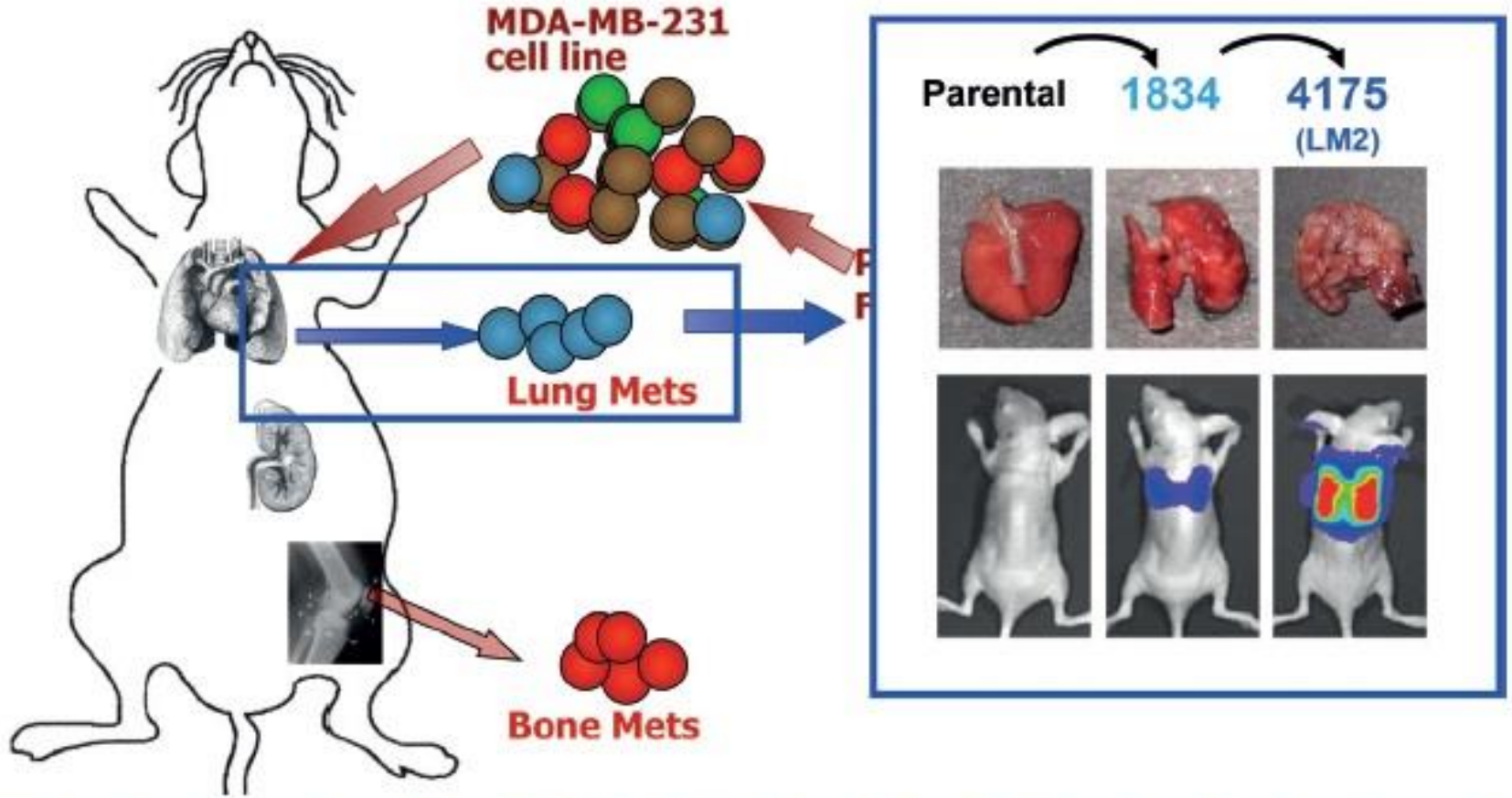
What determines organ-tropism of metastasis?

"Seed and soil" theory: the provision of a fertile environment in which compatible tumor cells could grow. *Stephen Paget 1889*

- 1950s-1970s injection of tumor cells into circulation of animals
  - Vast majority of injected cells died
  - The number of metastases was proportional to the number of tumor cells injected
  - The rate of tumor cell trapping in the microvasculature of different organs, and the survival and outgrowth of trapped cells varied.
  - Metastasis is largely clonal

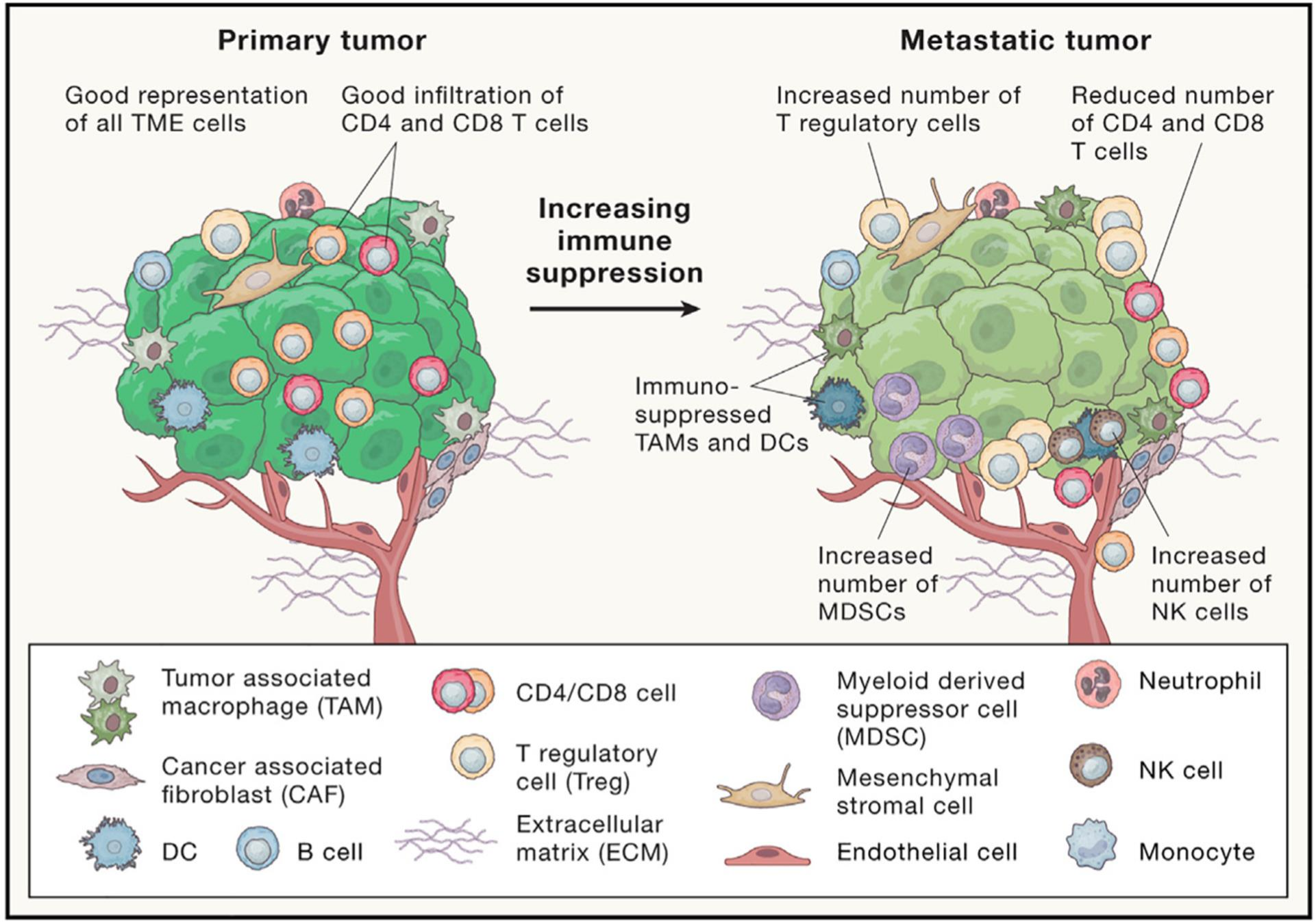
- 1973 Isiaih J. Fidler *Nature New Biology* **242**, 148–149
- 2000s Joan Massague
  - Selection of multiple metastatic lines with different organ tropism

IN VIVO SELECTION TO IDENTIFY METASTASIS MEDIATORS

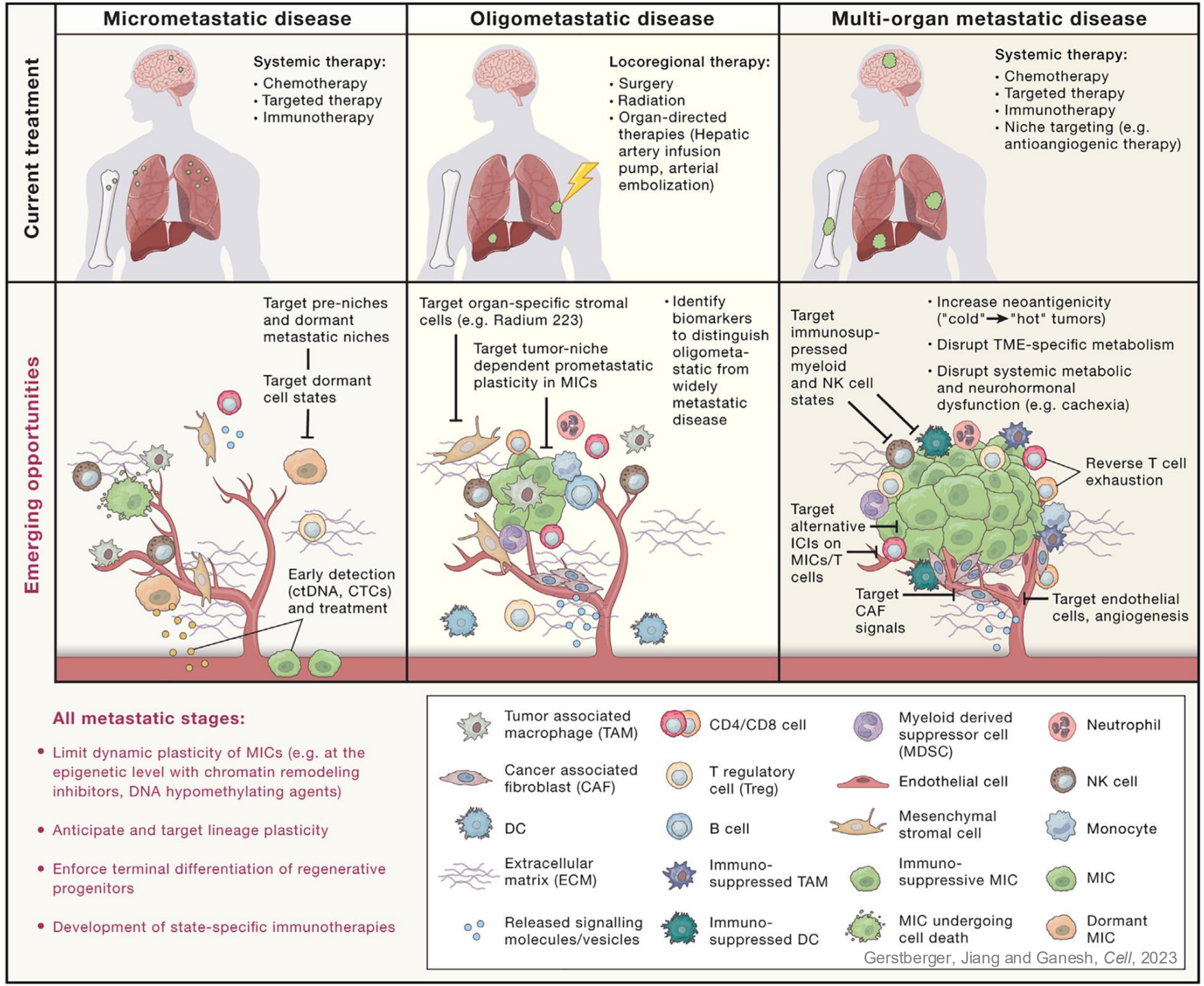


Different seeds can have different affinities for different sites in the body, as has been shown by studies that bred mice to have particular sub-clones of metastatic colonies that are either lung specific or bone specific

Source: IJ Fidler. (1973) *Nature* 242:148–149, reprinted with permission from Macmillan Publishers Ltd; Y Kang et al. (2003) *Cancer Cell* 3:537–549, reprinted with permission from Elsevier; AJ Minn et al (2005) *Nature* 436, 518–524, reprinted with permission from Macmillan Publishers Ltd

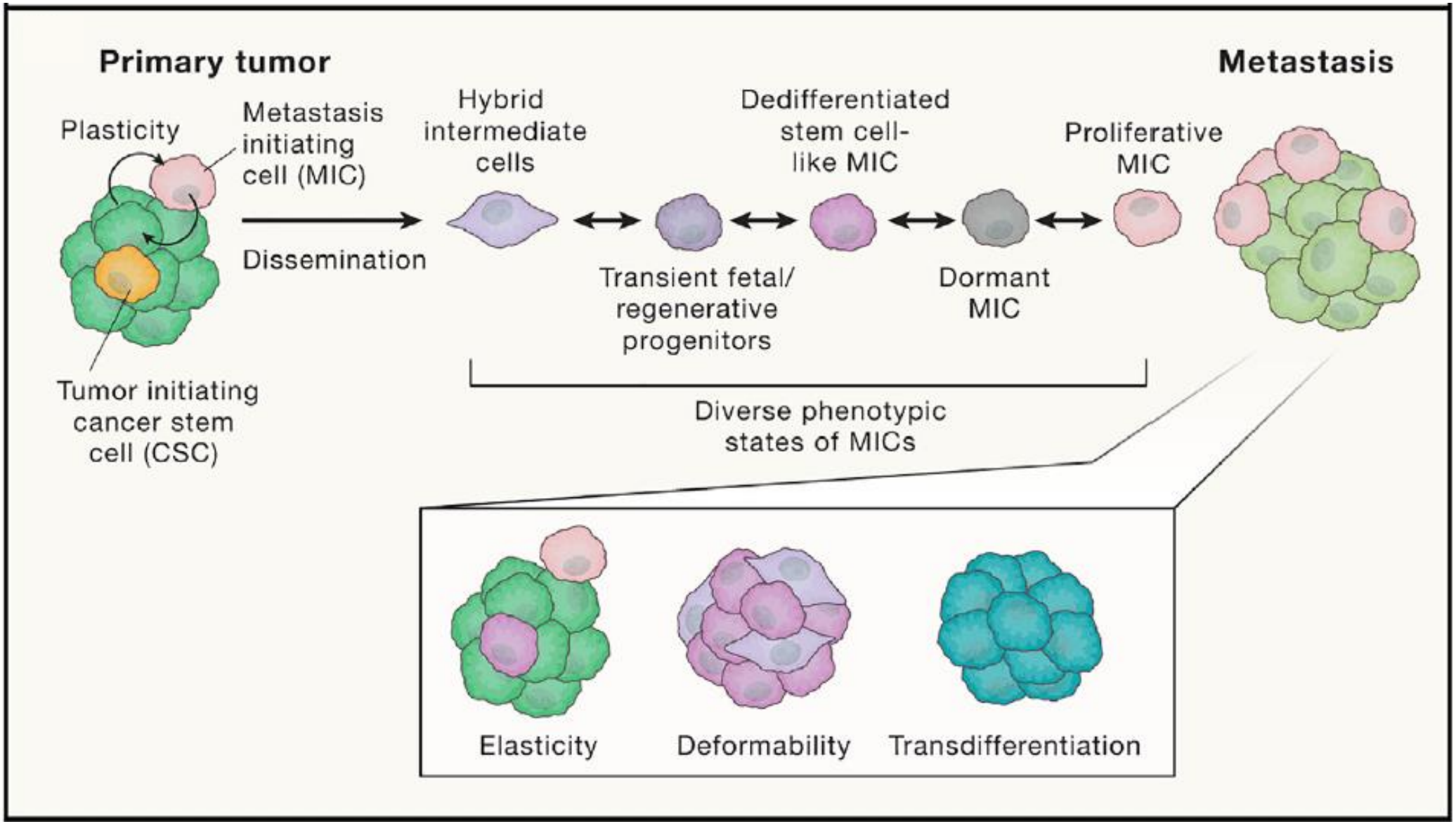


Gerstberger, Jiang and Ganesh, *Cell*, 2023



Gerstberger, Jiang and Ganesh, *Cell*, 2023

Plasticity is the overarching hallmark of metastasis

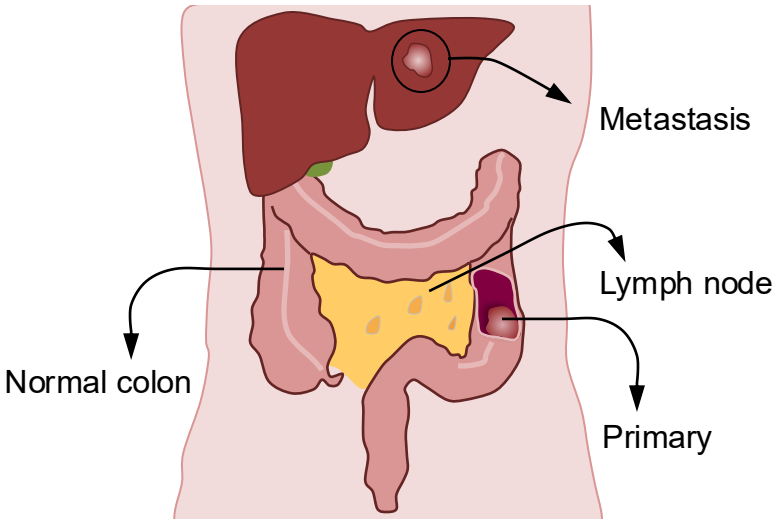


Gerstberger, Jiang and Ganesh, *Cell*, 2023

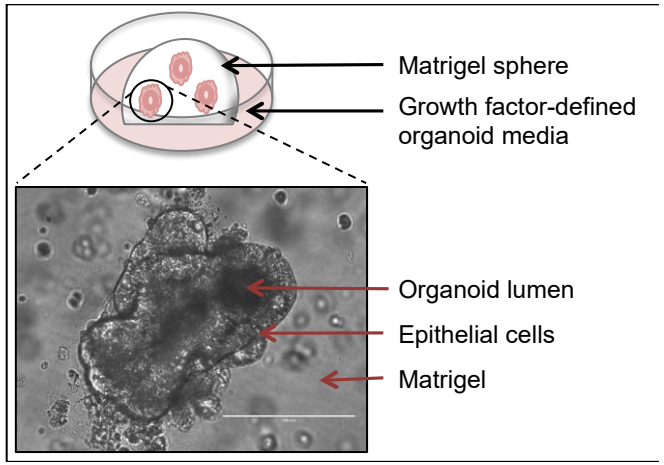
Models for studying cancer: pros and cons

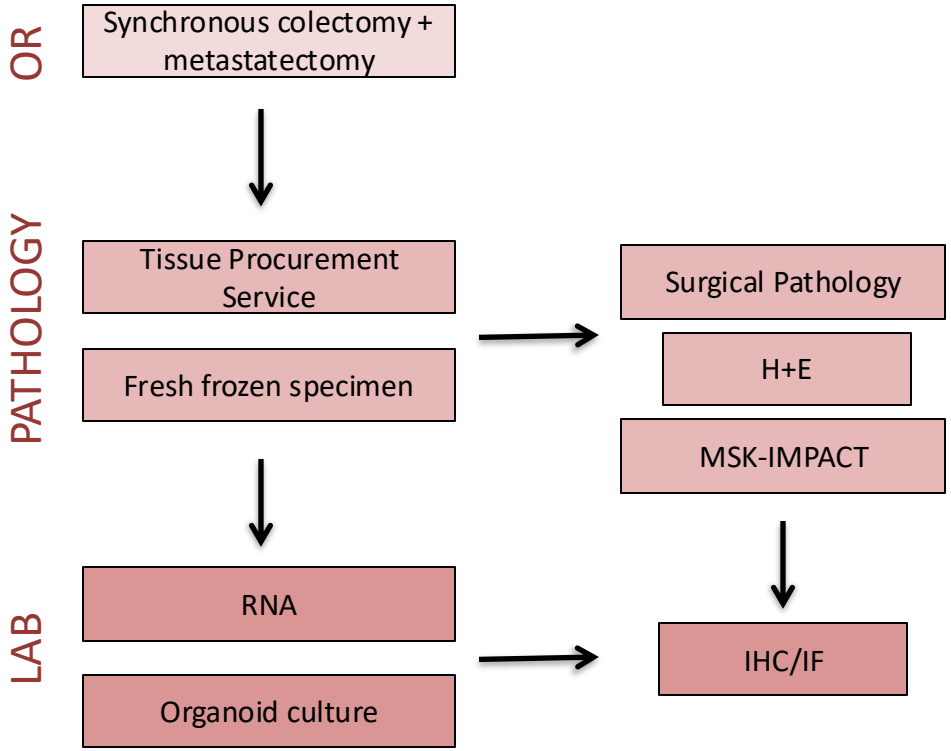
- Clinical samples
- Tissue culture
- GEMMs
- Xenograft mouse models
- NAMs
  - Patient-derived organoids
  - Bioengineered systems
  - AI models

MSK IRB#14-244: Generating Colorectal Cancer Organoid Cultures to Study Cancer Dissemination and Metastasis.



Metastatic CRC



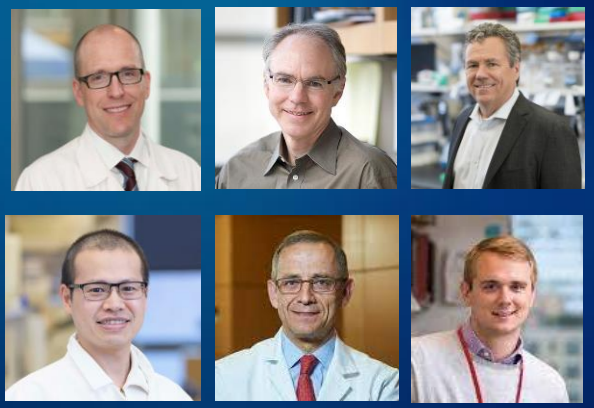


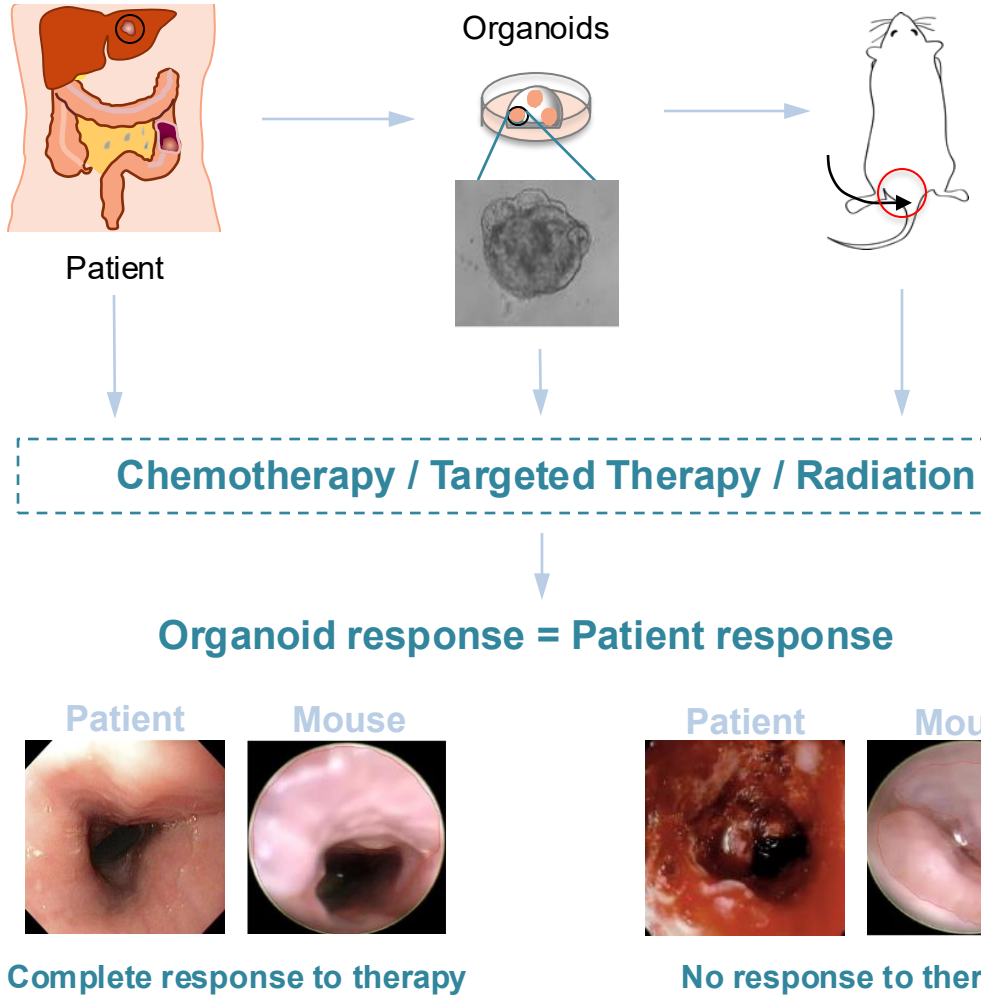
Patient-derived organoid advantages:

- High efficiency of generation (>80% CRC)
- Genetically tractable
- Transplantable into orthotopic sites in mice
- Retain metastatic tropisms
- Heterogeneity and plasticity

Organoids capture patient specific phenotypic states and treatment responses

MSKCC Rectal Biobank Project

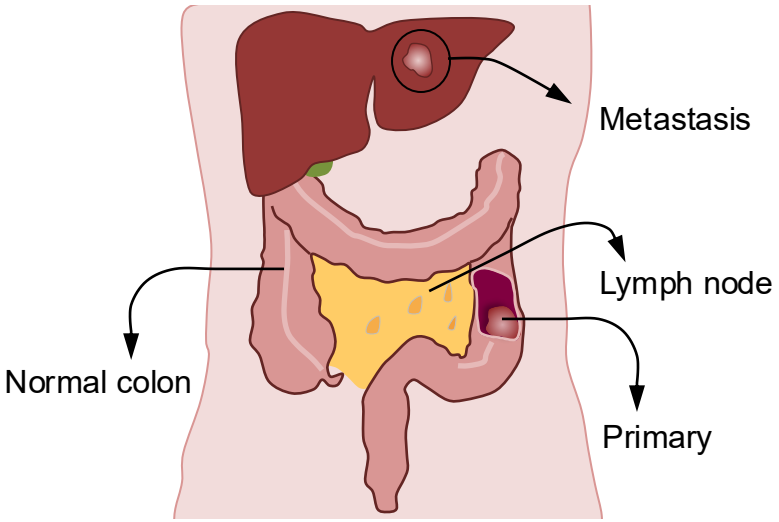




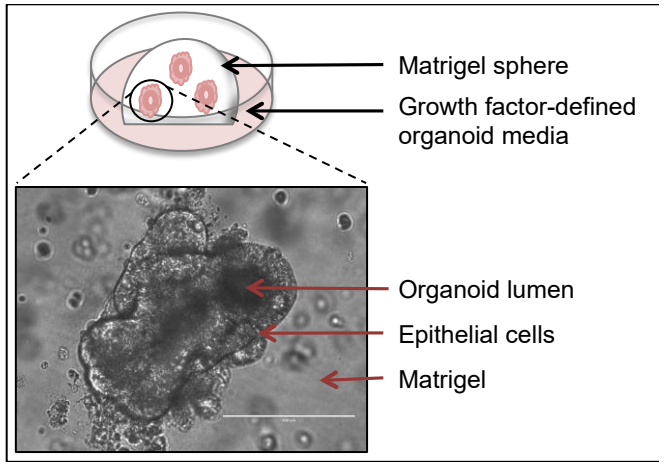
Ganesh et al, *Nature Medicine*, 2019

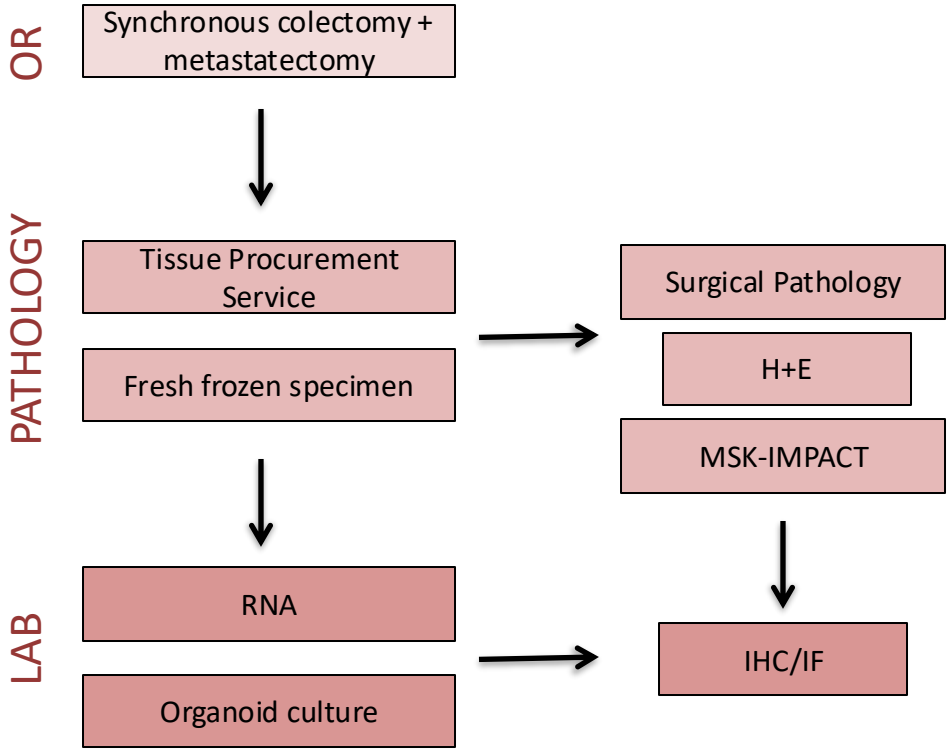
Can we use organoids to understand how cancers evolve during metastasis?

MSK IRB#14-244: Generating Colorectal Cancer Organoid Cultures to Study Cancer Dissemination and Metastasis.



Metastatic CRC





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Dana Pe'er

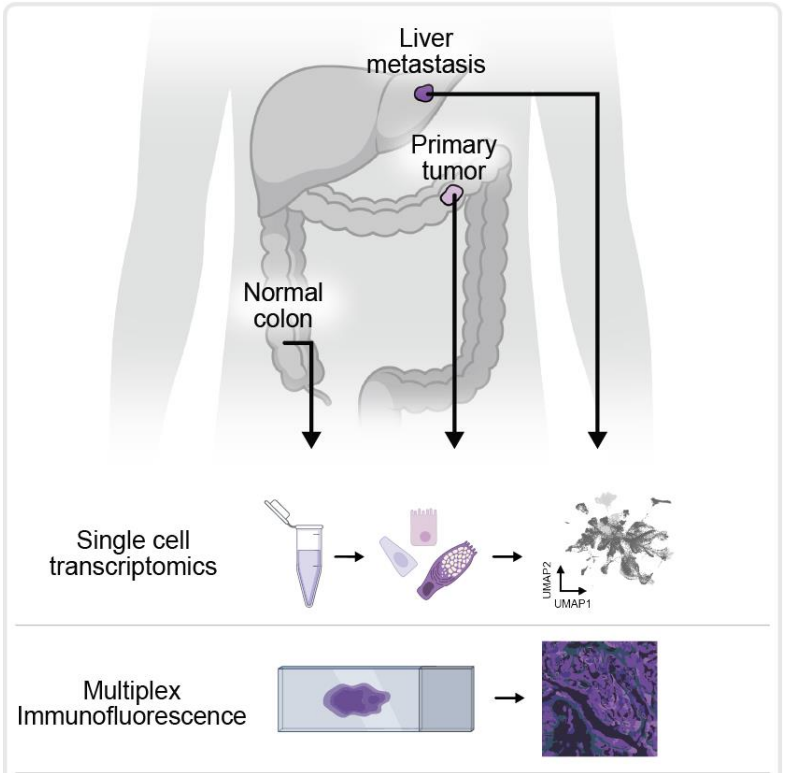
Andrew Moorman

Elizabeth Benitez

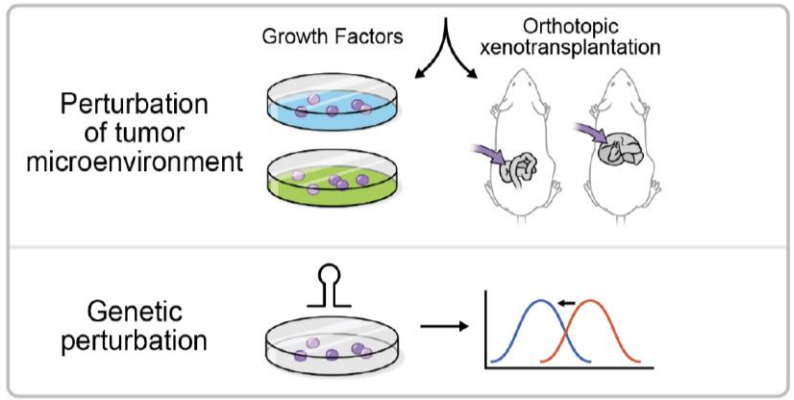
Francesco Cambuli

Patient-derived biospecimen platform to dissect transitions to metastatic state

Synchronous resection of metastatic colon cancer



Organoid perturbations



- How do tumors transition to metastasis?
- What are the shared metastatic mechanisms across patient tumors?

176 datasets: 31 patients, 9 untreated, 22 5FU chemotherapy treated, 6 metachronous metastases

NIH NATIONAL CANCER INSTITUTE

HTAN HUMAN TUMOR ATLAS NETWORK

Moorman*, Cambuli*, Benitez* et al. *bioRxiv* 2023

Progressive plasticity from canonical intestinal to non-canonical states during CRC metastasis

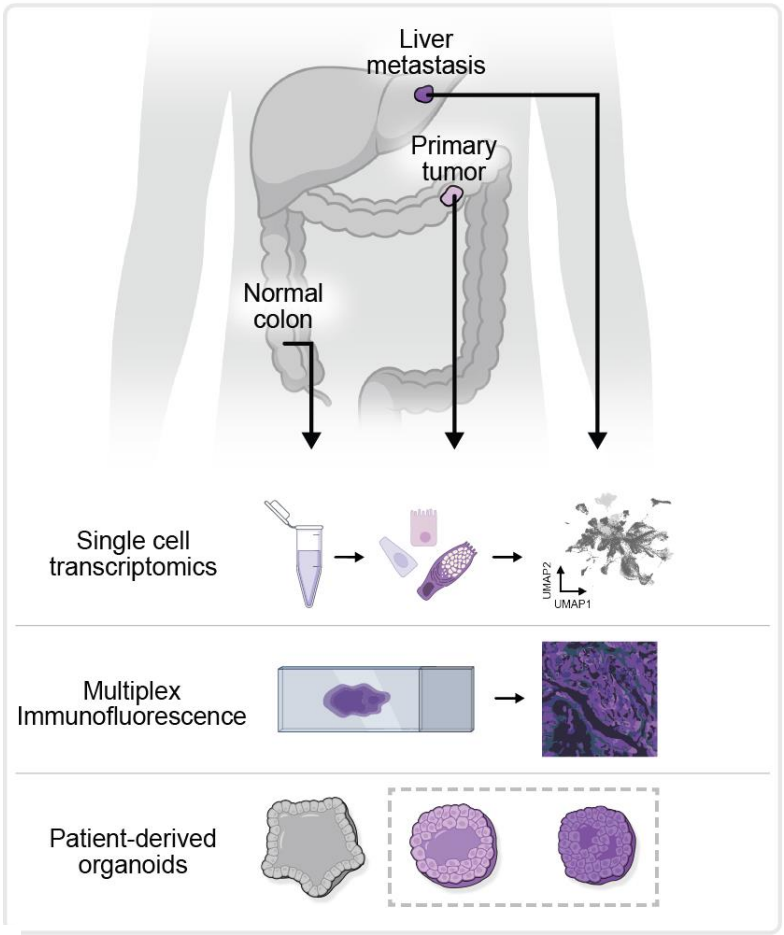
Dana Pe'er

Andrew Moorman

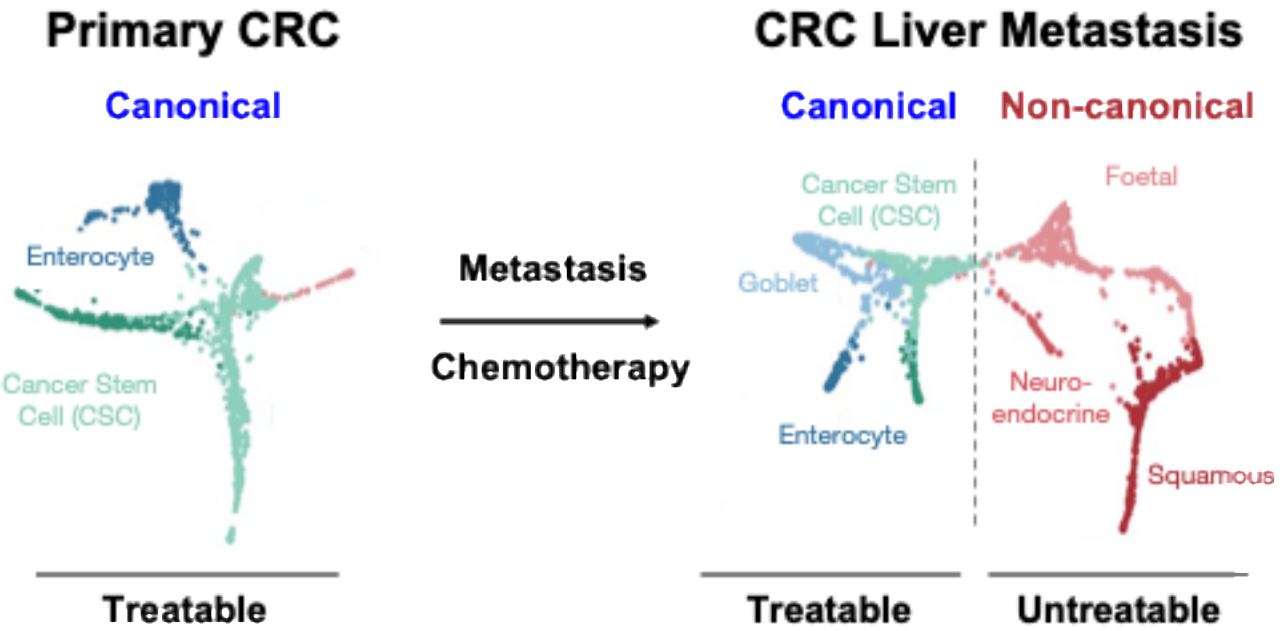
Elizabeth Benitez

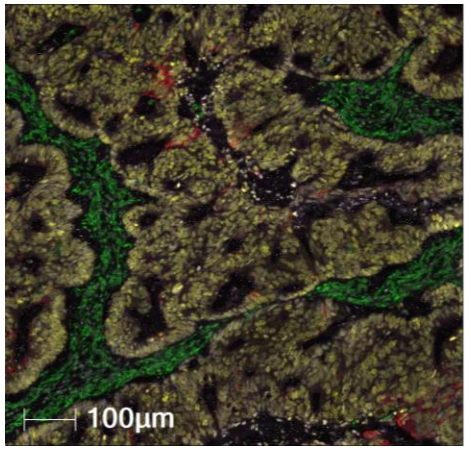
Francesco Cambuli

Synchronous surgical resection of metastatic colorectal cancer

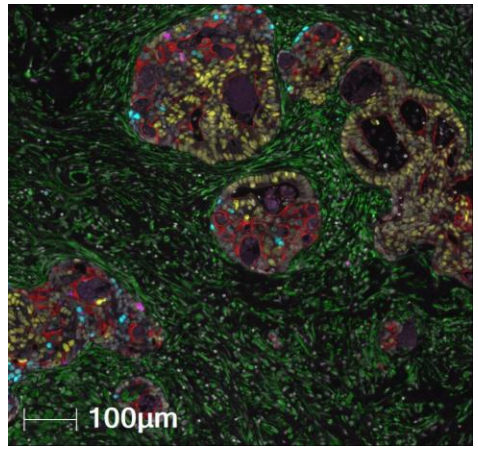


176 datasets from 31 patients





Canonical cell states



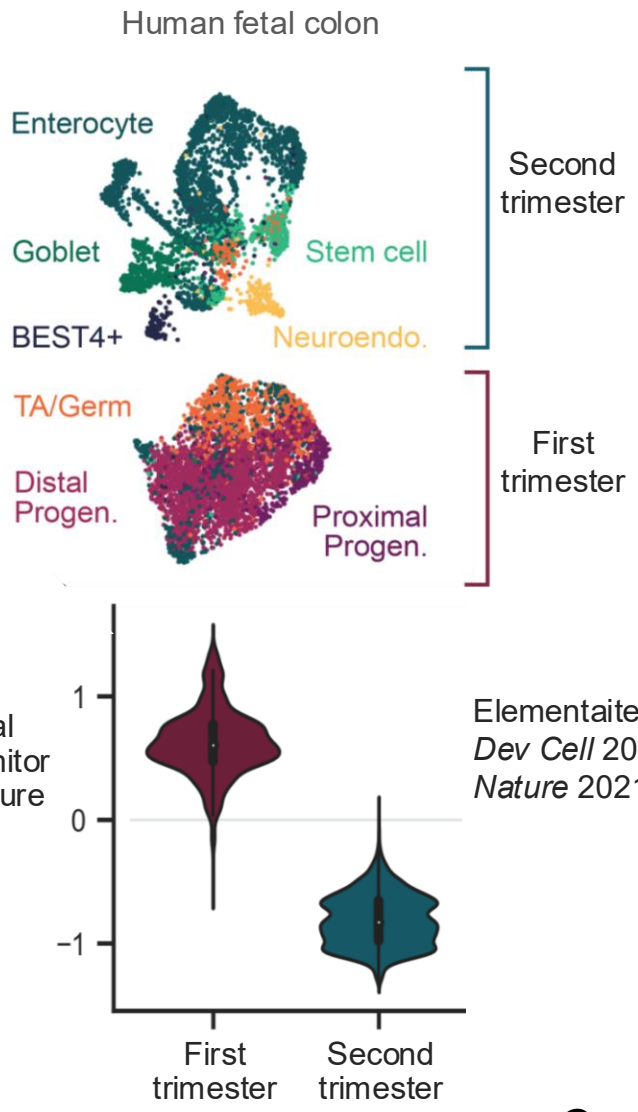
Canonical and non-canonical cell states

NIH NATIONAL CANCER INSTITUTE

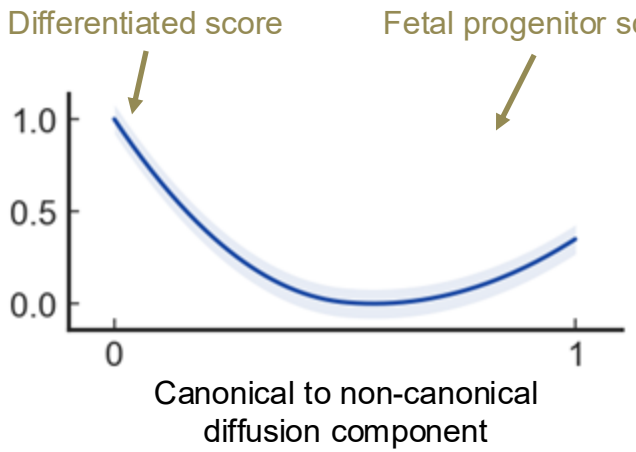
HTAN HUMAN TUMOR ATLAS NETWORK

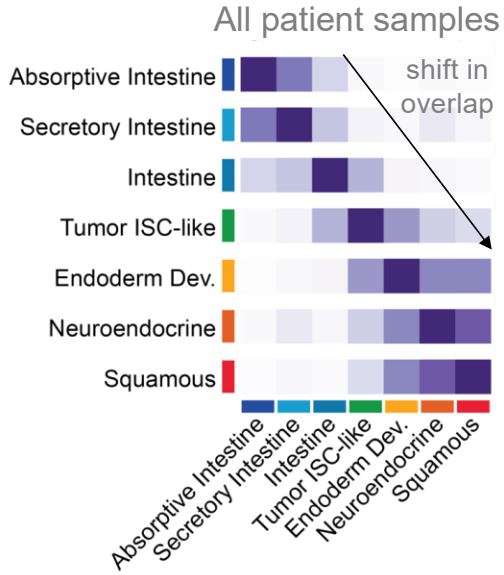
Moorman, Benitez, Cambuli, et al., *Nature*, 2025

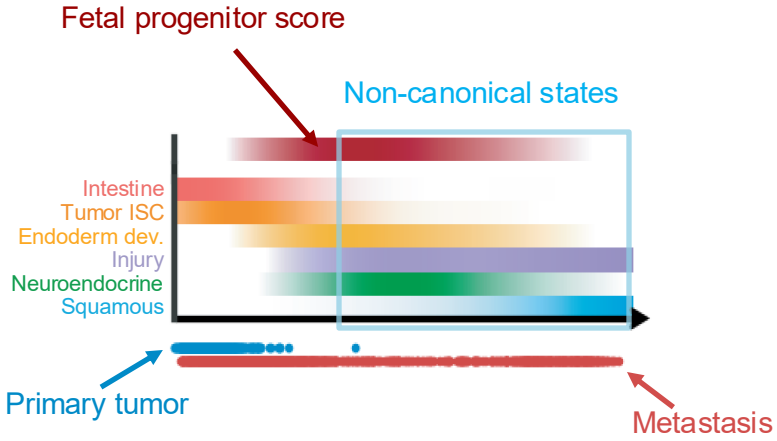
Tumors progress via a conserved fetal progenitor intermediate state

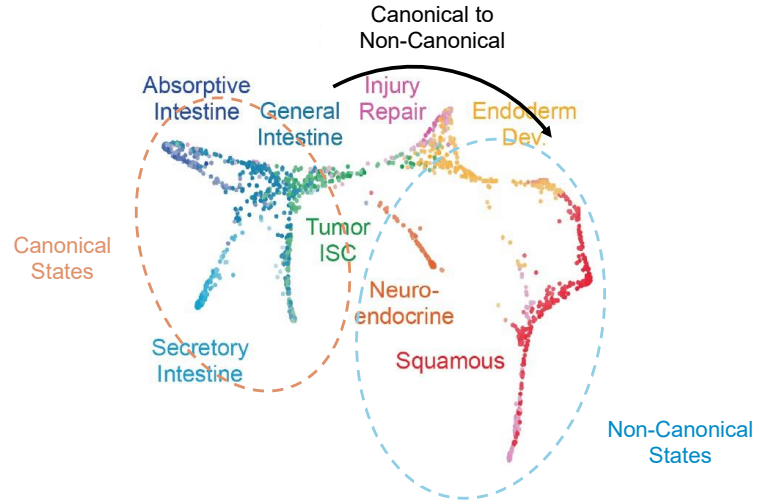


Elementaite et al.
Dev Cell 2020
Nature 2021









- Cancer cells display conserved, sequential cell-state transitions during progression
- Non-canonical states are pervasive across patients and correlate with worse outcomes

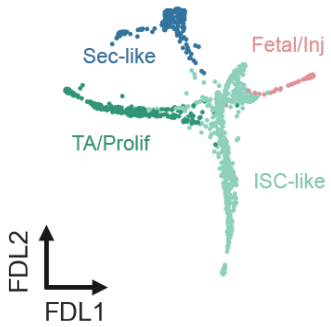
Moorman, Benitez, Cambuli, et al., *Nature*, 2025

Primary and met organoids retain distinct differentiation potential *ex vivo*

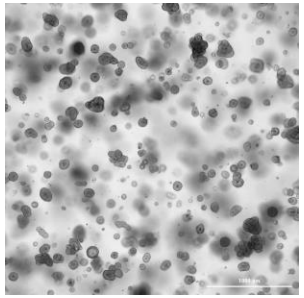
Patient KG146

Human Intestinal Stem Cell Media

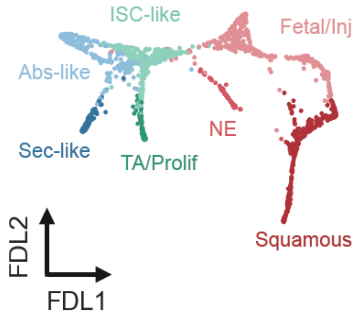
Patient Primary Tumor scRNAseq



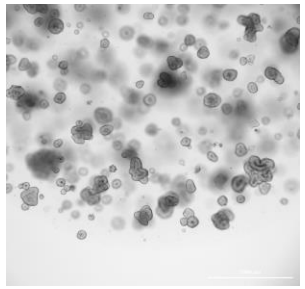
Primary Tumor Organoids



Patient Metastasis scRNAseq

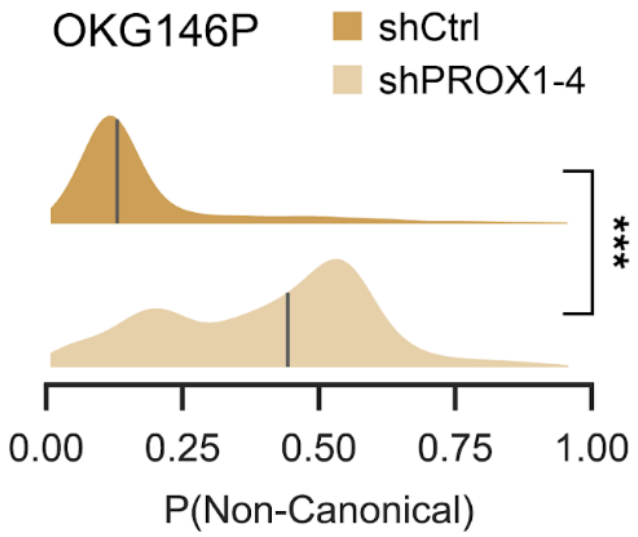


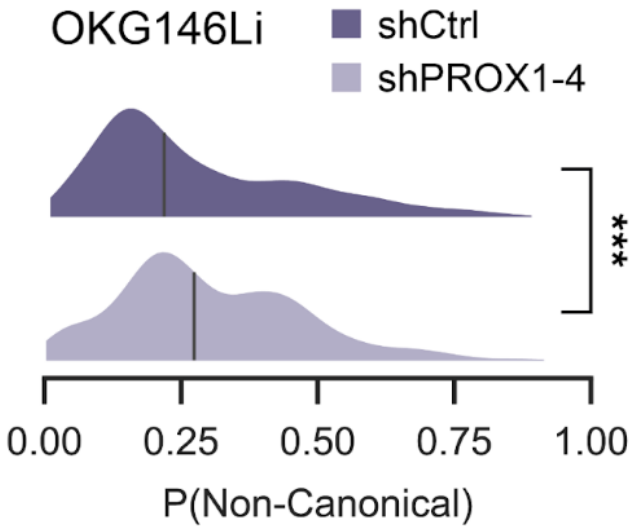
Metastasis Organoids



Moorman, Benitez, Cambuli, et al., *Nature*, 2025

PROX1 inhibits non-canonical transition in primary CRC



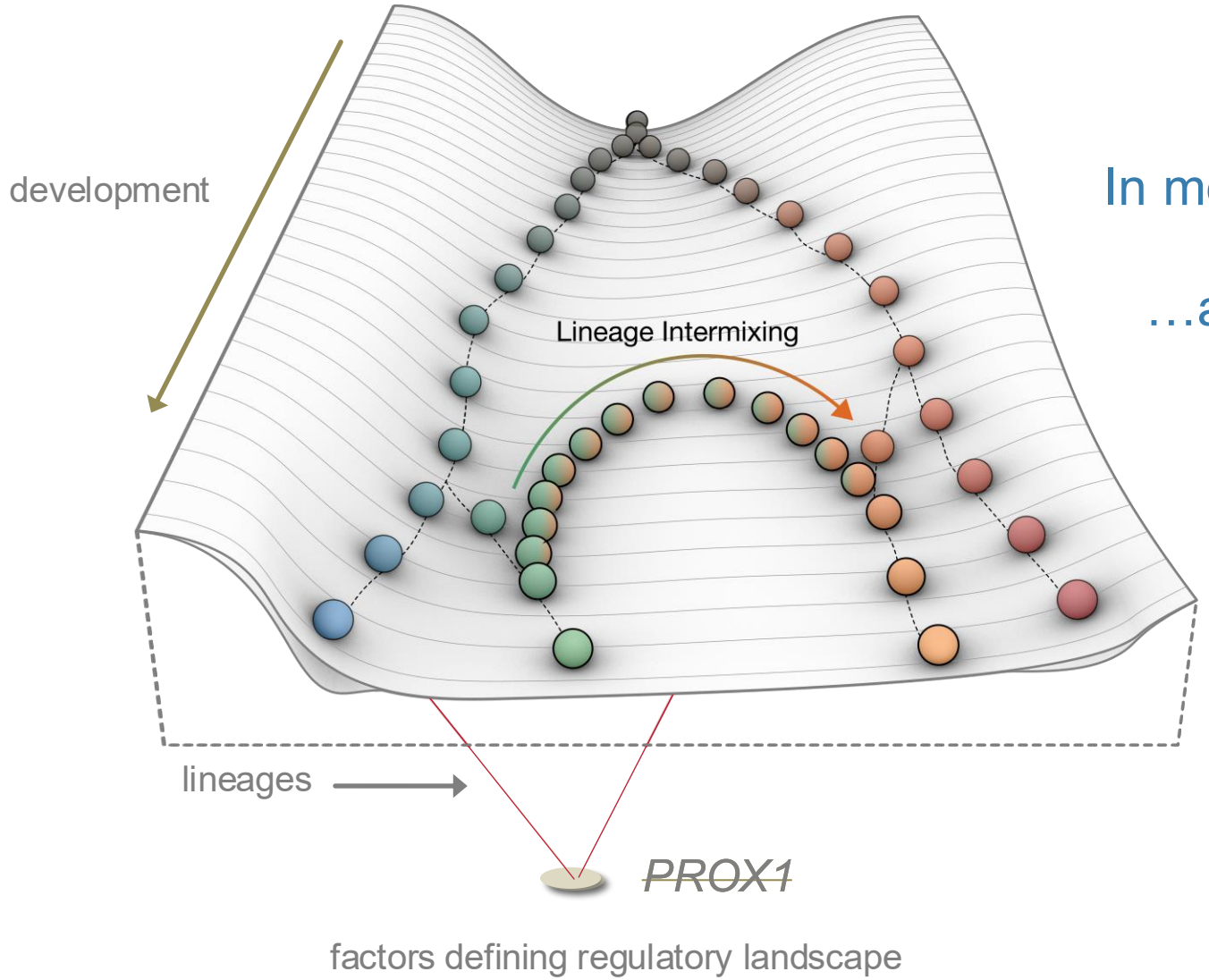


In **primary** organoids, *PROX1* knockdown releases inhibition and **induces non-canonical states**

In **metastasis** organoids, *PROX1* knockdown has **little impact** on transdifferentiated state

PROX1 dependency is weak in mets

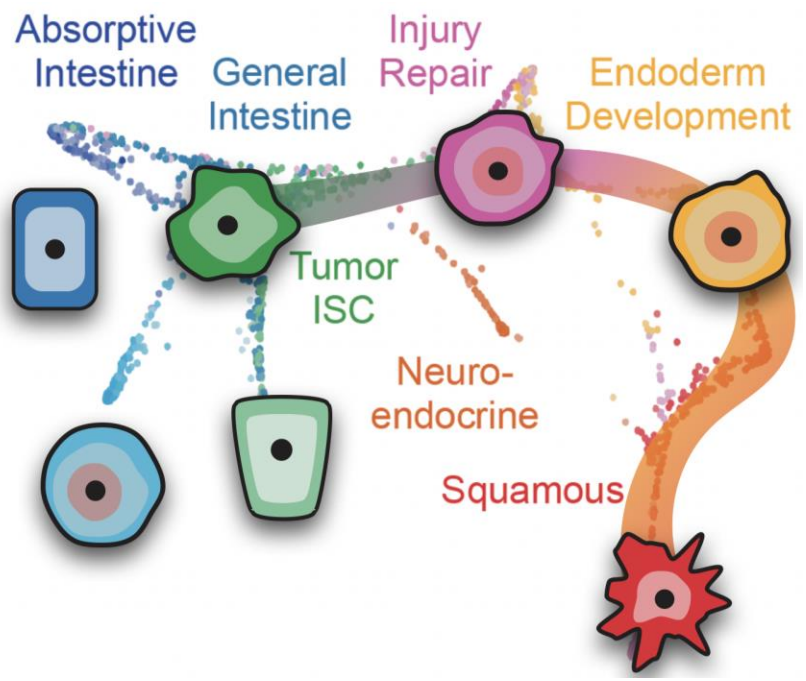
Cancer cell plasticity involves specific regulators



In metastasis, barriers fail

…allowing promiscuous expression from different lineages

Plasticity in colorectal metastasis



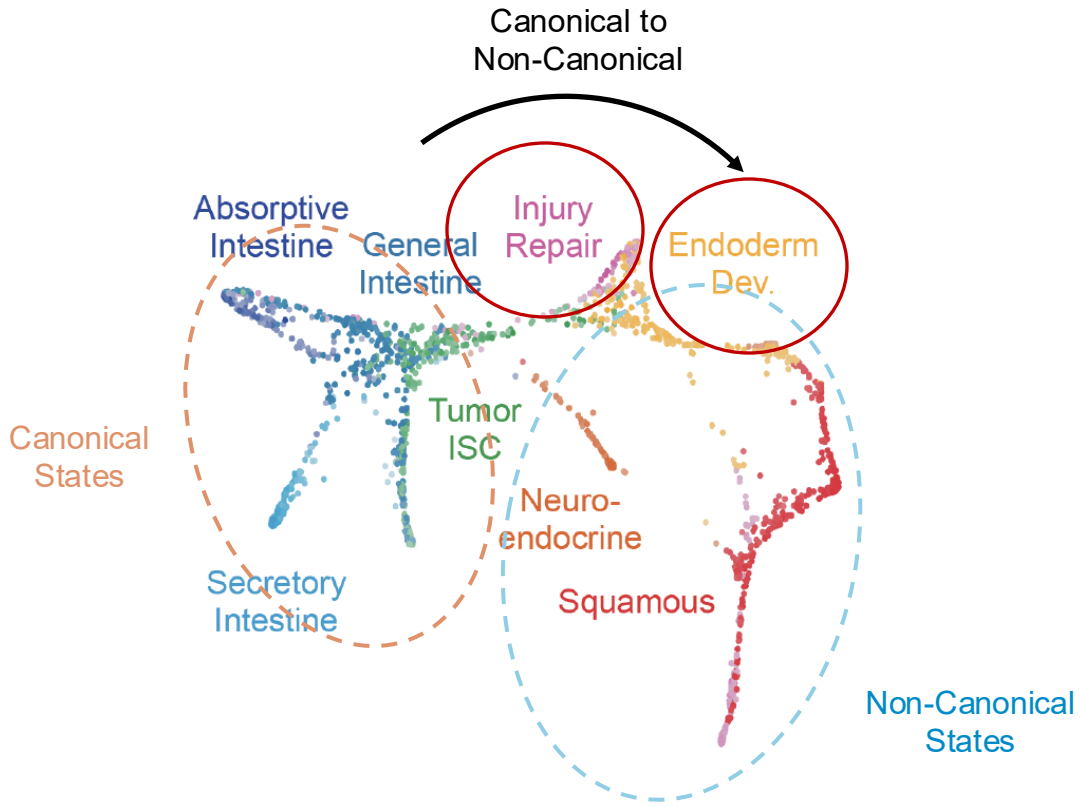
- Metastatic cells display **greater plasticity**, allowing them to adapt to different tissue environments
- **Epithelial injury** via metastasis or therapy promotes entry into **non-canonical states**
- CRC cells display **conserved, sequential cell state transitions** during tumor progression
- ***PROX1* buffers plasticity** in primary tumor contexts

These mechanisms are observed across multiple patients

How can we therapeutically target plasticity?

Target regulators of cell state transitions?

Target conserved tumor regenerative states



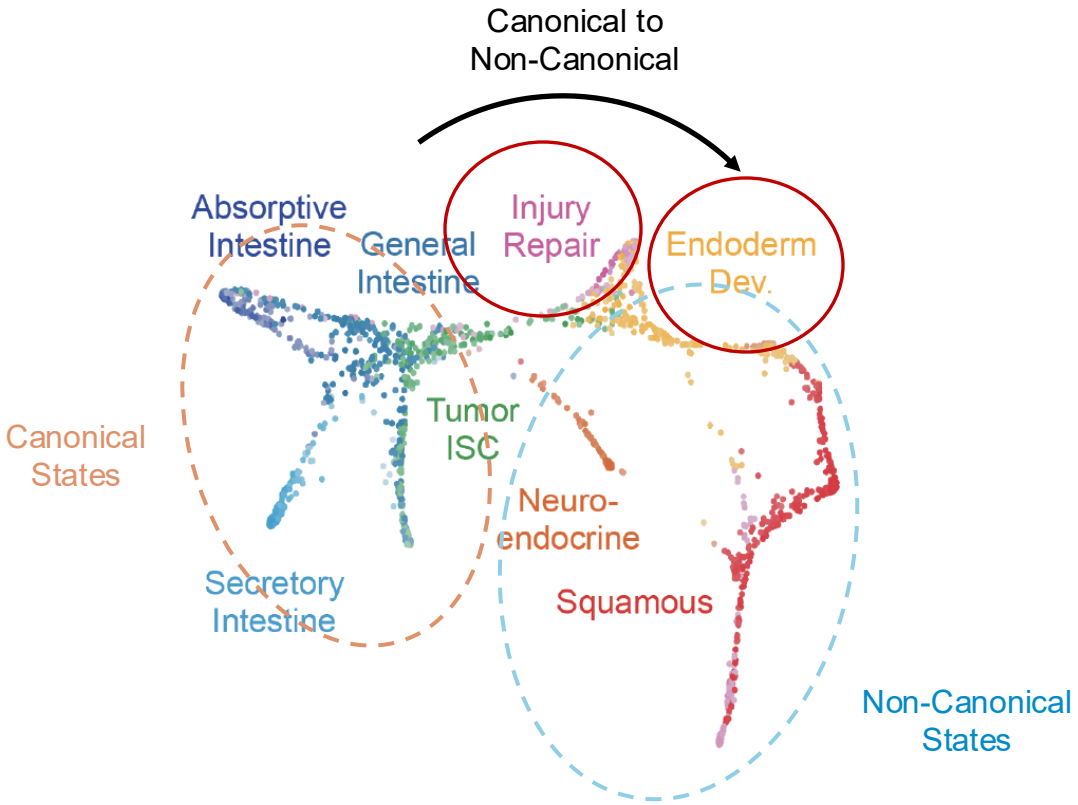
Challenges: heterogeneity, fetal-state specific targets are largely not at the cell surface

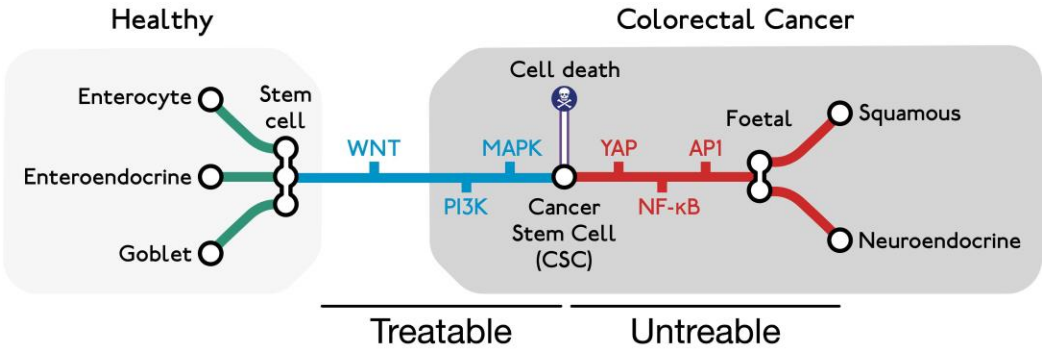
CANCER GRAND CHALLENGES

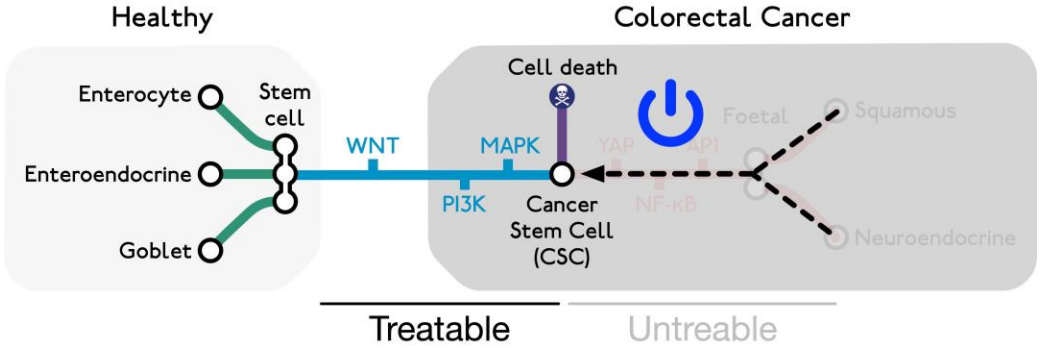
REWIRE-CAN
Reprogramming Epithelial WIRing to Eradicate CANcer

How can we therapeutically target plasticity?

Target regulators of cell state transitions?

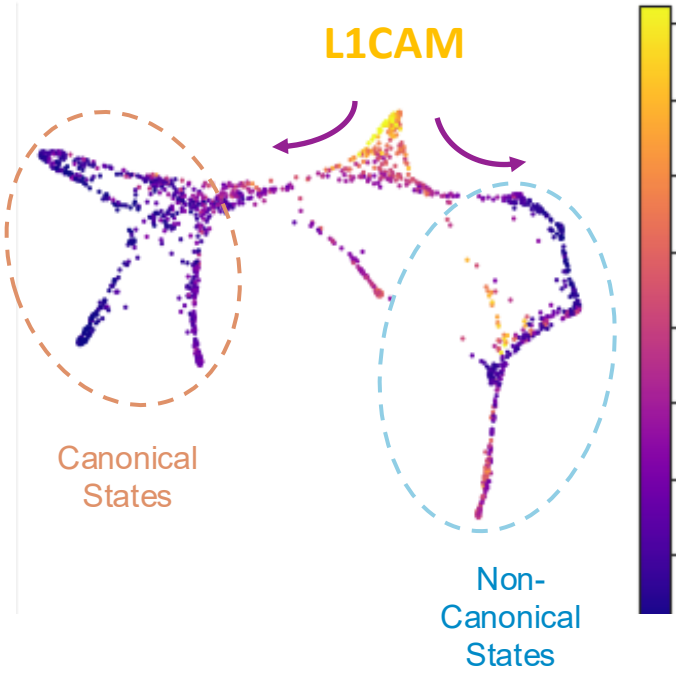




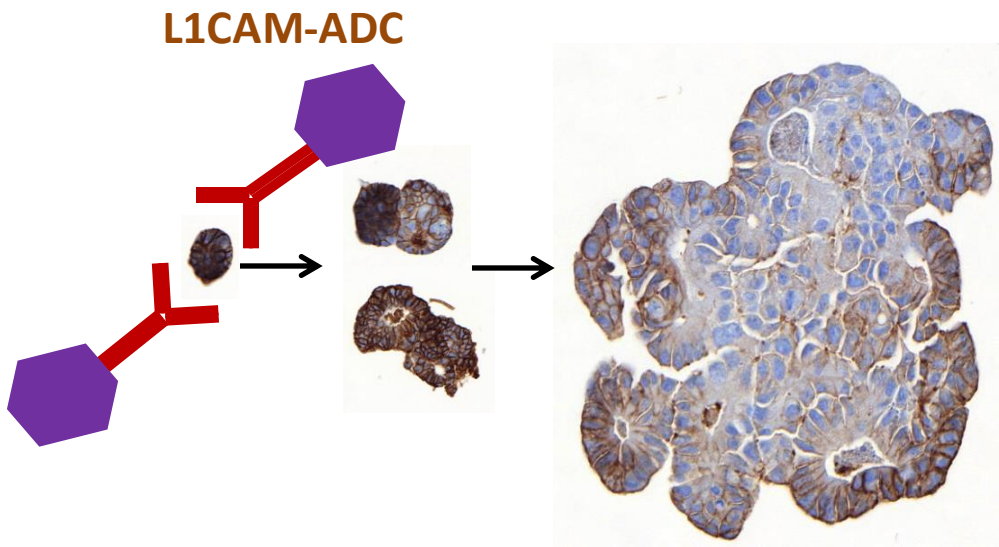


Targeting tumor regenerative transitional states

L1CAM marks a conserved tumor regenerative intermediate state



Patient metastatic tumor single cell RNA sequencing

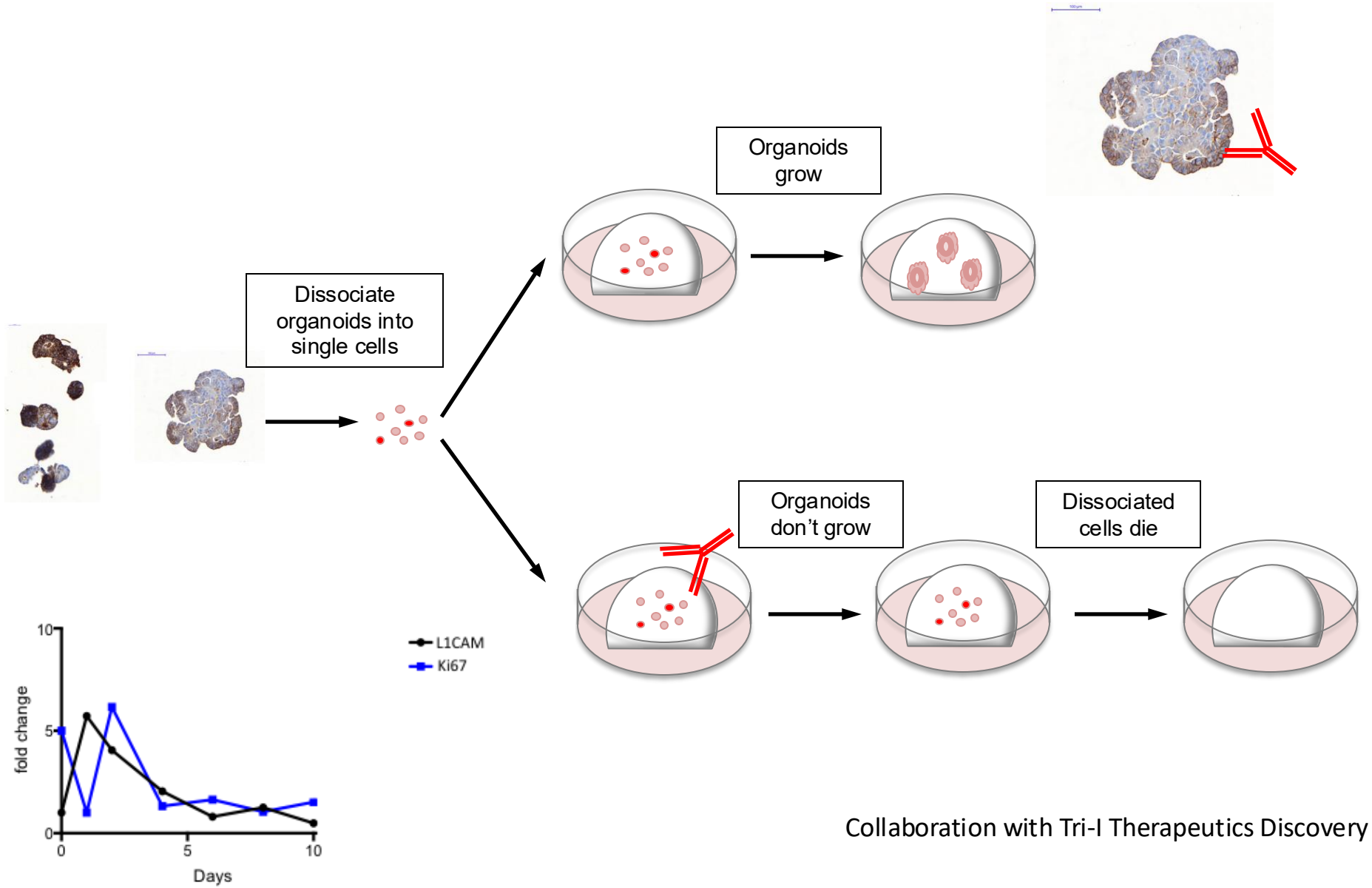


Patient-derived metastasis organoid

Could therapeutic targeting of L1CAM could block metastasis and cancer regrowth after therapy?

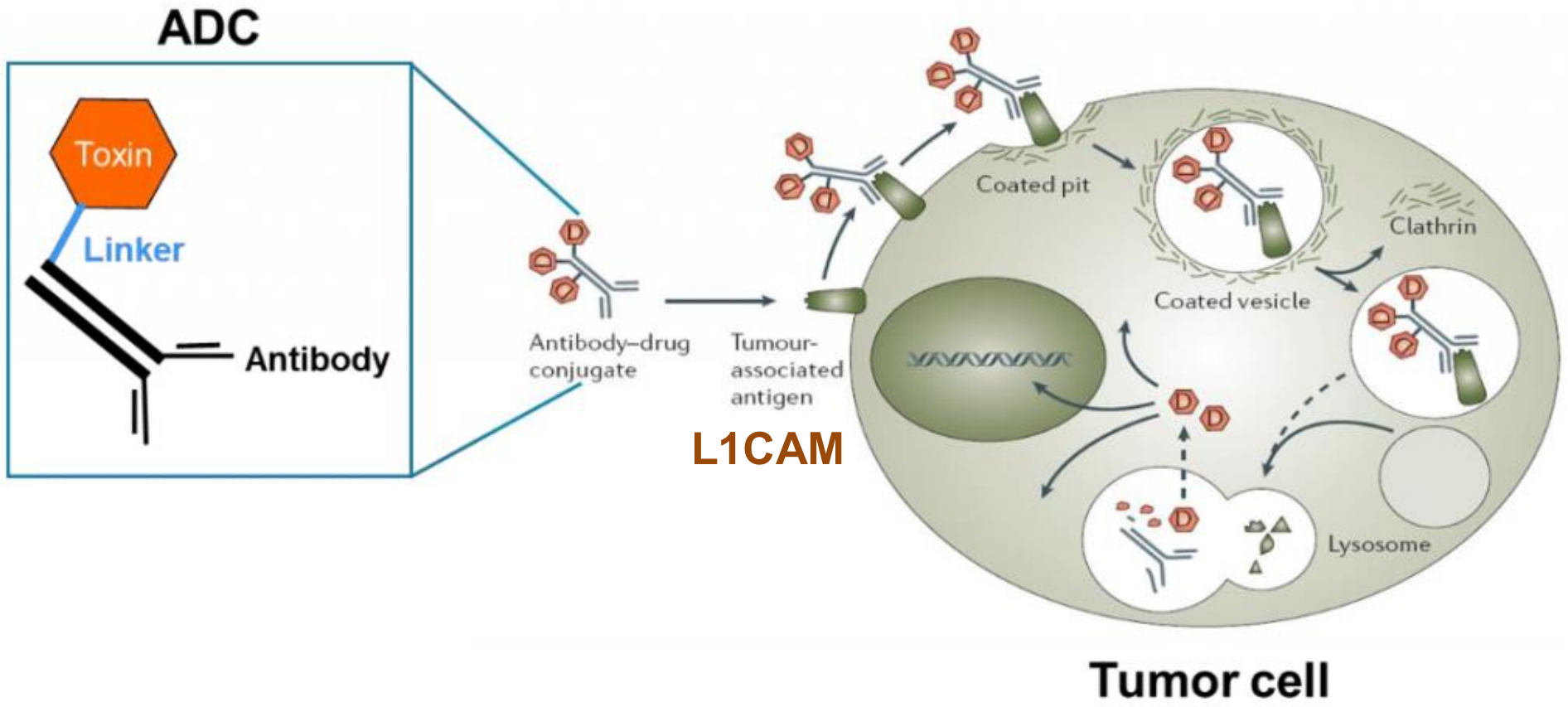
Ganesh et al. *Nature Cancer*, 2020
Chatila et al.. *Nature Medicine*, 2022
Moorman, Benitez, Cambuli et al., *Nature,* 2024
Park et al., *Molecular Cancer Therapeutics*, 2026

Using patient-derived organoids to find L1CAM inhibitors:
Collaboration with Tri-I Therapeutics Discovery Institute

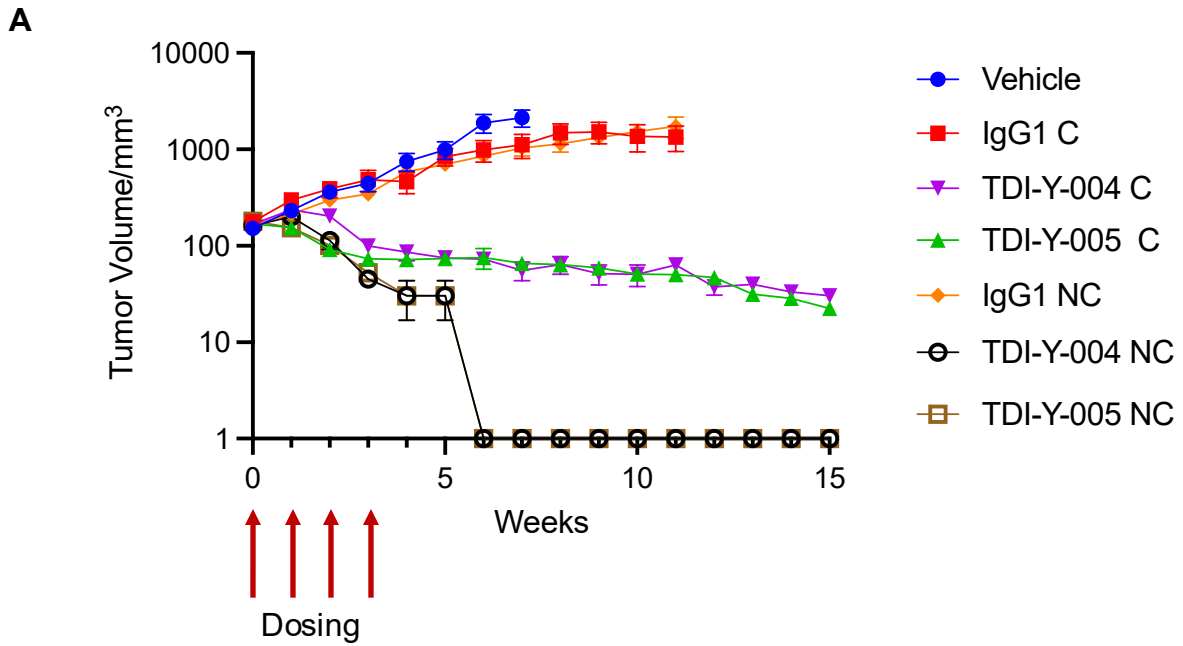


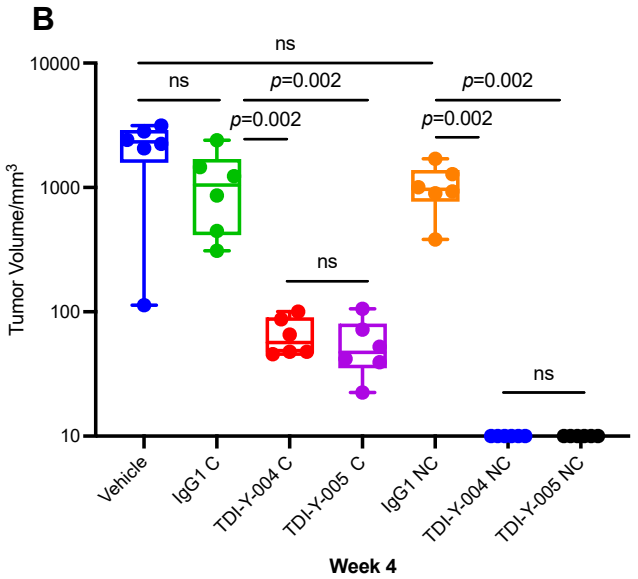
Collaboration with Tri-I Therapeutics Discovery Institute

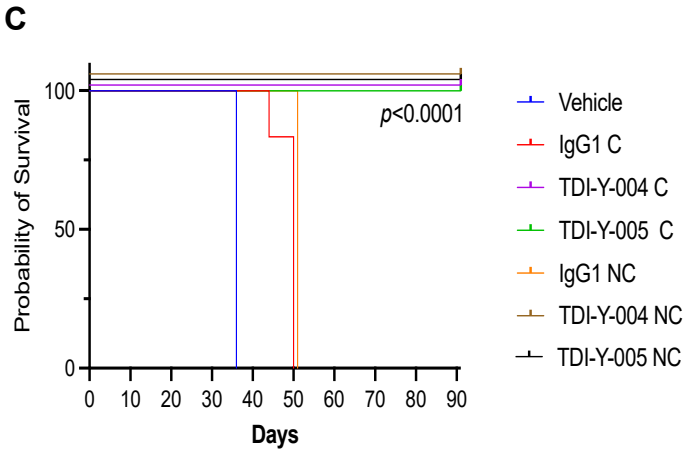
Technology: L1CAM-targeting antibody-drug conjugates (ADC)



L1CAM-targeting ADCs abrogate tumor growth *in vivo*

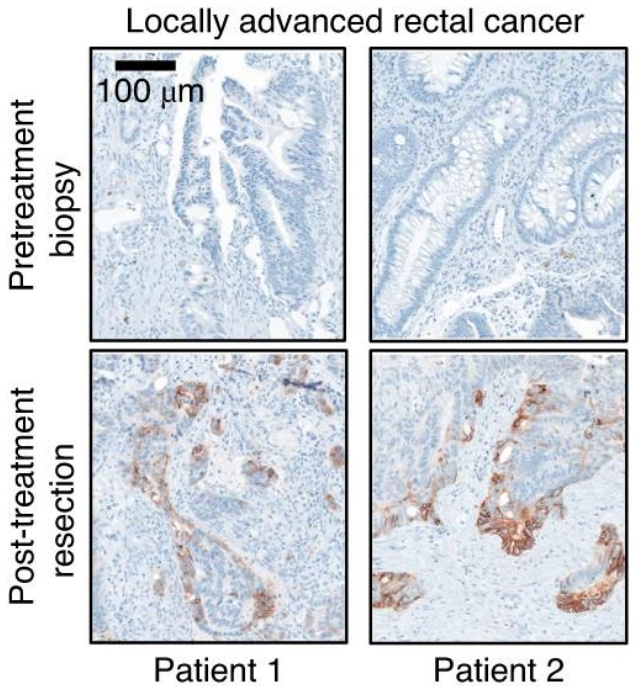


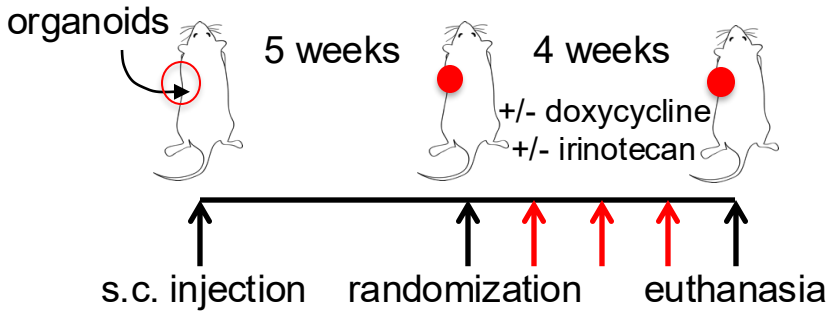


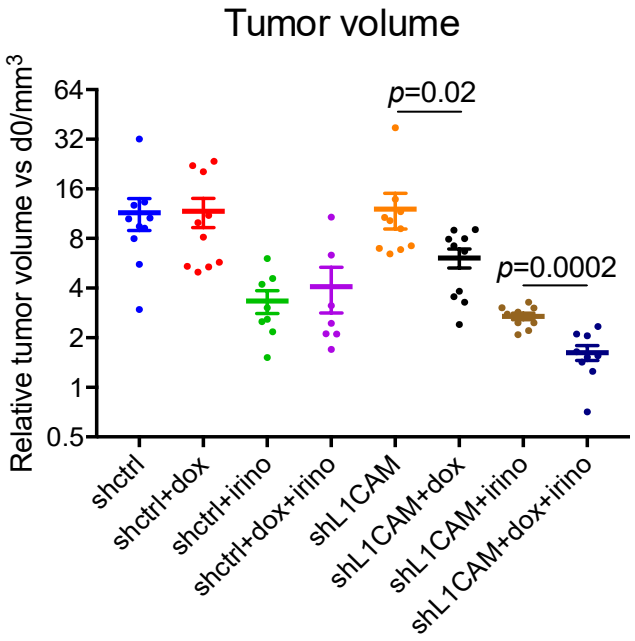


Clinical trial paradigm:

Physician's choice first line therapy + L1CAM ADC







Ganesh et al., *Nature Cancer*, 2020

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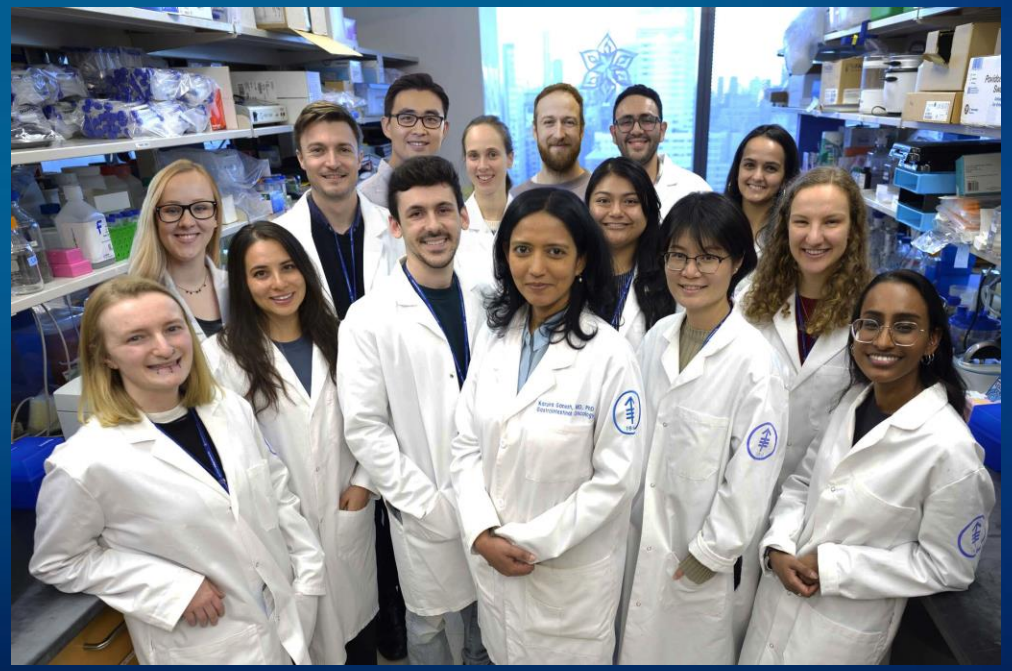
Our patients and their families



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U54CA209975
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