Dissecting and targeting metastatic plasticity

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National Cancer Advisory Board
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Disclosures

I have the following relevant financial relationships to disclose:

Employee of: Memorial Sloan Kettering Cancer Center

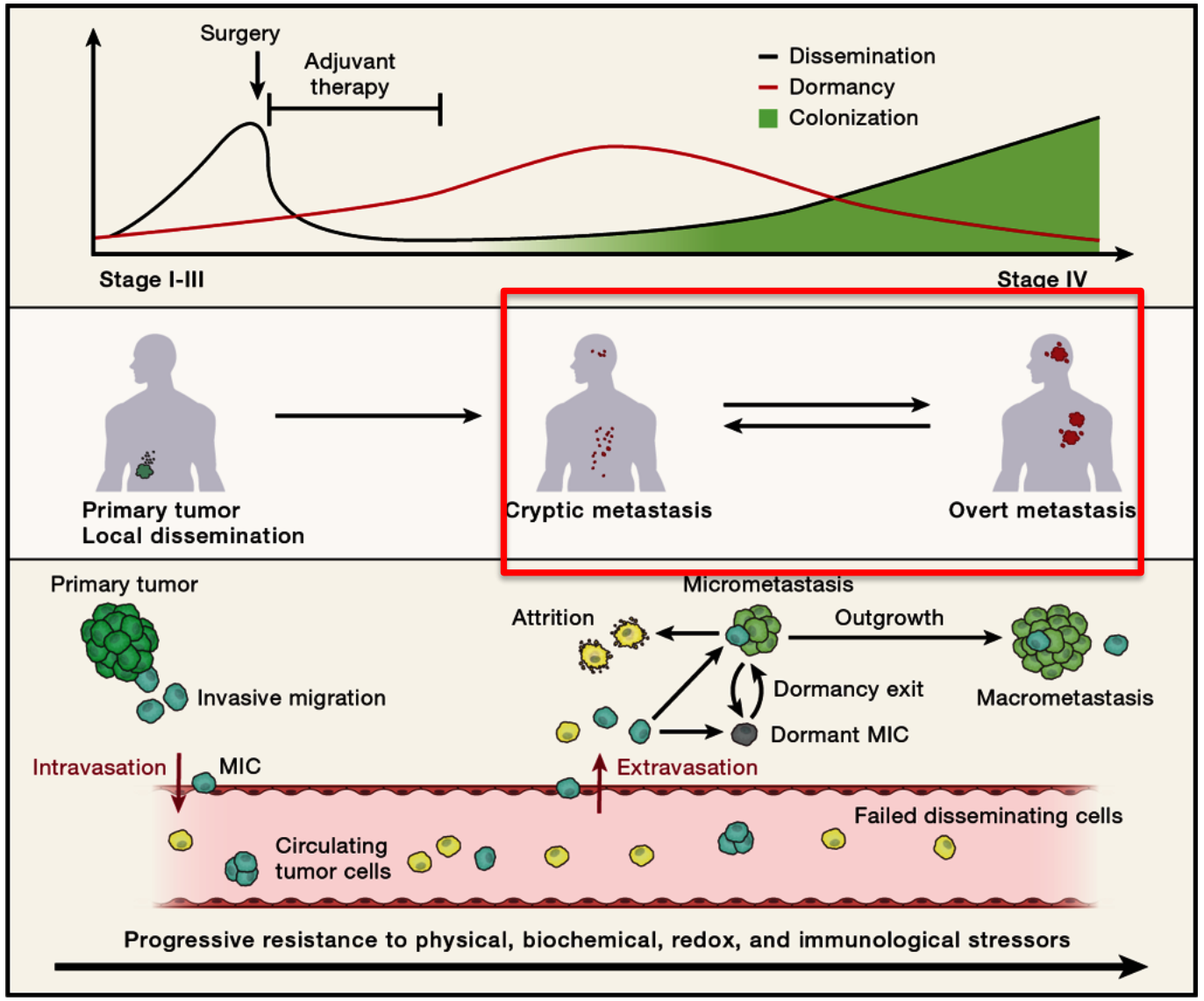
Co-Founder: CrossFlag Therapeutics

Consultant for: Genentech, AstraZeneca

Grant/Research Support from: NIH/NCI, Stand Up to Cancer, AACR, Burroughs Wellcome Funds, Damon Runyon Cancer Research Foundation,V 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, methods and molecules for targeting advanced cancer including L1CAM and NKD1

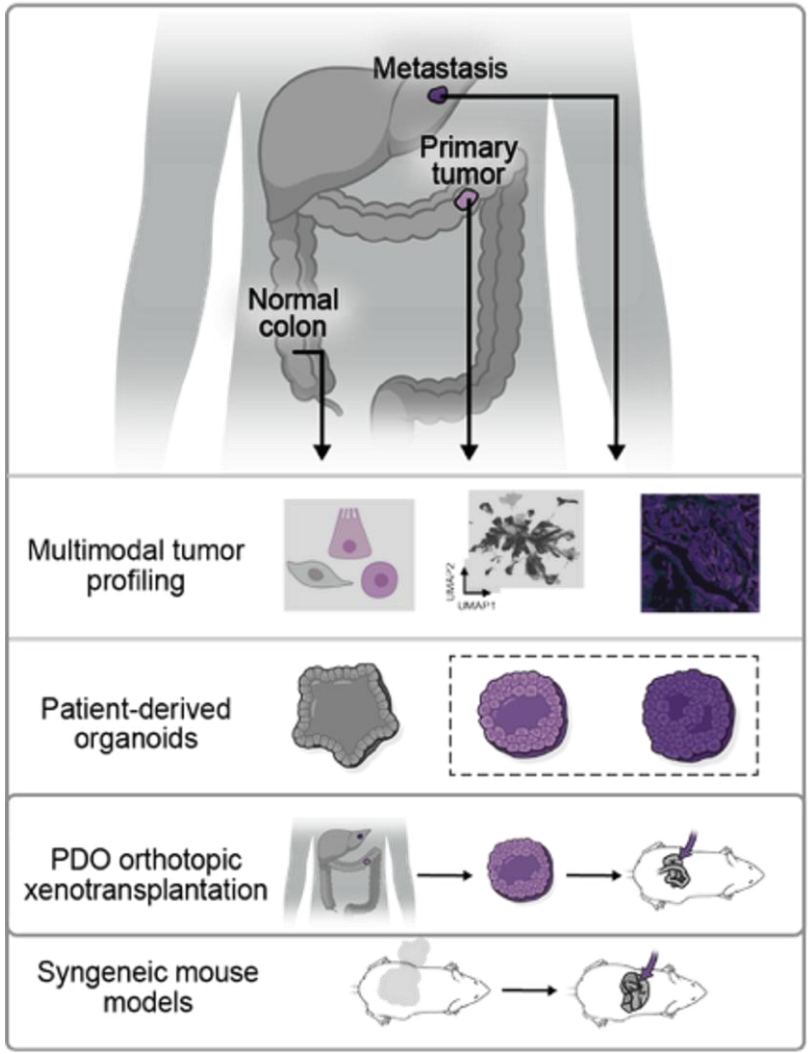
Co-evolution of tumor and host during tumor progression



Gerstberger, Jiang and Ganesh, Metastasis. *Cell*, 2023

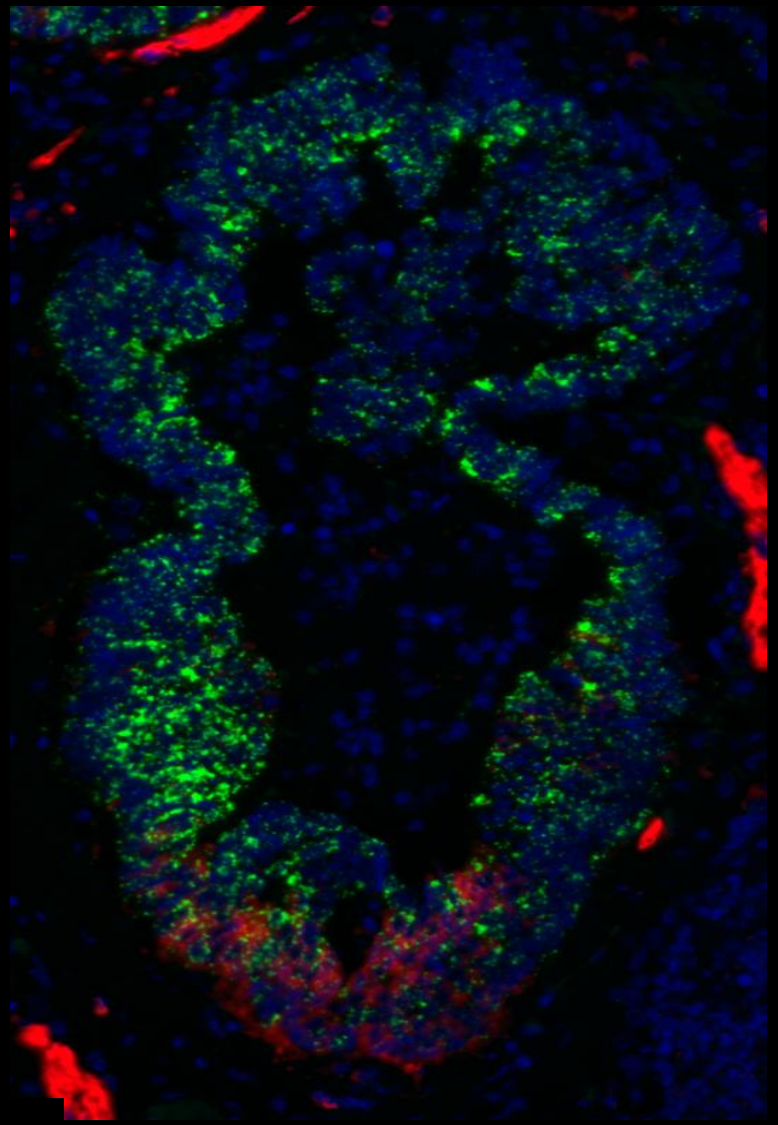
Colorectal Cancer (CRC): *An Unmet Need & Opportunity*

- 3rd most common cancer and 2nd leading cause of cancer death worldwide
- Increasing incidence in people <50 years
- Surgical metastatectomies and longitudinal biopsies
- Unparalleled representative models

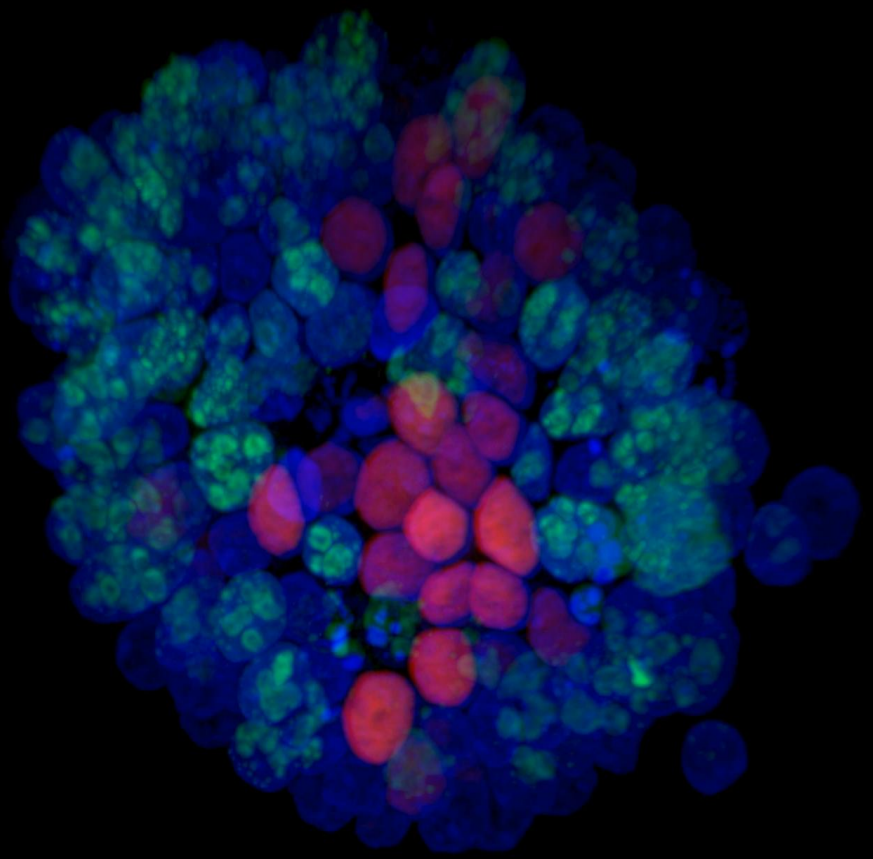


Patient colorectal cancer tissue

LGR5+ Cancer Stem Cells
L1CAM+ Metastasis Initiating Cells



Patient-derived colorectal cancer organoid

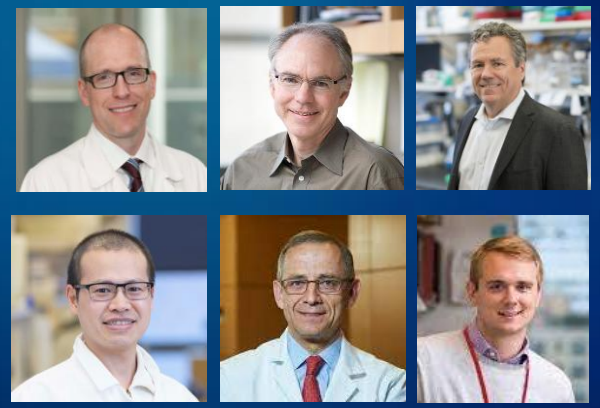


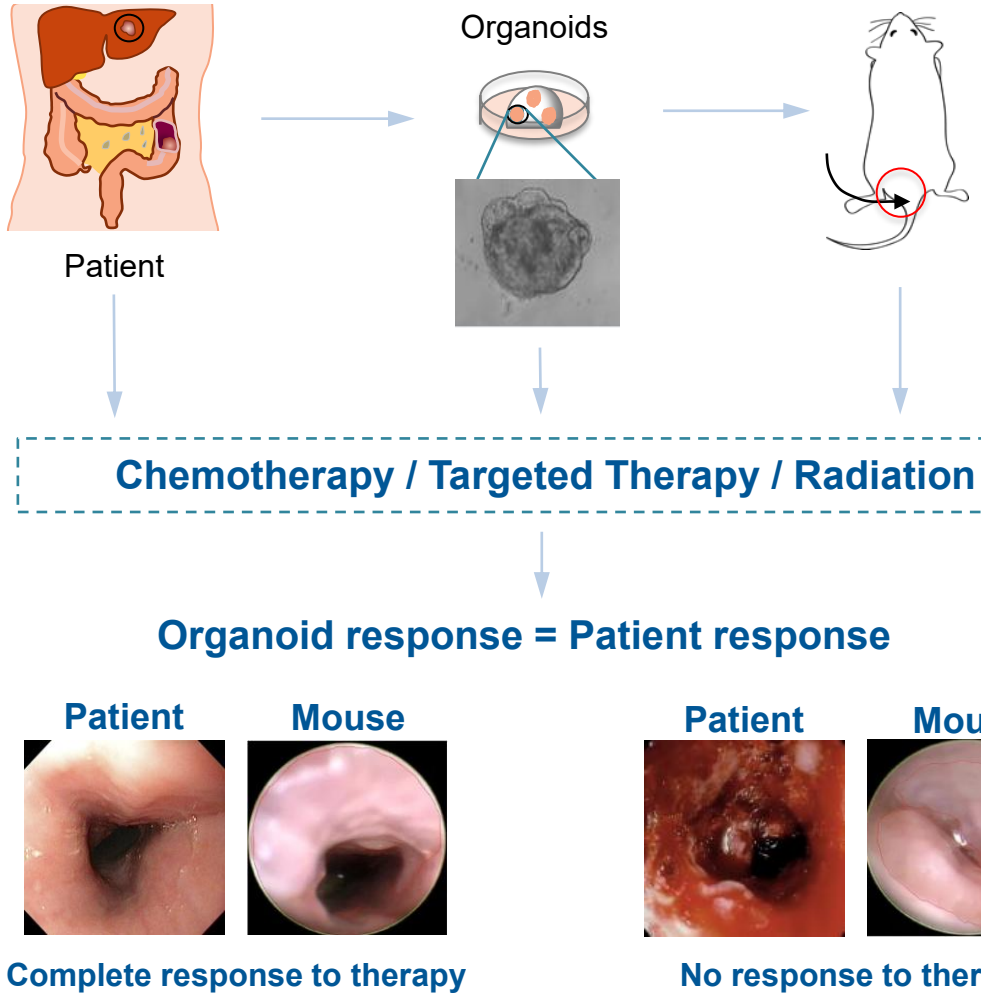
Ganesh *et al.*,
Nature Cancer, 2020

Organoids capture intra- and inter-patient heterogeneity and plasticity

Organoids capture patient specific phenotypic states and treatment responses

MSKCC Rectal Biobank Project





Ganesh et al, *Nature Medicine,* 2019

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

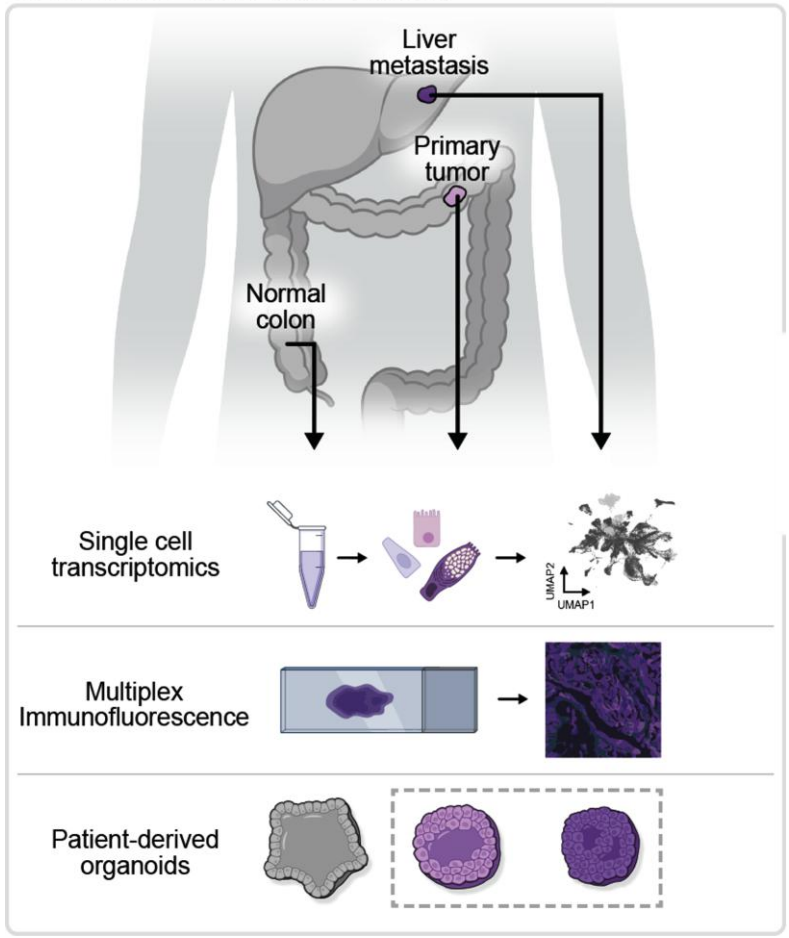
Dana Pe'er

Andrew Moorman

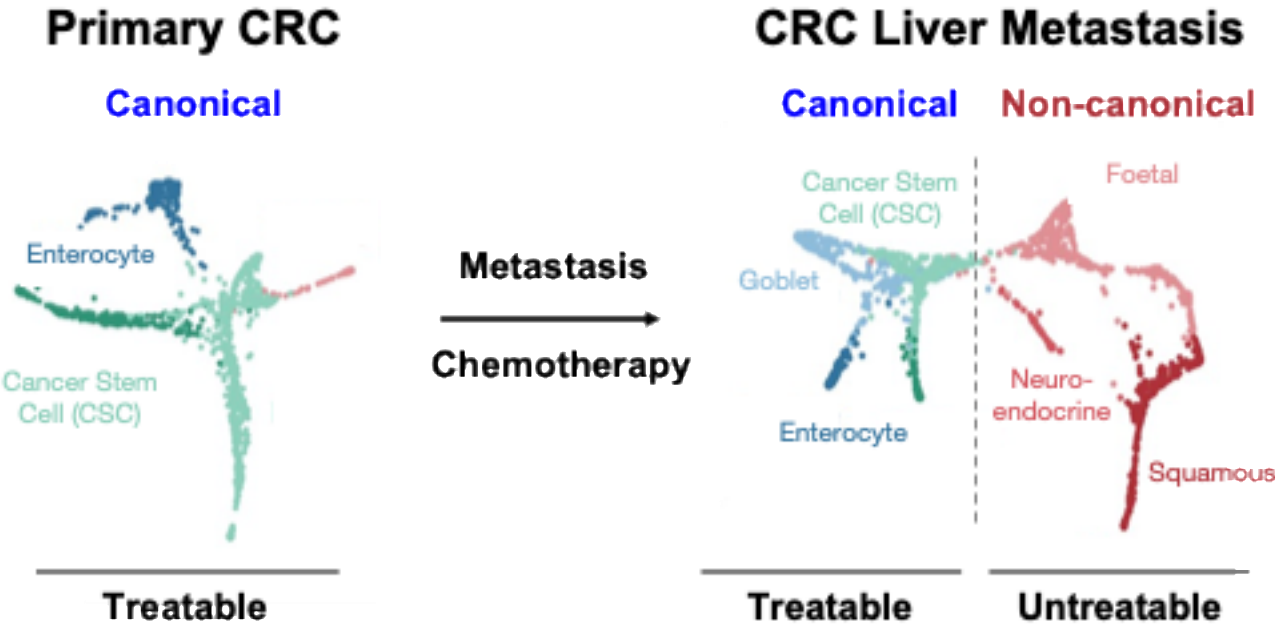
Elizabeth Benitez

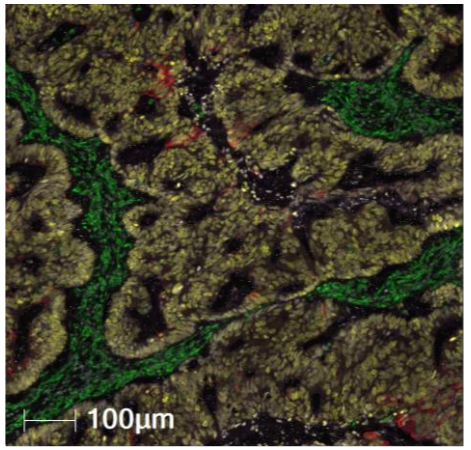
Francesco Cambuli

Synchronous surgical resection of metastatic colorectal cancer

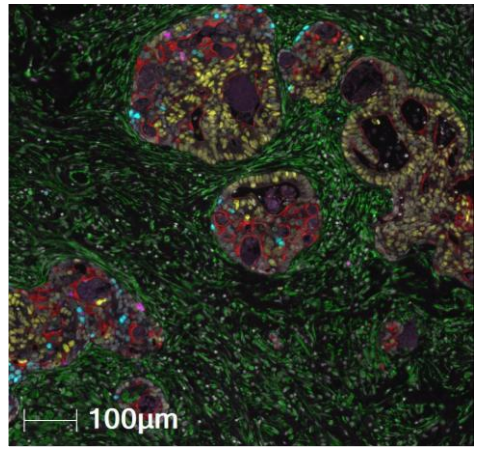


176 datasets from 31 patients





Canonical cell states



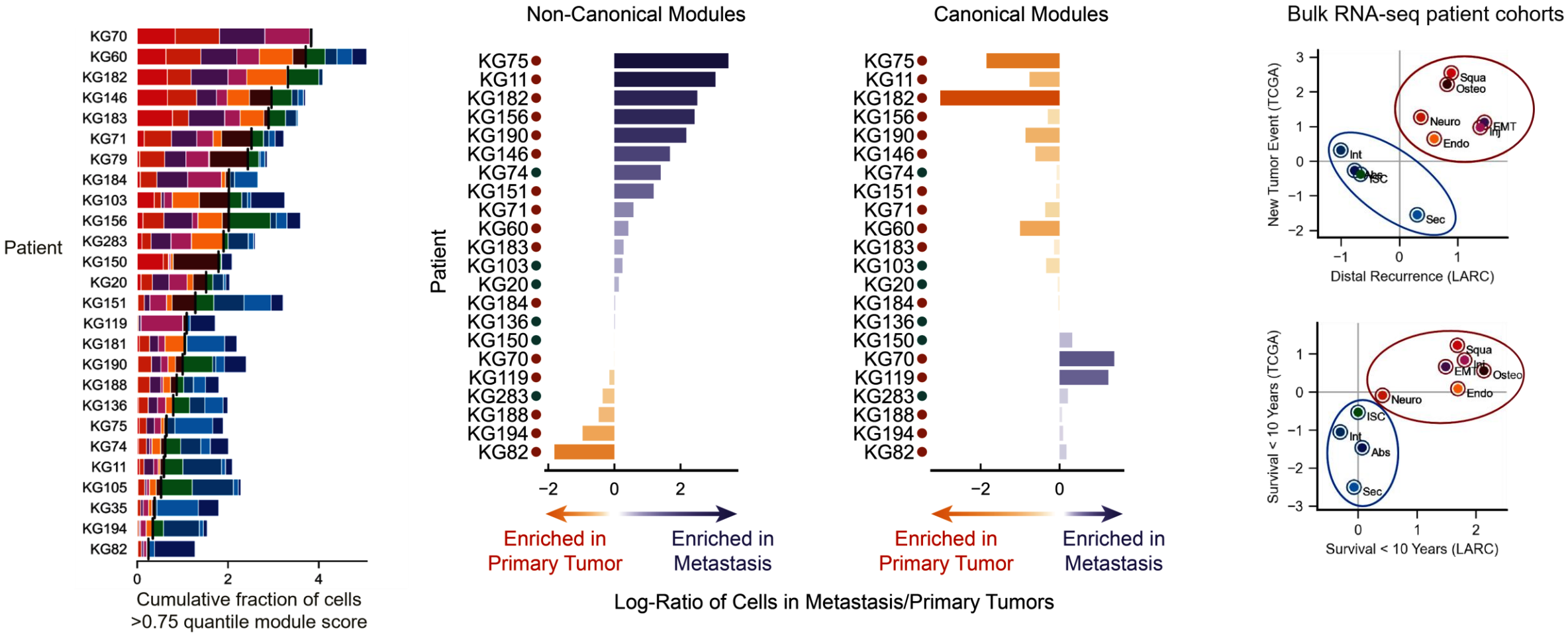
Canonical and non-canonical cell states

NIH NATIONAL CANCER INSTITUTE

HTAN HUMAN TUMOR ATLAS NETWORK

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

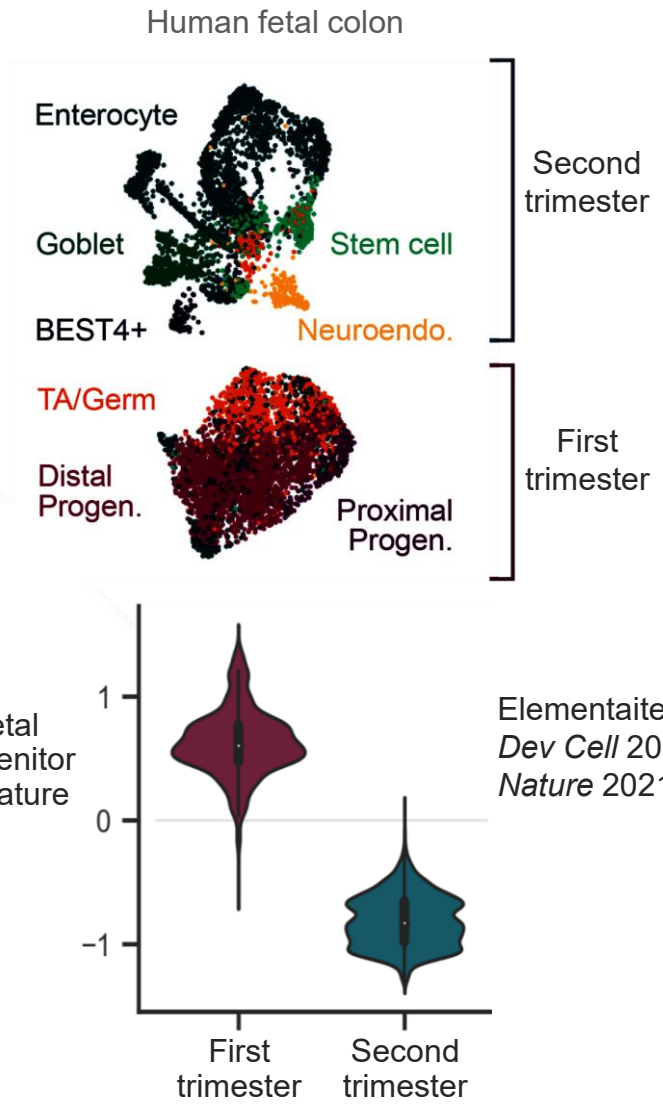
CRC tumors exhibit a canonical to non-canonical axis



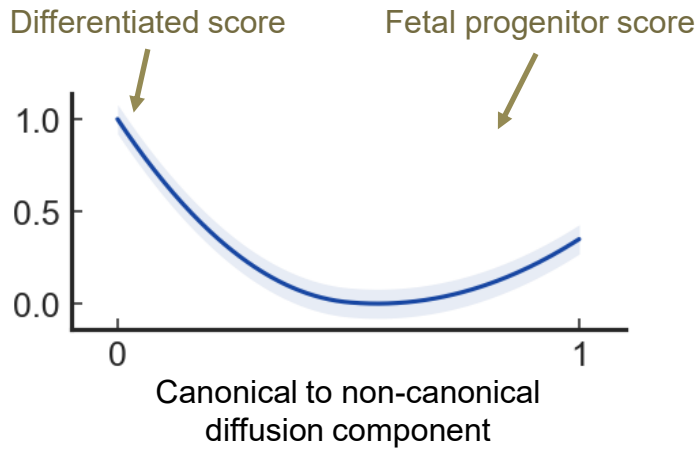
- Matched tumors show that metastatic progression shifts cell fates to non-canonical
- Non-canonical states are pervasive across patients and correlate with worse outcomes

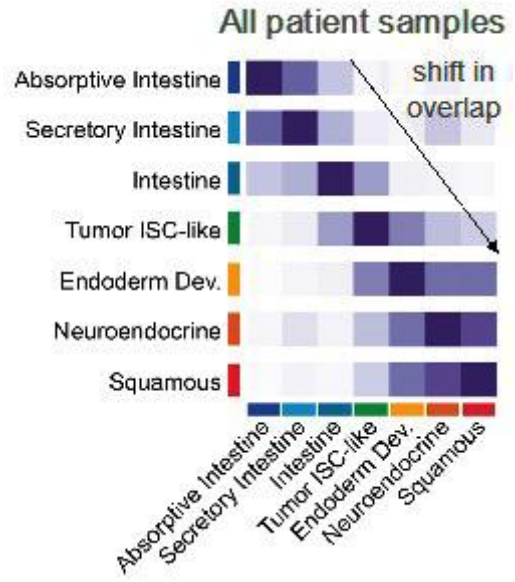
Moorman*, Benitez*, Cambuli*, et al. *Nature*, 2025

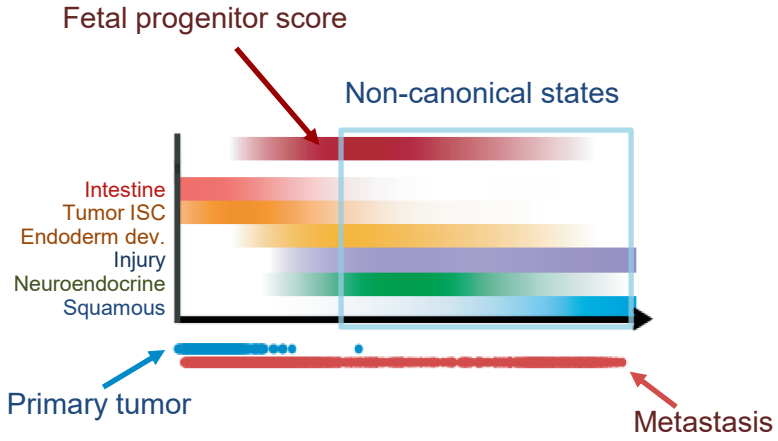
Tumors progress via a conserved fetal progenitor intermediate state

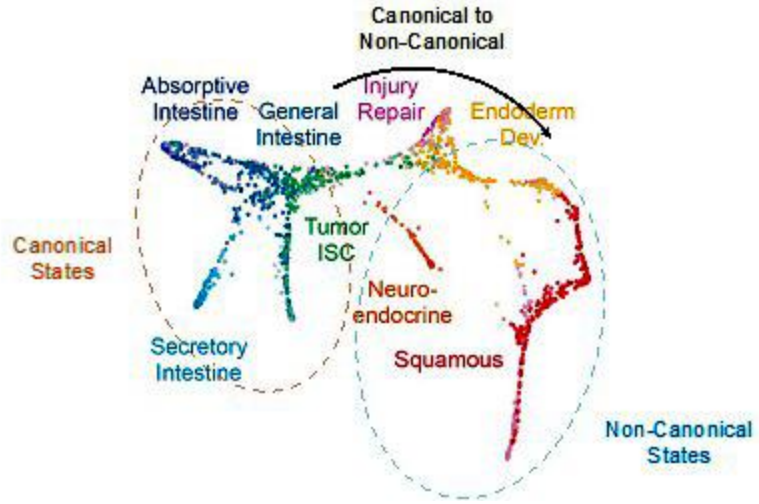


Elementaite et al.
Dev Cell 2020
Nature 2021







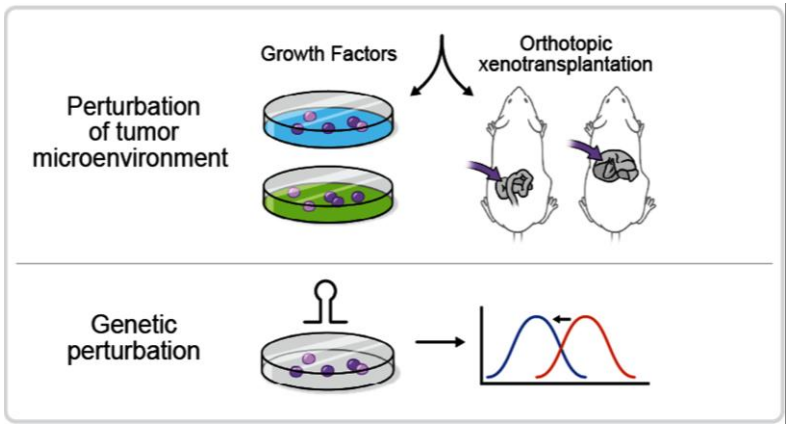


- Cancer cells display conserved, sequential cell-state transitions during progression
- Non-canonical states are pervasive across patients and correlate with worse outcomes

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

Is transdifferentiation due to cell autonomous or microenvironmental factors?

Organoid perturbations

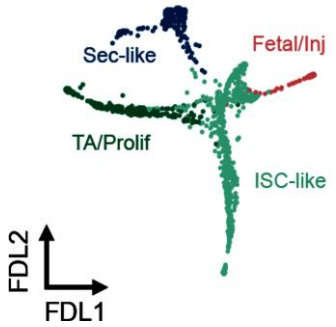


Primary and met organoids retain distinct differentiation potential *ex vivo*

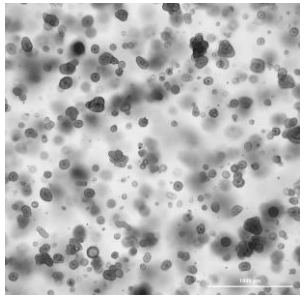
Patient KG146

Human Intestinal Stem Cell Media

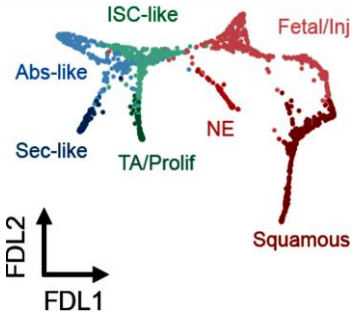
Patient Primary Tumor scRNAseq



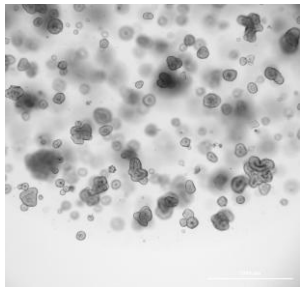
Primary Tumor Organoids



Patient Metastasis scRNAseq



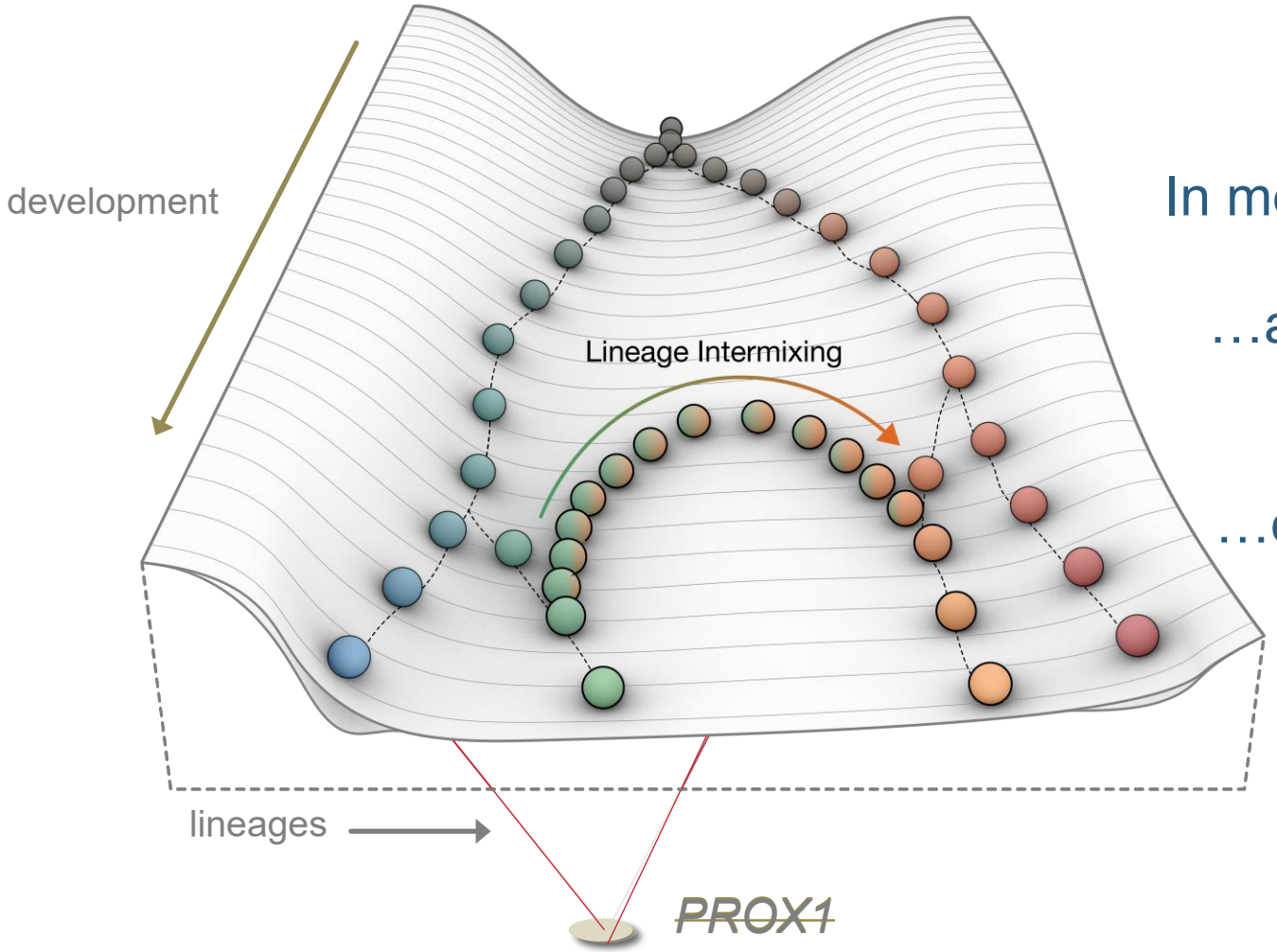
Metastasis Organoids



Metastatic cancer cells have increased cell autonomous plasticity.
Microenvironmental cues drive differentiation down distinct trajectories

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

Cancer cell plasticity involves specific regulators



In metastasis, barriers fail

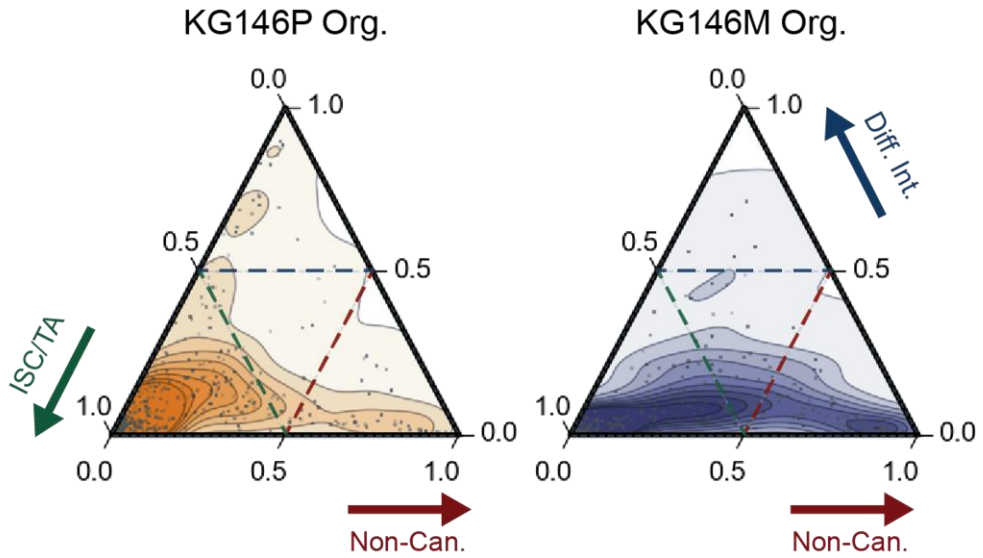
…allowing promiscuous expression from different lineages

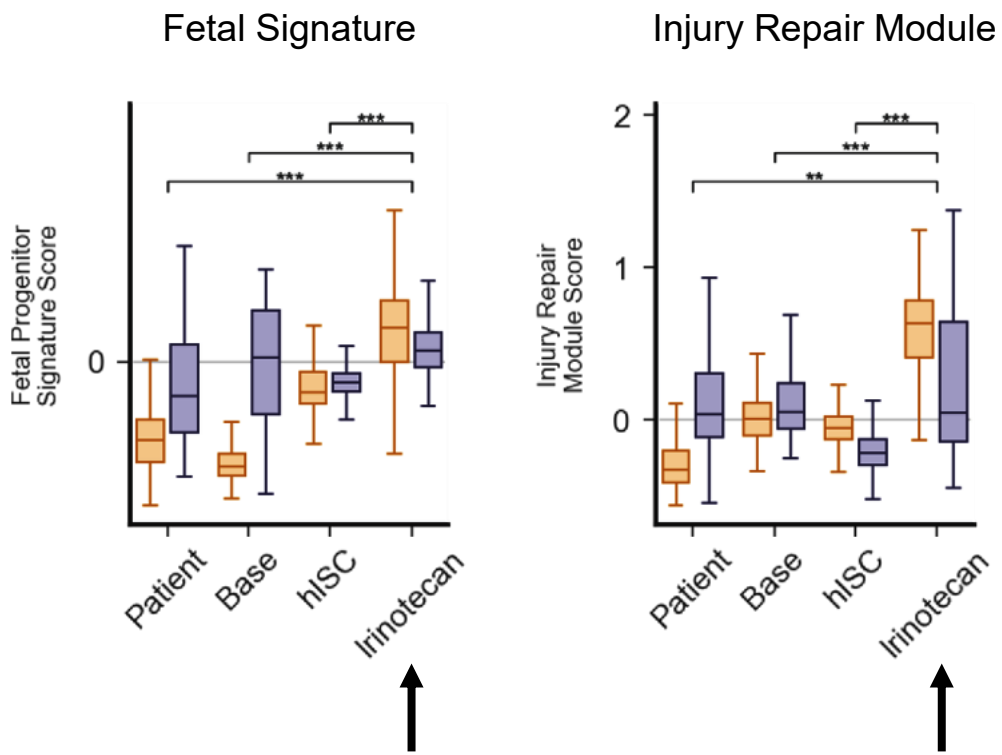
…coupling metastasis with therapy resistance

Moorman, Cambuli, Benitez et al., *Nature, 2025*
Jiang et al., *Nature,* Accepted in principle.

Chemo treatment of primary and met organoids increases fetal state and injury repair signals

Chemotherapy-Treated
HISC Media





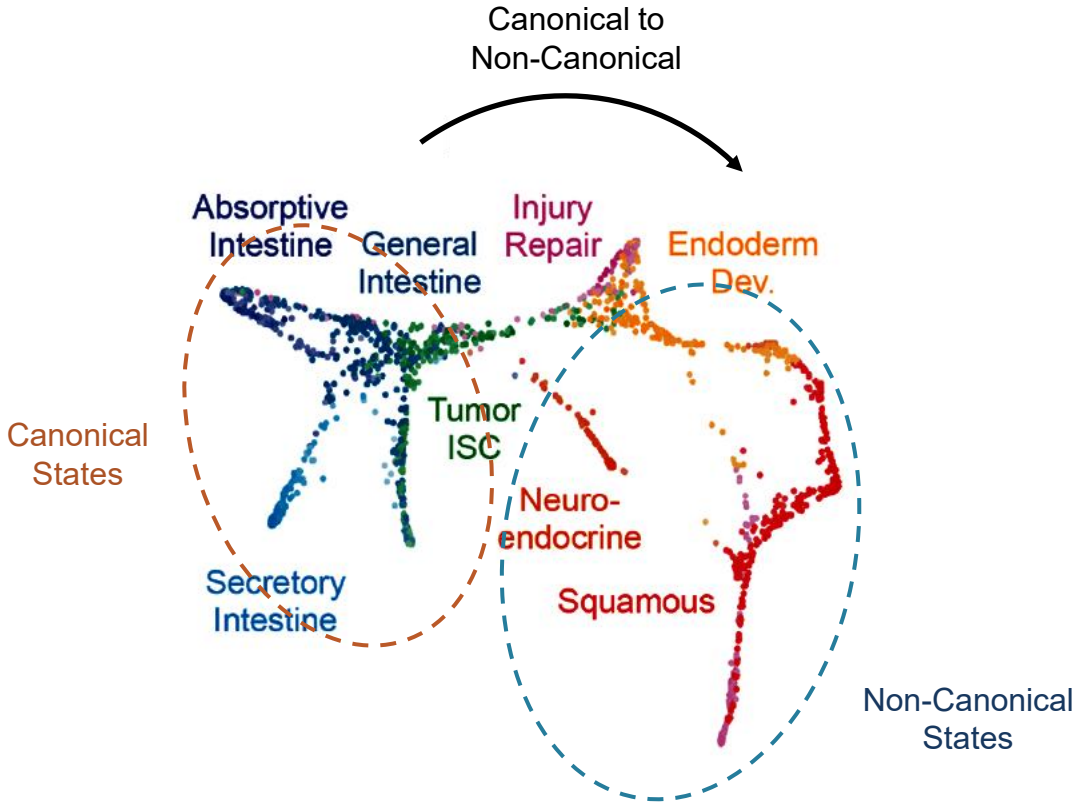
Moorman*, Benitez*, Cambuli*, et al. *Nature*, 2025

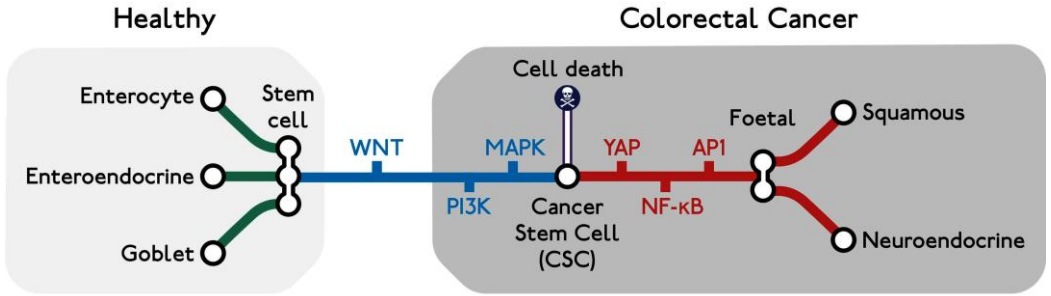
CANCER GRAND CHALLENGES

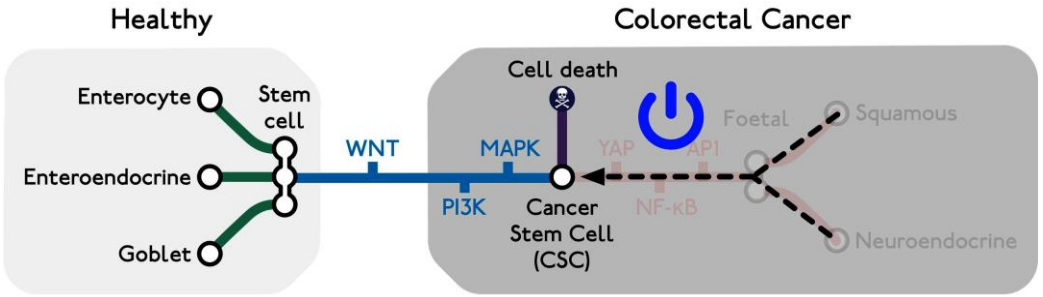
REWIRE-CAN
Reprogramming Epithelial WIRing to Eradicate CANcer

How can we therapeutically target plasticity?

Target regulators of cell state transitions?

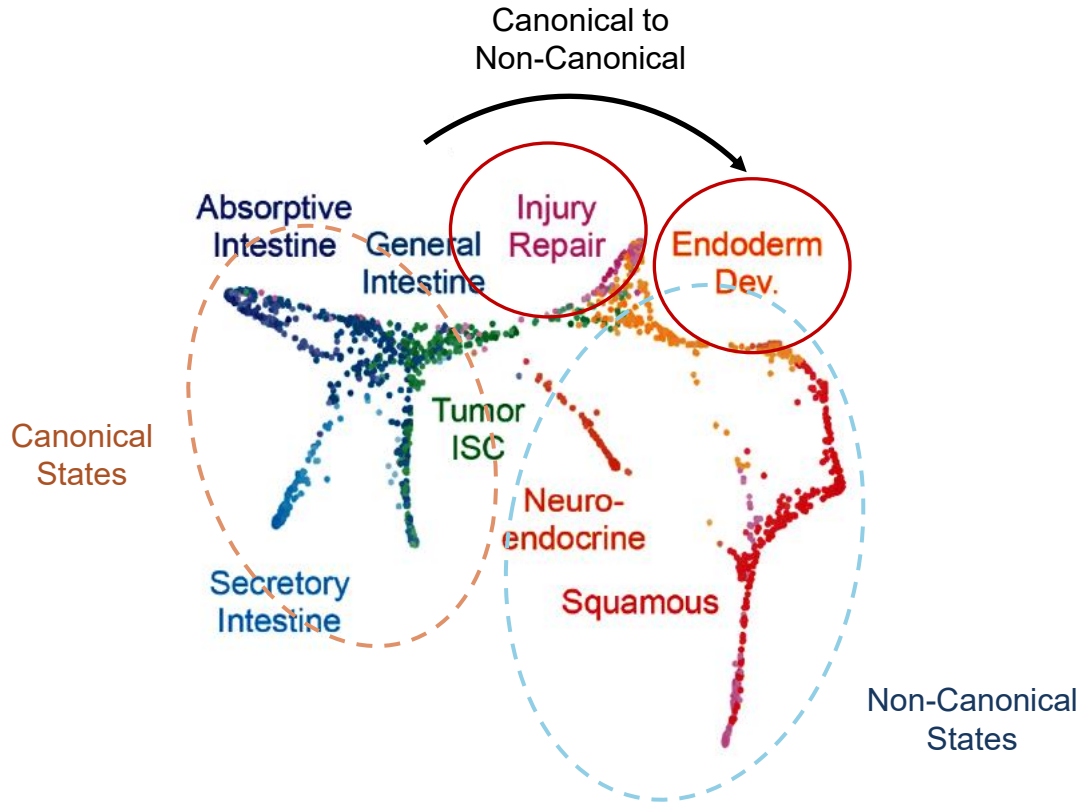




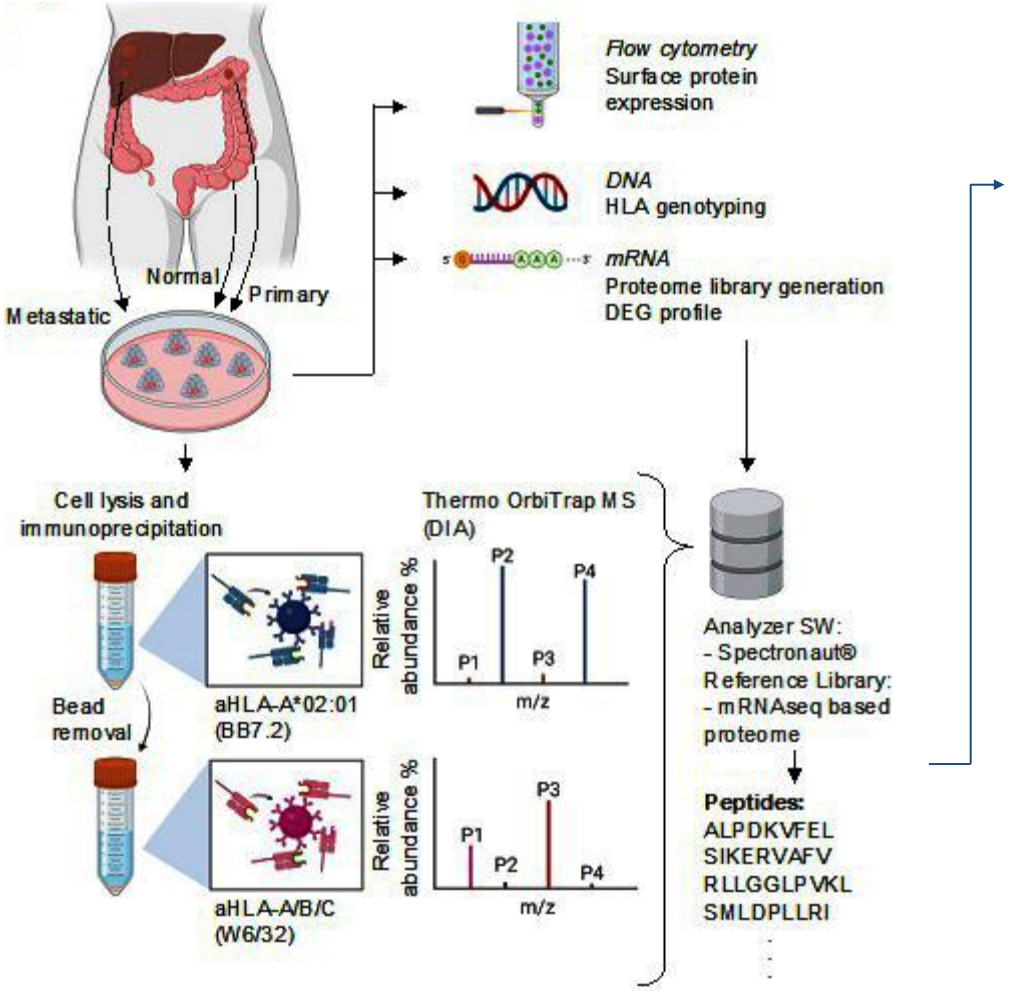


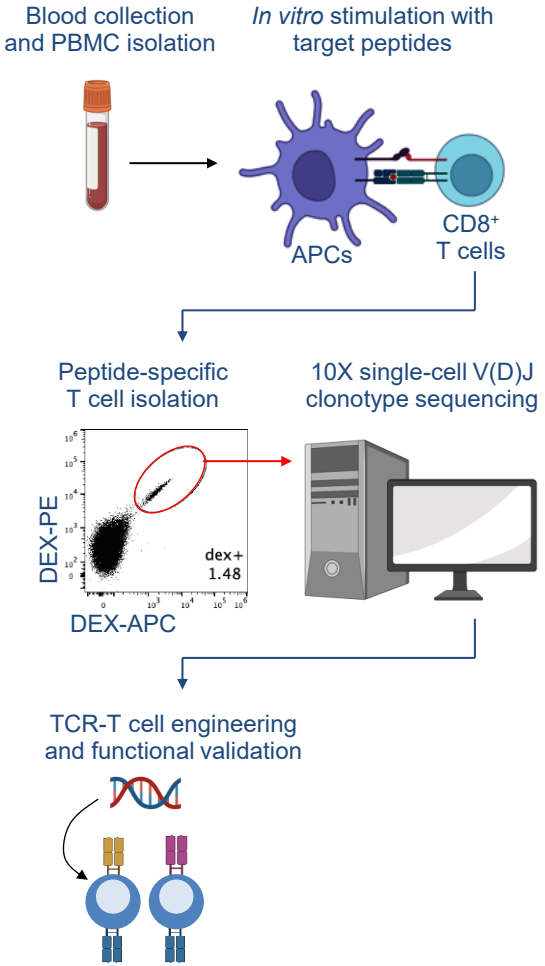
How can we therapeutically target plasticity?

Target conserved tumor regenerative states

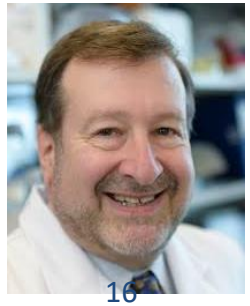


MSS/pMMR mCRC immunopeptidome analysis pipeline



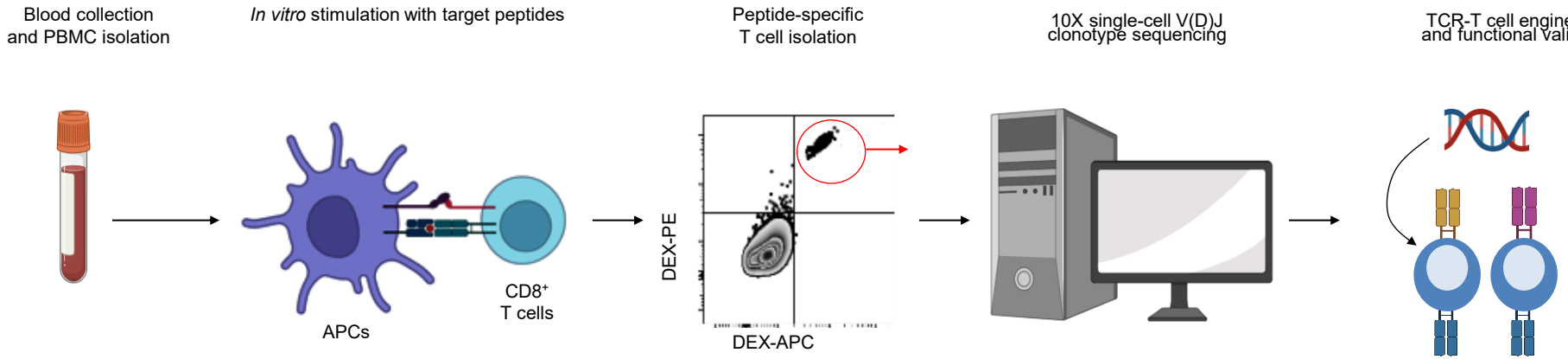


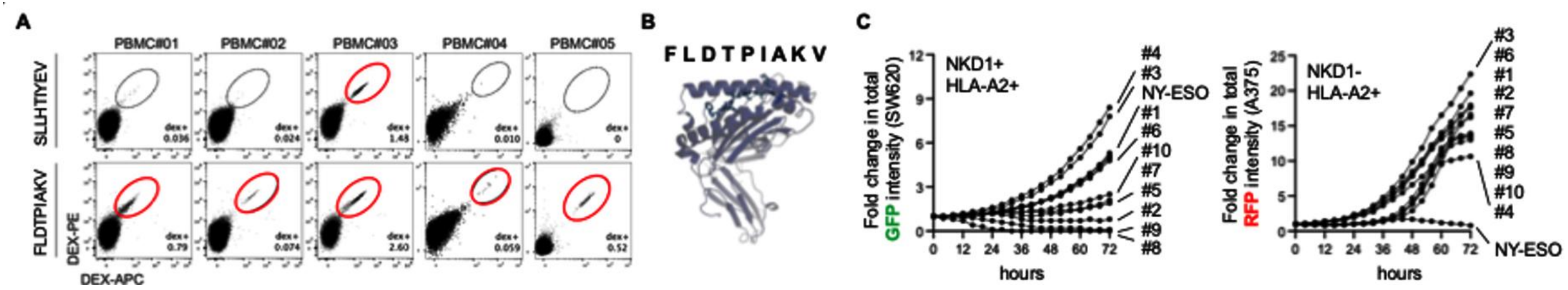
Jaeyop “Josh” Lee, MD, PhD



David Scheinberg, MD, PhD

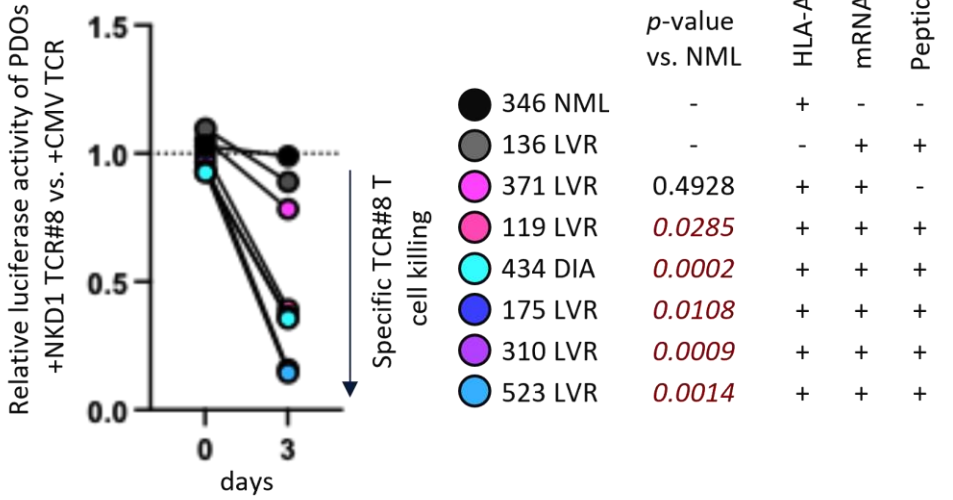
NKD1-specific TCR identification and testing
Hypothesis: No thymic selection against TCRs recognizing first trimester antigens



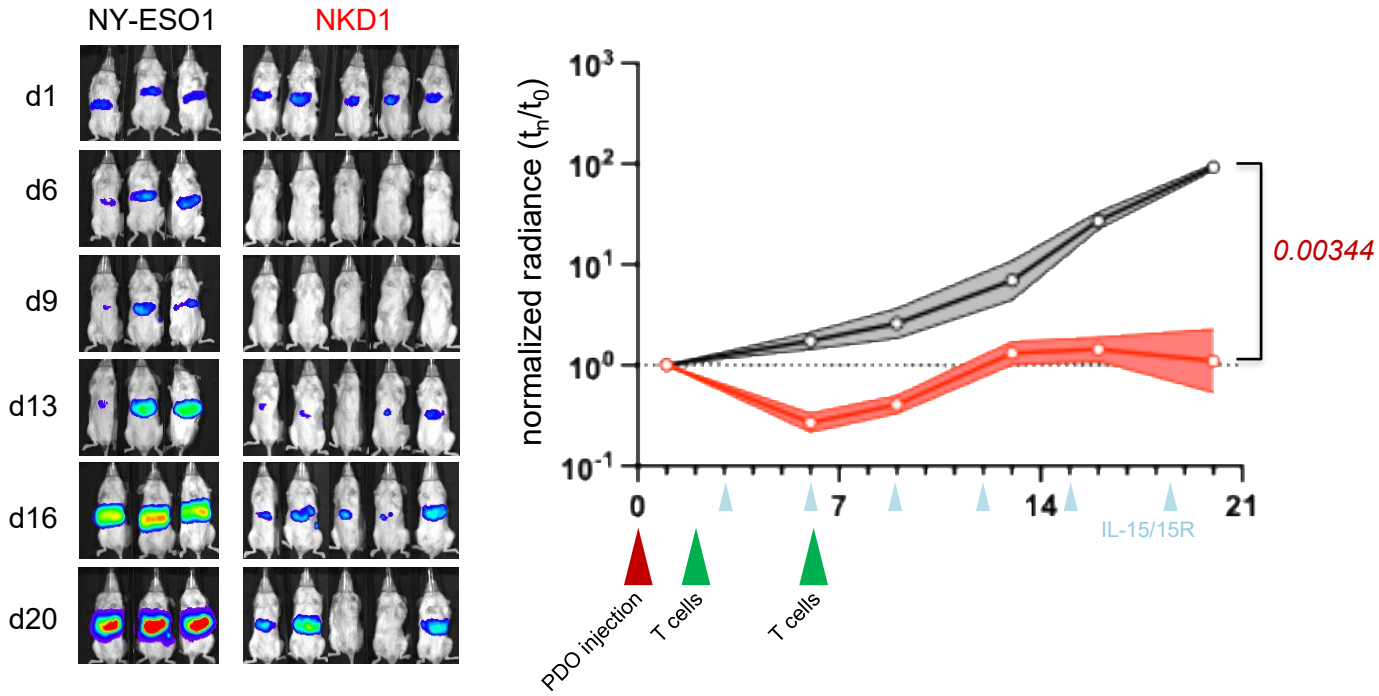


NKD1-TCR T cell therapy controls CRC liver metastasis in vivo

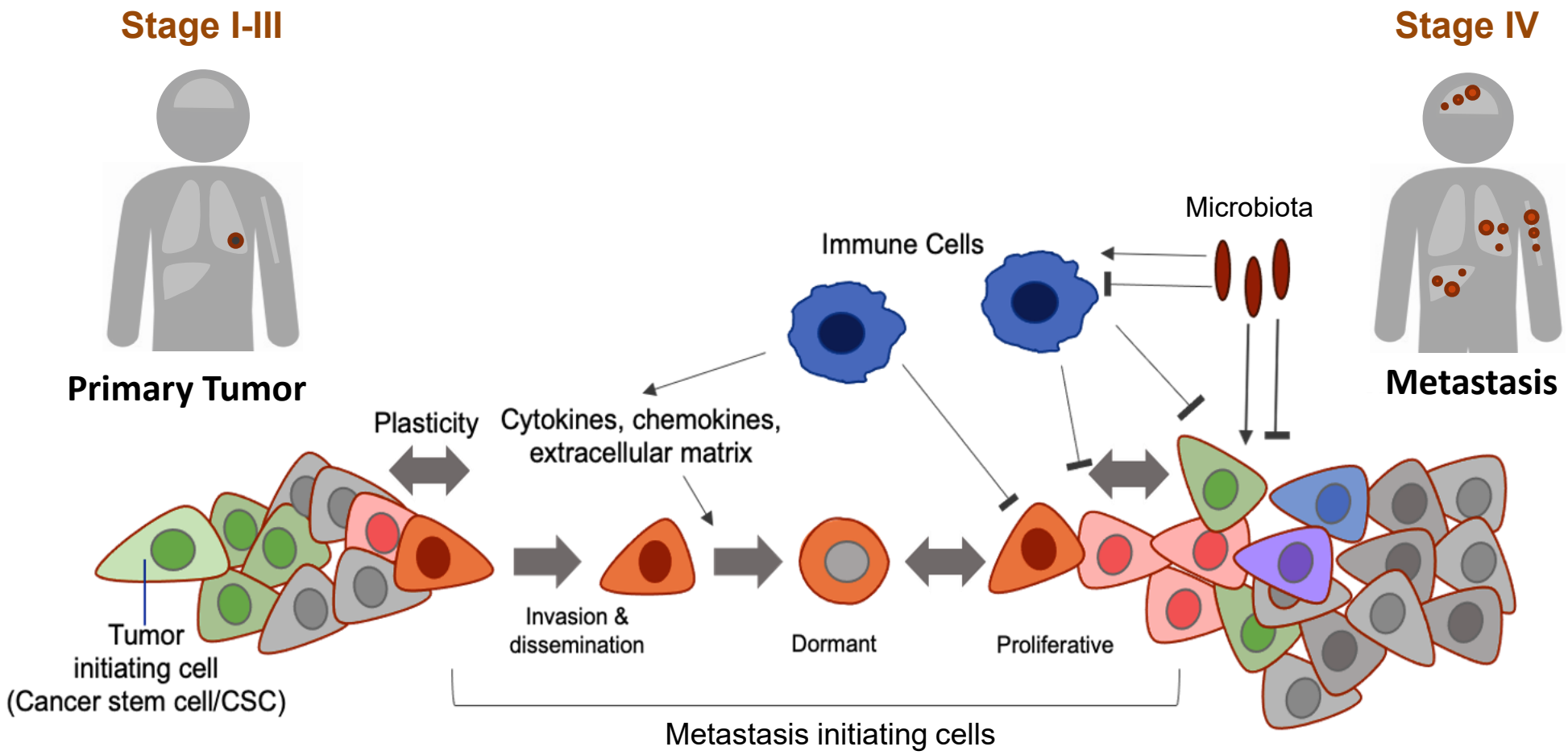
A **CRC patient-derived organoids**



B **CRC liver metastasis**



Understanding tumor: microenvironment coevolution is critical to cancer therapy

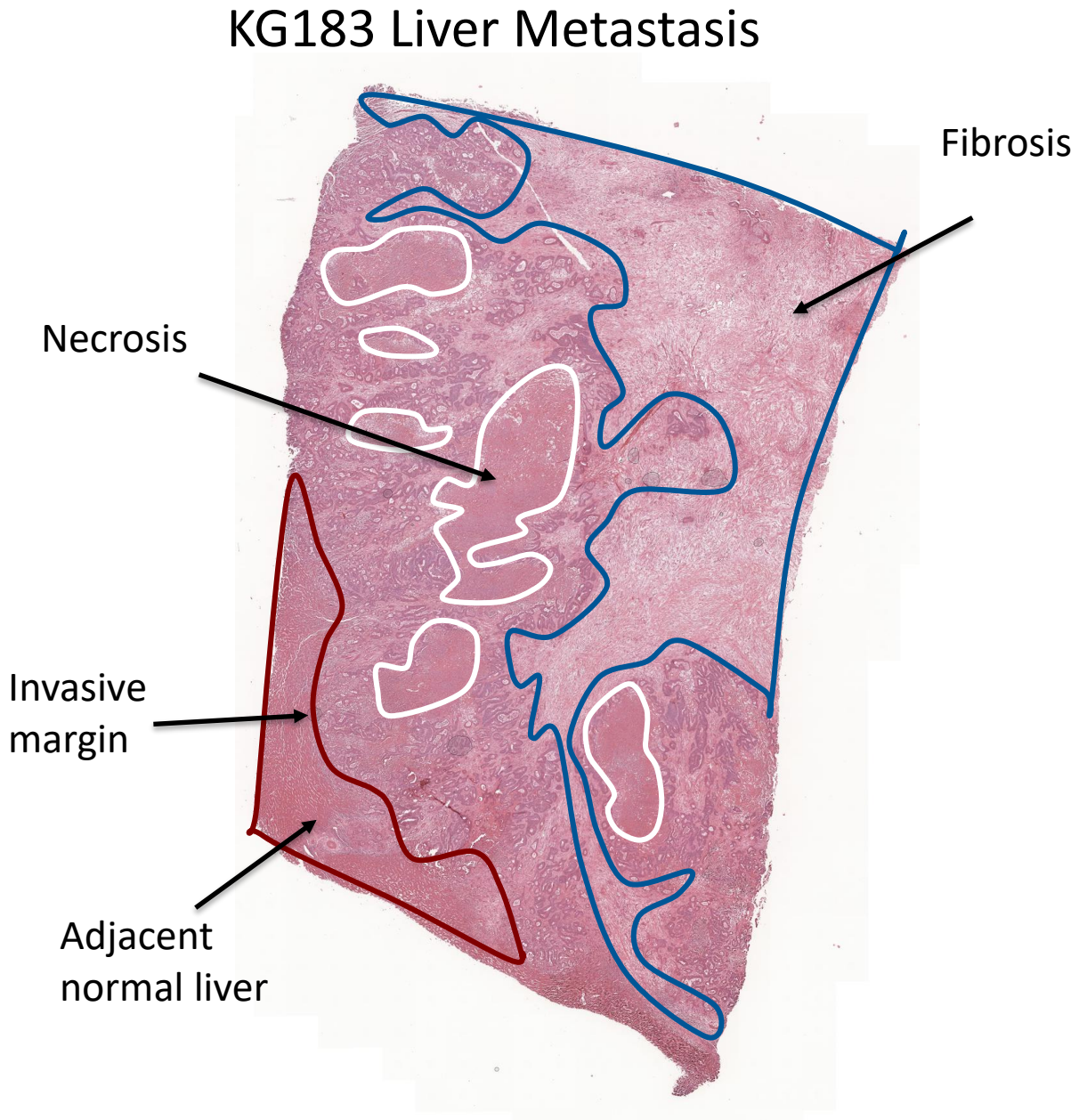


Gerstberger, Ganesh and Jiang, Cell, 2023..

Ganesh and Massagué, Nature Medicine 2021.

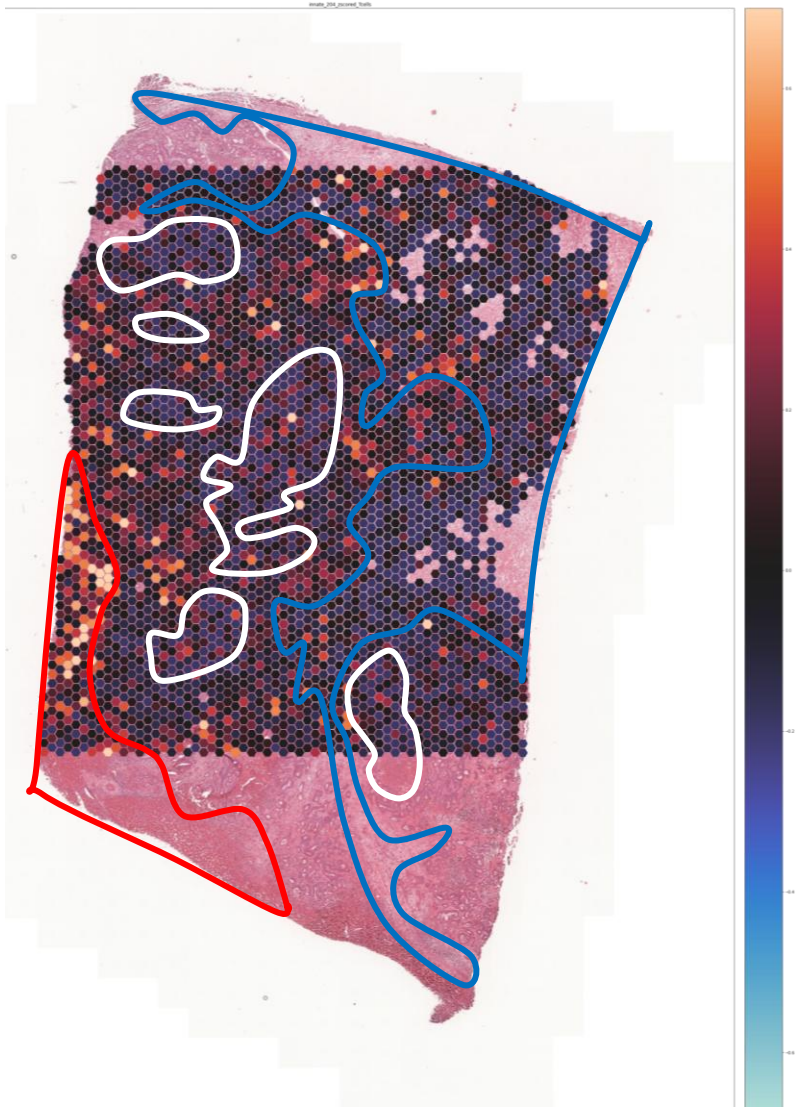
Massagué and Ganesh, Cancer Discovery 2021.

Canonical and Noncanonical cell states are spatially segregated in metastases

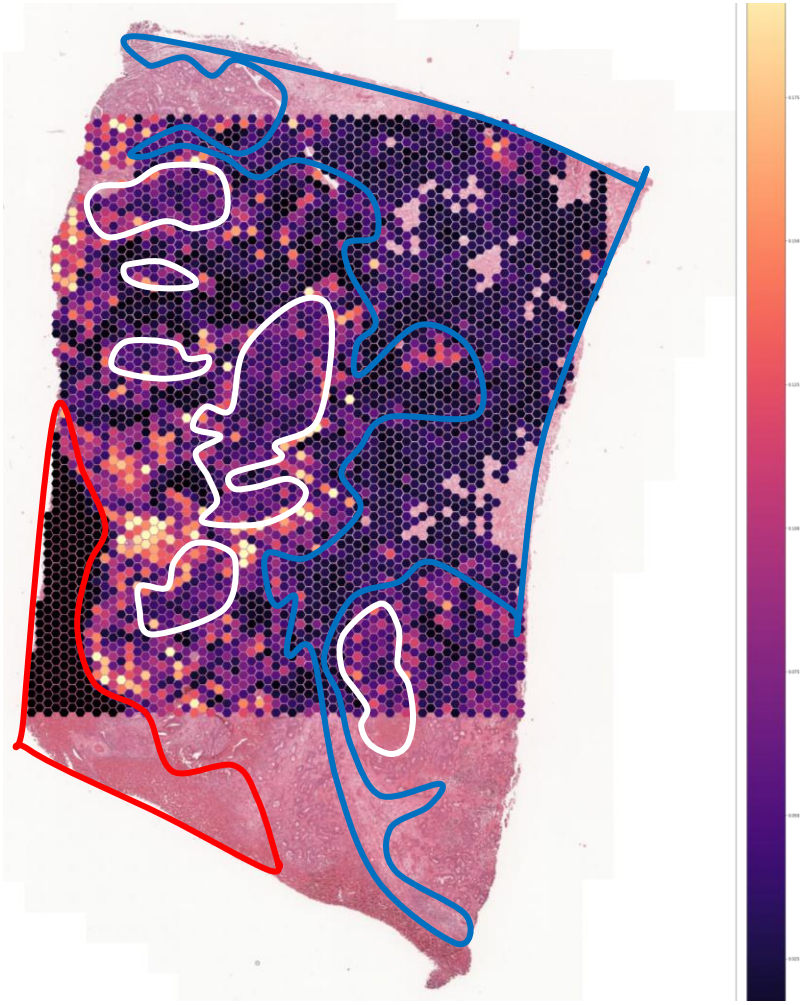


Immune crosstalk with transitional cell states at the invasive margin

Cytotoxic T cells



Injury repair



% of all cells in region

Unmet needs

- Longitudinal samples to track co-evolution of tumor, immune system and microbiome during tumor evolution in patients.

  What hypotheses should we test?

- Experimentally tractable, clinically representative model systems to define contributions of individual components of TME to specific steps of tumor progression.

  How can we test hypotheses?

- Dynamic biomarkers of tumor:host co-evolution in patients undergoing cancer therapy to guide plasticity-targeted therapeutics

  How do we overcome plasticity?

A functional biospecimen platform to dissect metastasis
MSK IRB: #20-554 PI: Ganesh

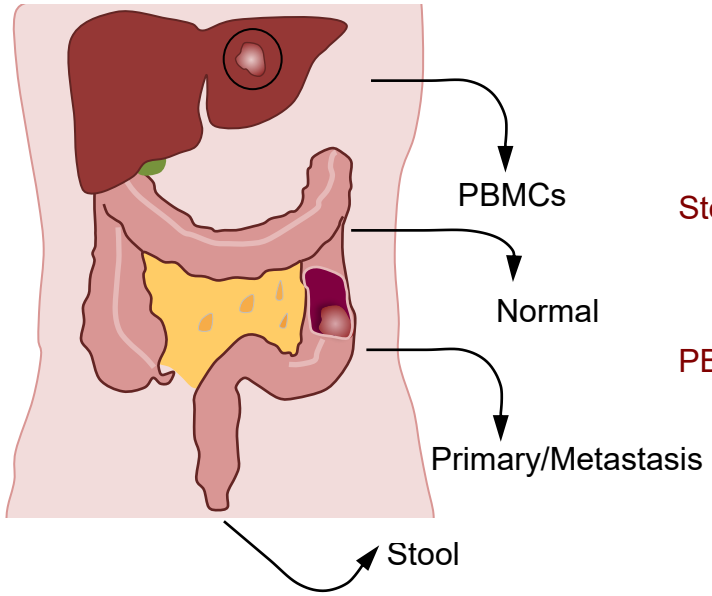
Tumor/Immune/Microbiome determinants of metastatic recurrence (Stage III) or response to first line therapy (Stage IV)

Stage III Esophagogastric and CRC

EG – ~50% recurrence
~80% recur within 2 years
CRC – ~30% recurrence
~80% recur within 2 years

Stage IV Esophagogastric and CRC

EG: Median PFS: 6.4 months
CRC: Median PFS: 8.4 months



Tumor/Normal:
- MSK-IMPACT exome sequencing
- Organoids
- FFPE tissue
- Banked frozen tissue for future RNA/ATACseq
- Banked DNA for intratumoral microbiome sequencing
- Tumor interstitial fluid protemonics

Stool:
- Frozen in anaerobic conditions
- 16S sequencing
- Banked DNA for shotgun sequencing

PBMCs:
- Immunophenotyping
- Immune cell expansion for organoid coculture
- Blood metabolite/microbiome profiling

Longitudinal collection pre-treatment, after first cycle of chemo, after 3 months of chemo, post-progression

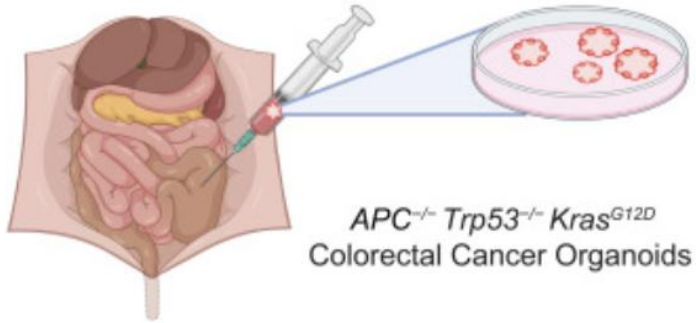
Spontaneous metastasis of syngeneic AKP organoid cecal allografts to liver and lung in C57/BL6 mice

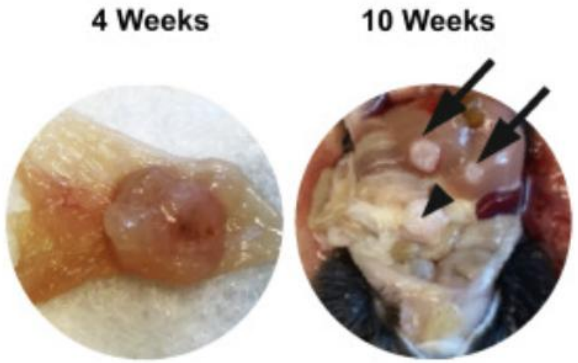
Immunity

Volume 59, Issue 1, 13 January 2026, Pages 145-160.e9

Article

Opposing functions of distinct regulatory T cell subsets in colorectal cancer

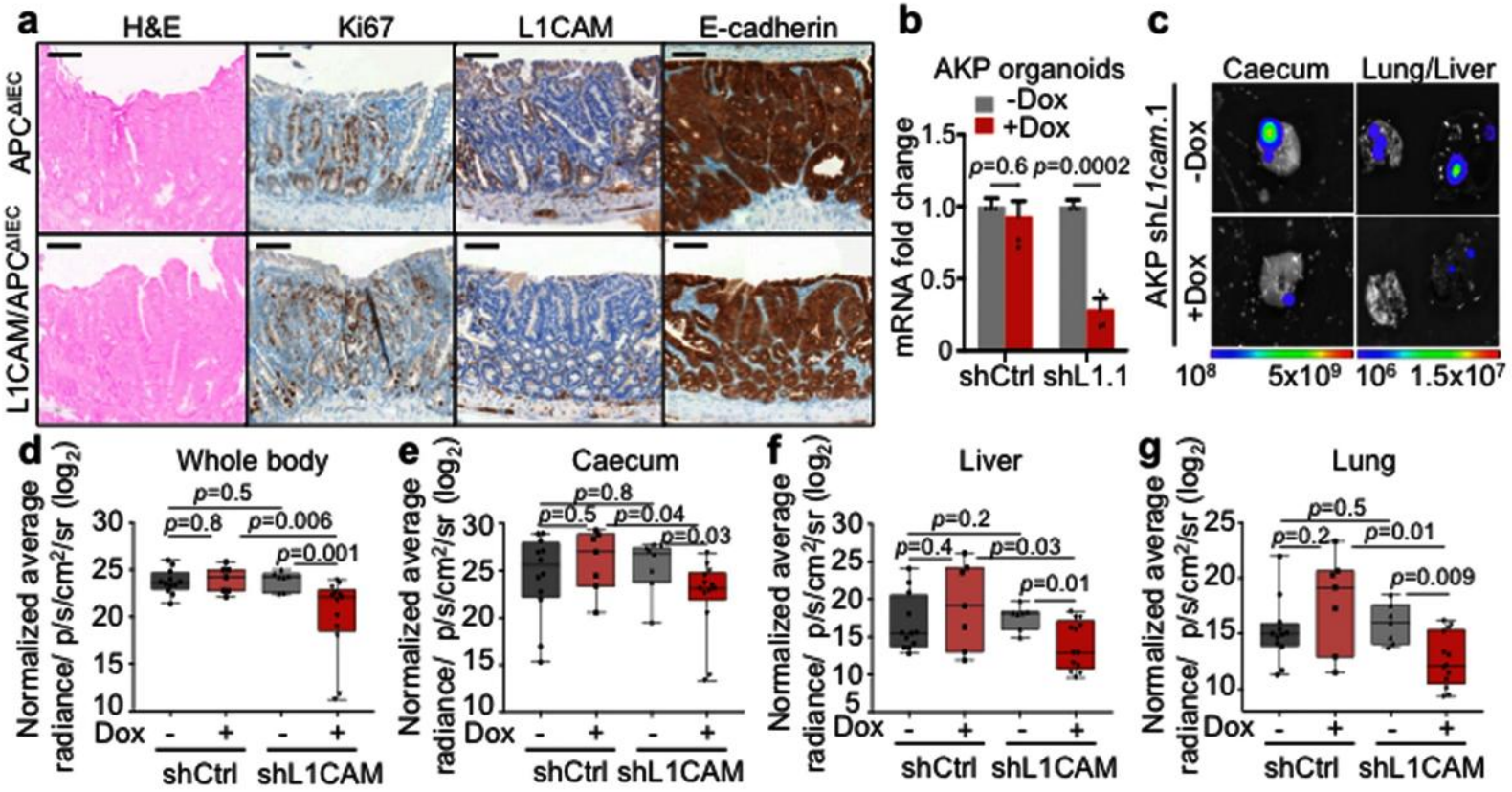




Huang et al, *Immunity,* 2026

ARTICLES
https://doi.org/10.1038/s43018-019-0006-x
nature cancer
There are amendments to this paper

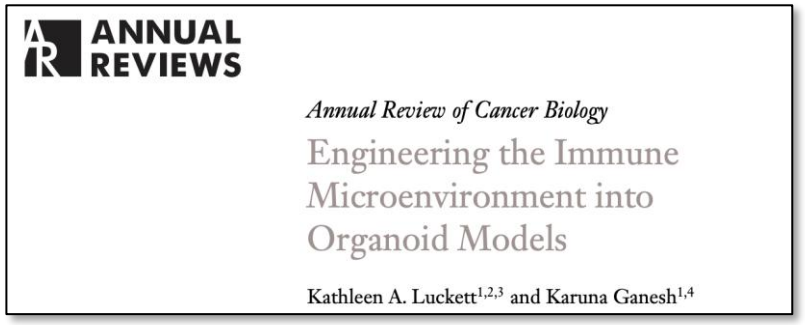
L1CAM defines the regenerative origin of metastasis-initiating cells in colorectal cancer

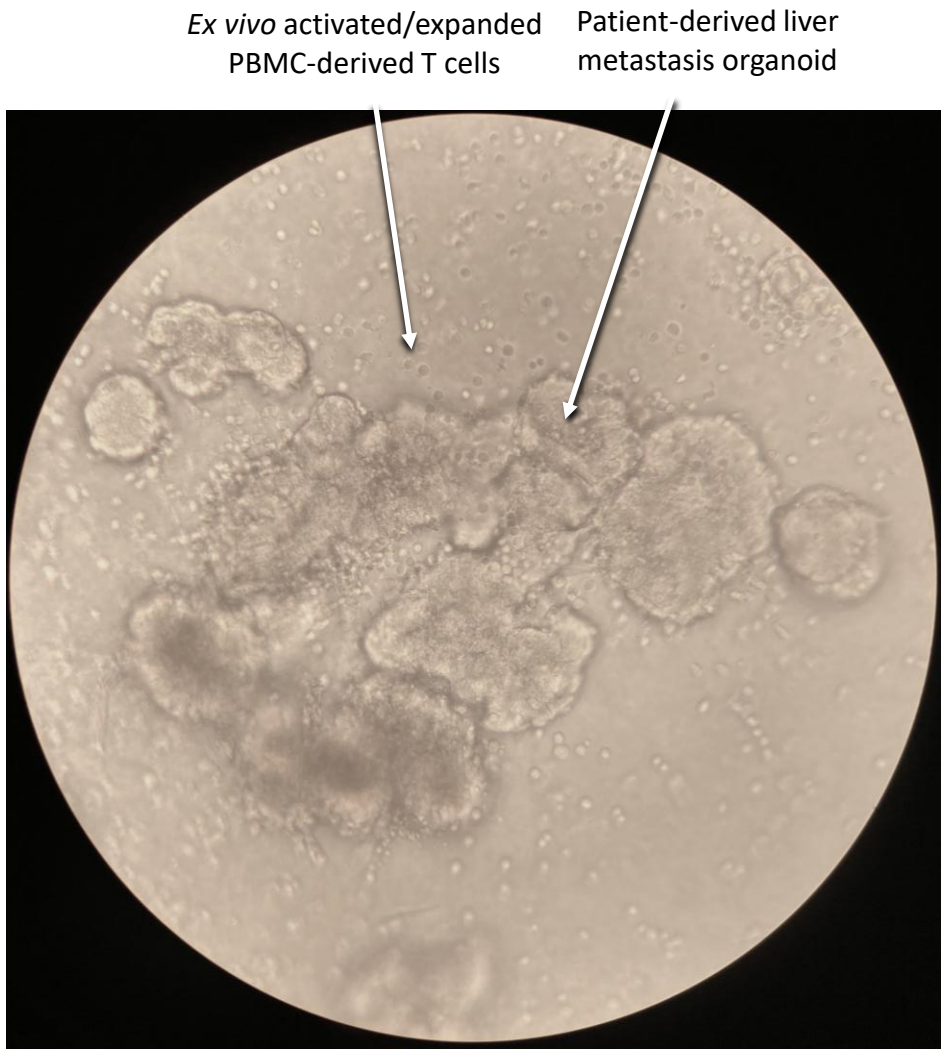


Ganesh et al, *Nature Cancer,* 2020

Interrogating immune and cancer cell interactions with organoid cocultures

- Living biobank of patient derived organoids and autologous PBMCs
- Visualize and characterize organoid immune crosstalk
- How do immune cells influence injury repair, fetal progenitor, and non-canonical cell states and transitions?



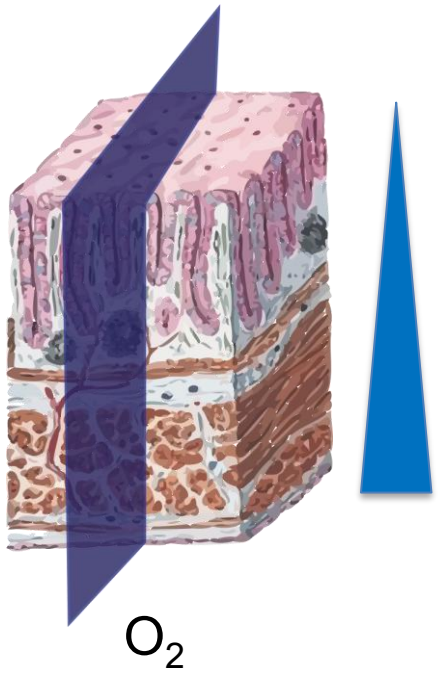


“Chemostatic” long-term human gut bioengineering

Scott Manalis

Jason Yu

Elizabeth Benitez



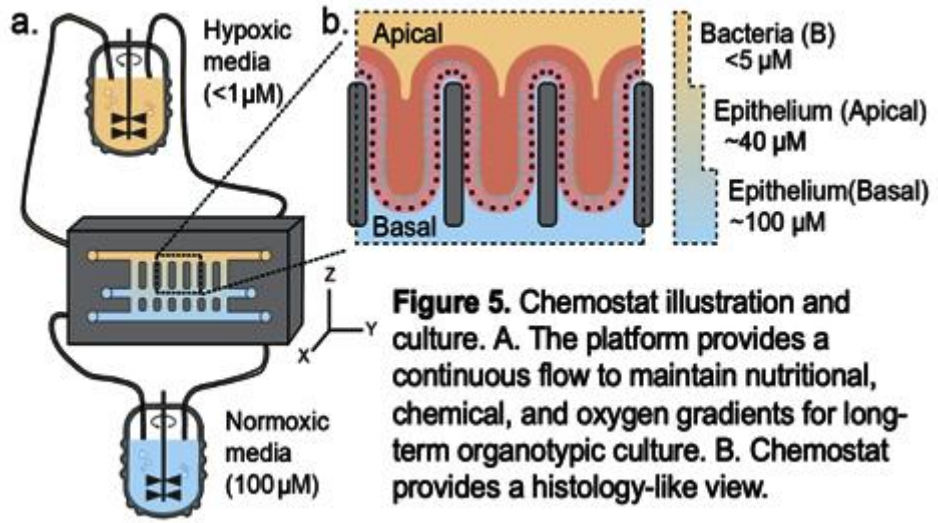
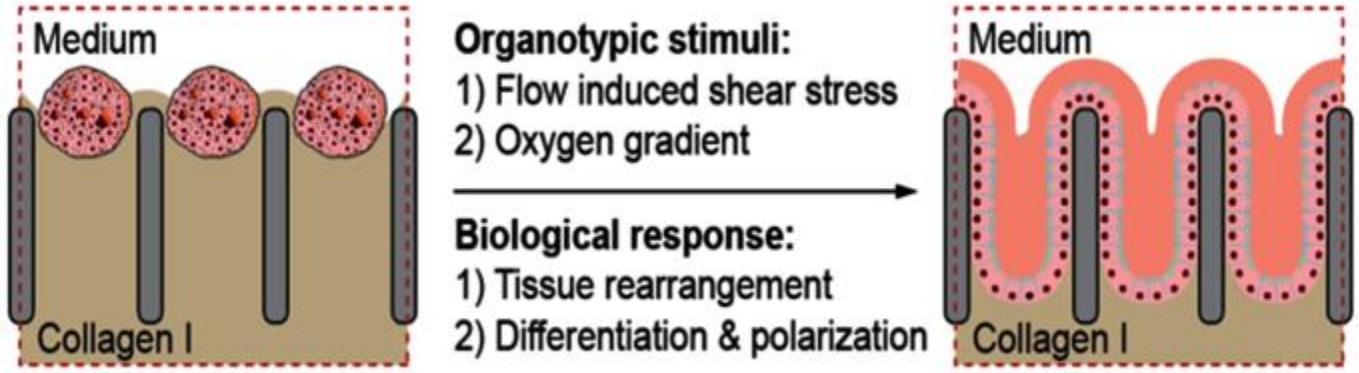


Figure 5. Chemostat illustration and culture. A. The platform provides a continuous flow to maintain nutritional, chemical, and oxygen gradients for long-term organotypic culture. B. Chemostat provides a histology-like view.



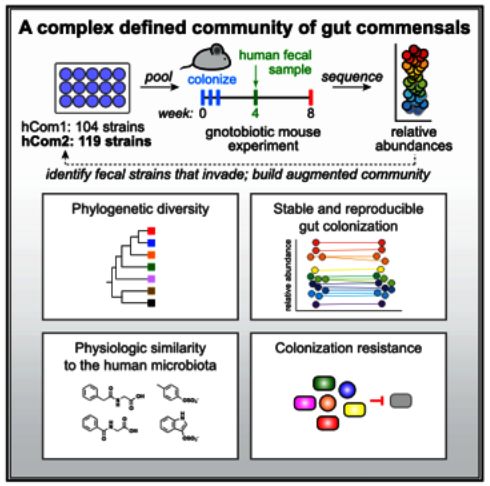
Yu et al., *biorXiv*,

Cell

Resource

Design, construction, and *in vivo* augmentation of a complex gut microbiome

Graphical abstract



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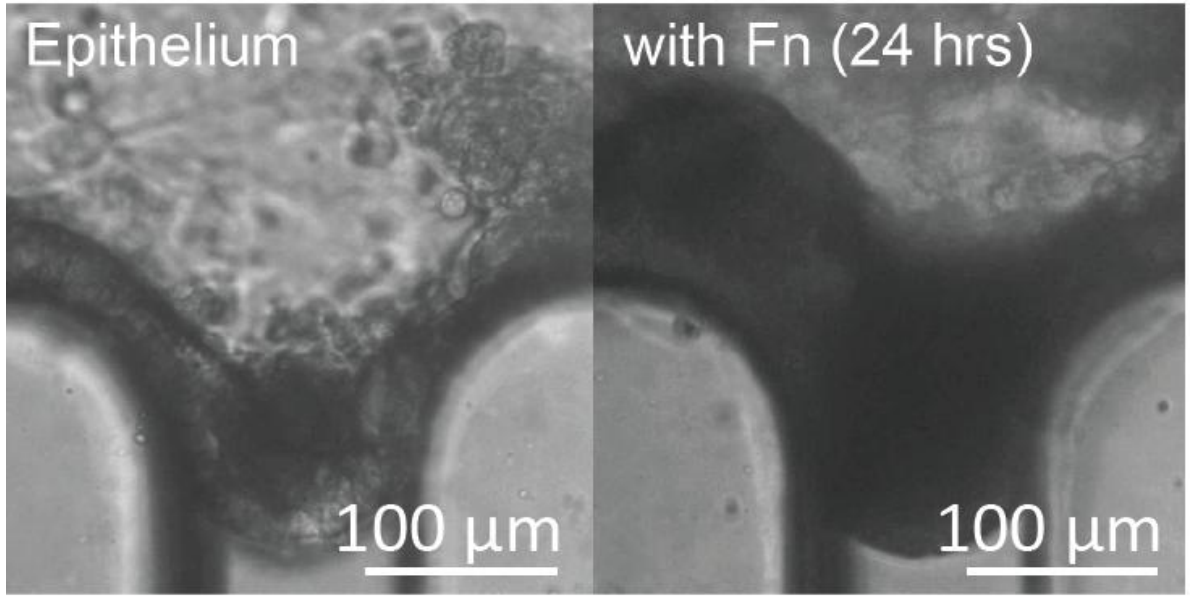
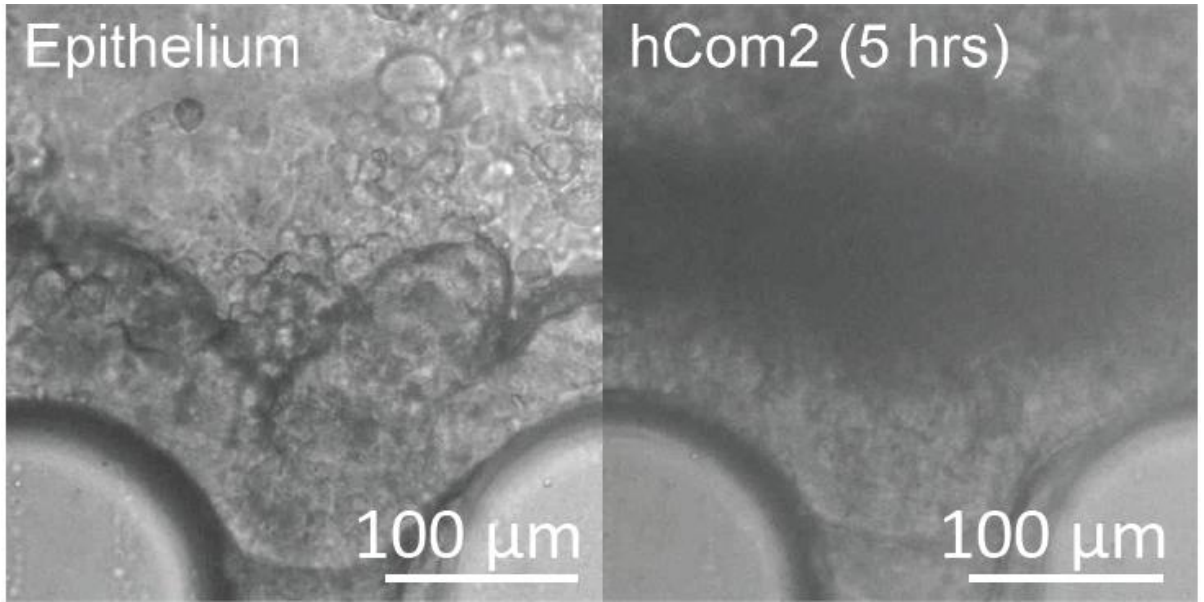
In brief

The development of a complex community of bacteria that represents the most common taxa from the human microbiome enables further mechanistic study of genes, pathways, and species that influence host physiology and health.

with Michael Fischbach lab, Stanford



Bacteria co-culture in chemostat



Dissecting and targeting cancer plasticity: implications for science and translation

- Plasticity is a pervasive hallmark of advanced cancer
- Understanding plasticity requires *clinical datasets of advanced metastatic cancer* and *clinically representative models*
- Cancer plasticity involves highly conserved cell state transitions that can be mechanistically defined and intercepted using rational drug design
- Models and drug development must take both cancer genomics and cell state into account
- Need to go beyond static baseline and genomic biomarkers in clinical trial development:
  e.g. cfDNA ChiPseq, radiotheranostics
- Targeting micrometastatic disease as an emerging clinical priority opportunity

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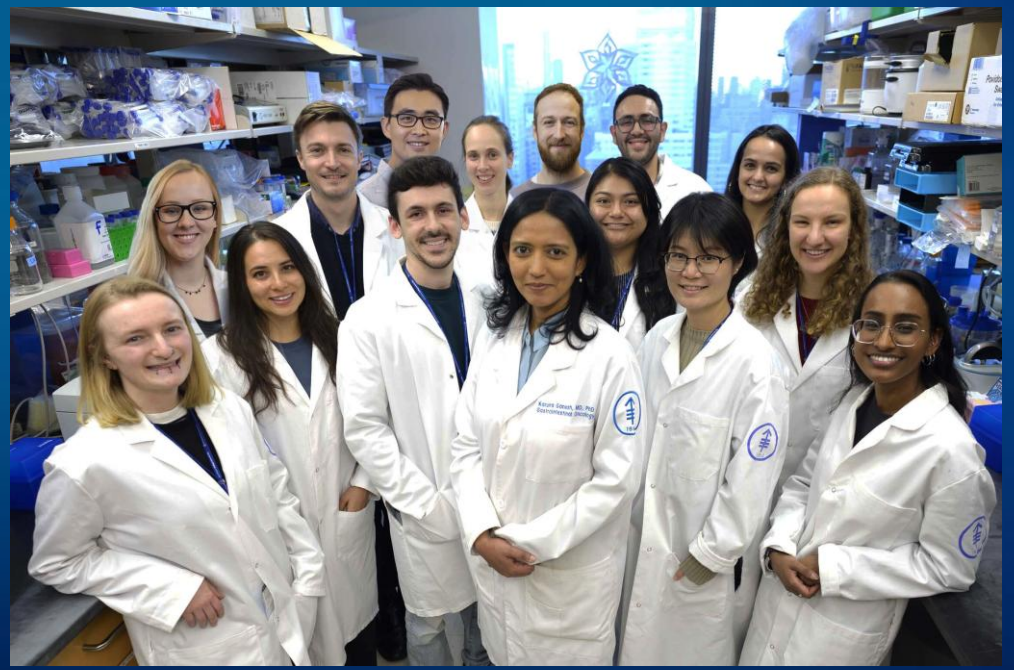
Our patients and their families



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