3D technologies to accelerate HTAN atlas building efforts

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NIH NATIONAL CANCER INSTITUTE

NCI CANCER MOONSHOT

Human Tumor Atlas Network
A program of the National Cancer Institute
of the National Institutes of Health

Recommendation I: *Generation of Human Tumor Atlases*

Create dynamic 3D maps of human tumor evolution to document the genetic lesions and cellular interactions of each tumor as it evolves from precancerous lesion to advanced cancer.

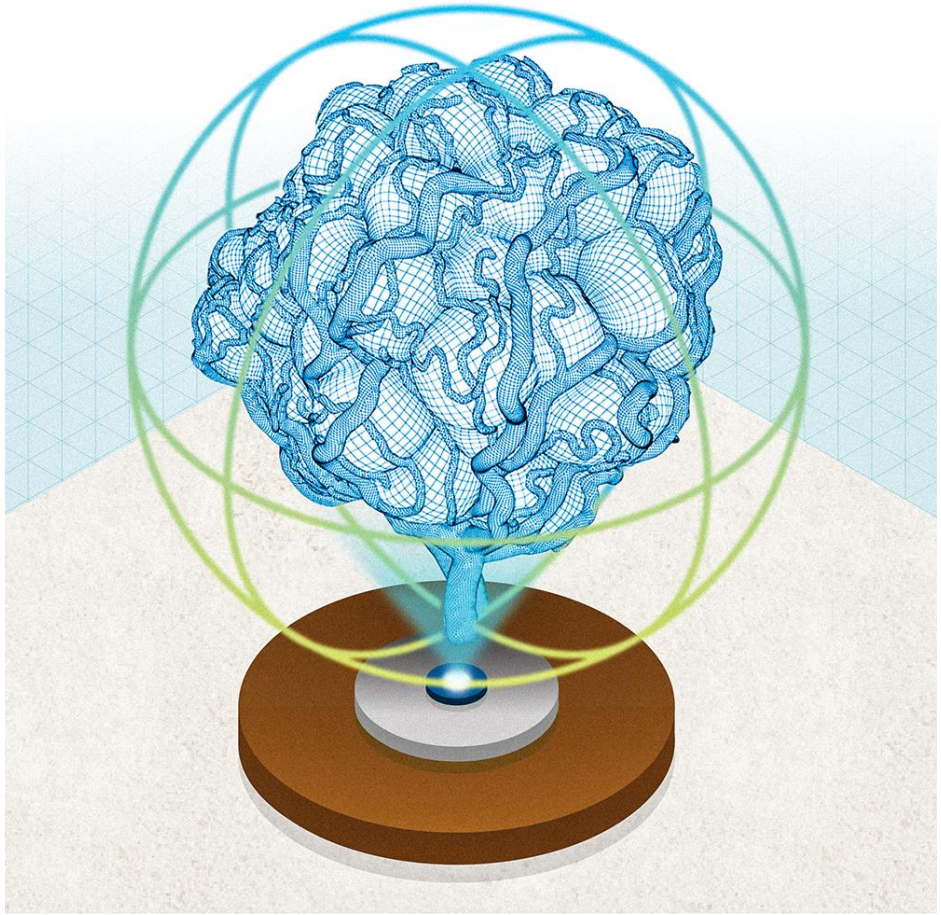
Overall Goal of this concept:

Rapid implementation of promising new technologies for **time-efficient, three-dimensional (3D) molecular characterization of intact human tumor tissue** for dynamic 3D tumor atlas construction.

The NCI Human Tumor Atlas Network

HTAN
HUMAN TUMOR ATLAS NETWORK

- Construct dynamic 3D atlases of human cancers
- ***Integrate*** molecular, cellular, and tumor tissue composition and architecture, including the microenvironment and immune milieu
- Focus on ***high-risk*** cancers; including those responsive / non-responsive to immunotherapy; pediatric cancers
- Represent a ***diverse patient population***, including minority and underserved patients
- Describe ***transitions during cancer****:* pre-malignant lesions to malignancy, locally invasive to metastatic cancer, & the development of therapeutic resistance
- Enable ***predictive modeling*** to refine therapeutic choices for patients.

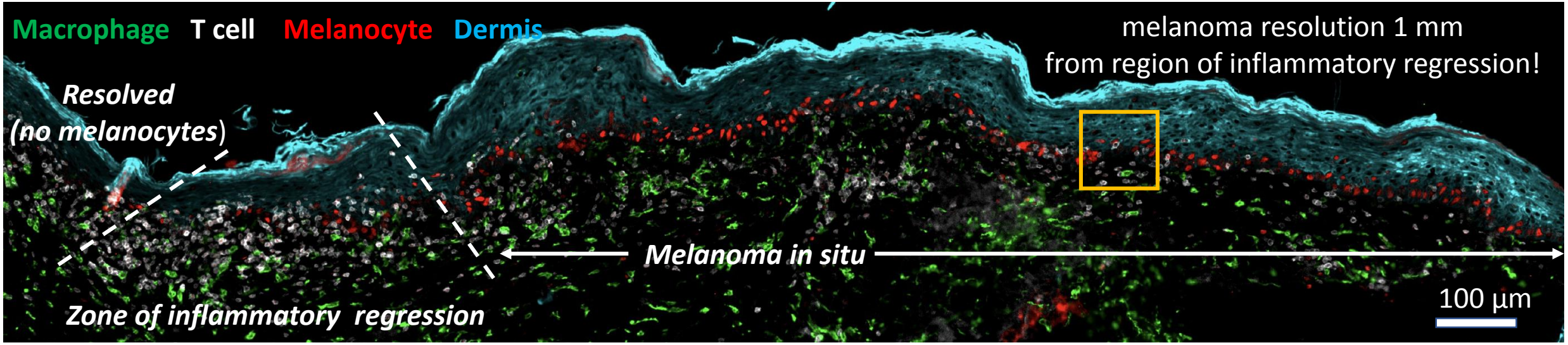


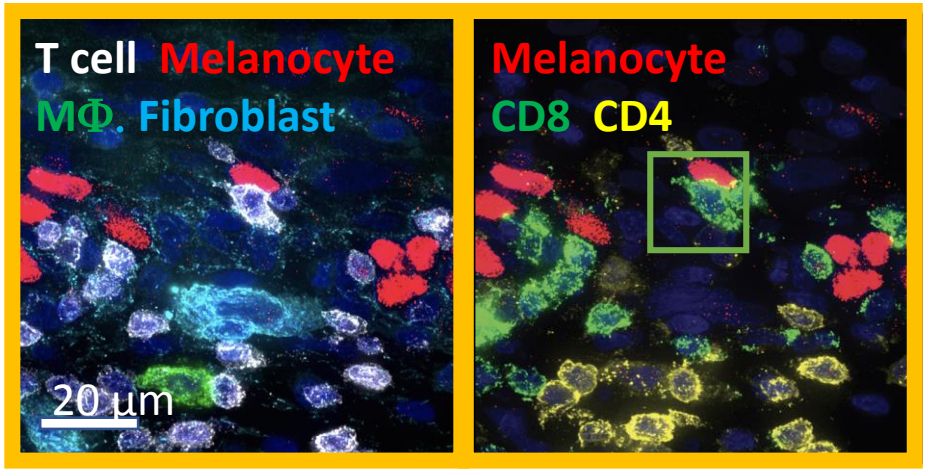
https://humantumoratlas.org/

Ongoing HTAN efforts illustrate the importance of spatial tumor context

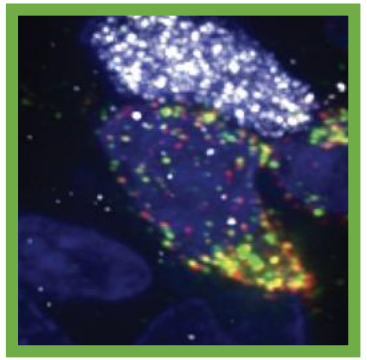
Multiplex imaging allows mapping of up to 100 proteins / 1000 transcripts to assess tumor heterogeneity

Cyclic IF reveals staged immunoediting in early cancer (melanoma *in situ)*





Exhaustion markers



Progression of distinct immune editing states across a ~ 2 mm tumor section.

Left: immune cells have cleared or are active against the tumor

Right: melanoma with horizontal growth,

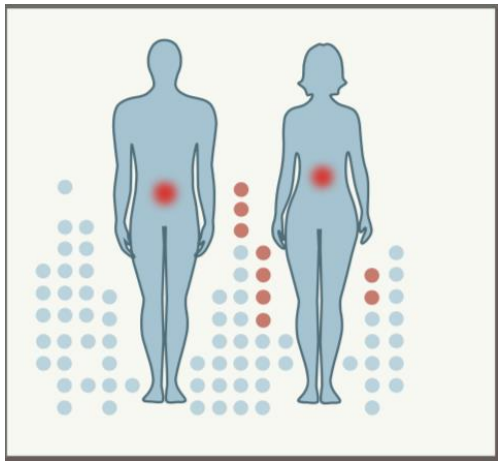
→ Drivers and mechanisms of progression?

Kindly provided by Peter Sorger, Harvard HTAN Center

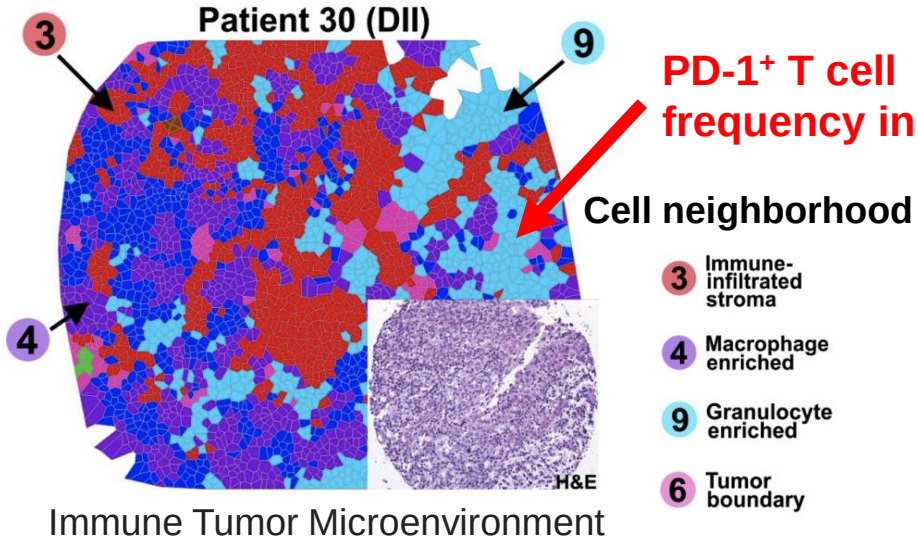
Ongoing HTAN efforts illustrate the importance of spatial tumor context

Diffuse Immune Infiltrate (DII) Colorectal Cancer

Clinical Annotations

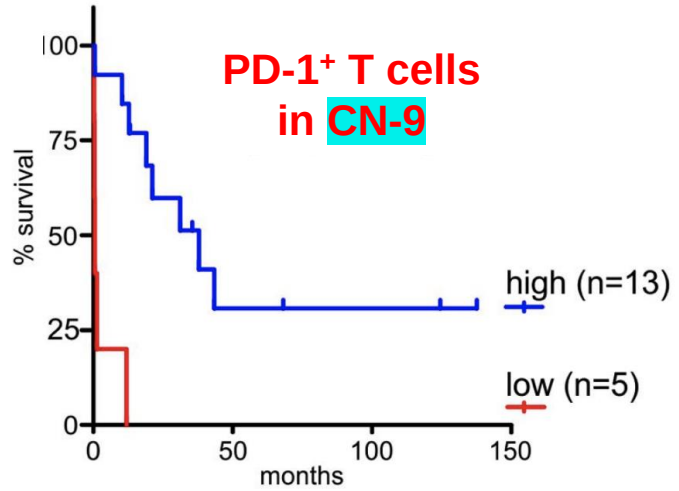


Multiplex imaging



Immune Tumor Microenvironment

Prognostic Value



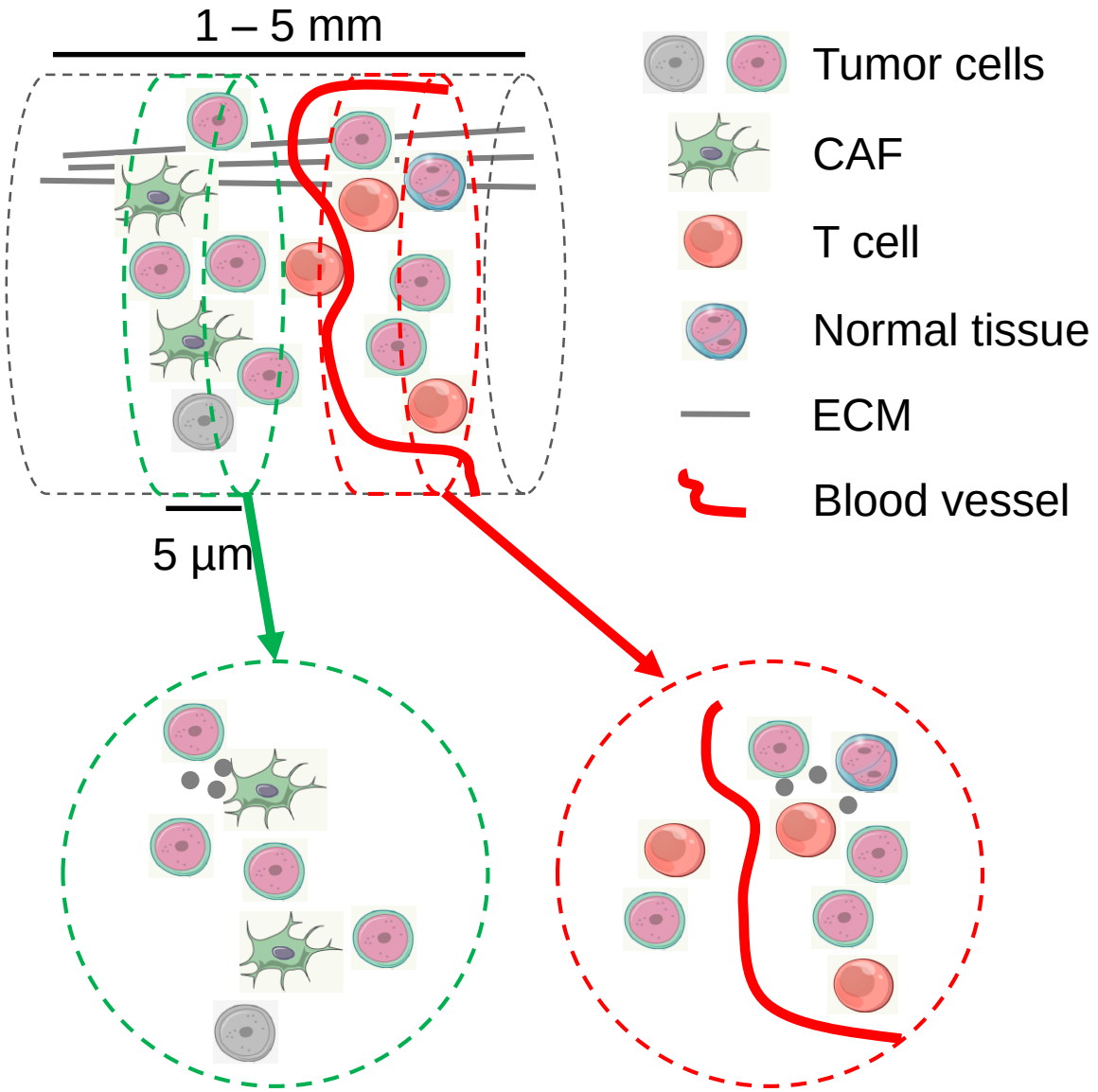
Tumor function is driven by complex cell-subset interactions

T cell frequency within CN, but not Cell Neighborhood or PD-1+ T cells alone are prognostic.

→ Current HTAN efforts are largely focused on **2D analyses** of ~ 5 µm tissue slices

Nolan Lab, BioRxiv, https://doi.org/10.1101/743989 – DCFI and BU HTAN Centers

Limitations of 2D spatio-molecular mapping



- Marked heterogeneity within single biopsies can result in image selection bias and **failure to detect rare cell types or key physiological landmarks**
- **Limited preservation of spatial relationships**, particularly irregular structures (vasculature, microenvironment)
- 3D views require sequential tissue sectioning, which is **time-consuming and destructive to tumor tissue**

→ **Impediment to the Blue Ribbon Panel recommendation to create dynamic 3D tumor maps**

Emerging examples for 3D characterization of intact tissue

3D Approach	Assay	Validated in…	Tissue Depth
Light Sheet Microscopy	IF	Human tumor tissue	~ 3 mm
Transparent tissue tomography (T3)	IF	Core needle biopsy	0.8 mm
StarMAP	RNA FISH	Mouse brain	0.15 mm
DNA microscopy	Custom RNA-Seq	Tissue culture	N/A
Paired-cell sequencing	scRNA-Seq	Mouse liver	N/A

→ **Suitable 3D technologies were not available or mature enough at time of HTAN awards**

Synergy

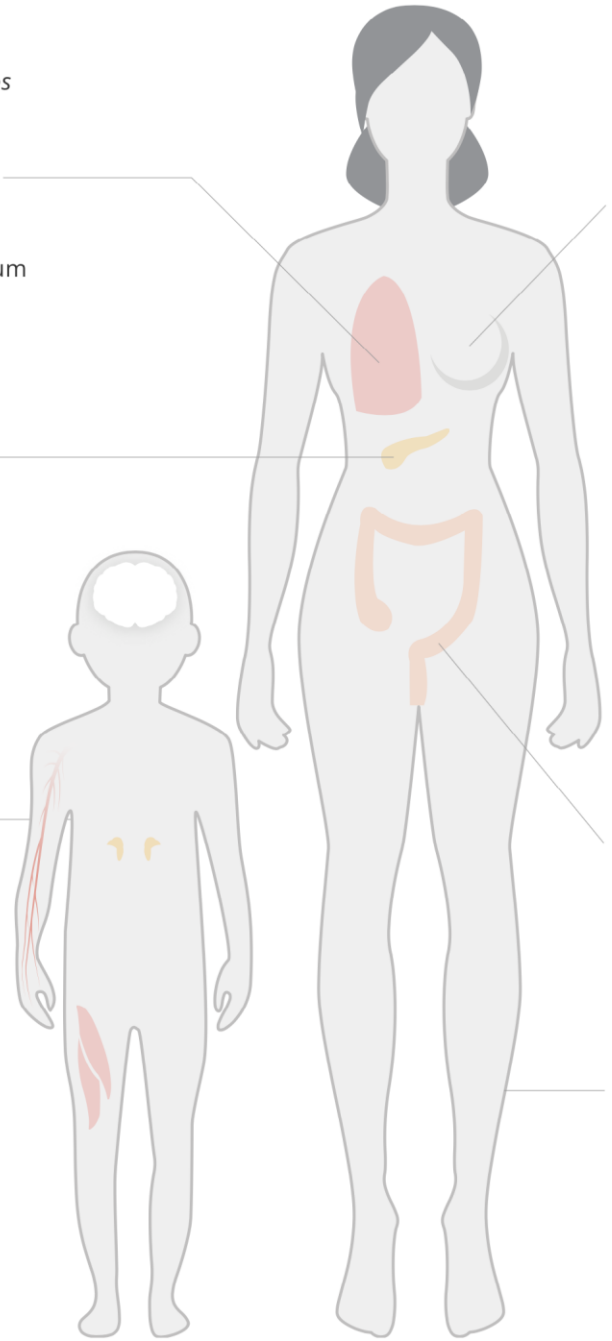
- **2D assays:** Discovery of tumor-specific cell types and suitable markers
- **3D assays:** Map cell types identified by 2D in the context of intact tumor microenvironment

Proposed funding mechanism – UH2

- UH2 Cooperative Agreement to integrate with existing HTAN U2C and U24 grants.
  - 3 - 4 UH2 Grants
  - $ 250,000 / year - informed by HTA pilot project
  - Duration: 2 years
  - Total costs for all years: ~ $ 3.3 M total cost for 4 awards
- All PIs with relevant expertise are encouraged to apply. Non-HTAN grantees are expected to be part of HTAN and encouraged to use HTAN-procured biospecimen.
- Preliminary data demonstrating the “shovel-readiness” of the technology in an HTAN-relevant tumor will be required.
- HTAN-focused program that leverages and complements other NIH and NCI imaging efforts.

Integration with existing HTAN Research Network

- Leverage **shared HTAN tumor sources** via trans-network efforts (currently colon, breast)
- Encourage identification of **collaborators** within HTAN-funded research centers
- Agree to data use and sharing policies
- Deposit data, protocols and SOPs with the HTAN Data Coordinating Center
- Participate in relevant HTAN Working Groups and biannual Face-to-Face meetings



LUNG

Avrum Spira & Steven Dubinett
Boston University & University of California Los Angeles

Dana Pe'er & Christine Icabuzio-Donahue
Memorial Sloan-Kettering Cancer Center

Molecular and Cellular Characterization of Screen Detected Lesions (MCL) Consortium Pre-Cancer Atlas Pilot

PANCREAS

Dana Pe'er & Christine Iacobuzio-Donahue
Memorial Sloan-Kettering Cancer Center

MCL Consortium Pre-Cancer Atlas Pilot

Li Ding, Ryan Fields, William Gillanders, & Samuel Achilefu
Washington University in St. Louis

PEDIATRIC

FNLCR & Broad Institute
Tumor Atlas Pilot
Glioma, neuroblastoma, and sarcoma (organs commonly affected by these cancers include the brain, adrenal glands, and muscle)

Kai Tan and Stephen Hunger
Children's Hospital of Philadelphia
Glioma, neuroblastoma, and very high risk acute lymphoblastic leukemia (organs commonly affected by these cancers include the brain, adrenal glands, and blood)

BREAST

Shelley Hwang, Carlo Maley, & Robert West
Duke University, Arizona State University, & Stanford University

Joe Gray, Gordon Mills, Jeremy Goecks, & Christopher Corless
Oregon Health & Science University

Bruce Johnson & Aviv Regev
Dana-Farber Cancer Institute & Broad Institute

Li Ding, Ryan Fields, William Gillanders, & Samuel Achilefu
Washington University in St. Louis

Frederick National Laboratory for Cancer Research (FNLCR) & Broad Institute Tumor Atlas Pilot

MCL Consortium Pre-Cancer Atlas Pilot

COLON

Michael Snyder & James Ford
Stanford University

Robert Coffey, Ken Lau, & Martha Shrubsole
Vanderbilt University

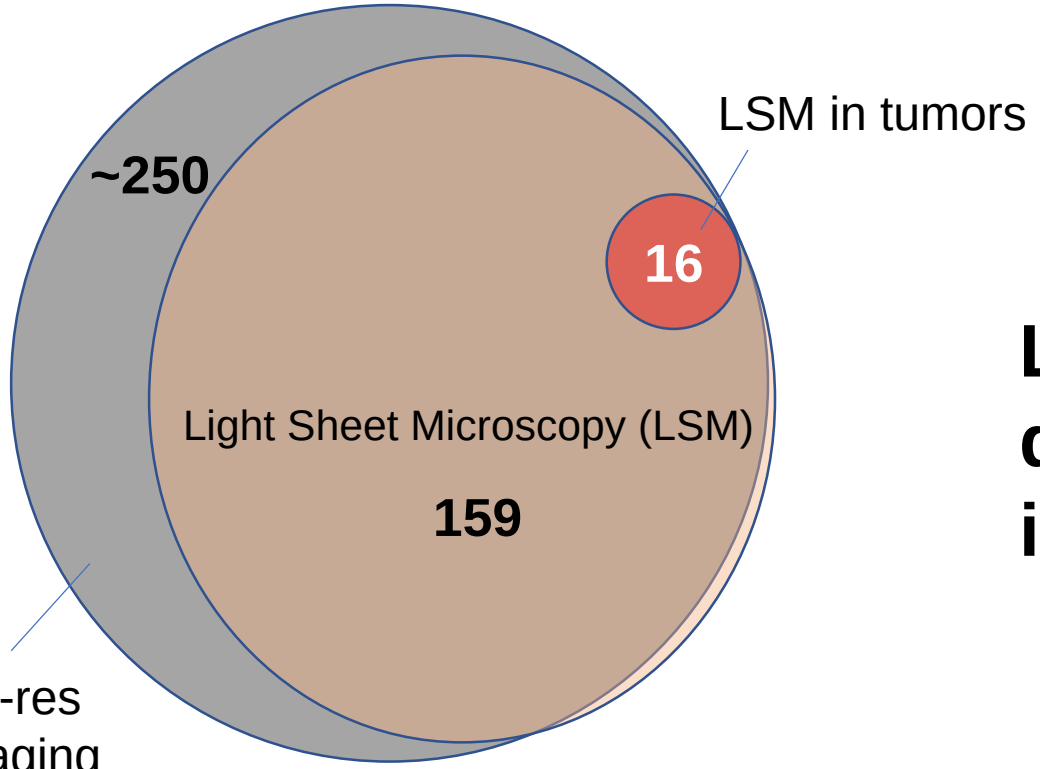
Bruce Johnson & Aviv Regev
Dana-Farber Cancer Institute & Broad Institute

SKIN

Peter Sorger, Sandro Santagata, & Jon Aster
Harvard University & Brigham and Women's Hospital

Bruce Johnson & Aviv Regev
Dana-Farber Cancer Institute & Broad Institute

Portfolio analysis of active 3D imaging awards across NIH



- Mostly low-res clinical imaging
- Core support
- BRAIN initiative

Transparent Tissue Tomography (1)

DNA microscopy (1)

STARMAP (1)

Limited support of non-destructive high-resolution imaging in the cancer space.

Thank you / Questions?