The NCI Human Tumor Atlas Network (HTAN)

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ITCR Monthly Meeting

NIH NATIONAL CANCER INSTITUTE

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The Cancer Moonshot Initiative

2016 State of the Union Address

Goals

- *Accelerate progress in cancer, including prevention & screening*

  From cutting-edge basic research to wider uptake of standard care

- *Encourage greater cooperation and collaboration*

  Break down silos within and between academia, government, and the private sector

- *Enhance data sharing*

  NCI Cancer Research Data Commons

  Annotated patient-level clinical data and ‘omics

The Process

Vice President's Office

Federal Task Force

NIH/NCI

National Cancer Advisory Board

Blue Ribbon Panel (BRP)

BRP Working Groups (WG)

- Cancer Immunology WG
- Tumor Evolution and Progression WG
- Pediatric Cancer WG

Blue Ribbon Panel Recommendations

A. Network for **Direct Patient Engagement**

B. Cancer **Immunotherapy** Clinical Trials Network

C. Therapeutic Target Identification to **Overcome Drug Resistance**

D. A National Cancer **Data Ecosystem** for Sharing and Analysis

E. Fusion Oncoproteins in **Childhood Cancers**

F. Symptom Management Research

G. Prevention and Early Detection: Implementation of Evidence-Based Approaches

H. Retrospective **Analysis of Biospecimens** from Patients Treated with Standard of Care

I. Generation of **Human Tumor Atlases**

J. Development of New Enabling **Cancer Technologies**

Recommendation I: Generation of Human Tumor Atlases

I. Develop a 3D cancer atlas

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

BRP Pediatric Cancer Working Group Report (pdf)
BRP Cancer Immunology Working Group Report (pdf)
BRP Tumor Evolution and Progression Working Group Report (pdf)
Final Blue Ribbon Panel Report (pdf)

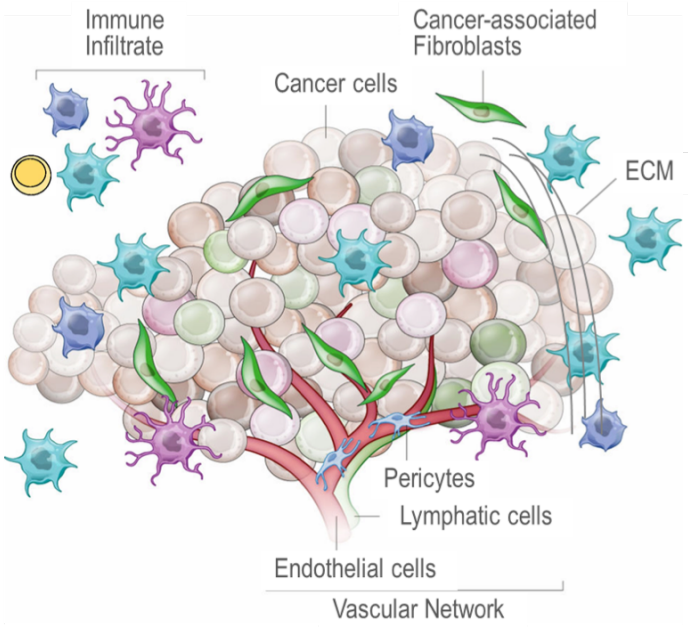
Objective of the Human Tumor Atlas Network (HTAN)

The main objective of the HTAN is the construction of tumor atlases for use by the scientific community that represent:

- High-resolution maps of the dynamic 3-dimensional architecture of an individual tumor, that
- Describes the molecular, cellular and physiological events that occur within individual cancer cells, the cancer mass, the tissue of origin and sites of metastasis, including the molecular, cellular and soluble components that can influence the immune response to the cancer, in order
- To enable predictive modeling to refine therapeutic choices for patients.
- Specific critical time points: transition from premalignancy to cancer, locally invasive to metastatic, and the response to and development of resistance to therapy.
- Initial focus on exemplary pediatric and adult cancers, including cancers in which immunotherapy responses have been good and in which such responses have been poor.

Spatial context is emphasized in the BRP recommendation

- Molecular, cellular and tissue-level interactions facilitate critical transitions in cancer.
- Gaps in our knowledge make it difficult to predict prognosis or develop risk stratification, precision screening and treatment strategies.



Modified from Junttilla and Sauvage. Nature 2013

A **comprehensive tumor atlas** will inform:

- Understanding of tumor heterogeneity and evolution
- Contribution of non-tumor components, such as stromal and immune cells, ECM
- Identification of markers of progression and drug resistance
- Development of early intervention strategies and robust therapies.

The Human Tumor Atlas Network (HTAN)

Goal: Pilot-scale, high-priority human tumor atlases that facilitate basic and clinical scientific discovery regarding important transitions during tumorigenesis.

Components of the HTAN:

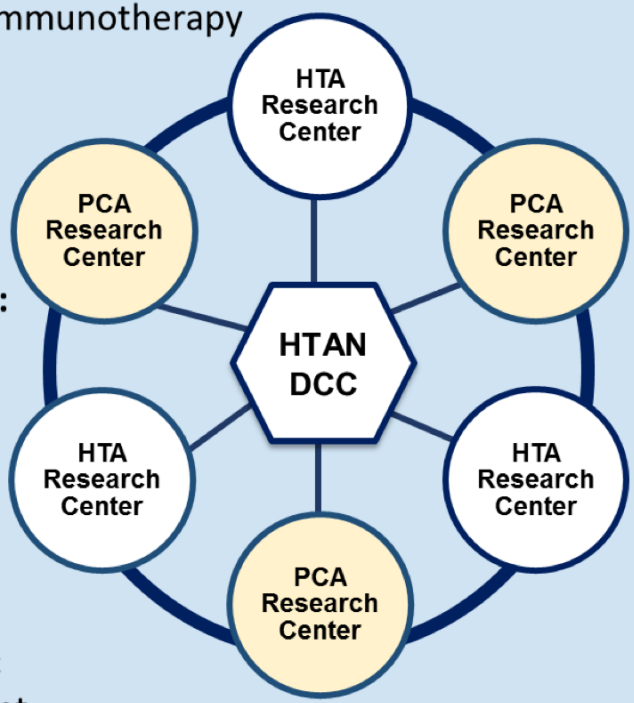
1. **Human Tumor Atlas (HTA) Research Centers** (U2C) focused on construction of dynamic 3D tumor atlases. RFA-CA-17-034 (closed)
2. **Pre-Cancer Atlas Research Centers** (U2C) focused on characterization of pre-malignant lesions. RFA-CA-17-035 (closed)
3. **Coordinating Center** (U24) focused on integration of the HTAN through administrative and scientific support. RFA-CA-17-036 (closed)

Human Tumor Atlas Network

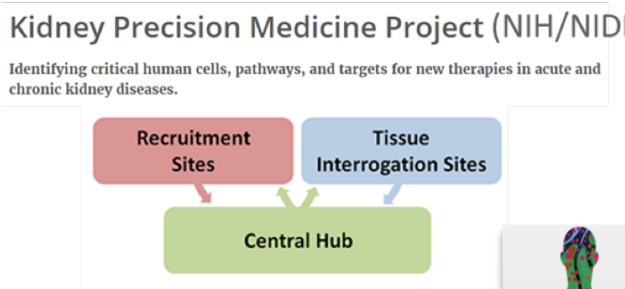
High Priority Tumors HTA Research Centers:
*(Non)Responsive to immunotherapy
*Highly metastatic
*High-risk hereditary
*Pediatric

Tumor Criteria for PCA Research Centers:
*Public Health Impact
*Access
*Feasibility
*Partnerships

Transitions:
Pre-cancer → Cancer
Invasive → Metastatic
Responsive → Resistant



The HTAN in the context of other “Atlas” initiatives:



Human Tumor Atlas Network

- Emphasis on spatial relationships and interactions
- Prospective/longitudinal sample collection (time)
- Extensive clinical data
- Atlases describing disease transitions

What is an Atlas?

- An **atlas** is a collection of **maps**; it is typically a bundle of maps of Earth or a region of Earth.

(en.wikipedia.org)

Imperii Orientalis et Circumjacentium Regionum by Guillaume Delisle (1742)

Slide modified from Dr. Sudhir Srivastava

What is an Atlas?

- An **atlas** is a collection of **maps**; it is typically a bundle of maps of Earth or a region of Earth.
- In addition to presenting **geographic features** and political boundaries, many atlases often feature **geopolitical**, **social**, religious and **economic statistics**

(en.wikipedia.org)

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Multiparameter data:
*3D Tumor architecture (ECM, native tissue, etc.)
*Tumor Microenvironment
*Cell-cell interactions (or not)
*Biophysical characteristics (pH, metabolites, etc.)

Slide modified from Dr. Sudhir Srivastava

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- Atlases have traditionally been bound into book form, but today many atlases are in **multimedia formats**.

Challenges in data visualization
*user dependent:
-patient
-clinician
-cancer researcher (basic or translational)
-informatician / computational biologist

(en.wikipedia.org)

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What is an Atlas?

- An **atlas** is a collection of **maps**; it is typically a bundle of maps of Earth or a region of Earth.
- They **also have information about the map** and places in it.

Connection to patient outcomes and clinical characteristics:
*highly annotated clinical data
*epidemiological data

Allows for 'navigation' of the atlas, setting directions for future research and/or treatment options.

(en.wikipedia.org)

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What is a human tumor atlas?

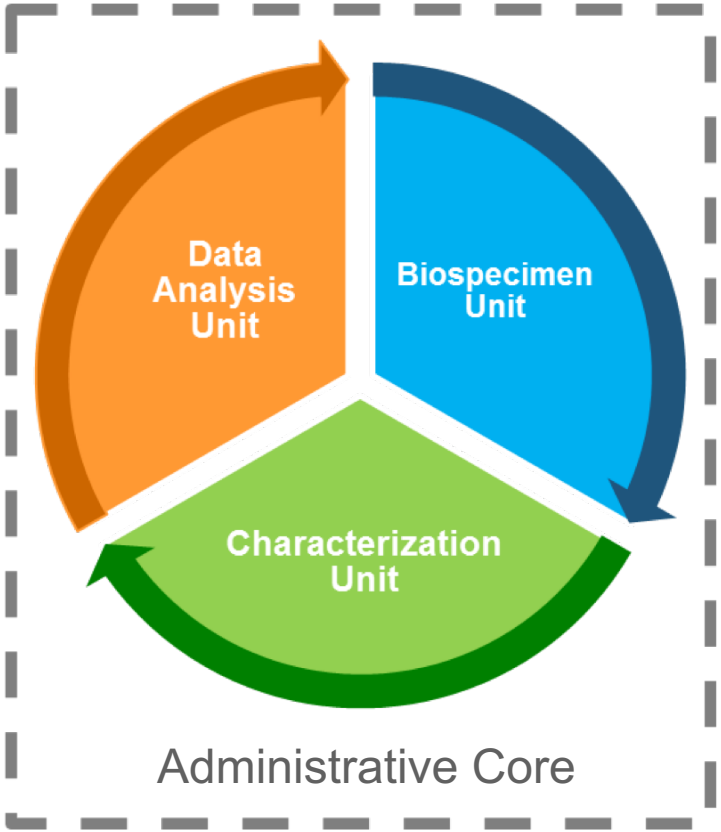
A comprehensive human tumor atlas is defined as the **multidimensional molecular, cellular, and morphological mapping** of human cancers, **complemented with critical spatial information** (at the molecular, cellular, and/or tissue level) that **facilitate visualization of the structure, composition, and multiscale interactions** within the tumor ecosystem.

Organization of HTA and PCA U2C Research Centers

The HTAN will include **U2C HTA and PCA Research Centers** whose research activities span the full range of atlas-building activities, including:

1) Development and transfer of SOPs for tissue acquisition, preservation, and processing.
2) Multi-scale, multi-parameter data collection using samples collected over time during important transitions in cancer.
3) Data integration, analysis and visualization to deliver a final atlas 'product'.

A highly multi- and interdisciplinary team of investigators is anticipated, including pathologists, clinical oncologists, cancer biologists, systems biologists, bioinformaticians, technology developers, computer scientists, etc.



We don't yet know the best data, but it is sure to be multi-dimensional

Clinical imaging modalities (radiomics); ing factors

Histology; Highly multiplexed 2D a imaging

Metabolomics (Mass spec, M maging, etc.)

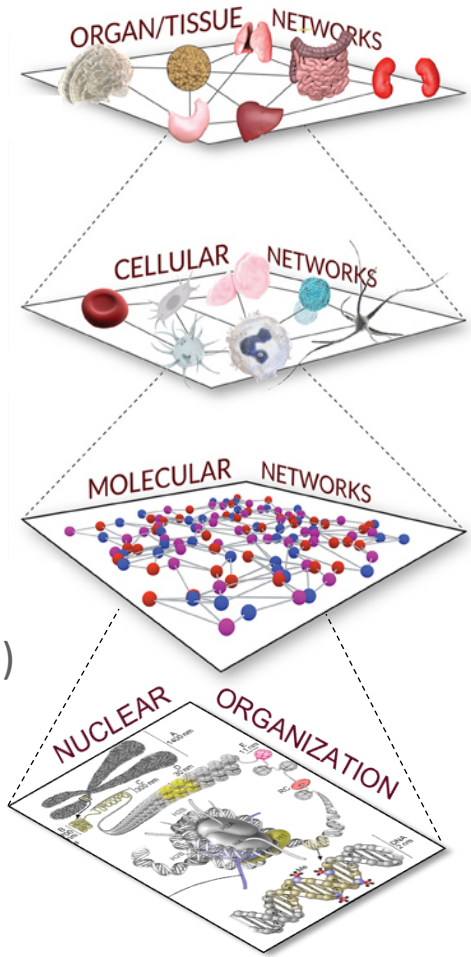
Proteomics (many bio al and imaging approaches)

Transcriptomics (q, smFISH, etc.); Epigenomics (ATAC-Seq)

Whole gen hole exome, targeted DNA seq

Chro onformation (4C, Hi-C, etc), EM imaging

Many at single-cell resolution



Multi-scale modeling!

Data Integration

The human tumor atlas will offer a variety of computational and data management challenges:

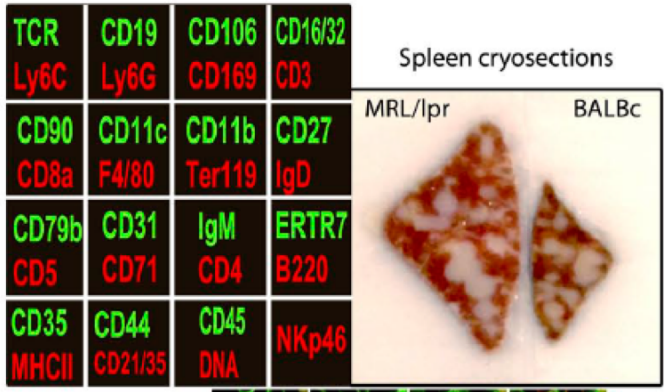
- Development of algorithms to support the analysis and integration of complex data sets arising from multiple biotechnologies for analyzing omic, imaging and another phenotypic features.
- Need for supporting experimental methodologies, especially for precancerous lesions where the amount of sample available is limited (fewer false discovery and biases).
- DATA VISUALIZATION
- Large-scale data management, sharing, and discovery systems that support researchers for HTAN data analysis and validation are a formidable challenge. It will include the development of data and metadata standards to enable data capture, sharing and analysis – interoperability and FAIR

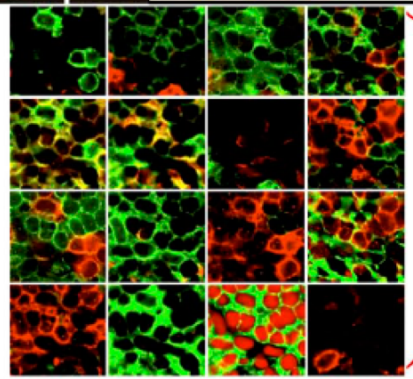
The human tumor atlas will offer a variety of computational and data management challenges:

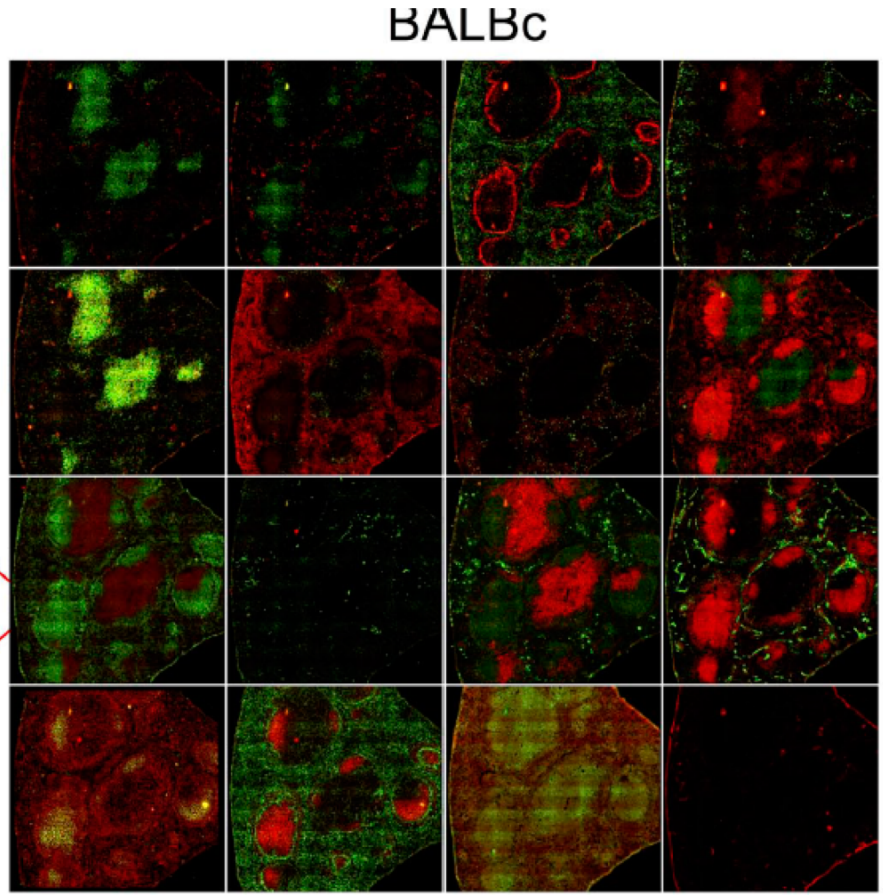
Integration of molecular data (over time) with imaging data (at many scales) will be a particular challenge.

Some examples of various imaging techniques:

Immunofluorescence of up to 100 markers on the same tissue

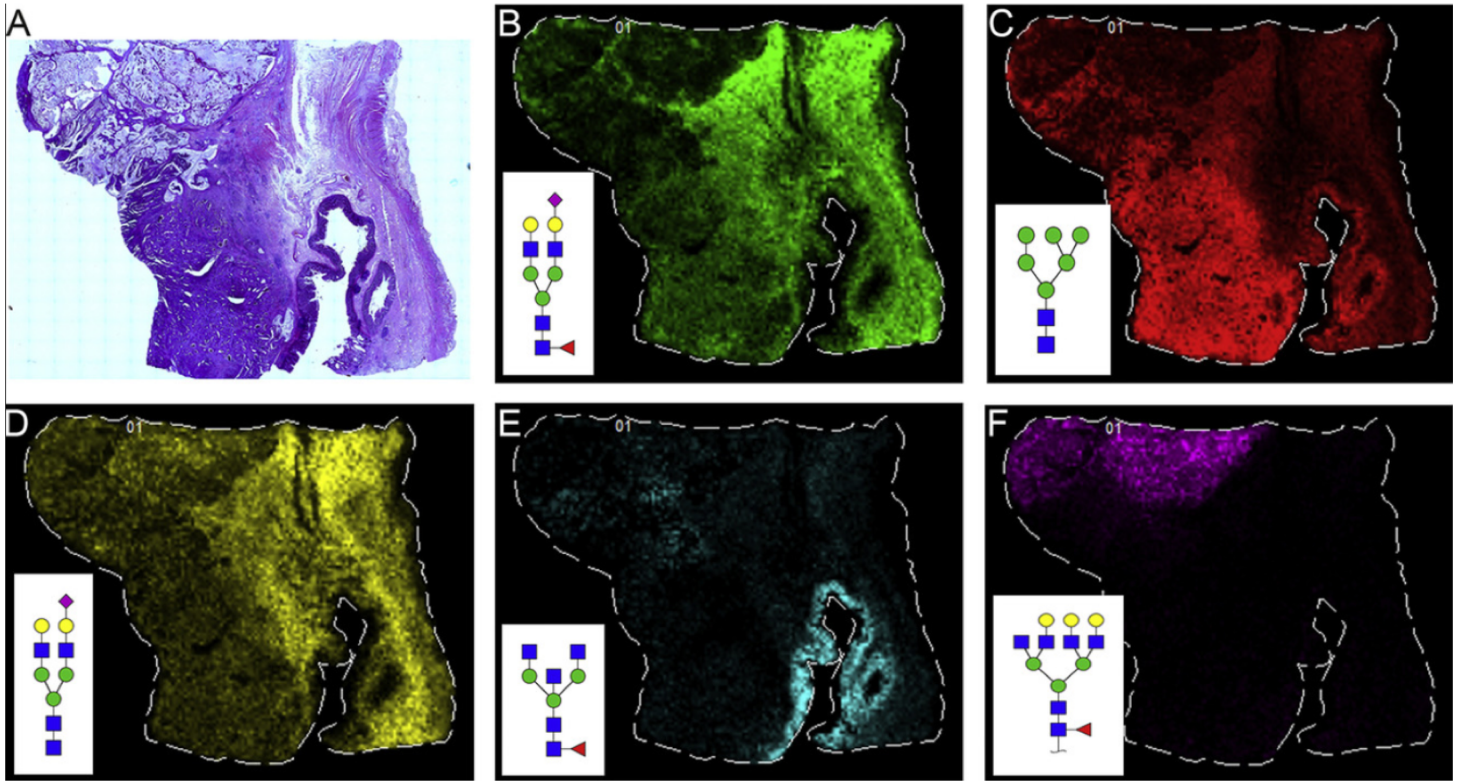






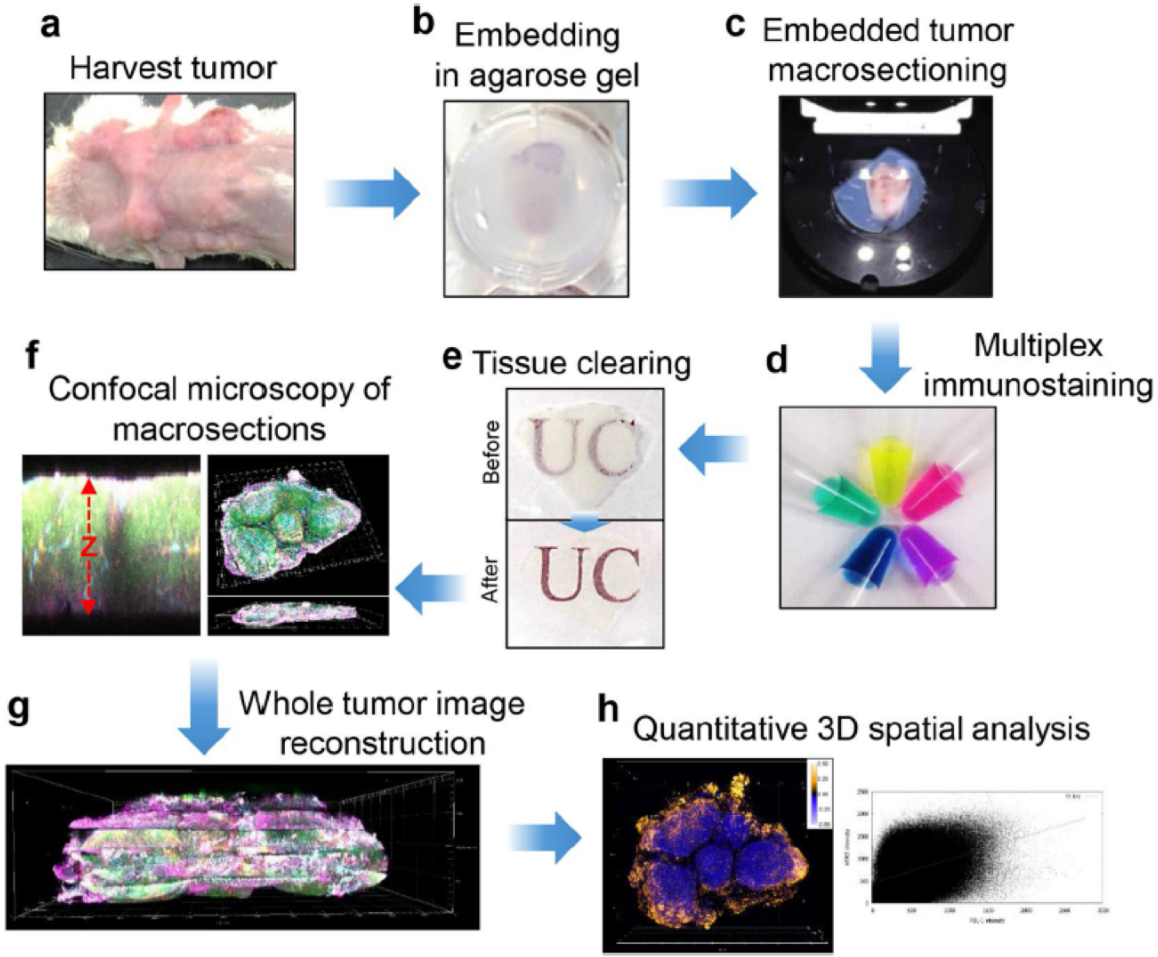
Goltsev et al. https://doi.org/10.1101/203166 Biorxiv

Label free imaging using MALDI Mass Spectrometry



Drake et al. Link

3D Tissue Imaging



Lee et al. Scientific Reports, Nov 2017

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Histology; Highly multiplexed 2D and 3D imaging

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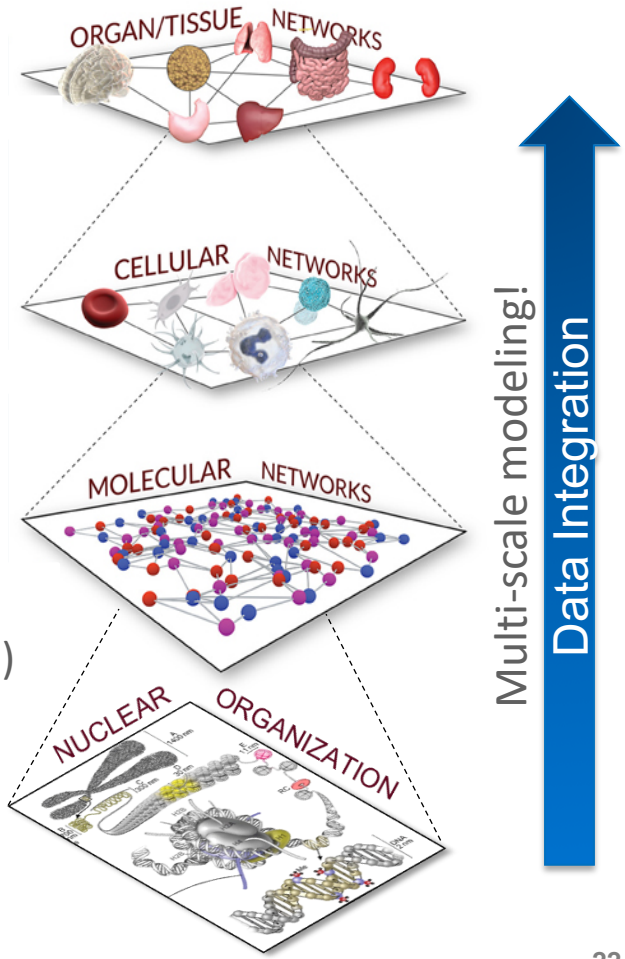

ITCR algorithms and tools will be of great interest to the HTAN investigators:

… “Leveraging, where feasible, technology from related NCI-sponsored informatics initiatives, for example the NCI Informatics Technology for Cancer Research (ITCR) program, which supports the development of informatics algorithms, tools, and resources across the continuum of cancer research.” (from Moonshot RFAs)

Expected outcome of the HTAN effort:

At the end a successful 5-year HTAN effort, we expect a preliminary set of comprehensive human tumor atlases that:

- Aid in defining tumor heterogeneity within and across patients in high-priority adult and pediatric cancers
- Quantify the dynamics and 3D architecture of the tumor ecosystem during important transitions
- Facilitate predictive modeling that leads to development of new risk stratification methods, better treatment options for patients, and improved understanding of disease mechanisms
- Provide direction for future atlas building efforts regarding the most impactful tumor atlas construction methods across tumor types

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