The Human Tumor Atlas Network (HTAN)

Pre-Application Webinar for RFA-CA-23-039

Human Tumor Atlas (HTA) Research Centers (U01)

- The HTA webinar will start at 3:05 PM EST
- All participants are muted upon entry to the webinar
- Please submit your questions in the Q&A box
- HTAN pre-application webinars will be recorded and posted on https://www.cancer.gov/about-nci/organization/dcb/news/past-events

NIH NATIONAL CANCER INSTITUTE

November 9, 2023
3:00–4:00 PM EST

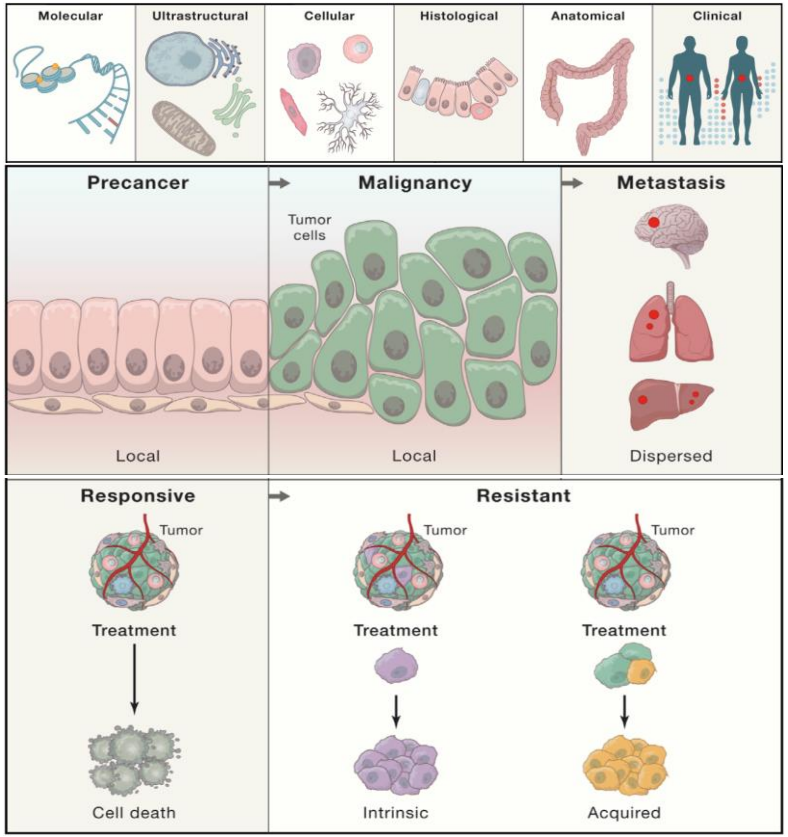
Agenda

3:05 – 3:15 PM EST	HTAN Overview
3:15 – 3:30 PM EST	HTA RFA Scope and Functions
3:30 – 4:00 PM EST	Q&A

The NCI Human Tumor Atlas Network (HTAN)

Overarching program goal: Construct dynamic 3D atlases of human cancers

- ***Integrate*** molecular, cellular, and tumor tissue composition and architecture, including the microenvironment and immune milieu.
- Describe ***transitions during cancer****:* pre-malignant lesions to malignancy, locally invasive to metastatic cancer, response to therapy.
- Represent a ***diverse patient population***, including underrepresented and underserved patients.
- Enable ***predictive modeling*** to discover biomarkers, understand basic cancer mechanisms, (eventually) refine therapeutic choices for patients.



Rozenblatt-Rosen et al., Cell 2020

Current HTAN Atlases

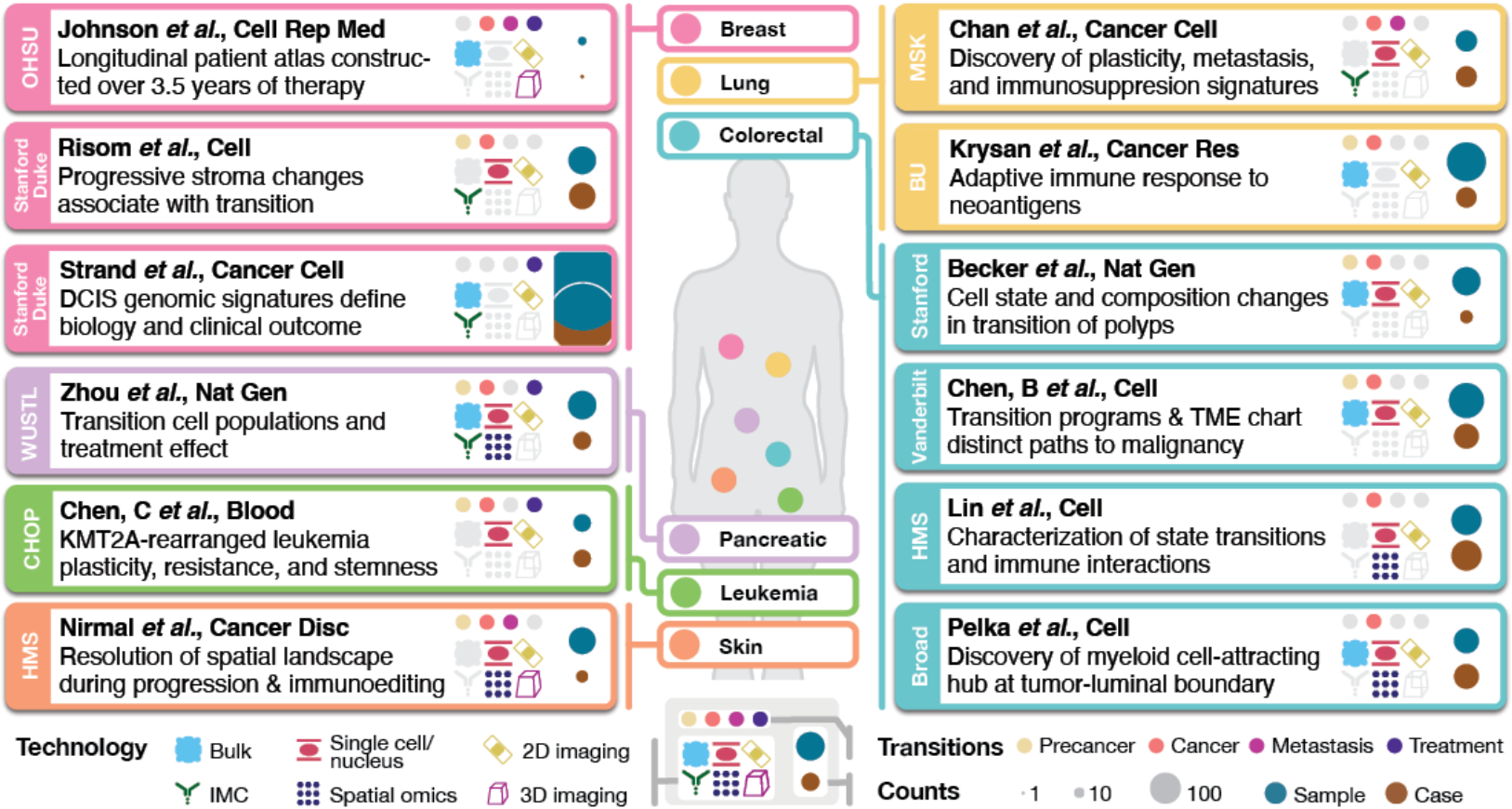
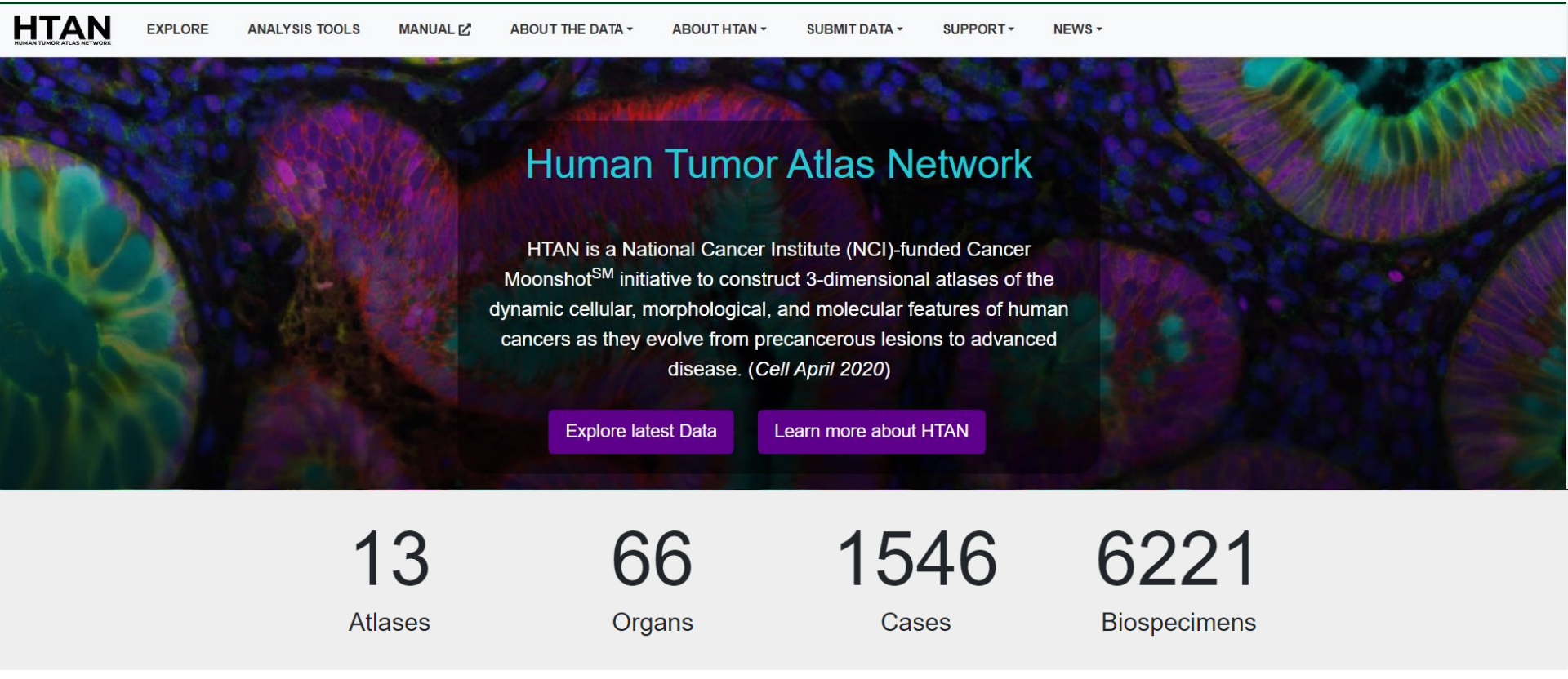


Figure courtesy of L. Ding, WUSTL HTAN

HTAN Data and Resources for the Cancer Research Community

https://data.humantumoratlas.org



HTAN Organization

Components of the HTAN:

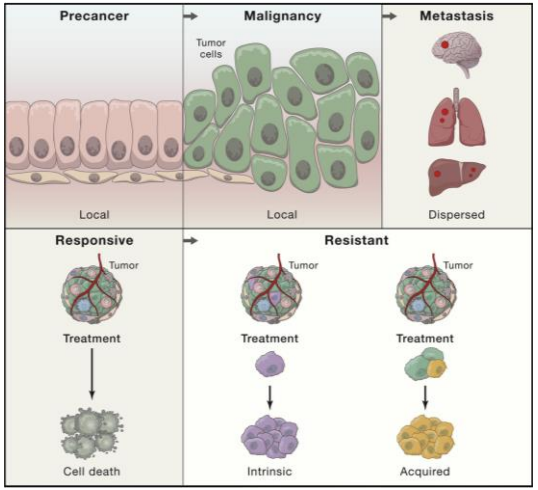
Human Tumor Atlas (HTA) Research Centers RFA-CA-23-039 (U01)

Pre-Cancer Atlas (PCA) Research Centers RFA-CA-23-040 (U01)

HTAN Data Coordinating Center (DCC) RFA-CA-23-041 (U24)

The number of HTA and PCA Research Centers will depend on availability of NCI FY24 funding.

Overarching Goal of the HTA RFA



Rozenblatt-Rosen et al., *Cell*, Volume 181, Issue 2, 2020, Pages 236-249

Each HTA Research Center will construct **one** atlas describing **one or more transitions spanning the entire cancer continuum**:

- *Transition from non-malignant to malignant disease;*
- *Transition from locally invasive to more advanced stages and metastatic cancer;*
- *Locoregional recurrence of disease within the same patient;*
- *Dynamic response to therapy;*
- *Development of therapeutic resistance.*

Building tumor atlases will deepen our understanding of precancer to invasive cancer progression at the earliest stages, further progression to more advanced cancer stages, recurrence, allow enhancement of diagnostic and treatment strategies, generate and test hypotheses and provide insights into biological mechanisms.

HTA RFA Scope and Objective

Each HTA Research Center is required to construct **one tumor atlas**. Atlas construction should be founded upon a **strong use case(s);** the atlas is expected to generate biological insights poised for translation at the conclusion of HTAN funding.

- ***Multimodal mapping requirement:*** Use of multimodal technological platforms. Leverage the existing HTAN infrastructure and assay types; the plan should include **at least two existing HTAN data types** for which data and metadata standards and levels exist (**at least one must be a spatial assay**).

- ***Spatial mapping requirement:*** Study the spatial contexts of the cells within the tumor and its microenvironment, including 3D characterization. (*Of note, atlases constructed using only bulk or dissociative-omics technologies in the absence of a spatial 2D or 3D mapping will be considered non-responsive).*

- ***Dynamic mapping requirement:*** Characterize the dynamic phenotype of precancers or advanced cancers based on the tumor transition being studied.

Some Important Elements

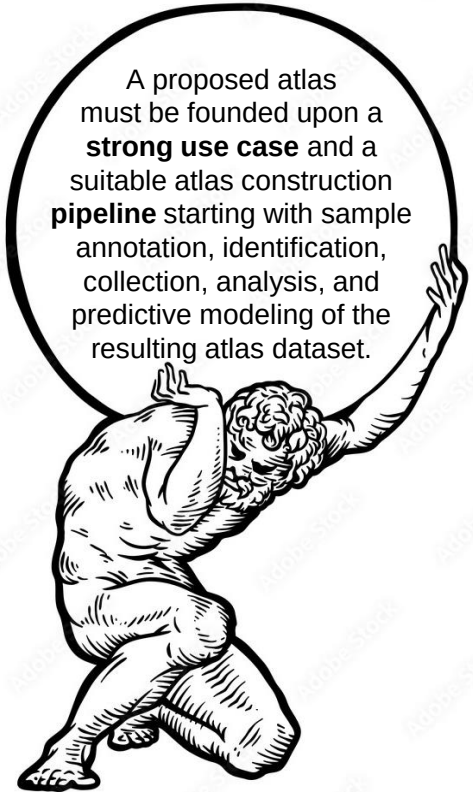
The cancer type is not prescribed, but atlases that **add significant value** to the current set of HTAN atlases (www.humantumoratlas.org) will be prioritized.

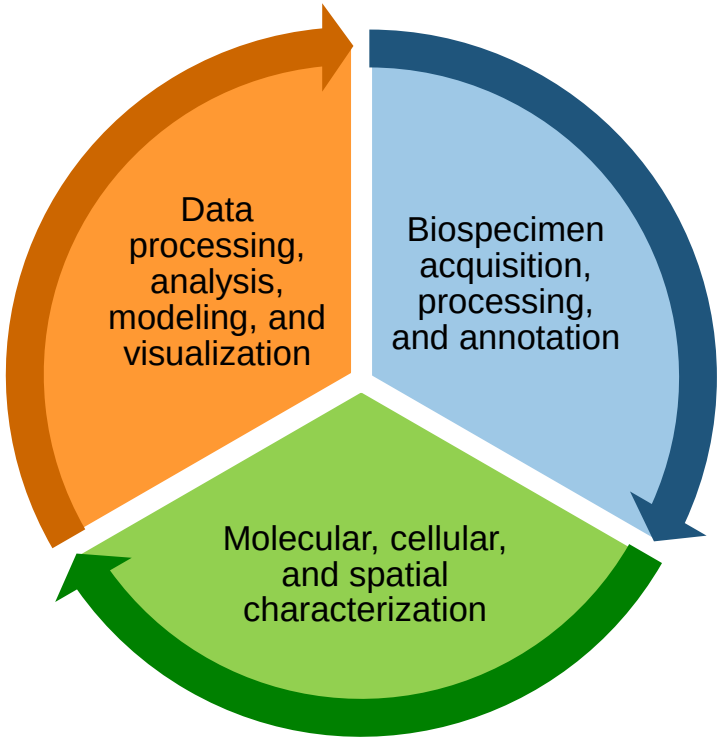
Significant value may be added through multiple approaches, including but not limited to:

- Proposing tumor types not included in the first phase of HTAN;
- Proposing to include a unique sample set that diversifies or extends the impact of an atlas constructed in the first phase of HTAN;
- Adding longitudinal samples that increase the insight and impact of atlases constructed during the first phase of HTAN;
- Putting emphasis on a diversity of patient populations and adding samples from patients traditionally underrepresented in large, organized collections.

HTA Research Center Organization

Main Areas of Responsibility





HTA Research Center

Leadership and Team Expertise

It is expected that applications will include multiple PDs/PIs to accomplish the goals of this RFA.

Team should have expertise in, but not limited to, the following:

- Pathology, biospecimen collection, annotation, and characterization of clinical biospecimens.
- Molecular, cellular and spatial profiling of human tissue samples using the proposed technologies.
- Analysis of large-scale, multidimensional, multimodal, and spatial data sets from human tissue samples, and predictive modeling.

Biospecimen Acquisition, Processing, and Annotation

Applications must demonstrate strong biospecimen science.

Information should include (but not limited to):

- **A biological and statistical justification** for biospecimen collection frequency, sample type, and volume of biospecimens to be acquired that is motivated by the specific atlas use case being proposed.
- **Evidence of access** to a source of human samples and epidemiological and clinical data relevant to the proposed precancer or tumor atlas immediately upon award.
- Information regarding the **quality assurance (QA) and quality control (QC) metrics**, how tissue will be processed and/or preserved to facilitate biospecimen characterization activities, including optimization of pre-analytical processing of tissue and minimizing confounding variables.
- Describe how the biospecimens submitted for characterization will be **verified by trained pathologist(s)** and how morphologic information will be preserved for correlation with characterization data.

Molecular, Cellular, and Spatial Characterization

Generate molecular, cellular and spatial characterization data to be utilized for atlas construction. It is required that each atlas include at least **two common HTAN data types** for which data and metadata standards have been developed **(one must be a spatial data type).**

Information should include (but not limited to):

- **A biological/statistical justification** for data collection frequency, data type, and data volume to be acquired based on the specific atlas use case.
- The data collection **technology(ies)/platform(s) to be employed**.
- A **strategy to monitor and ensure data quality**, including action plans for when quality issues are discovered.
- The expected **data collection workflow**, including all technologies and QA/QC nodes, potential challenges, strategies to minimize them.
- If technology platforms are located across institutions, include a **plan for how biospecimens will be divided** (or not) for analysis.

Data Processing, Analysis, Modeling, and Visualization

In addition to **data processing, analysis, modeling, and visualization** of atlas data, personnel responsible for this function must work closely with all HTA Center members to quickly determine **data quality** and provide **feedback for rapid course correction**.

Personnel within this functional unit are also responsible for **demonstrating the value of the atlas dataset through identification and coordination of atlas use cases**.

Information should include (but not limited to):

- Describe plans for **completion of the proposed use case** and the clinical or biological insight and hypotheses that will be gained from the modeling effort.
- Describe and demonstrate any **existing or proposed data processing pipelines** to be employed within the HTA Research Center, specifically with regards to imaging/spatial and omics data collection.
- Describe and **demonstrate plans to aggregate and integrate data and metadata** from the broad range of experimental and computational approaches outlined throughout the application into a tumor atlas.

Diversity and Disparity

All HTAN atlases should contain a diversity of patient populations consistent with the requirements of the NIH **Inclusion Policies for Research Involving Human Subjects** (as described in https://grants.nih.gov/policy/inclusion.htm).

NCI is particularly interested in applications where samples are collected from patients whose self-identified race and ethnicity and/or genetic ancestries are currently underrepresented in cancer research, underserved populations, or populations who experience disparate cancer outcomes.

The adequate breadth of samples included within each Center will enable future translational research based on the HTAN atlases to be relevant to and reflect all U.S. patient populations.

Non-Responsive Applications

Will Not Proceed to Review

- Applications primarily focused on the pursuit of a biological mechanism through basic research that does not result in an atlas.
- Applications proposing atlases constructed through exclusive use of non-human biospecimens.
- Applications based upon one experimental measurement and do not propose methods that provide multidimensional data/information regarding the spatial distribution of cellular and/or non-cellular components of the tumor.
- Applications that propose to primarily study biofluids for identification of biomarkers without any attempt to reconstruct the multidimensional tumor ecosystem.
- Applications that do not propose to collect at least two existing HTAN data types (at least one must be a spatial assay) for which data and metadata standards and levels exist.
- Applications that are not able to satisfy current HTAN policies.
- Applications that do not include biospecimens representative of patient diversity in the United States, as required by NIH policy.

Mechanism of Support and Funding

- **Mechanism of support**: **U01**; Research Project -- Cooperative Agreements
- **Application Type:** New applications (**Type 1**)
- **Budget:** Not to exceed **$800,000 per year (Direct Cost)** per Center.
  - *Cap is exclusive of 3rd party F&A costs.*
- **Project Period:** Not to exceed **5 years**.

Budgeting for Post-Award Activities

Set-Aside (Restricted) Funds for HTAN Pilot Projects and Trans-Network Projects (TNPs)

- **Applicants must set aside 15% (Direct Cost) of their annual budget in Years 2–5** to facilitate the testing of hypotheses derived from atlas construction and/or to develop TNPs.

- The set-aside amount should be presented in the "Other Direct Costs" category under the heading “Consortium Collaborative Funds". The use of the set-aside funds will be restricted until pilot projects and/or TNPs are developed.

- **<u>Do not include</u> a description of pilot projects or TNPs within the application.**

Terms & Conditions of Award

Please make sure to read Section VI: Terms & Conditions of Award

Awardees will be expected to abide by current HTAN policies, including rapid and complete sharing of data and resources. Please confirm that data generated from samples collected from ongoing clinical trials or other sources can be shared to the widest extent possible before applying.

Current HTAN policies can be found:
https://data.humantumoratlas.org/resources

Page Limit

All page limits described in the SF424 Application Guide must be followed, with an exception for the Research Strategy section.

For the **Research Strategy** section, applicants are strongly suggested (but not required) to **limit the sub-sections to the page lengths** indicated below. (*NB: Specific Aims page is not counted in this page limit*.)

Research Strategy Sub-Sections	**Suggested Page Limits**
Sub-section A: Proposed Atlas Overview	2
Sub-section B: Research Team	2
Sub-section C: Integrated Functions of the HTA Research Center	12
Sub-section D: Addressing Cancer Health Disparities	1
Sub-section E: Project Management Plan	1
TOTAL	**18**

Important Reminders

- **Please read the HTA RFA carefully** to understand the requirements; failure to follow the instructions will result in a ‘non-responsive’ application, which will not be reviewed.
- Please also **read the companion RFAs** to understand the HTAN program as a whole, as well as the requirements for data sharing and coordination.
- In the Research Strategy section, specific sub-sections are outlined in the RFA in lieu of standard subsections (Significance, Innovation, and Approach); however, applications must highlight aspects of the proposed activities that speak to the significance and innovation of the approach.
- Please read the **review criteria** carefully, including the **criteria listed in “Specific to this FOA”** section, and address those criteria in the body of your application, in appropriate places.
- Please demonstrate your knowledge of and experience in multimodal, spatial and dynamic mapping of tumors.
- Describe your experience with working collaboratively in multidisciplinary teams/projects.
- Please pay attention to the Cooperative Agreement Terms and Conditions of Award.
- For any specific questions, please reach out to the NCI scientific contacts mentioned in the RFA.

Application Due Date
December 5, 2023

- All applications are due by 5:00 PM local time of applicant organization.
- Applicants are encouraged to apply early to allow adequate time to make any corrections to errors found in the application during the submission process by the due date.
- No late applications will be accepted for this Notice of Funding Opportunity (NOFO).

Thank You and Good Luck!

www.cancer.gov

www.cancer.gov/espanol

RESERVE SLIDES

This webinar: Human Tumor Atlas Research Centers (U01)

- To solicit applications for developing the **Human Tumor Atlas (HTA) Research Centers**, one of the three scientific components of the Human Tumor Atlas Network (HTAN) (NCI Human Tumor Atlas Network).

- Each HTA Research Center will construct **one human precancer or advanced cancer atlas** with an explicit focus on how evolving **spatial blueprint at single-cell resolution** contribute to important transitions in cancer from tumor initiation to metastasis.

Which HTAN RFA is most suitable?

RFA-CA-23-040 (PCA)

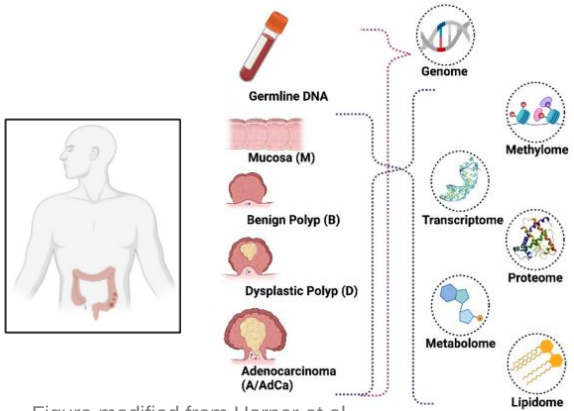
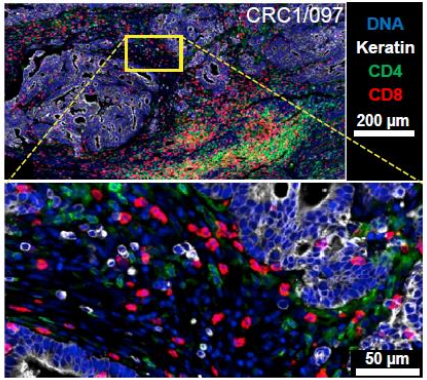


Figure modified from Horner et al.
https://doi.org/10.21203/rs.3.rs-515393/v1

Review the requirements outlined in the two RFAs.

Some applications focused on precancer may be suitable for both RFAs. Strongly encourage applicants to speak to an NCI PO.

RFA-CA-23-039 (HTA)

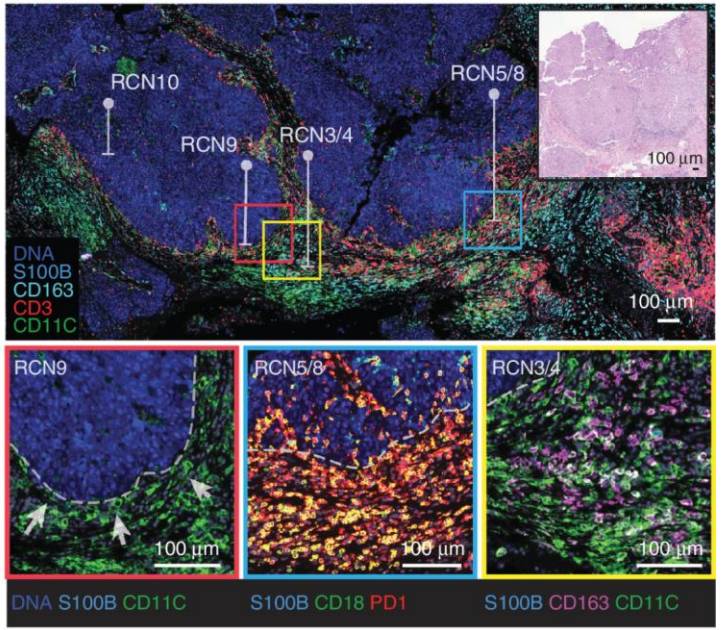


Lin et al. Cell 2023:
https://doi.org/10.1016/j.cell.2022.12.028

- Overall goal of the atlas is to **guide prevention and interception strategies**.
- **Streamlined technology to analyze adequate number of samples**; spatial assay can be a minor component; single-cell analysis is not required.
- **Longitudinal sample** from same patient is desired.

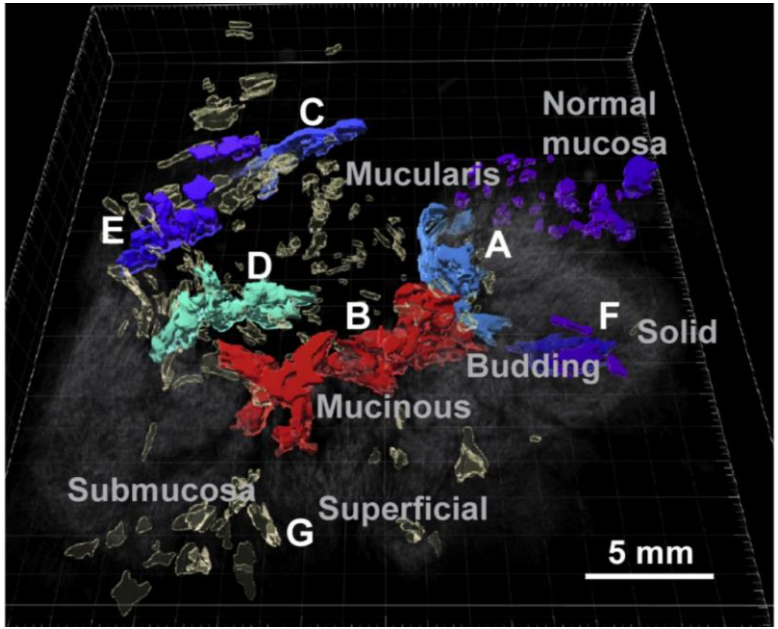
- Atlas must be founded upon a **strong use case** and **generate testable hypotheses**.
- Major focus is on **spatial mapping** and understand **cellular interactions in a spatial context** as tumors progress/evolve.
- Utilize dissociative single-cell ‘omics’ in a supporting role.

Charting the Spatial Landscape of Tumor and 3D Interrogations



RCN = Recurrent cellular neighborhood

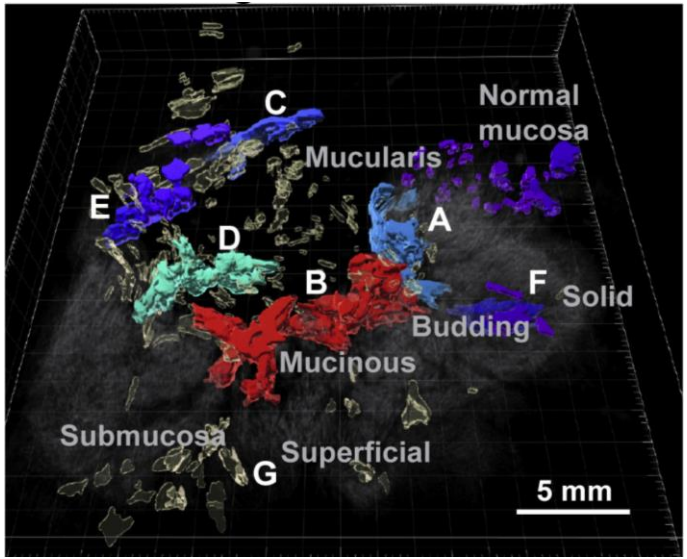
Nirmal et al. *Cancer Discov* (2022) 12 (6): 1518–1541.



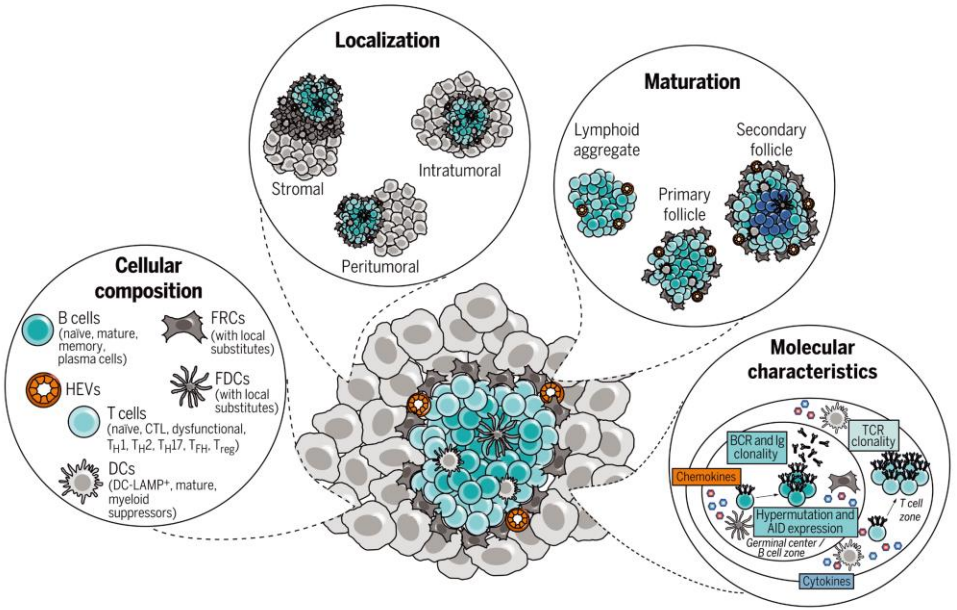
Lin et al., *Cell*, Volume 186(2), 2023.

3D Interrogations

An Example: Tertiary Lymphoid Structure (TLS) Networks



Lin et al., Cell, Volume 186(2), 2023.



Schumacher and Thommen, Science 375, 39, 2022.