

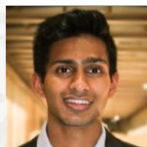
SenNet

Why + How We Construct the Human Reference Atlas

Katy Börner
(CODCC, Indiana University)

February 22, 2023

MC-IU HuBMAP+SenNet Team in Bloomington, IN



Avinash Boppana
Research Consultant



Katy Börner
MC-IU PI
CNS Director



Bruce Herr II
Sr. Systems Architect/PM



Mark Musen
Professor of Medicine
(Biomedical Informatics) and
of Biomedical Data Science



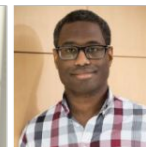
**David
Osumi-Sutherland**
Ontologist



Andrea Radtke
Associate Scientist/Staff
Scientist



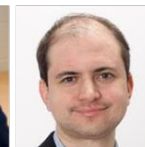
Lisel Record
MC-IU PM
CNS Associate Director



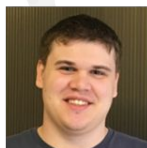
David Van Valen
Assistant Professor of
Biology and Biological
Engineering & Investigator



Fusheng Wang
Associate Professor of
Biomedical Informatics
and Computer Science



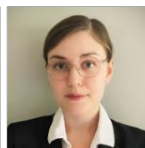
Griffin Weber
Associate Professor
of Medicine



Daniel Bolin
Software Developer



Andreas Bueckle
Research Scientist



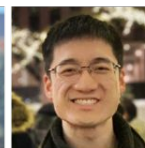
Kate Gustilo
Research Analyst



Josef Hardi
Software Developer



Yashvardhan Jain
Research Software Engineer
(Machine Learning)



Edward Lu
Software Developer



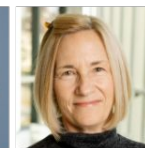
Libby Maier
User Experience Designer



Matthew Martindale
Center Assistant



Ellen Quardokus
Sr. Research Analyst



Nancy Ruschman
Project Manager



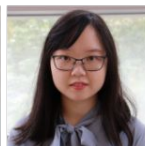
Devin Wright
PM Assistant



Rachel Bajema
2D Medical Illustrator



Supriya Bidanta
Research Assistant



Lu Chen
PhD Student



Xiaojie Fan
PhD Student



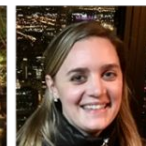
Aashay Gondalia
Research Assistant



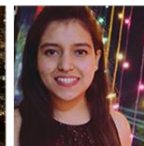
Yingnan Ju
Machine Learning



Shriya Mandarapu
Research Assistant



Heidi Schlein
3D Medical Illustrator



Naveksha Sood
Research Associate



Todd Theriault
Technical Writer



Larry Zhang
PhD Student

Principal Investigator,
Co-Principal Investigators,
and Consultants

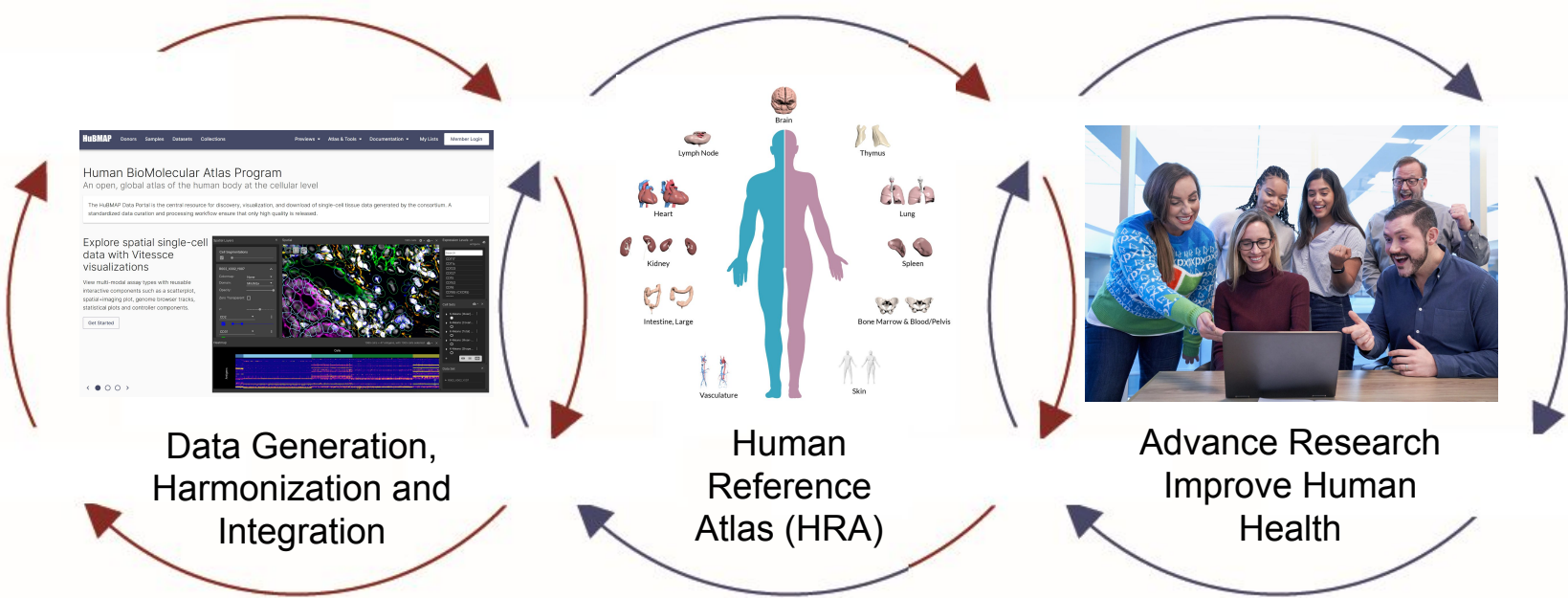
Full Time Staff

Part Time Staff
and Students

Funded by HuBMAP and SenNet and the ATLAS efforts within KPMP, GUDMAP4, CFDE.



Why construct a Human Reference Atlas (HRA)?



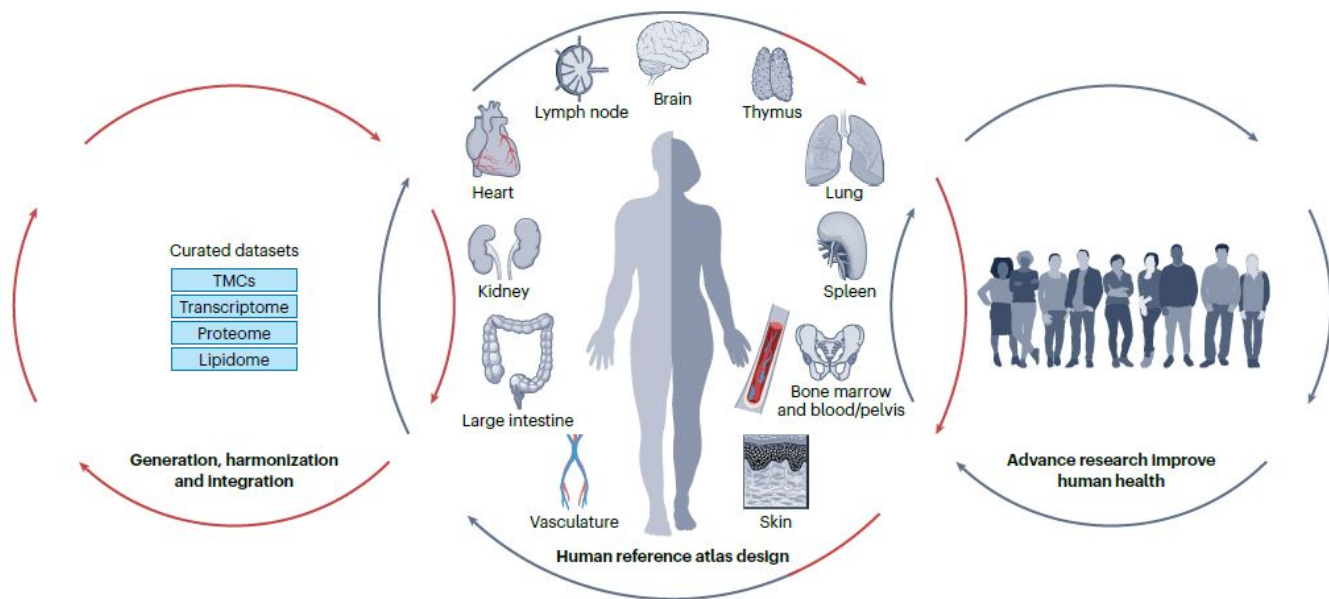


Fig. 5 | Schematic of the SenNet Consortium goals. SnC atlas building requires a framework for layering data. Data generated by the TMCs and TDA sites are input into the CODCC along with associated metadata. The datasets are organized and de-identified (curation), then analyzed and integrated. The goal is to create an atlas and public database of curated data that can be searched, analyzed and visualized as 3D images of organs using unified annotations. High-quality experimental data are needed to create a human reference atlas. The evolving reference atlas supports data standardization and federation, making it possible to integrate data from different specimens, laboratories and assay types. The atlas characterizes the healthy human—from the whole body down to the single-

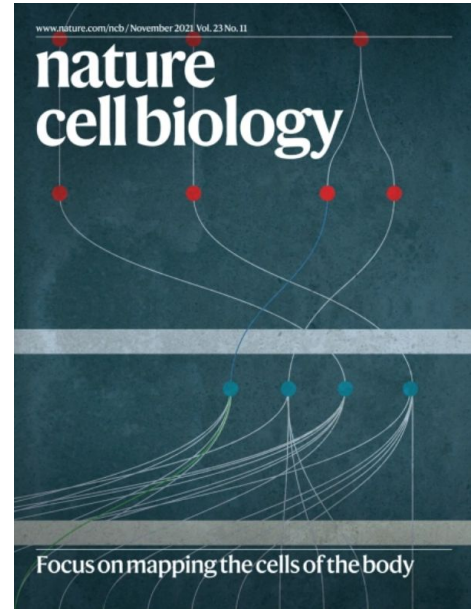
cell level; it can be compared across ages and diseases to understand differences, advance research and improve human health. Use case scenarios for different stakeholders (researchers, practitioners and students) guide atlas construction and usage but also experimental data acquisition and analysis. Of note, diversity in terms of human participant gender, race and socioeconomic status is emphasized in SenNet. However, these variables may impact SnC heterogeneity even further, meaning that, in the timeframe of the initial grants, statistically meaningful characterization of SnCs across diverse populations might not be achieved.

Defining the Human Reference Atlas (HRA)

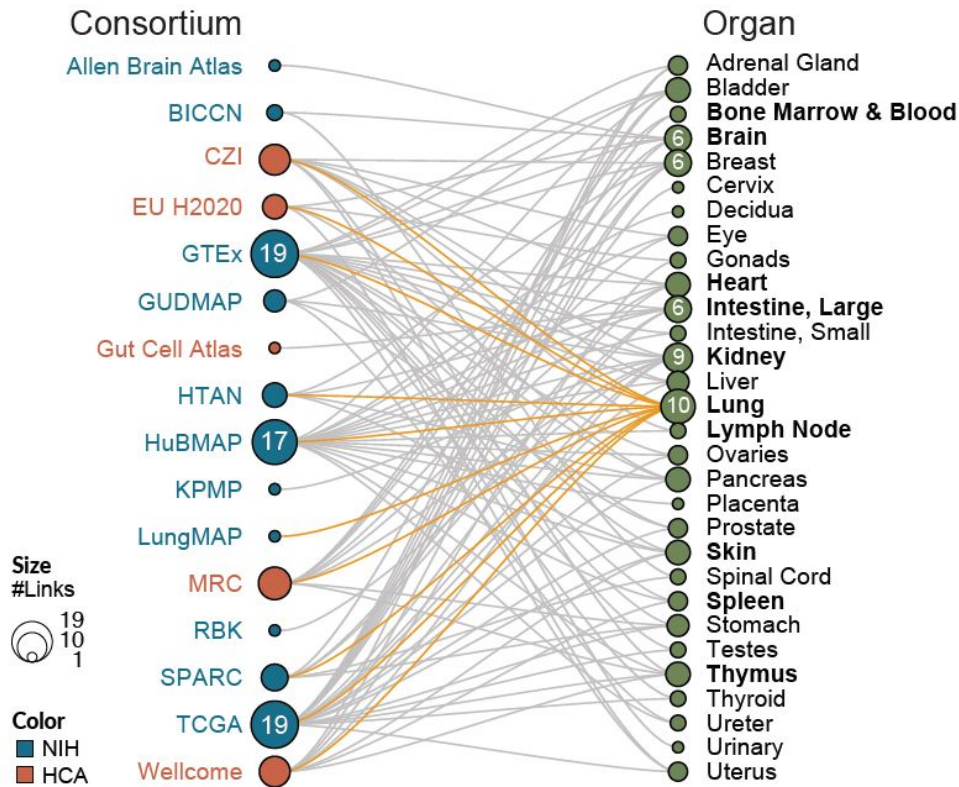
The Human Reference Atlas (HRA)

1. defines the 3D space and shape of anatomical structures and cell types that are of biomedical relevance plus the biomarkers used to characterize them. Anatomical structures, cell types and biomarkers are validated and represented in/added to ontologies (Uberon/FMA, CL, HGNC).
2. defines how new datasets can be mapped to the HRA, e.g., spatially using the Visible Human CCF or Vasculature CCF, via ASCT+B ontology terms/IDs, or via gene expression data as in Azimuth.
3. it is
 - authoritative (there exists expert agreement and it was validated by data),
 - computable (supports API queries, UIs),
 - published as LOD (connected to gene, disease, and other ontologies and data),
 - open (anyone can use the HRA data and code), and
 - continuously evolving (e.g., as new technologies become available).

<https://www.nature.com/articles/s41556-021-00788-6>



Constructing the Human Reference Atlas – Together!



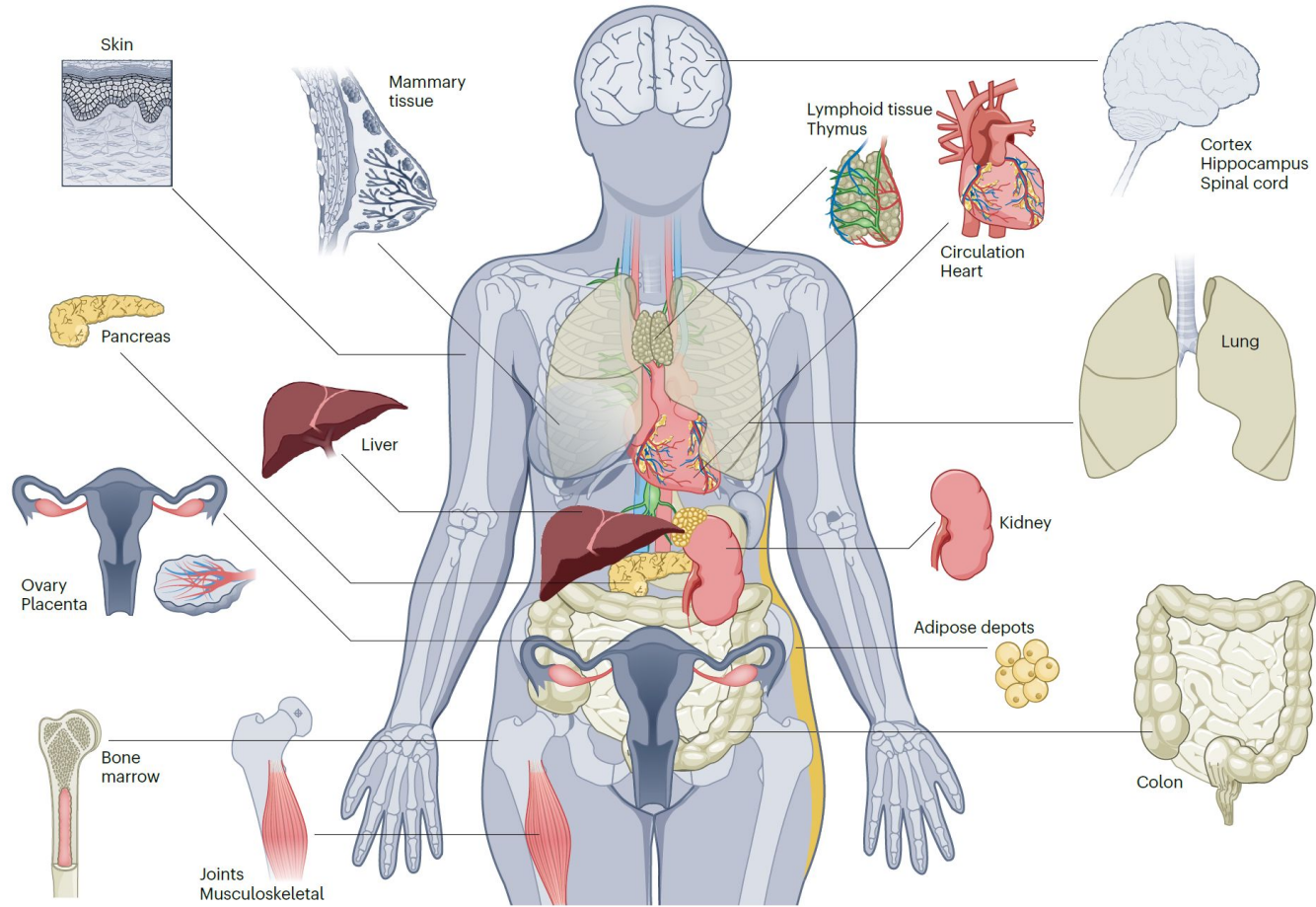


Fig. 2 | Organs in which SnCs will be mapped by SenNet. Human tissues in which SnCs will be identified and characterized by the SenNet Consortium to produce 4D atlases of senescence across the lifespan of humans.

Assay Types

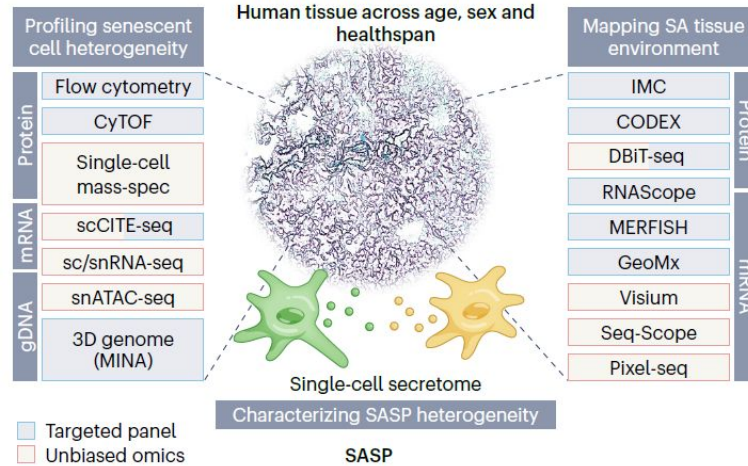


Fig. 3 | Overview of technologies that will be implemented and developed by SenNet Consortium scientists to detect, characterize and spatially map the location of SnCs. CyTOF, cytometry by time-of-flight; scCITE-seq, cellular indexing of transcriptomes and epitopes by sequencing; sc/snRNA-seq, single-cell or single-nucleus RNA sequencing; snATAC-seq, single-nucleus assay for transposase-accessible chromatin using sequencing; MINA, multiplexed imaging of nucleome architectures; IMC, imaging mass cytometry; CODEX, co-detection by indexing immunofluorescence; DBIT-seq, deterministic barcoding in tissue for spatial-omics sequencing for co-mapping mRNAs and proteins; RNAScope, RNA in situ hybridization visualization of single molecules; MERFISH, multiplexed error-robust fluorescence in situ hybridization; GeoMx, NanoString GeoMx digital spatial profiling; Visium, Visium 10x Genomics molecular profiling; Seq-Scope, a spatial barcoding technology with spatial resolution comparable to optical microscopy; Pixel-seq, polony-indexed library sequencing.

Anatomical Structures (AS)

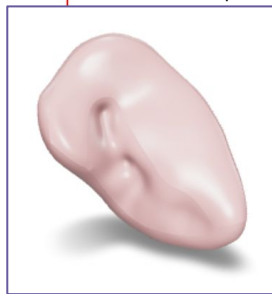
Cell Types (CT)

Biomarkers (B)

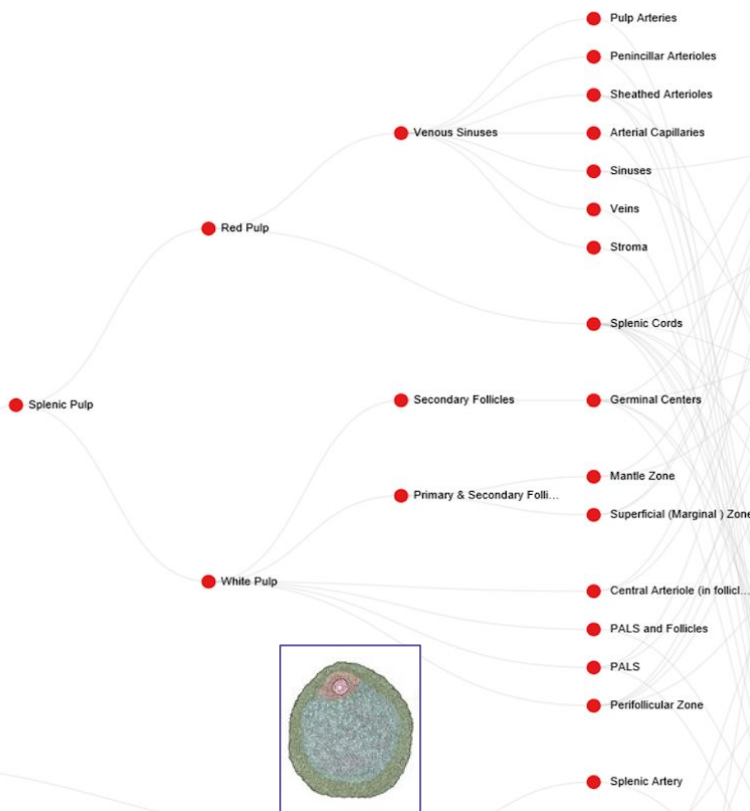
Partonomy Tree
part_of

SenNet
Organs

VHP F Spleen



Spleen



White pulp of spleen

Typology Tree
is_a

Bimodal network describing which CT are located_in what AS

- adventitial stromal cell
- B cell
- Dendritic cell
- Endothelial
- Endothelial cell
- Erythrocytes
- fibroblast
- Fibroblastic reticular cell
- Follicular Dendritic cell
- Granulocytes
- Littoral cell
- Lymphatic endothelium
- macrophage
- Monocytes
- Myofibroblast
- neurons
- NK cell
- Plasma cell
- Plasmablasts
- Platelets

Bimodal network describing which B characterize what CT

BG - Genes
BP - Proteins

- CD10
- CD11b
- CD11c
- CD138
- CD14
- CD141
- CD15
- CD163
- CD19
- CD20
- CD21
- CD22
- CD23+
- CD235a
- CD27
- CD27-
- CD271
- CD271-
- CD3
- CD3-
- CD31
- CD34
- CD4
- CD4 (helper)
- CD41

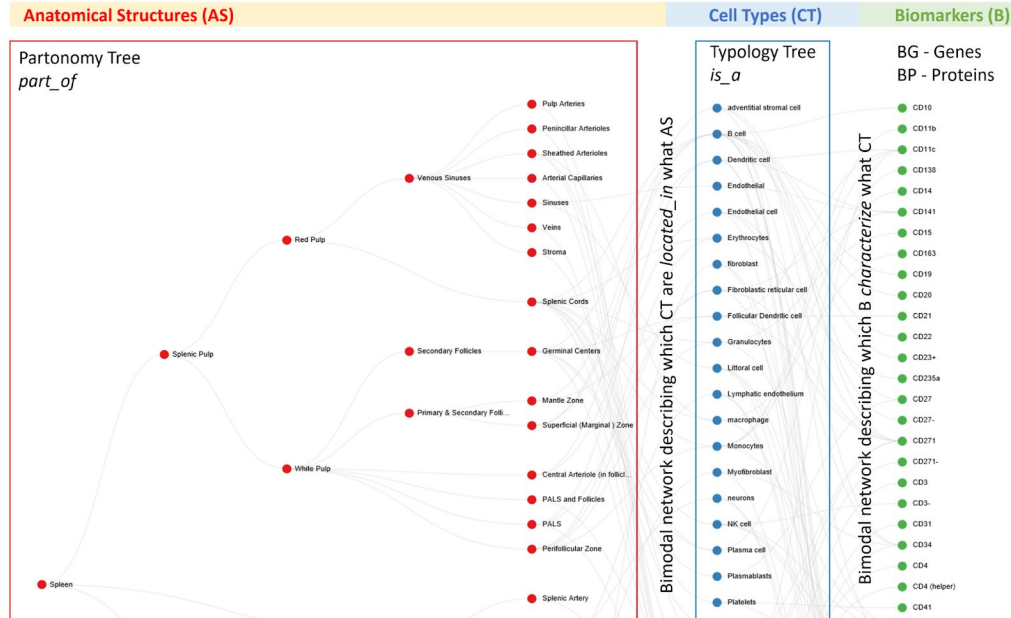
SenNet
Biomarkers

HRA Validation/ Expansion

2D/3D Maps
& Ontology
Crosswalks



New ATLAS publications



New ATLAS datasets

**Azimuth
Maps**
**Validated
Antibody
Panels
(OMAPs)**

BF – Proteoforms
BL – Lipids
BM – Metabolites

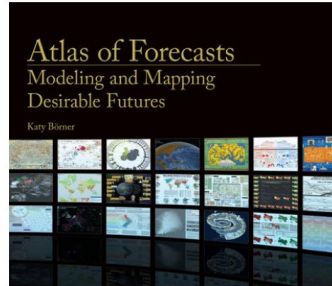
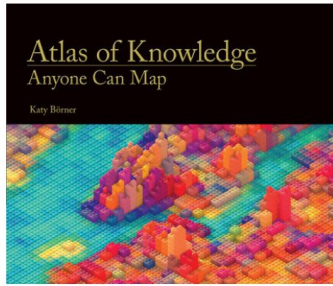
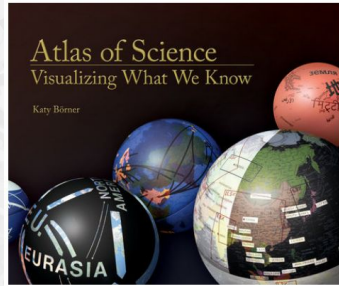


Atlas Construction



Atlas Construction

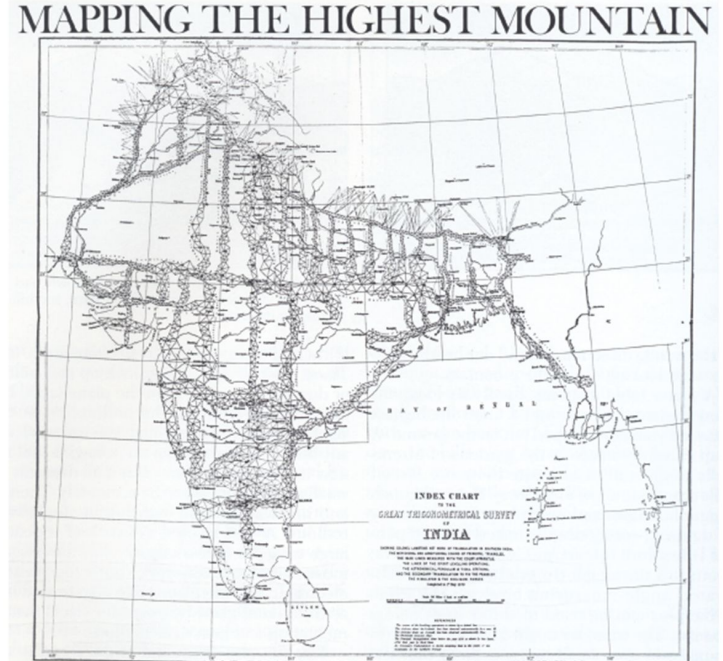
Requires careful data collection and processing, 100% provenance so all results can be reproduced.



<https://mitpress.mit.edu/60-off-the-atlas-trilogy-from-katy-borner/>

History of Map Mapmaking in *Atlas of Science*

For generations, a vast network of repeating sightline triangles was meticulously measured and recorded. What resembles a pattern of eyelashes on the northern border represents the sightlines to stations built above treetops. While analyzing the triangles in the calculating offices of Calcutta, the mapmakers discovered the highest peak in the world: Mount Everest.

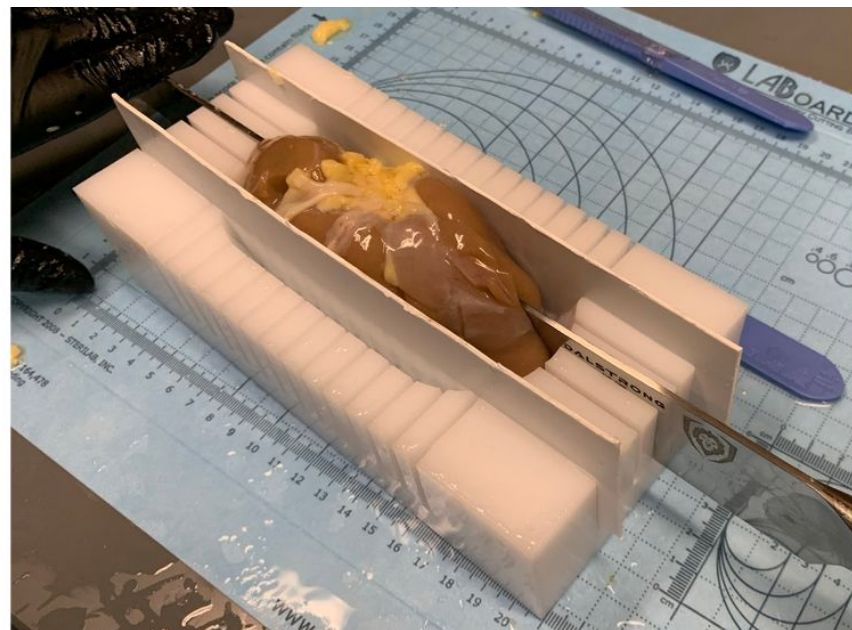
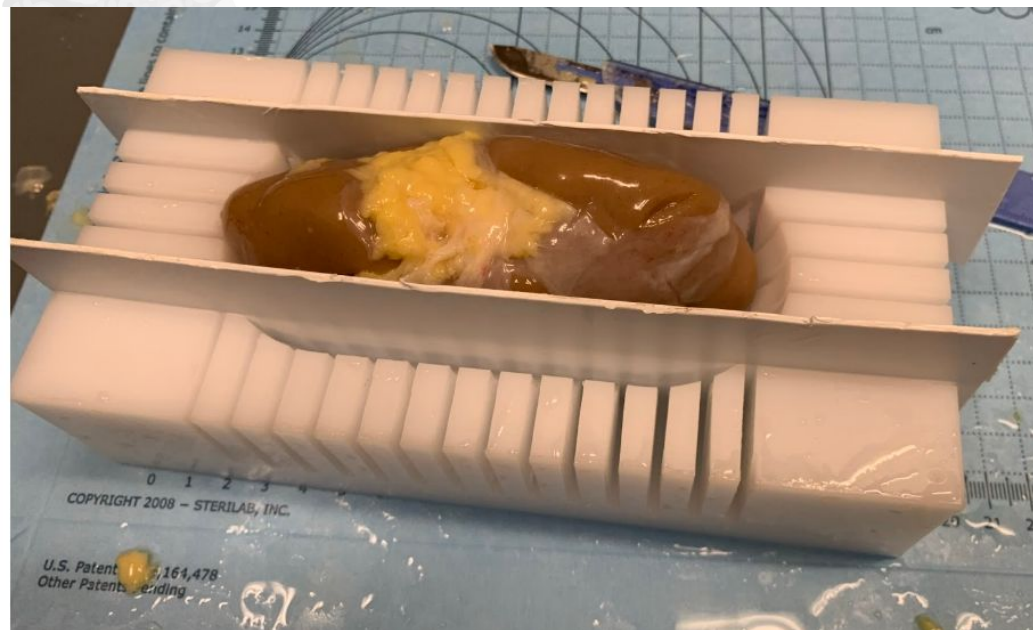


Atlas Construction

Requires careful data collection and processing, 100% provenance so all results can be reproduced.



Fig 2. Millitome process for the kidney (from left to right): Digital 3D model of left male kidney, millitome for the lower half of the kidney with 7 x 14 blocks, ice cube tray holding a subset of the tissue blocks, a screenshot showing 98 blocks registered in the EUI.



VU presented process in ASCT+B WG Meeting #22 on Jan 12, 2022, 11a ET



VU presented process in ASCT+B WG Meeting #22 on Jan 12, 2022, 11a ET

Atlas Construction



Requires careful data collection and processing, 100% provenance so all results can be reproduced.

Please make sure to generate/share for each tissue block/section/suspension

- All essential donor, organ, sample, and assay metadata
- Spatial RUI registration data
- High-resolution histopathology images--used for AS and FTU segmentation
- scRNAseq data--to generate cell type annotations via Azimuth
- CODEX/CellDive/MxIF--use/contribute to OMAPs, see next slide

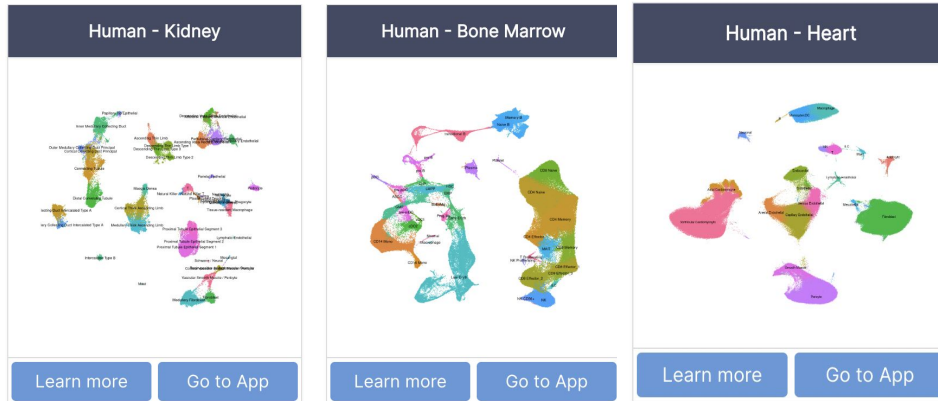
In addition, please consider

- Running the assays on the same or adjacent tissue sections
- Utilization of biomarkers mapped to ASCT+B via Azimuth references and OMAPs

Azimuth Reference Mapping

Mapping to Azimuth Single-cell References:

- Enables integration, re-use, and comparison of data across labs and consortia
- Encourages community adoption of ontologies and standards
- Projects HuBMAP data into consistent cell labels



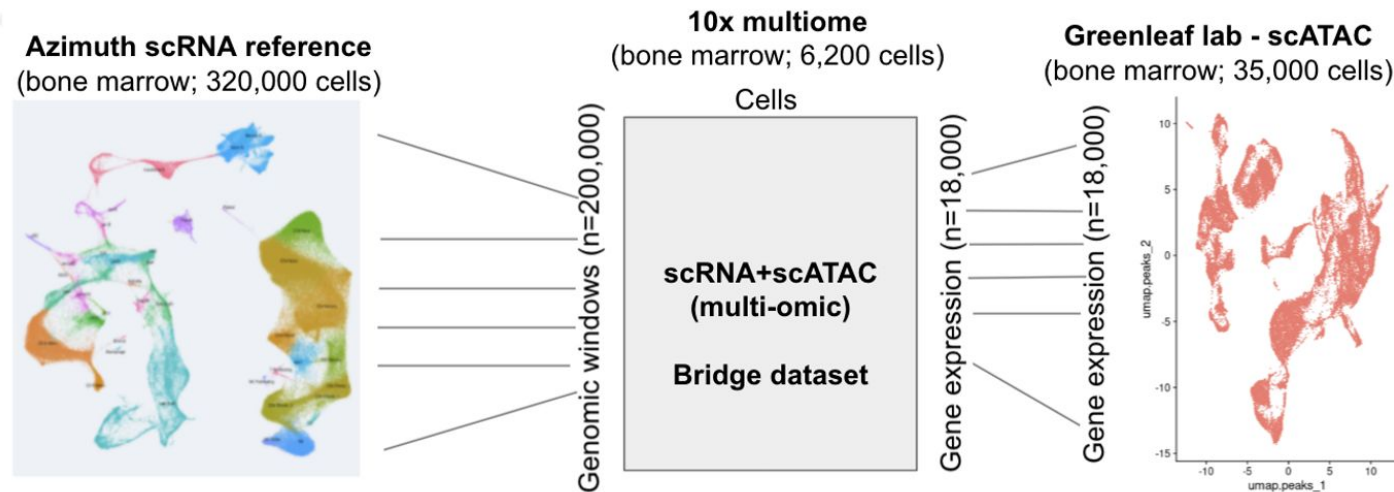
Azimuth: Bridge Integration to Annotate/Map scATAC-seq Data to HRA

scATAC-seq measures DNA accessibility per cell

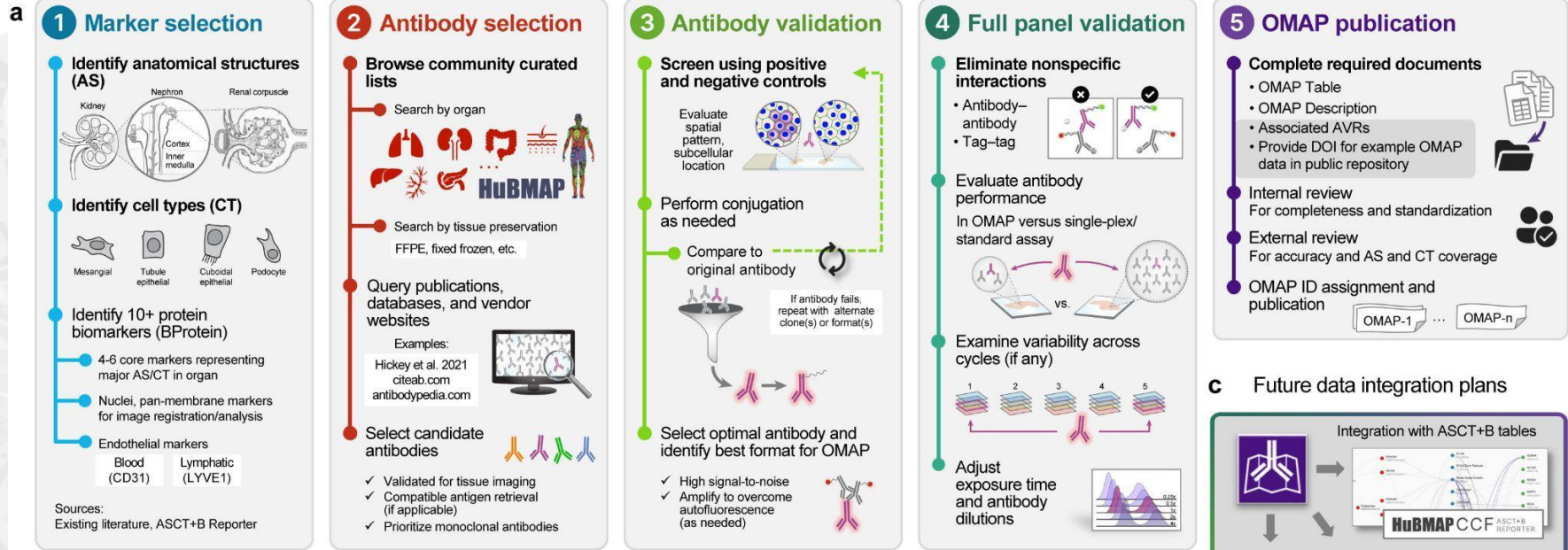
- Data is sparse and difficult to annotate

Goal: Use bridge integration (Hao et al., 2022) to map scATAC-seq query to scRNA-seq reference

- Learn dictionary representation of RNA reference and ATAC query to transfer annotations

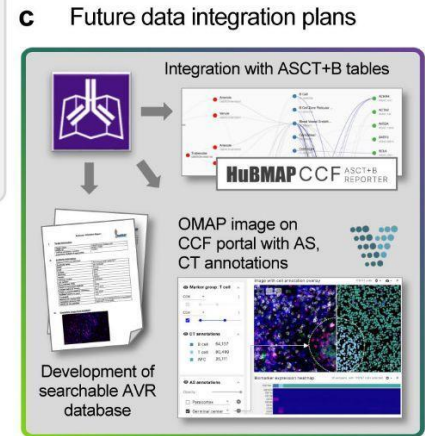


Organ Mapping Antibody Panels (OMAPs)



b Required metadata for multiplexed antibody-based imaging & standardization across related mapping efforts

	1 Target information	2 Antibody information							3 Methodology			4 OMAP-specific			5 Publication									
OMAP	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●								
AVR	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●								
ASCT+B	●	●													●	●								
	UniProt ID	HGNC ID	Target name	Host	Isotype	Clonality	Vendor	RRID	Catalog no.	Recombinant	Lot number	Dilute or concentration	Organ/tissue	Tissue preservation	Imaging method	Protocol DOI	Conjugate	Cycle number	Fluorescent reporter	Core panel	Rationale	Author ORCID	Reviewer ORCID	Dataset DOI



OMAPs How to Contribute (Andrea Radtke, NIAID, NIH)

Goals for OMAPs:

- Offset the considerable time (6-8 months) and cost (~\$30-60,000 in 2022 USD) associated with creating such resources de novo
- Standardize data acquisition for multiplexed tissue imaging studies
- Empower construction of atlases from healthy and diseased human tissues
- Support the spatial biology community by aggregating highly cited antibody clones
- Identify essential markers for anatomical structures and cell types in diverse human organs
- [SOP: Construction of Organ Mapping Antibody Panels for Multiplexed Antibody-Based Imaging of Human Tissues](#)
- [Frequently Asked Questions \(FAQs\) for OMAPs](#)
- [OMAP table template](#)
- [OMAP description document template](#)

Interested in contributing to OMAPs?

Contact:

Andrea Radtke andrea.radtke@nih.gov

Ellen Quardokus ellenmq@indiana.edu

Michael Caldwell michael.caldwell@northwestern.edu

Existing OMAPs

Choose CCF-HRA Release version: **3rd HRA Release (v1.2), June 2022**

OMAP ID	Organ	Tissue Preservation Method	Multiplexed antibody-based imaging method	#AS	#CT	#BP
OMAP-1	Lymph Node	Fixed Frozen	IBEX	29	31	40
OMAP-2	Intestines	Fresh Frozen	CODEX	42	29	51
OMAP-3	Kidney	Fresh Frozen	CODEX	30	37	26
OMAP-4	Skin	FFPE	Cell DIVE	16	15	18
OMAP-5	Liver	Fresh Frozen	SIMS	17	16	20
OMAP-6	Pancreas	FFPE	CODEX	3	9	12
OMAP-7	Lung	FFPE	Cell DIVE	50	42	30

Totals: 187 179 197

<https://hubmapconsortium.github.io/ccf/pages/omap.html>



Human Reference Atlas Standard Operating Procedures

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[Using a Millitome](#)

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[Manual Segmentation of Tissue](#)

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[Authoring ASCT+B Tables](#)

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Creating Crosswalks Between ASCT+B Tables and Azimuth Reference Maps

Mapping Experimental Data to the HRA Using OMAPs or Azimuth

[ASCT+B Table Communications](#)

[3D Reference Object Library](#)

[Creating 3D Models from Datasets](#)

Creating Crosswalks between ASCT+B Tables and 3D Reference Objects

[3D Reference Object Approval](#)

Using 3D Reference Objects

2D Functional Tissue Unit (FTU) Reference Object Library

[Creating 2D Illustrations of Functional Tissue Units](#)

[Style Guide: Human Reference Atlas 2D Functional Tissue Unit \(FTU\) Illustrations](#)

[Creating a Crosswalk between ASCT+B Tables and 2D Functional Tissue Unit Models](#)

HRA Validation and Review

Internal Validation of ASCT+B Tables, and 2D and 3D Reference Objects

External Review of ASCT+B Tables

Validation Checks Performed by the DO-CMS

ASCT+B Table Validation with CCF Tools

ASCT+B Reporter Validation Checks

HRA Editorial Process

[Human Reference Atlas Tracking and Publication](#)

Tracking Digital Object Status

Maintaining the HRA Portal

Designing Organ Icons

[Registering Digital Object Identifiers](#)

Publishing CCF.OWL on BioPortal and OLS

HRA Release Process

Planned Changes in HRA Digital Objects for 5th Release (April 1, 2023 Deadline)

Organ	Replied to email inquiry	ASCT+B Table (Authors)	2D FTU	3D Obj	OMAP	
Blood	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Blood Vasculature	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Bone Marrow	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Brain	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Breast	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Eye	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Fallopian Tube	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Heart	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Kidney	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Knee	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Large Intestine	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Liver	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Lung	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Lymph Node	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Lymph Vasculature	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Pancreas	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Peripheral Nervous System	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Placenta Full Term	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Prostate	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Skin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Small Intestine	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Spinal Cord	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Spleen	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Thymus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Uterus	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Ovary	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Tonsil	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Nasal Passage	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Azimuth

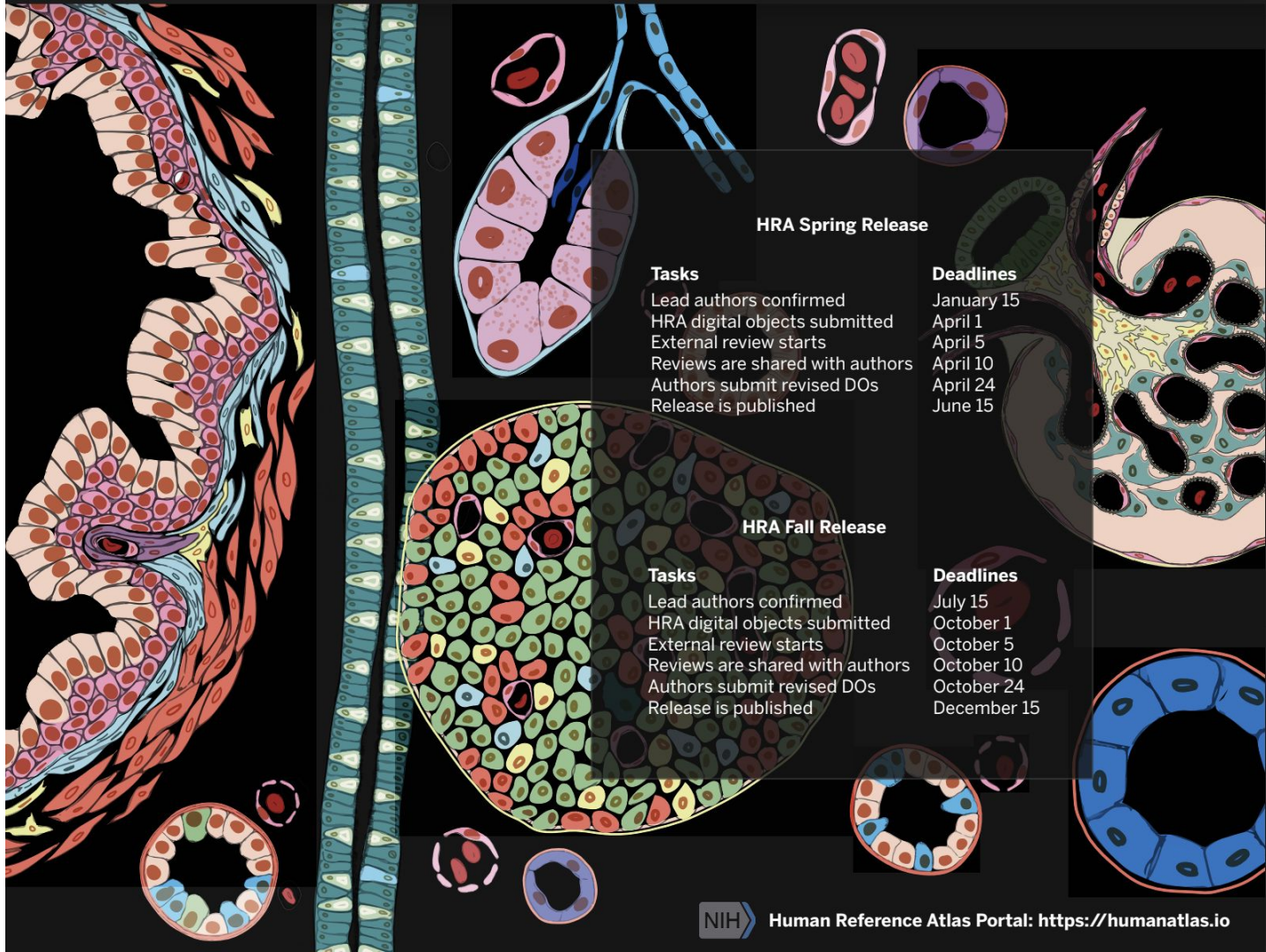
Organs in work:

- Liver
- Small and large intestine
- Skin
- Retina

HRA

29 Organs total

57 3D reference organs (L/R, M/F)



HRA Spring Release

Tasks

Lead authors confirmed
HRA digital objects submitted
External review starts
Reviews are shared with authors
Authors submit revised DOs
Release is published

Deadlines

January 15
April 1
April 5
April 10
April 24
June 15

HRA Fall Release

Tasks

Lead authors confirmed
HRA digital objects submitted
External review starts
Reviews are shared with authors
Authors submit revised DOs
Release is published

Deadlines

July 15
October 1
October 5
October 10
October 24
December 15



Human Reference Atlas



Human Reference Atlas (HRA) Portal

HuBMAP HUMAN REFERENCE ATLAS

Data ▾ CCF Ontology Tools ▾ Training & Outreach ▾ About ▾

Human Reference Atlas 3D Multiscale Biomolecular Human Reference Atlas Construction, Visualization and Usage

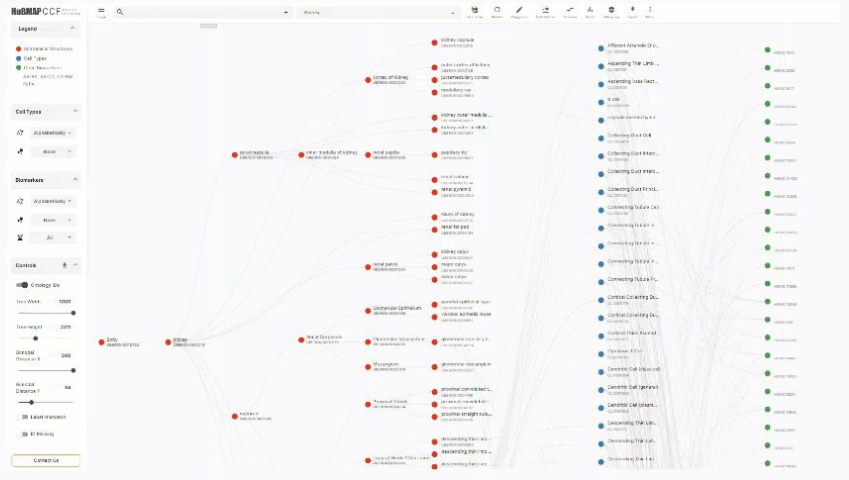
A **Common Coordinate Framework (CCF)** for a human body provides a unique address for each cell in the human body. It is similar to the latitude-longitude system used to navigate a world map.

A **Human Reference Atlas (HRA)** is a comprehensive, high-resolution, three-dimensional atlas of all the cells in the healthy human body. The Human Reference Atlas provides standard terminologies and data structures for describing specimens, biological structures, and spatial positions linked to existing ontologies.

Compare data to the Human Reference Atlas

Use the ASCT+B Reporter tool to explore data in the context of the Human Reference Atlas.

Get Started



<https://humanatlas.io>

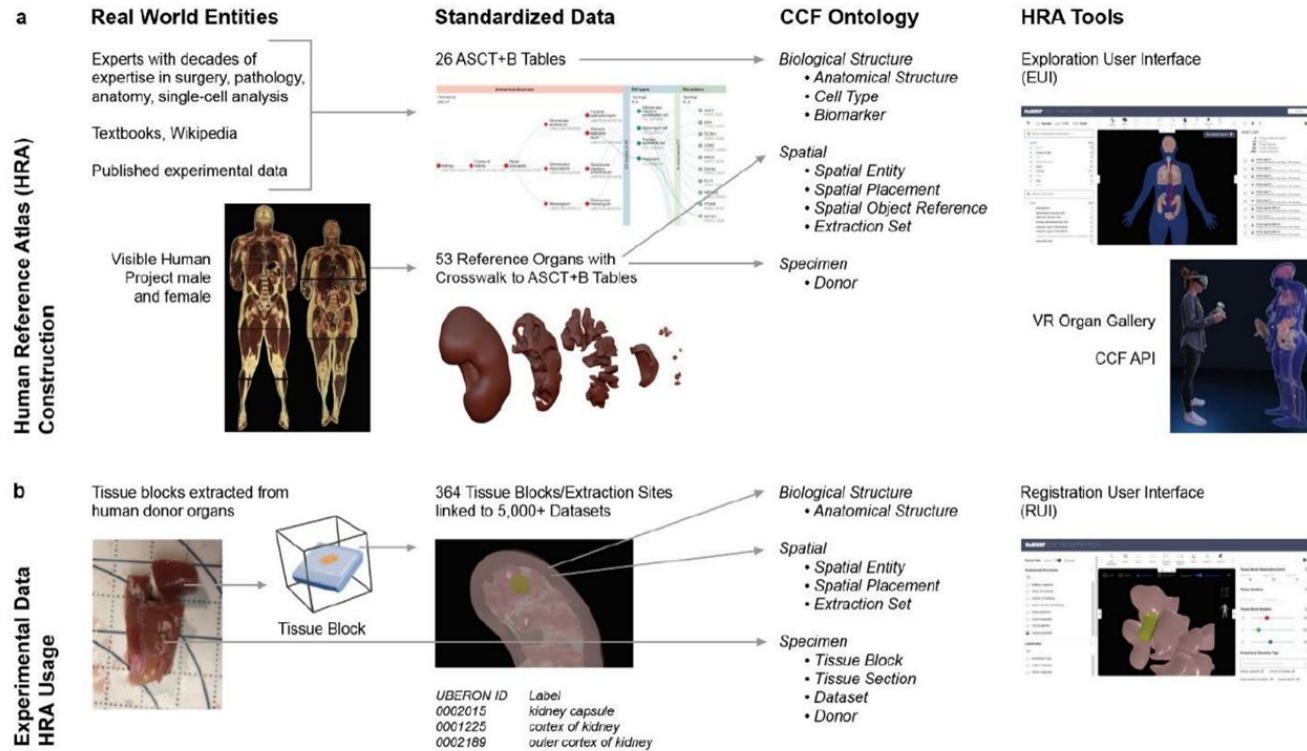
HRA Use Cases: Three key use cases have been identified, discussed with experts, and help prioritize HRA construction and usage:

US#1 API to HRA, e.g, to improve CT annotation

US#2 API to HRA to predict spatial location of tissue

US#3 Exploration of CTs, Bs to understand what changes with age or during disease

Human Reference Atlas data and APIs



Specimen, Biological Structure, and Spatial Ontologies in Support of a Human Reference Atlas

<https://biorxiv.org/cgi/content/short/2022.09.08.507220v1>

Figure 1. From real-world entities, to standardized data, to ontology. a. Human Reference Atlas construction takes real-world data and represents it in standardized data structures that are defined by the interlinked Biological Structure, Spatial, and Specimen ontologies.

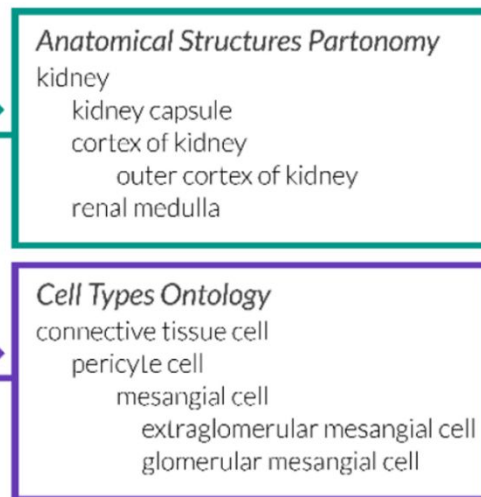
Human Reference Atlas (HRA)

Anatomical Structures, Cell Types, and Biomarkers or ASCT+B tables aim to capture the partonomy of anatomical structures, cell types, and major biomarkers (e.g., gene, protein, lipid or metabolic markers). 3D and 2D reference object capture the shape, size, and spatial composition of ASCT.

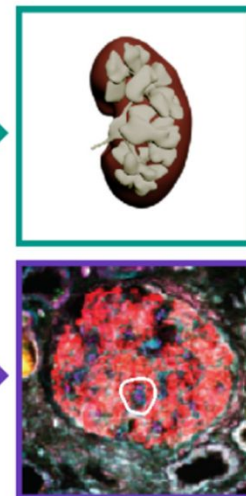
ASCT Table

Structure/Region	Sub structure/Sub region	Cell Type
Renal Corpuscle	Bowman's (glomerular) Capsule/parietal layer	Parietal epithelial Cell
	Bowman's (glomerular) Capsule/visceral layer	Podocyte
	Glomerular Tuft	Capillary Endothelial Cell Mesangial Cell
Tubules	Proximal Tubule	Proximal Tubule Epithelial Cell (general)
		Proximal Convoluted Tubule Epithelial Cell Segment 1
		Proximal Tubule Epithelial Cell Segment 2
		Proximal Tubule Epithelial Cell Segment 2
	Loop of Henle, Thin Limb	Descending Thin Limb Cell (general)
		Ascending Thin Limb Cell (general)
	Loop of Henle, Thick Limb	Thick Ascending Limb Cell (general)
		Cortex-TAL Cell
	Distal Convolution	Medulla-TAL Cell
		TAL-Macula Densa Cell
Distal Convoluted Tubule Cell (general)		
Connecting Tubule	DCT Type 1 Cell	
	DCT Type 2 Cell	
	Connecting Tubule Cell (general)	
		CNT-Principal Cell

Ontology



3D Reference Object Library



Sections

- Description
- Organ
- info
- Azimuth
- Search

Reference-Based Analysis

Open Azimuth App

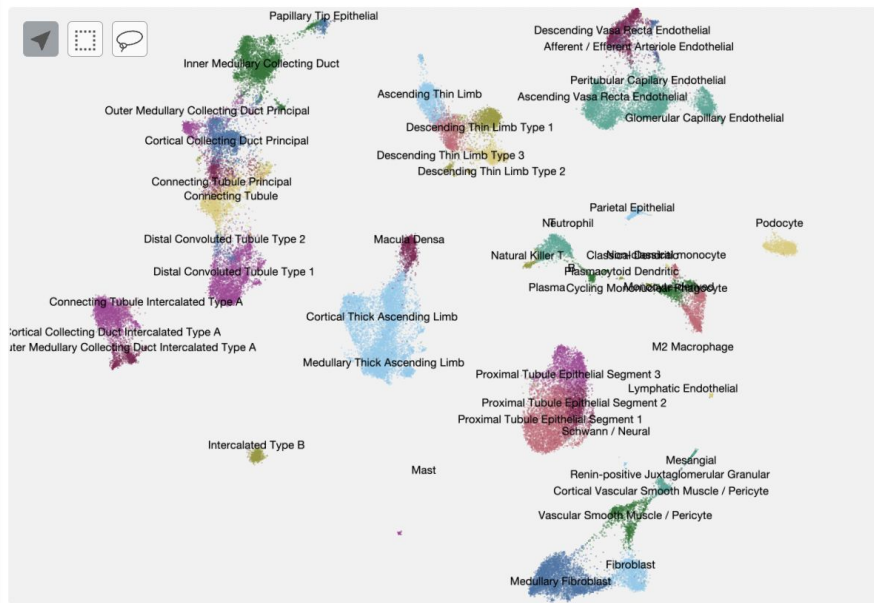
Modalities
 RNA
 Nuclei in reference
 64,693
 Reference dataset
[Lake et al, bioRxiv 2021](#)



Scatterplot (UMAP)

64693 cells

Cell Sets



Cell Sets

- ▶ annotation.I3
- annotation.I2
- annotation.I1
-

+

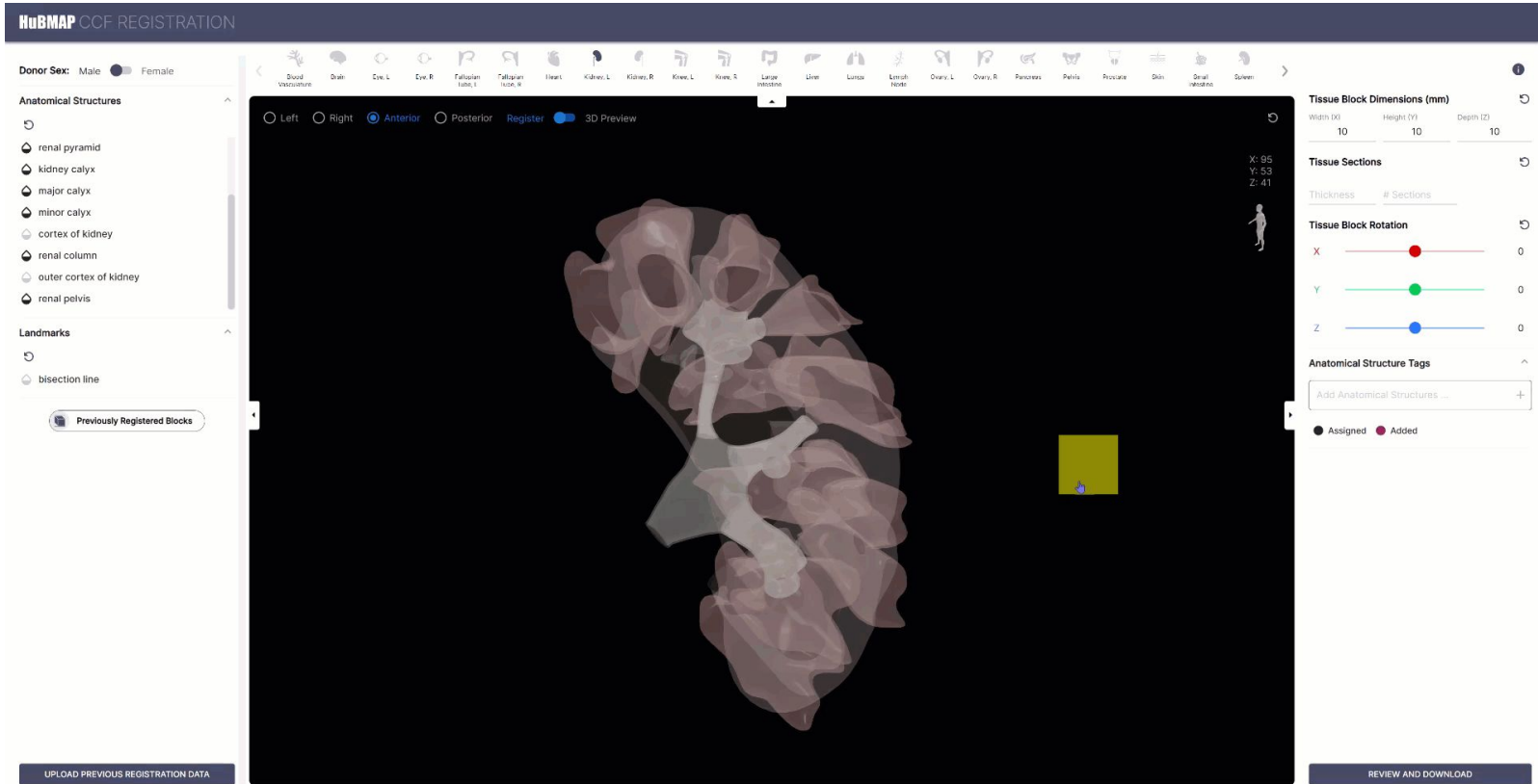
⏮ ⏪ ⏩ ⏭

Expression Levels 43513 genes

Search

- 5S-rRNA
- 7SK
- 7SK.1
- 7SK.2
- 7SK.3
- A1BG
- A1BG-AS1
- A1CF

Registration User Interface (RUI)



<https://hubmapconsortium.github.io/ccf-ui/rui>

RUI supports 57 organs (L/R, M/F) with 1,542 anatomically correct 3D anatomical structures.

Donor Sex: Male Female

Anatomical Structures

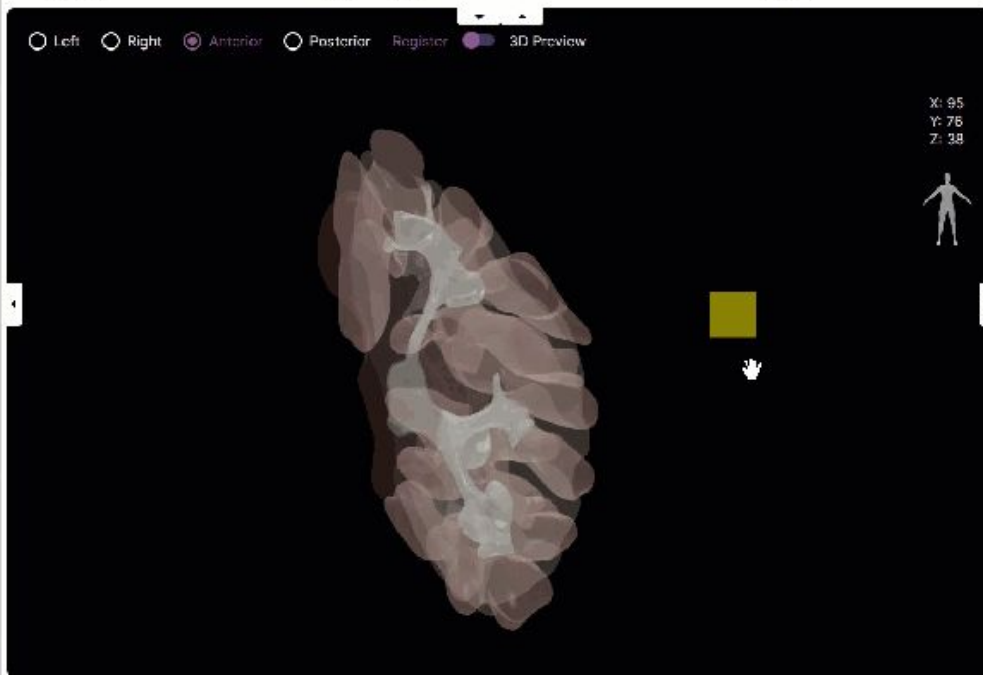
- renal pyramid
- cortex of kidney
- renal column
- outer cortex of kidney
- kidney calyx
- minor calyx
- major calyx
- renal pelvis

Landmarks

- bisection line

 Previously Registered Blocks

UPLOAD PREVIOUS REGISTRATION DATA



Tissue Block Dimensions (mm)

Width (X) 10 Height (Y) 10 Depth (Z) 10

Tissue Sections

Thickness # Sections

Tissue Block Rotation

X

Y

Z

Anatomical Structure Tags

Add Anatomical Structures ...

Assigned Added

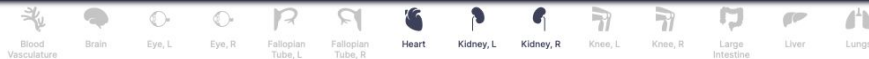
REVIEW AND DOWNLOAD

Exploration User Interface (EUI)

HuBMAP CCF EXPLORATION

LOGIN

Sex: **Both** Age: **1-110** BMI: **13-83**

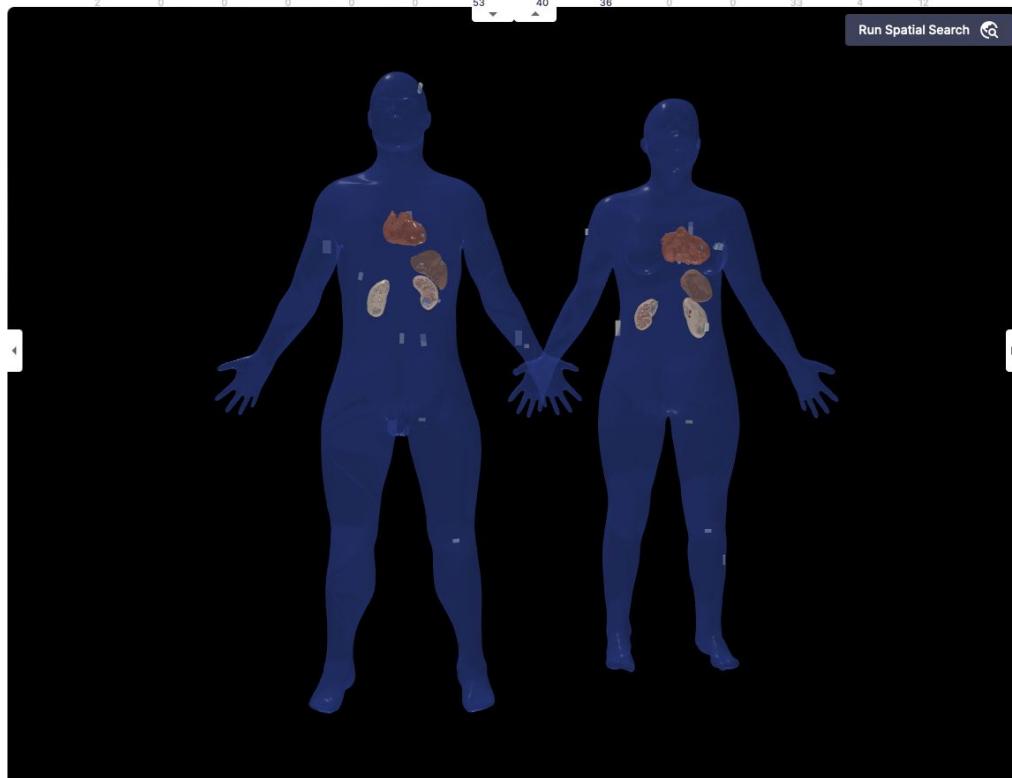


Search anatomical structures...

body	377
brain	0
lymph node	33
eye	0
fallopian tube	0
heart	53
kidney	76
knee	0
liver	4
lung	11
ovary	1
pancreas	4
pelvis	0

Search cell types...

cell	377
absorptive	43
adventitial stromal cell	67
afferent neuron cell	4
airway deuterosomal cell	12
alveolar type 1 fibroblast	12
alveolar type 2 fibroblast	12
amnion mesenchymal stromal cell (amsc)	0
apocrine cell	33
articular chondrocyte	0
astro I1 fgfr3 serpin12 primary motor cortex	0
astro I1-6 fgfr3 aqp1 primary motor cortex	0
astro I1-6 fafr3 plca1 primary motor cortex	0



body | cell

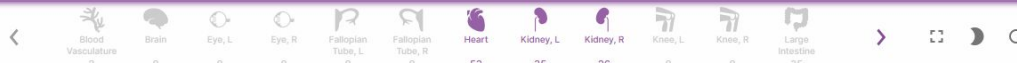
9 Tissue Data Providers
146 Donors
377 Tissue Blocks
622 Tissue Sections
1286 Tissue Datasets

- Apical Septum Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Right Ventricle Free Wall Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Septum Left Ventricle Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Septum Left Ventricle Male
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Left Ventricle Apex Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Left Ventricle Apex Male
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Anterior Left Ventricle Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Anterior Left Ventricle Male
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Lateral Left Ventricle Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Lateral Left Ventricle Male
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle posterior Left Ventricle Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Apical Septum Male
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle posterior Left Ventricle Male
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Septum Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA

<https://portal.hubmapconsortium.org/ccf-eui>

EUI supports search for 1,542 AS and 953 cell types. Will soon add search for biomarkers.

Sex: Both Age: 1-110 BMI: 13-83

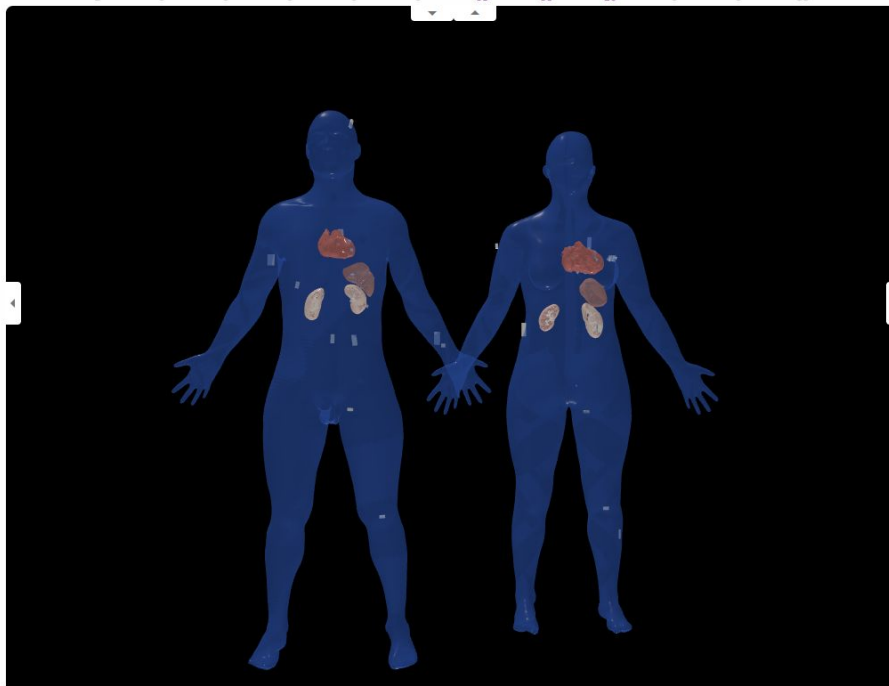


Search anatomical structures...

body	344
brain	0
lymph node	28
eye	0
fallopian tube	0
heart	53
kidney	61
knee	0
liver	4
lung	11
ovary	1

Search cell types...

cell	344
absorptive	47
absorptive	41
adipocyte	53
adipocyte	98
adipocyte	16
adventitial stromal cell	56
afferent arteriole endothelial cell	61
airway smooth muscle	11
alveolar macrophage	11
apocrine	35



body | cell

9	Tissue Data Providers
133	Donors
344	Tissue Blocks
576	Tissue Sections
1083	Tissue Datasets

- CoverNephrectomy**
Entered 5/18/2020, Seth Winfree, KPMP-IU/O...
- Patient A Cortical biopsy**
Entered 5/18/2020, Seth Winfree, KPMP-IU/O...
- Patient B Cortical biopsy**
Entered 5/18/2020, Seth Winfree, KPMP-IU/O...
- Apical Septum Female**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Right Ventricle Free Wall Female**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Septum Left Ventricle Female**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Septum Left Ventricle Male**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Left Ventricle Apex Female**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Left Ventricle Apex Male**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Anterior Left Ventricle Female**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Anterior Left Ventricle Male**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Middle Lateral Left Ventricle Female**
Entered 3/16/2021, Peter Hanna, SPARC/UCLA

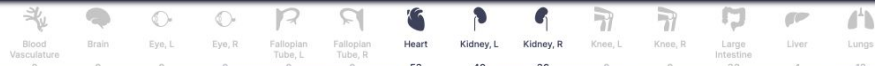
Note: The screenshot shows HuBMAP data

Exploration User Interface (EUI)

HuBMAP CCF EXPLORATION

LOGIN

Sex: **Both** Age: **1-110** BMI: **13-83**



Search anatomical structures...

body	377
brain	0
lymph node	33
eye	0
fallopian tube	0
heart	53
kidney	76
knee	0
liver	4
lung	11
ovary	1
pancreas	4
pelvis	0

Search cell types...

cell	377
absorptive	43
adventitial stromal cell	67
afferent neuron cell	4
airway deuterosomal cell	12
alveolar type 1 fibroblast	12
alveolar type 2 fibroblast	12
amnion mesenchymal stromal cell (amsc)	0
apocrine cell	33
articular chondrocyte	0
astro I1 fgfr3 serpinl2 primary motor cortex	0
astro I1-6 fgfr3 aqp1 primary motor cortex	0
astro I1-6 fafr3 plca1 primary motor cortex	0



body | cell

9	Tissue Data Providers
146	Donors
377	Tissue Blocks
622	Tissue Sections
1286	Tissue Datasets

Female, Age 44, BMI 28.0
Entered 12/26/2019, Jamie Allen, TMC-Vande... ^

Registered 6/10/2020, Jamie Allen, TMC-Van...
17 x 18 x 3 millimeter, 1.5 millimeter, fresh...

0 |-----| 2

MALDI MALDI PAS AF

Registered 12/27/2019, Jamie Allen, TMC-Van...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...

Registered 12/27/2019, Jamie Allen, TMC-Van...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...

Female, Age 44, BMI 28.0
Entered 12/26/2019, Jamie Allen, TMC-Vande... ^

Registered 6/10/2020, Jamie Allen, TMC-Van...
17 x 18 x 3 millimeter, 1.5 millimeter, fresh...

0 |-----| 2

OTHER PAS PAS OTHER

Registered 11/10/2020, Jamie Allen, TMC-Van...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...

Registered 11/10/2020, Jamie Allen, TMC-Van...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...

Apical Septum Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA

Basal Right Ventricle Free Wall Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA

Basal Septum Left Ventricle Female

<https://portal.hubmapconsortium.org/ccf-eui>

More than 5,000 tissue datasets from 4 consortia have been RUI registered.

Exploration User Interface (EUI) - Spatial Search

HuBMAP CCF EXPLORATION

LOGIN

Sex: Both Age: 1-110 BMI: 13-83

Search anatomical structures...

body	377
brain	0
lymph node	33
eye	0
fallopian tube	0
heart	53
kidney	76
knee	0
liver	4
lung	11
ovary	1
pancreas	4
pelvis	0

Search cell types...

cell	377
absorptive	43
adventitial stromal cell	67
afferent neuron cell	4
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apocrine cell	33
articular chondrocyte	0
astro I1 fgfr3 serpin12 primary motor cortex	0
astro I1-6 fgfr3 aqp1 primary motor cortex	0
astro I1-6 fafr3 plca1 primary motor cortex	0

Configure Spatial Search

Donor Sex: Female Organ: Kidney, L Edit

Probing Sphere Radius: 6 mm

Run Spatial Search

Use the keyboard or click a Tissue Block to move the Probing Sphere

X: 65
Y: 38
Z: 39

See demo of spatial search at <https://www.youtube.com/watch?v=UfxMpza towE>

Cell types in lower left are from ASCT+B Table data.

Explore spatial search at <https://portal.hubmapconsortium.org/ccf-eui> and <https://qtexportal.org/home/eui>

<https://portal.hubmapconsortium.org/ccf-eui>

Spatial search API is ready for HuBMAP portal wide usage.

Exploration User Interface (EUI) & Vitesse

HuBMAP CCF EXPLORATION LOGIN

HuBMAP Donors Samples Datasets Other Atlas & Tools Resources User Profile

HBM645.ZQSN.258 Kidney (Right) MALDI IMS

Sections

- Summary
- Visualization
- Provenance
- Metadata
- Files
- Collections
- Contributors
- Attribution

MALDI Imaging MS data collected from the Right Kidney of a 44 year old White Female donor by the Biomolecular Multimodal Imaging Center (BIOMC) at Vanderbilt University. BIOMIC is a Tissue Mapping Center that is part of the NIH funded Human Biomolecular Atlas Program (HuBMAP). Mass Spectrometry images of Lipids were collected with a Bruker Daltonics MALDI timsTOF Flex Prototype at 10 m from m/z 100-2000 in Positive Ion Mode. Support was provided by the NIH Common Fund and National Institute of Diabetes and Digestive and Kidney Diseases (U54 DK120058). Tissue was collected through the Cooperative Human Tissue Network with support provided by the NIH National Cancer Institute (5 UM1 CA183727-08).

Publication Date: 2020-09-08 Modification Date: 2022-02-11

Visualization

Spatial Layers x Spatial

- 700.564 CerP(d40) [checked]
- 701.512 PA(36:1)-I [checked]
- 718.538 PE(34:0)- [checked]
- 707.501 PA(O-38:E) [checked]
- 700.564 CerP(d40) [unchecked]

Data Set x

- VAN0012-RX-103-75-IMS_NegMode_multilayer.ome.tif

body | cell

- 9 Tissue Data Providers
- 146 Donors
- 377 Tissue Blocks
- 622 Tissue Sections
- 1286 Tissue Datasets

Female, Age 44, BMI 28.0
Entered 12/26/2019, Jamie Allen, TMC-Vande...
Registered 6/10/2020, Jamie Allen, TMC-Van...
17 x 18 x 3 millimeter, 1.5 millimeter, fresh_fro...
0 2
MALDI MALDI PAS AF P
Registered 12/27/2019, Jamie Allen, TMC-...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...
Registered 12/27/2019, Jamie Allen, TMC-...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...

Female, Age 44, BMI 28.0
Entered 12/26/2019, Jamie Allen, TMC-Vande...
Registered 6/10/2020, Jamie Allen, TMC-Van...
17 x 18 x 3 millimeter, 1.5 millimeter, fresh_fro...
0 2
OTHER PAS PAS OTHER
Registered 11/10/2020, Jamie Allen, TMC-...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...
Registered 11/10/2020, Jamie Allen, TMC-...
17 x 18 x 1.5 millimeter, 1.5 millimeter, fresh...

- Apical Septum Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Right Ventricle Free Wall Female
Entered 3/16/2021, Peter Hanna, SPARC/UCLA
- Basal Septum Left Ventricle Female

<https://portal.hubmapconsortium.org/ccf-eui>

Works. Need to connect OMAP data to 'Spatial Layers' image channels. TMCs have this info.

Interactive FTUs: Explore CT x B matrices for 19 FTUs across organs--what changes as we age, change BMI?

FTU Library

- ^ Kidney
 - Ascending thin limb
 - Cortical collecting duct
 - Collecting duct (inner medulla)
 - Collecting duct (outer medulla)
 - Descending thin limb
 - Nephron
 - Renal corpuscle
- ^ Large intestine
 - Crypt of Lieberkuhn
- ^ Liver
 - Liver lobule
- ^ Lung
 - Pulmonary alveolar parenchyma
 - Bronchial submucosal gland
- ^ Pancreas
 - Acinus
 - Intercalated duct
 - Islets of Langerhans
- ^ Prostate
 - Prostatic glandular acinus
- ^ Skin
 - Dermal papilla
 - Epidermal ridge
- ^ Spleen
 - Red pulp
 - White pulp
- ^ Thymus
 - Thymus lobule

Renal Corpuscle of the Kidney

50 µm

Cell Types by Gene Biomarkers [Expand](#)

Gene Biomarkers	Protein Biomarkers	Lipid Biomarkers	
Cell Type	Cell Count	VCAM1	CLDN1
parietal epithelial cell	5,758	●	●
glomerular visceral epithelial cell	13,224		
glomerular capillary endothelial cell	2,028		
glomerular mesangial cell	no data		

Gene Expression Mean in FTU	Percentage of cells in FTU

Source Data

1. Kidney Precision Medicine Project
[Ancillary Study Data, Clinical Data, HRT Codebook](#)
2. [Dataset Owner Title]
[<Dataset Title + Link to Dataset>](#)
3. [Dataset Owner Title]
[<Dataset Title + Link to Dataset>](#)
4. [Dataset Owner Title but extremely long and wraps around to the next line as you can see here in this example]
[<Extremely long dataset title that wraps around to the next line as you can see in this example + link to dataset>](#)
5. [Dataset Owner Title]
[<Dataset Title + Link to Dataset>](#)
6. [Dataset Owner Title]

[Illustration](#)

[Embed](#)

[Contact](#)


[HRA Portal](#)

Interactive FTUs: Data

Use Azimuth references + OMAPs to assign ontology aligned CT / B names to bulk or spatially explicit experimental data.


References

Human - PBMC



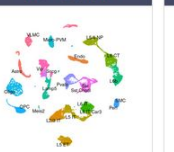
[Learn more](#) [Go to App](#)

Human - Motor Cortex




[Learn more](#) [Go to App](#)

Mouse - Motor Cortex




[Learn more](#) [Go to App](#)

Human - Pancreas




[Learn more](#) [Go to App](#)

Human - Fetal Development



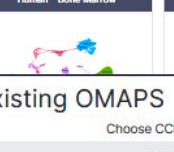
[Learn more](#) [Go to App](#)

Human - Kidney




[Learn more](#) [Go to App](#)

Human - Bone Marrow




[Learn more](#) [Go to App](#)

Human - Lung v2 (HLCA)




[Learn more](#) [Go to App](#)

Human - Tonsil



[Learn more](#) [Go to App](#)

Human - Adipose

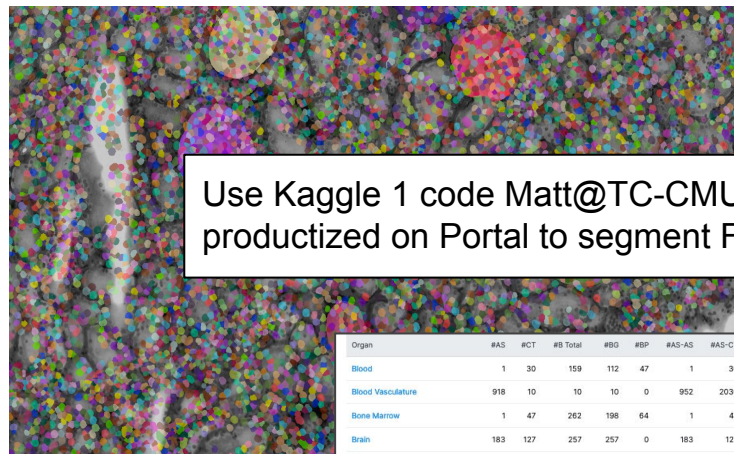


[Learn more](#) [Go to App](#)

Existing OMAPs

Choose CCF-HRA Release version: 3rd HRA Release (v1.2), June 2022

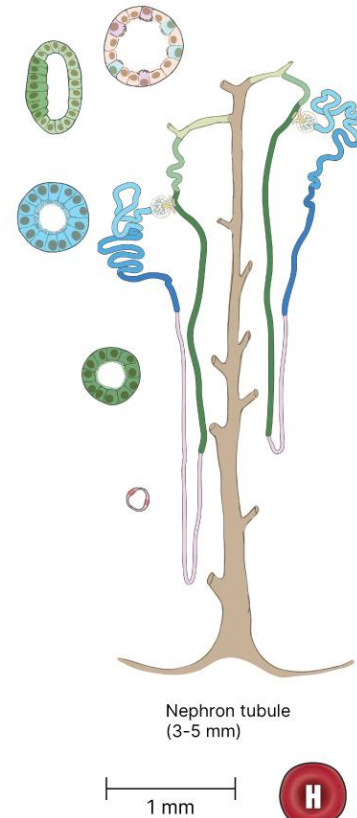
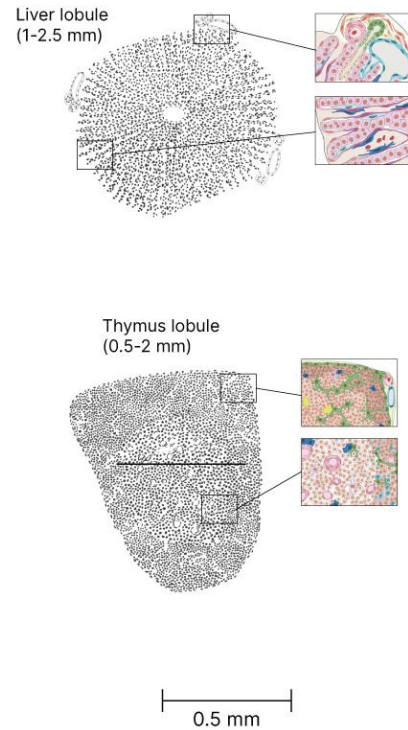
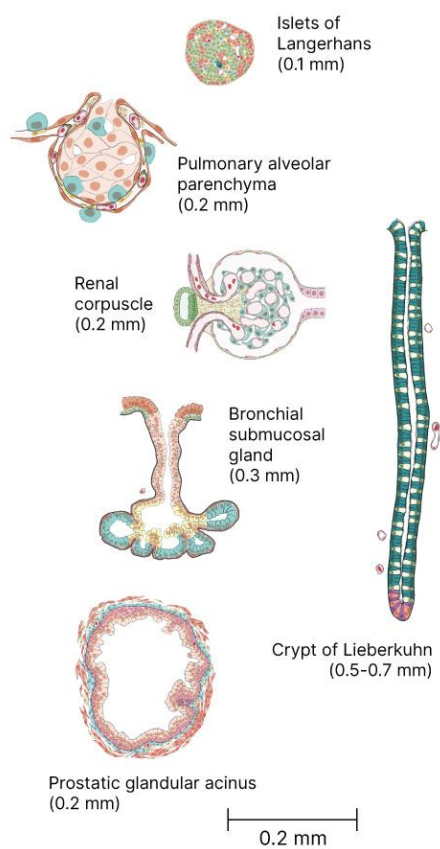
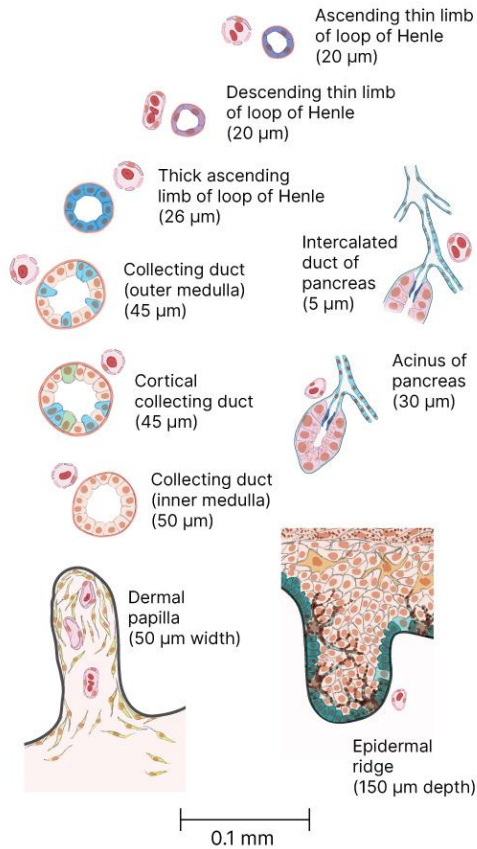
OMAP ID	Organ	Tissue Preservation Method	Multiplexed antibody-based imaging method	#AS	#CT	#BP
OMAP-1	Lymph Node	Fixed Frozen	IBEX	29	31	40
OMAP-2	Intestines	Fresh Frozen	CODEX	42	29	51
OMAP-3	Kidney	Fresh Frozen	CODEX	30	37	26
OMAP-4	Skin	FFPE	Cell DIVE	16	15	18
OMAP-5	Liver	Fresh Frozen	SIMS	17	16	20
OMAP-6	Pancreas	FFPE	CODEX	3	9	12
OMAP-7	Lung	FFPE	Cell DIVE	50	42	30



Use Kaggle 1 code Matt@TC-CMU productized on Portal to segment FTUs.

Organ	#AS	#CT	#B Total	#BG	#BP	#AS-AS	#AS-CT	#CT-B
Blood	1	30	159	112	47	1	30	506
Blood Vasculature	918	10	10	10	0	952	2030	11
Bone Marrow	1	47	262	198	64	1	47	838
Brain	183	127	257	257	0	183	127	346
Eye	26	53	140	61	75	27	58	404
Fallopian Tube	72	18	26	13	13	84	81	27
Heart	50	23	45	45	0	60	183	74
Kidney	57	67	184	184	0	72	75	300
Knee	33	41	12	0	12	33	21	47
Large Intestine	54	57	166	83	83	287	1156	360
Liver	17	31	85	29	56	17	32	116
Lung	76	76	280	191	89	121	168	456
								86
								499
								19
								1
								30
								11
								228
								126
								609
								2
								44
								74
Prostate	4	12	31	31	0	4	12	36
Skin	15	36	70	0	70	17	19	100
Small Intestine	39	48	89	43	46	69	178	131
Spleen	37	60	194	85	109	50	129	421
Thymus	17	51	394	318	76	28	39	603
Ureter	7	14	30	30	0	7	14	61
Urinary Bladder	16	15	30	30	0	16	16	63
Uterus	61	18	45	39	6	89	34	65
Totals:	2,685	953	2,842	1,959	878	3,306	5,465	5,678

ASCT+B tables record what CTs are found in which FTUs.



Scientific Map/Atlas construction requires data/code that is documented/shared so others can reproduce results

HuBMAP Donors Samples Datasets Other Atlas & Tools Resources User Profile

Human BioMolecular Atlas Program

An open, global atlas of the human body at the cellular level

The HuBMAP Data Portal is the central resource for discovery, visualization, and download of single-cell tissue data. Standardized data curation and processing workflow ensure that only high quality is released.

Explore spatial single-cell data with Vitesce visualizations

View multi-modal single-cell resolution measurements with reusable interactive components such as a scatterplot, spatial+imaging plot, genome browser tracks, statistical plots, and controller components.

[Get Started](#)

Spatial Layers Spatial 143673 cells

- reg001_expr
- Colormap: None
- Domain: Min/Ma
- Opacity: [slider]
- Zero Transparent:
- DAPI-02
- [slider]

Data Set Heatmap 143673 cells x 29 antigens, with 143673 cells selected

- reg001_expr
- reg001_mask

Cell Sets

- Cell ...
- Cell ...
- Cell ...
- Cell ...
- Cell ...
- Cell ...
- Cell ...
- Cell ...

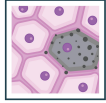
Navigation Menu:

- Human Reference Atlas (HRA) Portal
- ASCT+B Reporter
- Exploration User Interface (EUI)
- Registration User Interface (RUI)
- Azimuth: Reference-based single cell mapping
- HRA Preview: ASCT+B Reporter Comparison
- HRA Preview: Vasculature CCF Visualization
- HRA Preview: HRA vs. Experimental Data
- HRA Preview: Scrollytelling Series
- HRA Preview: Tabula Sapiens Comparison
- HRA Preview: FTU Segmentation
- HRA Preview: Mesh-Level Collision Detection

Footer:

- 105 Donors
- 1177 Samples
- 1259 Datasets
- 31 Organs
- 16 Collections

Previews explain new data, code, functionality.



SenNet

SenNet Talks on HRA construction and usage:

- 2022.06.01 **SenNet-Biomarkers** [Slides](#), [Recording](#) (at 35 min mark)
- 2022.04.27 **Onboarding SenNet TMCs** [Slides](#), [Recording](#)

Visible Human MOOC

<https://expand.iu.edu/browse/sice/cns/courses/hubmap-visible-human-mooc>

3rd HuBMAP Portal Release (June 2022)



HuBMAP Halfway Point

- HuBMAP consortia members reflect on the past four years and discuss their plans and hopes for the future.



Introduction to the HRA-CCF

- An introduction to the three ontologies at work in the Human Reference Atlas's Common Coordinate Framework: the specimen, biological structure, and spatial ontologies.



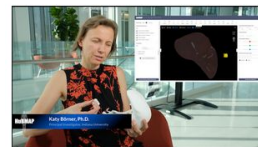
Using the EUI on the GTEx Portal

- How to cross-compare data from GTEx and HuBMAP by using the Exploration User Interface embedded in the GTEx Portal.



The Great VHMOOC Blooper Reel

Not everything goes according to plan when we make our VHMOOC videos. These outtakes give a humorous look behind the scenes!



Katy Börner—Atlas Construction and Usage

Also featuring a demonstration of tissue registration with 3D models.



Mike Snyder Explains How to Map Human Intestines

A lively demonstration of the crucial role the intestines play in human health, and what we can learn by mapping them at the single-cell level.



Richard Conroy—How HuBMAP Works

A big-picture overview of the first four years of HuBMAP.

December 10th-11th, 2022

Begins at 12PM EST

24 Hour Human Reference Atlas Event

Let's map the human body at single cell resolution!

<https://humanatlas.io/events/2022-24h/>



<https://humanatlas.io/events/2022-24h>



12PM

SPM in London (GMT), 2AM in Tokyo (GMT+9)

Welcome

With Katy Börner and Andreas Bueckle (*Indiana University*)

[Click here to learn more about the Human Reference Atlas that experts from 17 consortia are building.](#)

Trivia



1PM

8PM in London (GMT), 3AM in Tokyo (GMT+9)

Panel: What is a Human Reference Atlas?

Moderator: Todd Theriault (*Co-Curator, Places & Spaces, Indiana University*) with Aviv Regev (*Human Cell Atlas*), Sanjay Jain (*Washington University in St. Louis*), Kristin Ardlie (*Broad Institute of MIT & Harvard*), James C. Gee (*University of Pennsylvania*)



2PM

7PM in London (GMT), 4AM in Tokyo (GMT+9)

Panel: Who funds the Atlas?

Moderator: Katy Börner (*Indiana University*) with Christian Desaintes (*European Commission*), Yong Yao (*NIH/NIMH*), Amy Bernard (*Kavli*), Jonah Cool (*Chan Zuckerberg Initiative*)



3PM

8PM in London (GMT), 5AM in Tokyo (GMT+9)

Creation of Homo Perfectus

With Marie Dauenheimer (*Board Certified Medical Illustrator*)



Conclusions



Human Reference Atlas construction requires high-quality data

We understand that all TMCs are expected to generate and submit the following for their relevant tissue:

1. Histopathology images
2. scRNAseq data
3. CODEX/CellDive/MxIF

In addition to basic expectations on types of data generated per tissue, there are other important considerations such as:

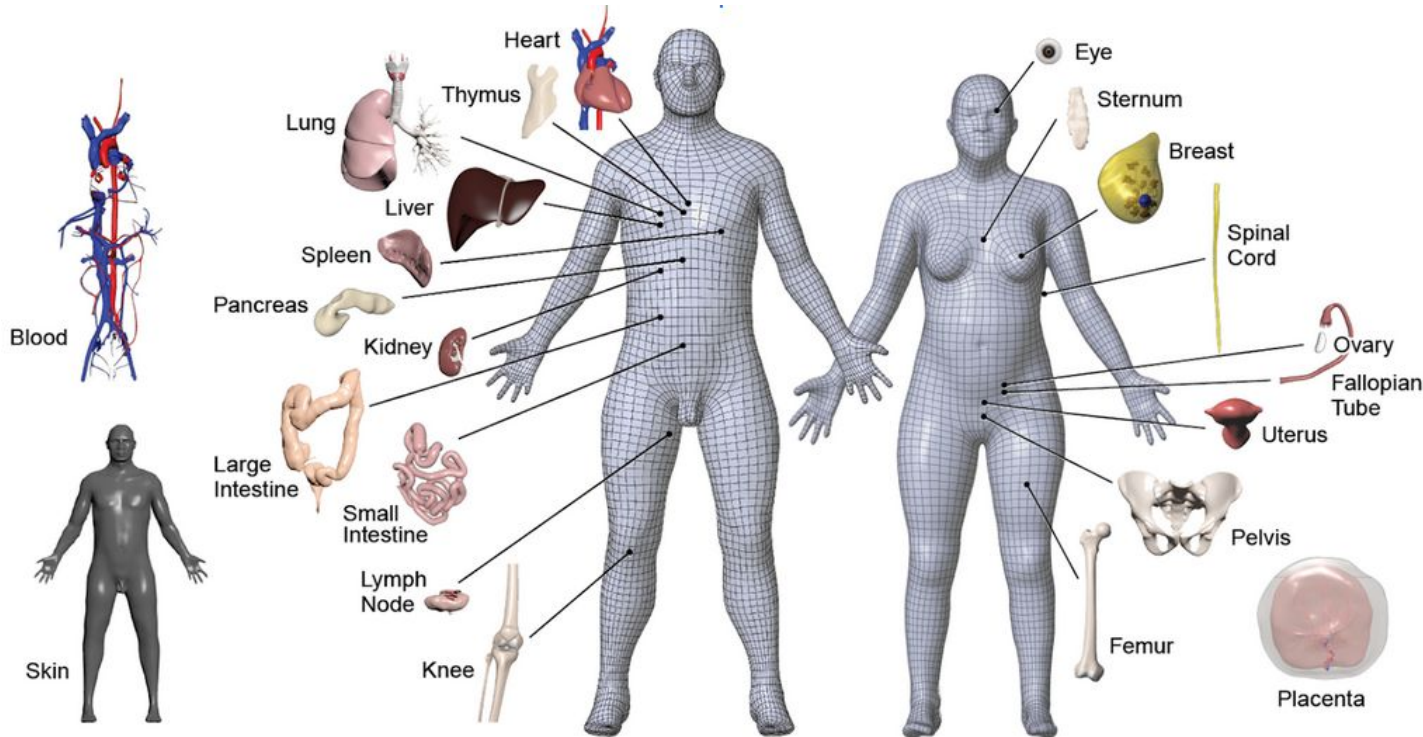
1. Running the assays above on the same or adjacent tissue sections
2. Including all essential donor, organ, sample, and assay metadata
3. RUI registration of all tissues
4. Utilization of biomarkers mapped to ASCT+B via Azimuth references and OMAPs

Plus, 3D data will be critically important to understand cell structure and function in their native 3D context. We would like to collaborate with teams that (will) generate 3D data.

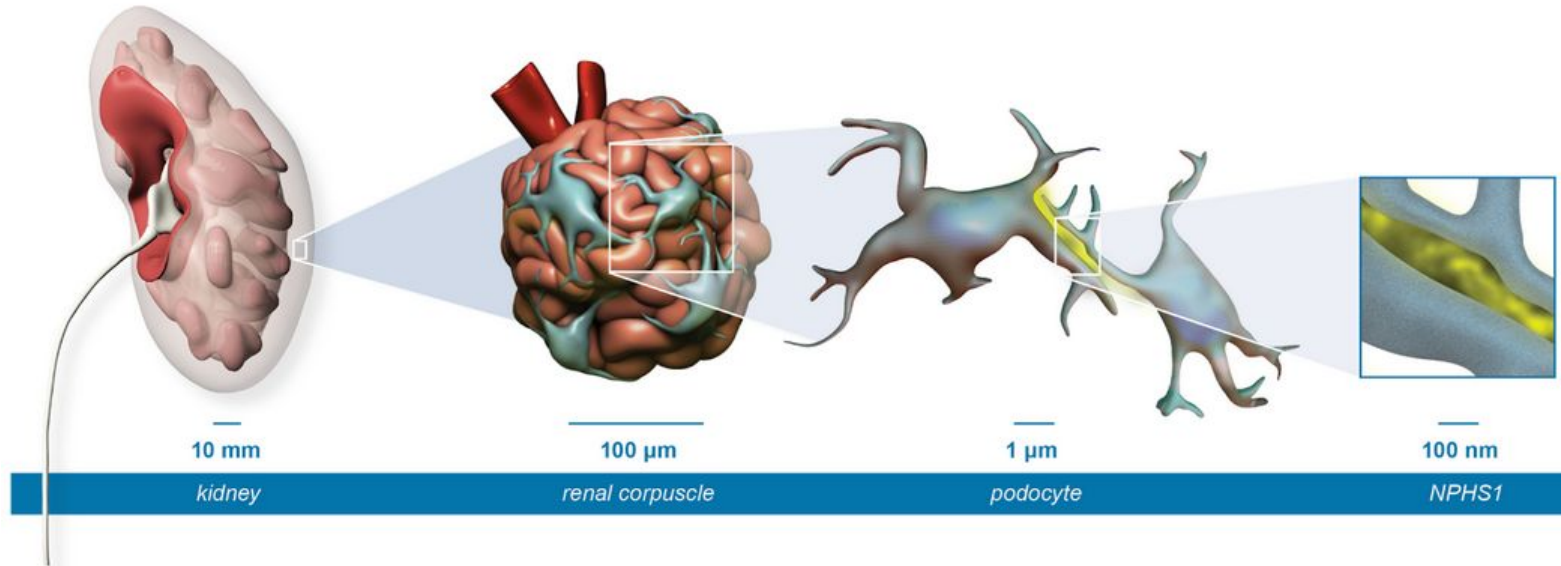
Early HRA will show organs that are funded.
It will NOT be perfect or complete.

First Phase

Organs added in Production Phase



HRA will be multiscale!



The multi-scale HRA covers more than 1,500 anatomical structures in the male and female body. A zoom into the kidney (10 mm level) reveals a representative view of a renal corpuscle (200 μm level), a subsegment of one of the ca. 1 million FTUs (nephron) of the kidney that is important in filtration. Podocytes, one of the cells important in filtration (μm level) with nucleus (in blue) and a protein NPHS1 that maintains the structural integrity of the filtration barrier (yellow) is illustrated.

Questions

