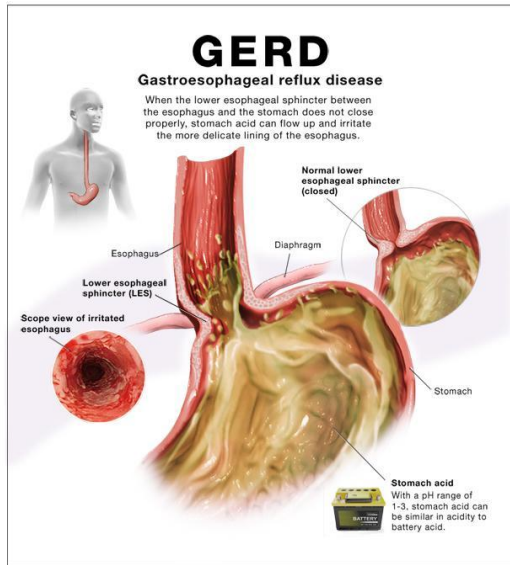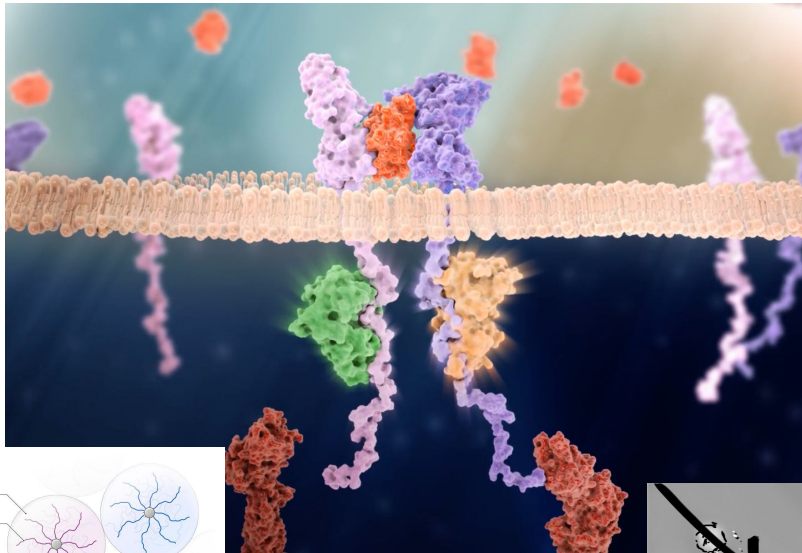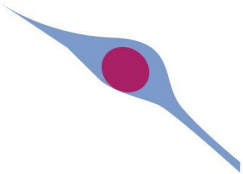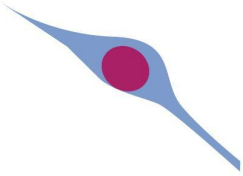# Mapping the Human Body at Single-Cell Resolution: Developing the Human Reference Atlas

Rachel Bajema, Indiana University- Bloomington
Heidi Schlehlein, Indiana University- Bloomington

Who are medical illustrators?
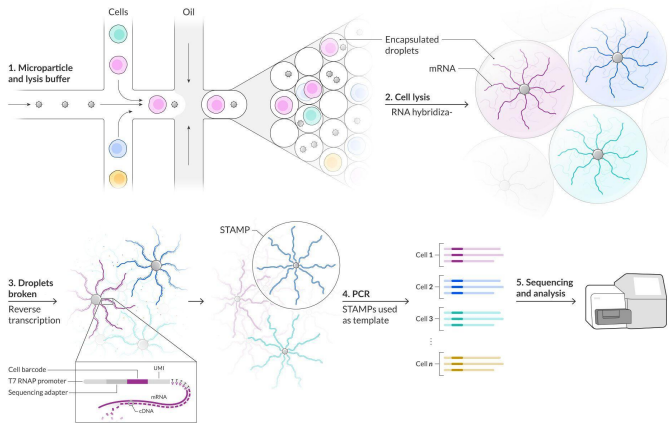
What is HuBMAP (The Human BioMolecular Atlas Program)?

- Creating a computable, open-source map of the human body at single-cell resolution
- 18 funded components with over 350 researchers in more than 50 research institutions across the U.S. and Europe
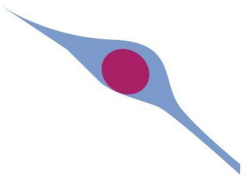- Initiatives:

1. *HuBMAP Integration, Visualization and Engagement*: Building an atlas tissue maps; tools for visualizing, searching and modeling data; Infrastructure, Engagement and Communications

   Indiana University Bloomington > Luddy School of Informatics, Computing, and Engineering > Cyberinfrastructure for Network Science Center (CNS)

2. Rapid Technology Implementation: Enhancing, large-scale validation, integration of emerging new technologies

3. Tissue Mapping Centers: Collect and analyze a range of normal tissues

4. Transformative Technology Development: Analyze tissue, validation of new methods for mapping the body at high resolution

Funded by the NIH Common Fund

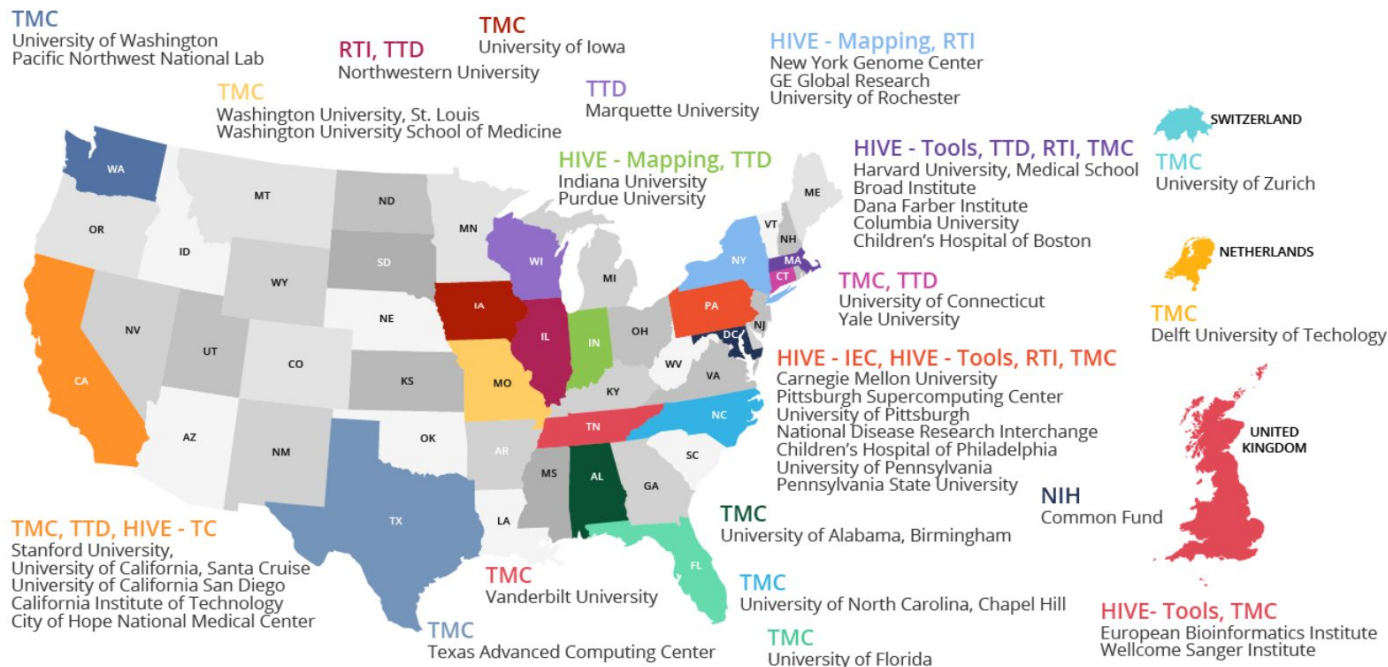# Tissue Mapping Centers (TMC)
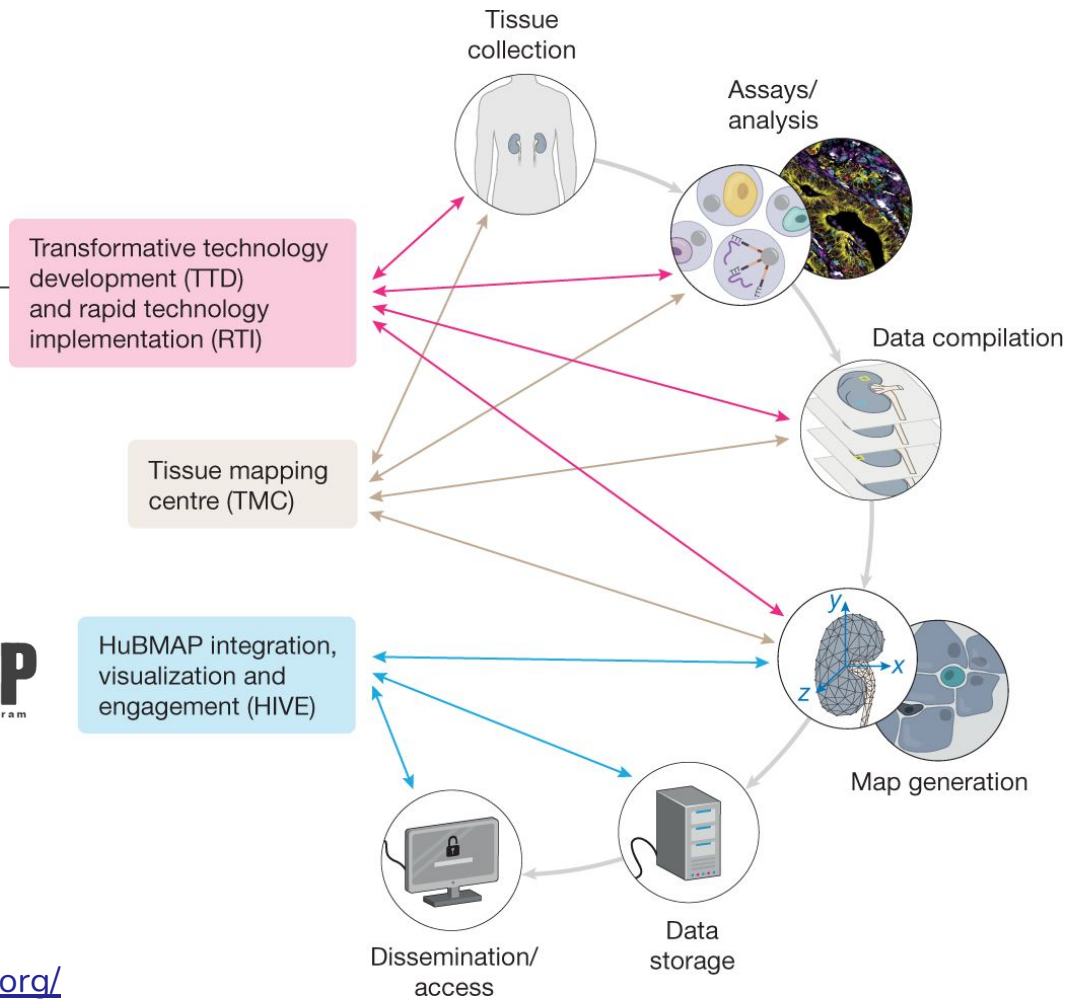
Where data comes from

Over 20 different organs from more than 80 donors comprise the samples and datasets (>1000 of each) across 3 main modalities:
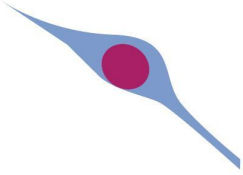- mass spectrometry
- microscopy
- sequencing

New Assay types are published as they become available.


HuBMAP Contributing Sites

TMC
University of Washington
Pacific Northwest National Lab

TMC
University of Iowa

RTI, TTD
Northwestern University

HIVE - Mapping, RTI
New York Genome Center
GE Global Research
University of Rochester

TMC
Washington University, St. Louis
Washington University School of Medicine

TTD
Marquette University

SWITZERLAND

HIVE - Mapping, TTD
Indiana University
Purdue University

HIVE - Tools, TTD, RTI, TMC
Harvard University, Medical School
Broad Institute
Dana Farber Institute
Columbia University
Children's Hospital of Boston

TMC
University of Zurich

TMC, TTD
University of Connecticut
Yale University

NETHERLANDS

TMC
Delft University of Techology

HIVE - IEC, HIVE - Tools, RTI, TMC
Carnegie Mellon University
Pittsburgh Supercomputing Center
University of Pittsburgh
National Disease Research Interchange
Children's Hospital of Philadelphia
University of Pennsylvania
Pennsylvania State University

TMC, TTD, HIVE - TC
Stanford University,
University of California, Santa Cruise
University of California San Diego
California Institute of Technology
City of Hope National Medical Center

NIH
Common Fund

UNITED KINGDOM

TMC
University of Alabama, Birmingham

TMC
Vanderbilt University

TMC
University of North Carolina, Chapel Hill

HIVE- Tools, TMC
European Bioinformatics Institute
Wellcome Sanger Institute

TMC
Texas Advanced Computing Center

TMC
University of Florida

KPMP

HUMAN CELL ATLAS

cell×gene

ALLEN INSTITUTE for BRAIN SCIENCE

GTEx Portal

THE HUMAN PROTEIN ATLAS

HuBMAP
Human BioMolecular Atlas Program

Transformative technology development (TTD) and rapid technology implementation (RTI)

Tissue mapping centre (TMC)

HuBMAP integration, visualization and engagement (HIVE)

Tissue collection

Assays/ analysis

Data compilation

Map generation

Data storage

Dissemination/ access

https://hubmapconsortium.org/

Why another Human Atlas? Why Single-Cell?

- Our goal is multiscale, multidimensional mapping of the human body from the whole body level to the individual cell

- Now possible to classify cells by their expression profiles (level at which RNA or protein is expressed from each gene)

- Large scale data sets can be interpreted by machine learning and visualization tools to find how cells are related to and interact with each other

- Enables the creation of cellular reference maps of the position, function and characteristics of every cell type in the human body

Human - Bone Marrow

Learn more   Go to App
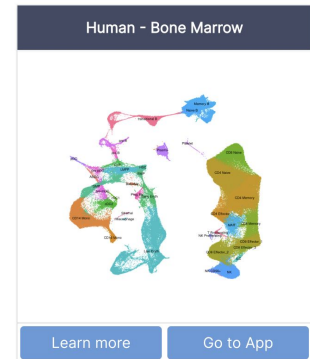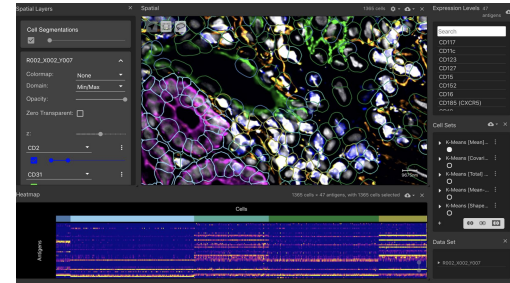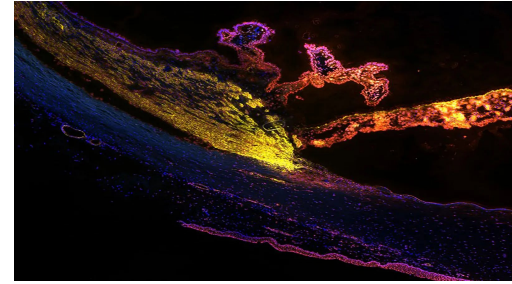
Registration User Interface (RUI)

A new way to preserve spatial relationships between different tissue samples from around the world into searchable one 3D space

Exploration User Interface (EUI)

A way to explore the vast amounts of data entered into the RUI

Anyone can access this data
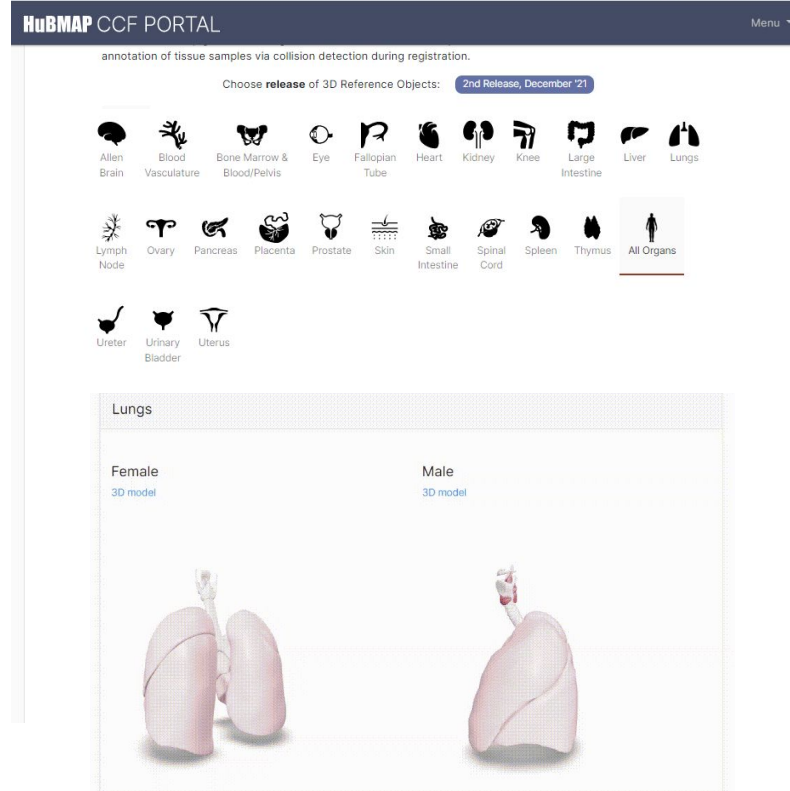
3D Reference Organ Library

Glb and fbx files of all 25 organs centrally located

- Free for all to use under Creative Commons license,
- Created for RUI
- Each organ has metadata related to Uberon terms that link to the ASCT+B Table

https://hubmapconsortium.github.io/ccf/pages/ccf-3d-reference-library.html

Anatomical Structures, Cell Types and Biomarkers (ASCT+B) tables
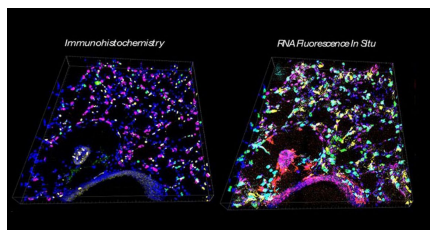
Data from assays/analysis indicates which anatomical structures, cell types and biomarkers are present in a tissue sample
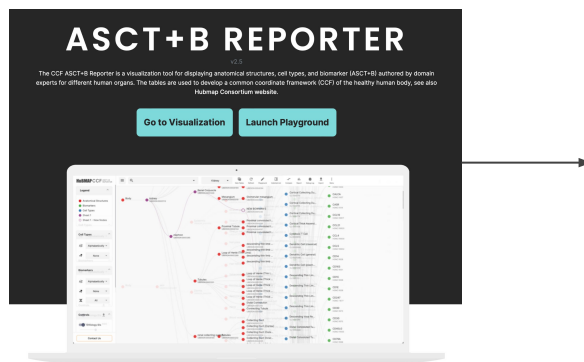
Connected to cell ontology: standard set of research-confirmed cell types

- Forces agreement on terminology and interpretation of data

- Text output (.csv) defines organizational hierarchy (relationships) for each organ
  - Organ
  - Anatomical structures
  - Cell types
  - Biomarkers

- Used to define functional tissue units (FTUs) for each organ

- FTUs are related to vascular mapping, a concurrent effort

- **FTUs chosen for illustration**

https://hubmapconsortium.github.io/ccf-asct-reporter/

Partial ASCT+B table for Large Intestine

AS/4/LABEL	AS/4/ID	AS/4/NOTES	CT/1	CT/1/LABEL	CT/1/ID
colonic epithelium	UBERON:0000397		absorptive	enterocyte of epithelium of large intestine	CL:0002071
colonic epithelium	UBERON:0000397		goblet	large intestine crypt goblet cell	CL:1000321
epithelium of crypt of Lieberkuhn	UBERON:0011184		epithelial stem cell	intestinal crypt stem cell of large intestine	CL:0009016
epithelium of crypt of Lieberkuhn	UBERON:0011184		Paneth	paneth cell of epithelium of large intestine	CL:0009009
epithelium of crypt of Lieberkuhn	UBERON:0011184		neuroendocrine	neuroendocrine cell	CL:0000165
epithelium of crypt of Lieberkuhn	UBERON:0011184		absorptive	enterocyte of epithelium of large intestine	CL:0002071
epithelium of crypt of Lieberkuhn	UBERON:0011184		goblet	large intestine crypt goblet cell	CL:1000321
epithelium of crypt of Lieberkuhn	UBERON:0011184		transient amplifying cell	transit amplifying cell of large intestine	CL:0009011
epithelium of crypt of Lieberkuhn	UBERON:0011184		tuft cell	intestinal tuft cell	CL:0019032
colonic epithelium	UBERON:0000397	Tissue resident lymphocytes; interepithelial lymphocytes	surface intraepithelial CD8+ alph alpha positive alpha/beta lymph	CD8-alpha-alpha-positive, alpha-beta intraepithelia	CL:0000915
colonic epithelium	UBERON:0000397	Tissue resident lymphocytes; interepithelial lymphocytes	surface intraepithelial CD8+ lymphocyte gamma/delta		CL:0008364
colonic epithelium	UBERON:0000397	Tissue resident lymphocytes; interepithelial lymphocytes	surface intraepithelial CD8+ alph beta positive alpha/beta lympho	CD8-alpha-beta-positive, alpha-beta intraepithelia	CL:0000796
colonic epithelium	UBERON:0000397	Tissue resident lymphocytes; interepithelial lymphocytes	surface intraepithelial CD4+ lymphocyte	CD4-positive, alpha-beta intraepithelial T cell	CL:0000793
colonic epithelium	UBERON:0000397	Tissue resident lymphocytes; interepithelial lymphocytes	surface intraepithelial CD4-CD8- lymphocyte alpha/beta	CD4-negative, CD8-negative, alpha-beta intraepith	CL:0000935
crypt of Lieberkuhn of colon	UBERON:0013485		eosinophil	mature eosinophil	CL:0000041
lamina propria of mucosa of colon	UBERON:0007177		subepithelial membrane		
lamina propria of mucosa of colon	UBERON:0007177		pericryptal fibroblastic sheath		
lamina propria of mucosa of colon	UBERON:0007177		capillary endothelium	capillary endothelial cell	CL:0002144
lamina propria of mucosa of colon	UBERON:0007177		lymphatic endothelium	endothelial cell of lymphatic vessel	CL:0002138
lamina propria of mucosa of colon	UBERON:0007177		pericyte	pericyte cell	CL:0000669
lamina propria of mucosa of colon	UBERON:0007177		myofibroblast	myofibroblast cell	CL:0000186
lamina propria of mucosa of colon	UBERON:0007177		fibroblast	fibroblast	CL:0000057
lamina propria of mucosa of colon	UBERON:0007177		nerve/schwann cell	Schwann cell	CL:0002573
lamina propria of mucosa of colon	UBERON:0007177		ganglion		
lamina propria of mucosa of colon	UBERON:0007177		neuroendocrine cell	neuroendocrine cell	CL:0000165
gut-associated lymphoid tissue	UBERON:0001962		M cell	M cell of gut	CL:0000682
gut-associated lymphoid tissue	UBERON:0001962		B cell	lymphocyte of large intestine lamina propria	CL:0009018
gut-associated lymphoid tissue	UBERON:0001962		CD4+ T cell	lymphocyte of large intestine lamina propria	CL:0009018
gut-associated lymphoid tissue	UBERON:0001962		regulatory CD4+ T cell	lymphocyte of large intestine lamina propria	CL:0009018
gut-associated lymphoid tissue	UBERON:0001962		CD8+ T cell	macrophage	CL:0009018
gut-associated lymphoid tissue	UBERON:0001962		macrophage	macrophage	CL:0000235
gut-associated lymphoid tissue	UBERON:0001962		NK cell	lymphocyte of large intestine lamina propria	CL:0009018
gut-associated lymphoid tissue	UBERON:0001962		ILF lymphatic endothelium	endothelial cell of lymphatic vessel	CL:0002138

Currently more than 25,000 nodes and edges in the ASCT+B knowledge graph

https://docs.google.com/spreadsheets/d/1d_KWKnQq3HT5nzDmfhlvFG4P_qdviu0vyhGZ6QHgNIk/edit#gid=2043181688

2D Functional Tissue Unit (FTU) Illustrations

Pancreas islets of Langerhans (0.1 mm)

Pulmonary alveolar parenchyma (0.2 mm)

Renal corpuscle (0.2 mm)

Prostatic glandular acinus (0.2 mm)

Crypt of Lieberkuhn (0.5-0.7 mm)

0.2 mm

Liver lobule (1-2.5 mm)

Thymus lobule (0.5-2 mm)

0.5 mm

Nephron tubule (3-5 mm)

1 mm
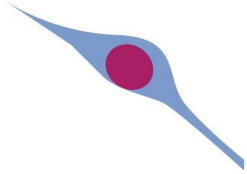
HuBMAP CCF Portal: where it all lives

Explore and use

Everything is open source- all recreatable, can be used for any purpose

Visual resource

Organ VR Gallery
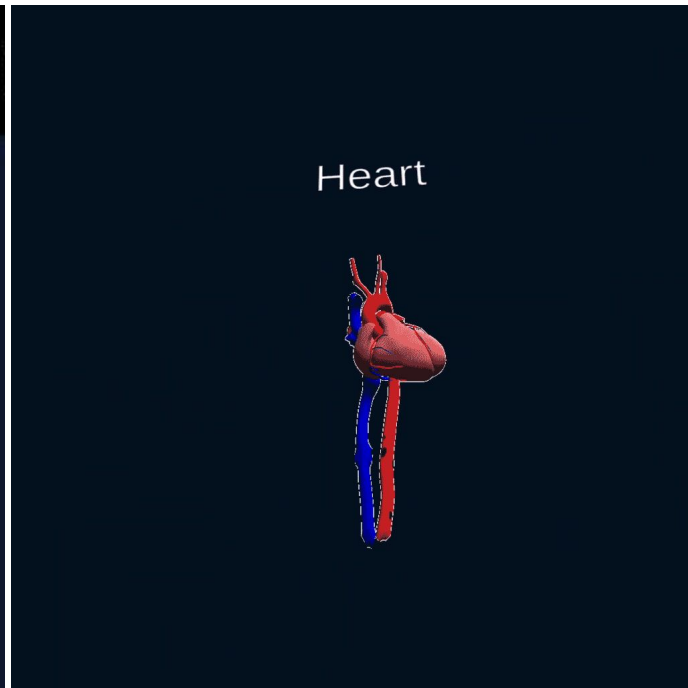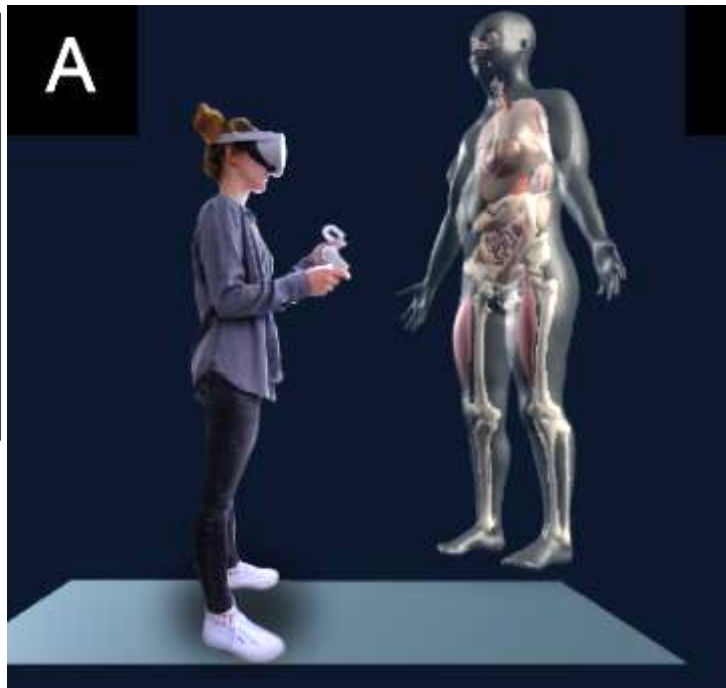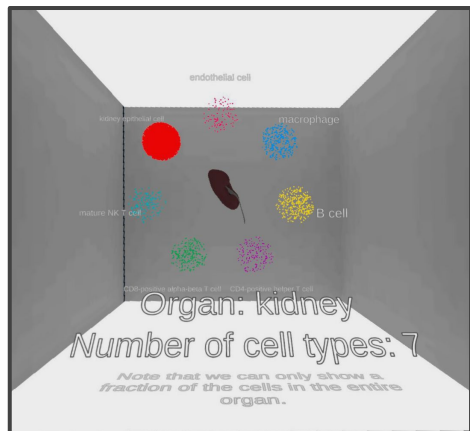
https://osf.io/z9gm3/
For test build: contact Andi Bueckle at abueckle@iu.edu
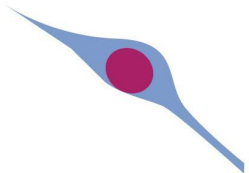
Visual resource

Vitessce

Principal Investigator:
Nils Gehlenborg

http://vitessce.io/
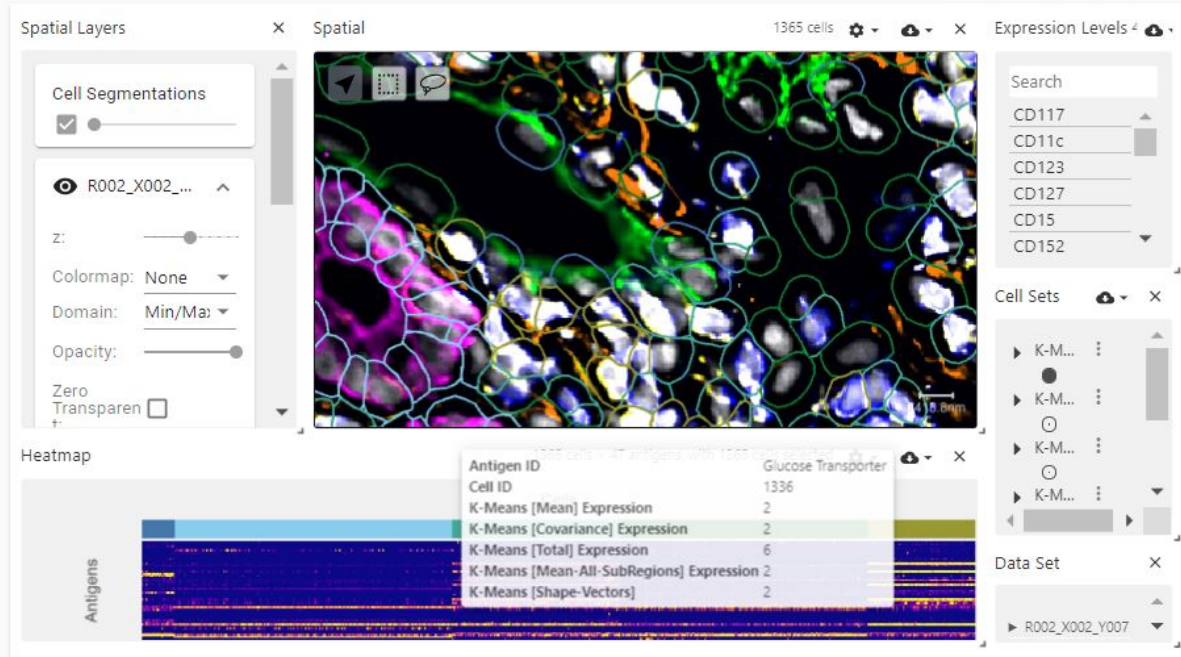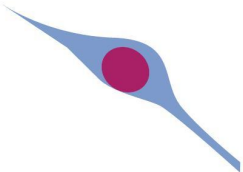
Visual resource
Vascular Common Coordinate Framework
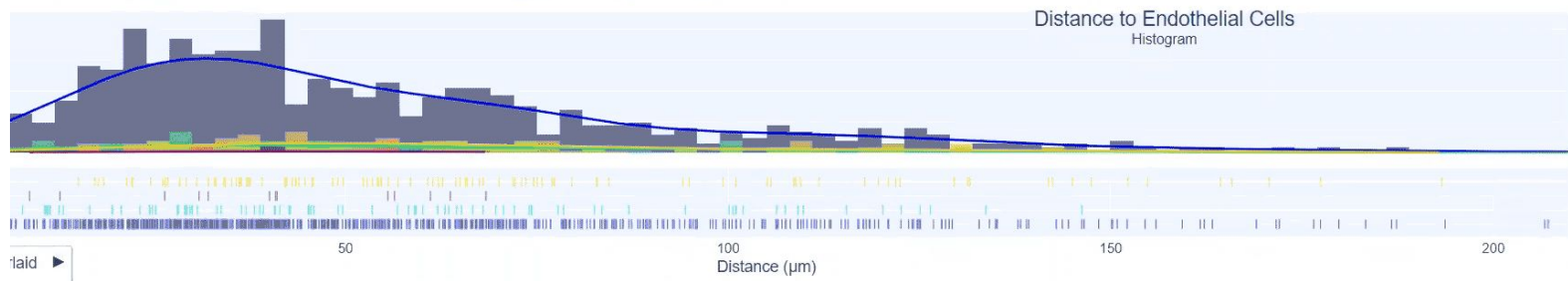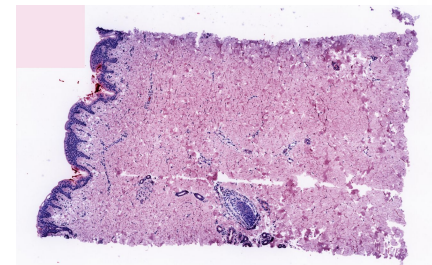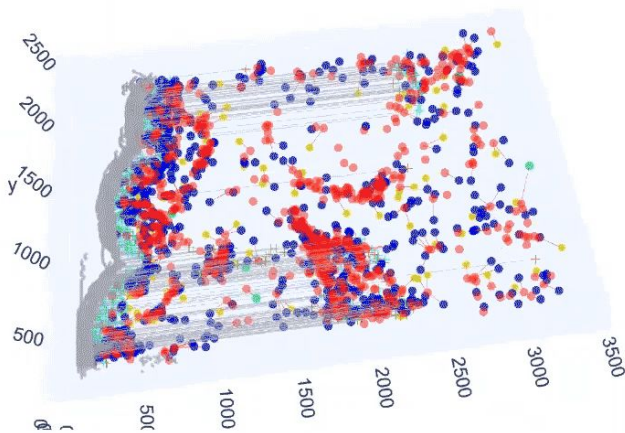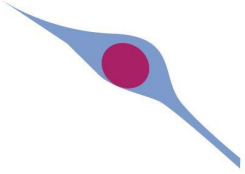
Call to action

- All 3D/2D files are open source, available for download

- Take the free [Visible Human MOOC tutorial](#) to learn more

- Explore the [HuBMAP Data Portal](#) and [CCF Portals](#), including the visualization tools

- Contribute to and the [ASCT+B tables](#) for research on anatomical structures, cell types and biomarkers, and their hierarchical relationships

- Register tissues blocks in the RUI

- Become an SMEs/external reviewers of 3D models and FTUs

    - Expert in an human anatomy organ system

    - Work with medical artist to edit and create 3D organs and FTU illustrations
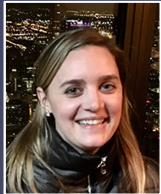
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