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

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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:

HuBMAP
Human BioMolecular Atlas Program

CNS
Cyberinfrastructure for Network Science Center

NIH

Funded by the NIH Common Fund

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

KPMP

HUMAN CELL ATLAS

cell×gene

ALLEN INSTITUTE for BRAIN SCIENCE

GTEx Portal

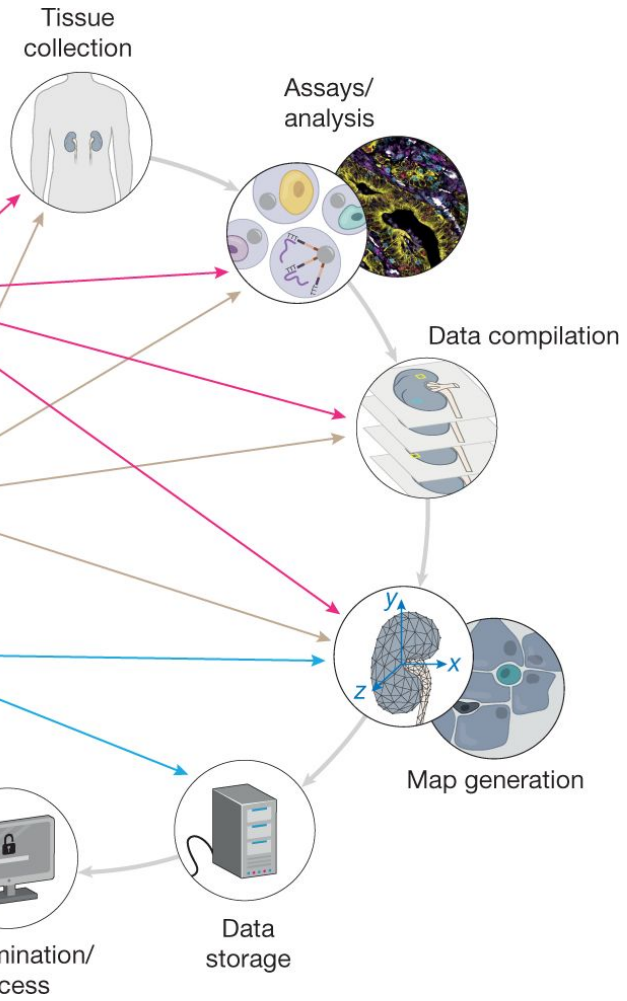
THE HUMAN PROTEIN ATLAS

HuBMAP
Human BioMolecular Atlas Program

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

Tissue mapping centre (TMC)

HuBMAP integration, visualization and engagement (HIVE)



https://hubmapconsortium.org/

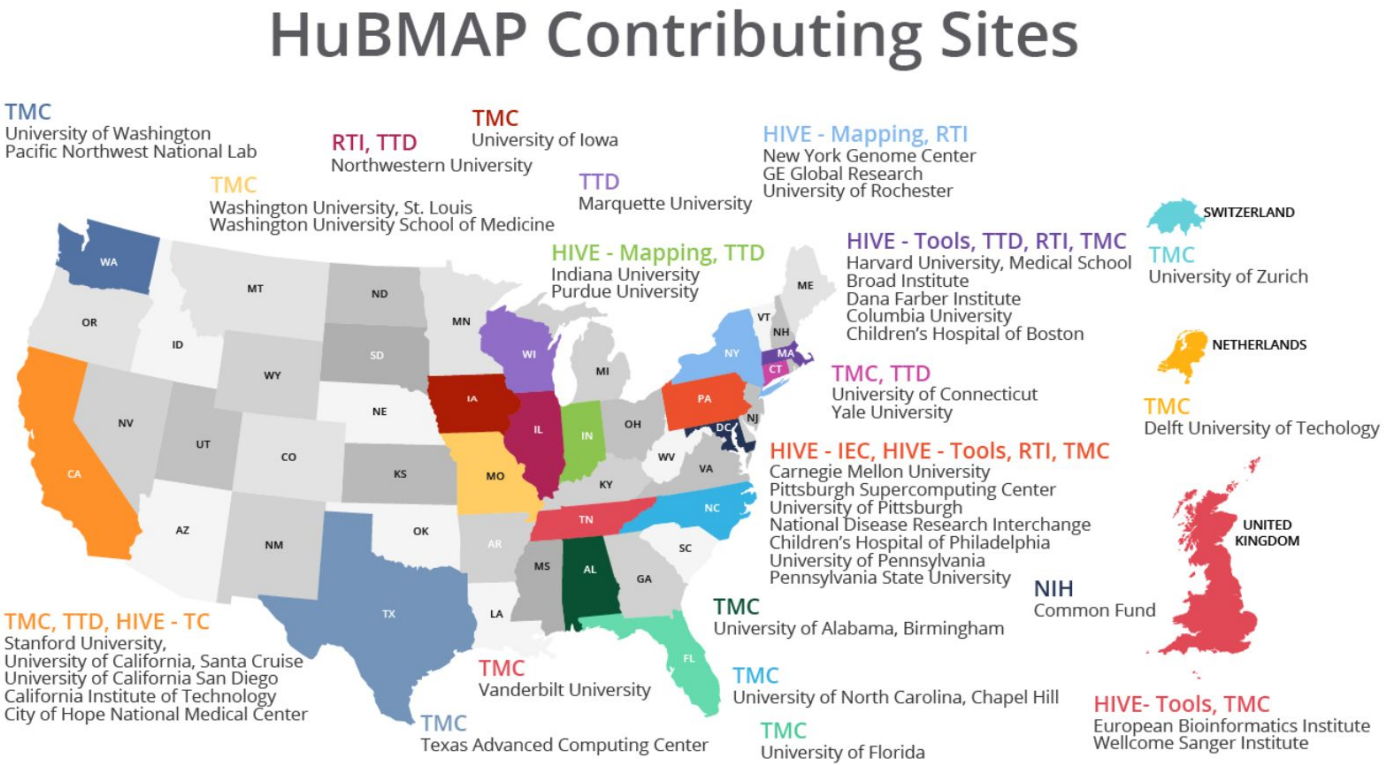
Tissue Mapping Centers (TMC)

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:

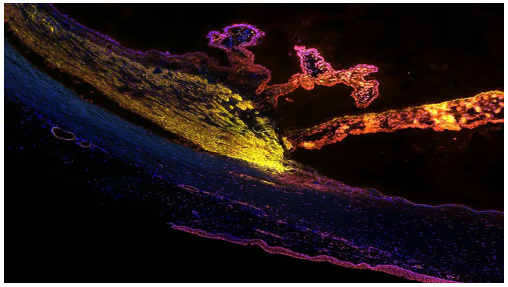
- mass spectrometry
- microscopy
- sequencing

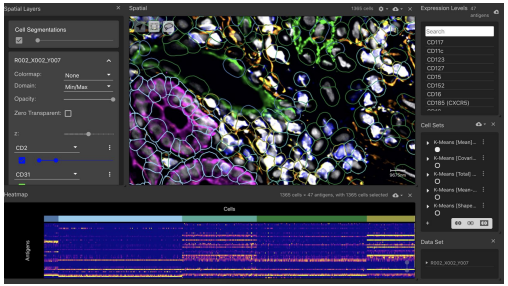
New Assay types are published as they become available.

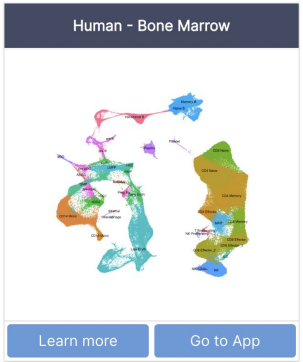


Why another Human Atlas? Why Single-Cell?

- 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







HuBMAP User Interfaces

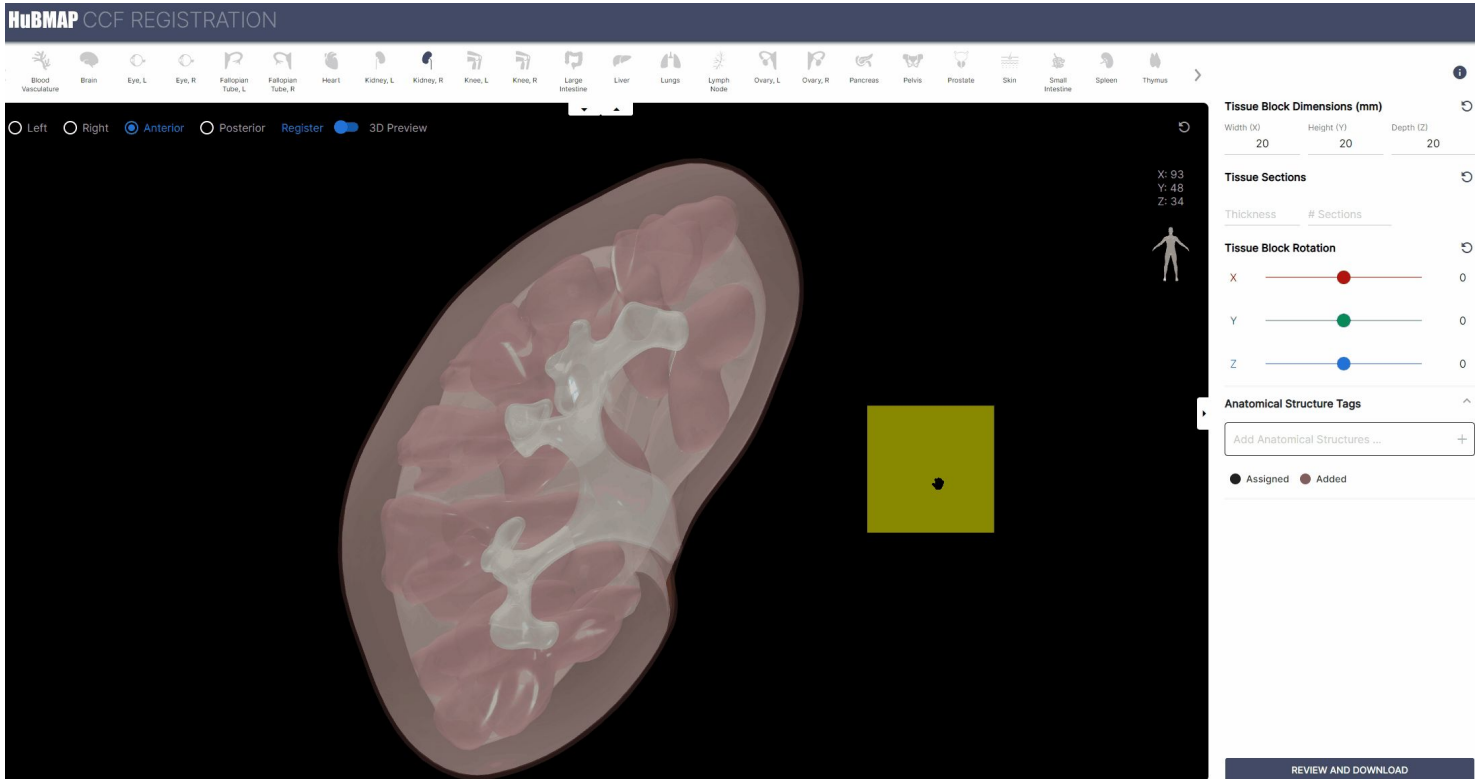
Place tissue samples and find data

Two challenges:

1. How to place a tissue sample into a virtual 3D system
2. How to search that data for cell types within anatomical structures, with various filters in place

Registration User Interface (RUI)

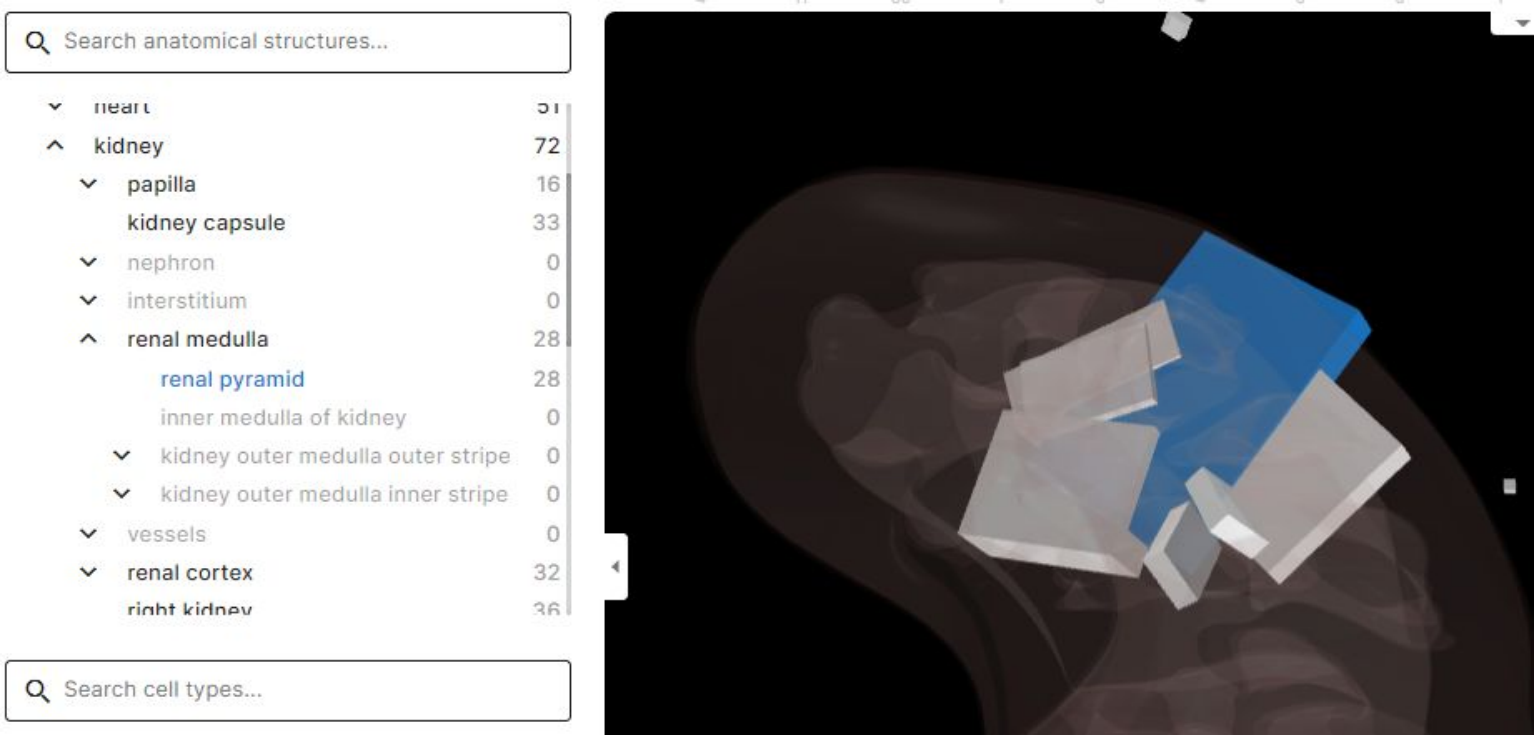
A new way to combine tissue samples from around the world into one 3D space



Exploration User Interface (EUI)

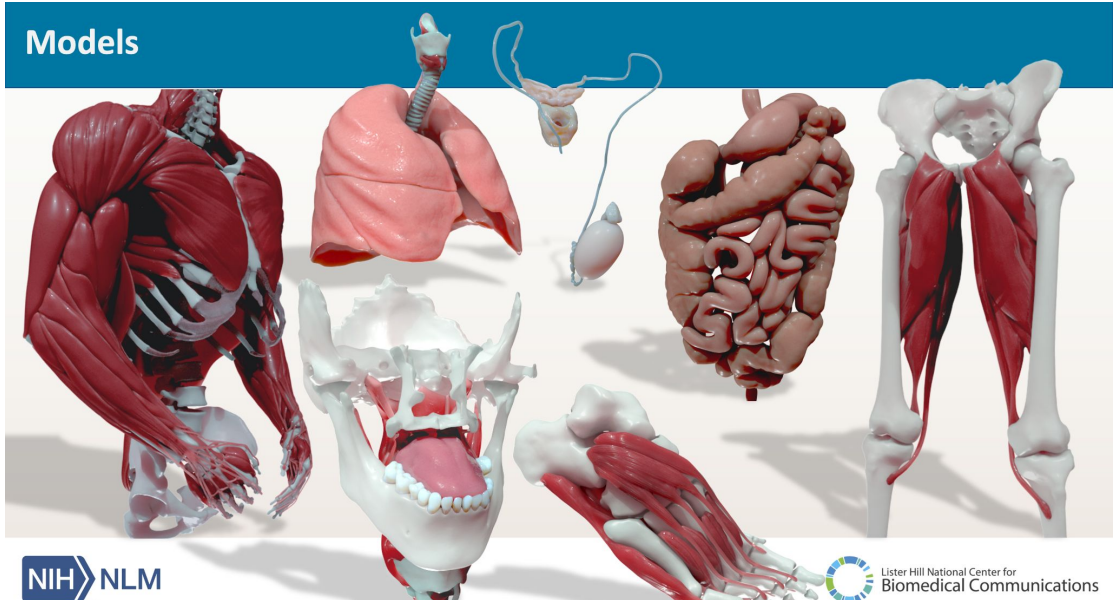
A way to explore the vast amounts of data entered into the RUI

Anyone can access this data



3D Reference Organs - NLM 3D

- Open-source library of 3D models derived from the Visible Human datasets ((https://youtu.be/-097PdgfhIU)
- Developed at National Library of Medicine from 2016-2019
- Moved to NIAID in 2019 to integrate into NIH 3D (coming Nov 2022)
- Repurposed for HuBMAP as part of collaboration with NIAID Fall 2019 - Dec 2021
- Further development of HuBMAP objects passed to HuBMAP HiVE team Jan 2022



3D Reference Organs - Challenges

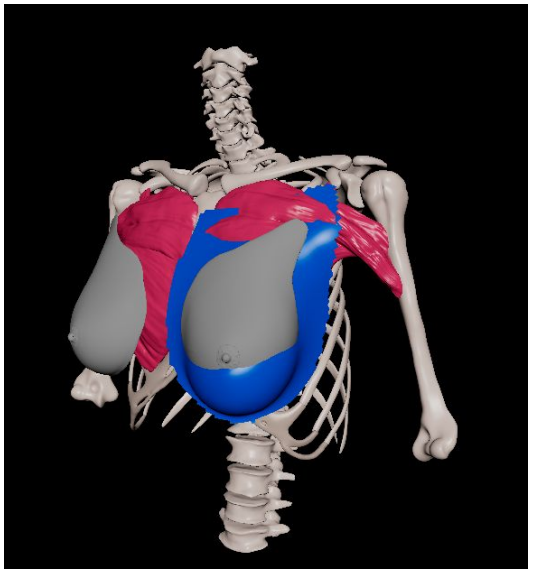
HuBMAP and NLM3D models did not have same requirements.

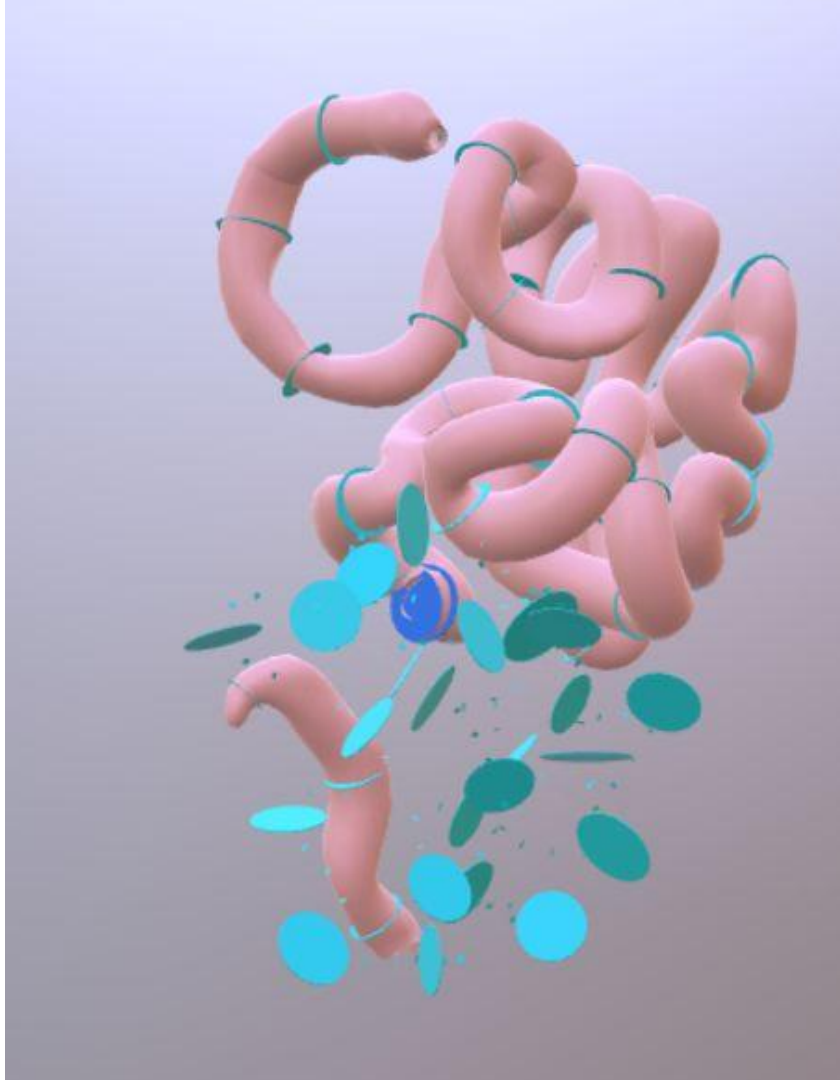
1. Adapt real data to “Textbook” appearance
2. Anatomical subdivisions dictated by ontology - overlapping jigsaw pieces carving up original model
3. High degree of variation in resolution between or within one model
4. Fitting VH organs and outside datasets (eg. Allen Brain) together inside bodies from which they were not derived.
5. Creating and placing organs in no particular order without surrounding structures to help orient (especially hard for vasculature).
6. Once an organ is published to the EUI/RUI, it is very problematic to make changes.

3D Reference Organs Challenges

Meeting the project's needs

- Fit skin with breast model
  - Blue is the original skin, grey is adjusted
- Small intestine measurements

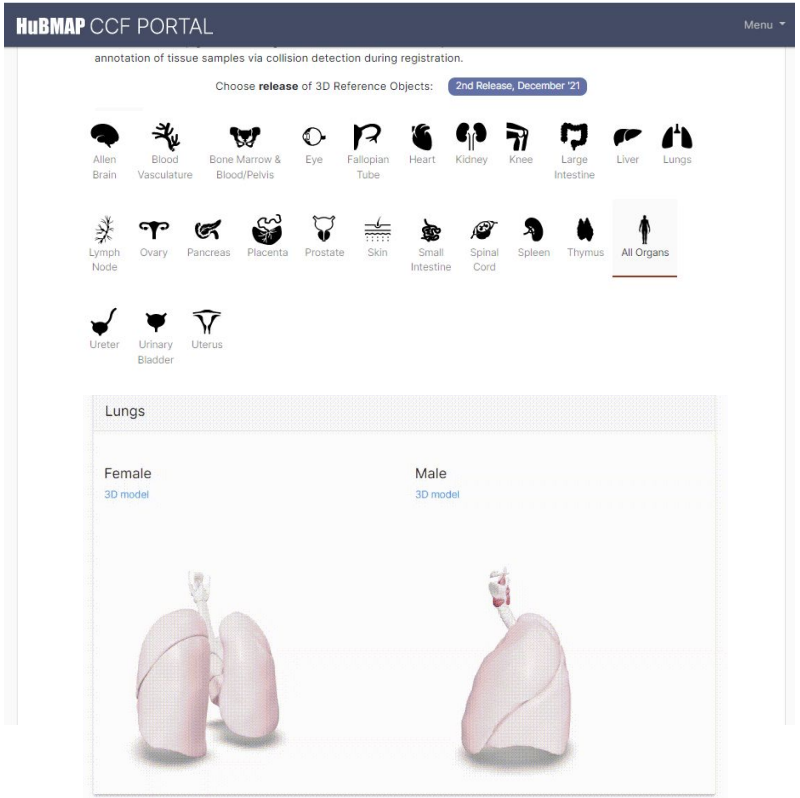




3D Reference Organ Library

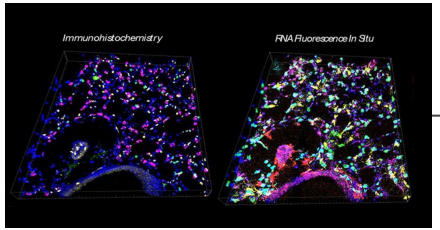
Glb and fbx files of all 25 organs centrally located

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

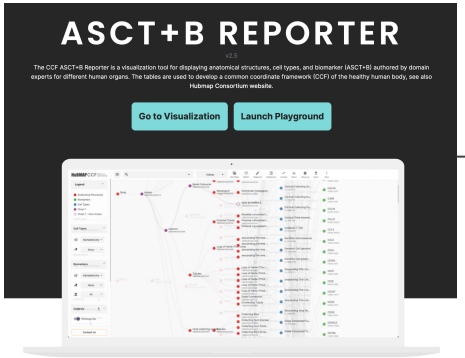


https://hubmapconsortium.github.io/ccf/pages/ccf-3d-reference-library.html

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

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

- 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

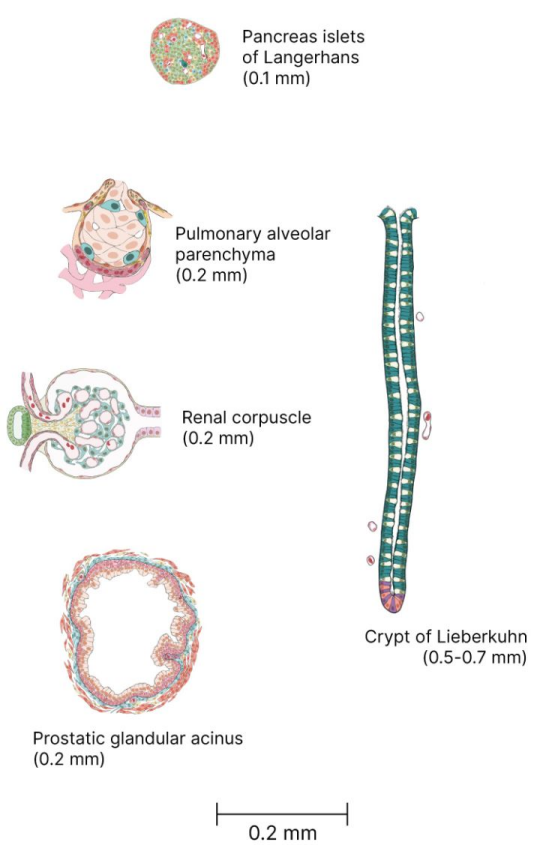
Partial ASCT+B table for Large Intestine

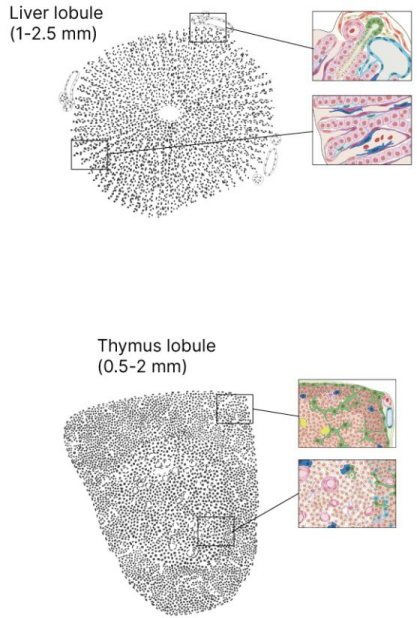
AS/4/LABEL	AS/4/ID	AS/4/NOTES	CT/1	CT/1/LABEL	CT/1/ID
colonic epithelium	UBERON:0000397		absorptive	enterocyte of epithelium of large intestine	CL:0002071
colonic epithelium	UBERON:0000397		goblet	large intestine crypt goblet cell	CL:1000321
epithelium of crypt of Lieberkuhn	UBERON:0011184		epithelial 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 intraepitheli	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

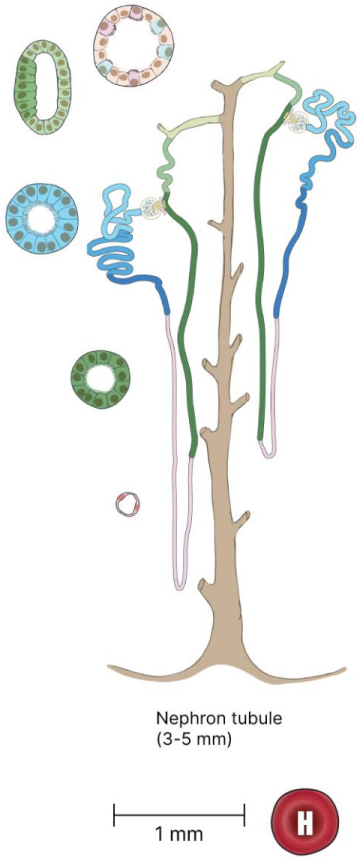
Currently more than 25,000 nodes and edges in the ASCT+B knowledge graph

https://docs.google.com/spreadsheets/d/1d_KWKnQq3HT5nzDmfhlvFG4P_qdviu0vyhGZ6QHgNlk/edit#gid=2043181688

2D Functional Tissue Unit (FTU) Illustrations





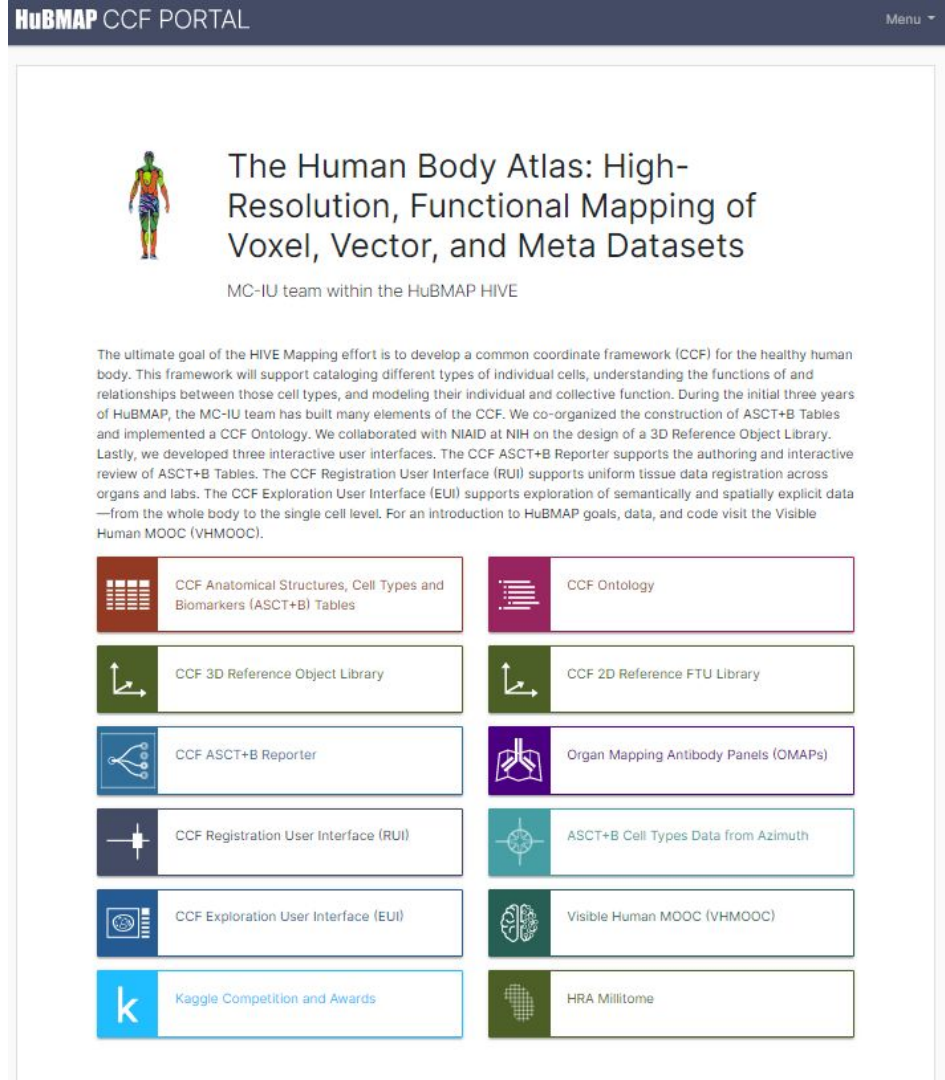


HuBMAP CCF Portal: where it all lives

Explore and use

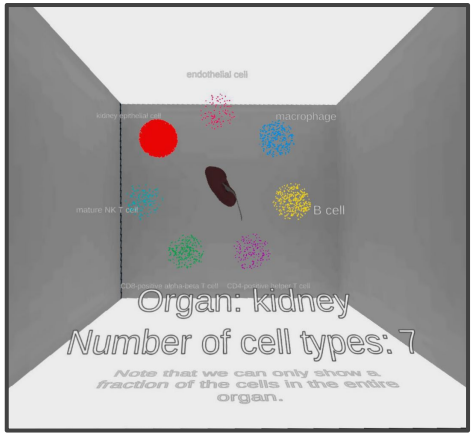
Everything is open source- all recreatable, can be used for any purpose

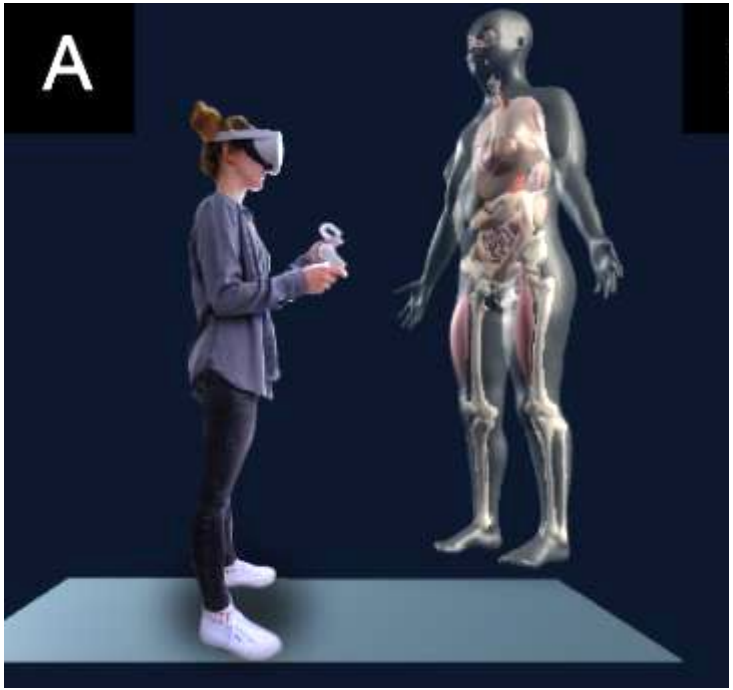
https://hubmapconsortium.github.io/ccf/index.html

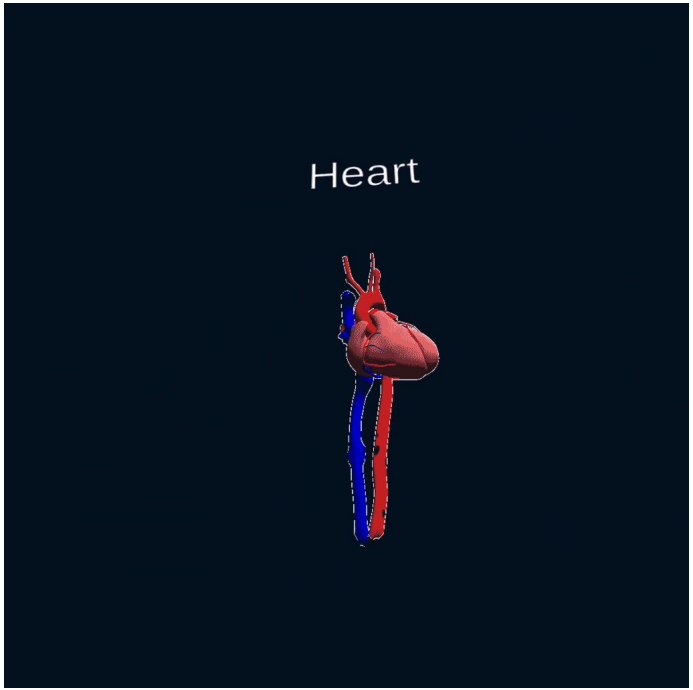


Visual resource

Organ VR Gallery







https://osf.io/z9gm3/

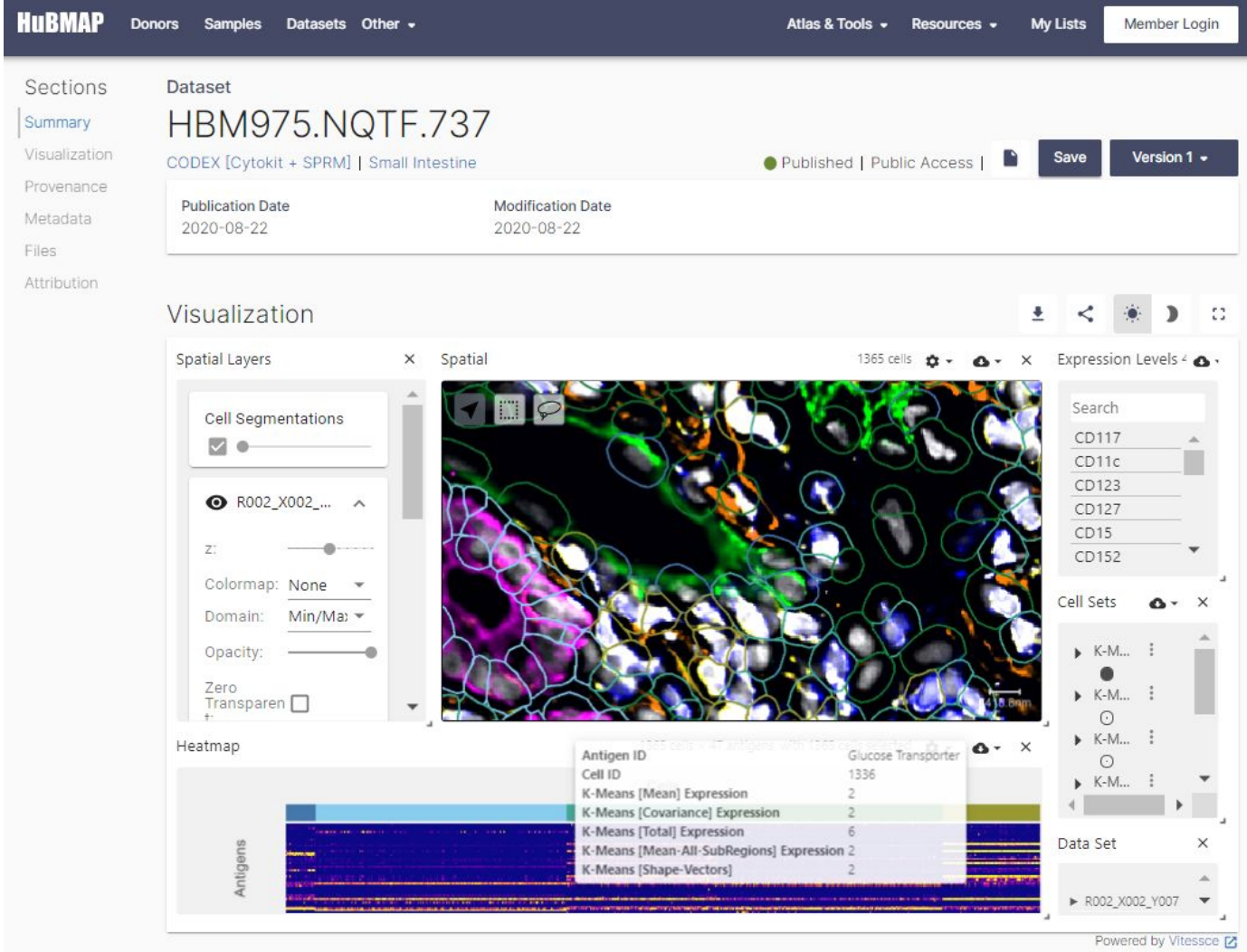
For test build: contact Andi Bueckle at abueckle@iu.edu

Visual resource

Vitessce

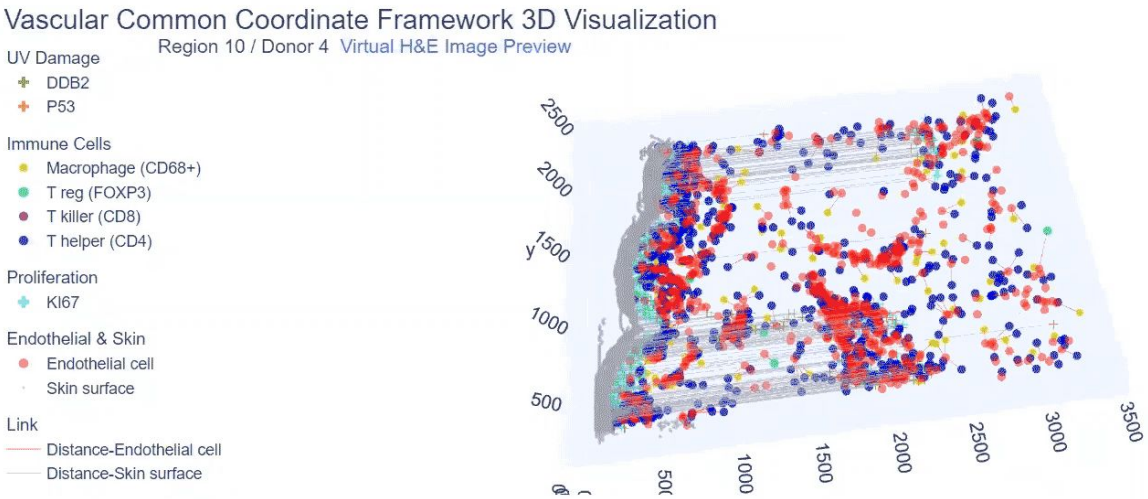
Principal Investigator:
Nils Gehlenborg

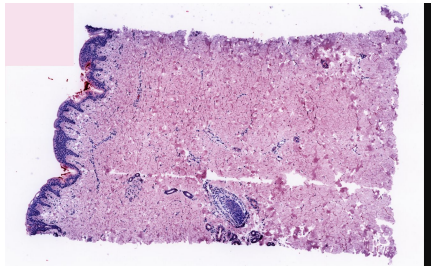
http://vitessce.io/

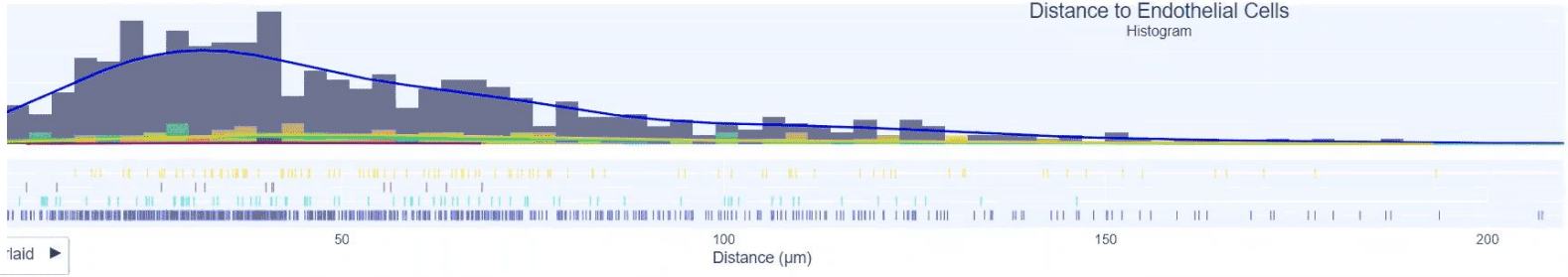


Visual resource

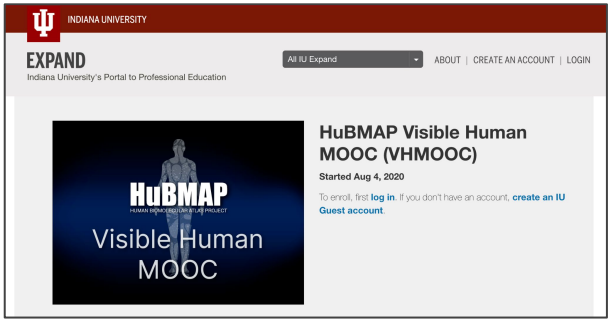
Vascular Common Coordinate Framework



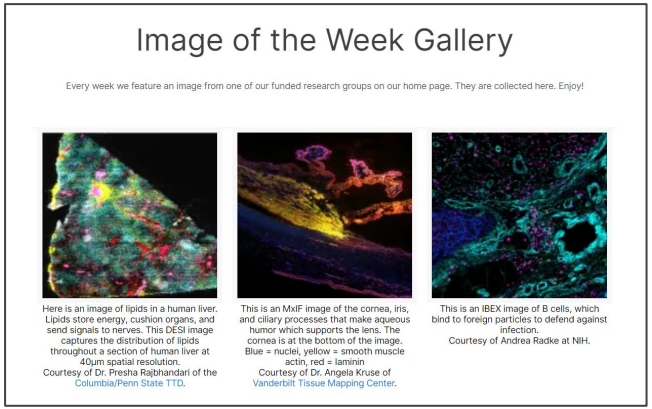




Call to action



- 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
- Use the ASCT+B tables for research on anatomical structures, cell types and biomarkers, and their hierarchical relationships
- Explore the Image of the Week Gallery and histology data sets for inspiration or reference material
- Student research projects



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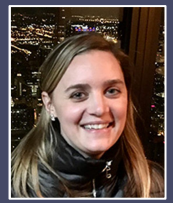

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