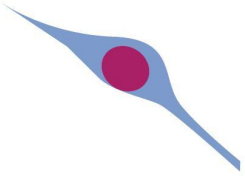


Mapping the Human Body at Single-Cell Resolution: Developing the Human Reference Atlas

Rachel Bajema, Indiana University- Bloomington
Kristen Browne, NIAID
Heidi Schlehlein, Indiana University- Bloomington





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:

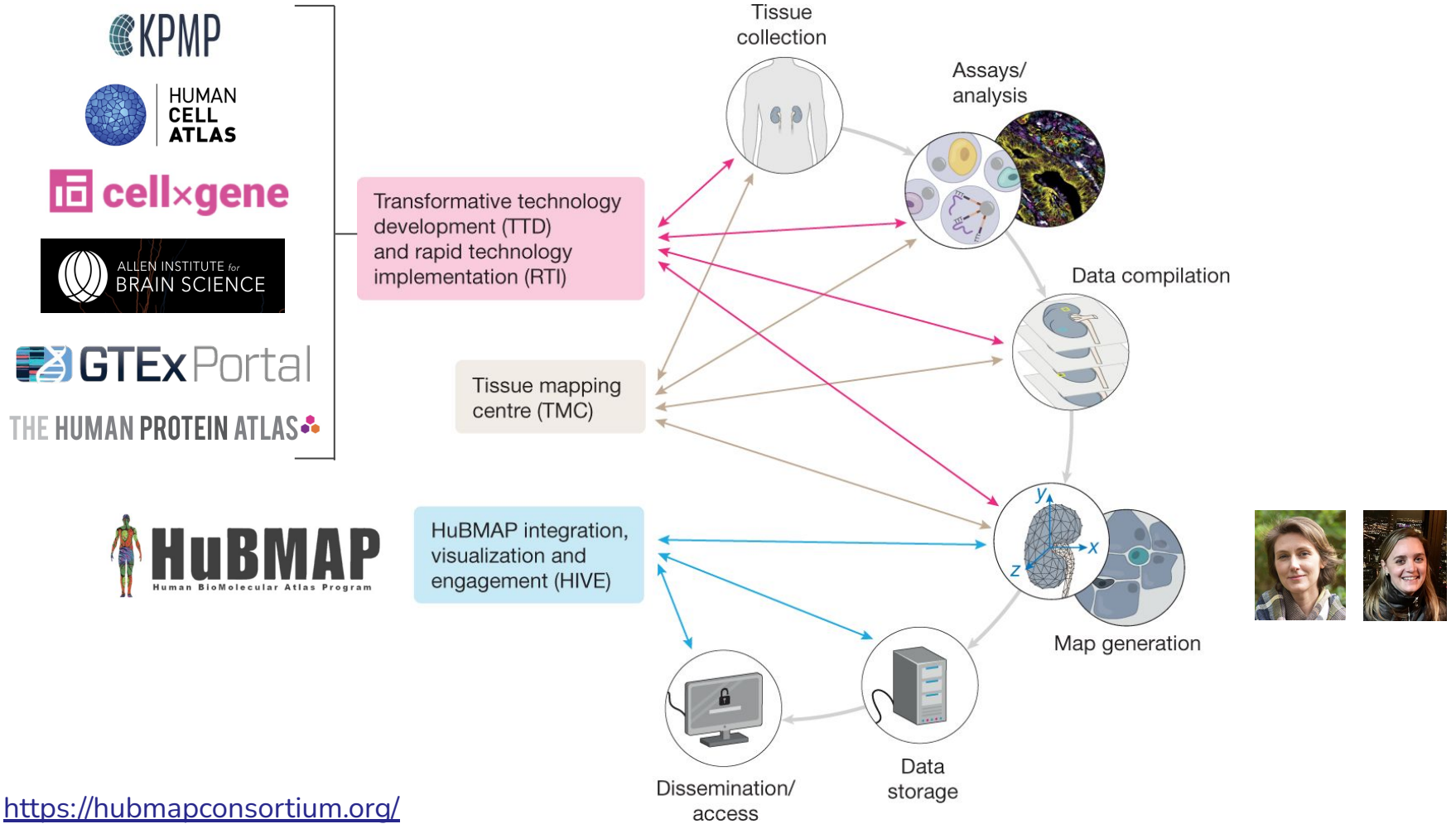


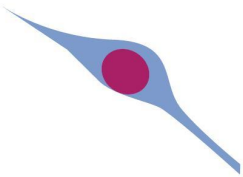
Funded by
the NIH
Common
Fund

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





Tissue Mapping Centers (TMC)

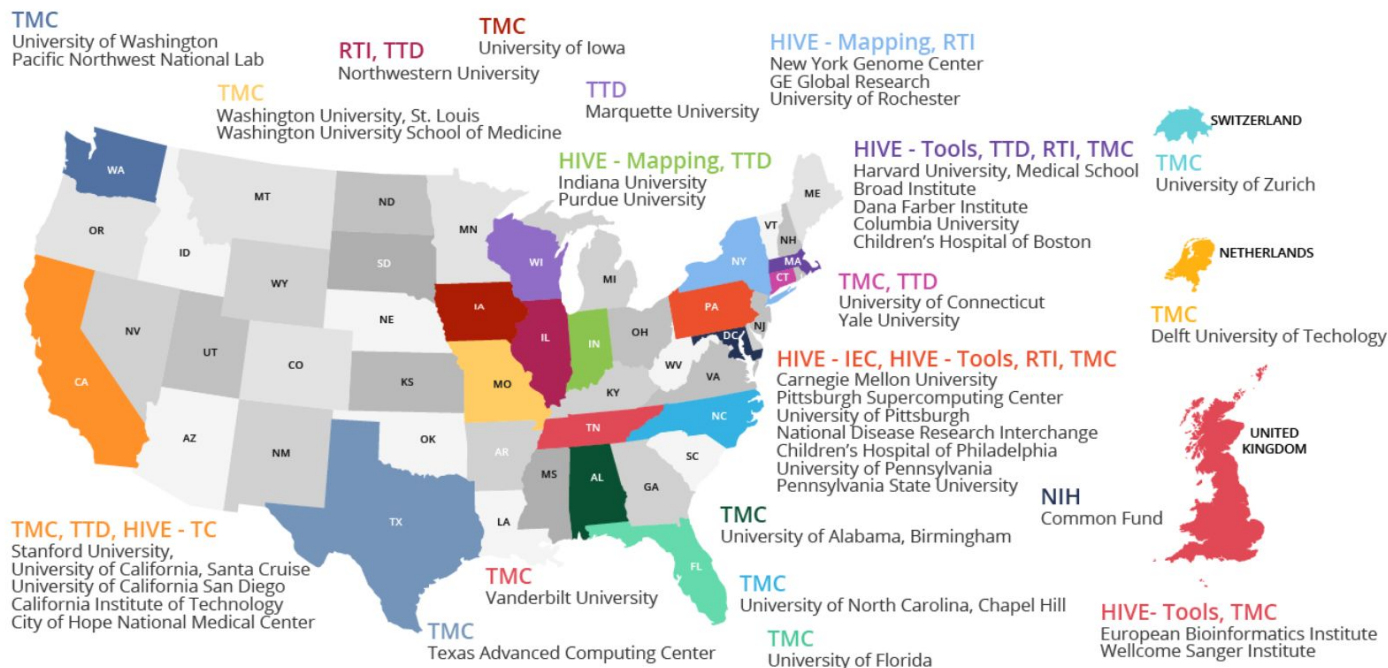
Where data comes from

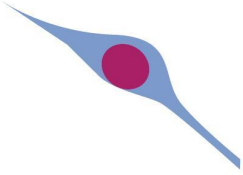
Over 20 different organs from more than 80 donors comprise the samples and datasets (>1000 of each) across 3 main modalities:

- mass spectrometry
- microscopy
- sequencing

New Assay types are published as they become available.

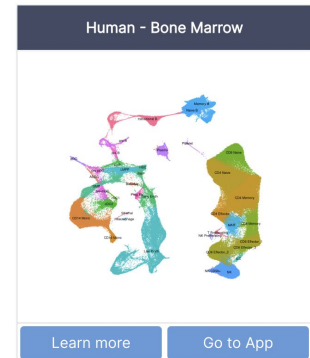
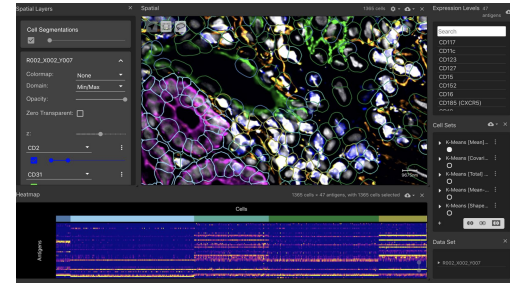
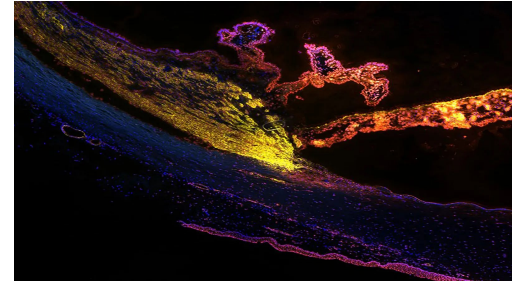
HuBMAP Contributing Sites

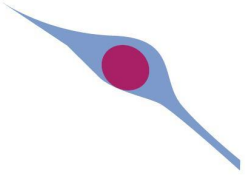




Why another Human Atlas? Why Single-Cell?

- 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



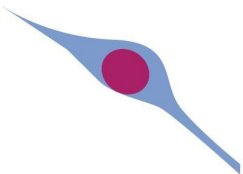


HuBMAP User Interfaces

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

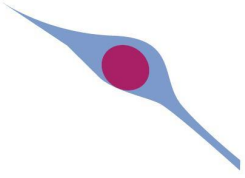


Registration User Interface (RUI)

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

The screenshot displays the HuBMAP CCF Registration User Interface (RUI). The interface is divided into several sections:

- Header:** "HuBMAP CCF REGISTRATION" with a navigation bar containing icons for various anatomical structures: Blood Vasculature, Brain, Eye, L, Eye, R, Fallopian Tube, L, Fallopian Tube, R, Heart, Kidney, L, Kidney, R, Knee, L, Knee, R, Large Intestine, Liver, Lungs, Lymph Node, Ovary, L, Ovary, R, Pancreas, Pelvis, Prostate, Skin, Small Intestine, Spleen, and Thymus.
- Navigation:** A row of buttons for "Left", "Right", "Anterior" (selected), "Posterior", "Register", and "3D Preview".
- Main View:** A large 3D anatomical model of a human torso, showing internal organs in pink and white. A small yellow square is visible on the right side of the model.
- Right Panel:** A control panel with the following sections:
 - Tissue Block Dimensions (mm):** A table with columns for Width (X), Height (Y), and Depth (Z). The values are 20, 20, and 20 respectively.
 - Tissue Sections:** A table with columns for Thickness and # Sections.
 - Tissue Block Rotation:** Three sliders for X, Y, and Z rotation, each with a value of 0.
 - Anatomical Structure Tags:** A section with a search box "Add Anatomical Structures ..." and a legend for "Assigned" (black dot) and "Added" (red dot).
- Bottom Right:** A "REVIEW AND DOWNLOAD" button.



Exploration User Interface (EUI)

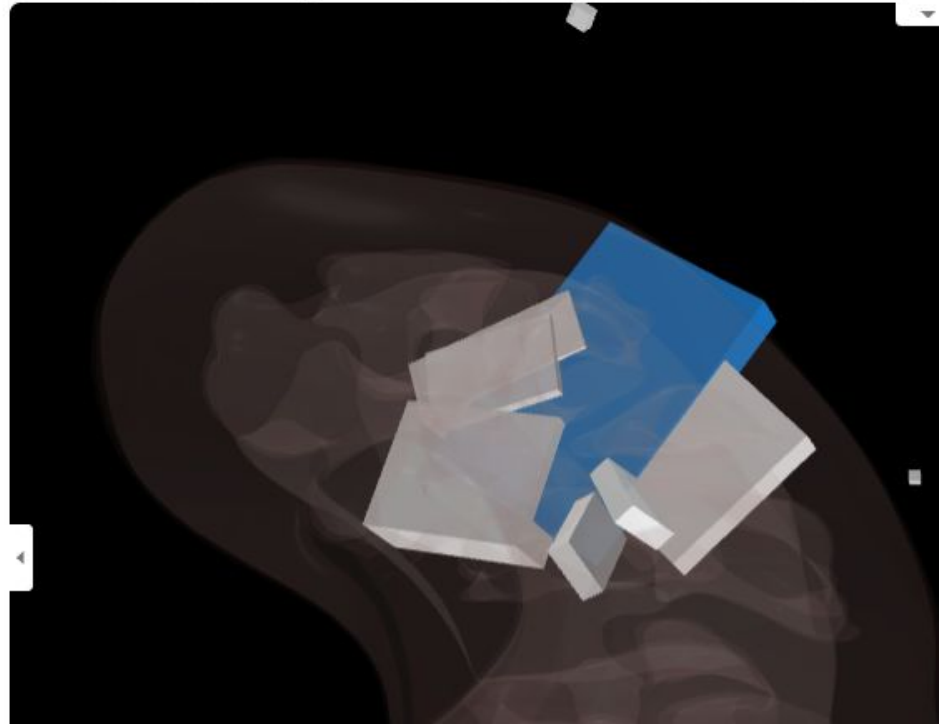
A way to explore the vast amounts of data entered into the RUI

Anyone can access this data

Q Search anatomical structures...

▼ heart	31
^ kidney	72
▼ papilla	16
kidney capsule	33
▼ nephron	0
▼ interstitium	0
^ renal medulla	28
renal pyramid	28
inner medulla of kidney	0
▼ kidney outer medulla outer stripe	0
▼ kidney outer medulla inner stripe	0
▼ vessels	0
▼ renal cortex	32
rihht kidney	36

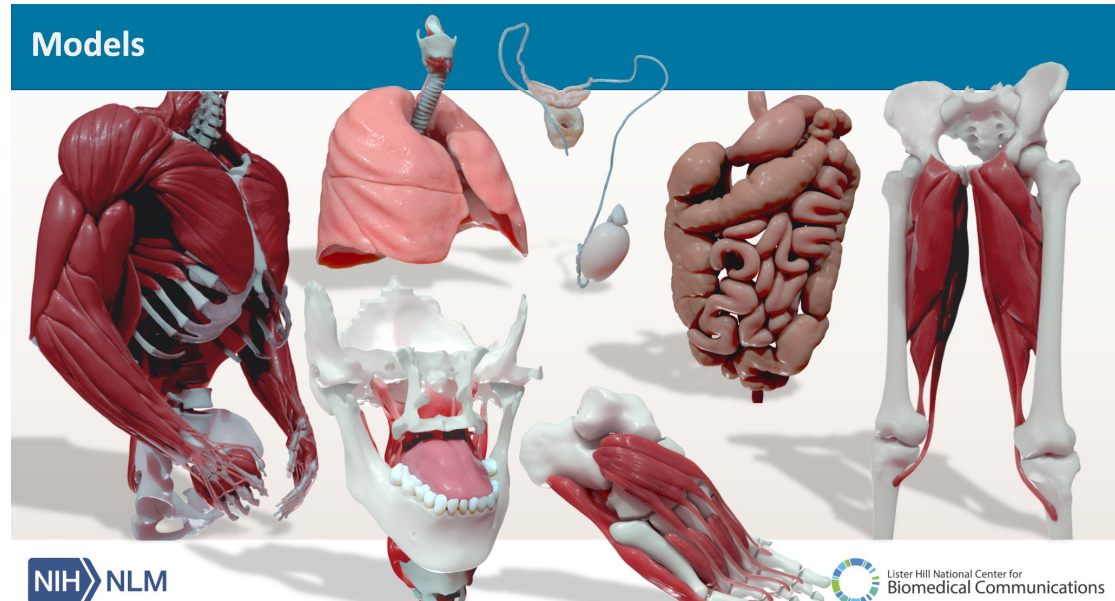
Q Search cell types...





3D Reference Organs - NLM 3D

- Open-source library of 3D models derived from the Visible Human datasets (<https://youtu.be/-097PdghfIU>)
- 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

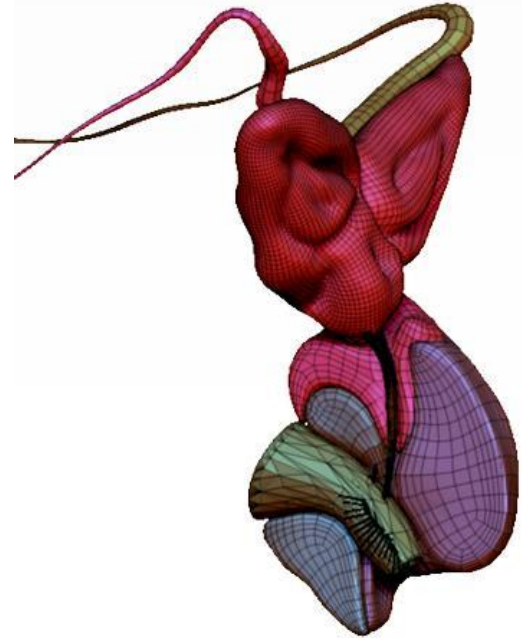


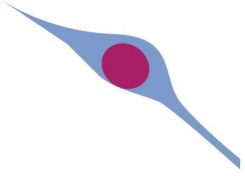


3D Reference Organs - Challenges

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.

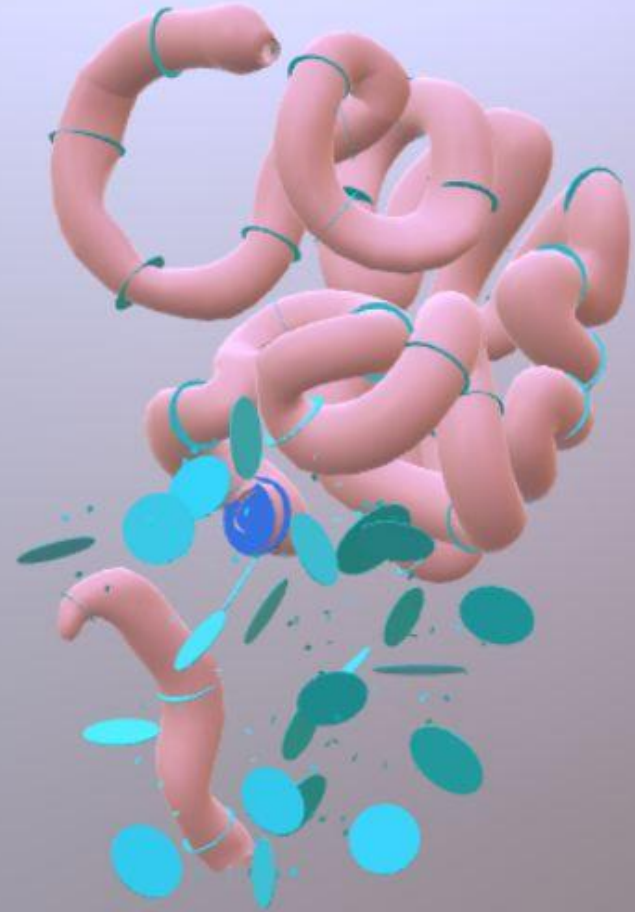
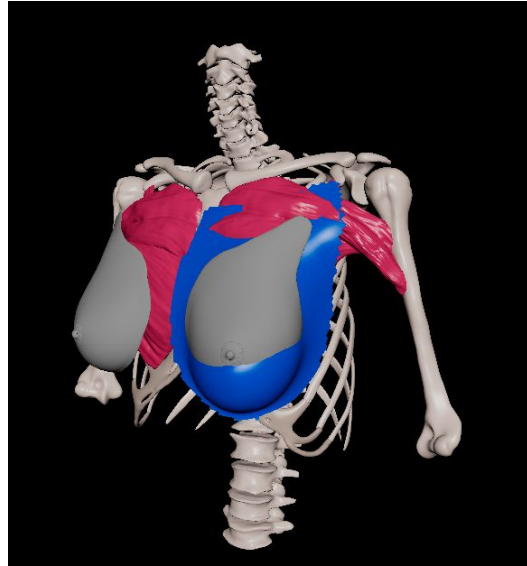




3D Reference Organs Challenges

Meeting the project's needs

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

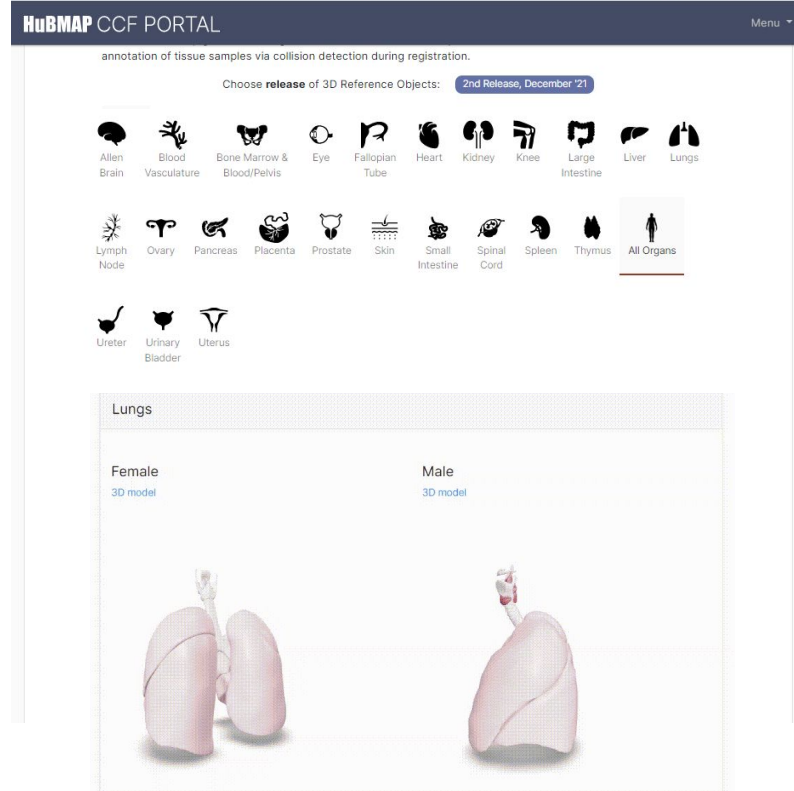




3D Reference Organ Library

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



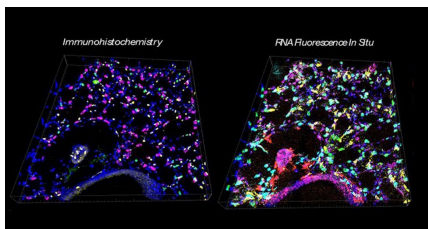
The screenshot shows the HuBMAP CCF Portal interface. At the top, it says "HuBMAP CCF PORTAL" and "Menu". Below that, it states "annotation of tissue samples via collision detection during registration." and "Choose release of 3D Reference Objects: 2nd Release, December '21".

The main content area displays a grid of 25 organ icons, each with a label: Allen Brain, Blood Vasculature, Bone Marrow & Blood/Pelvis, Eye, Fallopian Tube, Heart, Kidney, Knee, Large Intestine, Liver, Lungs, Lymph Node, Ovary, Pancreas, Placenta, Prostate, Skin, Small Intestine, Spinal Cord, Spleen, Thymus, Ureter, Urinary Bladder, and Uterus. The "All Organs" icon is highlighted with a red underline.

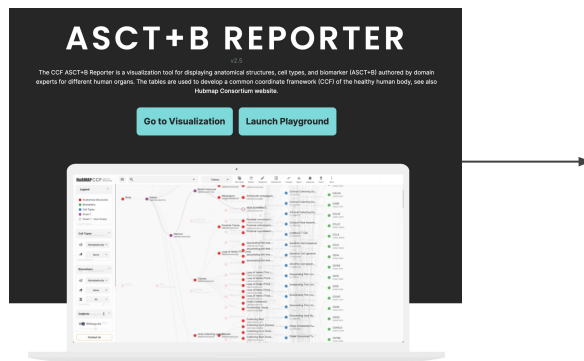
Below the grid, there is a section titled "Lungs" with two sub-sections: "Female 3D model" and "Male 3D model". Each sub-section shows a 3D model of the lungs.



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

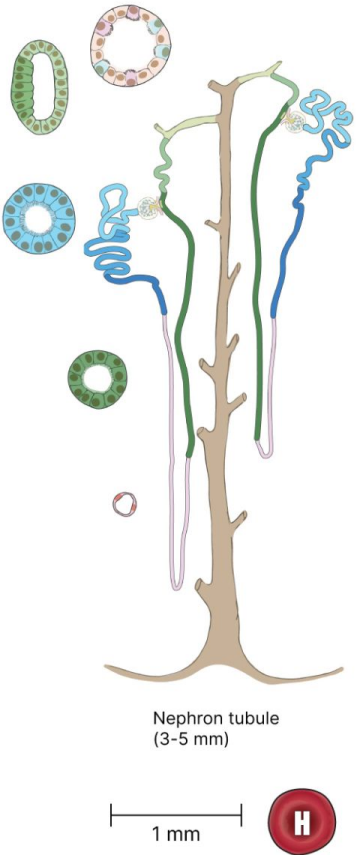
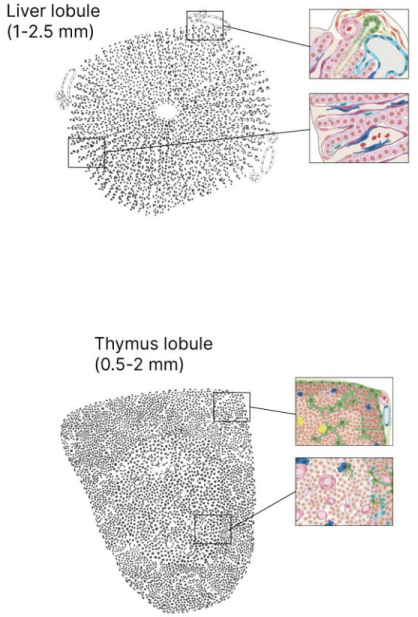
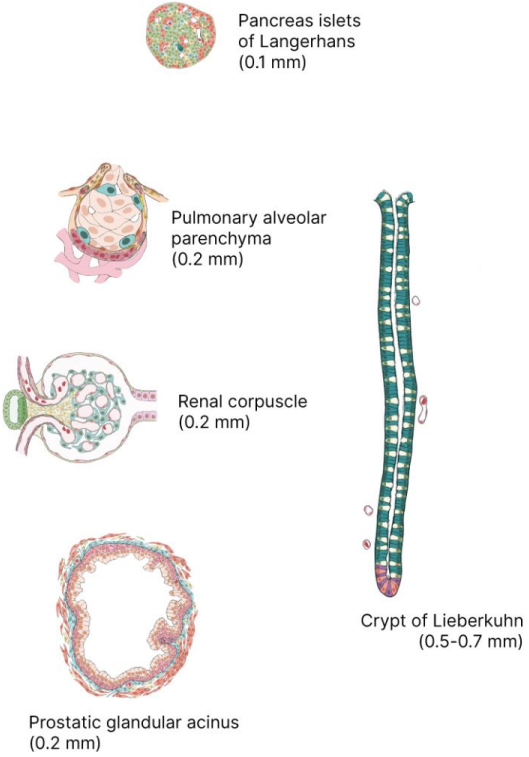
Partial ASCT+B table for Large Intestine

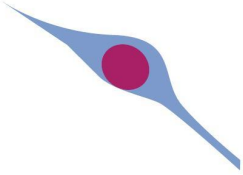
AS/4/LABEL	AS/4/ID	AS/4/NOTES	CT/1	CT/1/LABEL	CT/1/ID
colonic epithelium	UBERON:0000397		absorptive	enterocyte of epithelium of large intestine	CL:0002071
colonic epithelium	UBERON:0000397		goblet	large intestine crypt goblet cell	CL:1000321
epithelium of crypt of Lieberkuhn	UBERON:0011184		epithelial 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+ alpha positive alpha/beta lymphocyte	CD8-alpha-alpha-positive, alpha-beta intraepithelial T cell	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+ alpha beta positive alpha/beta lymphocyte	CD8-alpha-beta-positive, alpha-beta intraepithelial T cell	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 intraepithelial T cell	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





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>

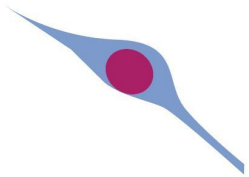


The Human Body Atlas: High-Resolution, Functional Mapping of Voxel, Vector, and Meta Datasets

MC-IU team within the HuBMAP HIVE

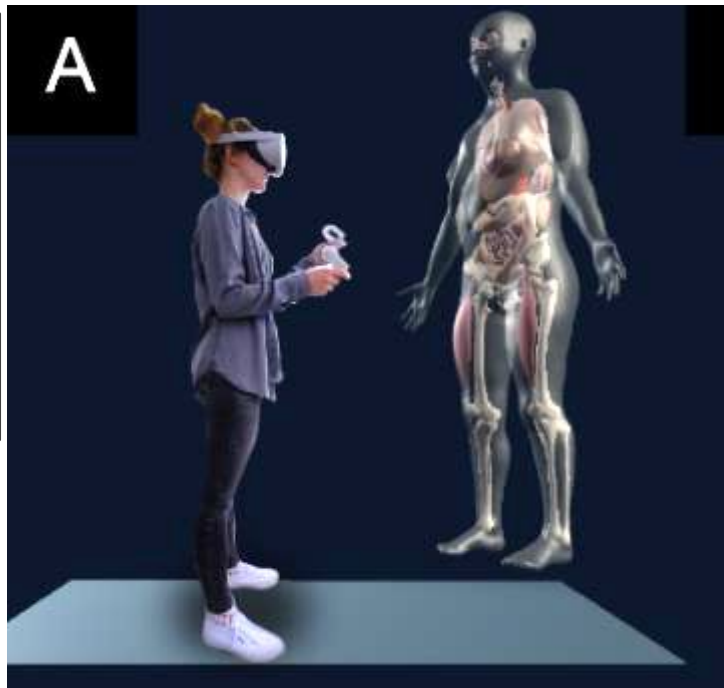
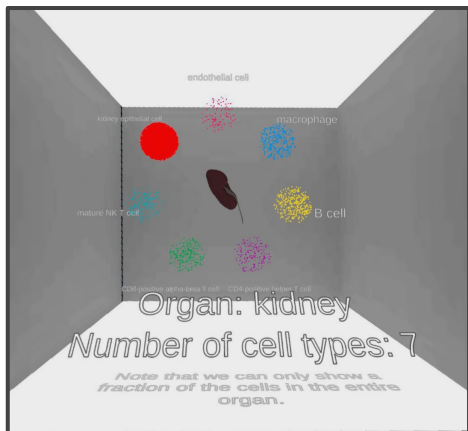
The ultimate goal of the HIVE Mapping effort is to develop a common coordinate framework (CCF) for the healthy human body. This framework will support cataloging different types of individual cells, understanding the functions of and relationships between those cell types, and modeling their individual and collective function. During the initial three years of HuBMAP, the MC-IU team has built many elements of the CCF. We co-organized the construction of ASCT+B Tables and implemented a CCF Ontology. We collaborated with NIAID at NIH on the design of a 3D Reference Object Library. Lastly, we developed three interactive user interfaces. The CCF ASCT+B Reporter supports the authoring and interactive review of ASCT+B Tables. The CCF Registration User Interface (RUI) supports uniform tissue data registration across organs and labs. The CCF Exploration User Interface (EUI) supports exploration of semantically and spatially explicit data—from the whole body to the single cell level. For an introduction to HuBMAP goals, data, and code visit the Visible Human MOOC (VHMOOC).

 CCF Anatomical Structures, Cell Types and Biomarkers (ASCT+B) Tables	 CCF Ontology
 CCF 3D Reference Object Library	 CCF 2D Reference FTU Library
 CCF ASCT+B Reporter	 Organ Mapping Antibody Panels (OMAPs)
 CCF Registration User Interface (RUI)	 ASCT+B Cell Types Data from Azimuth
 CCF Exploration User Interface (EUI)	 Visible Human MOOC (VHMOOC)
 Kaggle Competition and Awards	 HRA Millitome



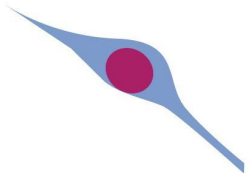
Visual resource

Organ VR Gallery



<https://osf.io/z9gm3/>

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



Visual resource

Vitesse

Principal Investigator:
Nils Gehlenborg

<http://vitesse.io/>



Sections

Summary

Visualization

Provenance

Metadata

Files

Attribution

Dataset

HBM975.NQTF.737

CODEX [Cytokit + SPRM] | Small Intestine

Published | Public Access |

Save

Version 1

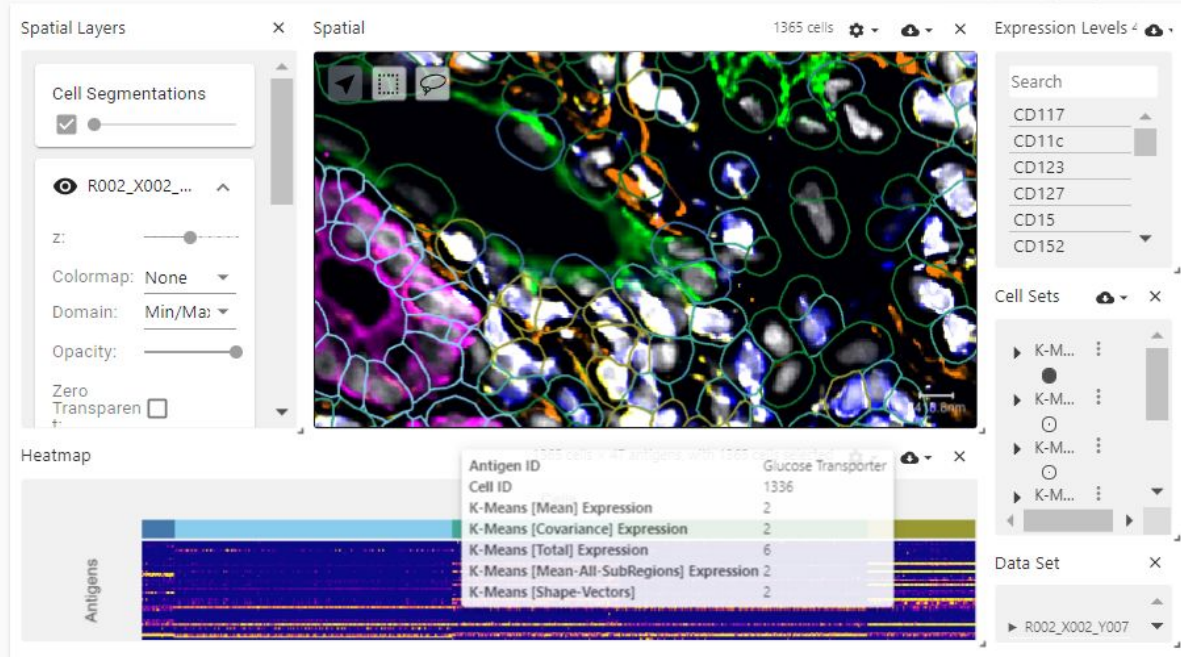
Publication Date

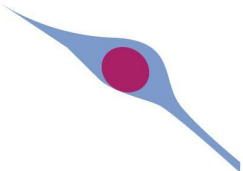
2020-08-22

Modification Date

2020-08-22

Visualization





Visual resource

Vascular Common Coordinate Framework

Vascular Common Coordinate Framework 3D Visualization

Region 10 / Donor 4 Virtual H&E Image Preview

UV Damage

- ✦ DDB2
- ✦ P53

Immune Cells

- Macrophage (CD68+)
- T reg (FOXP3)
- T killer (CD8)
- T helper (CD4)

Proliferation

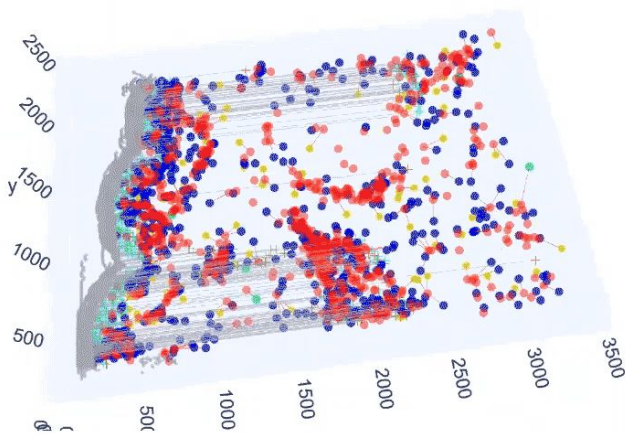
- ✦ Ki67

Endothelial & Skin

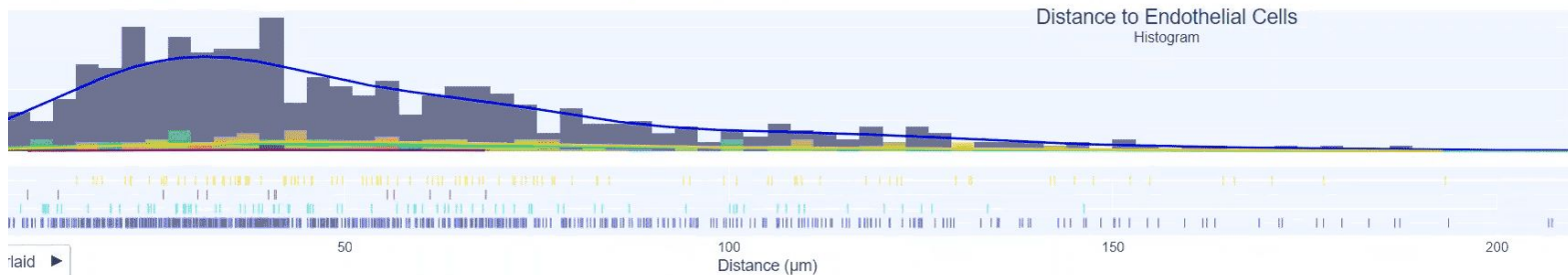
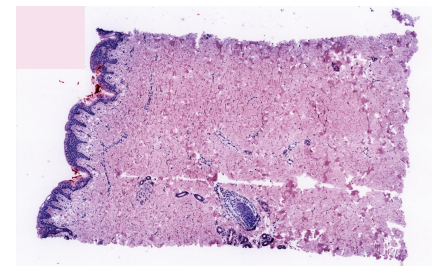
- Endothelial cell
- Skin surface

Link

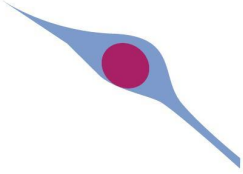
- Distance-Endothelial cell
- Distance-Skin surface



Slide: All



1aid ▶



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

The screenshot shows the Indiana University website header with the IU logo and the text "INDIANA UNIVERSITY". Below the header is a navigation bar with "EXPAND" and "All IU Expand" dropdown, and links for "ABOUT | CREATE AN ACCOUNT | LOGIN". The main content area features a large blue banner for "HuBMAP Visible Human MOOC" with a silhouette of a human figure. To the right of the banner, the text reads "HuBMAP Visible Human MOOC (VHMOOC)", "Started Aug 4, 2020", and "To enroll, first log in. If you don't have an account, create an IU Guest account".

The screenshot shows the "Image of the Week Gallery" website. The title "Image of the Week Gallery" is centered at the top. Below the title is a subtitle: "Every week we feature an image from one of our funded research groups on our home page. They are collected here. Enjoy!". The gallery contains three images with captions:

- Image 1:** A colorful fluorescence image of a human liver section. The caption reads: "Here is an image of lipids in a human liver. Lipids store energy, cushion organs, and send signals to nerves. This DESI image captures the distribution of lipids throughout a section of human liver at 40µm spatial resolution. Courtesy of Dr. Presha Rajbhandari of the Columbia/Penn State TTD."
- Image 2:** A fluorescence image of the cornea, iris, and ciliary processes. The caption reads: "This is an MxIF image of the cornea, iris, and ciliary processes that make aqueous humor which supports the lens. The cornea is at the bottom of the image. Blue = nuclei, yellow = smooth muscle actin, red = laminin. Courtesy of Dr. Angela Kruse of Vanderbilt Tissue Mapping Center."
- Image 3:** A fluorescence image of B cells. The caption reads: "This is an IBEX image of B cells, which bind to foreign particles to defend against infection. Courtesy of Andrea Radke at NIH."

Contact us

Facebook
@cnscenter

Instagram
@cns_at_iu

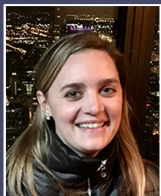
Twitter
@_hubmap



Rachel Bajema - rbajema@iu.edu



Kristen Browne - kristen.browne@nih.gov



Heidi Schlelein - hschleh@iu.edu



This project has been funded in part with Federal funds from the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, Department of Health and Human Services under BCBB Support Services Contract **HHSN316201300006W/HHSN27200002** to MSC, Inc.