5/29/2024

Human Reference Atlas

VCCF Cell Distance Visualizations

Yashvardhan Jain, Supriya Bidanta, and Katy Börner, MC-IU, CODCC

SenNet Science Talk

MC-IU CODCC

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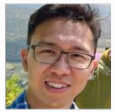
Senior Research Analyst



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3D Medical Illustrator

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Technical Writer

Jerin Thomas
Project Assistant

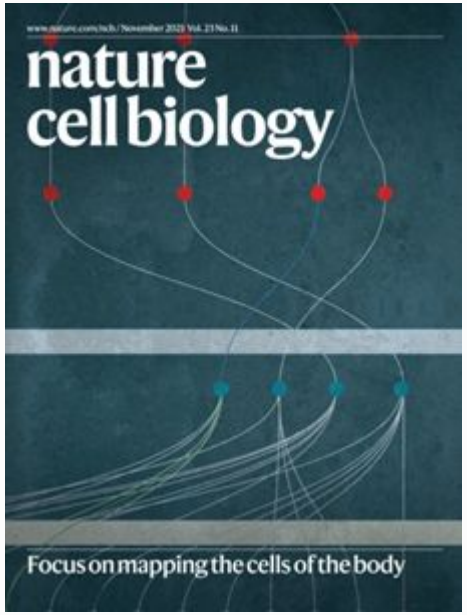
In close collaboration with SenNet, HuBMAP, KPMP, GUDMAP, HCA and other experts from 18+ consortia.
We thank all donors of healthy tissue data.

Human Reference Atlas (https://humanatlas.io)

The **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.

The 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/or experimental 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).



17	250+	1,000+	65	4,499	1,195	2,089	13	22
consortia	experts	publications	organs	anatomical structures	cell types	biomarkers	organ mapping antibody panels	functional tissue units

Börner, Teichmann, Quardokus, et al. 2021. "Anatomical structures, cell types and biomarkers of the Human Reference Atlas". Nature Cell Biology 23: 1117-1128. doi: 10.1038/s41556-021-00788-6. https://www.nature.com/articles/s41556-021-00788-6

Bridging Between Scales?

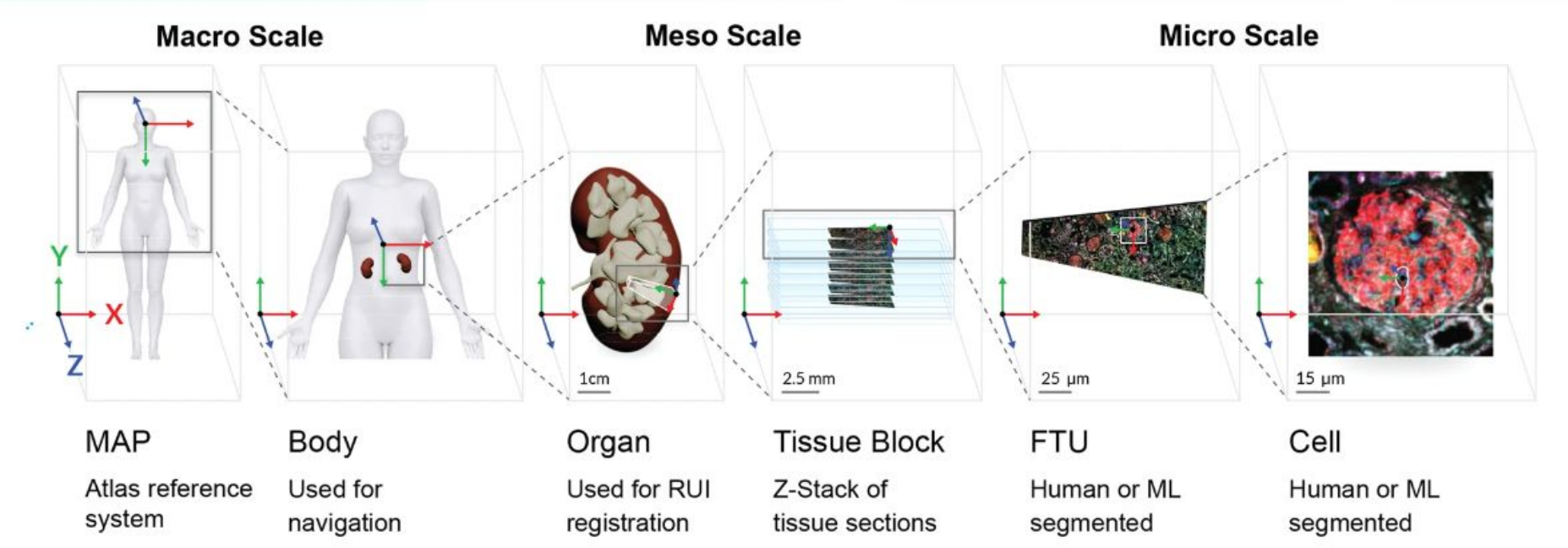
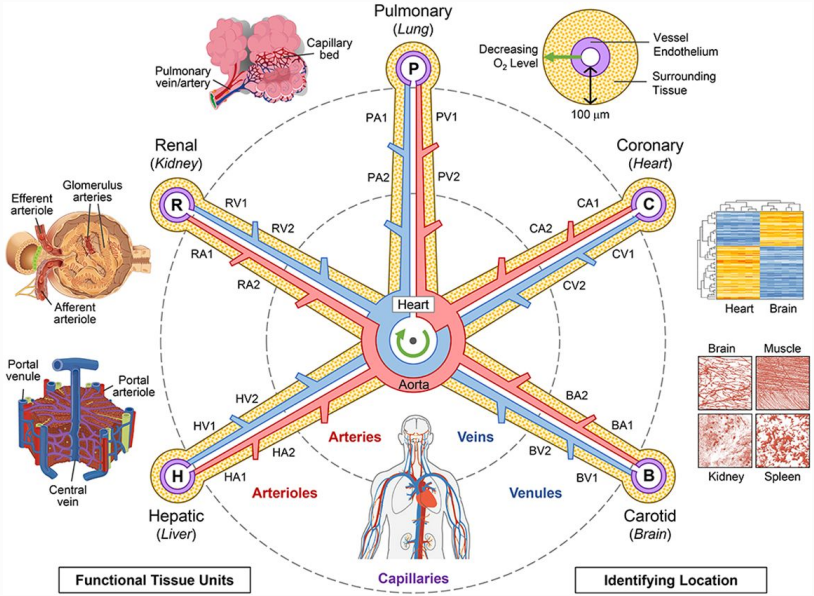


Image Source: Börner, K., Bueckle, A., Herr, B.W. *et al.* Tissue registration and exploration user interfaces in support of a human reference atlas. *Commun Biol* 5, 1369 (2022). https://doi.org/10.1038/s42003-022-03644-x

Vasculature Common Coordinate Framework



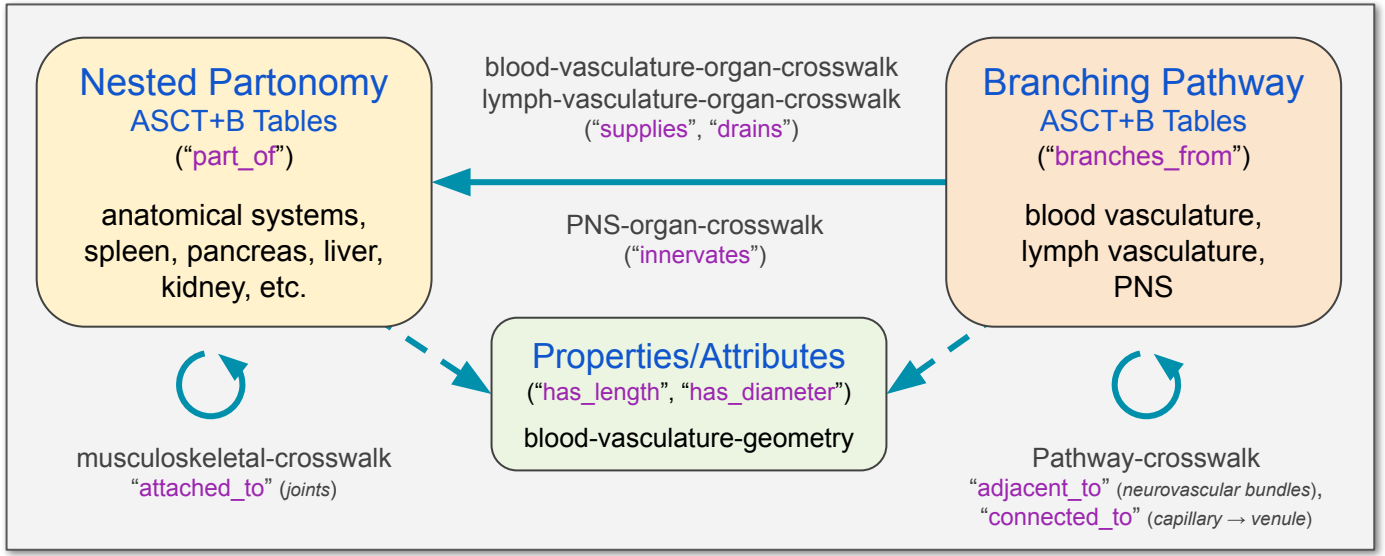
- The Vascular Common Coordinate Framework (VCCF) Database comprises 900+ vessels [1-2].
- Using experimental data, we can determine the pathway, throughput/vessel size, and 3D orientation in space of the human blood vasculature.
- Mapping the complex highway of blood flow will help examine exosome diffusion via the bloodstream to understand the role exosomes play in organ-to-organ communication or where exosomes might aggregate due to branches or tortuosity of the vessels.

- Weber GM, Ju Y, Börner K. Considerations for Using the Vasculature as a Coordinate System to Map All the Cells in the Human Body. *Front Cardiovasc Med*. 2020 Mar 13;7:29. https://www.frontiersin.org/articles/10.3389/fcvm.2020.00029/full
- Database: Boppana A, et al. Anatomical structures, cell types, and biomarkers of the healthy human blood vasculature. *Sci Data*. 2023 Jul 19;10(1):452. https://www.nature.com/articles/s41597-023-02018-0

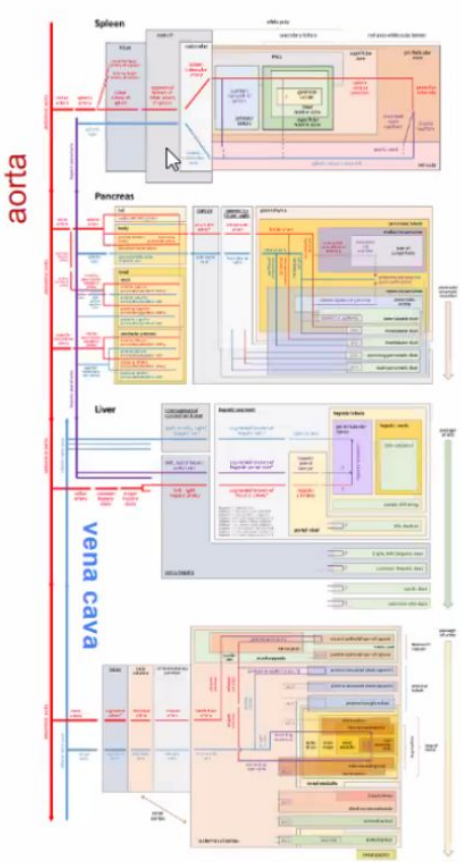
HRA Pathways and Crosswalks

- Blood vasculature, lymph vasculature, and PNS form pathways that extend from the heart and brain to all organs of the body
- Crosswalk files list relationships between the pathways and organs or other pathways; crosswalk diagrams visualize these relationships
- Geometry files describe pathway attributes (e.g., length and diameter) https://www.nature.com/articles/s41597-023-02018-0

Griffin Weber
Associate Professor of Medicine



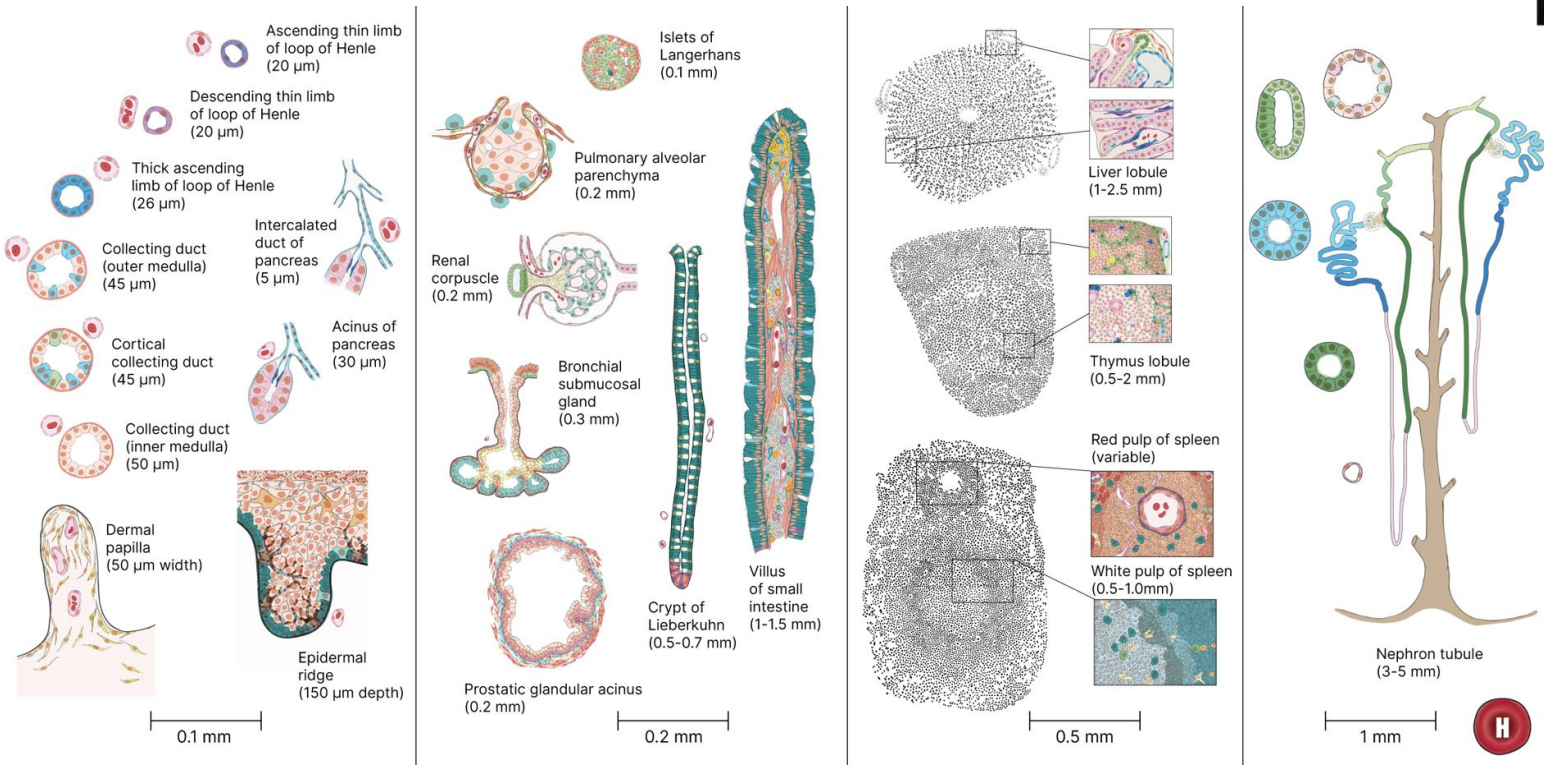
Crosswalk Diagrams



Blood Vasculature: Katherine S Gustilo, Avinash Boppana, Quinlan Cuddy **Lymph Vasculature**: Dhruv Singhal, Maxim Itkin, Ellen Quardokus **PNS**: Ilias Ziogas, Fahim Imam, Maryann Martone

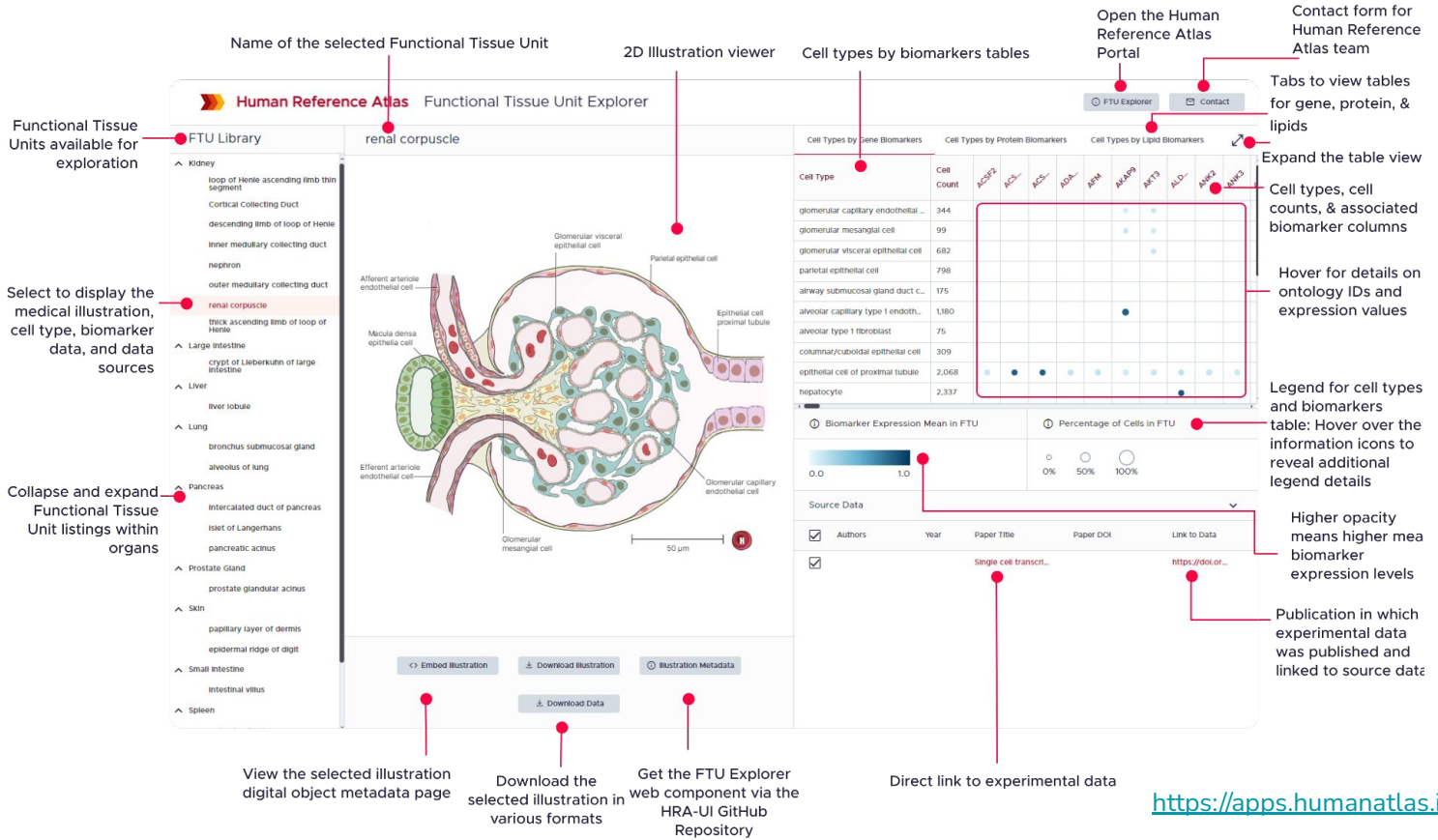
Functional Tissue Units (FTUs)

Supriya Bidanta
Research Assistant



https://www.biorxiv.org/content/10.1101/2023.10.16.562593v3 | Data: https://humanatlas.io/2d-ftu-illustrations

Interactive FTU Explorer

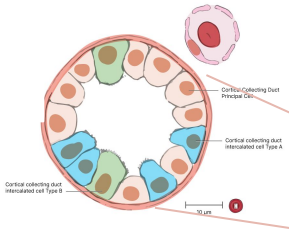


https://apps.humanatlas.io/ftu-explorer

Data for Interactive FTU Explorer

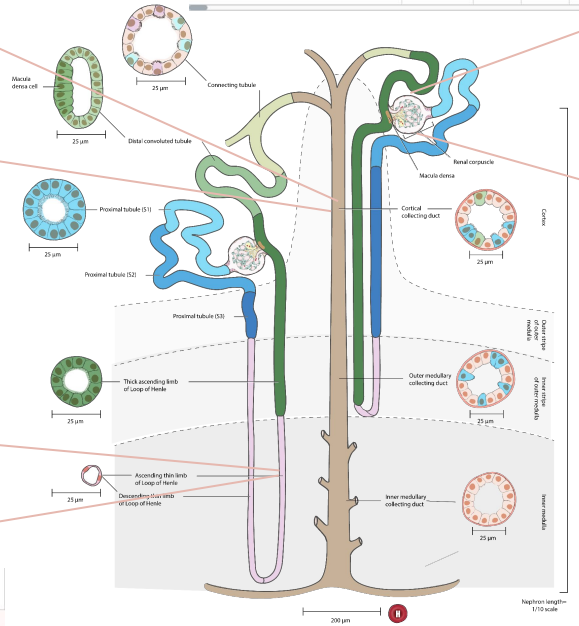
Experimental data mapped to Nephron (center), Ascending thin limb (lower left), Cortical Collecting Duct (upper left) and Renal Corpuscle of Kidney (upper right)

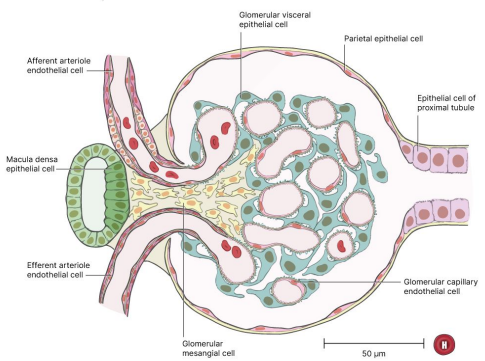
Kidney



Gene Biomarkers	Protein Biomarkers	Lipid Biomarkers

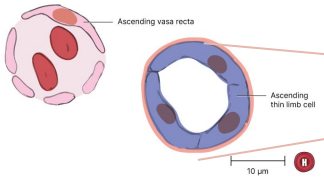
Cell Type	Cell Count	AASS	AKT3	ALS2...	ARG...
glomerular capillary endothelial cell	344		•		•
glomerular mesangial cell	99		•		•
glomerular visceral epithelial cell	341	•	•	•	•
parietal epithelial cell	266				•





Gene Biomarkers	Protein Biomarkers	Lipid Biomarkers

Cell Type	Cell Count	AKAP9	AKT3	ANK...
kidney collecting duct alpha-intercalated cell	746	•		
kidney collecting duct beta-intercalated cell	209	•		
kidney cortex collecting duct principal cell	562	•	•	
peritubular capillary endothelial cell	344	•	•	•



Gene Biomarkers	Protein Biomarkers	Lipid Biomarkers

Cell Type	Cell Count	AKAP9	AKT3	
kidney loop of henle thin ascending limb epithelia...	2,533	•		
vasa recta ascending limb cell	344	•	•	

Cell Types by Gene Biomarkers

Gene Biomarkers	Protein Biomarkers	Lipid Biomarkers

Cell Type	Cell Count	ACSF2	ACS...
epithelial cell of proximal tubule	2,068	•	•
kidney connecting tubule epithelial cell	1,052		
kidney distal convoluted tubule epithelial cell	1,878		
kidney loop of henle thick ascending limb epitheli...	2,533		

Biomarker Expression Mean in FTU

0.0 1.0

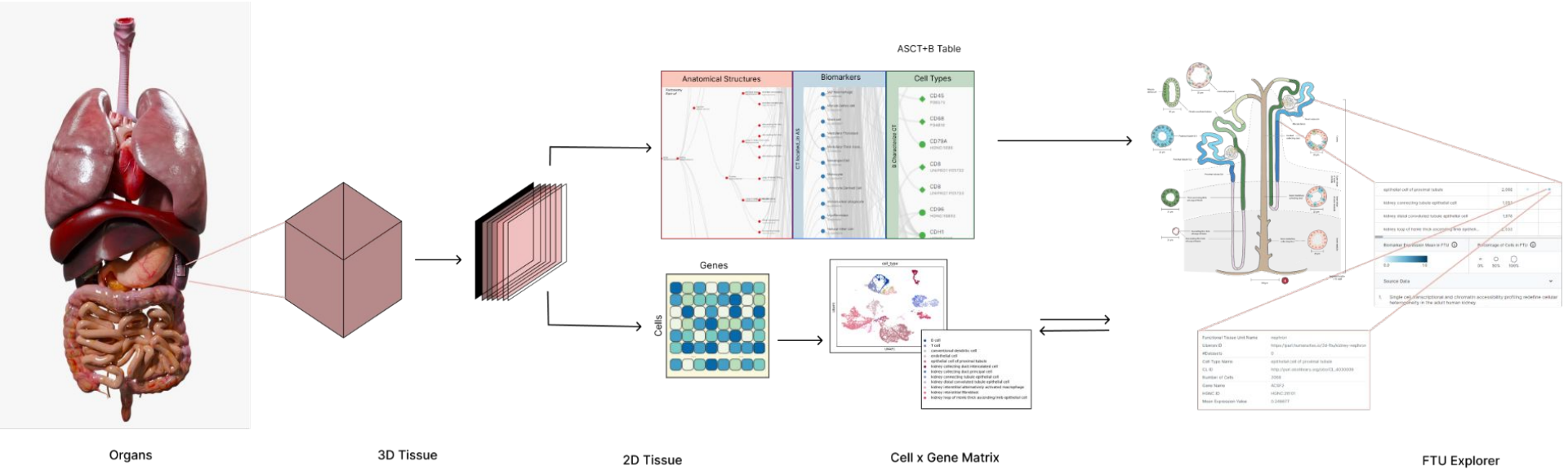
Percentage of Cells in FTU

0% 50% 100%

Source Data

1. Single cell transcriptional and chromatin accessibility profiling redefine cellular heterogeneity in the adult human kidney
snRNA-seq of Three Healthy Human Kidney Tissue

Data for Interactive FTU Explorer



The process of modeling a functional tissue unit (FTU) involves (1) gathering anatomical structure, cell type, and biomarker terminology and illustrations, (2) inviting organ experts to review the FTU illustration and terminology and suggest improvements, (3) working with a medical illustrator to create vector-based drawings of the FTUs, (4) reviewing FTUs for accuracy, (5) compiling experimental data on gene expressions specific to each cell type within the FTU, (6) adding data to the Human Reference Atlas (HRA), the FTU Explorer, and the HRA Organ Gallery.

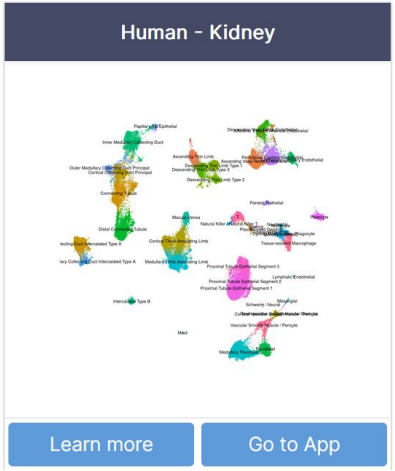
Data for Interactive FTU Explorer

Transcriptomics & Proteomics Data

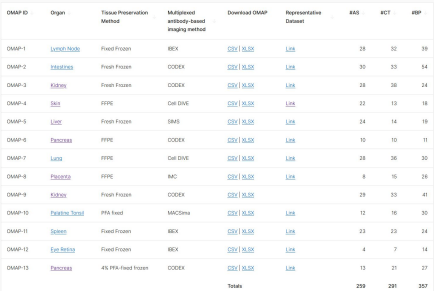
- **Transcriptomics:** Understanding gene expression across different cell types is crucial for tissue function. If you have human data from scRNA-seq and snRNA-seq studies for any of the 22 FTUs, annotated using Azimuth, CellTypist, and popV (compatible with the HRA), please share .h5ad or .hDF5 or .mtx file and link to primary publication.

- **Proteomics:** Protein expression, spatial transcriptomics (e.g., CODEX, MS-based Proteomics, Mass Cytometry). If you have data generated using an existing (or planned) Organ Mapping Antibody Panel (OMAP) for any of the 22 or other FTUs, please share TIFF, OME-TIFF, .fcs, .raw, .mzML, .mzXML, .txt formatted file and link to primary publication.

- **Multi-Omics:** We are interested to explore using Xenium and other multi-omics data to characterize FTUs.



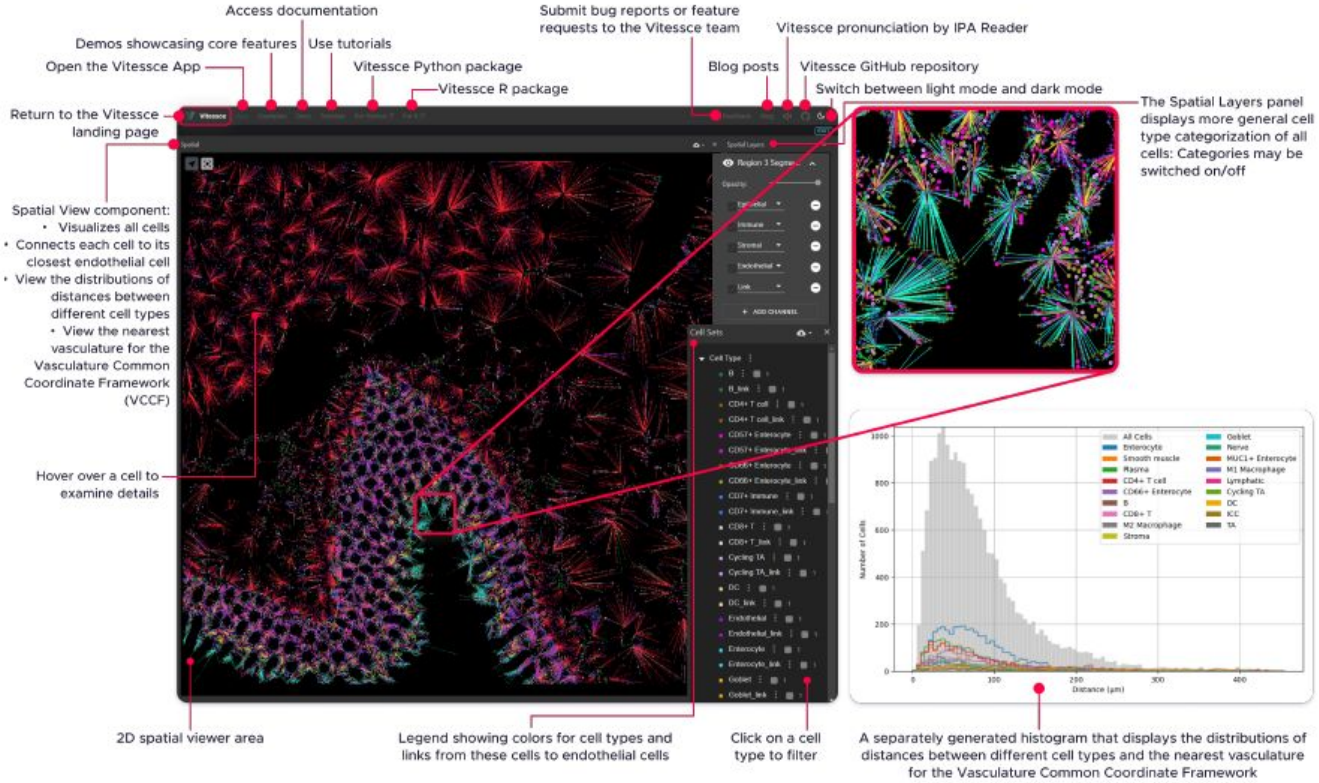
https://azimuth.hubmapconsortium.org



https://humanatlas.io/omap

If you have data to share, please reach out to Supriya Bidanta at sbidanta@iu.edu.

Cell Distance Visualizations



Yashvardhan Jain
Research Software Engineer
(Machine Learning)

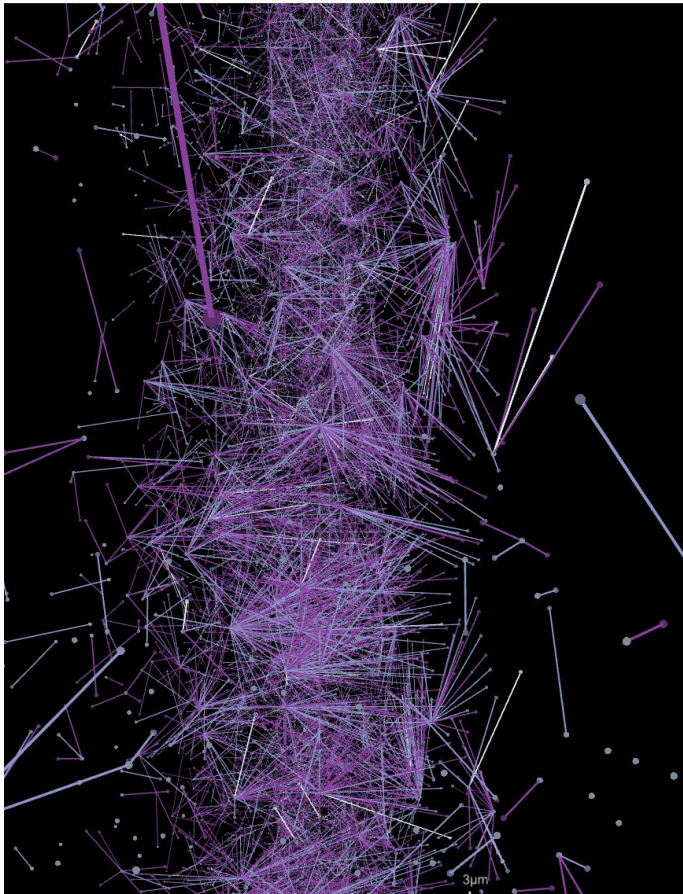
If you are interested to explore cell-cell, cell-FTU distance distributions, please share your data in this format:

x	y	z	Cell Type
555	756	4	Endothelial cell
765	231	3	B cell
356	235	7	T cell

With Yash Jain, MC-IU yashjain@iu.edu.

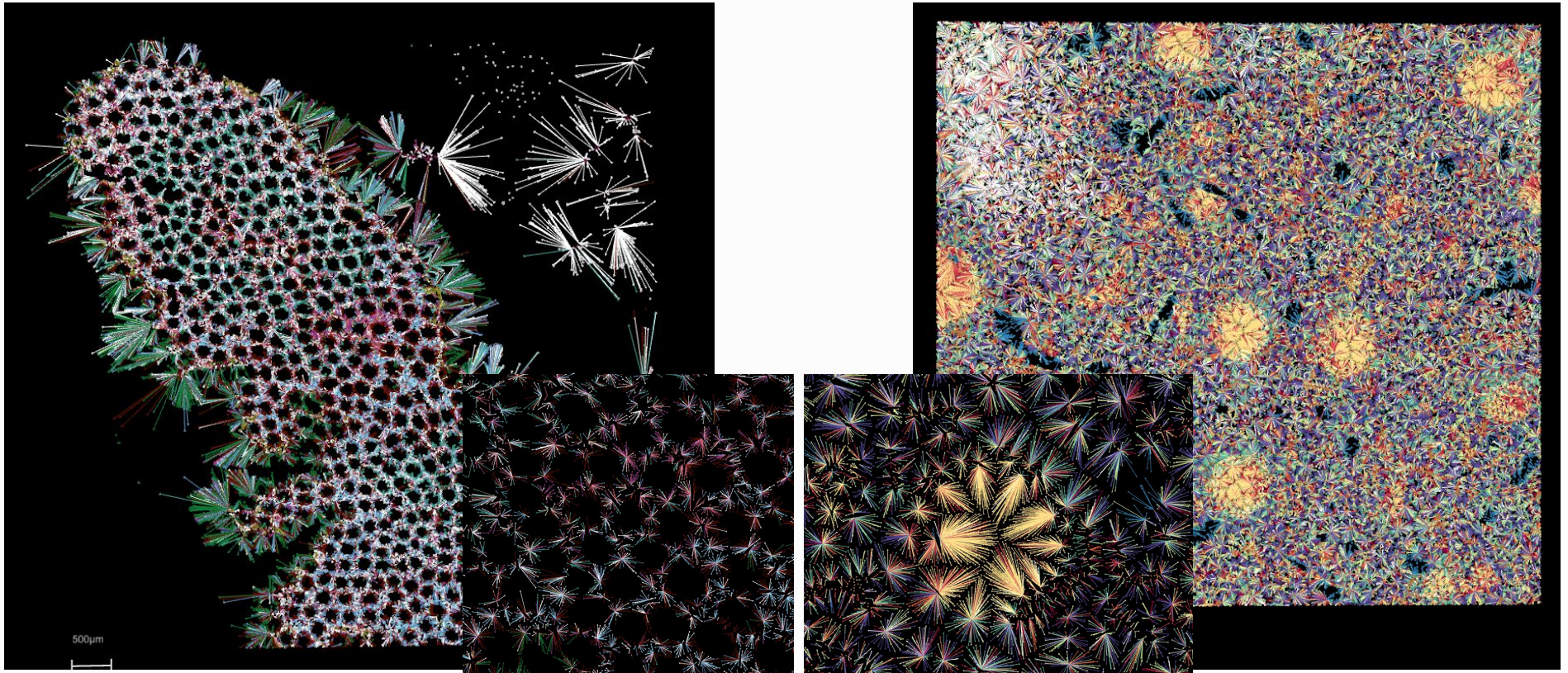
Join zoom next meeting on June 24, 2024 at 4-5p ET. Email Nancy Ruschman, nruschma@indiana.edu if you don't see invite in your cal.

VCCF at the Single Cell Level



Skin Data from Ghose, S., Ju, Y., McDonough, E. *et al.* 3D reconstruction of skin and spatial mapping of immune cell density, vascular distance and effects of sun exposure and aging. *Commun Biol* 6, 718 (2023). https://doi.org/10.1038/s42003-023-04991-z

VCCF at the Single Cell Level



Intestine Data from Hickey, J.W., Becker, W.R., Nevins, S.A. *et al.* Organization of the human intestine at single-cell resolution. *Nature* 619, 572–584 (2023). https://doi.org/10.1038/s41586-023-05915-x

Spleen Data from Currlin, Seth, et al. "Immune, endothelial and neuronal network map in human lymph node and spleen." *bioRxiv* (2021): 2021-10.

VCCF at the Single Cell Level

Slide Omitted - Unpublished CODEX Lymph Node Data from Rong Fan (Yale School of Medicine)

VCCF Teams and Datasets

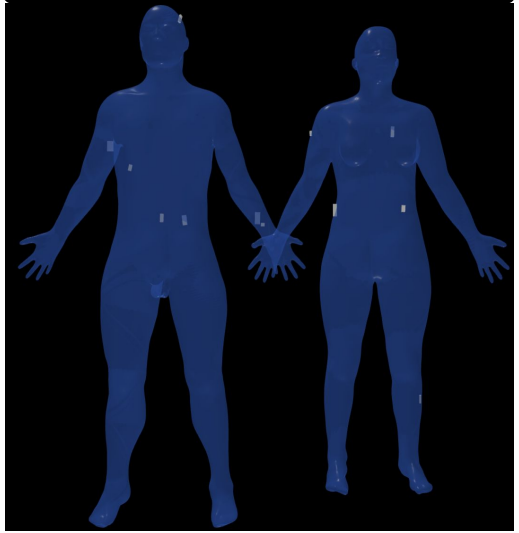
Lead PI	Lead contact	Institution	Organ	Technology	# of datasets	# of cells	Thickness (µm)	Pixel size (µm/px)	RUI Registered?	Data Published [Y/N]
Michael Snyder	John Hickey (Duke U)	Stanford University	S/L Intestines	CODEX	66	2,603,217	7	0.866	Y	Y [Paper page]
Michael Snyder	John Hickey	Stanford University	Esophagus	CODEX	1	45,958	7	0.377	IP	Y [Paper]
Michael Snyder	John Hickey	Stanford University	Tonsil	CODEX	1	1,73,968	7	0.377	N	Y [Paper]
Michael Snyder	Emma Marie Monte	Stanford University	Colon	Xenium	1 (29 layers)	2,639,215	5	0.2125	N	N
Jean Fan, Clive Wasserfall, M. Atkinson	Jean Fan	Johns Hopkins U, Data from UFL	Spleen	CODEX	6	992,398	5	0.377	Y	Y [Paper, Paper]
Peter Sorger	Clarence Yapp	Harvard Medical School	Colon	CyCIF	25	12,758,141	5	0.650	Y	Y [Paper]
Gloria Pryhuber	Gloria Pryhuber, Jeffrey Purkerson, Ravi Misra	U of Rochester Medical Center	Lung	CODEX	2*	1,236,464	5	0.5056	Y	N
Rong Fan	**Archibald Enninful**	**Yale School of Medicine**	**Lymph Node**	**CODEX**	**5**	**8,937,078**	**10**	**0.5**	IP	N
Fiona Ginty	Fiona Ginty	GE Research	Skin	3D Cell DIVE	12	98,049	5	0.325	Y	Y [Paper page]
Peter Sorger	Clarence Yapp	Harvard Medical School	Skin	True 3D from confocal	2	55,255	35 (3D)	140x140x 280 nm	N	Y [Paper]
Michael Angelo	Michael Angelo	Stanford University	Maternal-Fetal Interface	MIBI-TOF	209	477,747	4	0.391	IP	Y [Paper page]

VCCF: All Data is RUI Registered

If you encounter any issues, please contact Dan Qaurooni <dequeue@iu.edu>.

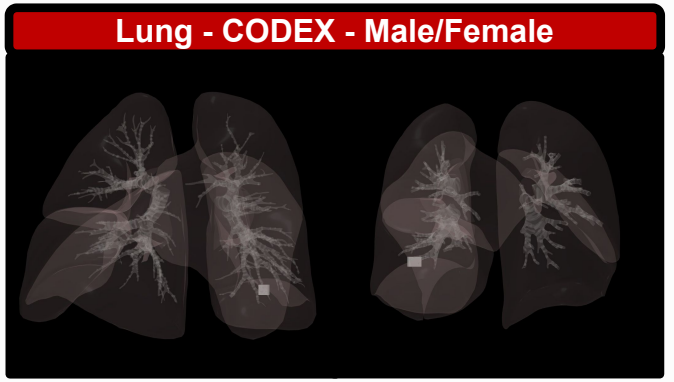
Daniel Qaurooni
Post-doctoral Fellow

Skin - Cell DIVE - Male/Female

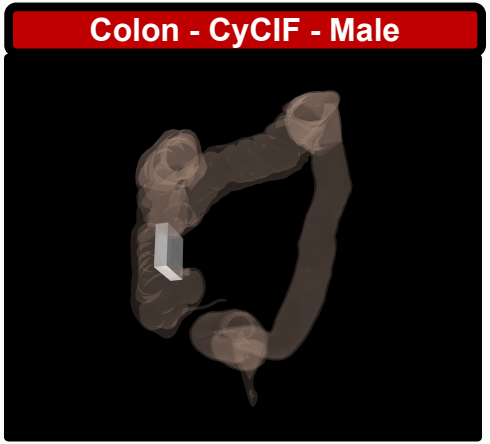


Spleen - CODEX - Male/Female

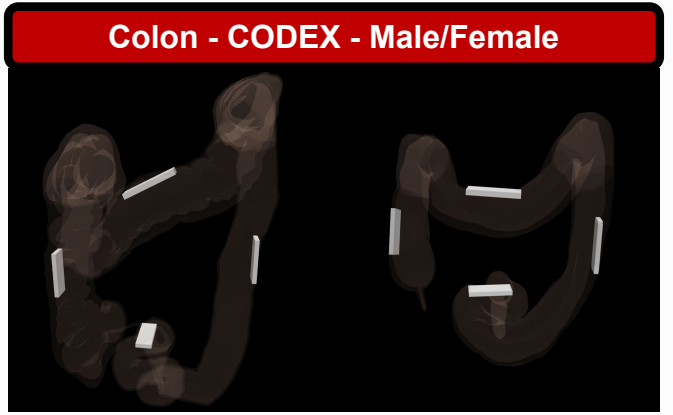
Lung - CODEX - Male/Female



Colon - CyCIF - Male



Colon - CODEX - Male/Female



VCCF: Data is mapped to HRA & CL

If you encounter any issues, please contact Ellen Quardokus <ellenmq@iu.edu>.

Ellen Quardokus
Senior Research Analyst

	A
1	**Tabs to crosswalk**
2	Colon-CODEX-Hickey-2023
✅ 3	BE-CODEX-Snyder (Barrett's esophagus)
✅ 4	Tonsil-CODEX-Snyder
5	Colon-Xenium-Snyder
6	Spleen-CODEX-UFL
7	Colon-CyCIF-Sorger
8	Lung-CODEX-Gloria
9	Lymph Node-CODEX-Rong Fan
10	Skin-CellDIVE-GE

	A	B	C	D	E	F	G
1	Crosswalk Cell Types CODEX Colon Hickey 2023						
2							
3	Author Name(s):	Ellen M. Quardokus					
4	Author ORCID(s):	0000-0001-7655-4833					
5	Reviewer(s):						
6	Reviewer ORCID(s):						
7	General Publication(s):						
8	Data DOI:						
9	Date:	revise for April 1, 2024					
10	Version Number:	v1.0					
11	**Cell Type**	**CL Label**	**CL ID**	**CL_Match**	**CL_level**	**Organ_Level**	**Organ_ID**
12	Enterocyte	enterocyte	CL:0000584	skos:exactMatch	superclass	large intestine	UBERON:0000059
13	Smooth Muscle	enteric smooth muscle cell	CL:0002504	skos:exactMatch	superclass	large intestine	UBERON:0000059
14	Plasma	plasma cell	CL:0000786	skos:exactMatch	specific	large intestine	UBERON:0000059
15	CD4+ T Cell	CD4-positive, alpha-beta T cell	CL:0000624	skos:exactMatch	superclass	large intestine	UBERON:0000059
16	CD66+ Enterocyte	enterocyte:CD66+	CL:0000584	skos:narrowMatch	specific	large intestine	UBERON:0000059
17	B	B cell	CL:0000236	skos:exactMatch	superclass	large intestine	UBERON:0000059
18	CD8+ T	CD8-positive, alpha-beta T cell	CL:0000625	skos:exactMatch	superclass	large intestine	UBERON:0000059
19	M2 Macrophage	alternatively activated macrophage	CL:0000890	skos:exactMatch	specific	large intestine	UBERON:0000059
20	Stroma	stromal cell	CL:0000499	skos:exactMatch	superclass	large intestine	UBERON:0000059
21	Goblet	goblet cell	CL:0000160	skos:exactMatch	superclass	large intestine	UBERON:0000059
22	Nerve	neuron	CL:0000540	skos:exactMatch	superclass	large intestine	UBERON:0000059
23	MUC1+ Enterocyte	enterocyte:MUC1+	CL:0000584	skos:narrowMatch	specific	large intestine	UBERON:0000059
24	M1 Macrophage	inflammatory macrophage	CL:0000863	skos:exactMatch	specific	large intestine	UBERON:0000059
25	Lymphatic	endothelial cell of lymphatic vessel	CL:0002138	skos:exactMatch	superclass	large intestine	UBERON:0000059
26	Cycling TA	transit amplifying cell:cycling	CL:0009010	skos:narrowMatch	cell state	large intestine	UBERON:0000059
27	DC	dendritic cell	CL:0000451	skos:exactMatch	superclass	large intestine	UBERON:0000059
28	ICC	interstitial cell of Cajal	CL:0002088	skos:exactMatch	specific	large intestine	UBERON:0000059
29	TA	transit amplifying cell	CL:0009010	skos:exactMatch	specific	large intestine	UBERON:0000059

US#5. Provide cell distance distribution visualizations

As a ...

Researcher or Pathologist

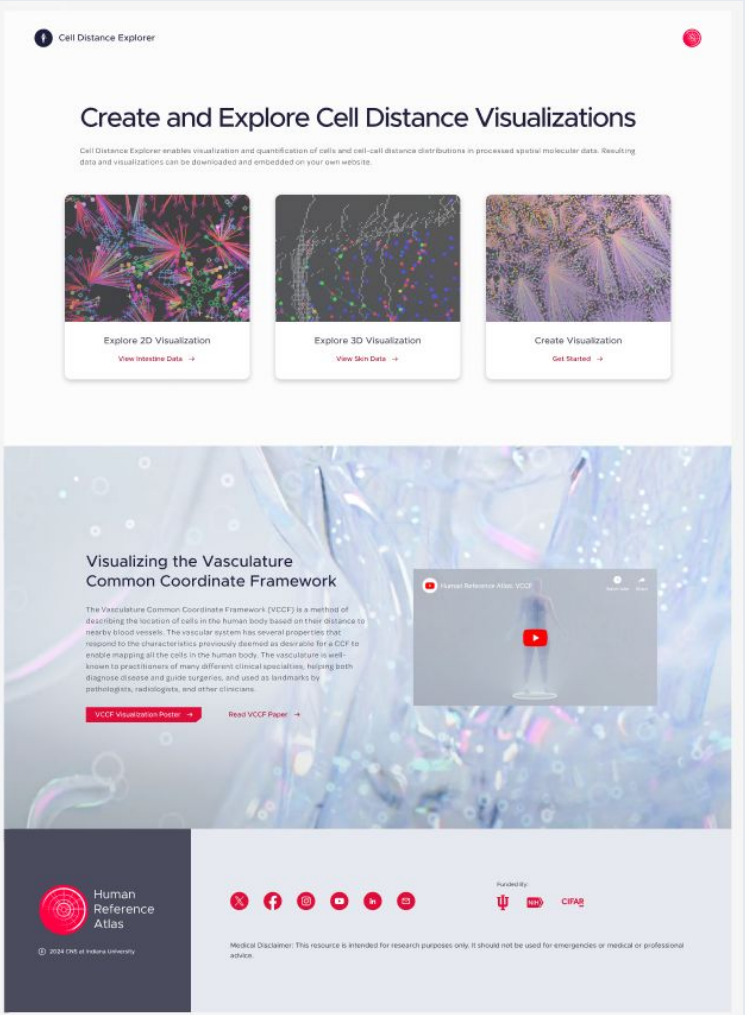
I want to ...

Compute, visualize, and explore distance distributions between different cells, cell types, and anatomical structures (e.g., FTUs), and cell types and morphological features (e.g., the edge of an organ).

, so that ...

I can improve our collective understanding of how we age (or, how disease develops, e.g., how tumor cells grow or metastasize) in support of targeted therapies.

US#5 UX (WIP)


Cell Distance Explorer
Create and Explore Cell Distance Visualizations
Cell Distance Explorer enables visualization and quantification of cells and cell-cell distance distributions in processed spatial molecular data. Resulting data and visualizations can be downloaded and embedded on your own website.
Explore 2D Visualization
View Intestine Data →
Explore 3D Visualization
View Skin Data →
Create Visualization
Get Started →
Visualizing the Vasculature Common Coordinate Framework
The Vasculature Common Coordinate Framework (VCCF) is a method of describing the location of cells in the human body based on their distance to nearby blood vessels. The vascular system has several properties that respond to the characteristics previously deemed as desirable for a CCF to enable mapping all the cells in the human body. The vasculature is well-known to practitioners of many different clinical specialties, helping both diagnose disease and guide surgeries, and used as landmarks by pathologists, radiologists, and other clinicians.
VCCF Visualization Poster →
Read VCCF Paper →
Human Reference Atlas
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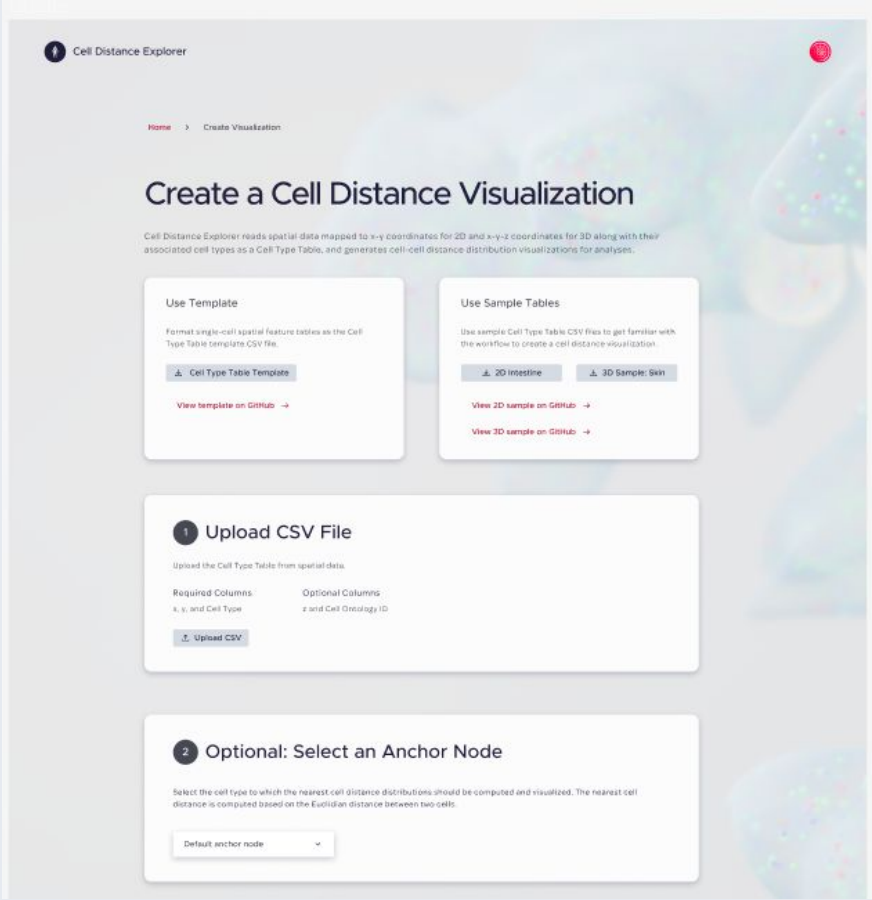
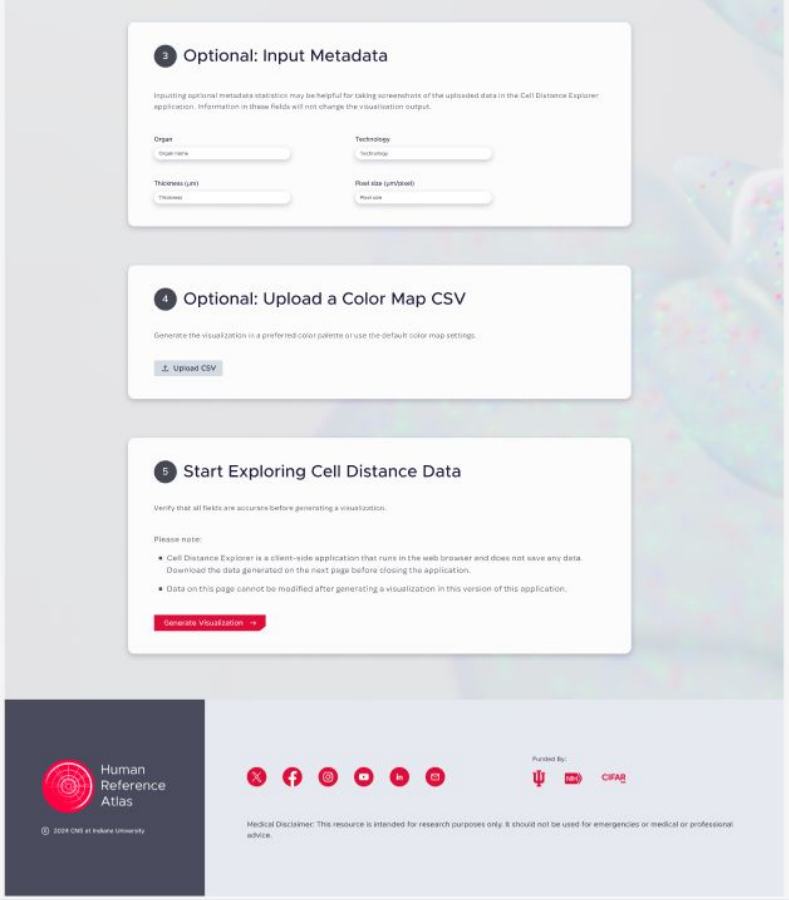
Funded by:
Medical Disclaimer: This resource is intended for research purposes only. It should not be used for emergencies or medical or professional advice.

US#5 UX (WIP)


Cell Distance Explorer
Home › Create Visualization
Create a Cell Distance Visualization
Cell Distance Explorer reads spatial data mapped to x-y coordinates for 2D and x-y-z coordinates for 3D along with their associated cell types as a Cell Type Table, and generates cell-cell distance distribution visualizations for analyses.
Use Template
Format single-cell spatial feature tables as the Cell Type Table template CSV file.
Cell Type Table Template
View template on GitHub →
Use Sample Tables
Use sample Cell Type Table CSV files to get familiar with the workflow to create a cell distance visualization.
2D Intestine
3D Sample: Skin
View 2D sample on GitHub →
View 3D sample on GitHub →
1 Upload CSV File
Upload the Cell Type Table from spatial data.
Required Columns
x, y, and Cell Type
Optional Columns
z and Cell Ontology ID
Upload CSV
2 Optional: Select an Anchor Node
Select the cell type to which the nearest cell distance distributions should be computed and visualized. The nearest cell distance is computed based on the Euclidian distance between two cells.
Default anchor node


3 Optional: Input Metadata
Inputting optional metadata statistics may be helpful for taking screenshots of the uploaded data in the Cell Distance Explorer application. Information in these fields will not change the visualization output.
Organ
Technology
Thickness (µm)
Pixel size (µm/pixel)
4 Optional: Upload a Color Map CSV
Generate the visualization in a preferred color palette or use the default color map settings.
Upload CSV
5 Start Exploring Cell Distance Data
Verify that all fields are accurate before generating a visualization.
Please note:
Cell Distance Explorer is a client-side application that runs in the web browser and does not save any data. Download the data generated on the next page before closing the application.
Data on this page cannot be modified after generating a visualization in this version of this application.
Generate Visualization →
Human Reference Atlas
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Funded By:
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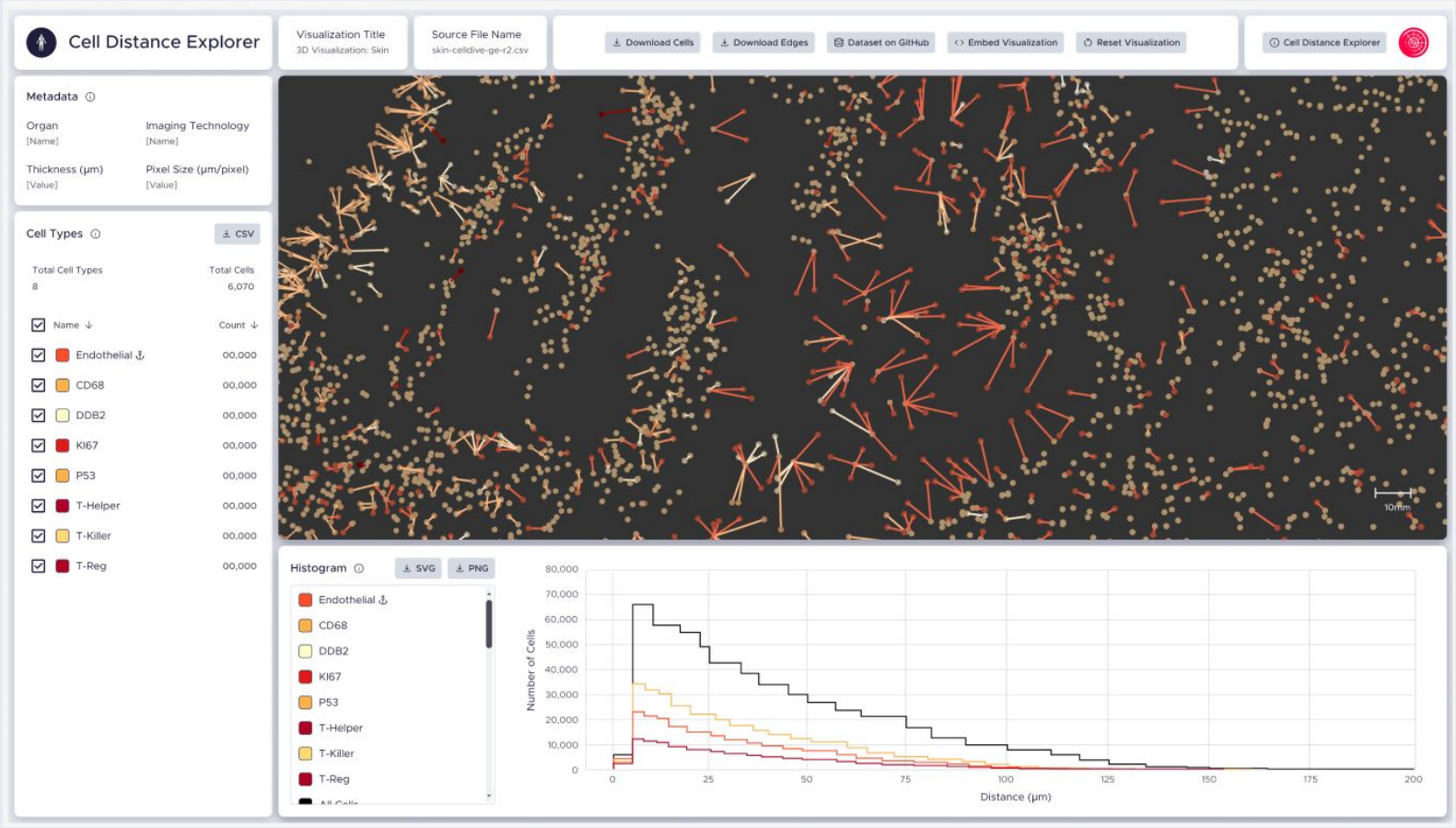
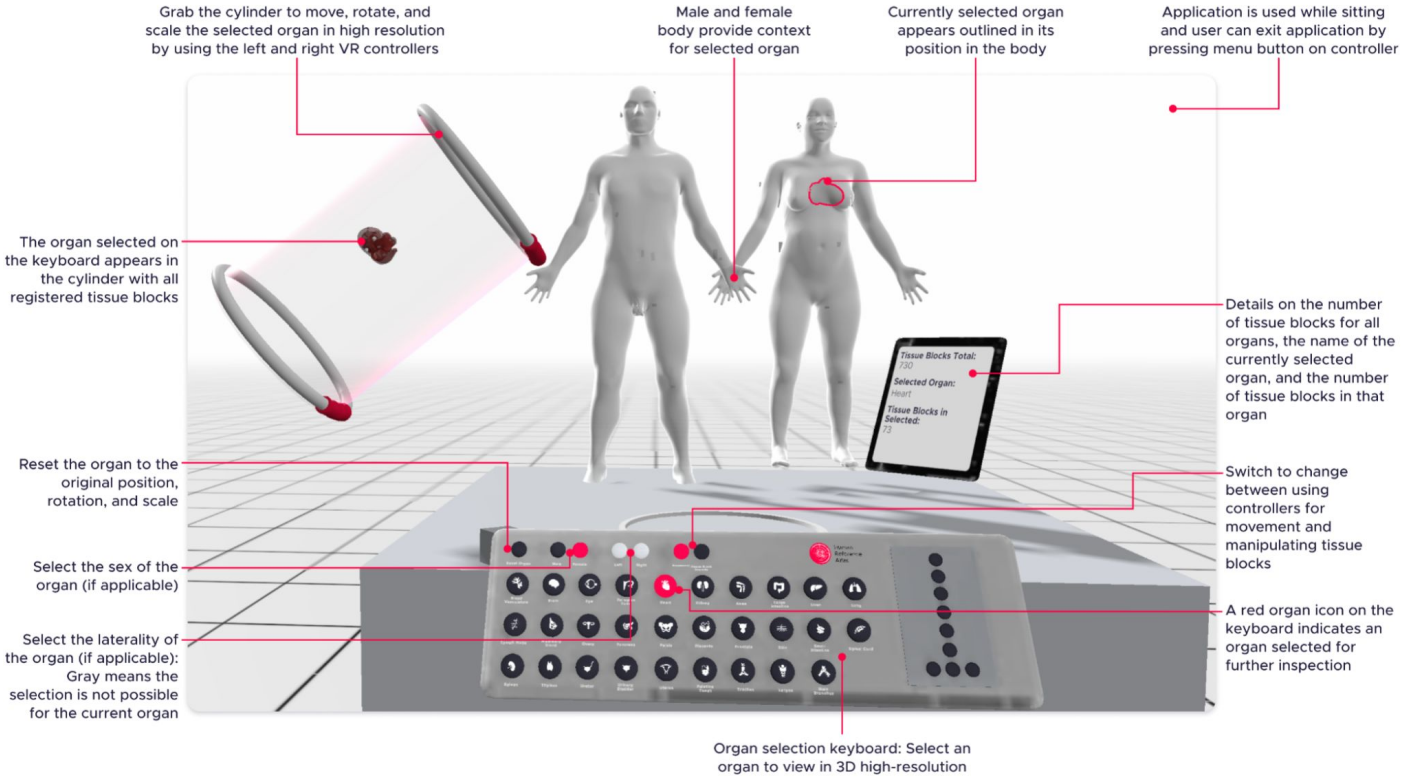
US#5 UX (WIP)


Cell Distance Explorer
Visualization Title
3D Visualization: Skin
Source File Name
skin-celldive-ge-r2.csv
Download Cells
Download Edges
Dataset on GitHub
Embed Visualization
Reset Visualization
Cell Distance Explorer
Metadata
Organ
[Name]
Imaging Technology
[Name]
Thickness (µm)
[Value]
Pixel Size (µm/pixel)
[Value]
Cell Types
CSV
Total Cell Types
8
Total Cells
6,070
Name
Count
Endothelial
00,000
CD68
00,000
DDB2
00,000
KI67
00,000
P53
00,000
T-Helper
00,000
T-Killer
00,000
T-Reg
00,000
10mm
Histogram
SVG
PNG
Endothelial
CD68
DDB2
KI67
P53
T-Helper
T-Killer
T-Reg
Number of Cells
80,000
70,000
60,000
50,000
40,000
30,000
20,000
10,000
0
0
25
50
75
100
125
150
175
200
Distance (µm)

Cells and Distances in HRA Organ Gallery in VR



Andreas Bueckle
Research Lead

https://www.meta.com/experiences/5696814507101529

Cells and Distances in HRA Organ Gallery in VR

Top left: Dual-hand zoom at 65-72 FPS
Endothelial cells are red.

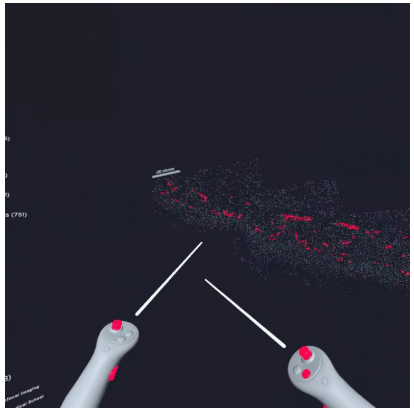
Top right: Anchor control allows moving and rotating the entire tissue stack.

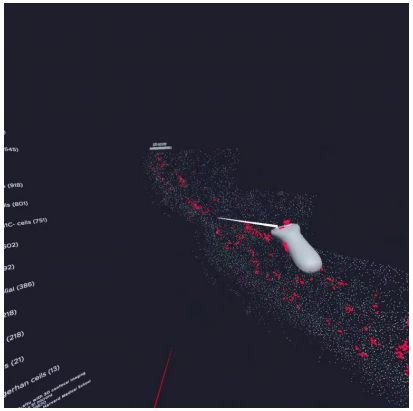
Bottom left: Custom-implemented brush-and-link allows highlighting all 13 cell types in VR.

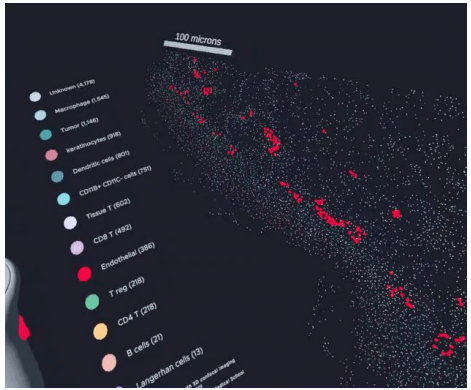
Bottom right: QR code to download app to Meta Quest 2, 3, and Pro.

For questions, please contact Andreas “Andi” Bueckle <abueckle@iu.edu>

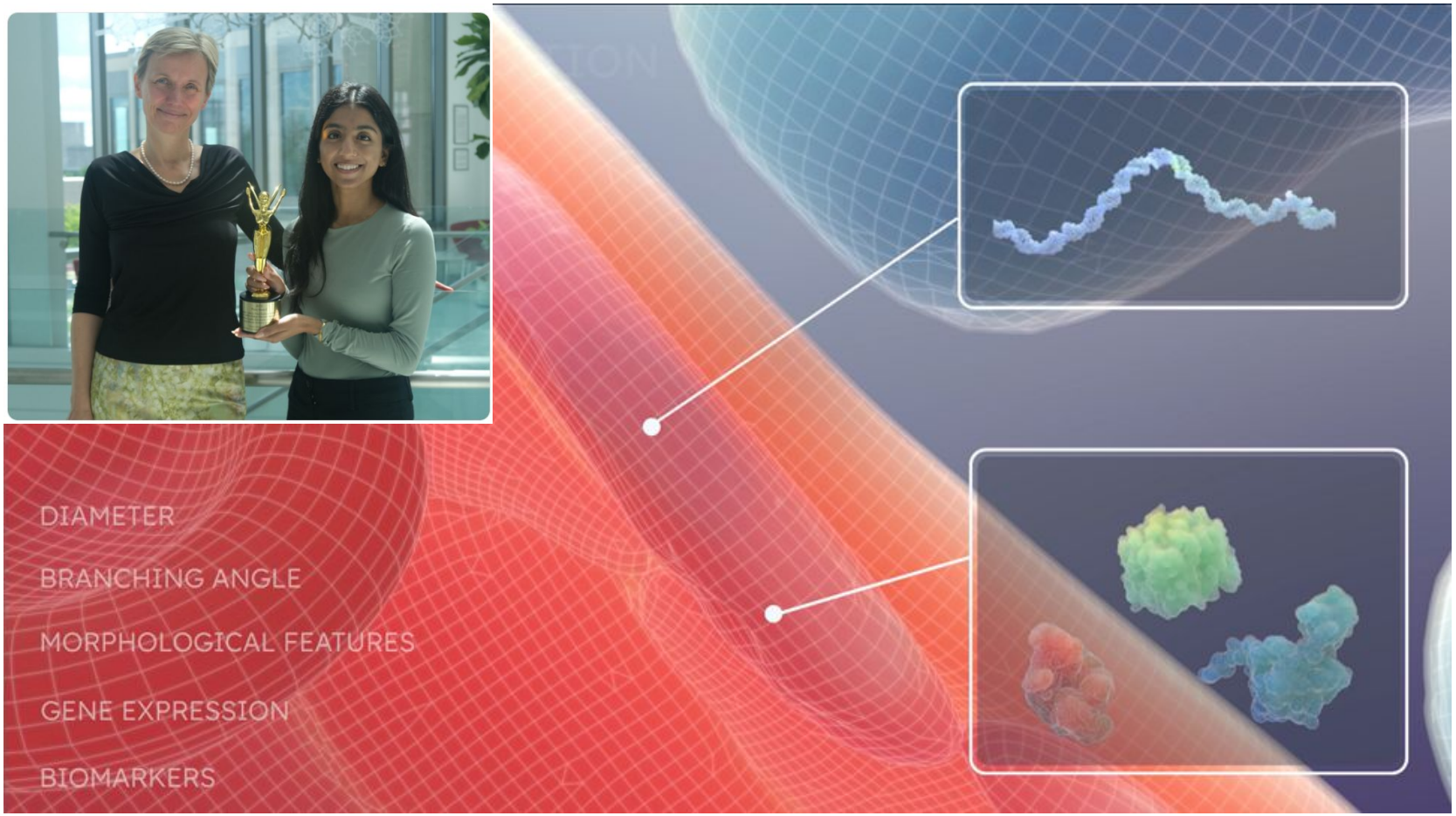
We would like to thank the NIH for the HuBMAP JumpStart Fellow that enables us to conduct this research and development.







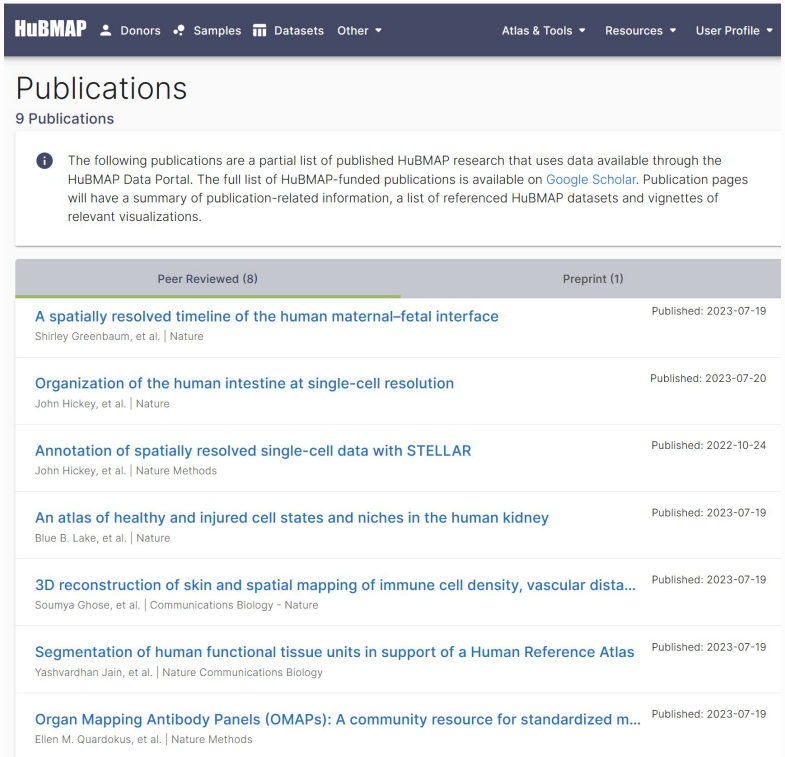
APP



HRA Vasculature Common Coordinate Framework (VCCF) Video, https://www.youtube.com/watch?v=zQeMgxo8n_U

VCCF Vis Publication Timeline

- Feb 28, 2024, 2-3pm: Zoom meeting to discuss focus and scope of paper & publication venue. Identify a lead contact per dataset.
- March - Nov, 2024: Monthly 1h meetings to discuss new data, alg, vis, write paper together. All are welcome to join, add data, suggest VCCF features. Email Nancy Ruschman, <nruschma@indiana.edu> if you don't see invite in your cal.
- Aug 26, 2024: Freeze data. No more data can be added.
- Sept - Oct, 2024: Compile Publication Pages on HuBMAP, SenNet, HTAN, and other portals.
- Nov 2024: Submit paper to *Nature Cell Biology*.



Thank You!

Contact: yashjain@iu.edu