

AUA
2024 MAY 3-6
San Antonio

Keynote:
The Human
Reference Atlas





Version 2.0

Human Reference Atlas

<https://humanatlas.io>



Keynote: The Human Reference Atlas



Bruce W. Herr II
Technical Director

Cyberinfrastructure for Network Science Center
Department of Intelligent Systems Engineering
Luddy School of Informatics, Computing, and Engineering
Indiana University, Bloomington, IN, USA



Human Reference Atlas Collaborators

- HuBMAP
- SenNet
- GTEx
- KPMP
- GUDMAP
- 13+ other consortia
- 250+ subject matter experts
- Funded by NIH and CIFAR
- Supported by HCA // Human Cell Atlas



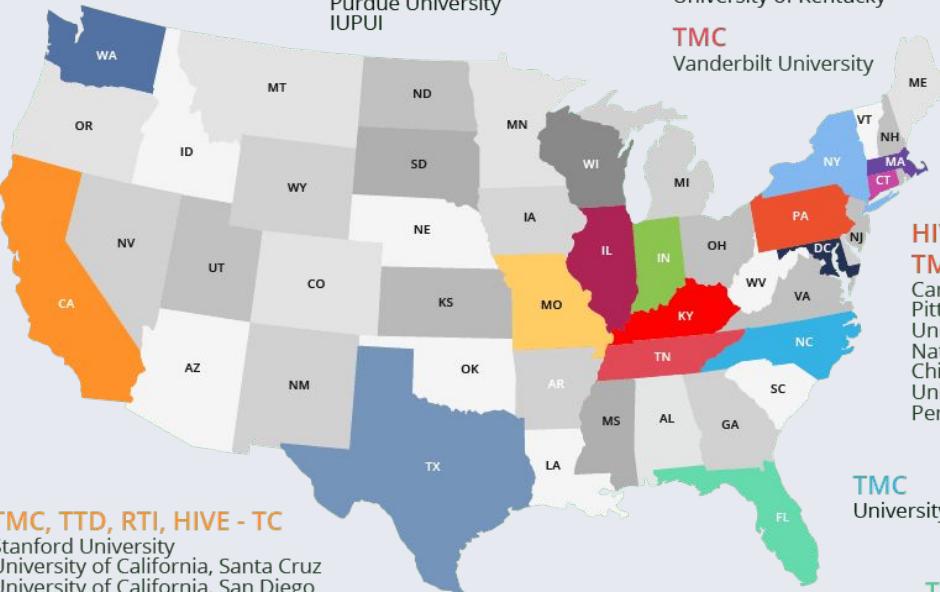
HuBMAP Contributing Sites

TMC, TTD

Pacific Northwest National Lab
Seattle Children's Hospital

TMC

Washington University, St. Louis



TMC, TTD, RTI, HIVE - TC

Stanford University
University of California, Santa Cruz
University of California, San Diego
City of Hope National Medical Center
Scripps Research

RTI, TTD, DP

Northwestern University
University of Illinois, Chicago
Lurie Children's Hospital of Chicago

HIVE - Mapping, TTD

Indiana University, Bloomington
Purdue University
IUPUI

HIVE - Mapping, RTI, TMC

New York Genome Center
University of Rochester Medical Center
General Electric Global Research Center

HIVE - TC

University of Kentucky

TMC

Vanderbilt University

NIH, TMC, DP

NIH Common Fund
Johns Hopkins University
Brigham and Women's Hospital



TMC

University of Zurich



TMC

Delft University of Technology



HIVE - TC, TMC

European Bioinformatics Institute

Wellcome Sanger Institute



Early history of the HRA and HuBMAP

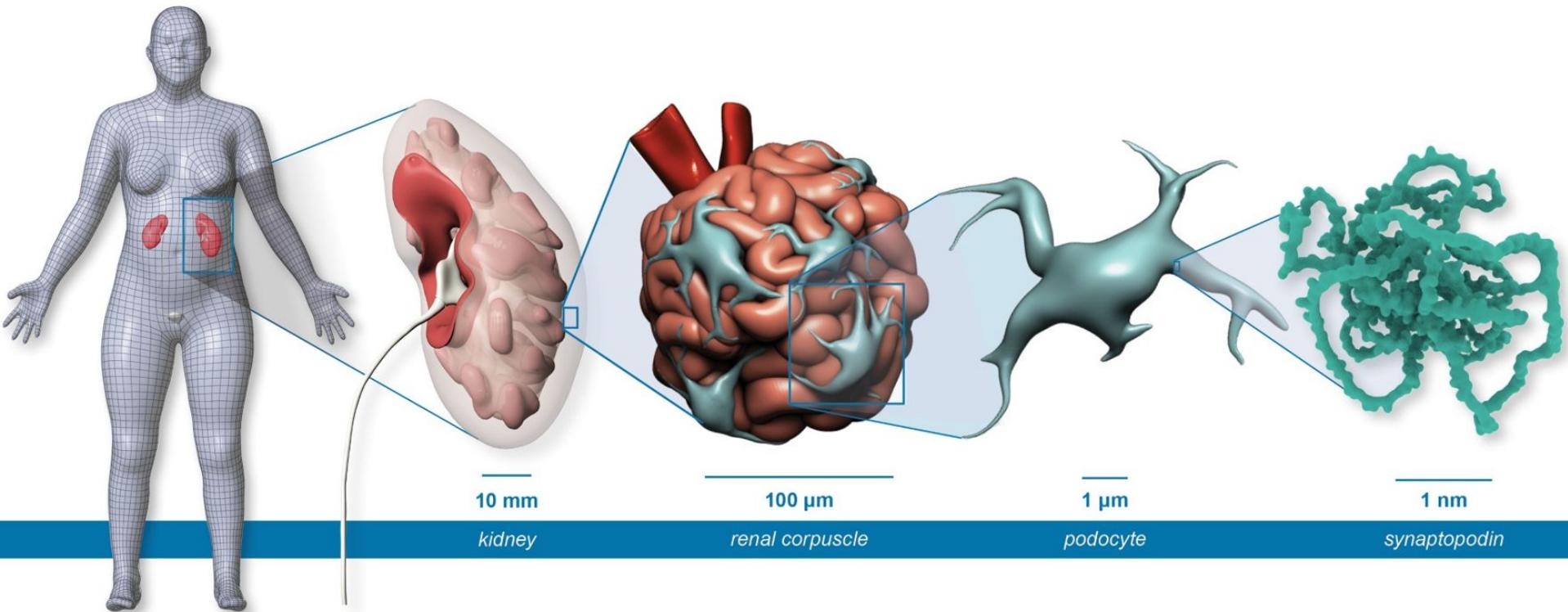
- HuBMAP started in 2018 with the goal of mapping the human body down to the cellular level
- The IU team started off with creating a common coordinate framework, that eventually evolved into the HRA
- In 2023, we published HRA v2.0
- We are now in the production phase of HuBMAP

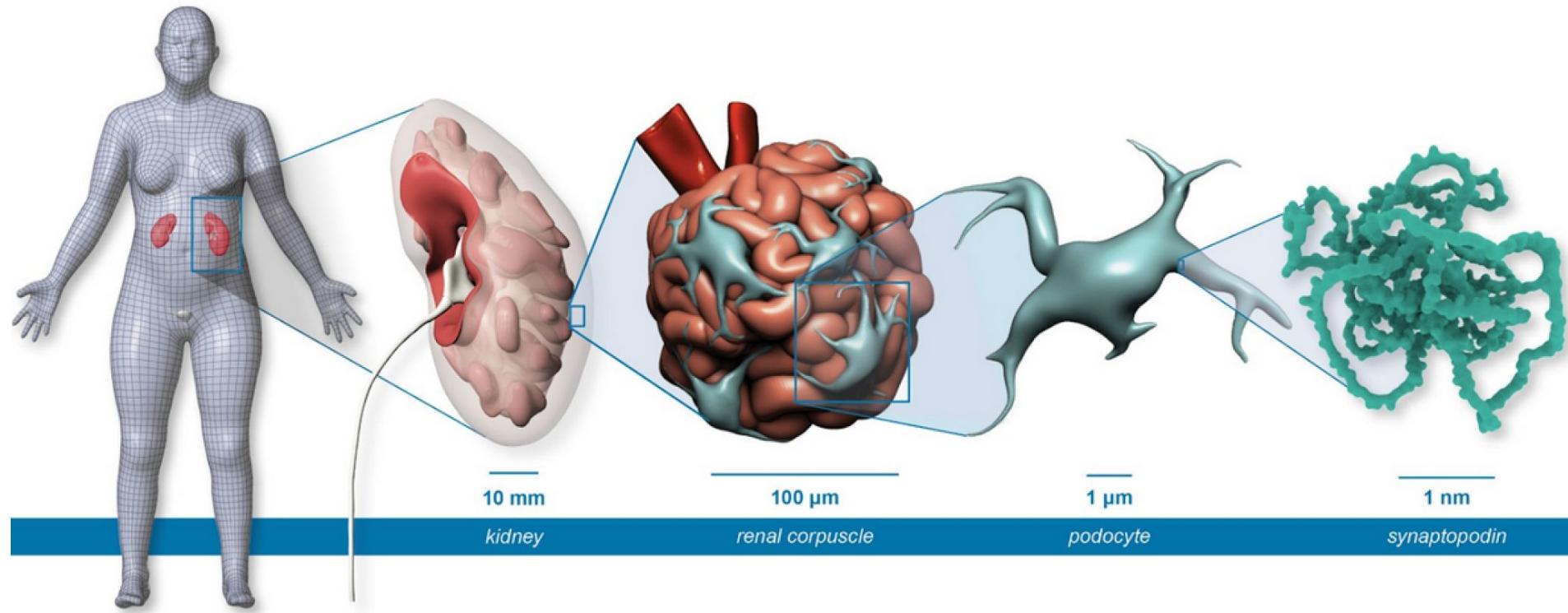
What is the HRA?



Human Reference Atlas (HRA)

A comprehensive, ontologically aligned, high-resolution, three-dimensional, multiscale atlas of anatomical structures and cells in the healthy human body





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

Vascular Geometry

Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

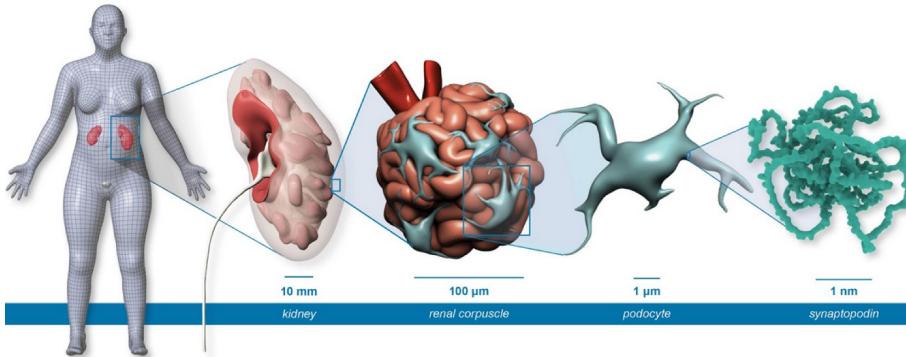
Vascular Geometry

Experimental Data (Donors, Tissues,
Extraction Sites, Datasets)

Atlas++

HRApop (Experimental Data + Cell Summaries)

HRAlit (HRA-relevant Literature)



Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

Vascular Geometry

Experimental Data (Donors, Tissues,
Extraction Sites, Datasets)

Atlas++

HRApop (Experimental Data + Cell Summaries)

HRAlit (HRA-relevant Literature)



Human Reference Atlas

User Stories guide the HRA development and keep it grounded in providing value

User stories are centered around

- **Construction** - Facilitate atlas construction by aligning new tissue blocks with existing data
- **Usage** - Use the atlas to gain insights into changes that occur at all levels in the body with aging or disease
- **Sustainability** - Ensure atlas sustainability with processes that encourage collaboration and guide future development

HRA User Stories

More than 30 one-on-one interviews were conducted with atlas architects, i.e., experts who serve as principal investigators or are otherwise intimately involved in the construction of the latest generation of human atlases, including BICCN, GTEx, GUDMAP, HCA, HuBMAP, Human Tumor Atlas Network (HTAN), KPMP, LungMAP, (Re)building the Kidney (RBK), and SenNet.

In addition, six programmers from different human atlas projects were surveyed.

Table on right shows feature summary, target user roles, user activities, and added value for seven user stories that drive HRA development.

Feature	User Role	User Activities	Added Value
<i>Facilitate atlas construction by aligning new tissue blocks with existing data</i>			
US#1. Predict cell type populations	Programmers that support Researchers, Clinicians, Pathologists	Predict and explore the likely cell type populations for a RUI-registered tissue block.	Improve cell type annotation through information on what cell type populations exist in what anatomical structures.
US#2. Predict spatial origin of tissue samples	Programmers that support Researchers, Clinicians	Predict and explore the likely 3D location in the human body for a given tissue block with known cell type population.	Compensate for the absence of spatial origin information in many single cell datasets.
<i>Use the atlas to gain insights into changes that occur at all levels in the body with aging or disease</i>			
US#3. Compare reference tissue with aging/diseased tissue	Researchers, Clinicians	Compare tissue blocks, cell types, and biomarker expression levels between healthy reference tissue and aging/diseased tissue.	Understand and communicate changes in tissue structure and function with age or disease.
US#4. Compare reference Functional Tissue Units with aging/diseased FTUs	Researchers, Clinicians	Compare FTUs in terms of cell types and mean biomarker expression levels for healthy reference tissue and aging/diseased tissue.	Understand and communicate changes in FTU structure and function with age or disease
US#5. Provide cell distance distribution visualizations	Researchers, Pathologists	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).	Add granularity to our understanding of how disease develops (e.g., how tumor cells grow or metastasize) in support of targeted therapies.
<i>Ensure atlas sustainability with processes that encourage collaboration and guide future development</i>			
US#6. Develop lightweight atlas components	Programmers that support Researchers and Clinicians	Implement usable and useful HRA components (interfaces and APIs) into other portals in the growing ecosystem of human atlases.	Facilitate collaboration and data/code reuse between the HRA and other portals in support of FAIR data principles.
US#7. Implement dashboard for HRA	Researchers, Clinicians, Funders	Track the evolution and usage of the HRA using data, code, and portal usage statistics in aggregate and divided by portal (e.g., HubMAP or SenNet) or PEDP survey results.	Enable evidence-based decision-making by providing insights into the atlas' construction and usage (e.g., gaps in data, application areas, user demographics, equitable access).



Human Reference Atlas

Naming and connecting across scales

- Anatomical Structures
- Functional Tissue Units
- Cell Types
- Biomarkers



Human Reference Atlas

Connecting and empowering people

- Subject Matter Experts
- Ontologists
- Programmers
- Experimentalists
- Researchers, Clinicians, and Pathologists



Human Reference Atlas

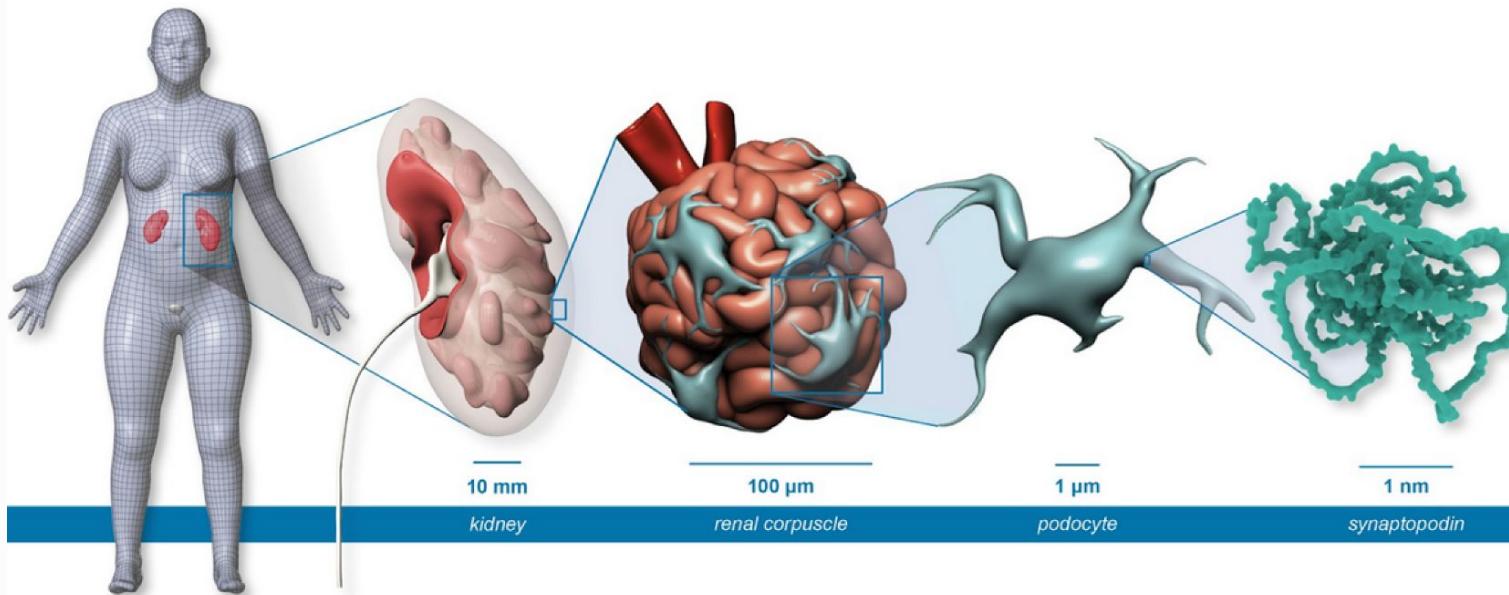
Relevance to Urology

- Measure what's healthy to compare to what's unhealthy
- Knowledge and data resource
- Open data and code, reproducible workflows, lightweight user interface components

NOTE: Not ready for clinical practice

Tour of the HRA





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

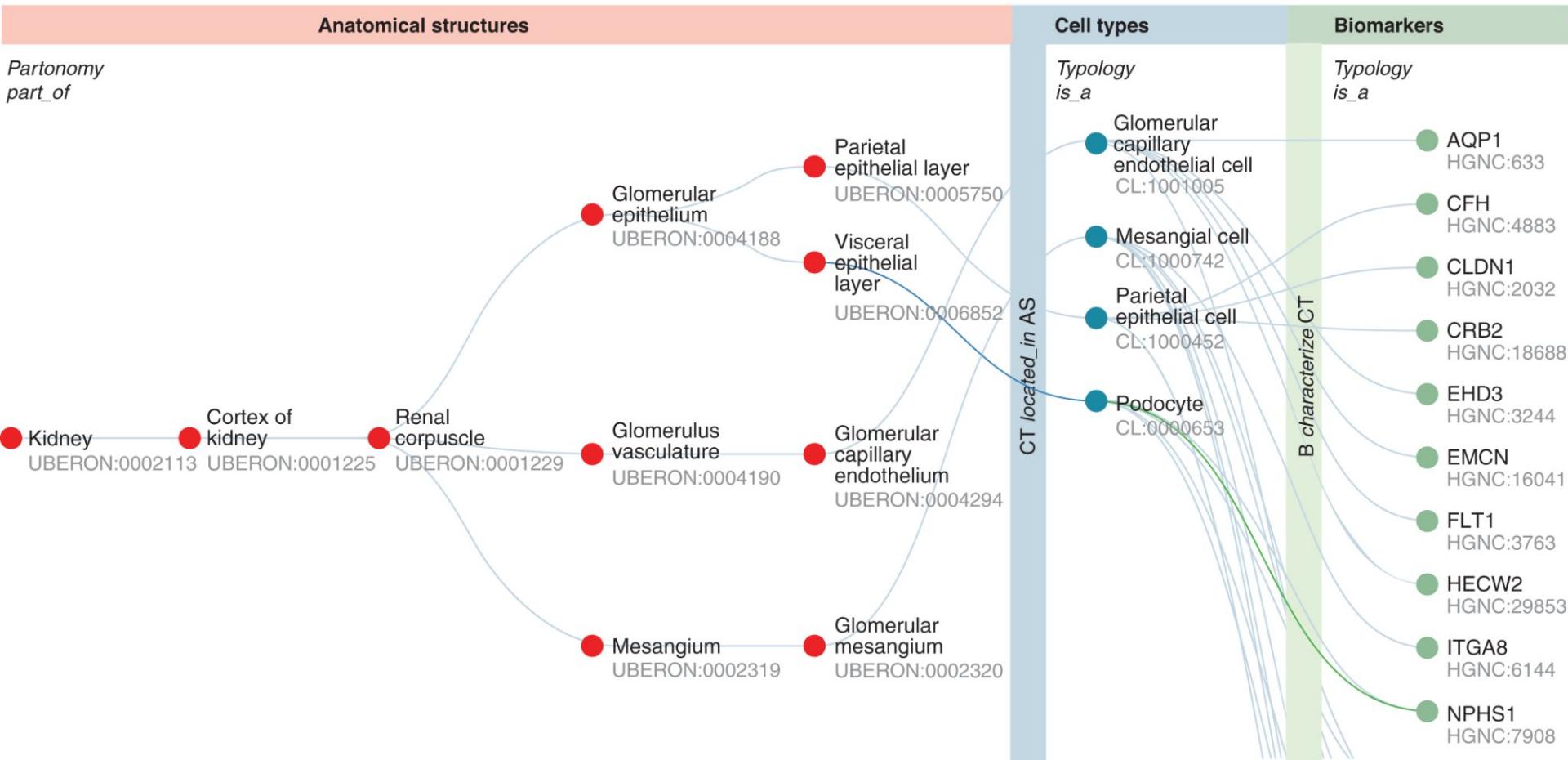
Atlas

3D Reference Organs

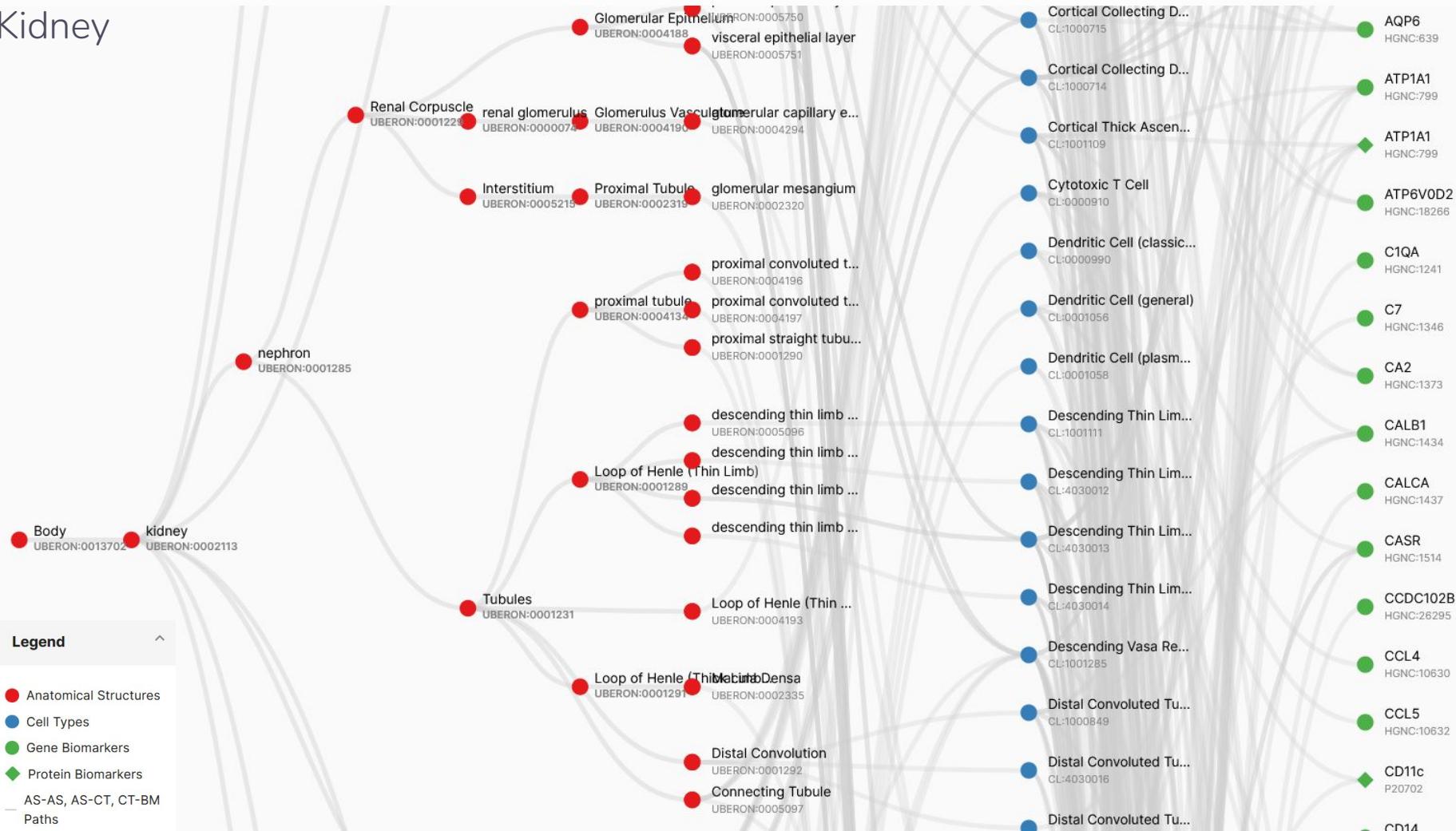
2D FTU
Illustrations

Organ Mapping Antibody Panels

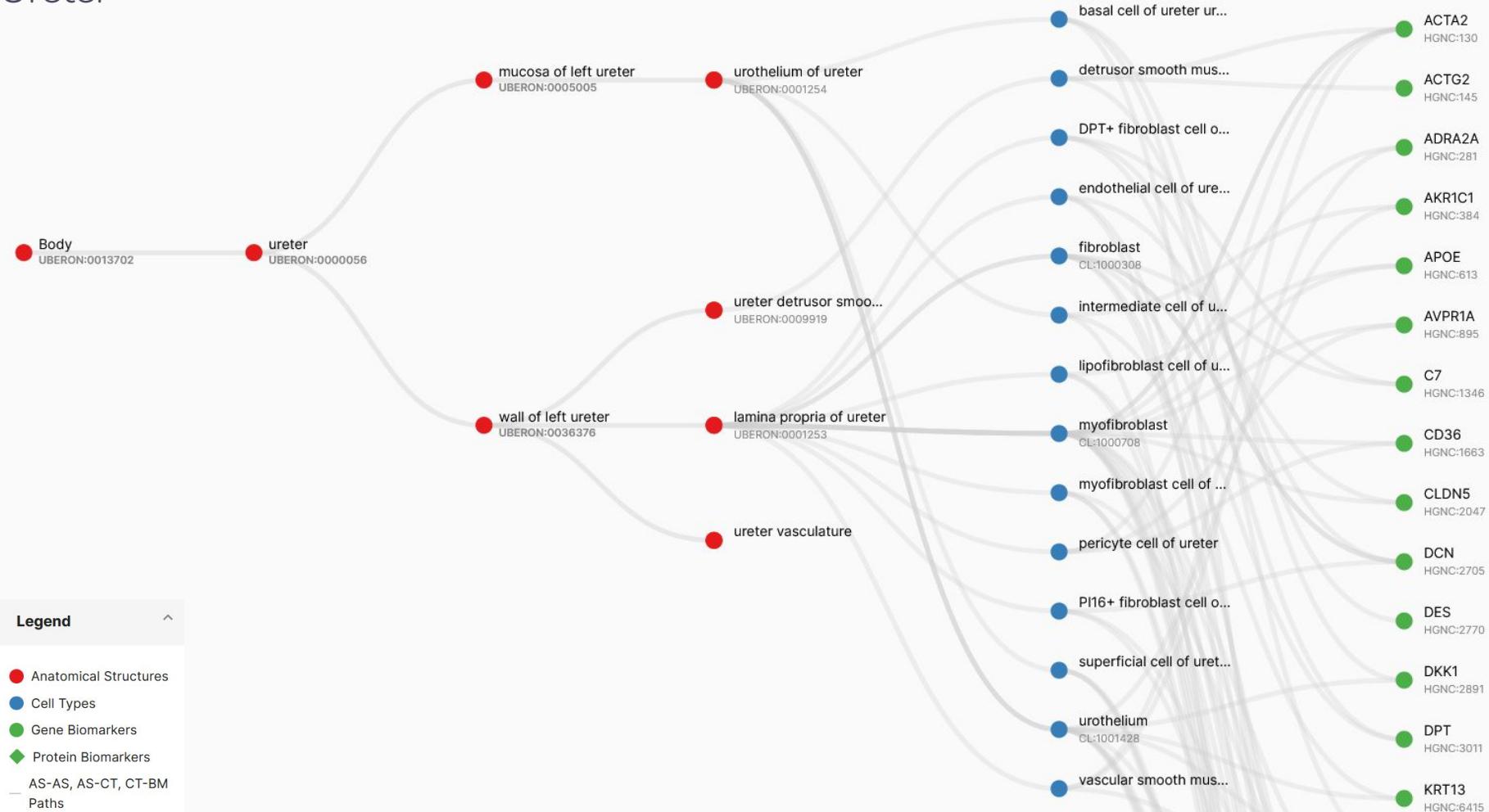
ASCT+B Table Framework



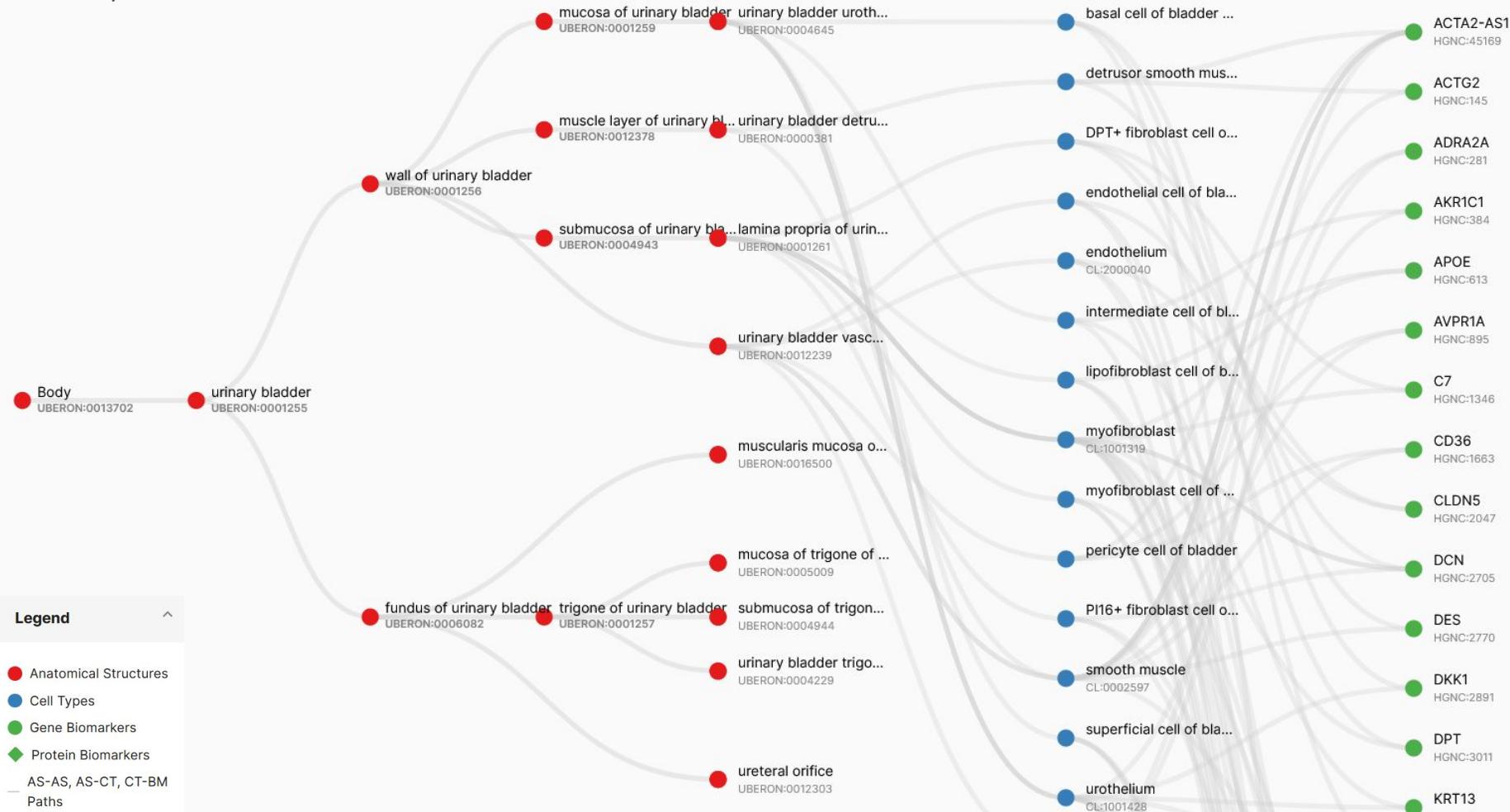
Kidney



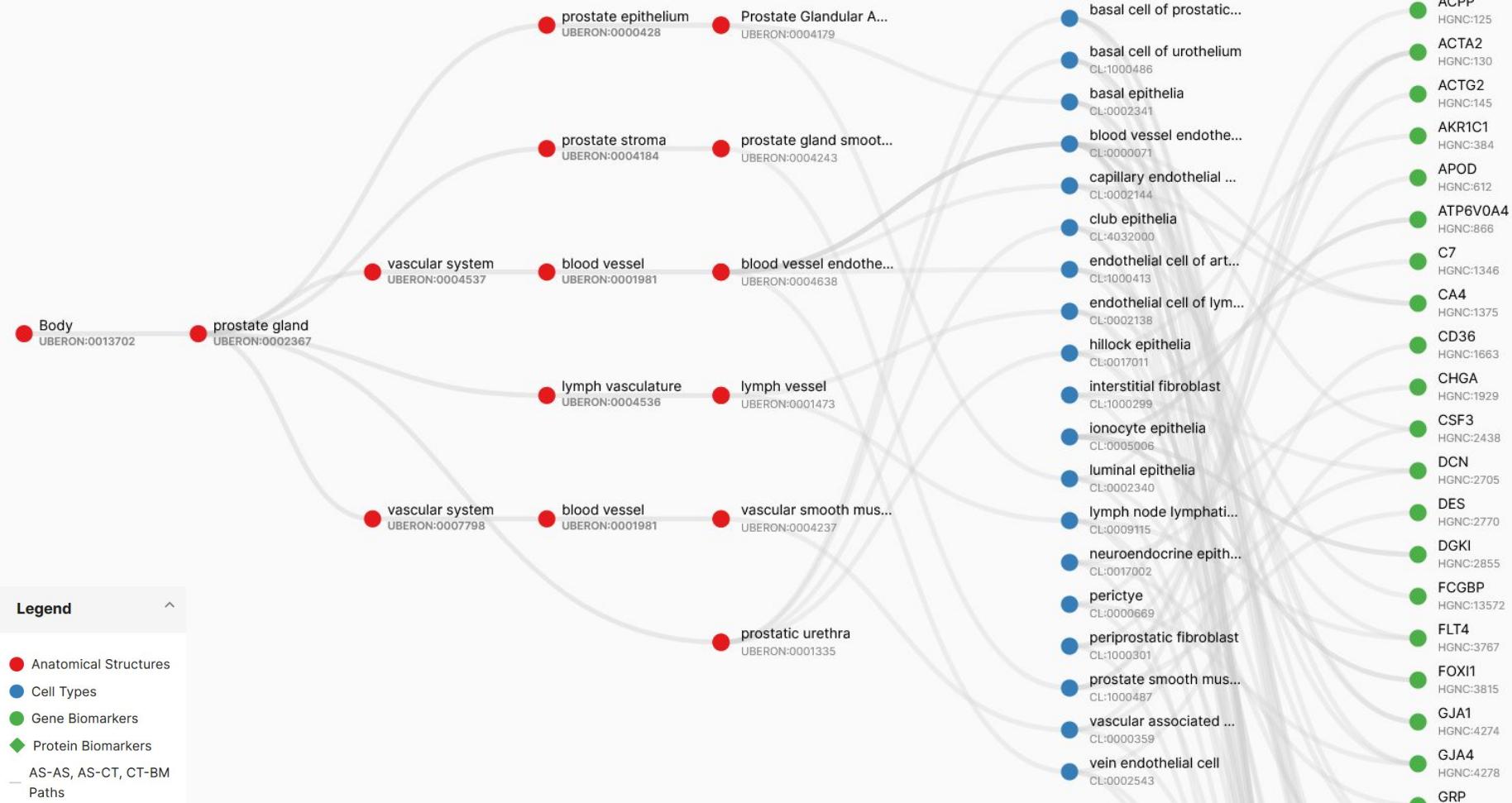
Ureter



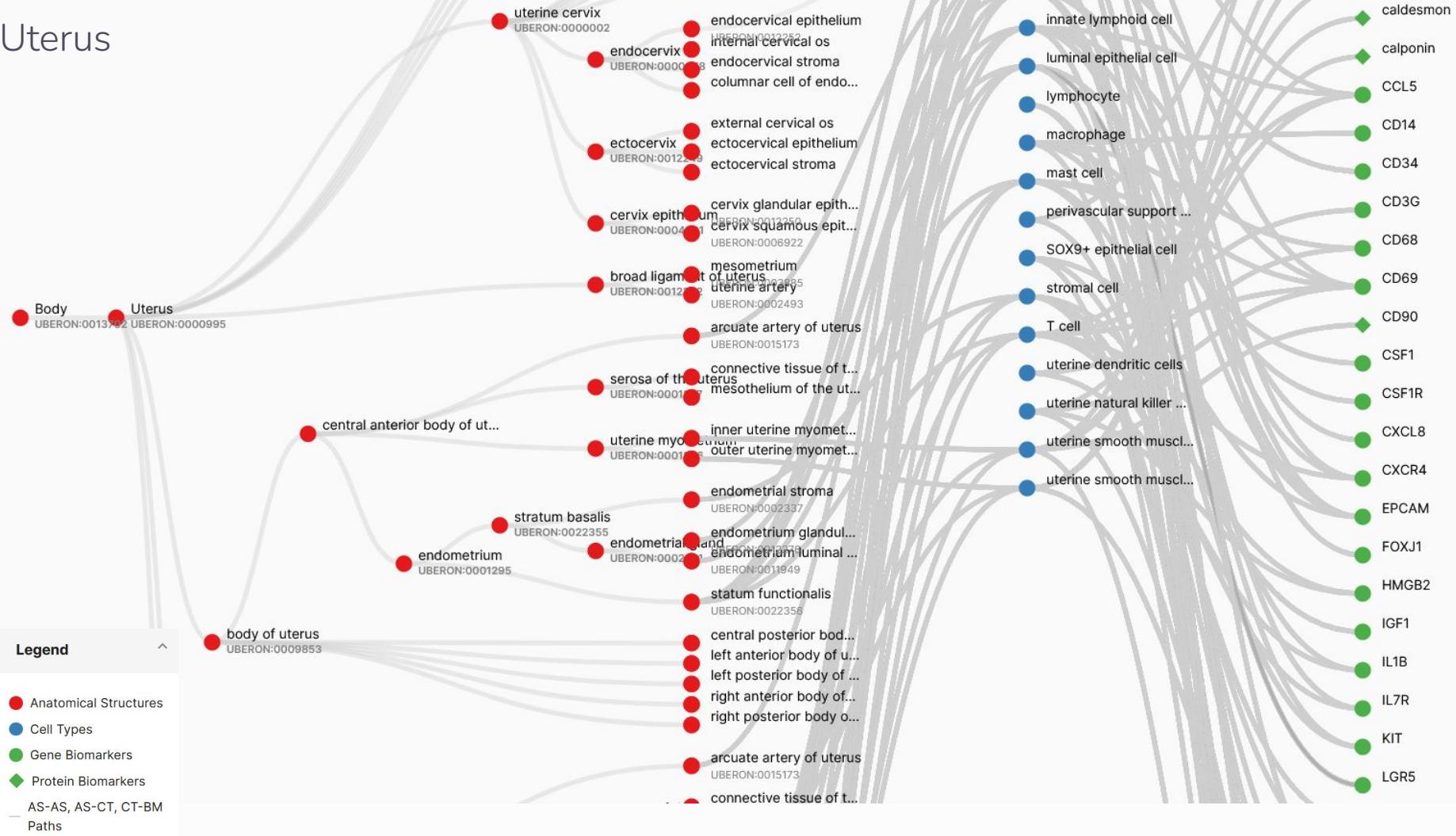
Urinary Bladder

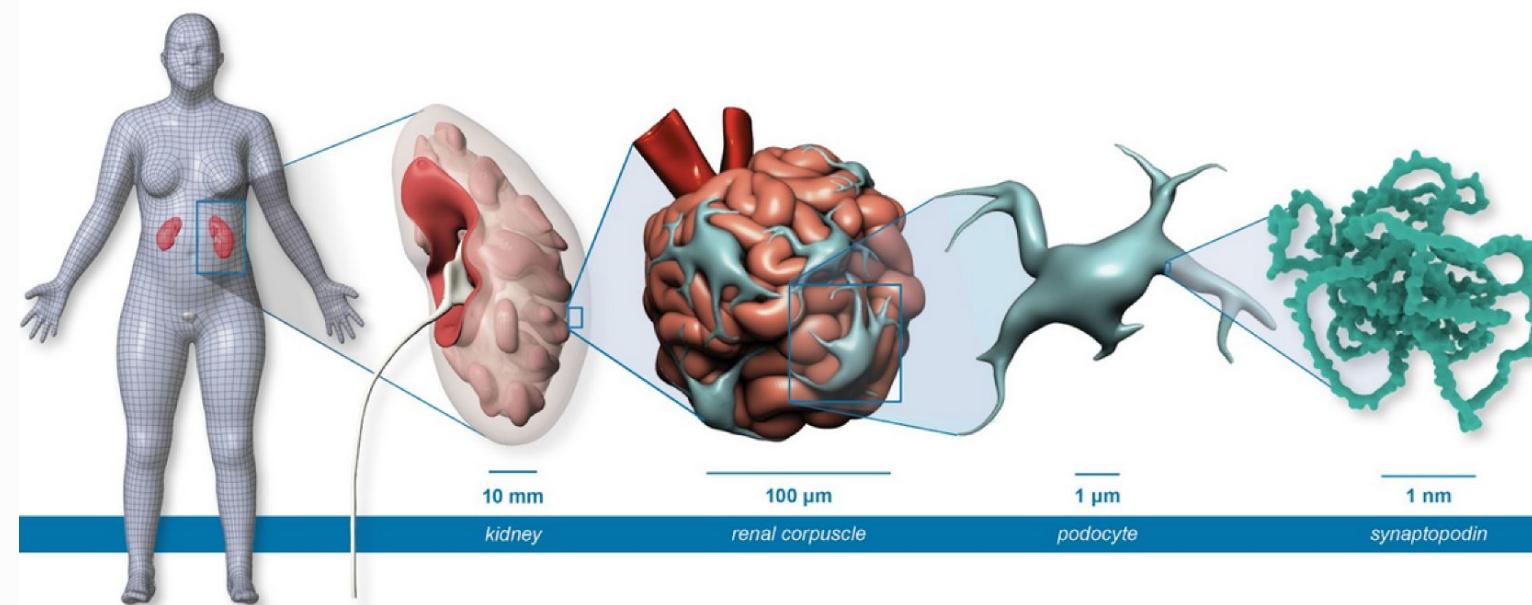


Prostate



Uterus





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

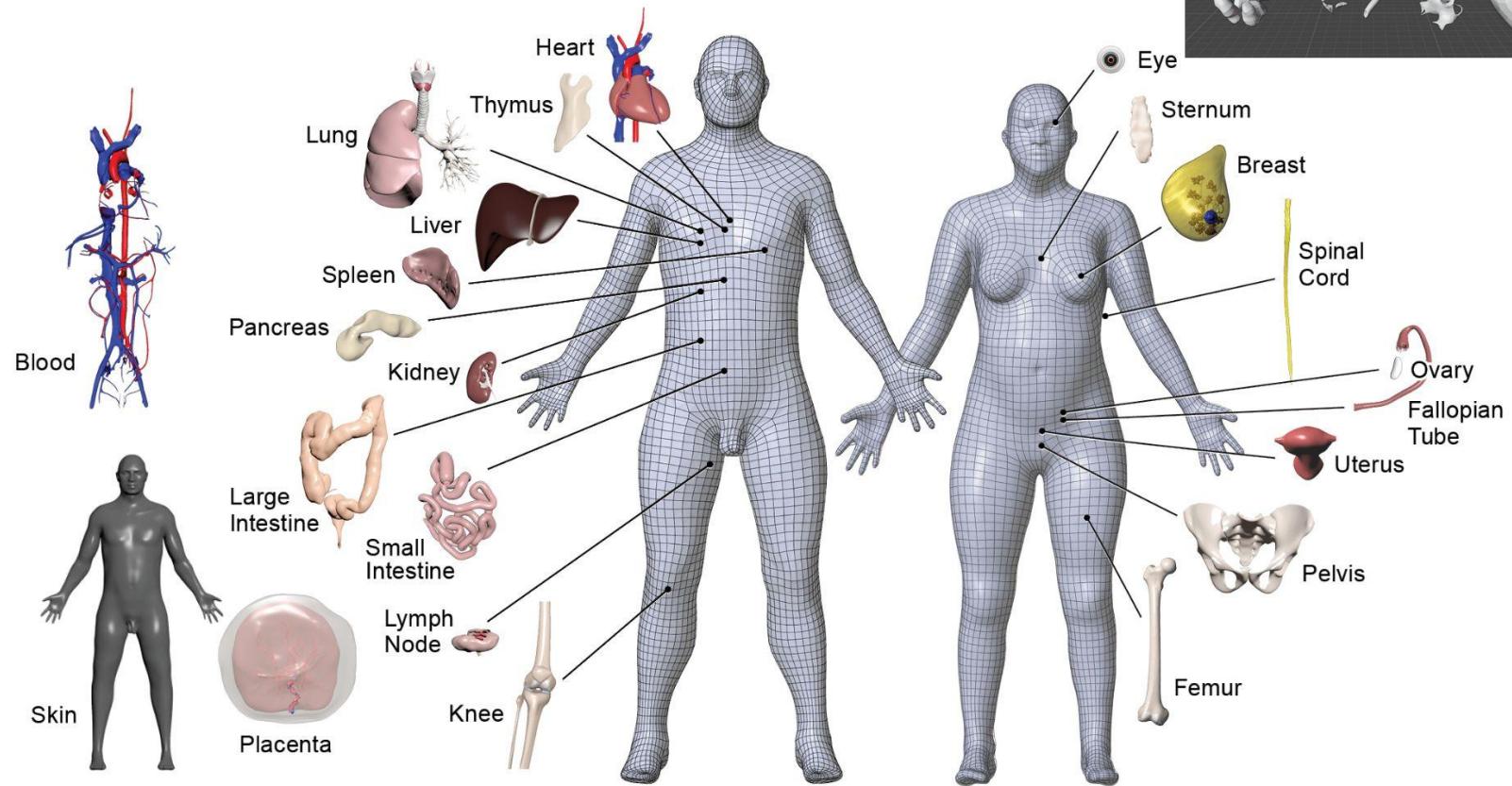
Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

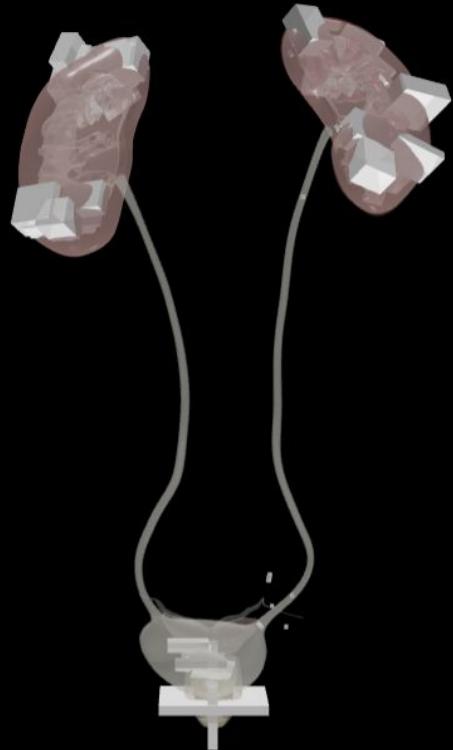
HRA 3D Reference Organs



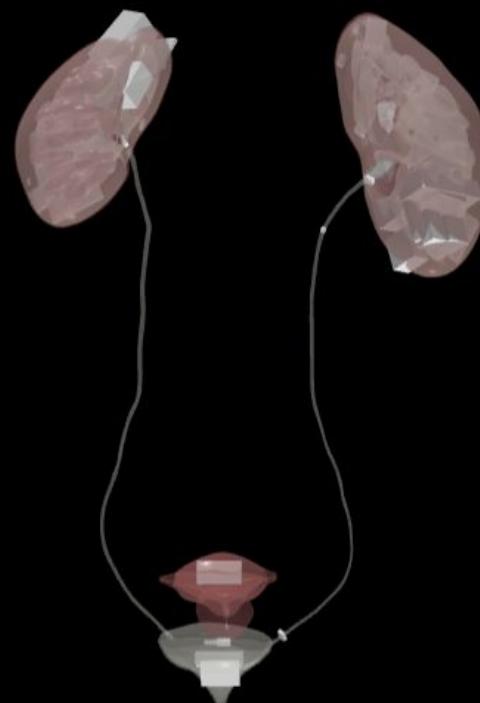


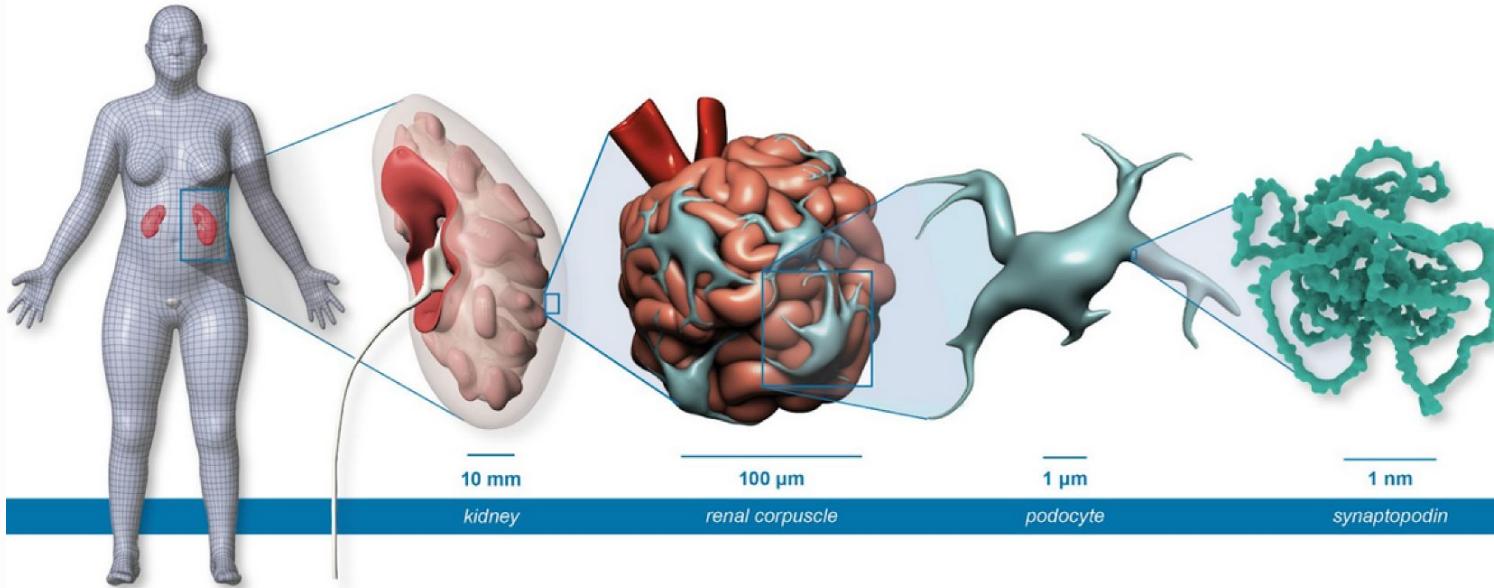
HRA 3D Reference Organs: kidney, ureter, bladder, prostate, and uterus

Male



Female





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

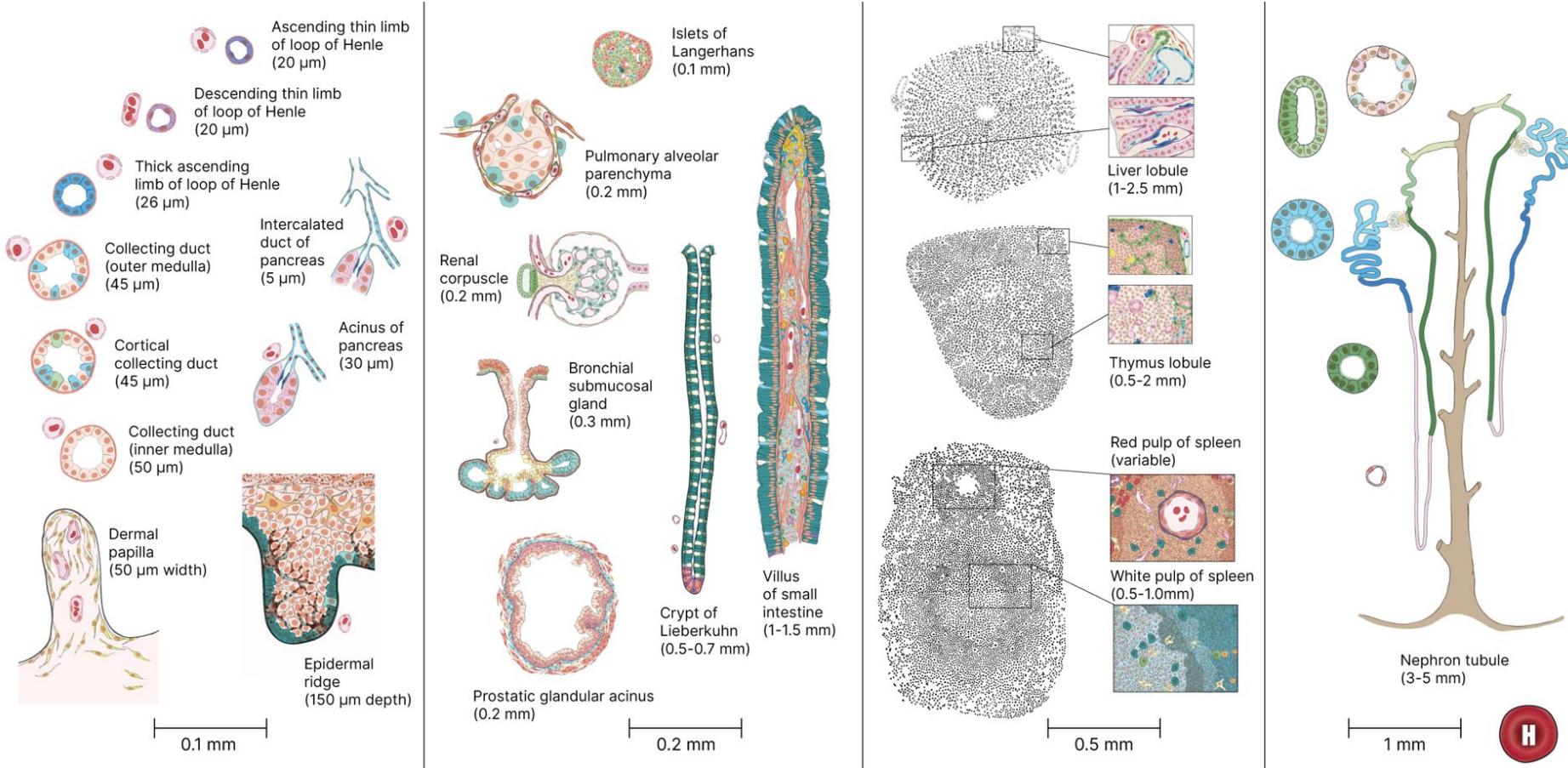
Atlas

3D Reference Organs

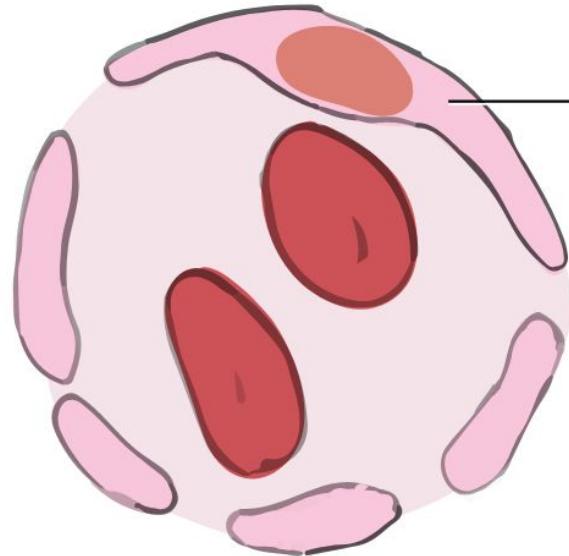
2D FTU
Illustrations

Organ Mapping Antibody Panels

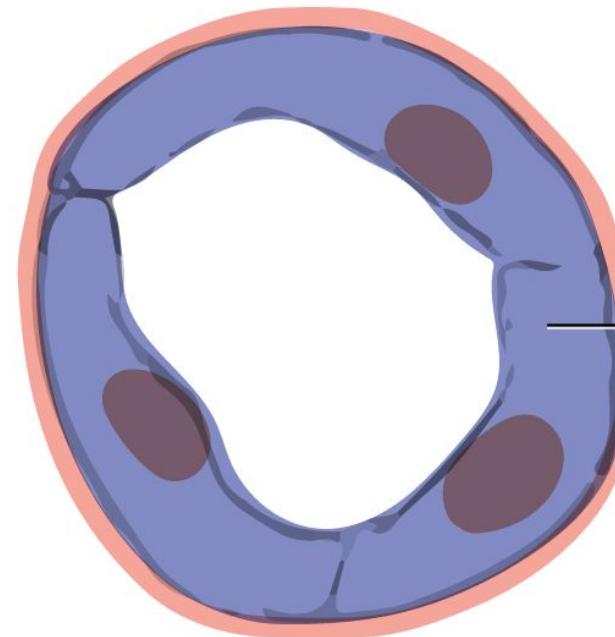
HRA Functional Tissue Units (FTUs)



Kidney - Ascending Thin Loop Of Henle



Ascending vasa recta

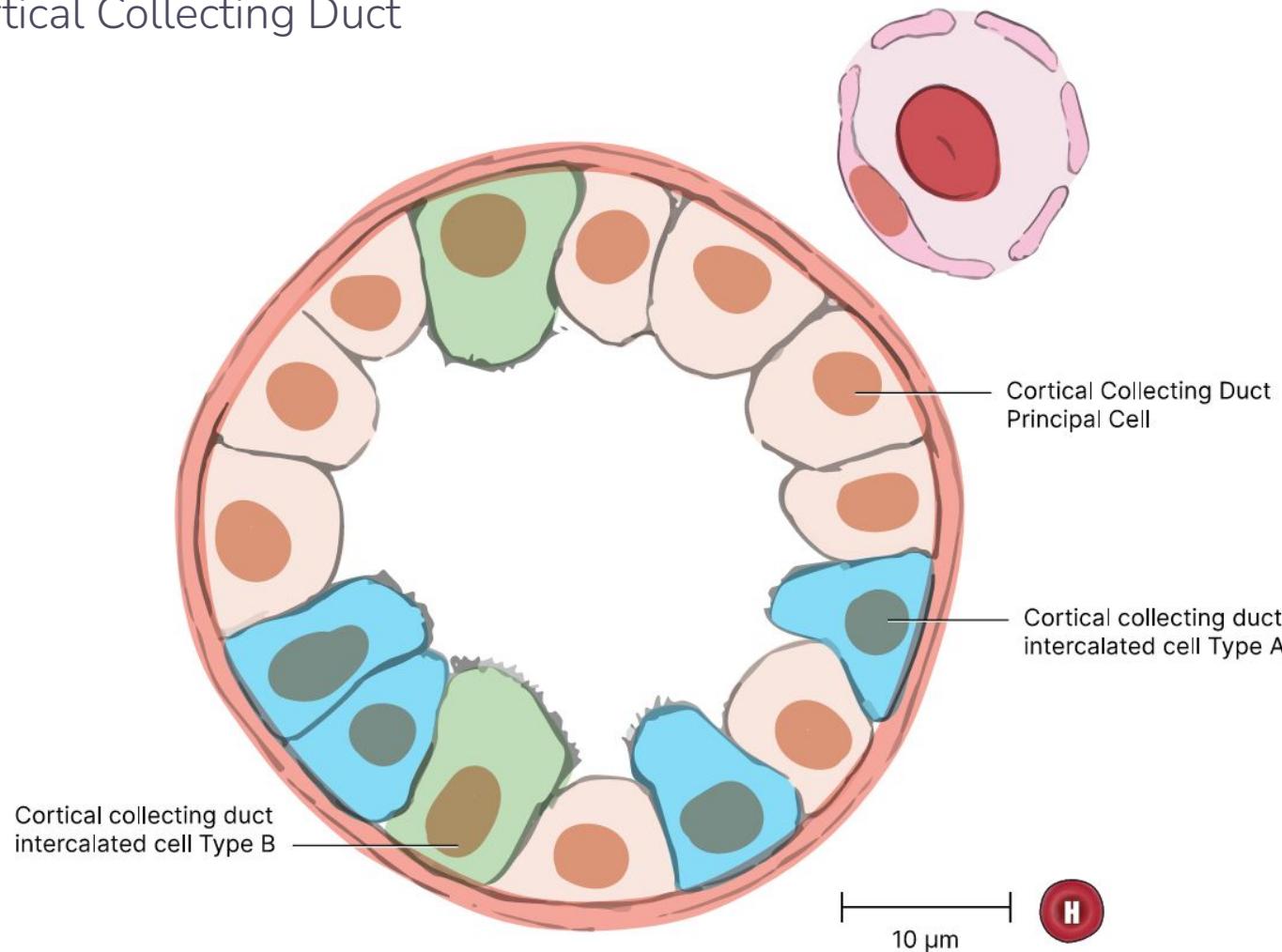


Ascending
thin limb cell

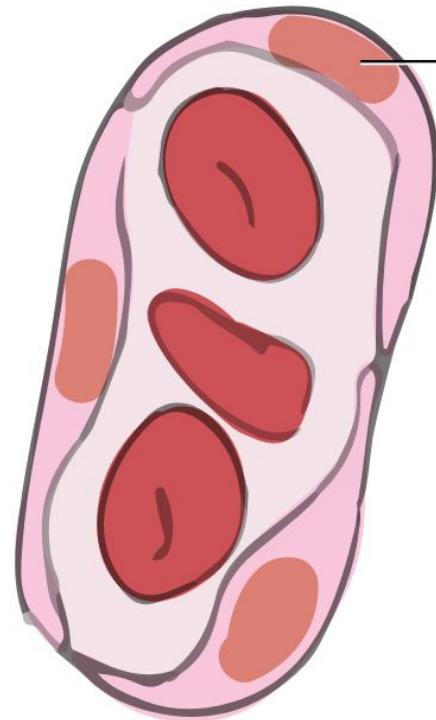
10 μm



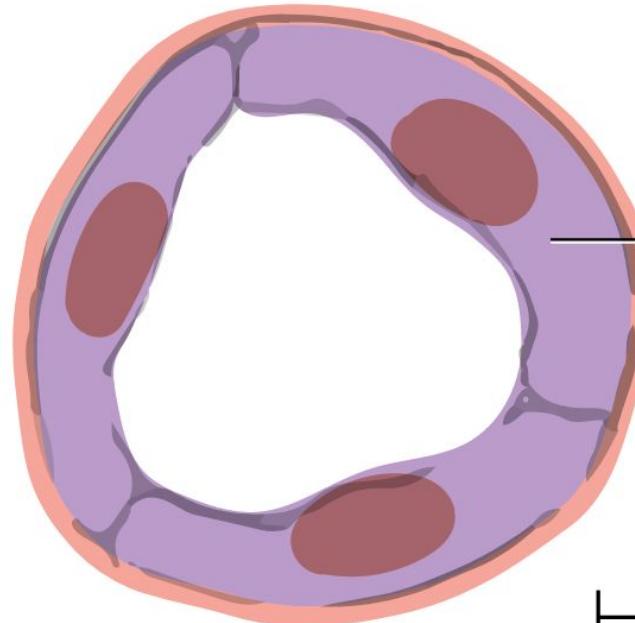
Kidney - Cortical Collecting Duct



Kidney - Descending Thin Loop Of Henle



Descending vasa recta

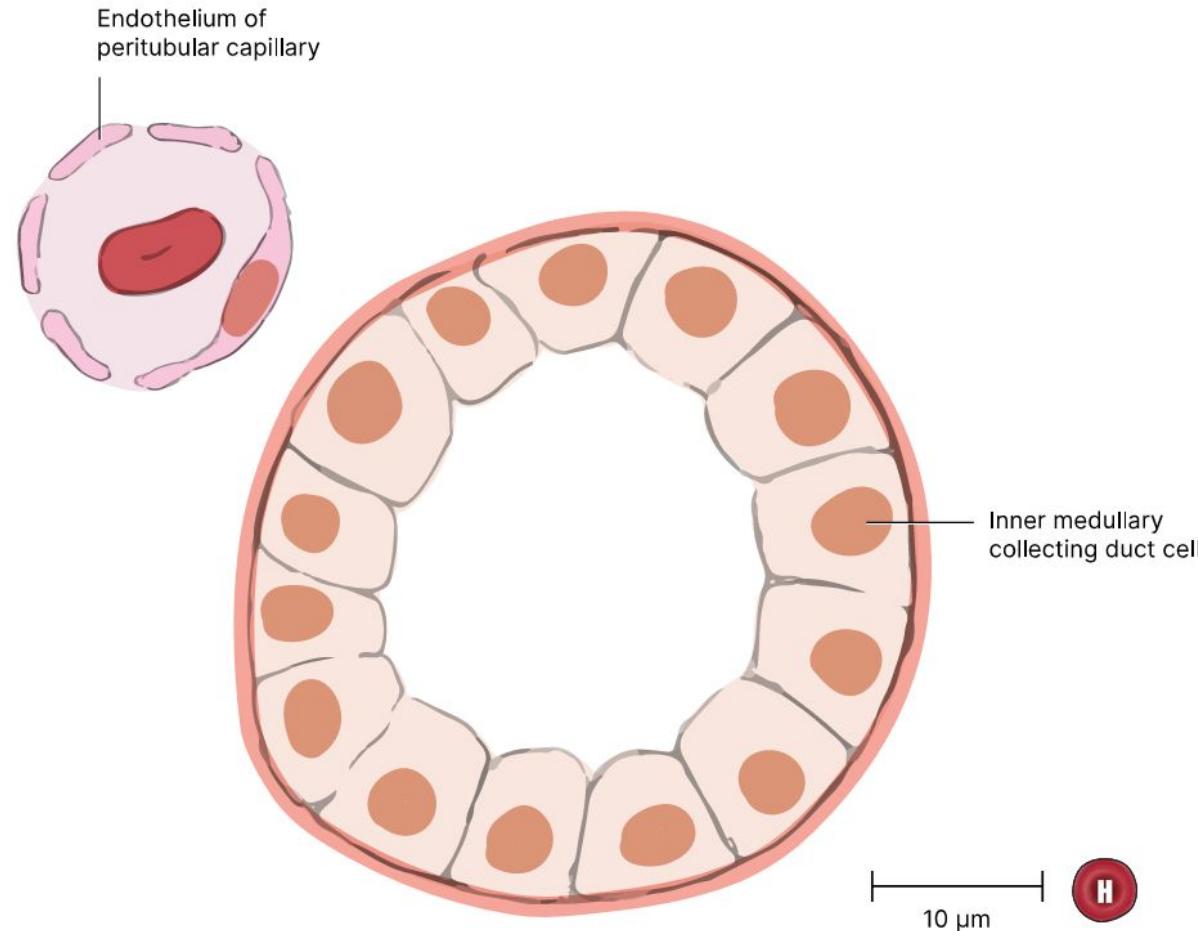


Descending
thin limb cell

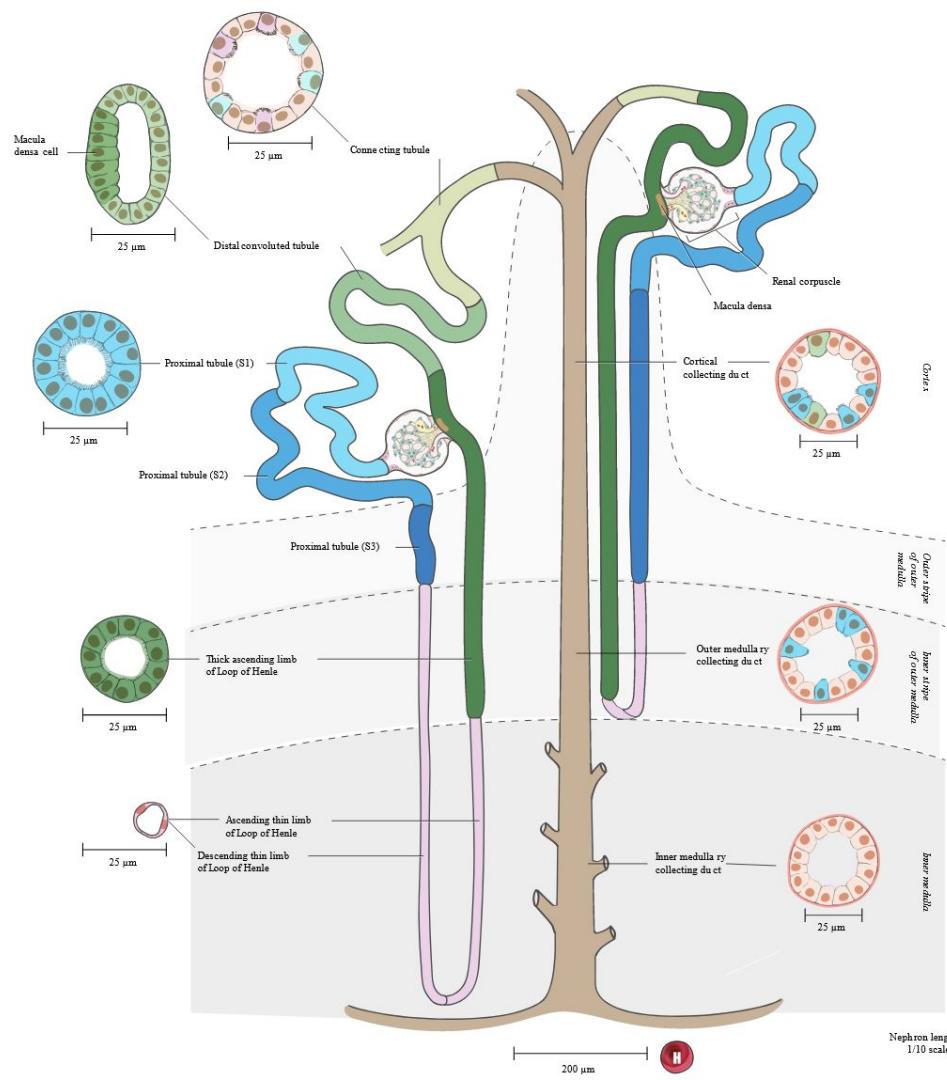
10 μm



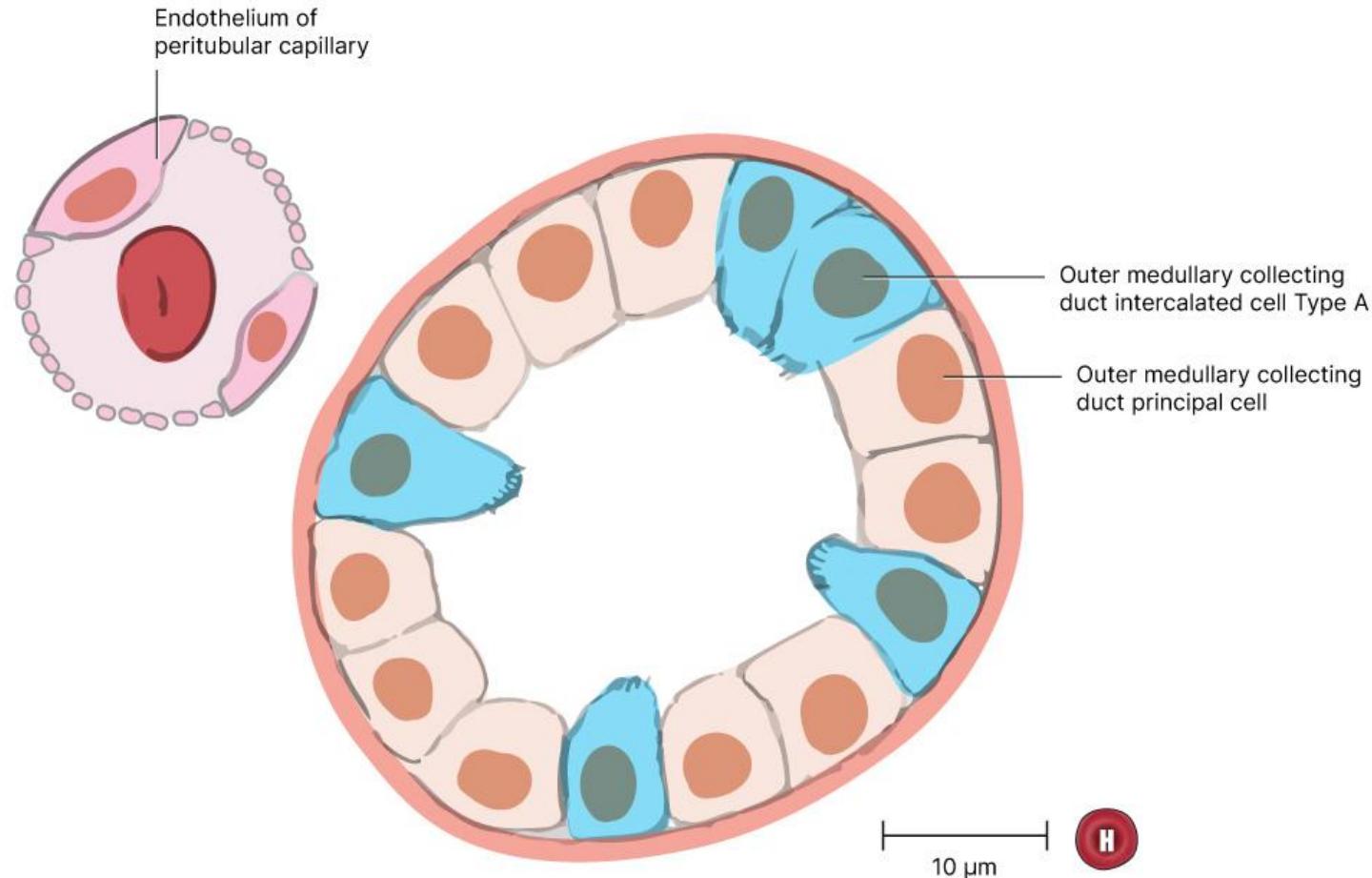
Kidney - Inner Medullary Collecting Duct



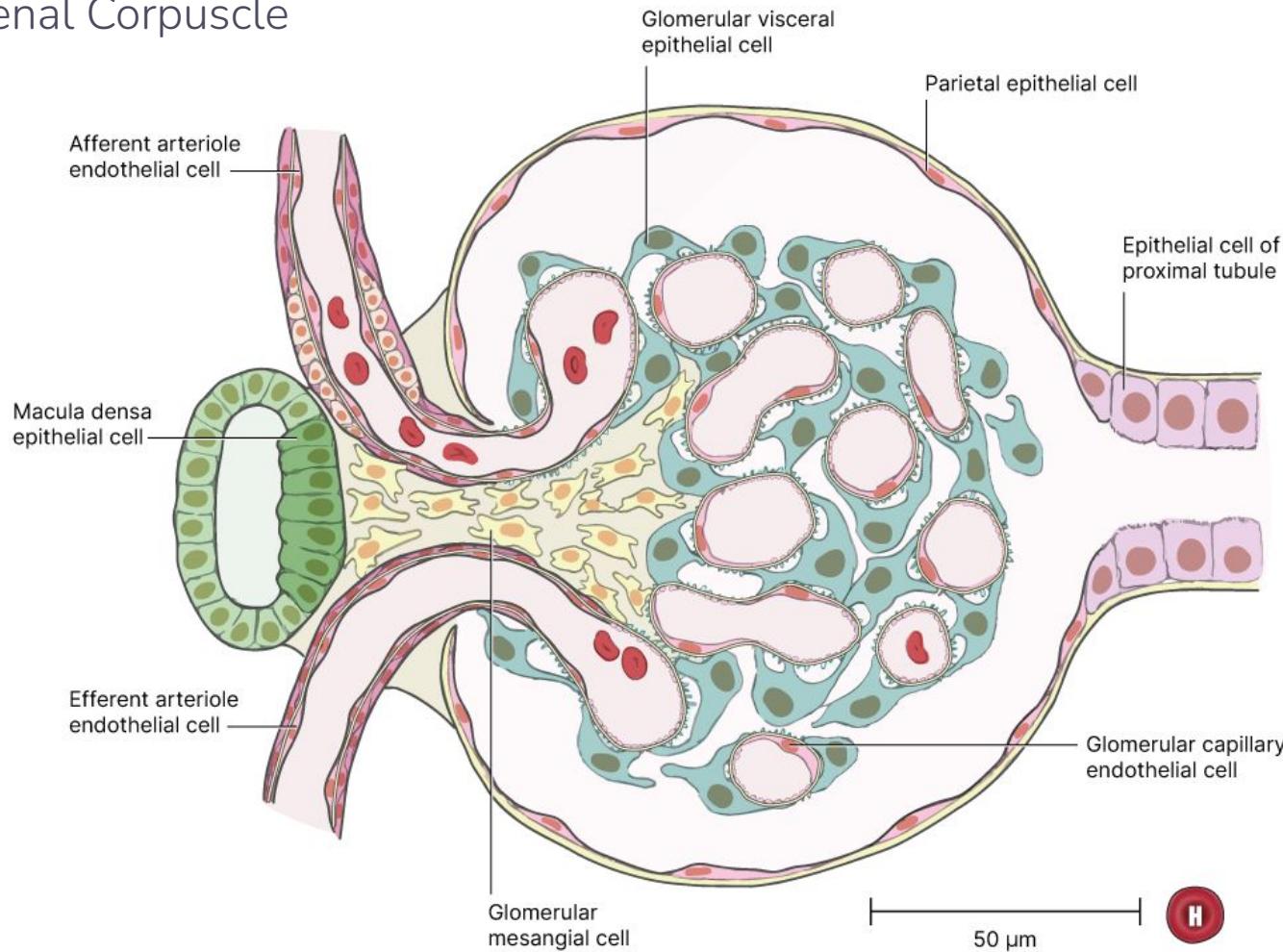
Kidney - Nephron



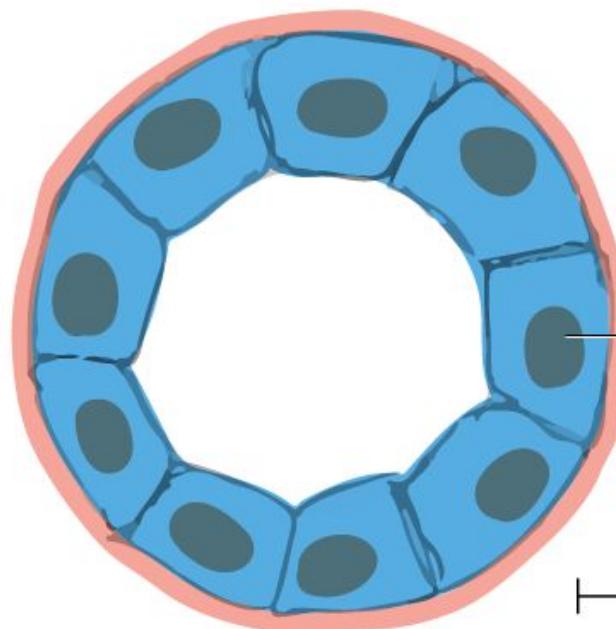
Kidney - Outer Medullary Collecting Duct



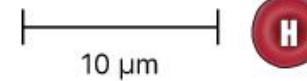
Kidney - Renal Corpuscle



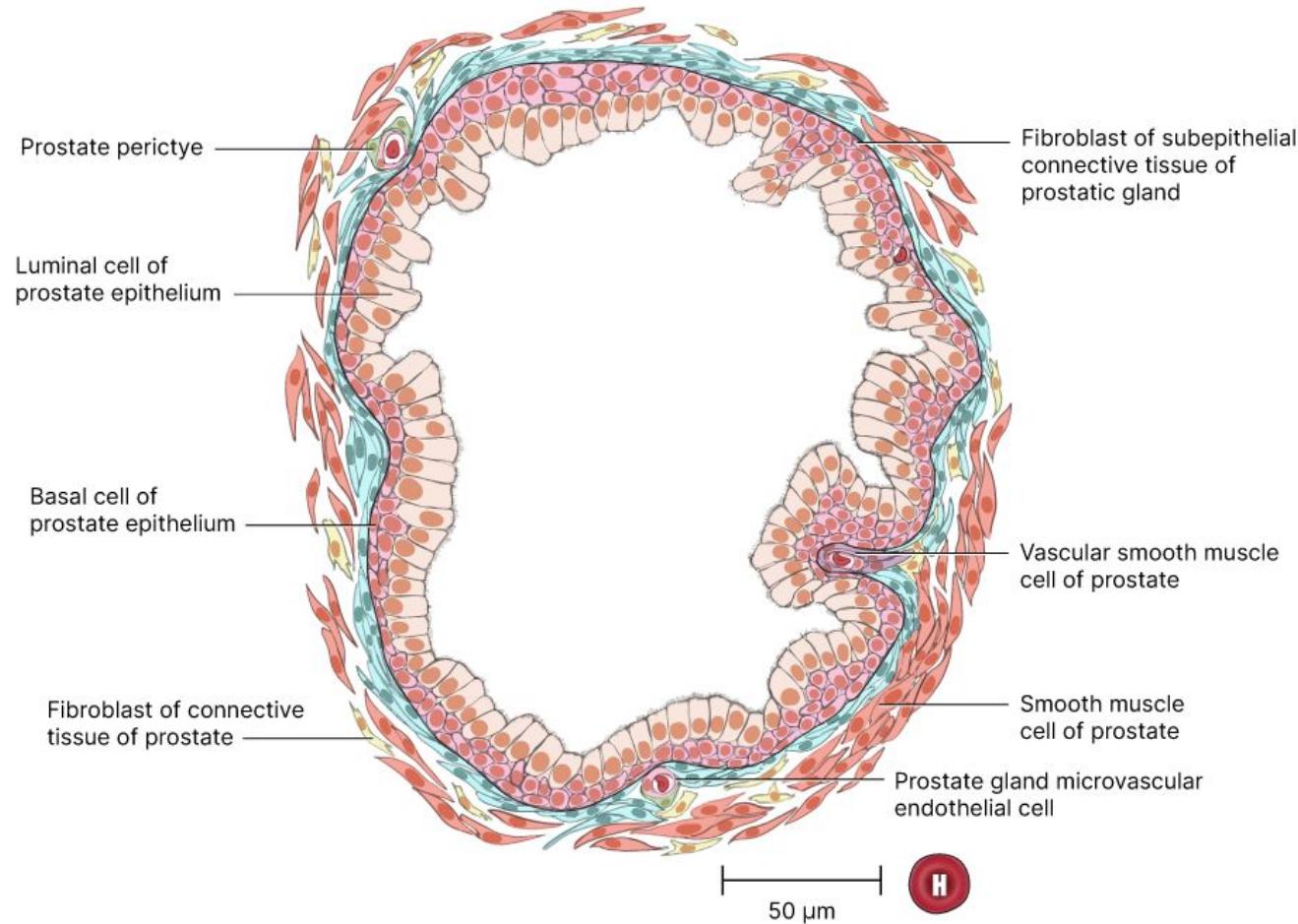
Kidney - Thick Ascending Loop Of Henle

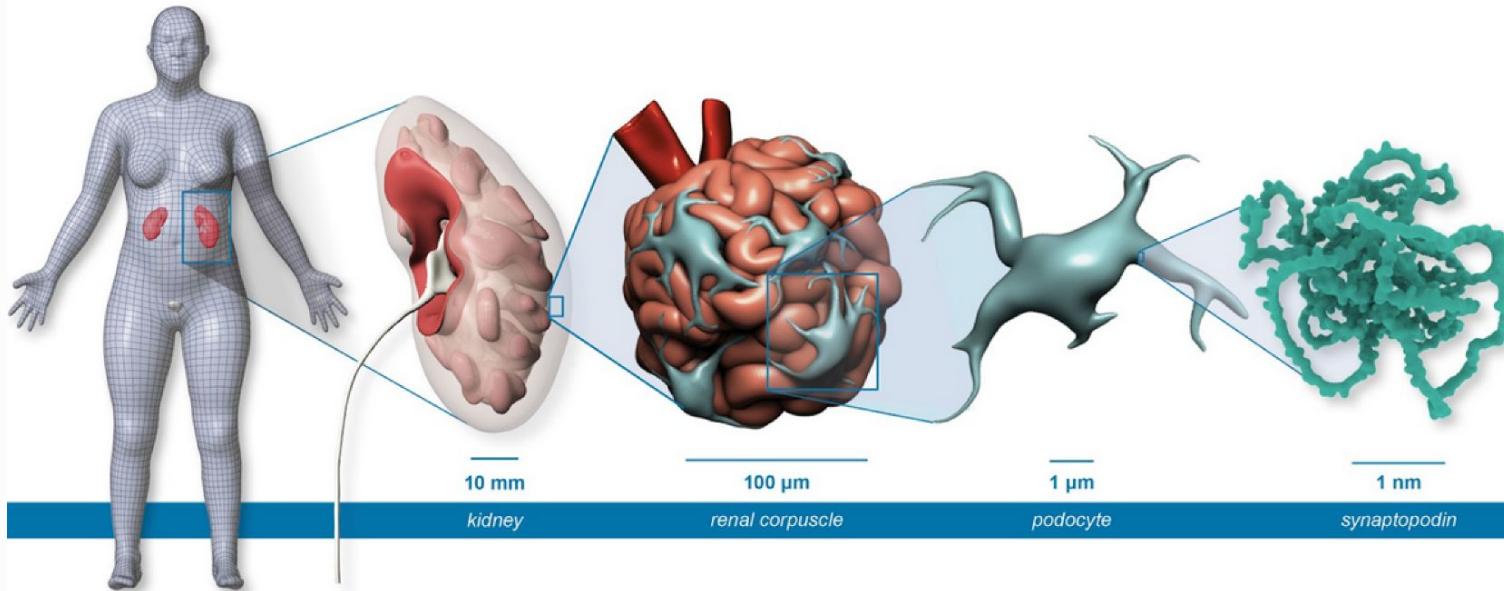


Thick ascending limb cell



Prostate - Glandular Aculus





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

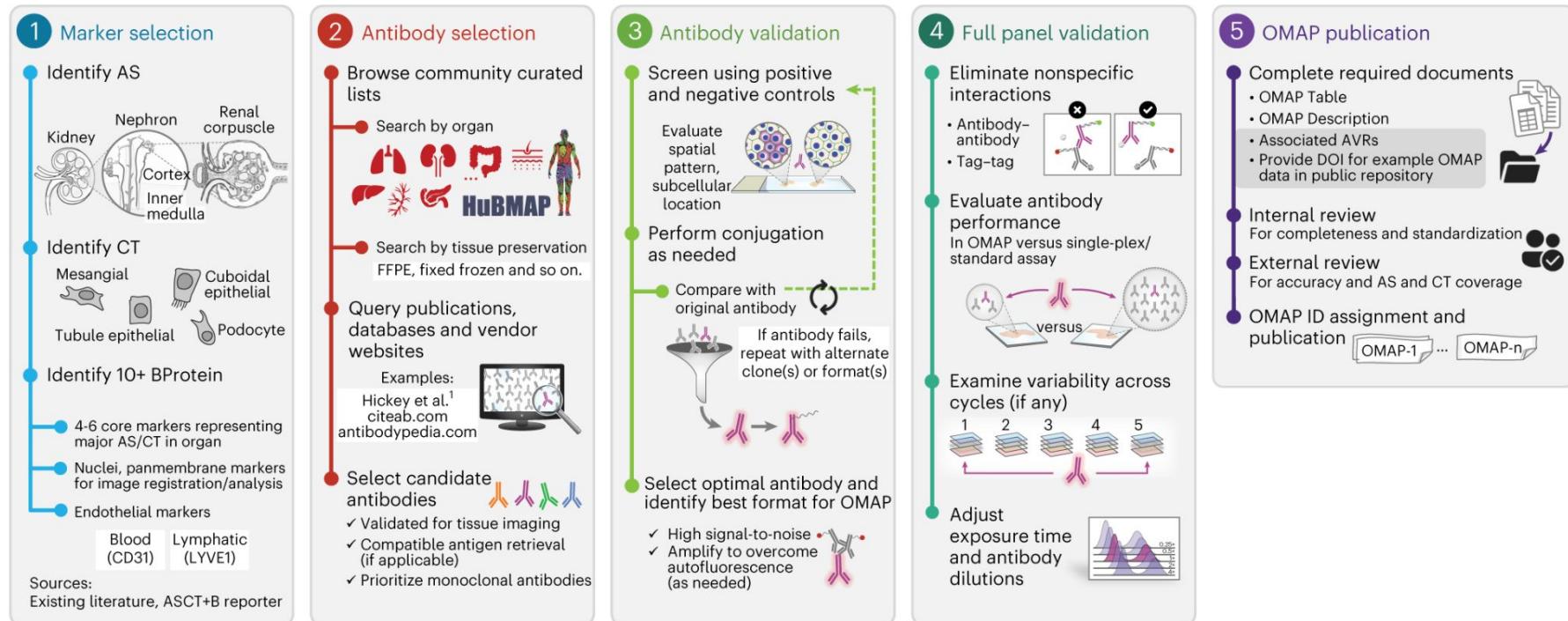
3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

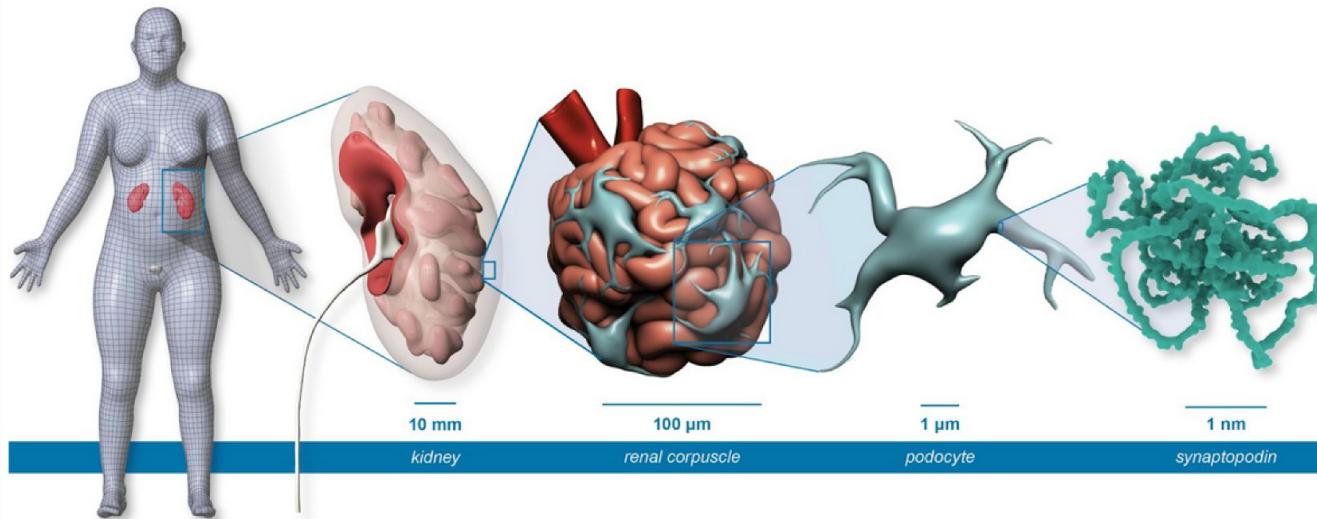
OMAP Framework

OMAPs are wet-bench validated collection of antibodies that are designed to work together in multiplex antibody imaging technologies (CODEX/Phenocycler, CellDive, SIMS, etc.) primarily for identifying specific classes of cell types or tissue regions/layers.



Kidney - OMAP-3





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

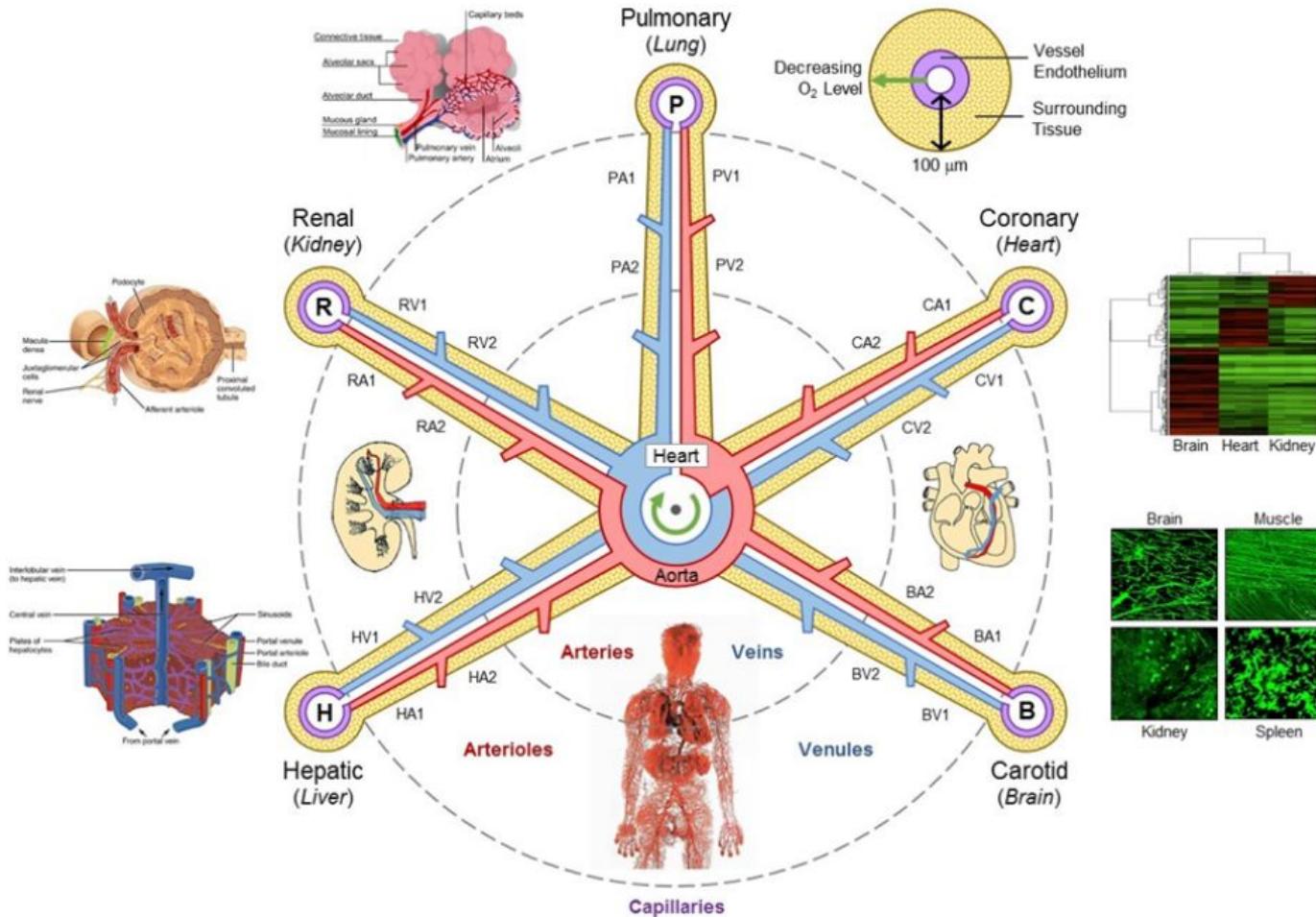
3D Reference Organs

2D FTU
Illustrations

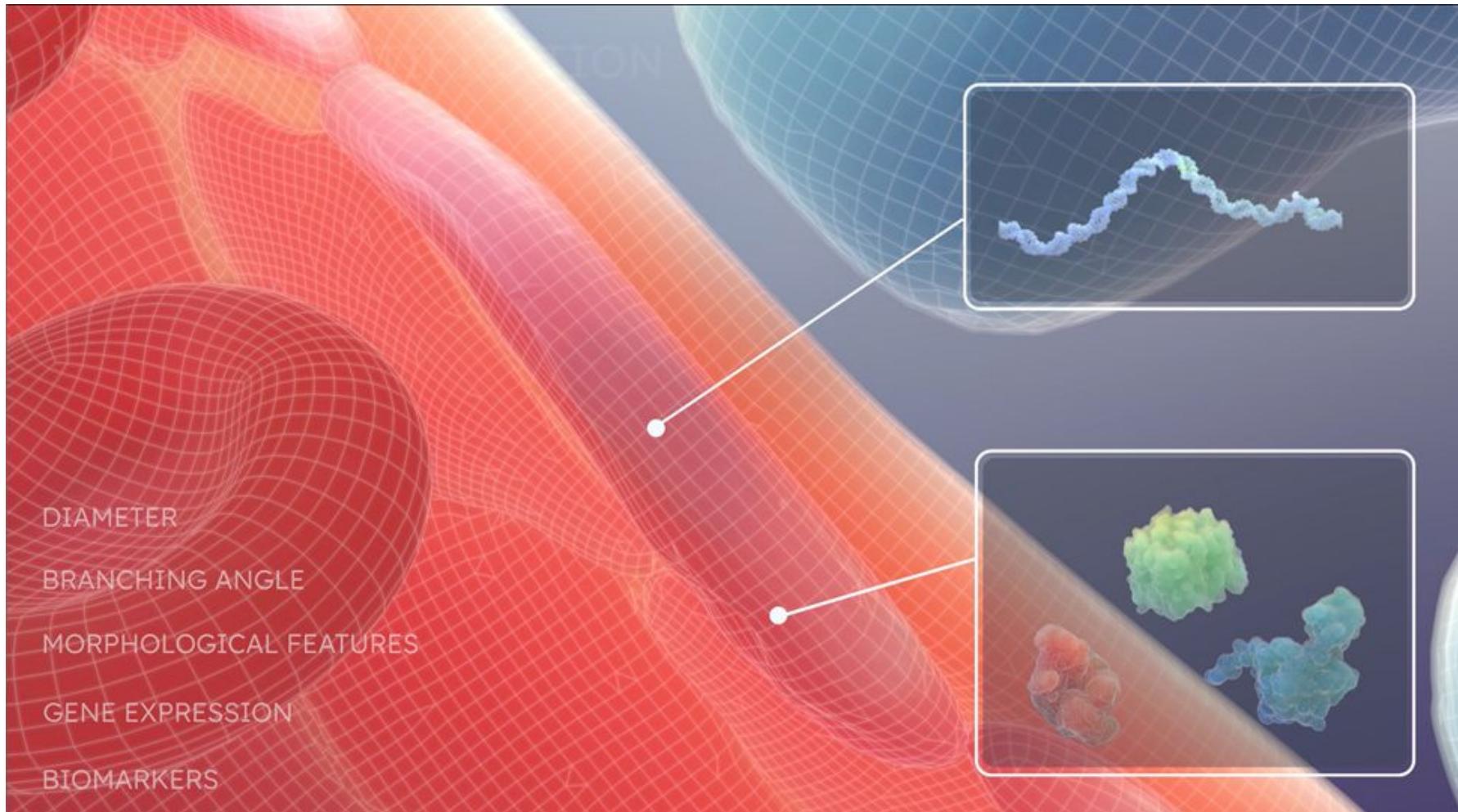
Organ Mapping Antibody Panels

Vascular Geometry

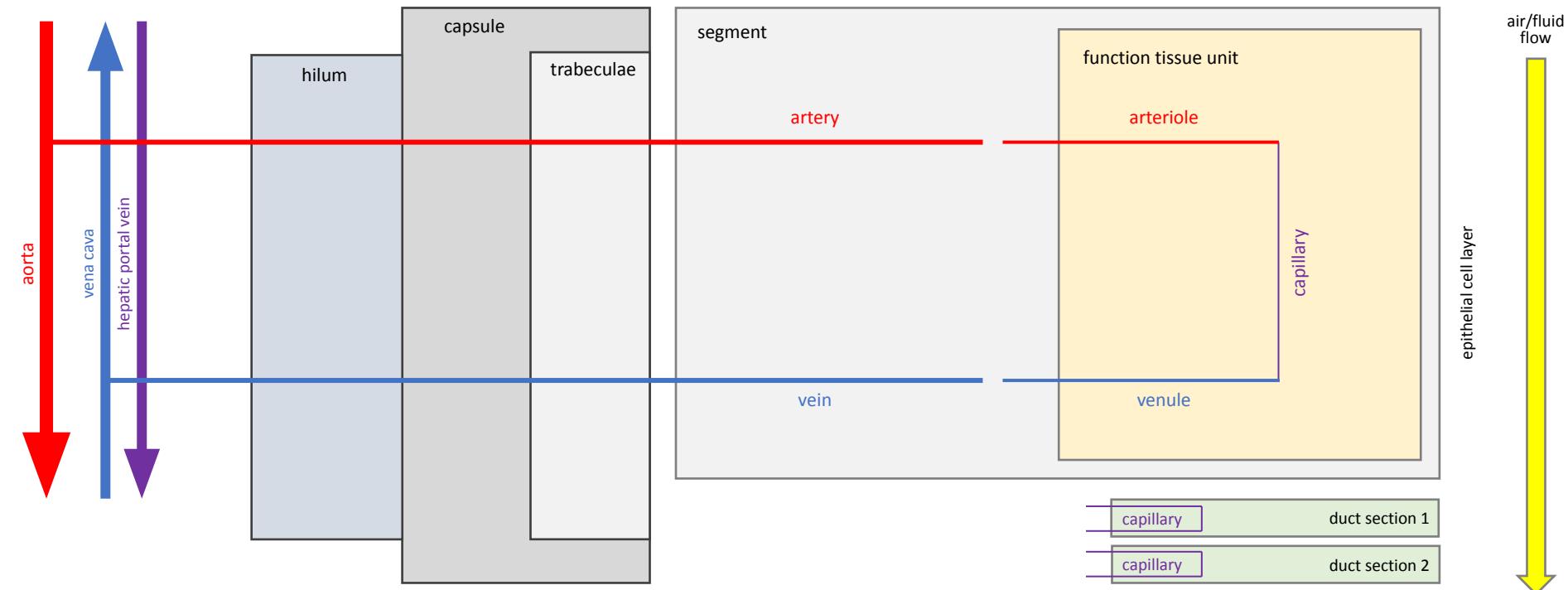
Vasculature Common Coordinate Framework



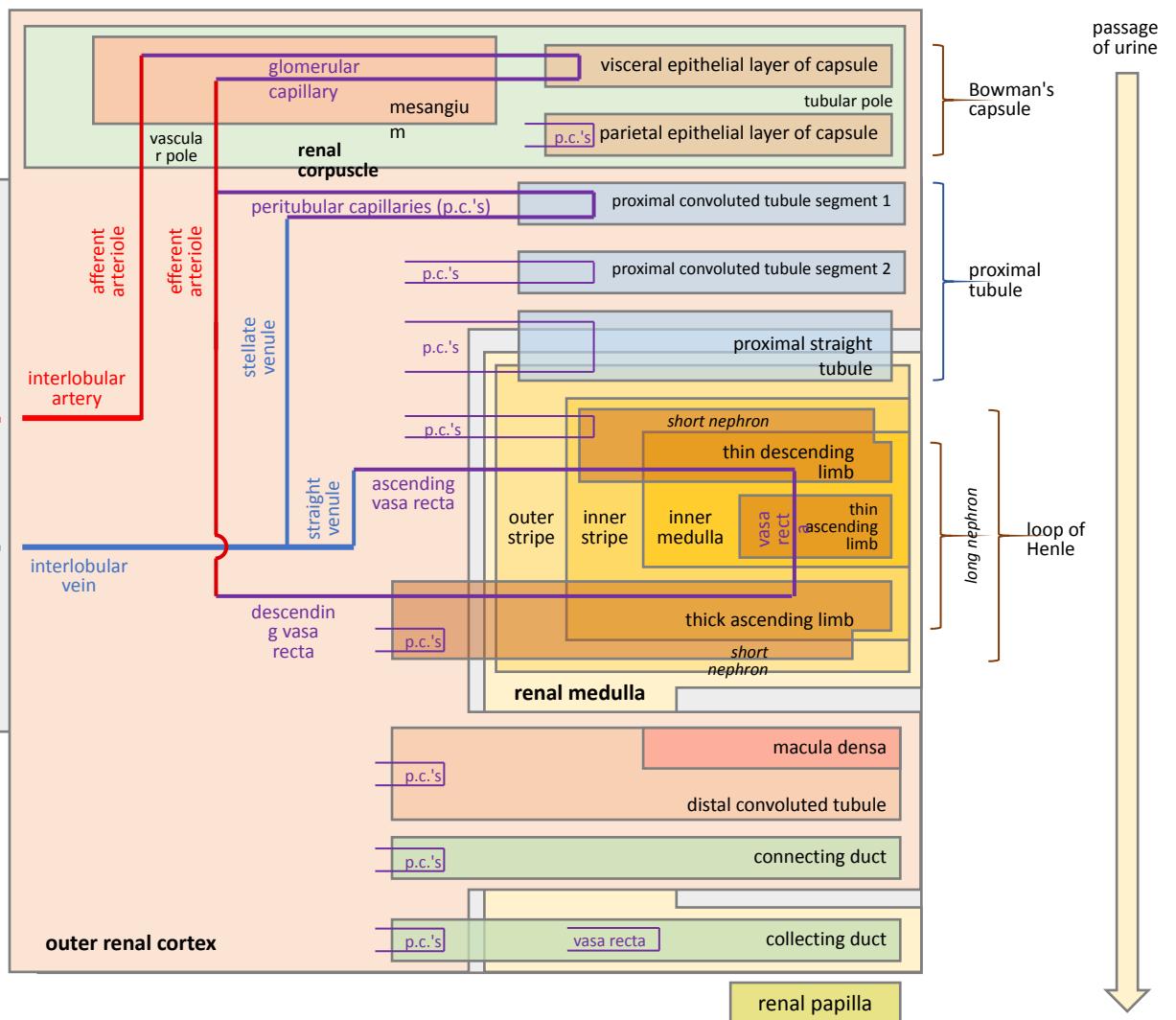
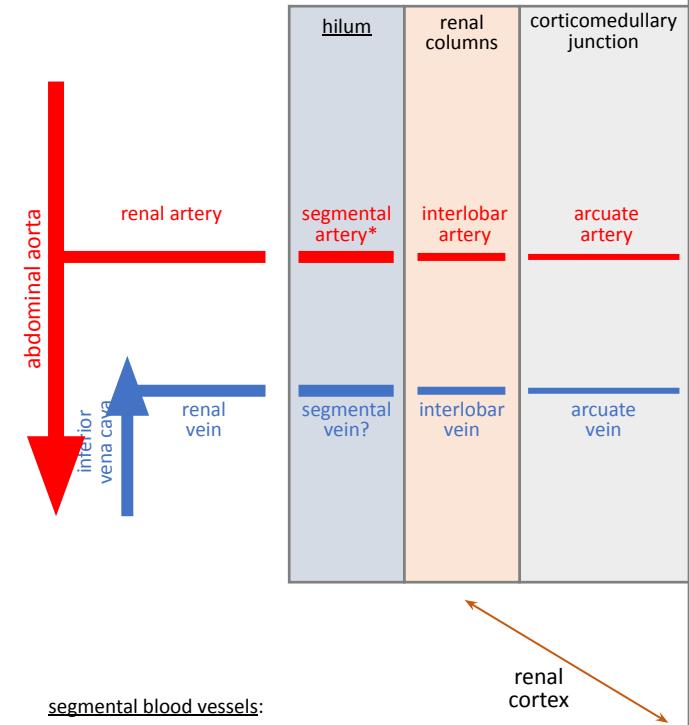
VCCF Video: https://youtu.be/zQeMgxo8n_U

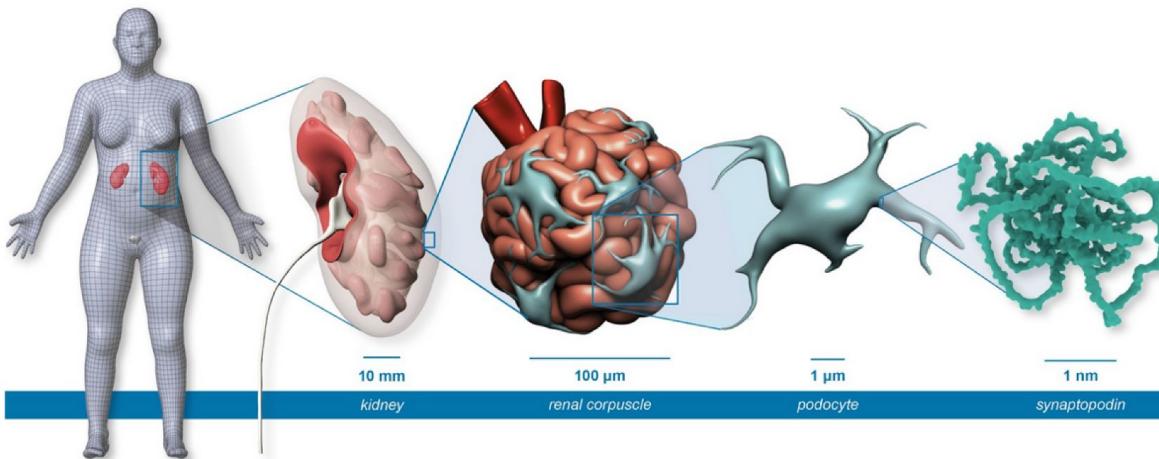


Template



Vascular Geometry for kidney





Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

3D Reference Organs

2D FTU
Illustrations

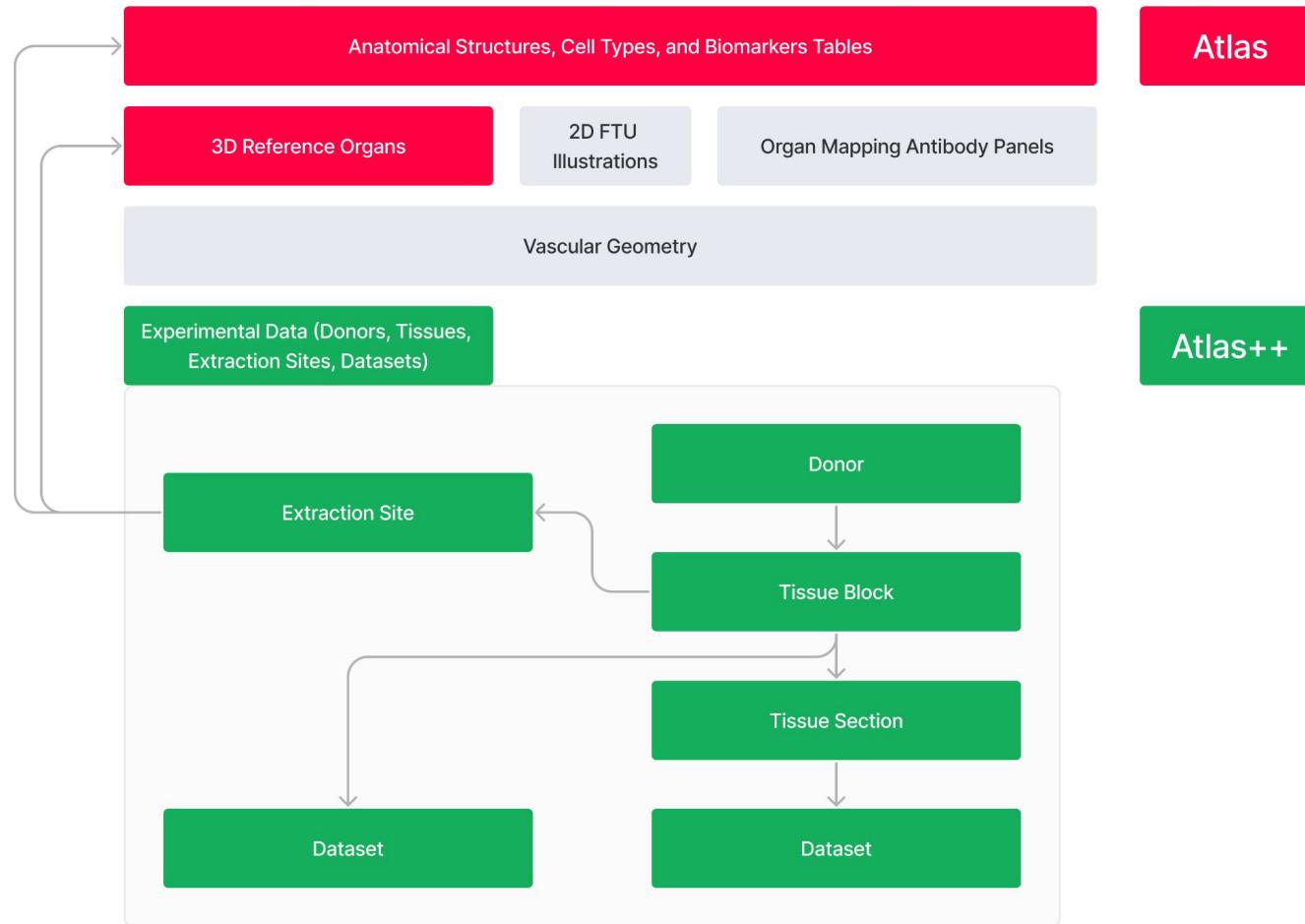
Organ Mapping Antibody Panels

Vascular Geometry

Experimental Data (Donors, Tissues,
Extraction Sites, Datasets)

Atlas++

Experimental Dataset Framework

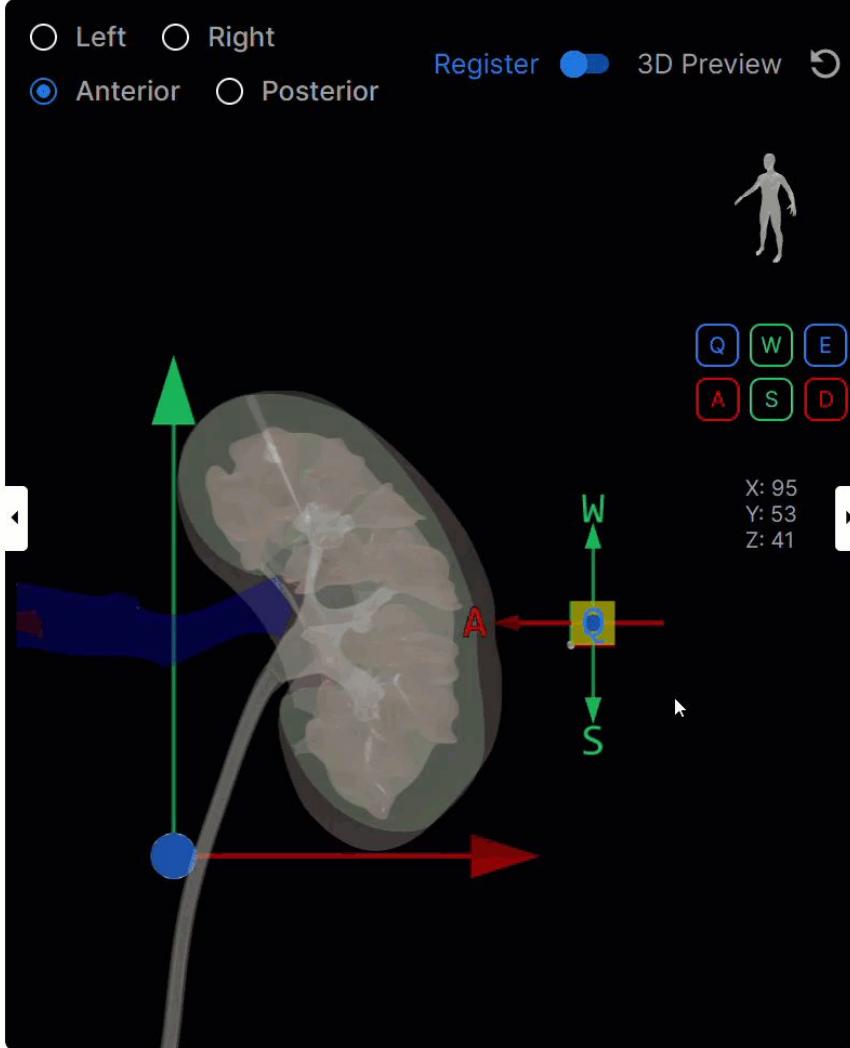


Anatomical Structures

- Left
 - Right
 - Anterior
 - Posterior
- Register 3D Preview
- all anatomical structures
 - kidney capsule
 - hilum of kidney
 - cortex of kidney
 - renal column
 - outer cortex of kidney
 - renal medulla
 - renal papilla
 - renal pyramid

Landmarks

- all landmarks
- bisection line
- left renal artery
- left renal pelvis
- left renal vein
- left ureter
- major calyces
- minor calyces



Tissue Block Controls

Tissue Block Dimensions (mm)

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

Tissue Sections

Thickness # Sections

Tissue Block Rotation

X

Y

Z

Anatomical Structure Tags

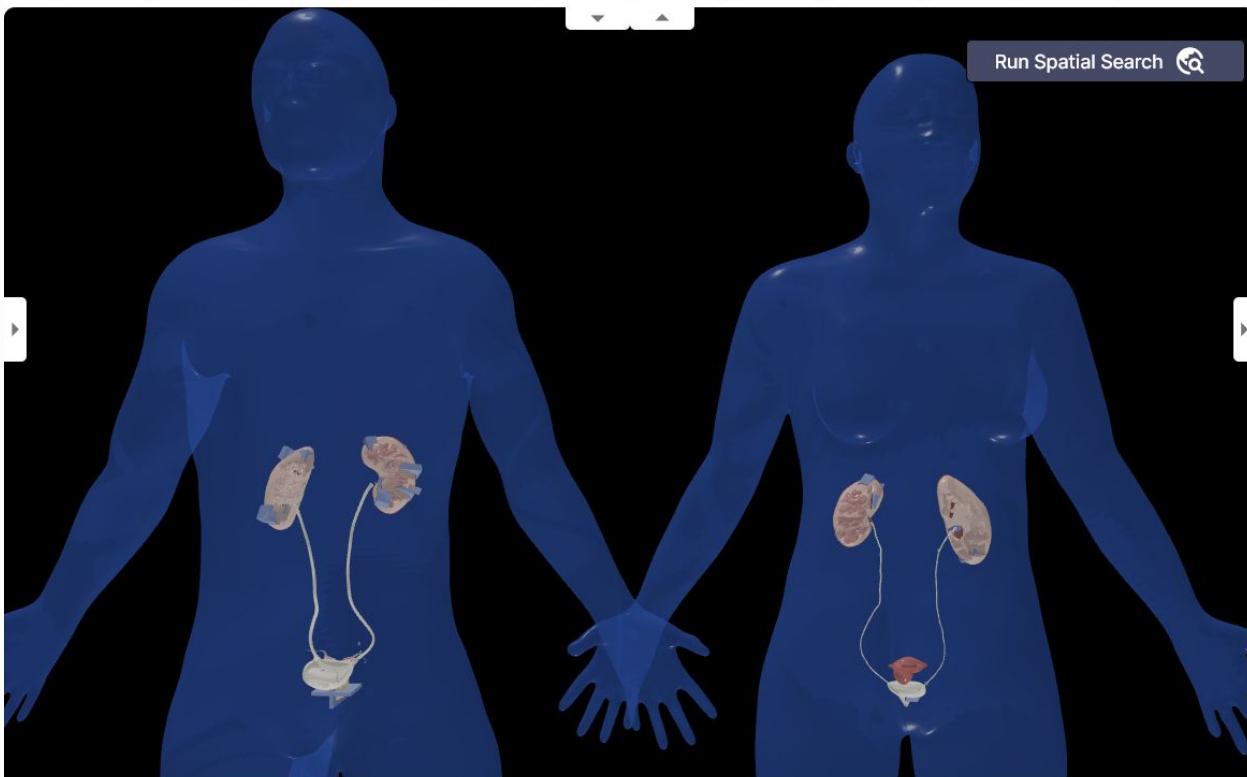
Add Anatomical Structures ...

Assigned Added

Review and Download

HRA-mapped Data: kidney, ureter, bladder, prostate, and uterus

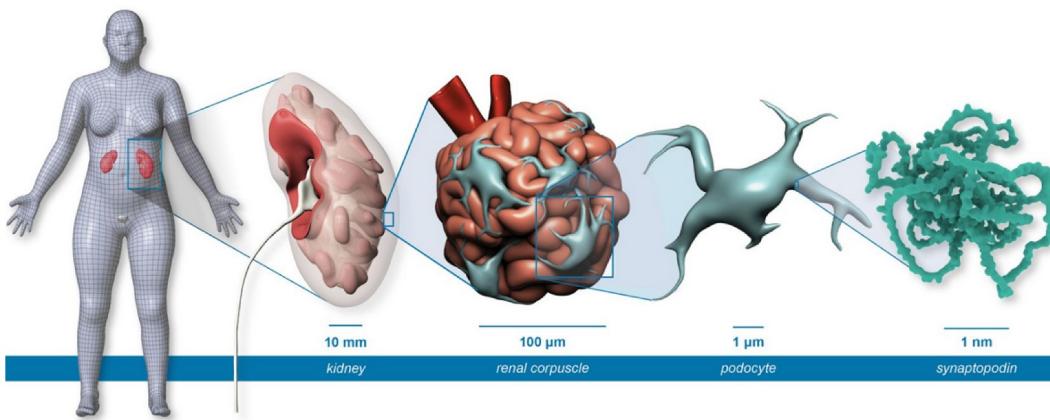
HuBMAP HRA EXPLORATION



kidney, ureter, urinary bladder, prostate, uterus | cell | biomarker

5 Tissue Data Providers
98 Donors
161 Tissue Blocks
131 Extraction Sites
400 Tissue Sections
1184 Tissue Datasets

- | | |
|--------------------------|---|
| <input type="checkbox"/> | Patient B Cortical biopsy
Entered 4/18/2020, Seth Winfree, KPMP-IU/O... |
| <input type="checkbox"/> | Patient A Cortical biopsy
Biopsy from Nephrology biobank-salvaged fro... |
| <input type="checkbox"/> | Cover Nephrectomy
Biopsy from Nephrology biobank-salvaged fro... |
| <input type="checkbox"/> | Male, Age 42, Donor ID D46
Entered 8/10/2023, John Lafin, UT Southwest... |
| <input type="checkbox"/> | Male, Age 25, Donor ID D38
Entered 8/10/2023, John Lafin, UT Southwest... |
| <input type="checkbox"/> | Male, Age 18, Donor ID D20
Entered 8/10/2023, John Lafin, UT Southwest... |
| <input type="checkbox"/> | Male, Age 36, Donor ID D80
Entered 8/10/2023, John Lafin, UT Southwest... |
| <input type="checkbox"/> | Male, Age 18, Donor ID D20 |



Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

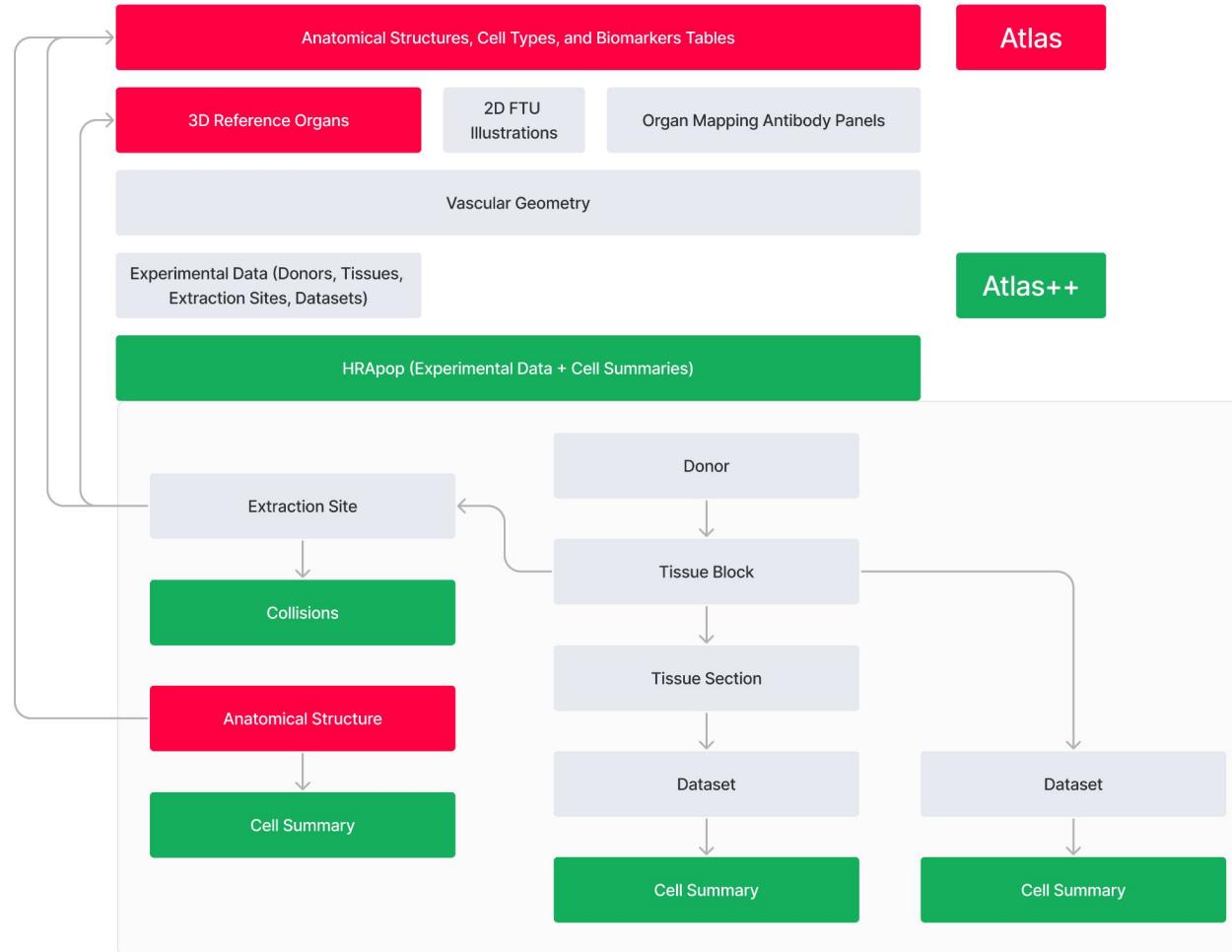
Vascular Geometry

Experimental Data (Donors, Tissues,
Extraction Sites, Datasets)

Atlas++

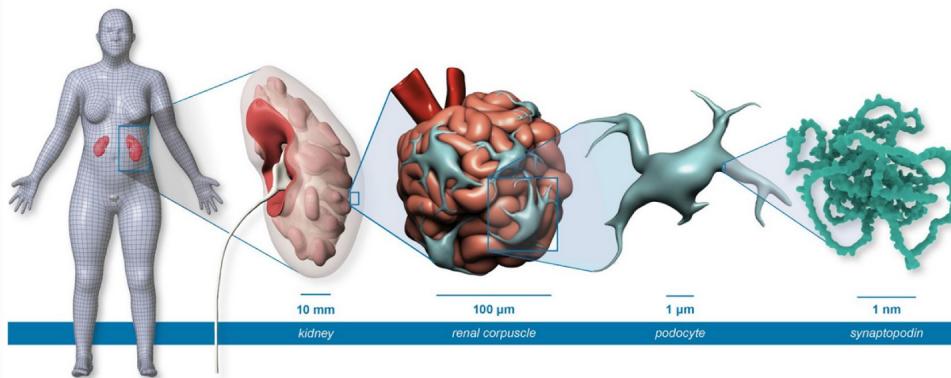
HRApop (Experimental Data + Cell Summaries)

HRApop Framework



HRApop data: kidney, ureter, bladder, prostate, and uterus

Organ	Datasets with H5AD file	ASCT+B and 3D Reference Organs			Cell Type Annotation Tools		
		#AS in 3D (male + female)	#AS	#CT	#CT in Azimuth	#CT in CellTypist	#CT in popV
kidney	207	116	61	70	58	34	0
prostate gland	34	18	13	19	0	0	13
urinary bladder	0	15	16	15	0	0	14
ureter	0	4	7	14	0	0	0
uterus	23	10	61	18	0	0	13
Total (sum, not unique)	264	159	151	122	58	34	40



Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

Vascular Geometry

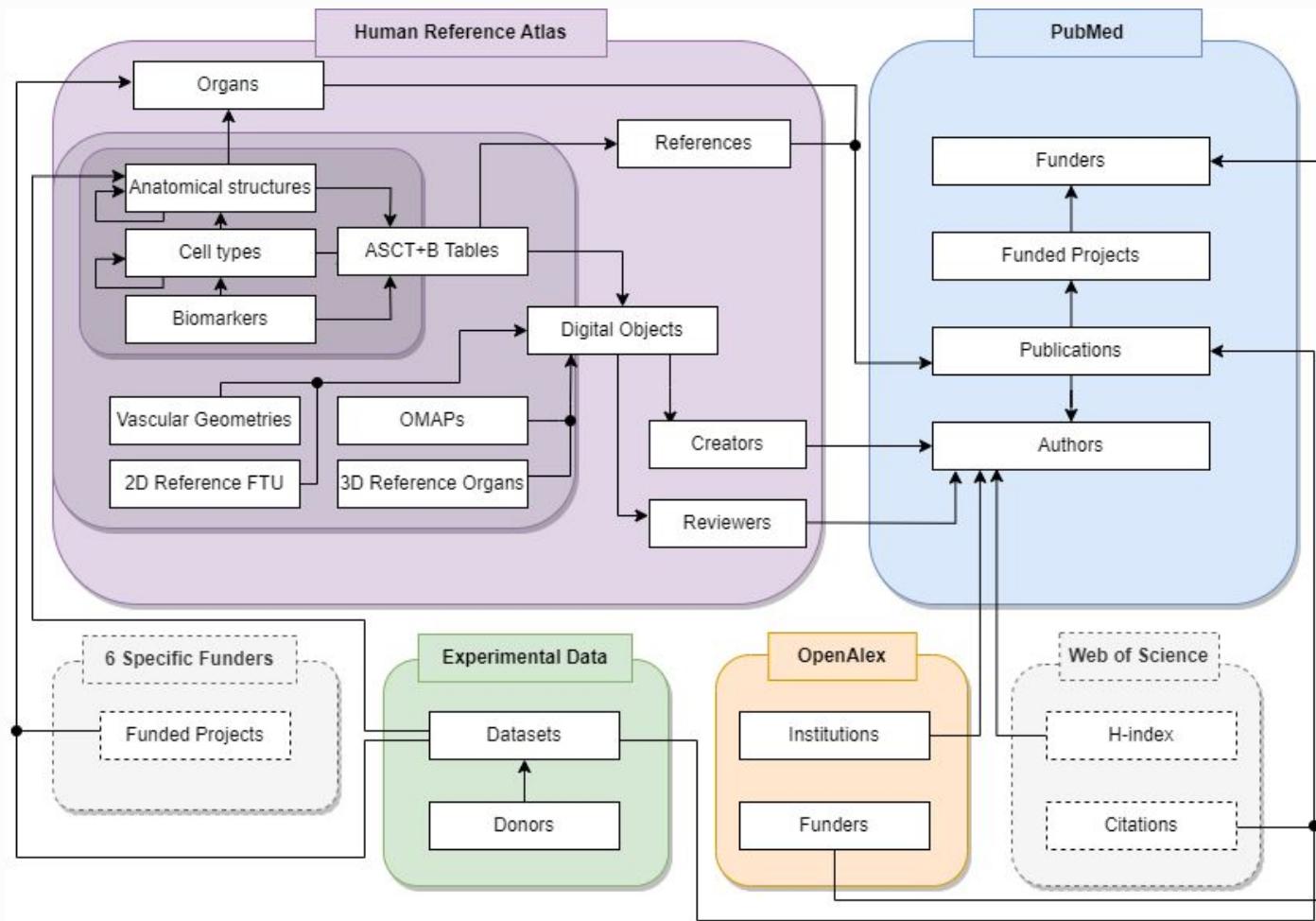
Experimental Data (Donors, Tissues,
Extraction Sites, Datasets)

Atlas++

HRApop (Experimental Data + Cell Summaries)

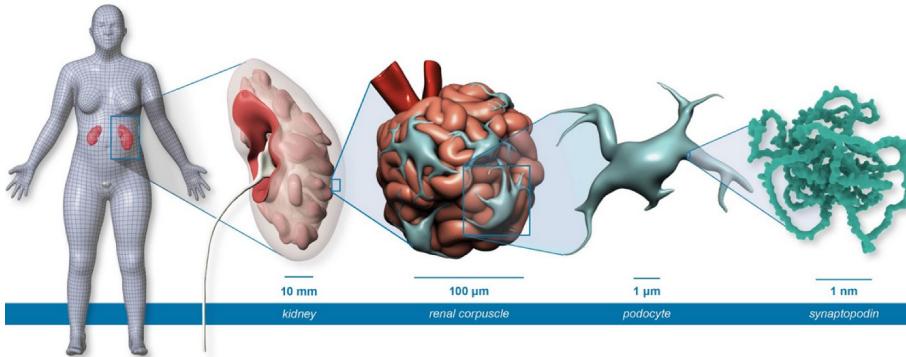
HRAlit (HRA-relevant Literature)

HRAlit Framework



HRAlit data: kidney, ureter, bladder, prostate, and uterus

Organ	#Publications	#Experts	#Institutions	#Funded Projects	#Funders
kidney	762,095	59,910	8,899	97,041	1,485
prostate	174,800	23,131	5,078	34,219	907
ureter	62,702	3,921	1,564	3,294	144
urinary bladder	133,489	10,343	3,131	14,713	460
uterus	71,489	3,266	1,417	8,470	177
Total (sum, not unique)	1,204,575	100,571	20,089	157,737	3,173



Anatomical Structures

Functional
Tissue Units

Cell Types

Biomarkers
Genes, Proteins, ..

Conceptual

Atlas

3D Reference Organs

2D FTU
Illustrations

Organ Mapping Antibody Panels

Vascular Geometry

Experimental Data (Donors, Tissues,
Extraction Sites, Datasets)

Atlas++

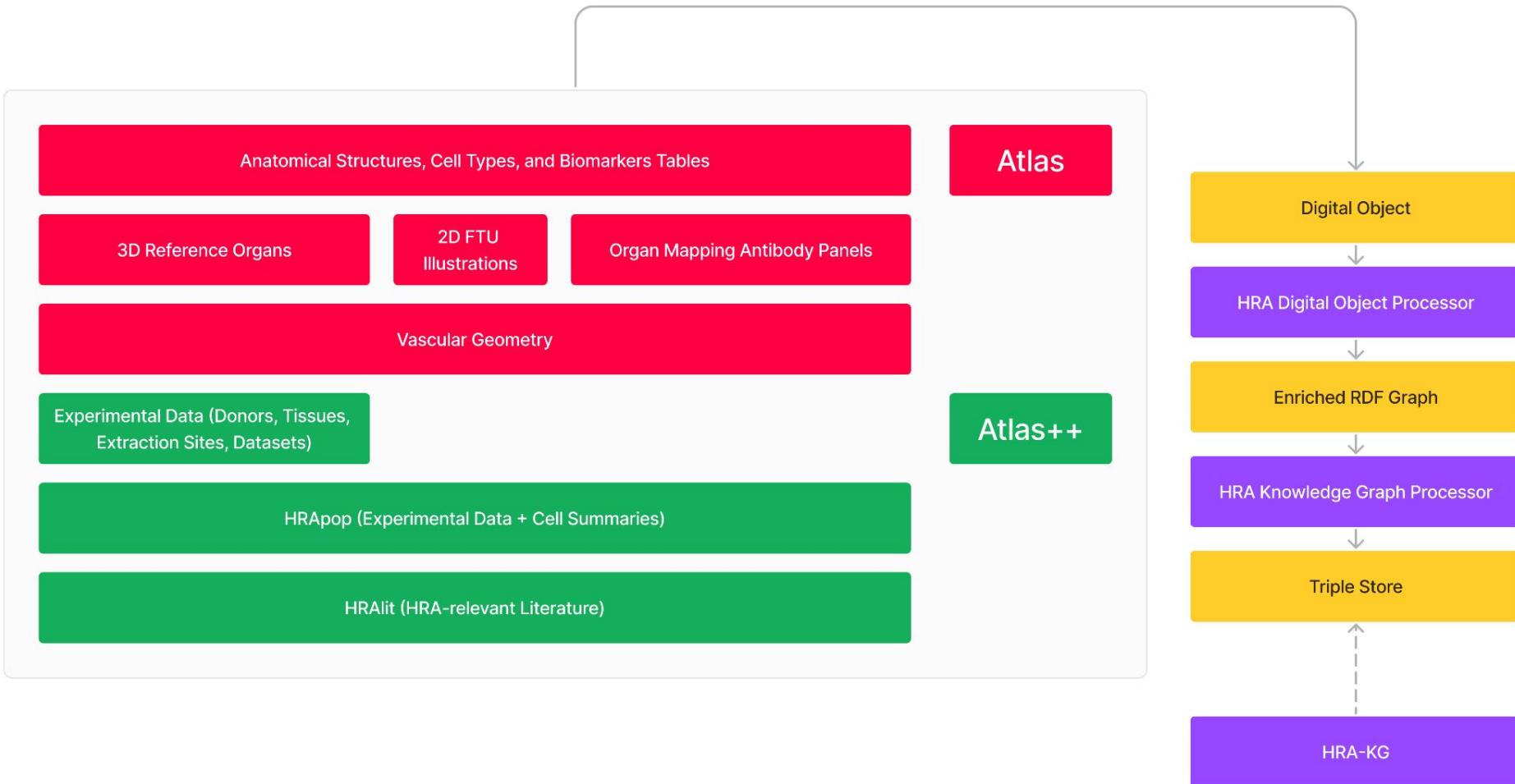
HRApop (Experimental Data + Cell Summaries)

HRAlit (HRA-relevant Literature)

Using the HRA



HRA Knowledge Graph Framework



HRA API and Applications



ASCT+B Reporter User Interface

The screenshot illustrates the ASCT+B Reporter User Interface, featuring a central network visualization and several interactive panels.

Left Side Panel:

- Search and filter menu for locating specific structures or reducing the tree visualization to specific anatomical structures, cell types, and biomarkers.
- Collapse the legend and display settings in the left side panel.
- Return to the ASCT+B Reporter home page.
- Tree visualization legend for color and node shape.
- Display settings for OMAP Tables.
- Display settings for cell types.
- Display settings for the tree visualization.
- Display settings for biomarkers.
- Top of legend and display settings left side panel.
- Hovering over a node reveals more information.
- Email questions and feedback to the Human Reference Atlas team.

Central Network Visualization:

- Select organs displayed in the tree visualization (e.g., ASCT+B-Liver).
- Refresh view.
- Open tables in Google Sheets.
- Playground view.
- Compare.
- Reset.
- Export.
- Front.
- View GitHub Repository and other information.
- Message log of the visualization generation process.
- Summary statistics right side panel.

Information Panels:

- Anatomical structure nodes (e.g., central axis).
- Cell type nodes (e.g., endothelial cell).
- Biomarker nodes (e.g., CD31, CD34).

Bottom Labels:

- Anatomical structure nodes.
- Cell type nodes.
- Biomarker nodes.

<https://humanatlas.io/overview-tools>

Registration User Interface (RUI)

The screenshot illustrates the HubMAP HRA Registration User Interface (RUI) for 3D registration of anatomical structures. The interface includes a central 3D viewer, a left sidebar for anatomical structures, and a right sidebar for registration metadata.

Central 3D Viewer:

- Default anterior view of the selected organ.
- Move tissue block either by dragging left mouse button or by pressing keys on keyboard as indicated on colored axes (red, green, blue).

Top Bar:

- Switch between Register mode (four camera angles only) and 3D Preview mode (free orbit camera).
- Select a predefined camera angle in Register mode (Left, Right, Anterior, Posterior).
- Current position of tissue block (X: 76, Y: 70, Z: 52).
- Keyboard keys highlight when pressed to move tissue block.
- Button to reset the scene.

Left Sidebar: HubMAP HRA REGISTRATION

- List of anatomical structures in selected 3D model.
- Hover over an individual anatomical structure to reveal a slider to modify the opacity.
- Button to show/hide anatomical structure.
- Button to reset opacity and show/hide status.
- Set of landmarks in the organ (if available).
- Dropdown for selecting a landmark set (e.g., Landmark set HCA (1)).
- 3 dimensional scene viewer.

Right Sidebar: Registration Metadata

- RUI information modal.
- Reset tissue block dimensions.
- Enter tissue block width, height, depth.
- Reset tissue section metadata.
- Add thickness and number of tissue section.
- Reset rotation around all axes.
- Rotation value input for axis.
- Drag slider to rotate around designated axis.
- Add anatomical structure tags manually via controlled vocabulary.
- List of anatomical structures colliding with the tissue block.
- Click the Review and Download button when finished to finalize the registration.

Bottom Buttons:

- Review and Download.

Exploration User Interface (EUI)

The screenshot illustrates the HRA Exploration interface, designed for exploring tissue blocks across various anatomical structures, cell types, and biomarkers.

Filter for exploring tissue blocks of interest: Located at the top left, this section includes dropdown menus for Sex (Both), Age (1-110), and BMI (13-83). It also features checkboxes for Anatomical Structures (AS), Cell Types (CT), and Biomarkers (B).

List of reference organs for exploration: A sidebar on the right lists reference organs with their corresponding tissue block counts: Skin (2), Brain (11), Lung (28), Eye (17), Fallopian Tube (1), Heart (159), and Kidney, L (66).

Number of tissue blocks per organ: A red callout points to the count of 159 tissue blocks associated with the Heart organ.

Spatial search tool for filtering by location: A search bar labeled "Run Spatial Search" is positioned above the 3D scene viewer.

Information modal for the interface: A modal window provides information about the current filters applied: body | cell | biomarker.

Results based on current filters: The main results panel displays three categories of data:

- Tissue Data Providers**: 19 entries, including 307 Donors, 729 Tissue Blocks, 892 Tissue Sections, and 3213 Tissue Datasets.
- Donor card in the expanded view**: A detailed card for a male donor, Liz McDonough, registered on 9/10/2021, showing details like age (72), BMI (27.4), and entry date (4/9/2021).
- Tissue block card with information on number of tissue sections**: A card for a tissue block registered on 1/12/2021, showing dimensions (28 x 11 x 0.3 millimeter) and section count (26).
- Tissue section card**: A card for a tissue section registered on 1/12/2021, showing dimensions (28 x 11 x 0.3 millimeter) and section count (26).
- Dataset cards for viewing relevant portals, publications, or other resources**: Cards for "Cell Dive" and "Publication" datasets, each listing multiple registered entries.

Anatomical Structures list: Shows the count of tissue blocks for various organs: brain (11), lymph node (36), eye (43), fallopian tube (0), and heart (159).

Number of tissue blocks that collide with this anatomical structure: A red callout points to the count of 159 tissue blocks associated with the heart.

Cell Types list: Shows the count of tissue blocks for various cell types: absorptive (67), adipocyte (159), adult endothelial progenitor cell (39), adventitial fibroblast (39), adventitial stromal cell (67), and afferent arteriole endothelial cell (121).

Number of tissue blocks that have this CT in colliding AS in ASCT+B table: A red callout points to the count of 159 tissue blocks associated with the heart.

Biomarkers list: Shows the count of tissue blocks for various biomarkers: a smooth muscle actin (0), A2M (253), ABCA10-43608400015.1 (0), ABCA1 (11), ABCA3 (11), ABCA4 (42), ABCA8 (11), ABCG9 (402), ABCG2 (0), ABCG2 (11), AB1BP (11), ABLIM1 (31), and AC002066.1 (0).

Show and hide lists for specific biomarkers (genes, lipids, metabolites, proteins, proteoforms): A red callout points to the biomarker list.

Number of tissue blocks that have this biomarker in colliding AS in ASCT+B table: A red callout points to the count of 159 tissue blocks associated with the heart.

3D scene viewer: The central feature of the interface, showing two blue human silhouettes with internal tissue blocks highlighted in orange.

Interactive FTU Explorer

Name of the selected Functional Tissue Unit

Functional Tissue Units available for exploration

Select to display the medical illustration, cell type, biomarker data, and data sources

Collapse and expand Functional Tissue Unit listings within organs

View the selected illustration digital object metadata page

Download the selected illustration in various formats

Get the FTU Explorer web component via the HRA-UI GitHub Repository

Direct link to experimental data

Expand the table view

Tabs to view tables for gene, protein, & lipids

Cell types, cell counts, & associated biomarker columns

Hover for details on ontology IDs and expression values

Legend for cell types and biomarkers table: Hover over the information icons to reveal additional legend details

Higher opacity means higher mean biomarker expression levels

Publication in which experimental data was published and linked to source data

Contact form for Human Reference Atlas team

Open the Human Reference Atlas Portal

<https://humanatlas.io/overview-tools>

Human Reference Atlas Functional Tissue Unit Explorer

FTU Library

- Kidney
 - loop of Henle ascending limb thin segment
 - Cortical Collecting Duct
 - descending limb of loop of Henle
 - inner medullary collecting duct
 - neprion
 - outer medullary collecting duct
 - renal corpuscle
 - thick ascending limb of loop of Henle
- Large intestine
- Colon
- Liver
- Lung
- Pancreas
- Prostate Gland
- Skin
- Sensory Insectile
- Spleen
- Thyroid

renal corpuscle

2D Illustration viewer

Cell types by biomarkers tables

Expand the table view

Cell Types by Gene Biomarkers

Gene Biomarkers	Protein Biomarkers	Lipid Biomarkers
DLL4	Cell Count	A2GZ
glomerular capillary endothelial cell	34,400	AKT2
glomerular mesangial cell	9,900	ALSO...
glomerular visceral epithelial cell	34,700	
parietal epithelial cell	36,600	

Biomarker Expression Mean in FTU

Percentage of Data in FTU

Source Data

Single cell transcriptional and chromatin accessibility profiling redefine cellular heterogeneity in the adult human kidney
scRNA-seq of Three Healthy Human Kidney Tissues

Illustration Download Embed

Contact HRA Portal

80 μm

Cell Distance Visualizations

The screenshot displays the Vitessce spatial viewer interface. On the left, a large 2D spatial viewer area shows a dense cluster of cells colored by type (e.g., red, green, blue) and connected by lines representing distances to the nearest endothelial cell. A legend below the viewer identifies colors for various cell types and links. A red box highlights a specific cell for closer examination. To the right of the viewer is a sidebar with a 'Spatial Layers' panel containing dropdown menus for 'Region', 'Type', 'Distance', 'Stromal', and 'Endothelial', along with a 'Link' button and an 'ADD CHANNEL' button. Below the sidebar is a 'Cell Sets' panel with a tree view of cell type categories. A red arrow points from the 'Cell Type' section of the sidebar to a separate histogram at the bottom right. At the top of the interface, there are several navigation and documentation links: 'Access documentation', 'Submit bug reports or feature requests to the Vitessce team', 'Vitessce pronunciation by IPA Reader', 'Blog posts', 'Vitessce GitHub repository', 'Switch between light mode and dark mode', 'Return to the Vitessce landing page', 'Open the Vitessce App', 'Demos showcasing core features', 'Use tutorials', 'Vitessce Python package', and 'Vitessce R package'. A red box highlights the 'Spatial View component' which includes a bulleted list: 'Visualizes all cells', 'Connects each cell to its closest endothelial cell', 'View the distributions of distances between different cell types', 'View the nearest vasculature for the Vasculature Common Coordinate Framework (VCCF)', and 'Hover over a cell to examine details'.

- Access documentation
- Submit bug reports or feature requests to the Vitessce team
- Vitessce pronunciation by IPA Reader
- Blog posts
- Vitessce GitHub repository
- Switch between light mode and dark mode
- Return to the Vitessce landing page
- Open the Vitessce App
- Demos showcasing core features
- Use tutorials
- Vitessce Python package
- Vitessce R package

Spatial View component:

- Visualizes all cells
- Connects each cell to its closest endothelial cell
- View the distributions of distances between different cell types
- View the nearest vasculature for the Vasculature Common Coordinate Framework (VCCF)

Hover over a cell to examine details

2D spatial viewer area

Legend showing colors for cell types and links from these cells to endothelial cells

Click on a cell type to filter

A separately generated histogram that displays the distributions of distances between different cell types and the nearest vasculature for the Vasculature Common Coordinate Framework

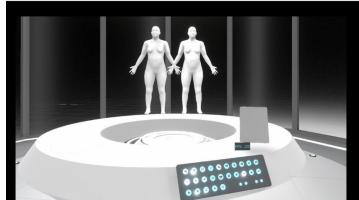
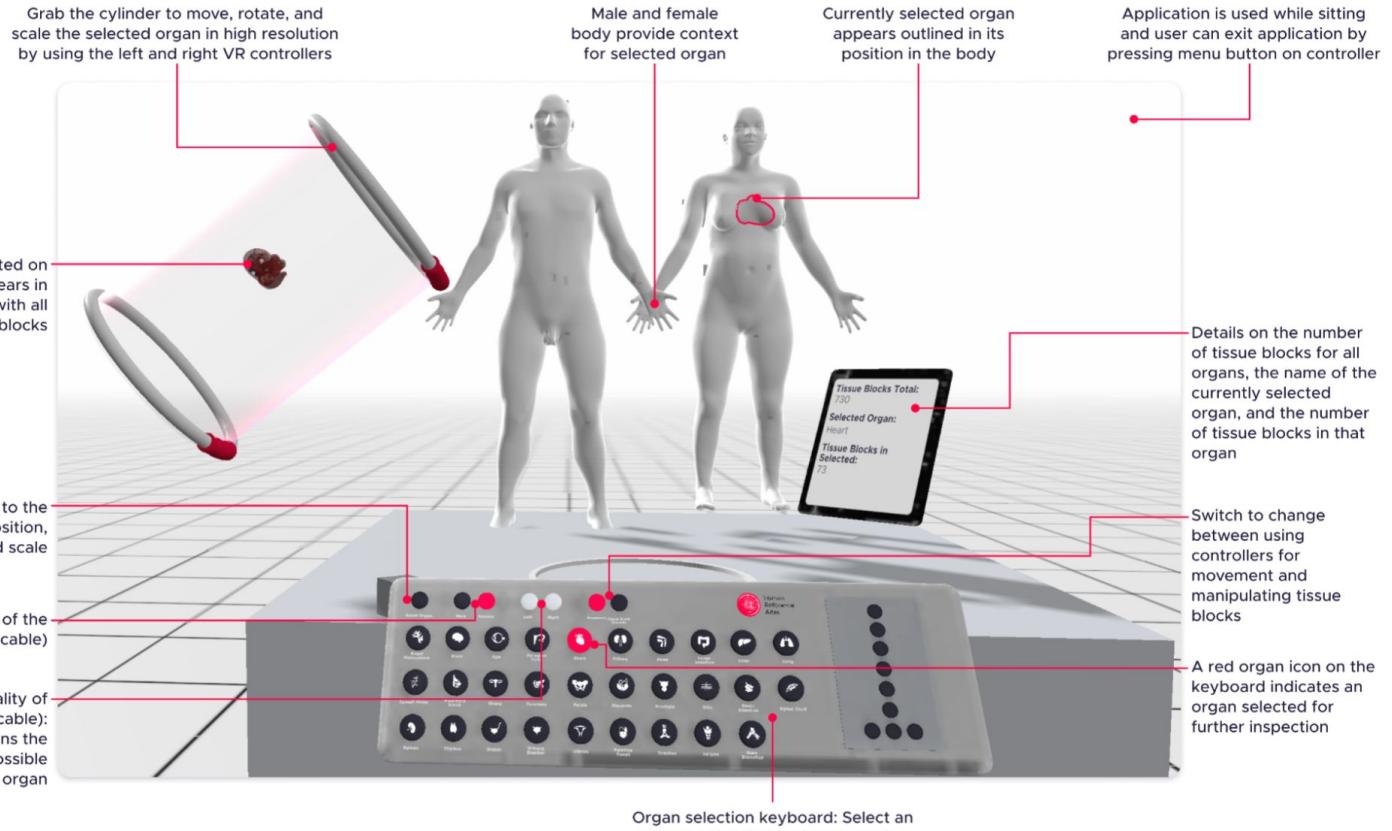
If you are interested to explore cell-cell, cell-FTU distance distributions, please share your data in this format:

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 March 25, 2024 at 4-5p ET. Email Nancy Ruschman, nruschma@indiana.edu if you don't see invite in your cal.

HRA Organ Gallery in VR



HRA Organ Gallery



Everyone

Discover the wonders of the Human Reference Atlas (HRA) in an immersive virtual reality (VR) experience! Created by 17+ international research consortia, including the NIH Human Biomolecular Atlas Program (HuBMAP), the HRA provides a comprehensive, open-source spatial reference of the healthy adult human body at the cellular level.

HRA API: Run an API Query

Input parameters for running an API query:
Fill in parameter values for the route

v1

HRA-API Workflow 3: Run an API Query

HRA-API v1.x Routes

REQUEST

QUERY-STRING PARAMETERS

- query string: SPARQL query to use
Examples: `SELECT * WHERE { ?sub ?pred ?obj. } LIMIT 10`
- token string: Authentication token to use for authenticated searches
- format enum: Allowed: application/json | application/d+json | application/n-quads | application/n-triples | application/sparql-results+json | application/sparql-results+xml | application/trig | simple | stats | table | text/csv | text/n3 | text/tab-separated-values | text/turtle | tree
Override SPARQL response format (Note that not all formats are supported for all SPARQL query types)

API Server: <https://apps.humanatlas.io/api>
Authentication: Not Required

FILL EXAMPLE CLEAR TRY

RESPONSE

Select a response code to view example response and schema doc

200 404

Successful operation. SPARQL responses vary by format/content negotiation.

EXAMPLE SCHEMA

```
[ { }, ]
```

Copy

Example response tab Schema documentation tab for the response

- A red arrow points from the 'Fill in parameter values for the route' text to the 'query string' input field.
- A red arrow points from the 'Select a response code to view example response and schema doc' text to the '200' and '404' buttons.
- A red arrow points from the 'Example response tab' text to the JSON example '[{ },]'.
- A red arrow points from the 'Schema documentation tab for the response' text to the 'SCHEMA' tab.
- A red arrow points from the 'Run the API query' text to the 'TRY' button.
- A red arrow points from the 'Reset parameters' text to the 'CLEAR' button.
- A red arrow points from the 'Fill parameters with example options' text to the 'FILL EXAMPLE' button.

<https://humanatlas.io/api>

HRA User Stories



HRA User Stories

More than 30 one-on-one interviews were conducted with atlas architects, i.e., experts who serve as principal investigators or are otherwise intimately involved in the construction of the latest generation of human atlases, including BICCN, GTEx, GUDMAP, HCA, HuBMAP, Human Tumor Atlas Network (HTAN), KPMP, LungMAP, (Re)building the Kidney (RBK), and SenNet.

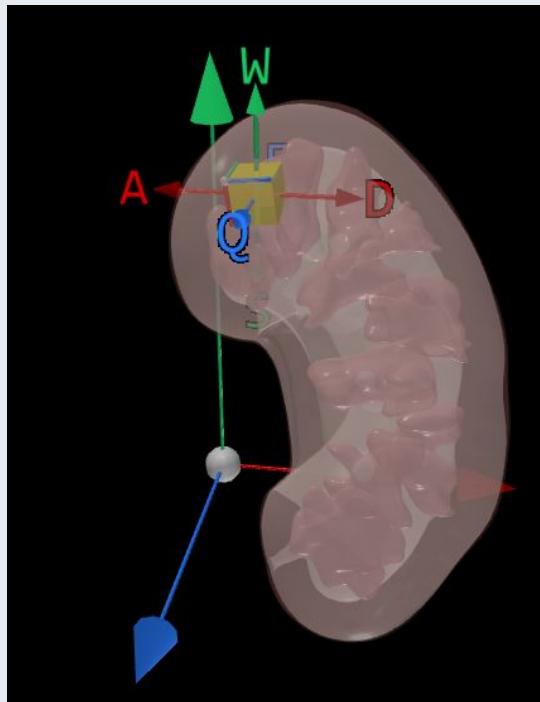
In addition, six programmers from different human atlas projects were surveyed.

Table on right shows feature summary, target user roles, user activities, and added value for seven user stories that drive HRA development.

Feature	User Role	User Activities	Added Value
<i>Facilitate atlas construction by aligning new tissue blocks with existing data</i>			
US#1. Predict cell type populations	Programmers that support Researchers, Clinicians, Pathologists	Predict and explore the likely cell type populations for a RUI-registered tissue block.	Improve cell type annotation through information on what cell type populations exist in what anatomical structures.
US#2. Predict spatial origin of tissue samples	Programmers that support Researchers, Clinicians	Predict and explore the likely 3D location in the human body for a given tissue block with known cell type population.	Compensate for the absence of spatial origin information in many single cell datasets.
<i>Use the atlas to gain insights into changes that occur at all levels in the body with aging or disease</i>			
US#3. Compare reference tissue with aging/diseased tissue	Researchers, Clinicians	Compare tissue blocks, cell types, and biomarker expression levels between healthy reference tissue and aging/diseased tissue.	Understand and communicate changes in tissue structure and function with age or disease.
US#4. Compare reference Functional Tissue Units with aging/diseased FTUs	Researchers, Clinicians	Compare FTUs in terms of cell types and mean biomarker expression levels for healthy reference tissue and aging/diseased tissue.	Understand and communicate changes in FTU structure and function with age or disease
US#5. Provide cell distance distribution visualizations	Researchers, Pathologists	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).	Add granularity to our understanding of how disease develops (e.g., how tumor cells grow or metastasize) in support of targeted therapies.
<i>Ensure atlas sustainability with processes that encourage collaboration and guide future development</i>			
US#6. Develop lightweight atlas components	Programmers that support Researchers and Clinicians	Implement usable and useful HRA components (interfaces and APIs) into other portals in the growing ecosystem of human atlases.	Facilitate collaboration and data/code reuse between the HRA and other portals in support of FAIR data principles.
US#7. Implement dashboard for HRA	Researchers, Clinicians, Funders	Track the evolution and usage of the HRA using data, code, and portal usage statistics in aggregate and divided by portal (e.g., HubMAP or SenNet) or PEDP survey results.	Enable evidence-based decision-making by providing insights into the atlas' construction and usage (e.g., gaps in data, application areas, user demographics, equitable access).

US#1. Predict cell type populations

Given a location in the body, what cell types and their distribution should I see?



% of Total	# Cells	Cell
17%	549,473	Cortical Thick Ascending Limb
15%	476,562	Inner Medullary Collecting Duct
8.0%	259,453	Proximal Tubule Epithelial Segment 1
7.4%	242,118	Distal Convoluted Tubule Type 1
6.3%	203,659	Ascending Thin Limb
6.0%	194,380	Connecting Tubule
5.7%	185,991	Descending Thin Limb Type 1
5.2%	168,763	Descending Thin Limb Type 2
4.7%	152,603	Proximal Tubule Epithelial Segment 3
3.9%	127,341	Medullary Thick Ascending Limb
2.9%	95,842	Fibroblast
2.7%	87,883	Cortical Collecting Duct Principal
2.1%	66,948	Macula Densa
1.8%	59,228	Medullary Fibroblast

<https://apps.humanatlas.io/us1/>

US#2. Predict spatial origin of tissue samples

Given a distribution of cells, where in the body might this have come from?

% of Total	# Cells	Cell
17%	549,473	Cortical Thick Ascending Limb
15%	476,562	Inner Medullary Collecting Duct
8.0%	259,453	Proximal Tubule Epithelial Segment 1
7.4%	242,118	Distal Convoluted Tubule Type 1
6.3%	203,659	Ascending Thin Limb
6.0%	194,380	Connecting Tubule
5.7%	185,991	Descending Thin Limb Type 1
5.2%	168,763	Descending Thin Limb Type 2
4.7%	152,603	Proximal Tubule Epithelial Segment 3
3.9%	127,341	Medullary Thick Ascending Limb
2.9%	95,842	Fibroblast
2.7%	87,883	Cortical Collecting Duct Principal
2.1%	66,948	Macula Densa
1.8%	59,228	Medullary Fibroblast



Similarity	Label
0.99	outer cortex of kidney
0.93	kidney pyramid
0.73	hilum of kidney
0.73	renal column
0.72	kidney capsule
0.50	renal papilla

Also, similar datasets and HRA extraction sites

<https://apps.humanatlas.io/us2/>

US#3. Compare reference tissue with aging/diseased tissue

The screenshot displays the Human Reference Atlas (HRA) Exploration interface. At the top, there's a header bar with a search icon, a brain icon, and a 'Run Spatial Search' button. Below the header is a navigation bar with icons for Brain, Eye, L, Eye, R, Fallopian Tube, L, Fallopian Tube, R, Heart, Kidney, L, and Kidney, R.

The main area features a 3D scene viewer with two human silhouettes. Tissue blocks are represented as colored shapes (e.g., red, orange, yellow) distributed across the body regions. A legend at the bottom right of the viewer identifies these colors: body (blue), cell (green), and biomarker (yellow).

On the left side, there are several filter panels:

- Filter for exploring tissue blocks of interest:** Includes dropdowns for Sex: Both, Age: 1-110, and BMI: 13-83.
- List of reference organs for exploration:** Shows a grid of icons for various organs: Brain, Eye, L, Eye, R, Fallopian Tube, L, Fallopian Tube, R, Heart, Kidney, L, and Kidney, R.
- Number of tissue blocks per organ:** A table showing the count of tissue blocks for each organ: Heart (159), Kidney, L (86), etc.
- Spatial search tool for filtering by location:** A search bar labeled 'Run Spatial Search'.
- Information modal for the interface:** A help icon (i).

Below these filters, there are three lists:

- Anatomical Structures list:** Shows a tree view of anatomical structures with counts: brain (11), lymph node (36), eye (43), fallopian tube (0), heart (159). A note indicates the total number of tissue blocks: 729.
- Cell Types list:** Shows a list of cell types with counts: absorptive (67), adipocyte (159), adult endothelial progenitor cell (39), adventitial fibroblast (39), adventitial stromal cell (67), afferent arteriole endothelial cell (121). A note indicates the total number of tissue blocks: 729.
- Biomarkers list:** Shows a list of biomarkers with counts: a smooth muscle actin (0), ABCA10-43608400015.1 (253), ABCA1 (0), ABCA13 (11), ABCA3 (42), ABCA4 (11), ABCA8 (11). A note indicates the total number of tissue blocks: 729.

On the right side, there are several cards and tables:

- Results based on current filters:** A table showing the count of various tissue components: 19 Tissue Data Providers, 307 Donors, 729 Tissue Blocks, 892 Tissue Sections, and 3213 Tissue Datasets.
- Donor card in the expanded view:** Details for a donor: Male, Age 72, BMI 27.4, Entered 4/9/2021, Liz McDonough, RTI-Gene...
- Tissue block card with information on number of tissue sections:** A table showing registered tissue blocks: 28 × 11 × 0.3 millimeter, 0.3 millimeter, block.
- Tissue section card:** A table showing registered tissue sections: 28 × 11 × 0.3 millimeter, 0.3 millimeter, block.
- Dataset cards for viewing relevant portals, publications, or other resources:** A table showing registered datasets: 28 × 11 × 0.3 millimeter, 0.3 millimeter, block.

At the bottom center, it says '3D scene viewer'.

<https://apps.humanatlas.io/eui/>

US#4. Compare reference FTUs with aging/diseased FTUs

This figure illustrates the Human Reference Atlas Functional Tissue Unit Explorer interface, showing how to compare reference FTUs with aging/diseased FTUs.

The interface consists of several panels:

- Functional Tissue Units available for exploration:** A tree view of organs and their subunits. Nodes can be collapsed or expanded. A red dot indicates the selected node: "renal corpuscle".
- Name of the selected Functional Tissue Unit:** "renal corpuscle".
- 2D Illustration viewer:** A detailed anatomical illustration of the renal corpuscle. Labels include: Glomerular visceral epithelial cell, Parietal epithelial cell, Epithelial cell proximal tubule, Glomerular capillary endothelial cell, Efferent arteriole endothelial cell, Macula densa epithelia cell, and Glomerular mesangial cell. A scale bar indicates 50 μm.
- Cell types by biomarkers tables:** A table showing cell types, gene biomarkers, protein biomarkers, and lipid biomarkers. A red box highlights the protein biomarker section for glomerular capillary endothelial cell.
- Expand the table view:** A button to expand the table view.
- Cell types, cell counts, & associated biomarker columns:** A legend for the table columns.
- Hover for details on ontology IDs and expression values:** A note about hovering over the table.
- Legend for cell types and biomarkers table:** A legend for the table, including a color scale from 0.0 to 1.0 and a size scale for 0%, 50%, and 100%.
- Biomarker Expression Mean in FTU:** A color scale for biomarker expression mean.
- Percentage of Cells in FTU:** A size scale for the percentage of cells.
- Source Data:** A dropdown menu for source data.
- Publication link:** A link to a publication: "Single cell transcriptional and chromatin accessibility profiling redefine cellular heterogeneity in the adult human kidney snRNA-seq of Three Healthy Human Kidney Tissue".
- Contact form:** A contact form for the Human Reference Atlas team.
- Open HRA Portal:** A link to open the Human Reference Atlas Portal.

At the bottom, there are buttons for "Illustration", "Download", and "Embed".

Annotations provide additional context for specific features:

- View the selected illustration digital object metadata page:** A link to the digital object metadata page.
- Download the selected illustration in various formats:** A link to download the illustration.
- Get the FTU Explorer web component via the HRA-UI GitHub Repository:** A link to the GitHub repository.
- Direct link to experimental data:** A link to experimental data.

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

US#5. Provide cell distance distribution visualizations

The screenshot displays the Vitesse application interface. At the top, there is a navigation bar with links to documentation, demos, tutorials, bug reports, GitHub, and mode switching. Below the navigation bar is a large 2D spatial viewer area showing a network of cells. A legend on the right identifies cell types by color and link type by shape. A separate histogram at the bottom shows the distribution of distances between different cell types.

- Access documentation
- Demos showcasing core features
- Use tutorials
- Submit bug reports or feature requests to the Vitesse team
- Vitesse pronunciation by IPA Reader
- Blog posts
- Vitesse GitHub repository
- Switch between light mode and dark mode

Return to the Vitesse landing page

Spatial View component:

- Visualizes all cells
- Connects each cell to its closest endothelial cell
- View the distributions of distances between different cell types
- View the nearest vasculature for the Vasculature Common Coordinate Framework (VCCF)

Hover over a cell to examine details

2D spatial viewer area

Legend showing colors for cell types and links from these cells to endothelial cells

Click on a cell type to filter

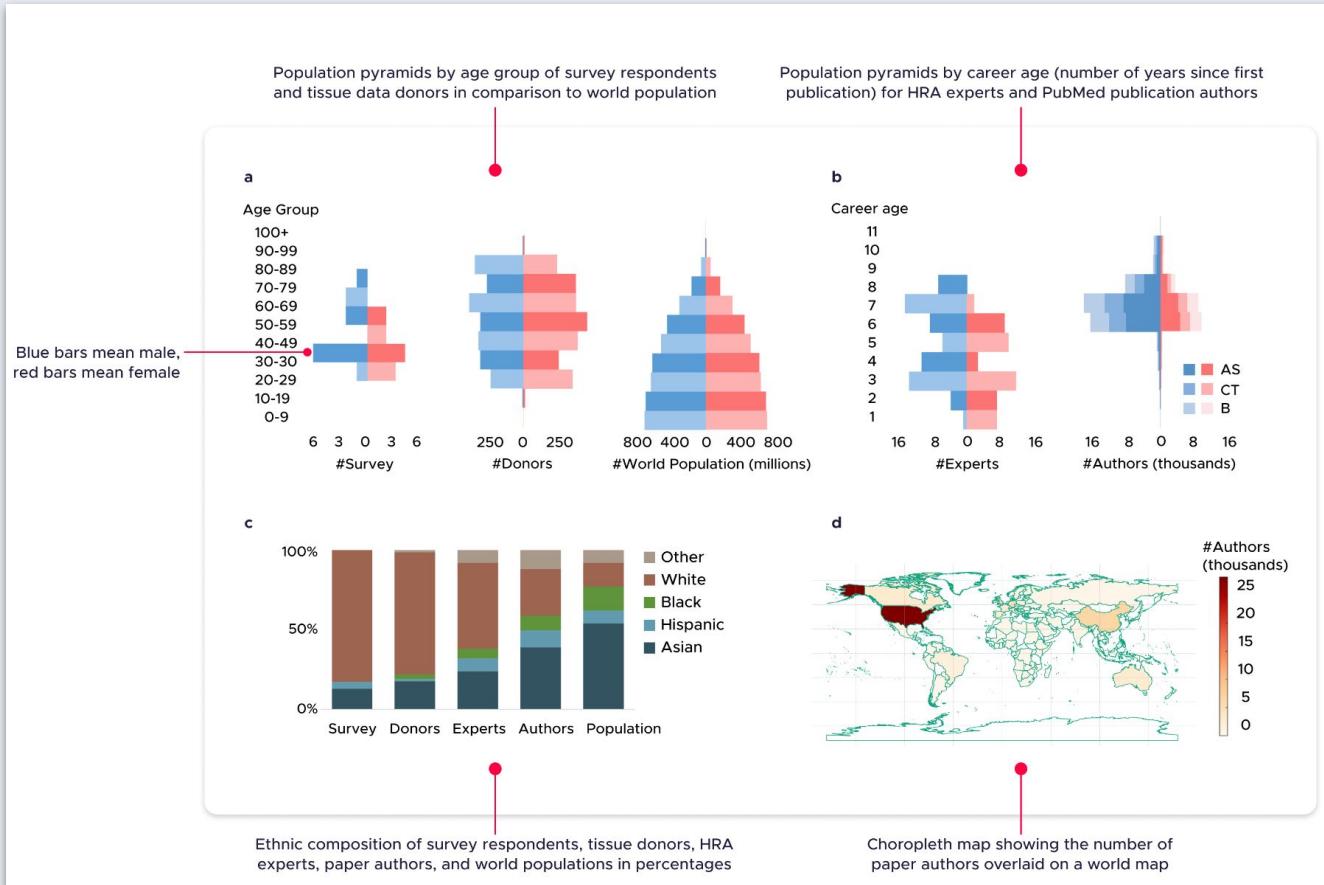
The Spatial Layers panel displays more general cell type categorization of all cells: Categories may be switched on/off

A separately generated histogram that displays the distributions of distances between different cell types and the nearest vasculature for the Vasculature Common Coordinate Framework

Cell Type	Color	Link Type	Color
All Cells	Grey	Object	Blue
Endothelial	Red	Revise	Green
Smooth muscle	Orange	MUCL+ Endothelio	Yellow
Macrophage	Dark Blue	M1 Macrophage	Dark Green
CD4+ T cell	Red	Lymphatic	Pink
CD4+ T cell_Link	Red	CD4+ Ectosyme	Light Green
CD8+ T cell	Blue	CD8+ Ectosyme	Dark Green
CD8+ T cell_Link	Blue	DC	Dark Blue
Cycling TA	Yellow	Cycling TA	Yellow
DC	Blue	DC_Link	Blue
Endothelial	Red	Endothelial	Red
Endothelial_Link	Red	Endothelial_Link	Red
Epithelial	Green	Epithelial	Green
Epithelial_Link	Green	Epithelial_Link	Green
Endothelial	Red	Endothelial	Red
Epithelial	Green	Epithelial	Green
Epithelial_Link	Green	Epithelial_Link	Green
Stroma	Grey	Stroma	Grey

Coming June 14th on humanatlas.io

US#7. Implement dashboard for HRA



Coming June 14th on humanatlas.io

Wrapping it up



Future work

- Releases every 6 months (June and December)
- More data, more collaborations, more organs, continued advancement of US#1-7
- HRA in clinical settings



Current Team

Principal Investigator,
Co-Principal Investigators,
and Consultants



Katy Börner
MC-IU PI
CNS Director

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

Helen Parkinson
Ontologist

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

Full Time Staff



Daniel Bolin
Software Developer

Andreas Bueckle
Research Lead

Josef Hardi
Software Developer

Bruce Herr II
MC-IU PM
CNS Technical Director

Yashvardhan Jain
Research Software Engineer
(Machine Learning)

Edward Lu
Software Developer

Libby Maier
User Experience Designer

Lisel Record
MC-IU PM
CNS Associate Director

Nancy Ruschman
Project Manager

Part Time Staff
and Students



Rachel Bajema
2D Medical Illustrator

Supriya Bidanta
Research Assistant

Avinash Boppana
Research Consultant

Lu Chen
PhD Student

Xiaojie Fan
PhD Student

Kate Gustilo
Research Analyst

Yingnan Ju
PhD Student

Bhushan Sanjay
Khope
Software Developer

Ushma Patel
Medical Illustrator

Connecting people is key to our success. Here are some of
our great collaborators (apologies to those I missed!)



Ellen Quardokus
Sr. Research Analyst

Heidi Schlelein
3D Medical Illustrator

Todd Theriault
Technical Writer

Jerin Thomas
Project Management
Assistant



Thank you!

Resources at:

<https://humanatlas.io/events/AUA2024>

Contact me:

Bruce Herr <bherr@iu.edu>

