

AUA  
2024 MAY 3-6  
*San Antonio*

Keynote:  
The Human  
Reference Atlas





Version 2.0

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# Human Reference Atlas

<https://humanatlas.io>



# Keynote: The Human Reference Atlas



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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



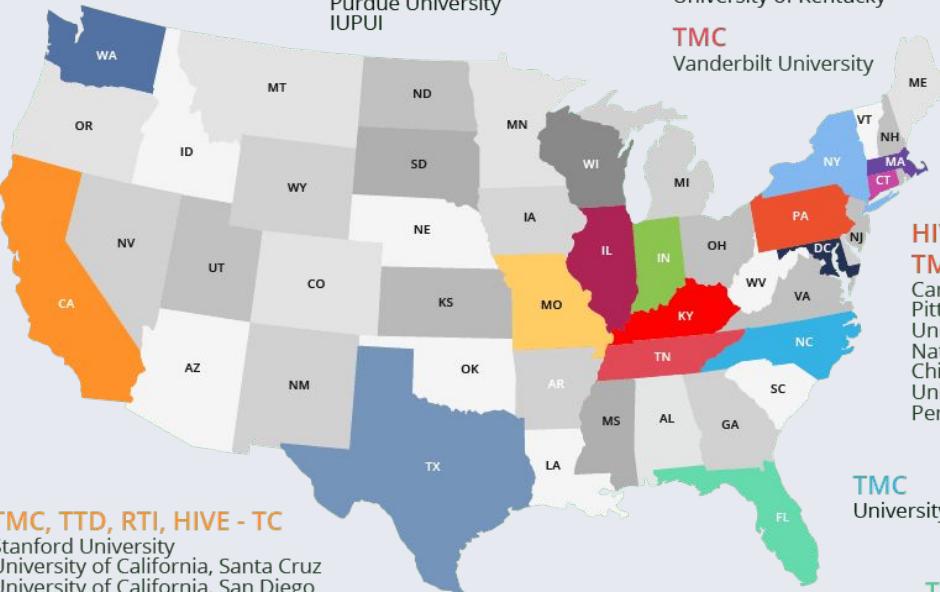
# HuBMAP Contributing Sites

## 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, TTD

University of Connecticut  
Yale University

## HIVE - TC, TTD, RTI, TMC, DP

Harvard University  
Harvard Medical School  
Columbia University  
Beth Israel Deaconess Medical Center



## TMC

University of Zurich



## TMC

Delft University of Technology



## TMC

University of North Carolina, Chapel Hill

## TMC, HIVE - TC

University of Florida

## HIVE - TC, TMC

European Bioinformatics Institute  
Wellcome Sanger Institute



# Early history of the HRA and HuBMAP

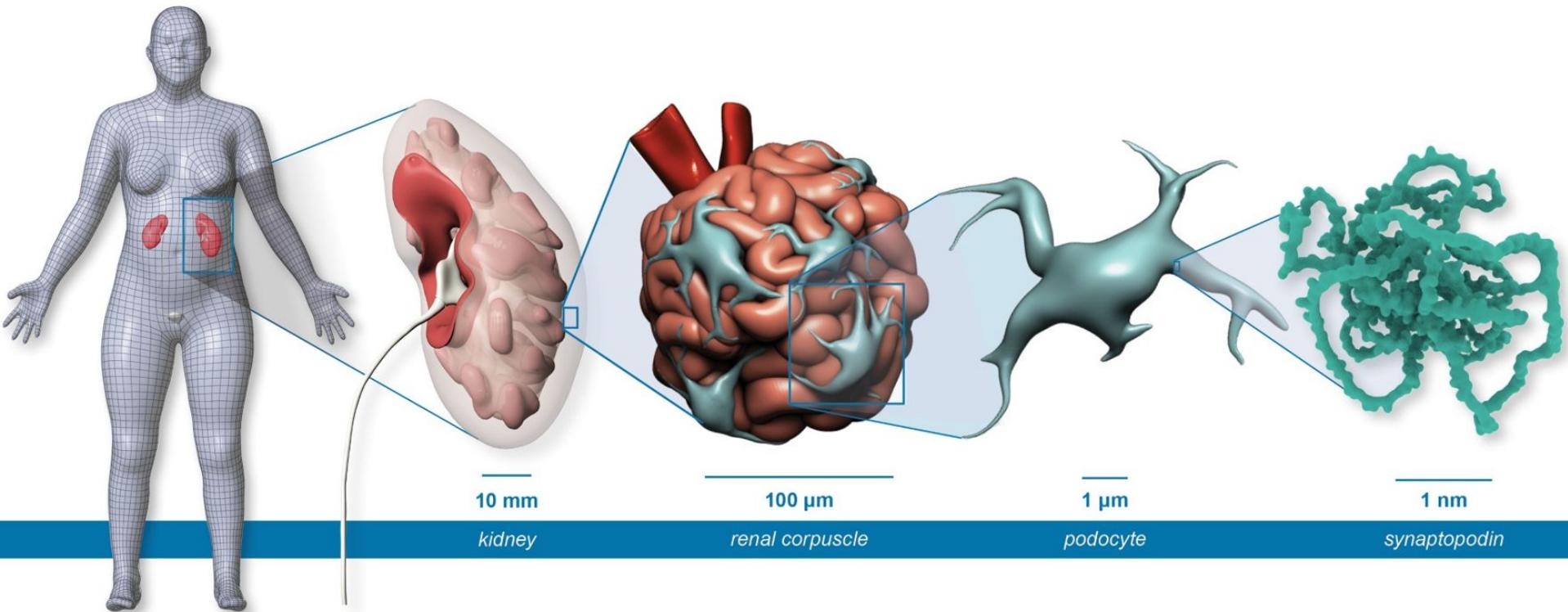
- HuBMAP started in 2018 with the goal of mapping the human body down to the cellular level
- The IU team started off with creating a common coordinate framework, that eventually evolved into the HRA
- In 2023, we published HRA v2.0
- We are now in the production phase of HuBMAP

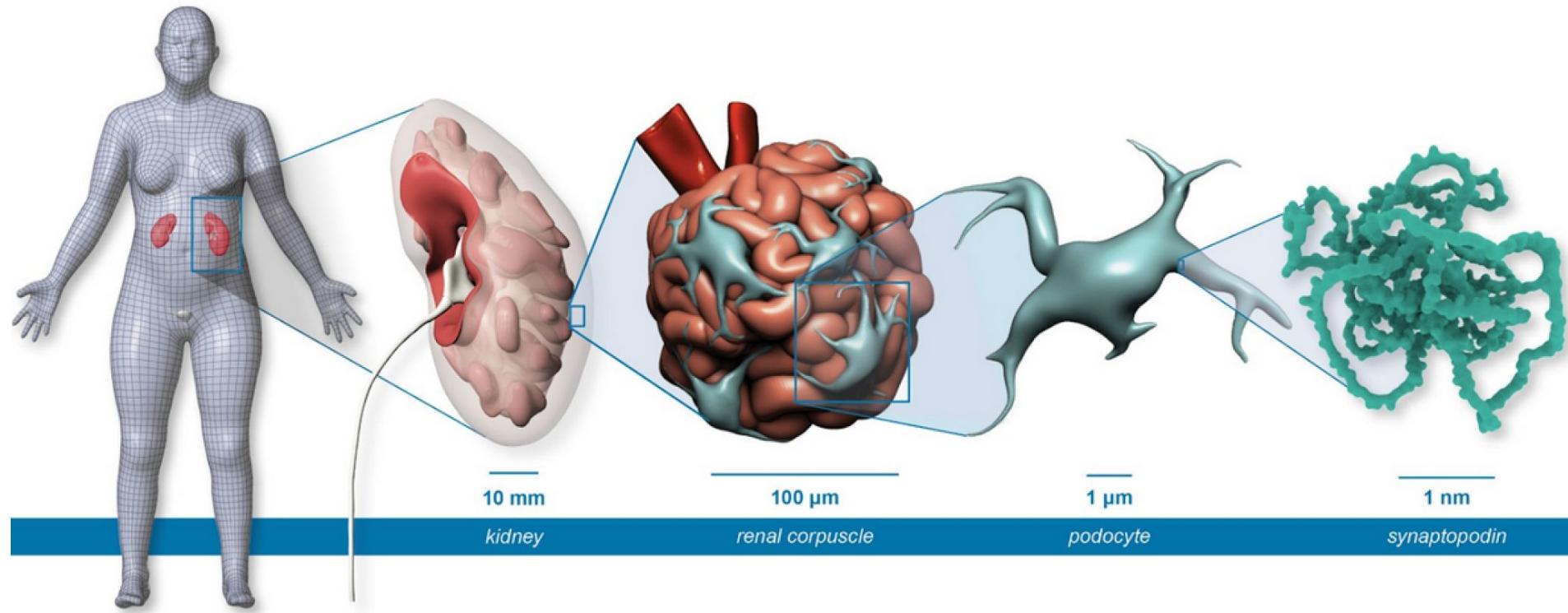
# What is the HRA?



# 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, ..

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Genes, Proteins, ..

Conceptual

Anatomical Structures, Cell Types, and Biomarkers Tables

Atlas

3D Reference Organs

2D FTU  
Illustrations

Organ Mapping Antibody Panels

Vascular Geometry

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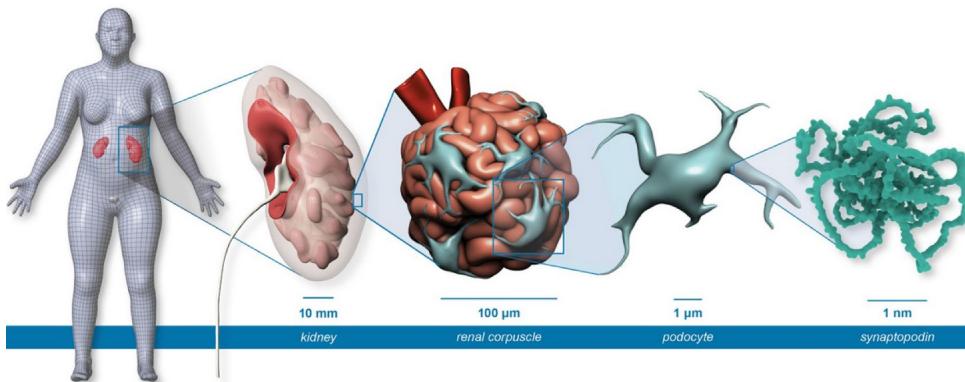
Vascular Geometry

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

Atlas++

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

HRAlit (HRA-relevant Literature)



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Atlas++

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# 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>			
<b>US#1.</b> 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.
<b>US#2.</b> 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>			
<b>US#3.</b> 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.
<b>US#4.</b> 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
<b>US#5.</b> 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>			
<b>US#6.</b> 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.
<b>US#7.</b> 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

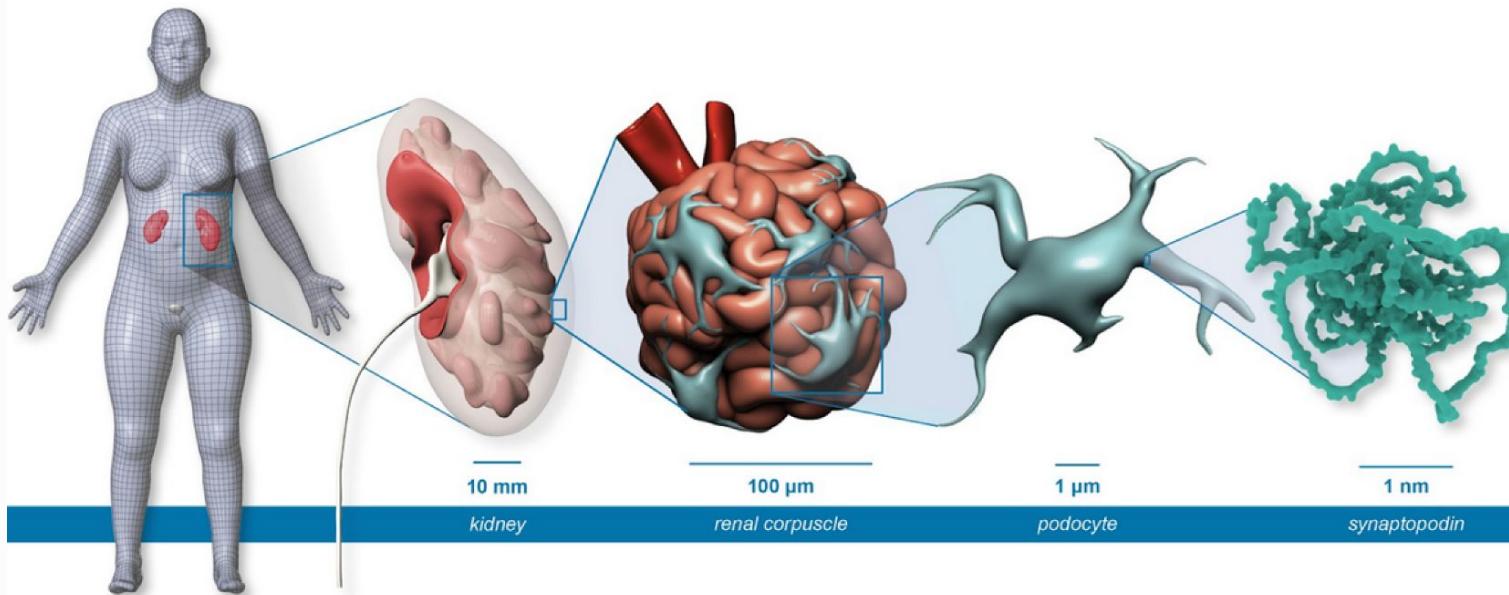
## Relevance to Urology

- 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





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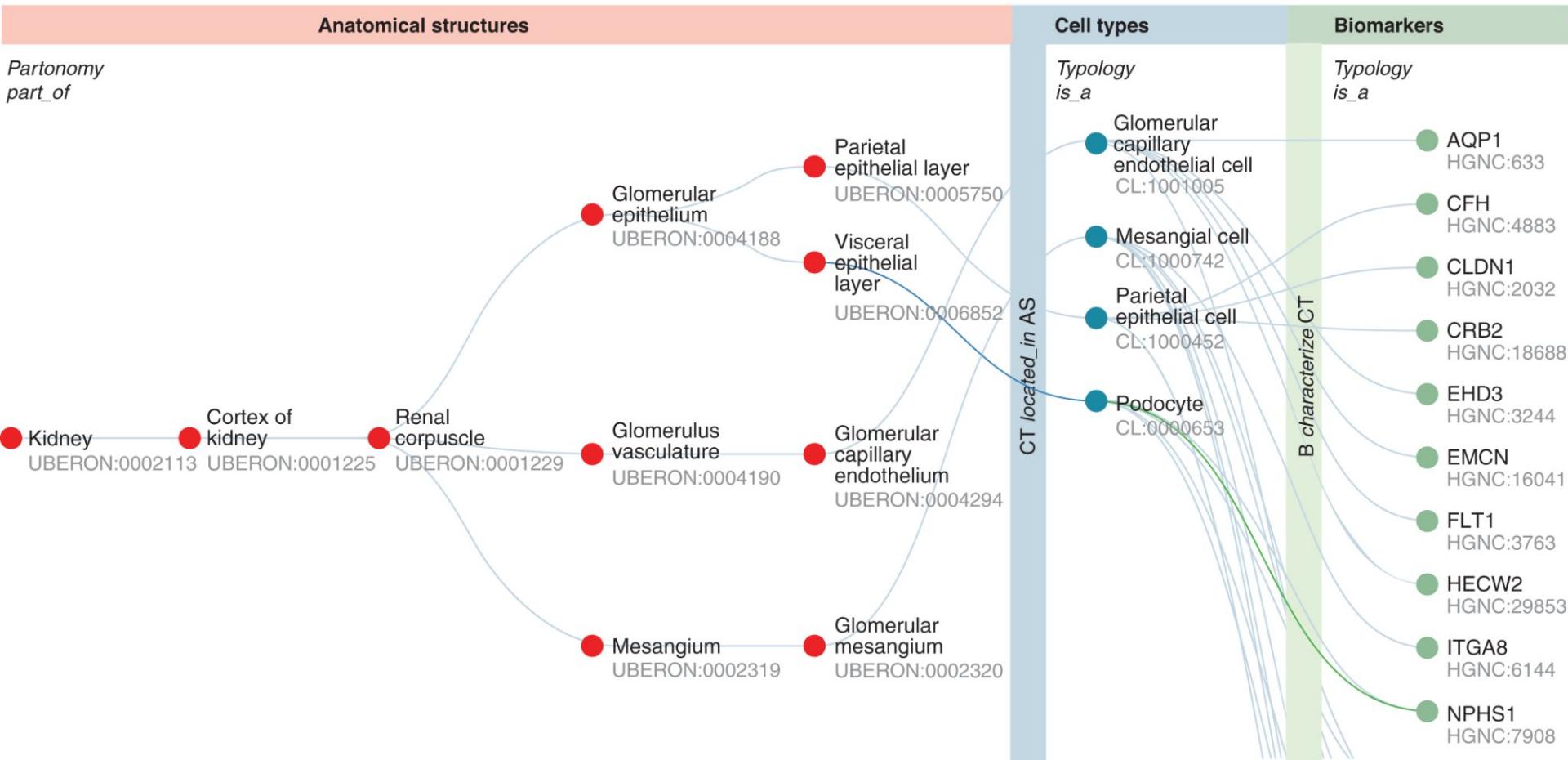
Atlas

3D Reference Organs

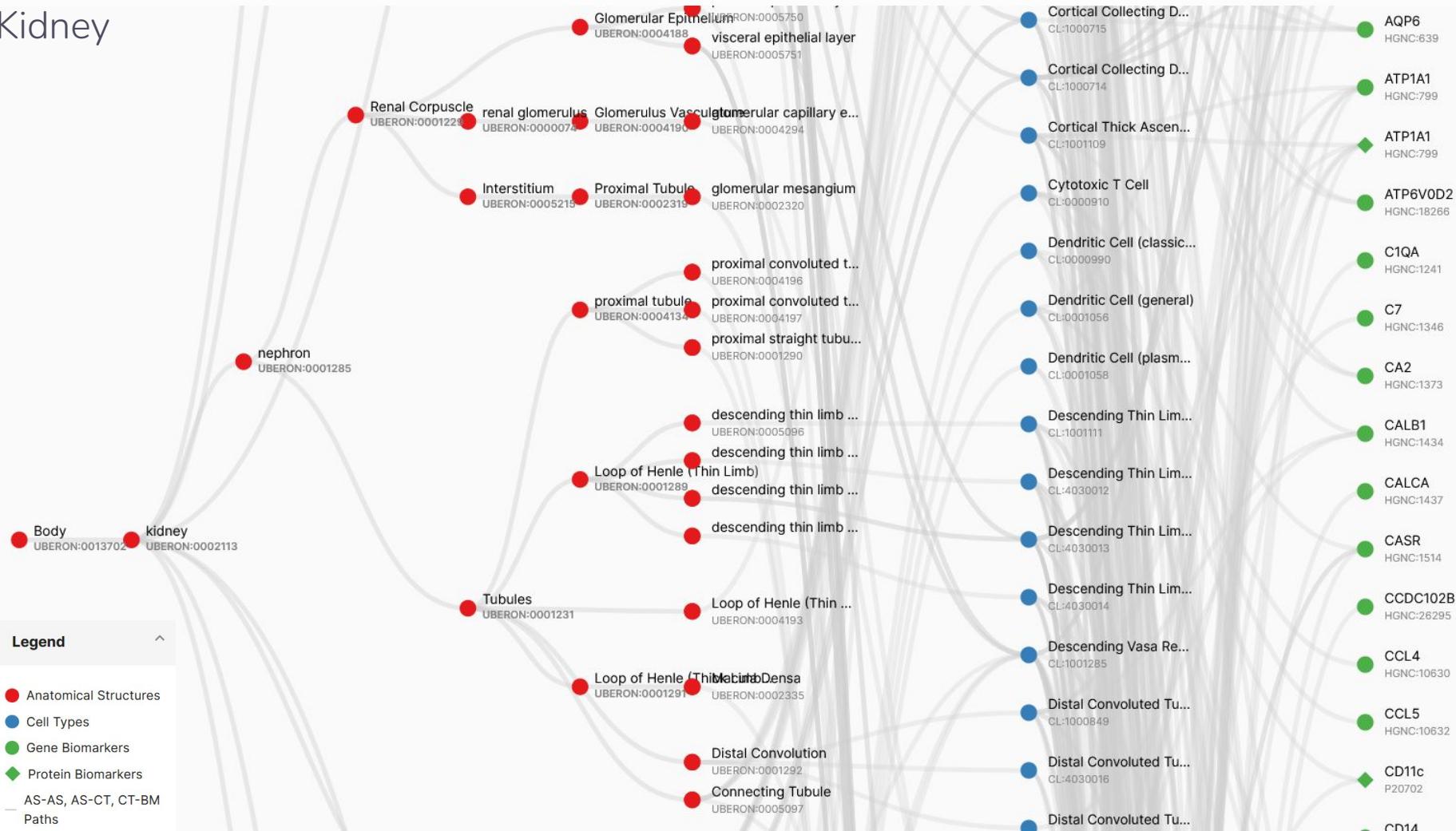
2D FTU  
Illustrations

Organ Mapping Antibody Panels

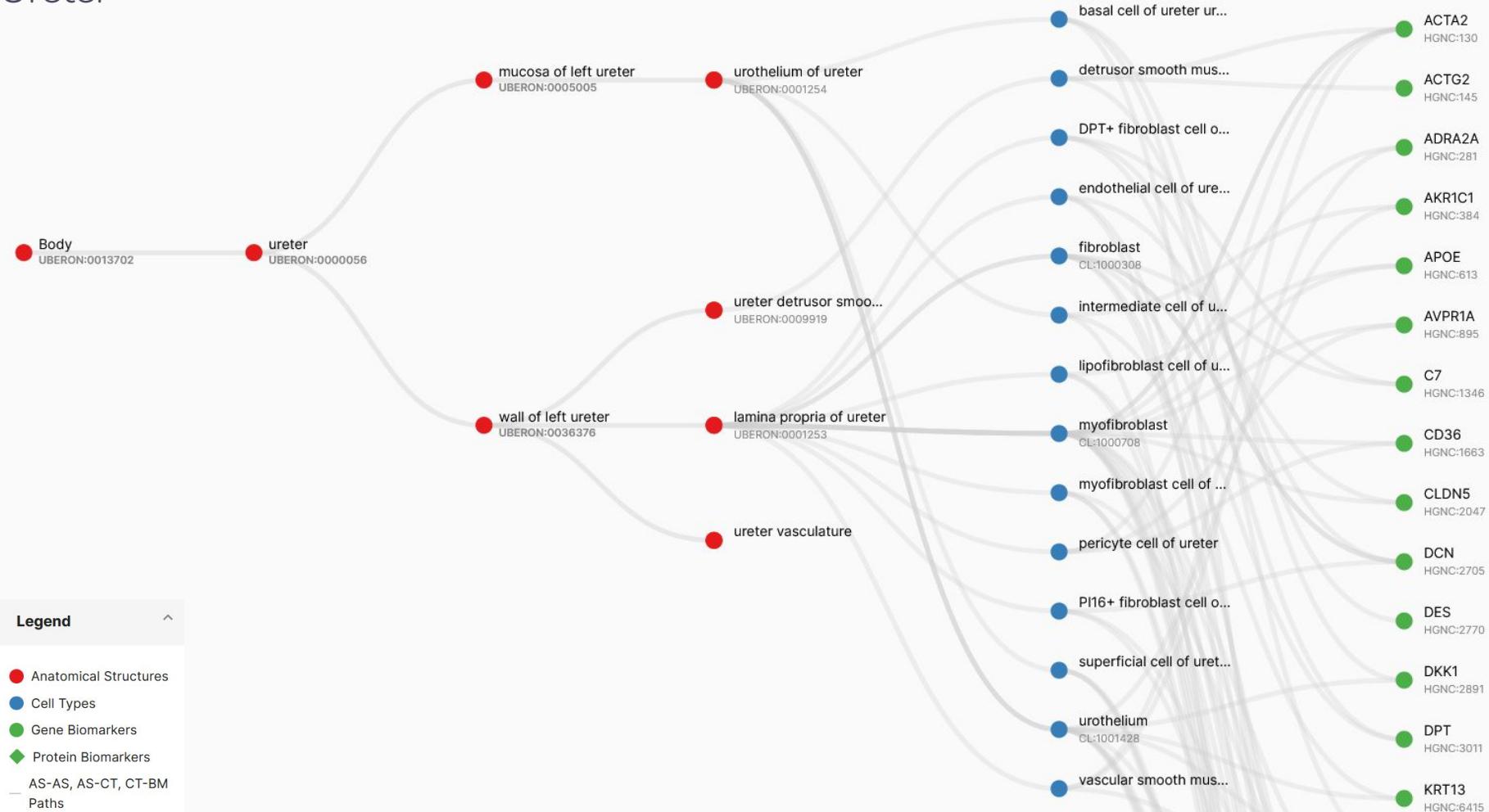
# ASCT+B Table Framework



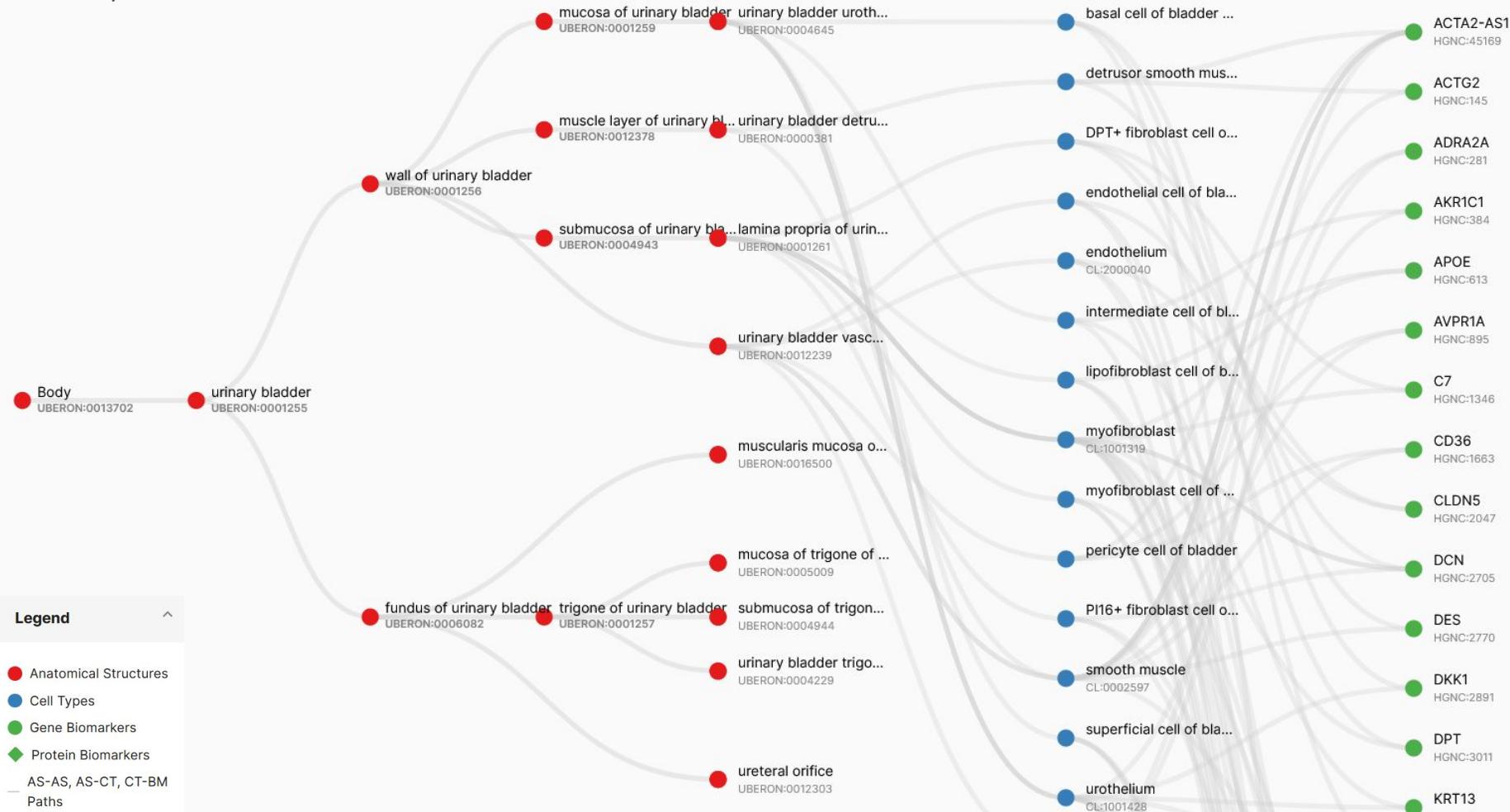
# Kidney



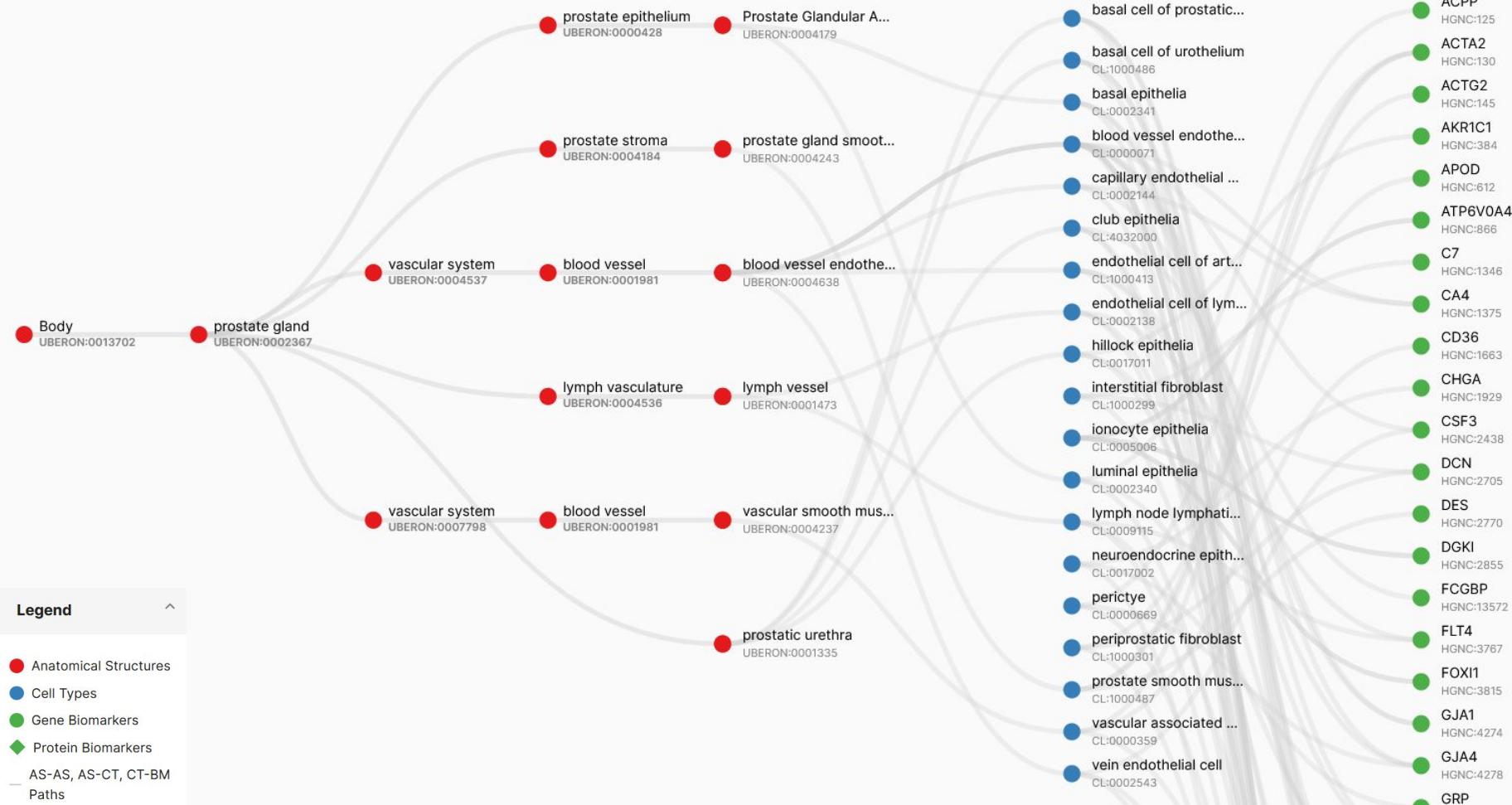
# Ureter



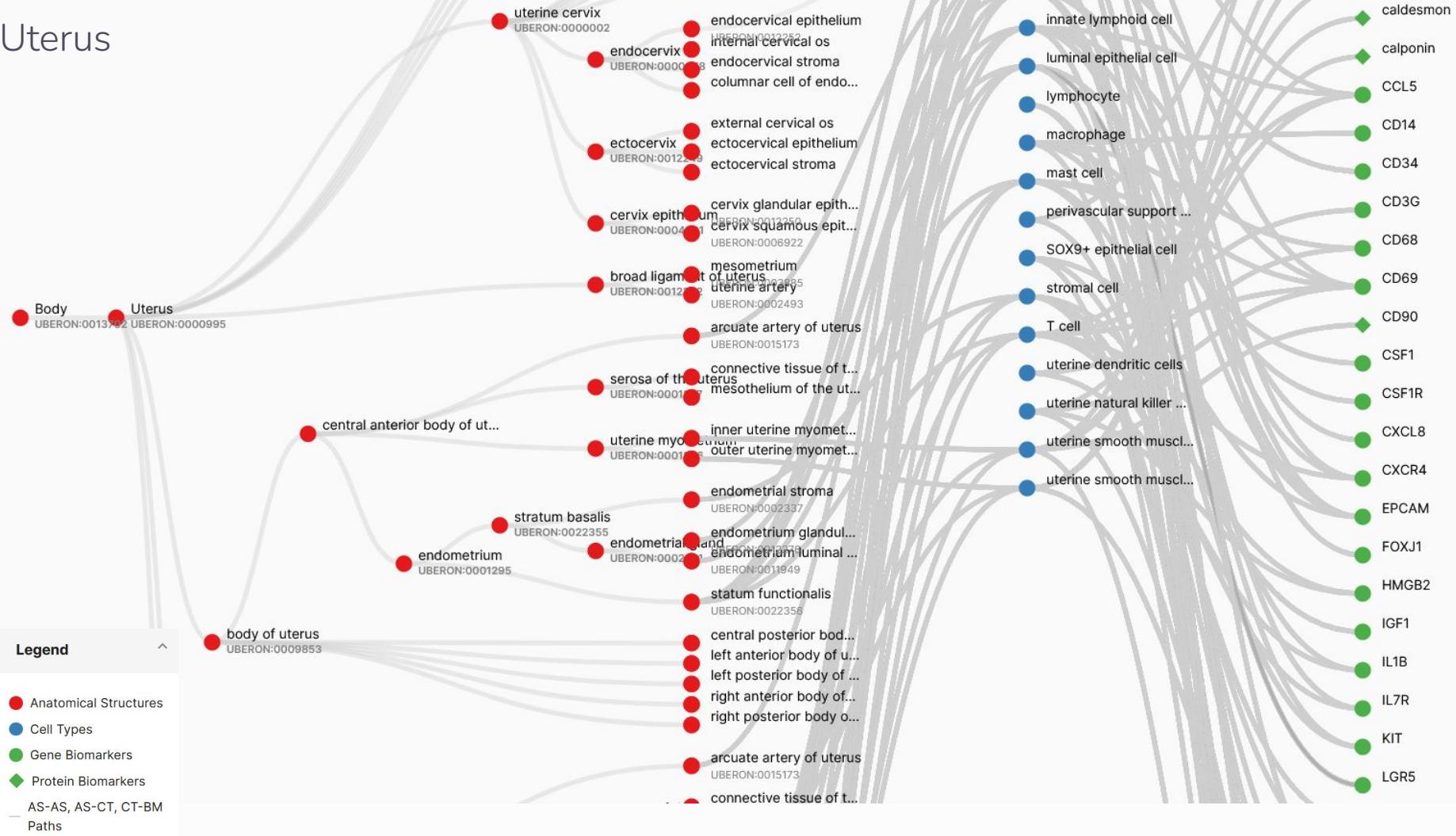
# Urinary Bladder

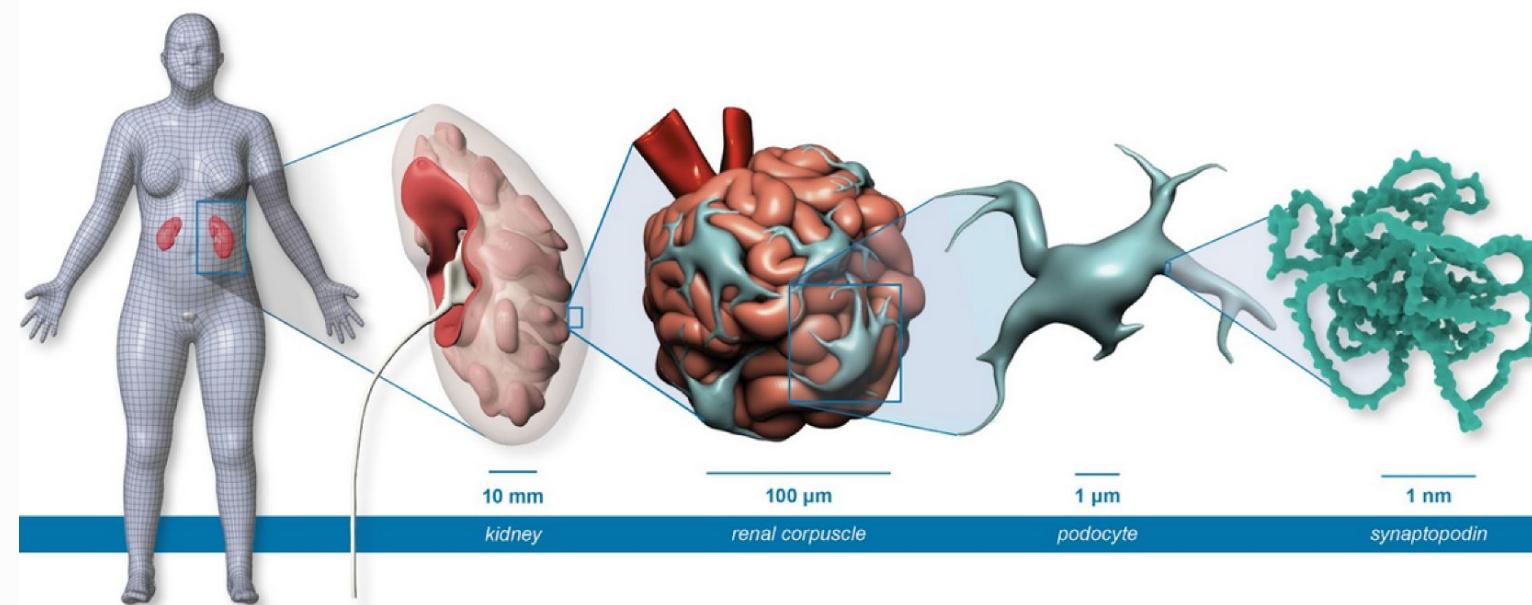


# Prostate



# Uterus





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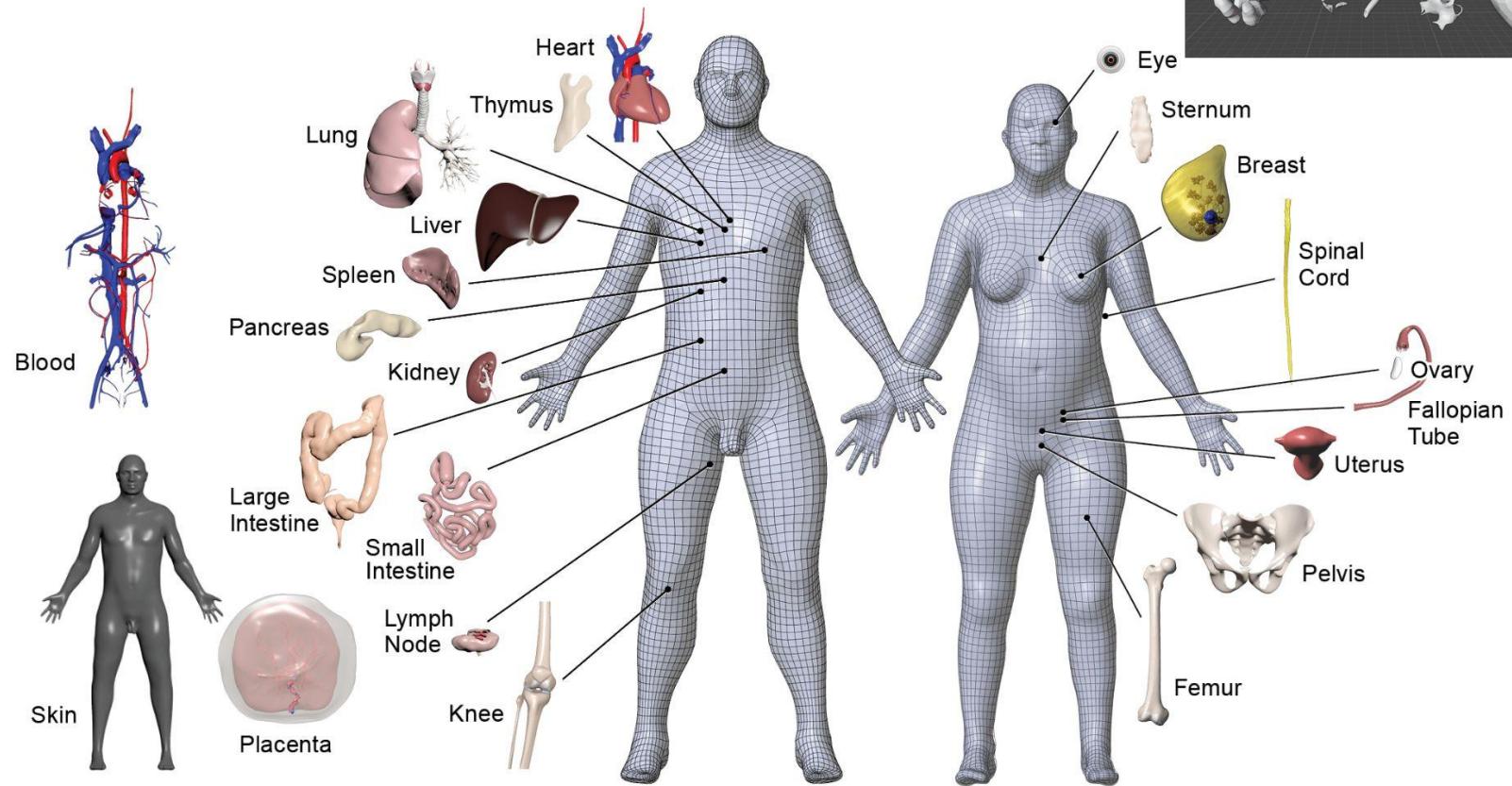
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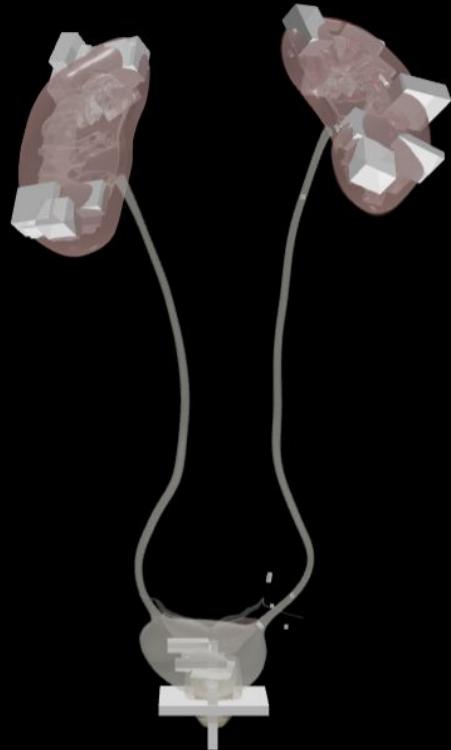
# HRA 3D Reference Organs



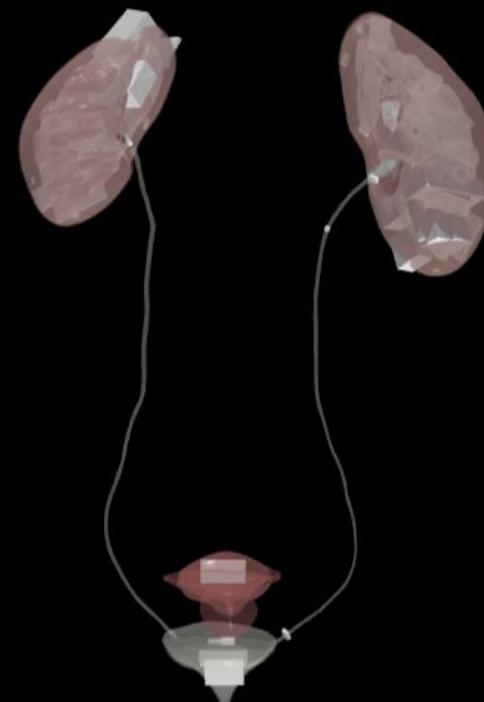


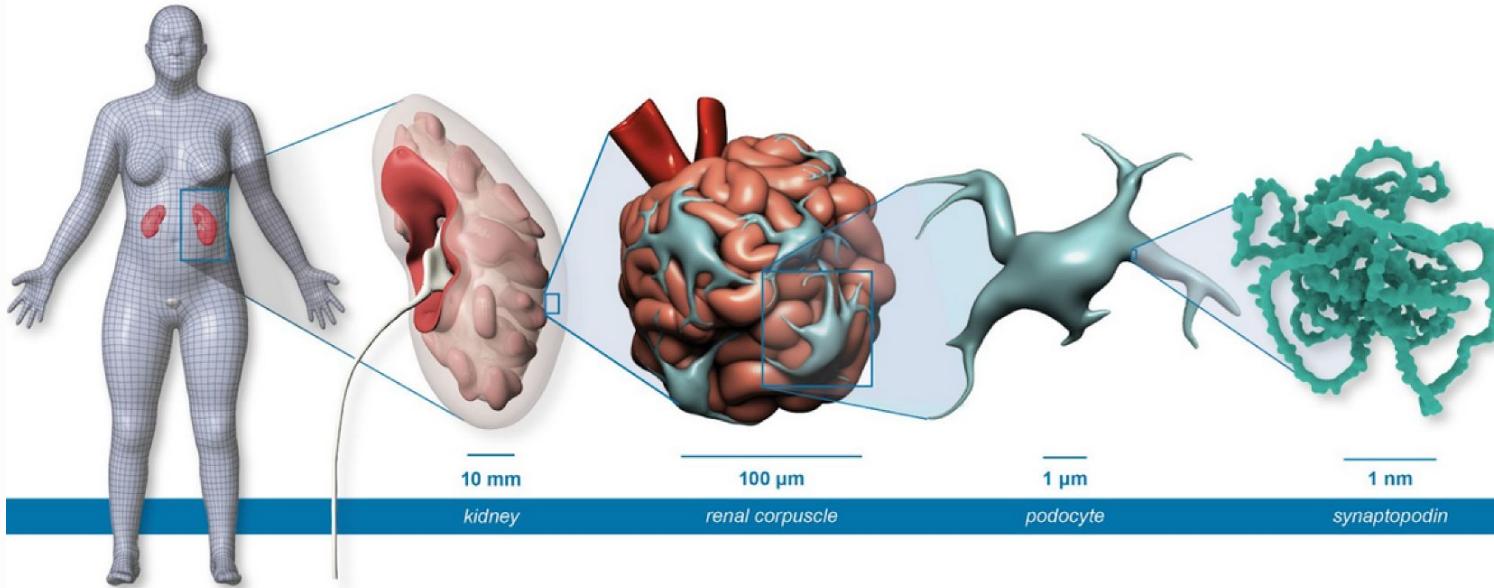
## HRA 3D Reference Organs: kidney, ureter, bladder, prostate, and uterus

Male



Female





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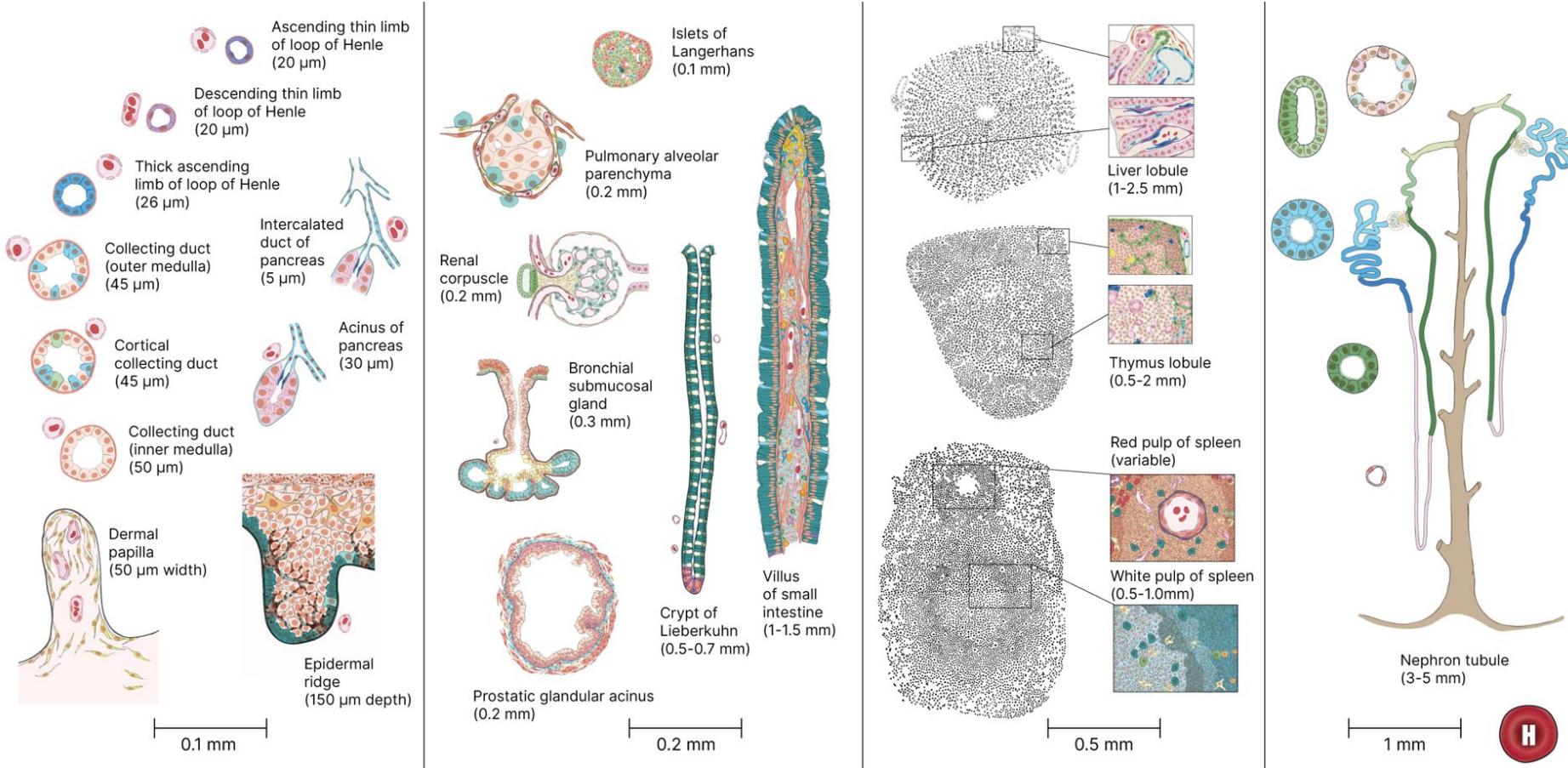
Atlas

3D Reference Organs

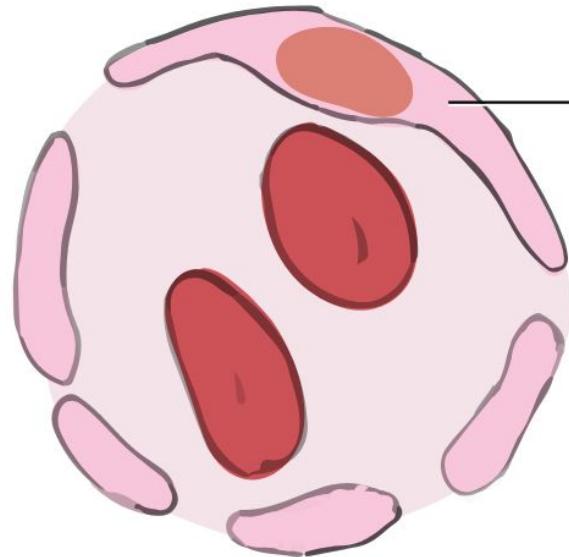
2D FTU  
Illustrations

Organ Mapping Antibody Panels

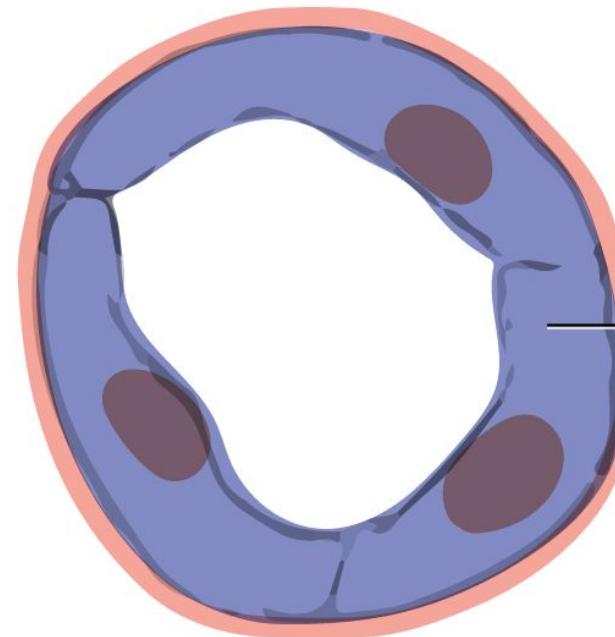
# HRA Functional Tissue Units (FTUs)



## Kidney - Ascending Thin Loop Of Henle



Ascending vasa recta

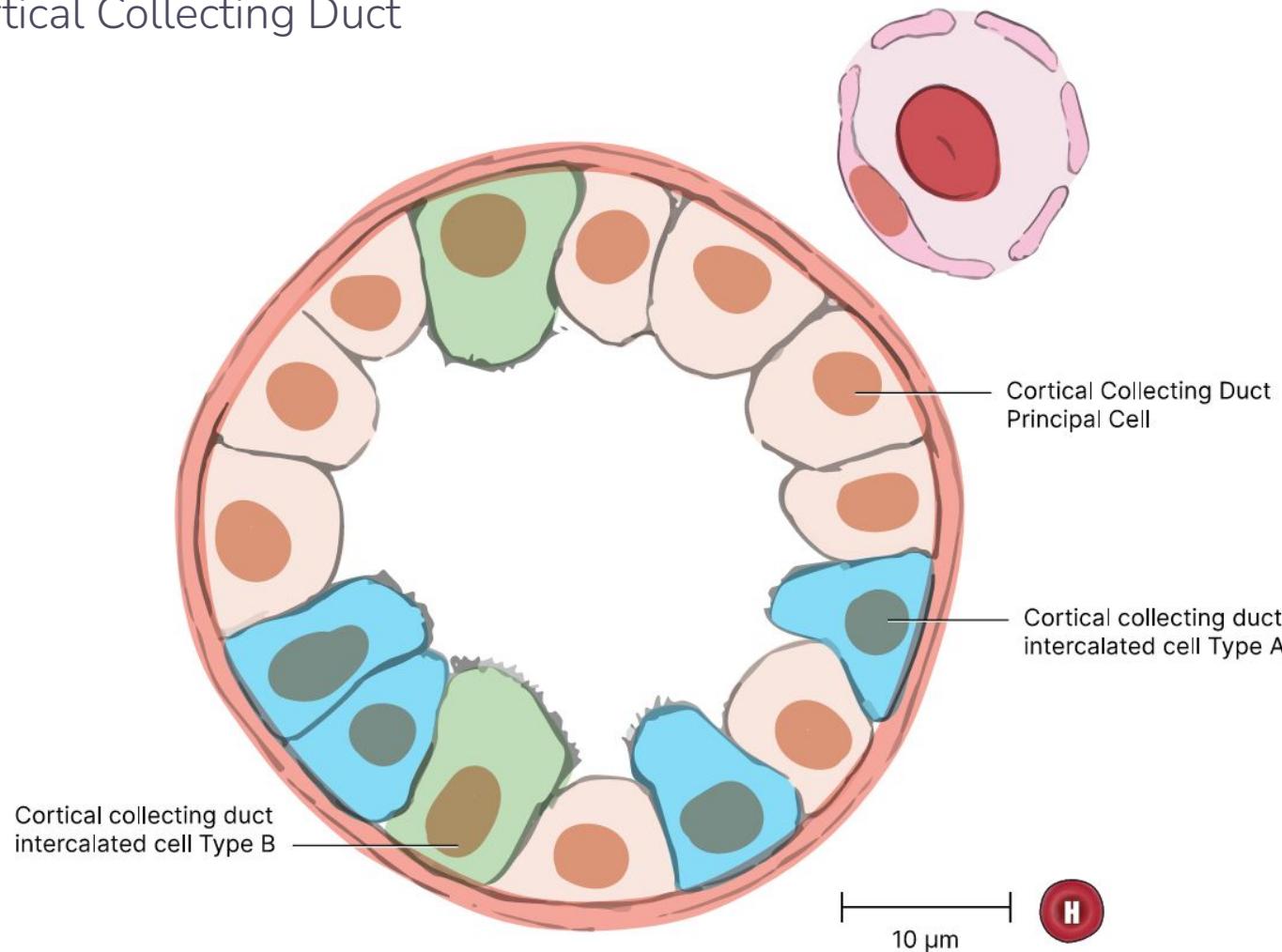


Ascending  
thin limb cell

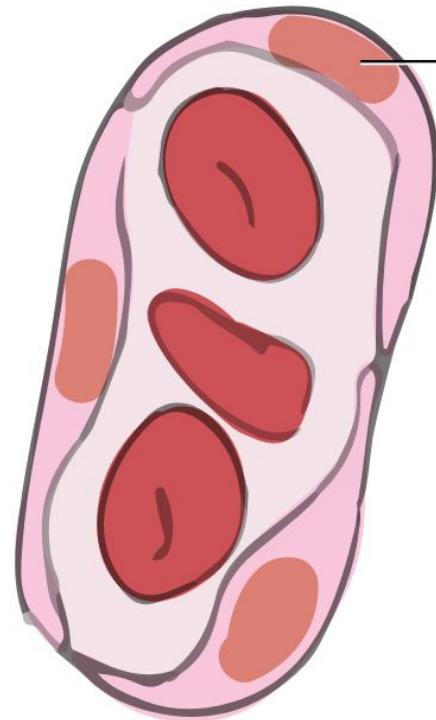
10  $\mu\text{m}$



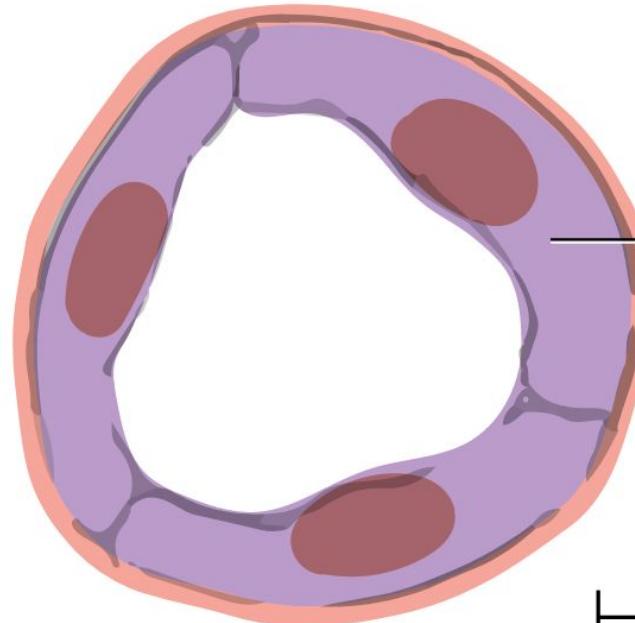
# Kidney - Cortical Collecting Duct



# Kidney - Descending Thin Loop Of Henle



Descending vasa recta

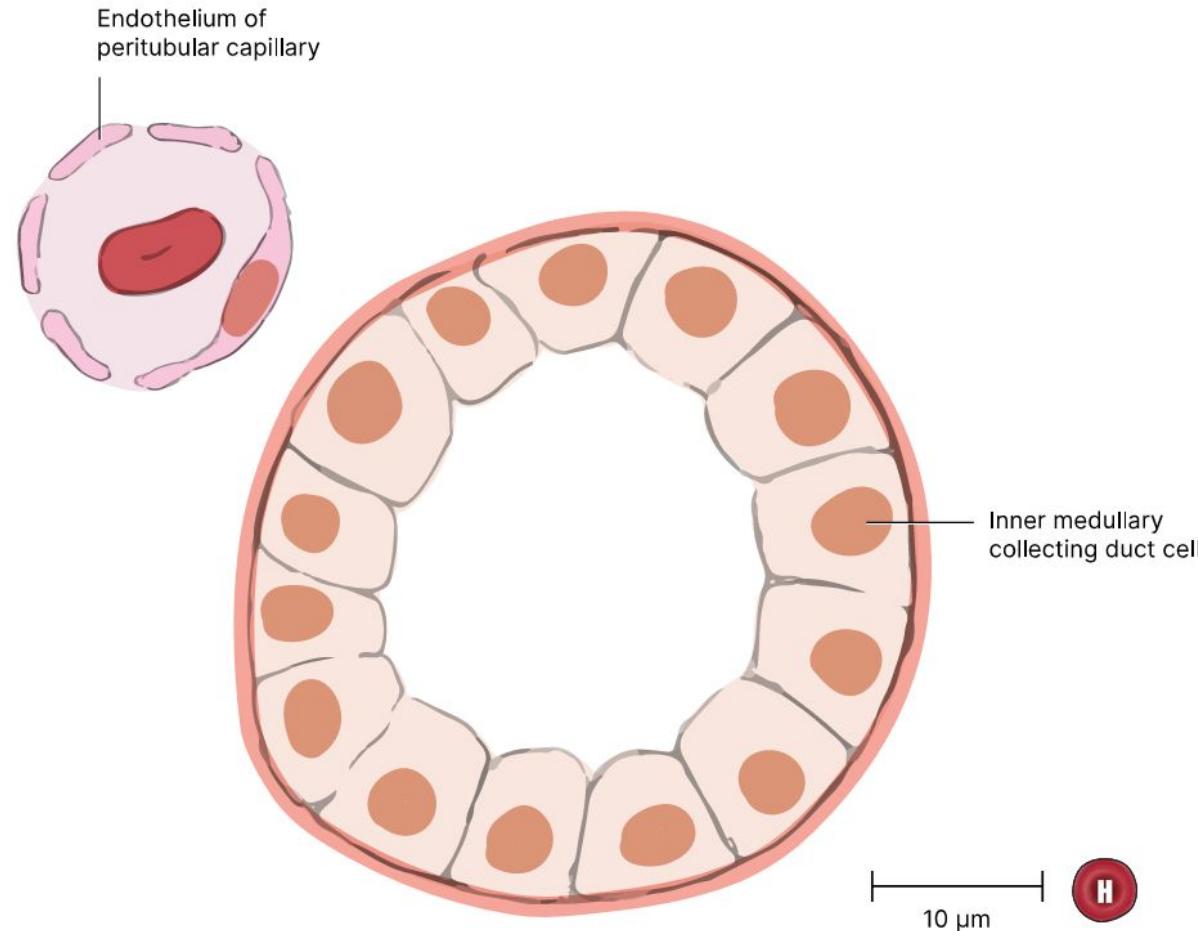


Descending  
thin limb cell

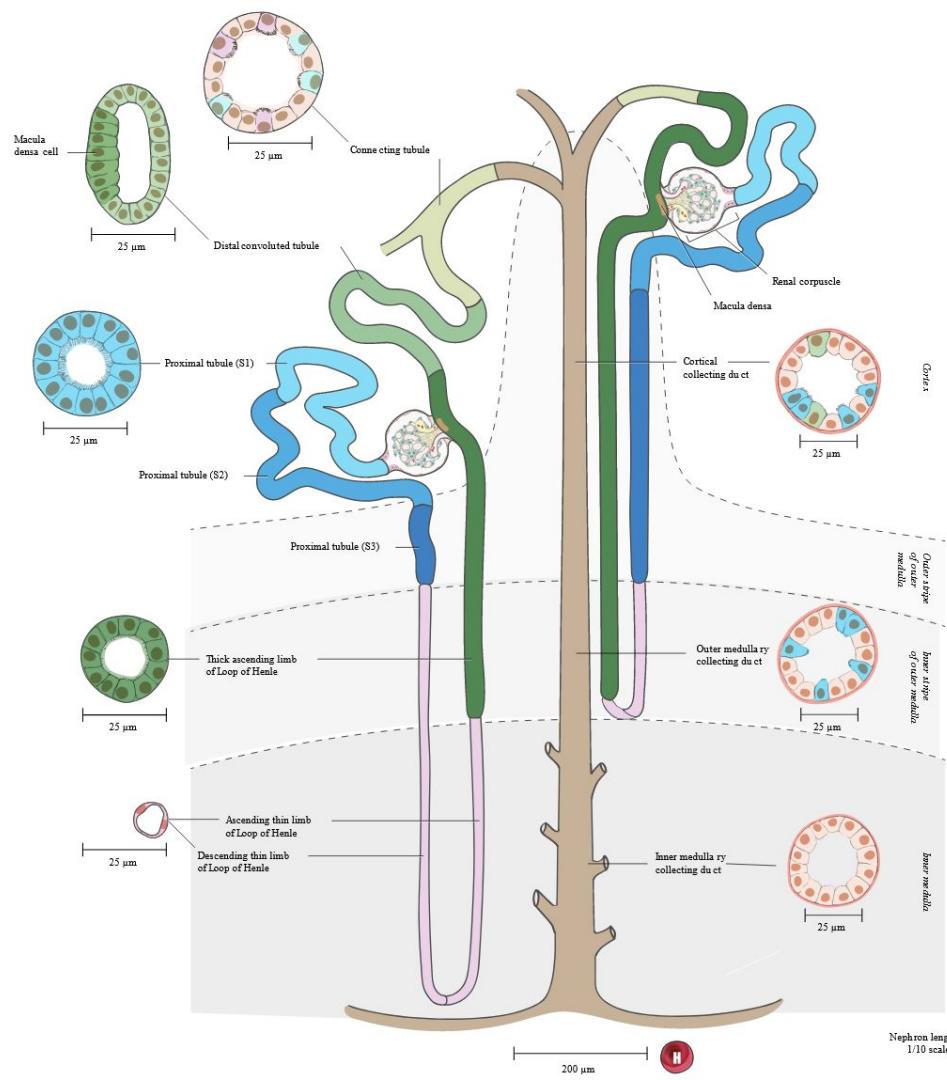
10  $\mu\text{m}$



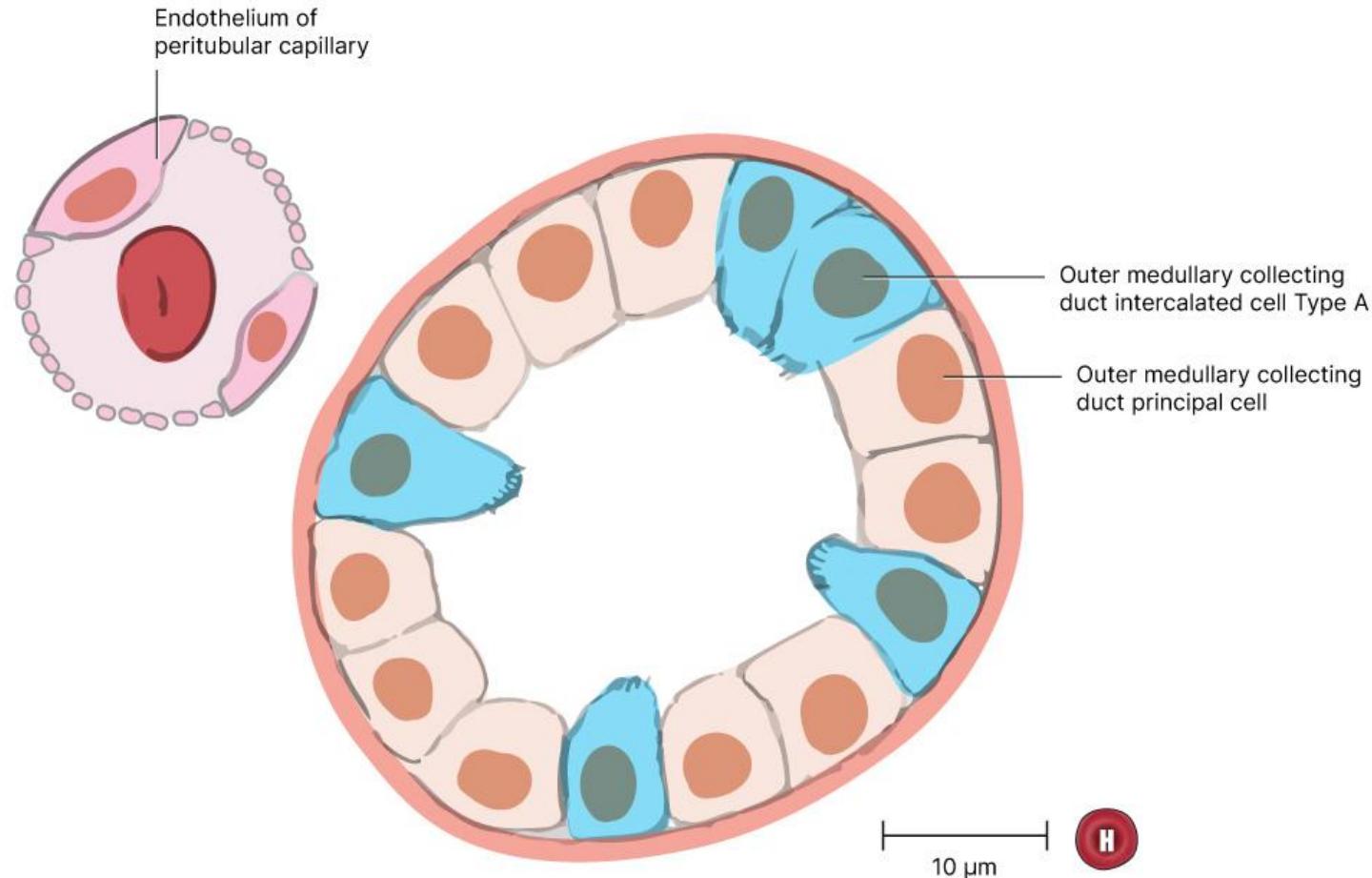
## Kidney - Inner Medullary Collecting Duct



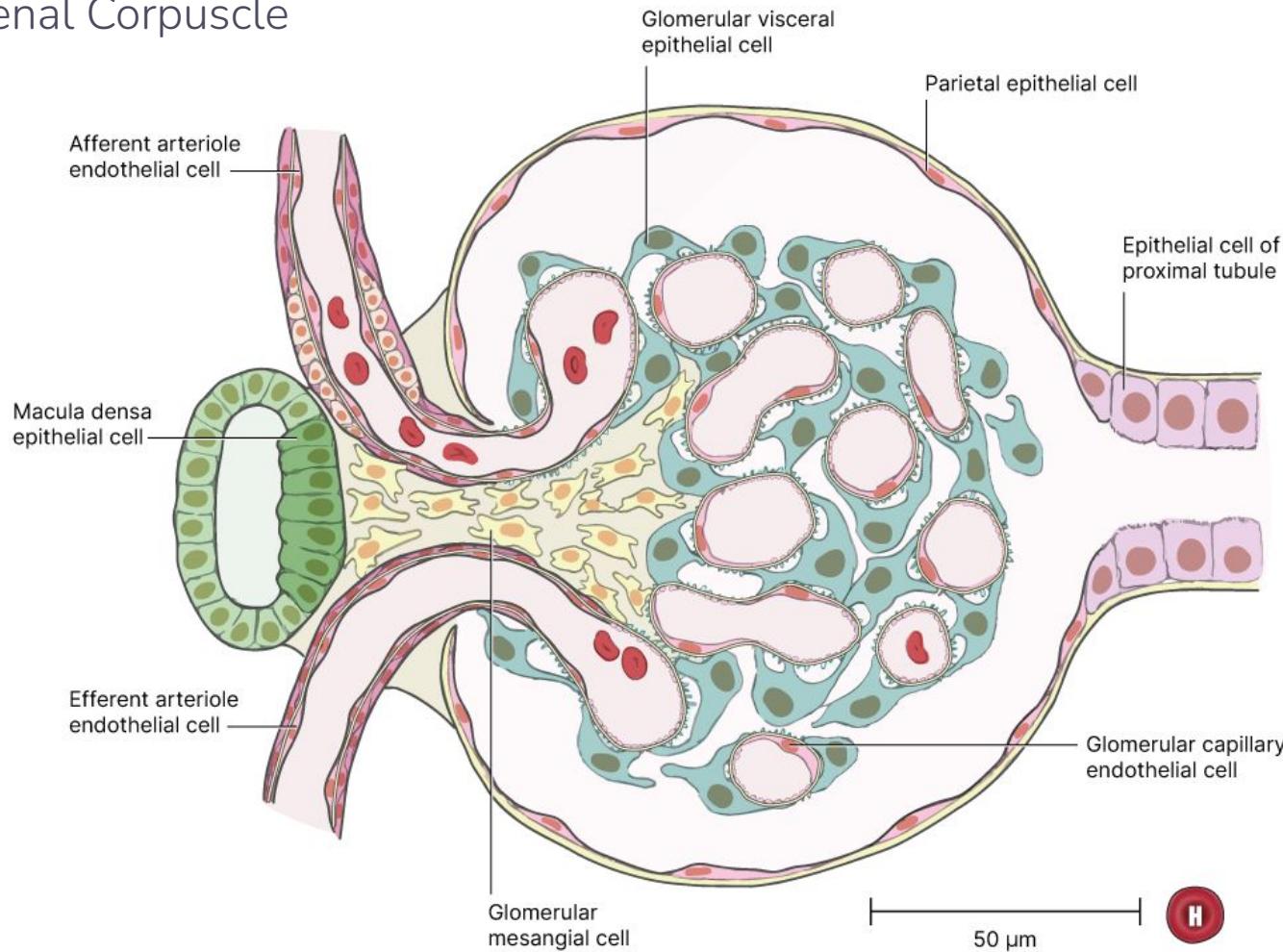
# Kidney - Nephron



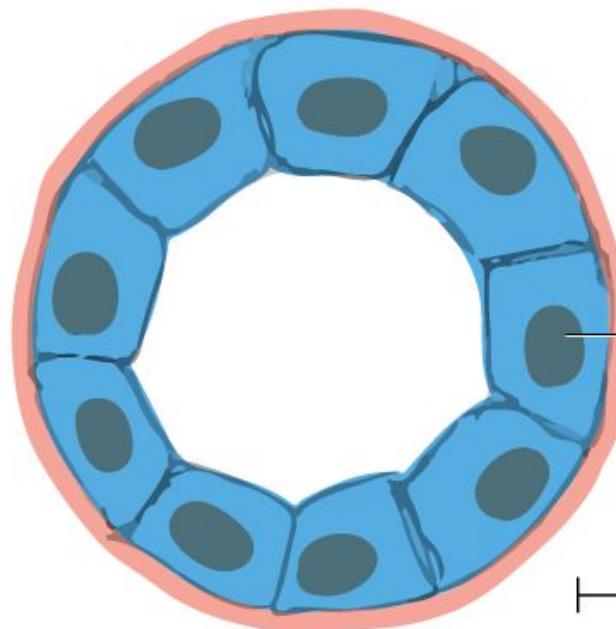
# Kidney - Outer Medullary Collecting Duct



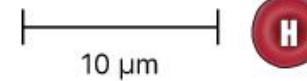
# Kidney - Renal Corpuscle



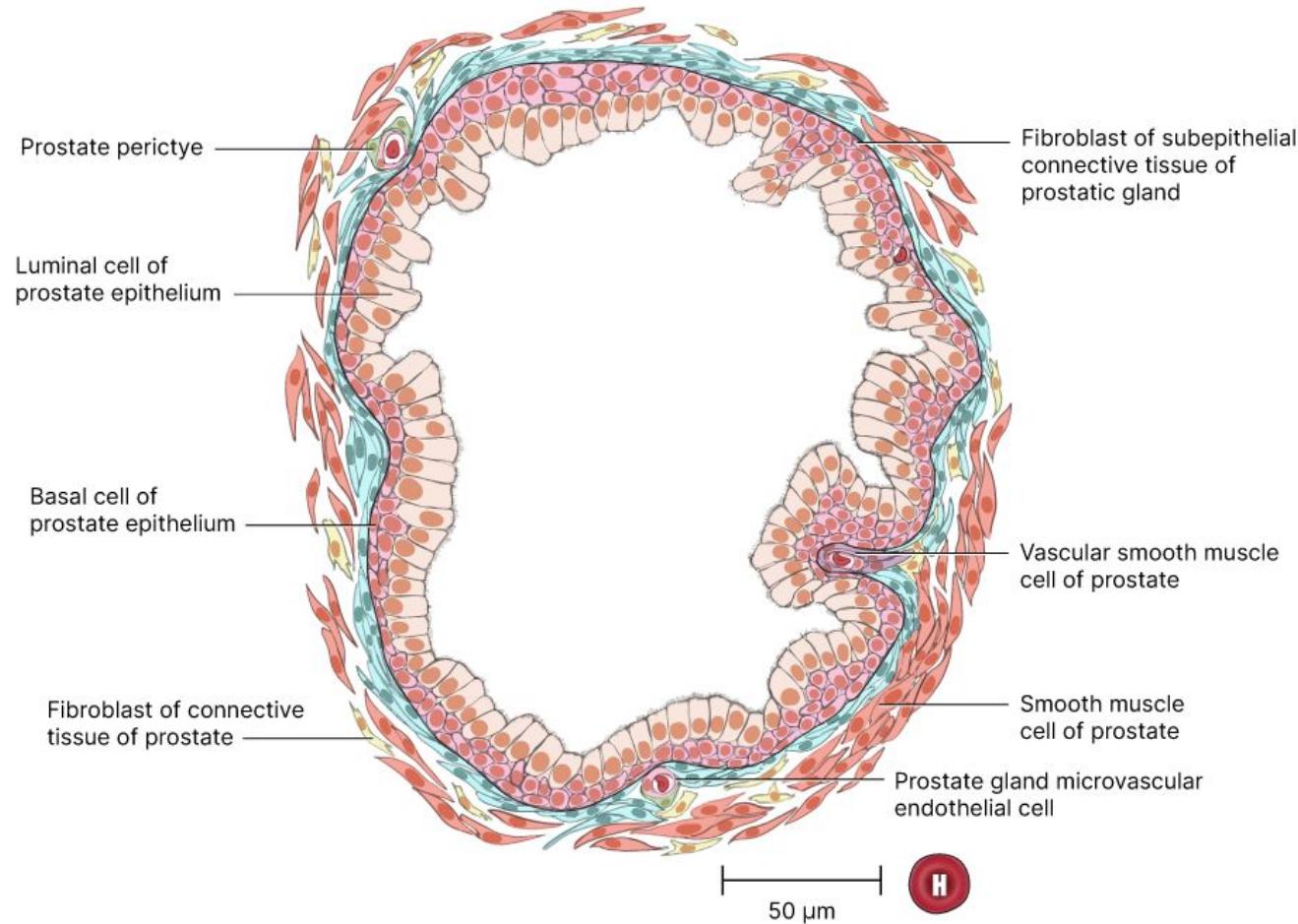
## Kidney - Thick Ascending Loop Of Henle

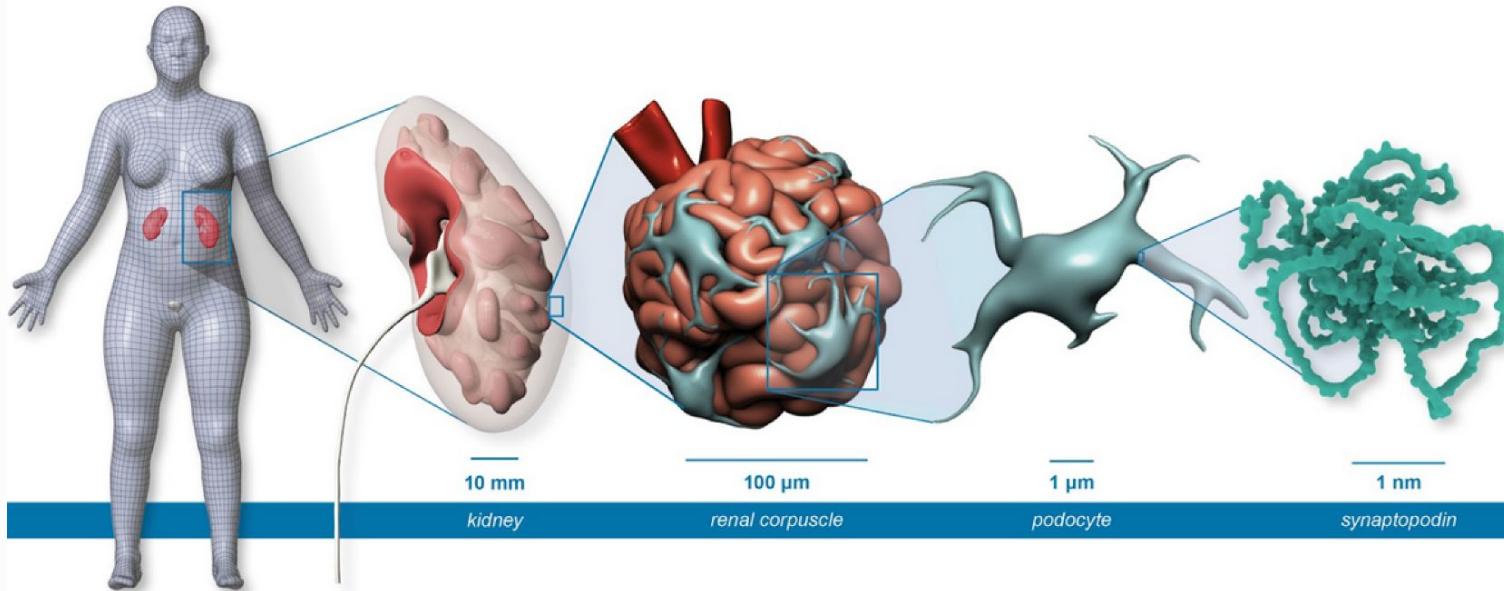


Thick ascending limb cell



# Prostate - Glandular Aculus





Anatomical Structures

Functional  
Tissue Units

Cell Types

Biomarkers  
Genes, Proteins, ..

Conceptual

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Atlas

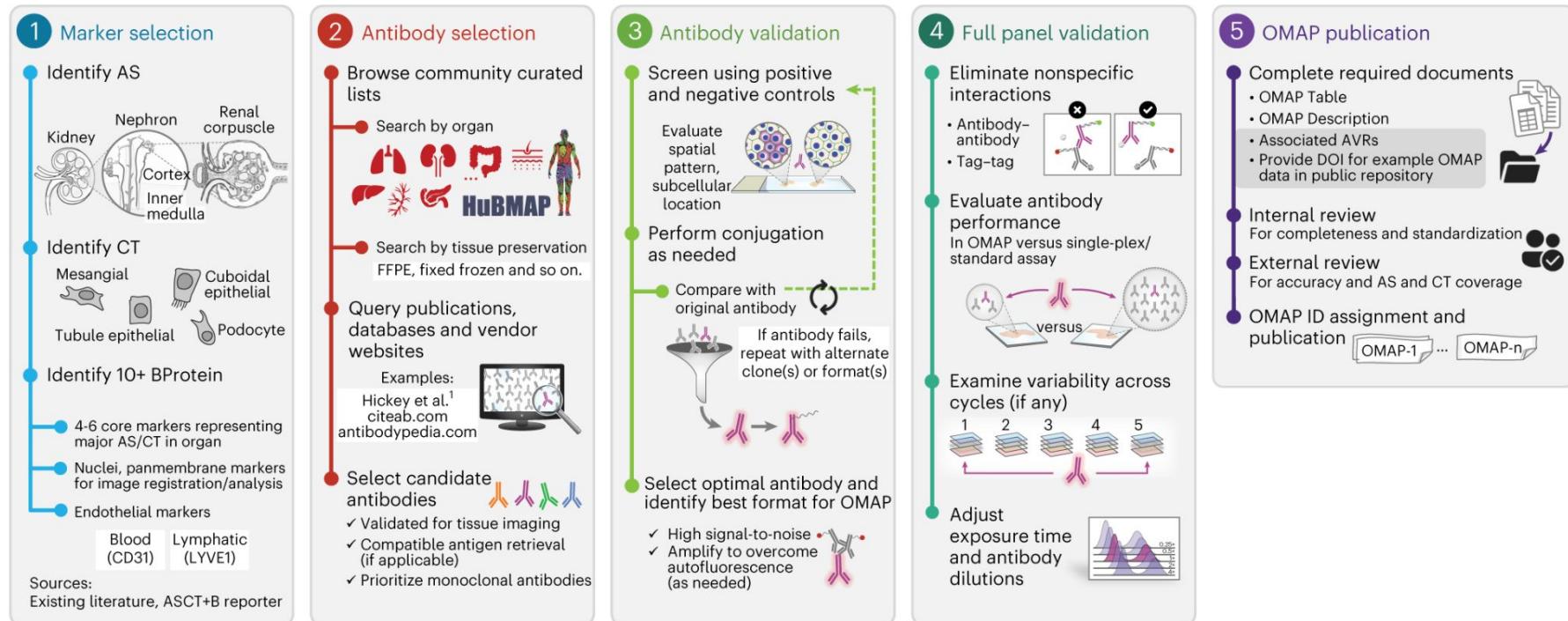
3D Reference Organs

2D FTU  
Illustrations

Organ Mapping Antibody Panels

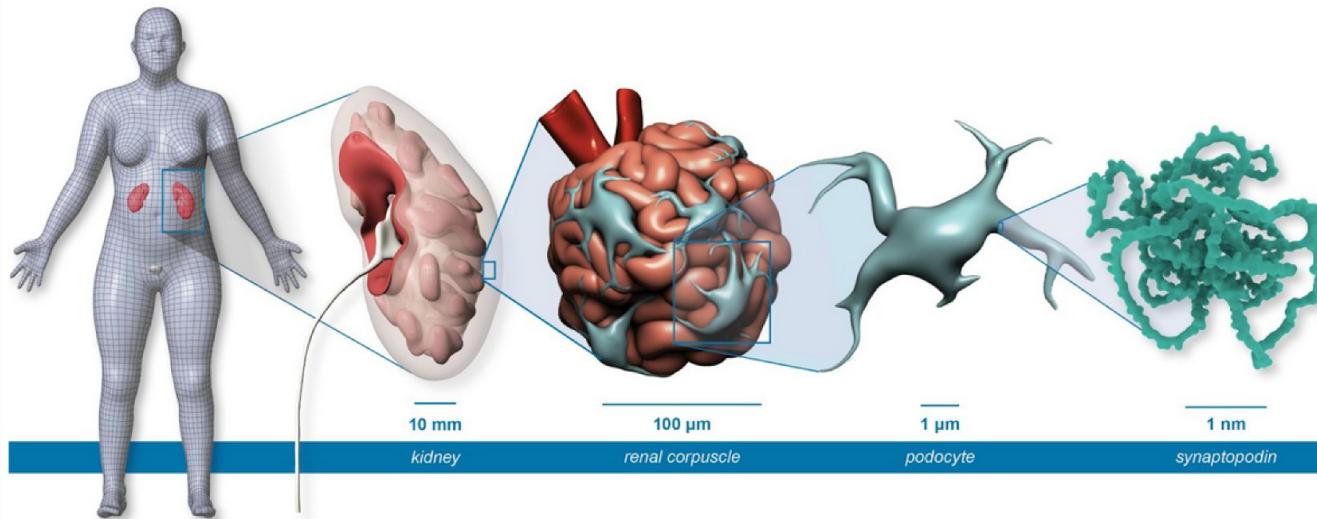
# OMAP Framework

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





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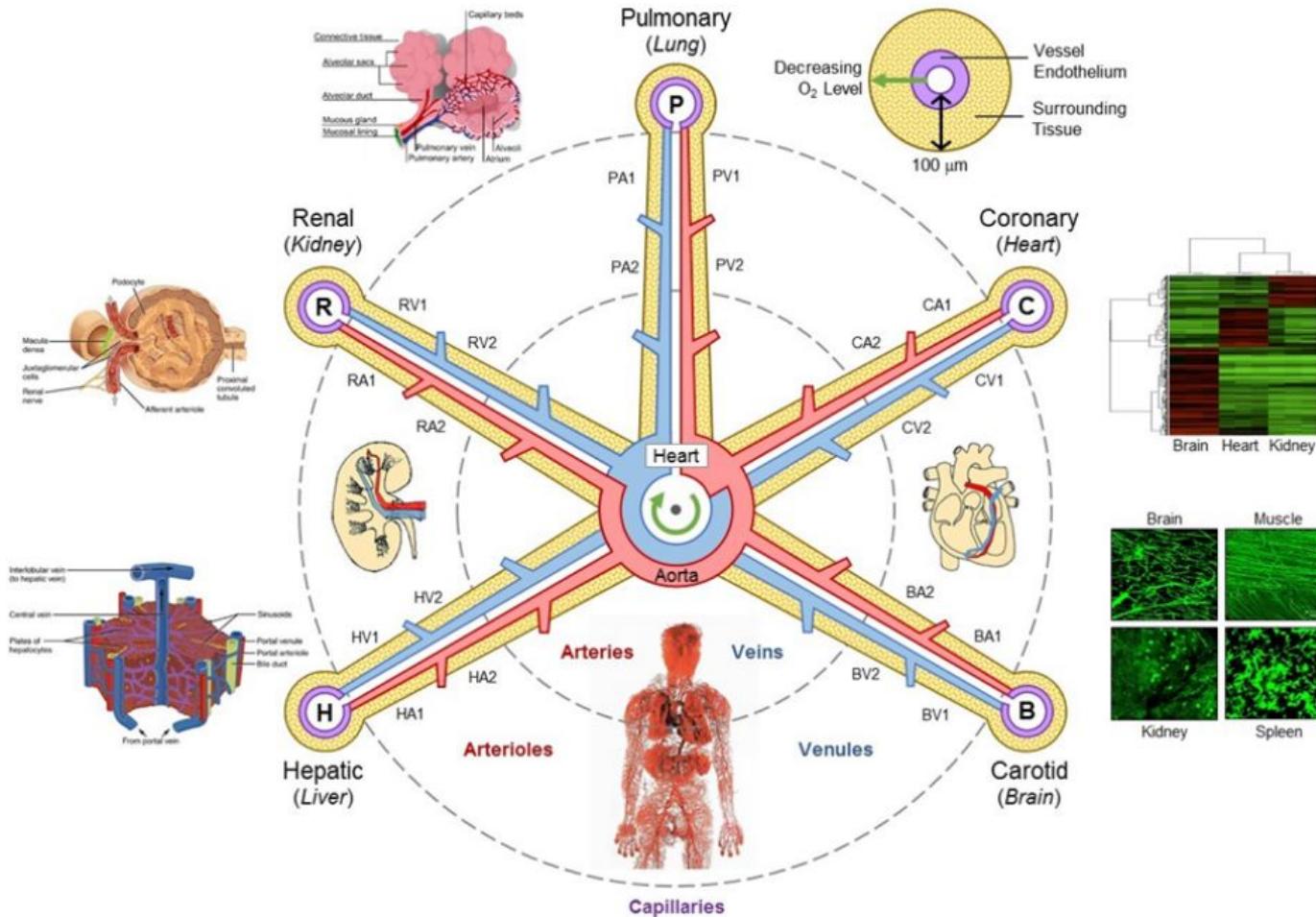
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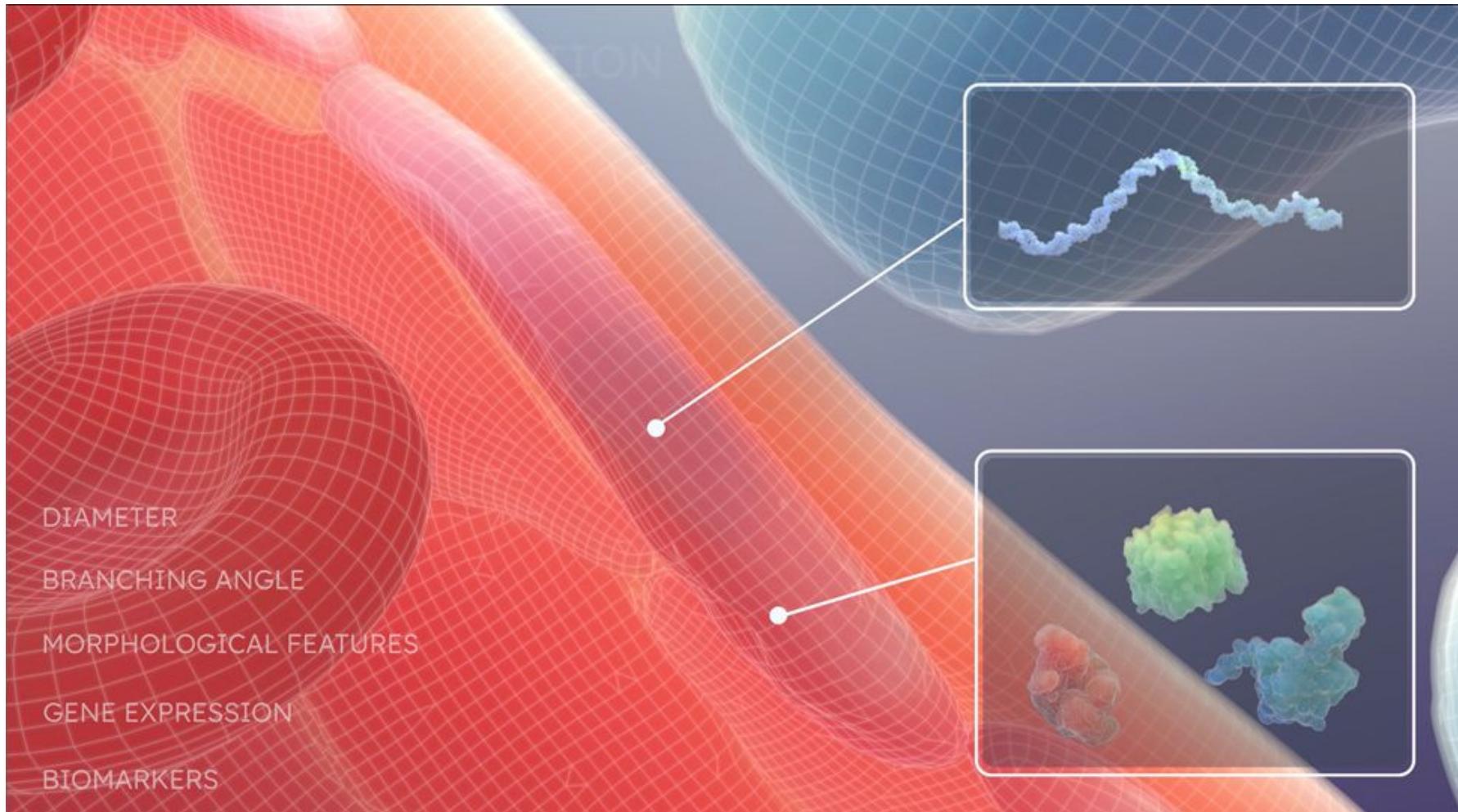
Organ Mapping Antibody Panels

Vascular Geometry

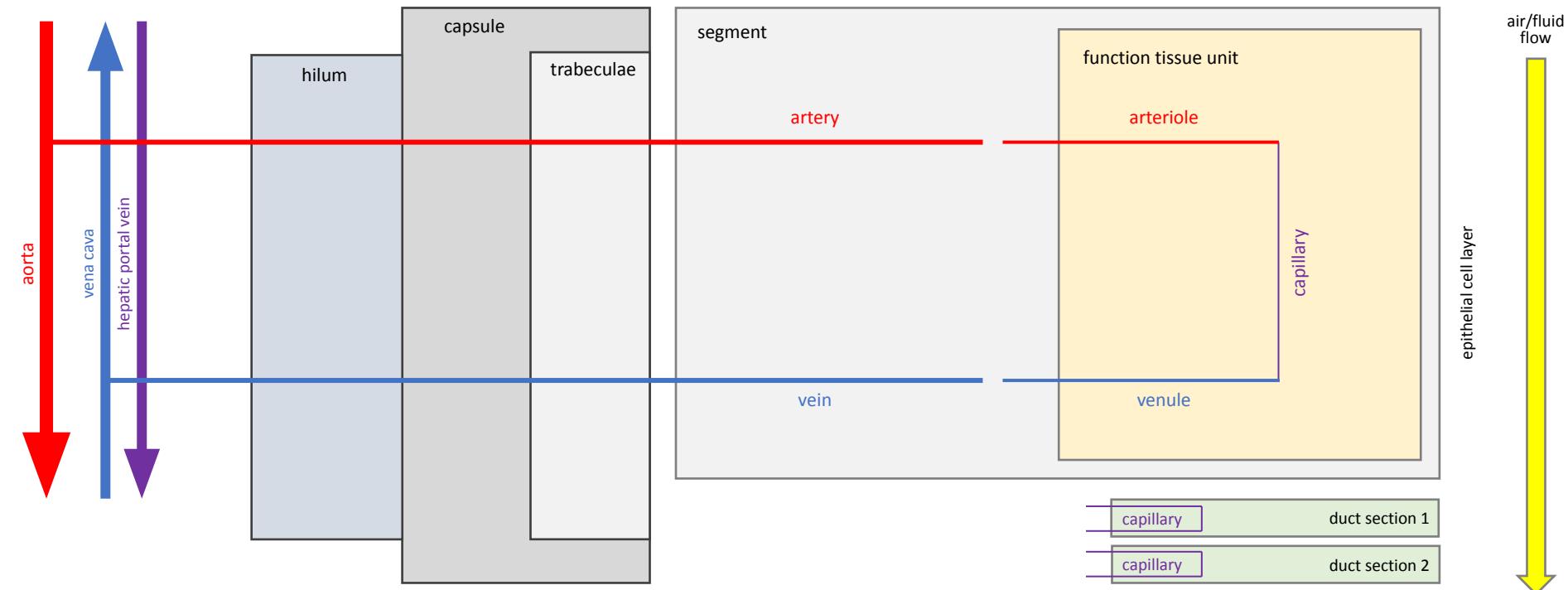
# Vasculature Common Coordinate Framework



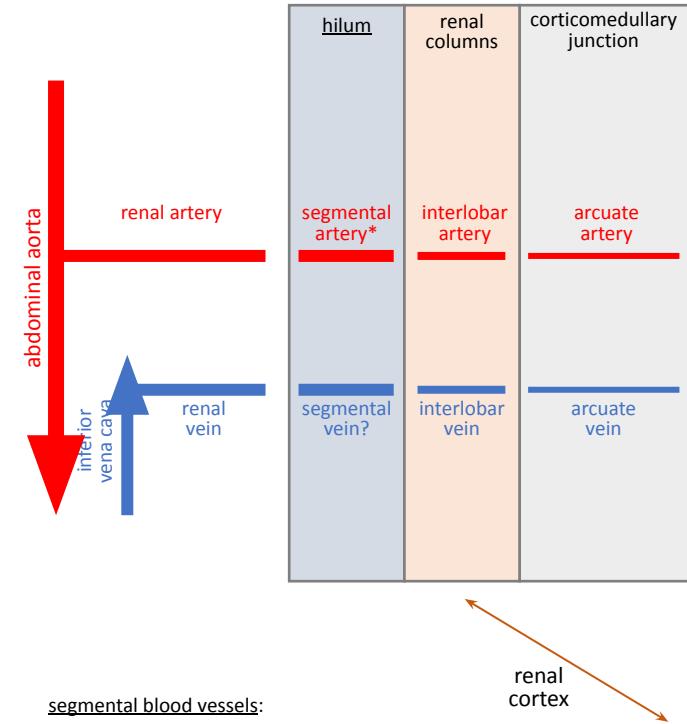
VCCF Video: [https://youtu.be/zQeMgxo8n\\_U](https://youtu.be/zQeMgxo8n_U)



# Template

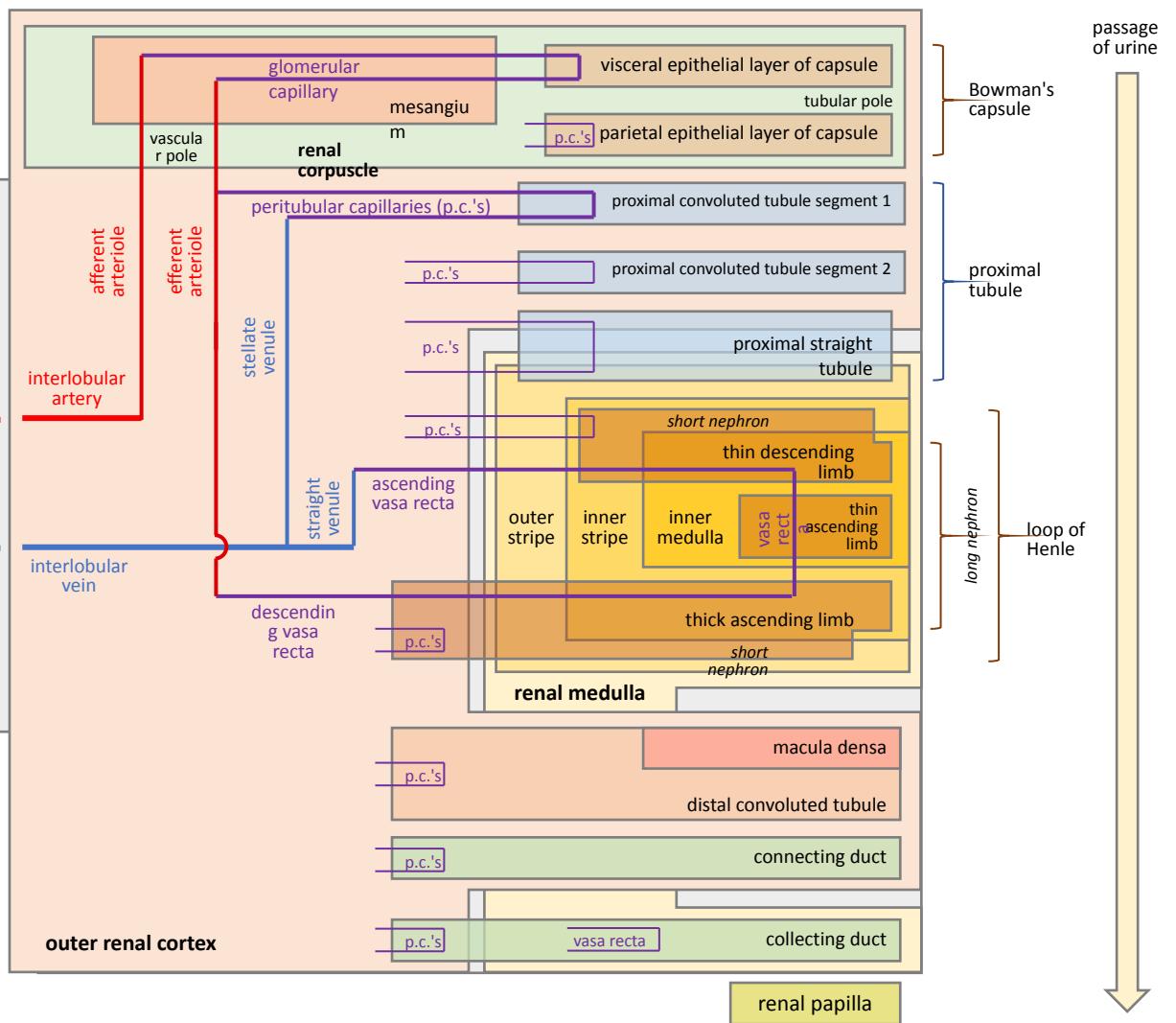


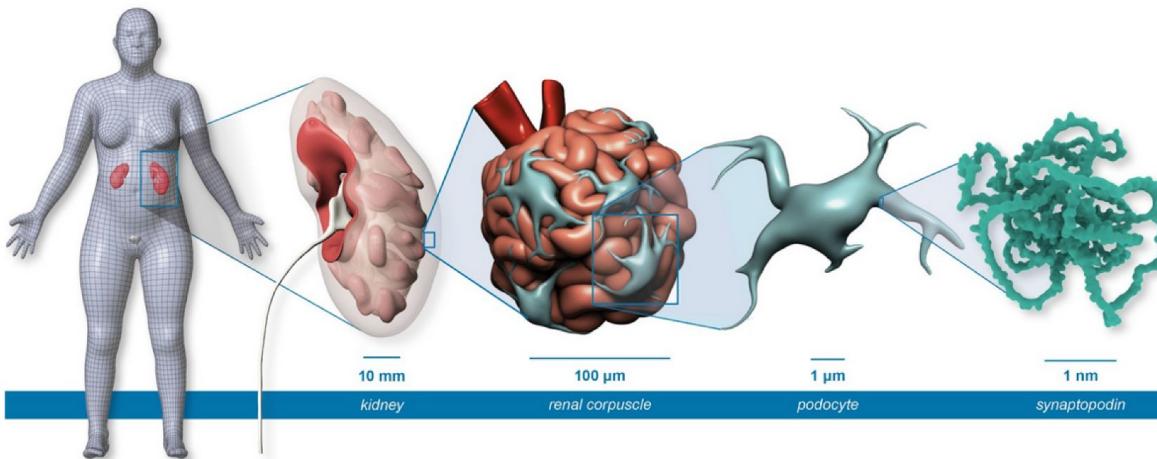
# Vascular Geometry for kidney



## segmental blood vessels:

- inferior segmental renal artery
- anterior inferior segmental renal artery
- anterior superior segmental renal artery
- posterior segmental renal artery
- superior segmental renal artery





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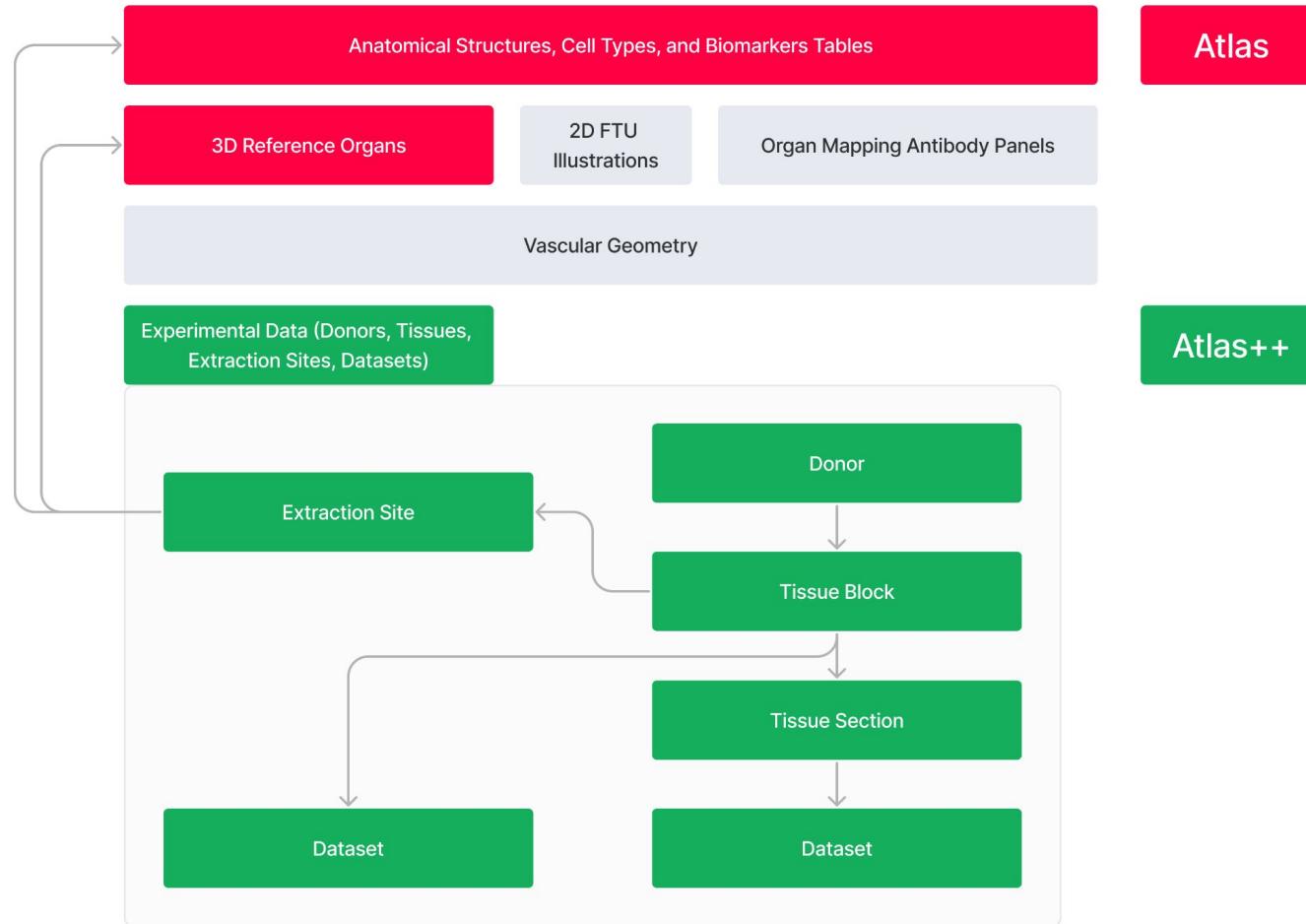
Organ Mapping Antibody Panels

Vascular Geometry

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

Atlas++

# Experimental Dataset Framework

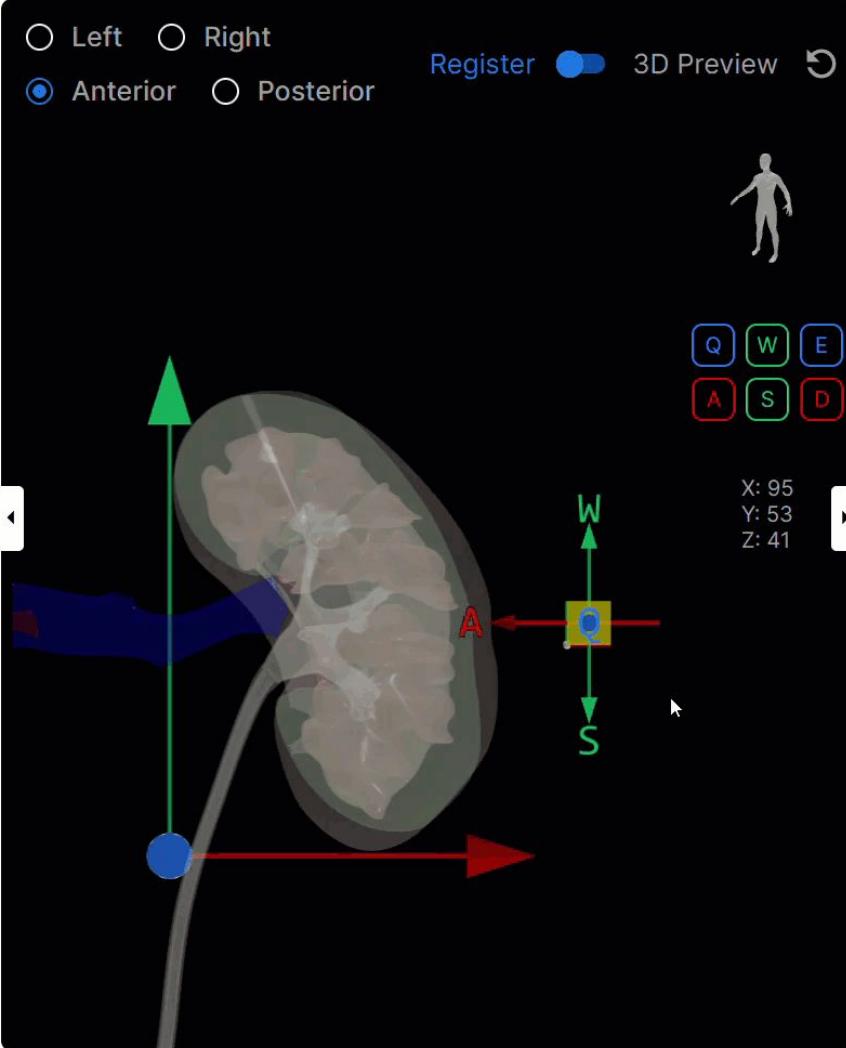


## Anatomical Structures

- 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

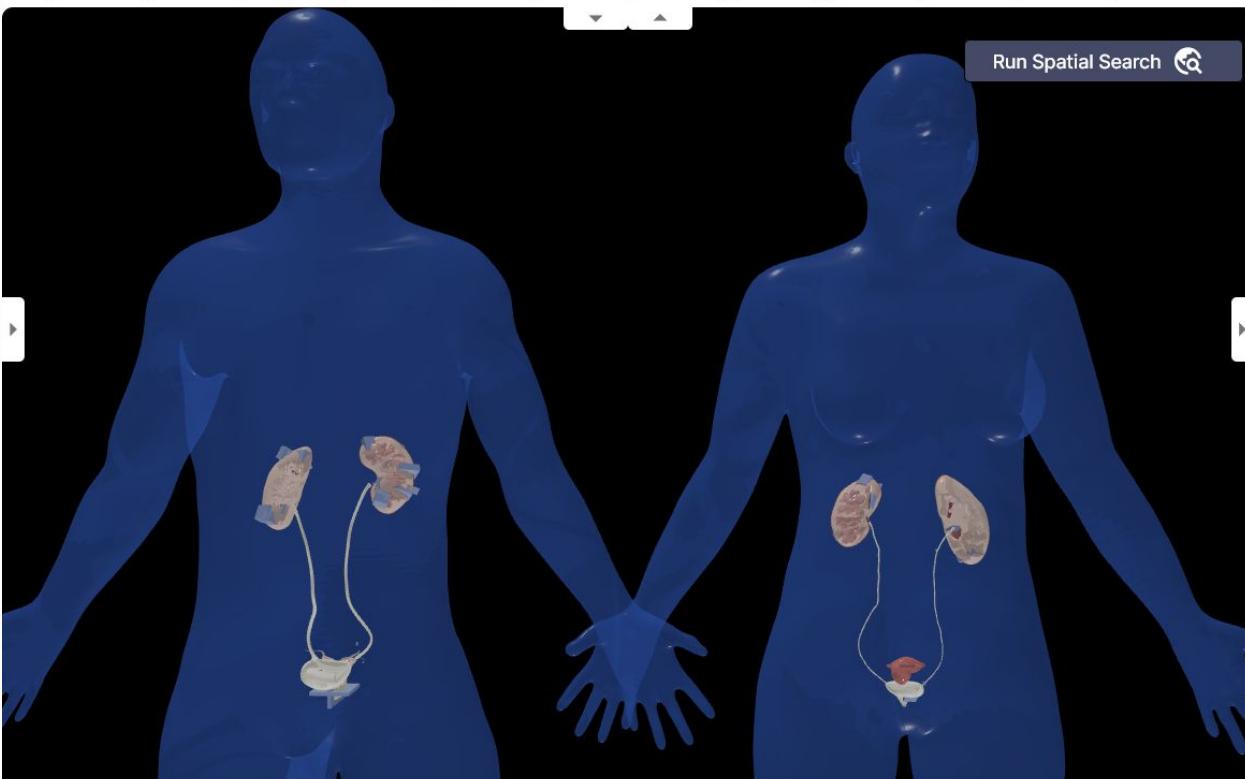
Review and Download

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

HuBMAP HRA EXPLORATION



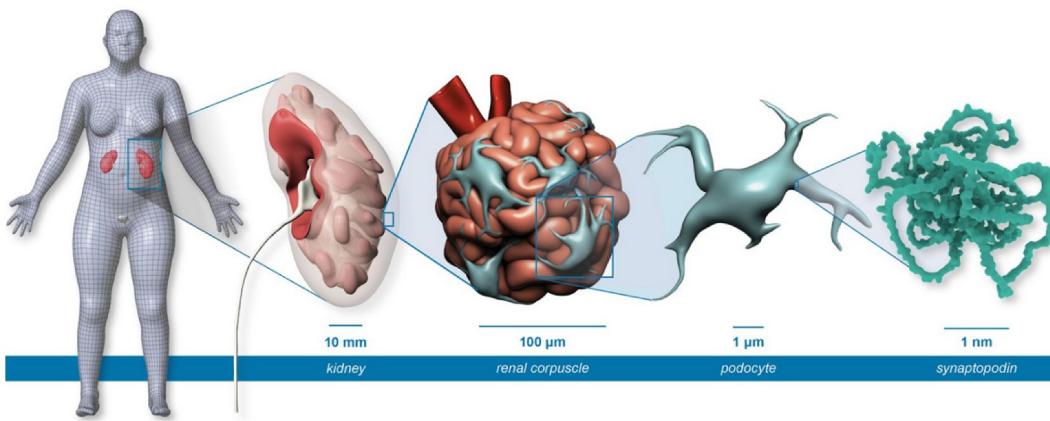
i



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



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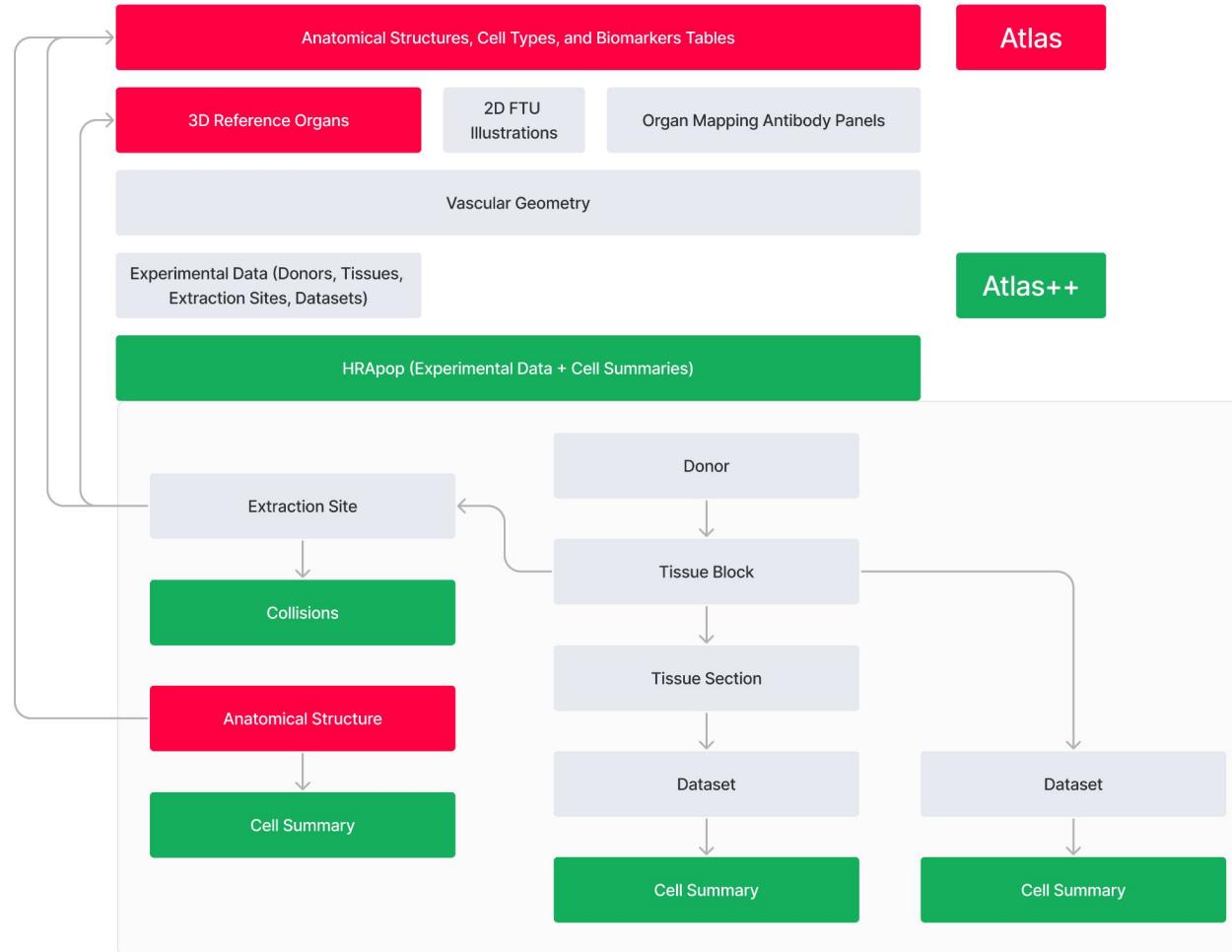
Vascular Geometry

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

Atlas++

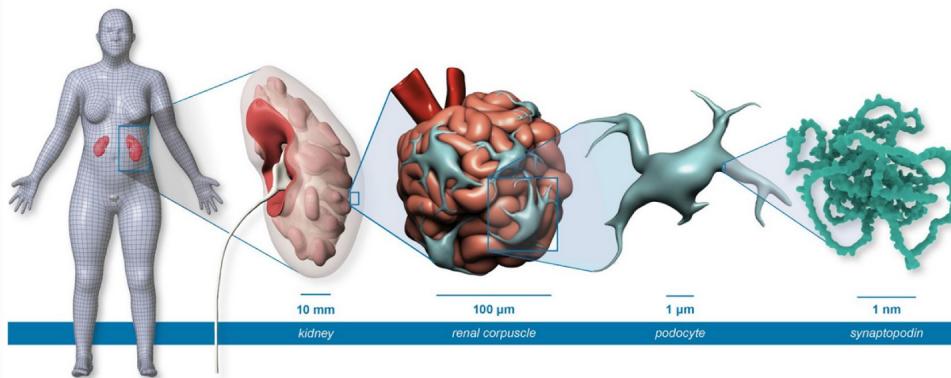
HRApop (Experimental Data + Cell Summaries)

# 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
<b>Total (sum, not unique)</b>	<b>264</b>	<b>159</b>	<b>151</b>	<b>122</b>	<b>58</b>	<b>34</b>	<b>40</b>



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Organ Mapping Antibody Panels

Vascular Geometry

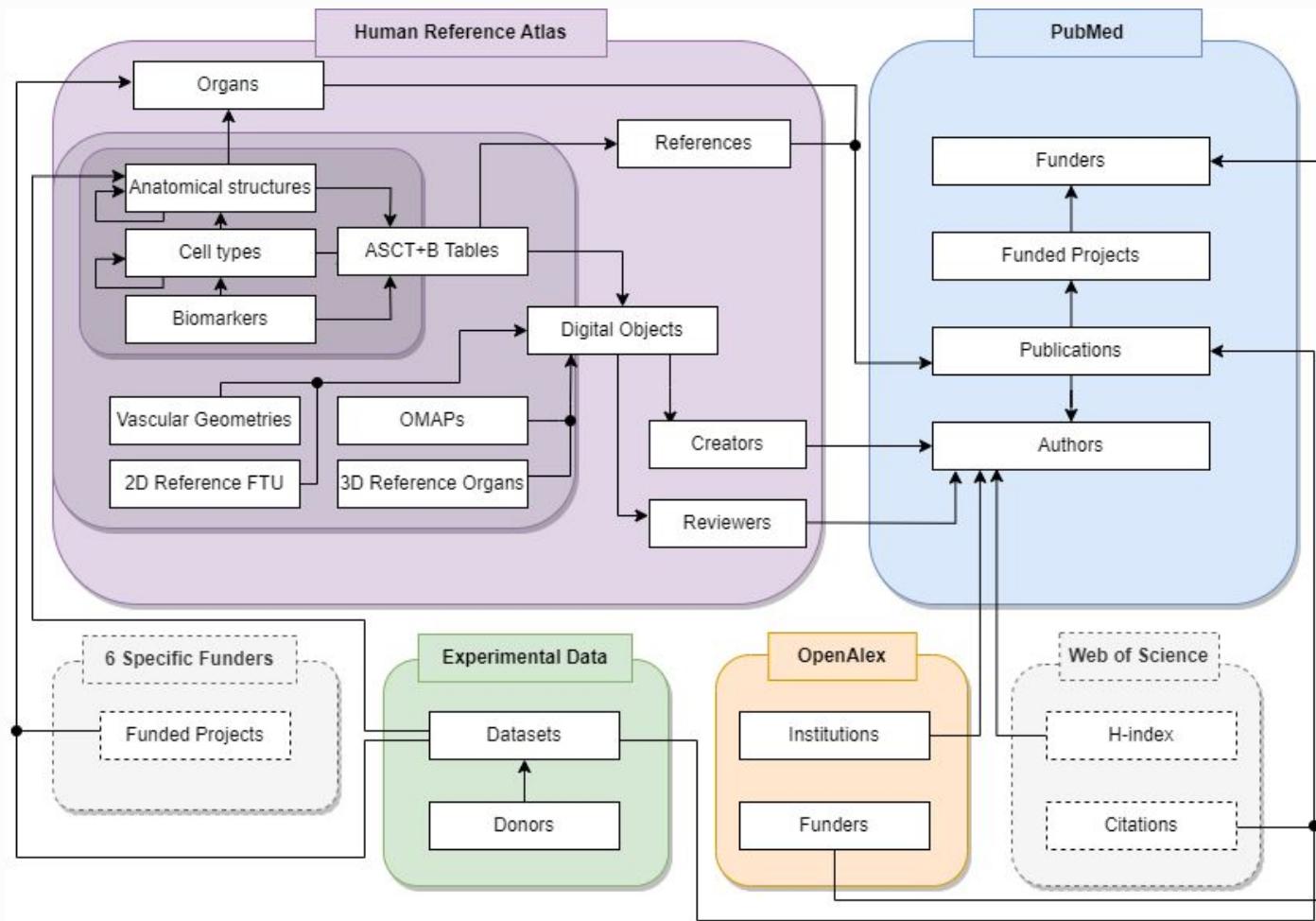
Experimental Data (Donors, Tissues,  
Extraction Sites, Datasets)

Atlas++

HRApop (Experimental Data + Cell Summaries)

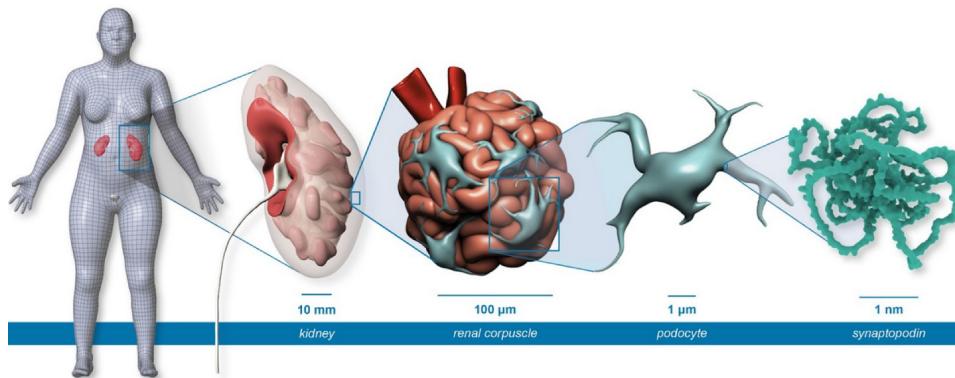
HRAlit (HRA-relevant Literature)

# 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
<b>Total (sum, not unique)</b>	<b>1,204,575</b>	<b>100,571</b>	<b>20,089</b>	<b>157,737</b>	<b>3,173</b>



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++

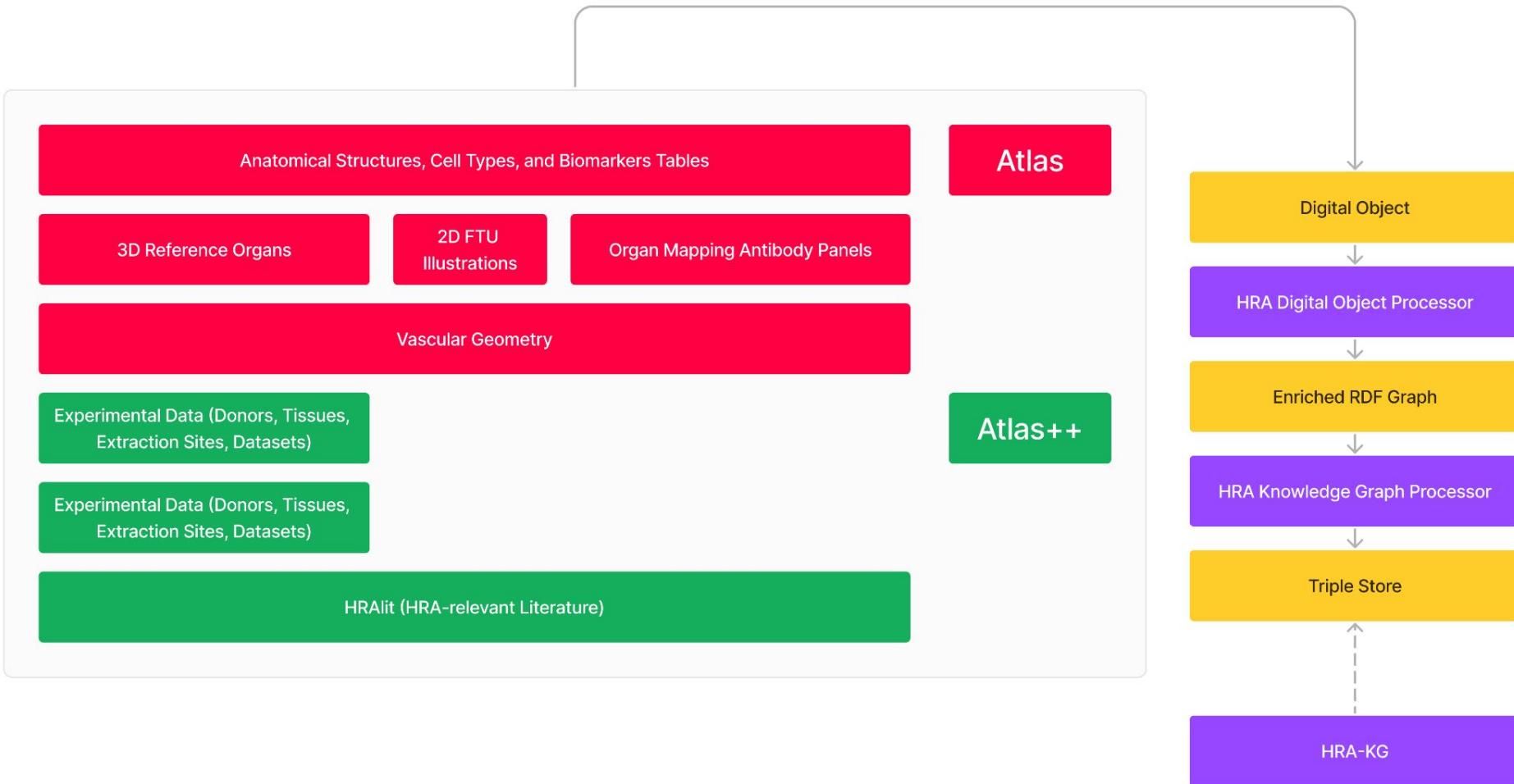
Experimental Data (Donors, Tissues,  
Extraction Sites, Datasets)

HRAlit (HRA-relevant Literature)

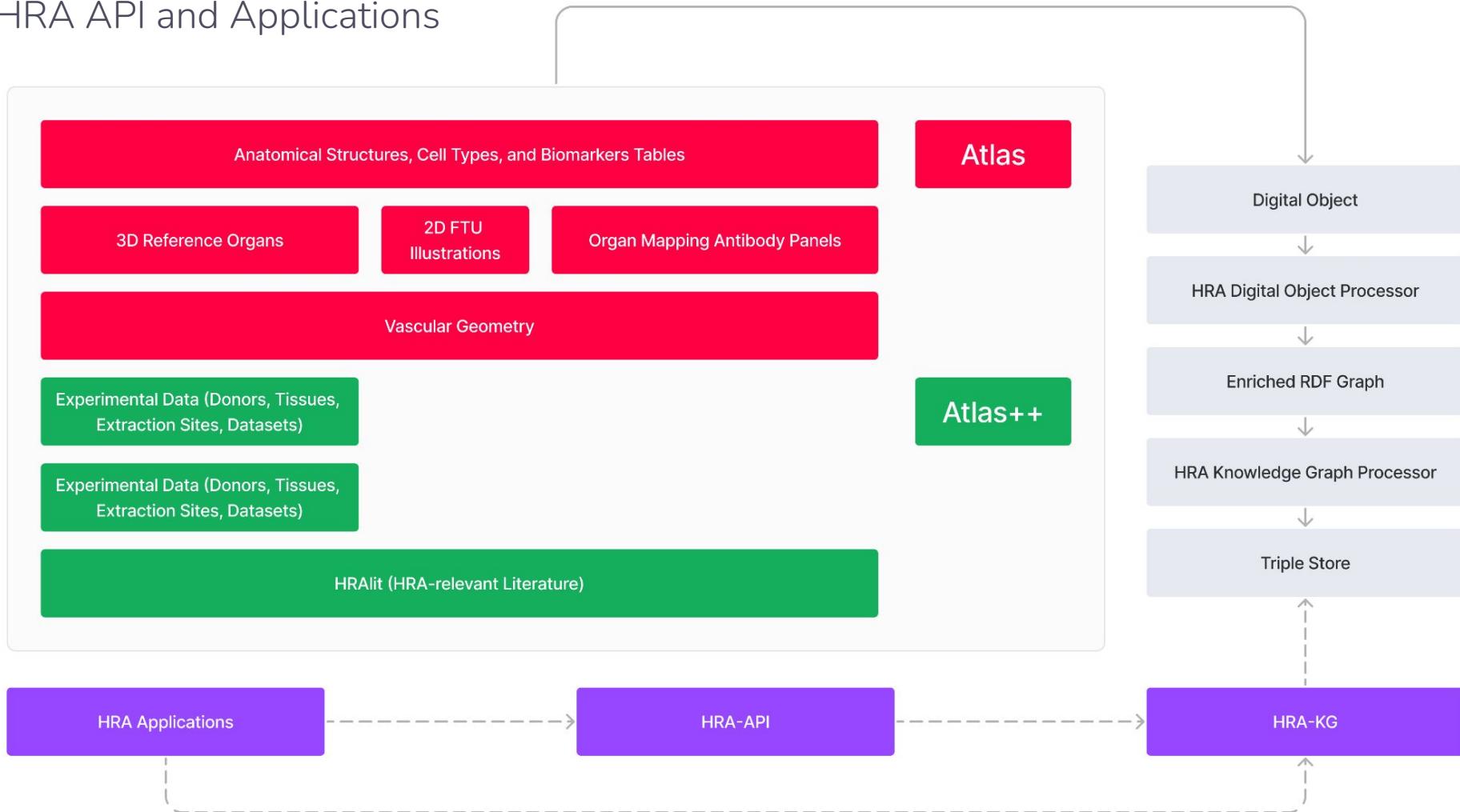
# Using the HRA



# 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, digital nerve).
- 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. It lists the following counts:

- 19 Tissue Data Providers
- 307 Donors
- 729 Tissue Blocks
- 892 Tissue Sections
- 3213 Tissue Datasets

**Results based on current filters**: This section displays a list of filtered results, each represented by a card. The first card shows a donor profile: Male, Age 72, BMI 27.4, Entered 4/9/2021, Liz McDonough, RTI-G... with a count of 26 tissue sections registered on 1/12/2021.

**Donor card in the expanded view**: The donor profile card is shown in expanded view, listing registered tissue sections.

**Tissue block card with information on number of tissue sections**: A card for a tissue block registered on 1/12/2021, Liz McDonough, RTI-G... with a size of 28 x 11 x 0.3 millimeter, 0.3 millimeter, block.

**Tissue section card**: A card for a tissue section registered on 1/12/2021, Liz McDonough, RTI-G... with a size of 28 x 11 x 0.3 millimeter, 0.3 millimeter, block.

**Dataset cards for viewing relevant portals, publications, or other resources**: Cards for "Cell Dive" and "Publication" are shown, each listing registered datasets.

**3D scene viewer**: The central feature is a 3D scene viewer showing two human figures with internal tissue blocks highlighted in orange.

**Annotations on the left side:**

- Show and hide lists for Anatomical Structures, Cell Types, and Biomarkers
- Anatomical Structures list: Anatomical Structures (AS) Tissue Blocks: 729. Sub-categories include brain (11), lymph node (36), eye (43), fallopian tube (0), and heart (159).
- Number of tissue blocks that collide with this anatomical structure
- Cell Types list: Cell Types (CT) Tissue Blocks: 729. Sub-categories include 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
- Biomarkers list: Biomarkers Tissue Blocks: 729. Sub-categories include a smooth muscle actin (0), A2M (253), ABCA10-43608400015.1 (0), ABCA1 (11), ABCA3 (11), ABCA4 (42), ABCA8 (11), ABCG9 (11), ABCG2 (0), ABCG2 (11), AB13BP (11), ABLIM1 (31), and AC002066.1 (0).
- Show and hide lists for specific biomarkers (genes, lipids, metabolites, proteins, proteoforms)
- Number of tissue blocks that have this biomarker in colliding AS in ASCT+B table

# 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 Tissue

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 with red, green, and blue highlights, representing different cell types. A legend at the bottom left identifies these colors. A red box highlights a specific cell, with a callout pointing to the 'Cell Sets' panel where 'CD45+' is selected. Another callout points to the 'Spatial View component' which lists features like visualizing all cells, connecting each cell to its closest endothelial cell, and viewing distributions of distances between different cell types. A red arrow points from this component to a smaller inset window on the right. The inset shows a network graph where nodes represent cells and edges represent distances to the nearest vasculature. A legend for this graph includes categories like All Cells, Endothelial, Smooth muscle, Macrophage, Lymphatic, DC, T cell, CD45+, CD4+, CD8+, B cell, CD45-, NK, KCC, M2 Macrophage, and Stroma. Above the inset, a histogram plots the 'Magnitude of Cells' (y-axis, 0-1000) against 'Distance (μm)' (x-axis, 0-400). The histogram bars are colored according to the cell types listed in the legend. The top of the main Vitessce window has several navigation and documentation links: 'Access documentation', 'Submit bug reports or feature requests to the Vitessce team', 'Vitessce pronunciation by IPA Reader', 'Vitessce GitHub repository', 'Switch between light mode and dark mode', 'Blog posts', 'Vitessce R package', 'Vitessce Python package', 'Use tutorials', 'Demos showcasing core features', 'Open the Vitessce App', and 'Return to the Vitessce landing page'.

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

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

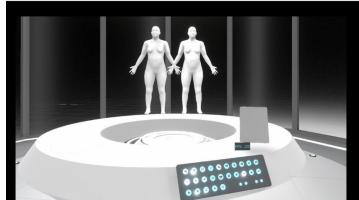
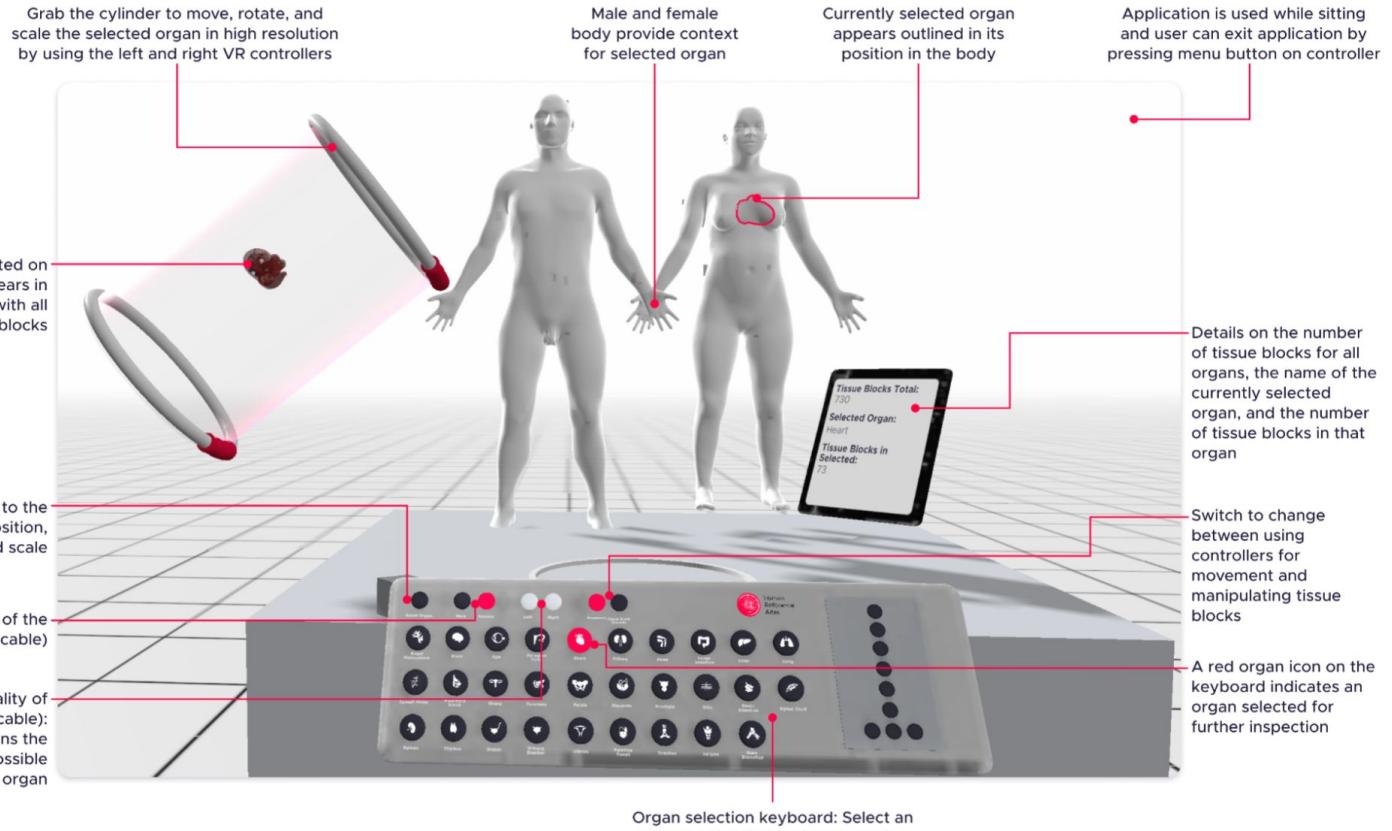
If you are interested to explore cell-cell, cell-FTU distance distributions, please share your data in this format:

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](mailto:yashjain@iu.edu).

Join zoom next meeting on March 25, 2024 at 4-5p ET. Email Nancy Ruschman, [nruschma@indiana.edu](mailto: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

**HRA-API Workflow 3: Run an API Query**

v1

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/ld+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

**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

**Run the API query**

**Reset parameters**

**Fill parameters with example options**

<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.

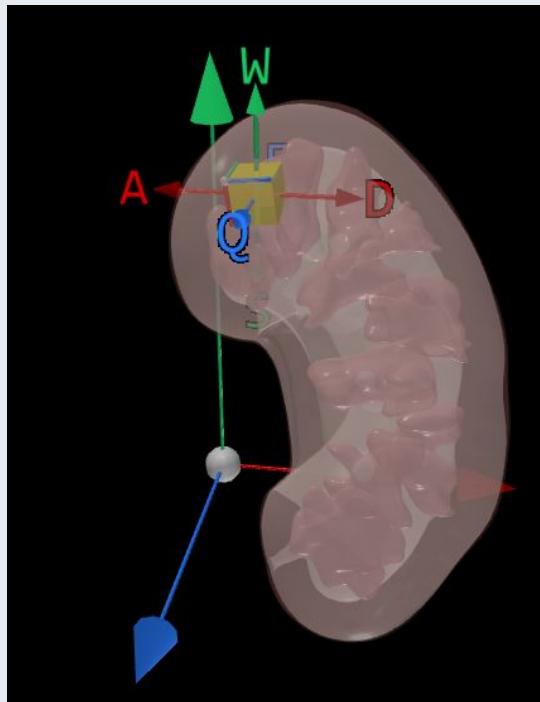
In addition, six programmers from different human atlas projects were surveyed.

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>			
<b>US#1.</b> 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.
<b>US#2.</b> 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>			
<b>US#3.</b> 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.
<b>US#4.</b> 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
<b>US#5.</b> 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>			
<b>US#6.</b> 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.
<b>US#7.</b> 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
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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 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.
- Number of tissue blocks per organ:** A table showing counts for Brain (11), Lymph node (36), Eye (43), Fallopian tube (0), and Heart (159).
- Spatial search tool for filtering by location:** A dropdown menu with options like body, cell, and biomarker.
- Information modal for the interface:** A help icon (i) in the top right corner.

Below these filters are detailed lists for each category:

- Anatomical Structures list:** Shows a tree view of structures: brain (11), lymph node (36), eye (43), fallopian tube (0), and heart (159). A summary table shows 729 tissue blocks.
- Cell Types list:** Shows a table of cell types: absorptive (67), adipocyte (159), adult endothelial progenitor cell (39), adventitial fibroblast (39), adventitial stromal cell (67), and afferent arteriole endothelial cell (121). A summary table shows 729 tissue blocks.
- Biomarkers list:** Shows a table of biomarkers: a smooth muscle actin (0), ABCM (253), ABC10-43608400015.1 (0), ABCA1 (11), ABCA13 (11), ABCA3 (42), ABCA4 (11), ABCA8 (11), ABCG9 (402), ABCG2 (0), ABCG6 (11), ABC13BP (11), ABIM1 (31), and AC002068.1 (0). A summary table shows 729 tissue blocks.

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

- Results based on current filters:** A table showing 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 male donor aged 72, BMI 27.4, entered 4/9/2021, Liz McDonough, RTI-Gene...
- Tissue block card:** A card for a tissue block registered on 9/10/2021, Liz McDonough, RTI-G... with dimensions 28 x 11 x 0.3 millimeter, 0.3 millimeter, block.
- Tissue section card:** A card for a tissue section registered on 1/12/2021, Liz McDonough, RTI-G... with dimensions 28 x 11 x 0.3 millimeter, 0.3 millimeter, block.
- Dataset cards:** Cards for viewing relevant portals, publications, or other resources.

At the bottom center is a label '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 the FTU Library. Nodes can be collapsed or expanded. A red dot indicates the selected node: **renal corpuscle**.
- Name of the selected Functional Tissue Unit:** Displays the selected FTU name: **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, Glomerular mesangial cell, Macula densa epithelia cell, Afferent arteriole endothelial cell, Efferent arteriole endothelial cell. A scale bar indicates 50 μm.
- Cell types by biomarkers tables:** Three tables showing cell types by gene, protein, and lipid biomarkers. The first table shows:

Cell Type	Cell Count	AASS	AKT3	ALS2...
glomerular capillary endothelial cell	34,400			
glomerular mesangial cell	9,900			
glomerular visceral epithelial cell	34,100			
parietal epithelial cell	26,600			
- Expand the table view:** A button to expand the table view for more details.
- Cell types, cell counts, & associated biomarker columns:** A legend indicating that higher opacity in the heatmap represents higher mean biomarker expression levels.
- Hover for details on ontology IDs and expression values:** A note that hovering over the heatmap cells provides additional information.
- Legend for cell types and biomarkers table:** A legend for the Biomarker Expression Mean in FTU and Percentage of Cells in FTU scales.
- Publication in which experimental data was published and linked to source data:** 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 for Human Reference Atlas team:** A contact button.
- Open the Human Reference Atlas Portal:** A button to open the HRA Portal.

At the bottom, there are links to view the selected illustration digital object metadata page, download the illustration, embed it, get the FTU Explorer web component via GitHub, and a direct link to experimental data.

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

# US#5. Provide cell distance distribution visualizations

The screenshot shows the Vitessce spatial viewer interface. A large central area displays a 2D spatial viewer with a network of red lines connecting cells to their nearest endothelial neighbors. A legend below the viewer identifies cell types by color: Endothelial (blue), Endothelial\_link (light blue), Endothelial\_stromal (green), Endothelial\_stromal\_link (light green), Endothelial\_stromal\_stromal (yellow), Endothelial\_stromal\_stromal\_link (light yellow), Endothelial\_stromal\_stromal\_stromal (orange), Endothelial\_stromal\_stromal\_stromal\_link (light orange), Endothelial\_stromal\_stromal\_stromal\_stromal (purple), Endothelial\_stromal\_stromal\_stromal\_stromal\_link (light purple), Endothelial\_stromal\_stromal\_stromal\_stromal\_stromal (pink), Endothelial\_stromal\_stromal\_stromal\_stromal\_stromal\_link (light pink), Endothelial\_stromal\_stromal\_stromal\_stromal\_stromal\_stromal (grey), Endothelial\_stromal\_stromal\_stromal\_stromal\_stromal\_stromal\_link (light grey), Endothelial\_stromal\_stromal\_stromal\_stromal\_stromal\_stromal\_stromal (black), Endothelial\_stromal\_stromal\_stromal\_stromal\_stromal\_stromal\_stromal\_link (light black). A smaller inset window shows a zoomed-in view of the network. To the right is a histogram showing the distribution of distances between different cell types and the nearest vasculature for the Vasculature Common Coordinate Framework (VCCF).

Annotations:

- Access documentation
- Demos showcasing core features
- Open the Vitessce App
- Use tutorials
- Vitessce Python package
- Vitessce R package
- 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
- 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

Coming June 14th on [humanatlas.io](https://humanatlas.io)

## **US#6. Develop lightweight atlas components**

The screenshot displays the NetMAP-HRA Registration software interface. At the top, there's a navigation bar with tabs for 'Left', 'Right', 'Anterior', 'Posterior', 'Rightest' (selected), and '3D Preview'. To the right of the preview are 'Registration Metrics' and 'Registration Details' sections. The main area features a semi-transparent 3D model of a heart. A coordinate system is overlaid on the heart, with a vertical green arrow pointing upwards, a horizontal red arrow pointing to the right, and a diagonal blue arrow pointing towards the bottom-left. Several small colored dots (red, blue, green) are placed on specific anatomical structures of the heart model. On the left side, there are two lists: 'Anatomical Structures' and 'Landmarks'. The 'Anatomical Structures' list includes: atrium, all atrioventricular structures, valve, mitral valve, tricuspid valve, aortic valve, coronary artery, papillary muscle of heart, anterior papillary muscle of left ventricle, anterolateral head of septal papillary muscle, anterolateral head of posterior papillary muscle, posterior papillary muscle of apex vca, posteroanterior head of posterior papillary muscle, and left cardiac atrium. The 'Landmarks' list includes: atrium, apex, aorta, left atrium, left ventricle free wall, right atrium, and right ventricle. At the bottom right, there are buttons for 'Home and Download'.

The screenshot shows the HuBMAP HRA Exploration interface. At the top, there's a navigation bar with icons for Home, Help, Logout, and a search bar labeled "Run Spatial Search". Below the navigation bar is a header with "Sex: Both", "Age: 1-10", and "BMI: 13-83". The main area features a 3D human body model with various organs highlighted in different colors (e.g., brain, heart, lungs, liver). To the left of the body model, there are two tables:

- Anatomical Structures (AG)**: Tissue Blocks: 729
  - brain: 11
  - lymph node: 36
  - esophagus: 43
  - urinary tube: 0
  - heart: 159
- Cell Types (ICT)**: Tissue Blocks: 729
  - absorptive: 67
  - adipocyte: 60
  - adipocyte: 224
  - adipocyte: 18
  - adipocyte: 1
  - adipocyte 1: 1

Below these tables is a section for **Biomarkers** (Tissue Blocks: 729):
 

	✓ AS	✓ CT	✓ BM	✓ BP	✓ SF
a smooth muscle actin	0				
ATM	253				
ATM (ENSG00000240005)	0				
ABCAB1	11				
ABCAB3	11				
ABCAB3A	42				
ABCAB4	11				
ABCAB4A	11				
ABCBC9	402				
ABCBC9	0				
ABCBC9	11				
ABCBD9	11				
ABCDD1	21				
AC0039981	0				



**Main: Green**

- 2 Tissue Data Providers
- 10 Donors
- 44 Tissue Blocks
- 19 Tissue Sections
- 90 Tissue Datasets

**All tissue sections using the HKA registration user interface (RUI):**

Block ID	Block Name	Specimen ID	Specimen Name	Donor ID	Donor Name	Registration Date
HKA_001	HKA_001	Specimen_001	Specimen_001	Donor_001	Donor_001	2023-01-01
HKA_002	HKA_002	Specimen_002	Specimen_002	Donor_002	Donor_002	2023-01-02
HKA_003	HKA_003	Specimen_003	Specimen_003	Donor_003	Donor_003	2023-01-03
HKA_004	HKA_004	Specimen_004	Specimen_004	Donor_004	Donor_004	2023-01-04
HKA_005	HKA_005	Specimen_005	Specimen_005	Donor_005	Donor_005	2023-01-05
HKA_006	HKA_006	Specimen_006	Specimen_006	Donor_006	Donor_006	2023-01-06
HKA_007	HKA_007	Specimen_007	Specimen_007	Donor_007	Donor_007	2023-01-07
HKA_008	HKA_008	Specimen_008	Specimen_008	Donor_008	Donor_008	2023-01-08
HKA_009	HKA_009	Specimen_009	Specimen_009	Donor_009	Donor_009	2023-01-09
HKA_010	HKA_010	Specimen_010	Specimen_010	Donor_010	Donor_010	2023-01-10

**Explore Tissue:**

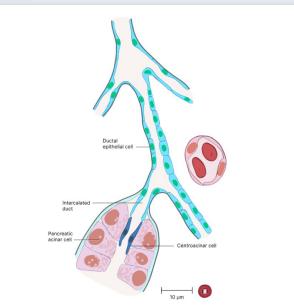
- [View](#)
- [Download](#)
- [Report](#)

**ASCT-HKA Report:**

- [View](#)
- [Download](#)

**Human Reference Atlas (HRA): Deep Dive**

[Web Portal](#)
[Online Course](#)
[Paper](#)



**HRA-API 2.0**

HuBMAP Help Doc <https://hubmapconsortium.org> | License: [MIT License](#)

This API provides programmatic access to data registered to the Human Reference Atlas (HRA). See the [HuBMAP HRA Portal](#) for details.

### API SERVER

- 🌐 <https://apps.humanatlas.io/api> - HRA 2.0 Production
- 🌐 <https://apps.humanatlas.io/hra-api> - HRA 1.x Production
- 🌐 <https://apps.humanatlas.io/hra-api--staging> - HRA 1.x Staging
- 🌐 <https://apps.humanatlas.io/> - Local Server

**SELECTED:** <https://apps.humanatlas.io/api>

[Expand all](#) | [Collapse all](#) sections

#### v1

HRA-API v1.x Routes

Method	Path	Description
GET	/v1/db-status	Get current status of database
GET	/v1/sparql	Run a SPARQL query
POST	/v1/sparql	Run a SPARQL query (POST)
GET	/v1/aggregate-results	Get aggregate results / statistics
POST	/v1/get-spatial-placements	Given a SpatialEntity already placed relative to a reference SpatialEntity, retrieve a new direct SpatialPlacements to the given SpatialEntity
GET	/v1/hubmap/rvi/locations.jsonld	Get all hubmap rvi locations (if enabled)
GET	/v1/hubmap/rvi/locations.jsonld	Get all hubmap rvi locations (if enabled)

Welcome to the Functional Tissue Unit Explorer

Explore functional tissue units (FTUs) featuring experimental datasets and Human Reference Atlas (HRA) technologies. Read more about this effort at [HRA Portal: FTU Explorer](#)

The FTU Explorer was designed in close collaboration with [Kidney Precision Medicine Project](#) and [European Bioinformatics Institute](#).

FTU Library

loop of Henle ascending limb thin segment: FTU Illustration

FTU Illustration Gene Biomarkers Protein Biomarkers Lipid Biomarkers Source Data

Ascending vasa recta

Ascending thin limb cell

10  $\mu$ m

Kidney

- loop of Henle ascending limb thin segment
- Cortical Collecting Duct
- descending limb of loop of Henle
- inner medullary collecting duct
- nephron
- outer medullary collecting duct
- renal capsule
- thick ascending limb of loop of Henle

Large Intestine

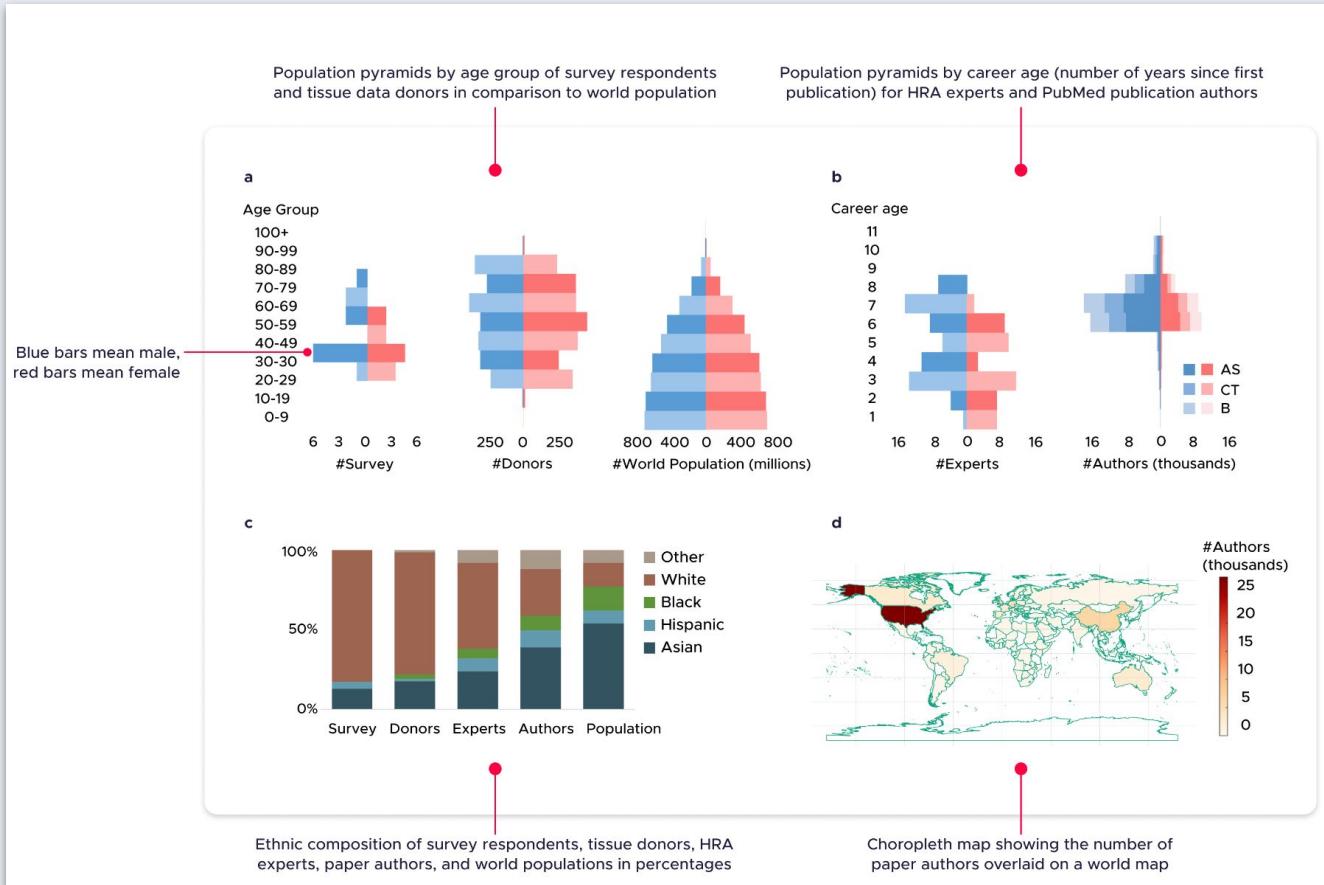
- crypt of Lieberkuhn of large intestine

Liver

Illustration Download Embed Contact HRA Portal

Coming June 14th on [humanatlas.io](http://humanatlas.io)

# US#7. Implement dashboard for HRA



Coming June 14th on [humanatlas.io](https://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



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CNS Director

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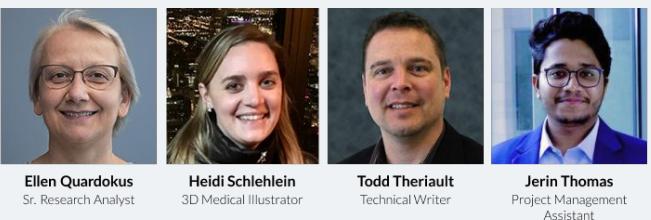
Kate Gustilo  
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Ushma Patel  
Medical Illustrator

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



Ellen Quardokus  
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Heidi Schlelein  
3D Medical Illustrator

Todd Theriault  
Technical Writer

Jerin Thomas  
Project Management  
Assistant



# Thank you!

Resources at:

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

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