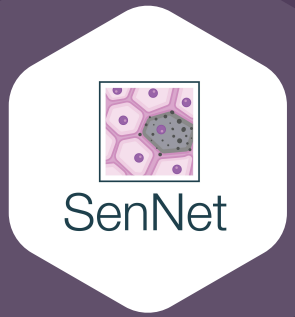
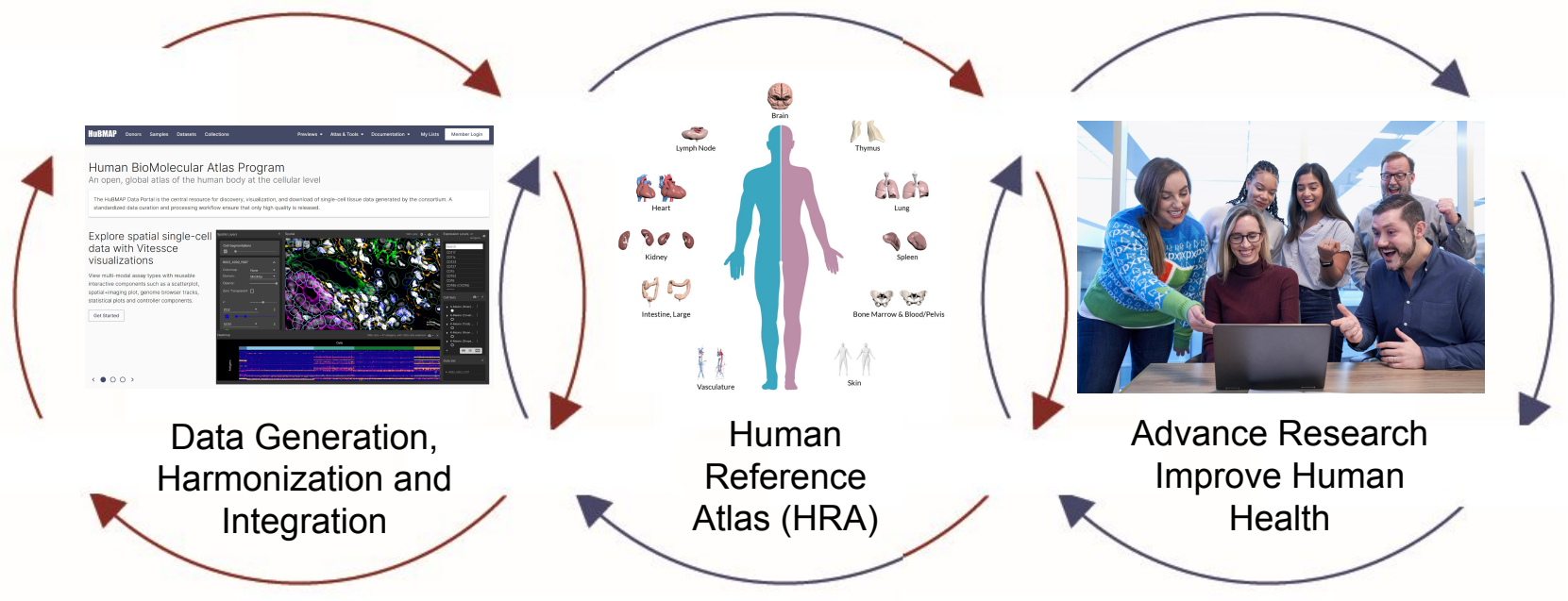


ASCT+B Tables and SenNet Biomarkers

Katy Börner & Ellen M. Quardokus
(CODCC, Indiana University)

June 1, 2022

Why construct a Human Reference Atlas (HRA)?

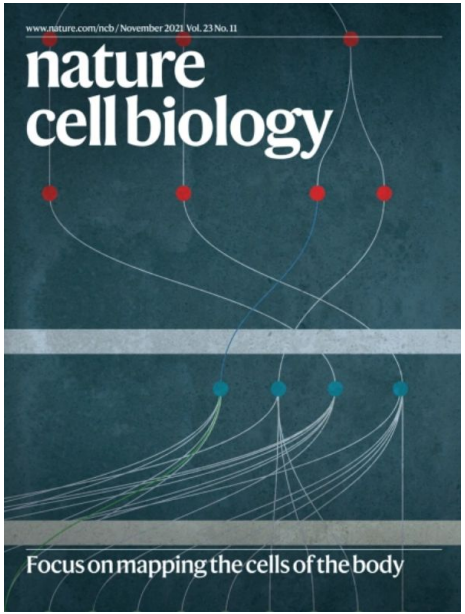


Defining the Human Reference Atlas (HRA)

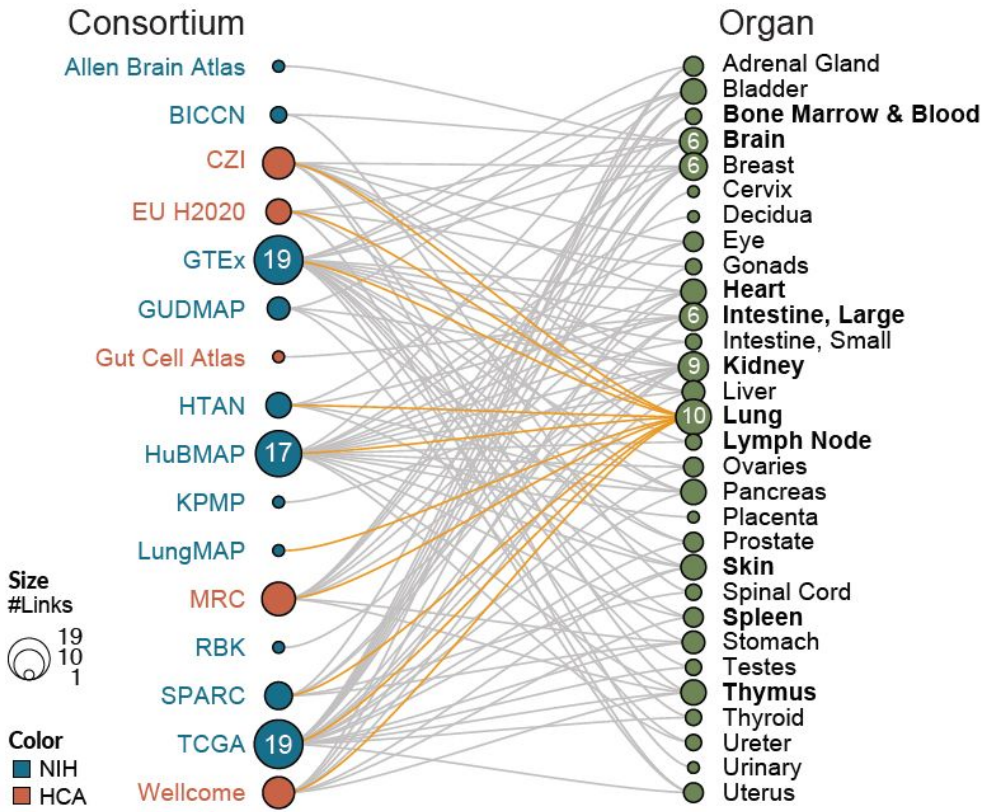
The Human Reference Atlas (HRA)

1. defines the 3D space and shape of anatomical structures and cell types that are of biomedical relevance plus the biomarkers used to characterize them. Anatomical structures, cell types and biomarkers are validated and represented in/added to ontologies (Uberon/FMA, CL, HGNC).
2. defines how new datasets can be mapped to the HRA, e.g., spatially using the Visible Human CCF or Vasculature CCF (or both, see next slide), via ASCT+B ontology terms/IDs, or via gene expression data as in Azimuth.
3. it is
    - authoritative (there exists expert agreement and it was validated by data),
    - computable (supports API queries, UIs),
    - published as LOD (connected to gene, disease, and other ontologies and data),
    - open (anyone can use the HRA data and code), and
    - continuously evolving (e.g., as new technologies become available).

https://www.nature.com/articles/s41556-021-00788-6



Constructing the Human Reference Atlas – Together!



Anatomical Structures (AS)

Cell Types (CT)

Biomarkers (B)

Partonomy Tree
part_of

Spleen
- Splenic Pulp
  - Red Pulp
    - Venous Sinuses
      - Pulp Arteries
      - Penicillar Arterioles
      - Sheathed Arterioles
      - Arterial Capillaries
      - Sinuses
      - Veins
    - Stroma
    - Splenic Cords
  - White Pulp
    - Secondary Follicles
      - Germinal Centers
    - Primary & Secondary Folli...
      - Mantle Zone
      - Superficial (Marginal) Zone
    - Central Arteriole (in follicl...
    - PALS and Follicles
    - PALS
    - Perifollicular Zone
- Splenic Artery

VHP F Spleen

White pulp of spleen

Bimodal network describing which CT are *located_in* what AS

Typology Tree
is_a

- adventitial stromal cell
- B cell
- Dendritic cell
- Endothelial
- Endothelial cell
- Erythrocytes
- fibroblast
- Fibroblastic reticular cell
- Follicular Dendritic cell
- Granulocytes
- Littoral cell
- Lymphatic endothelium
- macrophage
- Monocytes
- Myofibroblast
- neurons
- NK cell
- Plasma cell
- Plasmablasts
- Platelets

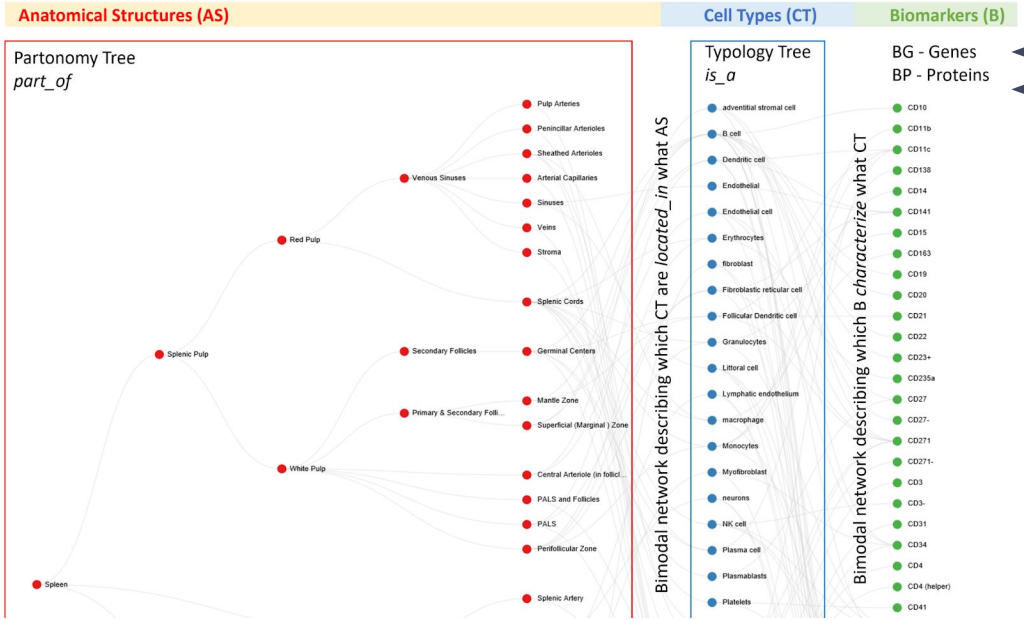
BG - Genes
BP - Proteins

Bimodal network describing which B *characterize* what CT

- CD10
- CD11b
- CD11c
- CD138
- CD14
- CD141
- CD15
- CD163
- CD19
- CD20
- CD21
- CD22
- CD23+
- CD235a
- CD27
- CD27-
- CD271
- CD271-
- CD3
- CD3-
- CD31
- CD34
- CD4
- CD4 (helper)
- CD41

HRA Validation/ Expansion

New ATLAS publications



Azimuth Maps

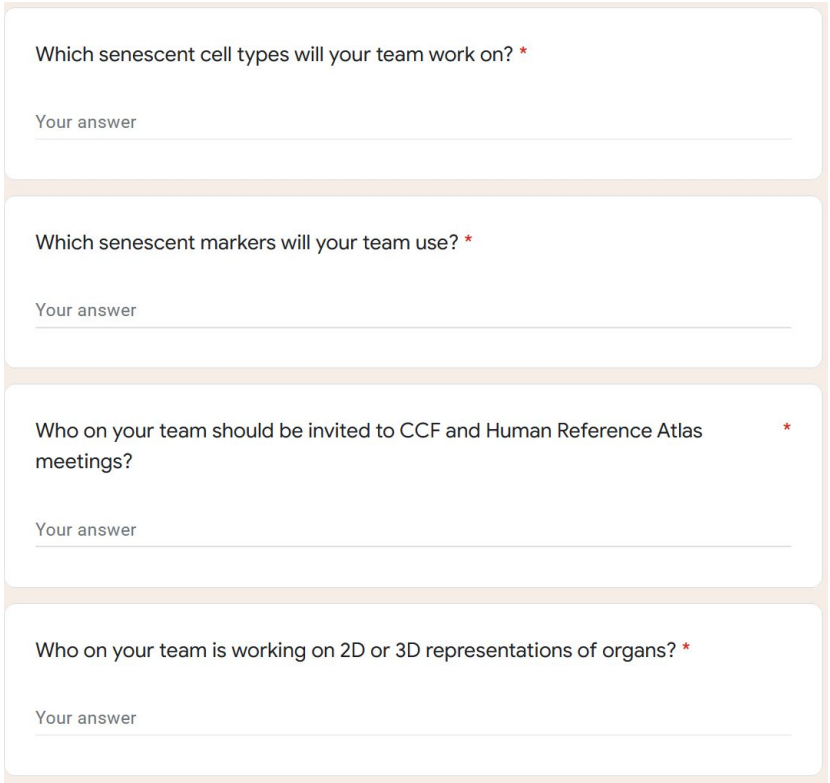
Validated Antibodies

2D/3D Maps & Ontology Crosswalks

New ATLAS datasets

BF – Proteoforms
BL – Lipids
BM – Metabolites

“Common Coordinate Framework (CCF) in Support of Human Reference Atlas (HRA) Construction and Usage” survey in Nov 2021:



SenNetMarkers_To_HGNC-UniProt_shared was shared to SenNet Biomarkers working group: https://docs.google.com/spreadsheets/d/1VHqmY1mDo7XeVXWqiWXXp2O0Dbyy6rnTKbvIgzoX8GI/edit?usp=sharing

	A	B	C	D	E	F	G	H	I
1	**SenNet CCF Survey, Nov '21**	**SenNet Gene Name**	**HGNC approved label**	**HGNC ID**	**UniProt ID**	**Aliases**	**full name**	**Comments**	
2	CCL2	CCL2	C-C motif chemokine ligand 2	HGNC:10618	P13500		C-C motif chemokine ligand 2		
3	CCNA2	CCNA2	cyclin A2	HGNC:1578	P20248 O96020		cyclin A2		
4	CCNE2	CCNE2	cyclin E2	HGNC:1590			cyclin E2		
5	cell size	Cell size	cell size			this is a measurement of a cell not a gene			
6	DDR	DDR	DNA damage response			this is a pathway not a gene			
7	Gamma-H2AX // same as gamma-H2AX; need to (	gamma-H2AX	H2AX	HGNC:4739	P16104	gH2AX H2A histone family member X H2A histone family, member X H2A.X H2a/x H2AFX H2AX histone H2AX Histone H2A.x Histone H2AX YH2AX	H2A.X variant histone		
8	GM-CSF	GM-CSF	CSF2	HGNC:2434	P04141	sargramostim molgramostim granulocyte-macrophage colony stimulating factor	colony stimulating factor 2		
9	HMGB1	HMGB1	high mobility group box 1	HGNC:4983	P09429				
10	HMGB2	HMGB2	high mobility group box 2	HGNC:5000	P26583				
11	IGFBP7	IGFBP7	insulin like growth factor binding protein 7	HGNC:5476	Q16270				
12	IL1	IL1	interleukin 1 alpha	HGNC:5991	P01583	IL1 IL1F1 IL-1A IL1-ALPHA	interleukin 1 alpha	IL1 is the same as IL1alpha	
13	IL1a	IL1A	interleukin 1 alpha	HGNC:5991	P01583		interleukin 1 alpha		
14	IL1b	IL1B	interleukin 1 beta	HGNC:5992	P01584				
15	IL6	IL6	interleukin 6	HGNC:6018	P05231				
16	IL8	IL8	CXCL8	HGNC:6025	P10145		C-X-C motif chemokine ligand 8	IL8 is no longer approved name	
17	Ki67	Ki67	MKI67	HGNC:7107	P46013	protein phosphatase 1 regulatory subunit 105 Molecular Immunology Borstel antibody 1	marker of proliferation Ki-67		
18	lipofuscin	lipofuscin	lipofusion			this is a fluorescent pigment that accumulates with age in the lysosomal compartment of postmitotic cells in several tissues			
19	LMNB1	LMNB1	lamin B1	HGNC:6637	P20700				
20	MMP1	MMP1	matrix metallopeptidase 1	HGNC:7155	P03956				
21	MMP2	MMP2	matrix metallopeptidase 2	HGNC:7166	P08253				
22	MMP3	MMP3	matrix metallopeptidase 3	HGNC:7173	P08254				
23	MMP9	MMP9	matrix metallopeptidase 9	HGNC:7176	P14780				
24	p15	p15	CDKN2B	HGNC:1788	P42772	P15 MTS2 INK4B TP15 CDK4I p15INK4b	cyclin dependent kinase inhibitor 2B	p15 is no longer approved name	
25	p16	p16	CDKN2A	HGNC:1787	P42771	CDK4I p16 INK4a MTS1 CMM2 ARF p19 p14 INK4 p16INK4a p19Arf p14ARF	cyclin dependent kinase inhibitor 2A	p16 is no longer approved name	
26	p19	p19	CDKN2A	HGNC:1787	P42771	CDK4I p16 INK4a MTS1 CMM2 ARF p19 p14 INK4 p16INK4a p19Arf p14ARF	cyclin dependent kinase inhibitor 2A	NOTE: p16 and p19 are the same gene!	
27	p21	p21	CDKN1A	HGNC:1784	P38936	P21 CIP1 WAF1 SDI1 CAP20 p21CIP1 p21Cip1/Waf1 p21	cyclin dependent kinase inhibitor 1A		
28	p53	p53	TP53	HGNC:11998	P04637	p53 LFS1	tumor protein p53		
29	PAI-1	PAI-1	SERPINE1	HGNC:8583	P05121	PAI	serpin family E member 1	alias previous name: plasminogen activator inhibitor, type I	
30	PCNA	PCNA	PCNA	HGNC:8729	P12004		proliferating cell nuclear antigen		
31	SPIDER-beta-Gal	SA-beta-Gal	GLB1	HGNC:4298	P16278	elastin receptor 1, 67kDa elastin receptor 1 (67kD) galactosidase, beta 1	galactosidase beta 1		
32	SASP factors	SASP	senescence-associated secretory phenotype			this is senescence-associated secretory phenotype (SASP) not a gene			
33	Serpine1	Serpine1	SERPINE1	HGNC:8583	P05121		serpin family E member 1		
34	TNFa	TNFa	TNF	HGNC:11892	P01375	TNFA TNFSF2 DIF TNF-alpha	tumor necrosis factor		

	A	B	C	D	E	F	G
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8	GM-CSF	GM-CSF	CSF2	HGNC:2434	P04141	sargramostim molgramostim granulocyte-macrophage colony stimulating factor	colony stimulating factor 2
9	HMGB1	HMGB1	high mobility group box 1	HGNC:4983	P09429		
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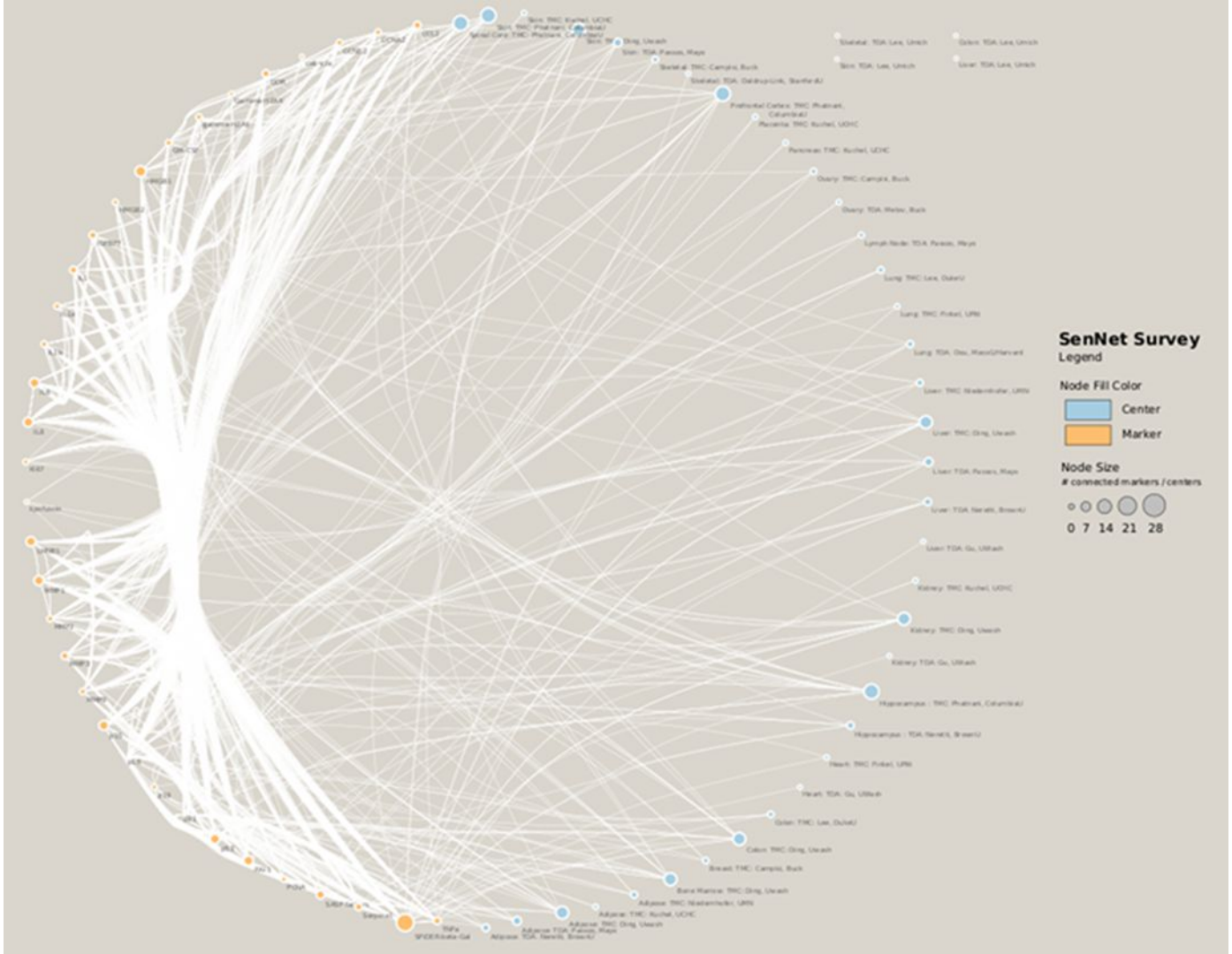
12	IL1	IL1	interleukin 1 alpha	HGNC:5991	P01583	IL1 IL1F1 IL-1A IL1-ALPHA	interleukin 1 alpha
13	IL1a	IL1A	interleukin 1 alpha	HGNC:5991	P01583		interleukin 1 alpha
14	IL1b	IL1B	interleukin 1 beta	HGNC:5992	P01584		
15	IL6	IL6	interleukin 6	HGNC:6018	P05231		
16	IL8	IL8	CXCL8	HGNC:6025	P10145		C-X-C motif chemokine ligand 8


SenNet Survey
Legend
Node Fill Color
Center
Marker
Node Size
connected markers / centers
0 7 14 21 28

SenNet

MONTHLY SCIENCE TALK

APRIL 27, 2022
2:30 PM EST

DR. ANDREAS BUECKLE
&
ELLEN M. QUARDOKUS

Cellular Senescence Network (SenNet) Consortium Organization
and Data Coordinating Center (CODCC)

Onboarding TMCs – CCF Registration User Interface (RUI) and CCF Exploration User Interface (EUI)

Presenter: Dr. Andreas Bueckle, Research Scientist, Cyberinfrastructure for Network Science Center, Department of Intelligent Systems Engineering, Luddy School of Informatics, Computing, and Engineering, Indiana University;

Abstract: Constructing the Human Reference Atlas (HRA) requires spatial annotations for registered human tissue across all organs. In this demo, we will introduce the CCF Registration User Interface (RUI) and CCF Exploration User Interface (EUI) which allow users to spatially register and semantically annotate tissue blocks and to spatially/semantically explore them across 50+ adult human reference organs via a web browser.

Learning Objective: Learn how to 3D register tissue and explore tissue blocks spatially and semantically.

Onboarding TMCs - Authoring and Using Anatomical structures, Cell types and Biomarker tables (ASCT+B), design of 3D organ reference library models

Presenter: Ellen M. Quardokus, Senior Research Analyst Biologist, Cyberinfrastructure for Network Science Center, Department of Intelligent Systems Engineering, Luddy School of Informatics, Computing, and Engineering, Indiana University;

Abstract: Constructing the Human Reference Atlas (HRA) requires spatial and semantic annotations for registered human tissue across all organs. ASCT+B tables capture into structured tables the nomenclature for each organ on three scales: anatomy, cell types located in the anatomy, and the biomarkers that characterize the cell types. The information is used to annotate 3D models, which are used in the Tissue Registration User Interface (RUI), Exploration User Interface (EUI) and data search. 3D organ models are designed with expert user input to capture the gross anatomical level needed to virtually register tissue blocks.

Learning Objective: Learn how to author and use ASCT+B tables and 3D reference organs efficiently.

Recordings

Recordings are at
Andi: https://youtu.be/FrbIrWjeLRs
Ellen: https://youtu.be/QDP58N8JYRk

Visible Human Massive Open Online Course (VHMOOC):
https://expand.iu.edu/browse/sice/cns/courses/hubmap-visible-human-mooc

Relevant Papers

- K. Börner et al., “Anatomical structures, cell types and biomarkers of the Human Reference Atlas,” *Nature Cell Biology*, vol. 23, no. 11, 2021. doi: doi.org/10.1038/s41556-021-00788-6.
- K. Börner et al., “Tissue Registration and Exploration User Interfaces in support of a Human Reference Atlas,” biorXiv preprint bioRxiv:2021.12.30.474265, 2021.

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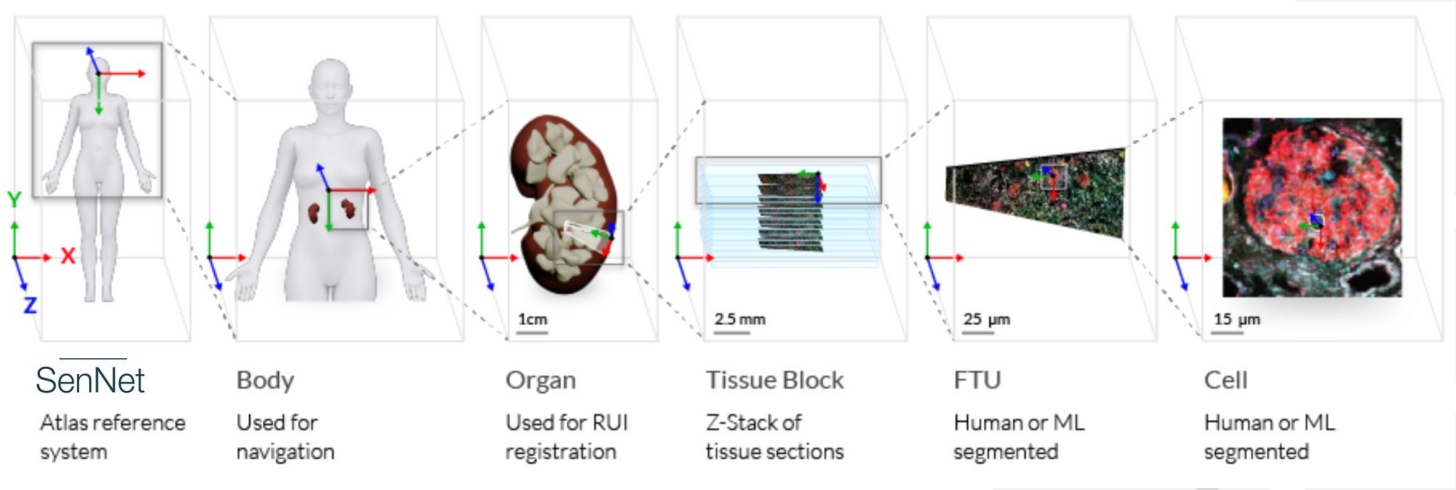
Standardized Tissue Registration

Learn how to 3D register tissue and explore tissue blocks spatially and semantically.



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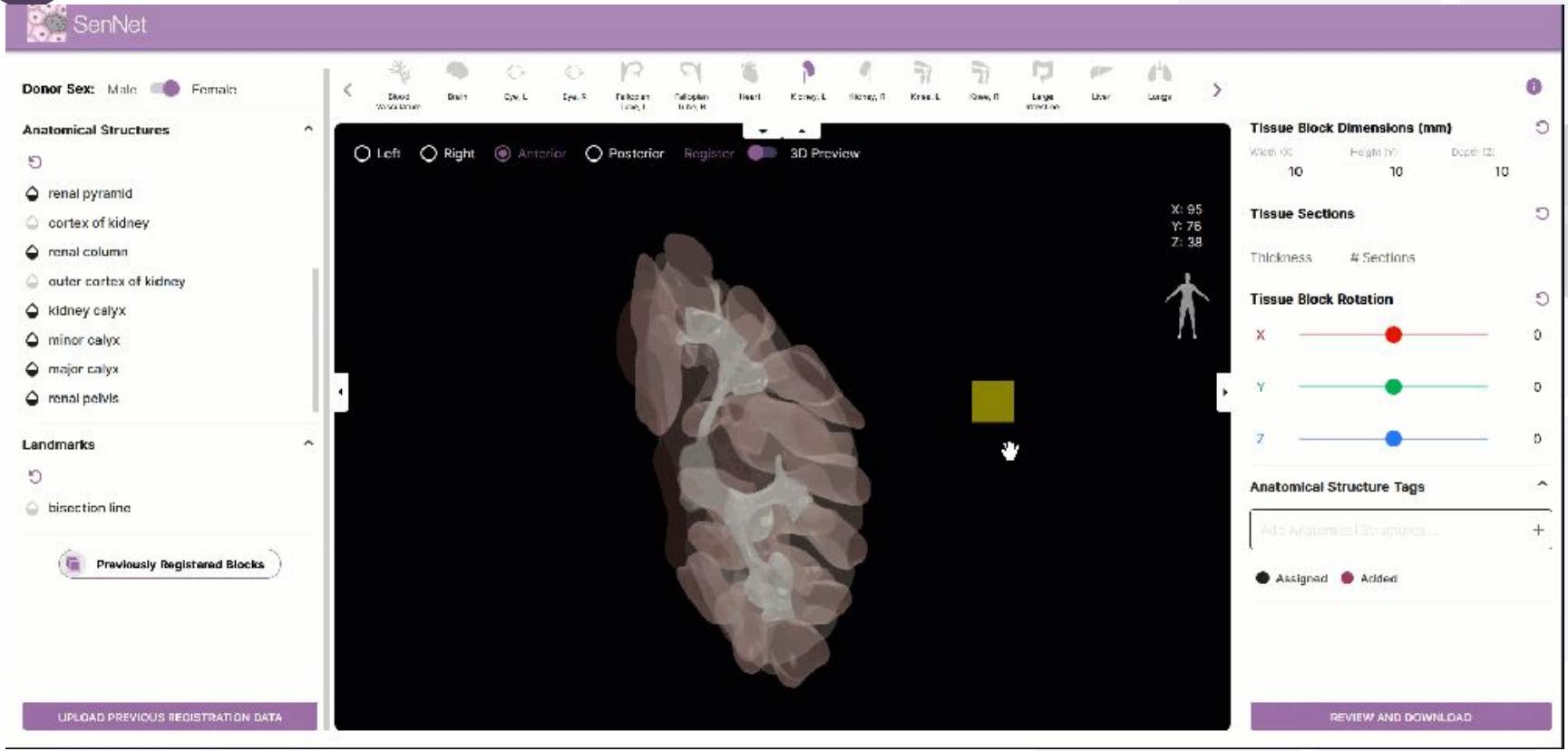
CCF Registration User Interface (RUI)



https://hubmapconsortium.github.io/ccf-ui/rui/

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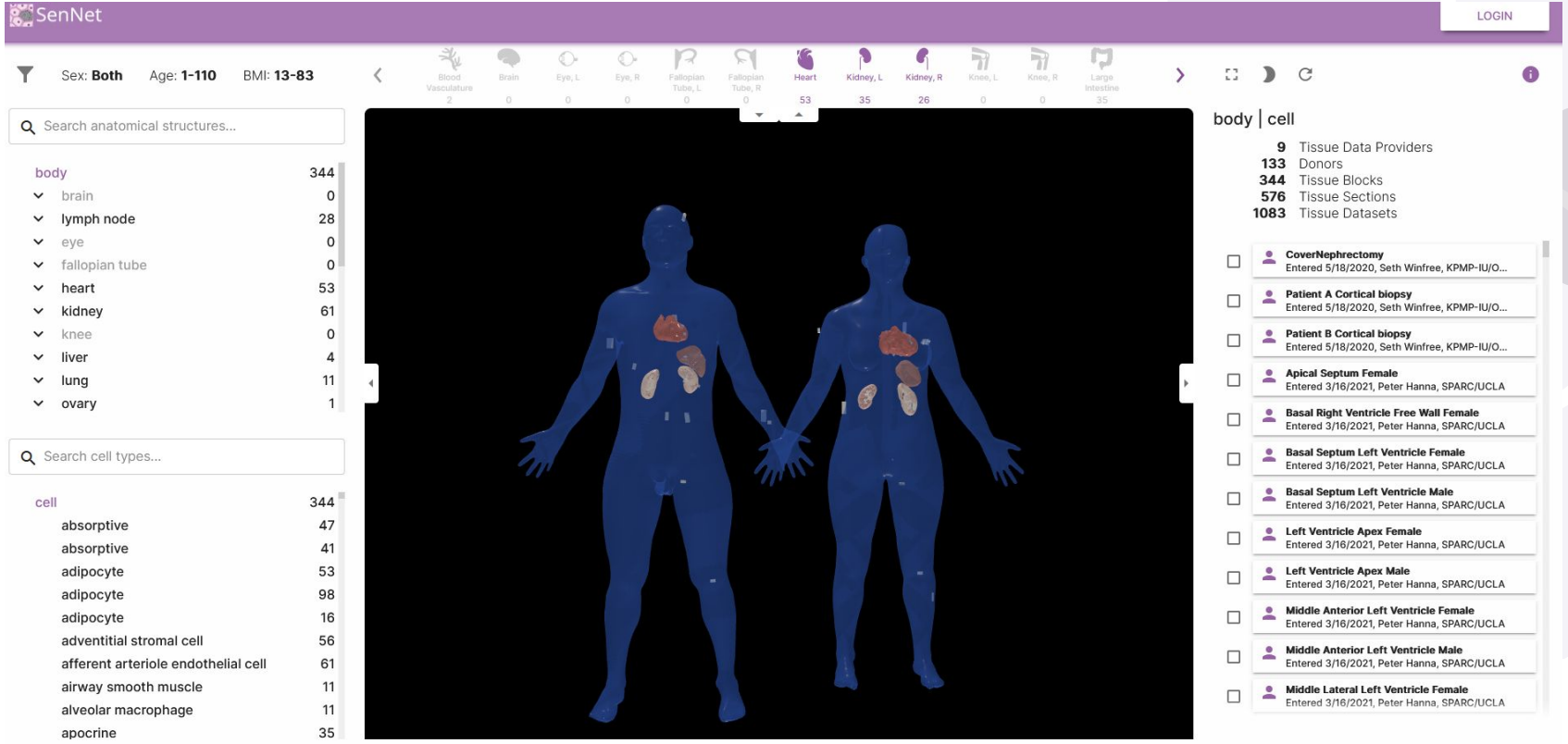
CCF Exploration User Interface (EUI)



https://portal.hubmapconsortium.org/ccf-eui

Note: The screenshot above shows HuBMAP data

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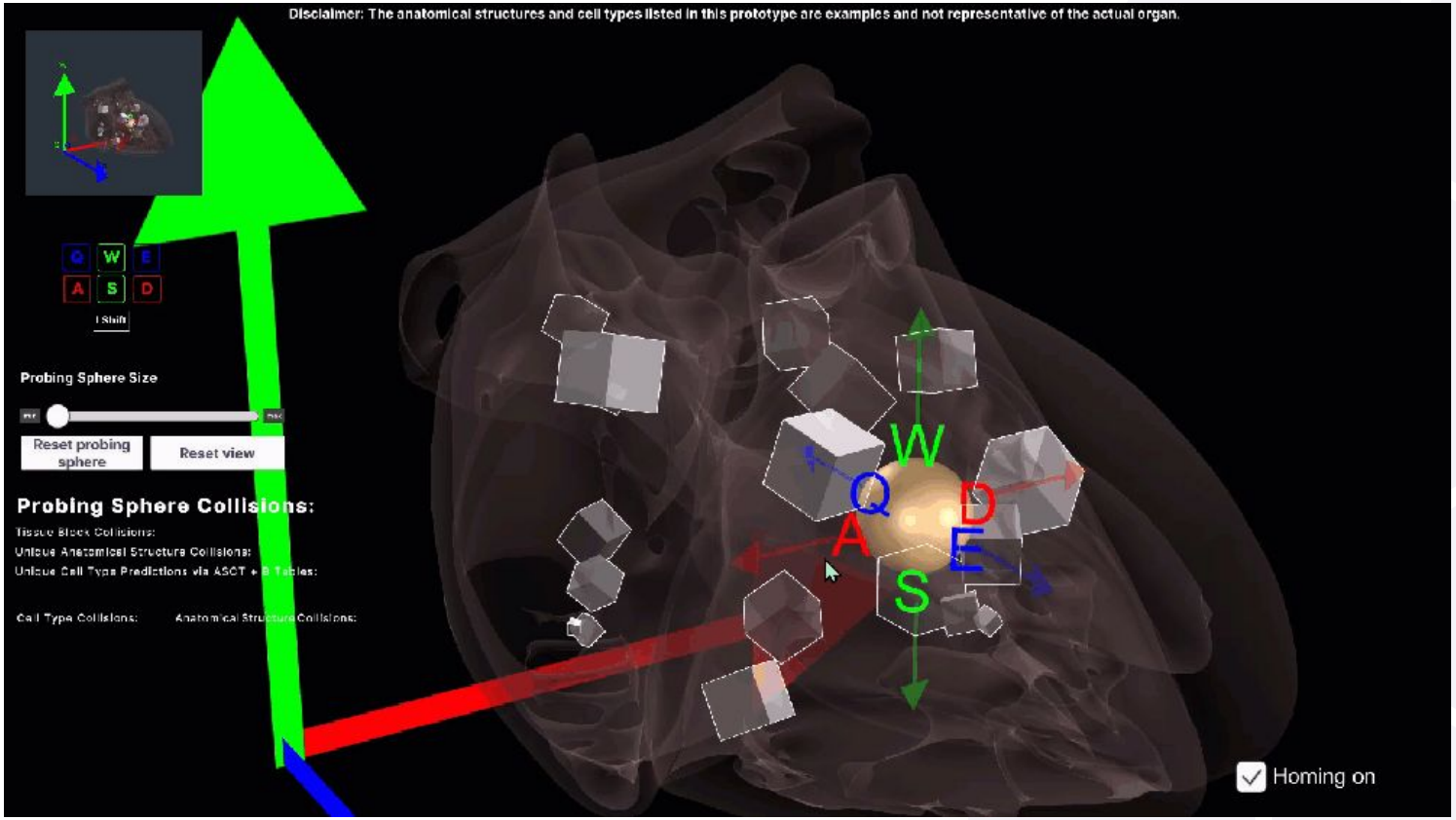
Exclusive Preview: Spatial Search



https://andreasbueckle.github.io/rui-3d-interactions/

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Relevant SOPs and Videos

- SOP: Using the CCF Registration User Interface: https://doi.org/10.5281/zenodo.5575776
- RUI 3.0.0 Tutorial: https://youtu.be/gY3_-LIoKaU
- How to Double-check a RUI Registration with the Exploration User Interface: https://youtu.be/UloDIG0S64w
- SOP: Assigning the Same RUI Location to Multiple Tissue Blocks: https://doi.org/10.5281/zenodo.5746143

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Onboarding TMCs - Authoring and Using Anatomical structures, Cell types and Biomarker tables (ASCT+B), and design of 3D organ reference library models

Presenting:
Ellen M. Quardokus (CODCC, Indiana University)

April 27, 2022

Learning Objective

Learning Objective: Learn how to author and use ASCT+B tables and 3D reference organs efficiently

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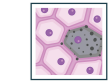

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Background–Structuring knowledge

What does an ASCT+B table do?

Standardize how information is captured, formatted, labeled

→

Knowledge about organs, anatomical structures, cell types, biomarker sets that uniquely define cell types

→

Ontologies like the multi-species Uber Anatomy (Uberon) and Cell Ontology (CL) capture Nomenclature, synonyms, descriptions, relationships between entities, provenance for knowledge, assigns unique ID for this unit of knowledge

Unstructured Knowledge sources ~80% of biomedical knowledge

Structured knowledge unifies nomenclature that describe datasets so we are all speaking in the same language

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ASCT+B Working Group Meetings

- **WG Charter**
  https://docs.google.com/document/d/1KxcZfKiDtSYx0BrCro9NucFaixPTdMixvlohZe6BkzY/edit
- **WG Expert Registration**
  https://iu.co1.qualtrics.com/jfe/form/SV_bpaBhIr8XfdiNRH
- **WG Listserv:**
  https://lists.hubmapconsortium.org/g/ASCT-B
- **WG Slack:** https://asct-b.slack.com
- **2022 Meetings:** First Wednesdays, 11-noon ET: June 1, July 6, ...

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What are ASCT+B tables?

ASCT+B table per organ = AS + CT + B sets + citation evidence + ontology mappings

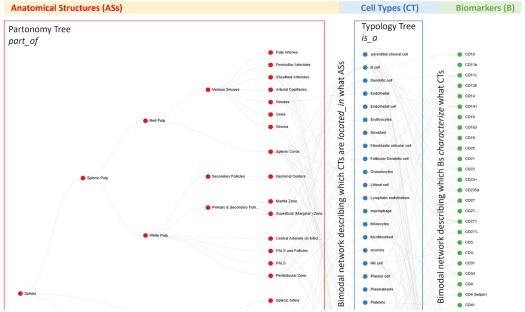
Subject matter Experts (SMEs)

ASCT+B table per organ

Structure/Region	Substructure/Sub region	Cell Type	Subset of Marker Genes
Renal	Bowman's Capsule	Parietal epithelial cell	*CRB2*, CLDN1**
Corpuscle	Glomerulus	Podocyte	*NPHS2*, PODXL*, NPHS1**
		Capillary Endothelial Cell	*EHD3*, EMCN*, HECW2*, FLT1*, AQP1**
		Mesangial Cell	*POSTN*, PIEZO2*, ROBO1*, ITGA8**

Partial ASCT Table from
- El-Achkar et al. A Multimodal and Integrated Approach to Interrogate Human Kidney Biopsies with Rigor and Reproducibility: The Kidney Precision Medicine Project. bioRxiv. 2019; 828665. doi:10.1101/828665

ASCT+B table vis (ASCT+B Reporter)



ASCT+B tables capture:

- organ name,
- anatomical structures,
- cell types,
- biomarker sets that uniquely define cell types (differentially expressed genes, proteins, proteoforms, lipids, metabolites)
- Citations providing evidence for relationships

Ontologies like multi-species Uber Anatomy (Uberon) and Cell Ontology (CL) capture :

- nomenclature,
- synonyms,
- relationships between entities,
- Descriptions of the entities
- provenance for knowledge,
- **assigns unique ID for this unit of knowledge to unite information**

Ontologies do NOT have everything we need yet to map every AS+CT+B sets:

The ASCT+B WG facilitates bringing SMEs together with ontology experts to capture new knowledge.
This knowledge is directly used in our Tissue Registration and our Data Exploration user interfaces.

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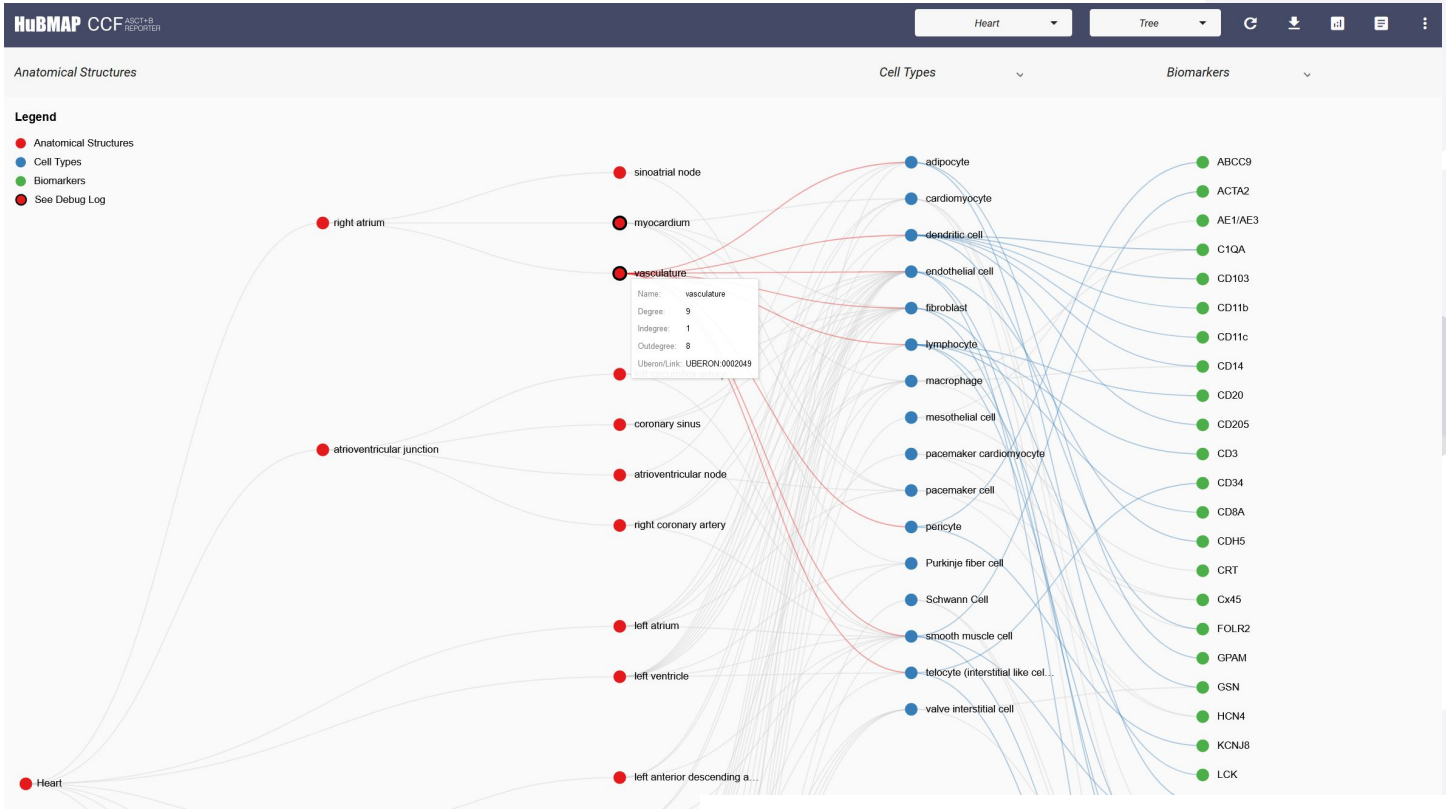
ASCT+B Reporter Vis of ASCT+B tables



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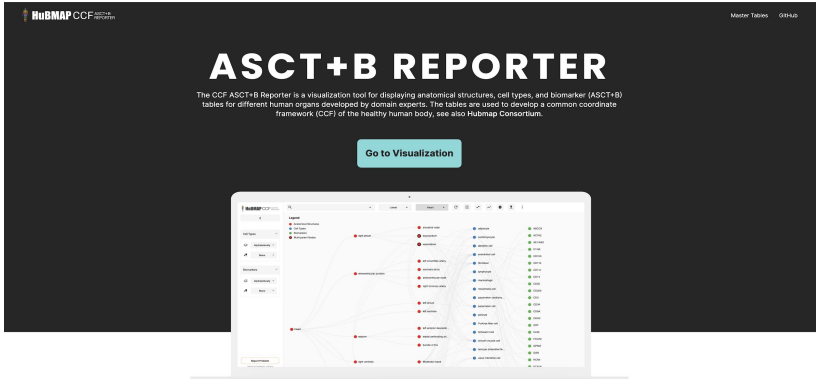
https://hubmapconsortium.github.io/ccf-asct-reporter

ASCT+B Reporter Visualization



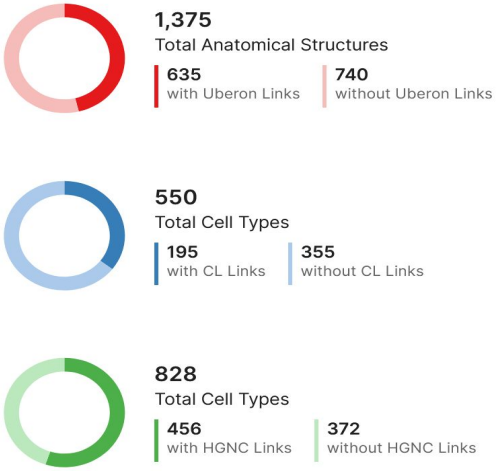
- Metrics for ASCT+B tables can be found using the downloadable reports feature
- We are adding report types that researchers may find helpful for different applications
- This information has been useful for another working group for developing organ mapping antibody panels (OMAPs)

Anatomical structures	1375
Cell types	550
Biomarkers	828

ENTITY LINKS

Anatomical Structures part_of AS links	1791
Cell Types located_in AS links	2836
Biomarker characterizes CT links	1367

ONTOLOGY LINKS



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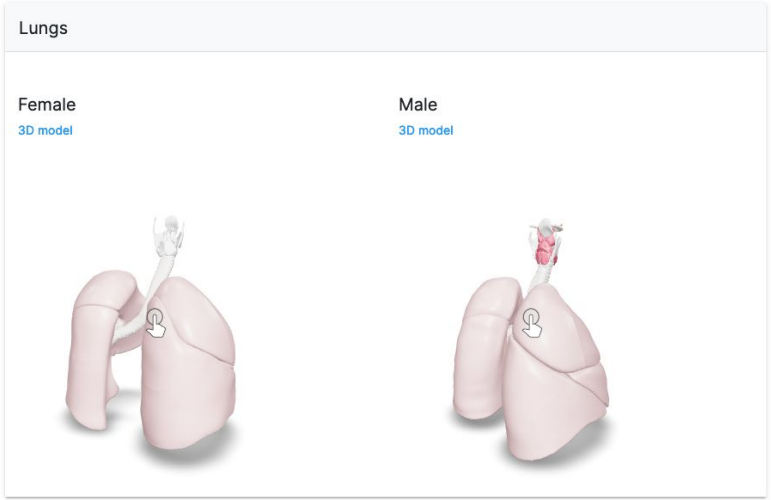
3D reference models

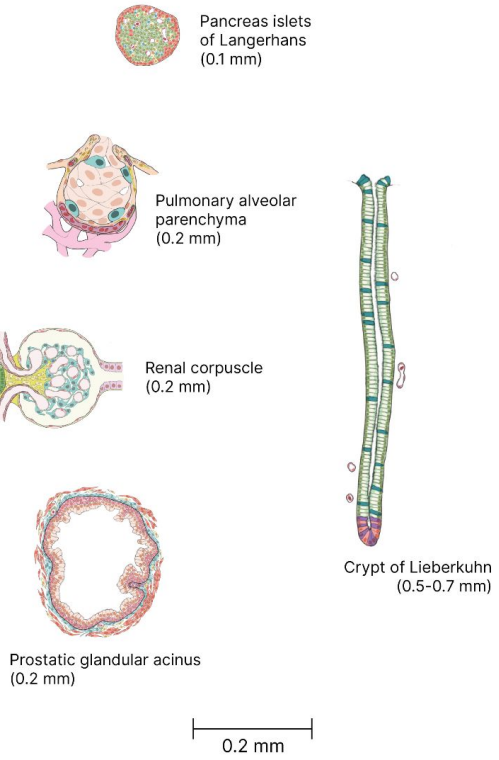


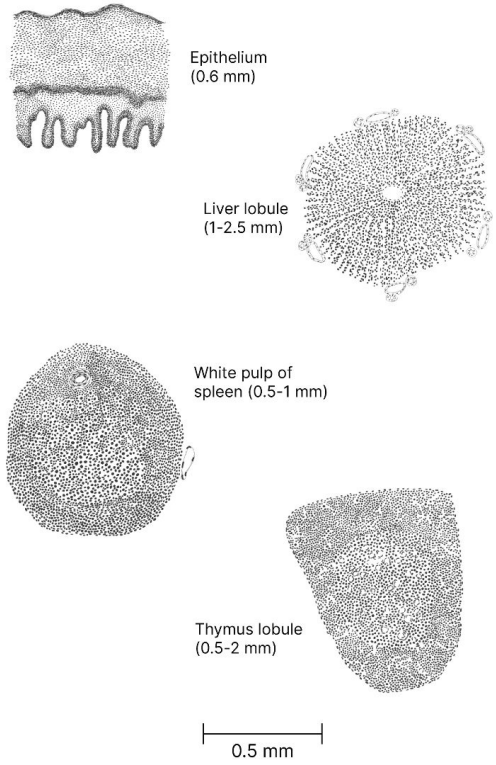
- Custom built by our medical illustrator (current Heidi Schlehlein; former: Kristen Brown, NIAID) using Visible Human Project Male and Female data based on Subject Matter Expert input
- Support the Tissue Registration (RUI) and Exploration User Interfaces
- Anatomical structures are labeled with ontology IDs which are used by the RUI during collision detection that brings the ontology labels with the registered block coordinates when tissue blocks are registered
- 3D reference models and ontology labels are also used for Dataset exploration in EUI.

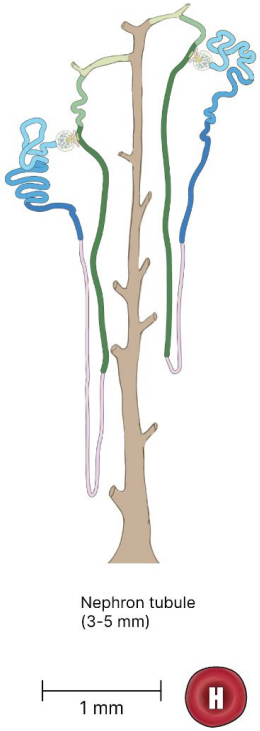
https://hubmapconsortium.github.io/ccf/pages/ccf-3d-reference-library.html

SenNet

NEW: 2D functional tissue unit (FTU) illustrations







- Custom built by our medical illustrator Rachel Bajema based on Subject Matter Expert input through ASCT+B table knowledge capture
- Support Dataset exploration in EUI at microanatomical levels.
- These will have clickable cell types and structures for cell type exploration

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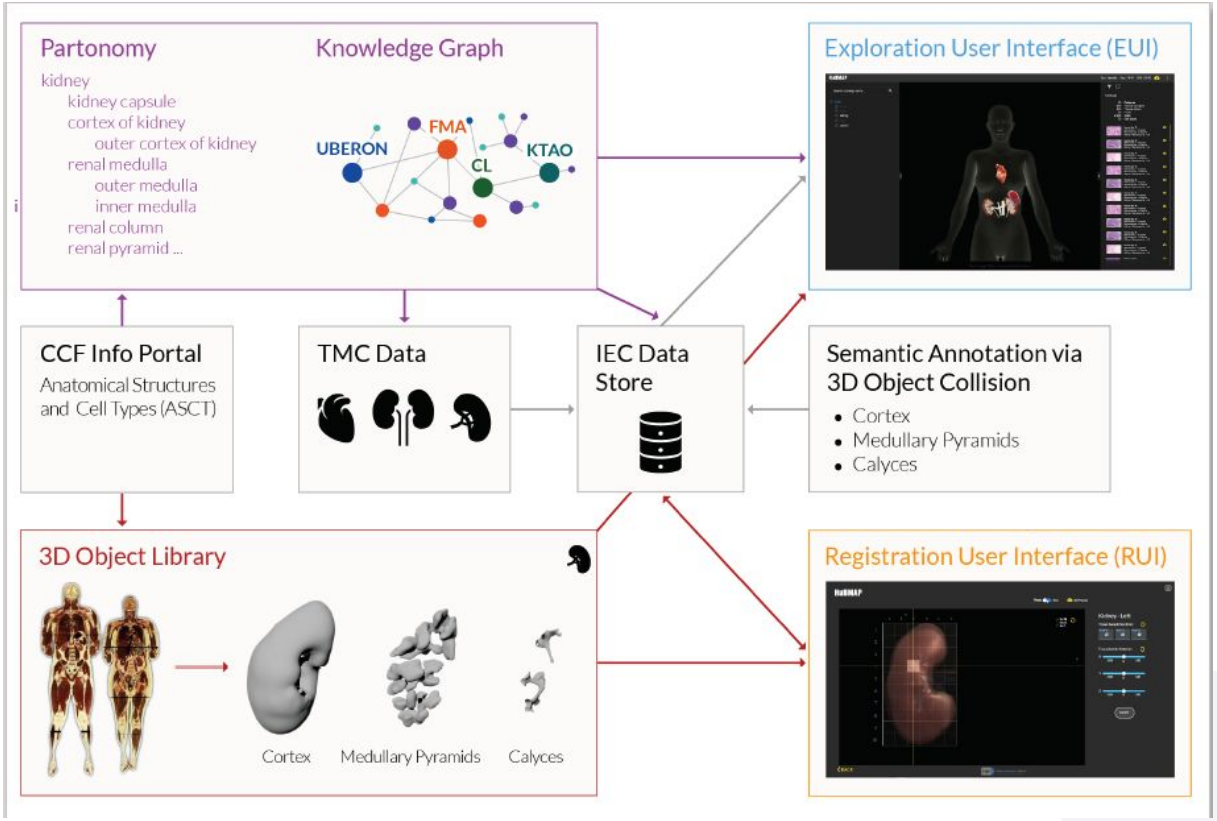
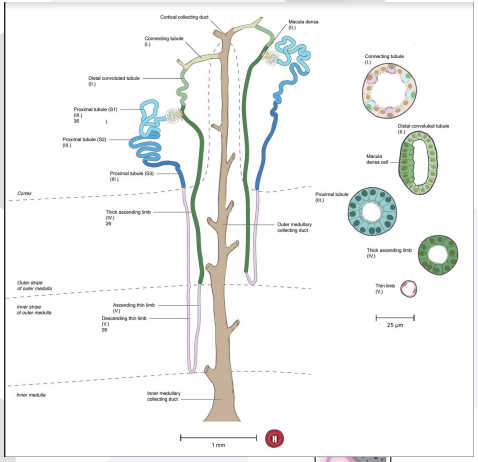
Workflow: CCF Registration to CCF Exploration



Clickable FTU illustrations for exploring microanatomy and cell types



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Where do I start? Relevant SOPs and Videos

- SOP: Authoring ASCT+B Tables (Updated: February 1, 2022) https://zenodo.org/record/5944386#.YfnrsPnMJaQ
- ASCT+B Reporter Visualization Tool https://hubmapconsortium.github.io/ccf-asct-reporter/
- SOP:3D Reference Object Approval (Updated: February 1, 2022) https://zenodo.org/record/5944197#.YfntS_IKhaQ
- SOP: Construction of Organ Mapping Antibody Panels for Multiplexed Antibody-Based Imaging of Human Tissues https://doi.org/10.5281/zenodo.5749883 (with Affinity Reagents WG)
- Visible Human Massive Open Online Course (VHMOOC): https://expand.iu.edu/browse/sice/cns/courses/hubmap-visible-human-mooc

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Ways you can help

Use your cell phone camera or a QR code reader to go directly to these website urls
Questions: email infoccf@indiana.edu

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