#### **NAVBO Webinar**

Mapping Knowledge about Human Vasculature Across Body Scales Aug 31, 2021

## From Mapping the Vasculome to Mapping the Human Body. And Back!

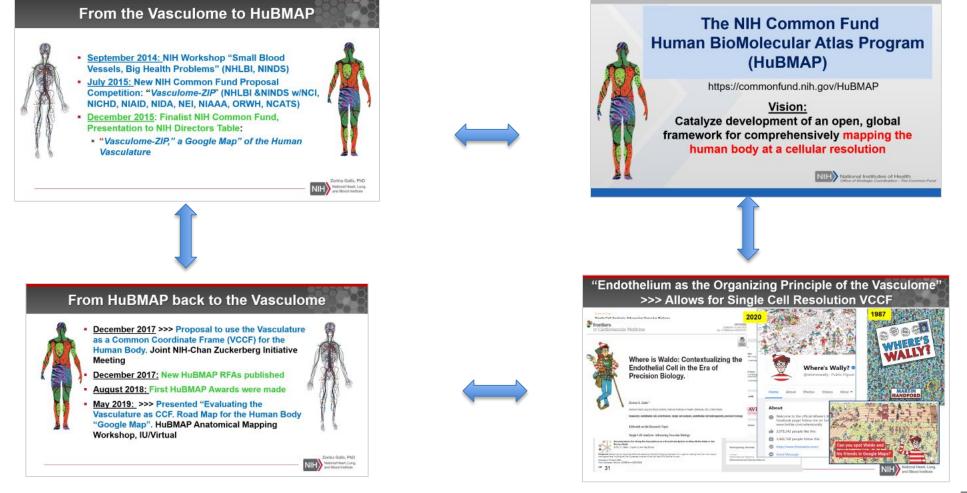
#### Zorina Galis, PhD Chief, Vascular and Hypertension Branch NIH / NHLBI

Note: The opinions presented do not necessarily represent the NIH/NHLBI opinions.



Zorina Galis, PhD National Heart, Lung, and Blood Institute

### **Main Points**





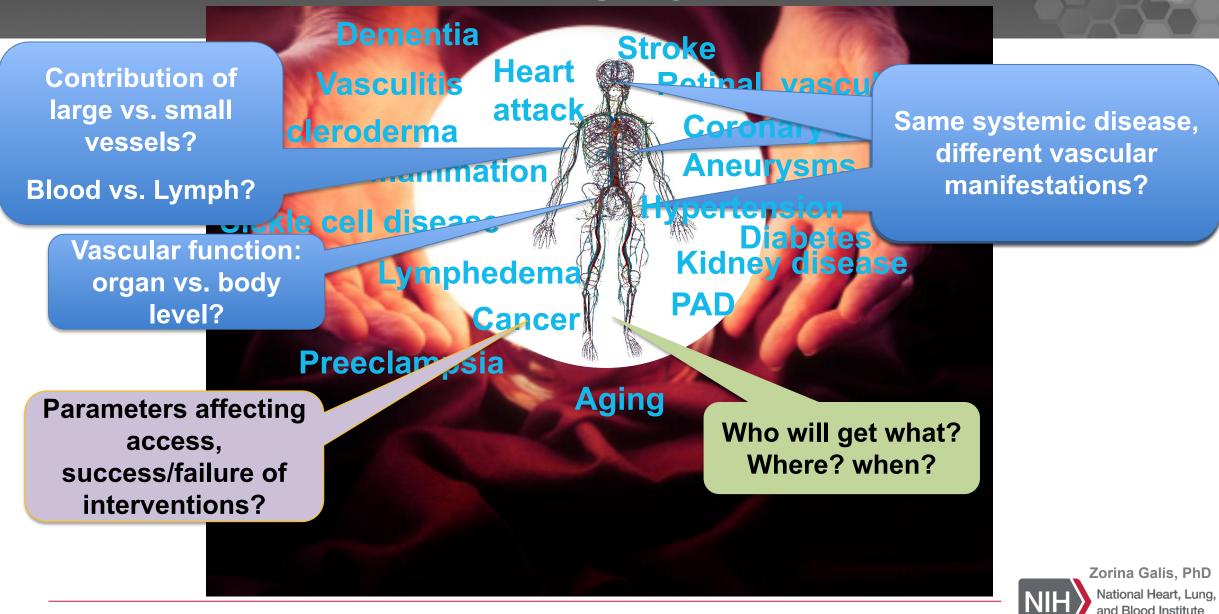
## From the Vasculome to HuBMAP

- <u>September 2014:</u> NIH Workshop "Small Blood Vessels, Big Health Problems" (NHLBI, NINDS)
- July 2015: New NIH Common Fund Proposal Competition: "Vasculome-ZIP" (NHLBI &NINDS w/NCI, NICHD, NIAID, NIDA, NEI, NIAAA, ORWH, NCATS)
- <u>December 2015</u>: Finalist NIH Common Fund, Presentation to NIH Directors Table:
  - "Vasculome-ZIP," a Google Map" of the Human Vasculature

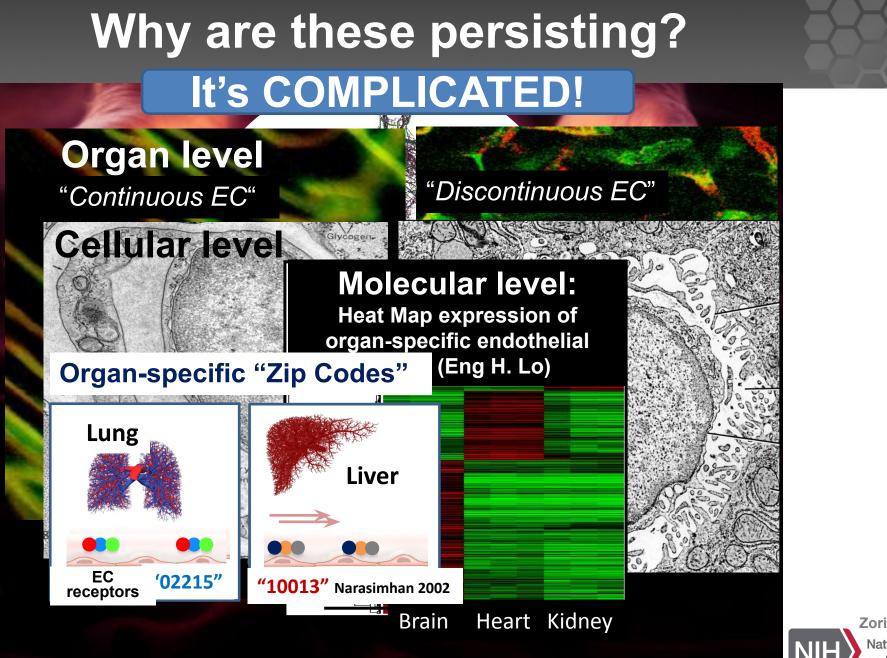




### Enduring Mysteries...

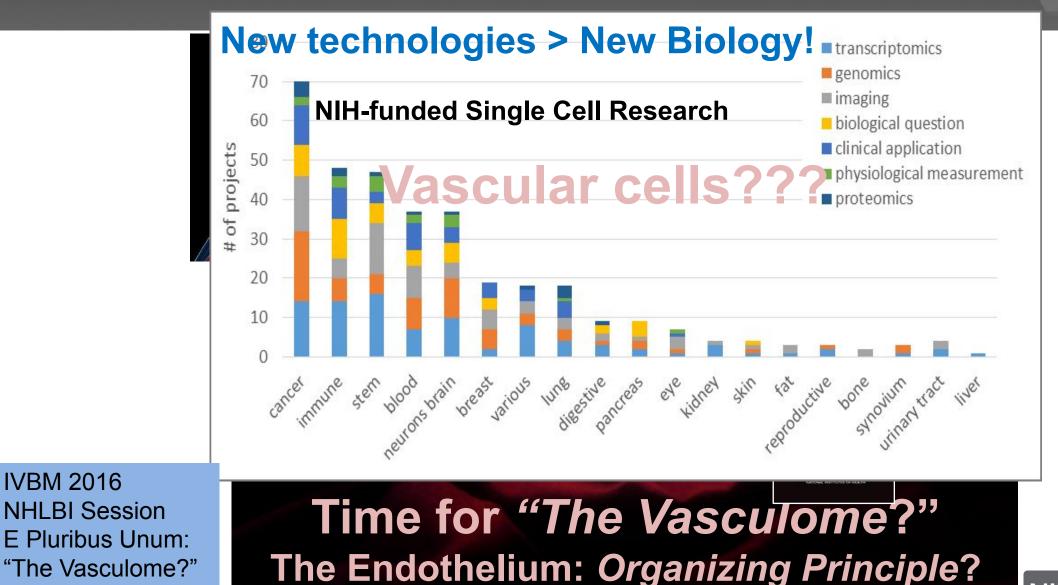


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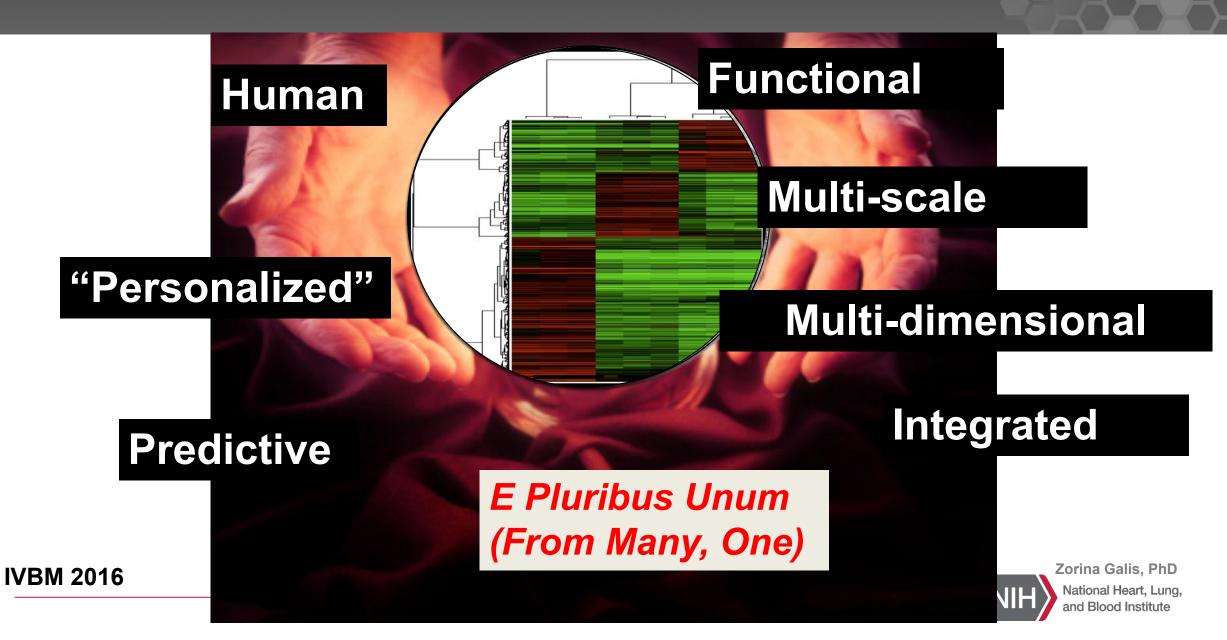
#### **Current Solution For Understanding Vascular Complexity?**



**IVBM 2016** 

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#### "The Vasculome"...



#### "Vasculome ZIP" (V-ZIP) NIH Common Fund Proposals Final Audition, December 14, 2015 NHLBI & NINDS W/NCI, NICHD, NIAID, NIDA, NEI, NIAAA, ORWH, NCATS

Whole body/organ analysis





# From the Vasculome to HuBMAP

#### >>> Approved December 2015... as Google map for the entire Human Body!

- Single Cell Analysis Program (SCAP) 2.0 (NIBIB&NIMH w/NIAID, NCI, NIGMS, NIDDK)
- January 2016: New Common Fund "Concept" Presented at the NIH Council of Councils (NHLBI, NIBIB, NIDDK): The Human Biomolecular Atlas Program (HuBMAP)
- September 2016: NIH Council of Councils Approves New "HuBMAP" Common Fund
- October 2106: IVBM 2016: E Pluribus Unum: "The Vasculome?"
- December 2017: New HuBMAP RFAs published
- <u>August 2018:</u> First HuBMAP Awards
- August 2020: First Data Release!
- To be continued...

#### https://commonfund.nih.gov/hubmap



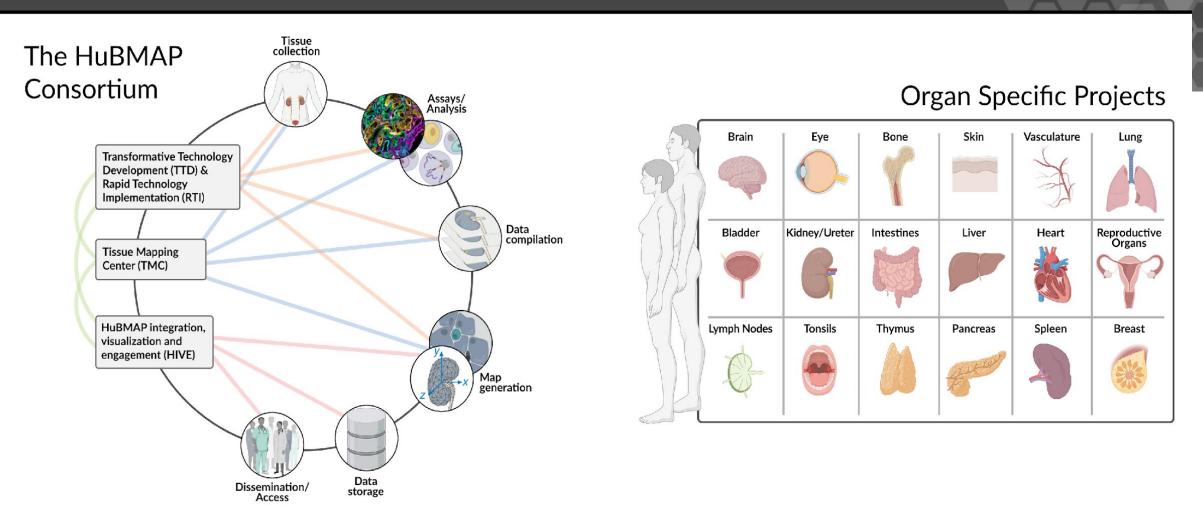
# The NIH Common Fund Human BioMolecular Atlas Program (HuBMAP)

https://commonfund.nih.gov/HuBMAP

### Vision:

Catalyze development of an open, global framework for comprehensively mapping the human body at a cellular resolution





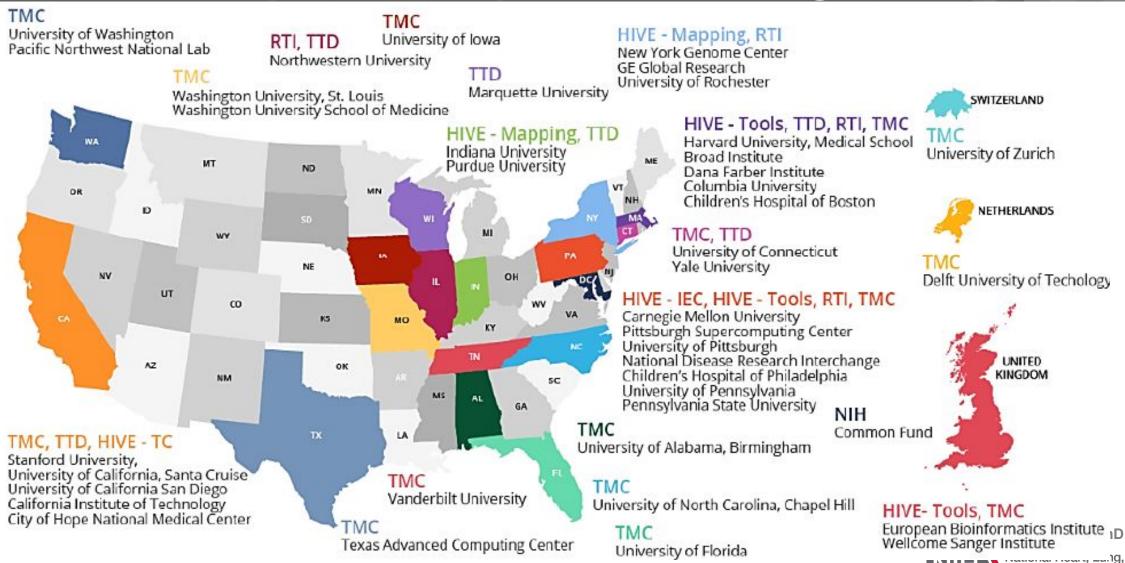
The Human Body at Cellular Resolution: The NIH Human Biomolecular Atlas Program.

Snyder et al. 2019, *Nature* 574, 187-192.

https://hubmapconsortium.org/



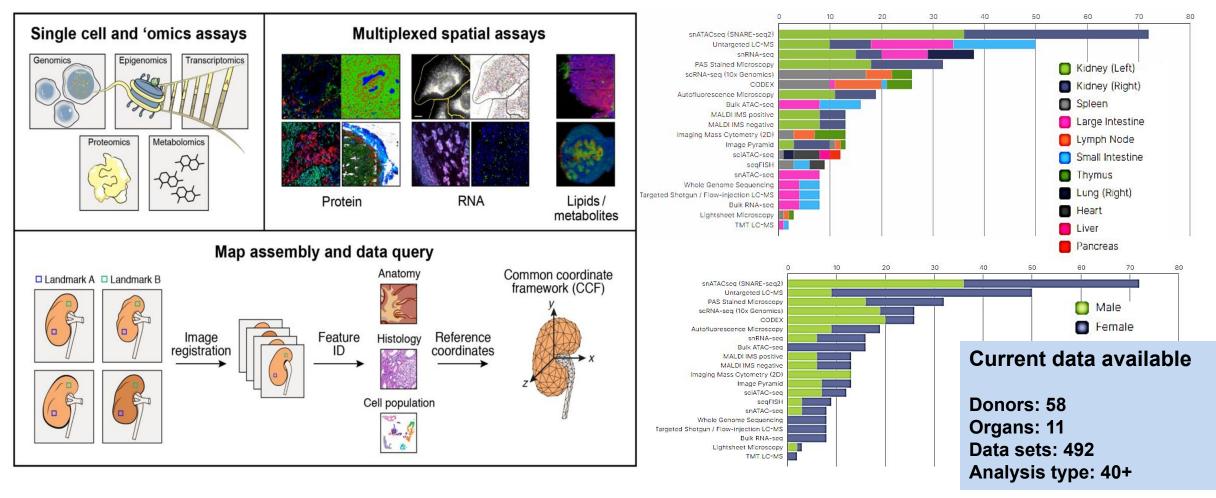
### HuBMAP Consortium Contributing Sites https://hubmapconsortium.org/



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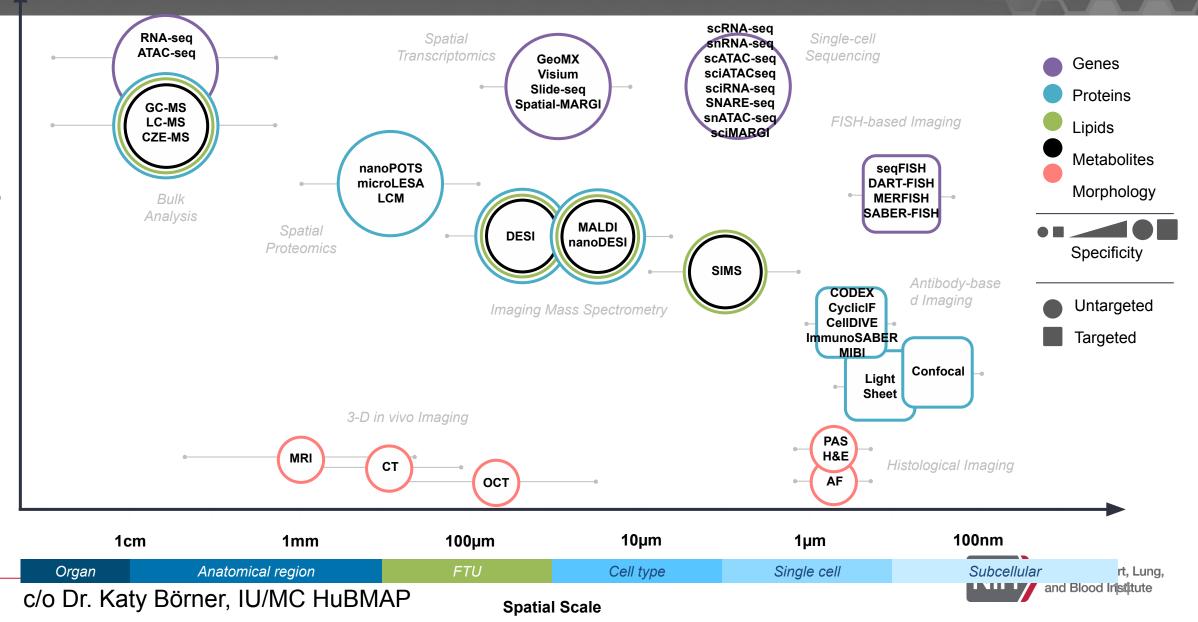
#### HuBMAP: Richness of open-access data sets and analysis tools





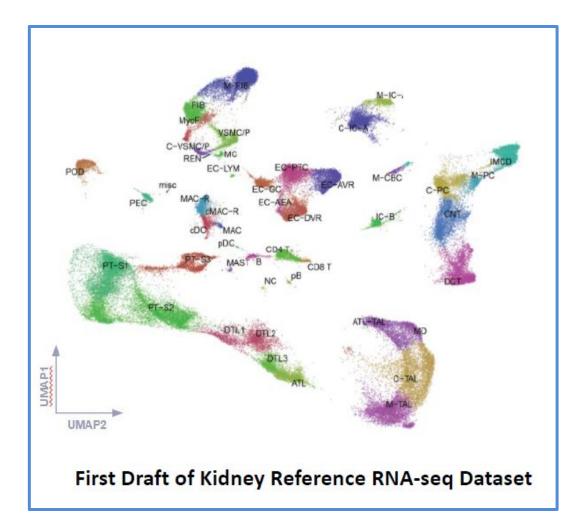
National Heart, Lung, and Blood Institute

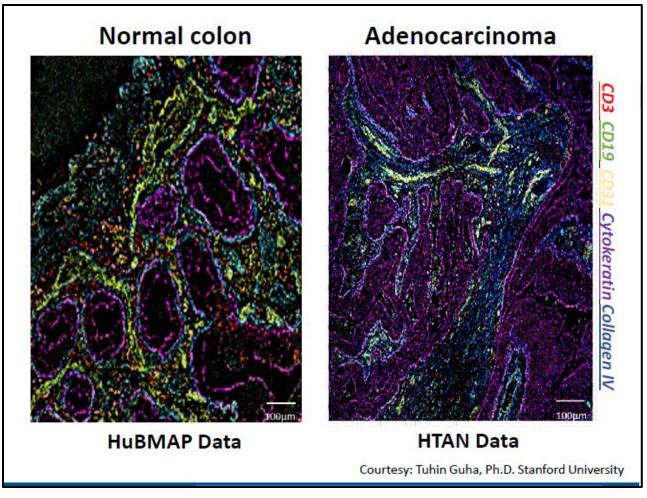
#### **Coverage of HuBMAP Analyses by Target and Scale**



**Molecular Coverage** 

### HuBMAP Provides a normal reference for human tissues





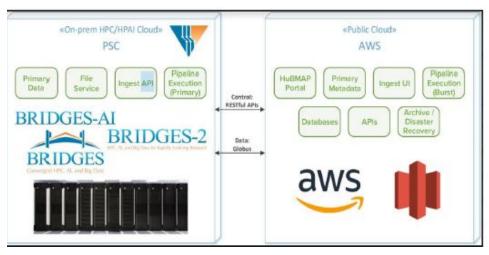


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# HuBMAP also provides a platform for management of internal and external data

#### **Internal and External Coordination**

#### PLATFORM FOR DATA MANAGEMENT



First data release (2020): over 23 TB data, 450 data sets, over 90 coders, etc.





### HuBMAP Provides Tools

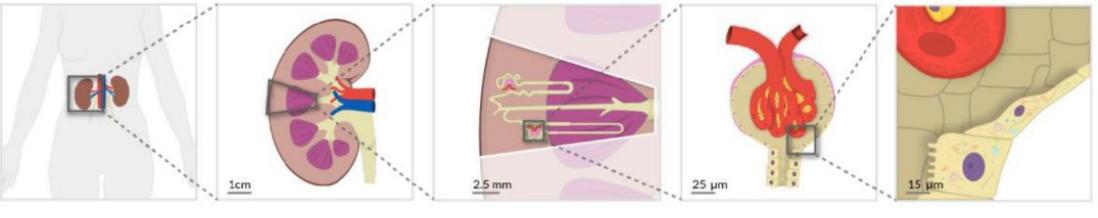
- Visualization, Search, Modeling
- Tissue Atlassing >>> Knowledge Management
  - Registration and Exploration User interface
  - Semantic Ontology: Common Coordinate Frame (CCF), Anatomical Structure Cell Type +Biomarker (ASCT+B) Tables
  - Reference tools



### Semantic Representation of a Kidney

Börner et al https://arxiv.org/ftp/arxiv/papers/2007/2007.14474.pdf

The Semantic Ontology divides the body into a set of nested named anatomical structures and cell types, from larger (left) to smaller (right) objects.



#### Body

- Body
- Kidney (Left, Right)
- Aorta
- Renal artery
- Renal vein
- Ureter

#### Organ

- Renal capsule
- Renal pyramid
- Renal cortex
- Renal medulla
- Renal calyx
- Renal pelvis

#### Functional Tissue Unit

- Nephron
- Renal corpuscle
- Proximal convoluted tubule
- Loop of Henle
- Distal convoluted tubule
- Connecting tubule
- Collecting duct

#### FTU Sub-structure(s) Cellular

- Bowman's capsule
- Glomerulus
- Efferent arteriole
- Afferent arteriole
- Parietal epithelial cell
  - Capillary
    - endothelial cell
  - Mesangial cell
  - Podocyte

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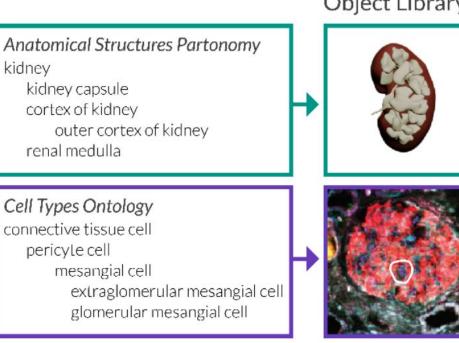
### **ASCT+B** Tables

Construction begins with domain experts manually developing ASCT+B tables, which indicate the most important anatomical structures (AS) and cell types (CT), organize them into a hierarchy, and map them to the 3D Reference Object Library.

Ontology

#### ASCT Table

Structure/Region	Sub structure/Sub region	Cell Type	
Renal Corpuscle	Bowman's (glomular) Capsule/parietal layer	Parietal epithelial Cell	
	Bowman's (glomular) Capsule/visceral layer	Podocyte	
	Glomerular Tuft	Capillary Endothelial Cell	
		Mesangial Cell	
Tubules	Proximal Tubule	Proximal Tubule Epithelial Cell (general)	
		Proximal Convoluted Tubule Epithelial Cell Segment 1	
		Proximal Tubule Epithelial Cell Segment 2	
		Proximal Tubule Epithelial Cell Segment 2	
	Loop of Henle, Thin Limb	Descending Thin Limb Cell (general)	
		Ascending Thin Limb Cell (general)	
	Loop of Henle, Thick Limb	Thick Ascending Limb Cell (general)	
		Cortex-TAL Cell	
		Medulla-TAL Cell	
		TAL-Macula Densa Cell	
	Distal Convolution	Distal Convoluted Tubule Cell (general)	
		DCT Type 1 Cell	
		DCT Type 2 Cell	
	Connecting Tubule	Connecting Tubule Cell (general)	
		CNT-Principal Cell	



3D Reference Object Library

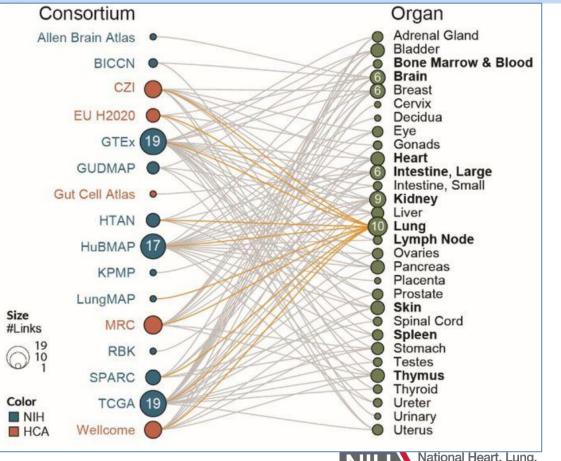
t, Lung,

c/o Dr. Katy Börner, IU/MC HuBMAP

### Human Anatomical Structures, Cell Types, and Biomarkers (ASCT+B) Tables



Work of 16 international consortia to construct human ASCT+B tables and three-dimensional reference organs in support of a Human Reference Atlas



and Blood Institute

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

#### New Results

#### Anatomical Structures, Cell Types, and Biomarkers Tables Plus 3D Reference Organs in Support of a Human Reference Atlas

<sup>(b)</sup> Katy Börner, <sup>(b)</sup> Sarah A. Teichmann, <sup>(b)</sup> Ellen M. Quardokus, <sup>(b)</sup> James Gee, <sup>(b)</sup> Kristen Browne,
<sup>(b)</sup> David Osumi-Sutherland, <sup>(b)</sup> Bruce W. Herr II, <sup>(b)</sup> Andreas Bueckle, <sup>(b)</sup> Hrishikesh Paul, <sup>(b)</sup> Muzlifah A. Haniffa,
<sup>(b)</sup> Laura Jardine, <sup>(b)</sup> Amy Bernard, <sup>(b)</sup> Song-Lin Ding, <sup>(b)</sup> Jeremy A. Miller, Shin Lin, <sup>(b)</sup> Marc Halushka,
<sup>(b)</sup> Avinash Boppana, <sup>(b)</sup> Teri A. Longacre, <sup>(b)</sup> John Hickey, <sup>(b)</sup> Yiing Lin, <sup>(b)</sup> M.Todd Valerius, <sup>(b)</sup> Yongqun He,
<sup>(b)</sup> Gloria Pryhuber, <sup>(b)</sup> Xin Sun, <sup>(b)</sup> Marda Jorgensen, <sup>(b)</sup> Andrea J. Radtke, <sup>(b)</sup> Clive Wasserfall, <sup>(b)</sup> Fiona Ginty,
<sup>(b)</sup> Johnan Ho, <sup>(b)</sup> Joel Sunshine, <sup>(b)</sup> Rebecca T. Beuschel, <sup>(b)</sup> Maigan Brusko, <sup>(b)</sup> Sujin Lee, <sup>(b)</sup> Rajeev Malhotra,
<sup>(b)</sup> Sanjay Jain, <sup>(b)</sup> Griffin Weber

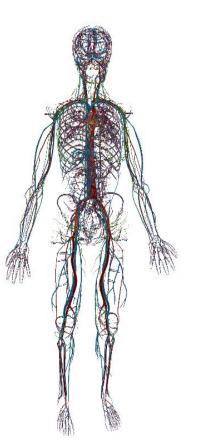
doi: https://doi.org/10.1101/2021.05.31.446440

#### https://www.biorxiv.org/content/10.1101/2021.05.31.446440v2.full

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

## From HuBMAP back to the Vasculome

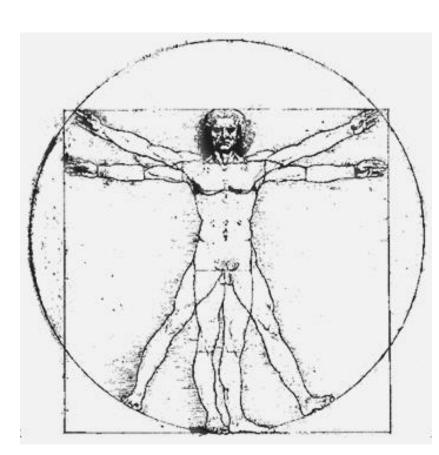
- <u>December 2017</u> >>> Proposal to use the Vasculature as a Common Coordinate Frame (VCCF) for the Human Body. Joint NIH-Chan Zuckerberg Initiative Meeting
- December 2017: New HuBMAP RFAs published
- August 2018: First HuBMAP Awards were made
- <u>May 2019</u>: >>> Presented "Evaluating the Vasculature as CCF. Road Map for the Human Body "Google Map". HuBMAP Anatomical Mapping Workshop, IU/Virtual





### Major challenge for mapping the human body: Finding a Common Coordinates Frame (CCF)

Joint NIH-Chan Zuckerberg Initiative Meeting (Dec 2017)

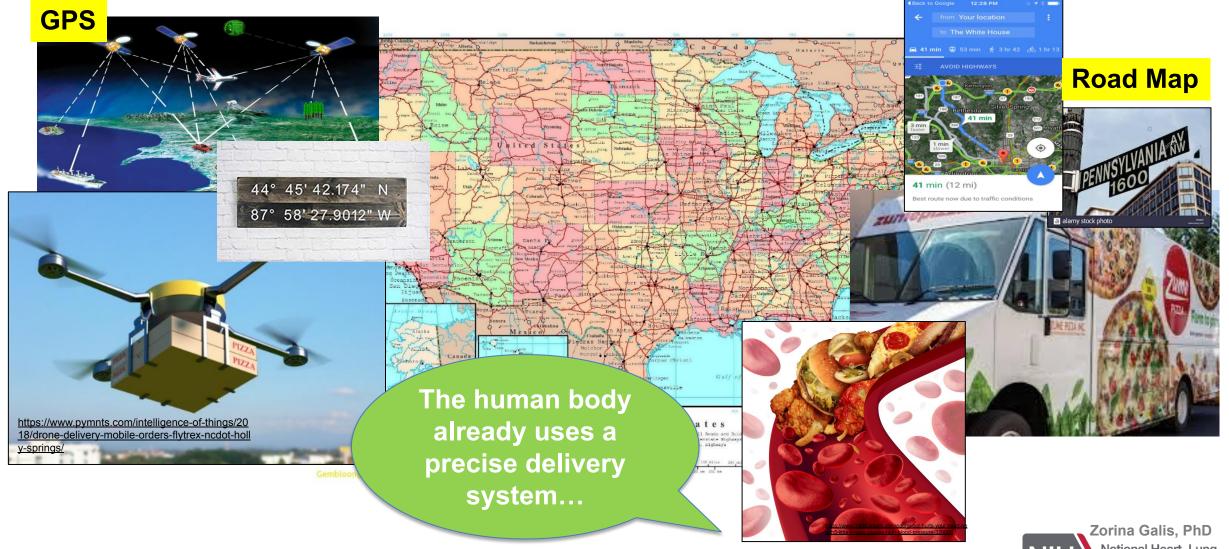


Desirable Features for a Body CCF ? (The "needs assessment")

- 1. Works across several scales: cell <> tissue/organ <> whole body
- 2. Applicable to all (most) body tissues
- 3. Accounts for donor differences (e.g., size, shape, sex)
- 4. Useful/Acceptable across various specialty domains



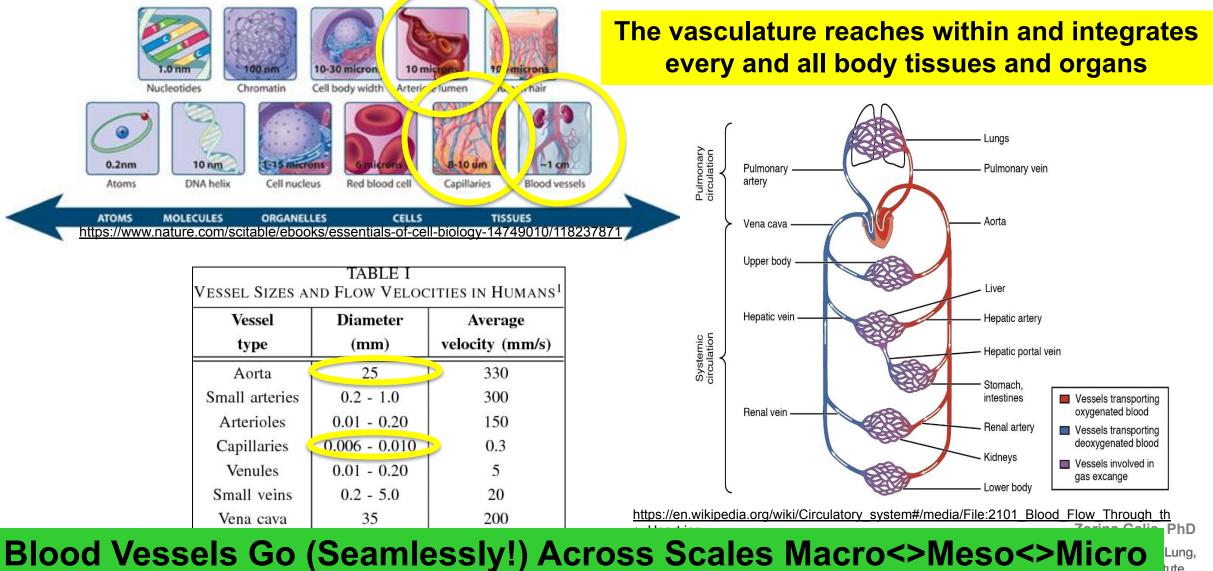
### Many Ways to Identify and Reach a Specific Location....





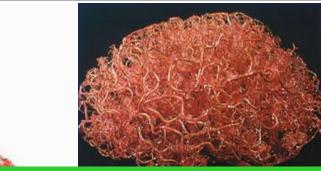


#### CCF Desirable # 1: "Works across several scales (cell <> tissue <> whole body)"



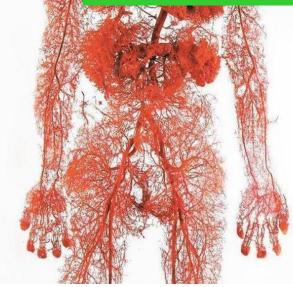
tute

### CCF Desirable #2: "Applicable to all (most) body tissues"



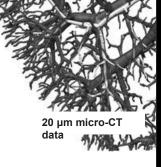


#### The Vasculature is "Framing" the Organ/Tissue Architecture Across Scales

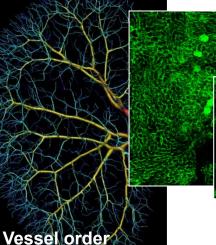


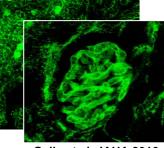
https://www.pinterest.jp/pin/522699100479032485/





Nordsletten et al, 2006 Am J Physiol



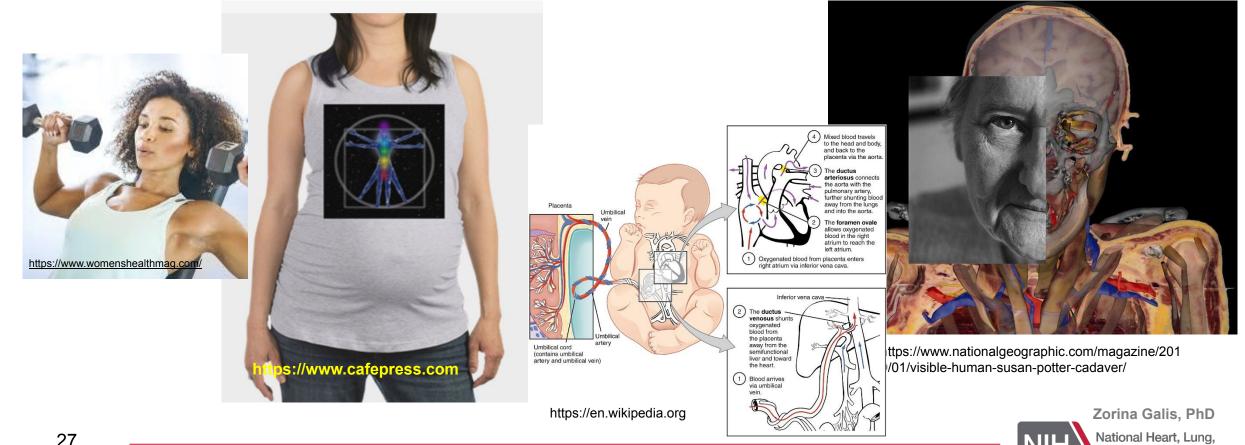


Galis et al, JAHA 2016



### CCF Desirable # 3: "Accounts for donor differences (e.g., size, shape, sex)"

Vasculature Keeps Up With Individual Body Characteristics (Size, Shape, Sex etc.) and with Changes (Development, Aging, etc.)

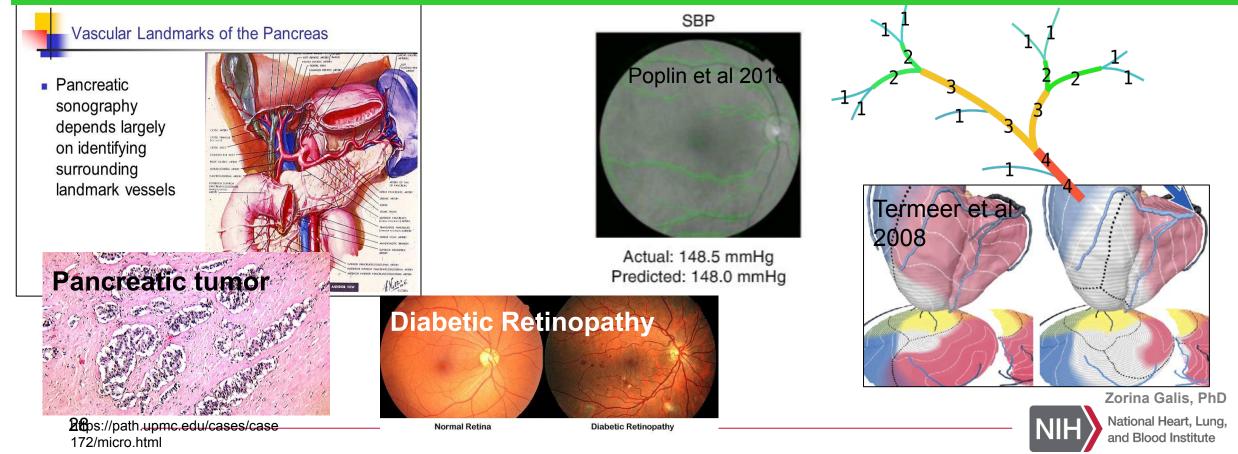


and Blood Institute

### CCF Desirable #4:

"Useful/Acceptable across specialty domains"

- Scientists, clinicians, modelers know many vessels by their own names!
- Vessels are used as body landmarks and conduits for clinical interventions (e.g. surgery planning, drug delivery) and diagnostic (biopsy, predictions, etc.)



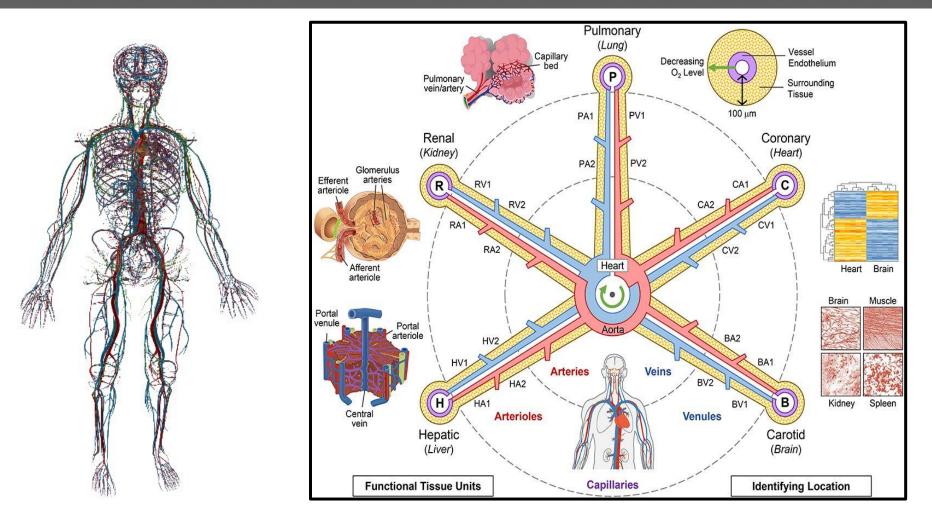


2019 HuBMAP Anatomical Mapping Workshop (IU/virtual): "Evaluating the Vasculature as Common Coordinate Frame (CCF) Road Map for the Human Body "Google Map"?

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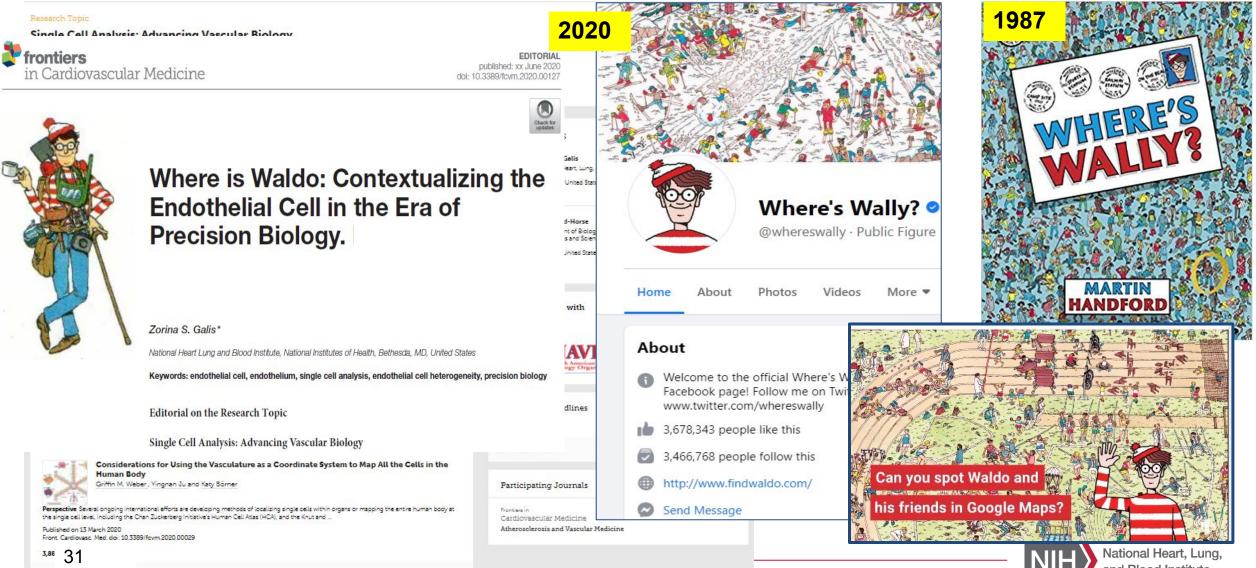


### The Hub-and-Spoke Model of a Vascular Coordinate System



Weber, Griffin M, Yingnan Ju, and Katy Börner. 2020. "Considerations for Using the Vasculature as a Coordinate System to Map Zorina Galis, PhD All the Cells in the Human Body". Frontiers in Cardiovascular Medicine 7 (29): doi: 10.3389/fcvm.2020.00029. 30

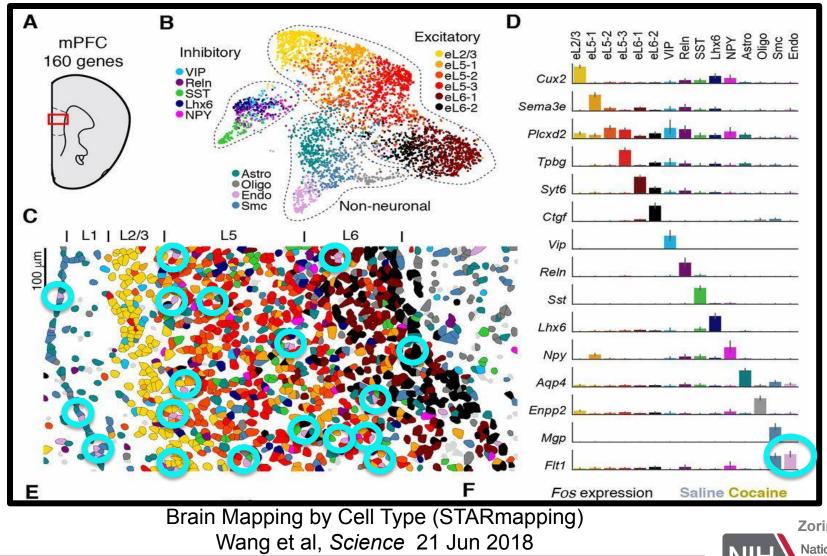
### "Endothelium as the Organizing Principle of the Vasculome" >>> Allows for Single Cell Resolution VCCF



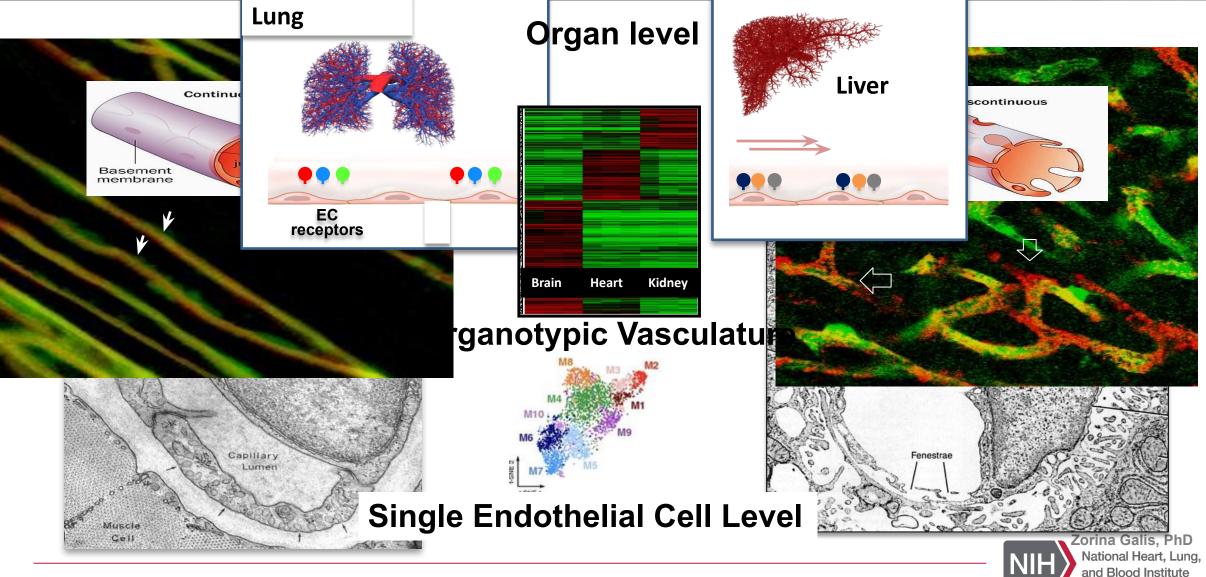
and Blood Institute

#### Like Waldo, The Endothelial Cell (EC) Is Hiding In Plain Sight Everywhere!

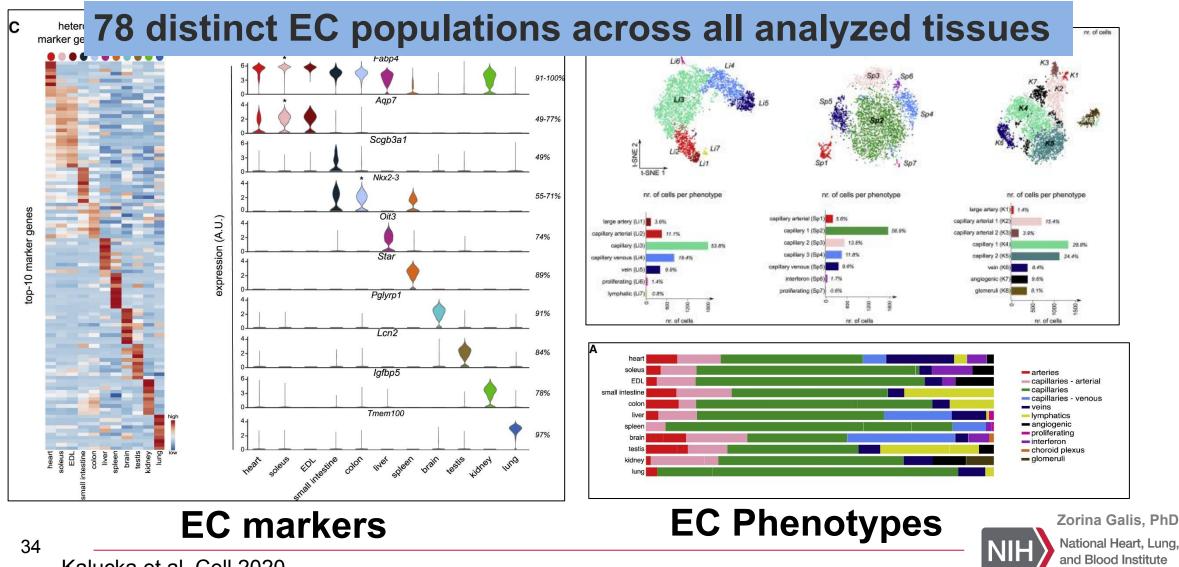




#### As Observers Have Grown Astute, Just Like Waldo, ECs Become Recognizable in Ever More Complex Scenarios



# EC Heterogeneity Across Tissues >> Vascular Bed Heterogeneity within the Organ



Kalucka et al, Cell 2020

#### EC Holds Important Contextual Information, Revealing Its Precise Context : Understanding Brain Vasculature Zonation



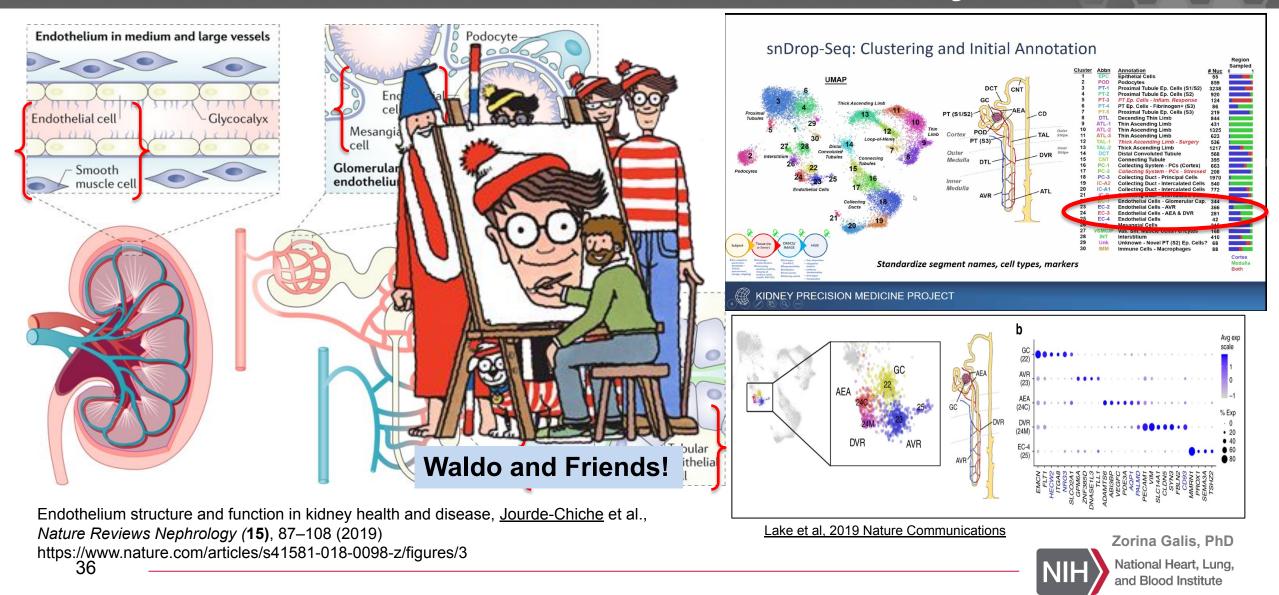
# EC can be precisely positioned along the blood vessel while walking from the arterial to venous side

(Vanlandewijck et al, Nature 2018)



Zorina Galis, PhD National Heart, Lung, and Blood Institute

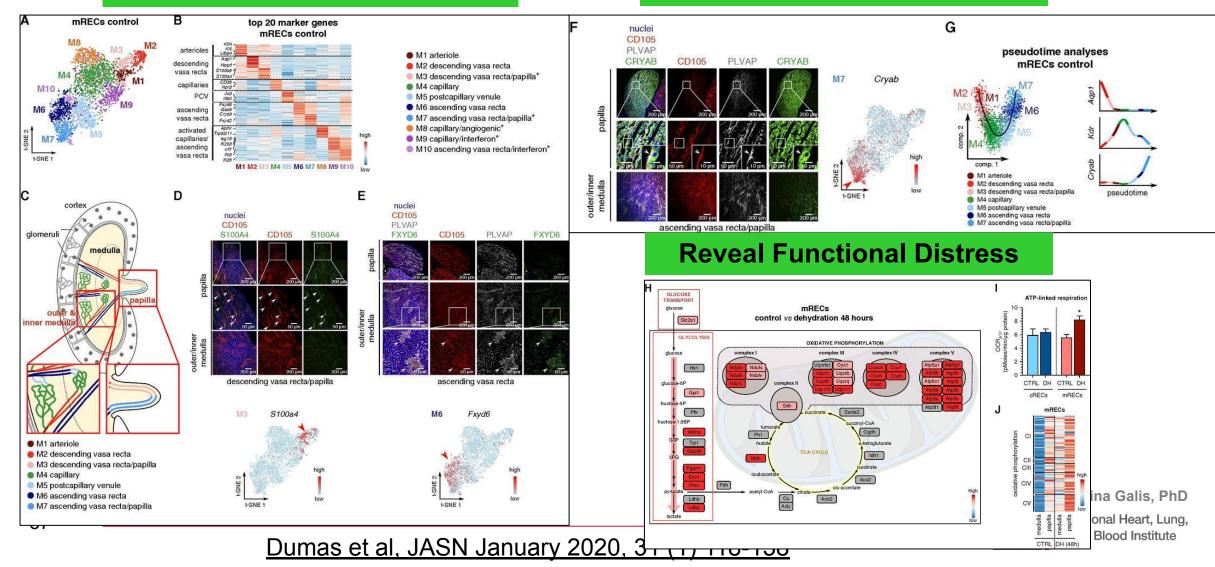
#### Diverse Endothelial Cell Populations Associate With Different Cells of The Kidney



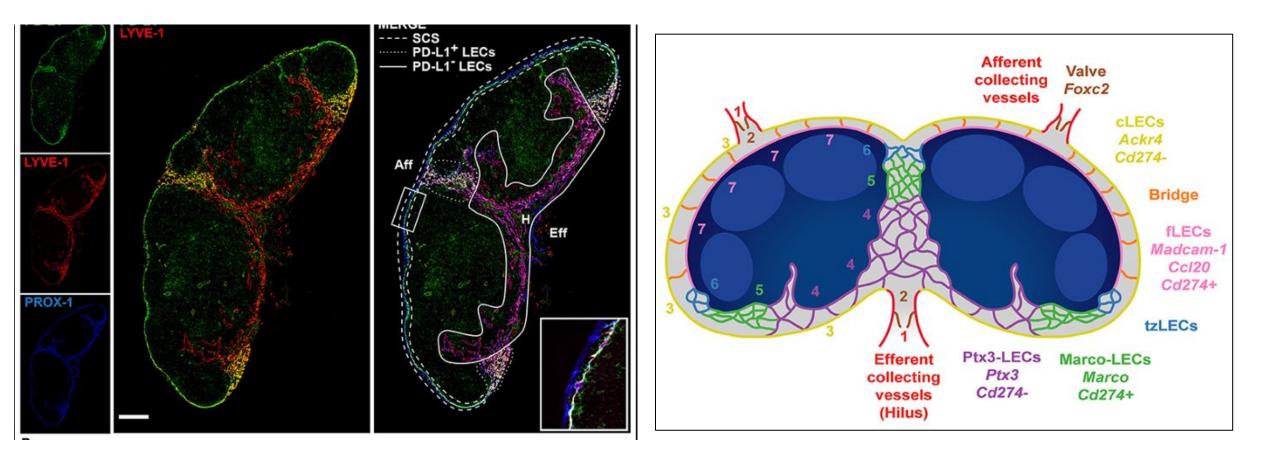
# Renal ECs Indicate Kidney Compartment-specific Gene Signatures

### **Precise Spatial Information**

### **Predict Temporal Information**



# Lymphatic ECs Help Map Lymph Nodes Architecture



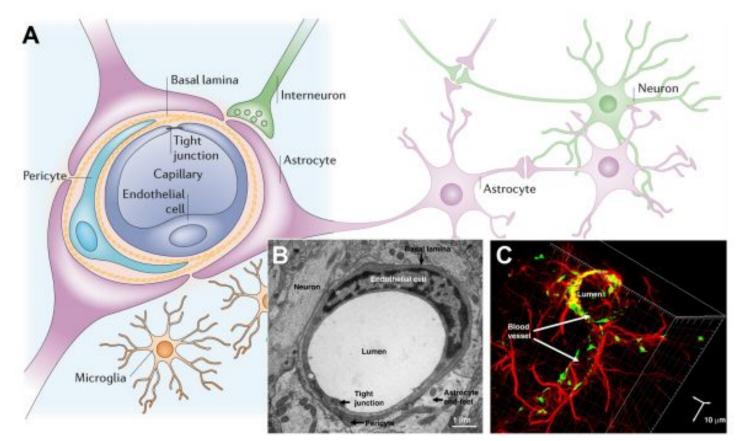
### Xiang et al, Frontiers in Cardiovascualr Medicine 2020



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# Endothelial Cells Are Central To Functional Tissue Units The Brain Neurovascular Unit

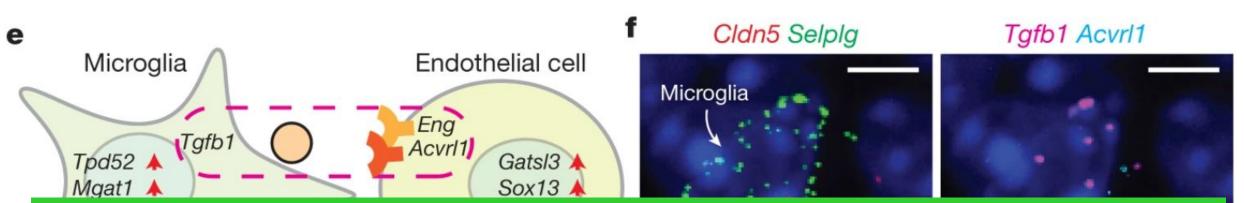
The Translational Significance of the Neurovascular Unit: A Mini-Review, McConnell et al, 2016 JCI



A single endothelial cell = blood vessel (capillary) is at the center of the neurovascular unithD



# Ears dropping on EC "intimate conversations"



### Vascular Neighborhoods:

Other individual cell types may be precisely localized based on interactions with different neighboring EC types

<u>httr</u> <u>/s4</u> >>> A GPS-Like Localization Approach Using Endothelial Cells? sequisity reveals liganu-receptor repertones in neighboring cells Zorina Galis, PhD National Heart. Lung

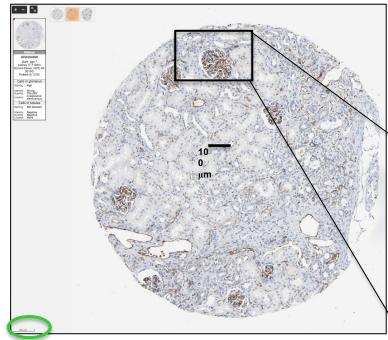




# Tissue Organization/Pattern and Vasculature (Utility of a 100 μmeter "tissue-stick"?)

100 um

Kidney Histology PECAM-1 Staining (EC, endothelial cells)



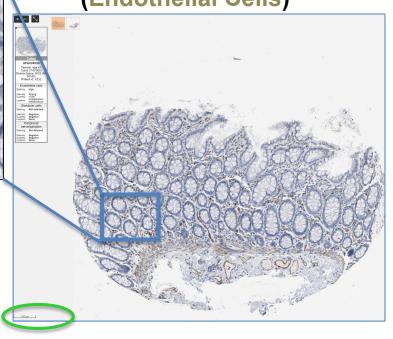
### Protein Atlas

https://www.proteinatlas.org/ENSG00000261371-PECAM1/tis sue/kidney#img Kidney

Close-up: Kidney Corpuscule (glomerulus)

100 µm

Colon Histology PECAM1 (CD31) staining (Endothelial Cells)

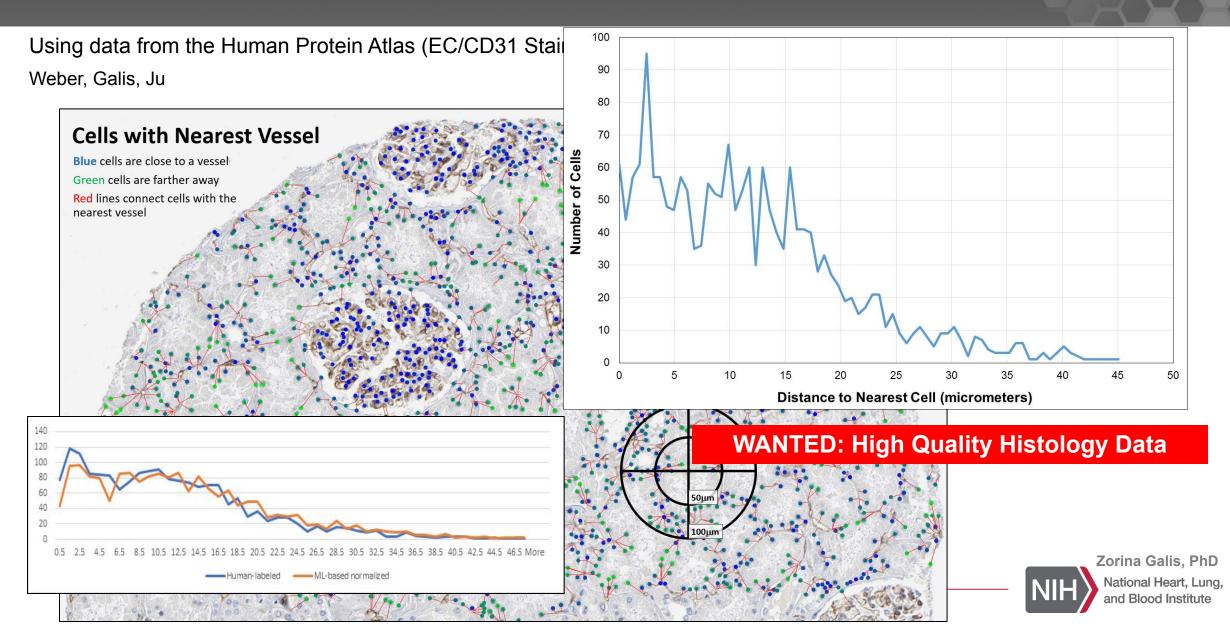


Protein Atlas https://www.proteinatlas.org/ENSG00000261371-PECA M1/tissue/colon#img

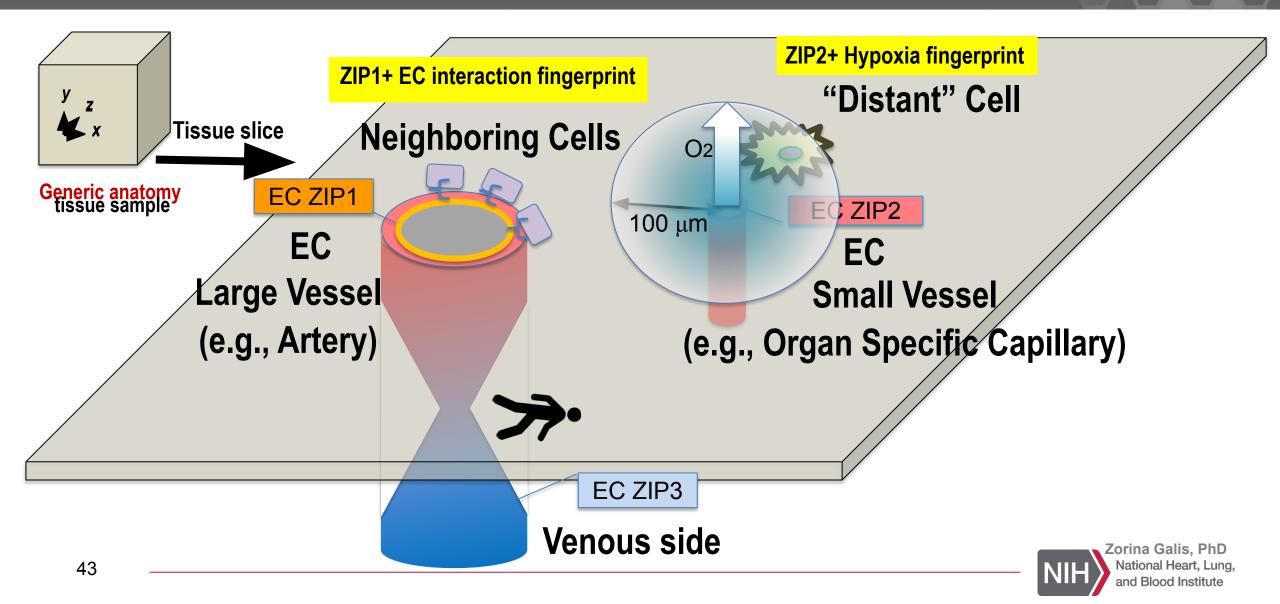


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# Distance from Closest Endothelial Cell (EC) - Kidney



### Endothelial Cell Gene Expression Can Be Used To Establish the Precise Location and Functional State of Other Cells



#### HUBMAP CCF PORTAL



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

MC-IU team within the HuBMAP HIVE

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

CCF Anatomical Structures, Cell Types and Biomarkers (ASCT+B) Tables	CCF Ontology
CCF 3D Reference Object Library	CCF ASCT+B Reporter
CCF Registration User Interface (RUI)	CCF Exploration User Interface (EUI)
Visible Human MOOC (VHMOOC)	Kaggle Competition and Awards

#### Anatomical Structures, Cell Types, plus Biomarkers (ASCT+B) table for Vasculature v1.0

#### Description

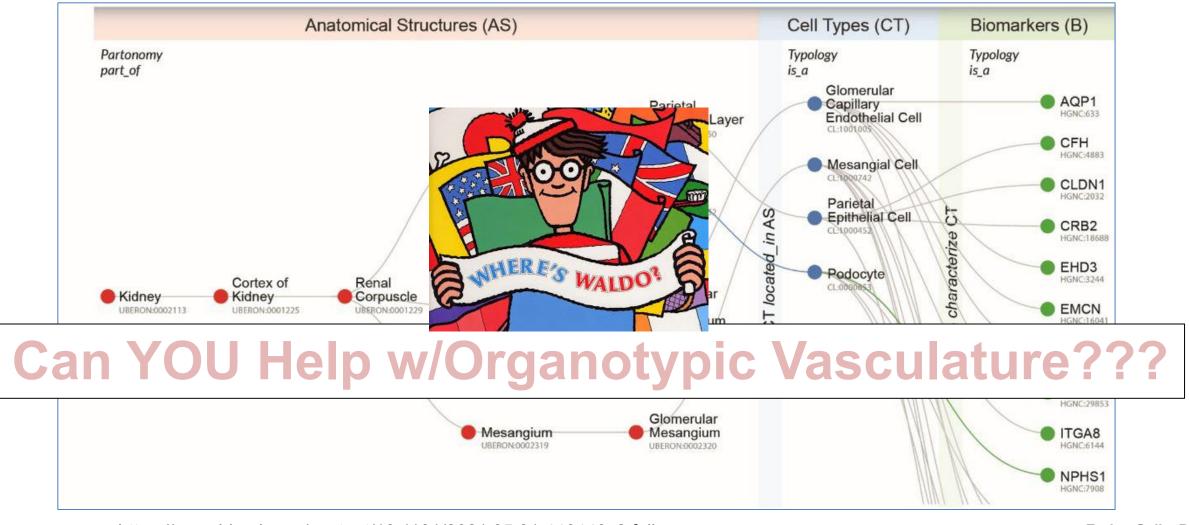
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Exis Anatomical Structures, Cell Types, plus Biomarkers (ASCT+B) tables aim to capture the nested *part\_of* structure of anatomical human body parts, the typology of cells, and biomarkers used to identify cell types. The tables are authored and reviewed by an international team of experts.

	Totals:	1,534	622	2,154	1,492	632	3,393	14,987	3,580		
scula	ature	870	2	1	1	0	869	606	2		
ymu	S	25	41	<mark>511</mark>	388	123	38	180	657		
een		46	66	255	80	145	68	172	414		
n		16	42	70	0	70	17	19	105		
mp	Funder:	National Institutes of Health									
ng	Publisher:	HuBMAP									
Ine	License:	Creative Commons Attribution 4.0 International (CC BY 4.0)									
Creation Date:	2021-03-12										
	Project Lead ORCID:	0000-0002-3321-6137									
art	Project Lead: Katy Börner										
in	Creator ORCID:	0000-0002-2597-881X; 0000-0002-6692-6880; 0000-0003-0120-4630; 0000- 0002-7112-7389; 0000-0003-0834-8274									
ne	Creator(s):	Griffin Weber; Sujin Lee; Rajeev Malhotra; Marc Halushka; Avinash Boppana									
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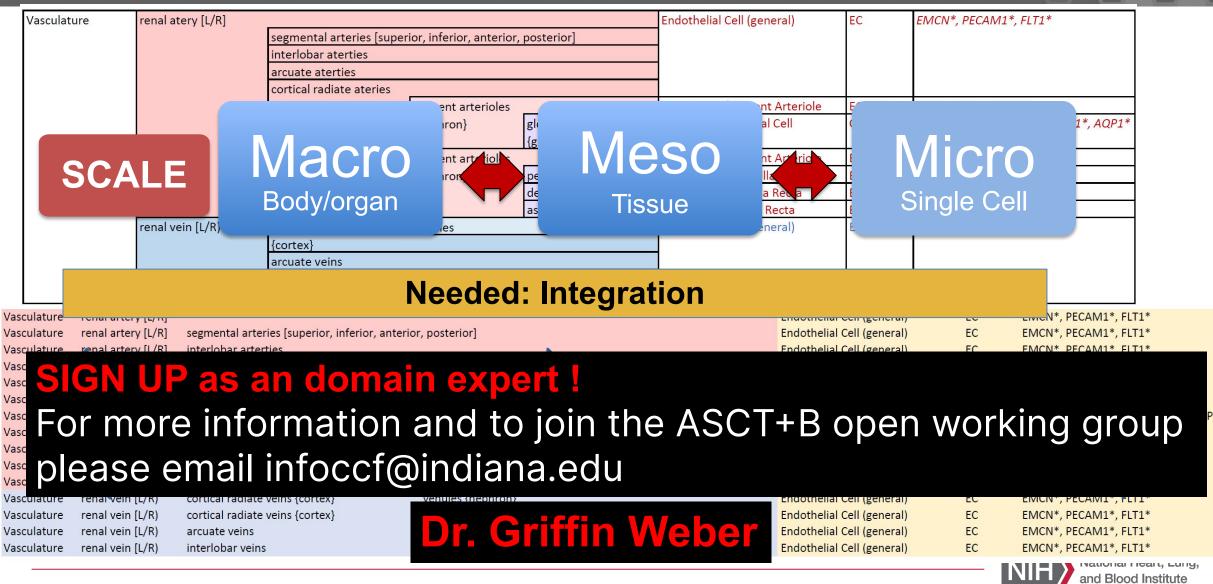
# Case Study: Kidney ASCT+B



https://www.biorxiv.org/content/10.1101/2021.05.31.446440v2.full

Zorina Galis, PhD National Heart, Lung, and Blood Institute

# Wanted: Seamless Integration of VASCULAR Anatomical Structures and Cell Types (ASCT) in ALL Organ Tables



## New HuBMAP Initiatives Approved by the NIH Council of Councils May 2019/2021

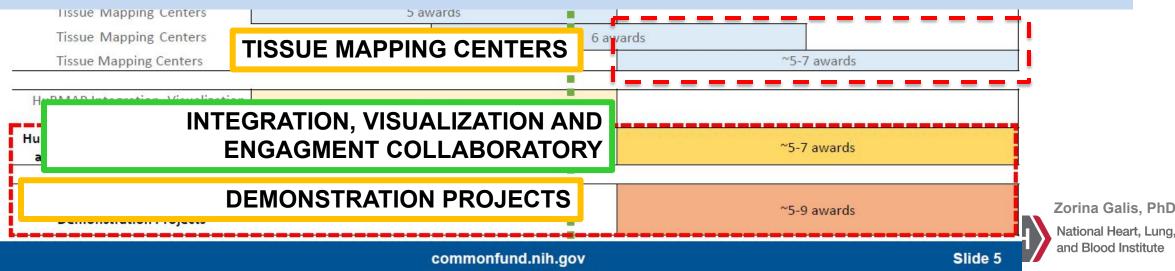




Check for latest updates at NIH Common Fund HuBMAP
 https://commonfund.nih.gov/hubmap

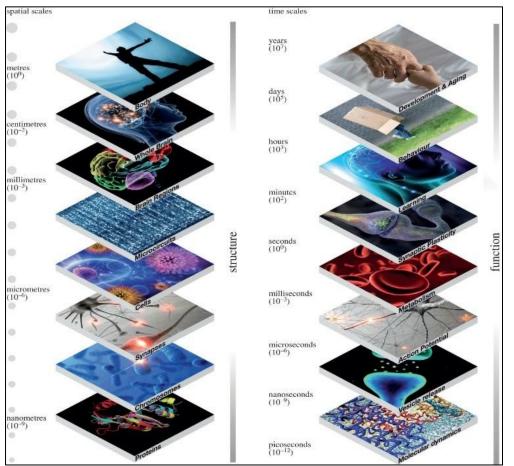
# Sign up for HuBMAP mailing list for updates <u>https://hubmapconsortium.org/hubmap-mailing-list/</u>

### • Follow HuBMAP on Twitter \_HuBMAP





# From Precision Vascular Biology to Precision Medicine



Frackowiak et al., The future of human cerebral cartography: a novel approach. Phil Trans R Soc B (2015)

- WHAT: Assembling and analyzing high content spatial/temporal and functional biological information
- HOW: new investigative and computational technologies, including ML
- WHY: Identifying the molecular/cellular bases of local and individual variations, signaling transitions from health to disease, targeted interventions
- >>basis for "Precision Medicine!"



### Seeking to Enable Solutions for Important Biomedical Challenges ...is a (Fun) Team Sport!



HuBMAP NIH Core Group, NIH Director Award 2019 for "building exceptional collaborations inside and outside the NIH to create a transformative paradigm that enables cooperative worldwide efforts to map the human body "

The Human BioMolecular Atlas Program (HuBMAP) Team https://commonfund.nih.gov/hubmap



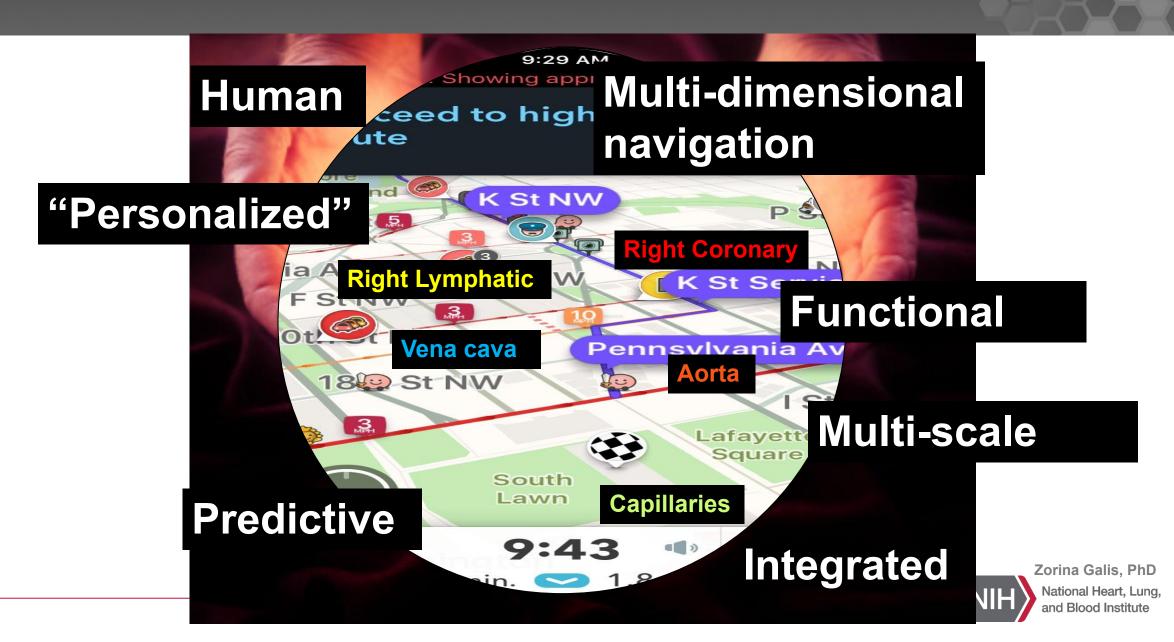








### "The Vasculome"...



# HuBMAP Types of Analyses

### IMAGING

DNA/RNA DART-FISH seqFISH smFISH MERFISH Slide-seq SABER-FISH GeoMx

Lipids/Metabolites MALDI Imaging MS SIMS Imaging DESI Imaging MS NanoDESI Imaging MS <u>Proteins</u> Multiplexed IF IHC Lightsheet CODEX Cell DIVE DART-FISH CyTOF Imaging MALDI Imaging MS nanoPOTS MIBI Immuno-SABER

### <u>Other</u>

MR Imaging CT Imaging Autofluorescence Stained Microscopy

### SEQUENCING

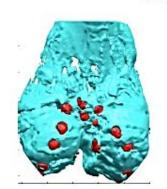
snDropseq scRNAseq snRNA-seq snATAC-seq sciRNAseq sciATACseq scTHSseq SNAREseq scATACseq

### **BULK OMICS**

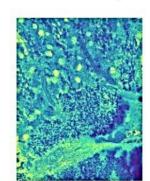
Lipids/Metabolites LC-MS/MS

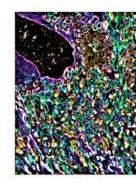
Proteins Bottom-up LC-MS/MS Top-down LC-MS/MS TMT LC-MS/MS















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