Creating a map of the human blood vasculature:
anatomical level and beyond

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Vasculature doman experts: Sujin Lee, Rajeev Malhotra, Marc Halushka

Funding from NIH Award OT2OD026671

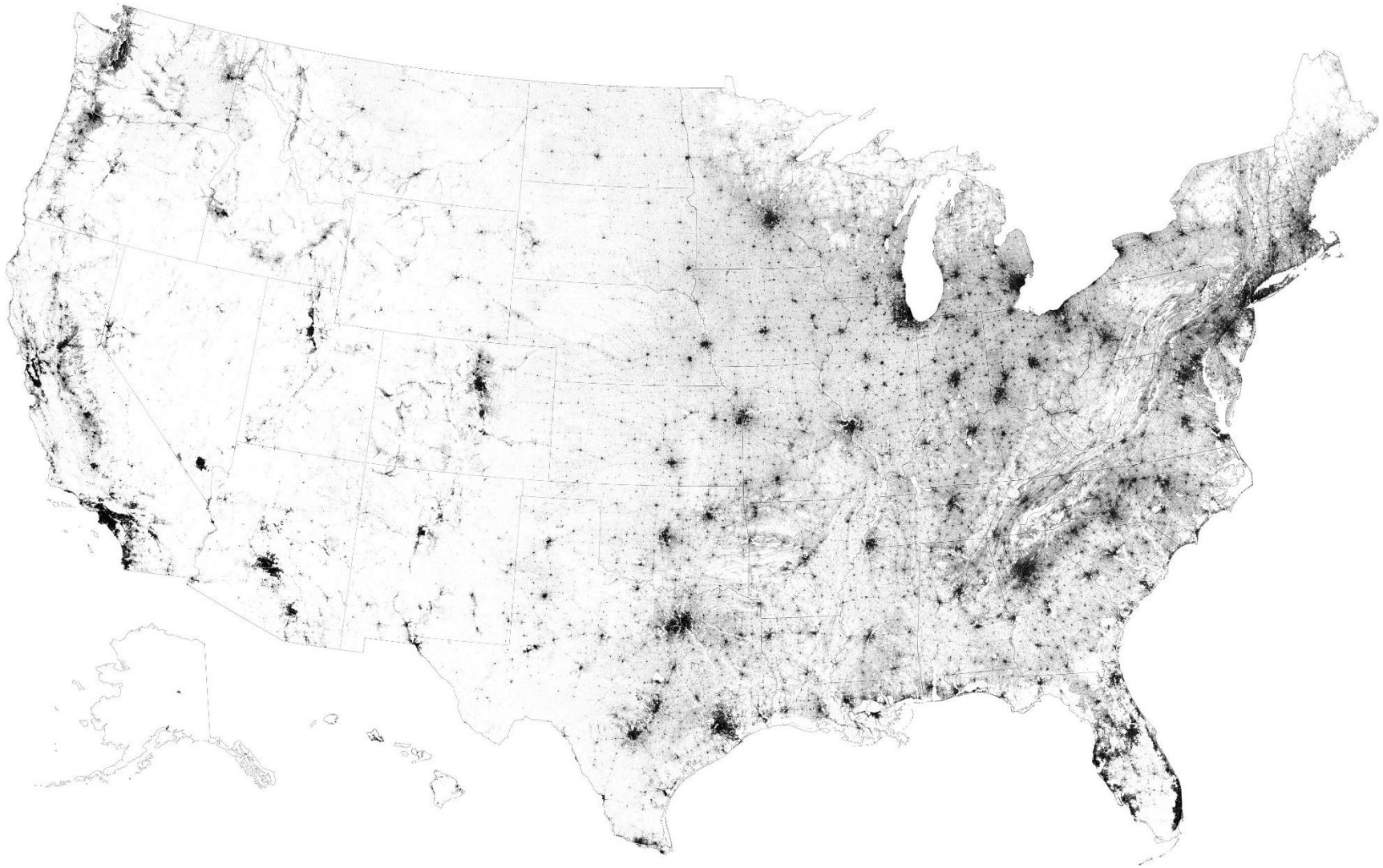
Create a map of all the **cells** in the human body

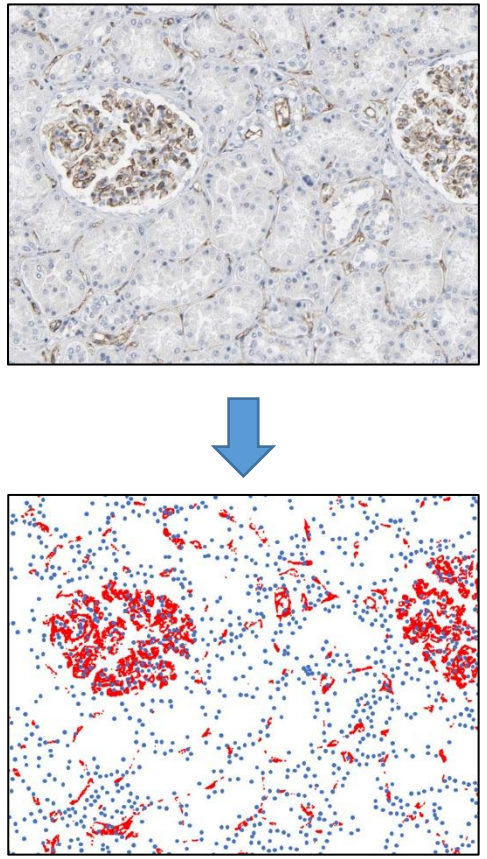
Create a map of all the **buildings** in a country

Create a map of all the **blood vessels**

Create a map of all the **roads**

Create a map of all the **buildings** in the country





https://www.nytimes.com/interactive/2018/10/12/us/map-of-every-building-in-the-united-states.html

Describing a building's location

42.302708, -71.072105 → Latitude-Longitude Coordinate System

49 Oldfields Rd
Boston, MA 02121 → Road-based Coordinate System

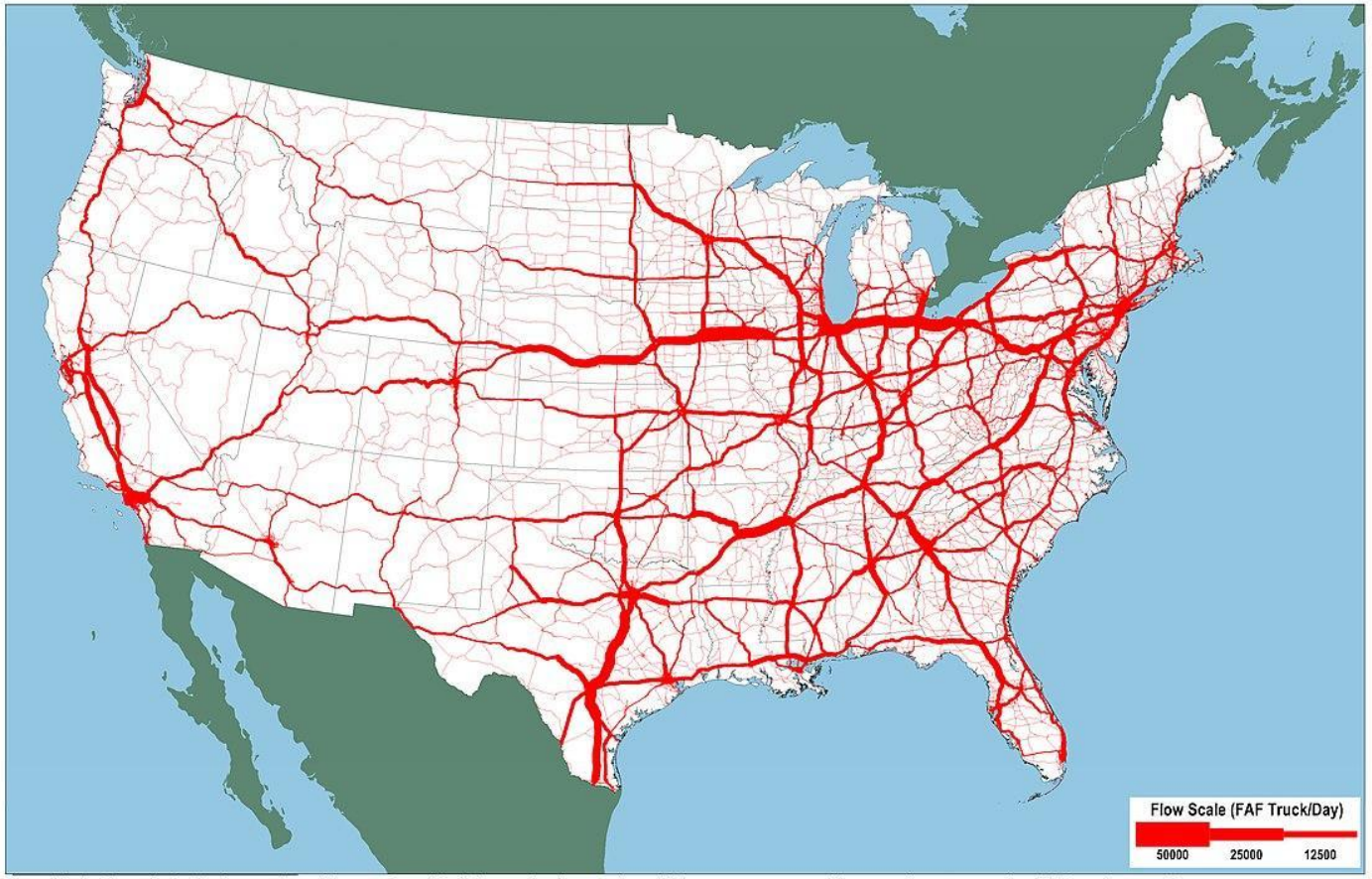
Can we describe the location of cells based on position relative to a nearby blood vessel?

Cells need to be near blood vessels to receive oxygen and nutrients

Buildings need to be near roads so that people and packages can get to them

Creating a map of roads by starting with the highways

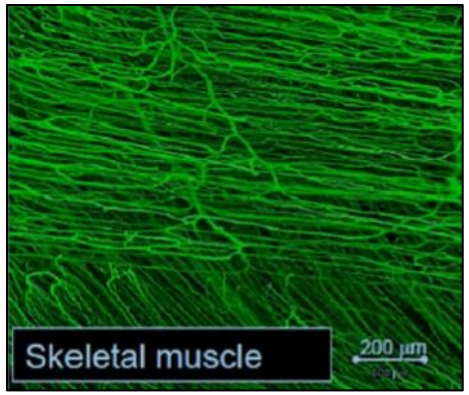
Average Daily Long-Haul Truck Traffic on the National Highway System: 2015

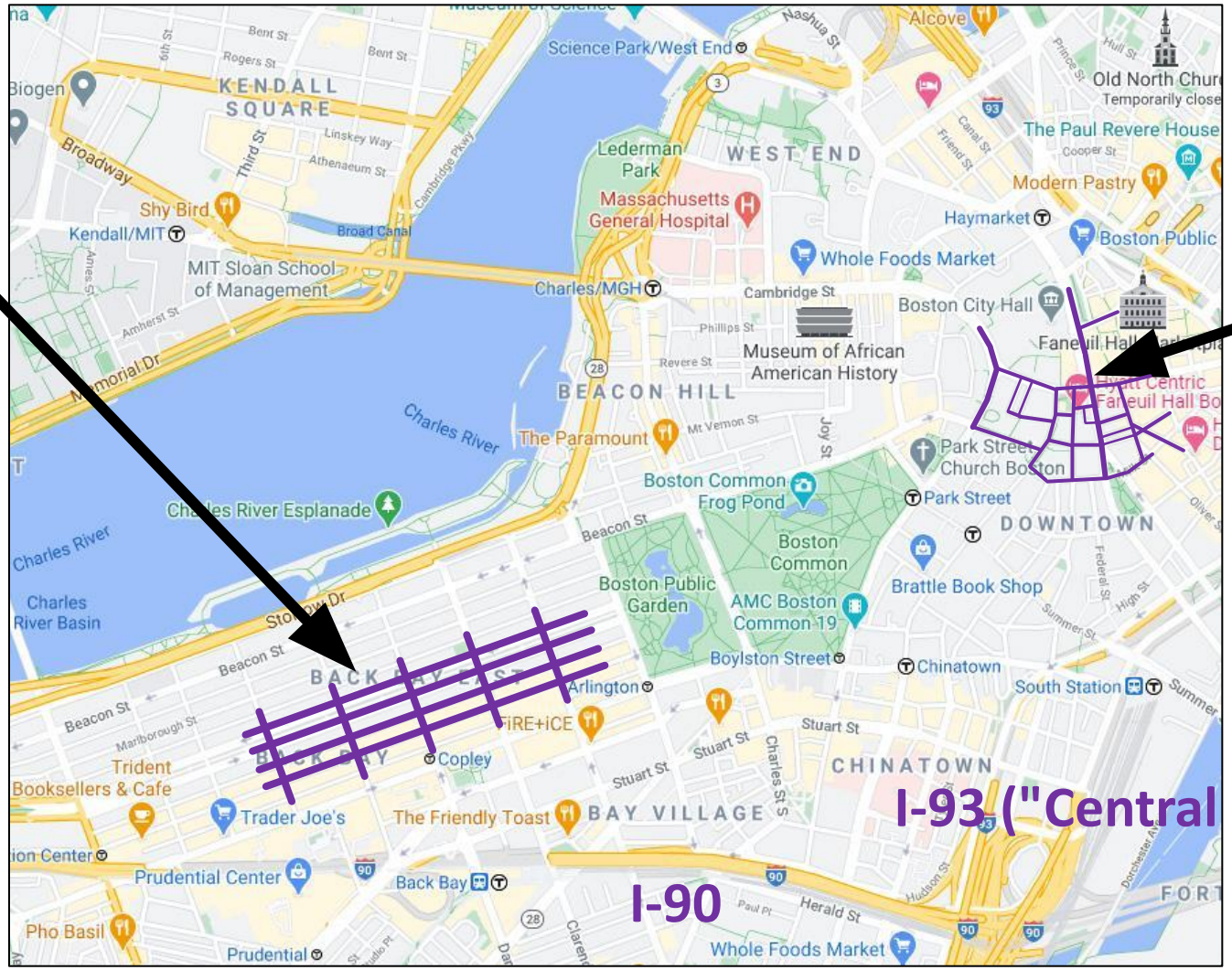


Note: Major flows include domestic and international freight moving by truck on highway segments with more than twenty five FAF trucks per day and between places typically more than fifty miles apart.
Source: U.S. Department of Transportation, Federal Highway Administration, Office of Freight Management and Operations, Freight Analysis Framework, version 4.3, 2017.

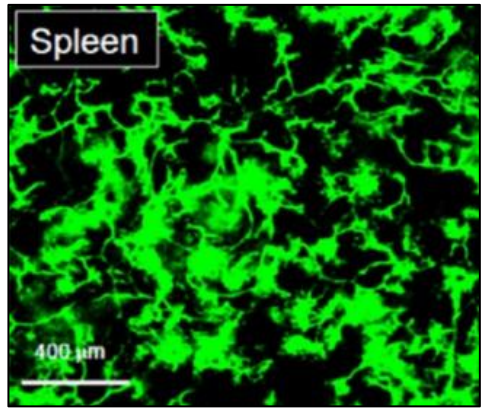
https://interestingengineering.com/the-complex-history-of-the-us-interstate-highway-system

Back Bay





Downtown

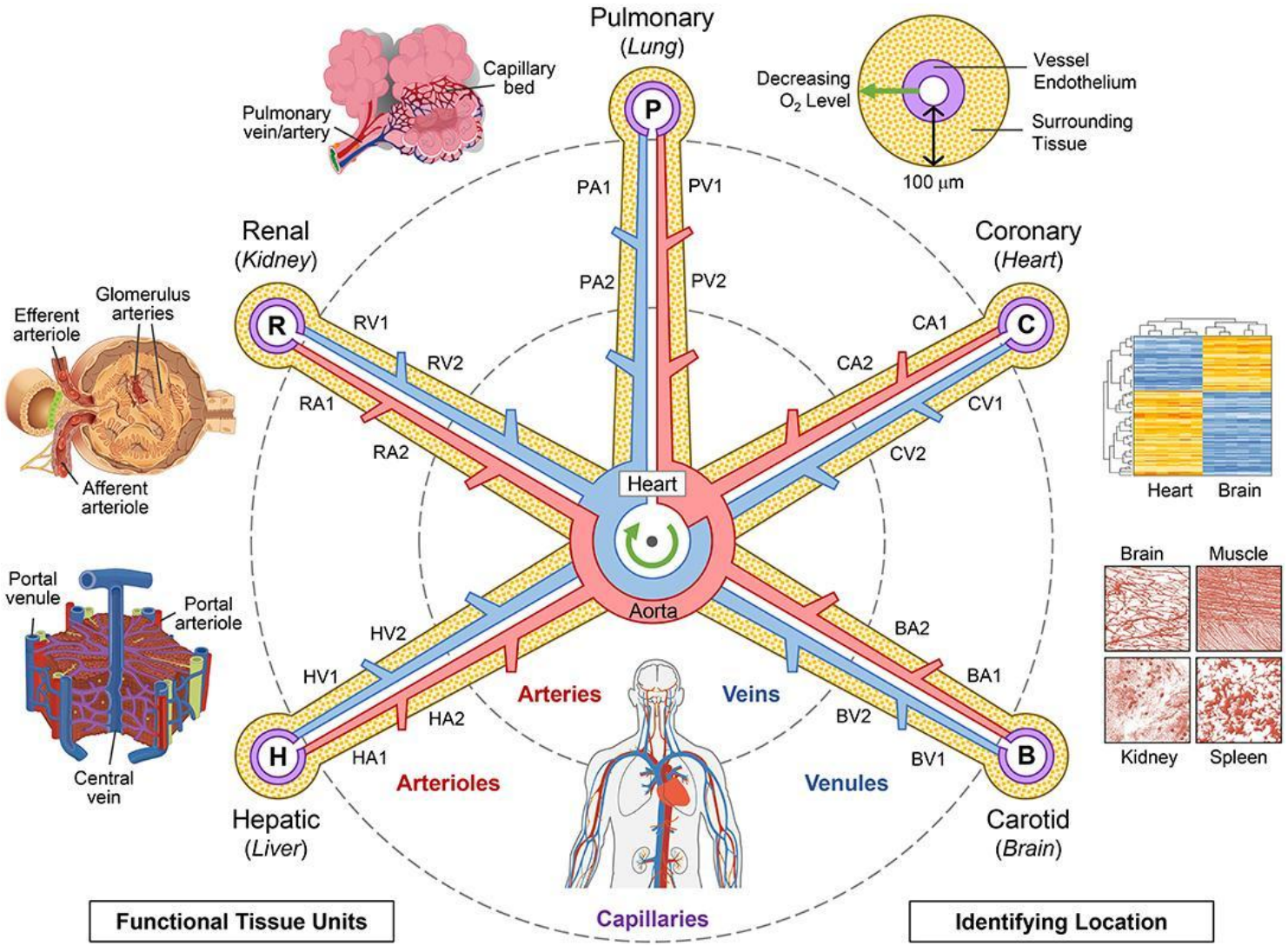


https://www.zumper.com/blog/best-neighborhoods-in-boston-for-newcomers/

https://www.75statestreetgarage.com/nearby-destinations/financial-district/

https://pubmed.ncbi.nlm.nih.gov/27815267/

Vascular Common Coordinate Framework (VCCF)



Weber GM, Ju Y, Börner K. Considerations for Using the Vasculature as a Coordinate System to Map All the Cells in the Human Body. Front Cardiovasc Med. 2020 Mar 13;7:29. doi: 10.3389/fcvm.2020.00029. PMID: 32232057; PMCID: PMC7082726.

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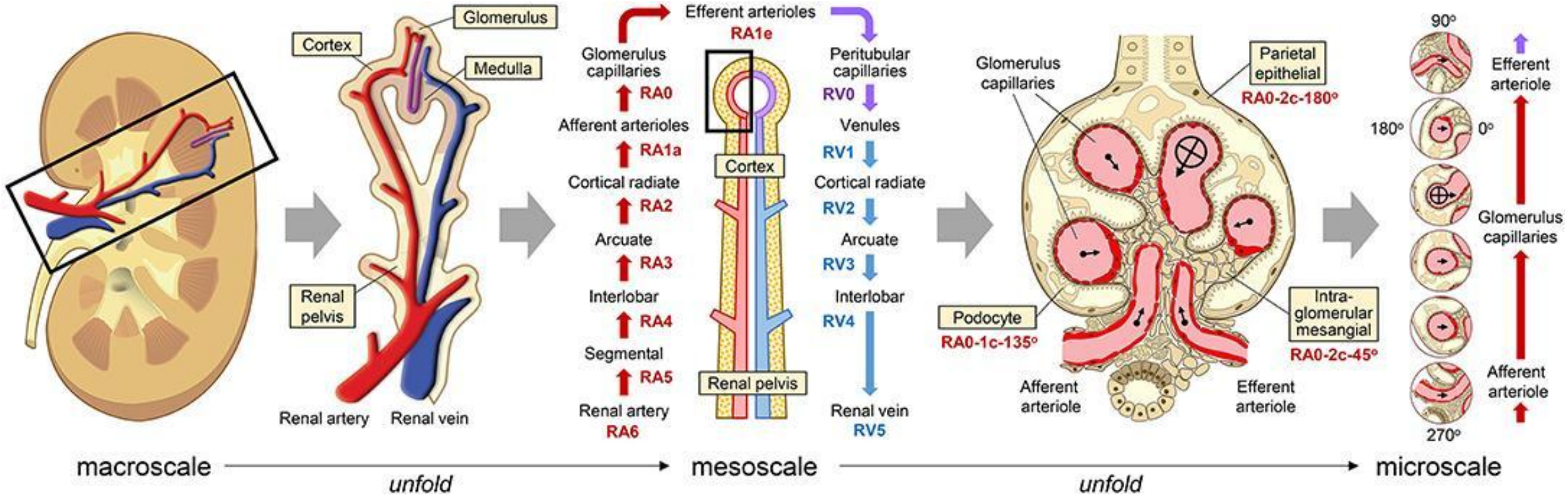
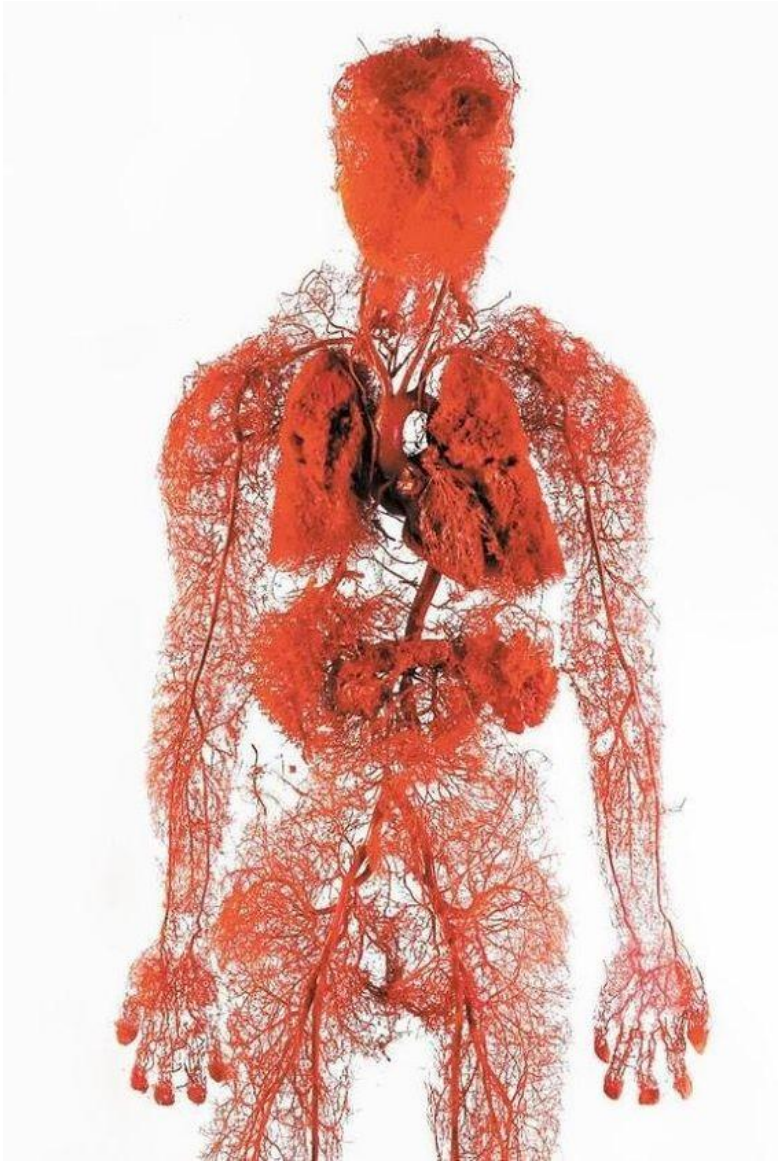
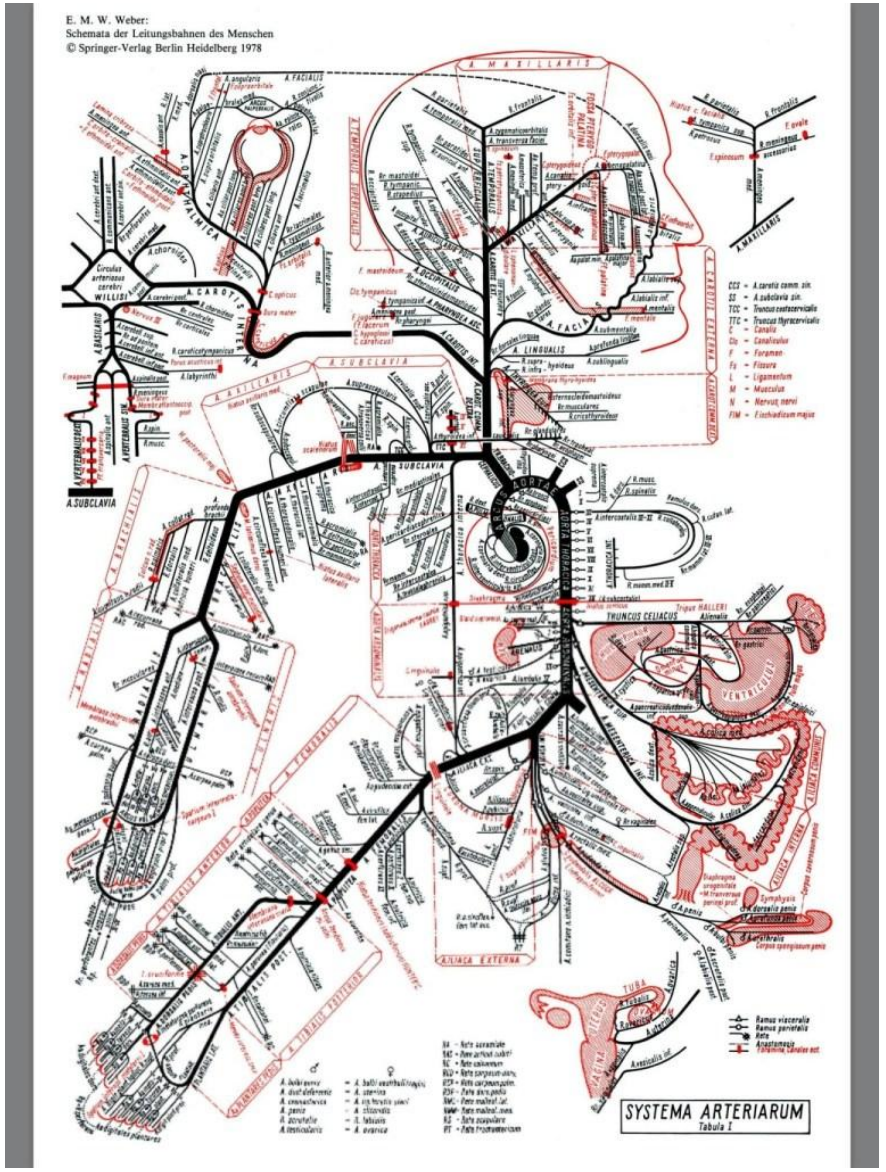


Weber GM, Ju Y, Börner K. Considerations for Using the Vasculature as a Coordinate System to Map All the Cells in the Human Body. Front Cardiovasc Med. 2020 Mar 13;7:29. doi: 10.3389/fcvm.2020.00029. PMID: 32232057; PMCID: PMC7082726.

Complexity of the VCCF



Body Worlds?



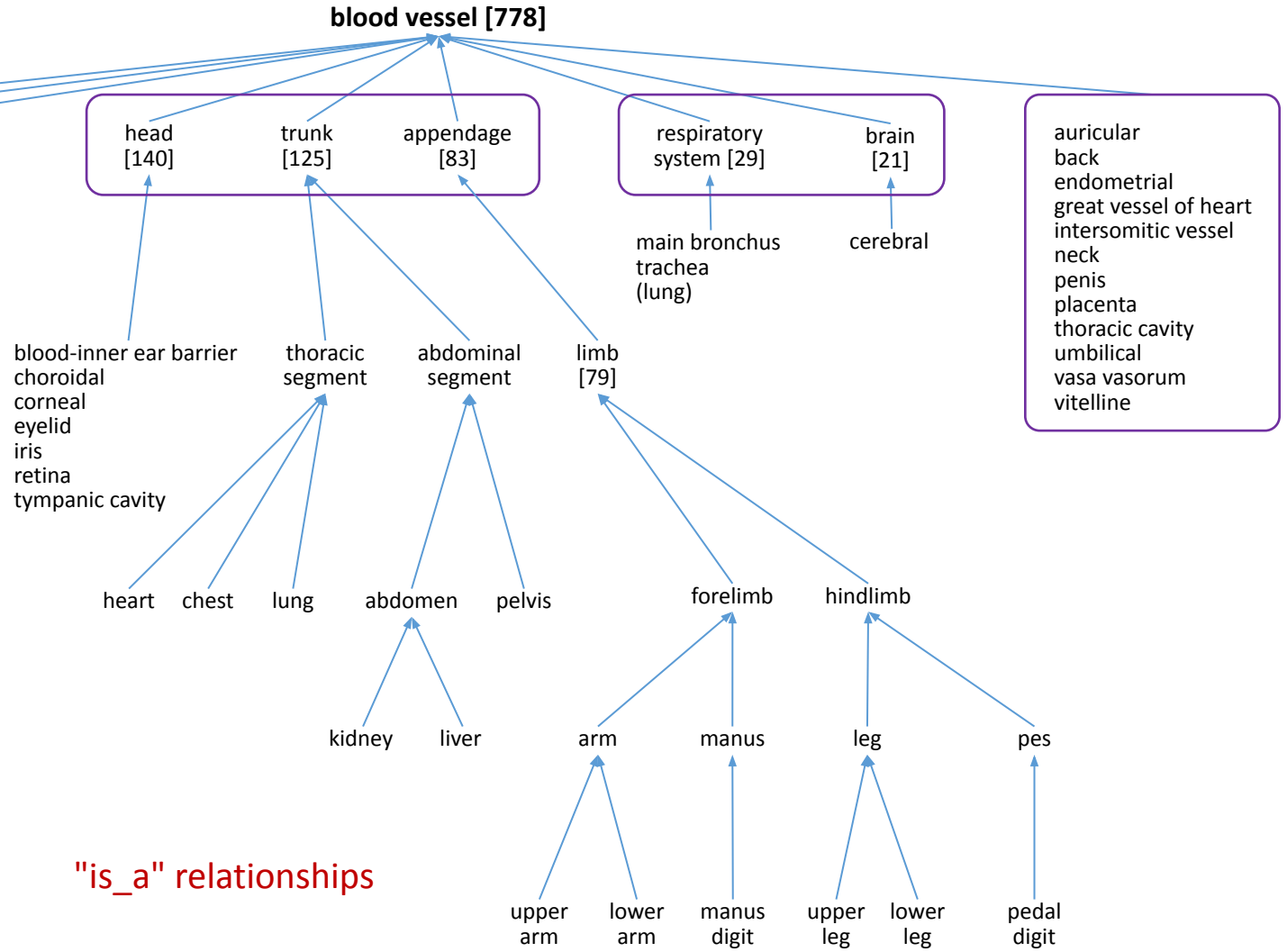
Eduard Weber 1978

VCCF Construction – UBERON "Top-Down" Approach

arterial blood vessel [378]
artery [361]
--systemic a. [197]
--respiratory system a.
arteriole [7]
aorta
=====
kidney arterial
respiratory arterial

venous blood vessel [322]
vein [297]
--systemic v. [62]
----craniocervical region v. [51]
--thoracic cavity v.
----vena cava
--thoracic v. [10]
--vein of abdomen [16]
venule [2]
venous sinus
=====
coronary sinus
renal venous

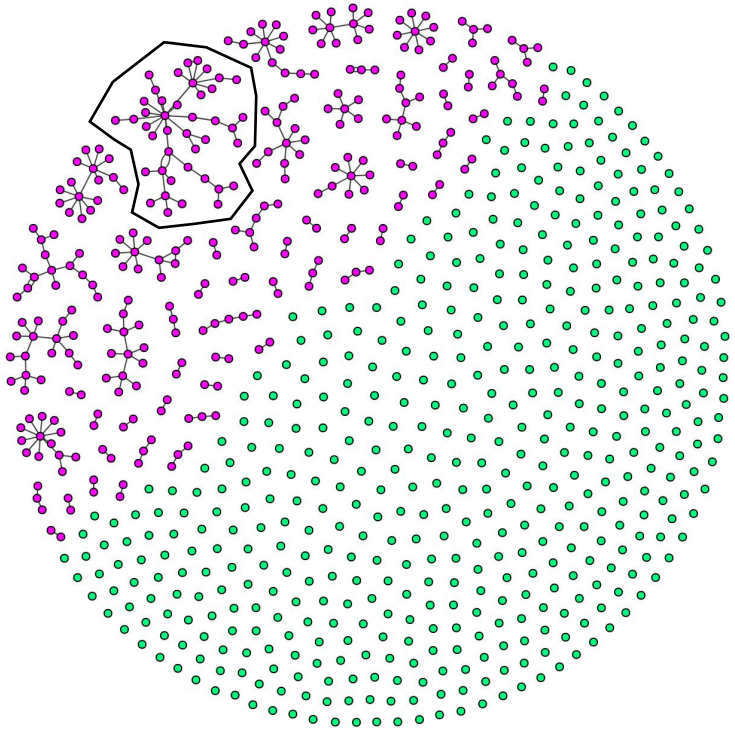
capillary [21]
continuous
fenestrated
--sinusoid
----hepatic sinusoid
----splenic sinusoid
=====
kidney
--glomerular
--peritubular
respiratory
--pulmonary
coronary
liver

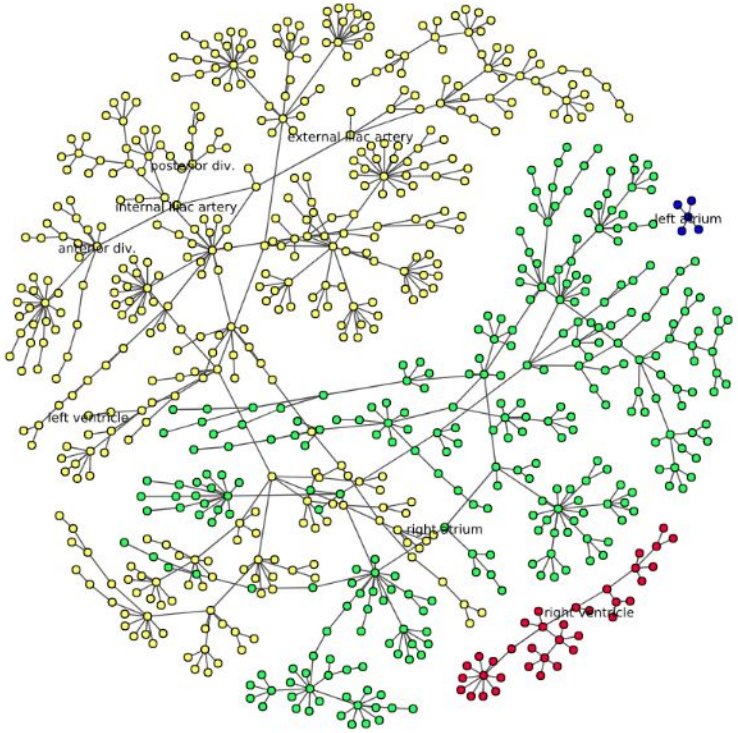


720 items in arterial/venous/capillary classes
439 items in body part blood vessel classes
[N] = number of vessels in subtree

VCCF Construction – UBERON "Bottom-Up" Approach

Connecting 747 Individual Vessels in UBERON





UBERON Only

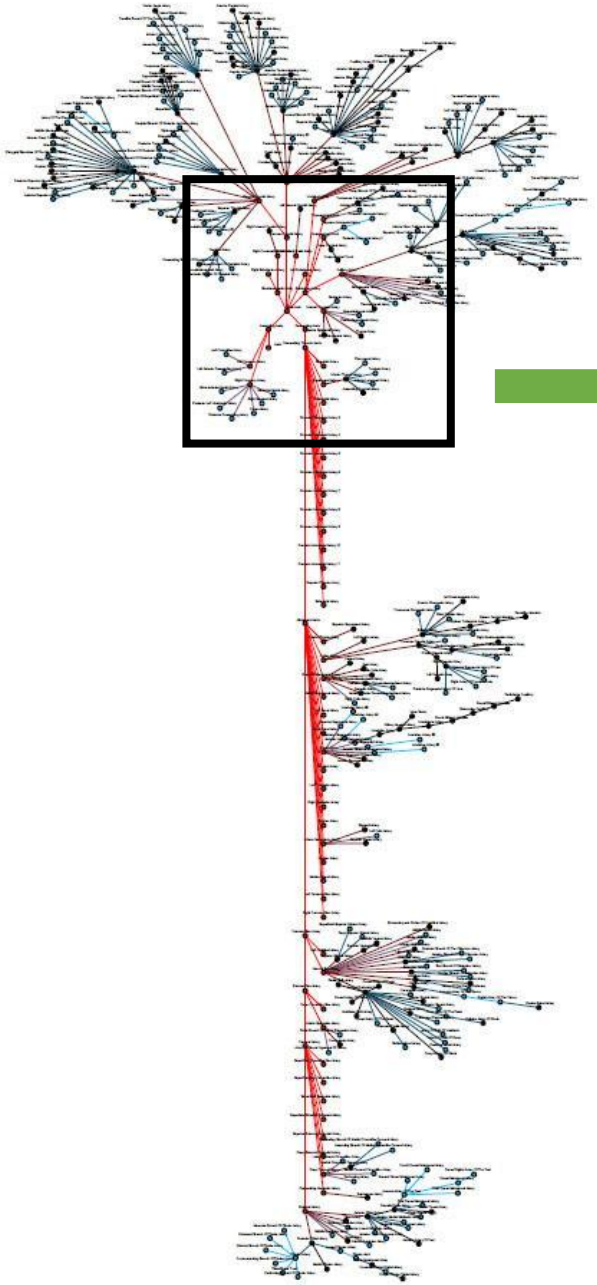
- Connected vessels
- Unconnected vessels

294 "part_of", "branching_part_of", "develops_from", and "tributary_of" relations

UBERON + Manually Added Links

- Left ventricle - arteries
- Right atrium - veins
- Left atrium - pulmonary veins
- Right ventricle - pulmonary arteries

Visualizing branching connections for quality checks



Review Process

Subject matter experts

- Marc Halushka – Vascular pathology (Johns Hopkins)
- Rajeev Malhotra – Vascular biology (Mass General Hospital, Harvard)
- Sujin Lee – Vascular surgery (Mass General Hospital, Harvard)

Merge process

- Kept change if made by both MH and RM+SL
- Kept change if made one and the other made no change
- Manually reviewed if each made a different change

Cleanup

- Misspellings, standardizing dashes, duplicates
- Paired vessels, anastomoses, variants

Publish

- 869 vessels; 19 levels of depth; 371 vessels (43%) in UBERON
- Construct HuBMAP Anatomical Structures, Cell Types, Biomarker (ASCT+B) table
- References to Wikipedia, Radiopaedia, Gray's Anatomy (1858); Netter (1981)
- Saved additional information we collected into an "extended" VCCF data table

Connections to other organ ASCT+B tables

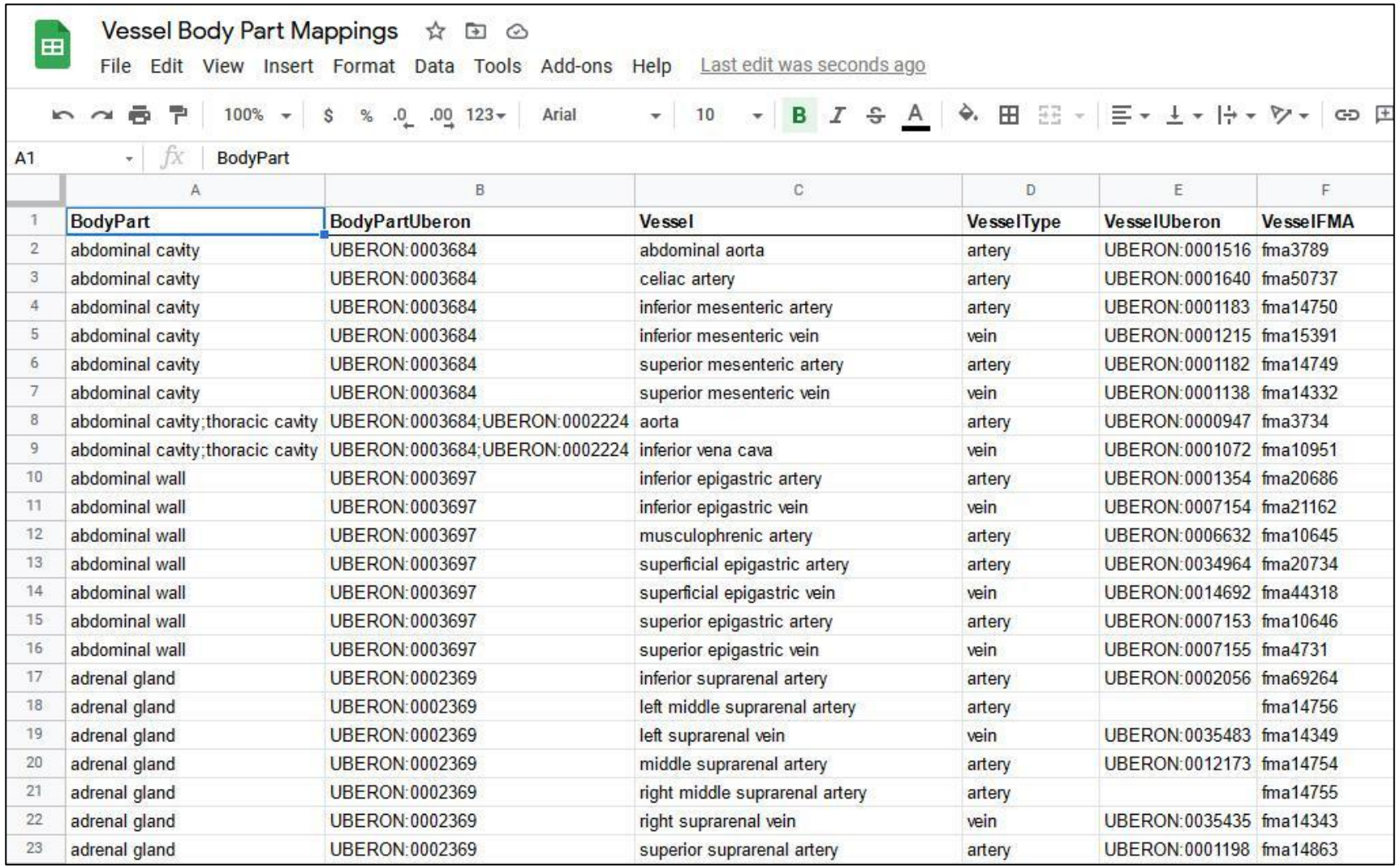
https://docs.google.com/spreadsheets/d/1RNNywmOjb2MmWFFC62VlG08mSQKnspsuSlqsPiiGbl8/edit#gid=0

BodyPart	Vessels
abdominal cavity	6
abdominal cavity;thoracic cavity	2
abdominal wall	7
adrenal gland	7
arm	25
brain	65
brainstem	2
cerebellum	6
clitoris	2
diaphragm	13
ear	12
esophagus	4
eye	21
face	57
foot	32
hand	25
head	48
heart	21
heart chamber	4
kidney	26
large intestine	20
larynx	2
leg	48
liver	20
lung	38

BodyPart	Vessels
neck	39
nose	1
ovary	5
pancreas	4
pancreas;small intestine	10
pelvis	65
penis	11
pituitary gland	2
rectum	3
scrotum	2
shoulder	14
small intestine	12
spinal cord	41
spleen	7
stomach	10
stomach;small intestine	1
testis	6
thoracic cavity	13
thoracic wall	77
thymus	2
thyroid gland	9
urinary bladder	6
uterus	7
vagina	8

Connections to other organ ASCT+B tables

https://docs.google.com/spreadsheets/d/1RNNywmOjb2MmWFFC62VlG08mSQKnspsuSlqsPiiGbl8/edit#gid=0



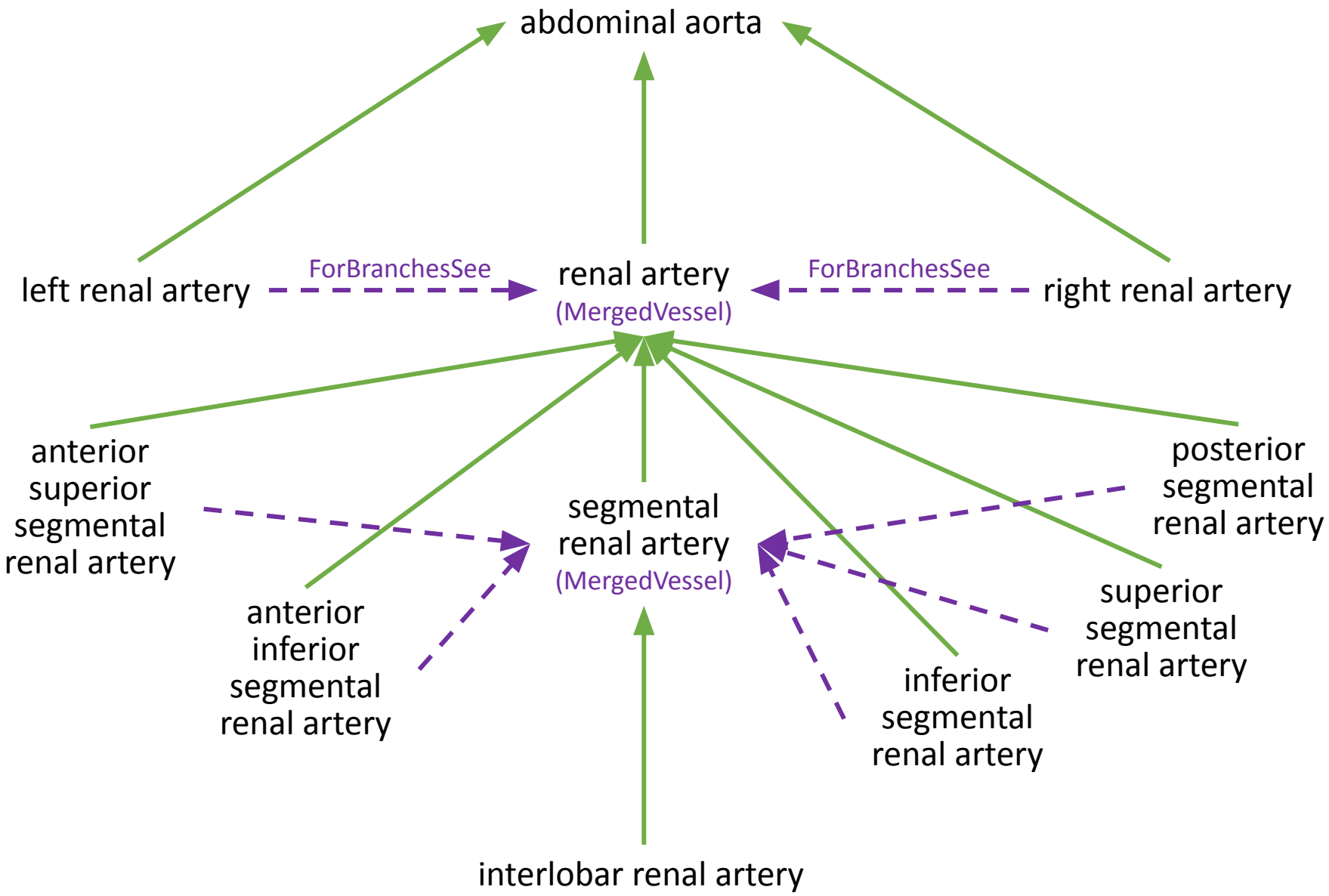
Vessel Body Part Mappings

File Edit View Insert Format Data Tools Add-ons Help Last edit was seconds ago

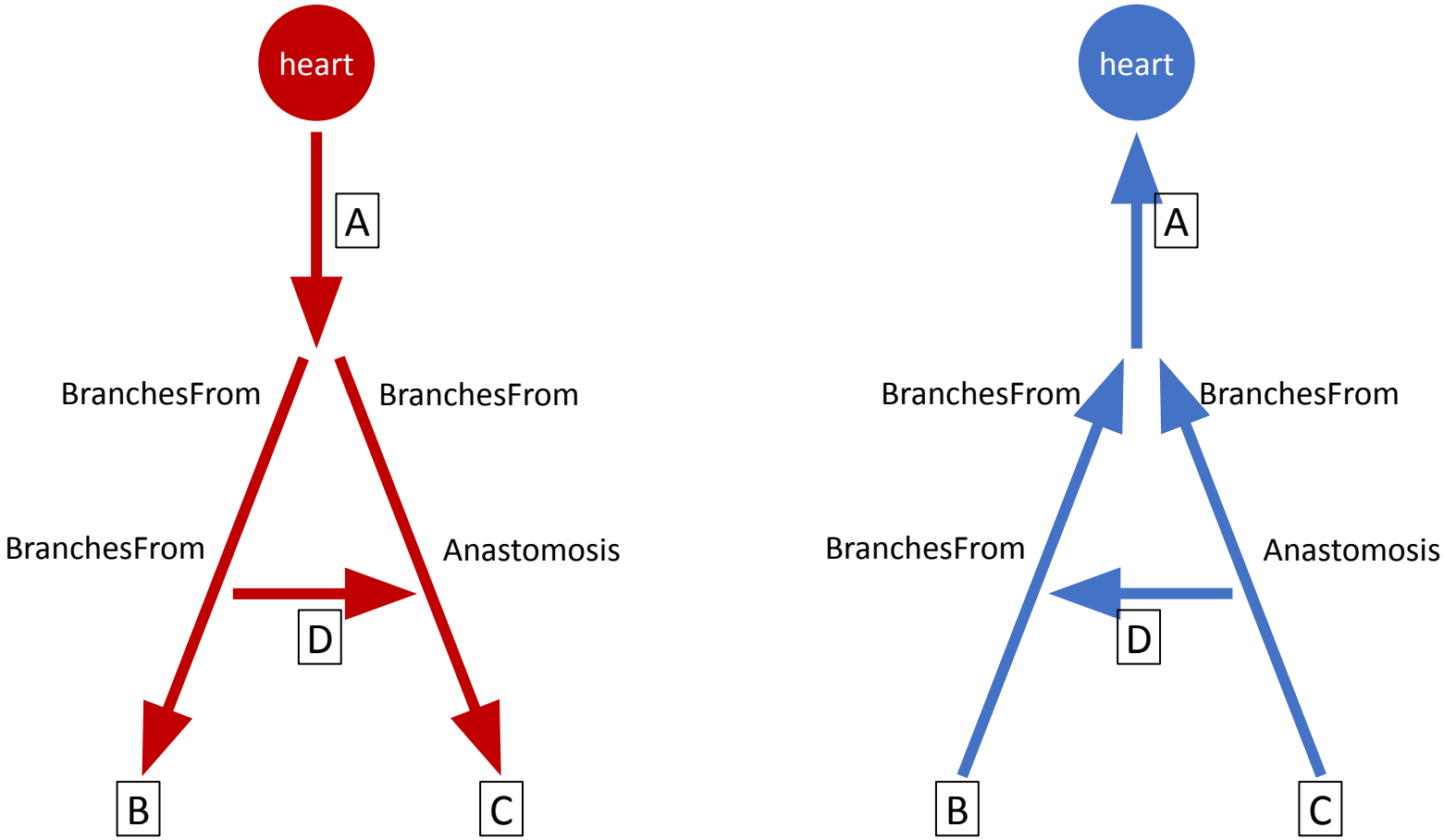
A1 BodyPart

	A	B	C	D	E	F
1	BodyPart	BodyPartUberon	Vessel	VesselType	VesselUberon	VesselFMA
2	abdominal cavity	UBERON:0003684	abdominal aorta	artery	UBERON:0001516	fma3789
3	abdominal cavity	UBERON:0003684	celiac artery	artery	UBERON:0001640	fma50737
4	abdominal cavity	UBERON:0003684	inferior mesenteric artery	artery	UBERON:0001183	fma14750
5	abdominal cavity	UBERON:0003684	inferior mesenteric vein	vein	UBERON:0001215	fma15391
6	abdominal cavity	UBERON:0003684	superior mesenteric artery	artery	UBERON:0001182	fma14749
7	abdominal cavity	UBERON:0003684	superior mesenteric vein	vein	UBERON:0001138	fma14332
8	abdominal cavity;thoracic cavity	UBERON:0003684;UBERON:0002224	aorta	artery	UBERON:0000947	fma3734
9	abdominal cavity;thoracic cavity	UBERON:0003684;UBERON:0002224	inferior vena cava	vein	UBERON:0001072	fma10951
10	abdominal wall	UBERON:0003697	inferior epigastric artery	artery	UBERON:0001354	fma20686
11	abdominal wall	UBERON:0003697	inferior epigastric vein	vein	UBERON:0007154	fma21162
12	abdominal wall	UBERON:0003697	musculophrenic artery	artery	UBERON:0006632	fma10645
13	abdominal wall	UBERON:0003697	superficial epigastric artery	artery	UBERON:0034964	fma20734
14	abdominal wall	UBERON:0003697	superficial epigastric vein	vein	UBERON:0014692	fma44318
15	abdominal wall	UBERON:0003697	superior epigastric artery	artery	UBERON:0007153	fma10646
16	abdominal wall	UBERON:0003697	superior epigastric vein	vein	UBERON:0007155	fma4731
17	adrenal gland	UBERON:0002369	inferior suprarenal artery	artery	UBERON:0002056	fma69264
18	adrenal gland	UBERON:0002369	left middle suprarenal artery	artery		fma14756
19	adrenal gland	UBERON:0002369	left suprarenal vein	vein	UBERON:0035483	fma14349
20	adrenal gland	UBERON:0002369	middle suprarenal artery	artery	UBERON:0012173	fma14754
21	adrenal gland	UBERON:0002369	right middle suprarenal artery	artery		fma14755
22	adrenal gland	UBERON:0002369	right suprarenal vein	vein	UBERON:0035435	fma14343
23	adrenal gland	UBERON:0002369	superior suprarenal artery	artery	UBERON:0001198	fma14863

Merging Paired Vessels and Sets of Vessels



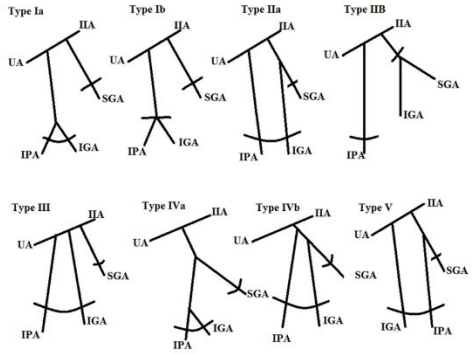
Selecting a Vessel Direction and Removing Loops



BranchesFrom side of vessel is side closer to the heart based on blood flow direction

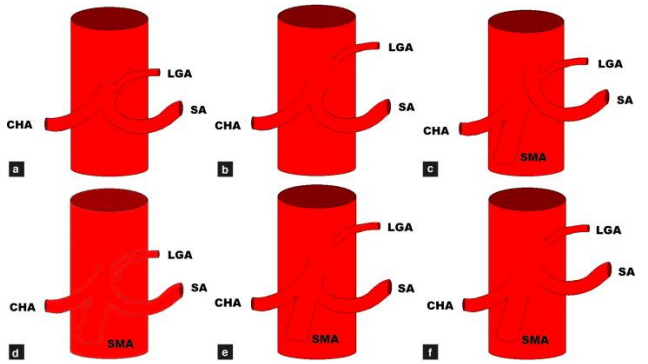
Variants (Many Examples)

Internal Iliac Artery



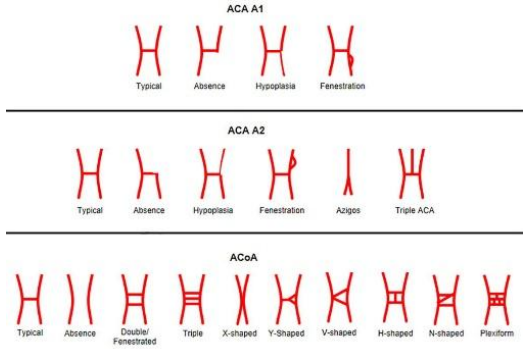
http://www.bmrat.org/index.php/BMRAT/article/view/546

Liver Arteries



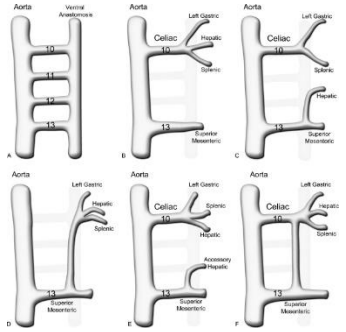
https://www.sciencedirect.com/science/article/pii/S2211568413003781#fig0010

Anterior Communicating Artery Complex



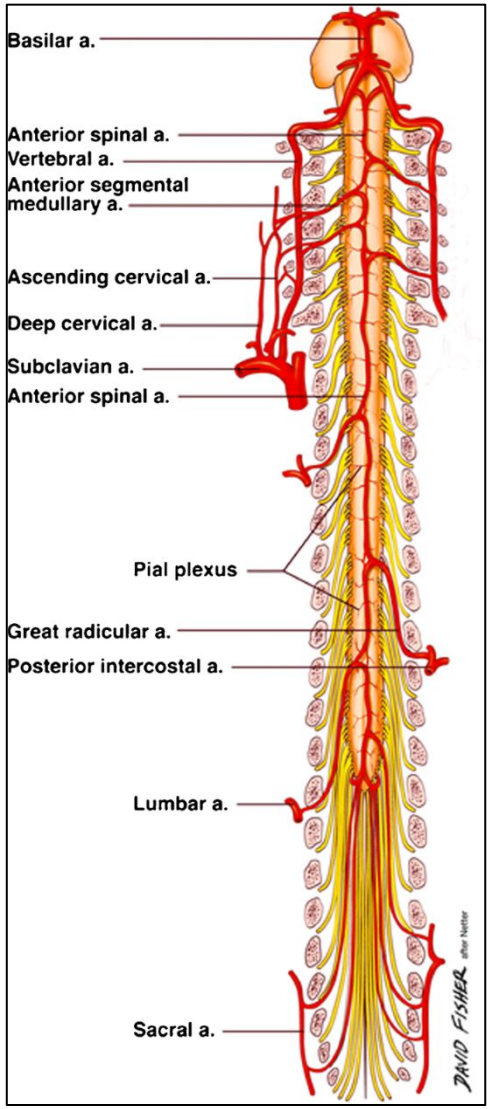
https://www.jocn-journal.com/article/S0967-5868(20)31460-0/fulltext

Mesenteric Vasculature



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3036491/

Variants - Spinal Arteries



vertebral artery

deep cervical artery

ascending cervical artery

posterior intercostal artery

lumbar artery

segmental spinal artery

anterior segmental medullary artery

anterior redicular artery

posterior redicular artery

posterior segmental medullary artery

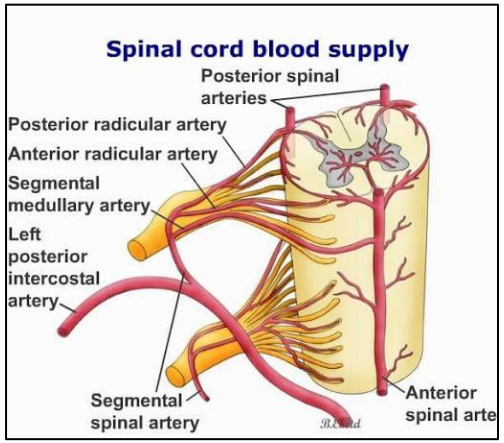
anterior spinal artery

vertebral artery

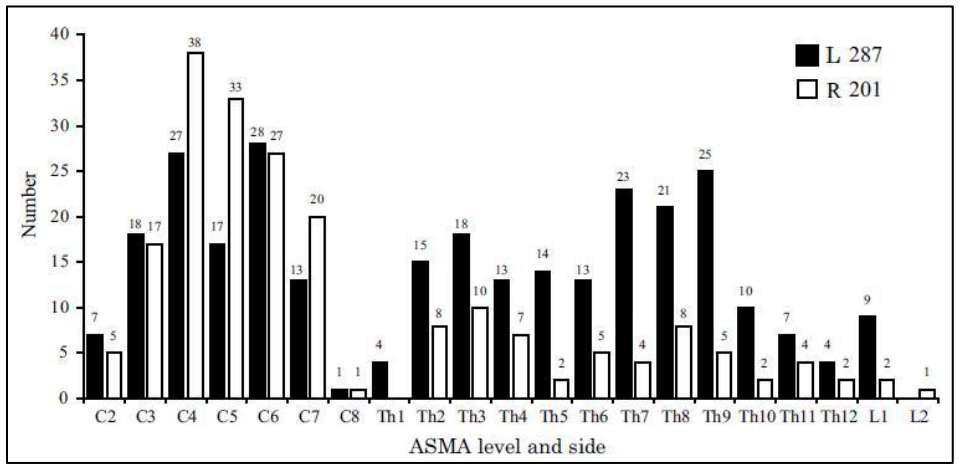
posterior spinal artery

BranchesFrom

Anastomoses



Kanazawa, 2019, Anatomical Science International, 95:97-103



Vasculature Cell Types and Biomarkers (From Rajeev Malhotra)

Vascular Endothelial Cells:
- VE-Cadherin (CD144)
- PECAM-1 (CD31)
- Tie-1
- Tie-2
- Von Willebrand Factor (VWF)
- Thrombomodulin (CD141): also expressed on VSMCs and macrophages
- Angiotensin converting enzyme (ACE or CD143)
- Nitric oxide
- Prostacyclin (PGI2)
- CD34 (non-specific)

Cardiac Endocardium:
challenging since different types of progenitor cells (eg, precardiac mesoderm and vascular endothelium)
- VE-Cadherin (CD144)
- PECAM-1 (CD31)
- FLK1 (non-specific marker)

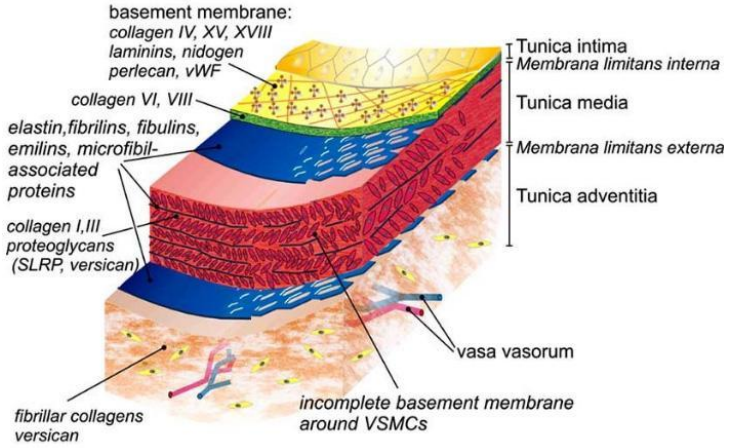
Specific Subpopulations of Endothelial Cells:
- Blood Brain Barrier: alkaline phosphatase (TNAP), γ-glutamyltranspeptidase (GGT), monoamine oxidase (MAO), lack of leukocyte adhesion molecules (ie, VCAM, ICAM), lack of thrombomodulin
- Sinusoidal (liver, spleen, bone marrow) that have minimal basement membrane and lack classical tight junctions: lack of thrombomodulin (CD141) and CD34; presence of E-selectin (CD62E) under normal conditions, expression of VAP-1, Stabilin-1, L-SIGN
- Lymphatic Endothelial Cells: Flt-4 (VEGFR-3), Desmoplakin, LYVE-1, lack CD34
- High Endothelial Venule: VAP-1, VAP-2, MECA79

Vascular Smooth Muscle Cells:
- α-Smooth muscle actin
- SM22α
- Calponin
- Myocardin
- H-caldesmon
- Smoothelin
- Telokin
- Meta-vinculin
- Desmin
- CRBP-1
- Matrix gla protein
- Smemb

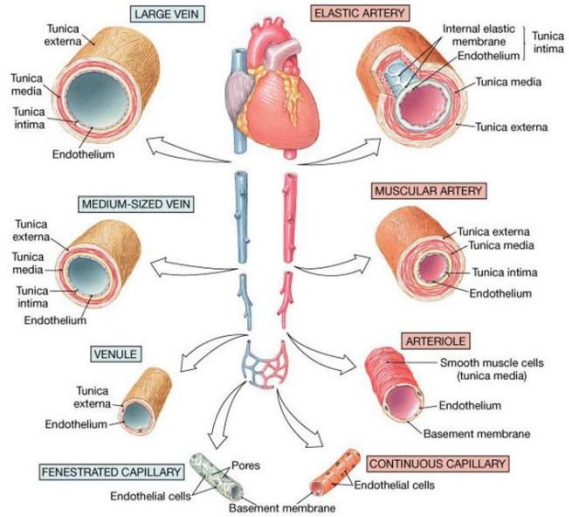
Fibroblasts in the vascular adventitial layer:
responsible for depositing abundant collagen fibrils around vessels
- Fibroblast specific protein 1 (FSP-1)
- Discoidin domain receptor 2 (DDR2)
- Collagen1a1
- Enolase 2
- Gli1
- Patched-1 and Patched-2
- Tcf21

Pericytes (periendothelial/subendothelial location):
- Proximity to capillaries
- Express PDGFRβ, NG2 (chondroitin sulfate proteoglycan 4), CD146, CD13, and Desmin, but none of these are specific for pericytes.

Vascular progenitor cells in the adventitial layer:
- Stem cell antigen-1 (Sca1)
- CD34 (non-specific)



Eble, Johannes & Niland, Stephan. (2009). The Extracellular Matrix of Blood Vessels. Current pharmaceutical design. 15. 1385-400. 10.2174/138161209787846757.



https://www.earthslab.com/physiology/types-blood-vessels-structure-function-arteries-arte%C2%ACrioles-capillaries-venules-veins/

Extended VCCF Table

Currently in Extended VCCF Table

- Vessel name
- Branches from
- Male or female
- Anastomoses
- Part of the body supplies or drains [roughly]
- Branching sequence [mostly]
- Paired and sets of vessels

Still in development

- Anatomical variants and prevalence
- Vessel geometry (length and diameter)
- Cell types and biomarkers
- Microvasculature (branching depth, branching angle, diameter, length, number)

https://docs.google.com/spreadsheets/d/13g01JtzQJYNrKZx7eF6njWtkMl5O6JNSwwWvzpGyZqE/edit#gid=144480668

Field	Example (Left Renal Artery)
BranchesFrom	abdominal aorta
Vessel	left renal artery
VesselType	artery
BodyPart	kidney
Sex	
Anastomoses	
ForBranchesSee	renal artery
MergedVessel	0
CoordX	50
CoordY	-170
BranchSequence	4
CellType	blood vessel endothelial cell
CellTypeLabel	blood vessel endothelial cell
CellTypeID	CL:0000071
Biomarkers	PECAM1 (CD31)
BiomarkersLabel	PECAM1
BiomarkersID	HGNC:8823
ReferenceURL	https://en.wikipedia.org/wiki/Renal_artery
Reference	https://en.wikipedia.org/wiki/Renal_artery
ReferenceDOI	
UBERON	UBERON:0001186
FMA	fma14753
BodyPartUberon	UBERON:0002113
UBERONLabel	left renal artery
FMALabel	Left renal artery
PathFromHeart	left ventricle;aorta;ascending aorta;aortic arch;descending aorta; descending thoracic aorta;abdominal aorta;left renal artery

Thank you!