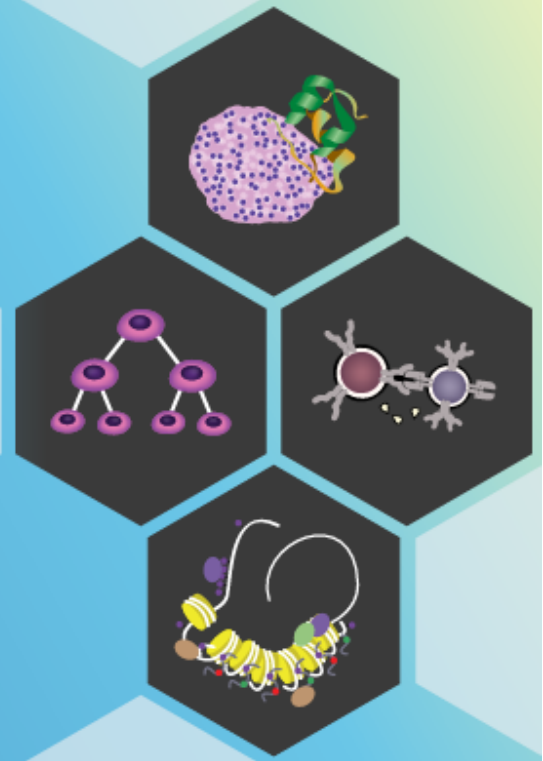
2024 RACHMIEL LEVINE-ARTHUR RIGGS

Diabetes Research Symposium

Diabetic Retinopathy: Stem Cells and New Insights



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Department of Ophthalmology and Visual Science

University of Alabama at Birmingham

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

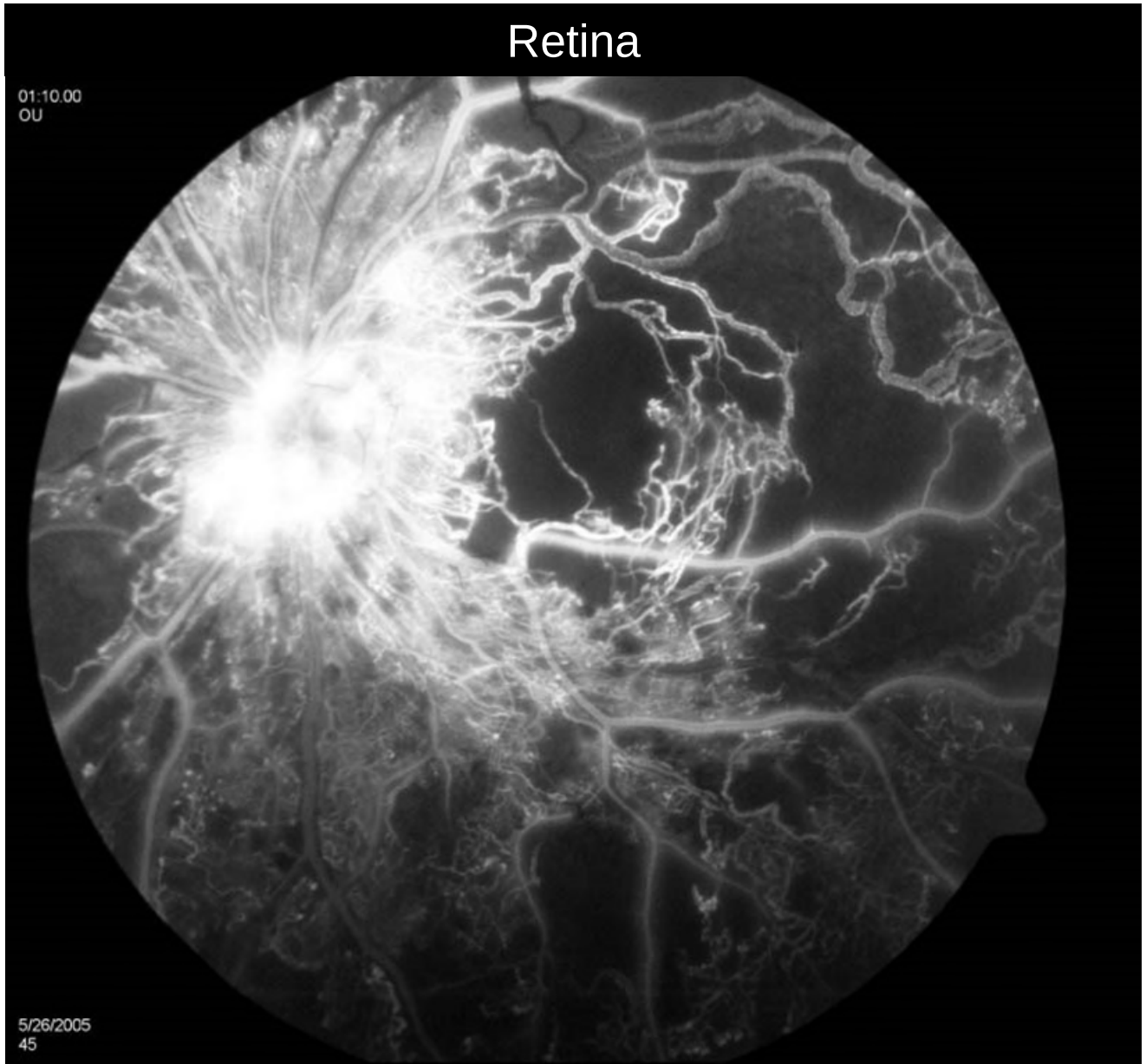
The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

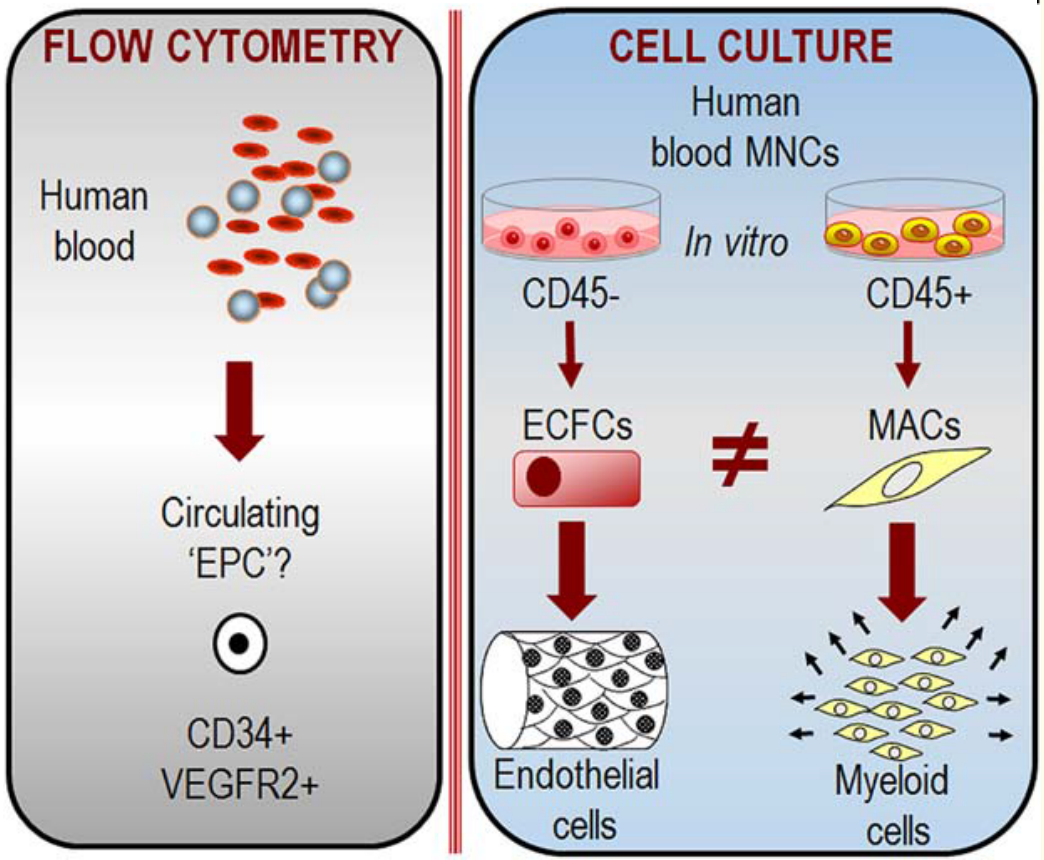
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.

Diabetes is associated with vascular dysfunction and nonperfusion of both small and large vessels

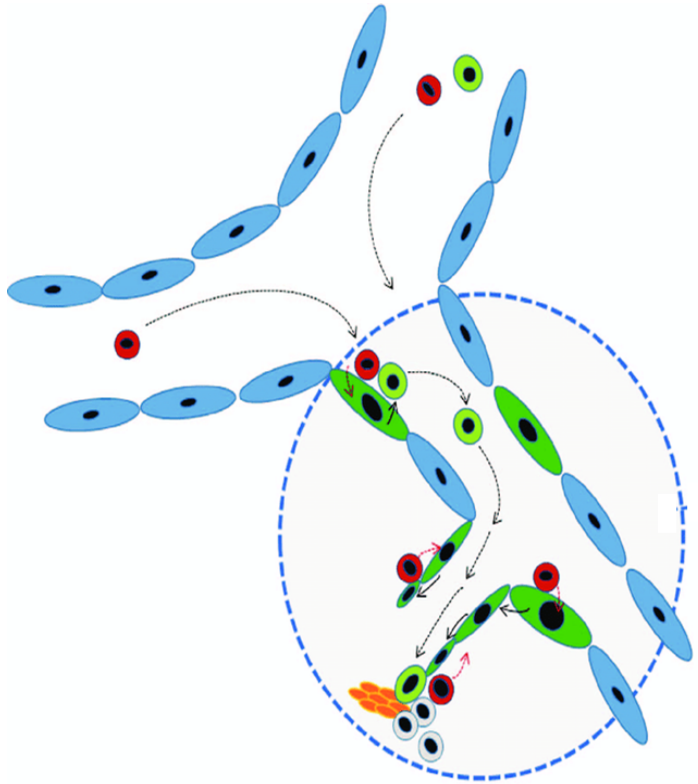


Vascular reparative cells



Peripehral Blood-derived CD34⁺ Cells

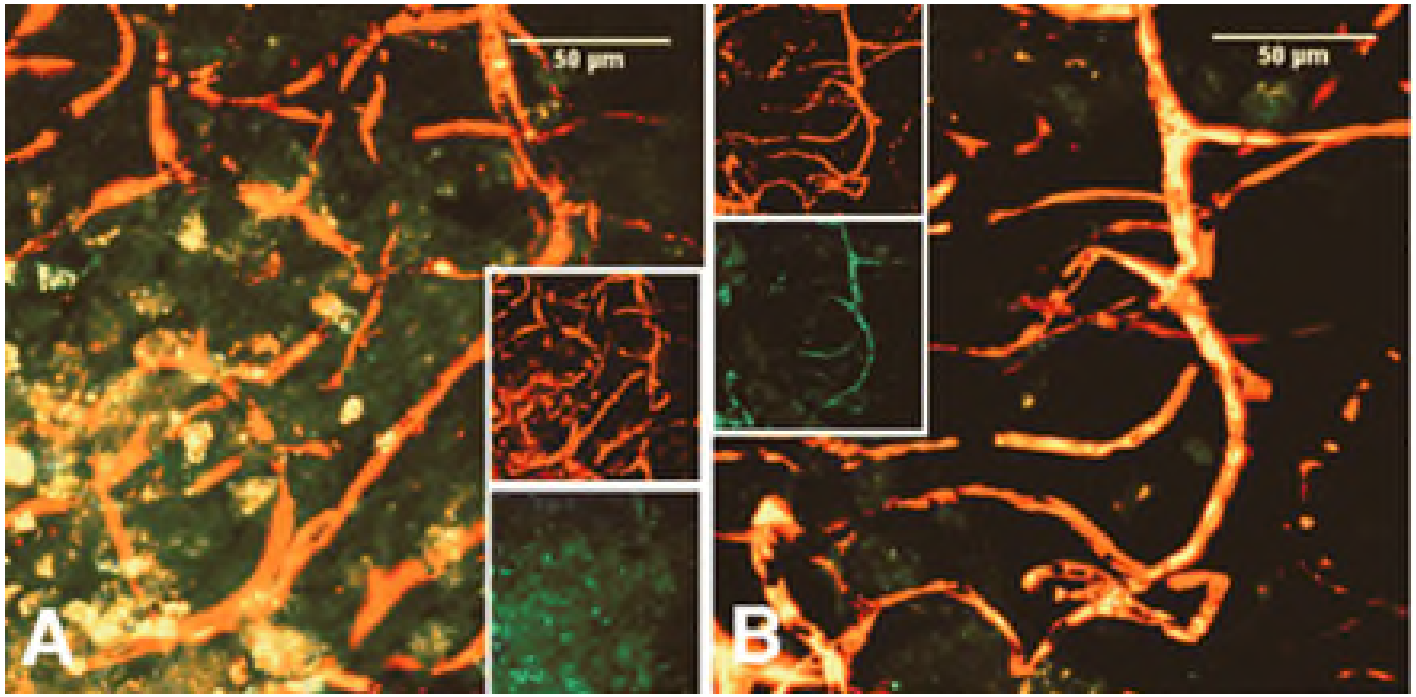
Bone Marrow-derived Hematopoietic Origin eEPCs/CACs	Vascular Wall-derived ECFCs
$CD45^{+}$	$CD45^{-}$
$CD14^{+}$	$CD14^{-}$
$CD115^{+}$	$CD115^{-}$
$CD145^{low}$	$CD31^{+}$
$VE\text{-}CAD^{+/-}$	$CD146^{high}$
$CD105^{+}$	$VE\text{-}CAD^{+/+}$
$vWF^{+/-}$	$CD105^{+}$
$CD133^{+}$	vWF^{+}
$CD117^{+}$	$CD133^{-}$
$VEGF\text{-}R1^{+}$	$CD117^{+/-}$
$VEGF\text{-}R2^{+}$	$VEGF\text{-}R1^{+}$
$TIE\text{-}2^{+}$	$VEGF\text{-}R2^{+/+}$
$CXCR4^{+}$	$TIE\text{-}2^{+}$
$AcLDL^{uptake+}$	$CXCR4^{+/-}$
$ALDH^{high+}$	$AcLDL^{uptake+}$
	$ALDH^{high+}$



Shaw et al., 2011;11:265–274
Stewart 2016,
Chew, Davis et al. 2014

Diabetes results in dysfunction of reparative cells

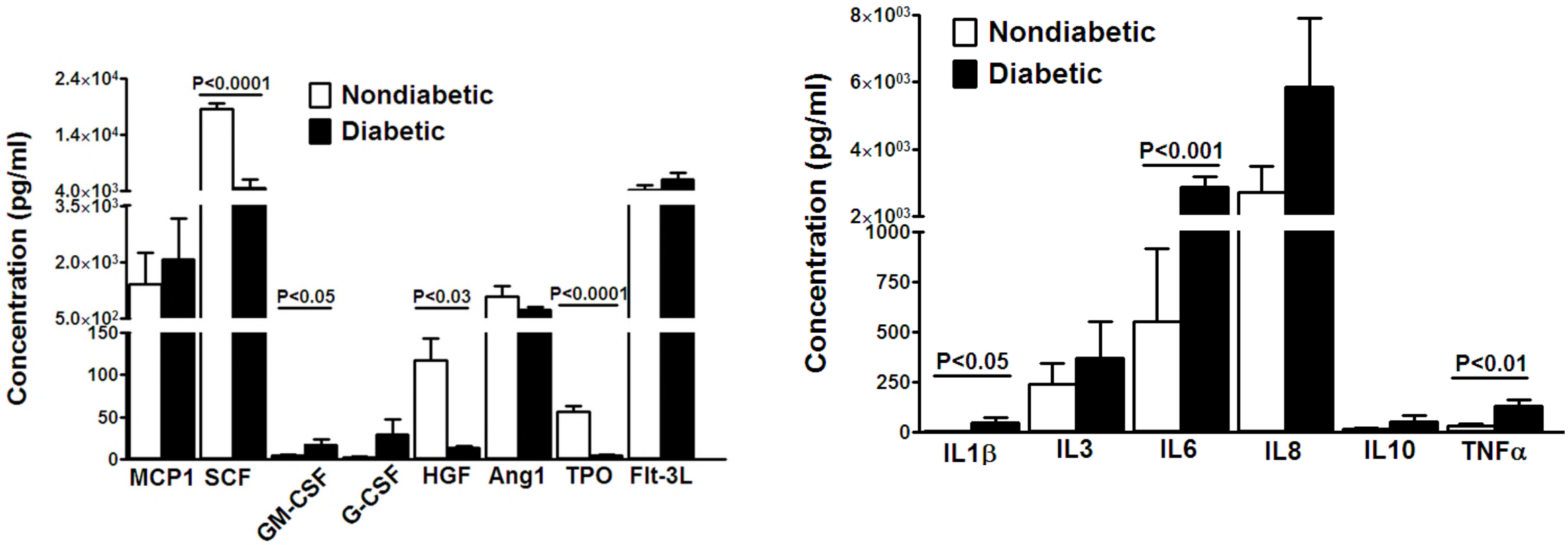
Murine model of retinal injury by ischemia/reperfusion; intravitreal injection of CD34$^+$ cells; Perfusion with rhodamine-conjugated dextran; Green – human cells; Caballero et al 2007



Diabetic cells **Non-diabetic cells**

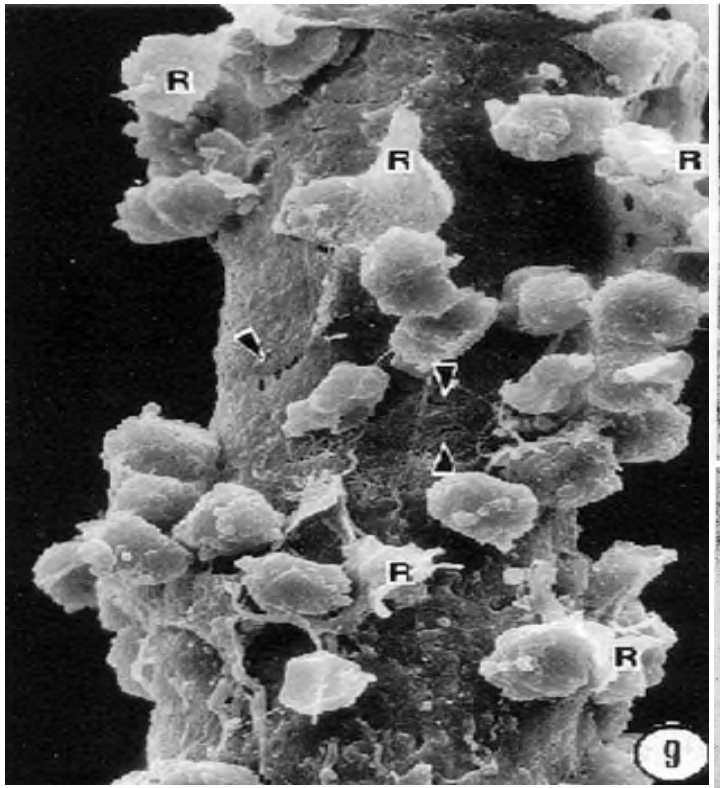
Human CD34$^+$ cells of non-diabetic origin home to areas of degenerate vasculature in mouse eyes injured by ischemia/reperfusion

MACs of diabetic origin have altered paracrine function



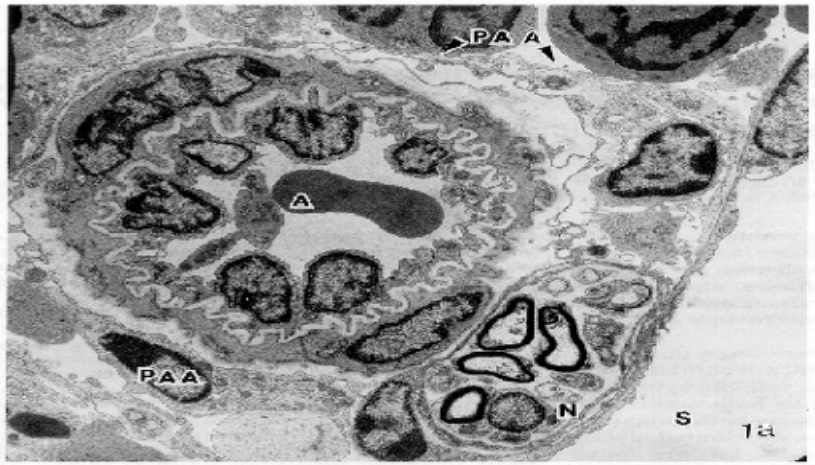
Jarajapu YP PLoS One. 2014

BM innervation critical for mobilization



Perivascular cells completely ensheath blood vessels and form an effective barrier to cell movement.

Perivascular cells are targeted by nerve fibres that synapse onto them.



The bone marrow only site where a “true” synaptic interaction between nerve and hematopoietic components has been identified

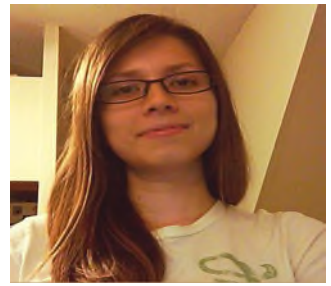
The mechanical gate

Yamazaki & Allen (1990)

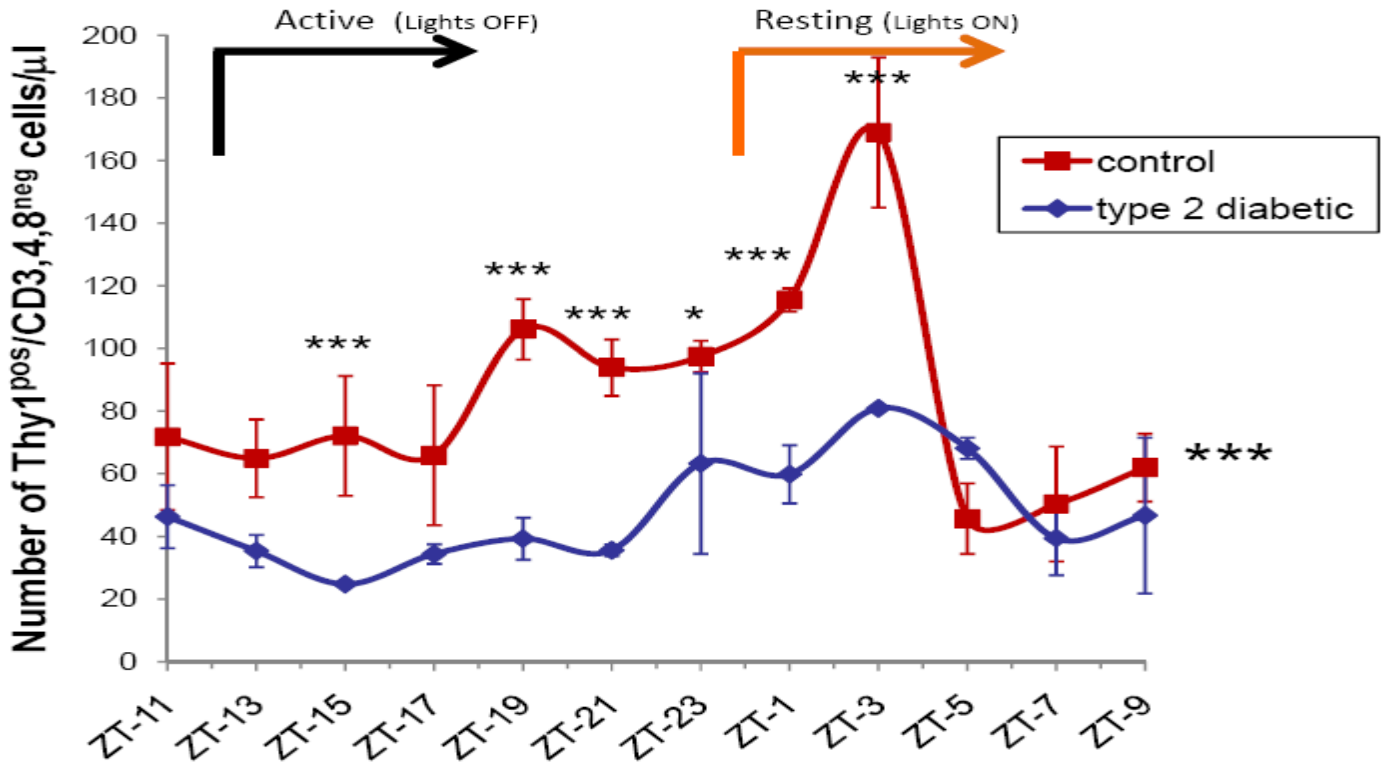
Am.J.Anat. 187(3): 261-76

Pattern of circadian release of HSPC in control and diabetic rats

Yuanqing Yan

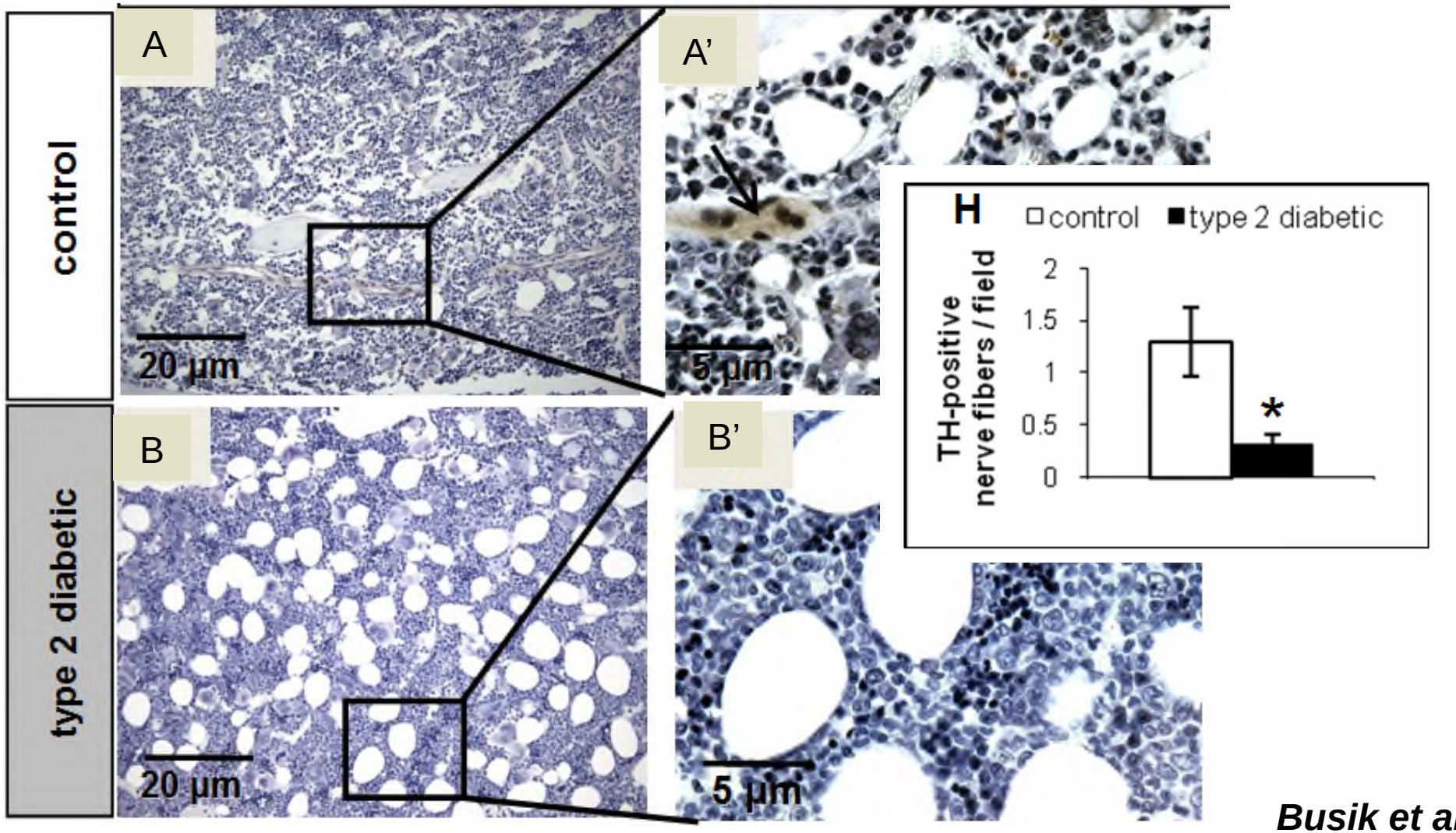


Tatiana Salzer



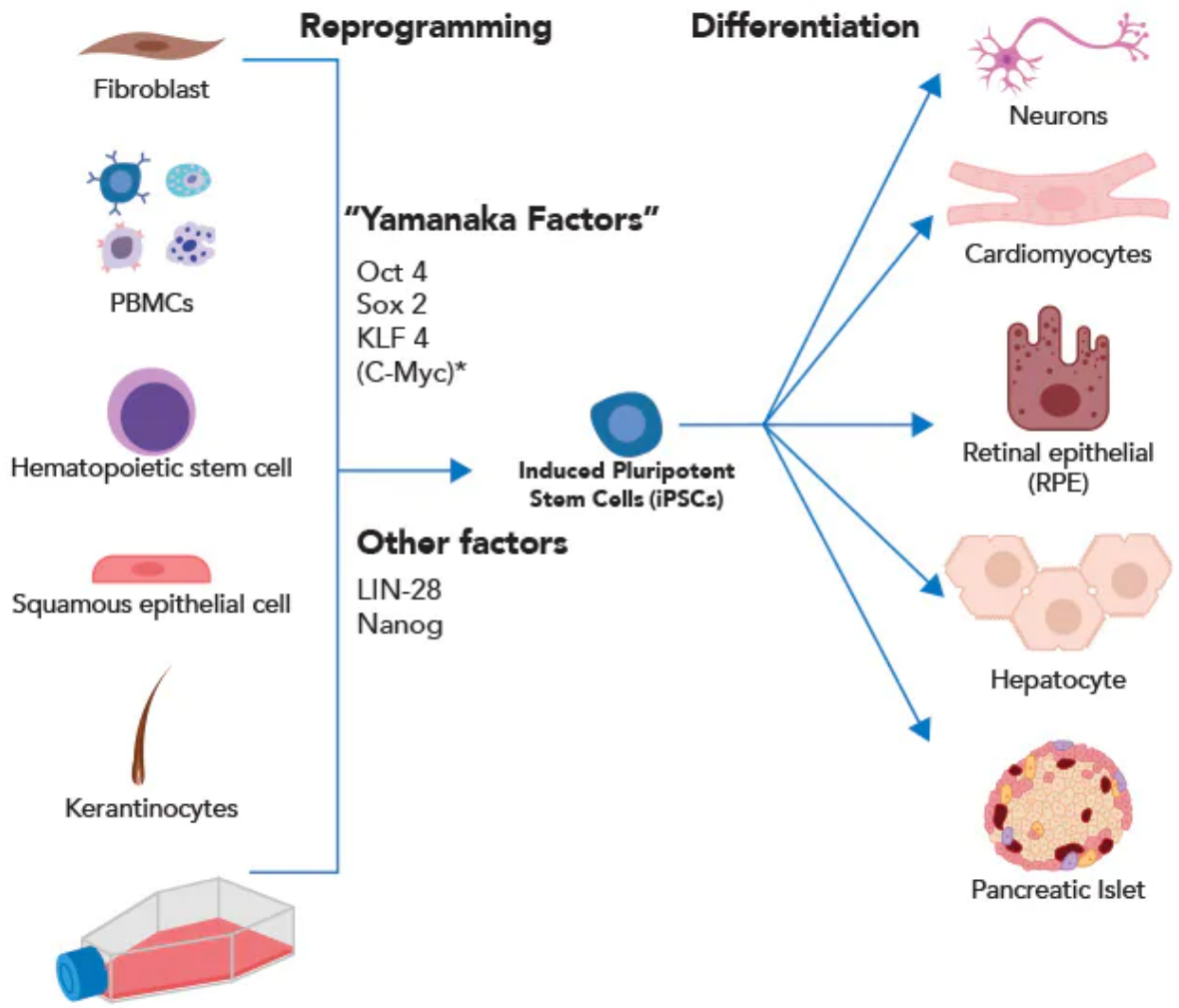
Busik et al., JEM (2009)

Bone marrow neuropathy in diabetes

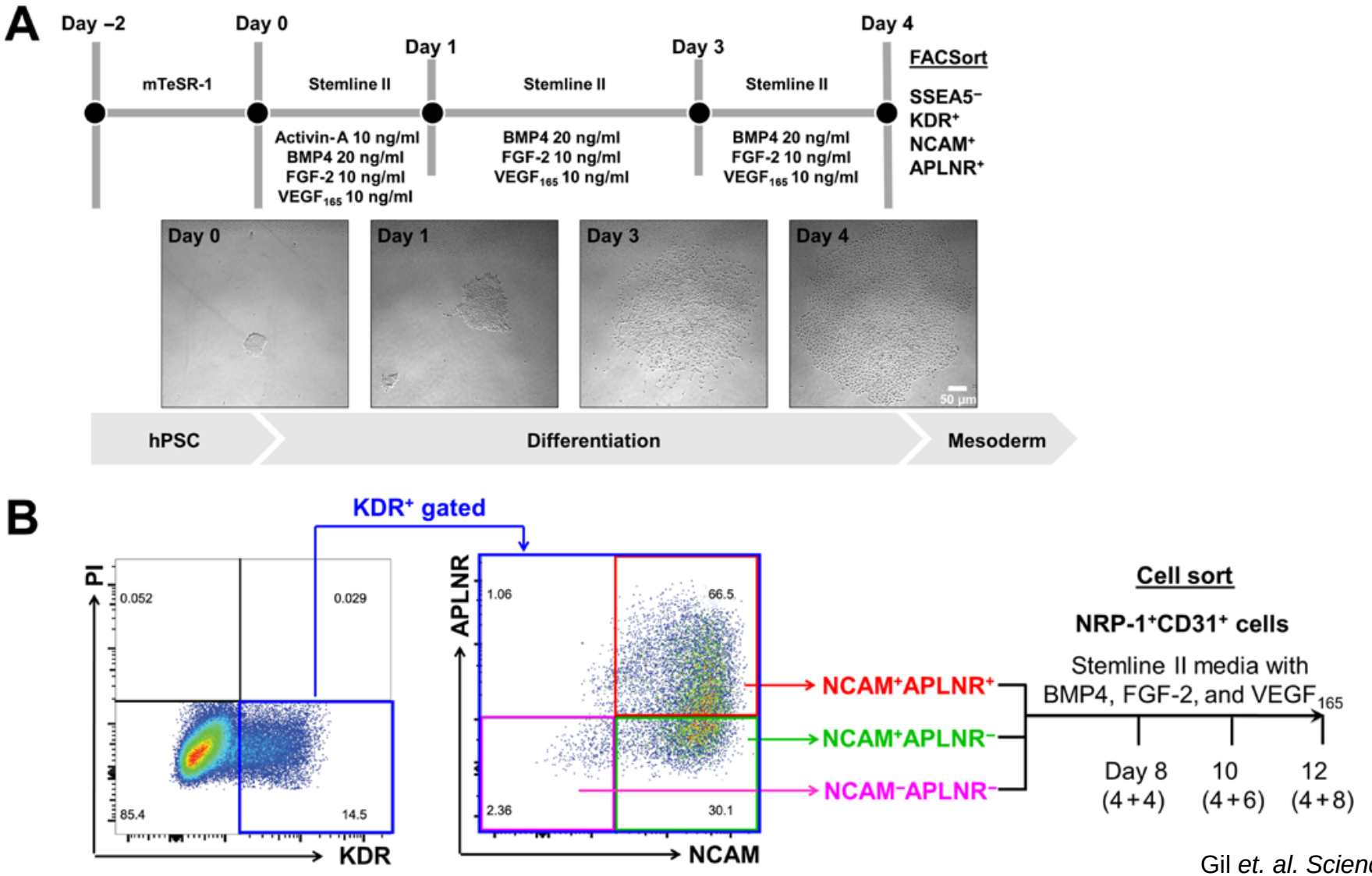


Busik et al., JEM (2009)

iPSCs for retinal repair- source of MACs and ECFCs



NCAM and APLNR co-expressing cells within KDR^{+} mesoderm cells give rise to NRP-1^{+}CD31^{+} ECs with ECFC competence



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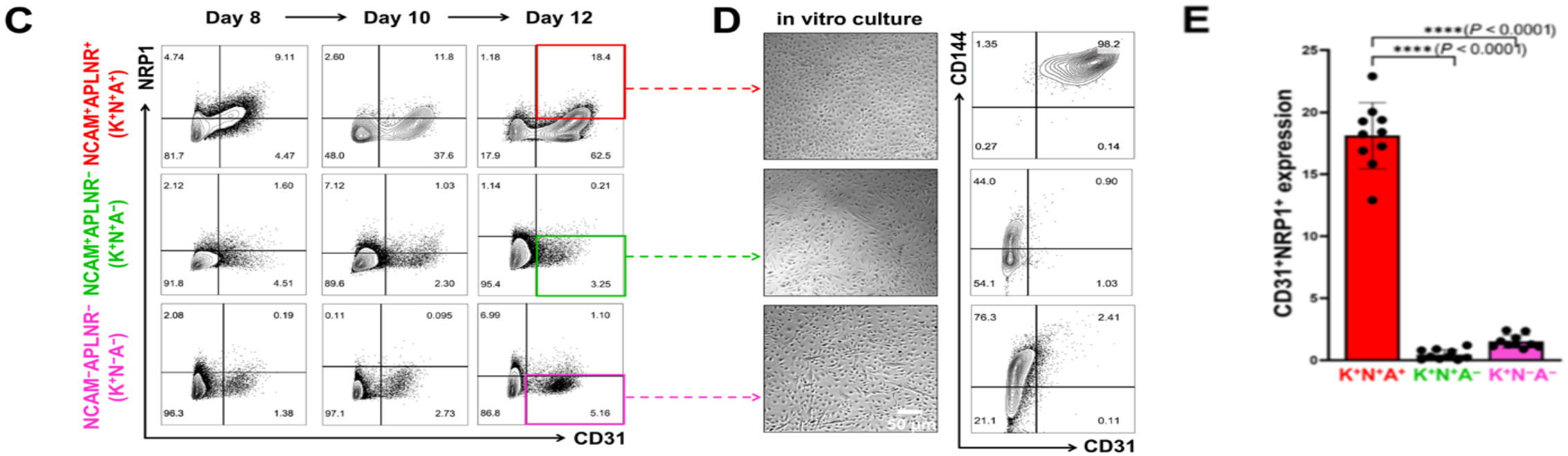
NCAM and APLNR co-expressing cells within D4 KDR^{+} mesoderm cells give rise to NRP-1^{+}CD31^{+} ECs with ECFC competence



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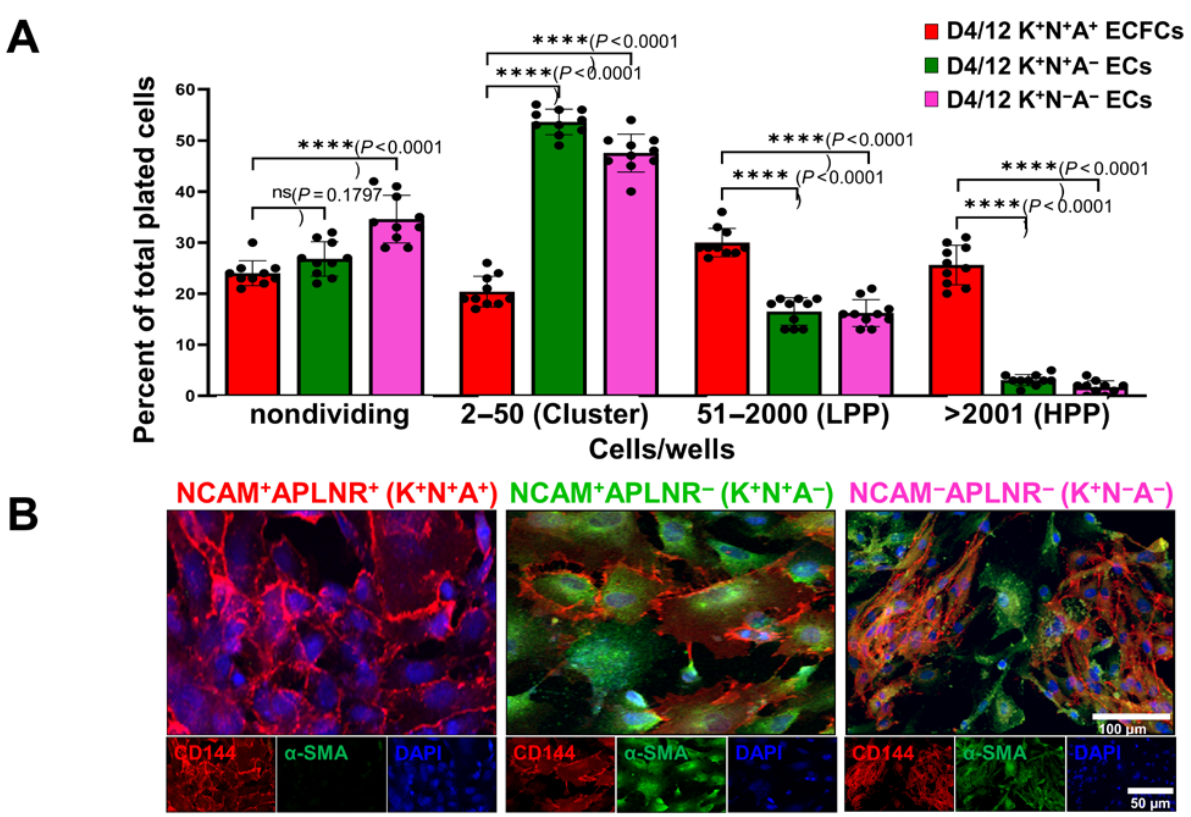
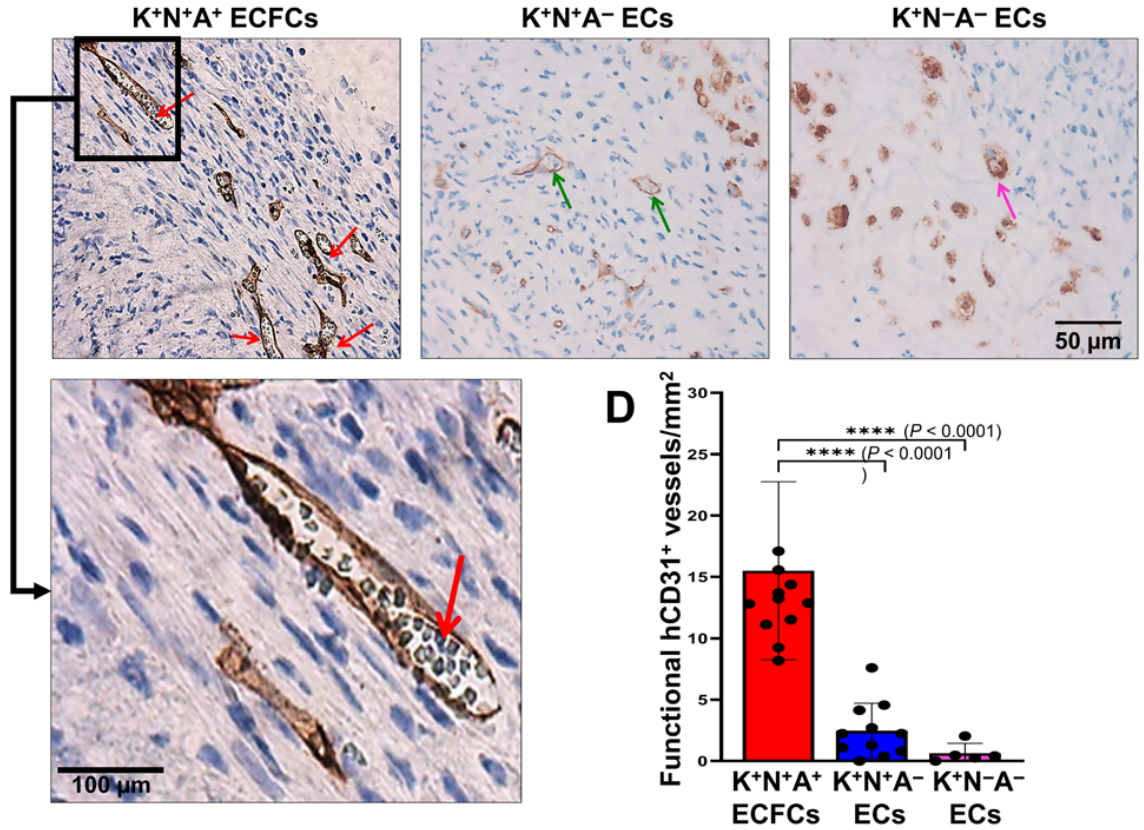
NRP-1^{+}CD31^{+} ECs exhibit ECFC competence





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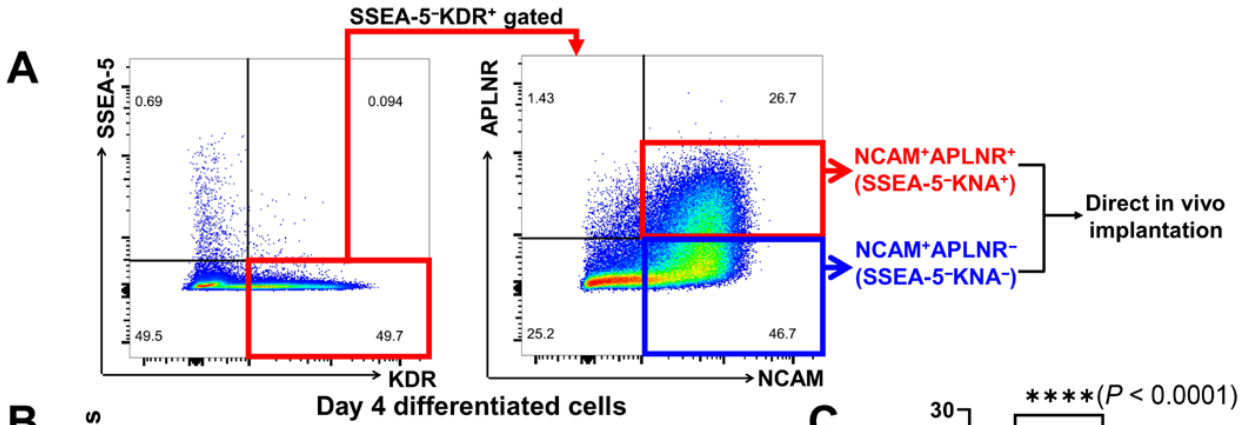
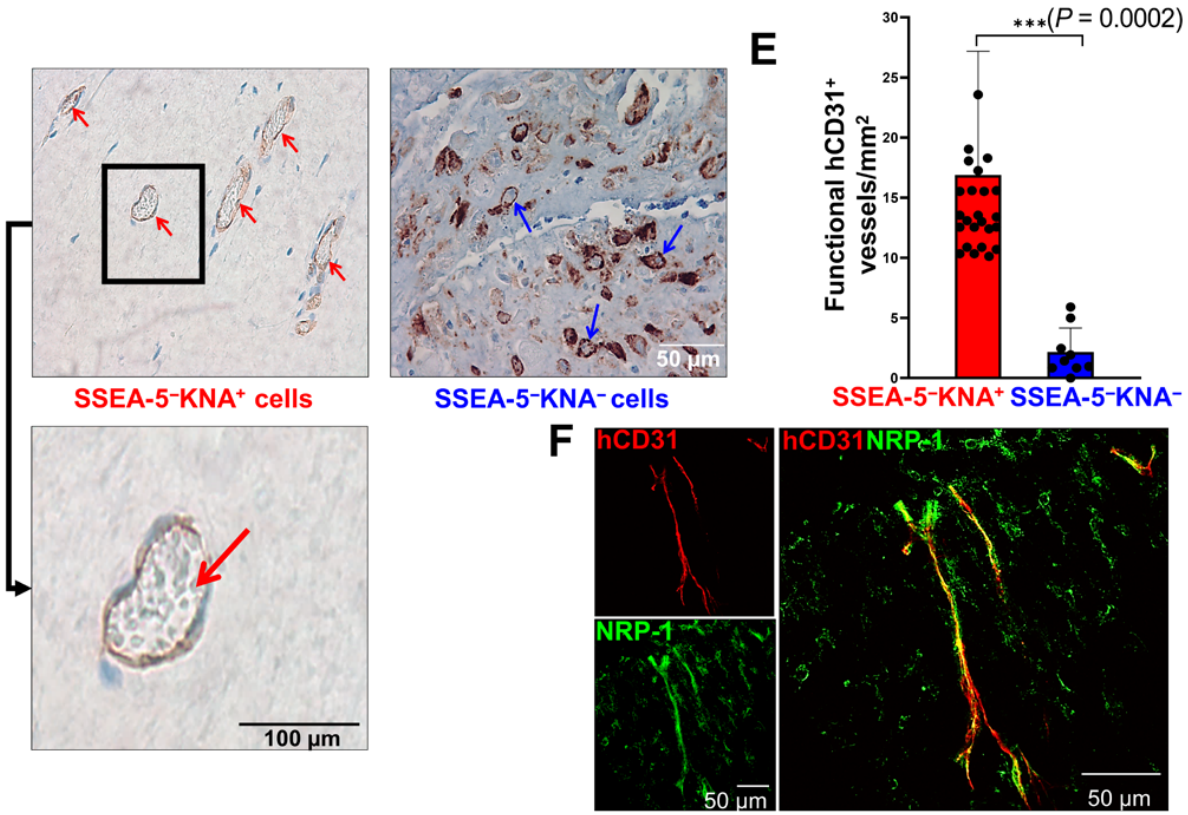
Cell sorting strategy for D4 SSEA-5 depleted KNA$^+$ mesoderm cells and direct in vivo differentiation of SSEA-5$^-$ KNA$^+$ mesoderm cells that formed robust human blood vessels without giving rise to teratomas





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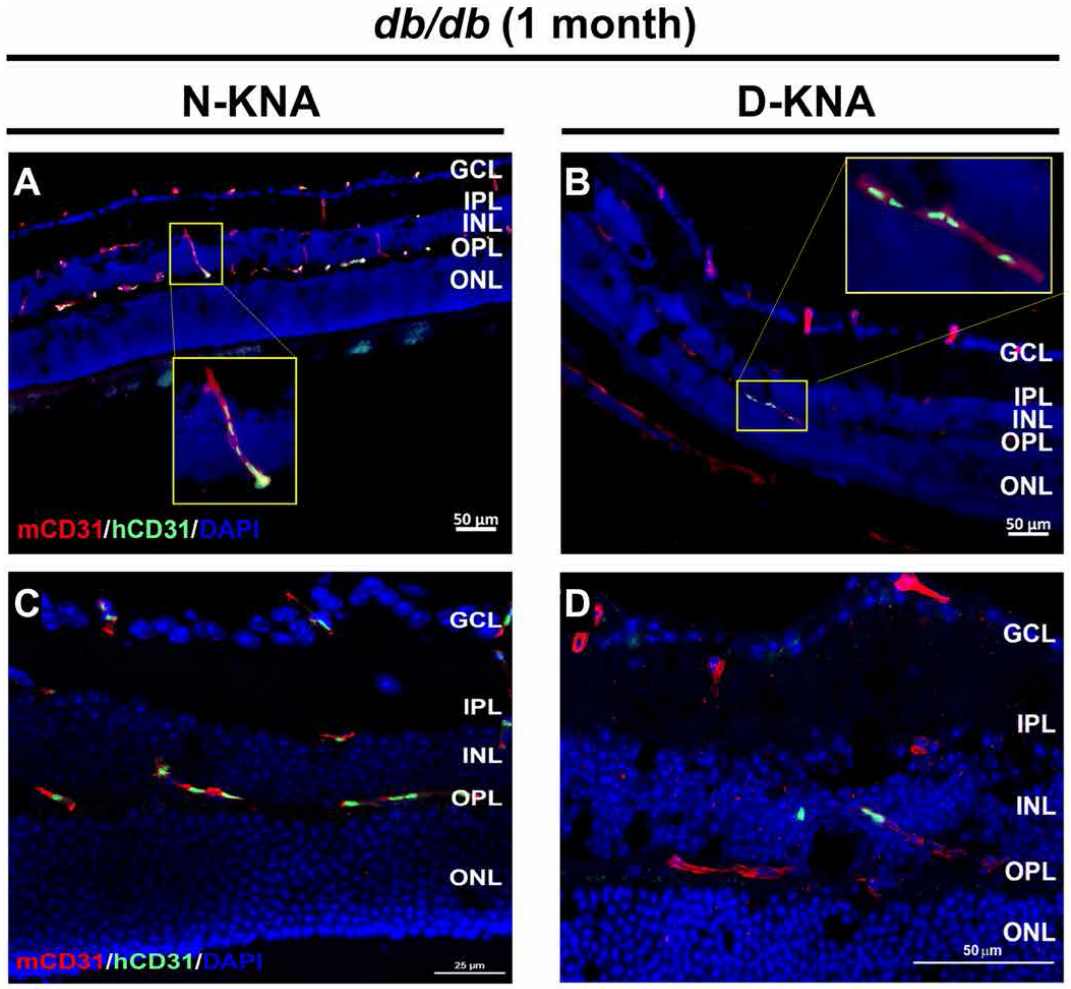
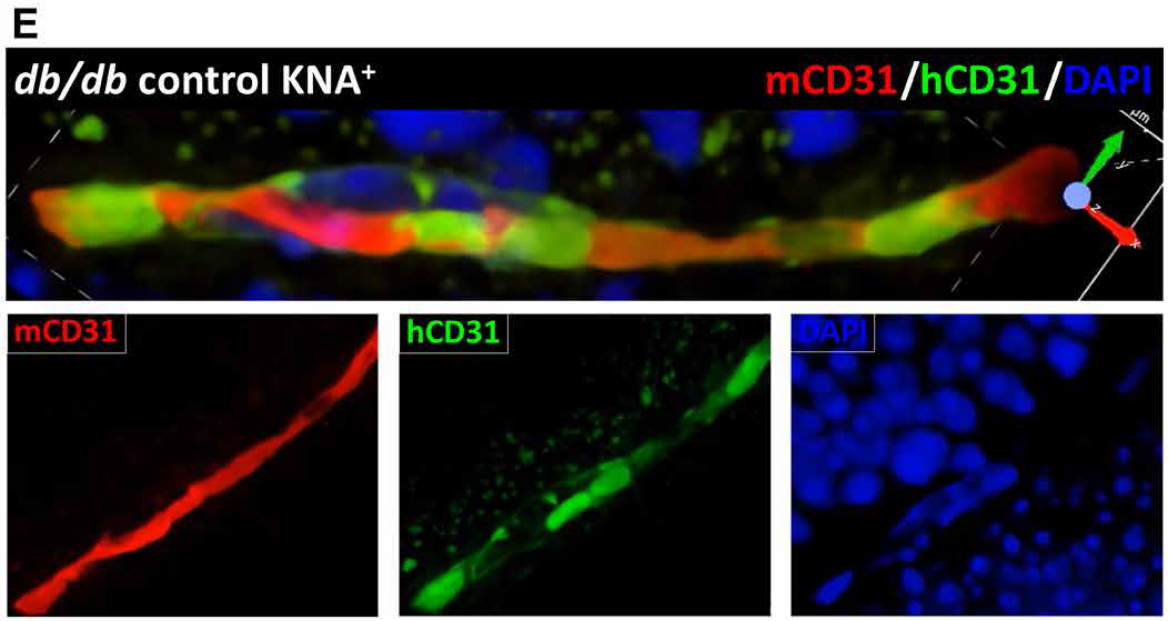
NA$^+$ cells from nondiabetic and diabetic donors integrate into retinal blood vessels of *db/db* mice 1 month after injection

Sergio Li Calzi





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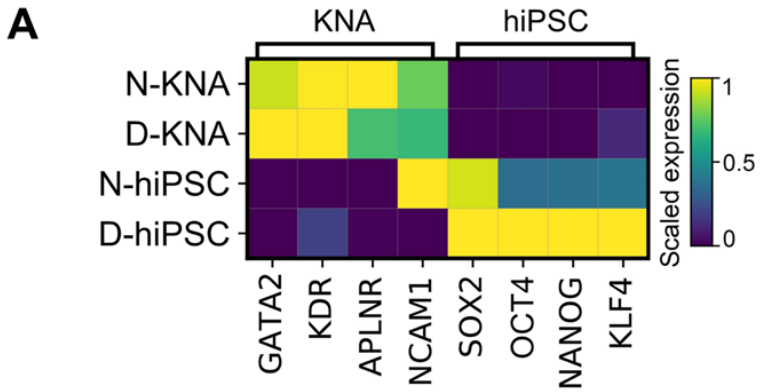
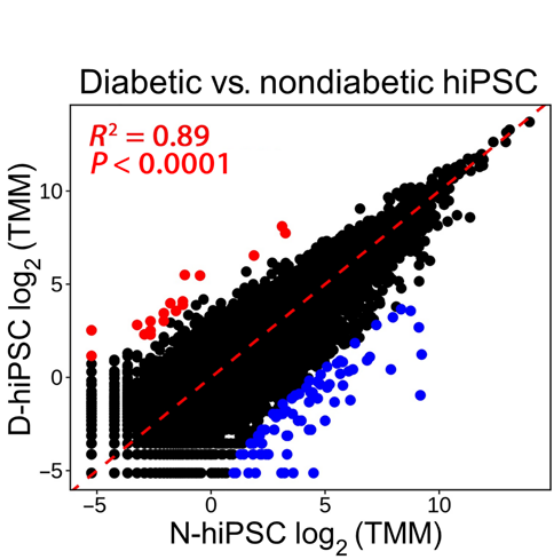
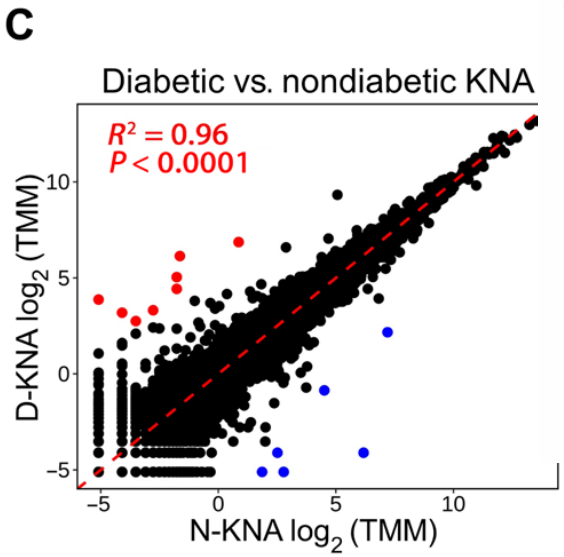
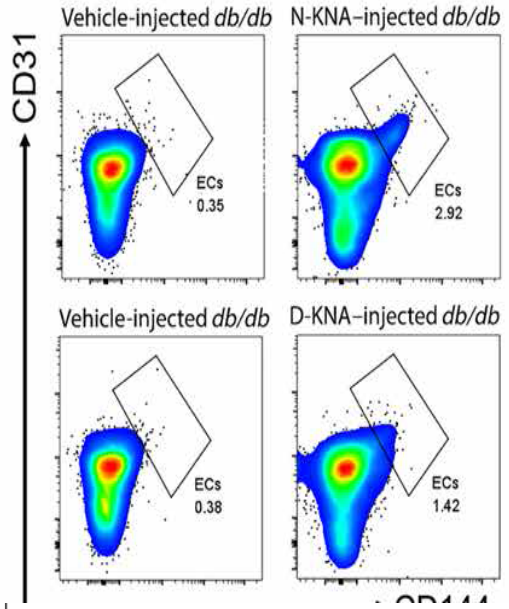
Transcriptomic analysis demonstrates that KNA cells from nondiabetic and diabetic donors are highly similar

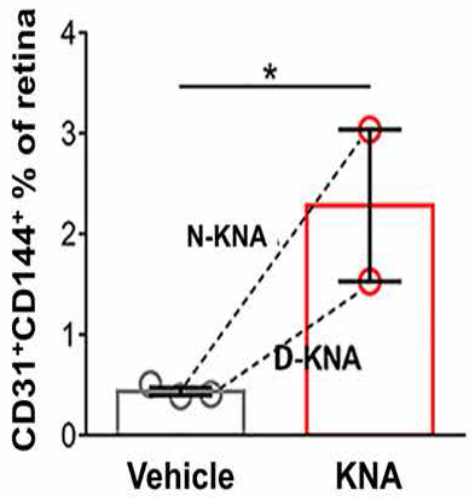
Seth Fortmann











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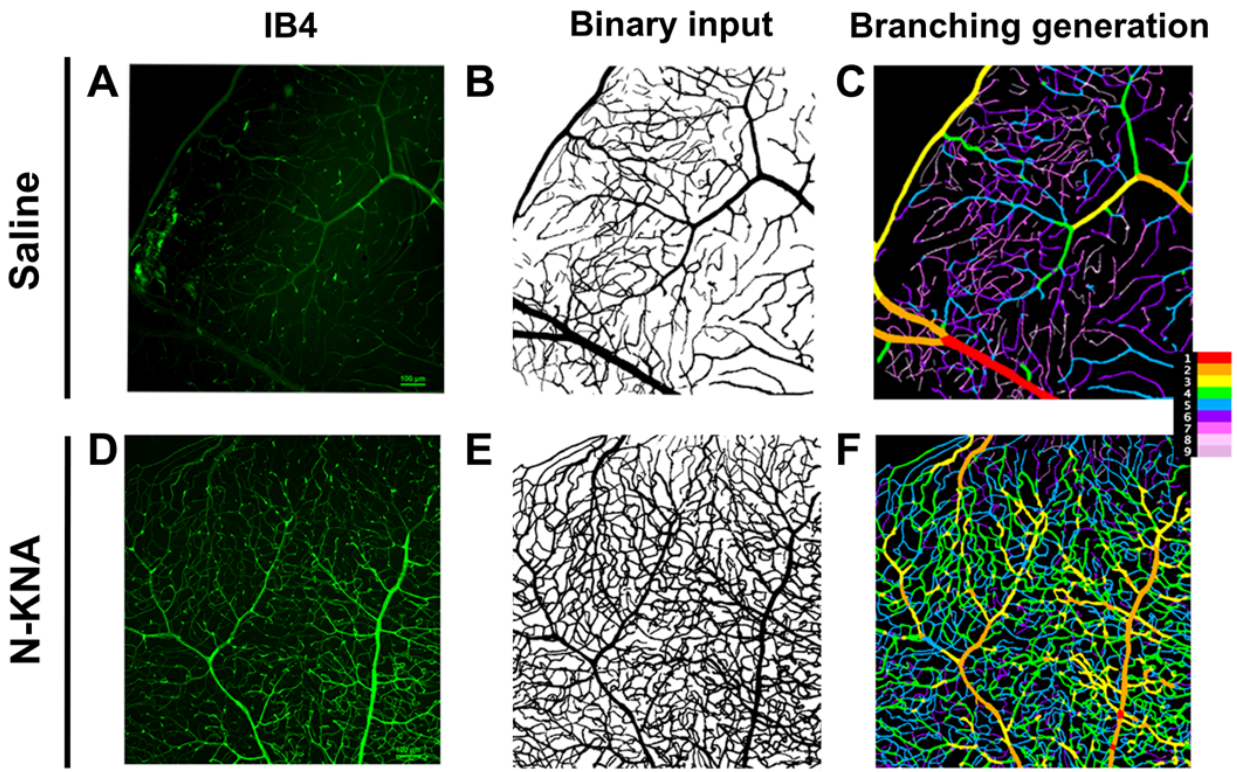
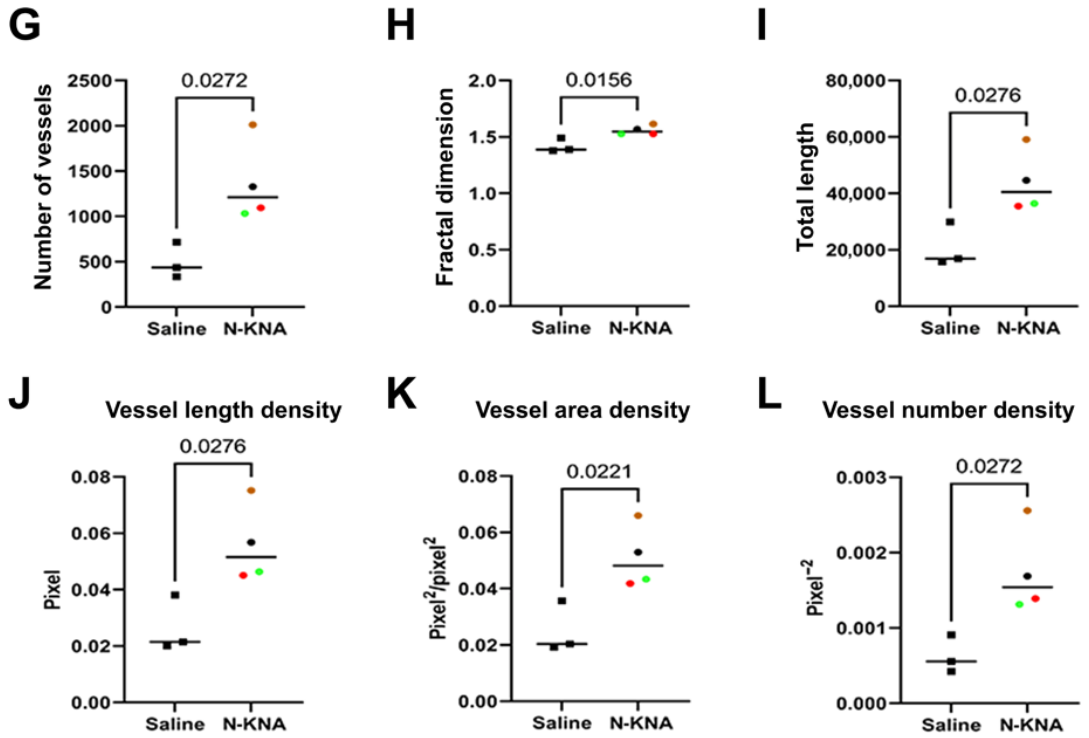
Vascular density assessment in retinas of *db/db* mice injected intravitreally with either saline or N-KNA cells.

Mariana Dupont





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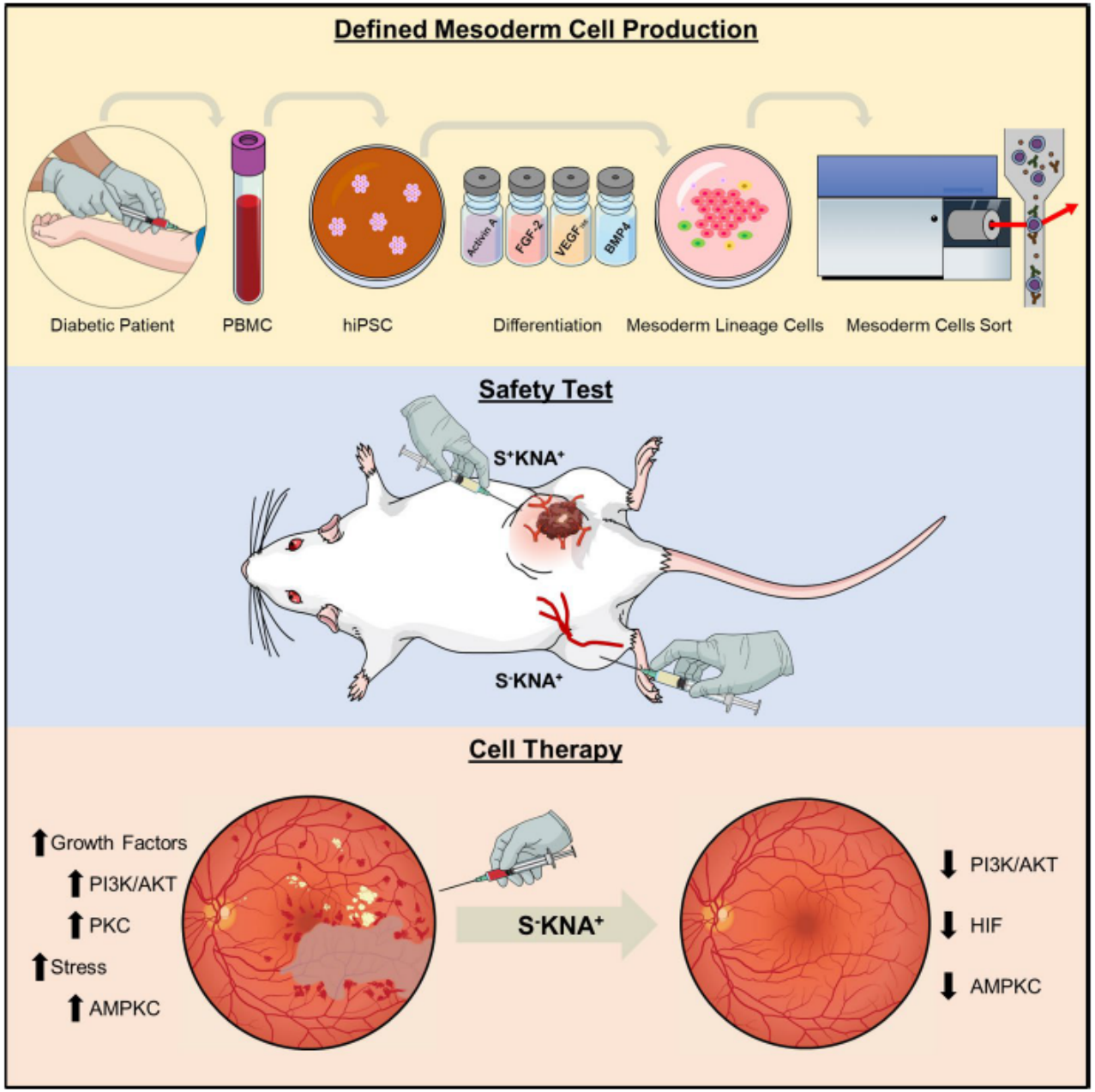
Summary 1

- Unique hiPSC –derived mesoderm population promotes robust microvascular repair in the retina
- KNA$^+$ cells from nondiabetic and diabetic sources express similar chemokine receptors, in vitro tube formation, and transcriptome
- Intravitreally injected N-KNA and D-KNA incorporate into resident vasculature of diabetic mice and remain viable for up to 4 months.



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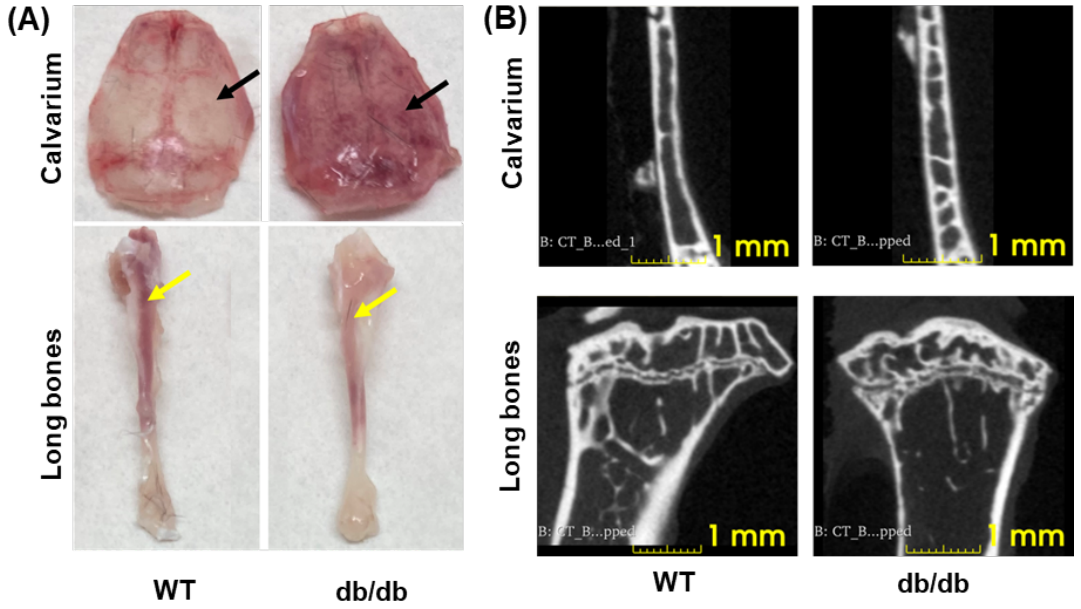
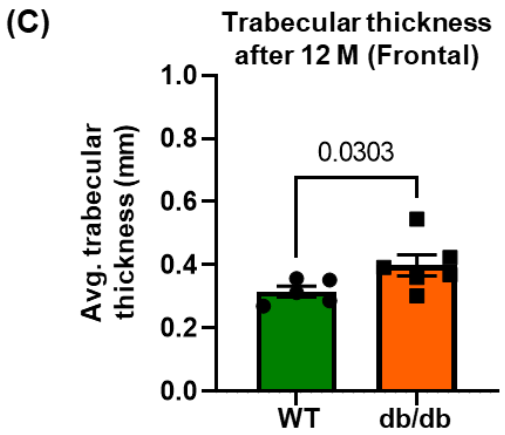
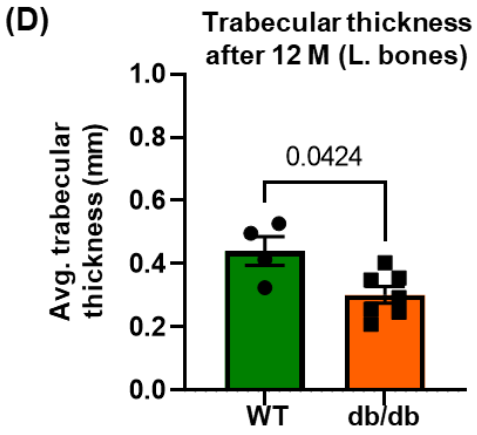
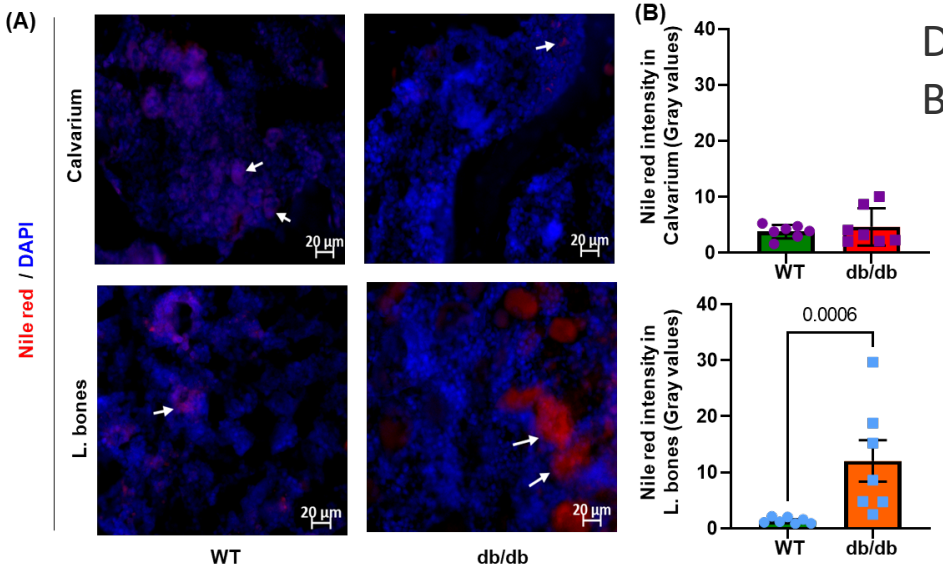
Differences in bone marrow content between the calvarium (flat bone) vs tibia (long bones) in diabetes after 12 months

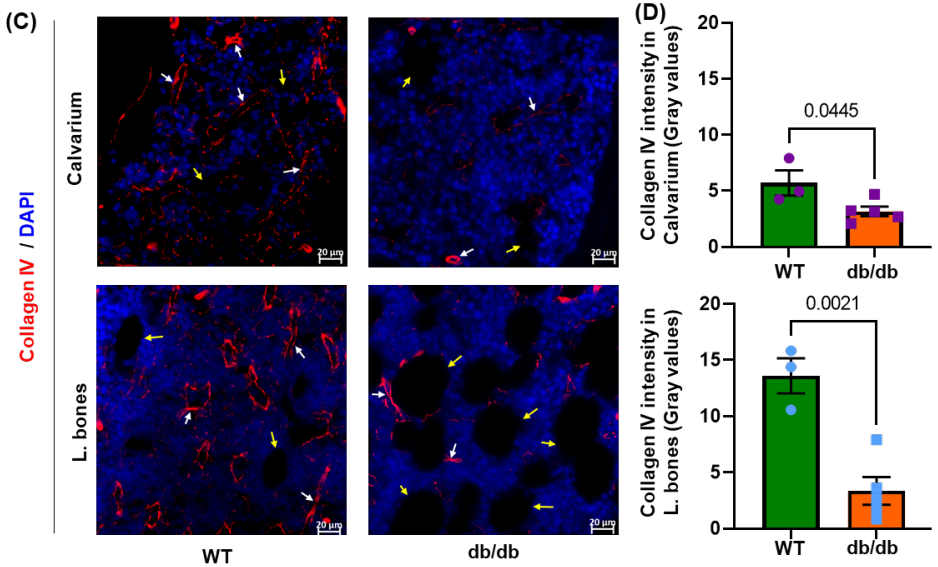
Dr. Bright Asare-Bediako





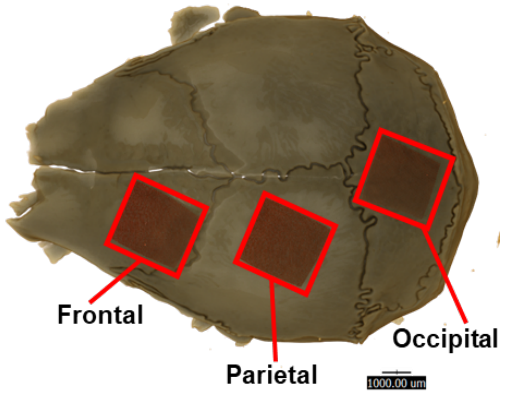




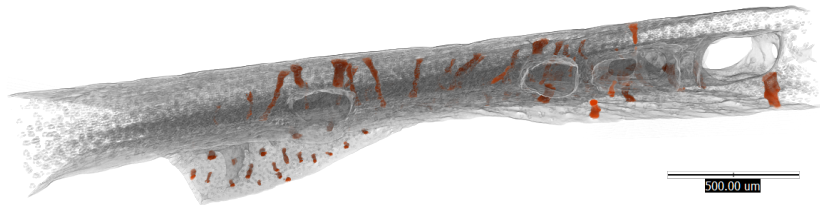


Ex vivo micro-CT Imaging of mouse calvarium reveals skull channels

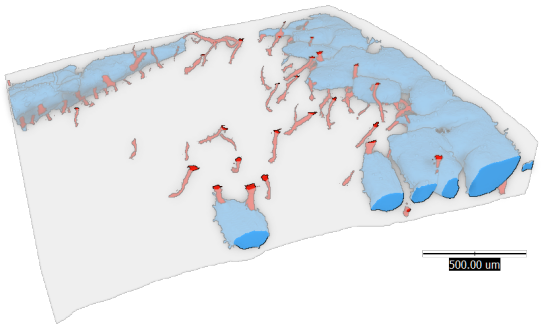
(A)



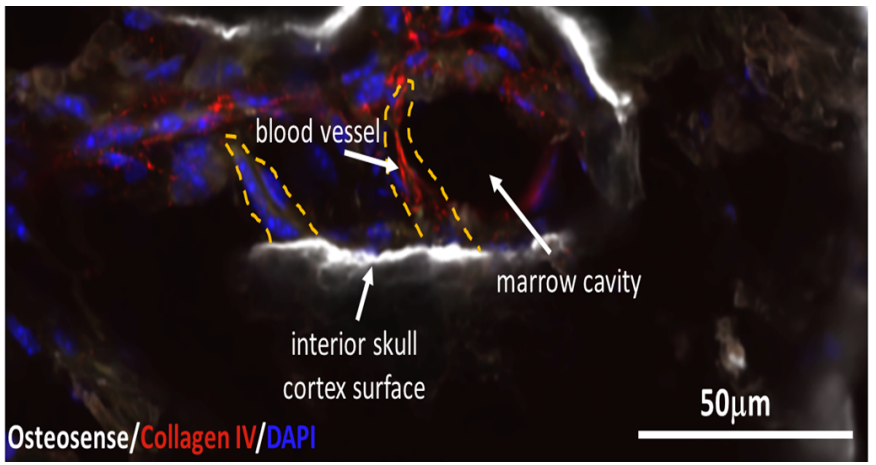
(B)



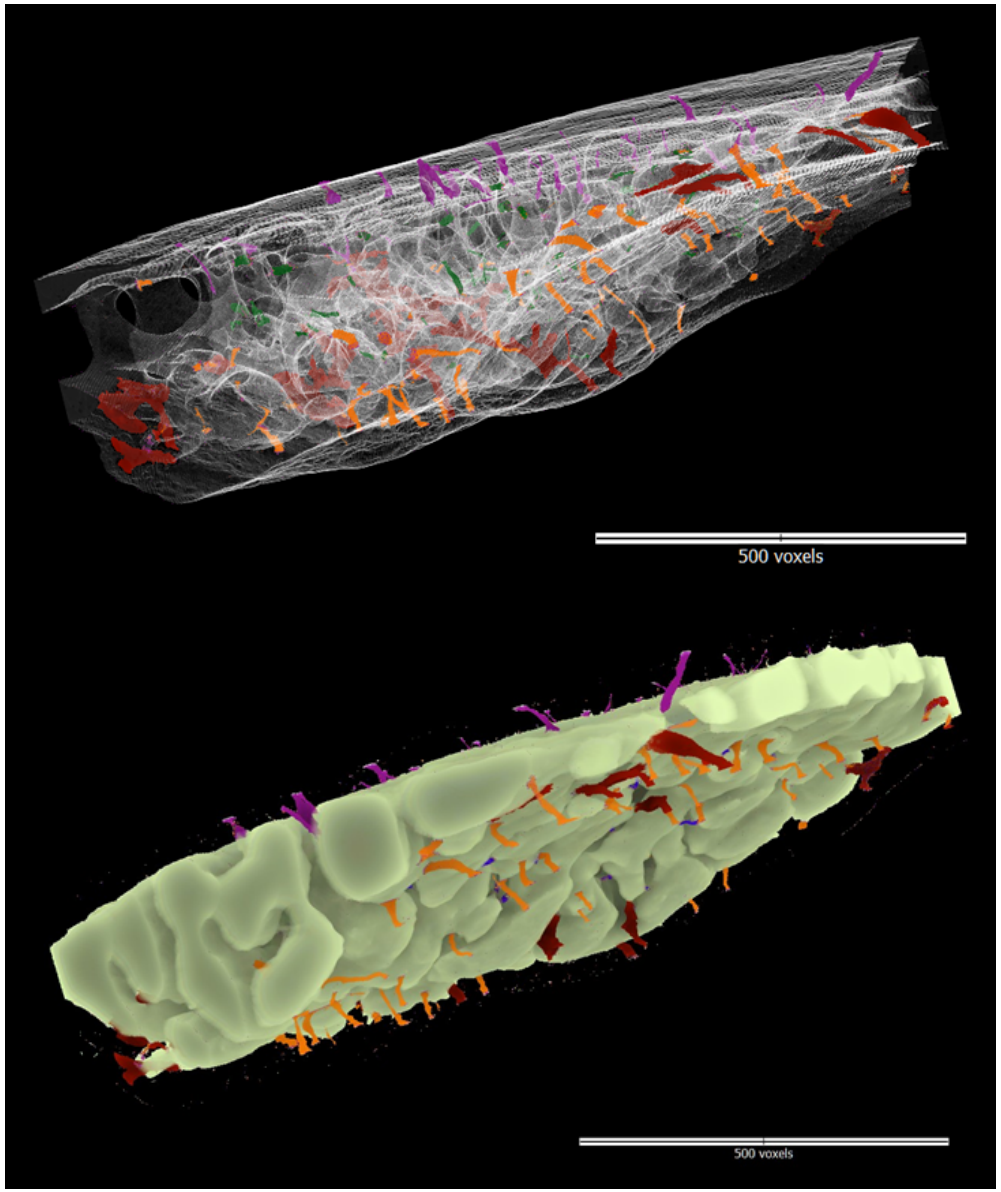
(C)

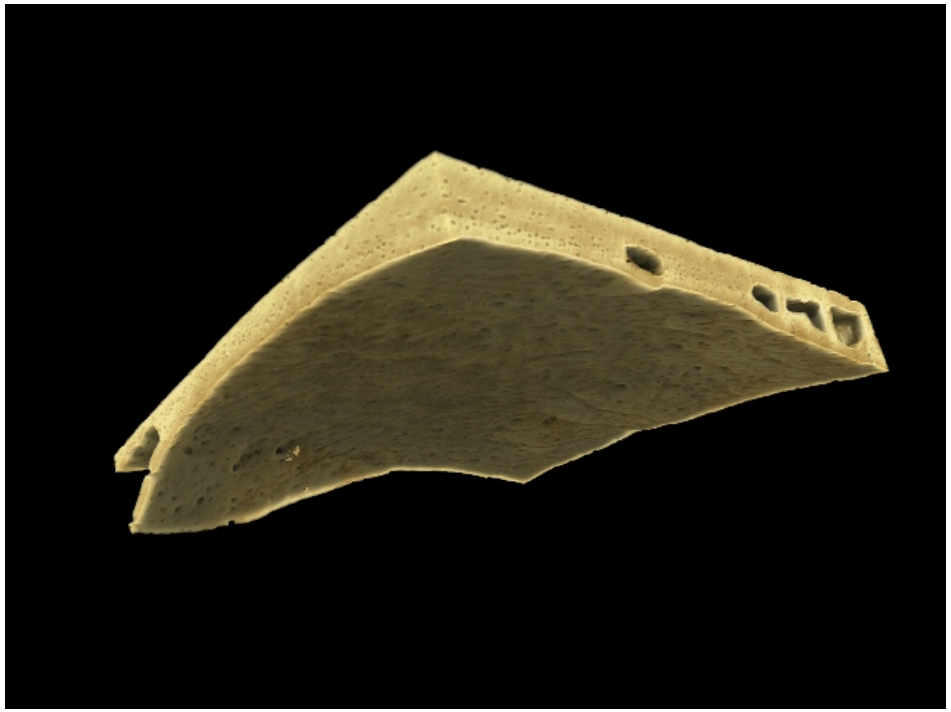


(D)



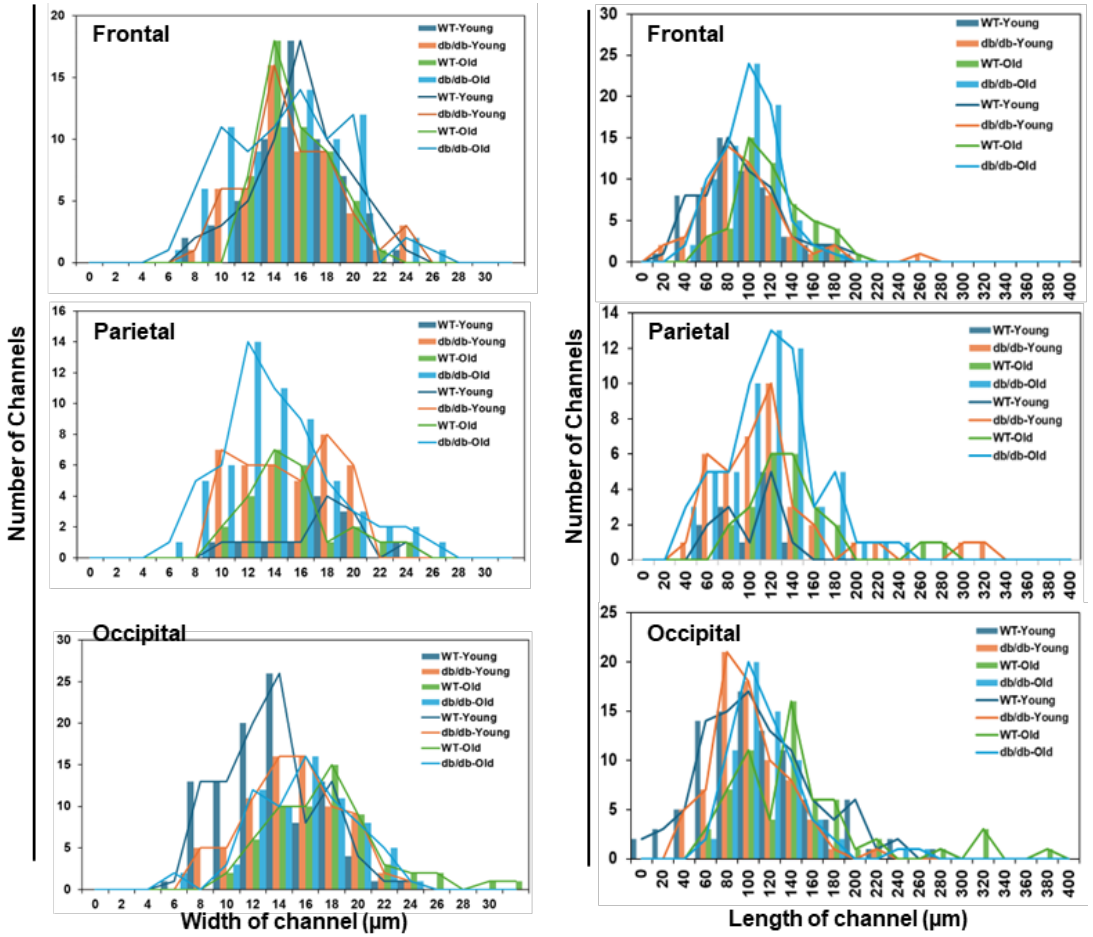
Rendering of the occipital and parietal skull sections



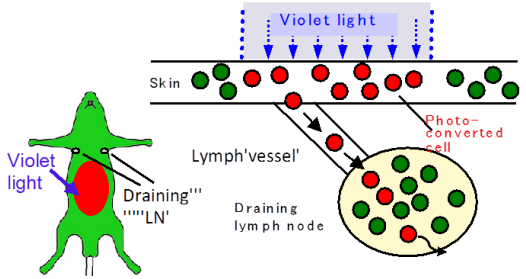


Supplementary Video File 1:

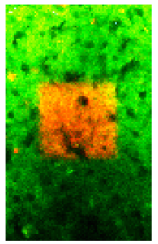
The structural features of the skull channels are similar in wild type and diabetic mice.



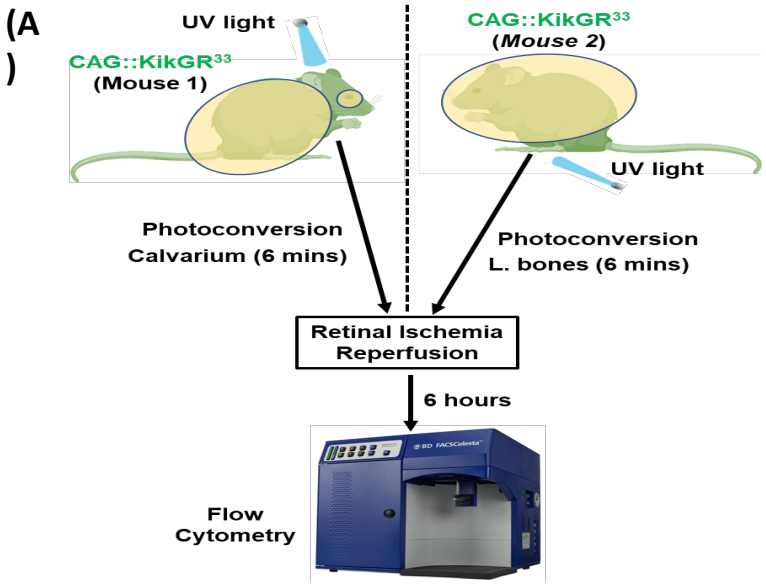
In vivo bone marrow cell labelling by photoconverting calvarial and tibial marrow of KIKGR mice for BM cell tracking

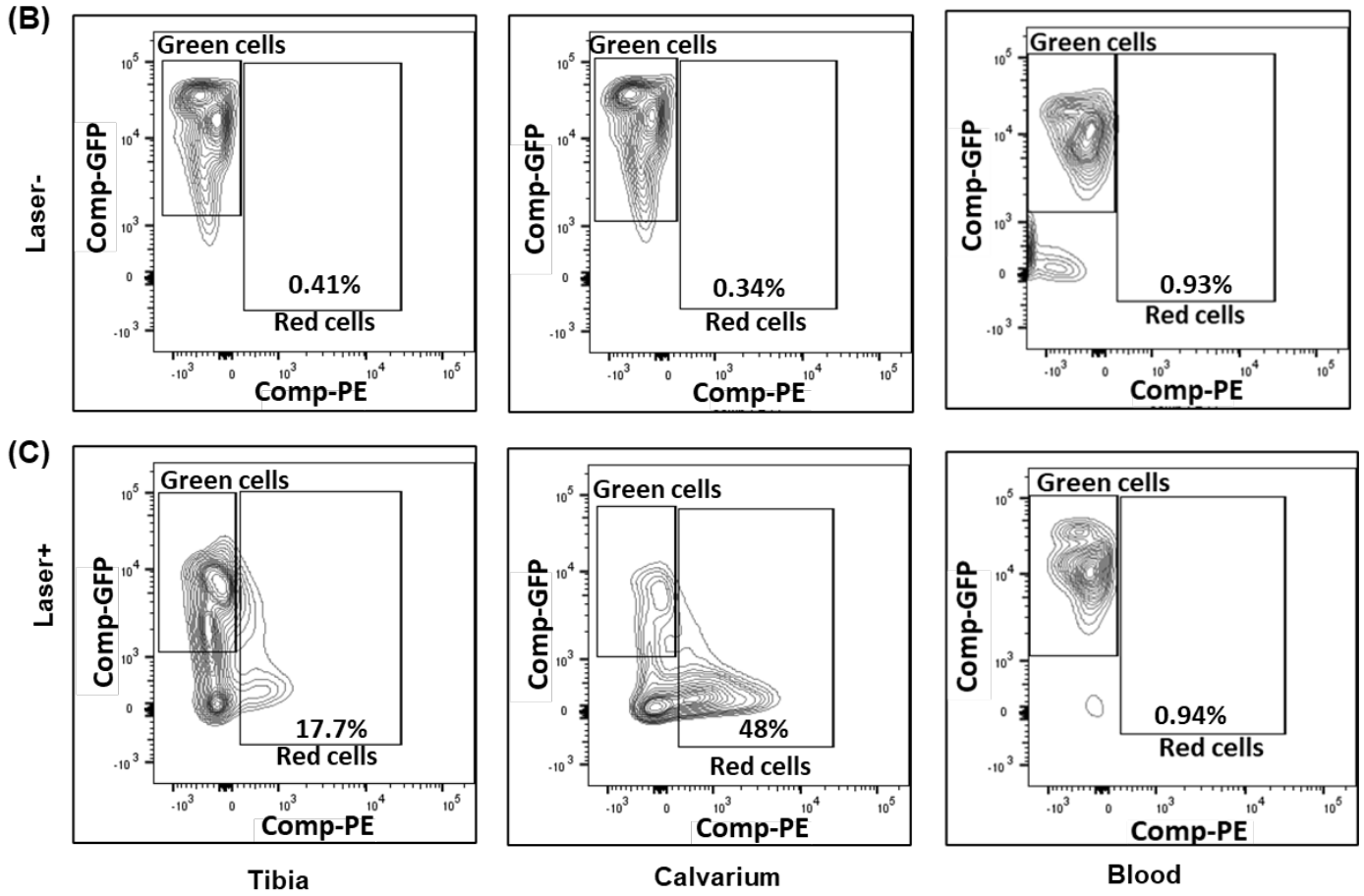


After labeling cells in skin as red color by photoconversion of KikGR, photoconverted cells migrate to draining LN. KikGR mice allow us to track cellular migration between organs in the whole body.

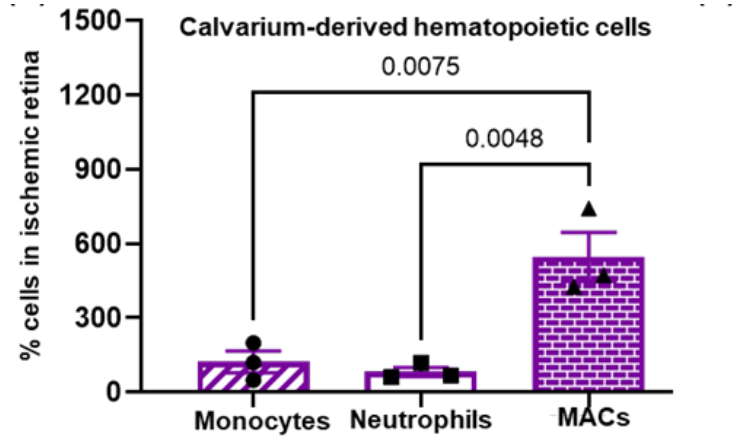


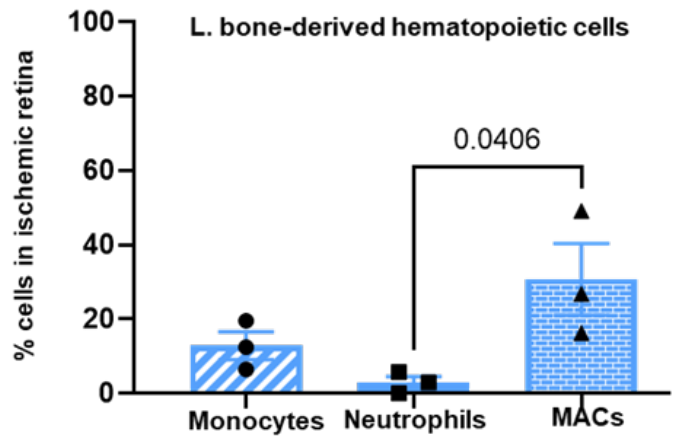
Region after exposure to two-photon laser was labeled red color.

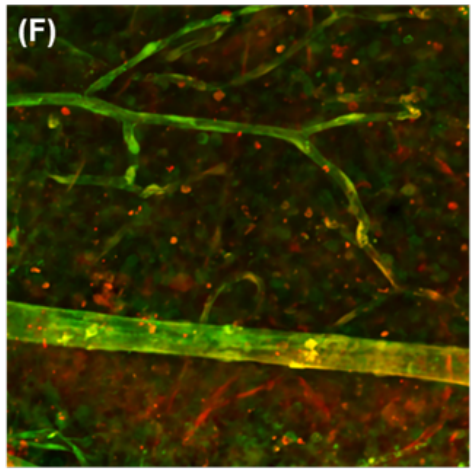




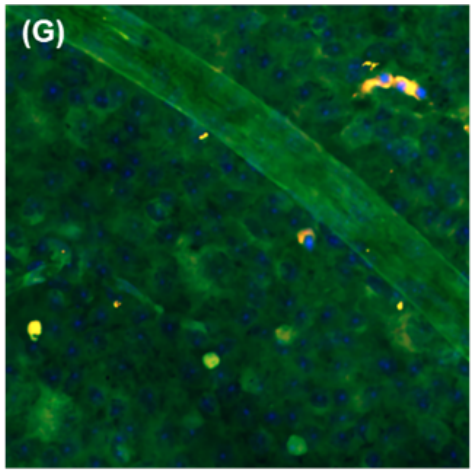
: In vivo BM cell labelling by photoconverting calvaria and tibia marrow of KIKGR mice for cell tracking.



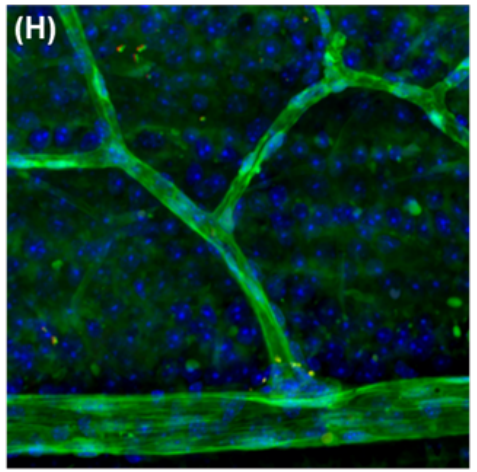




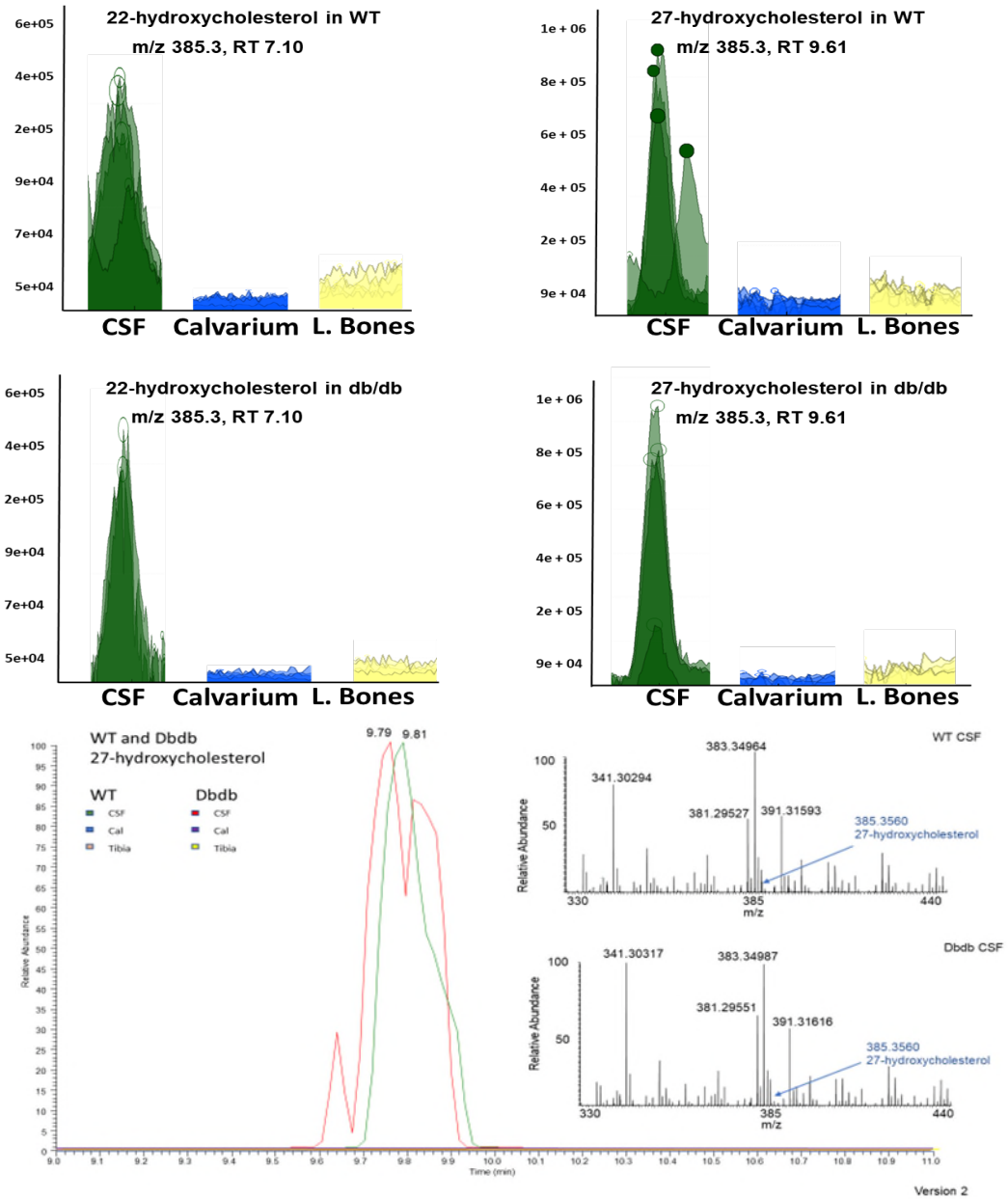
Calvarium Photoconversion followed by I/R

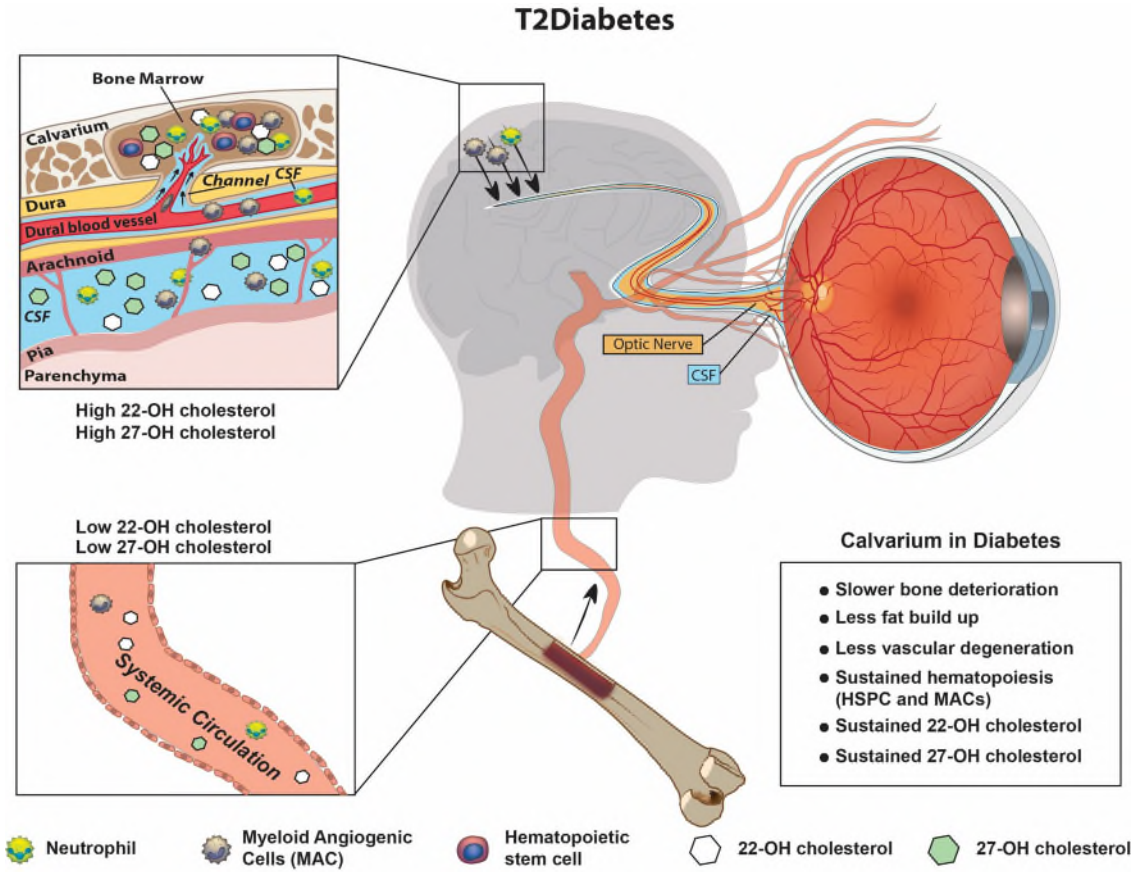


Tibia Photoconversion followed by I/R



Tibia Photoconversion, Contralateral control eye


22-hydroxycholesterol in WT
m/z 385.3, RT 7.10
CSF Calvarium L. Bones
27-hydroxycholesterol in WT
m/z 385.3, RT 9.61
CSF Calvarium L. Bones
22-hydroxycholesterol in db/db
m/z 385.3, RT 7.10
CSF Calvarium L. Bones
27-hydroxycholesterol in db/db
m/z 385.3, RT 9.61
CSF Calvarium L. Bones
WT and Dbdb
27-hydroxycholesterol
WT
Dbdb
9.79
9.81
Time (min)
WT CSF
383.34964
341.30294
381.29527
391.31593
385.3560
27-hydroxycholesterol
Relative Abundance
m/z
Dbdb CSF
341.30317
383.34987
381.29551
391.31616
385.3560
27-hydroxycholesterol
Version 2


T2Diabetes
Bone Marrow
Calvarium
Channel CSF
Dura
Dural blood vessel
Arachnoid
CSF
Pia
Parenchyma
High 22-OH cholesterol
High 27-OH cholesterol
Optic Nerve
CSF
Low 22-OH cholesterol
Low 27-OH cholesterol
Systemic Circulation
Calvarium in Diabetes
• Slower bone deterioration
• Less fat build up
• Less vascular degeneration
• Sustained hematopoiesis (HSPC and MACs)
• Sustained 22-OH cholesterol
• Sustained 27-OH cholesterol
Neutrophil
Myeloid Angiogenic Cells (MAC)
Hematopoietic stem cell
22-OH cholesterol
27-OH cholesterol

Summary 2

- Calvarium is protected from diabetes-induced damage
- Bone marrow compartment is directly connected with CSF, rich source of growth factors and anti-inflammatory factors
- Following CNV or I/R ocular injury robust recruitment of MACs and neutrophils occurs from the calvarium and monocytes from the tibia

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