

5th INTERNATIONAL OTTAWA HEART CONFERENCE
30-31 March 2017, Ottawa, Canada

Impaired Interstitial HDL Transit in Psoriasis: an Immunological Clue in Atherosclerosis

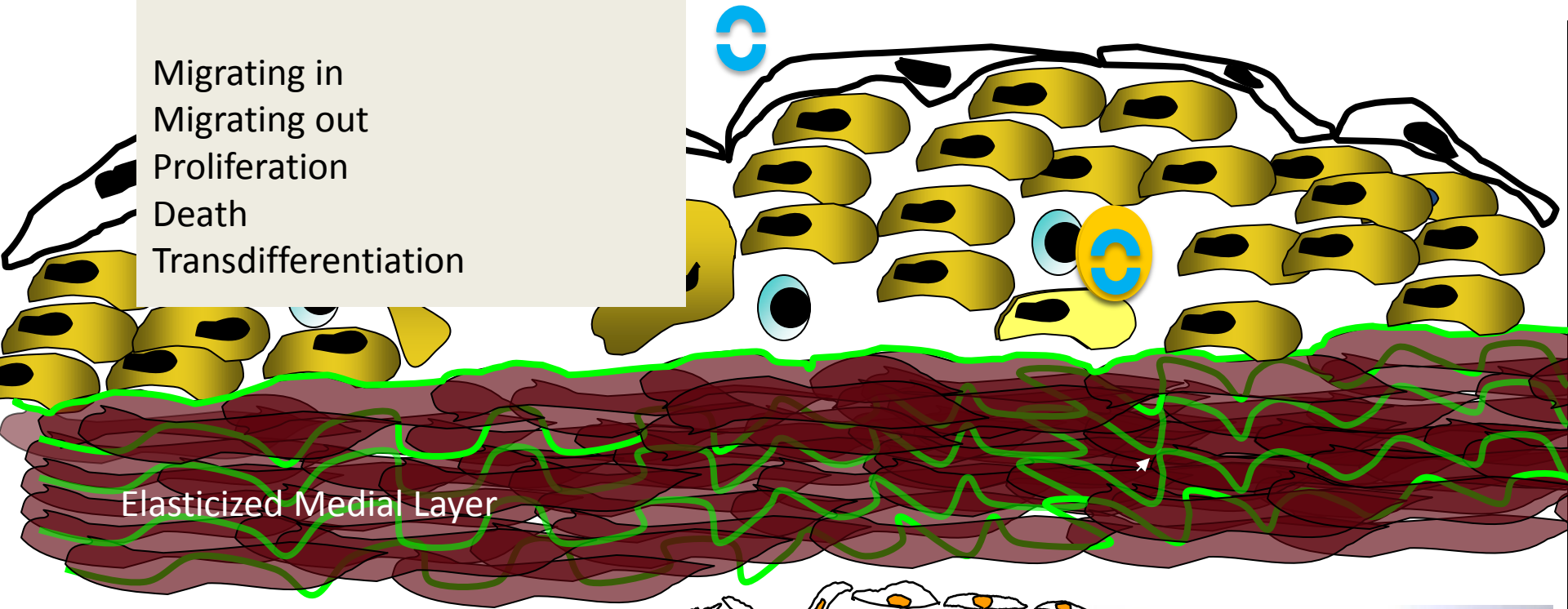
Li-Hao “Paul” Huang
Gwen Randolph Lab

Department of Pathology and Immunology
Washington University in St. Louis

I have no disclosure.

Macrophage Content:

- Migrating in
- Migrating out
- Proliferation
- Death
- Transdifferentiation

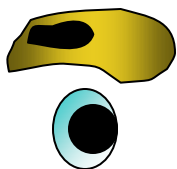


Elasticized Medial Layer

Adventitia

Capillary

Lymphatic



Macrophage

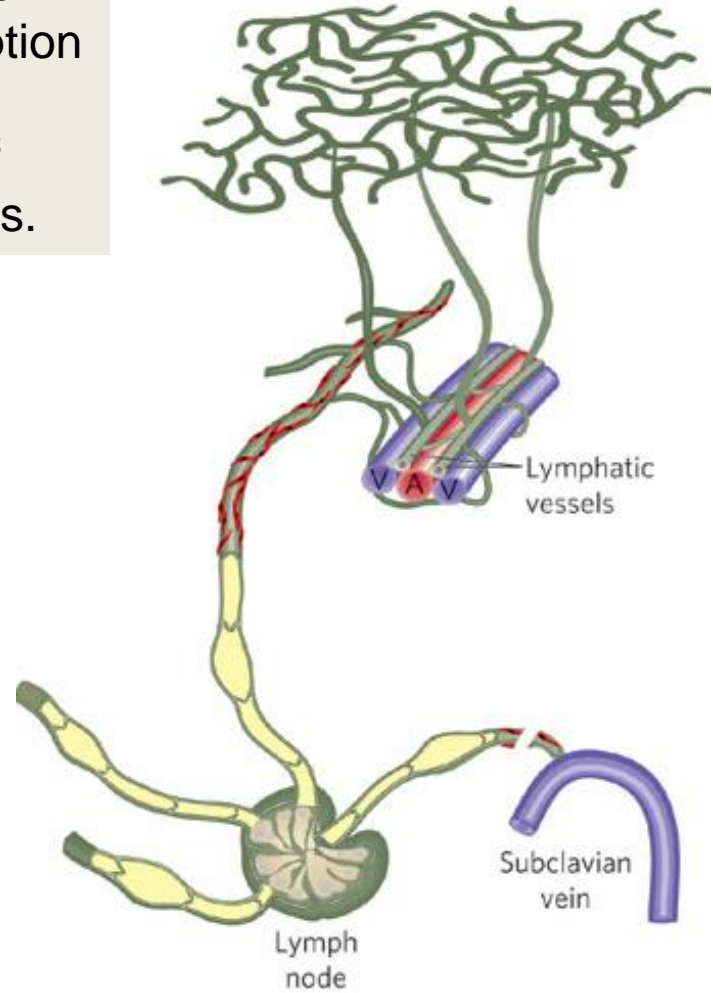
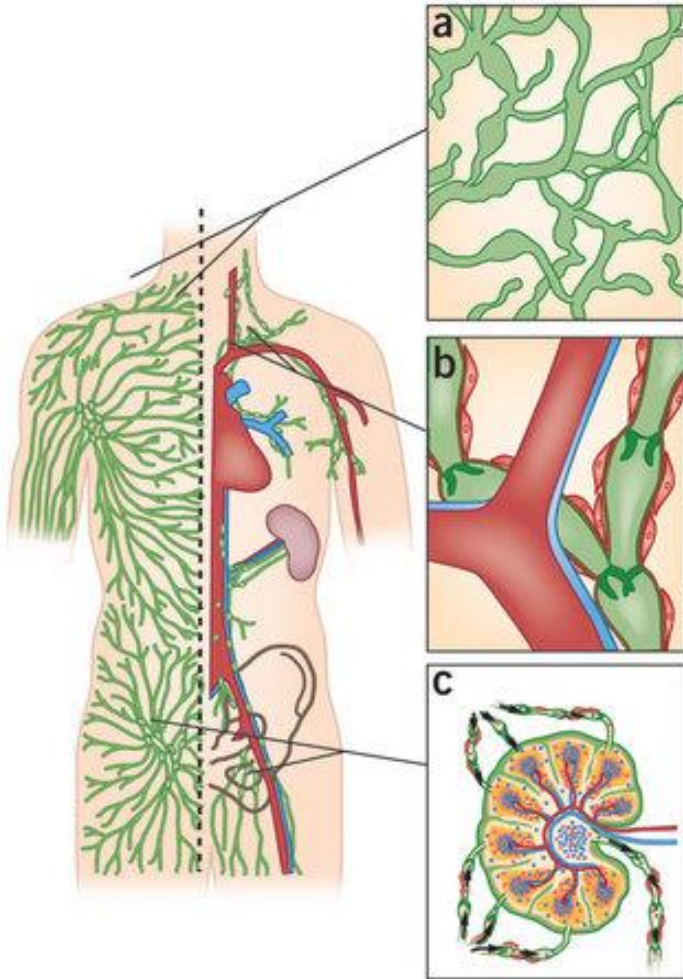
Lymphocyte

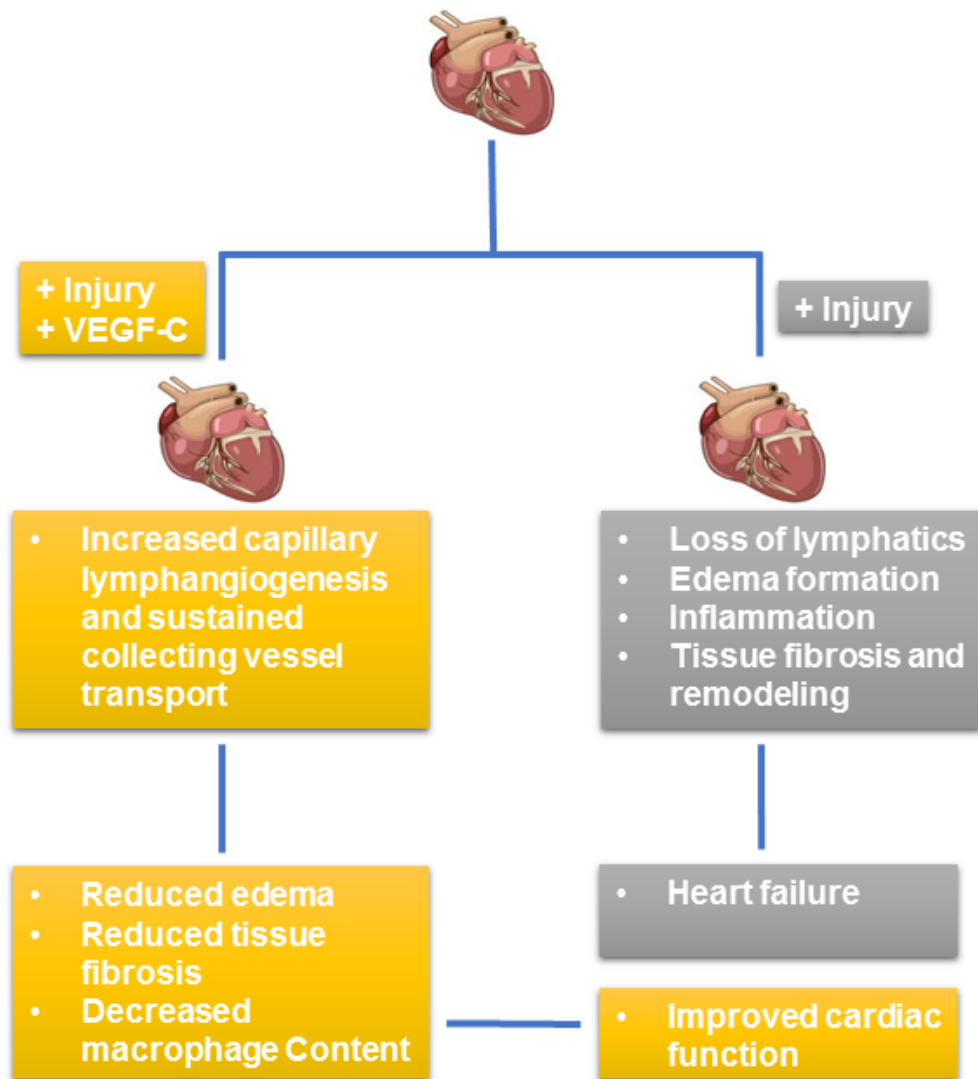
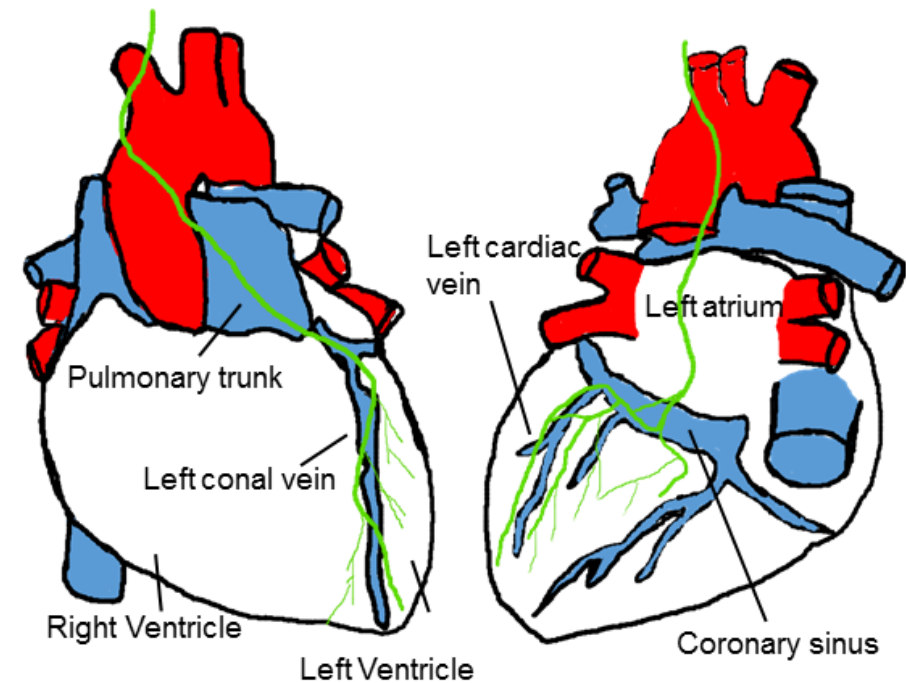
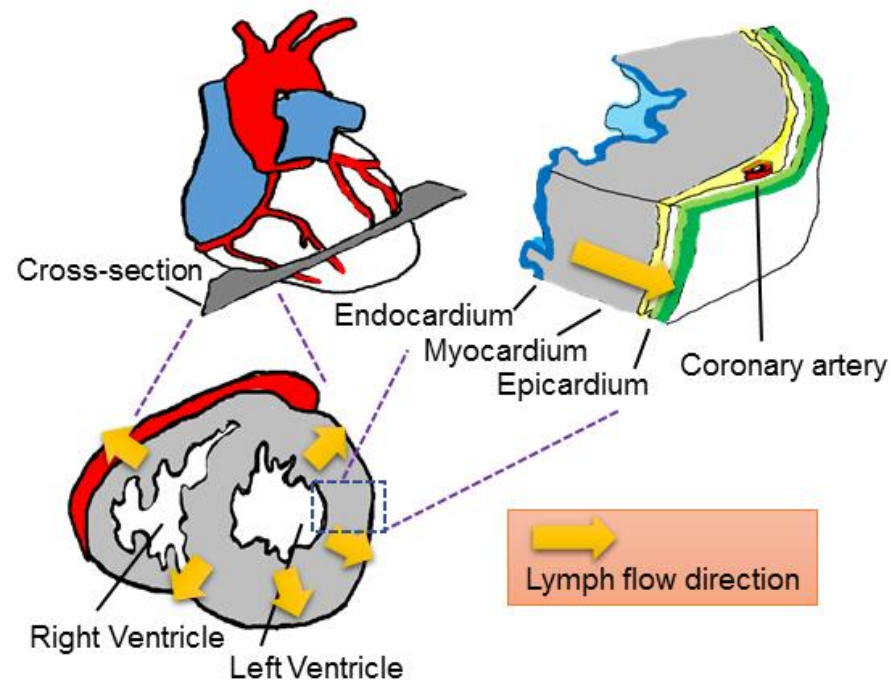


5 times faster

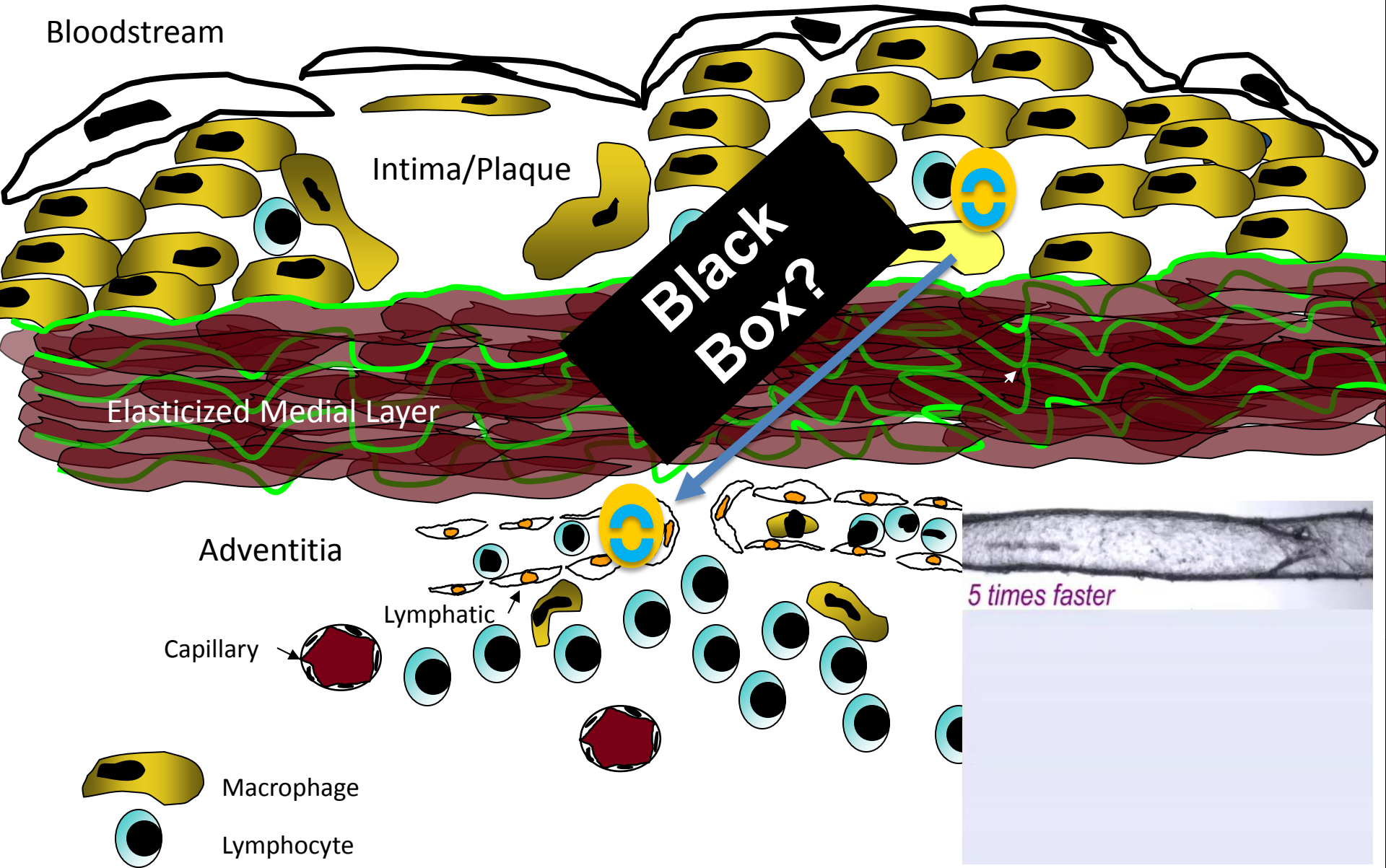
Lymphatic Vasculature

1. Fluid homeostasis.
2. Lipid absorption in gut.
3. Transport of immune cells.

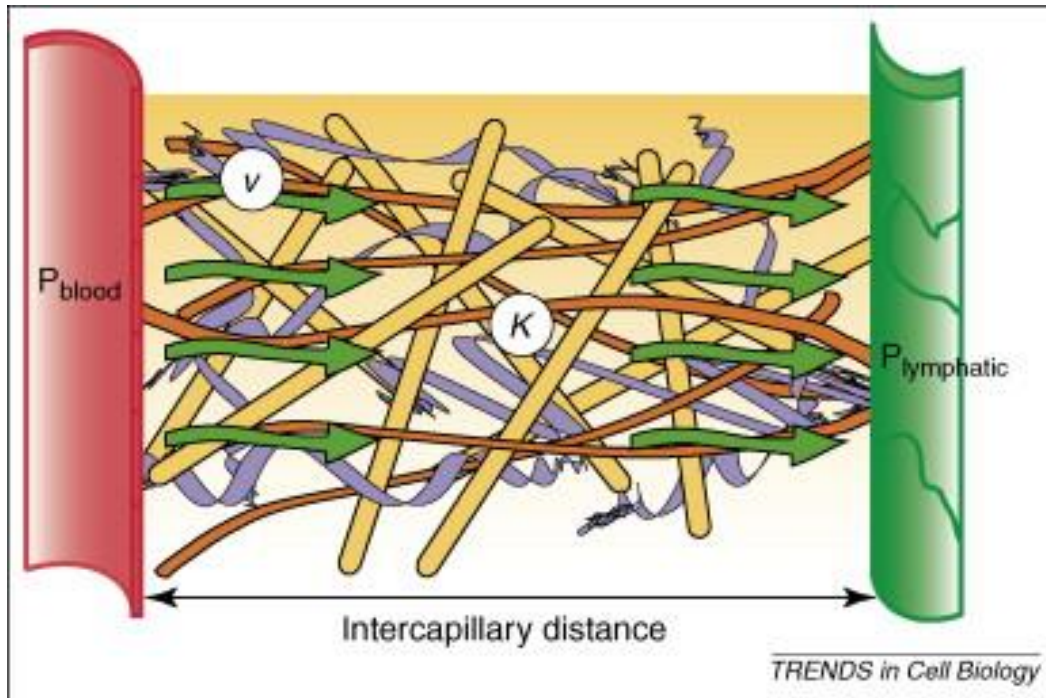




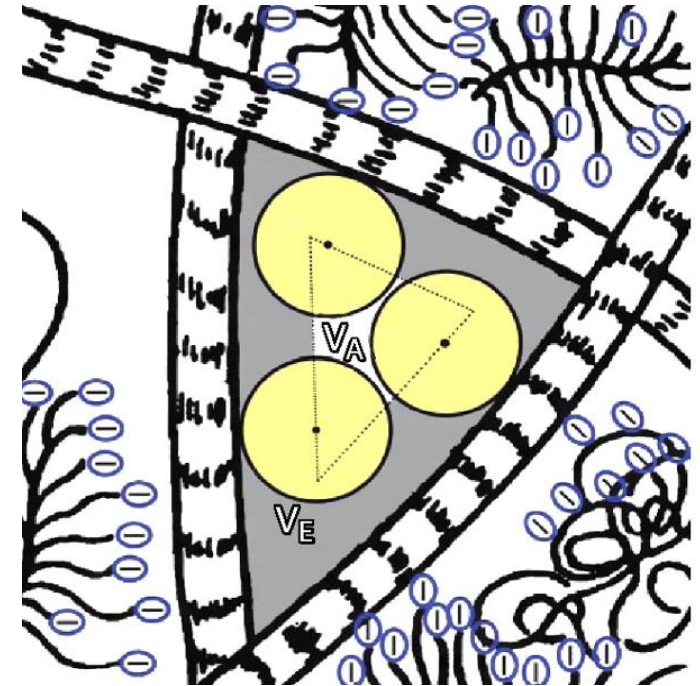
HDL passage through tissue is a black box.....



Schematic Models of the Interstitium and the Exclusion Phenomenon

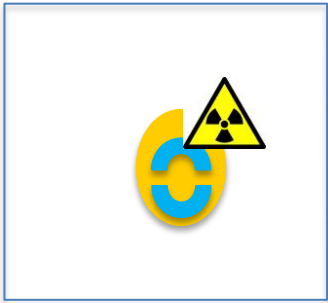


Joseph M. Rutkowski, Melody A. Swartz. Trends Cell Biology, 2007.

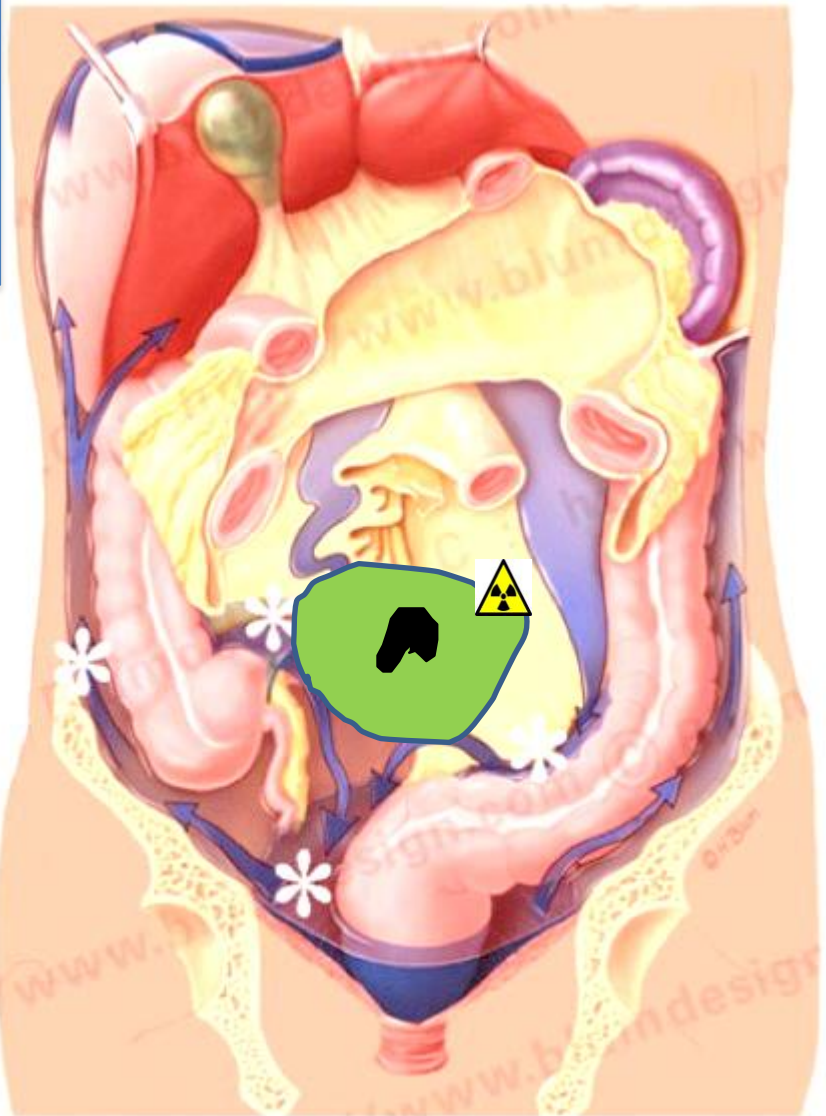


Helge Wiig, and Melody A. Swartz Physiol Rev 2012

Current Gold Standard for Studies on How HDL Moves out of Tissues

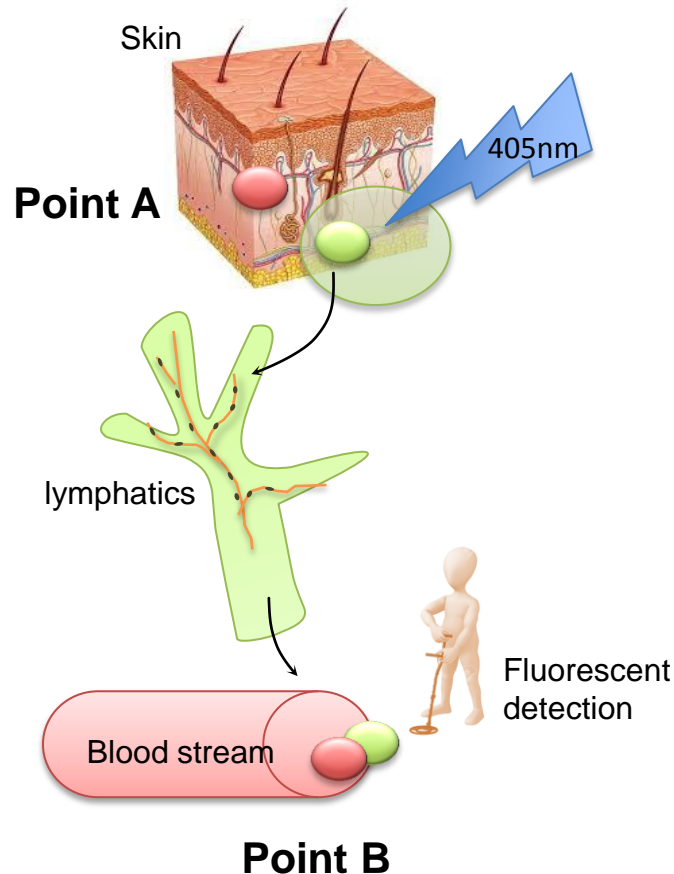


plasma

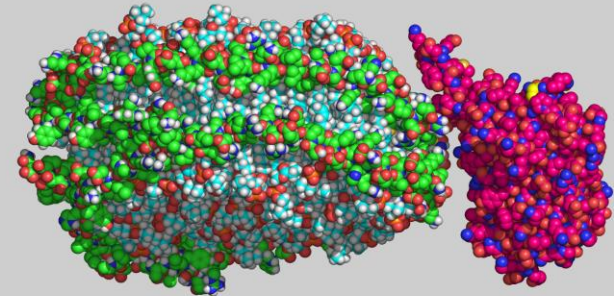


- Good way to study requirements in macrophages.
- Limited to peritoneal cavity.
- Does not assess how local changes in a tissue might influence HDL trafficking dynamics.

A New Tool to Follow Molecular Export from Tissue to Plasma...



PGA1: photoactivated GFP-hApoA1



hApoA1

PAGFP

- *In vitro*, PGA1 accepts cholesterol like native HDL
- Linear photoactivation in the presence of 405 nm laser light

PGA1 HDL Can be Reconstituted *in Vivo*

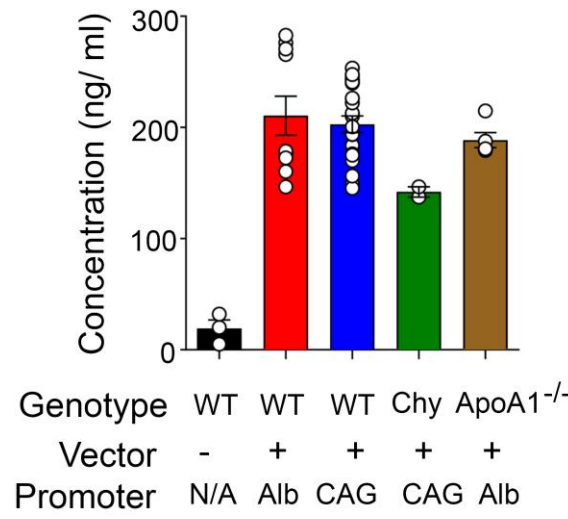
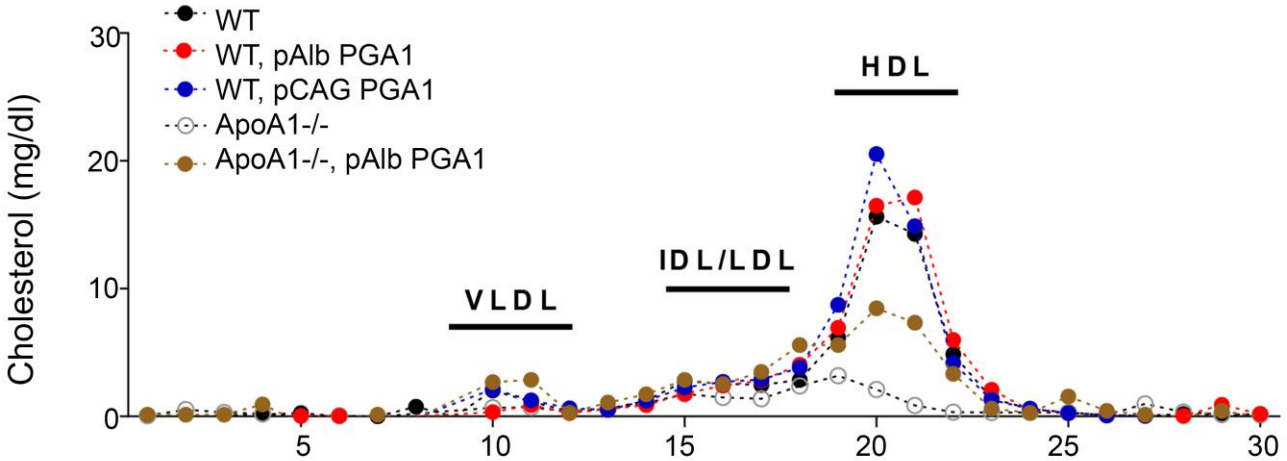
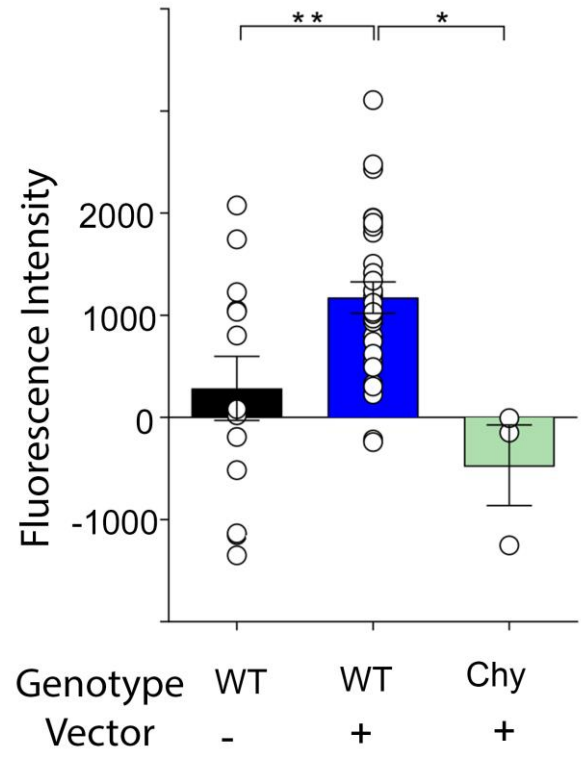
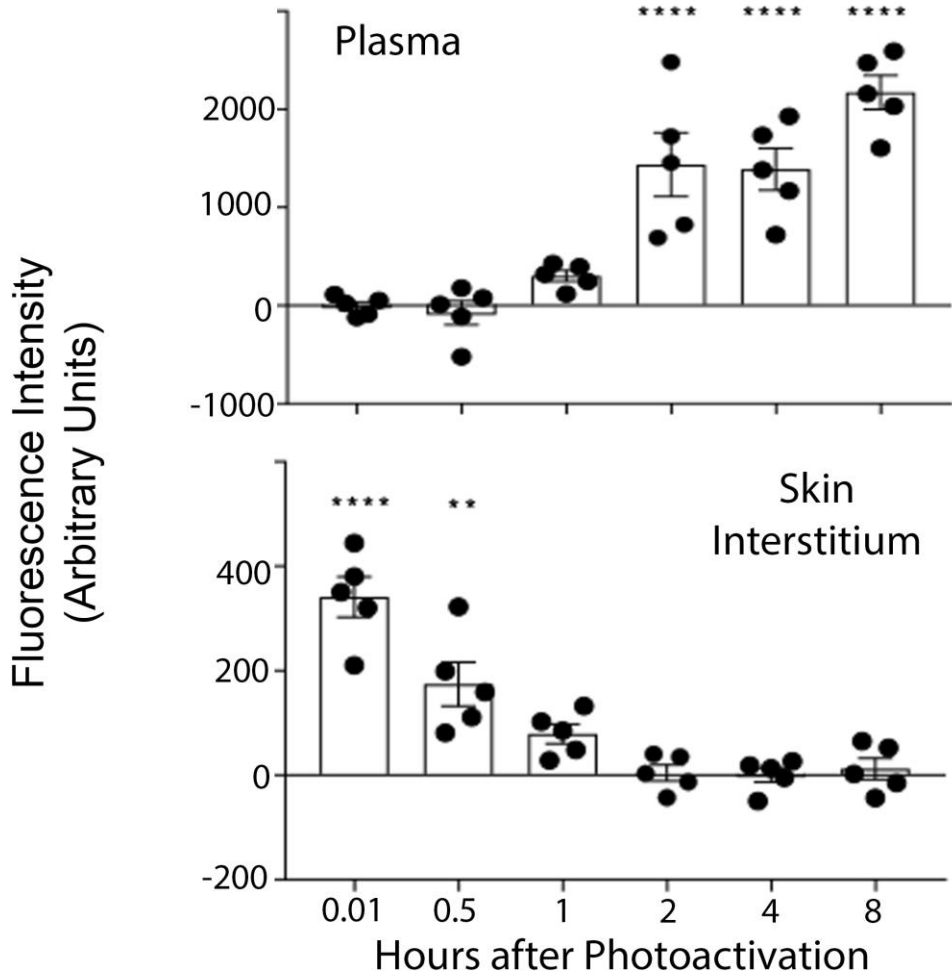
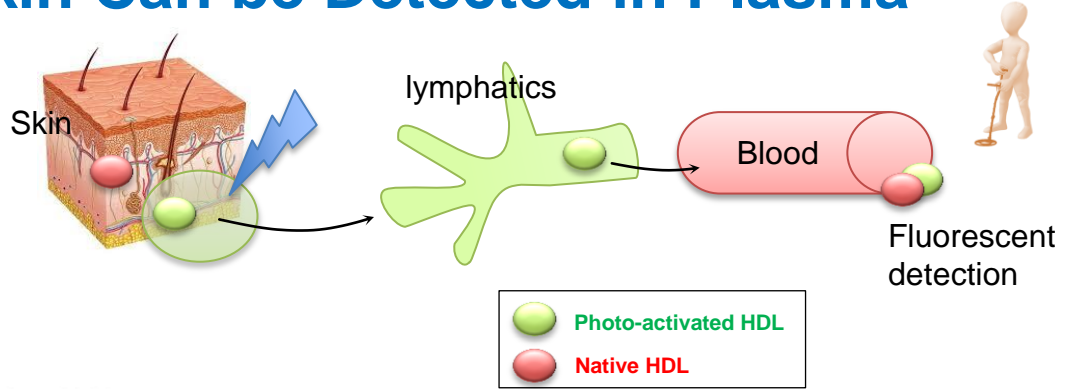
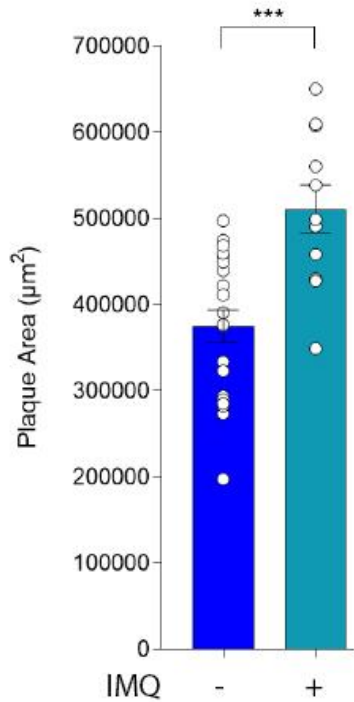


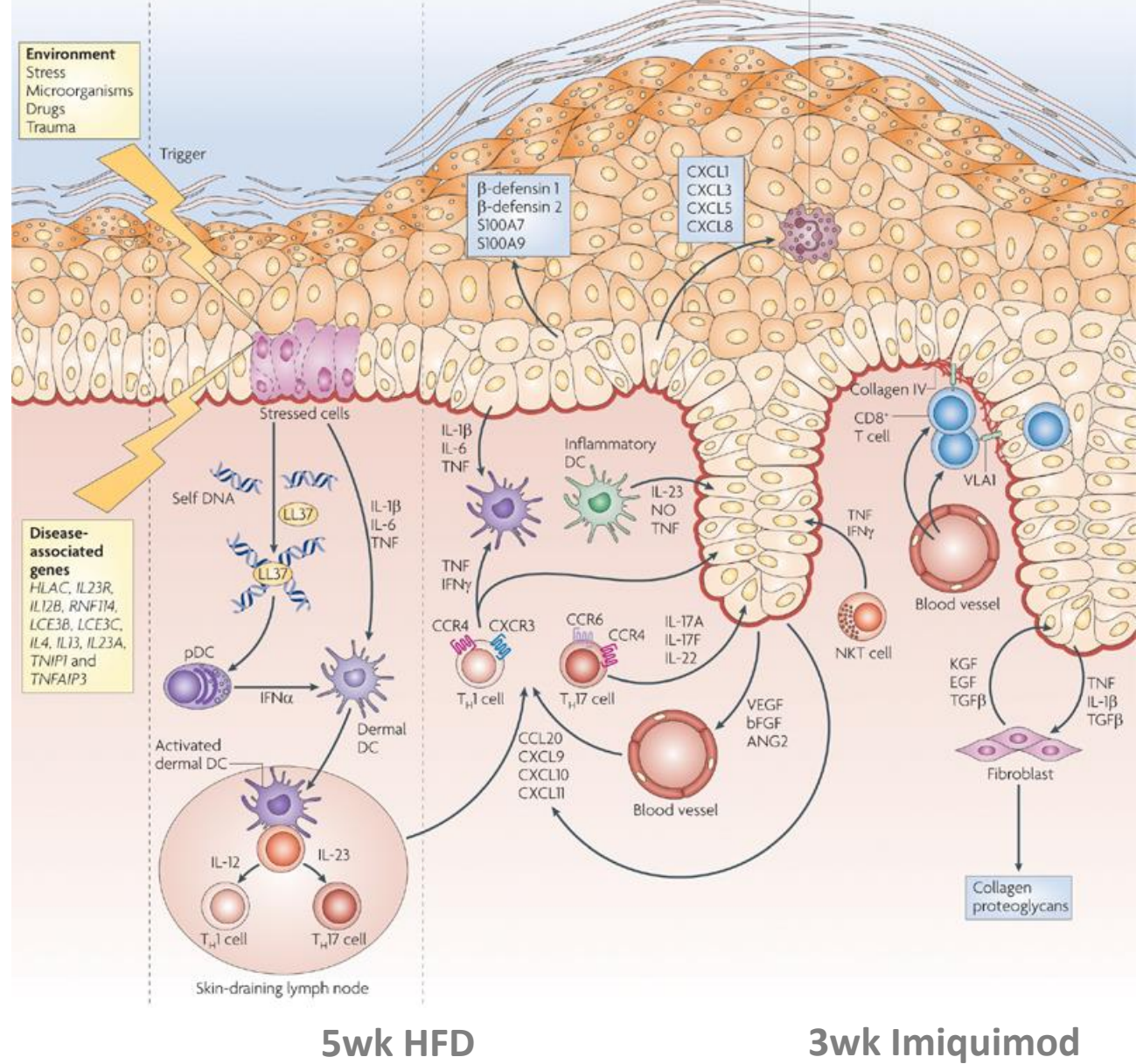
Photo-activated PGA1 in Skin Can be Detected in Plasma



Cardiovascular co-morbidity of psoriasis is prevalent and unexplained



ApoE KO
Male



IMQ Application Displays Systemic Effects

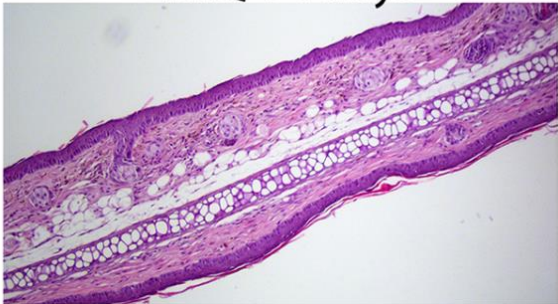


IMQ : daily x 14

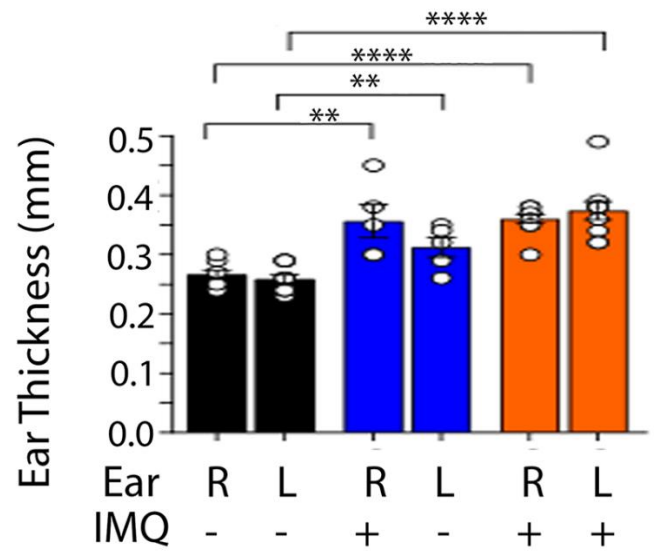
No IMQ



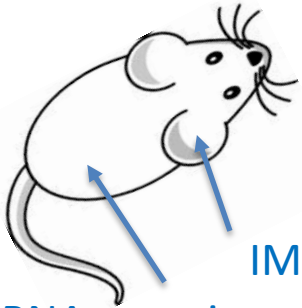
IMQ 14 days



Ear



Remote Skin Increases mRNA for Psoriasis-linked Cytokines



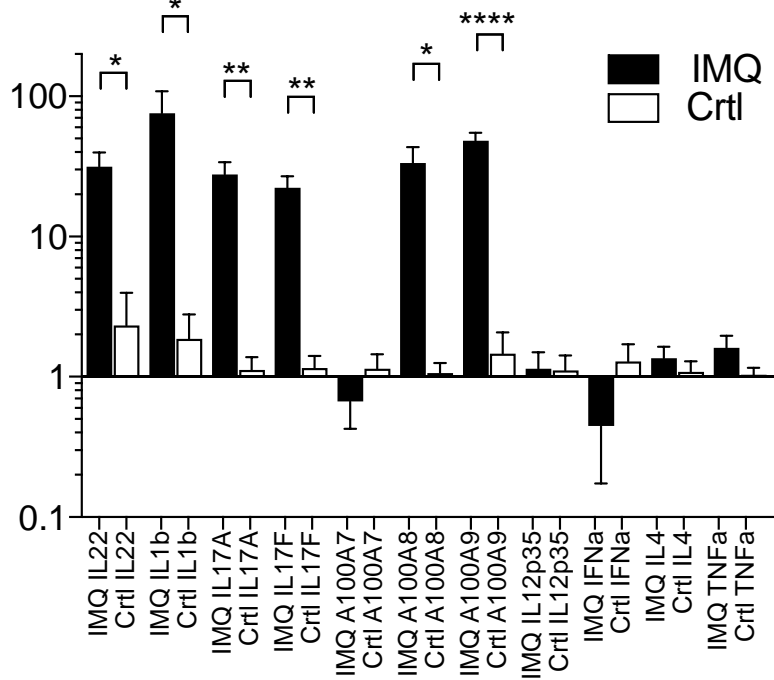
IMQ : daily x 14

mRNA analysis

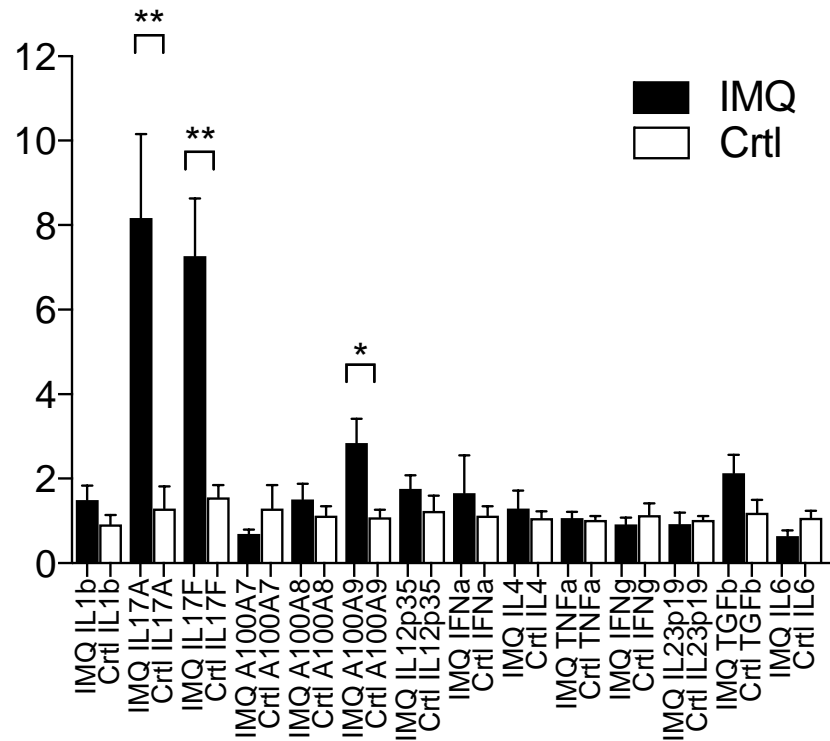
Mouse Dermis

Mouse Back Skin

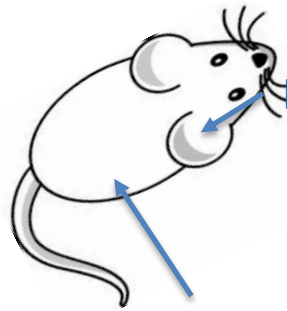
Relative expression
(Normalized to HPRT)



Relative expression
(Normalized to HPRT)



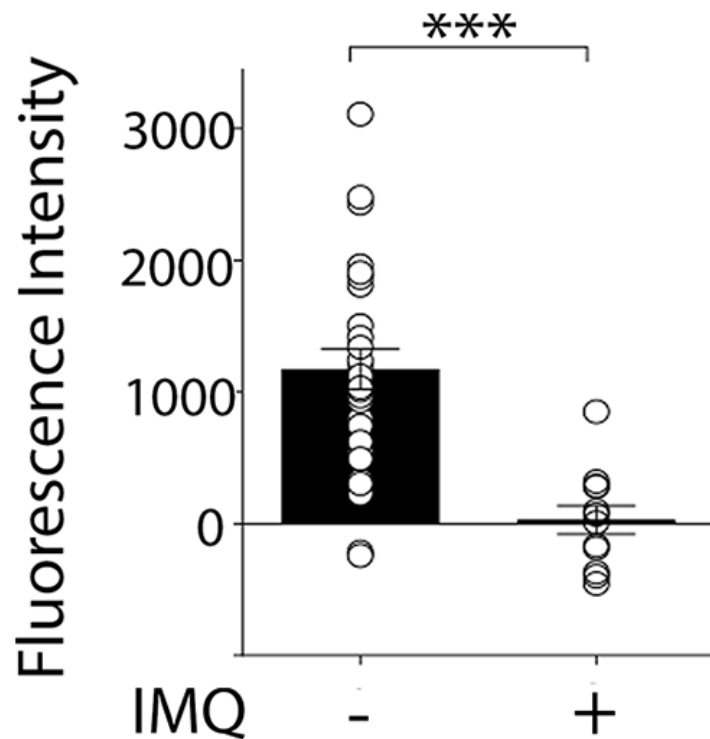
HDL Does Not Efficiently Transit through Skin in the IMQ Model of Psoriasis



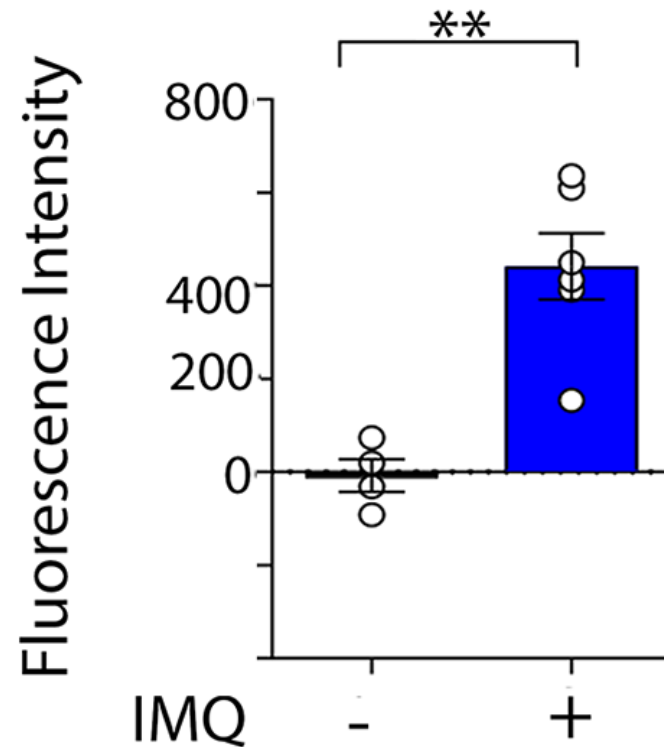
IMQ : daily x 14

photoactivation

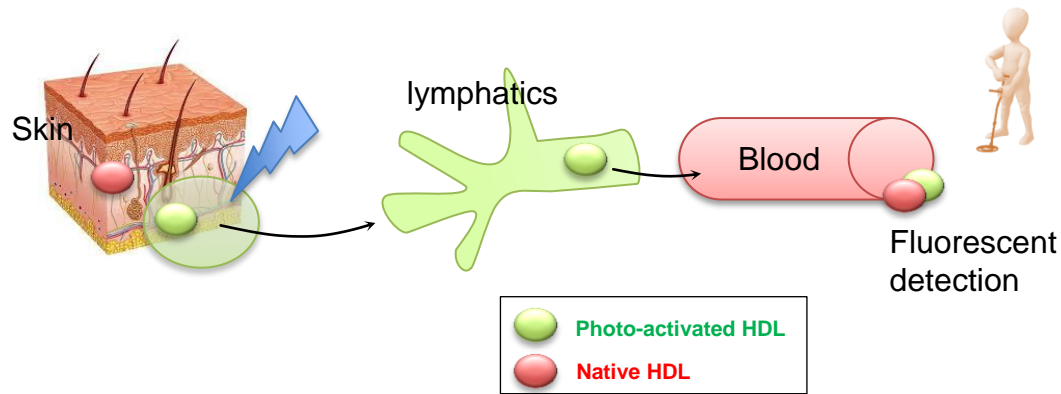
Plasma



Skin Interstitial Fluid



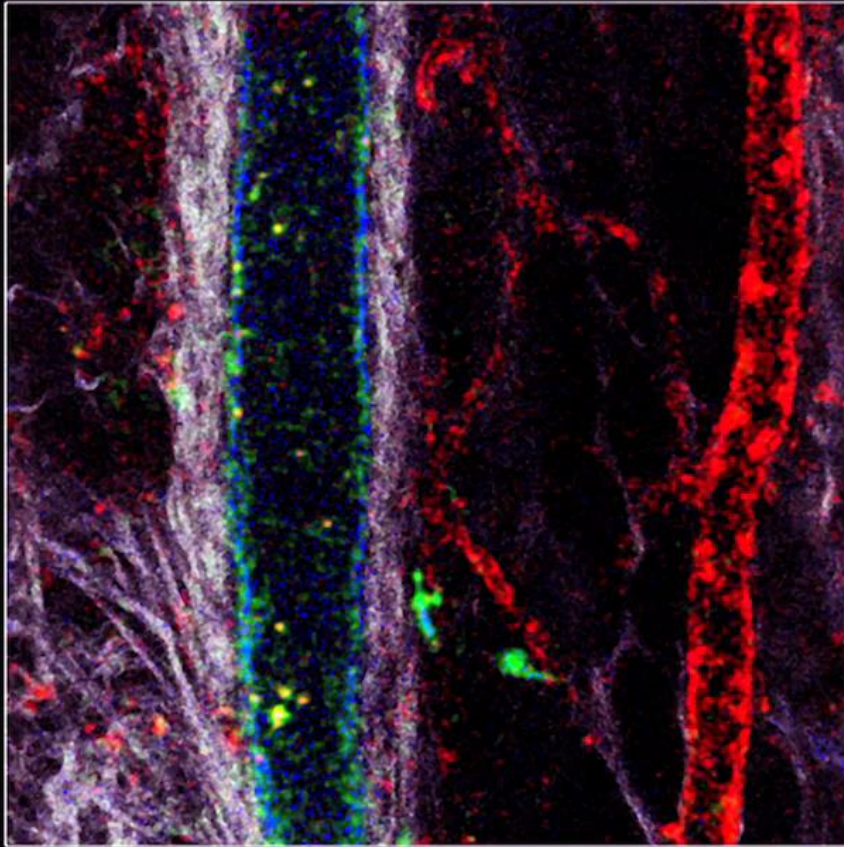
Why HDL Transport is Blocked?



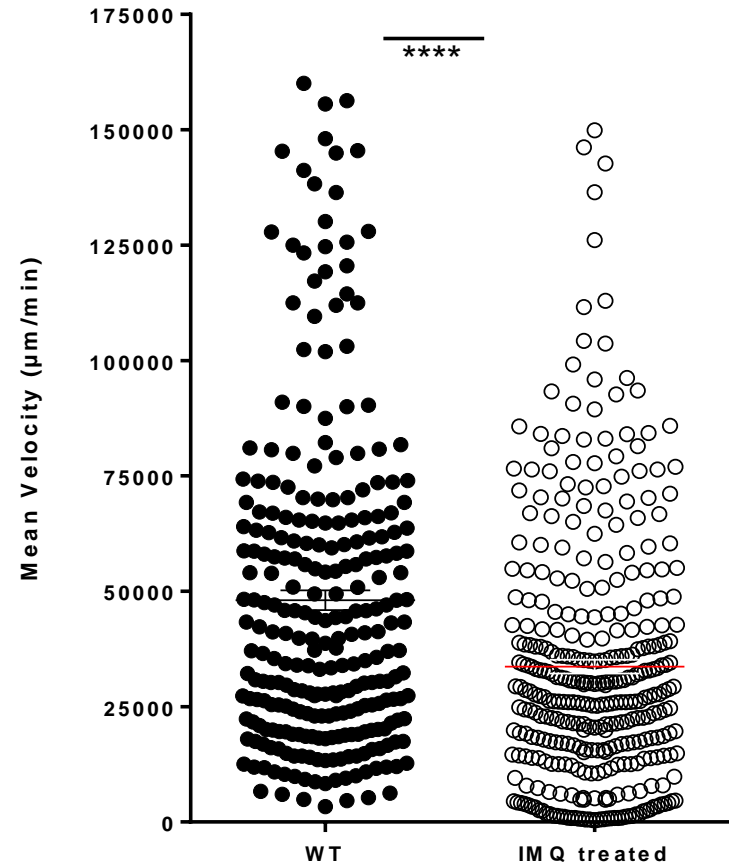
Since lymphatic flow does not alter completely, is that the interstitium (eg., extra-cellular matrix modification) that accounts for impaired flux?

A Bead-based Method to Quantify Lymphatic Flow

2P-imaging of the vascular system

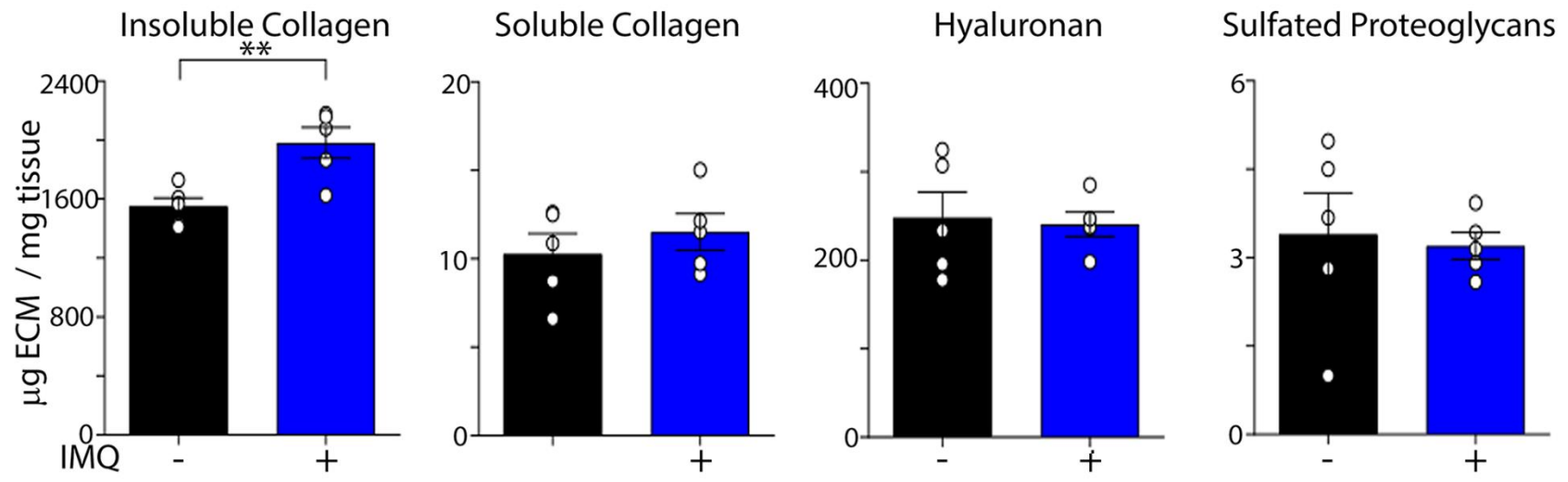


80µm [min:sec.msec]
YFP 1µm Microspheres Collagen
DyLight 594-Lectin DyLight 488-Lectin

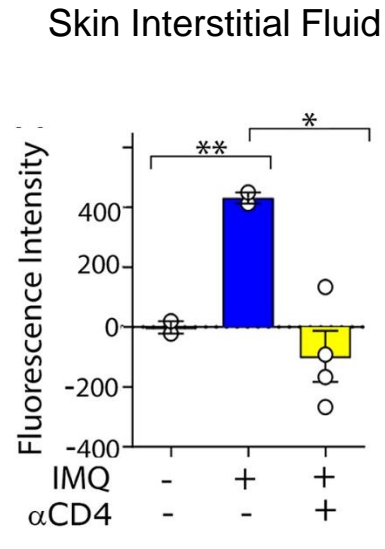
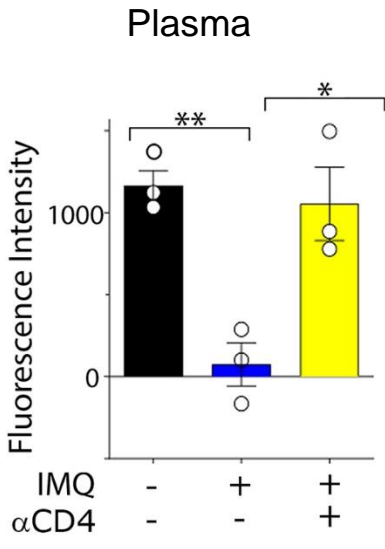
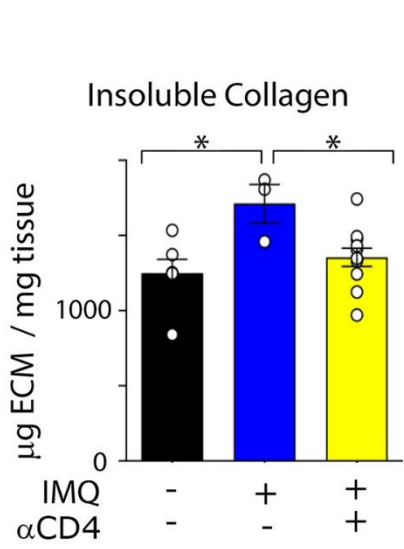
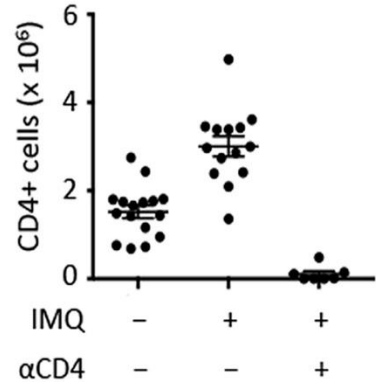
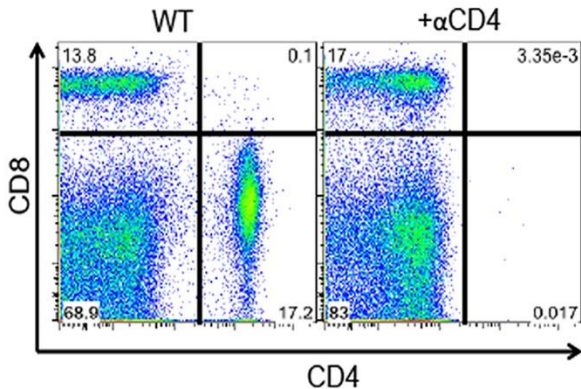


In collaboration with Brian Saunders and Bernd Zinselmeyer

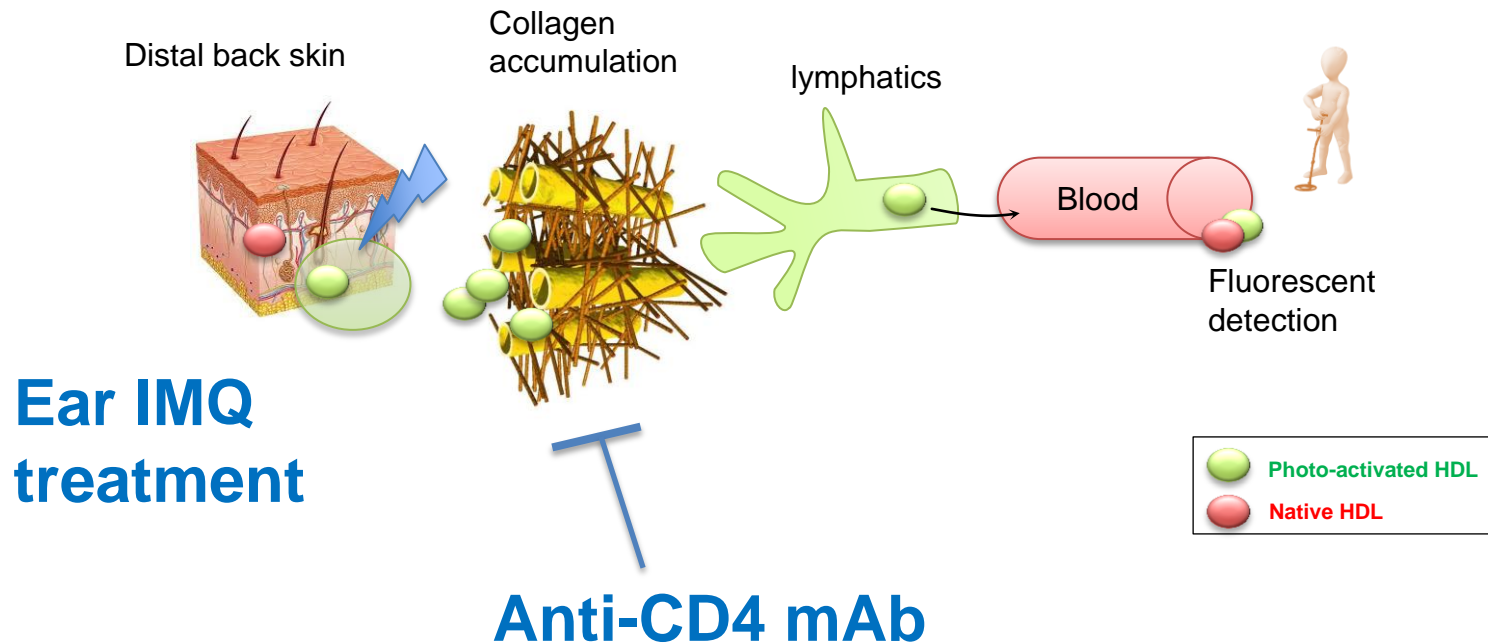
IMQ Application Systemically Increases Collagen Deposition in Skin



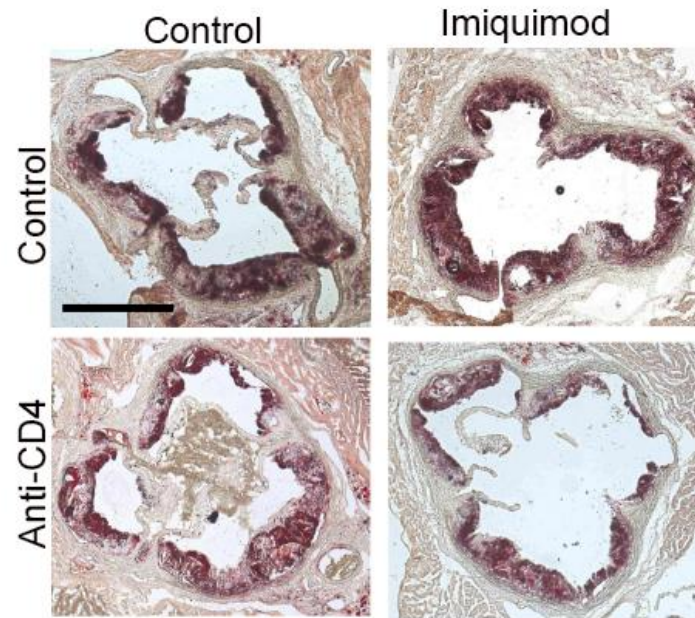
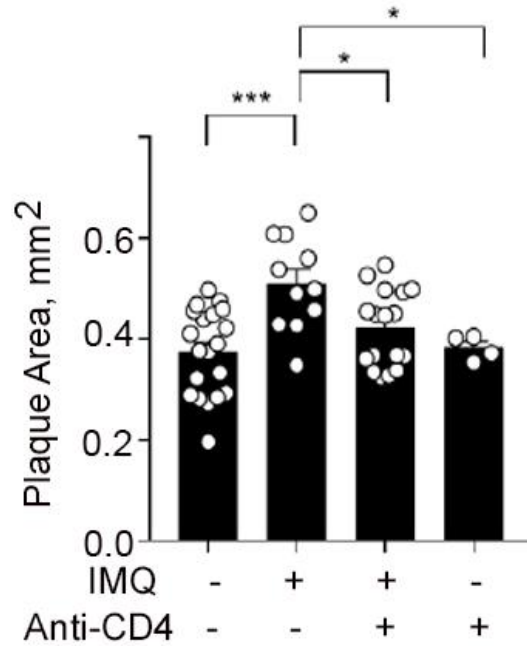
Depletion of CD4⁺ T cells reverses collagen accumulation and defective HDL trafficking in skin



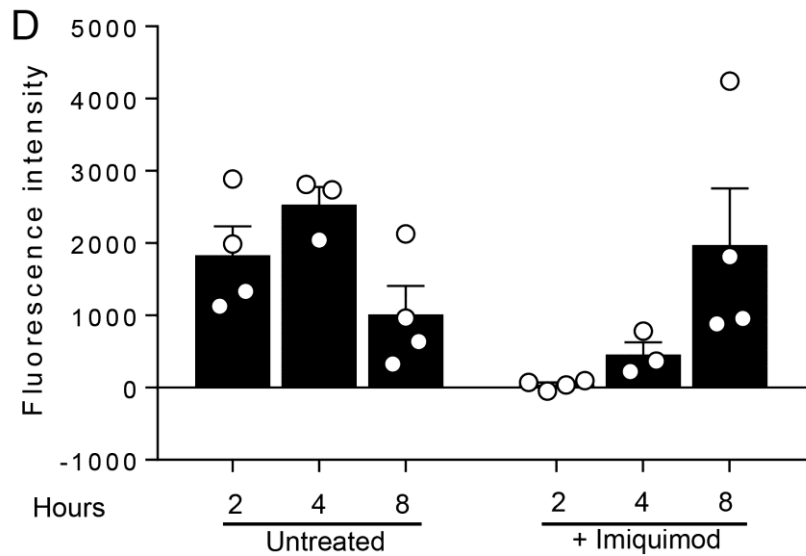
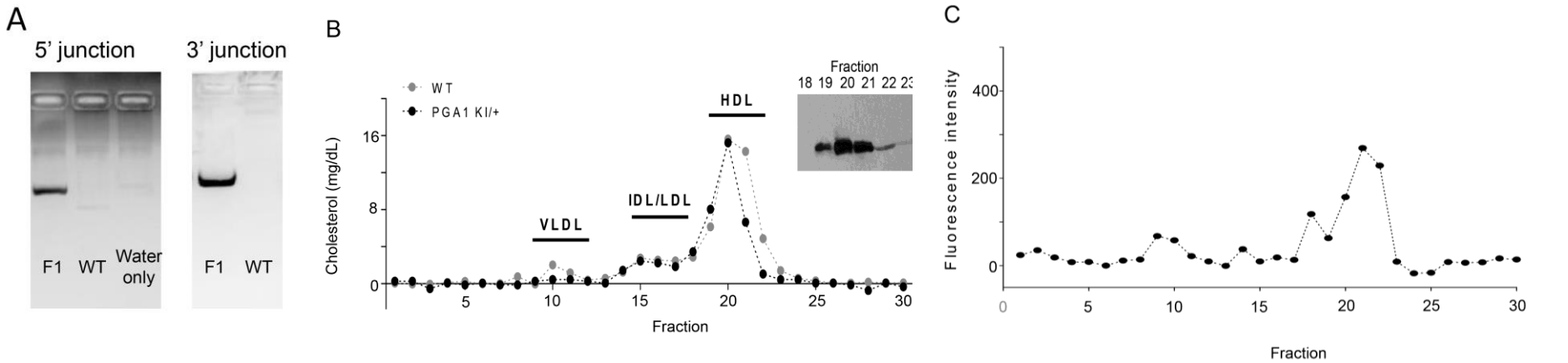
Collagen Accumulation Blocks HDL Transport in a CD4⁺ T Cell Dependent Manner



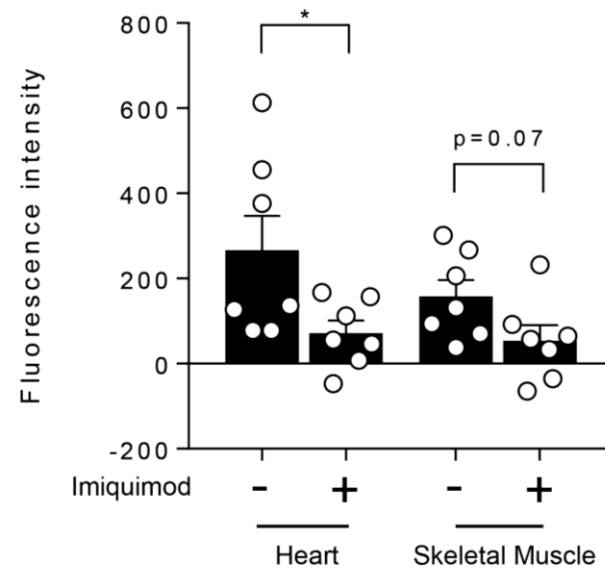
Depletion of CD4⁺ T cells reverses IMQ-enhanced atherosclerosis



Generation of PGA1 Knock-in mouse

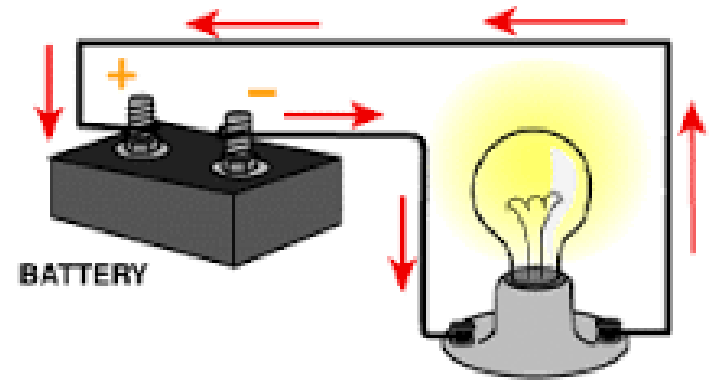
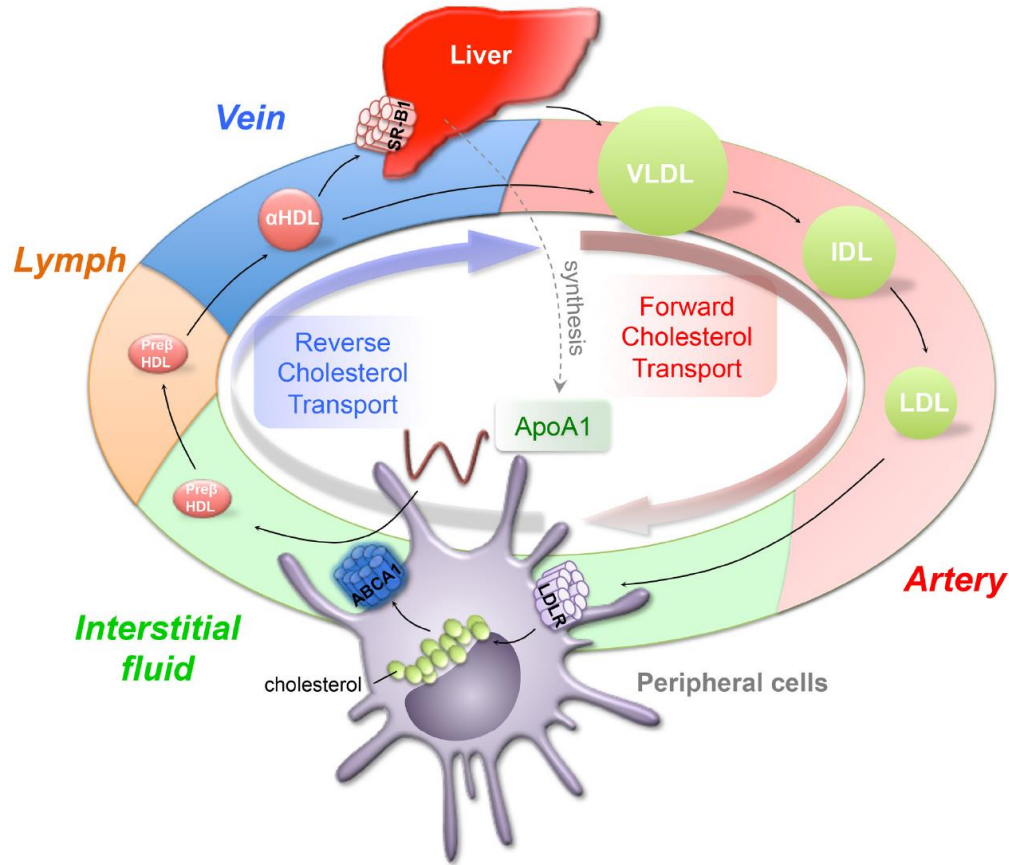


4hr post photoactivation



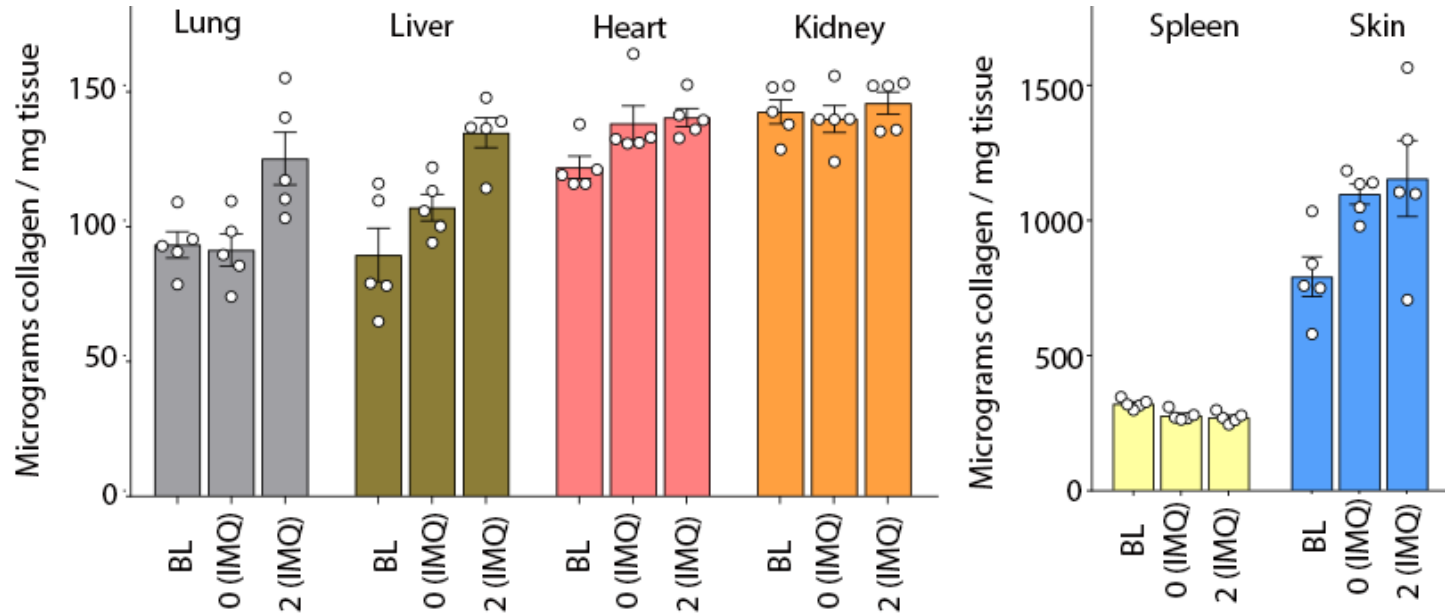
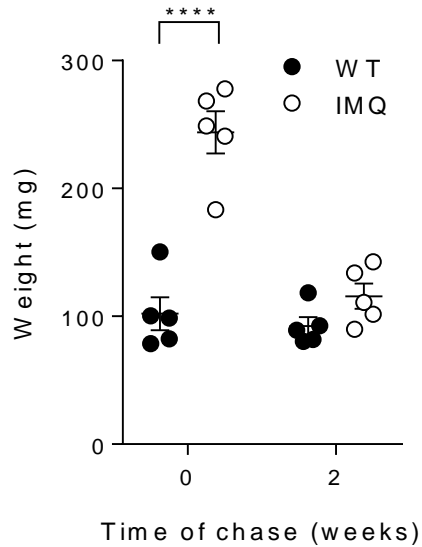
In collaboration with GEIC core at Wash U

HDL Cycle

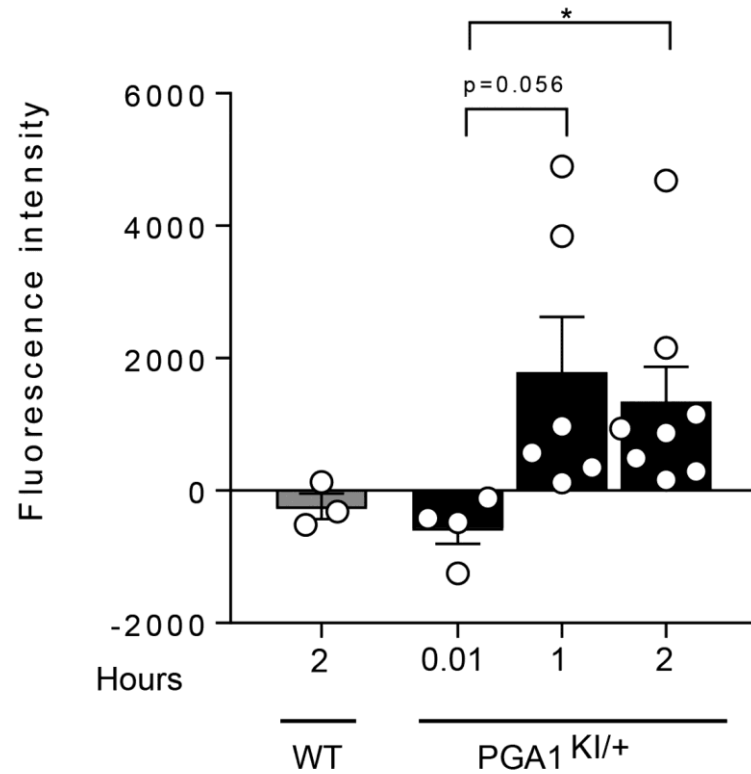


Huang et al; 2015 Front. Pharmacol.

The TLR7 Agonist IMQ Induces a Systemic and Sustained Accumulation of Collagen in Multiple Organs - is HDL Trafficking Impaired in All of Them?



We Can Now Detect and Quantify HDL Trafficking from the Artery Wall!



Conclusions:

To appreciate the importance of HDL transport through tissues, how it can be modulated by immunological responses, and its link to atherosclerosis...

- Two tools include a knock-in mouse line and AAV vectors of the fusion protein to monitor HDL transport through tissues.
- HDL becomes trapped in collagen-rich skin that arises in a model of psoriasis and HDL entrapment can be reversed by depletion of CD4⁺ T cells.
- HDL transport through artery wall can be monitored.



Gwen Randolph

Chih-Hao
Chang

Brain Sanders

Bernd Zinselmeyer

University of Bergen, Norway
Helge Wiig

Medical College Wisconsin
Mary Sorci-Thomas
Mike Thomas

University of Chicago
Melody Swartz

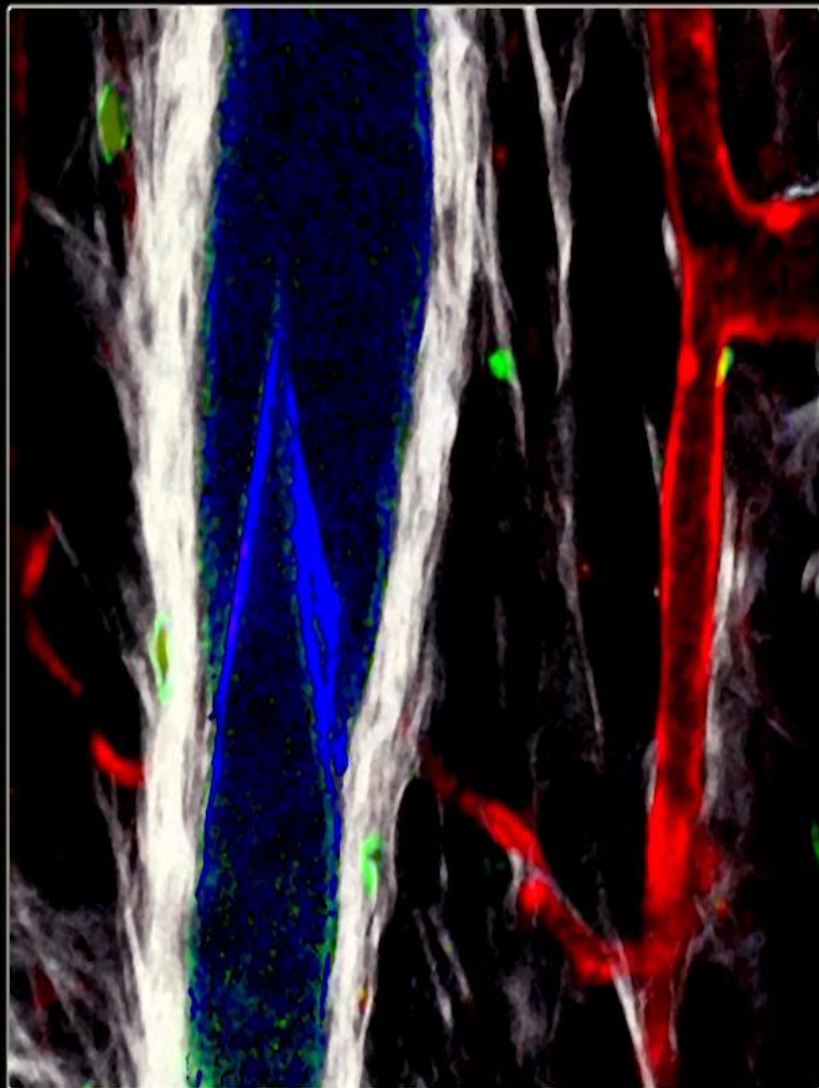
Washington University
Brian Kim

Washington University (GEiC core)
Shondra Miller
Mike White

Interesting Questions:

- How collagen deposition in artery/adventitia affects HDL transport?
- How is HDL transport in artery regulated by immune cells/TLO?
- Does HDL transport from the lesser curvature region differ from other regions?
- Why multiple CETP inhibitors fail in clinical trials?

2P-imaging of the vascular system



80 μ m

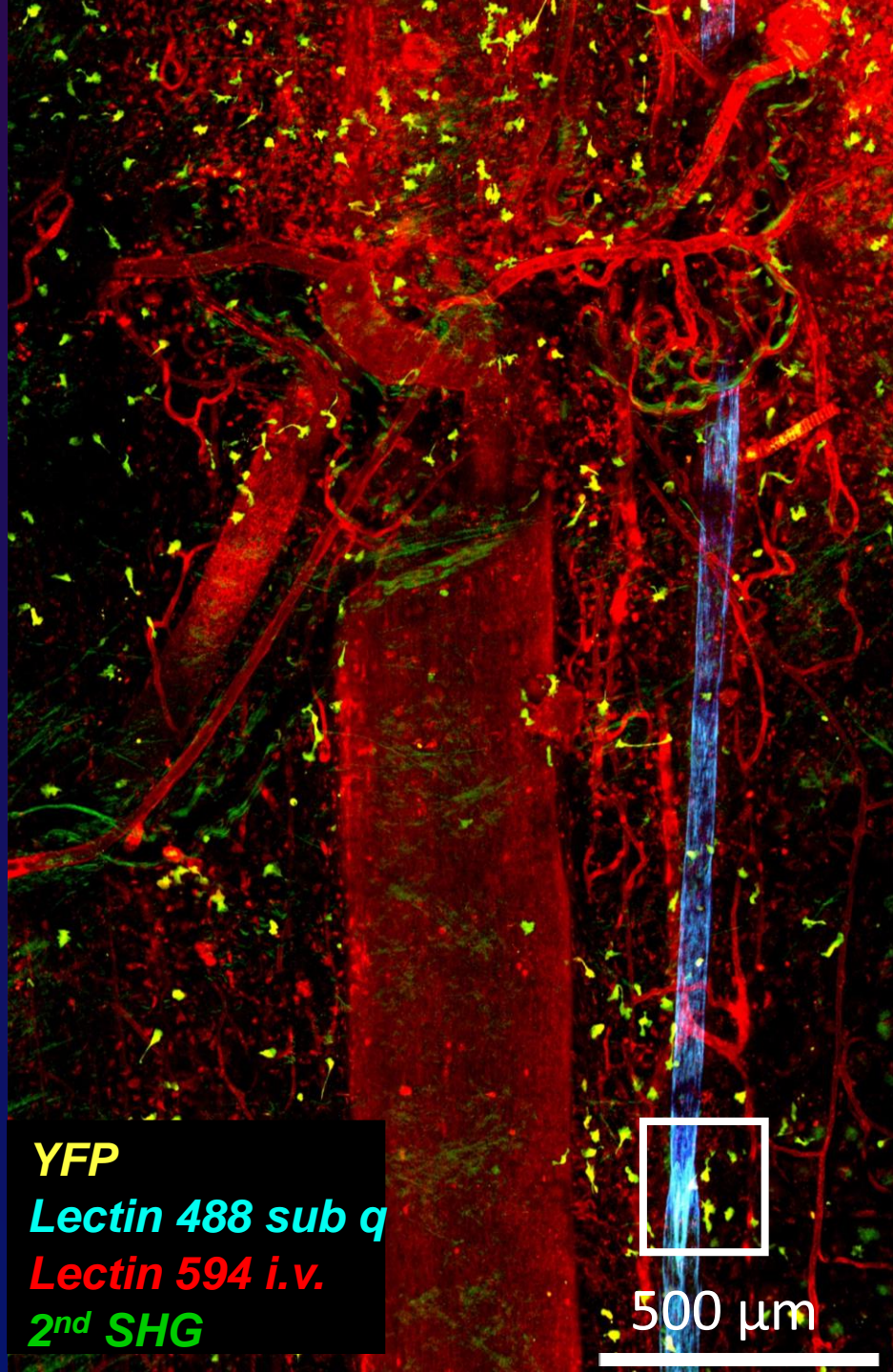
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cCD11c-YFP

Collagen

DyLight 594-Lectin

DyLight 488-Lectin

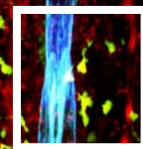


YFP

Lectin 488 sub q

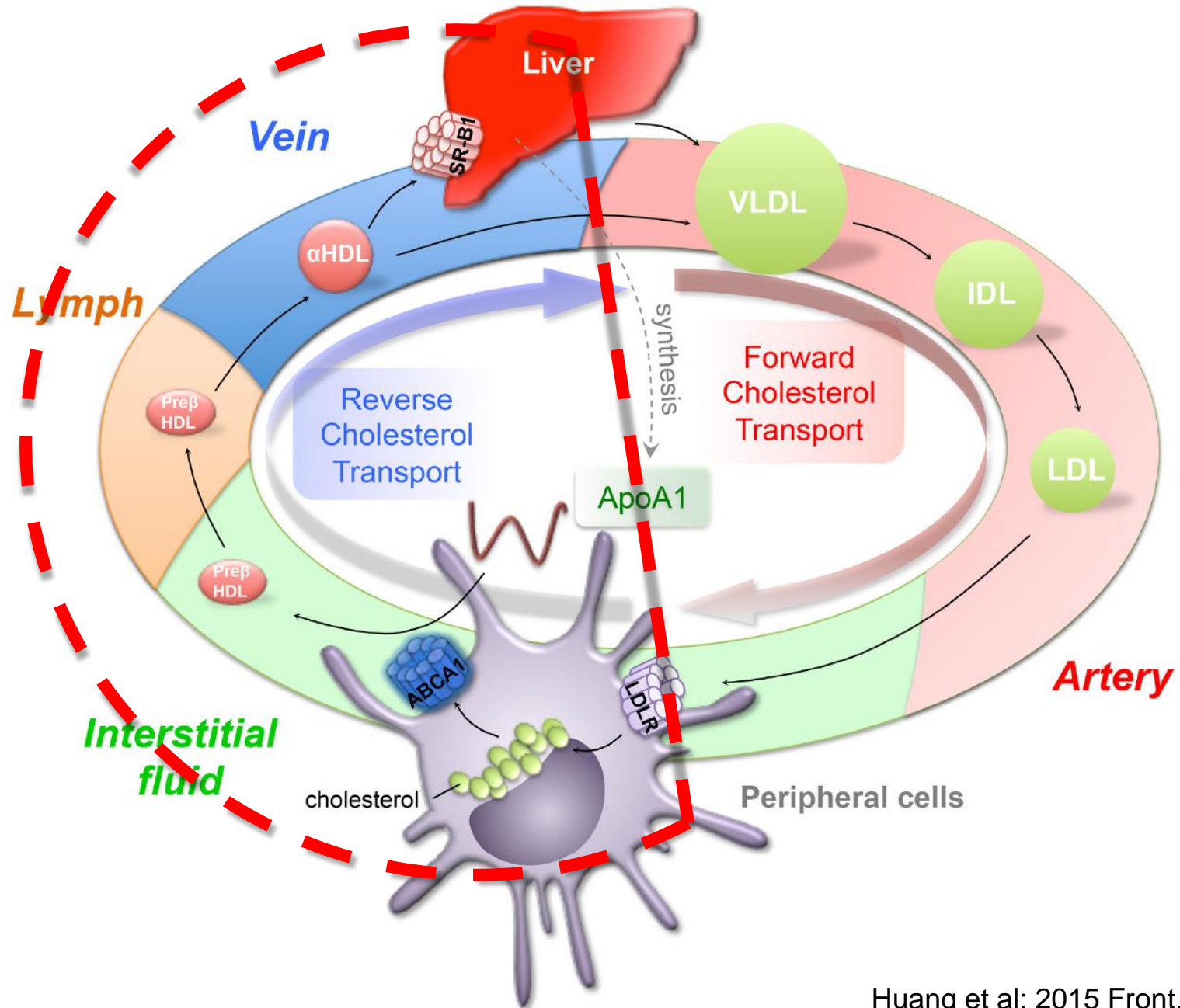
Lectin 594 i.v.

2nd SHG



500 μ m

Forward and Reverse Cholesterol Transport



HEALTHCARE

Merck & Co., Inc. (MRK) CETP Inhibitor Has Low Chances Of Success

Merck's CETP inhibitor seems to have very low chances of success after Eli Lilly's similar drug failed in its late stages



By [Hannah Ishmael](#) on Oct 14, 2015 at 2:03 pm EST



Zanoni et al; 2016 Science; Keene et al; 2014 BMJ; Voight et al; 2012 The Lancet; Gursky et al; 2013 JLR.

Barter et al; 2014 N. Engl. J. Med; Schwartz et al; 2012 N. Engl. Med; Keene et al; 2014 BMJ.

