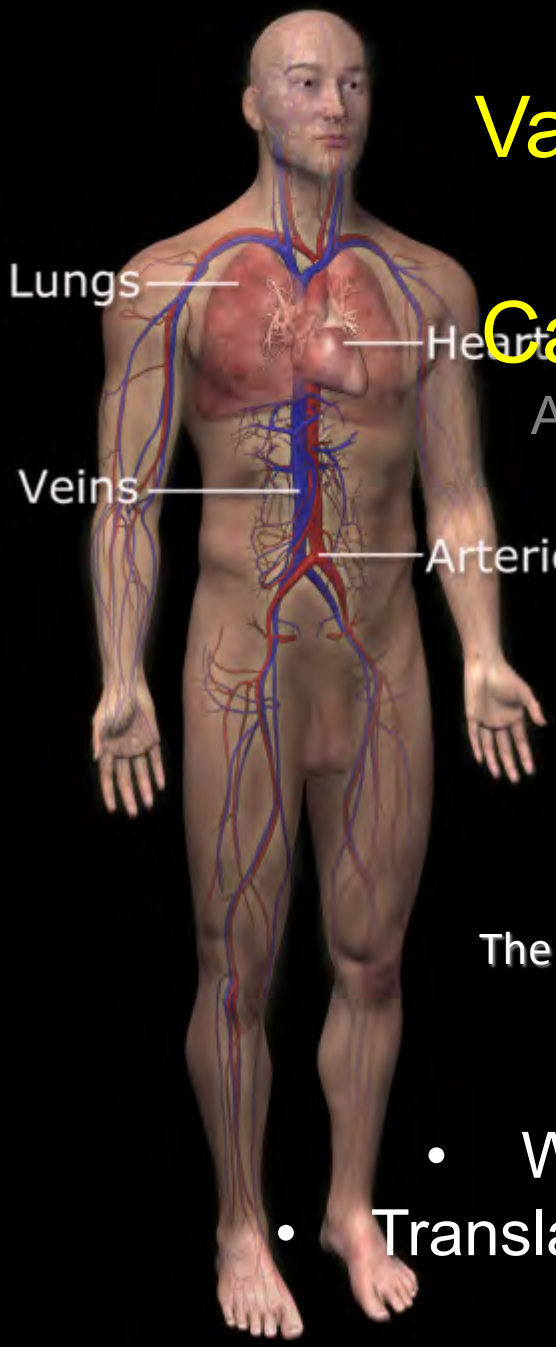

Marmot
MAKIA
CLOTHING COMPANY
HELSINKI HARBOUR

Robert Wingvist	1983-1989
Tomi Mäkelä	1986-1990
Päivi Koskinen	1988-1991
Juha Partanen	1988-1991
Harri Hirvonen	1988-1994
Imre Västrik	1990-1997
Mathias Bergma	1990-1996
Elina Armstrong	1990-1995
Olga Aprelikova	1991-1996
Juha Klefström	1992-1994
Anne Polvi	1993-1997
Erika Hatva	1993-1995
Isto Lahtinen	1994-1999
Birgitta Olofsson	1995-1998
Eola Kukk-Valdr	1995-2003
Yuji Gunji	1996-2003
Elena Arighi	1996-2002

Thank You!

Vascular Growth Factors in Cancer and Cardiovascular Diseases

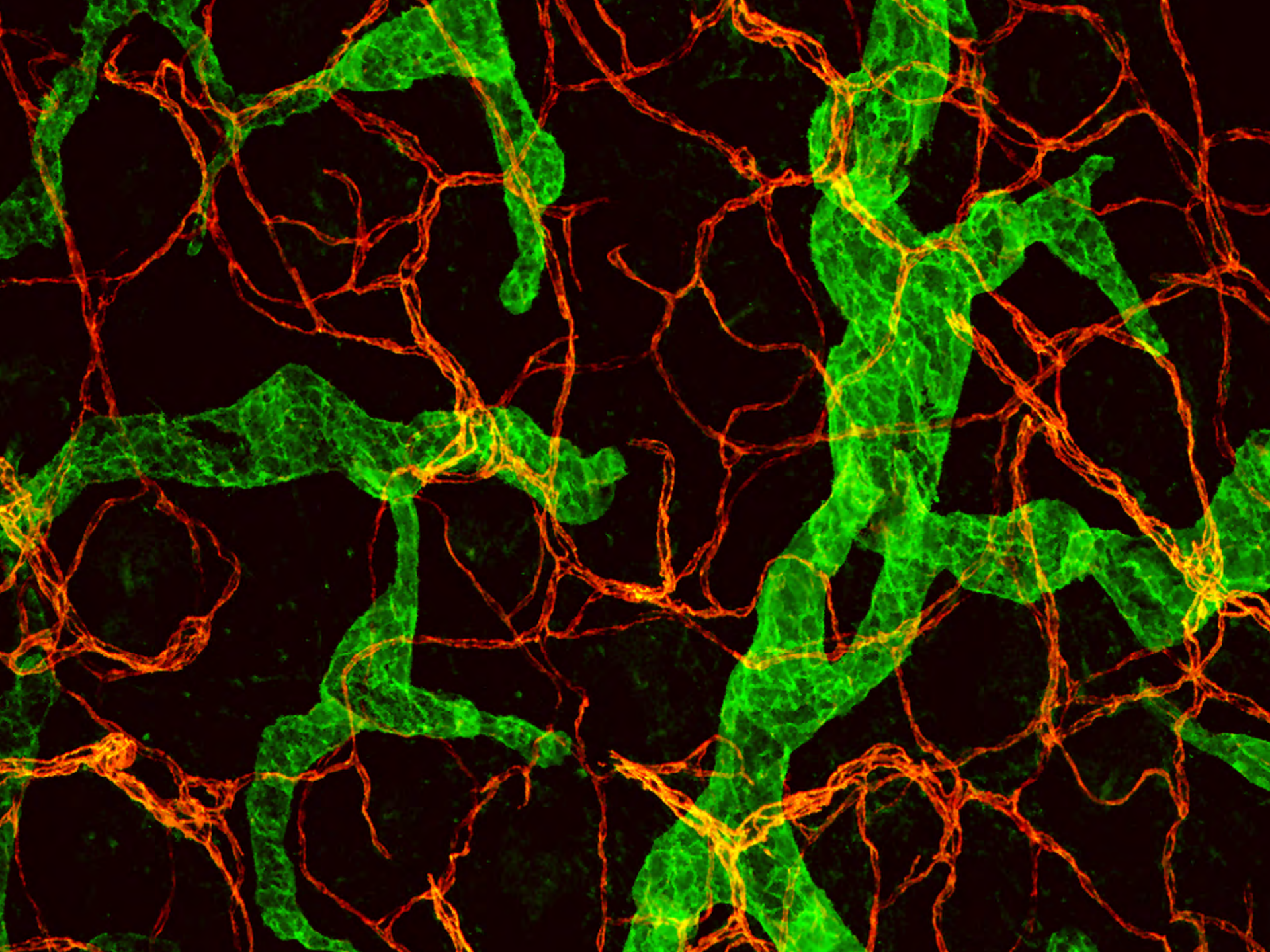
A personal translational perspective



The cardiovascular system

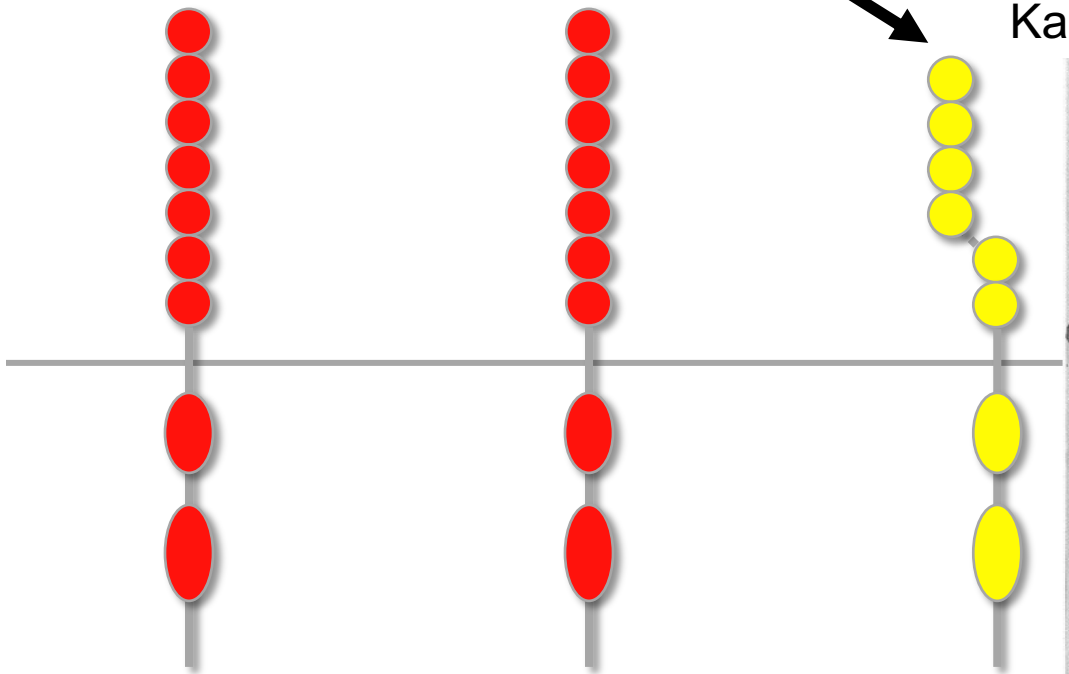
The lymphatic "immuno"vascular system

- Wihuri Research Institute (wri.fi)
- Translational Cancer Biology Program, UH



Endothelial Growth Factors and Receptors

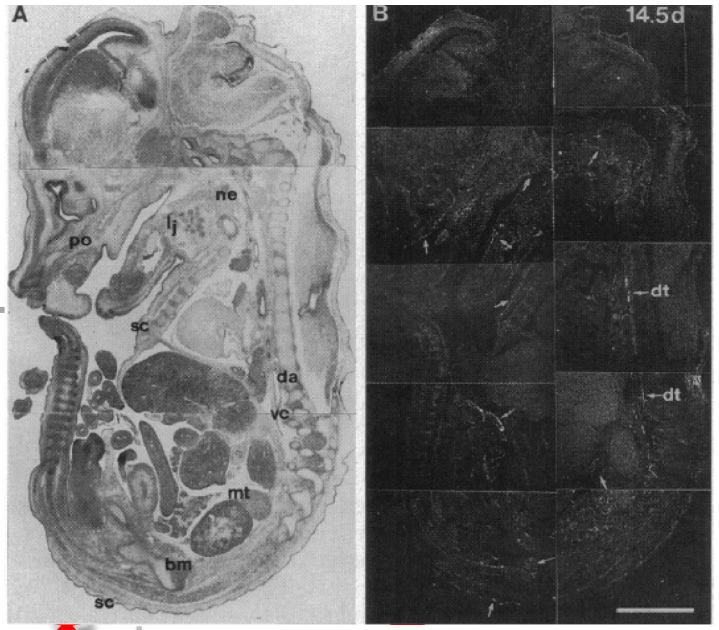
PlGF
VEGF-B *
VEGF
VEGF-C *
VEGF-D*
Ang1, 2, 4



VEGFR-1
VEGFR-2
VEGFR-3 *

Angiogenesis
Lymphangiogenesis

Kaipainen et al., Proc Natl Acad Sci



25 years ago

Vessel stabilization

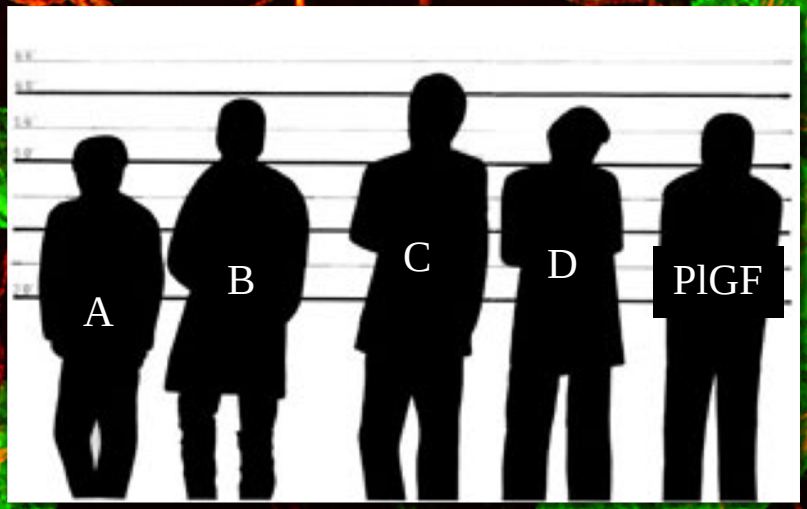
TCB

Gaspare Aselli (1581 – 1626)

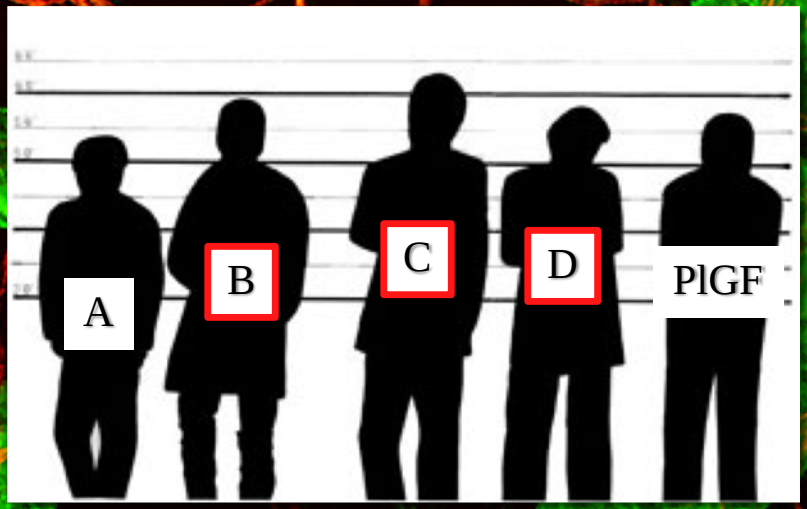
Anatomist and Surgeon

- (Re-)Discovered lymphatics in dogs1622 in Milan
- Chylous vessels
- *Venae albae* were already known to Hippocrates and Aristoteles
- *Ductus lactei* were described by physicians of the ‚Alexandrian School‘

The VEGF Family



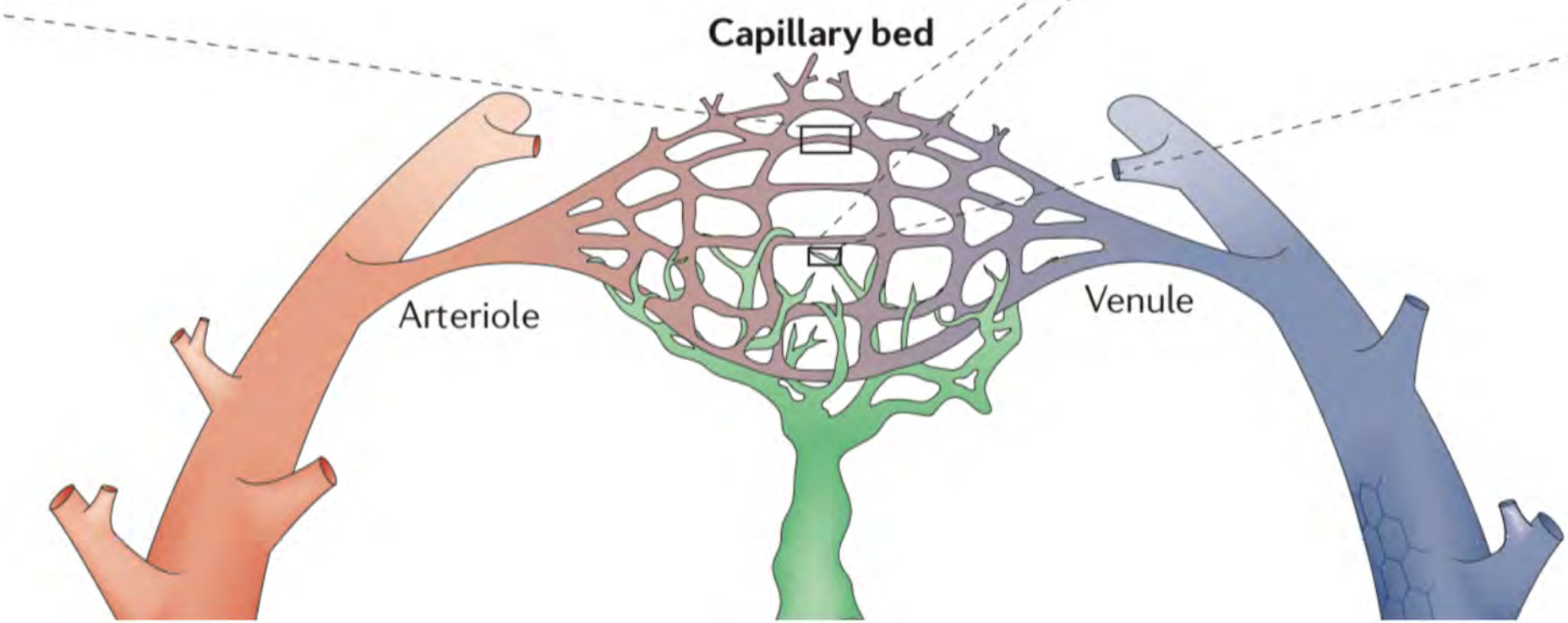
The VEGF Family The Next Generation of Therapeutics?



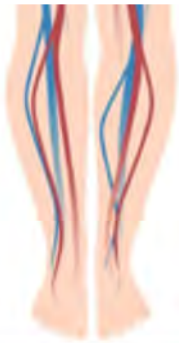
Vascular systems

The Circulatory System

The Lymphatic System

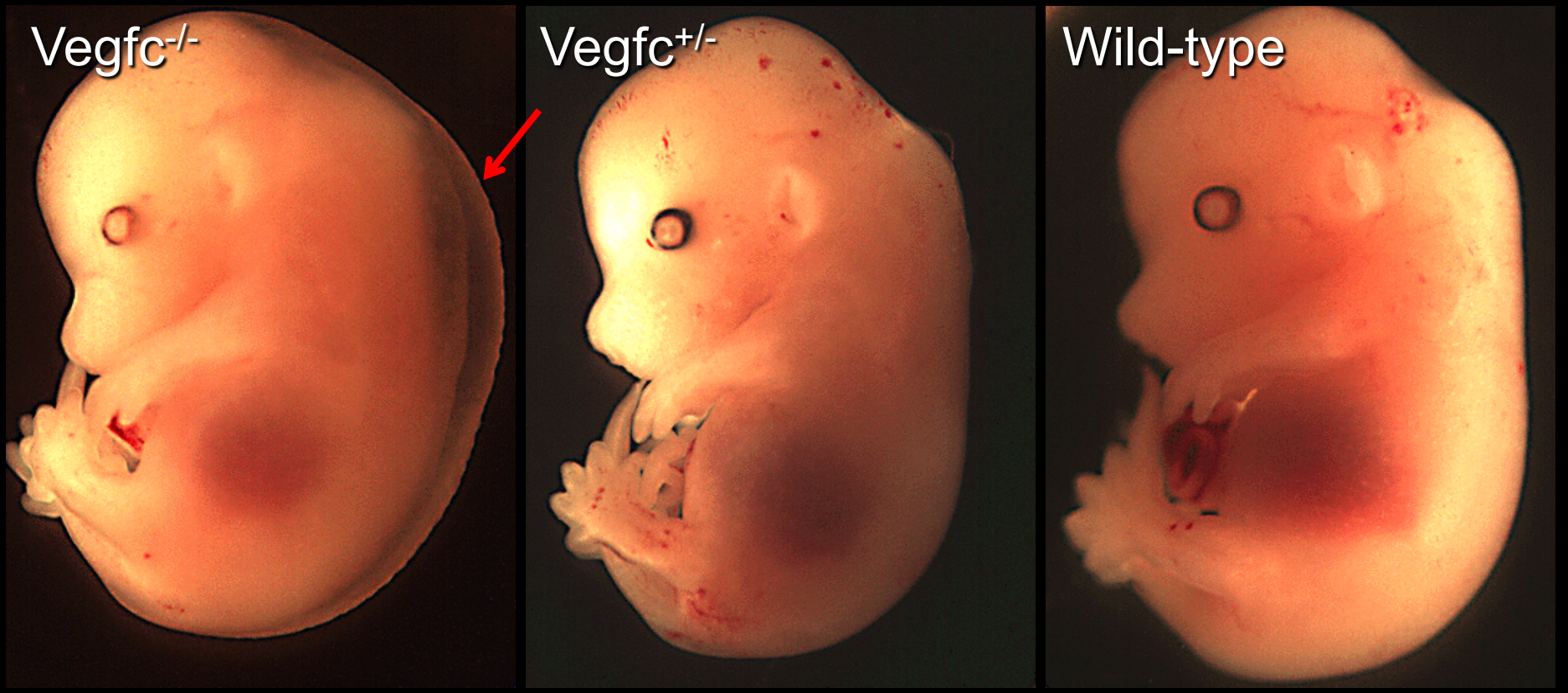


-Central pump
-Closed circuit



-No central pump
-One-way conduit

VEGF-C is required for development of the lymphatic vascular system

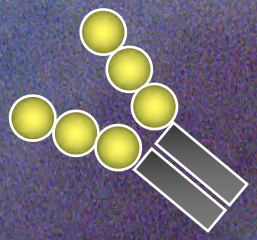


Kärkkäinen et al. Nature Immunology, 2004

Lymphatic vessels in the gut

Transgenic

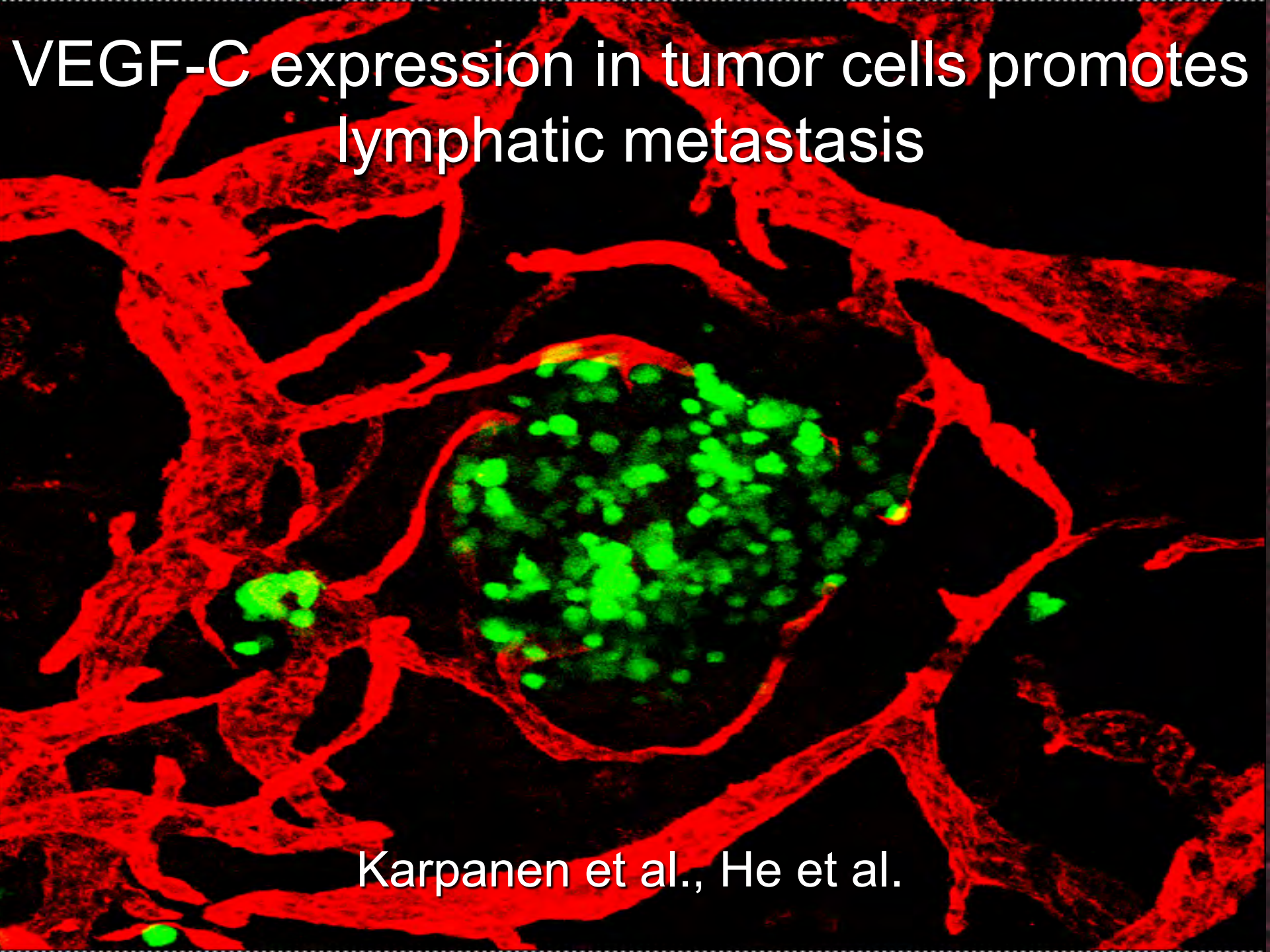
VEGFR-3-Ig



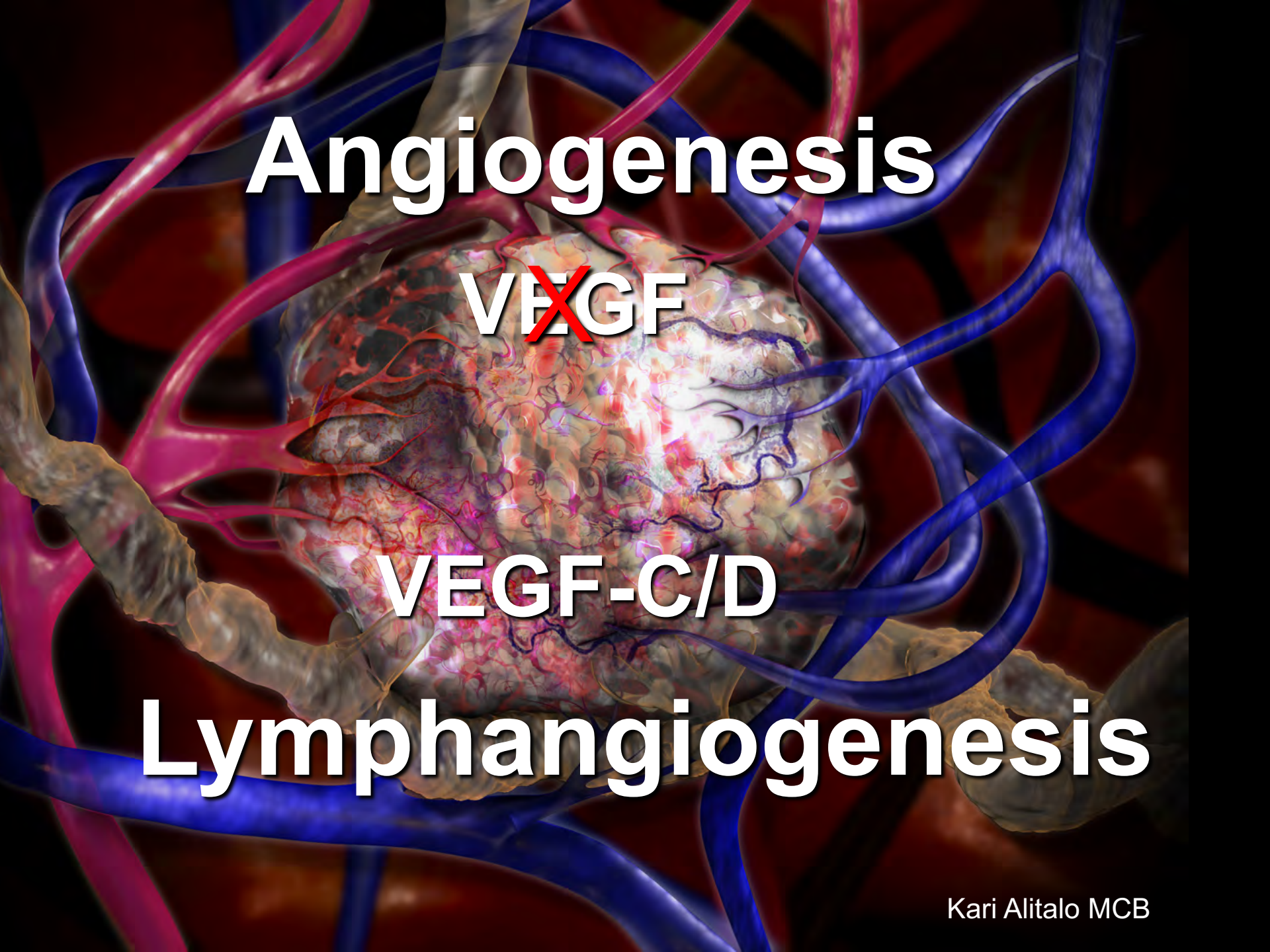
Control

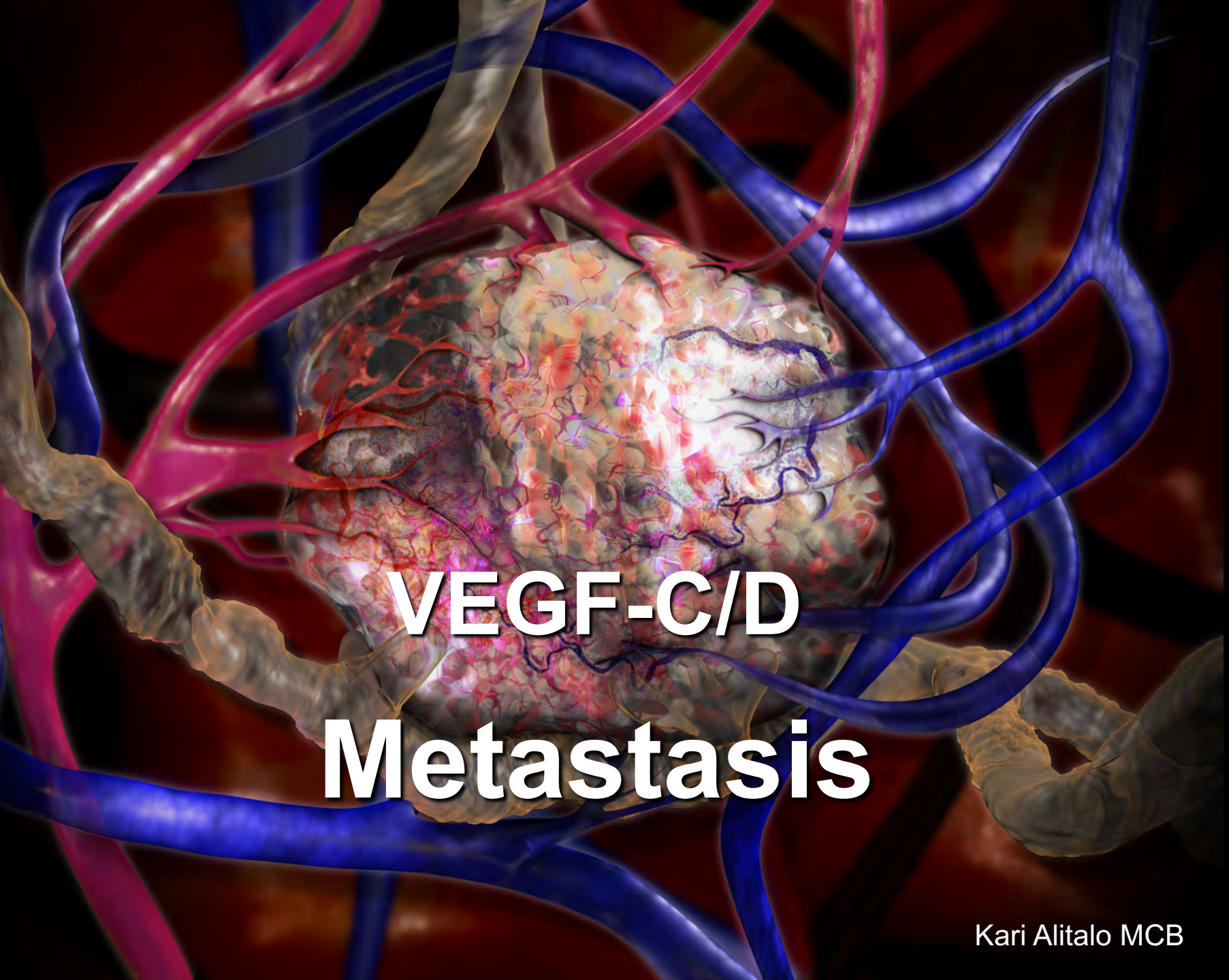
Makinen et al., Nature Mediine

VEGF-C expression in tumor cells promotes lymphatic metastasis

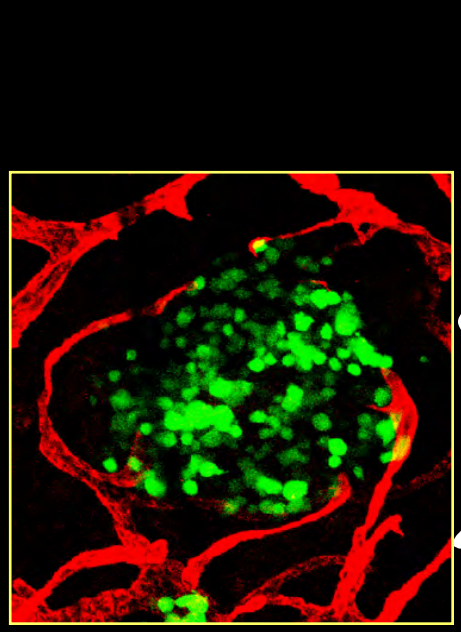


Karpanen et al., He et al.


Angiogenesis
VEGF
VEGF-C/D
Lymphangiogenesis
Kari Alitalo MCB

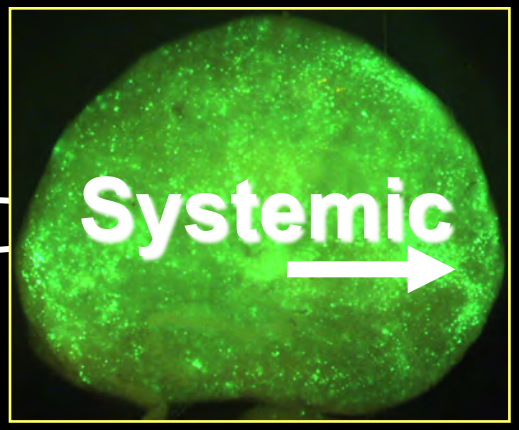

VEGF-C/D
Metastasis
Kari Alitalo MCB

Mechanisms of VEGF-C/D induced lymphatic metastasis



1. Lymphangiogenic sprouting

2. Dilation of collecting lymph vessels, incompetent lymphatic valves, increased flow

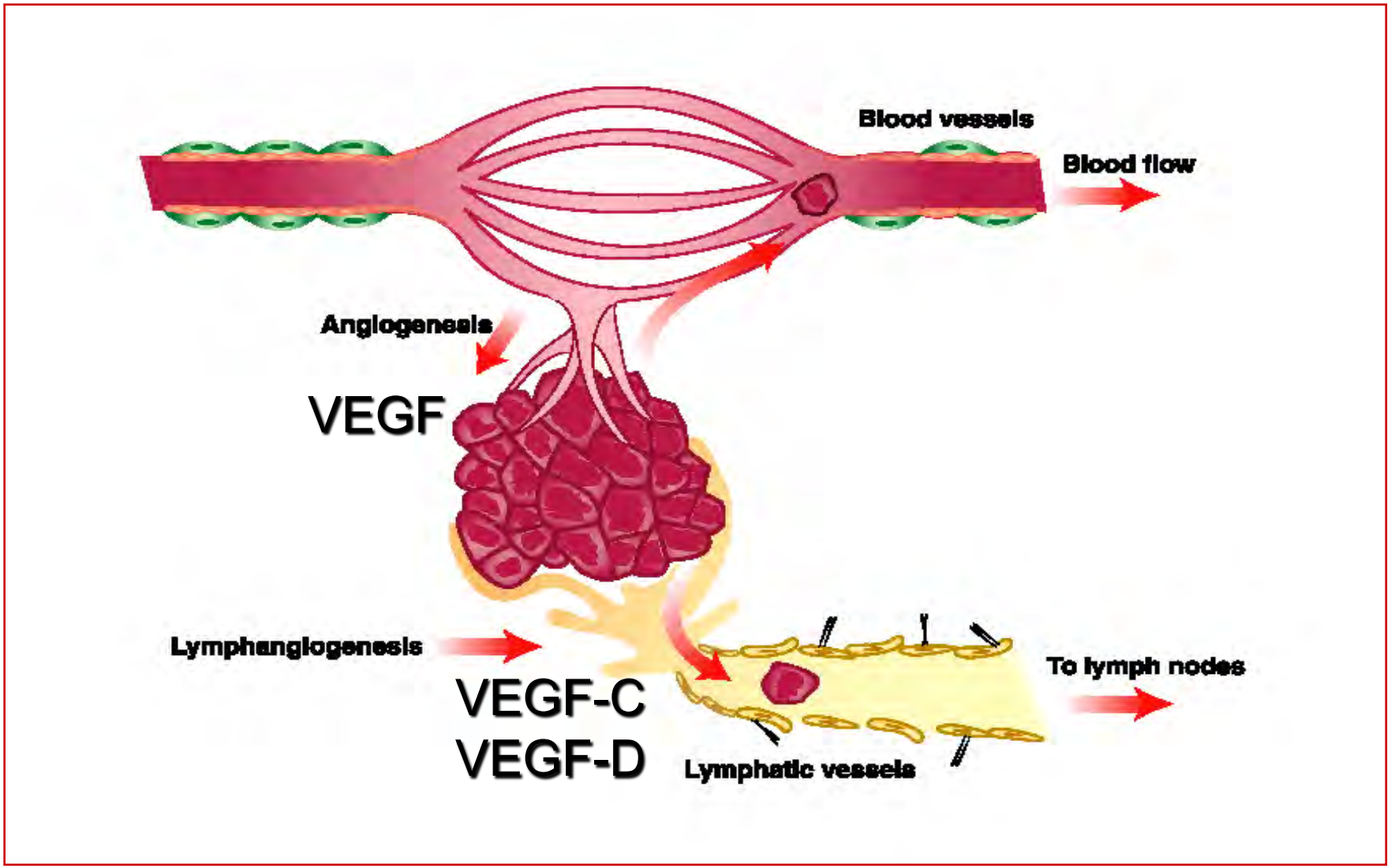


3. LN lymphangiogenesis

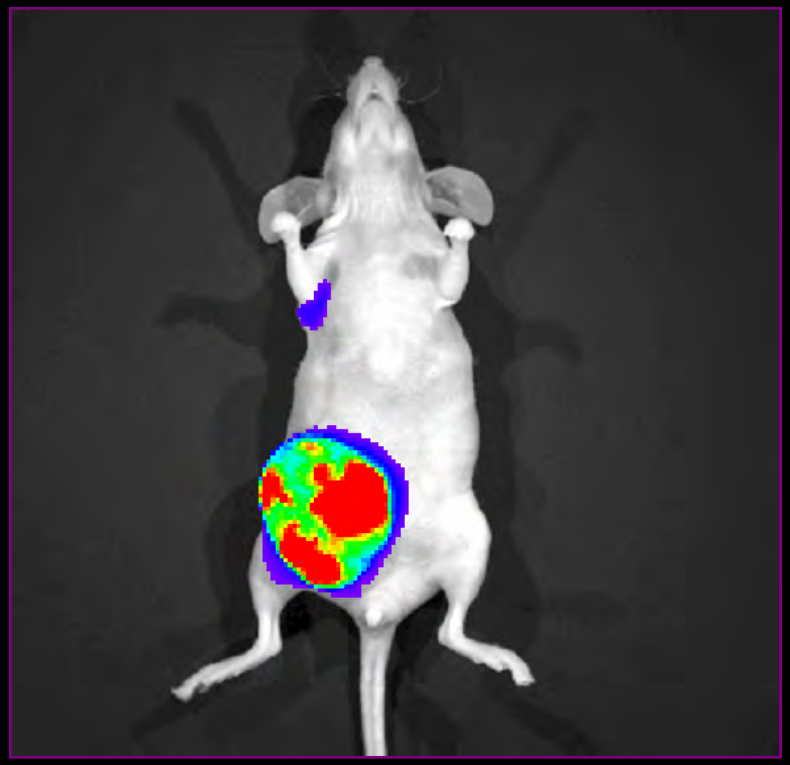
$\Rightarrow$ Blocking of VEGF-C/VEGFR-3 signalling effective for prevention of early steps of the metastatic process

Kari Alitalo MCB

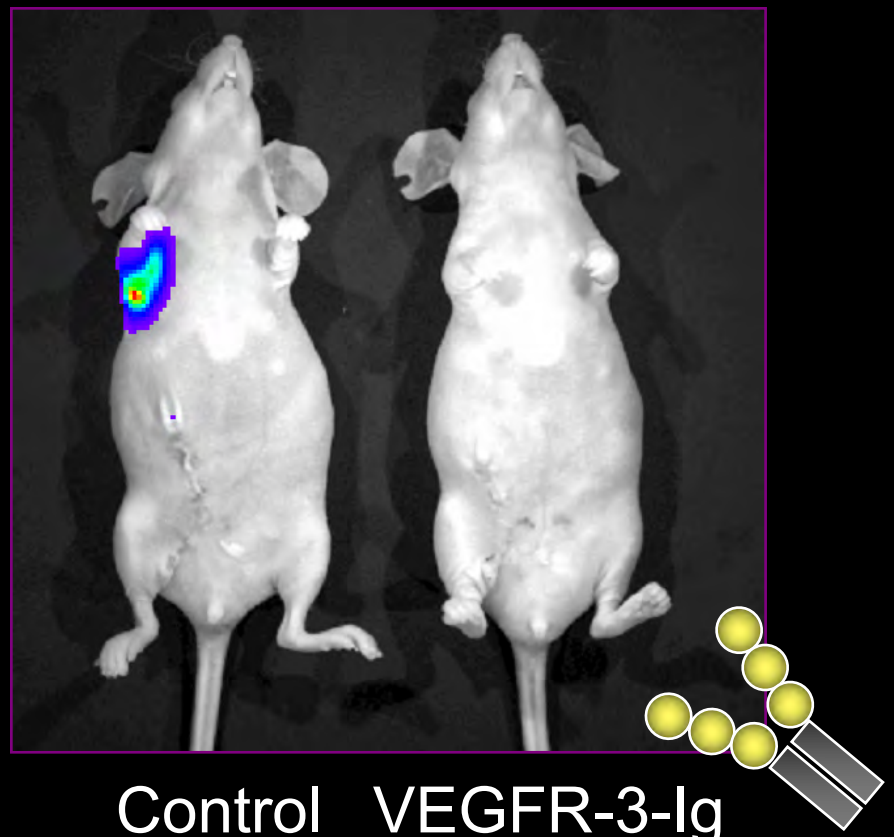
Metastasis via blood or lymphatic vessels



Imaging of luciferase-expressing tumors and lymph node metastasis



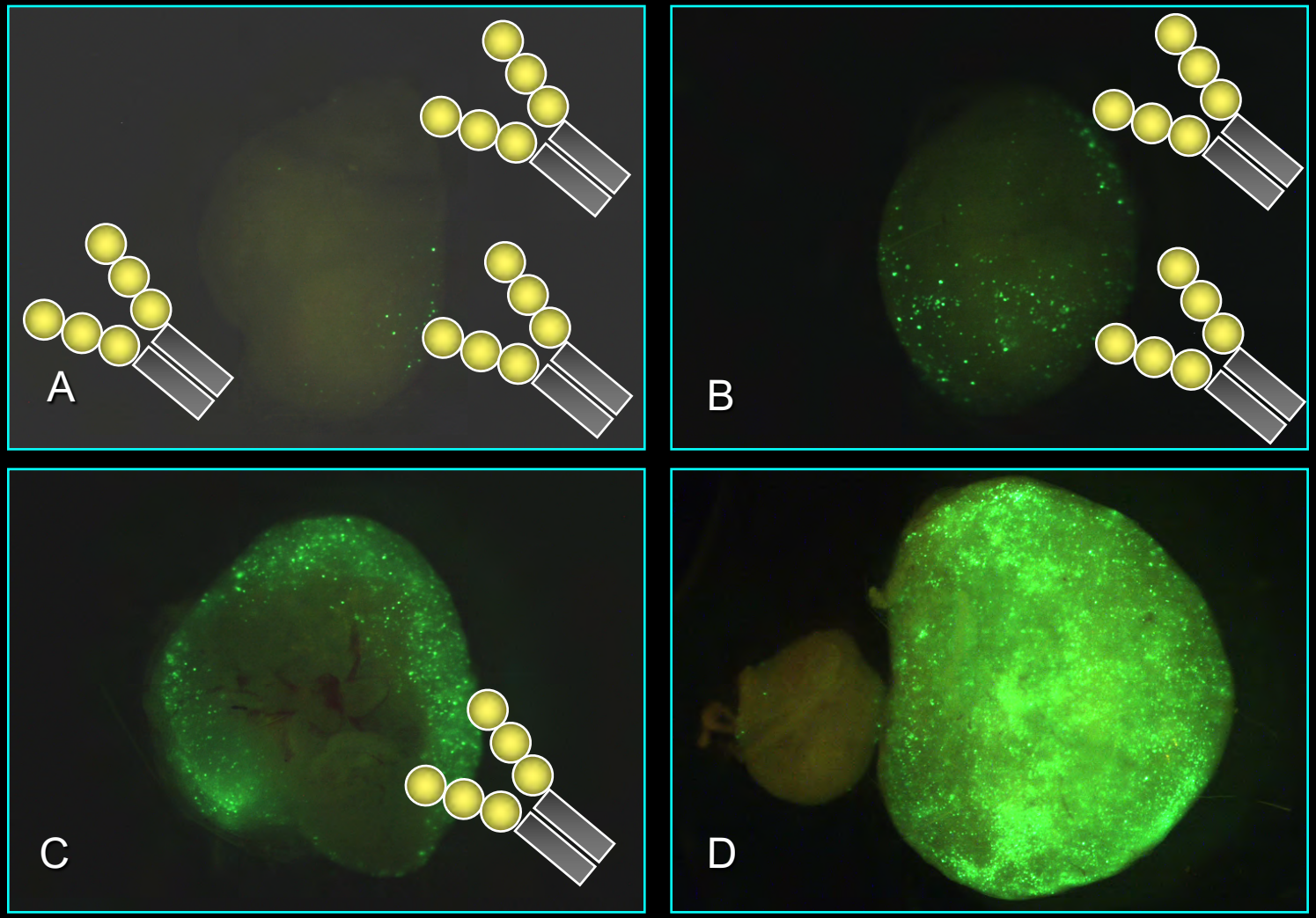
LNM35 tumor and metastasis



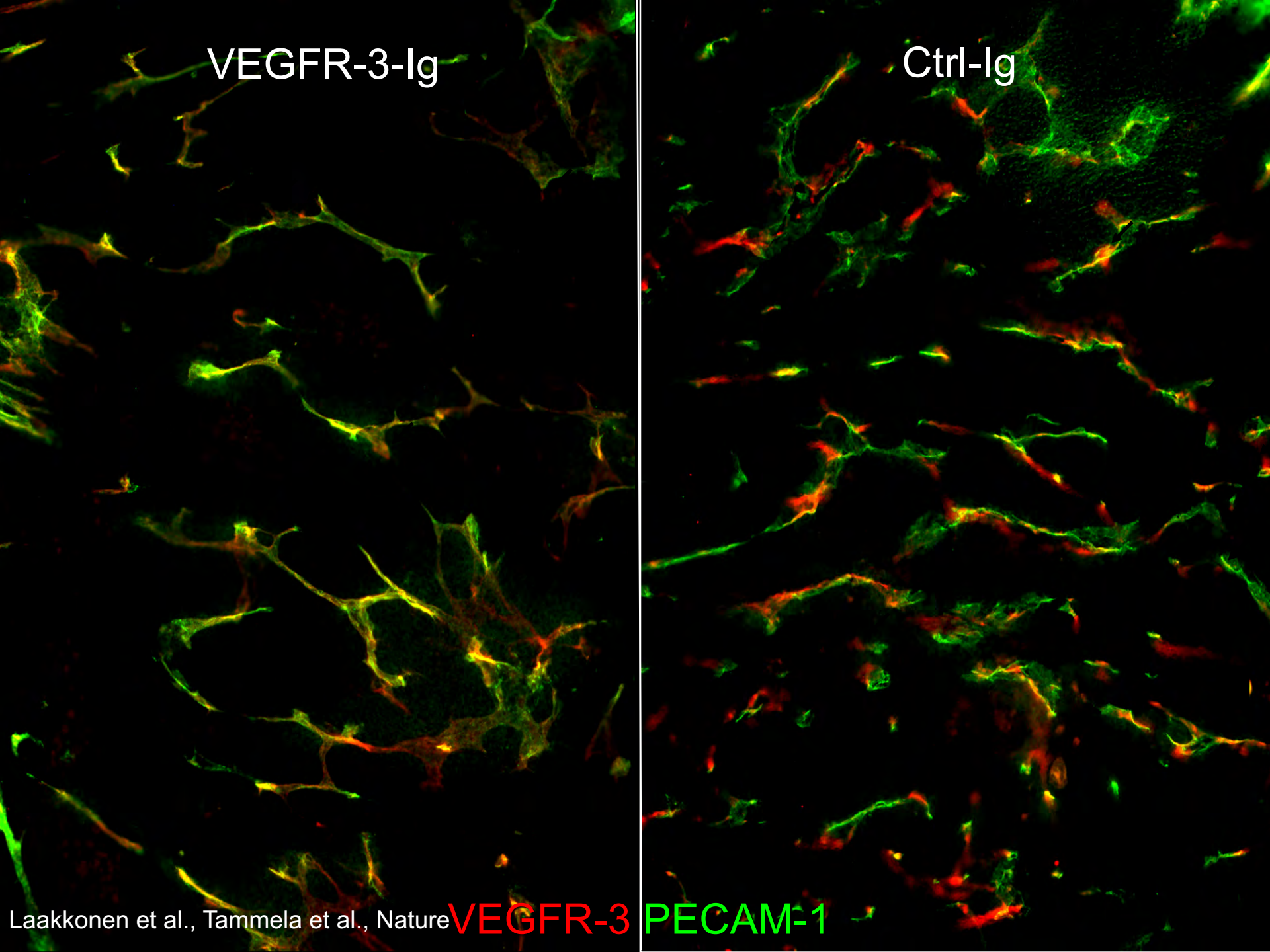
Control VEGFR-3-Ig treated

He et al., Cancer Res, 2005

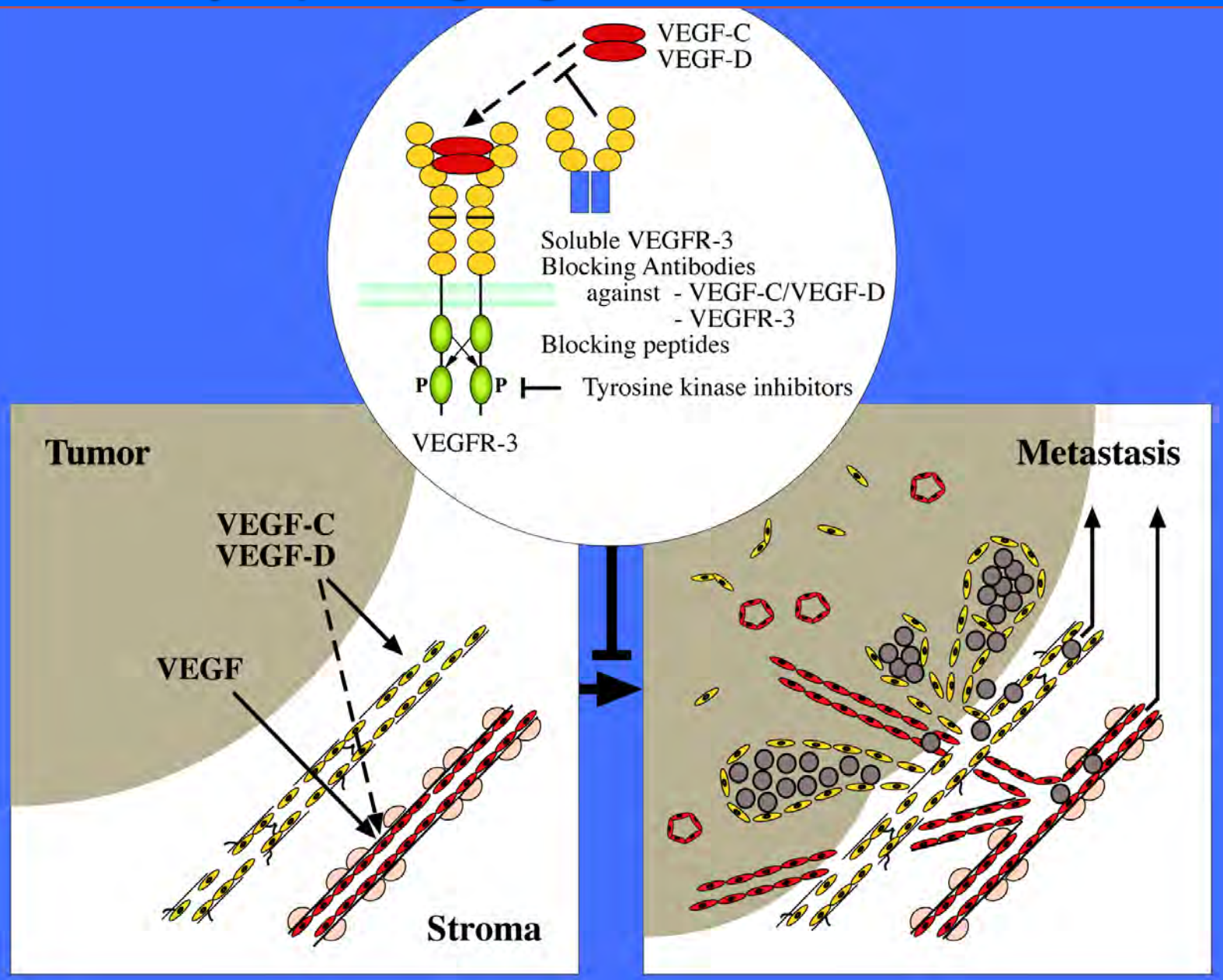
Titration of VEGFR-3-Ig and lymph node metastasis



He et al., Cancer Res, 2005

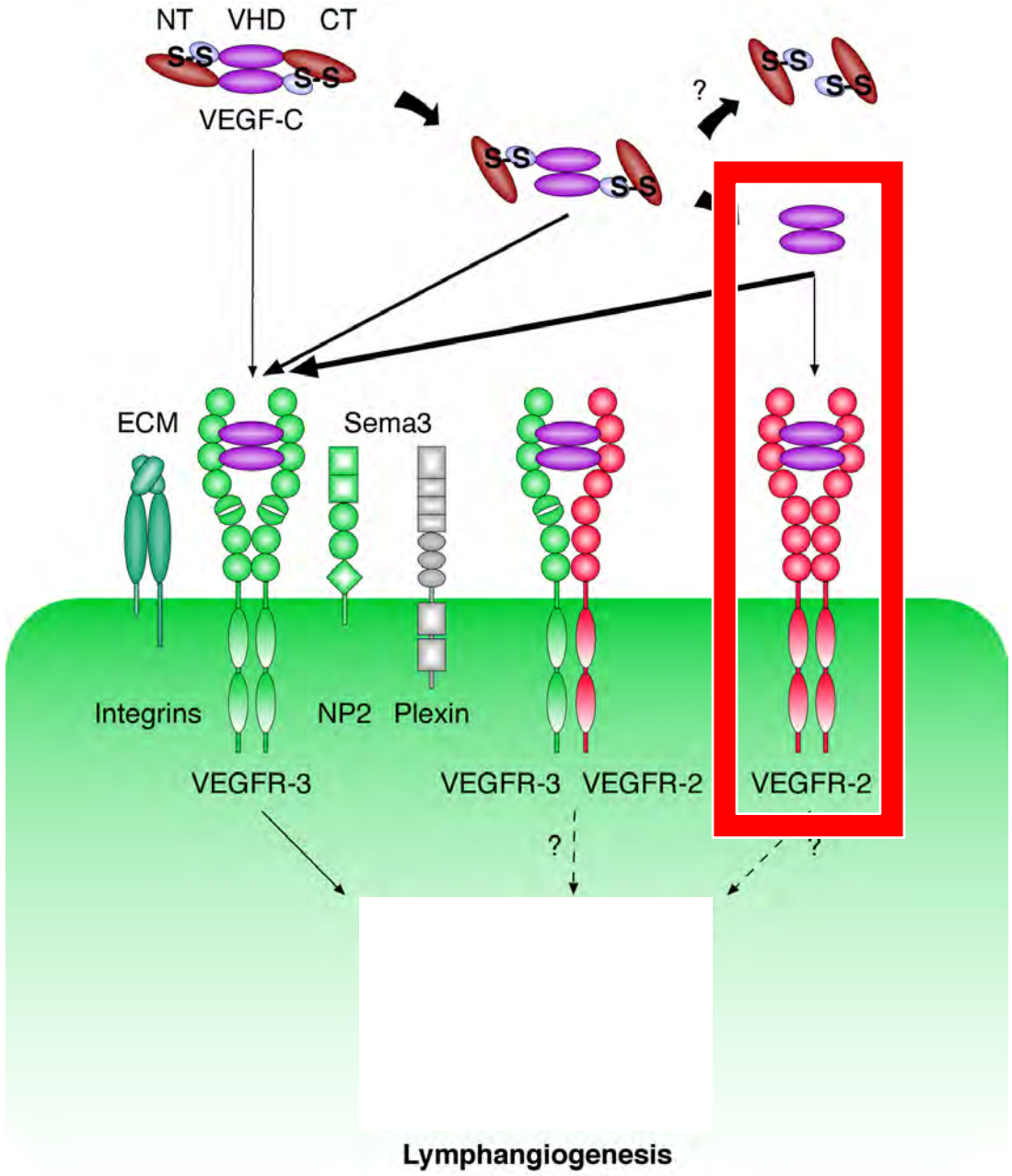

VEGFR-3-Ig
Ctrl-Ig
Laakkonen et al., Tammela et al., Nature
VEGFR-3
PECAM-1

Tumor Lymphangiogenesis and its Inhibition



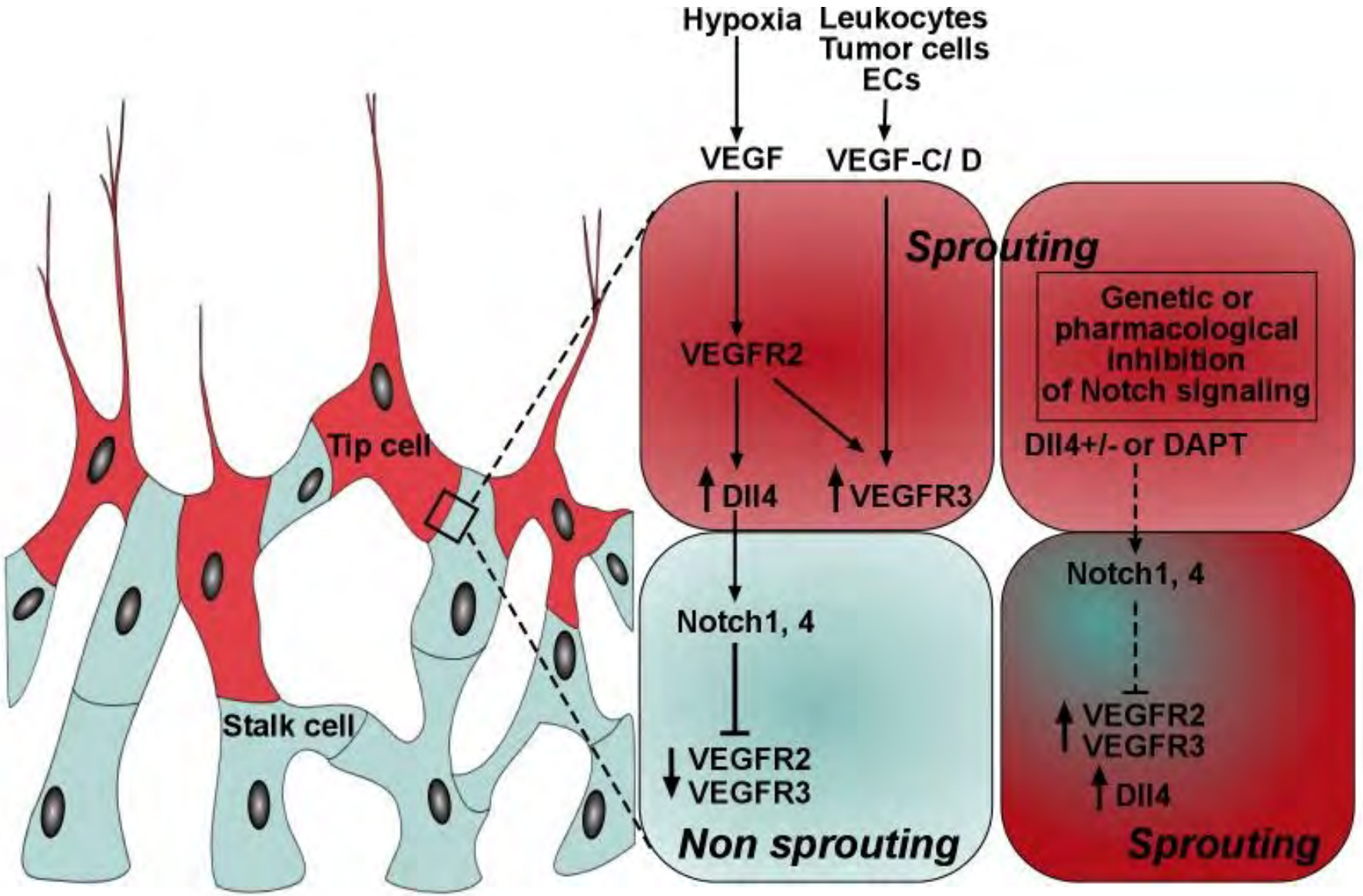
Karpanen and Alitalo, 2001

VEGF-C can also stimulate blood vessel growth



Karpanen MCBL

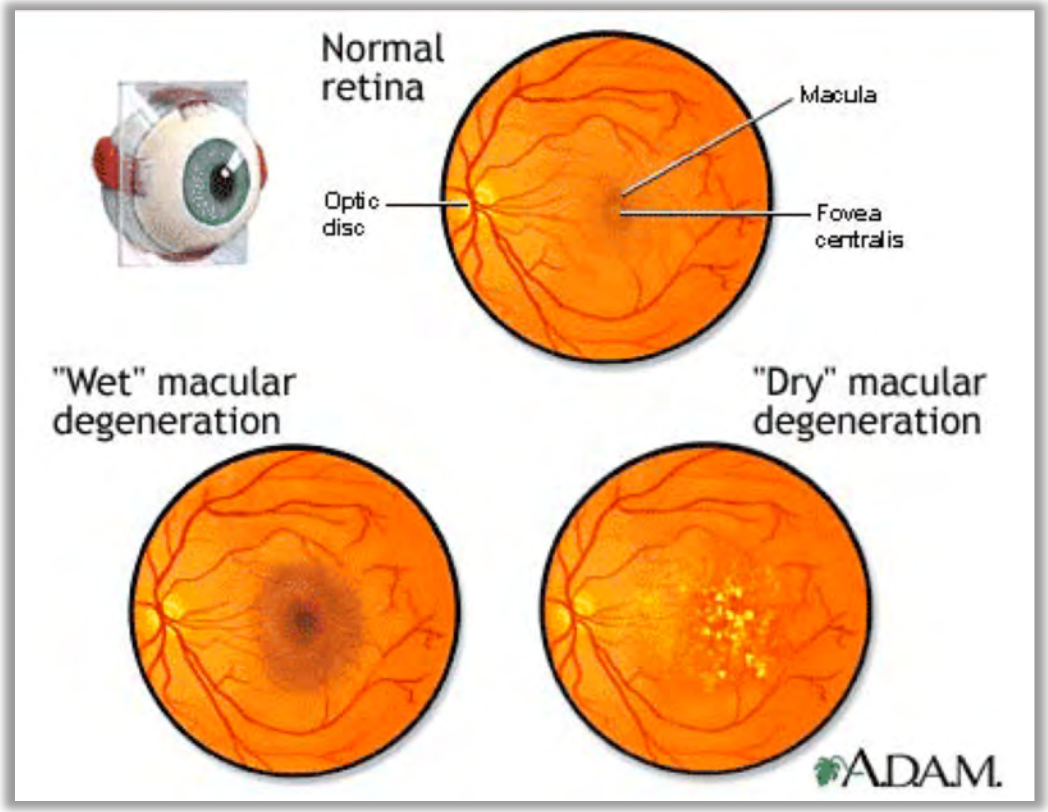
VEGF-C/VEGFR3 also functions in blood vessels

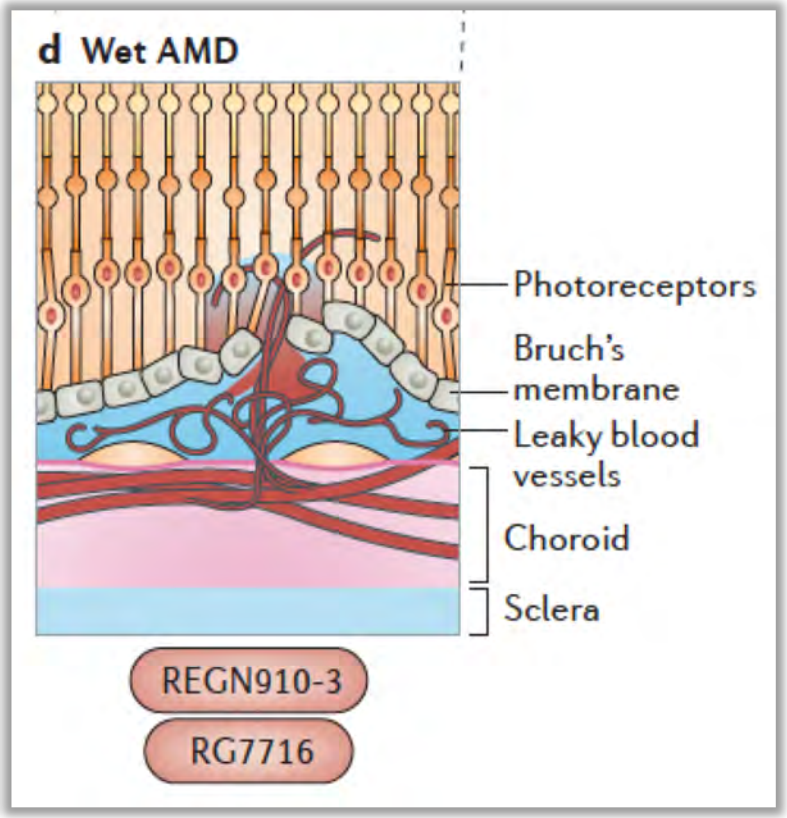


Tammela et al., Nature

VEGF-C/D trap

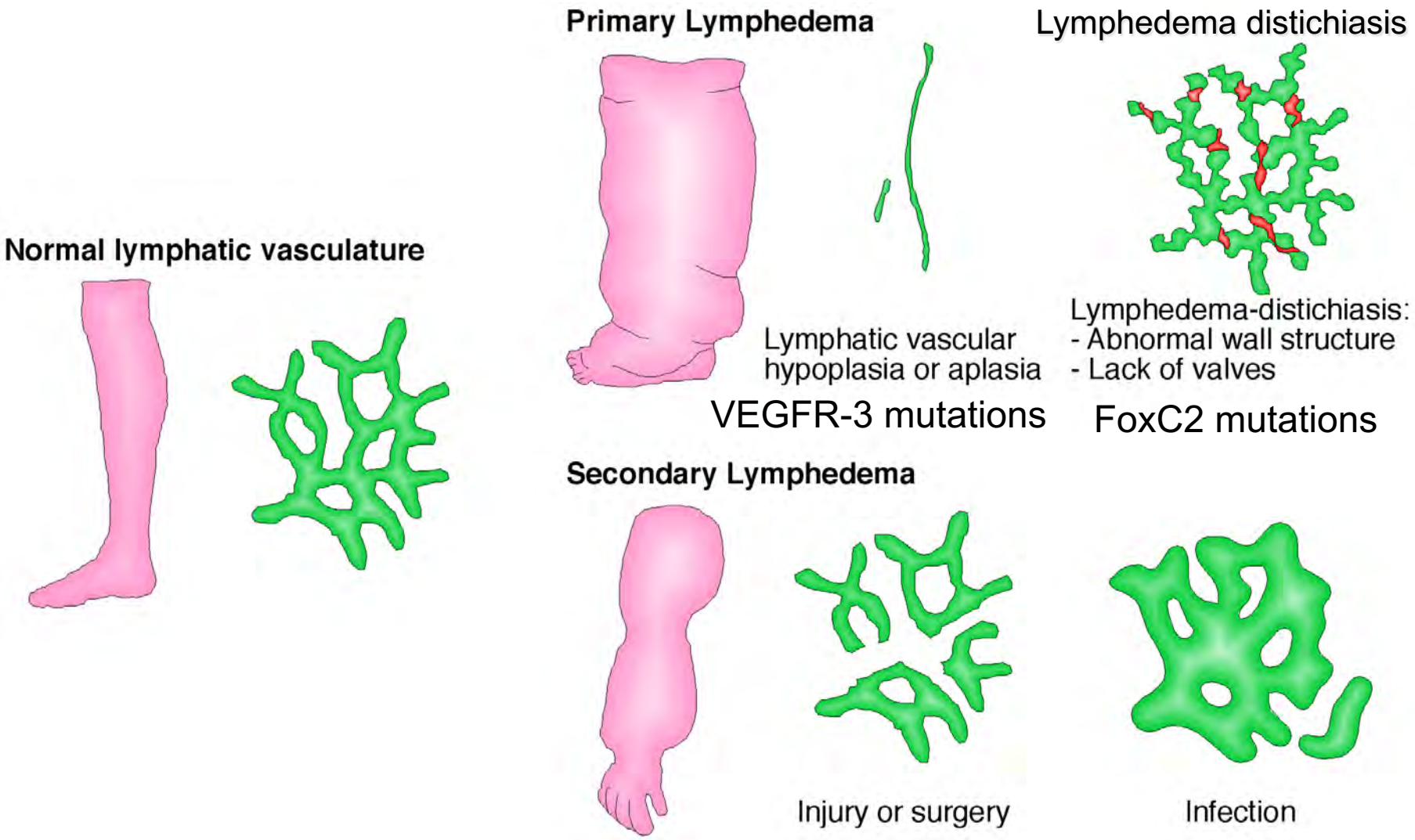
In phase 2b clinical trial with anti-VEGF (Lucentis®) in wet **age-related macular degeneration (wAMD)**.





Now also in phase 2b in diabetic macular edema (DME)

Failure of lymphatic vessel function in lymphedema



Karpanen & Alitalo, Ann. Rev. Pathol.
Petrova et al., Nature Medicine

Fluid pressure - extravasation

Drainage

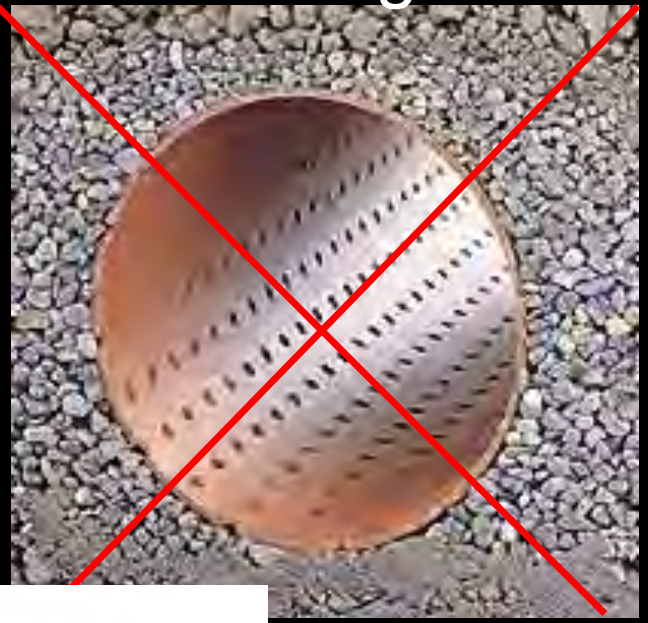
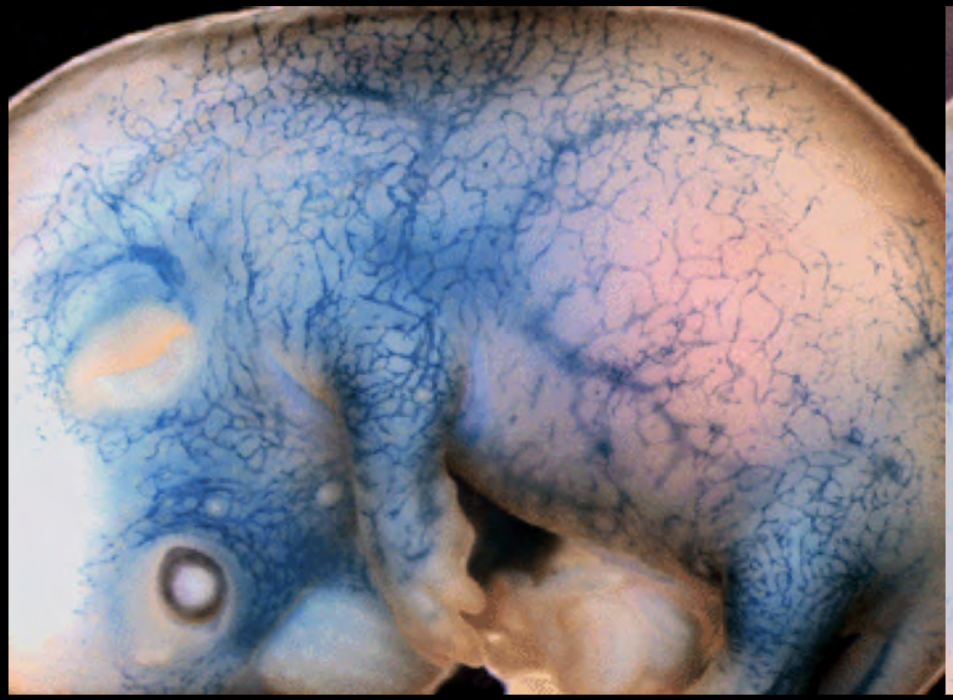


Image Source: Be a Survivor, By Vladmir Lange, M.D.

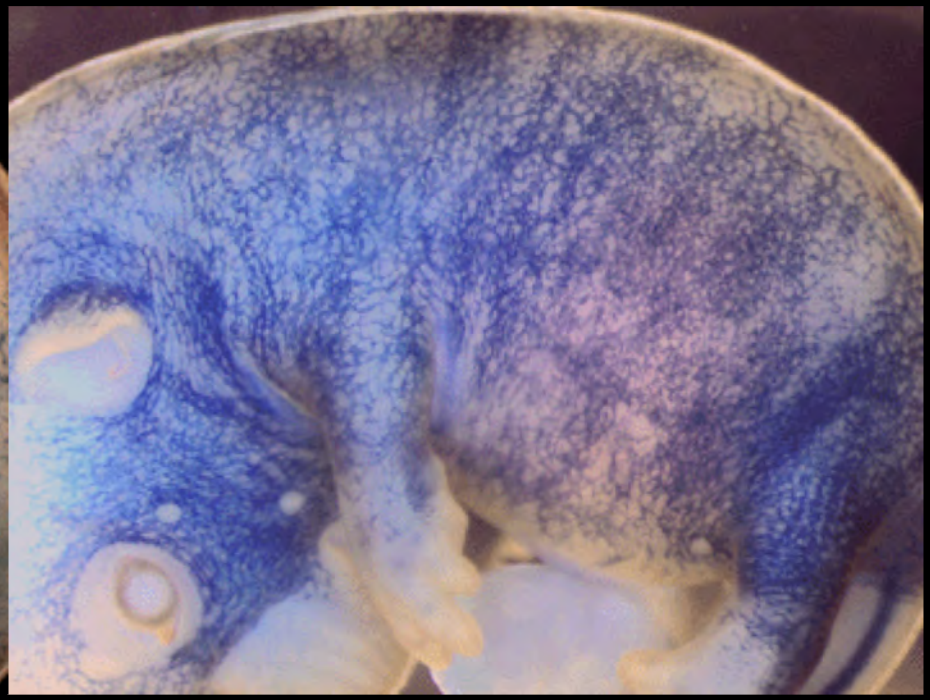
Lymphedema

Lymphatic hyperplasia in VEGF-C transgenic mice

Wild-type

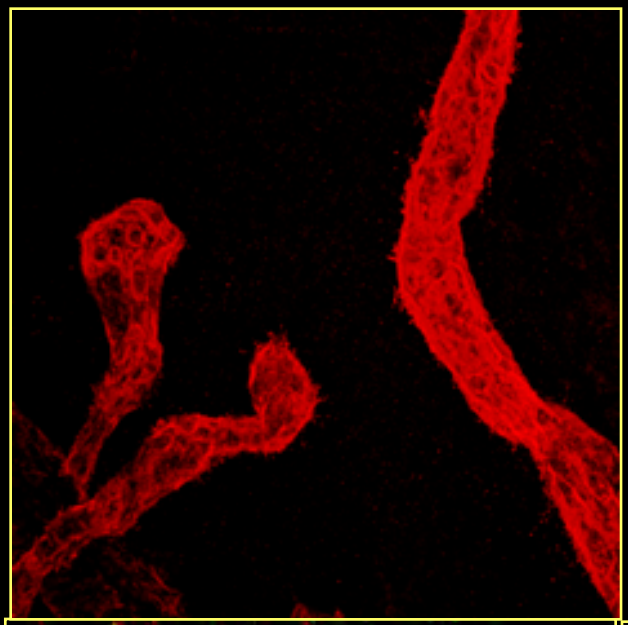


K14-VEGF-C

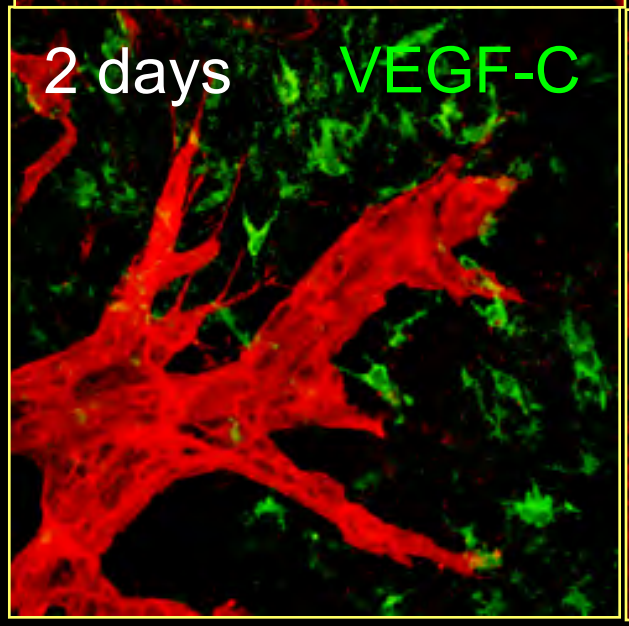


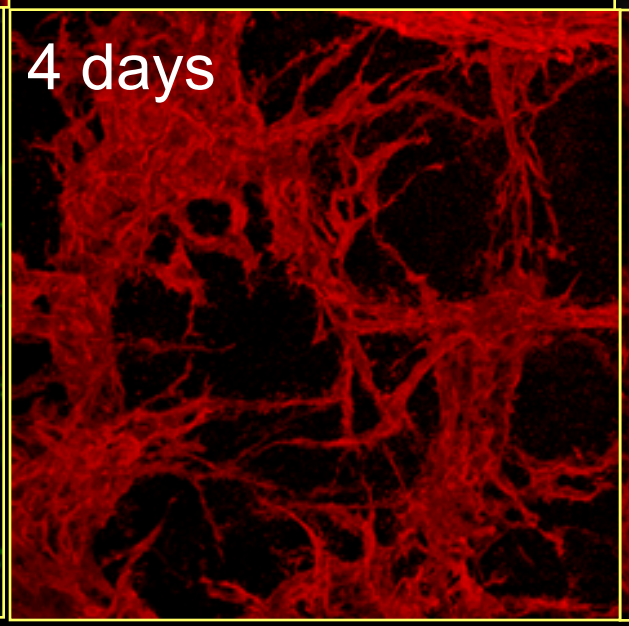
Jeltsch et al., Science, Saaristo et al., J Exp. Med.

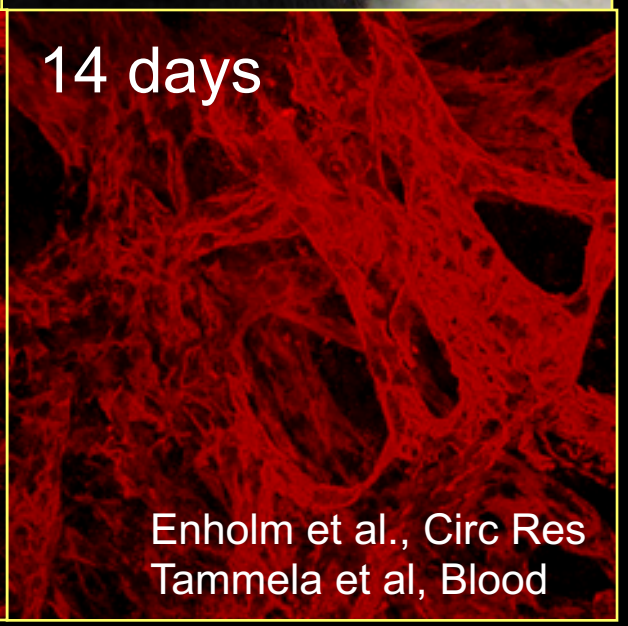
Lymphangiogenesis



induced by VEGF-C

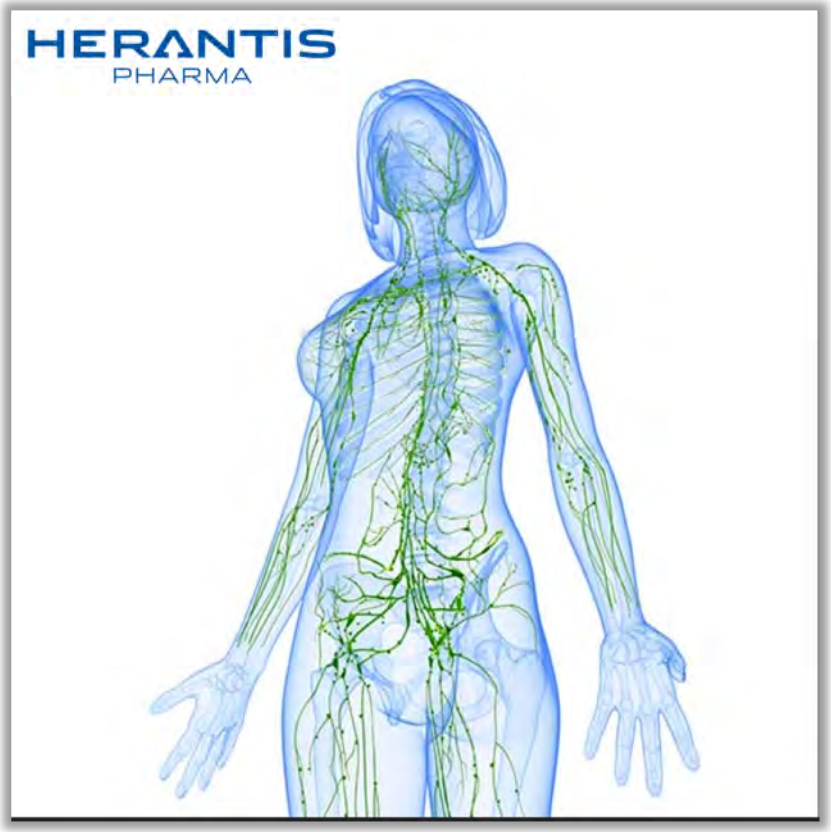


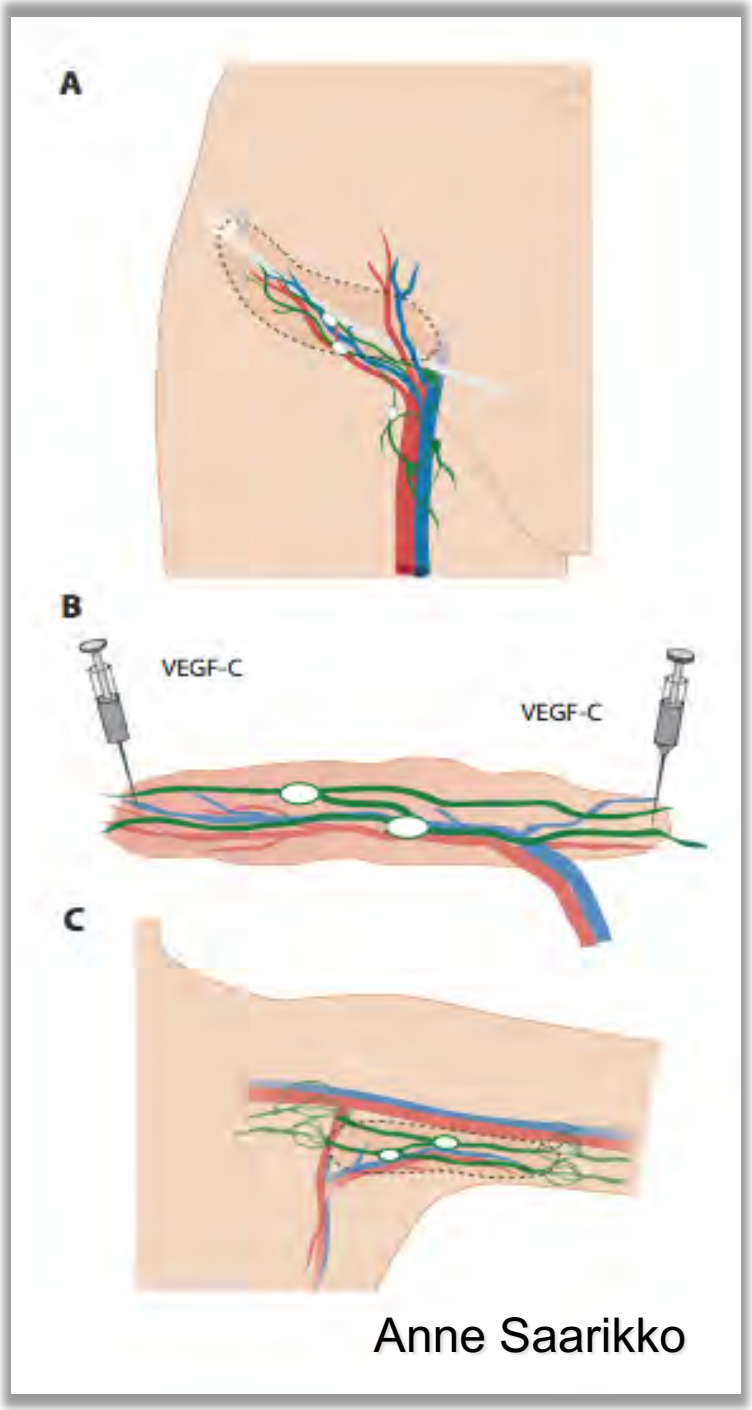




Clinical study on Lymphactin

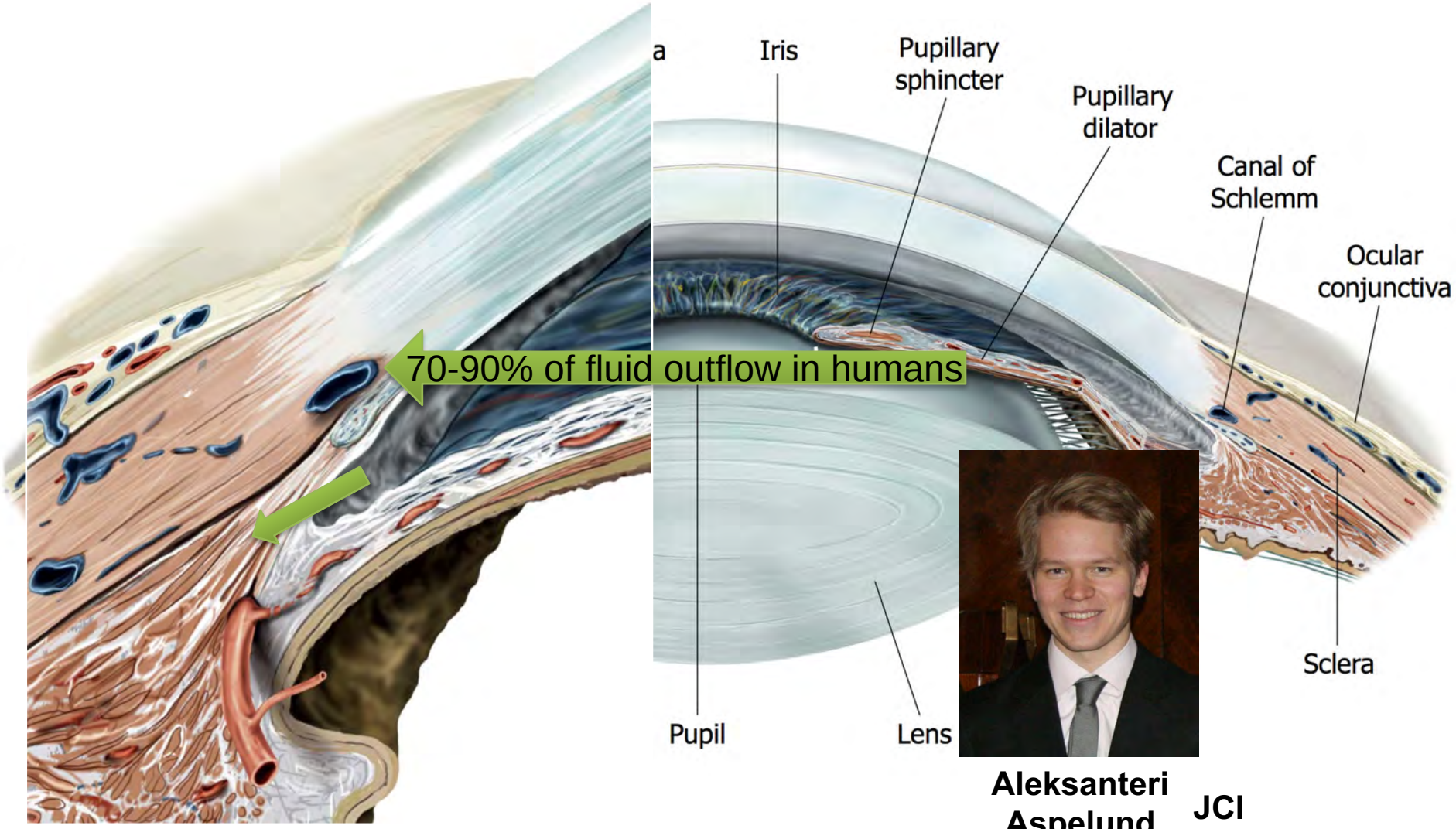
- Breast cancer associated secondary lymphedema
- Recruitment started in May 2016
- 1. Primary endpoint: safety and tolerability of Lymfactin®
- Preliminary efficacy of the treatment
- Now in phase 2 clinical trial





Anne Saarikko

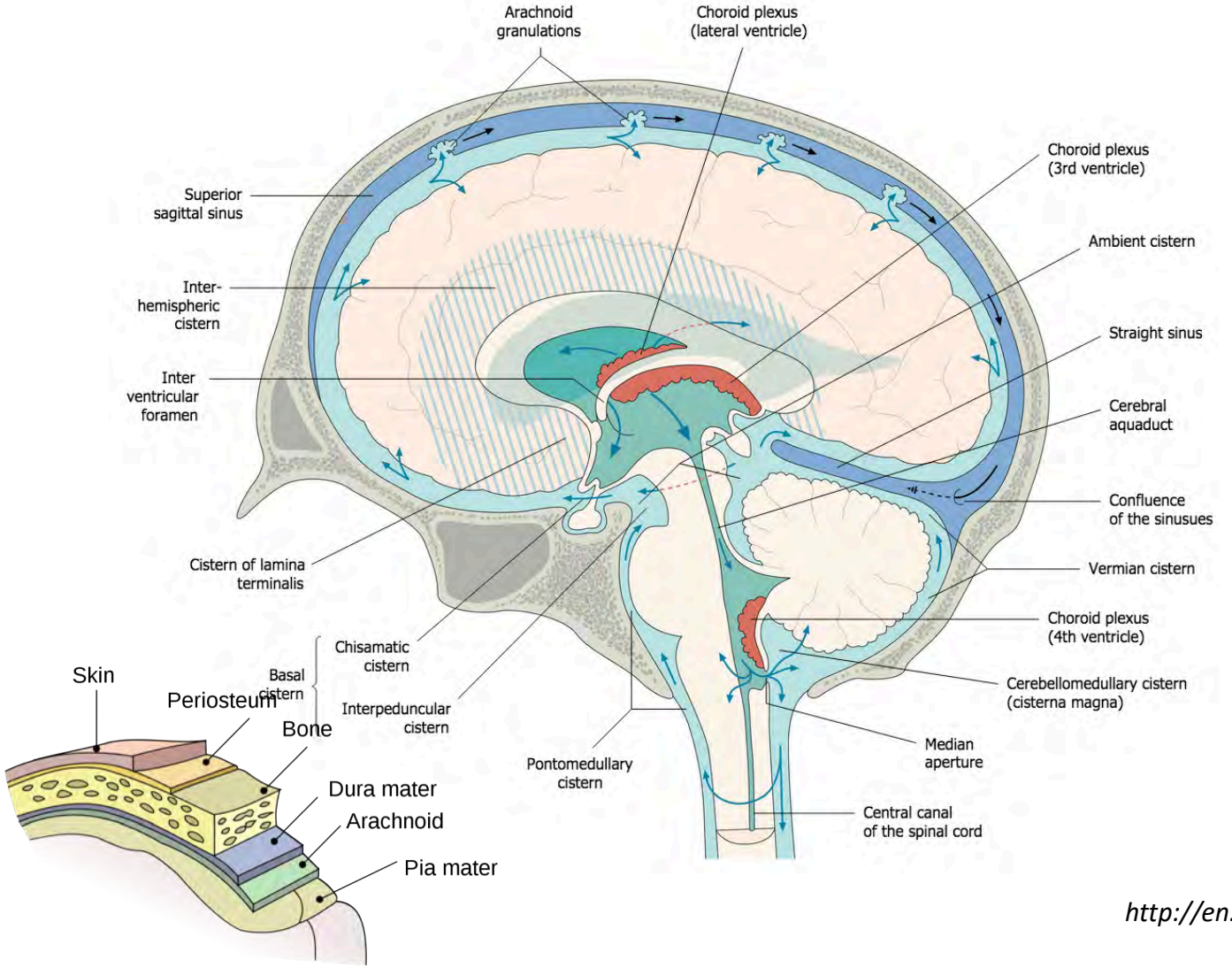
VEGF-C stimulates growth of the Canal of Schlemm, reducing intraocular pressure



Aleksanteri Aspelund **JCI**

Gilroy et al: Atlas of Anatomy. © 2008-2012 Thieme Medical Publishers, Inc.

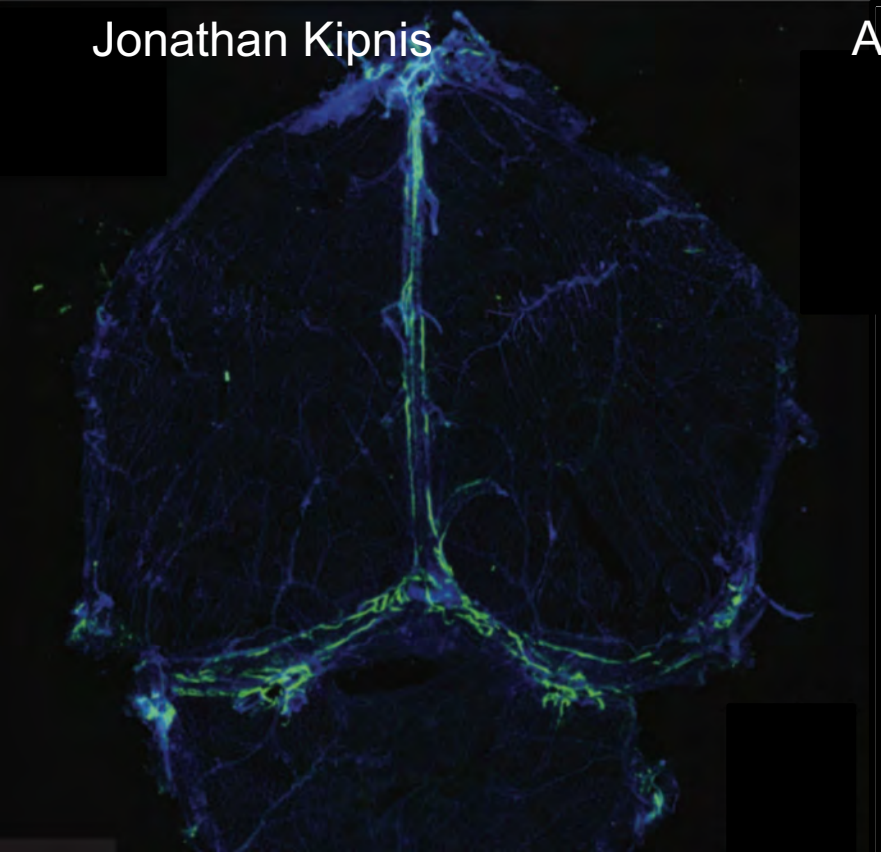
Cerebrospinal fluid flow

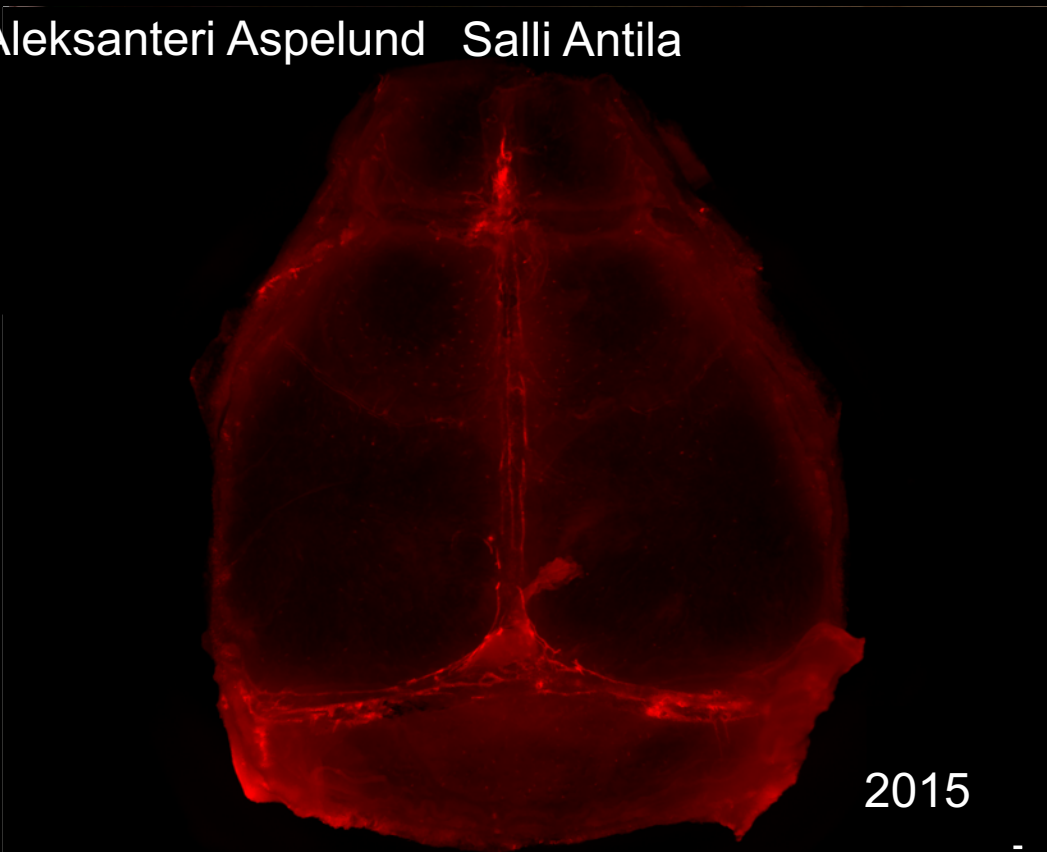


http://en.wikipedia.org/wiki/Cerebrospinal_fluid

Jonathan Kipnis

Aleksanteri Aspelund Salli Antila



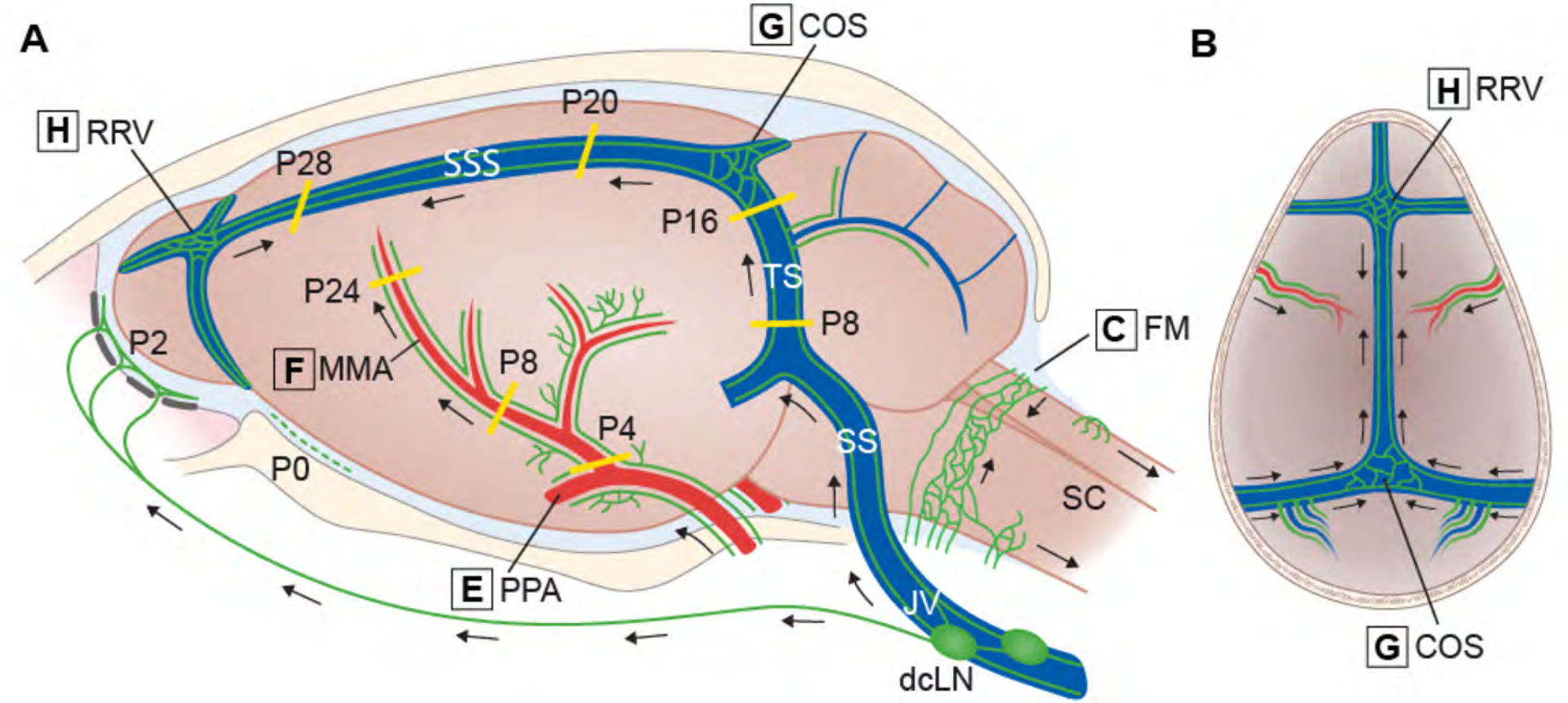


2015

Salli Antila, Sinem Karaman, Harri Nurmi, Mikko Airavaara, Merja Voutilainen, Thomas Mathivet, Dmitri Chilov, Zhilin Li, Tapani Koppinen, Jun-Hee Park, Shentong Fang, Aleksanteri Aspelund, Mart Saarma, Anne Eichmann, Jean-Léon Thomas, and Kari Alitalo

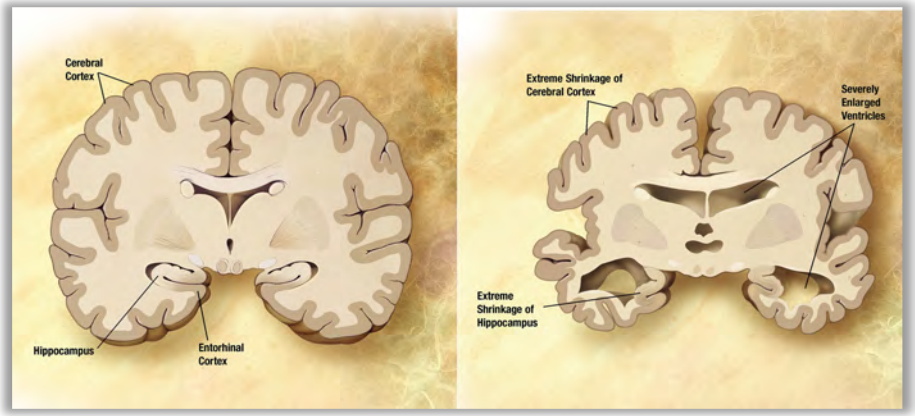
Development and plasticity of meningeal lymphatic vessels

J. Exp. Med. December 2017 Vol. 214 No. 12 3645–3667

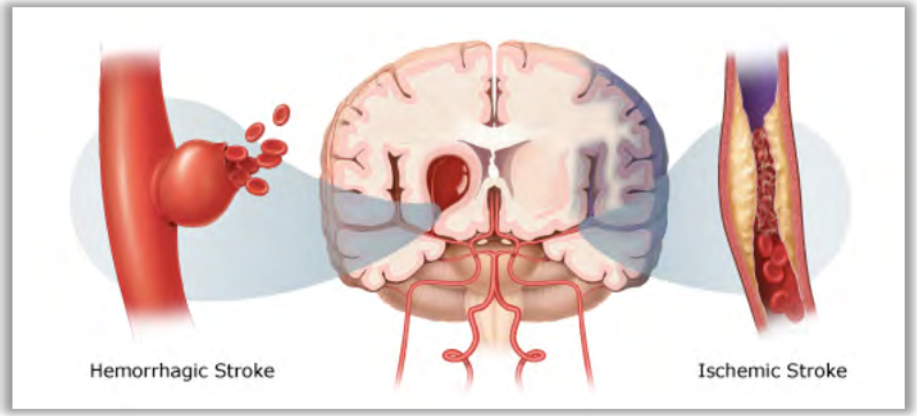


Are lymphatic vessels involved in neuropathology?

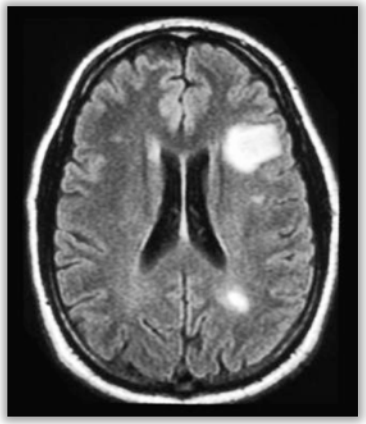
Alzheimer's disease



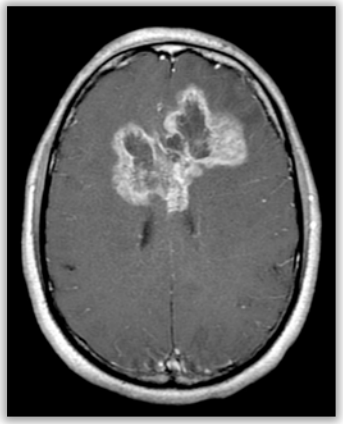
Stroke



Multiple sclerosis



Glioblastoma

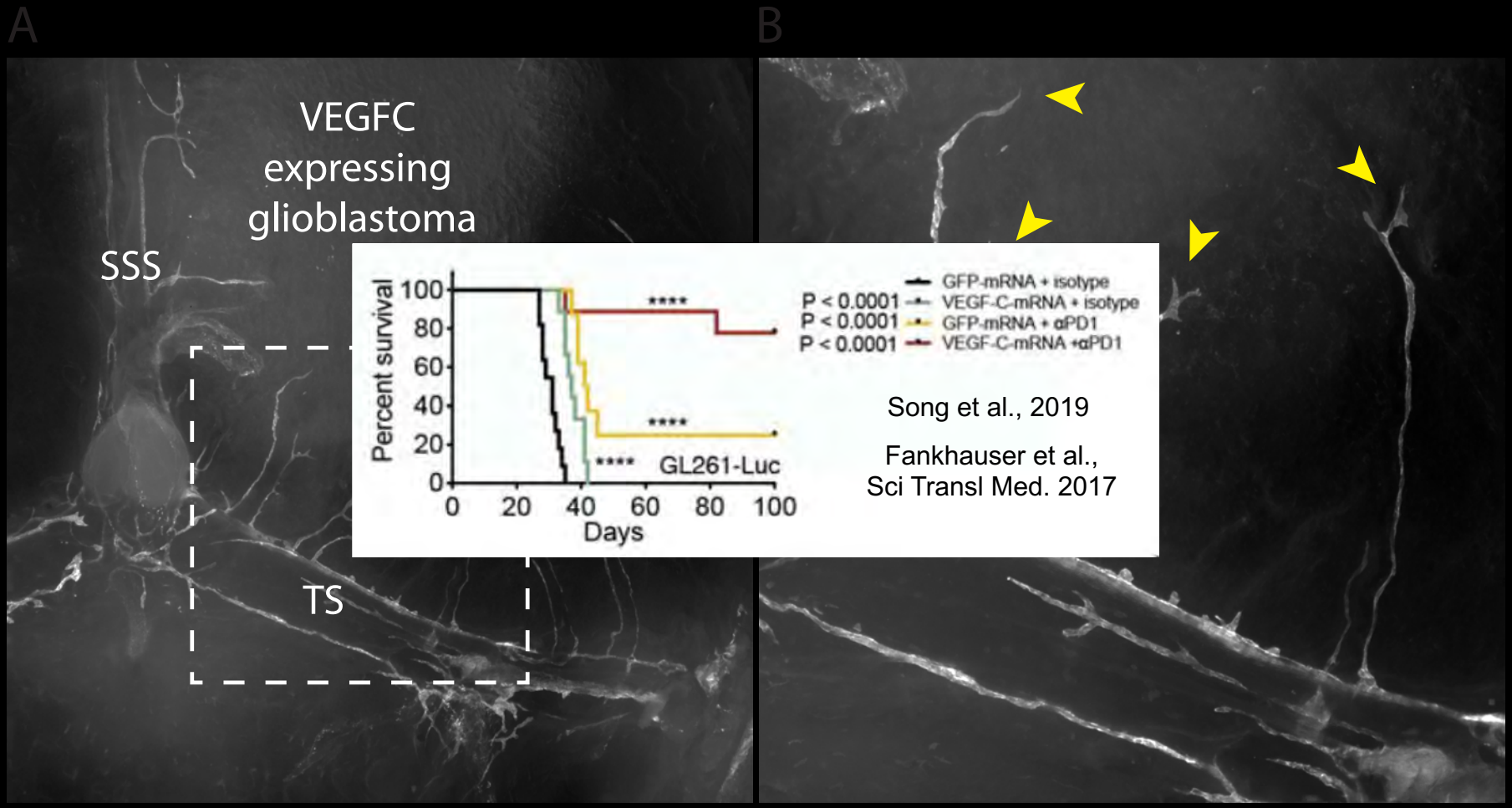


Migraine

Traumatic brain injury

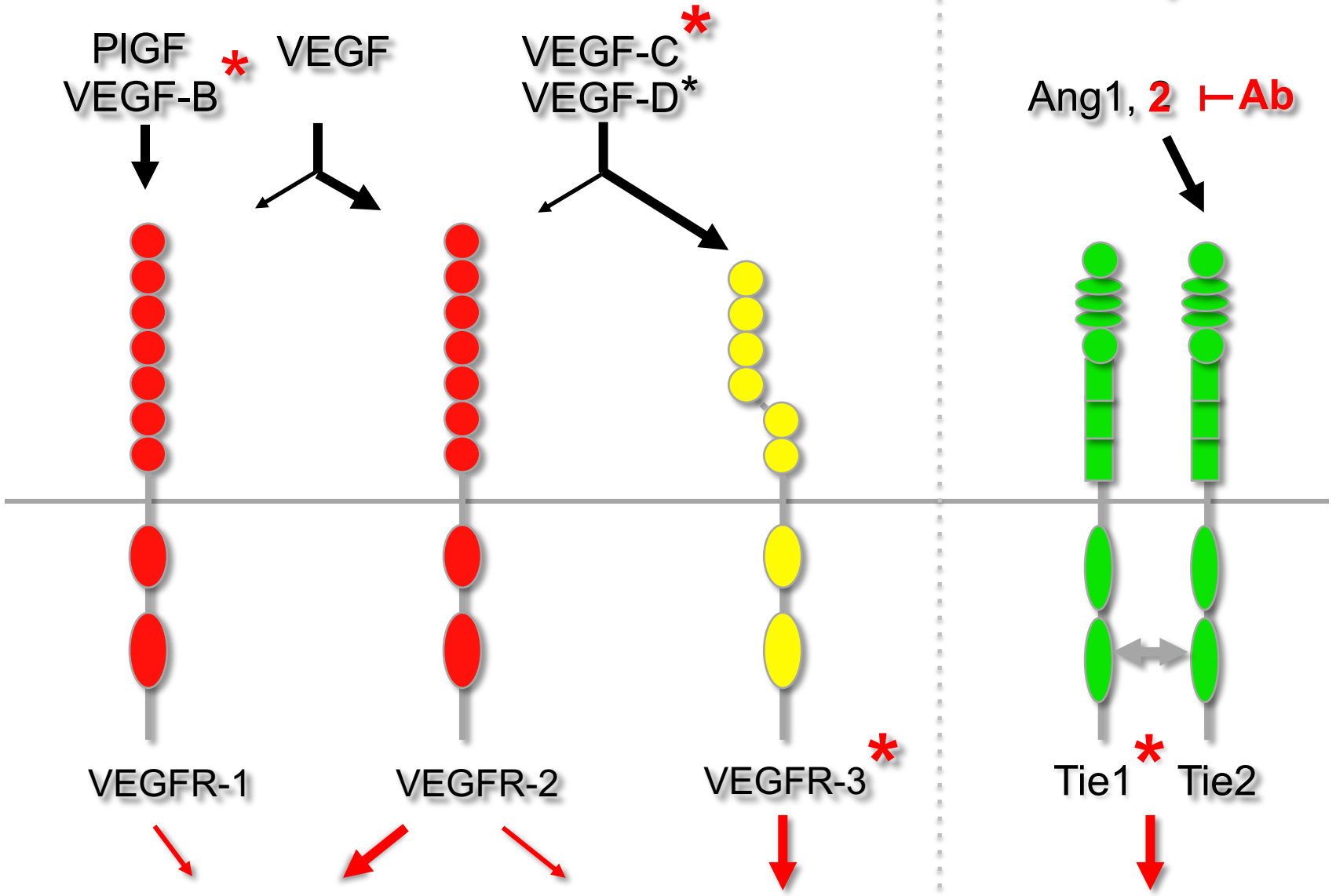
…Parkinson's, Lewy body disease, primary intracranial hypertension, prion-like proteinopathies…

Lymphangiogenesis to boost immunotherapy in brain tumors?



Antila, Aspelund et al. unpublished

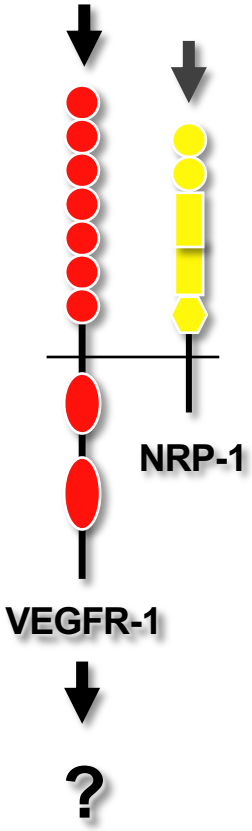
Endothelial Growth Factors and Receptors

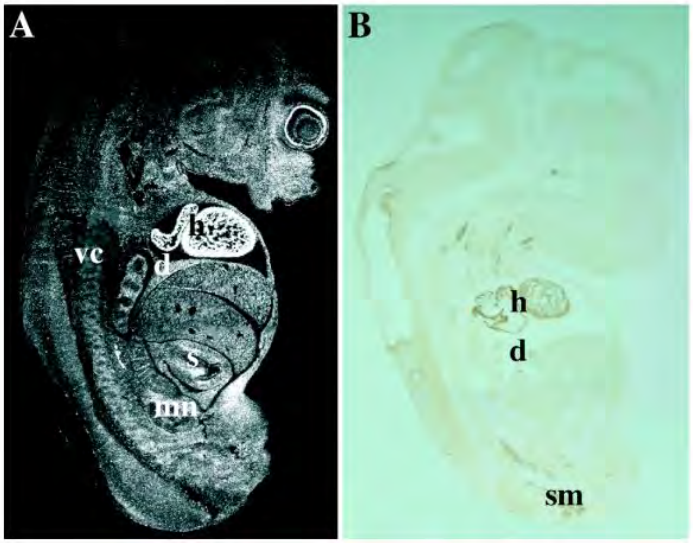


TCB

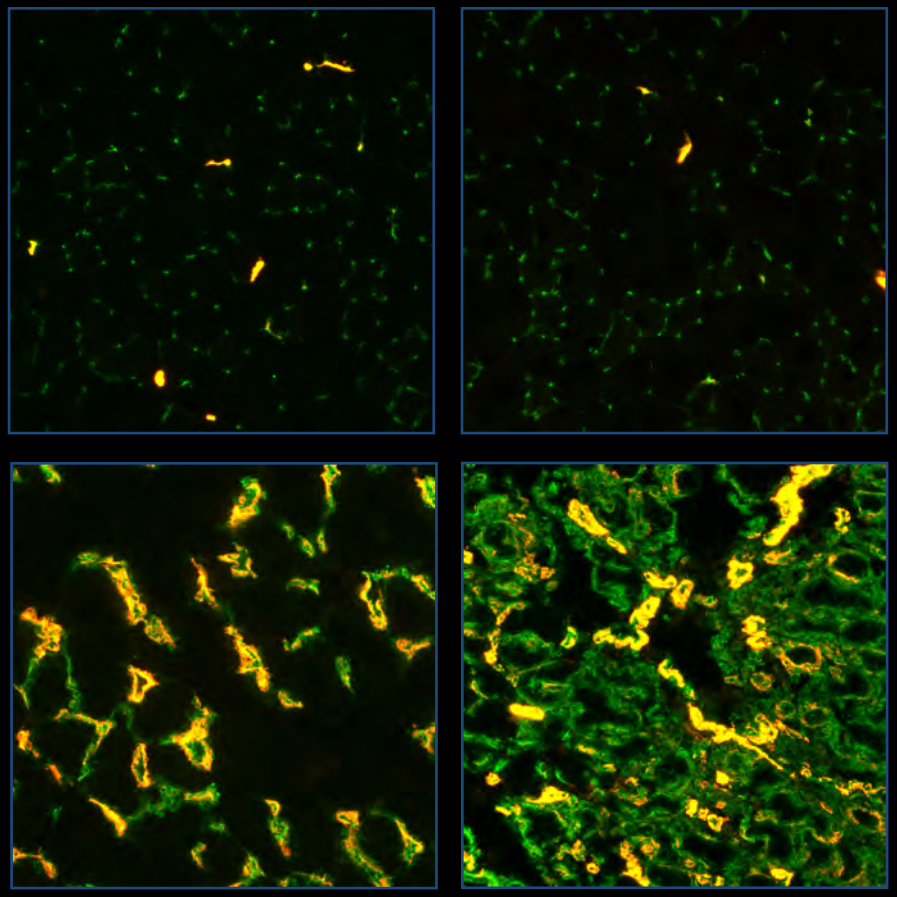
Vascular endothelial growth factor B

Olofsson B, Pajusola K*, Kaipainen A, von Euler G, Joukov V, Saksela O, Orpana A, Pettersson RF, Alitalo K*, Eriksson U*
Proc Natl Acad Sci U S A. 93: 2576-81, 1996*





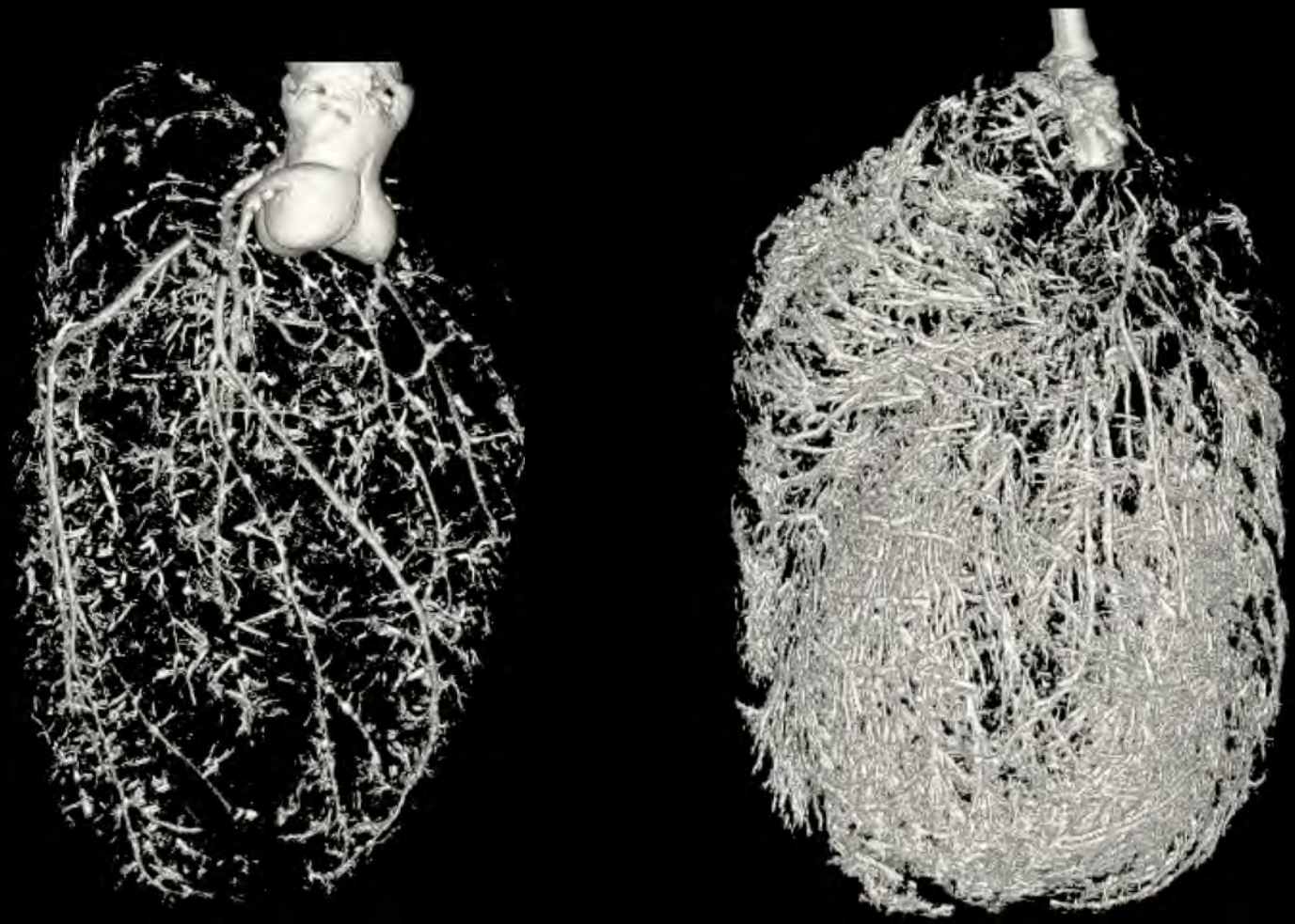
Blood vessels after AAV-mediated gene delivery to skeletal muscle



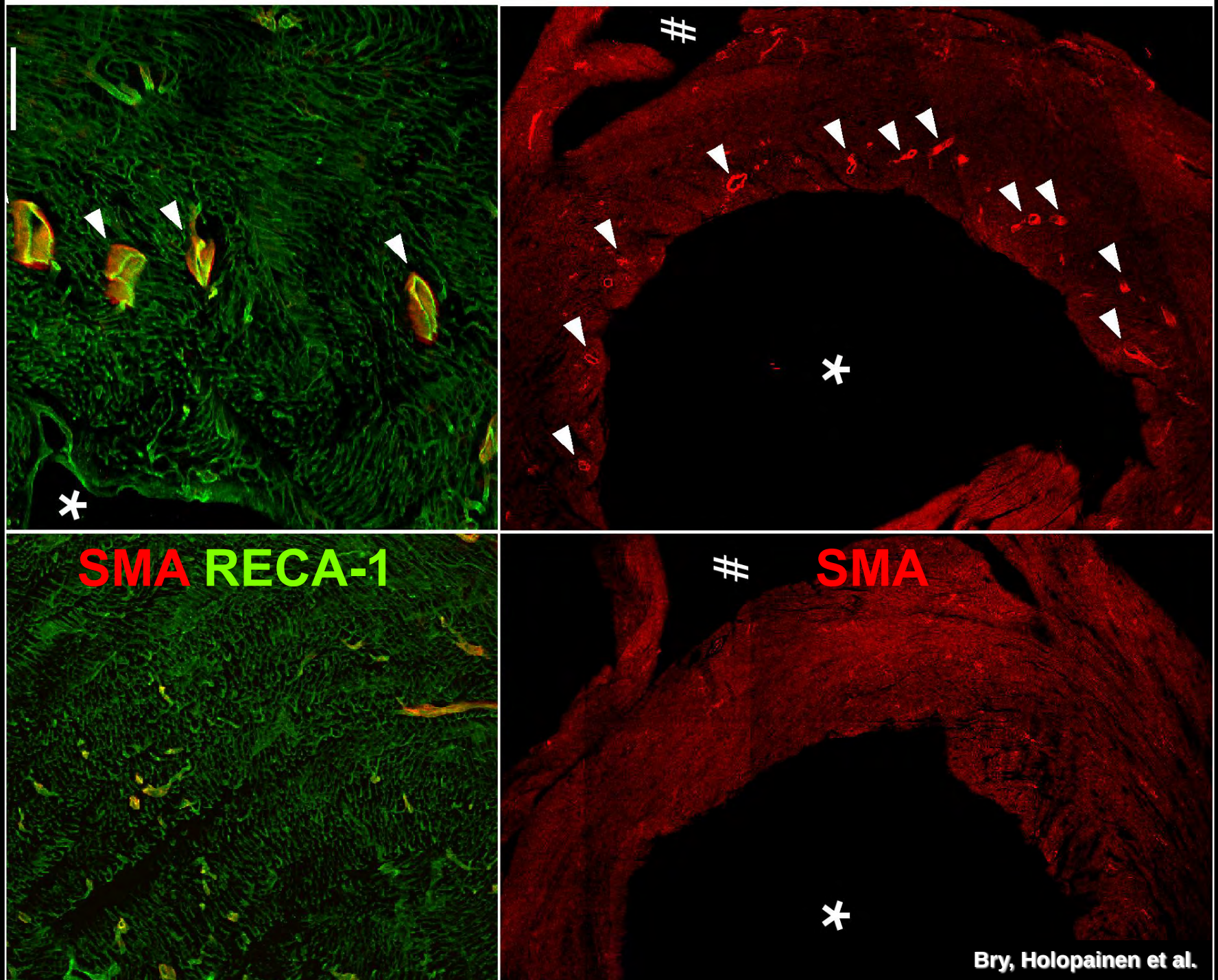
Anisimov et al.

VEGF-B WT and TG hearts

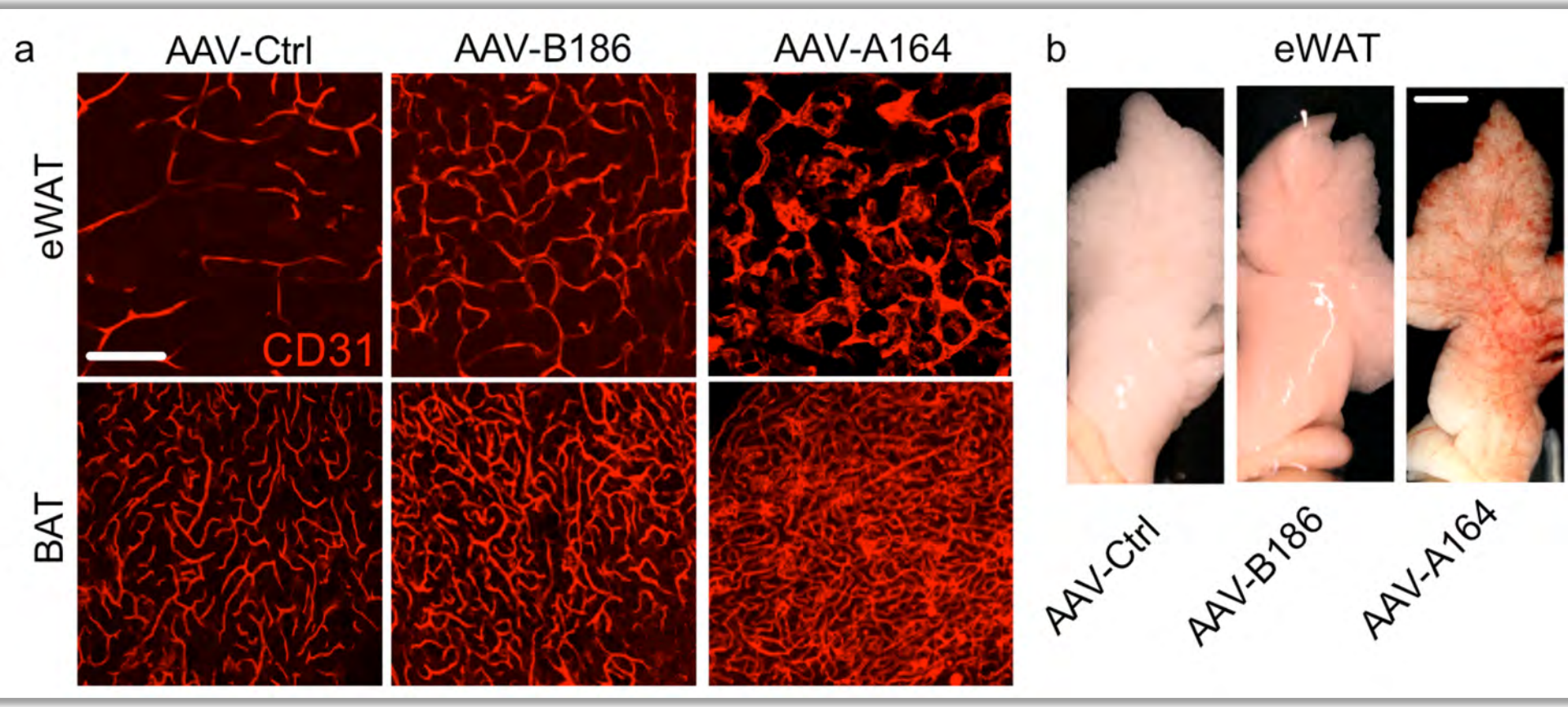
μCT imaging of the arterial phase



Kivelä et al., 2014

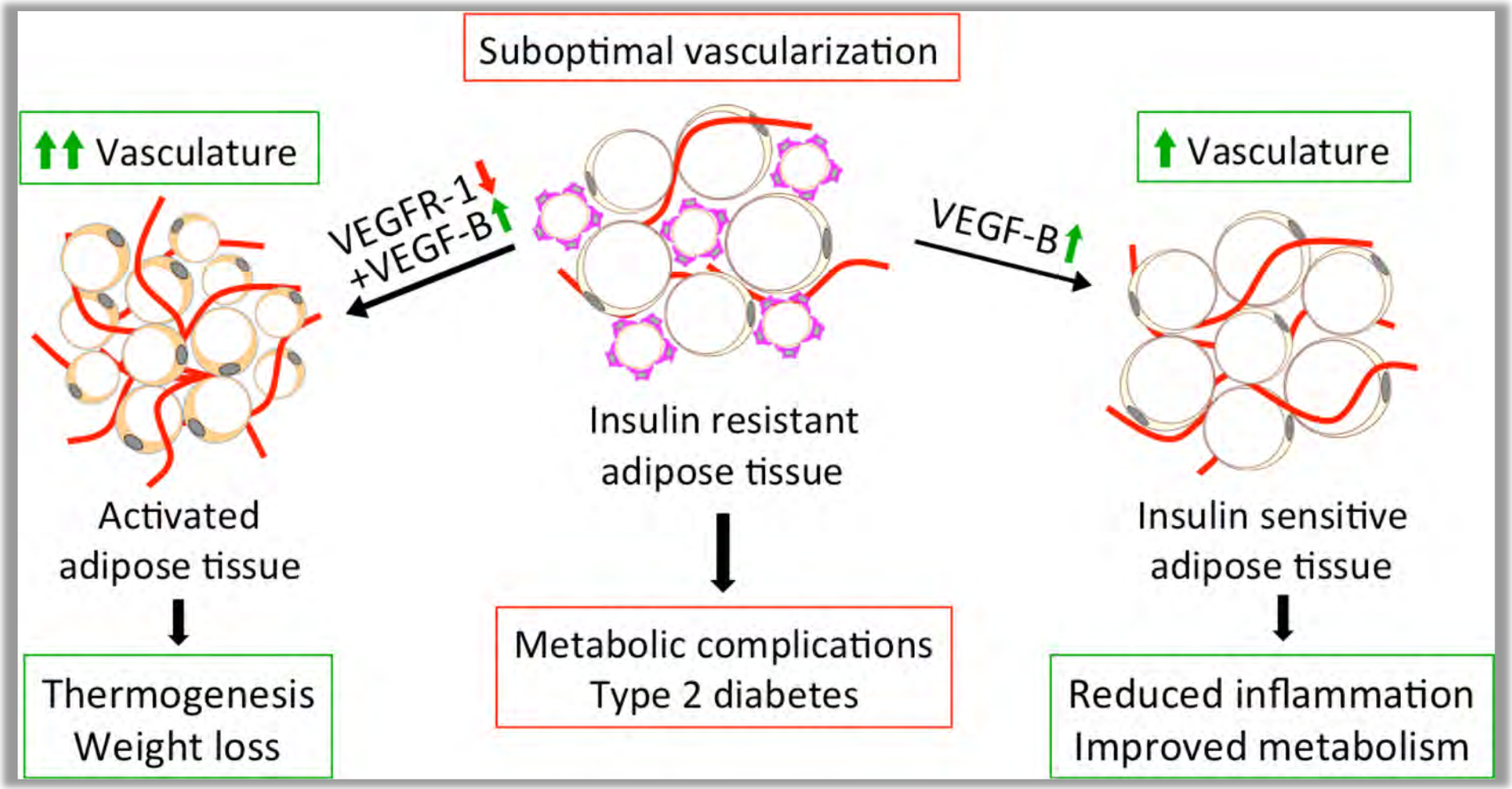

SMA RECA-1
SMA
Bry, Holopainen et al.

VEGF-B increases “healthy” vesssels in white and brown adipose tissue



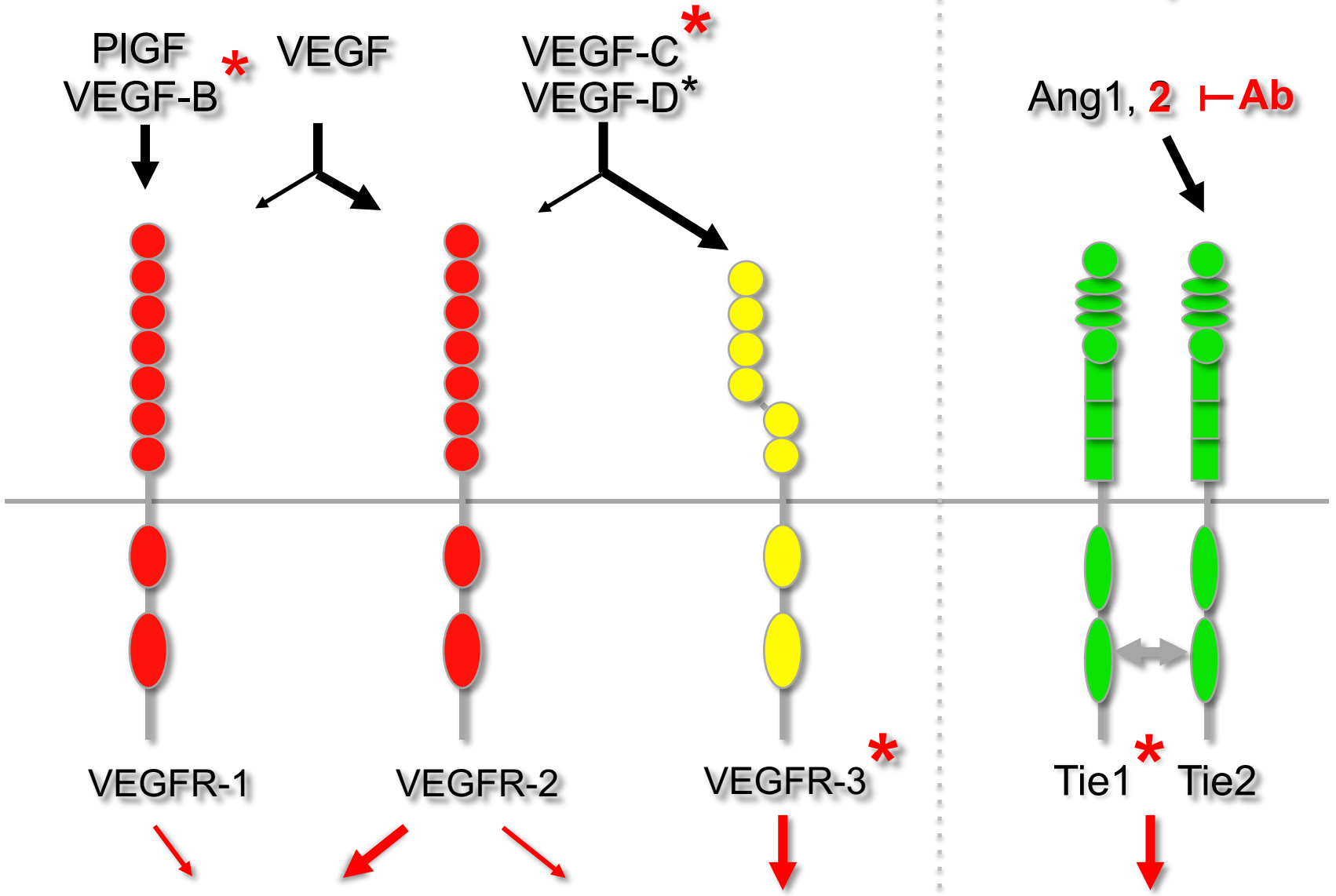
Robciuc et al., Cell Metabolism

Therapeutic angiogenesis in adipose tissue?



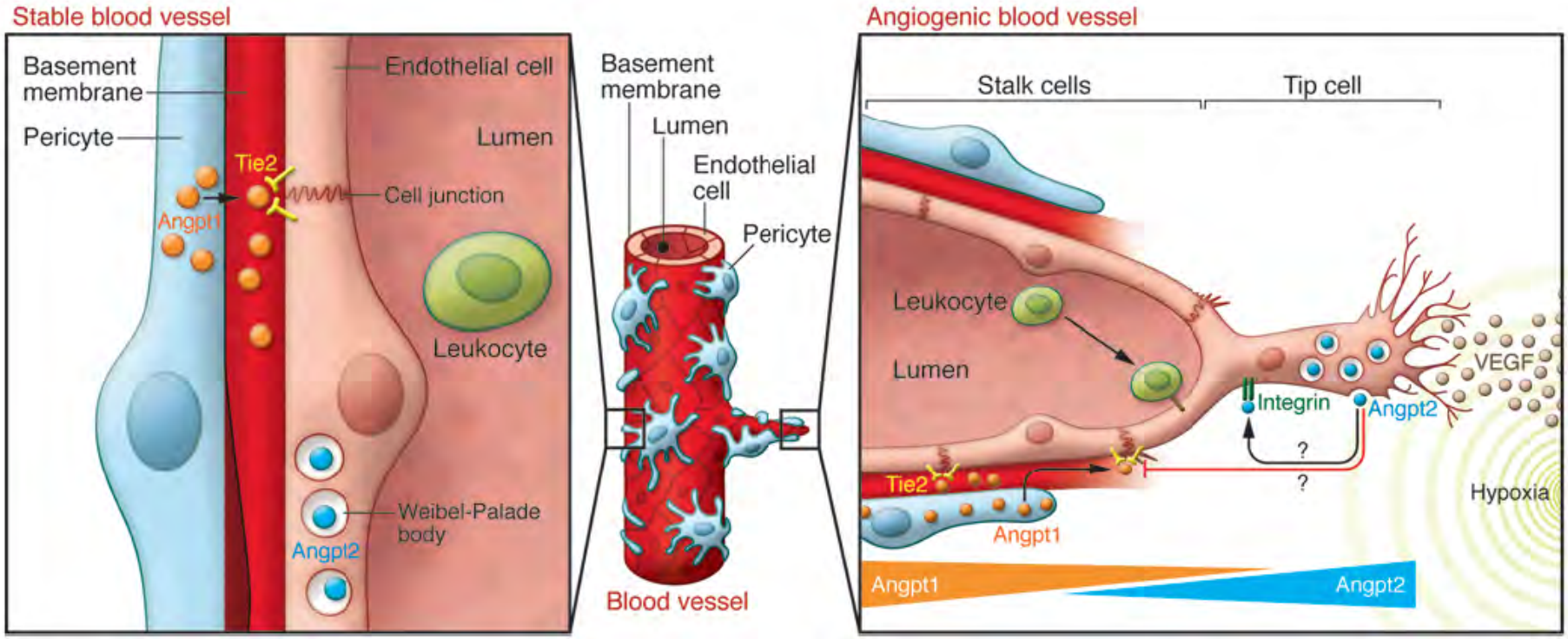
Robciuc et al., Cell metabolism

Endothelial Growth Factors and Receptors



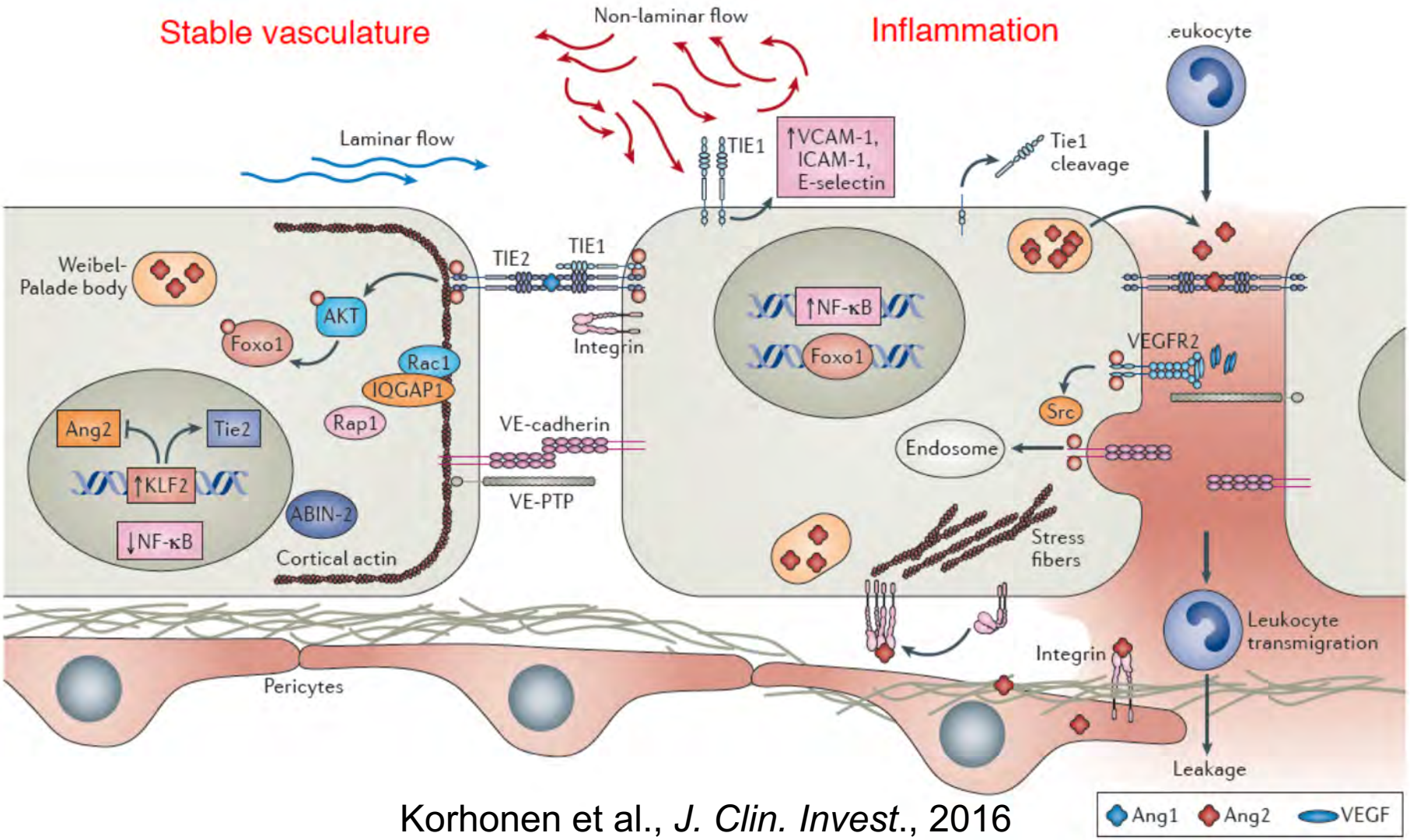
TCB

The angiopoietin-Tie system



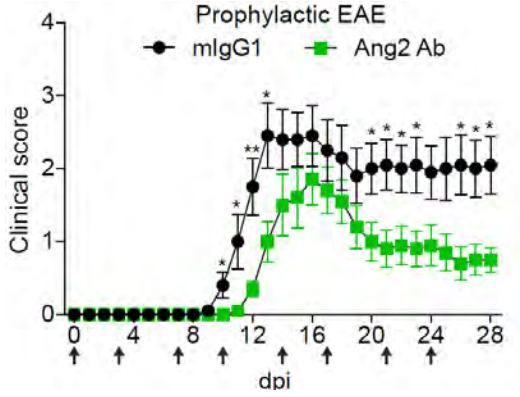
Saharinen & Alitalo, JCI, 2011

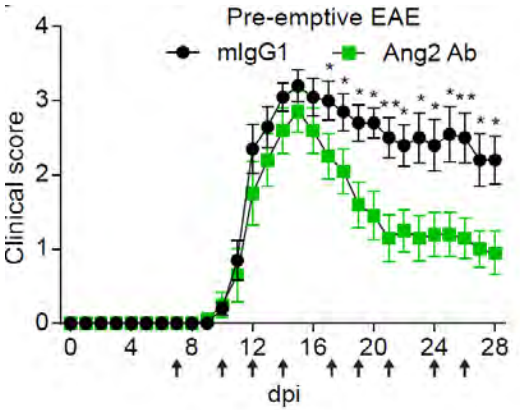
Ang-Tie system provides a molecular switch in inflammation

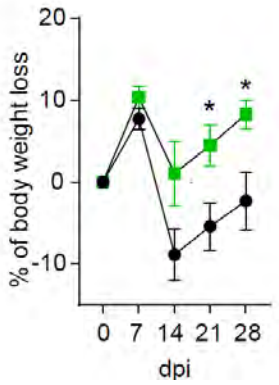


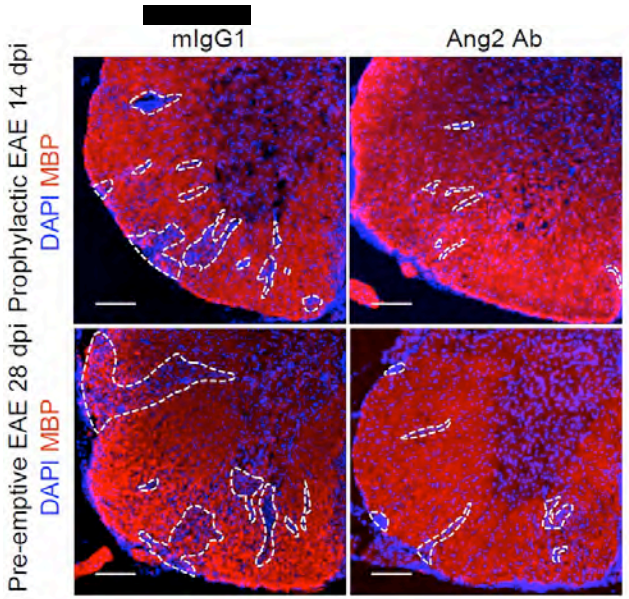
Korhonen et al., *J. Clin. Invest*., 2016
Kim et al., *J. Clin Invest*., 2016
Saharinen, Eklund and Alitalo, *Nature Reviews Drug Discovery*, 2017

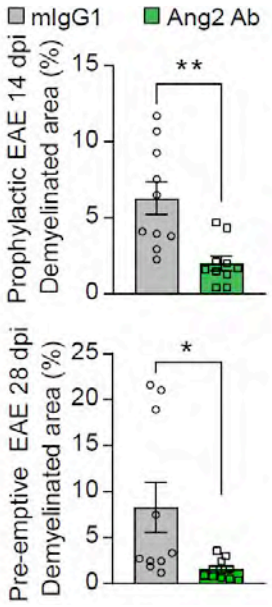
Ang2 blockade ameliorates neuroinflammation











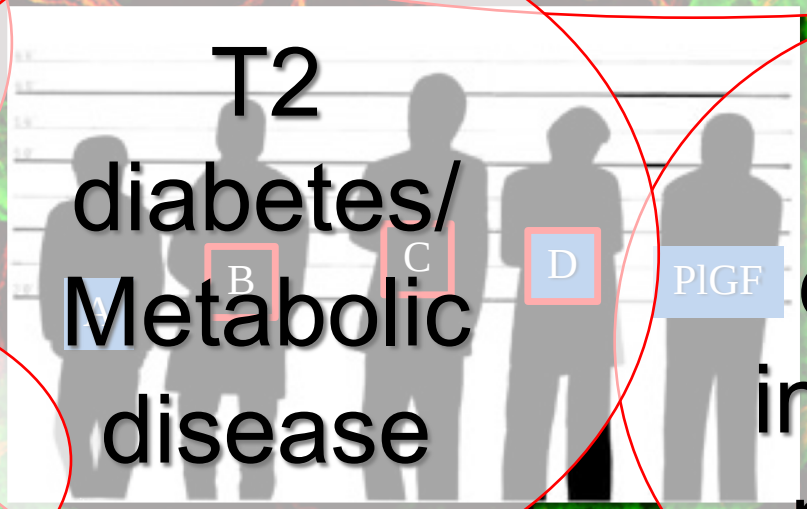
Li*, Korhonen* et al., submitted

Tumor angiogenesis

Lymphatic metastasis

Cardiac ischemia, atrophy

Lymphedema



T2 diabetes/ Metabolic disease

Retinal disease, intraocular pressure

Radiation therapy

Fluid leakage/sepsis

Neurovascular disease

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Thanks again!
MAKIA
CLOTHING COMPANY

“Brain lymphatics”

Nature medicine
“Notable advances 2015”

nature medicine

■ Neuroscience

Brain drain

The central nervous system was thought to be devoid of a classic lymphatic system, a network of vessels that moves immune cells throughout the body and aids in the clearance of excess fluid, macromolecules and waste. Two studies have overturned this assumption by identifying lymphatic vessels underneath the skulls of mice.

One group of researchers from the University of Virginia (*Nature* **523**, 337–341, 2015) found vessels in the meninges—a layer of tissue between the skull and the brain—that express markers that are specifically associated with lymphatic vessels. These vessels can transport a fluorescent dye injected into the ventricles of the brain to the deep cervical lymph nodes (dCLNs). Removal of a dCLN resulted in the accumulation of T cells in these vessels, whereas ligation of the vessel adjacent to a dCLN increased the diameter of these vessels, suggesting that these lymphatic vessels are involved in the drainage of cerebrospinal fluid and the exit of immune cells from the brain.

An independent group from the University of Helsinki (*J. Exp. Med.* **212**, 991–999, 2015) revealed these lymphatic vessels using reporter mice that expressed markers of lymphatic vessels. The team found that clearance of fluorescently labeled macromolecules is impaired in transgenic mice lacking these lymphatic vessels. Whether these vessels contribute to immune cell surveillance and disorders of the central nervous system awaits further investigation.

Science
“Breakthrough of the year”

Science
AAAS

Lymphatic vessels: The brain's well-hidden secret

A. Louveau *et al.*, “Structural and functional features of central nervous system lymphatic vessel,” *Nature* **523**, 337 (1 June 2015).

A. Aspelund *et al.*, “A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules,” *Journal of Experimental Medicine* **212**, 991 (15 June 2015).