

Die Molekularbiologie der Lymphangiogenese

Von den molekulargenetischen und molekularbiologischen Ursachen zur ursächlichen Behandlung des Lymphödems

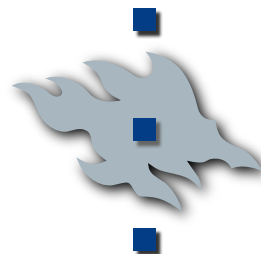
3. Oktober 2014

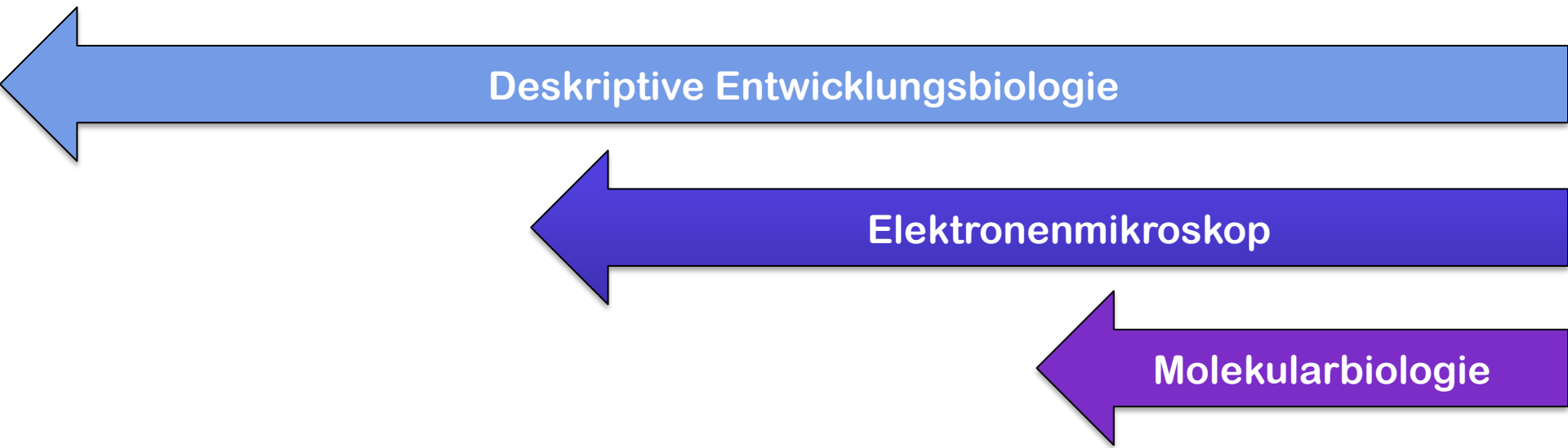
PD Dr. Michael Jeltsch

Wihuri Research Institute & Institute of Biomedicine

Universität Helsinki, Finnland

<http://lab.jeltsch.org>





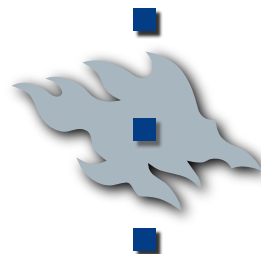
1900

1930

1960

1990

2020

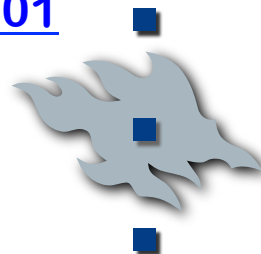




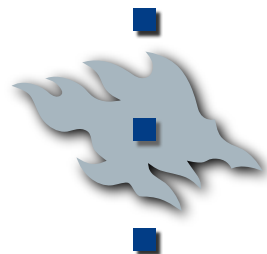
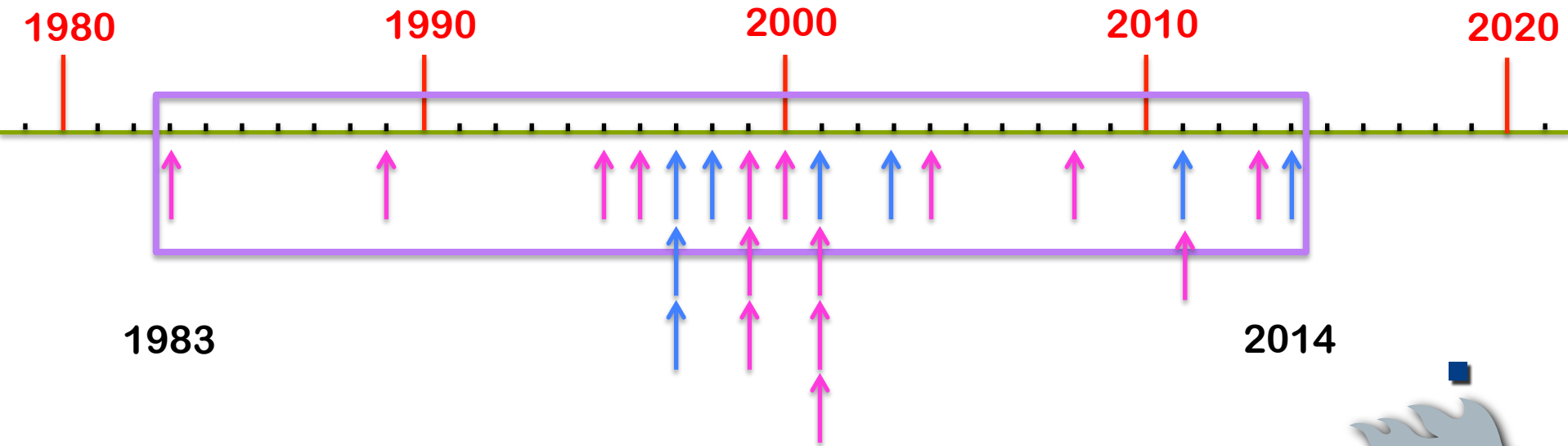
Florence Sabin 1902

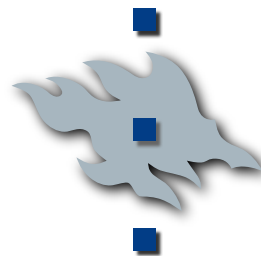
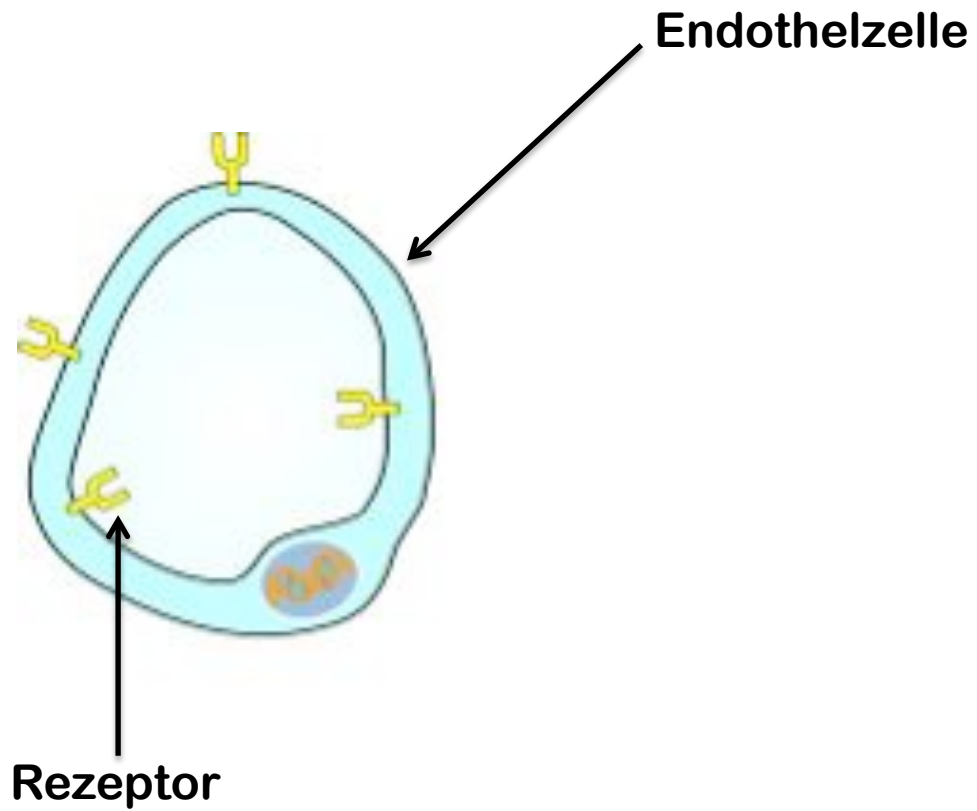


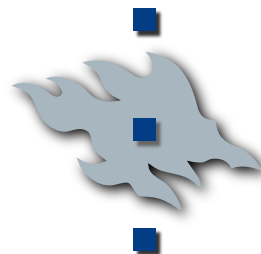
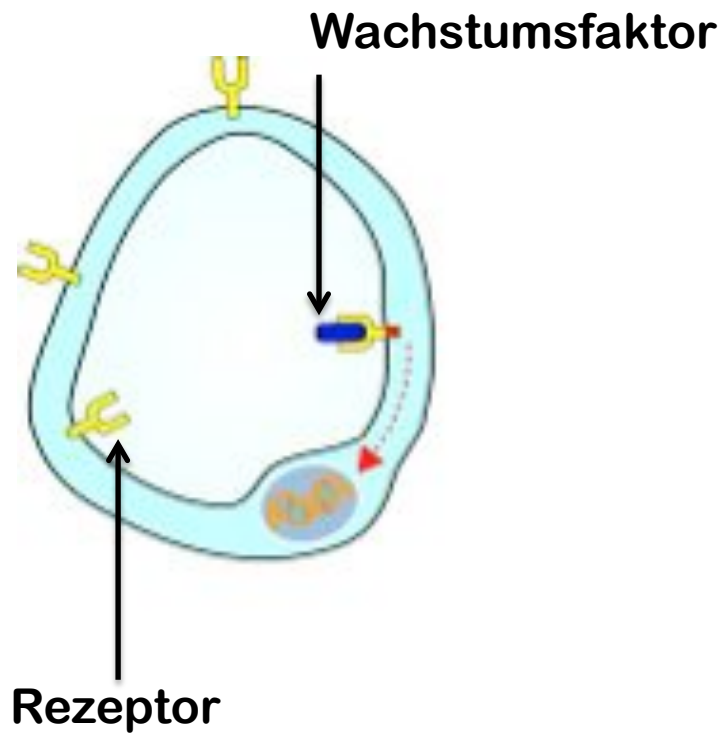
Marika Kärkkäinen et al. 2001

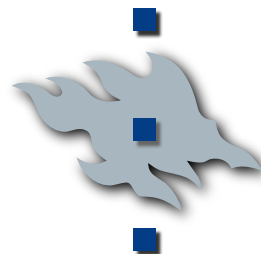
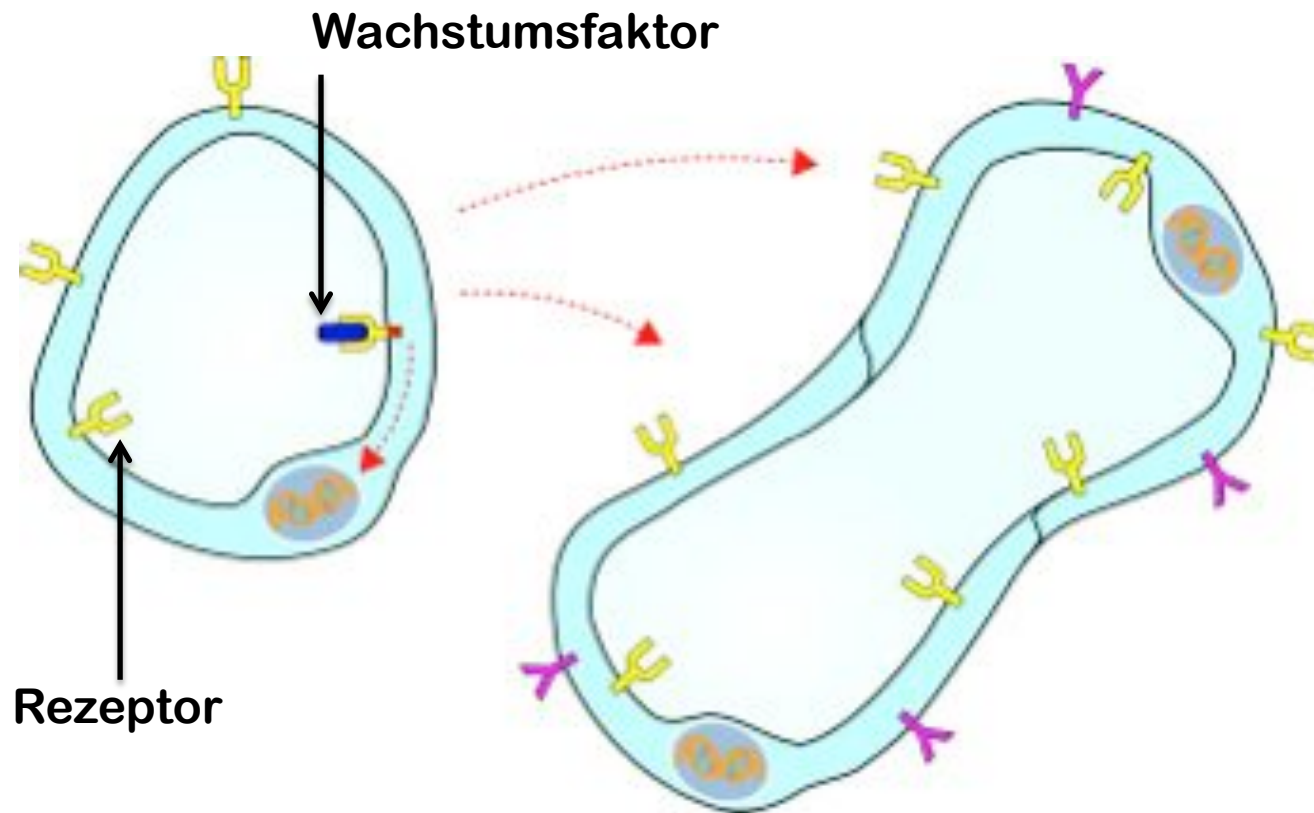


Molekularbiologie







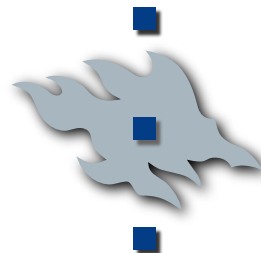


1983

Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid

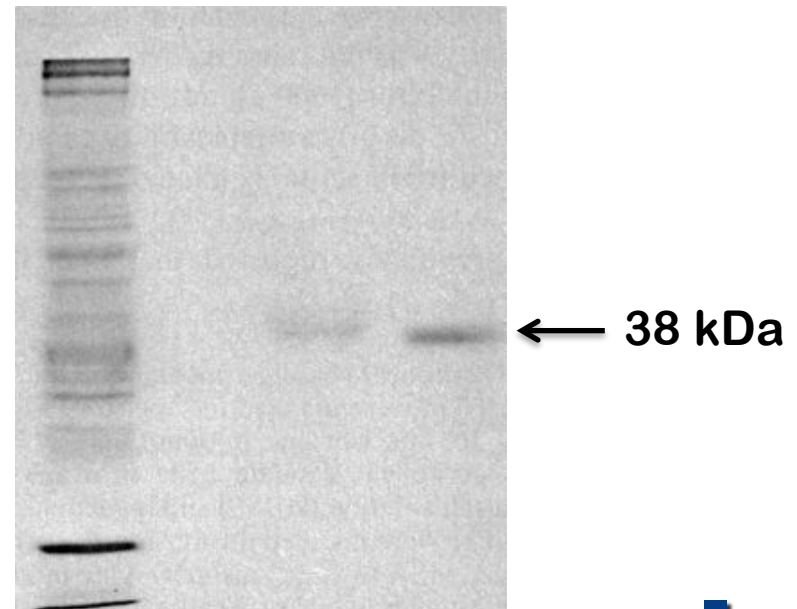
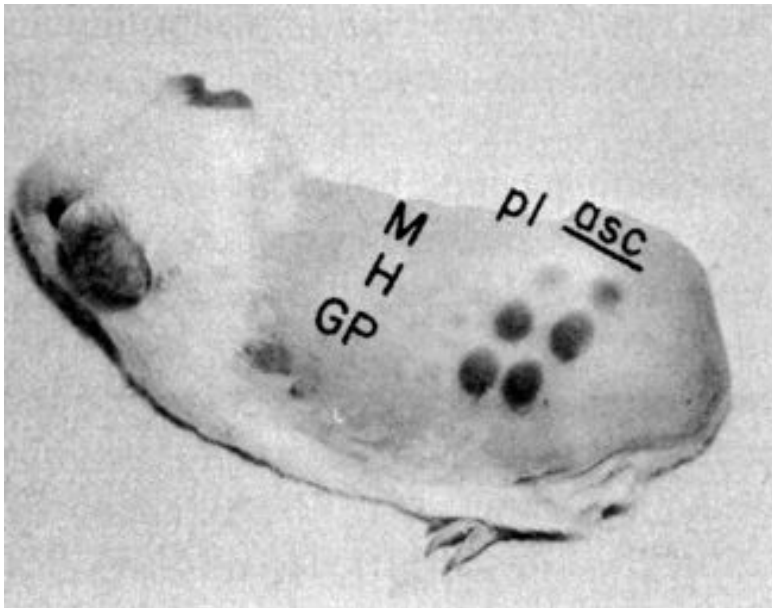
Donald Senger, ... & Harold Dvorak

Science 219, 983-985

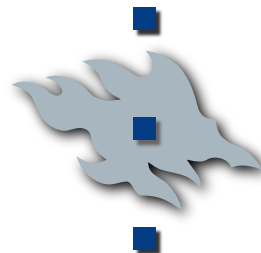


1983

Die Aszitesflüssigkeit von Tumoren enthält einen Faktor,
der im Miles-Assay die Permeabilität von Blutgefäßen erhöht:
VPF (Vascular Permeability Factor)



[Senger et al. 1989](#)

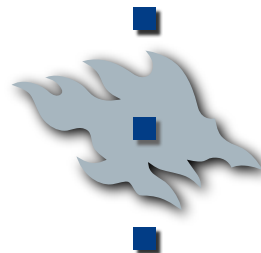


1989

Vascular endothelial growth factor is a secreted angiogenic molecule.

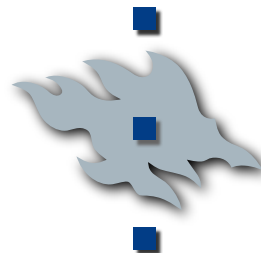
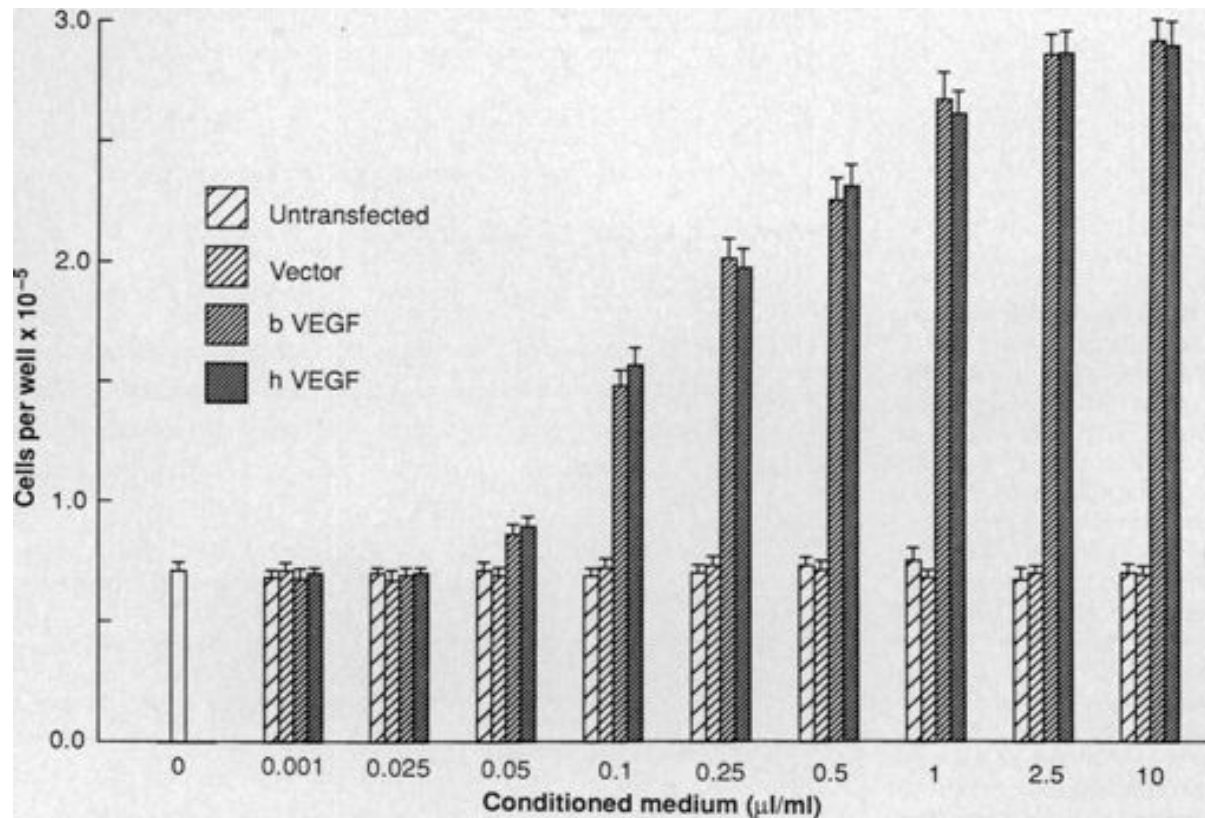
David Leung, ... & Napoleone Ferrara

Science 246, 1306-1309.

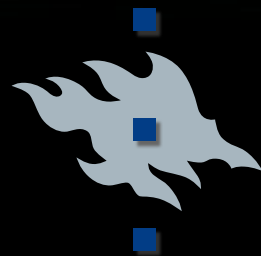
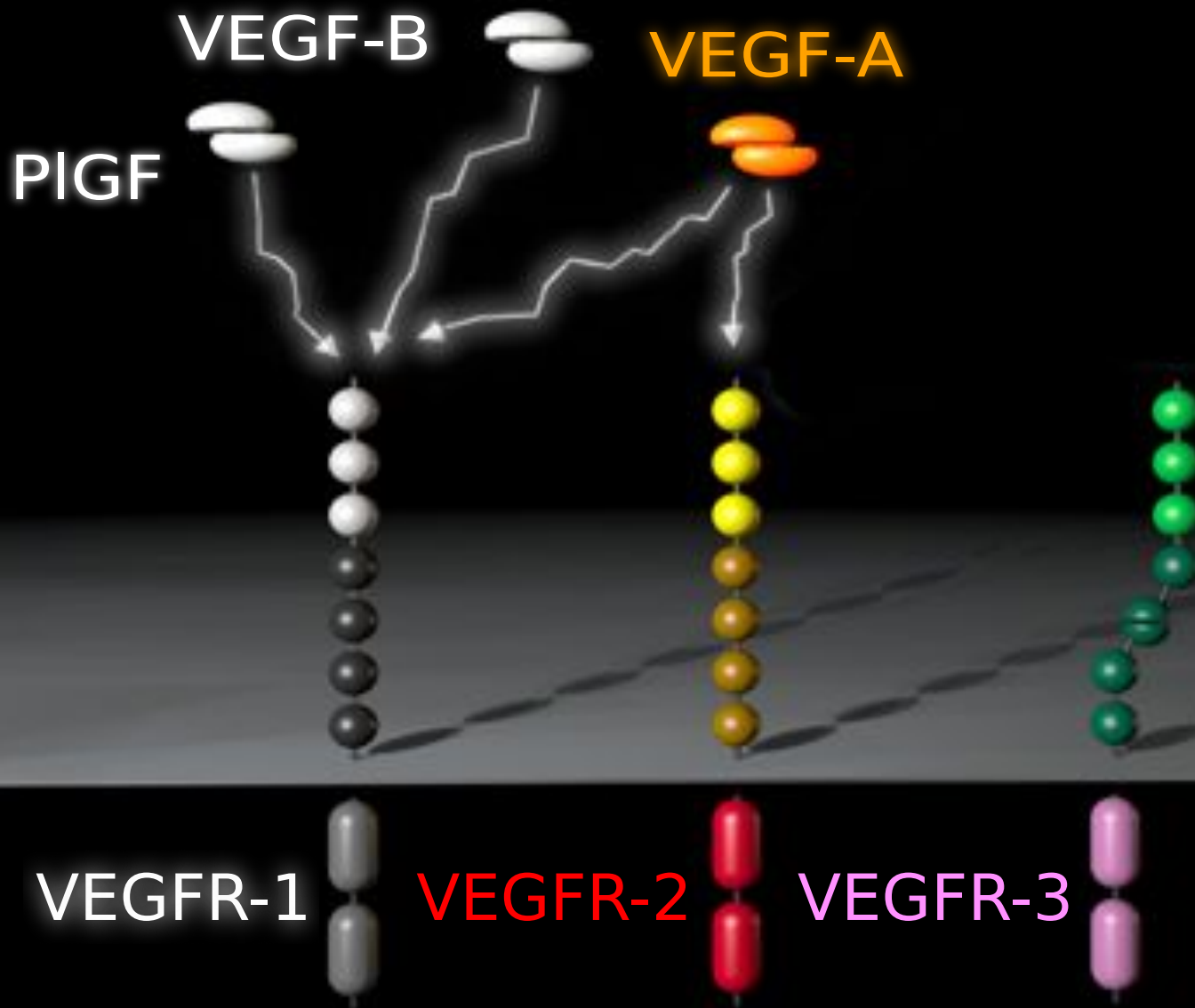


1989

Klonierung von VPF/VEGF, VEGF ist ein spezifischer Wachstumsfaktor für Endothelzellen



1989

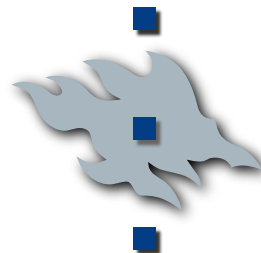


1995

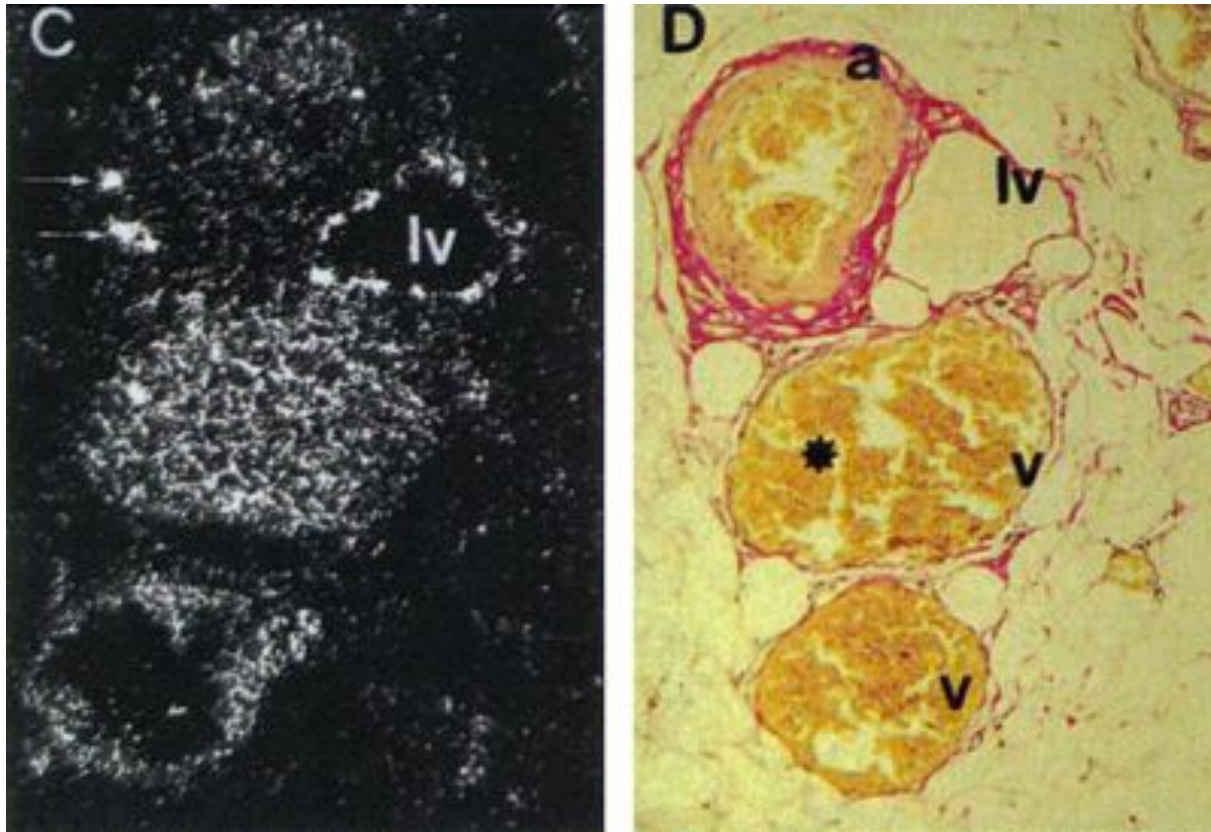
Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development.

Arja Kaipainen, ... & Kari Alitalo

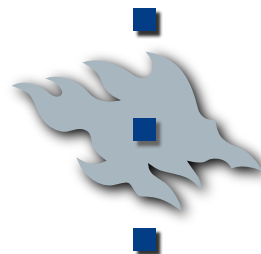
PNAS 92, 3566-70.



1995



[Kaipainen et al. 1995](#)

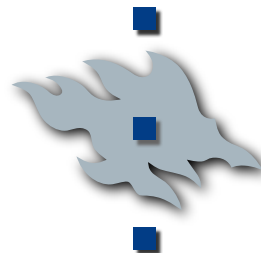


1995 1996

A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases.

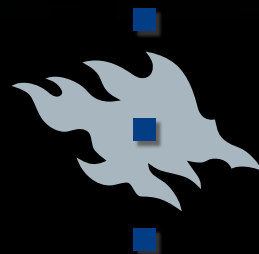
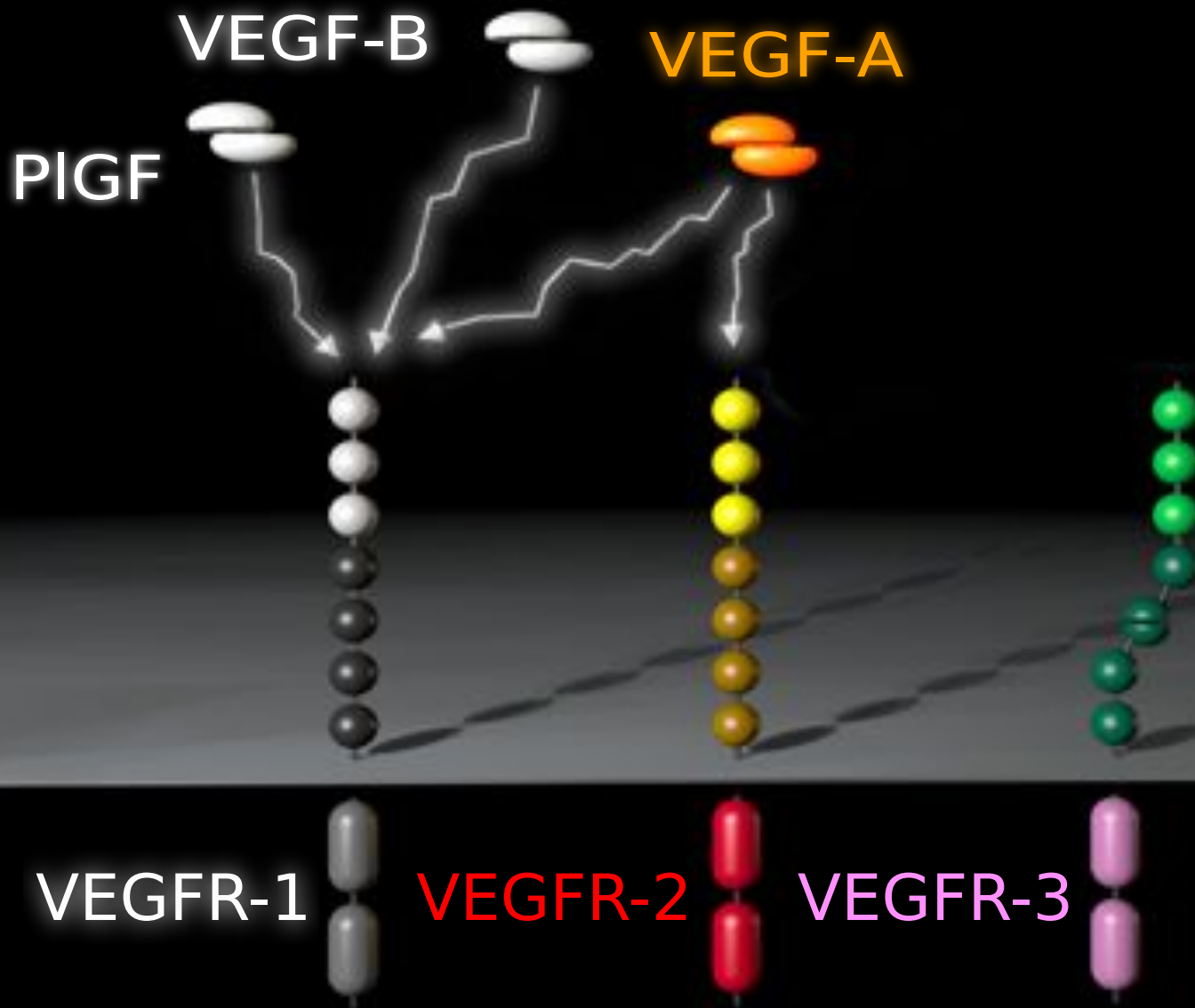
Vladimir Joukov, ... & Kari Alitalo

EMBO J 15, 290-98



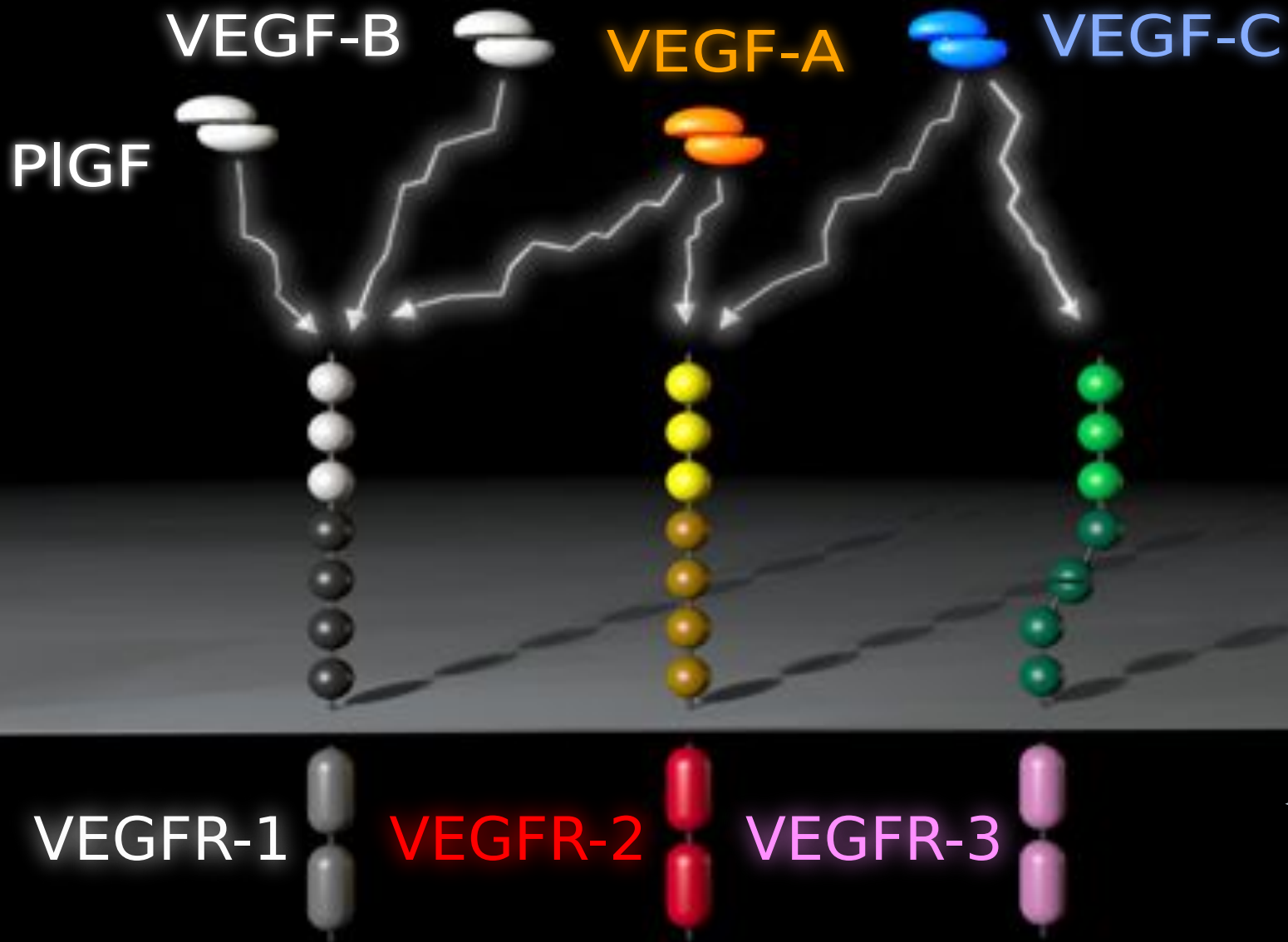
1995

1996

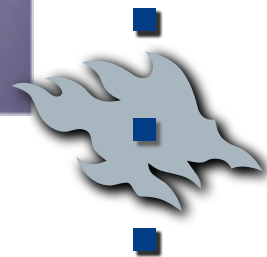


1995

1996



1995 1996



1995

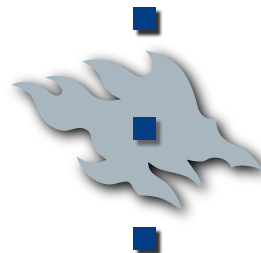
1996

1997

Hyperplasia of lymphatic vessels in VEGF-C transgenic mice.

Michael Jeltsch, ... & Kari Alitalo

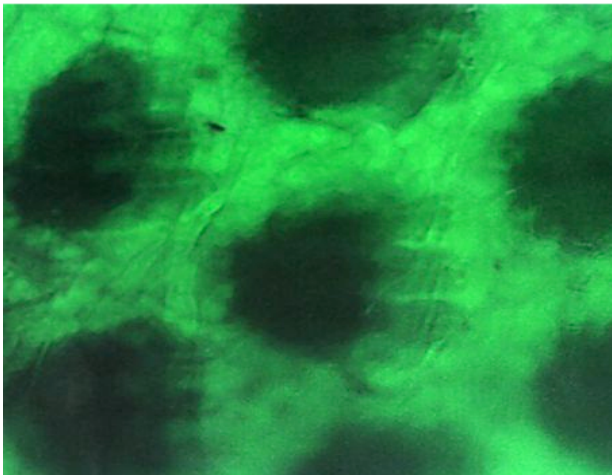
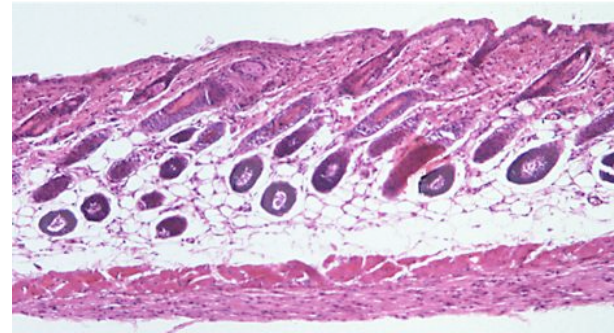
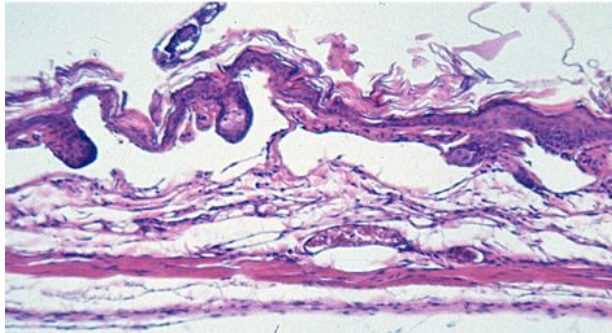
Science 276, 1423-25.



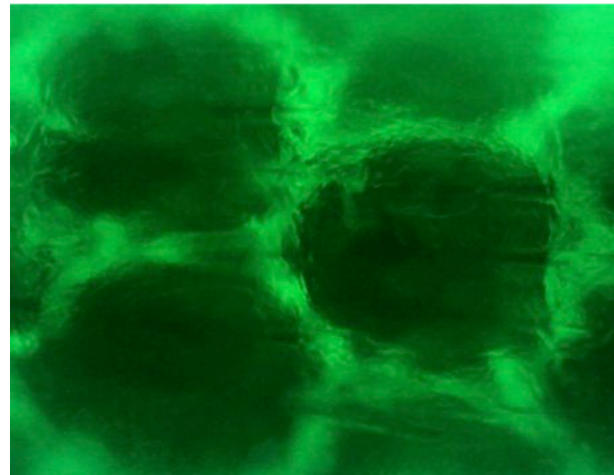
1995

1996

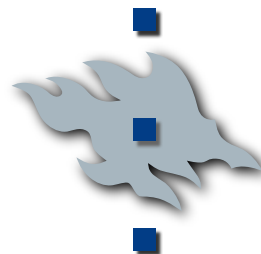
1997



VEGF-C



Kontrolle



1995

1996

1997

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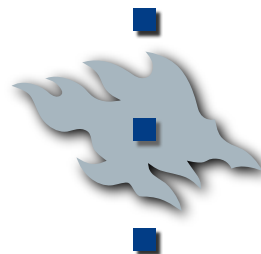
Michael Jeltsch, ... & Kari Alitalo

Science 276, 1423-25.

VEGF and VEGF-C: specific induction of angiogenesis and lymphangiogenesis in the differentiated avian chorioallantoic membrane.

Su-Ja Oh, ... & Jörg Wilting

Dev Biol 188, 96-109.



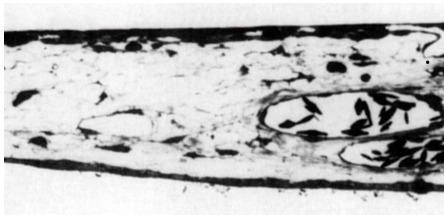
1995

1996

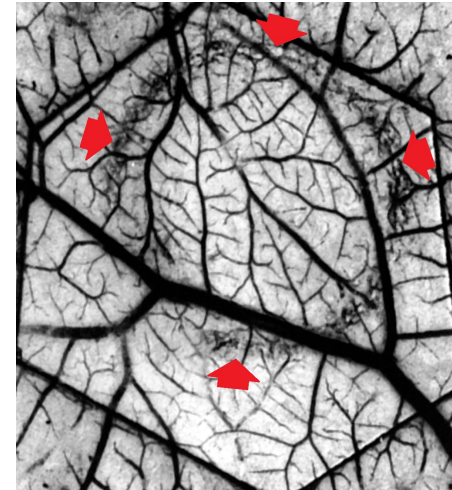
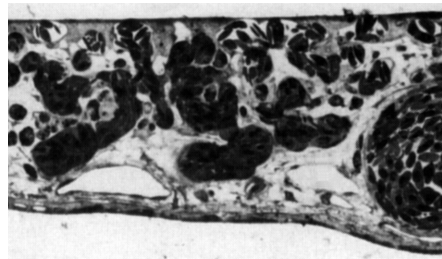
1997



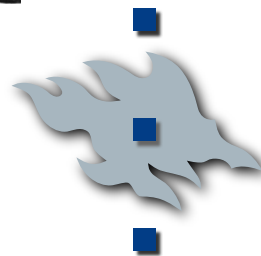
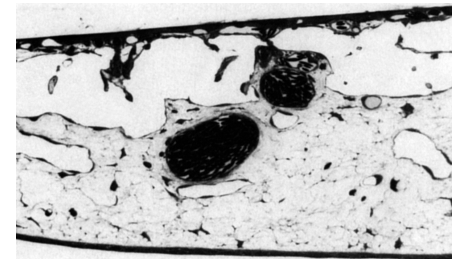
control



VEGF-A₁₆₅



mature VEGF-C



1995

1996

1997

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Science 276, 1423-25.

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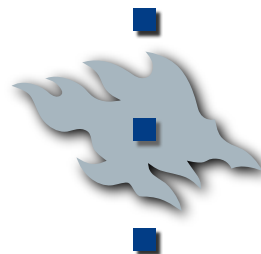
Su-Ja Oh, ... & Jörg Wilting

Dev Biol 188, 96-109.

Proteolytic processing regulates receptor specificity and activity of VEGF-C.

Vladimir Joukov, ... & Kari Alitalo

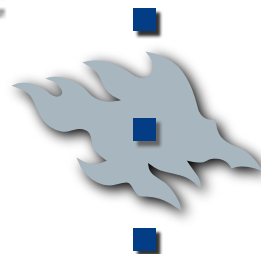
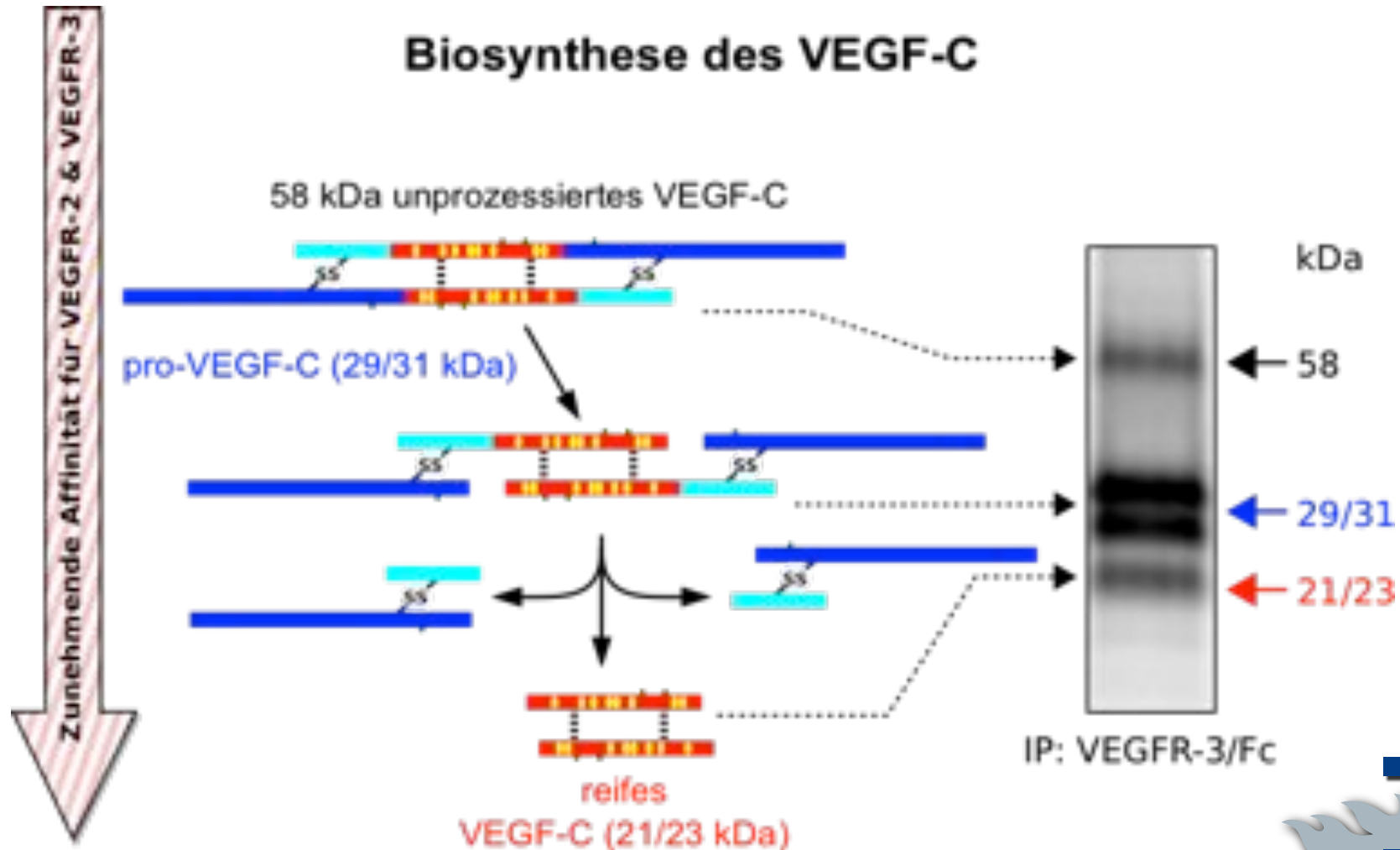
EMBO J 16, 3898-911.



1995

1996

1997



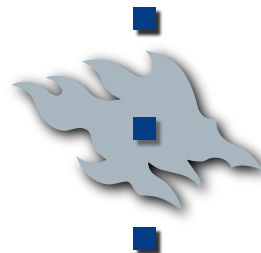
1998

A horizontal timeline graphic with a green bar at the bottom. Several vertical lines of varying heights are positioned along the bar. The third line from the left is colored red, while the others are black.

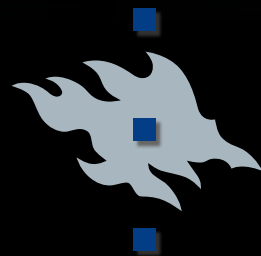
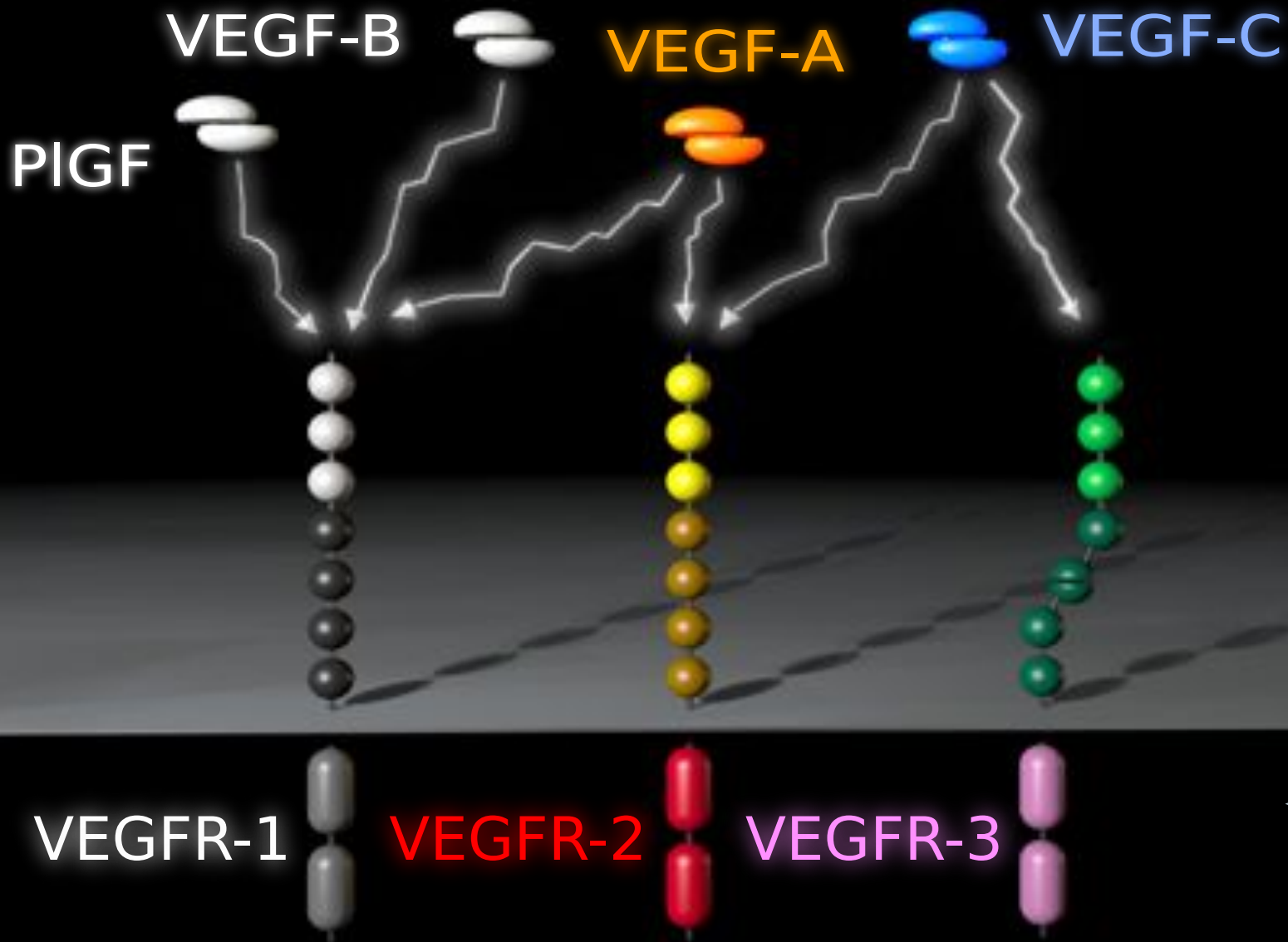
Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4).

Marc Achen, ... & Steven Stacker

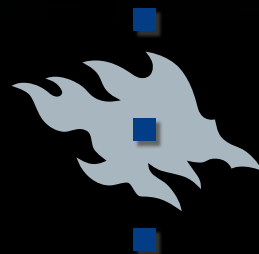
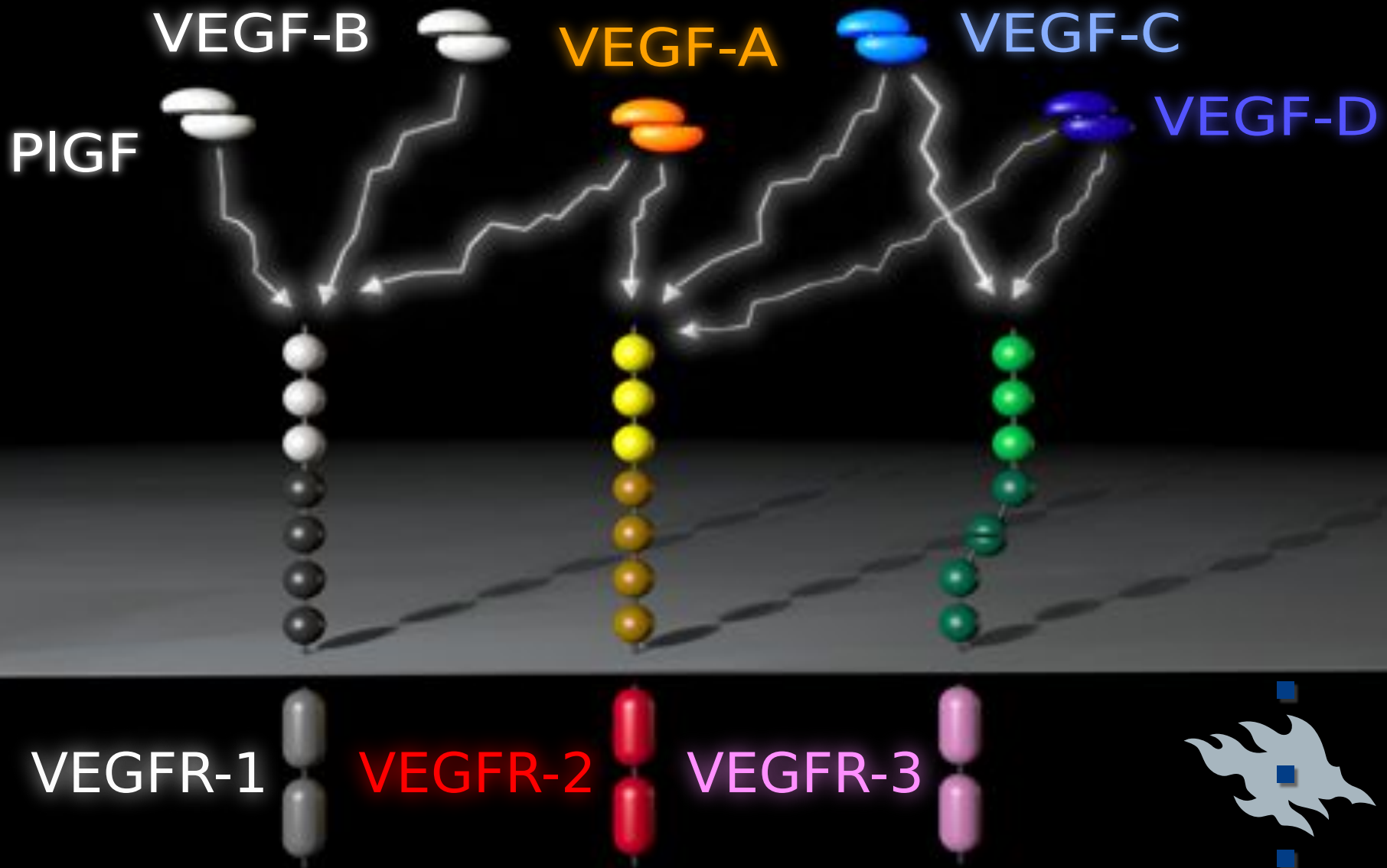
PNAS 95, 548-553.



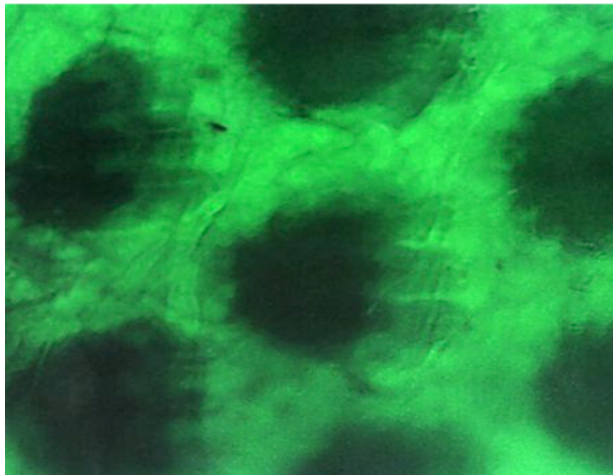
1998



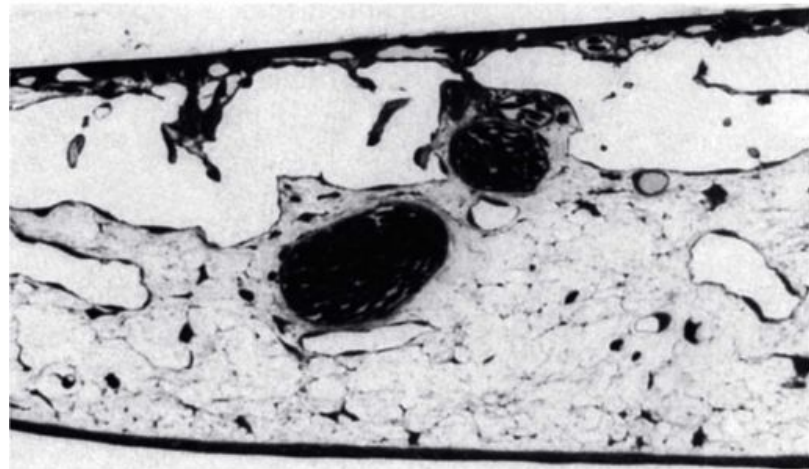
1998



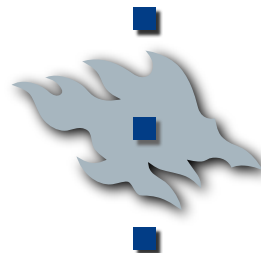
Wie unterscheidet man immunohistologisch zwischen Lymph- und Blutgefäß-Endothel?



funktionell



strukturell



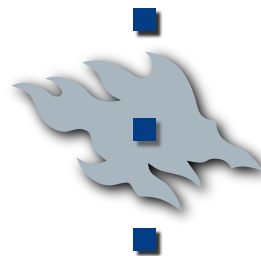
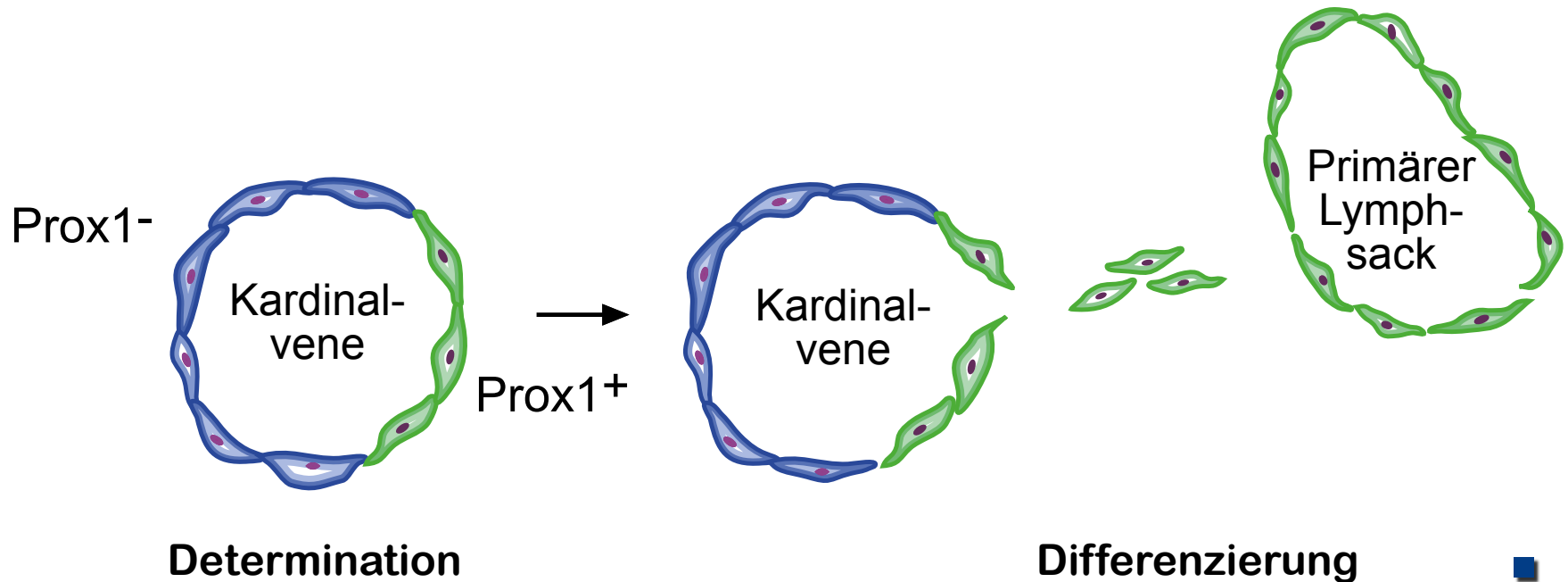
1998

1999

Prox1 Function Is Required for the Development of the Murine Lymphatic System.

Jeffrey Wigle & Guillermo Oliver

Cell 98, 769-78.



1998

1999

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Jeffrey Wigle & Guillermo Oliver

Cell 98, 769-78.

LYVE-1, a New Homologue of the CD44 Glycoprotein, Is a Lymph-specific Receptor for Hyaluronan.

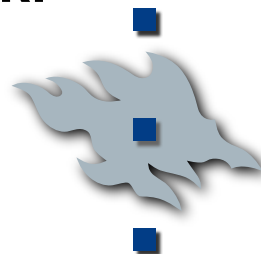
Suneale Banerji, ... & David Jackson

J Cell Biol 144, 789-801.

Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium.

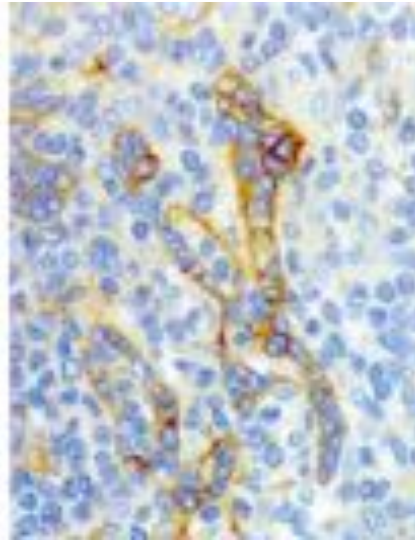
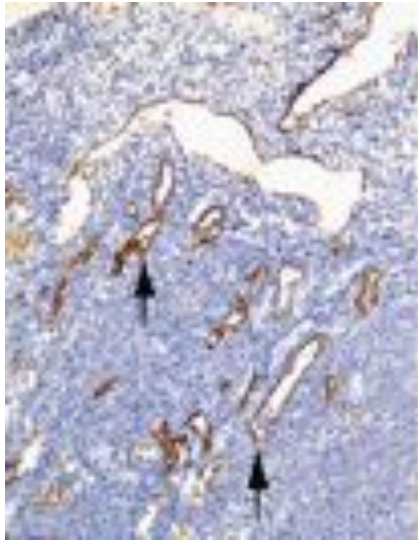
Silvana Breiteneder-Geleff, ... & Dentscho Kerjaschki

Am J Pathol 154, 385-94.



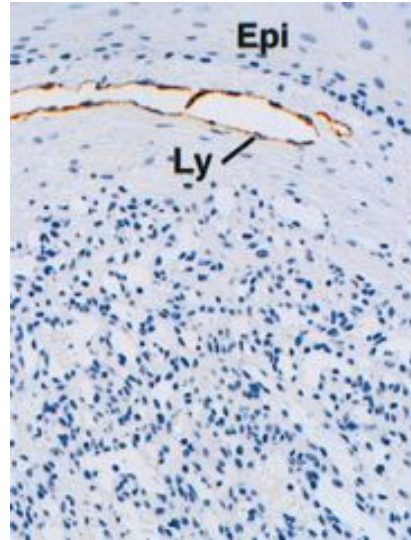
1998

1999



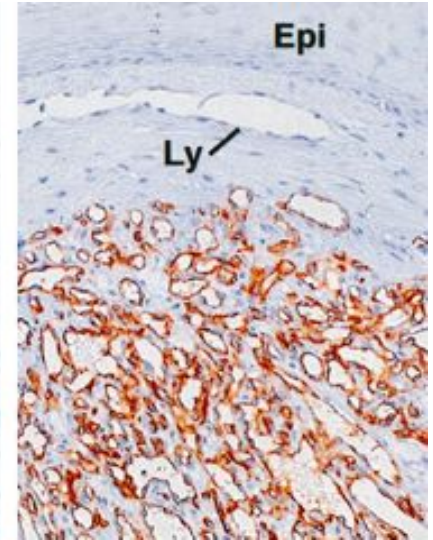
[Banerji et al. 1999](#)

LYVE-1 = Hyaluronsäure-Rezeptor
der lymphatischen Endothelzellen



[Breiteneder-Geleff et al. 1999](#)

Podoplanin



CD34

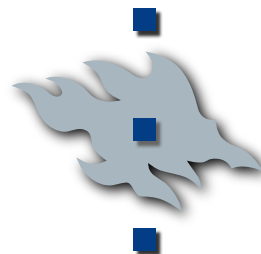
Marker für lymphatische Endothelzellen

VEGFR-3

Prox-1

LYVE-1

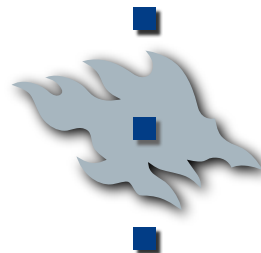
Podoplanin



1998

1999

Welche Rolle spielen VEGF-C und VEGFR-3 in Krankheiten, für die Lymphangiogenese (oder das Fehlen derselben) begünstigend oder ursächlich sind?



1998

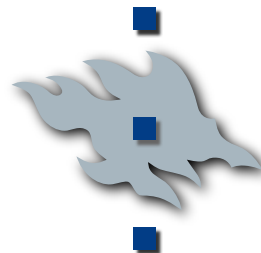
1999

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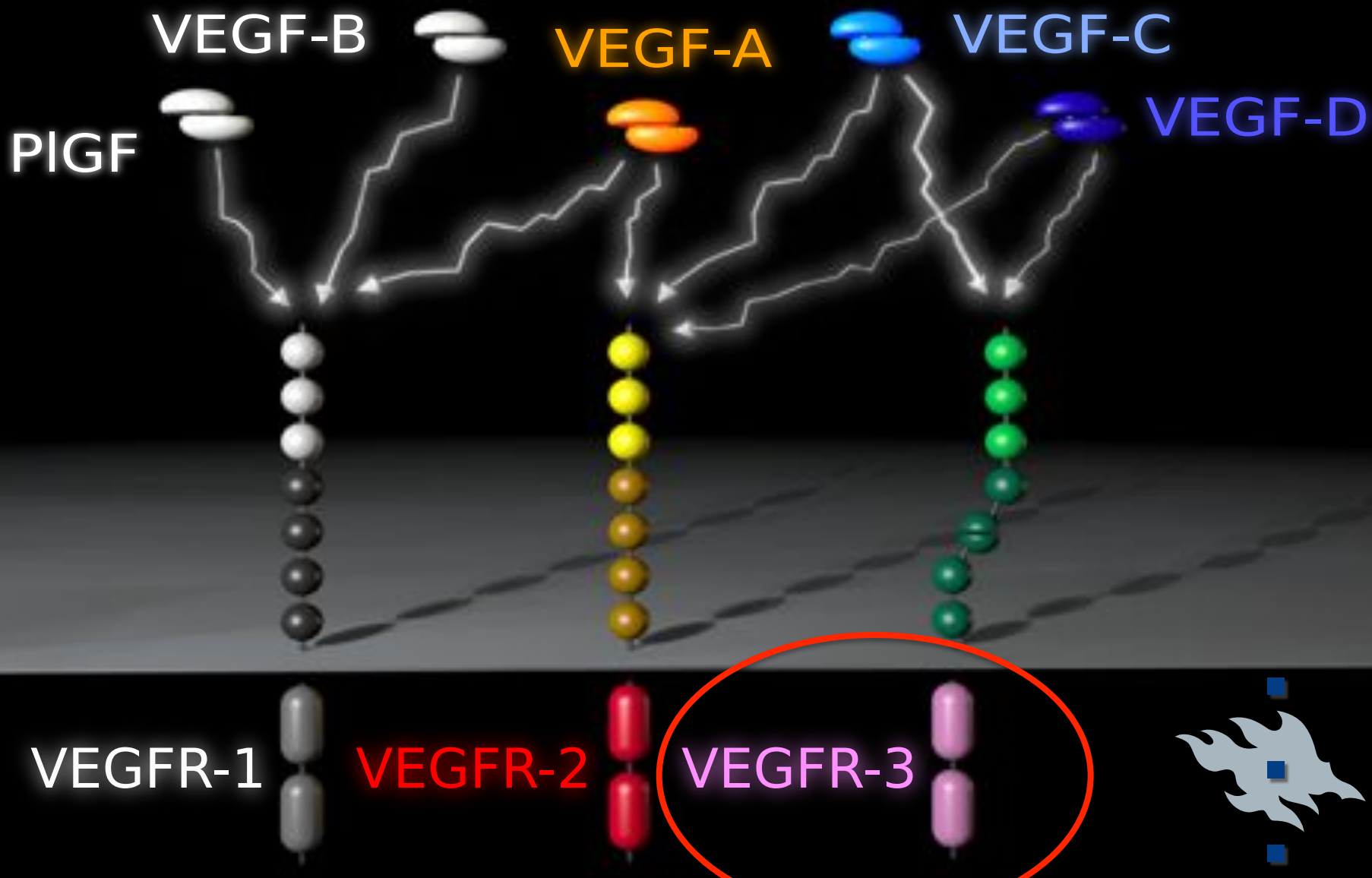
Congenital hereditary lymphedema caused by a mutation that inactivates VEGFR3 tyrosine kinase.

Alexandre Irrthum, ... & Miikka Vikkula

Am J Hum Genet 67, 295-301.



1998 1999 2000



1998

1999

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2001

Vascular endothelial growth factor-C-mediated lymphangiogenesis promotes tumour metastasis.

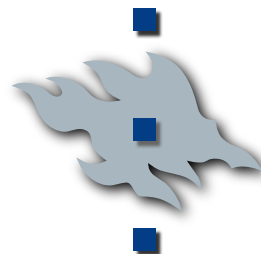
Stefano Mandriota, ... & Michael Pepper

EMBO J 20, 672-82.

Vascular endothelial growth factor C promotes tumor lymphangiogenesis and intralymphatic tumor growth.

Terhi Kärpänen, ... & Kari Alitalo

Cancer Res 61, 1786-90.

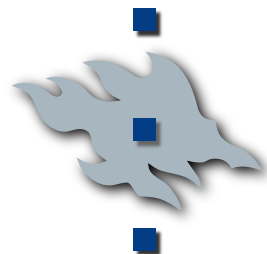
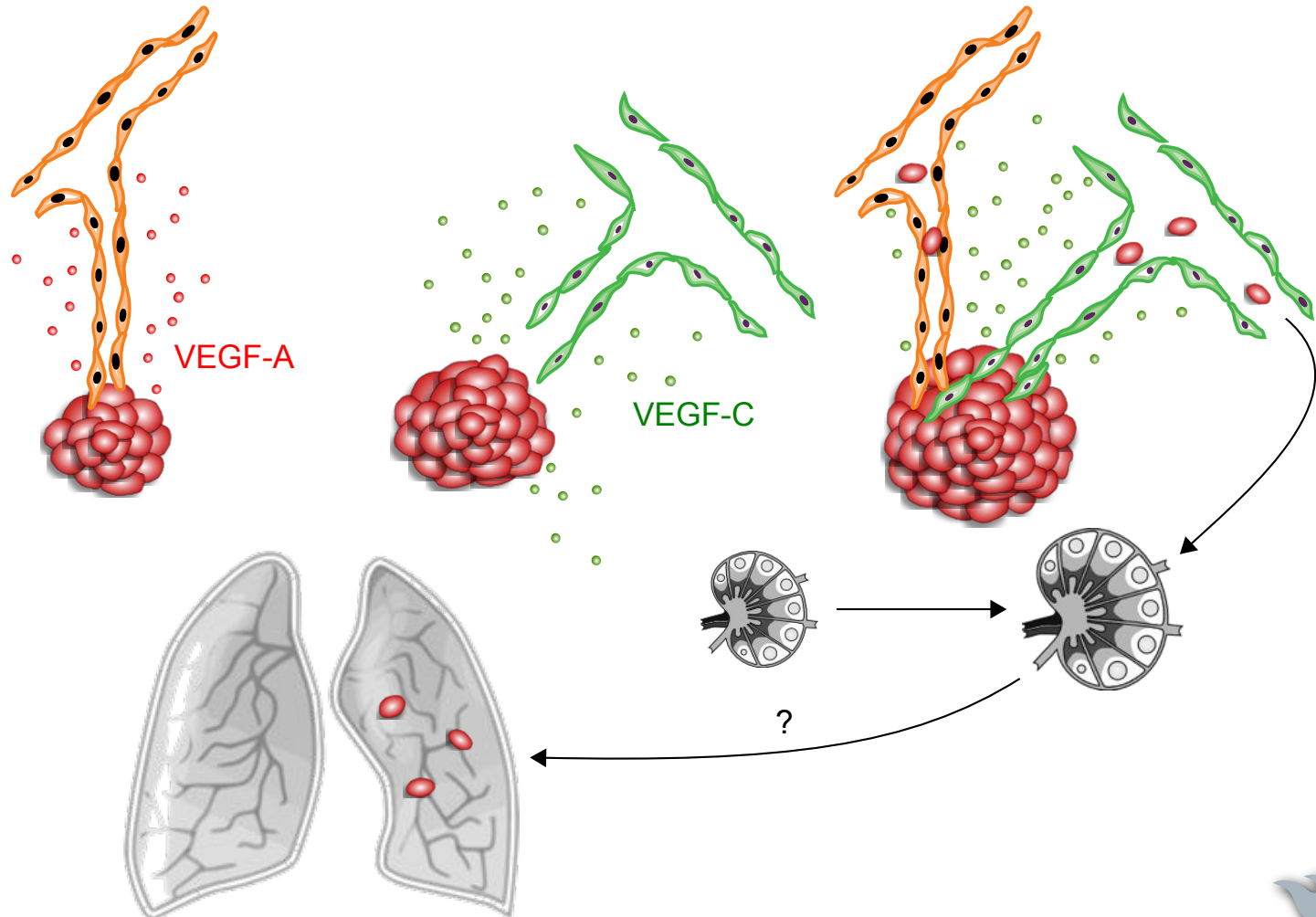


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2001



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2000

2001

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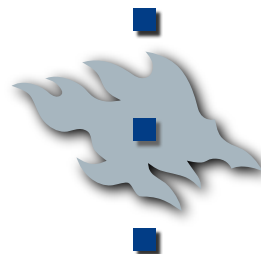
Terhi Kärpänen, ... & Kari Alitalo

Cancer Res 61, 1786-90.

Inhibition of lymphangiogenesis with resulting lymphedema in transgenic mice expressing soluble VEGF receptor-3.

Taija Mäkinen, ... & Kari Alitalo

Nature Med 7, 199-205.

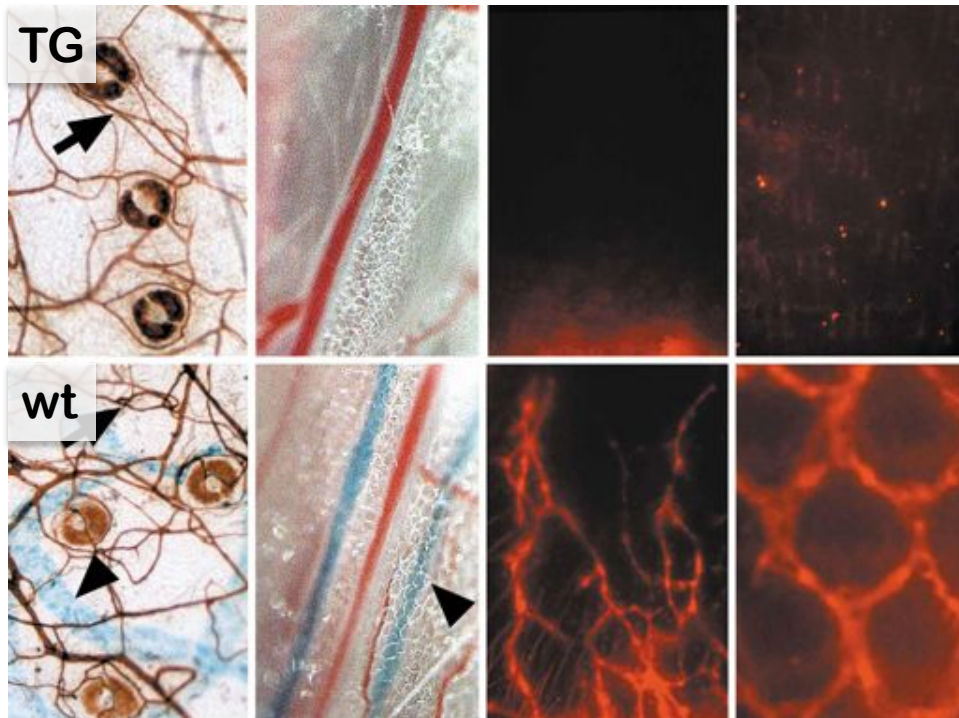


1998

1999

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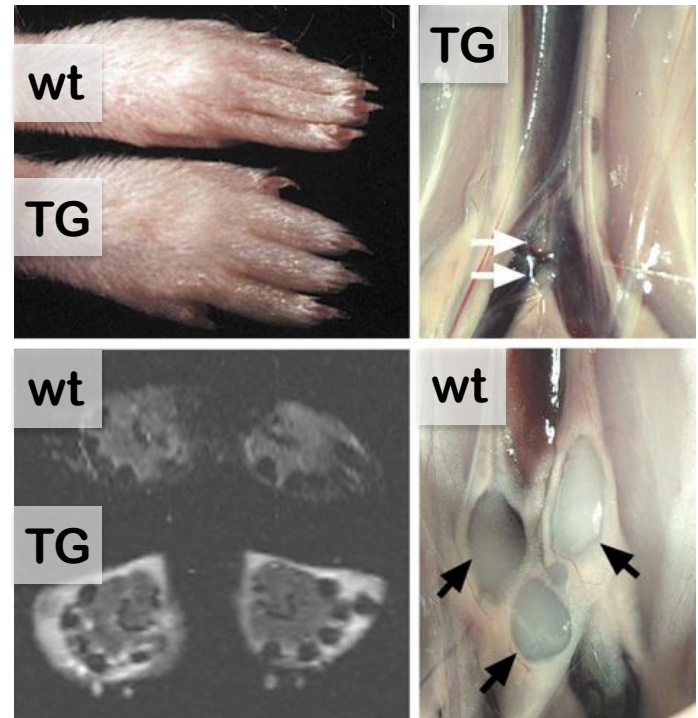


Ohr

Ischias-
vene

Ohr

Schwanz



wt

TG

wt

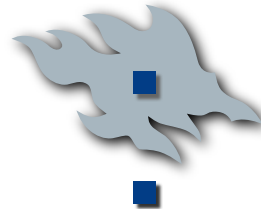
TG

TG

wt

[Mäkinen et al. 2001](#)

Pfoten

Lymph-
knoten

1998

1999

2000

2001

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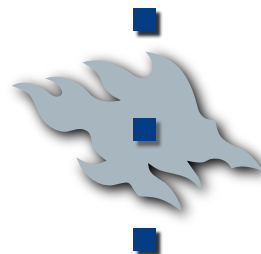
Taija Mäkinen, ... & Kari Alitalo

Nature Med 7, 199-205.

A model for gene therapy of human hereditary lymphedema.

Marika Kärkkäinen, ... & Kari Alitalo

PNAS 98, 12677-82.

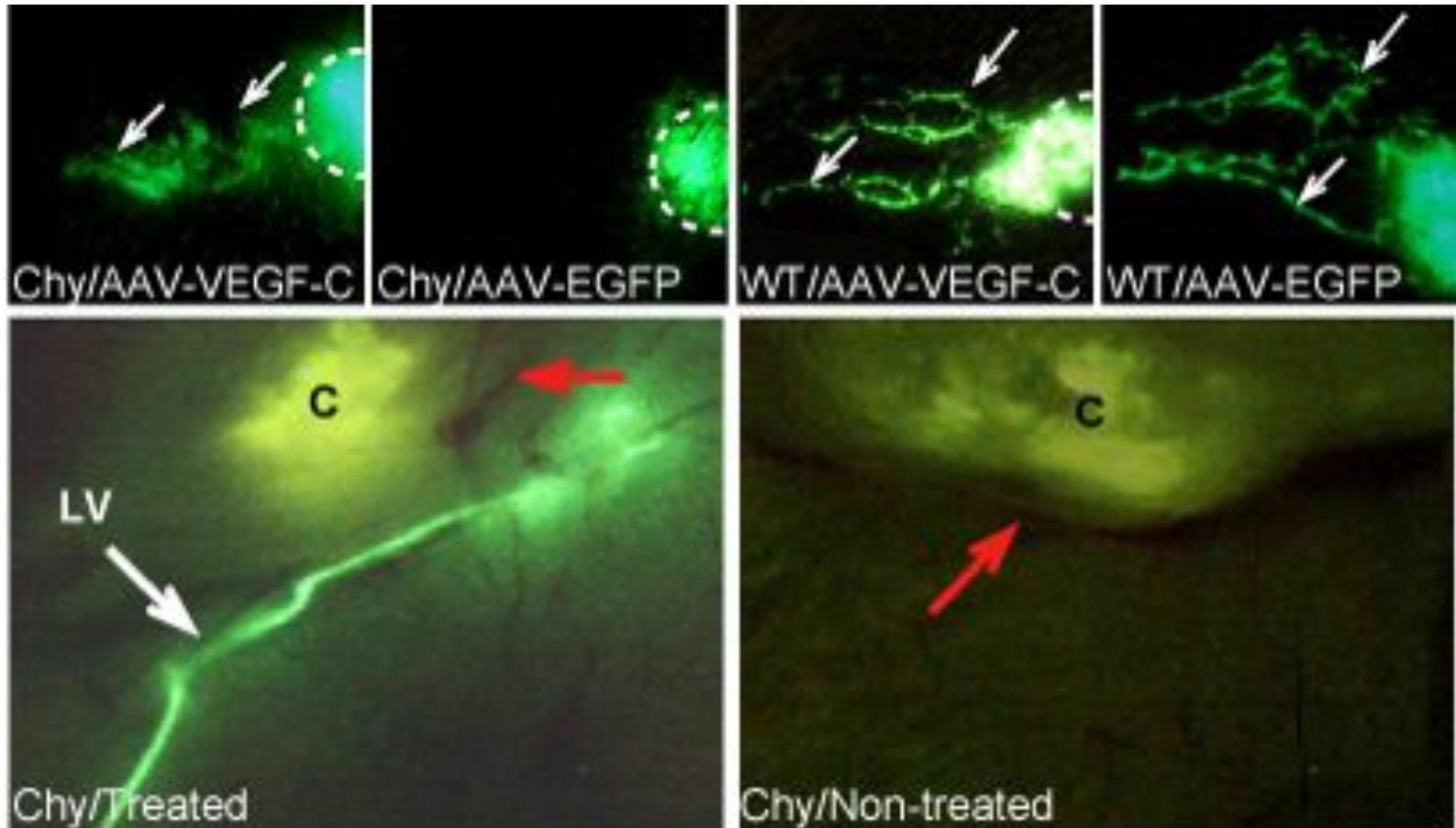


1998

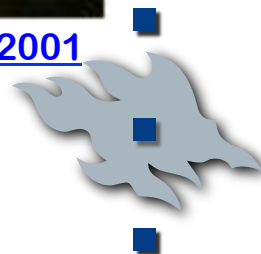
1999

2000

2001



[Kärkkäinen et al. 2001](#)



1998

1999

2000

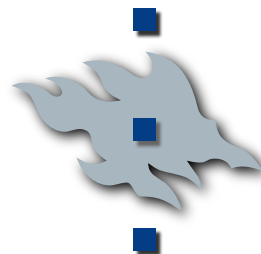
2001

2003

Vascular endothelial growth factor C is required for sprouting of the first lymphatic vessels from embryonic veins.

Marika Kärkkäinen, ... & Kari Alitalo

Nat Immunol 5, 74-80.



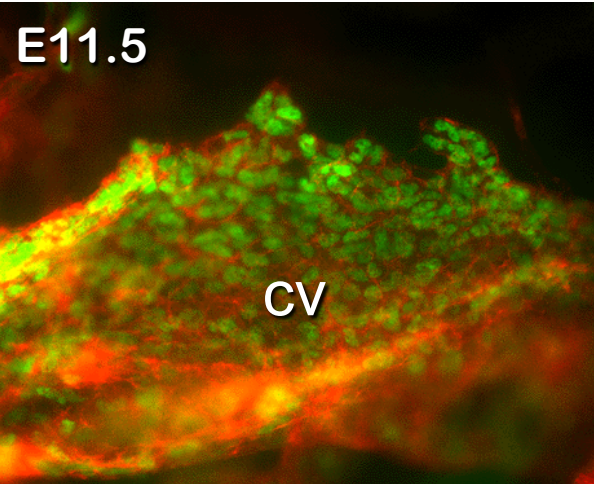
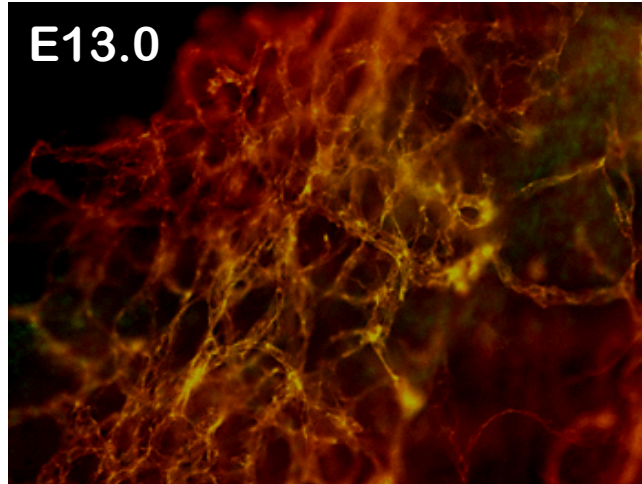
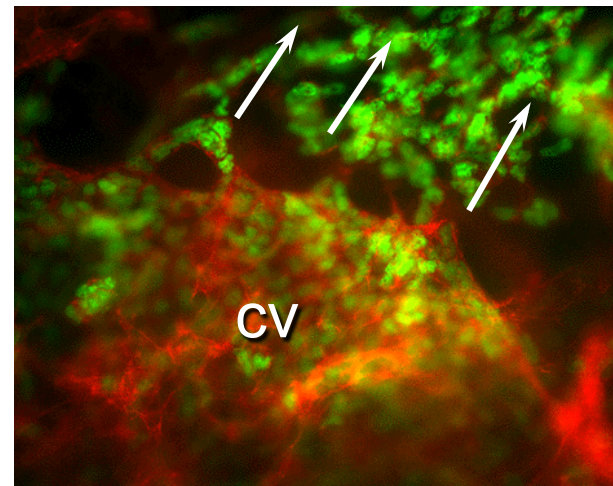
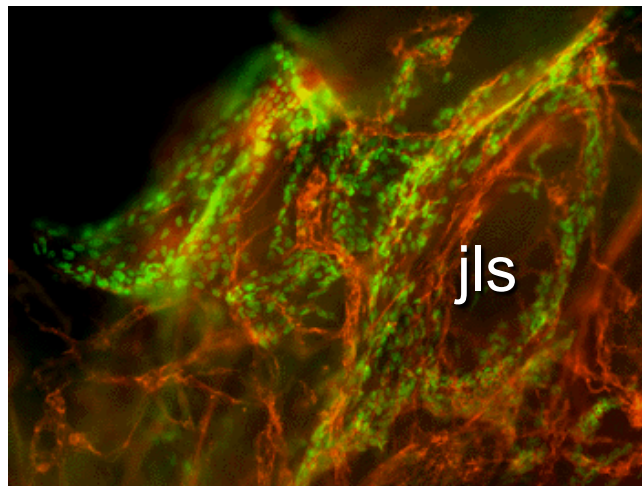
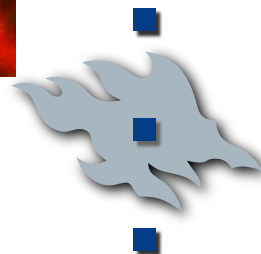
1998

1999

2000

2001

2003

Vegfc^{-/-}**Vegfc^{+/+}****Prox-1 PECAM**[Kärkkäinen et al. 2003](#)

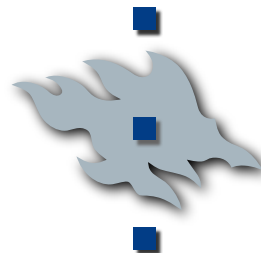
2004



Defective valves and abnormal mural cell recruitment underlie lymphatic vascular failure in lymphedema distichiasis.

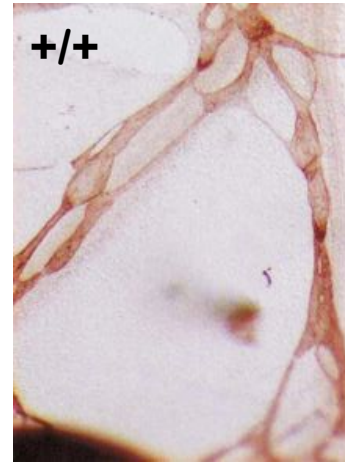
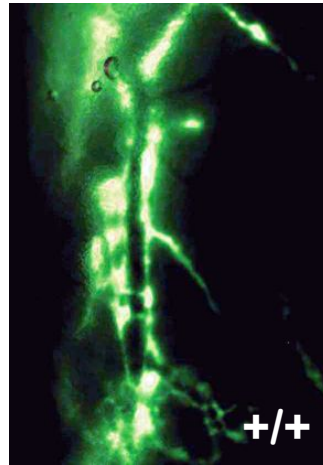
Tatiana Petrova, ... & Kari Alitalo

Nat Med 10, 974-81.

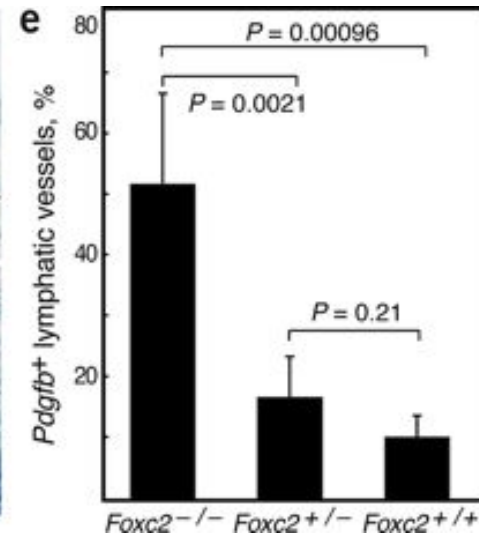
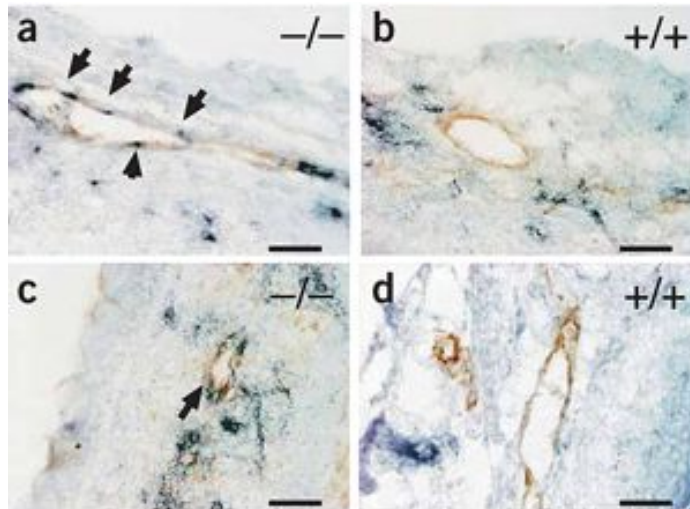


2004

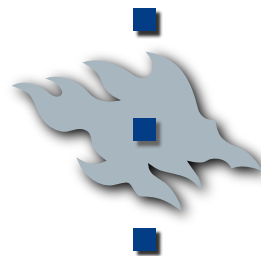
FOXC2^{-/-}
Lymph-
klappen-
Aplasie



FOXC2^{-/-}
Abnormal
hohe Ab-
deckung der
Lymphkapil-
laren mit
Perizyten



[Petrova
et al. 2004](#)



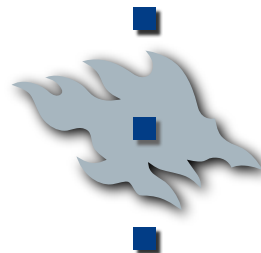
2004

2008

Blocking VEGFR-3 suppresses angiogenic sprouting and vascular network formation.

Tuomas Tammela, ... & Kari Alitalo

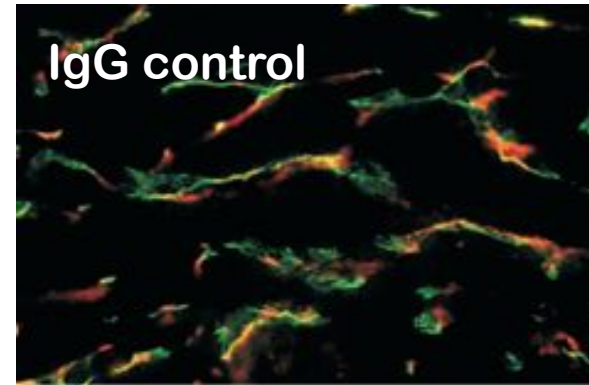
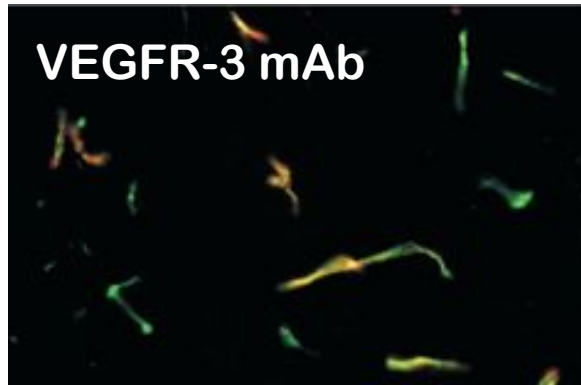
Nature 454, 656-60.



2004

2008

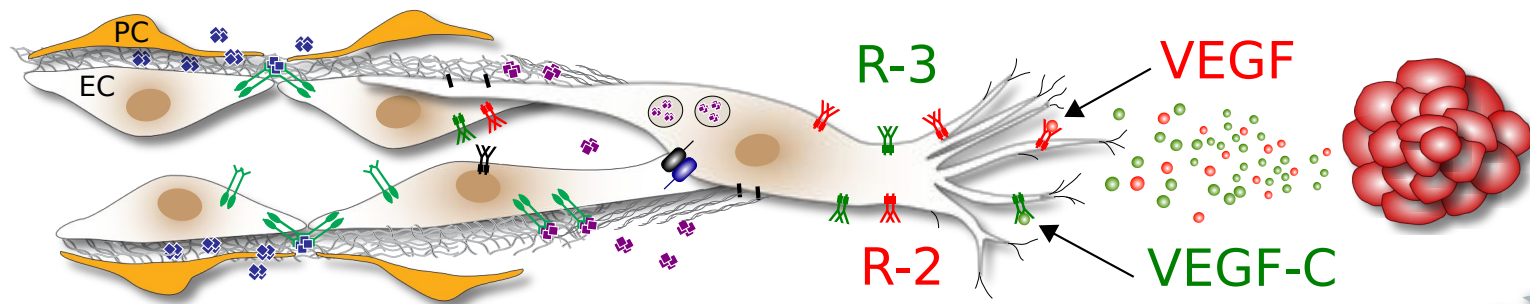
VEGFR-3
PECAM



[Tammela et al. 2008](#)

stalk cells

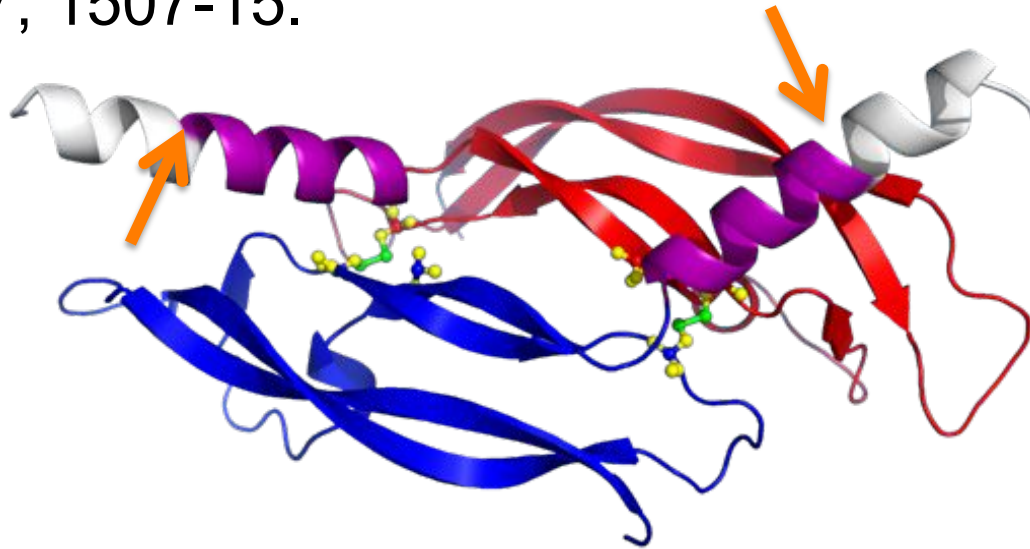
tip cell



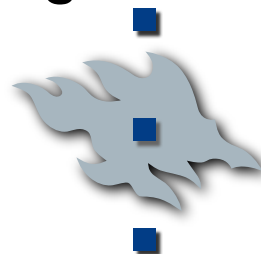
2011

Structural determinants of vascular endothelial growth factor-D receptor binding and specificity.

Veli-Matti Leppänen/Michael Jeltsch, ... & Kari Alitalo
Blood 117, 1507-15.



Vollständig prozessiertes VEGF-D ist nicht mehr lymphangiogen!



2011

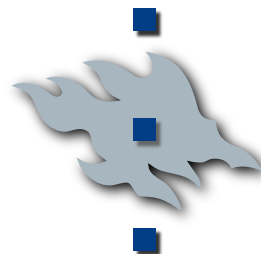
Ist VEGF-D irrelevant für Lymphangiogenese?

Humanes VEGF-D verliert seine lymphangiogenen Eigenschaften (VEGFR-3-Aktivierung) durch enzymatische Abspaltung der distalen N-terminalen Helix.

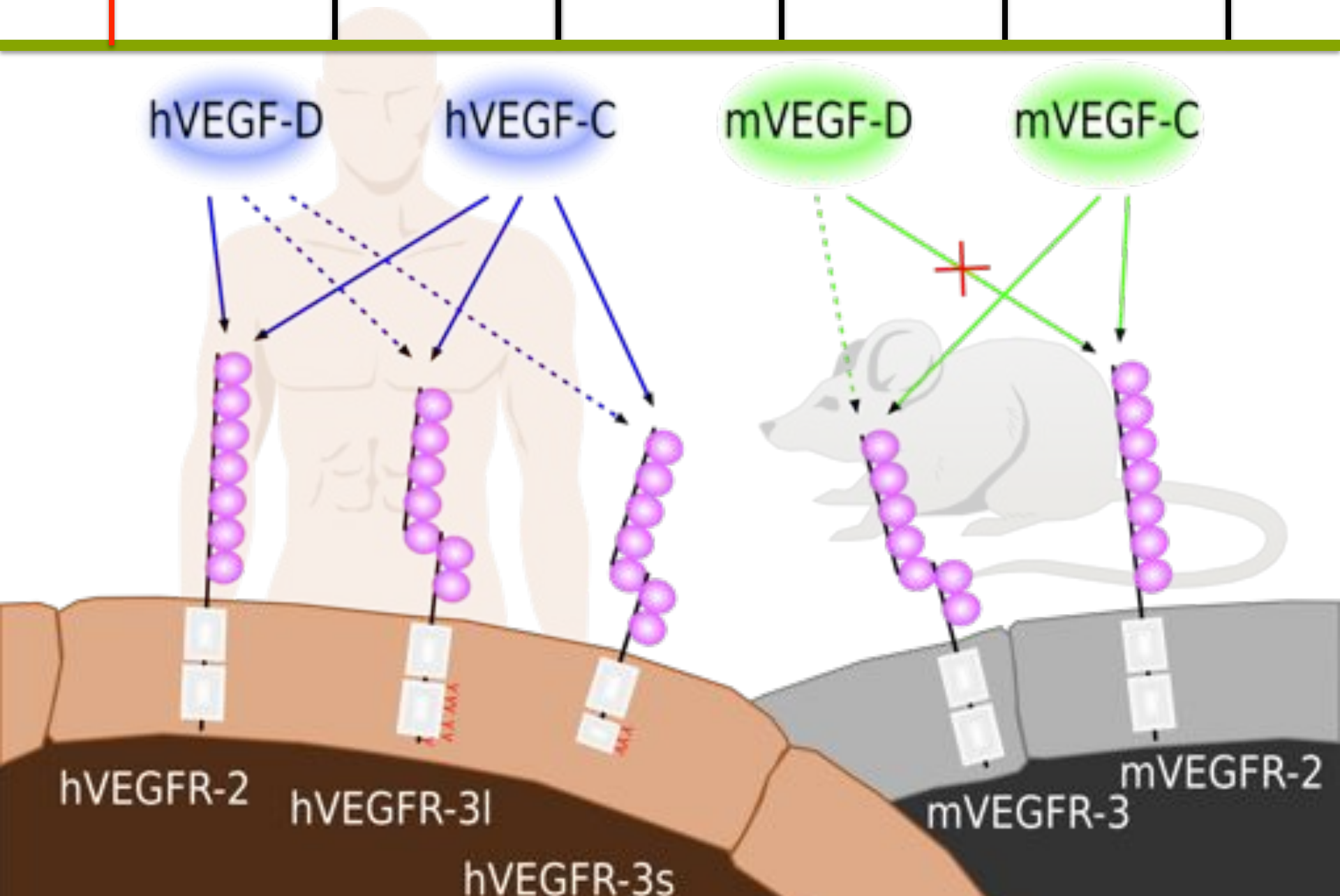
⇒ Funktion in der Angiogenese

In Mäusen führt die Inaktivierung des VEGF-D-Gens zu keinem nennenswerten Phänotyp.

Mäuse sind nicht Menschen...



2011



2010

2011

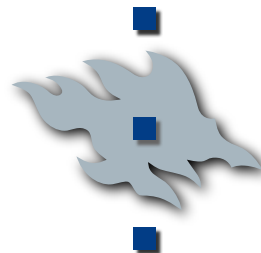
2012

2013

Lymph Node Transfer and Perinodal Lymphatic Growth
Factor Treatment for Lymphedema.

Krista Honkonen, ... & Anne Saaristo

Annals of Surgery 257, 961-67.

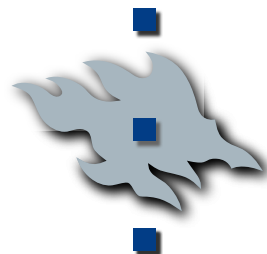
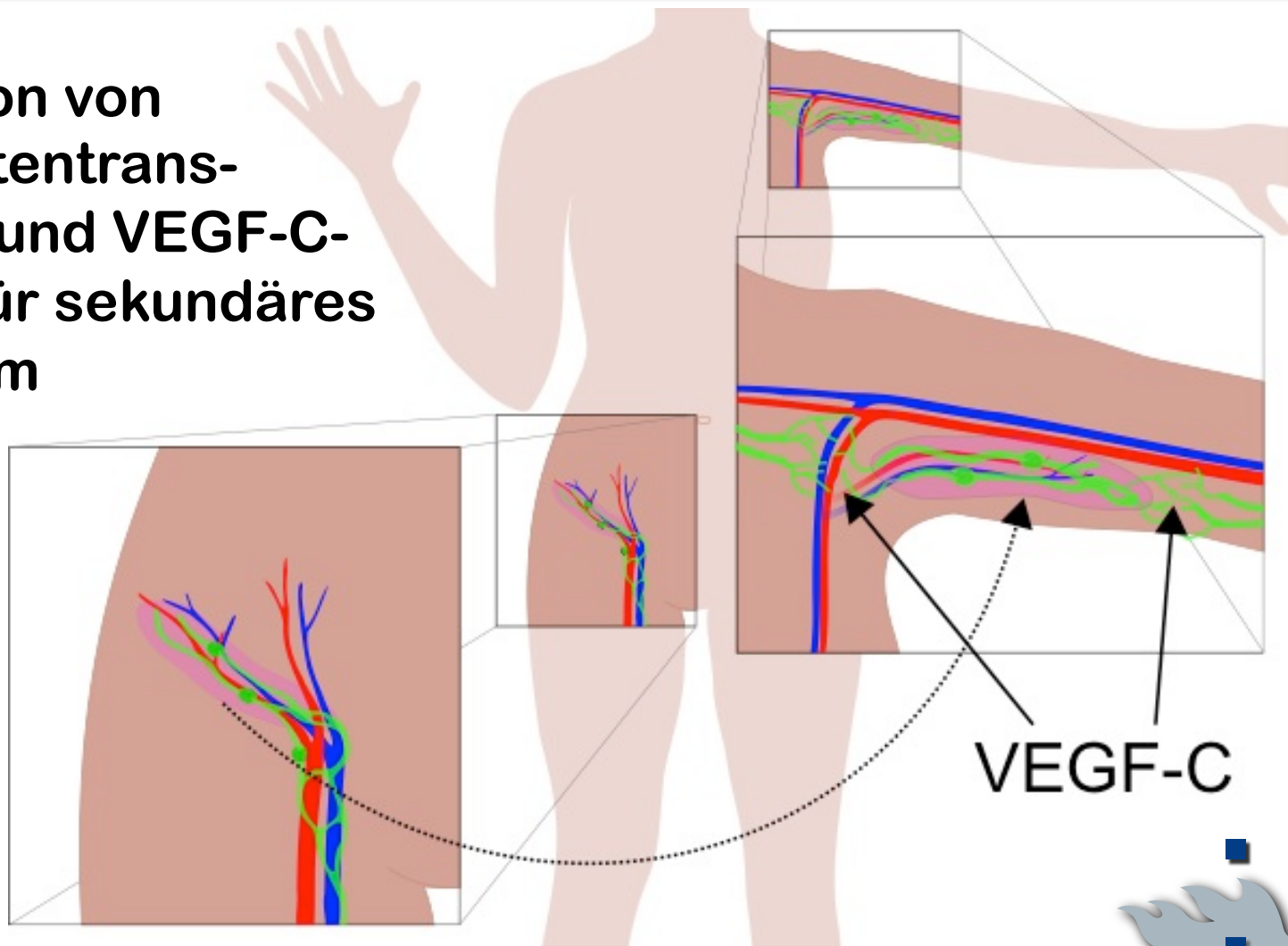


2011

2012

2013

Kombination von Lymphknotentrans- plantation und VEGF-C- Therapie für sekundäres Lymphödem



2011

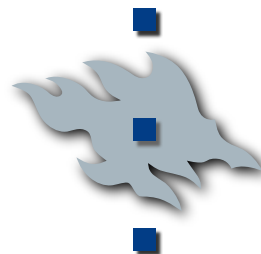
2013

2014

CCBE1 Enhances Lymphangiogenesis via ADAMTS3–
Mediated Vascular Endothelial Growth Factor-C Activation.

Michael Jeltsch, ... & Kari Alitalo

Circulation 129, 1962-71.



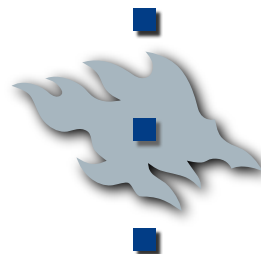
2011

2013

2014

Hennekam Lymphangiektasie- Lymphödem Syndrom

- **Eine seltene Erbkrankheit (OMIM #235510)**
- **Autosomal rezessiv**
- **Lymphödem & Lymphangiektasie**
- **Mentale Retardierung variabler Ausprägung**

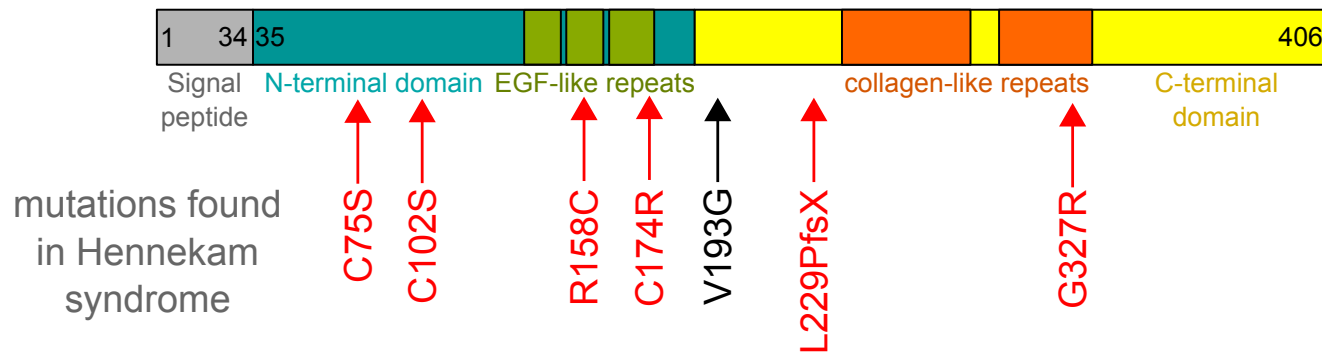


2011

2013

2014

Collagen and calcium-binding EGF domain-containing protein 1 (CCBE1)



[Kärkkäinen et al. 2003](#)



$-/-$



$+/-$

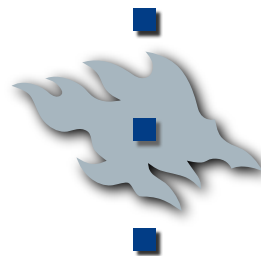
[Bos et al. 2011](#)



$-/-$



$+/-$

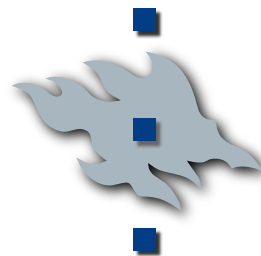
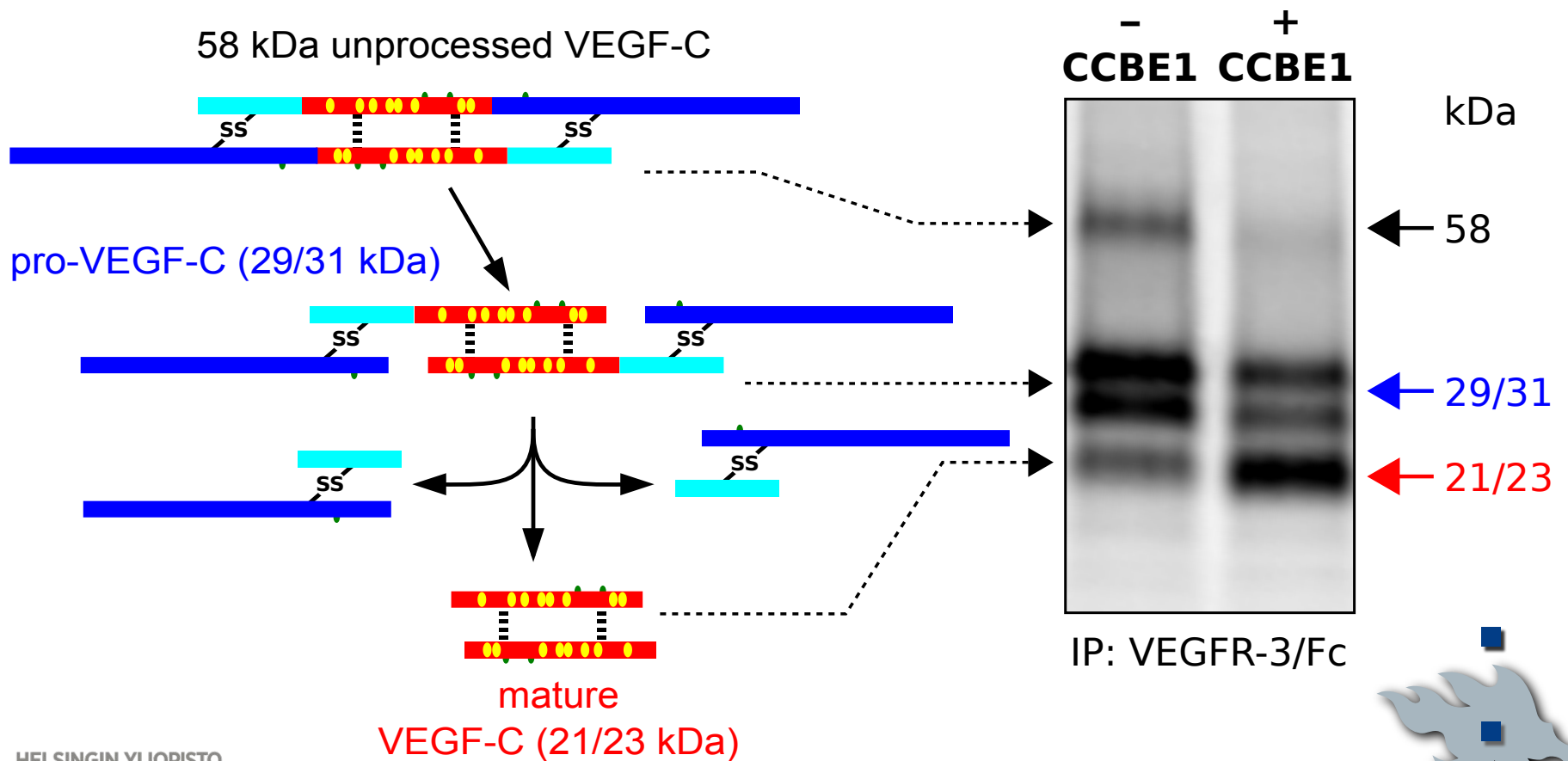


2011

2013

2014

CCBE1 beschleunigt die enzymatische Reifung von VEGF-C

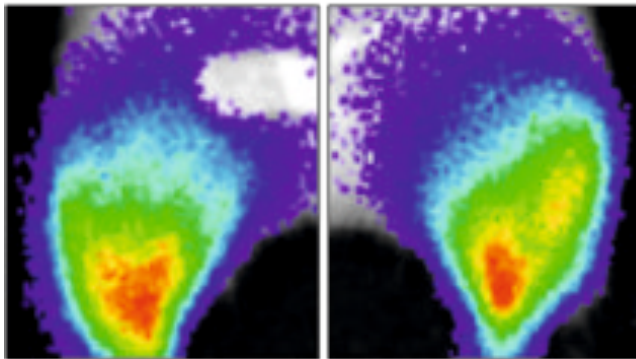


2011

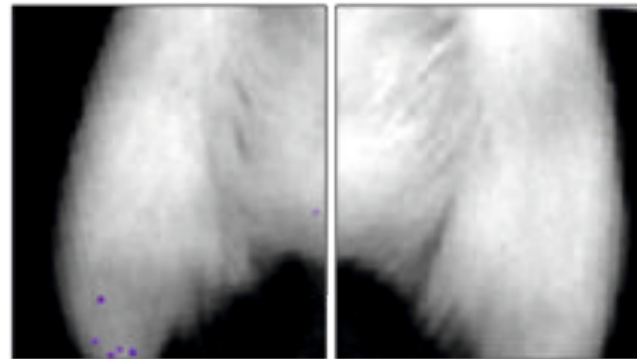
2013

2014

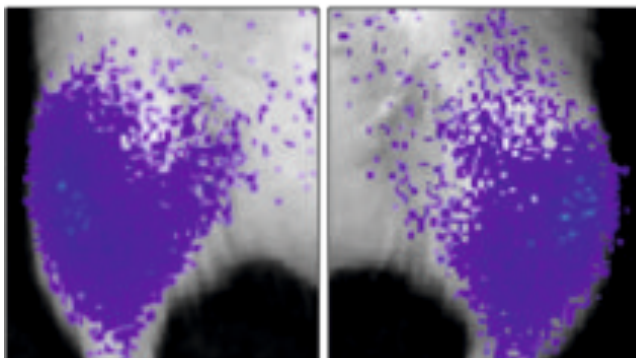
VEGF-C + CCBE1



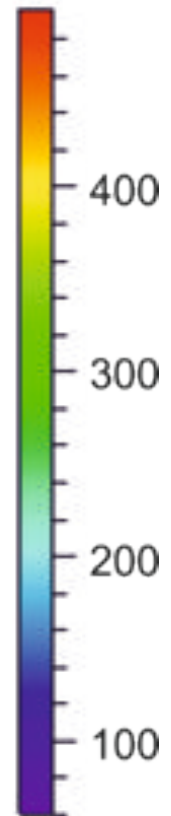
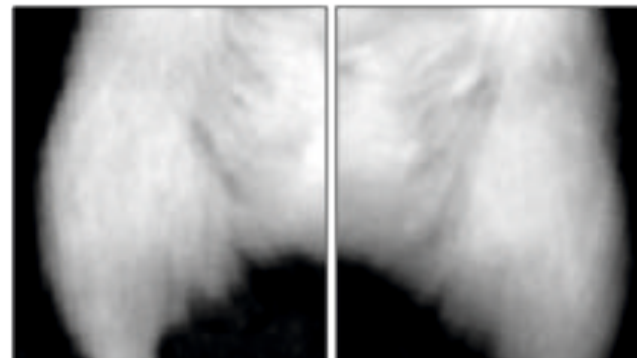
HSA + CCBE1



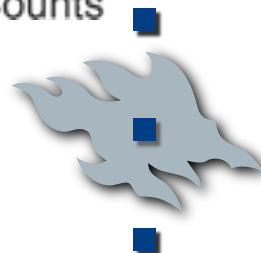
VEGF-C + HSA



HSA



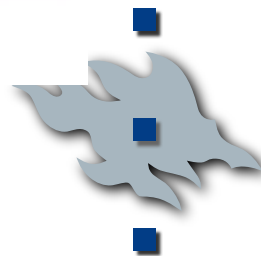
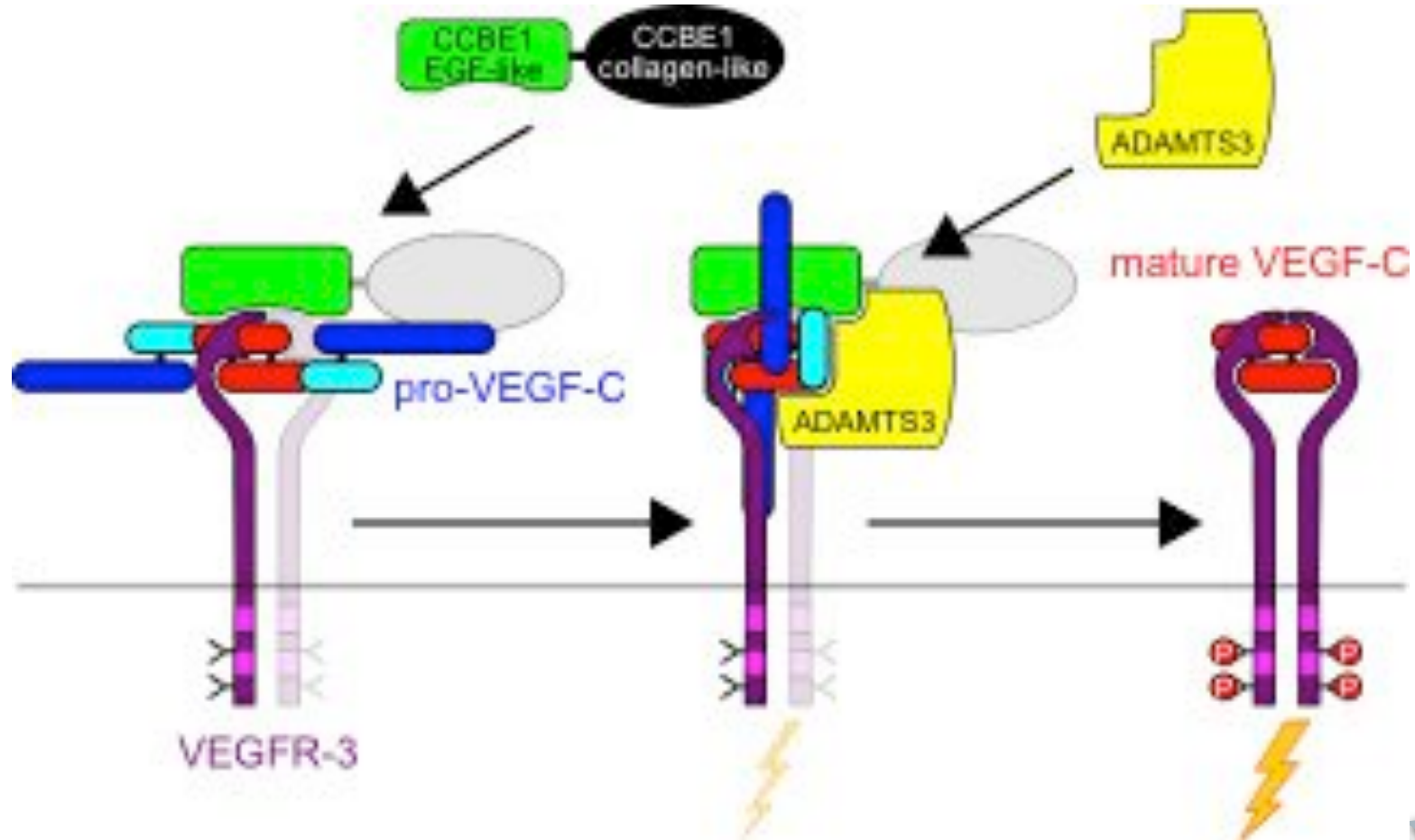
Counts



2011

2013

2014



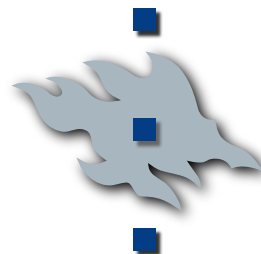
2011

2013

2014

“Hot topics” und offene Fragen

- Rolle des Lymphgefäßsystems in der Osmoregulation
- Ist das Glaukom eine Lymphgefäßkrankheit?
- Identifizierung neuer molekularer Faktoren und Mechanismen (für Hennekam Syndrome e.g. FAT4)
- Welche anderen Enzyme können VEGF-C aktivieren?

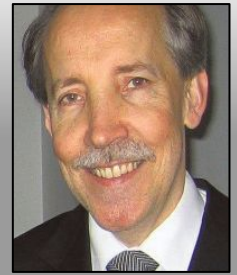




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Kumar
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**Jaana
Vulli**

