



Lymphangiogenesis in health and disease

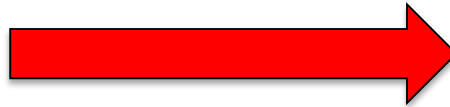
41 st European Society of Lymphology (ESL) Congress

Michael Jeltsch

June 4, 2015



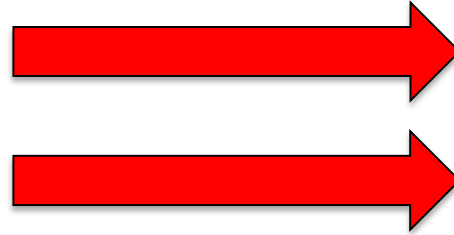
**Understanding
of the
Physiology**



Pathology



VEGFR-3
VEGF-C



**Hereditary
Lymphedema
Type 1A
Type 1D**

VEGF-C
CCBE1
ADAMTS3

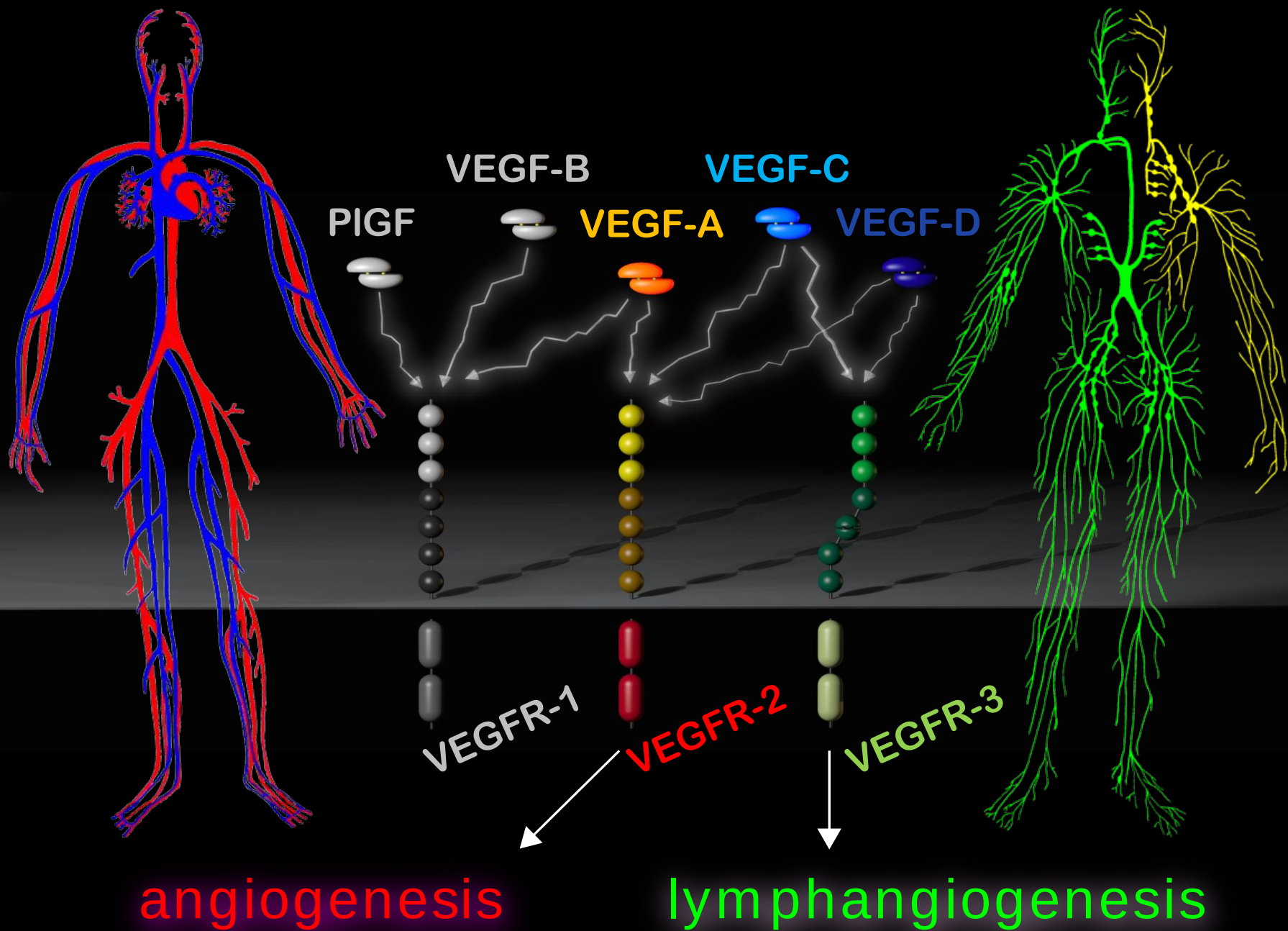


**Hennekam
Syndrome**



Hennekam Lymphangiectasia-Lymphedema Syndrome

- **A rare hereditary disorder**
- **Autosomal recessive**
- **Lymphedema & lymphangiectasia**
- **Mental retardation of variable severity**

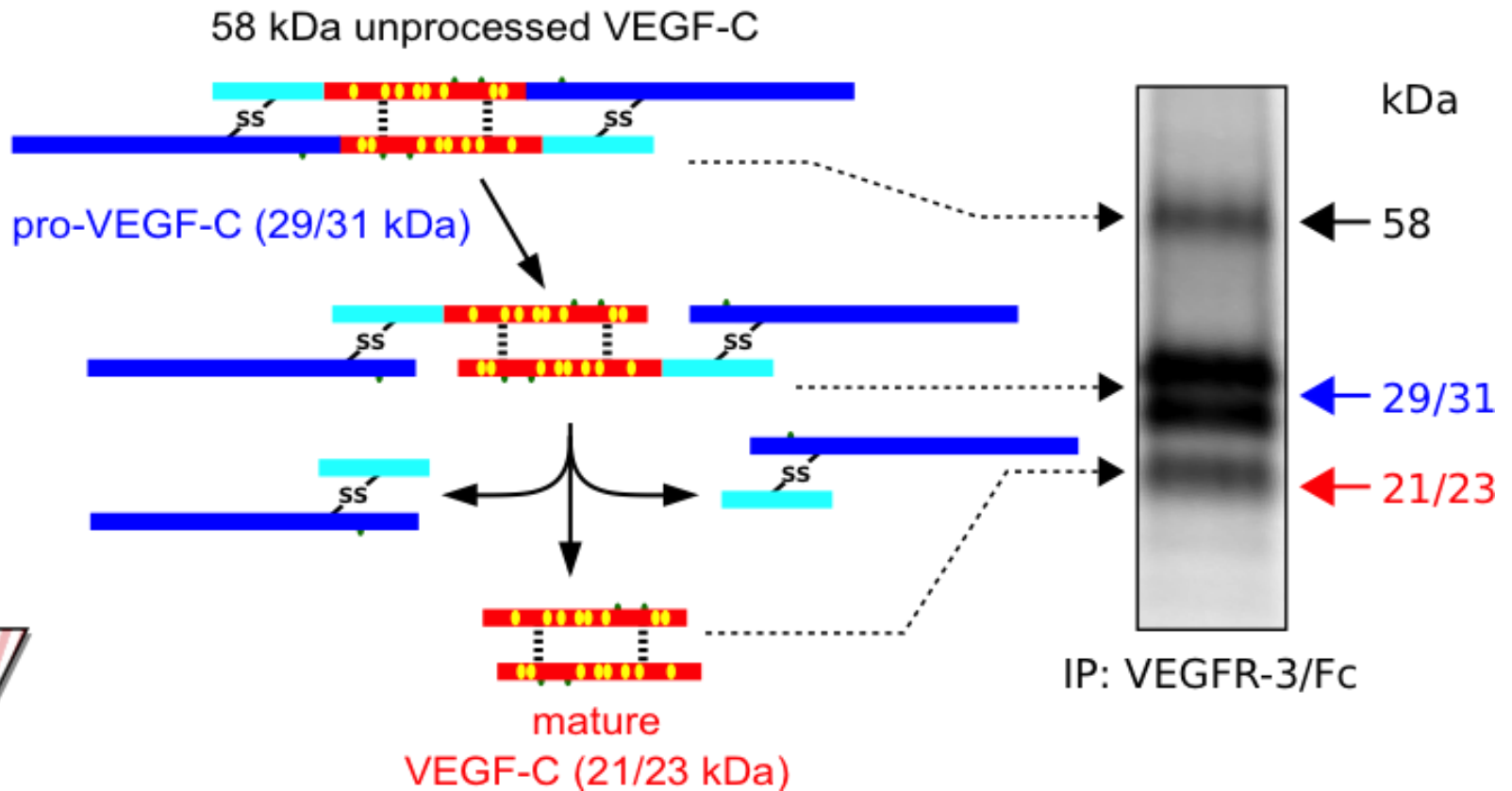




Vascular Endothelial Growth Factor-C

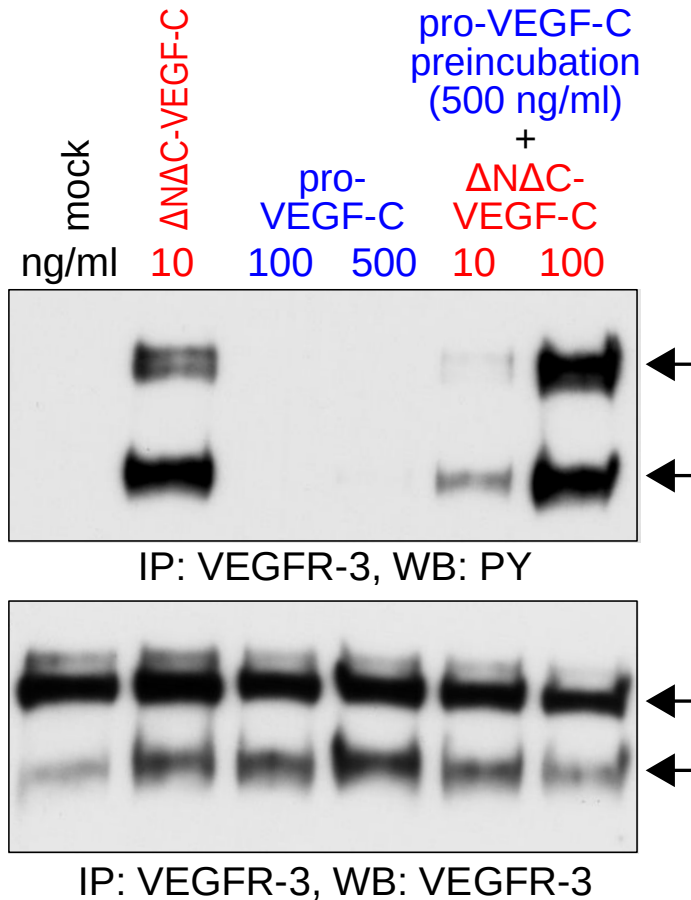


The biosynthesis of VEGF-C



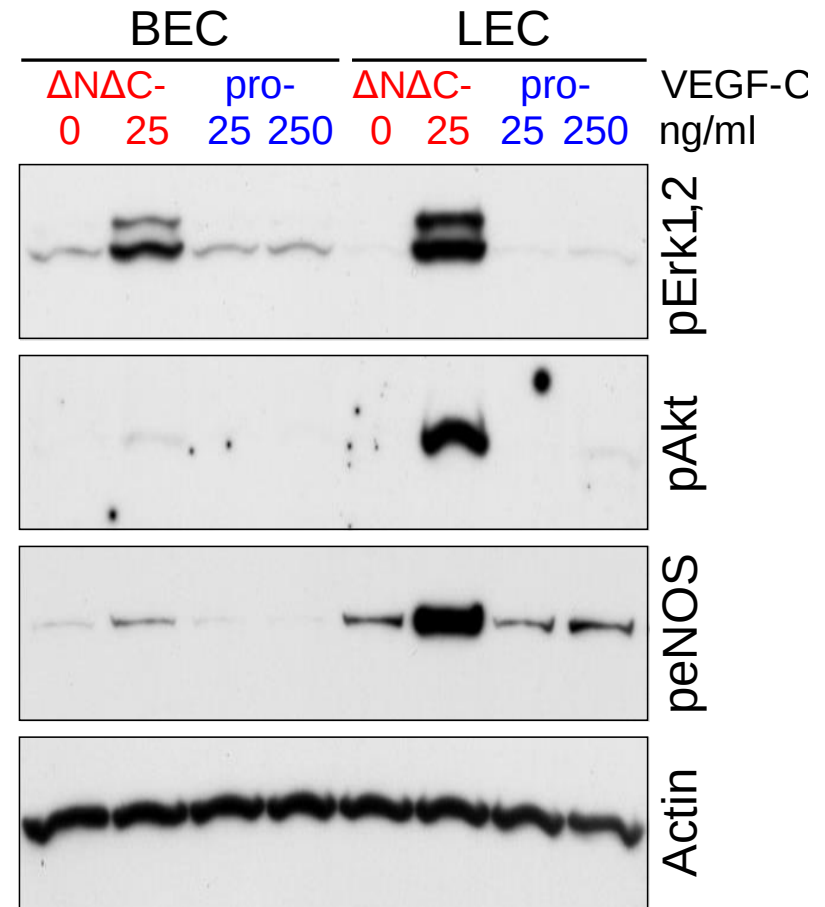
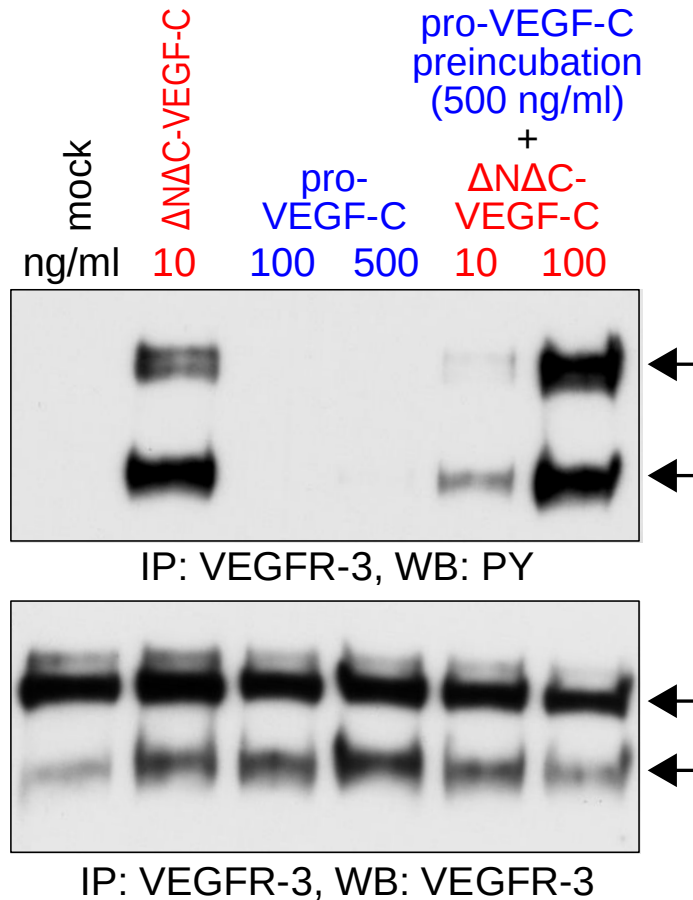


pro-VEGF-C inhibits the activation of VEGFR-3 by mature VEGF-C





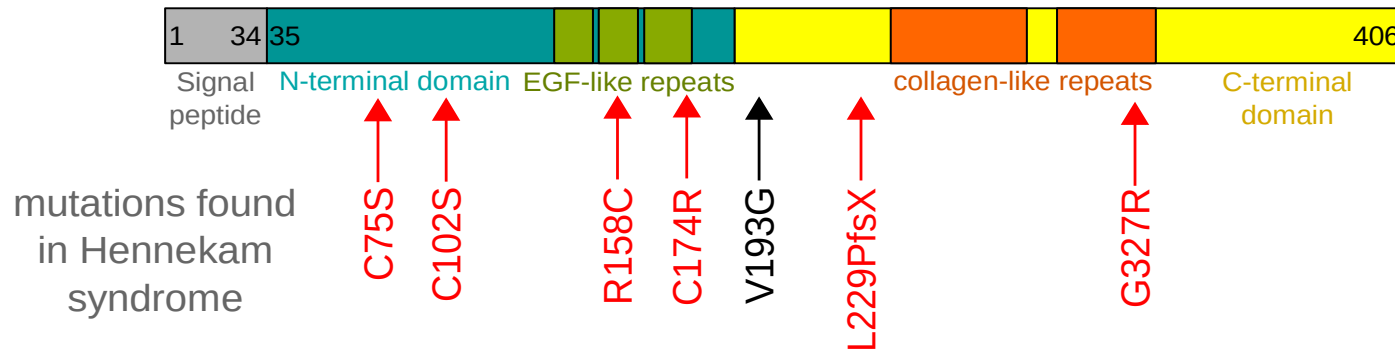
pro-VEGF-C inhibits the activation of VEGFR-3 by mature VEGF-C





CCBE1

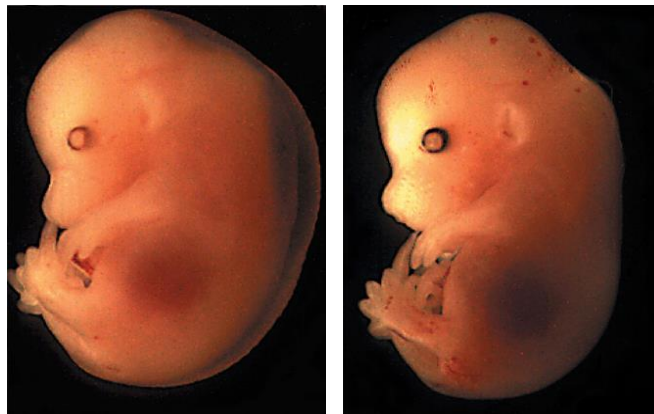
(Collagen and calcium-binding EGF domain-containing protein 1)



Similarity of VEGF-C^{-/-} and CCBE1^{-/-} phenotype

VEGF-C

Kärkkäinen et al. 2004

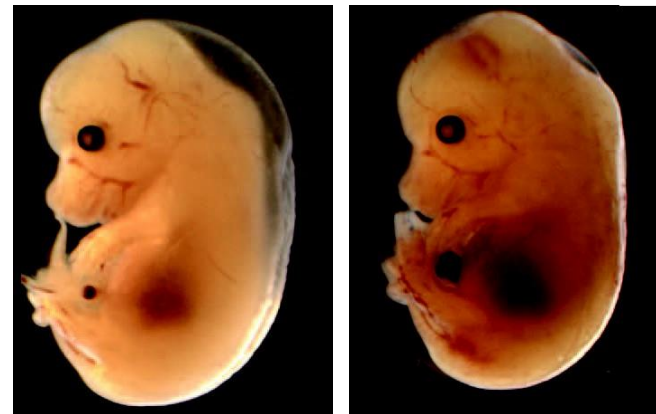


-/-

+/-

CCBE1

Bos et al., 2011

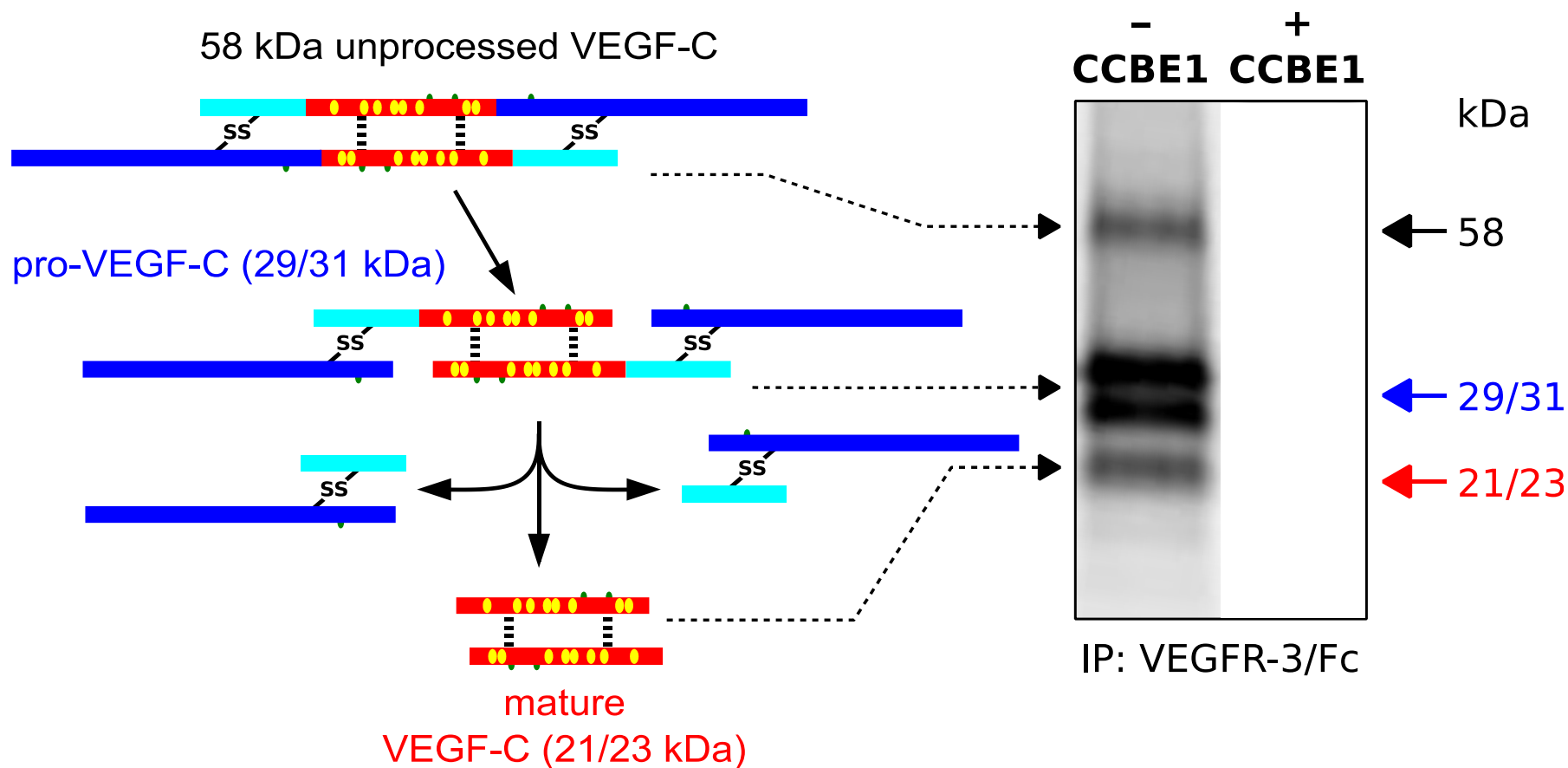


-/-

+/-

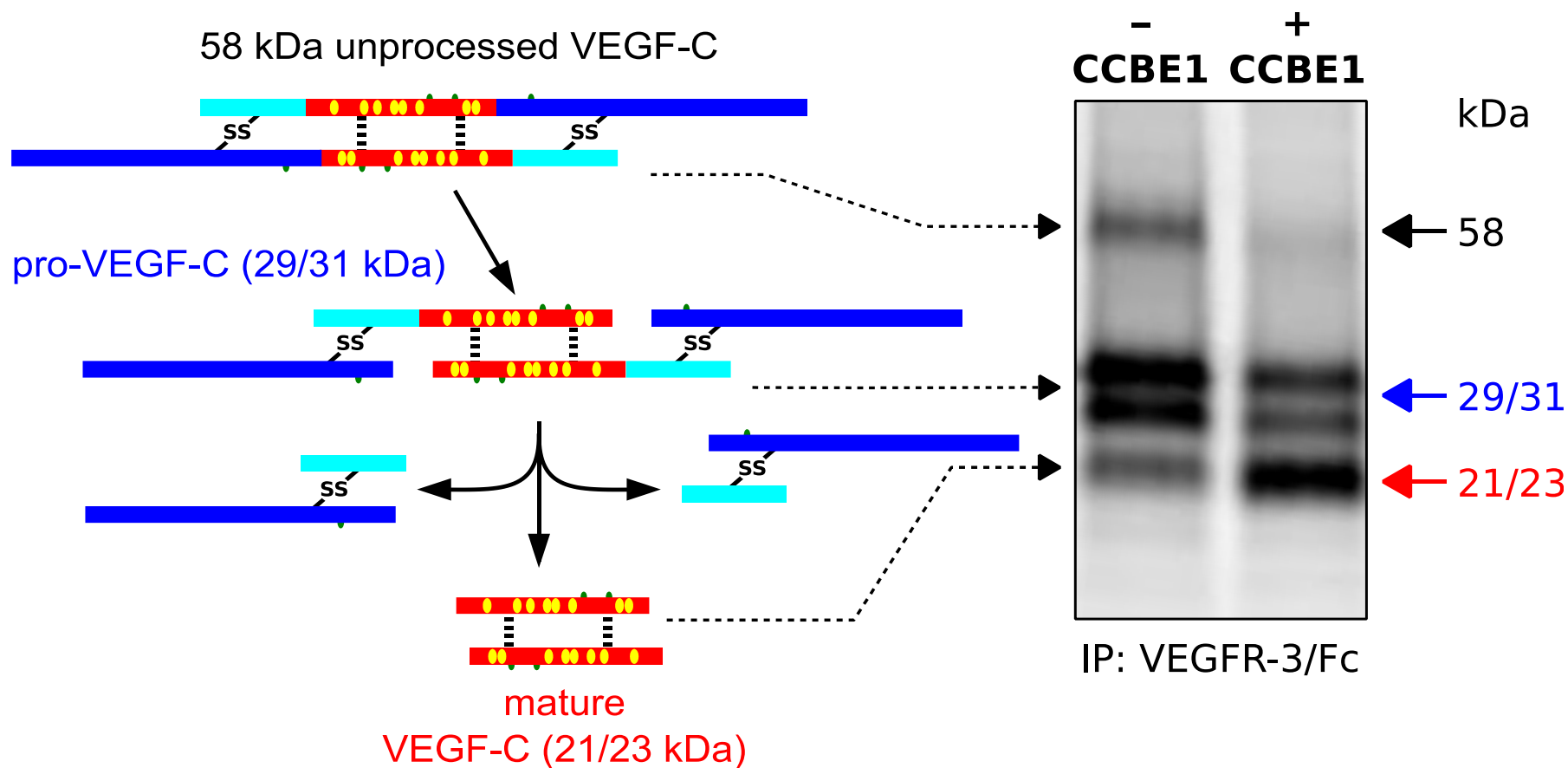


CCBE1 enhances VEGF-C processing



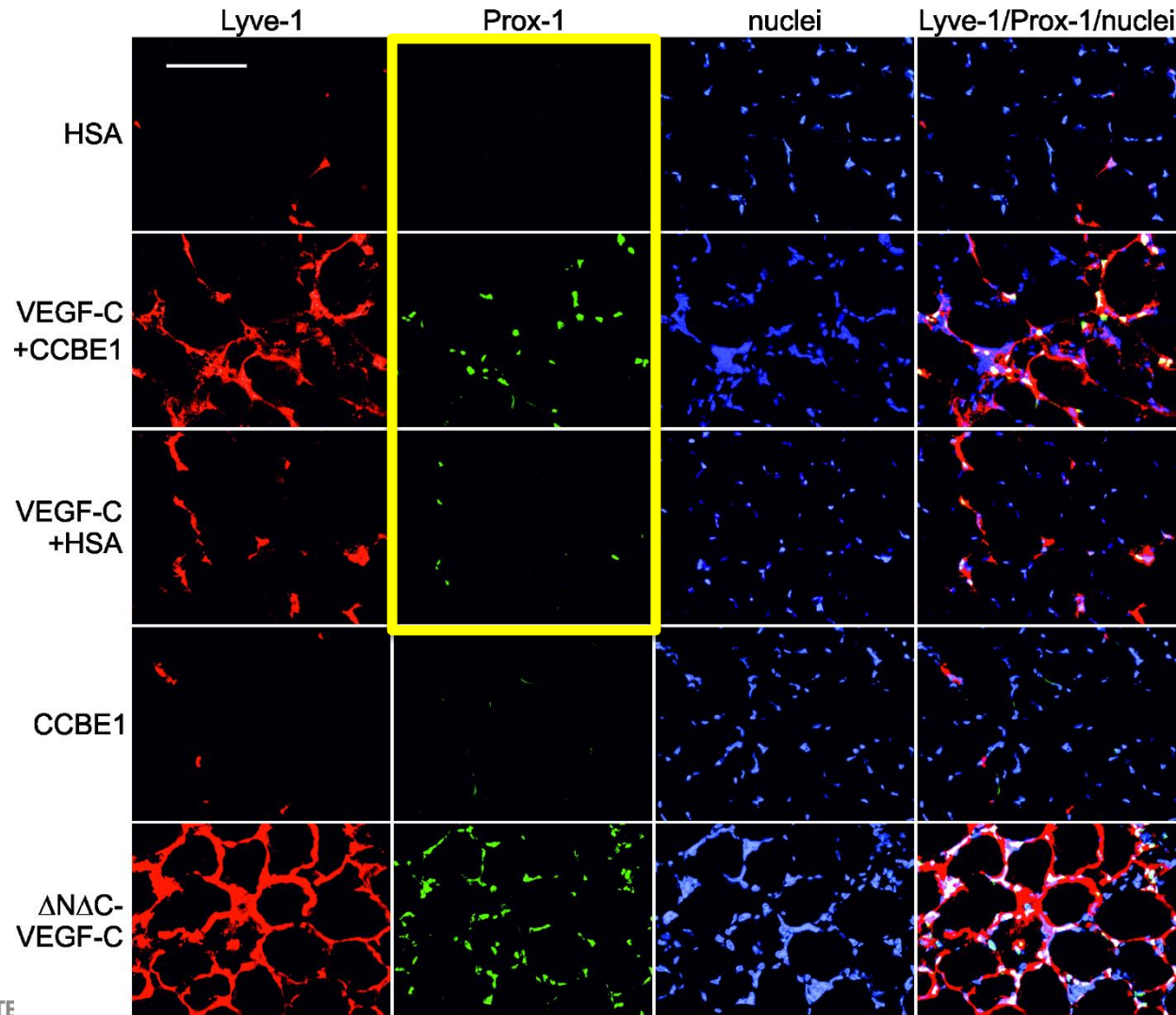


CCBE1 enhances VEGF-C processing



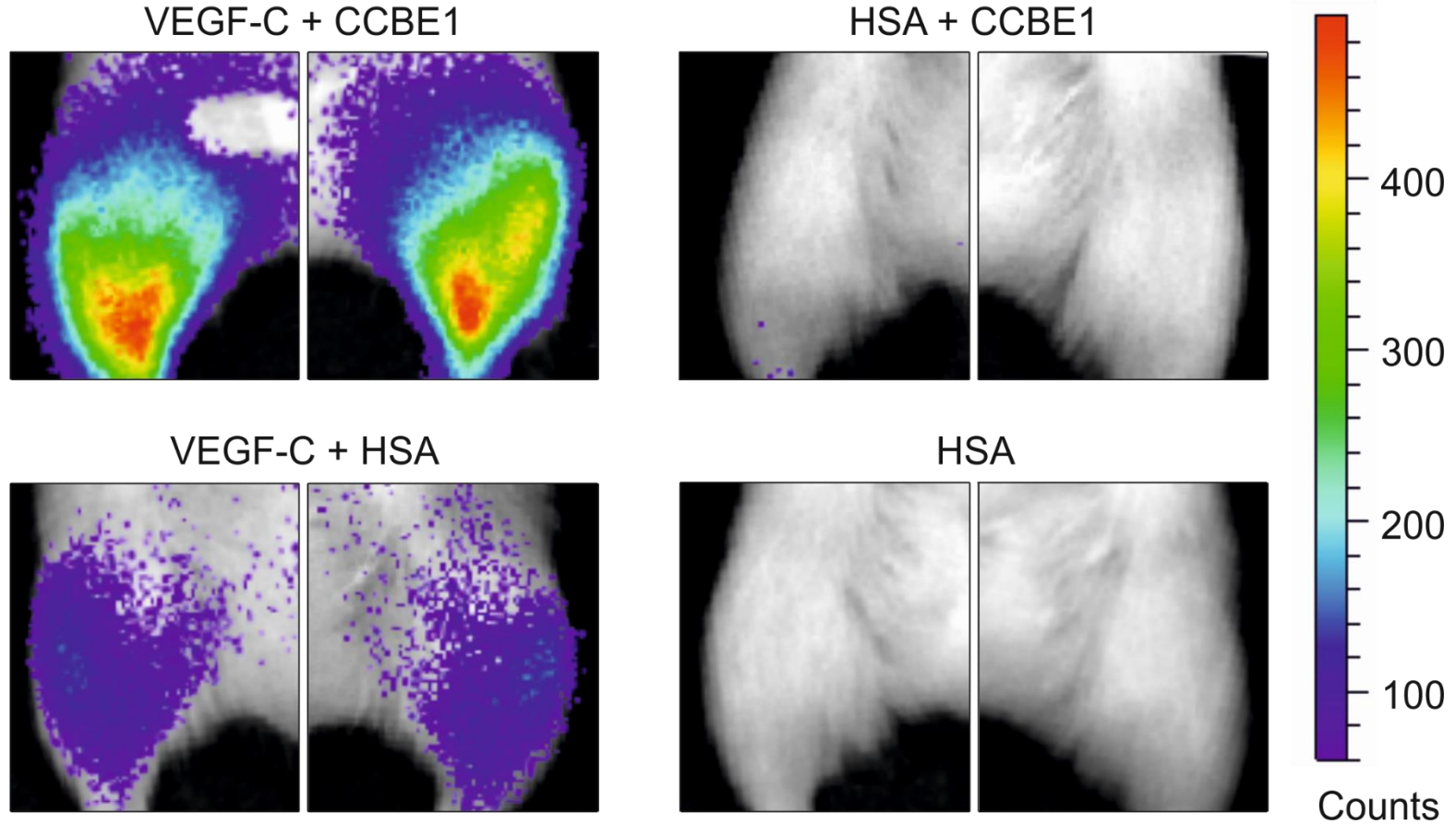


CCBE1 enhances VEGF-C-induced lymphangiogenesis in-vivo





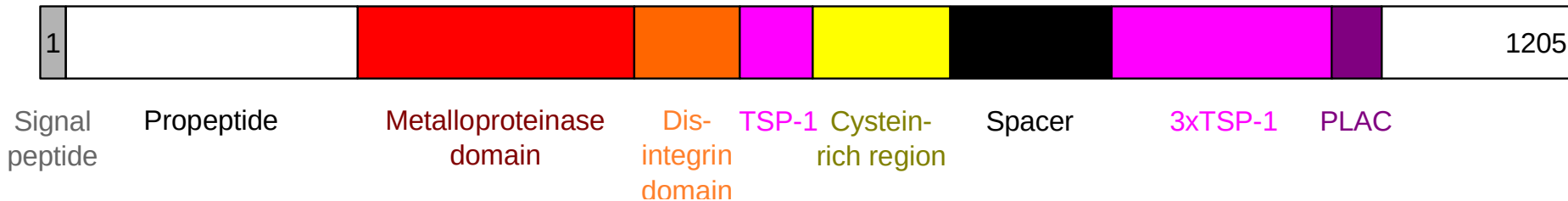
CCBE1 enhances VEGF-C-induced lymphangiogenesis in vivo





ADAMTS3

(A Disintegrin And Metalloproteinase With Thrombospondin Type 1 Motif-3)



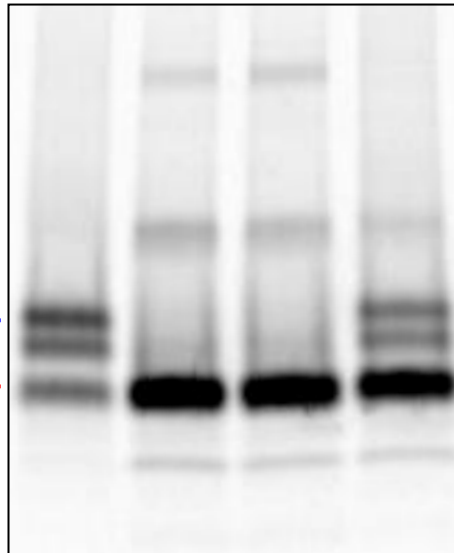
- Identification by protein mass spec analysis of purified CCBE1
 - Only known substrate so far: collagen



CCBE1 enhances VEGF-C cleavage by ADAMTS3

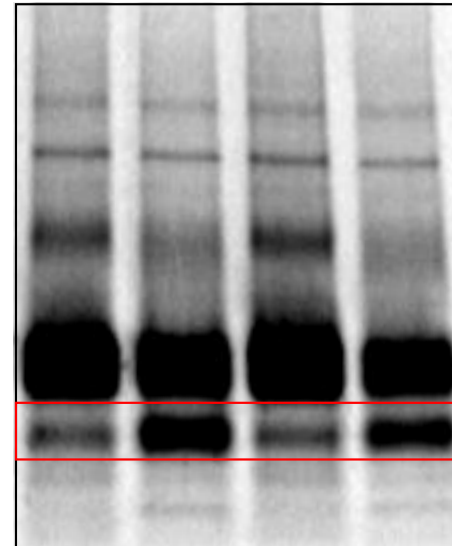
CCBE1	—	—	+	+
ADAMTS3	—	+	+	—

29/31 →
21/23 →



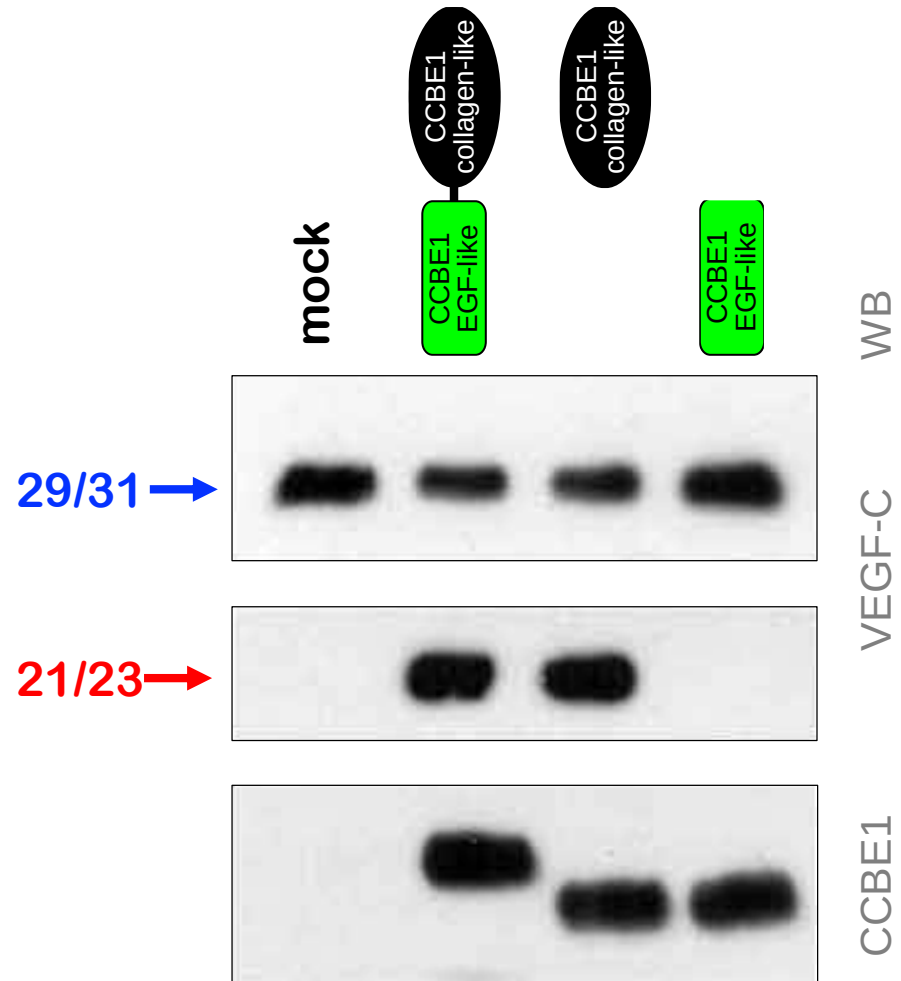
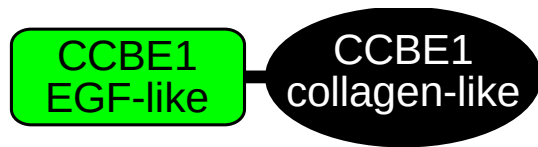
IP: VEGFR-3/Fc

—	+	—	+
+	+	—	—



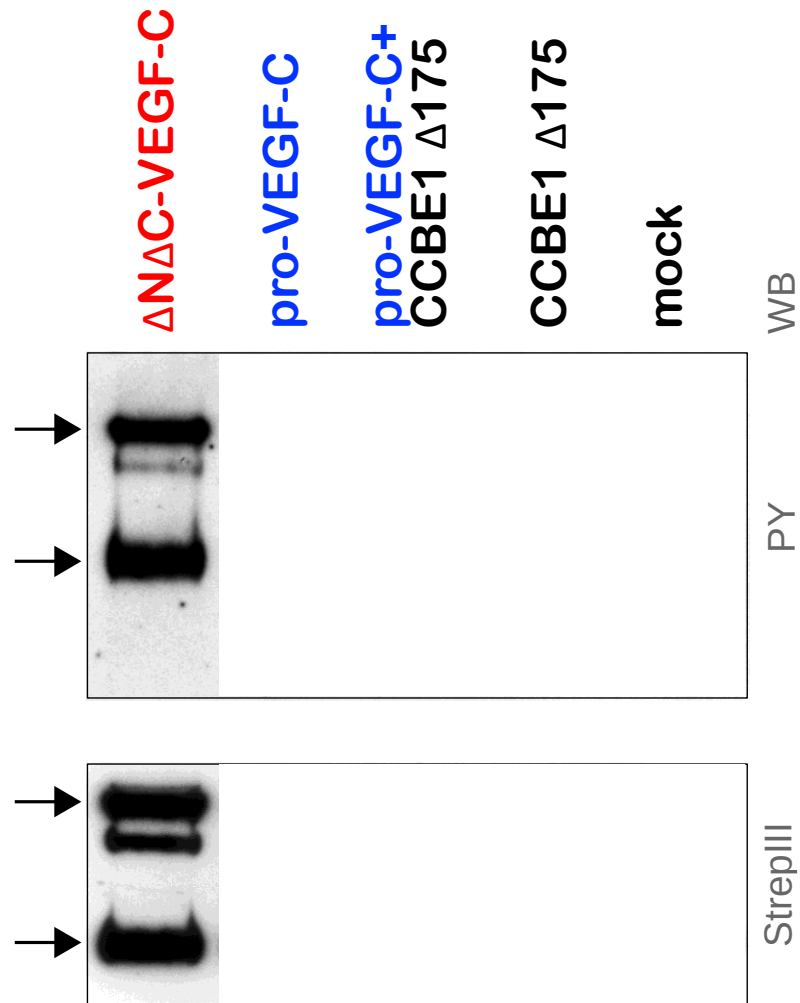
1.0 4.8 1.0 2.2

IP: VEGFR-3/Fc





+/- pro-VEGF-C
 +/- CCBE1 Δ 175
 +/- Δ N Δ C-VEGF-C





+/- pro-VEGF-C
 +/- CCBE1 Δ 175
 +/- Δ N Δ C-VEGF-C



Δ N Δ C-VEGF-C

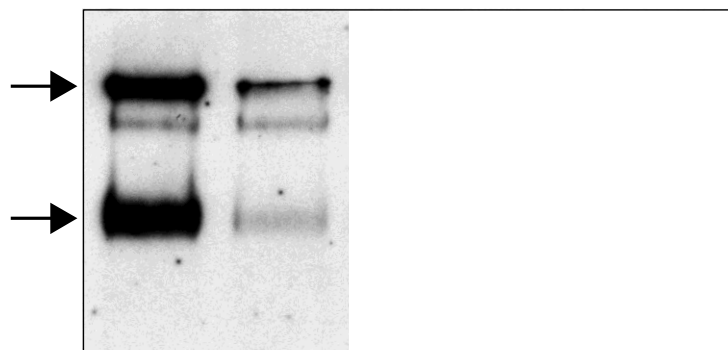
pro-VEGF-C

pro-VEGF-C+
CCBE1 Δ 175

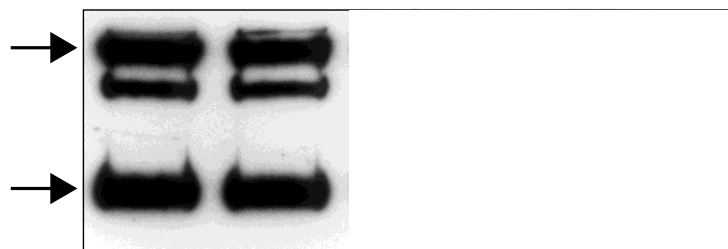
CCBE1 Δ 175

mock

WB



PY



StrepIII



+/- pro-VEGF-C
 +/- CCBE1 Δ 175
 +/- Δ N Δ C-VEGF-C



Δ N Δ C-VEGF-C

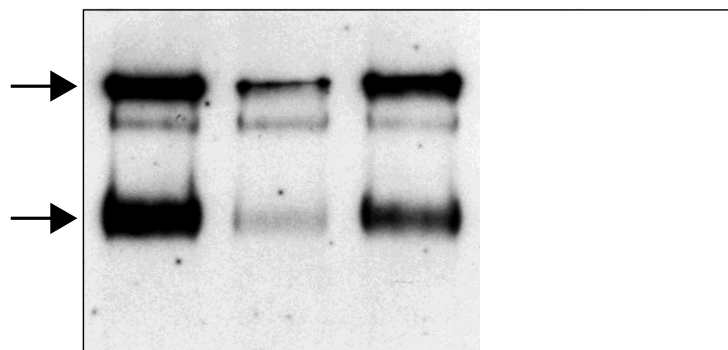
pro-VEGF-C

pro-VEGF-C+
CCBE1 Δ 175

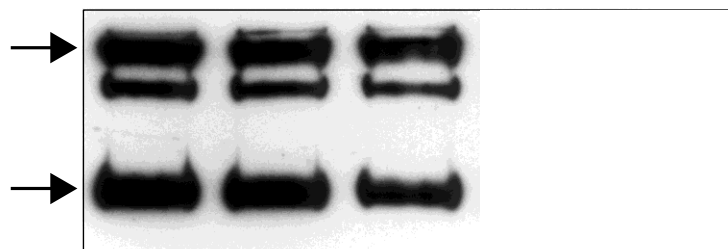
CCBE1 Δ 175

mock

WB



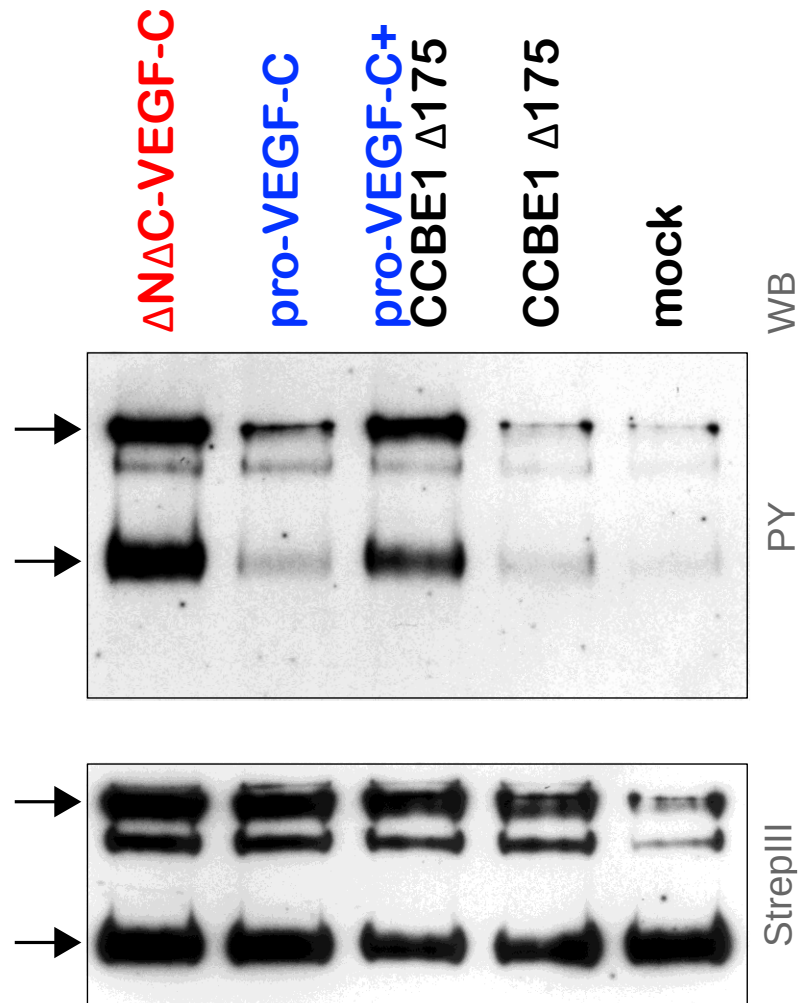
PY



StrepIII

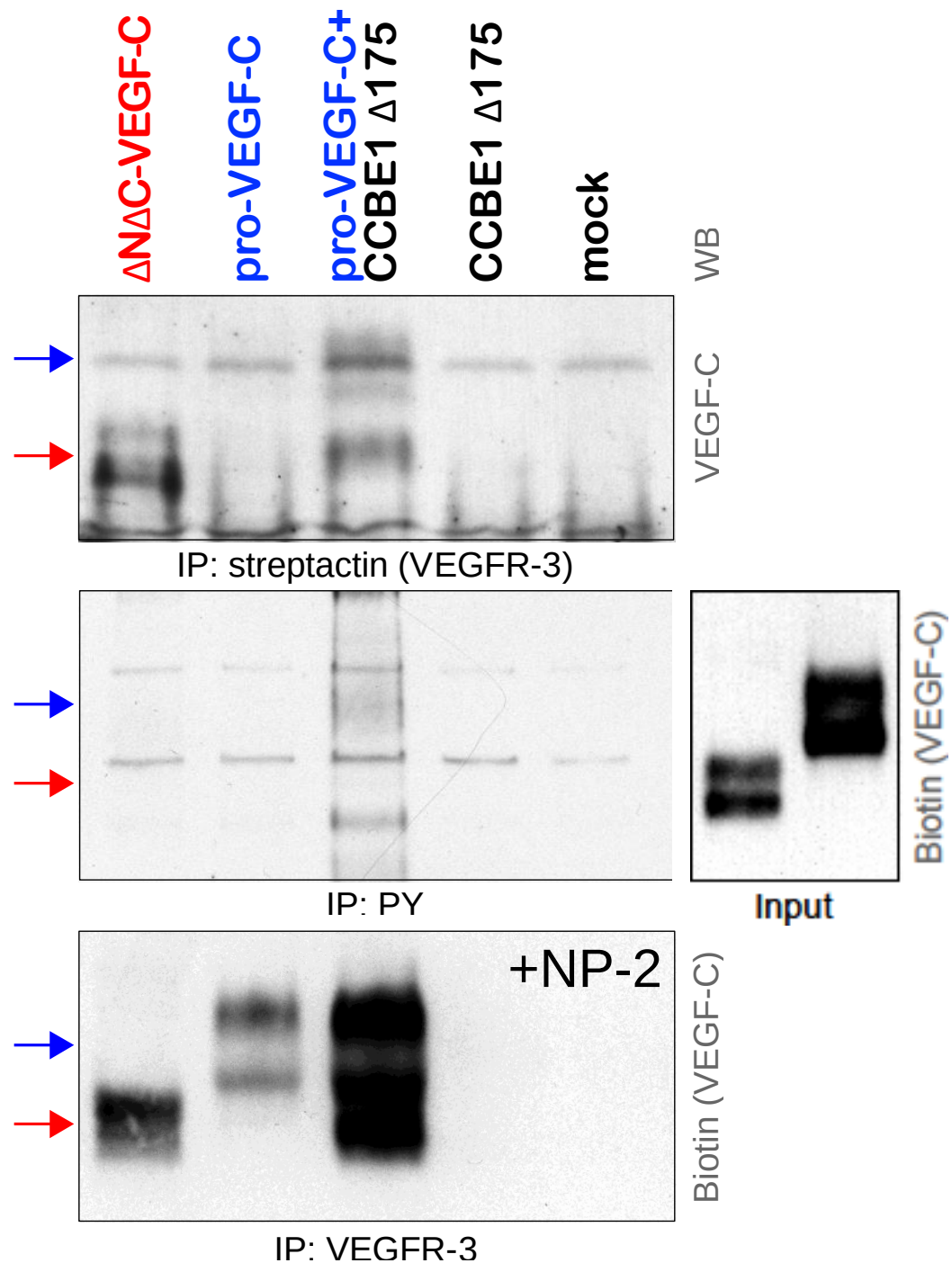


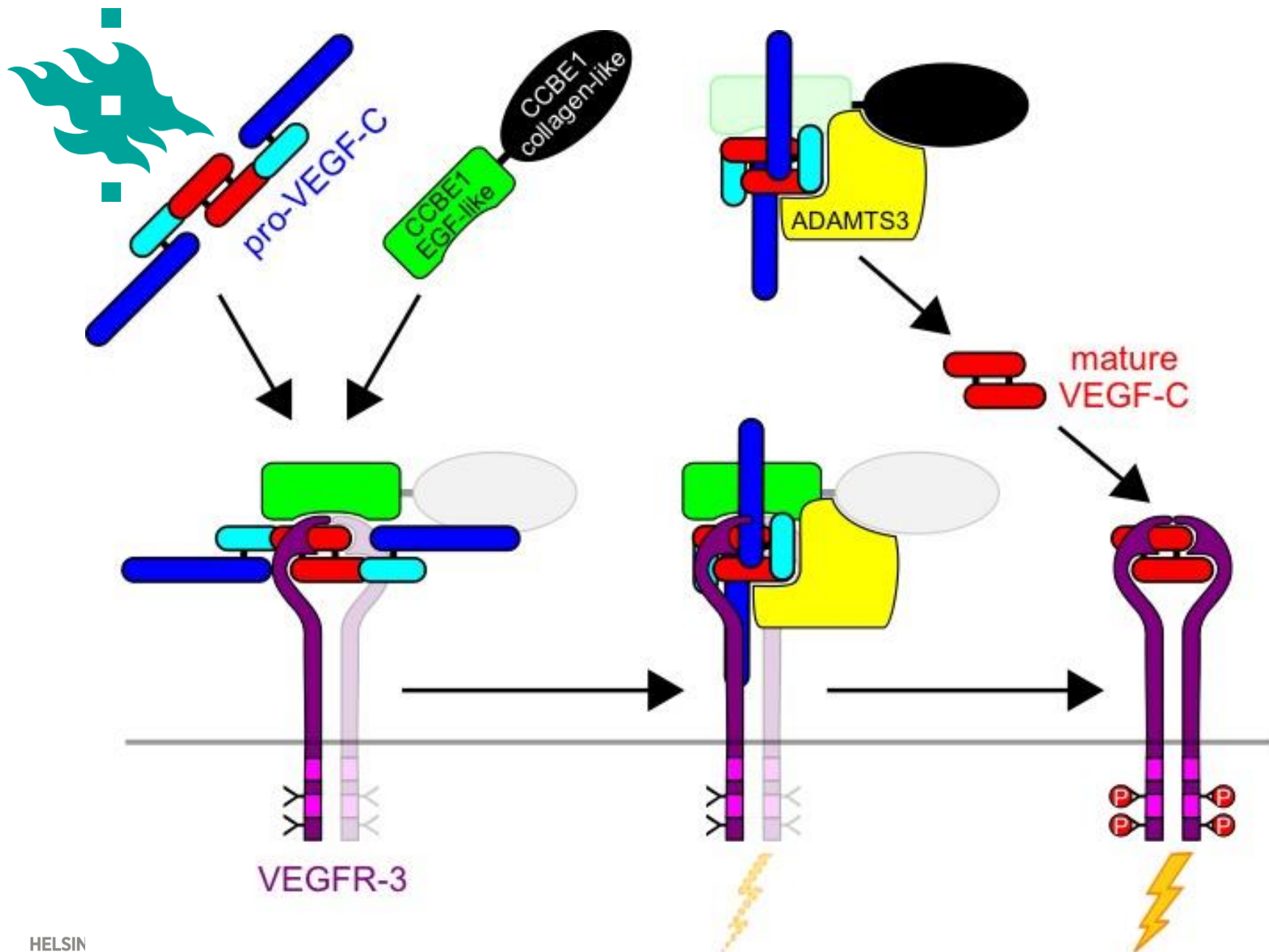
+/- pro-VEGF-C
 +/- CCBE1 Δ 175
 +/- Δ N Δ C-VEGF-C





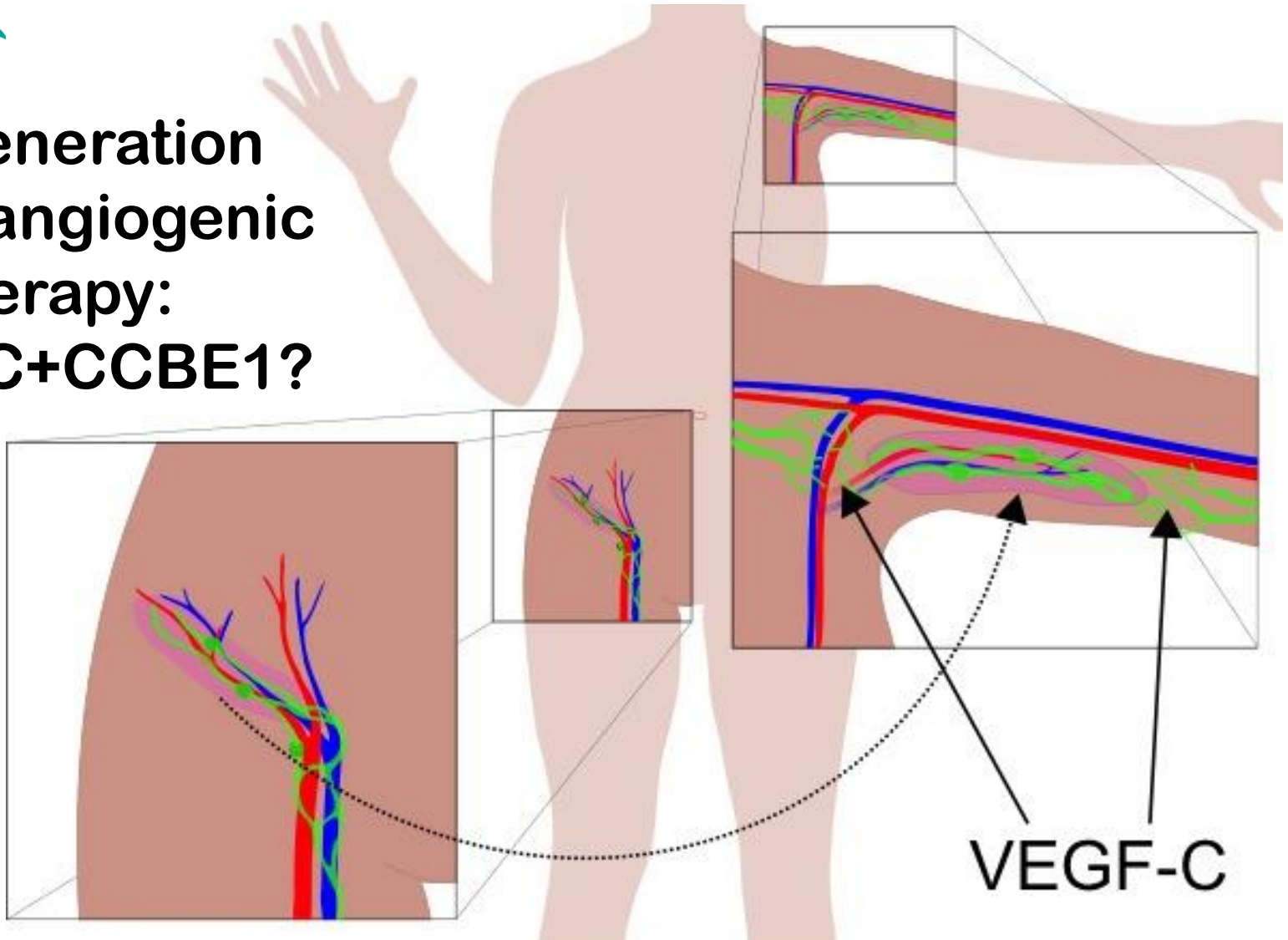
+/- pro-VEGF-C
+/- CCBE1 Δ 175
+/- Δ N Δ C-VEGF-C







2nd generation lymphangiogenic therapy: VEGF-C+CCBE1?





Take-home messages

1. **pro-VEGF-C** binds VEGFR-3, but does not signal,
mature VEGF-C binds VEGFR-3 and signals
(VEGF-C level measurements don't discriminate!)
2. The conversion of **pro-VEGF-C** into **mature VEGF-C** can be performed by **ADAMTS3**
(other enzymes?)
3. **CCBE1** localizes and accelerates the conversion of
pro-VEGF-C into **mature VEGF-C** by **ADAMTS3**
(EGF-like domain localizes,
collagen-like domain accelerates cleavage)



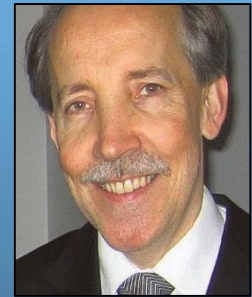
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