Engineering *new* networks of blood vessels

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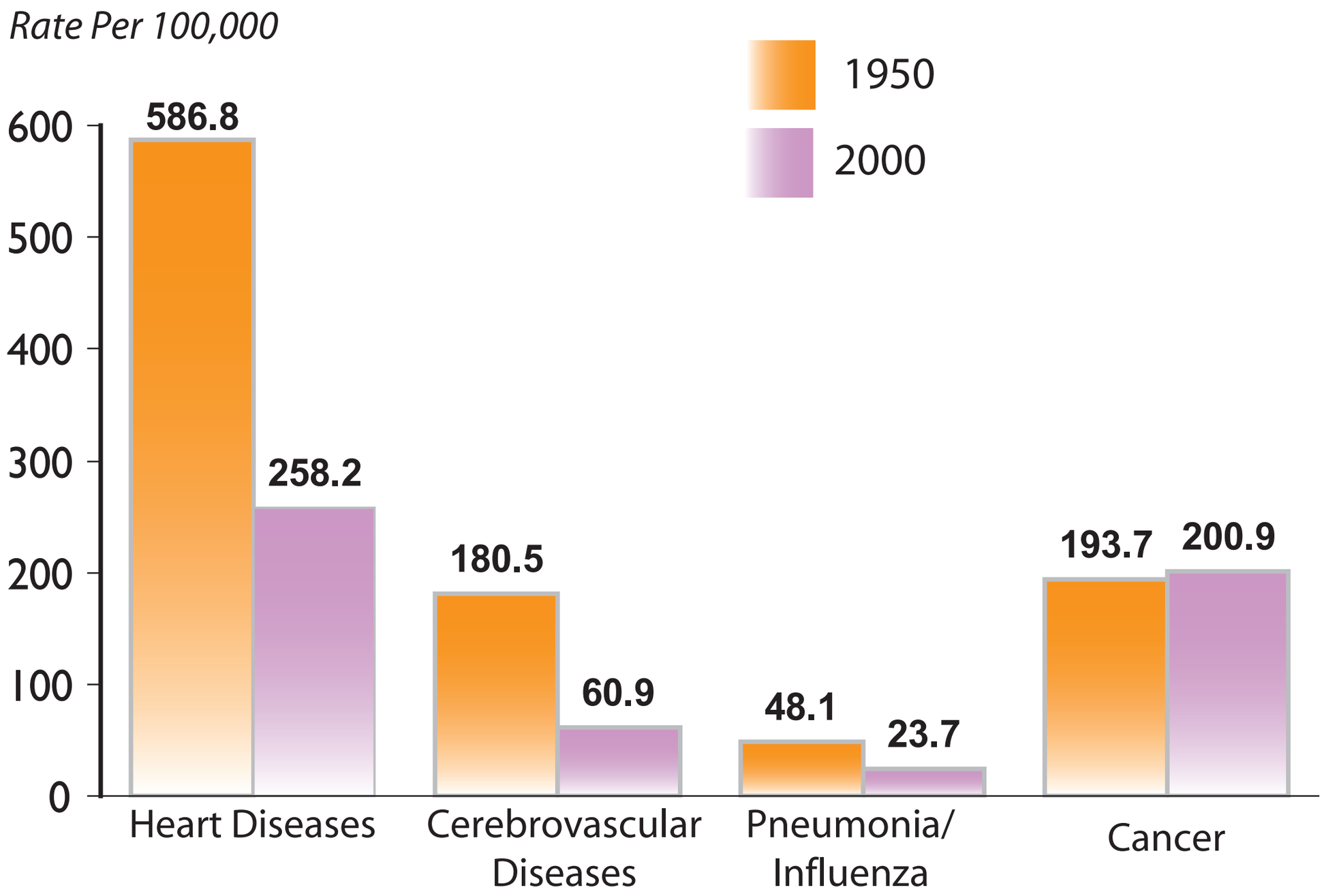
http://www.deas.harvard.edu/mooneylab/

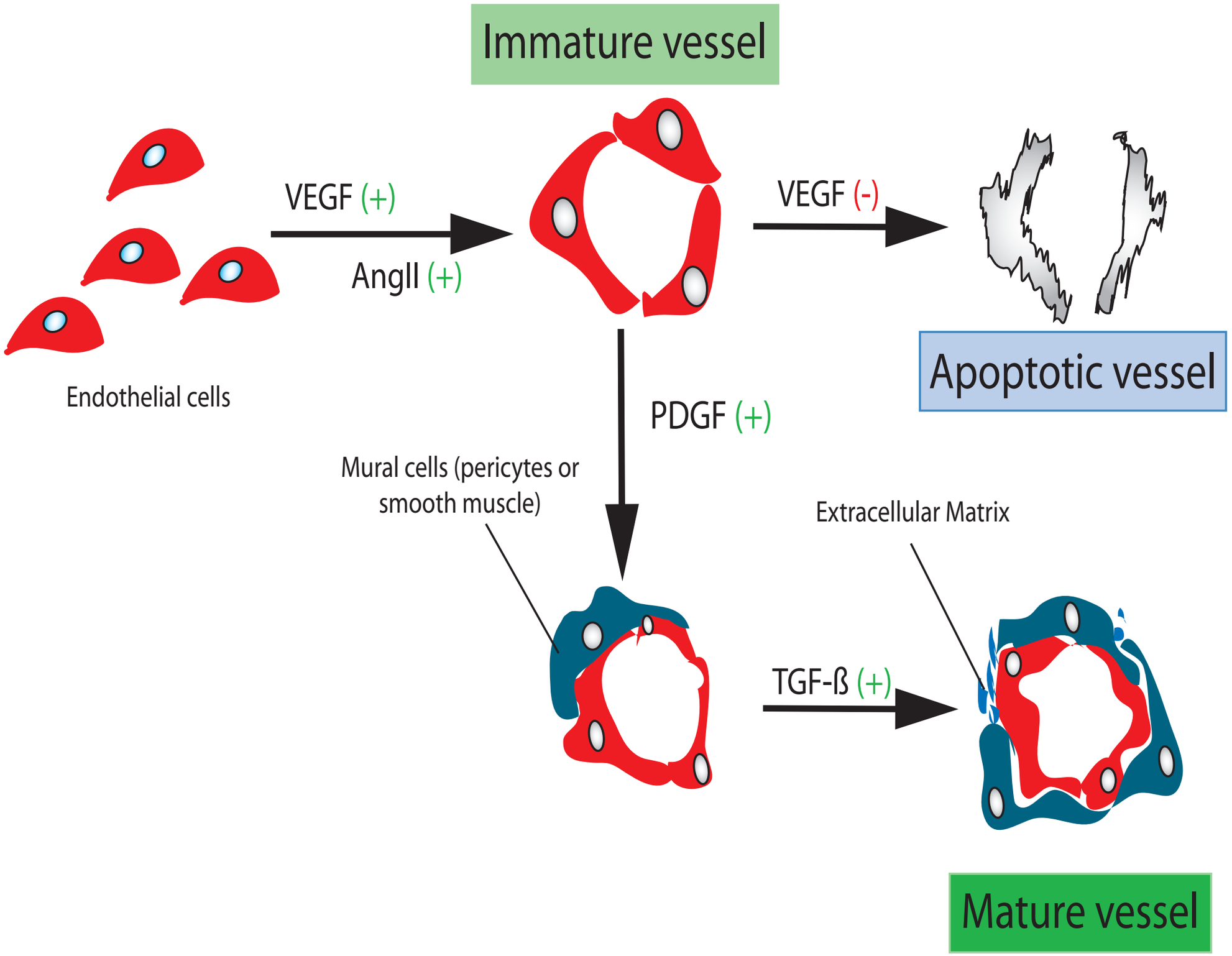
December 2005

US Death Rates* by Cause,
-1950 & 2000-



** Age-adjusted to the 2000 US standard population*
Source: US Mortality Volume 1950, National Vital Statistics Report, 2002, Vol. 50, No 15.

Angiogenesis



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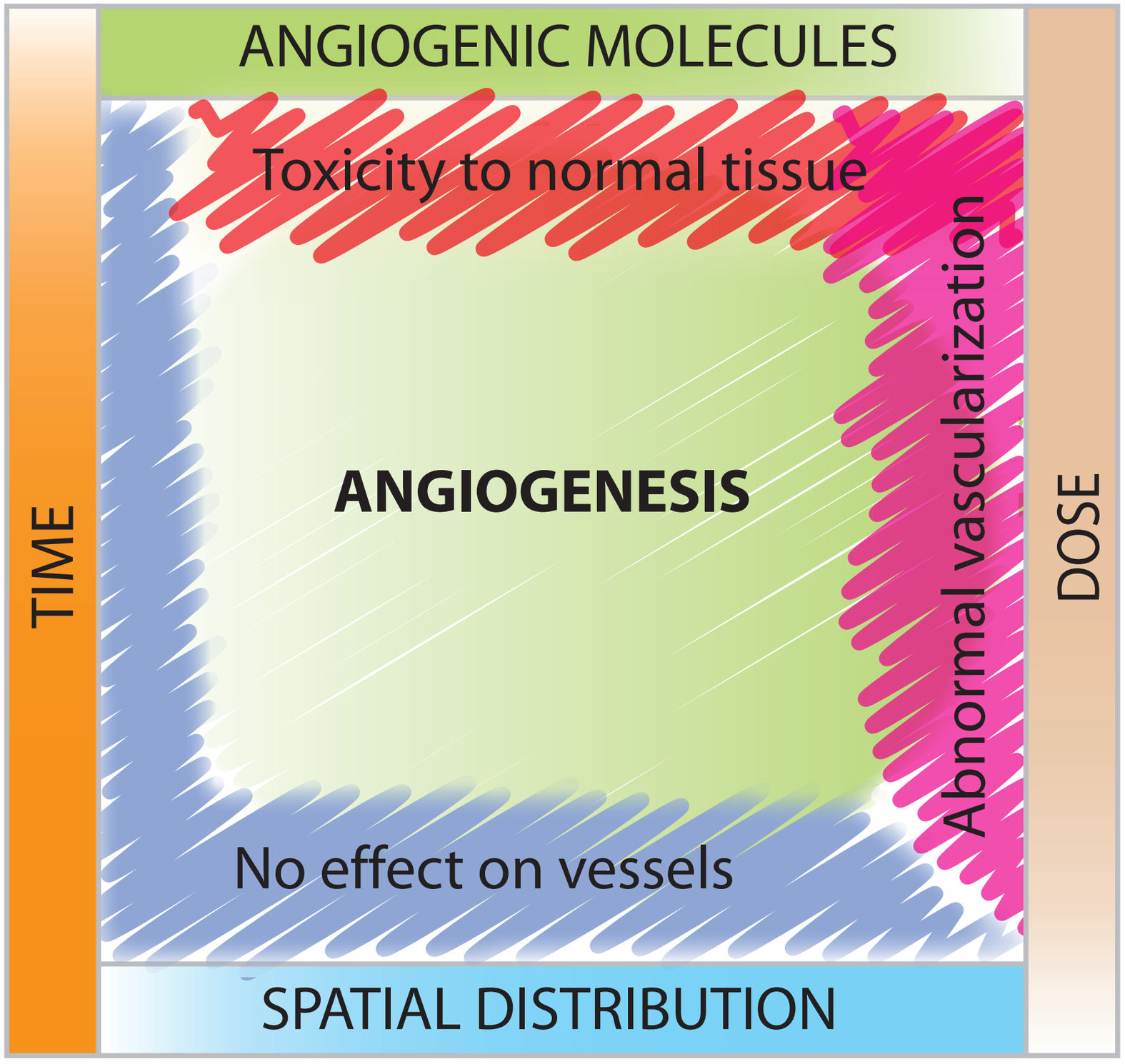
Angiogenesis: Normalization window



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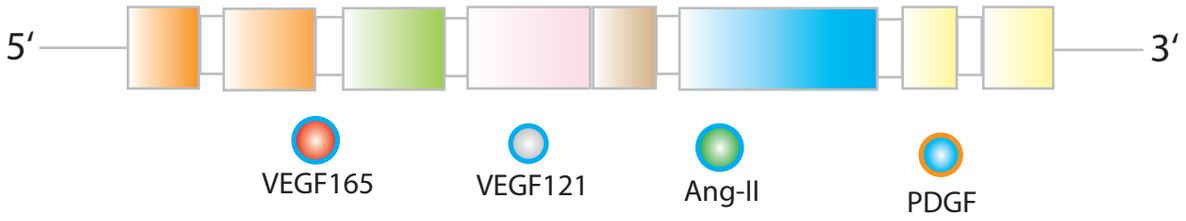
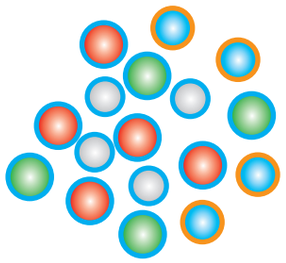
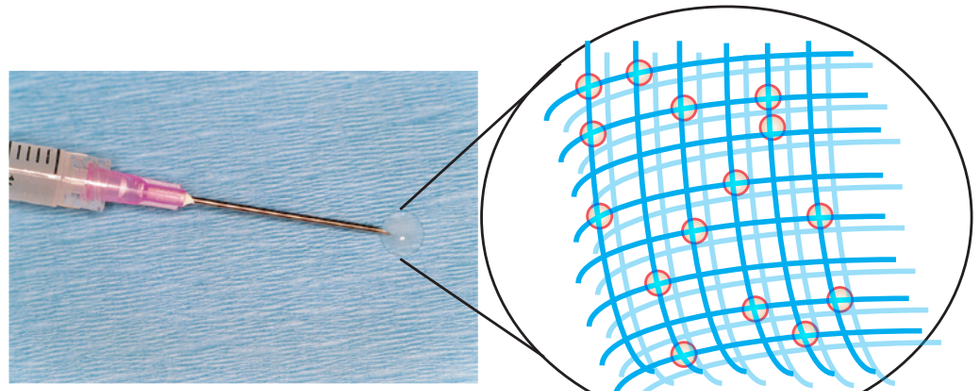
Vascular Endothelial Growth Factor (VEGF) gene

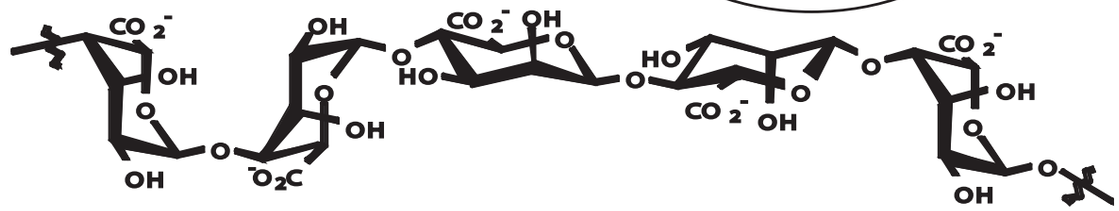


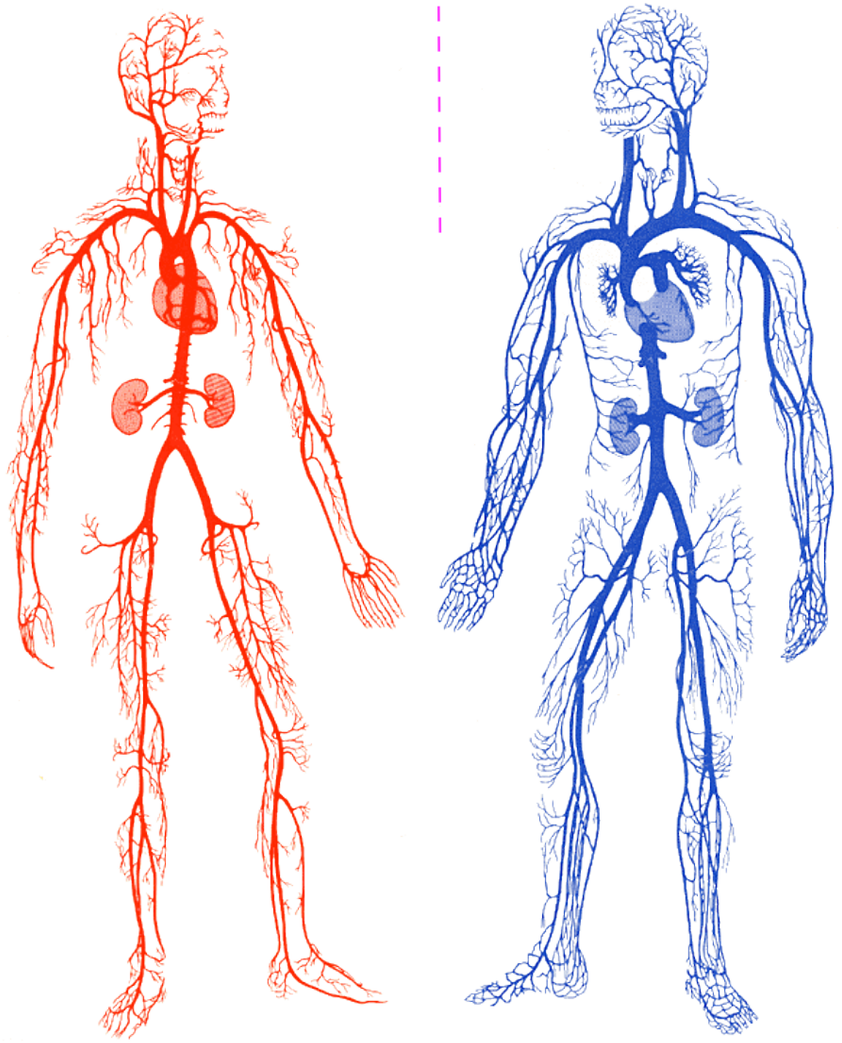


Angiogenic agents

Synthetic Extracellular Matrice







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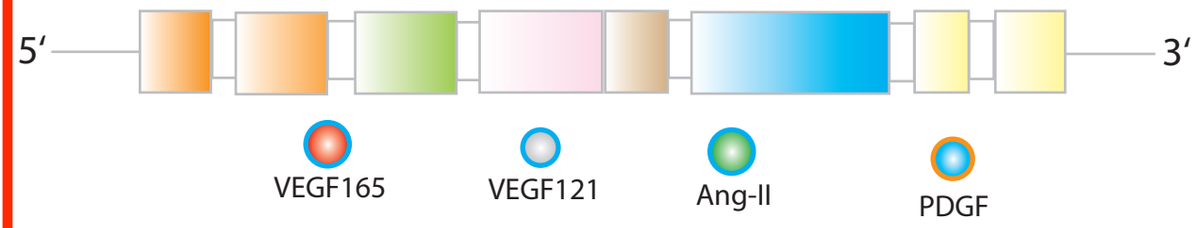

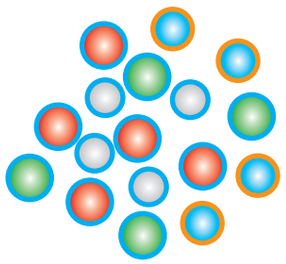

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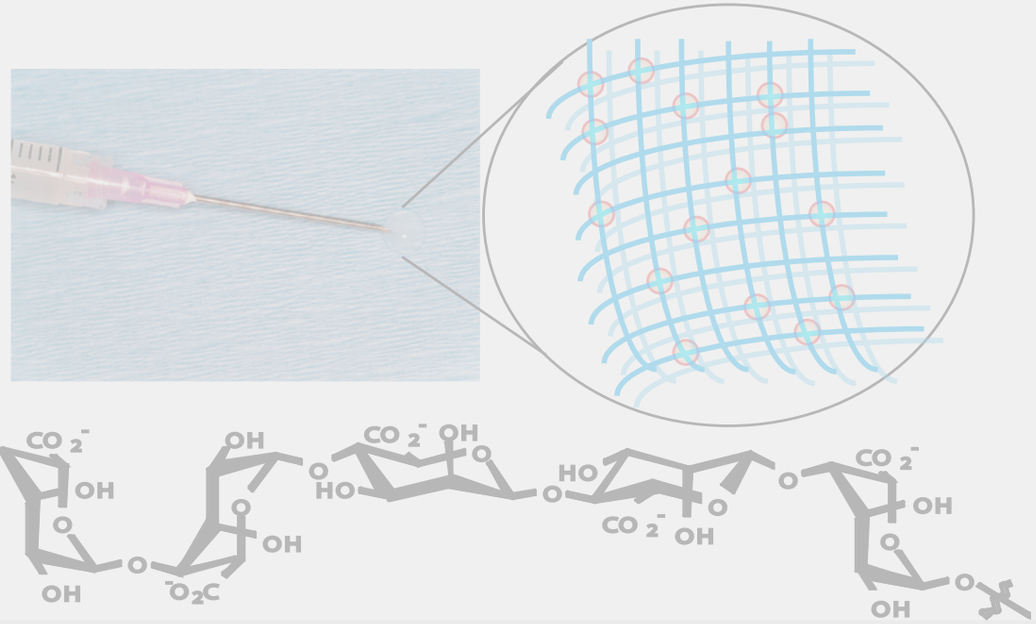

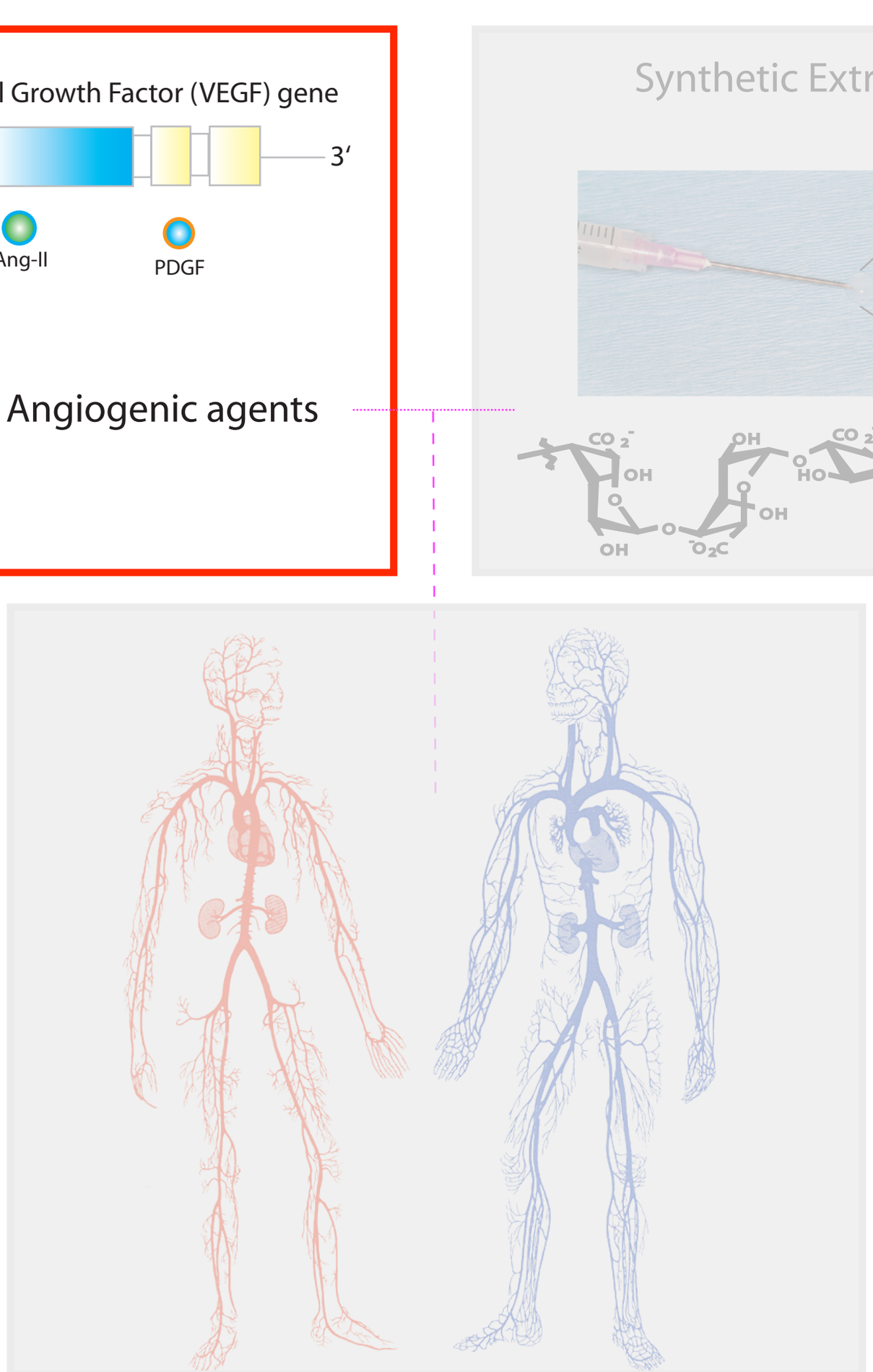

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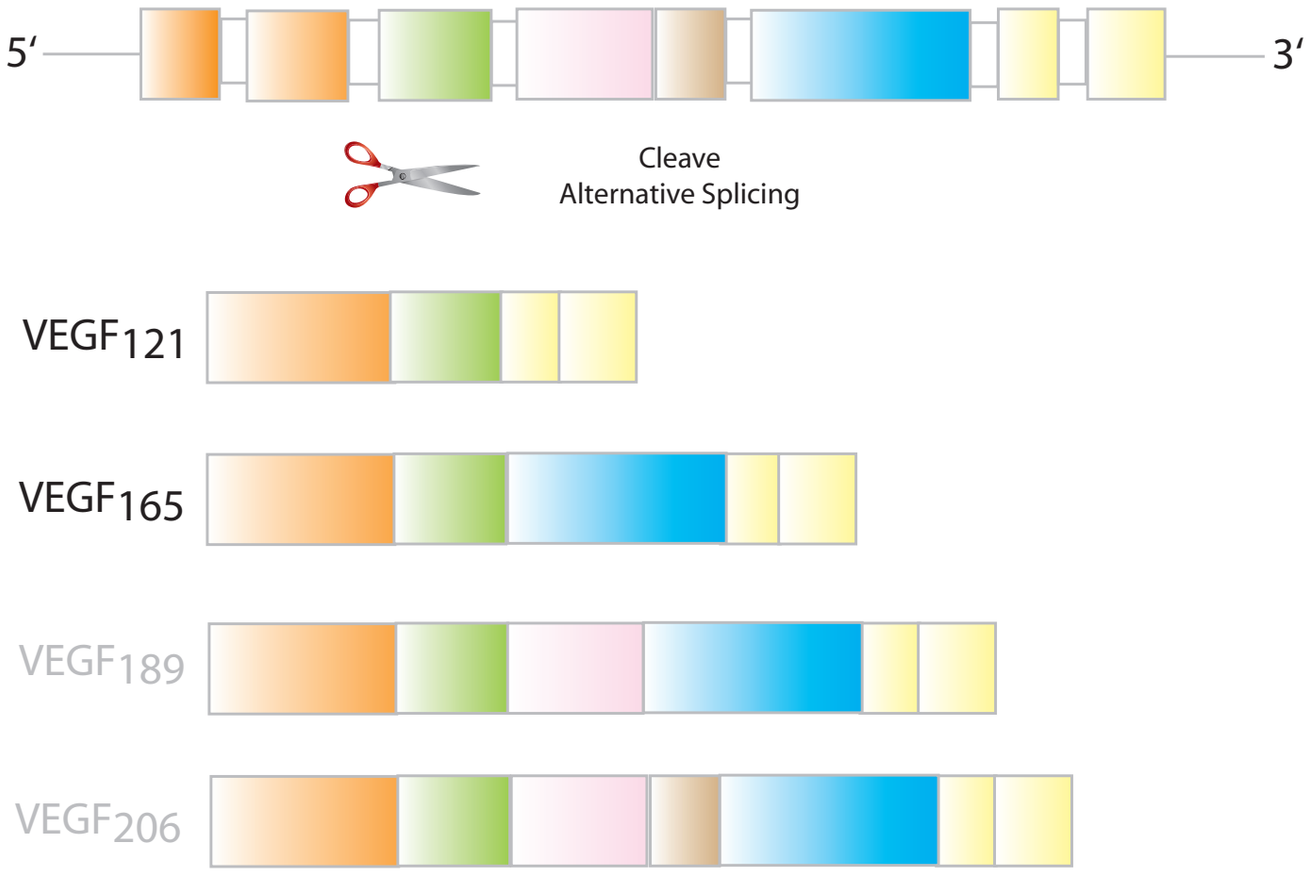
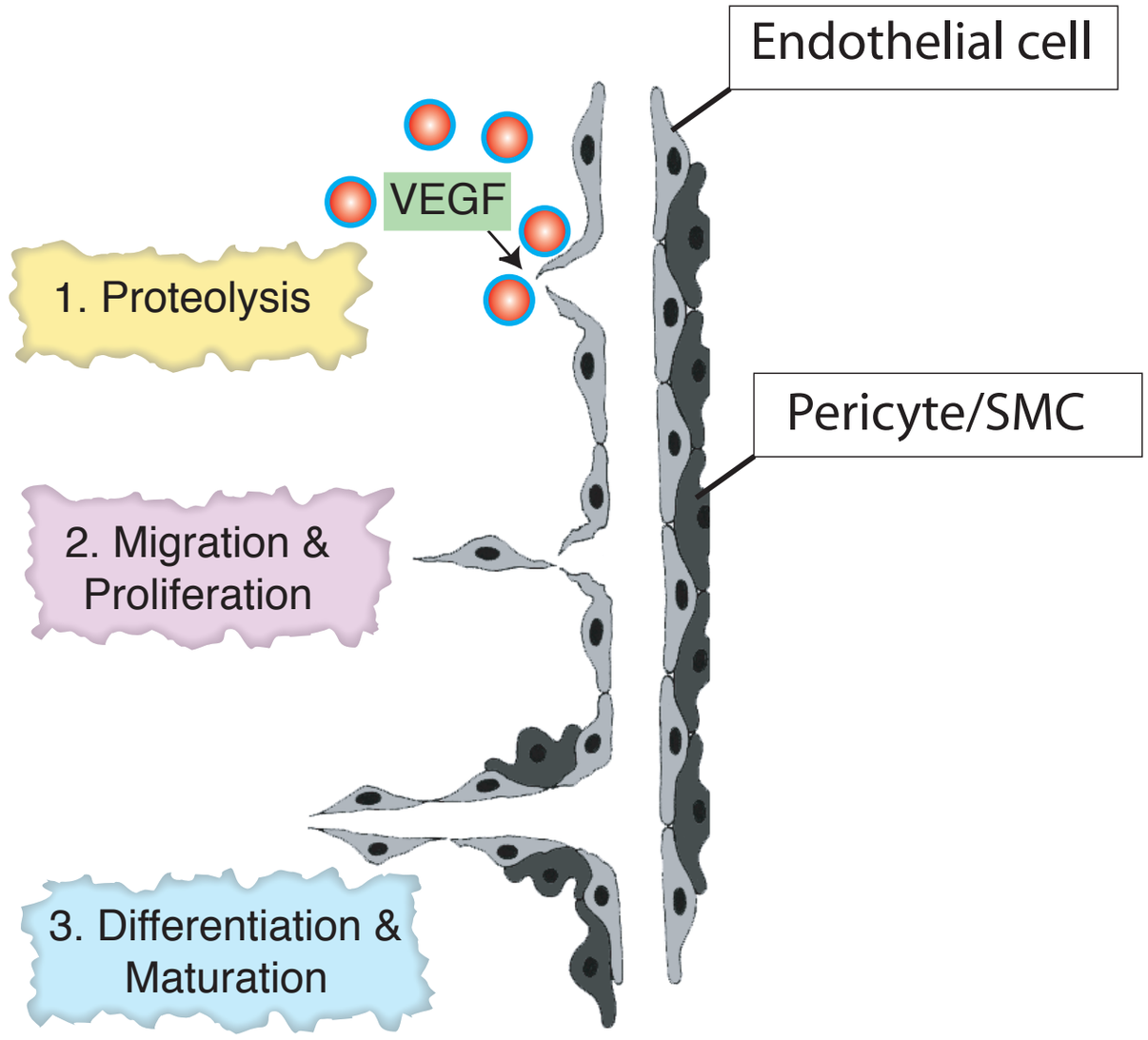
VEGF Biology

Vascular Endothelial Growth Factor (VEGF) gene



ANGIOGENESIS



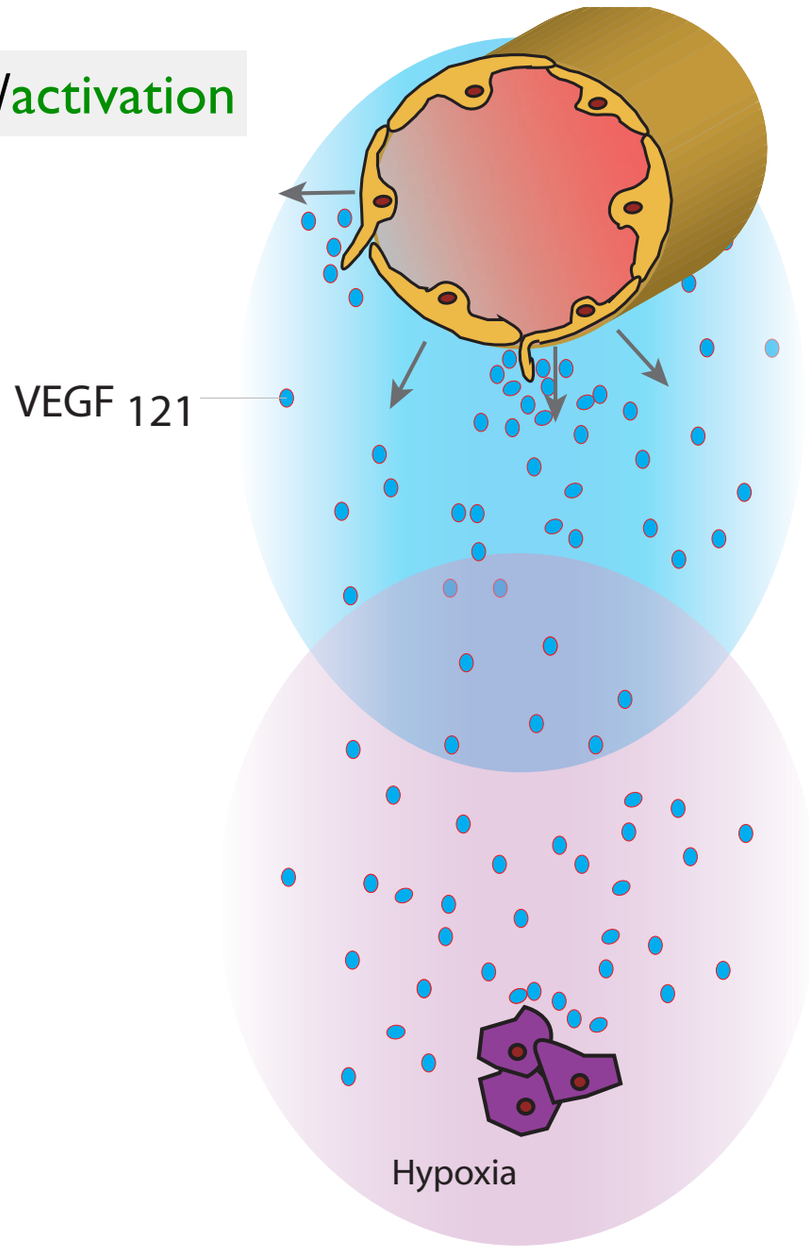
VEGF121 - not heparin-binding

$VEGF_{165}$ - heparin-binding

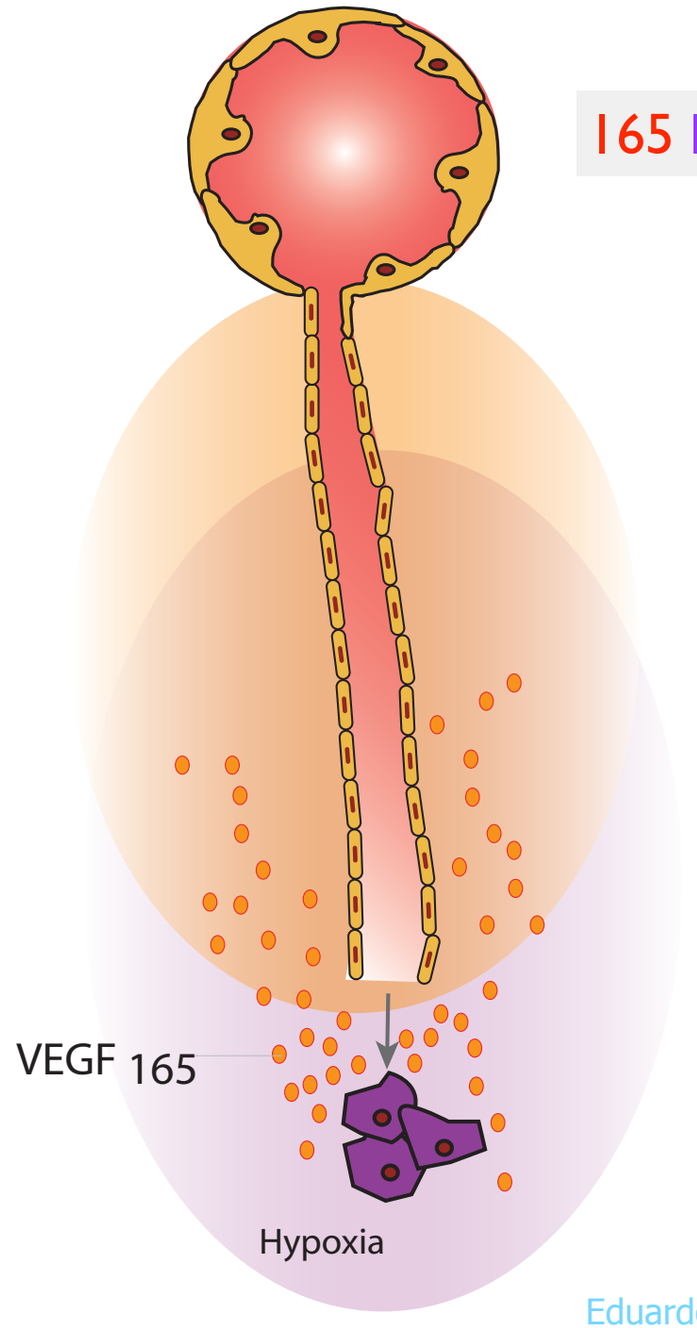
Hypothesis

Sustained and localized delivery of different angiogenic factors play distinct roles in the stimulation of collateral vessel and blood flow re-establishment in ischemic tissues

121 distant/activation



165 local/guiding



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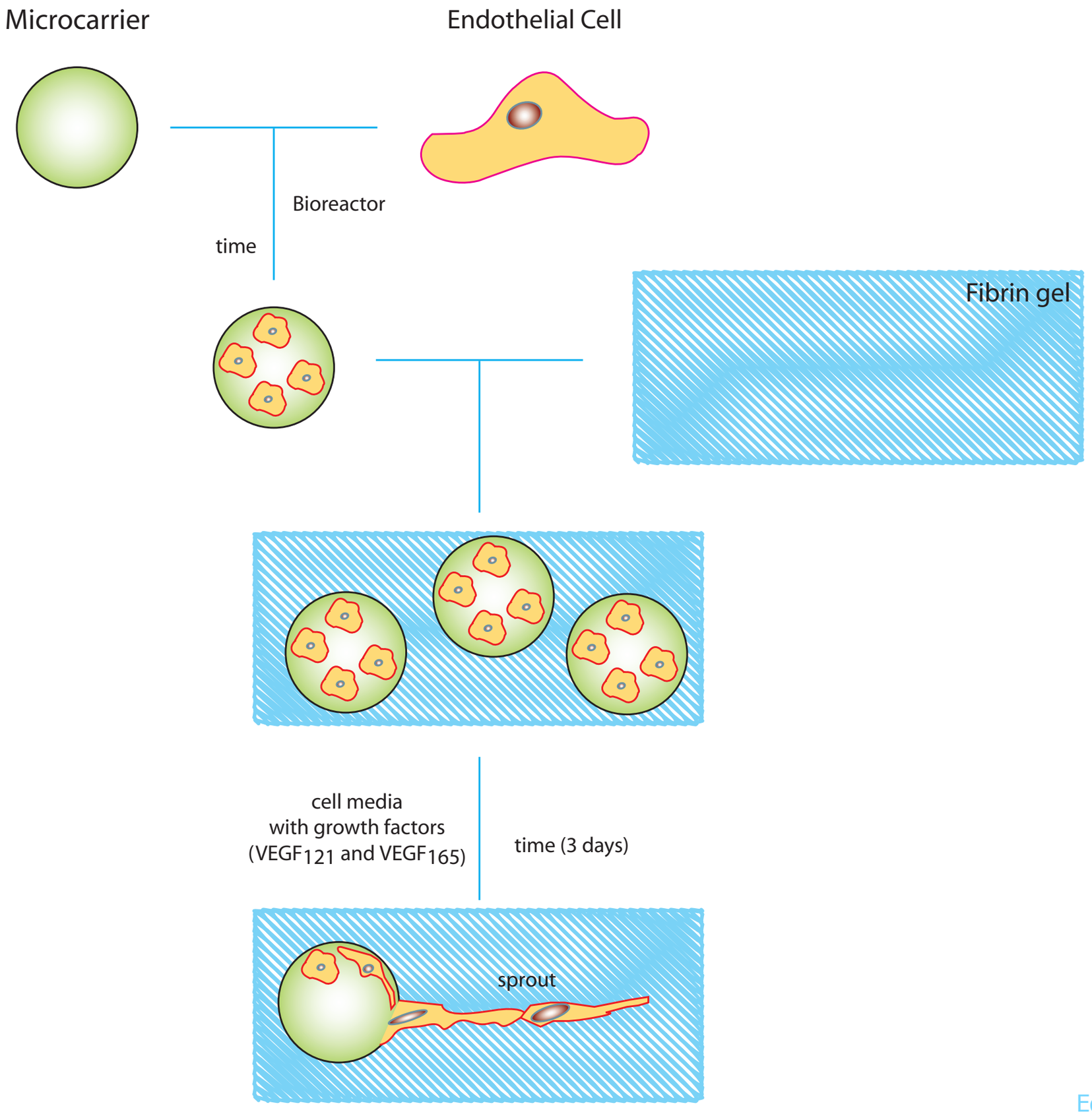
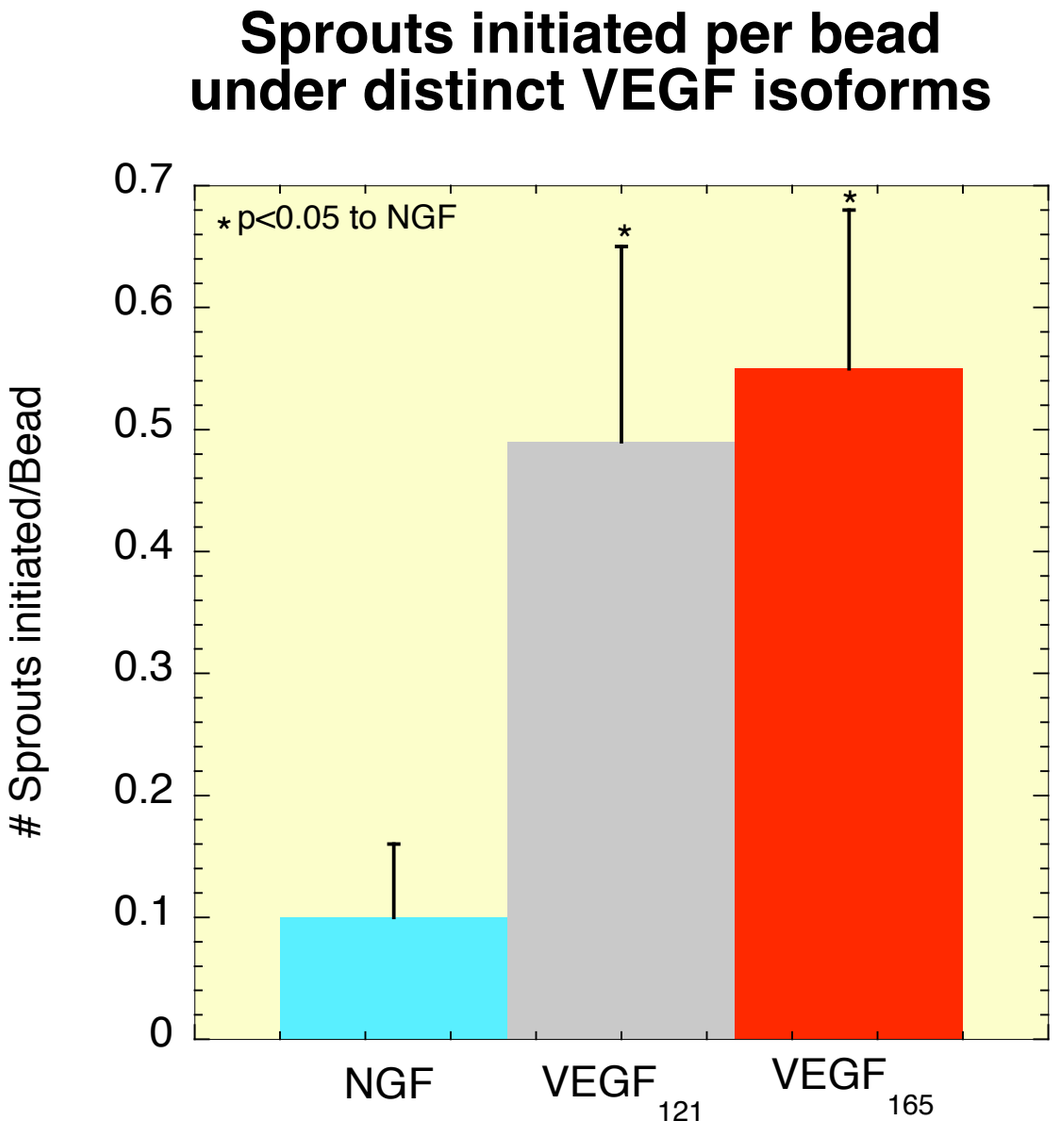
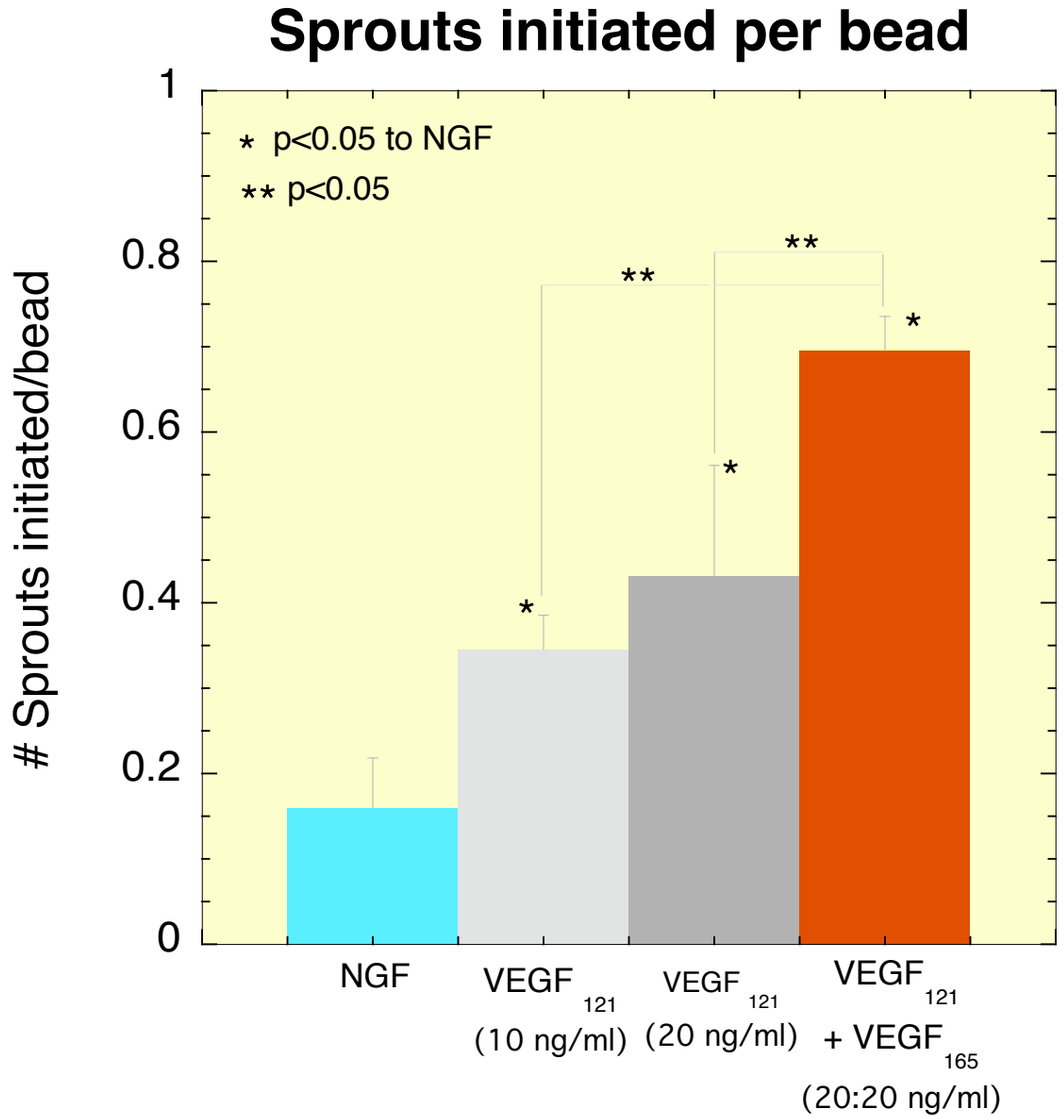
In Vitro 3D Angiogenesis Model



Angiogenesis In vitro: Sprout activation





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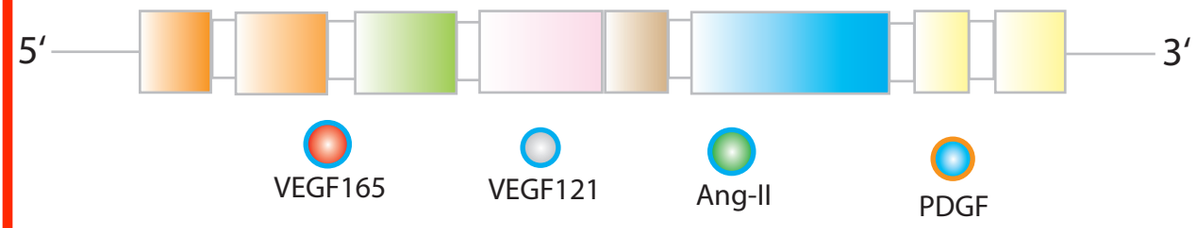

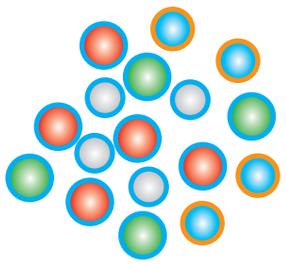

Angiogenic agents

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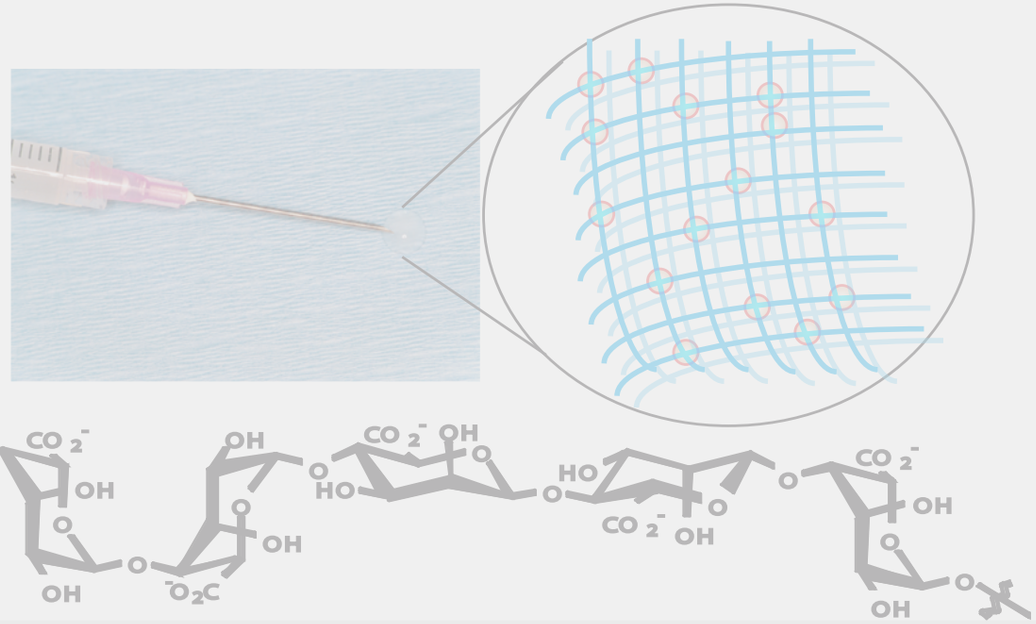

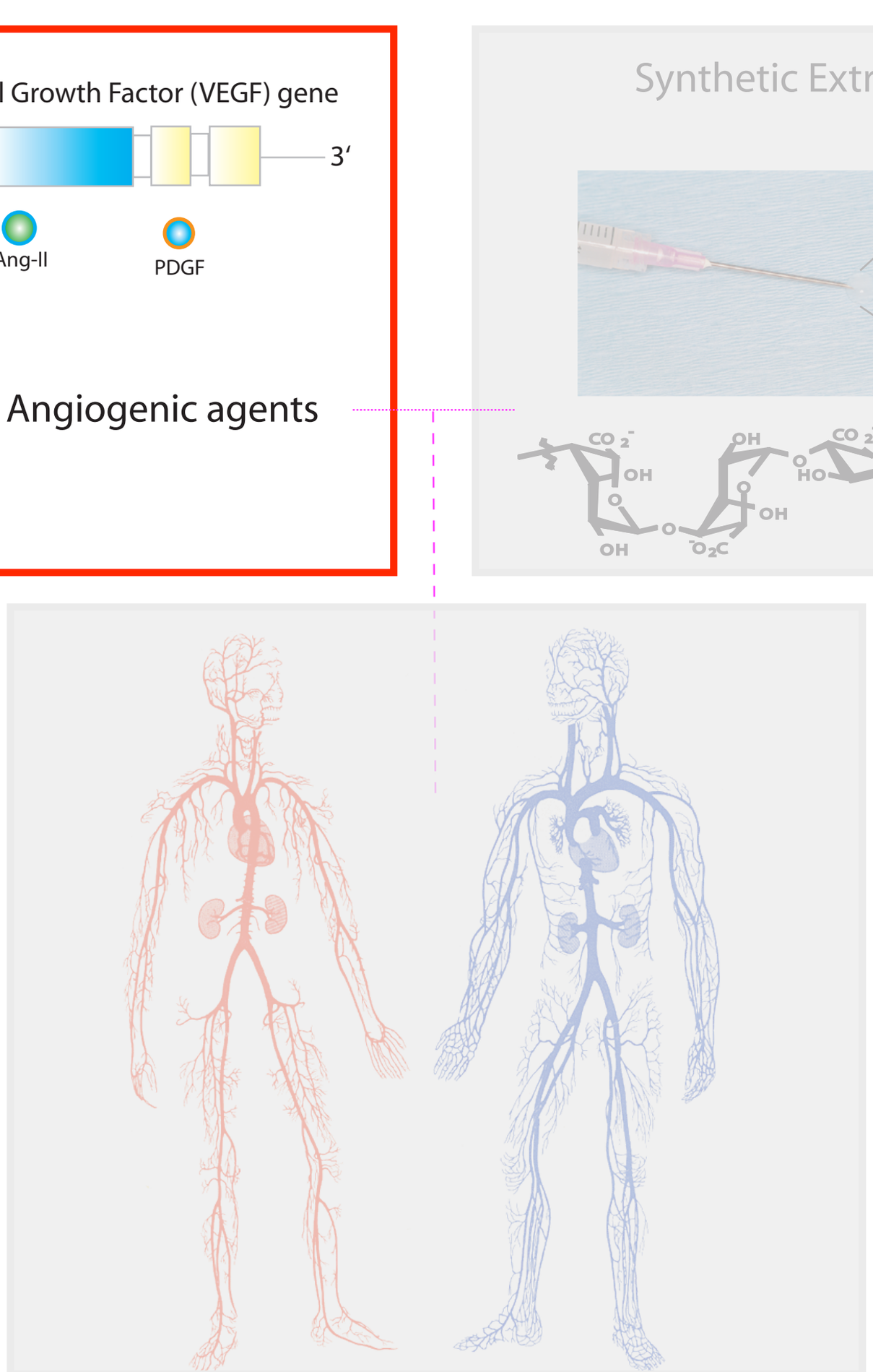

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5′ 3′

VEGF165 VEGF121 Ang-II PDGF

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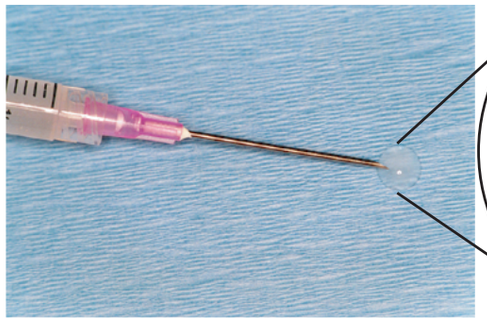

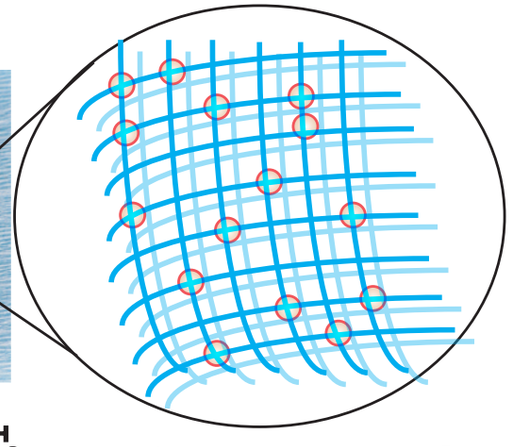

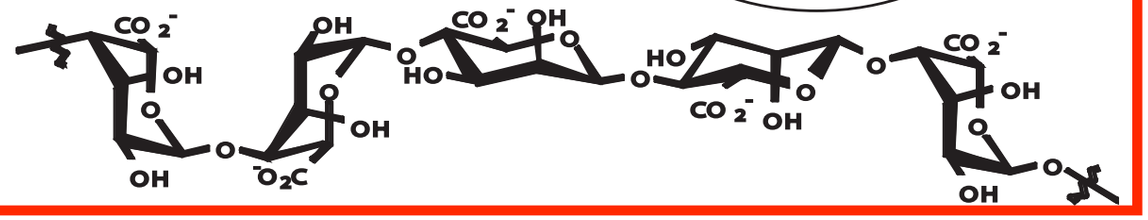

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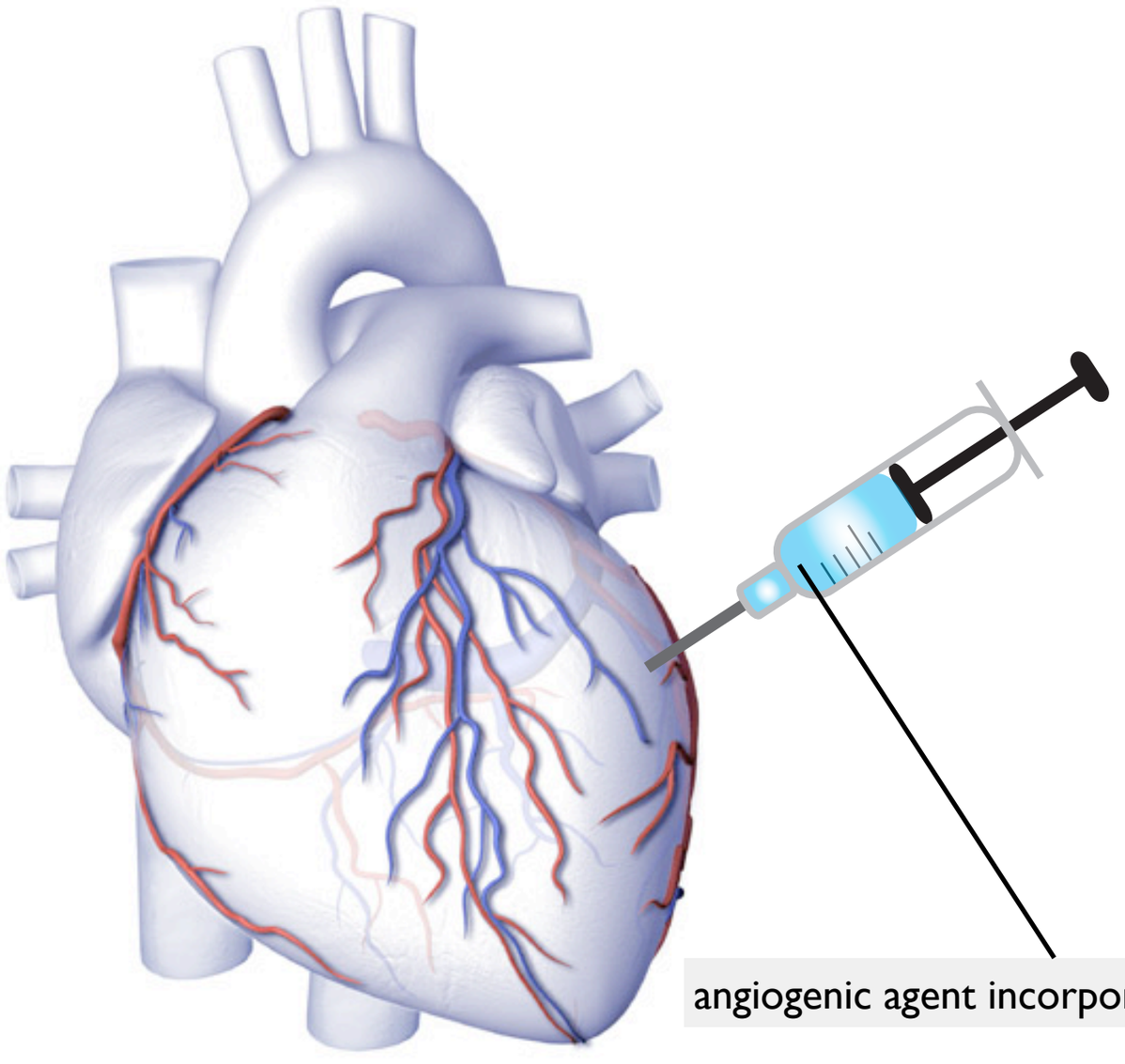
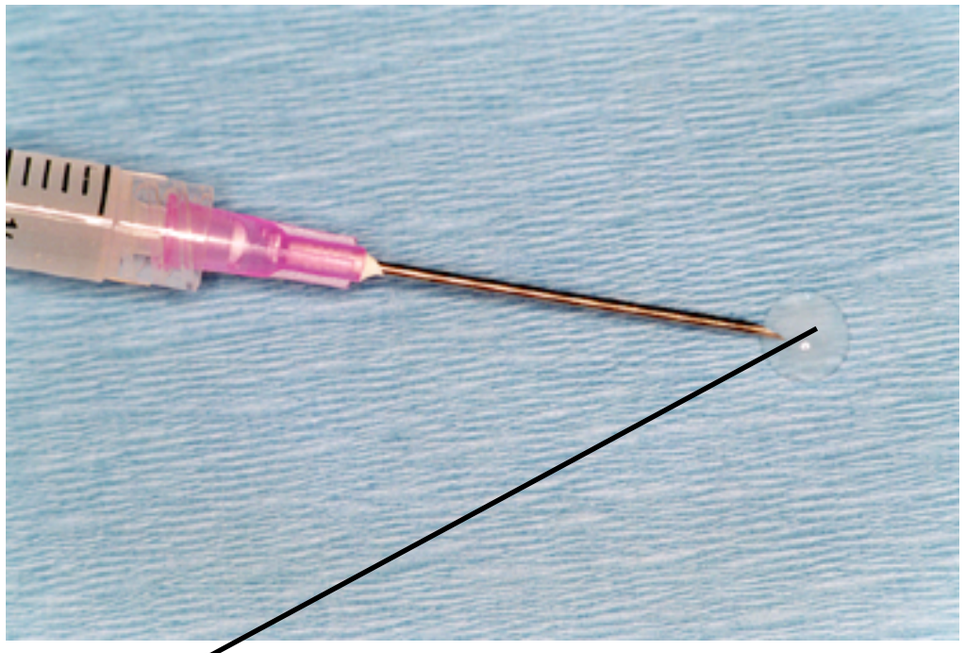
Engineering aim

Development of an injectable polymeric system for controlled and defined delivery of angiogenic agents

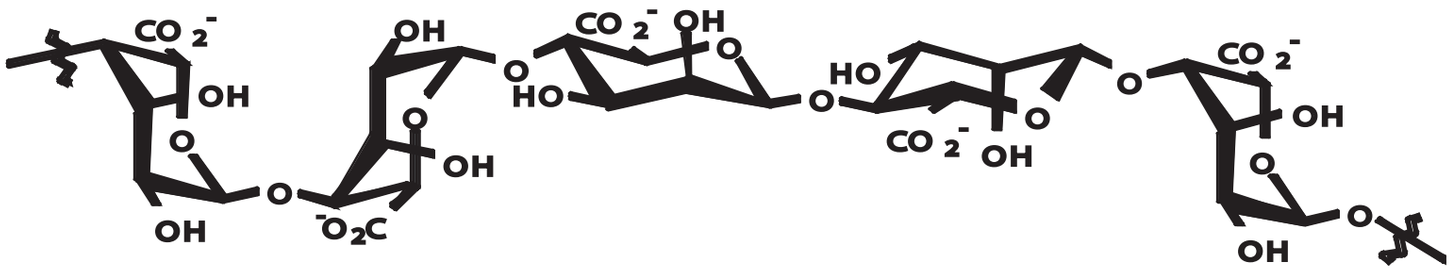




angiogenic agent incorporated in an injectable polymer

Polymeric System

ALGINATE



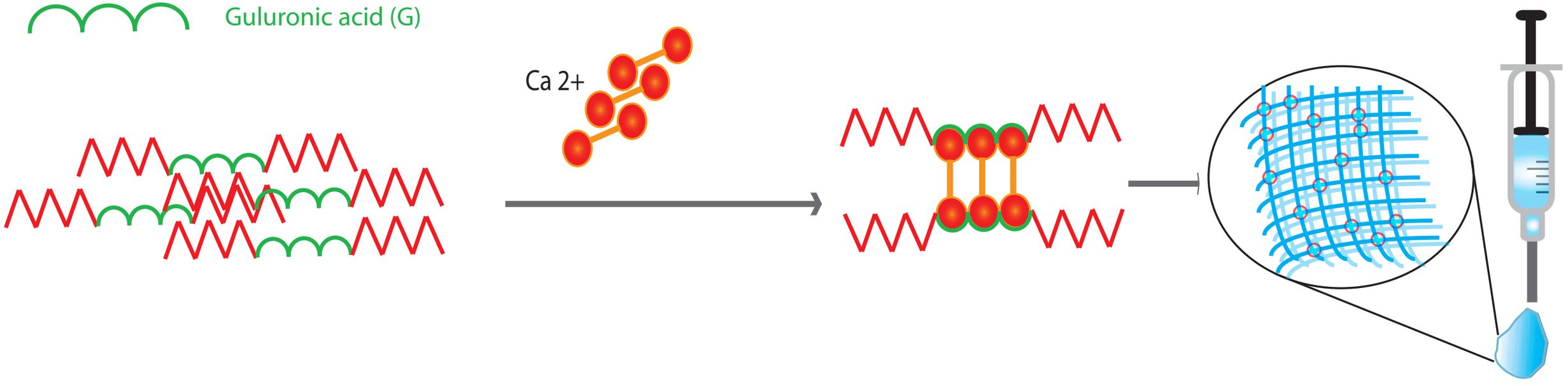
G G M M G

Mannuronic acid (M)

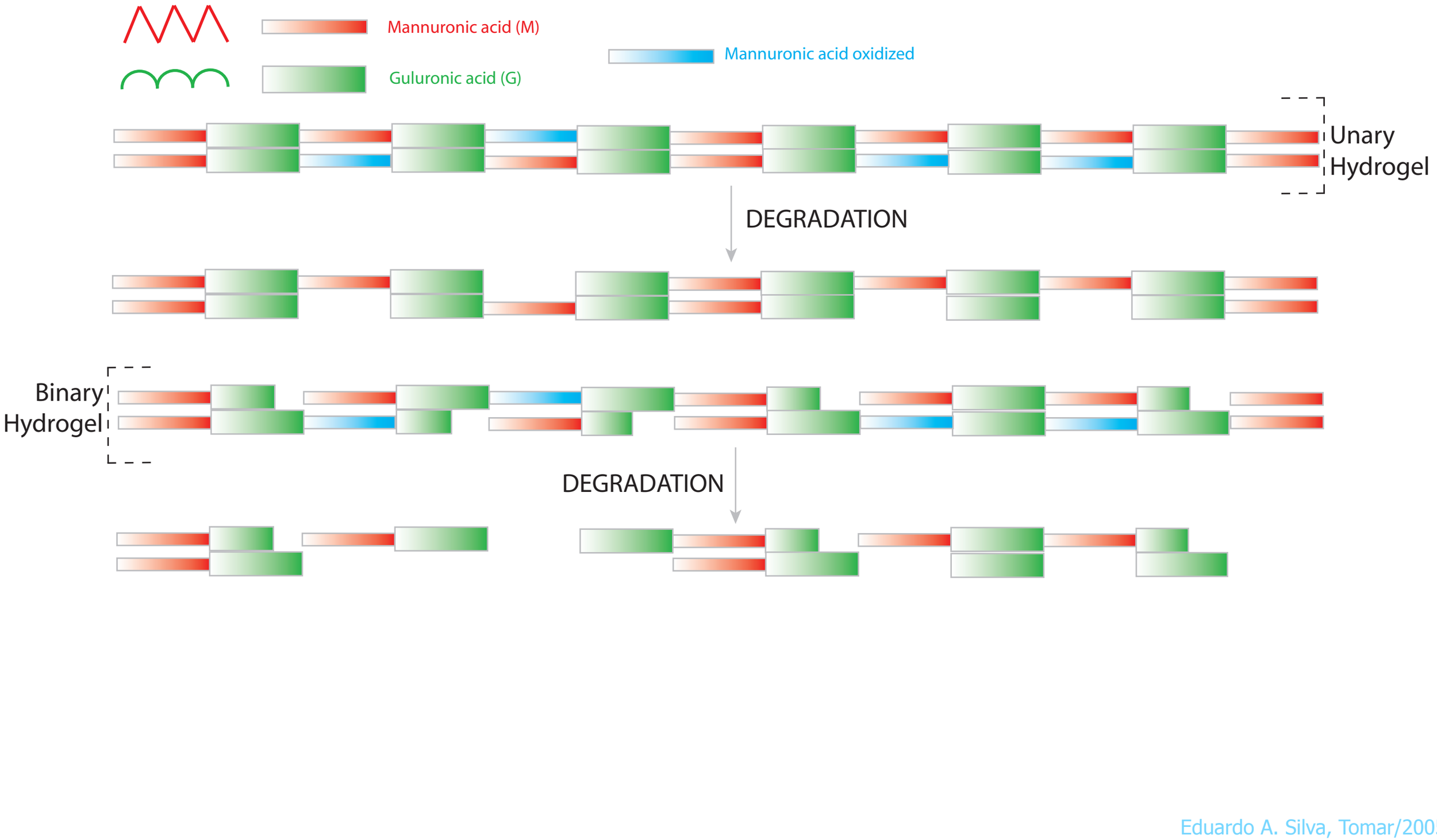
Guluronic acid (G)

Biocompatible
Drug/cell vehicle delivery
Non degradable

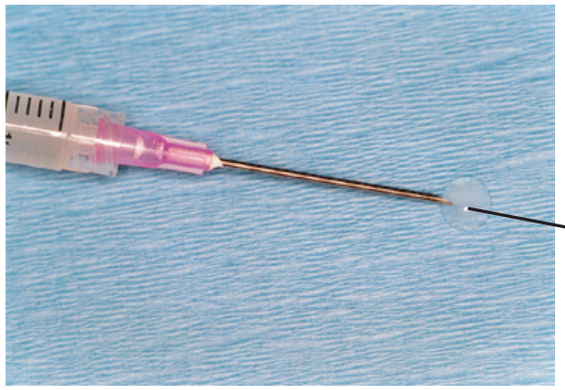
Alginate GEL



Alginate Modifications

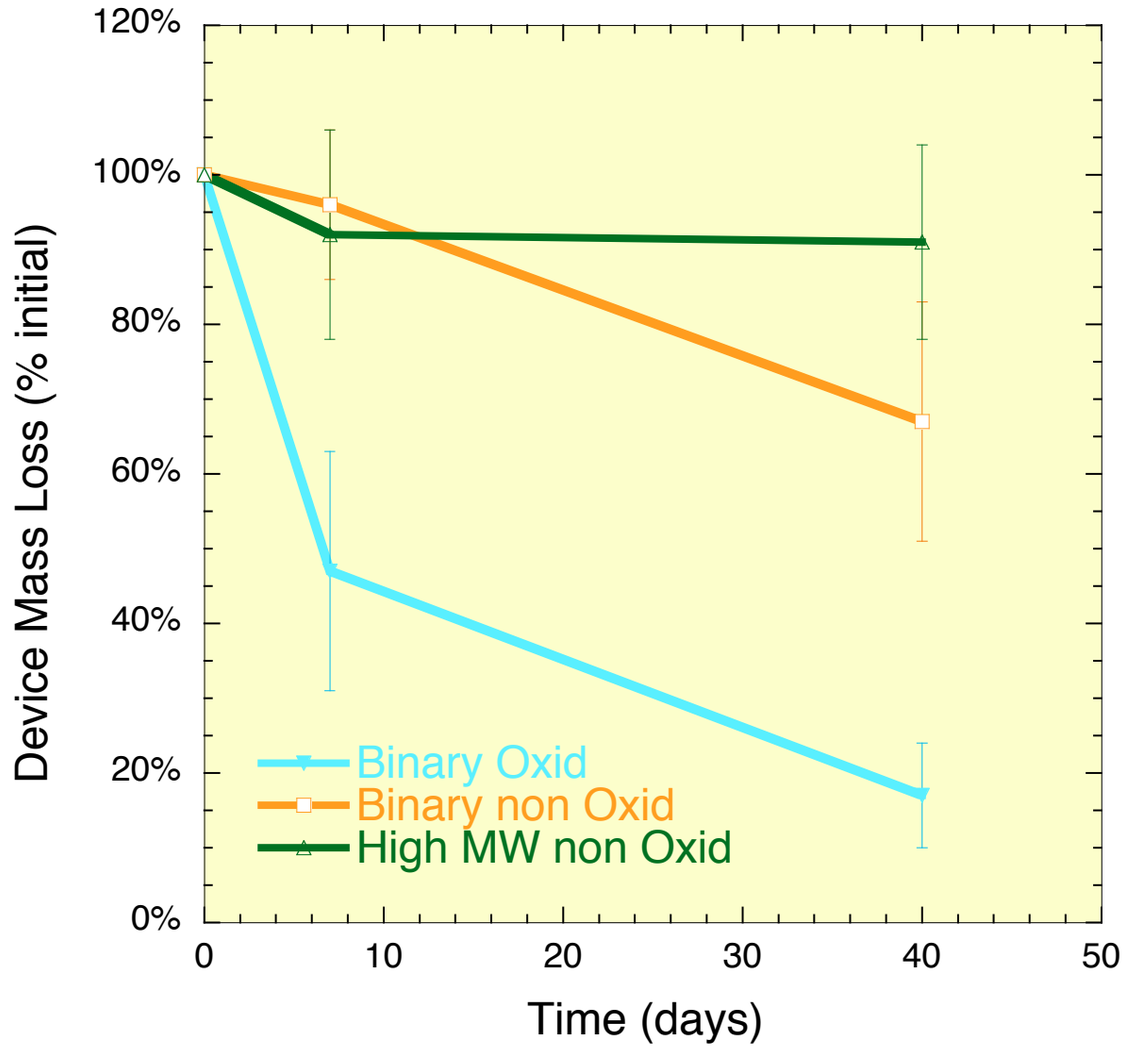


Alginate Properties

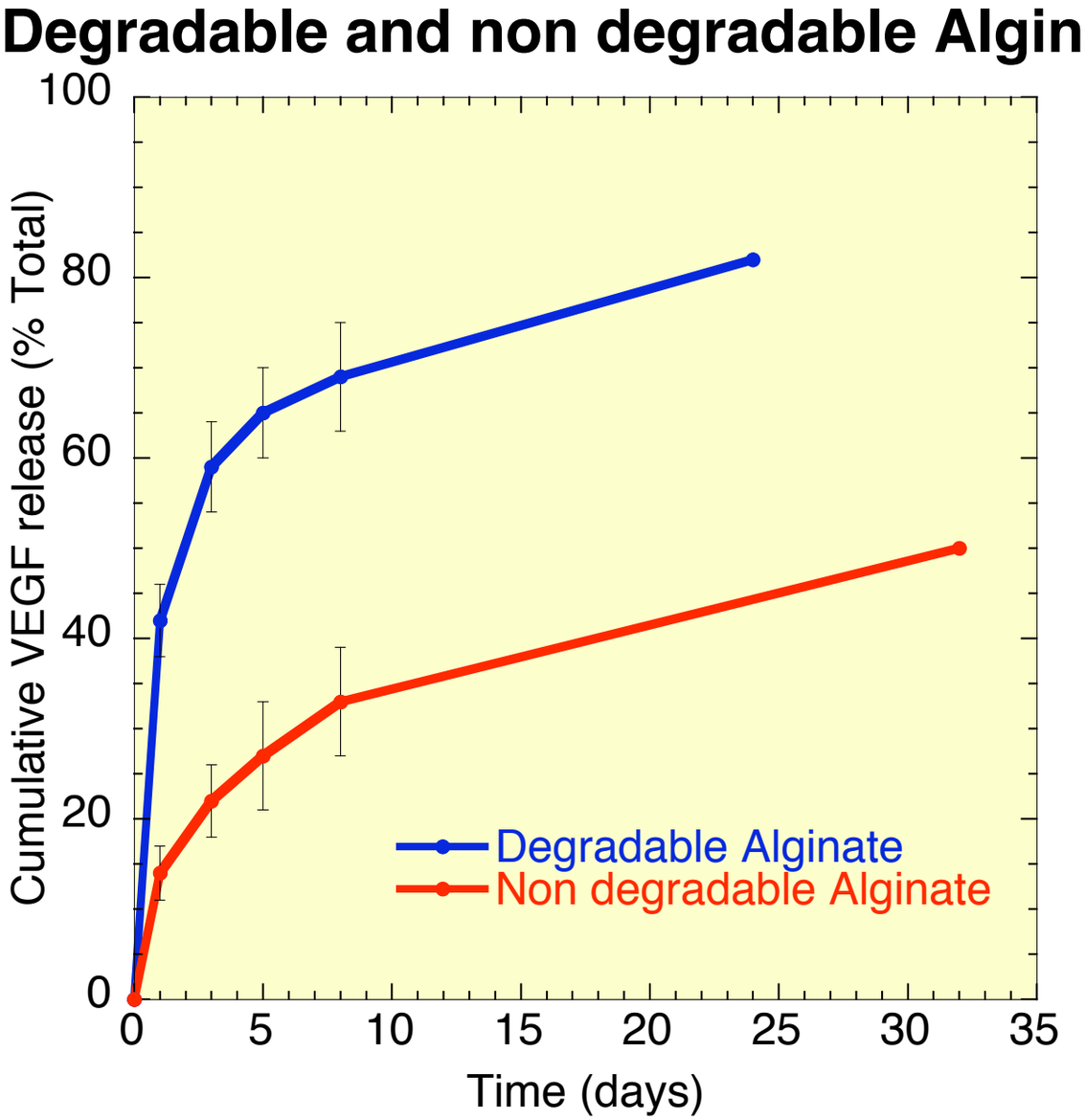


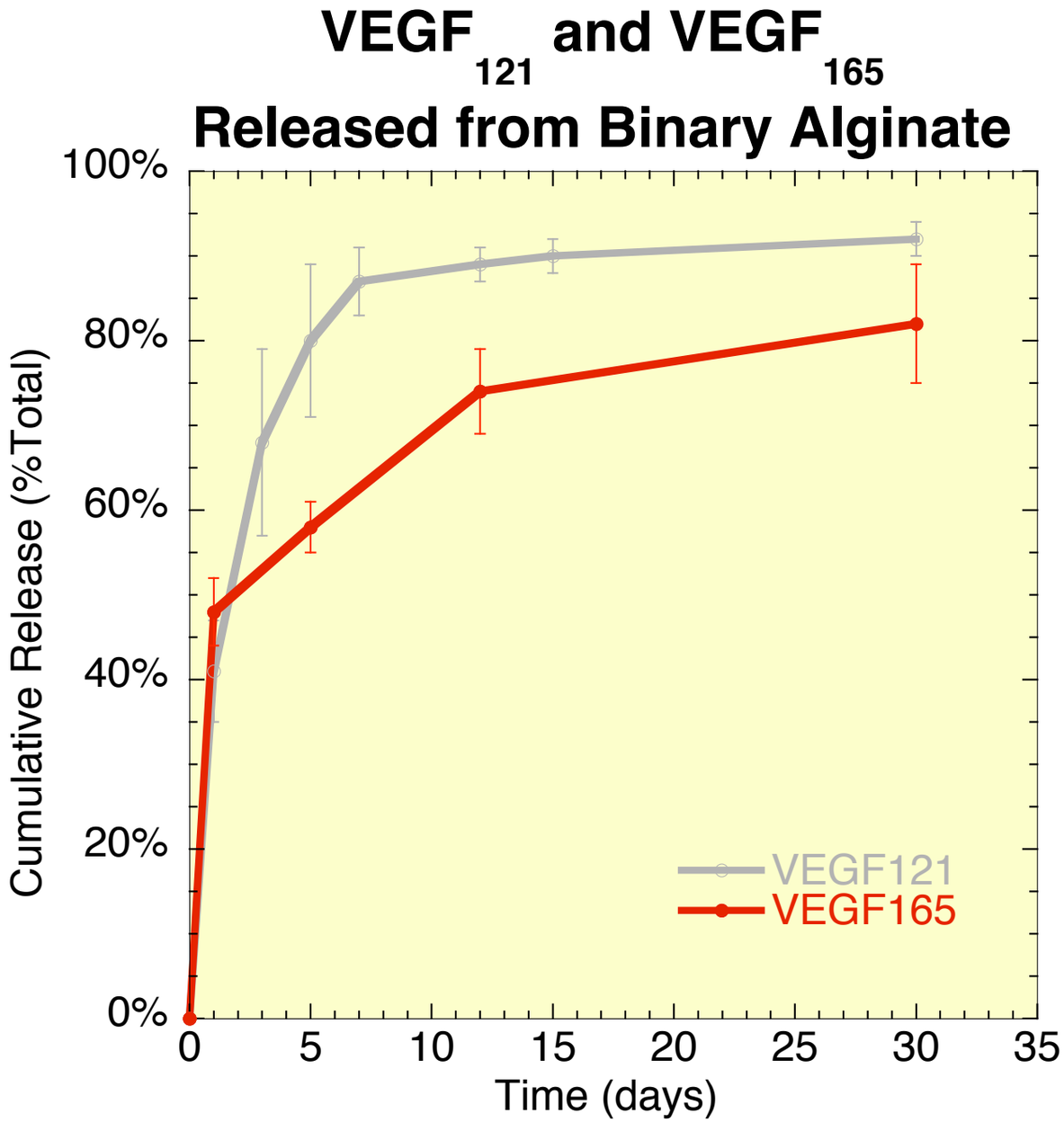
	(Relative %)	Mw (Kg/mol)
High Molecular Weight (25%)		± 250
low Molecular Weight (75%)		± 50

Alginate Hydrogel
(Binary Molecular Weight Distribution)



Manipulating VEGF Release





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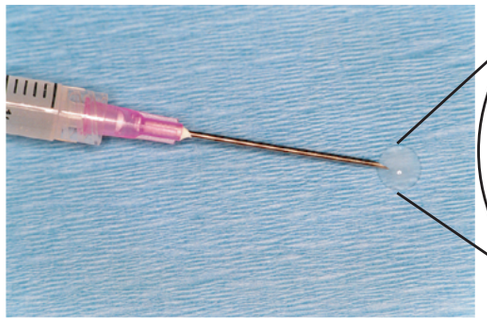

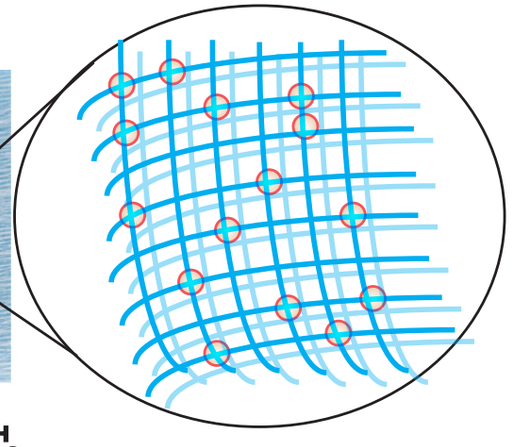

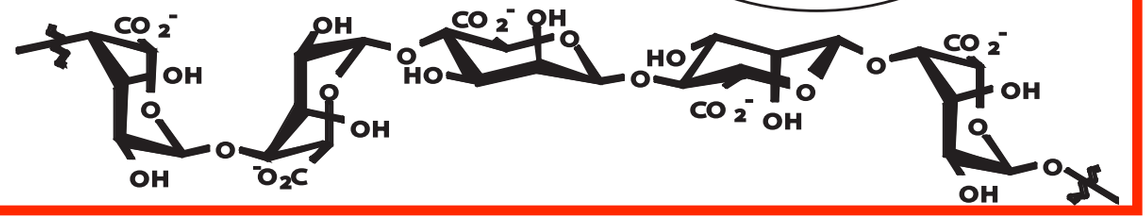

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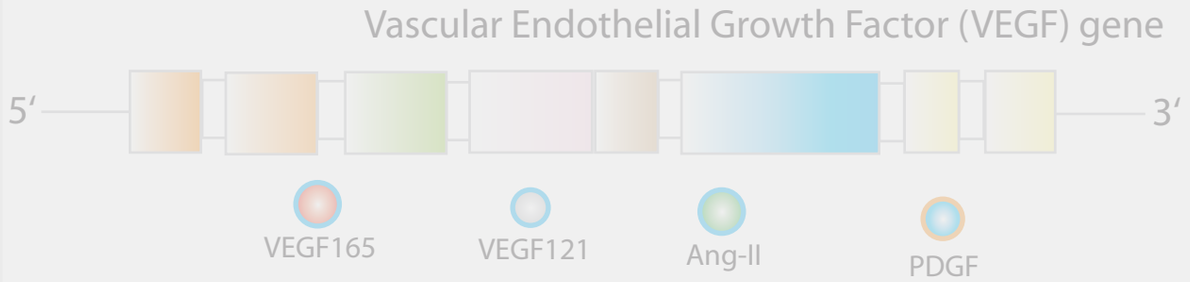

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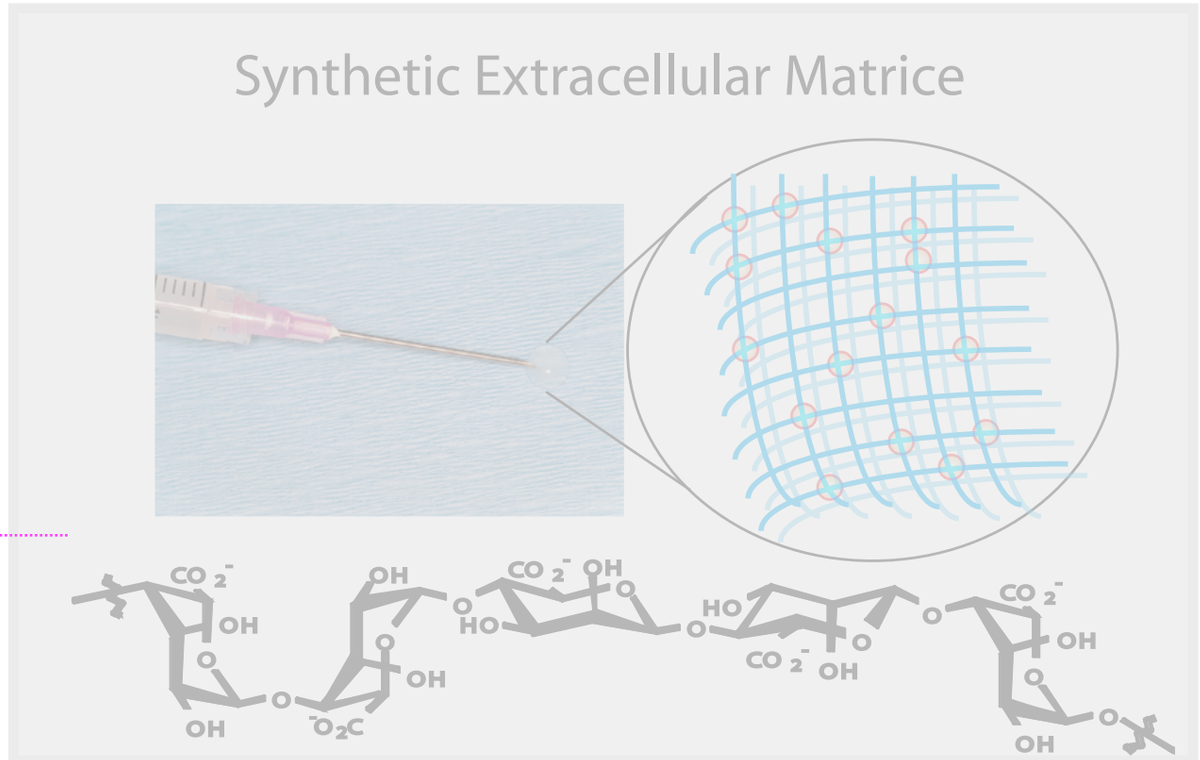
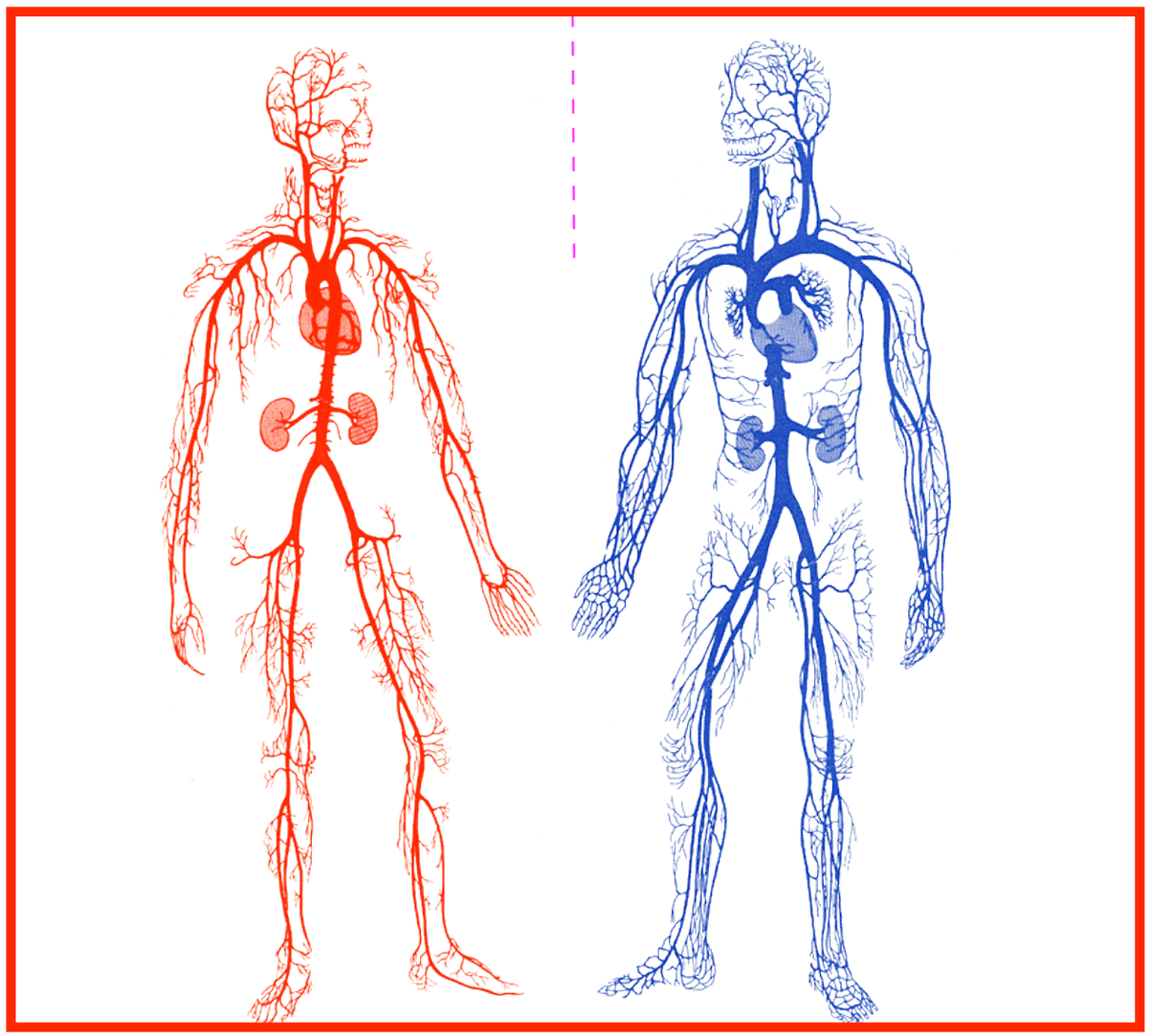
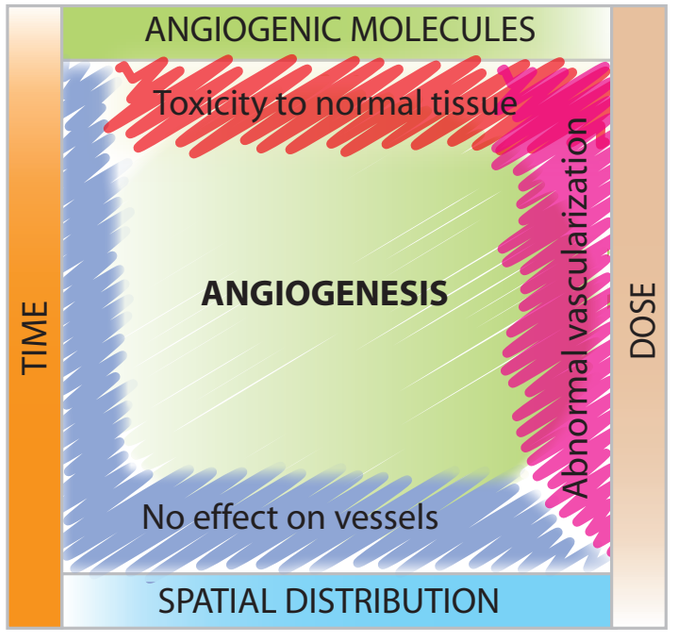
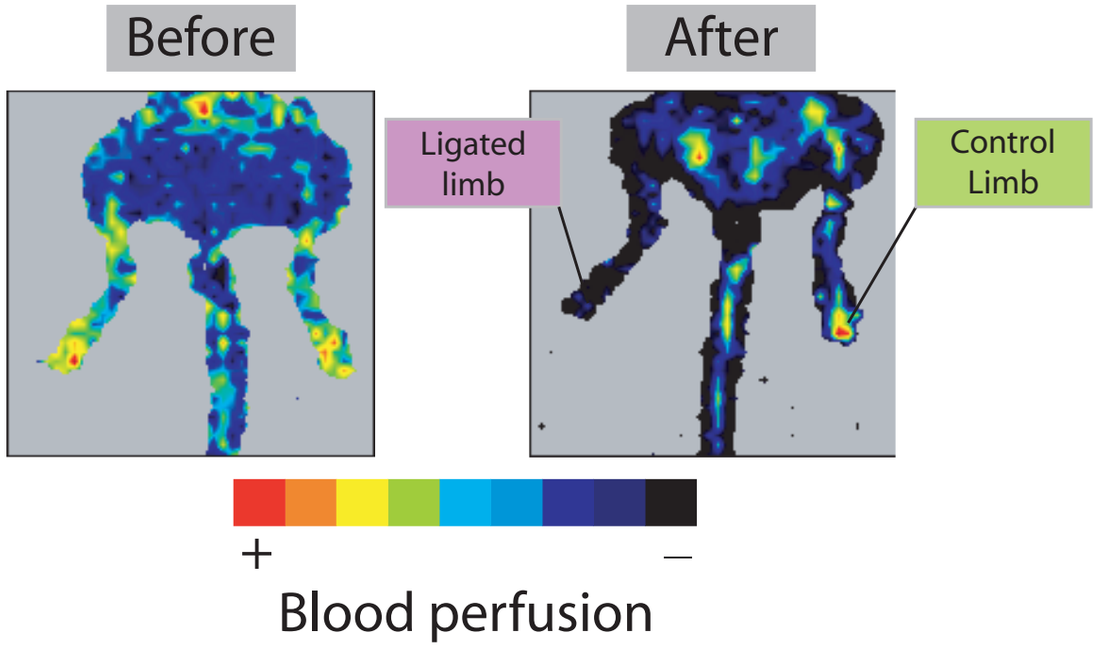




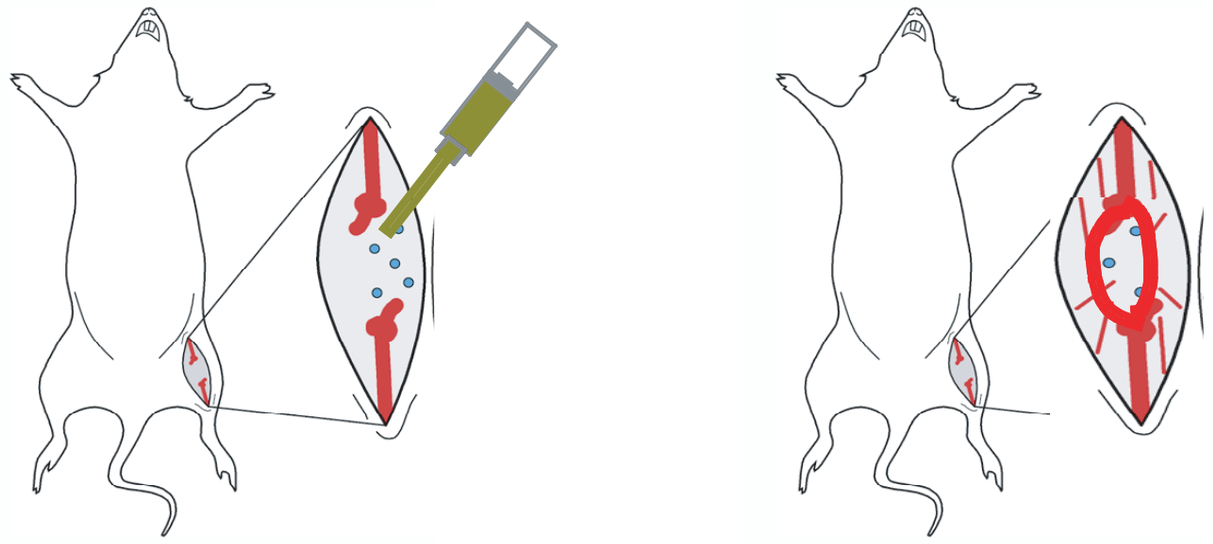
Angiogenesis *In vivo:* Technical Approach



Laser Doppler Perfusion Imaging system (LDPI)



ApoE -/- Ischemic HindLimb Model



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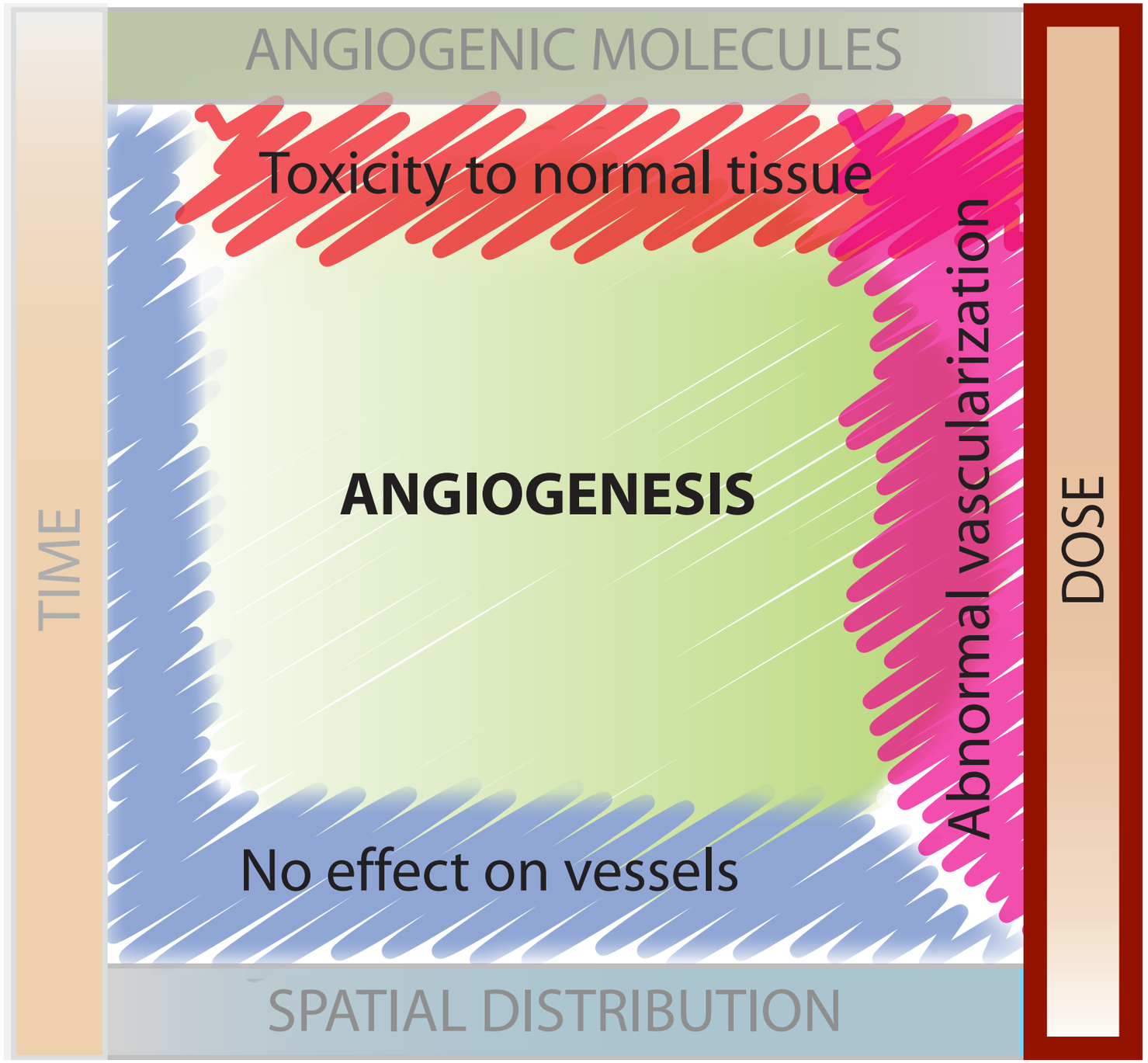
Angiogenesis: Normalization Window - Dose



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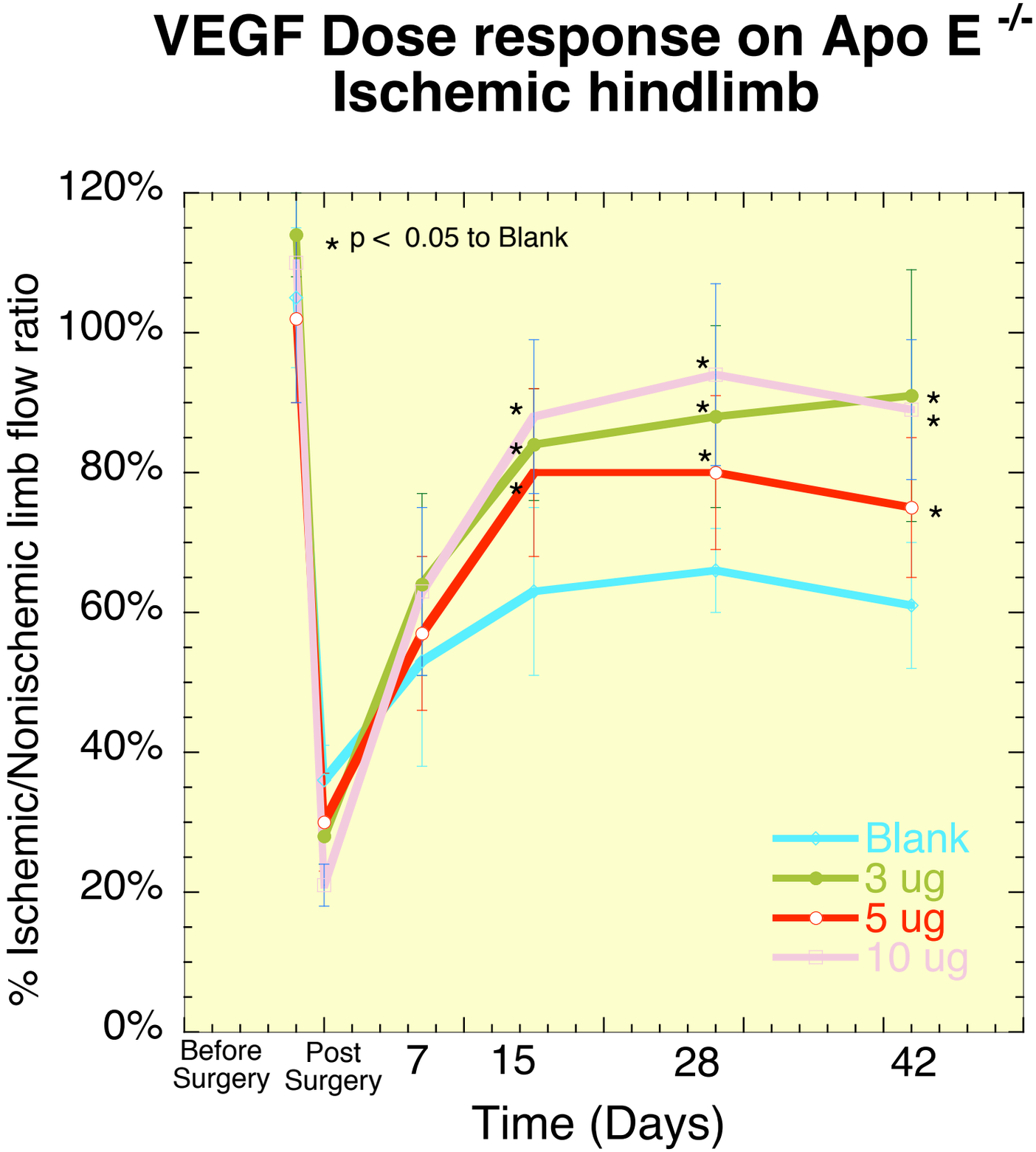
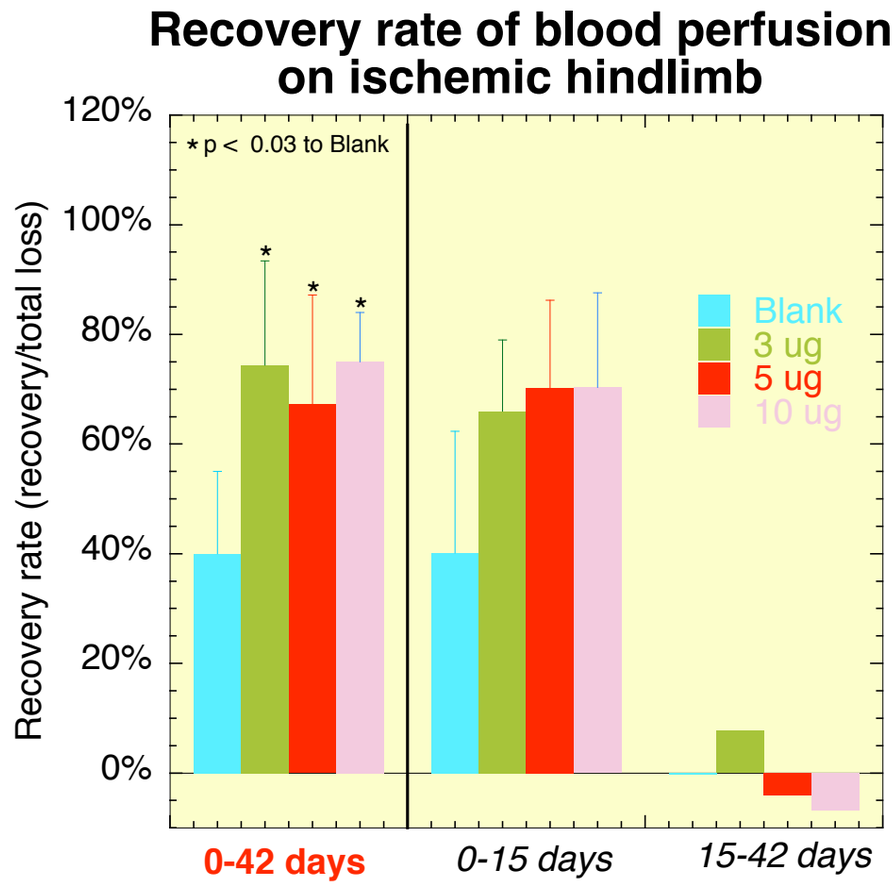
Angiogenesis *In vivo:* Dose Dependence





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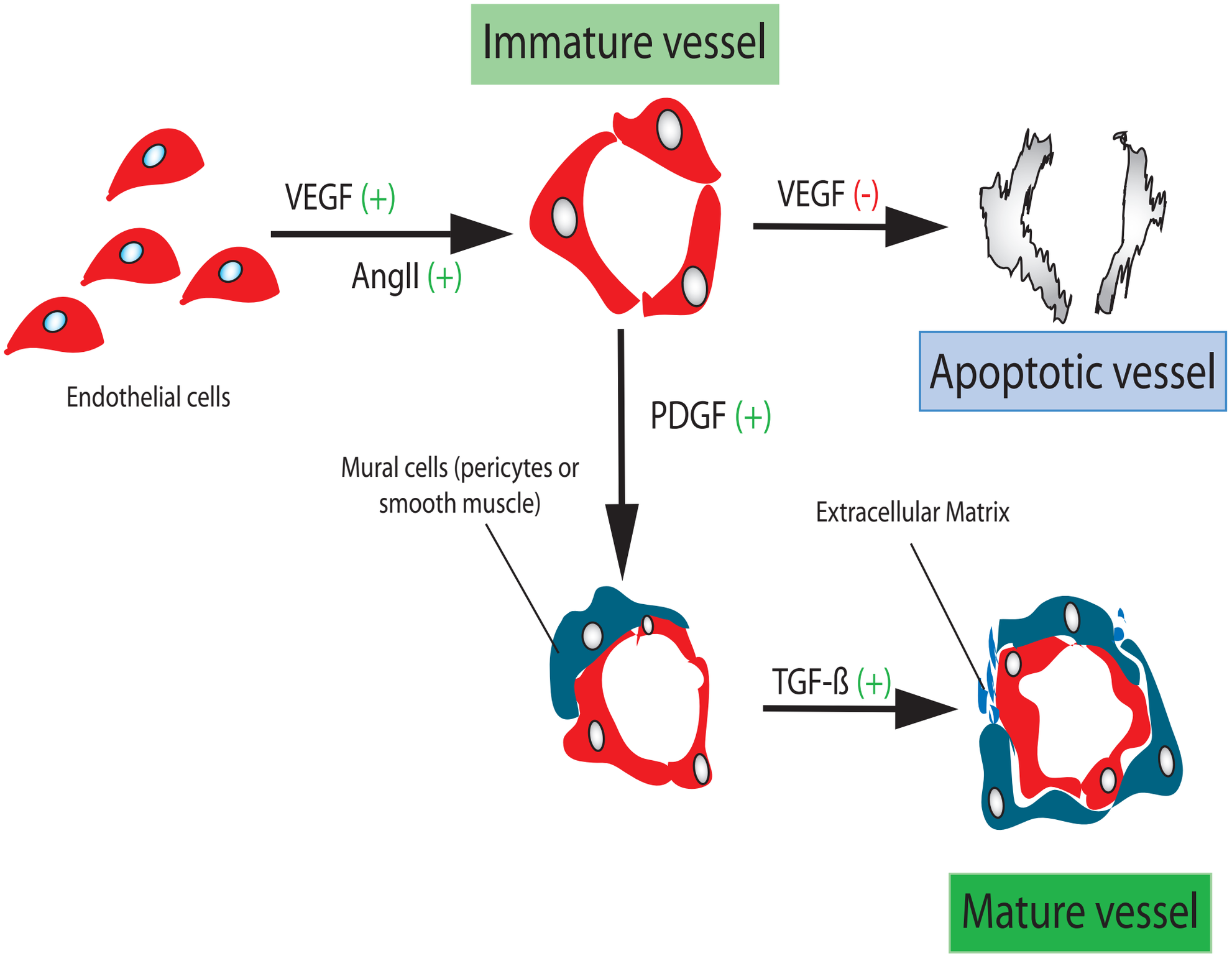
Angiogenesis: Early events...



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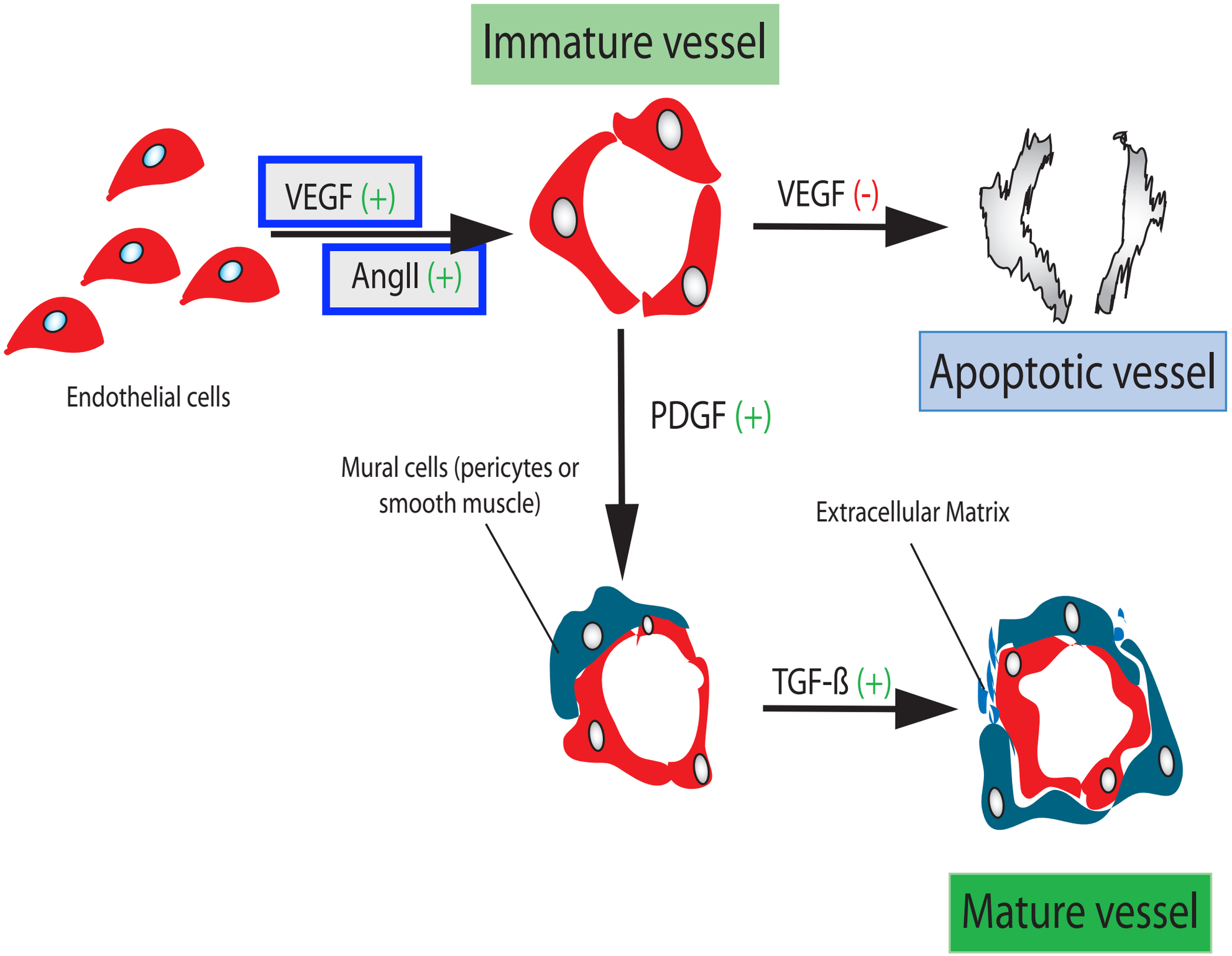
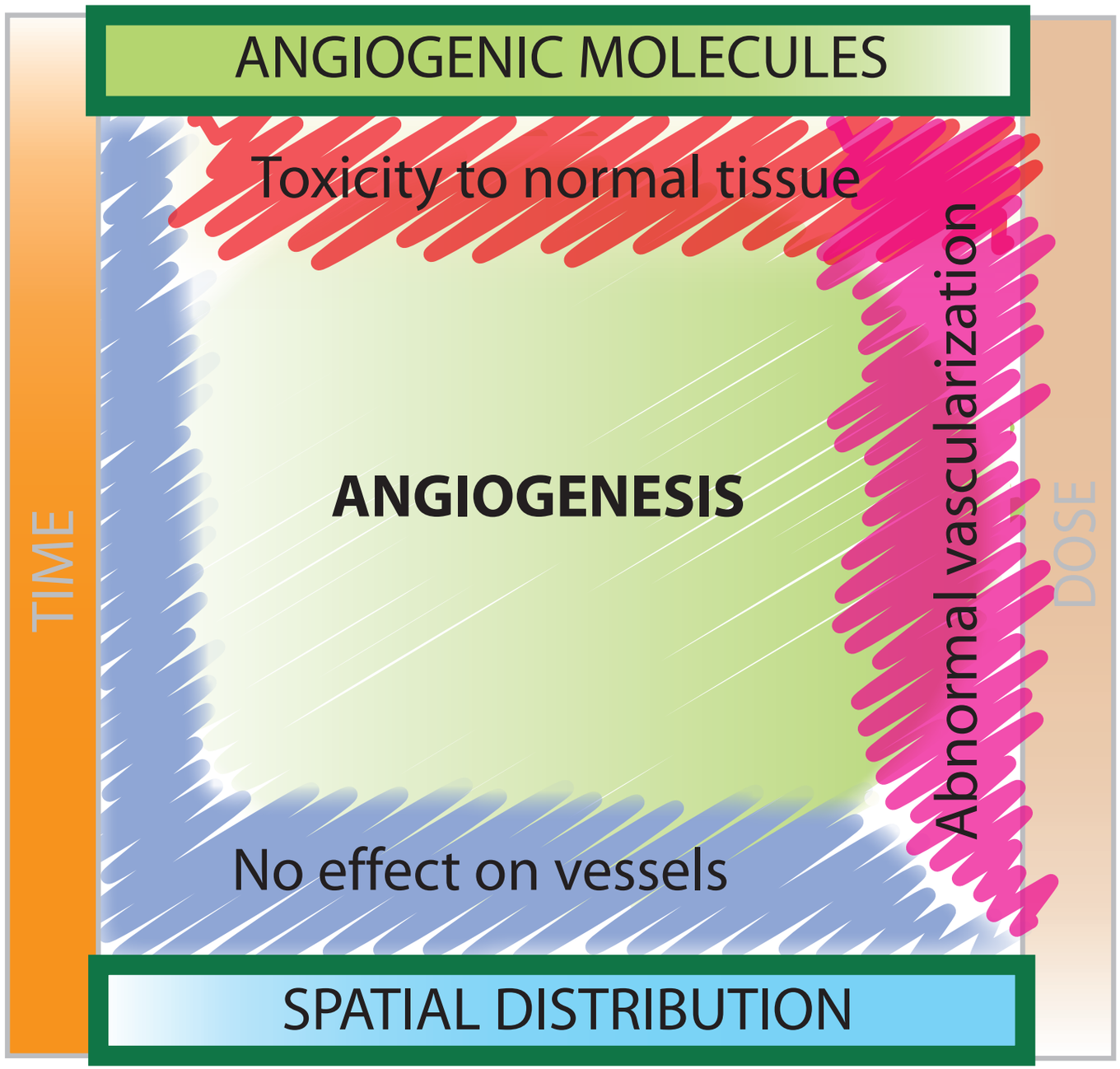


Angiogenesis :Normalization Window



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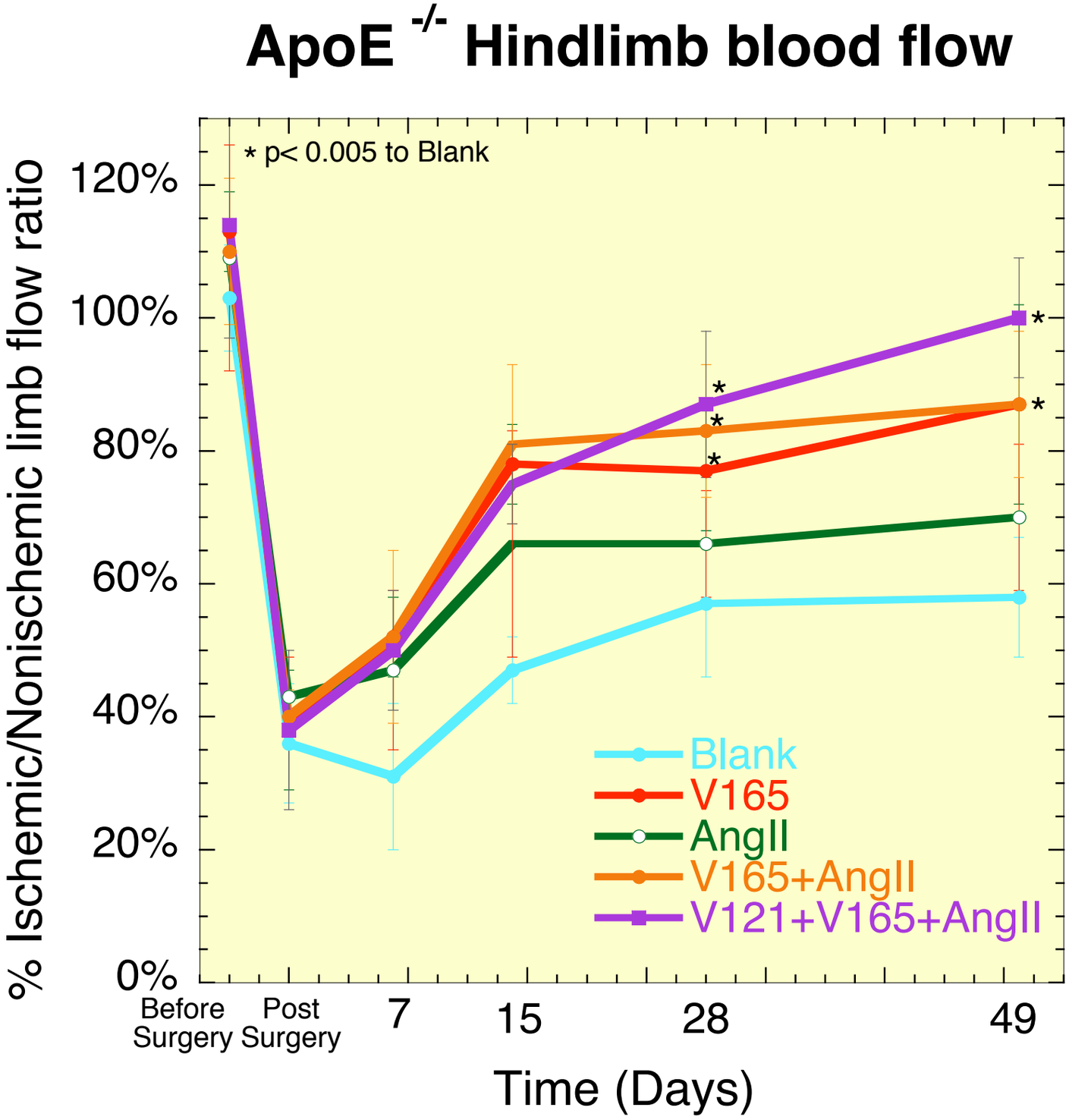
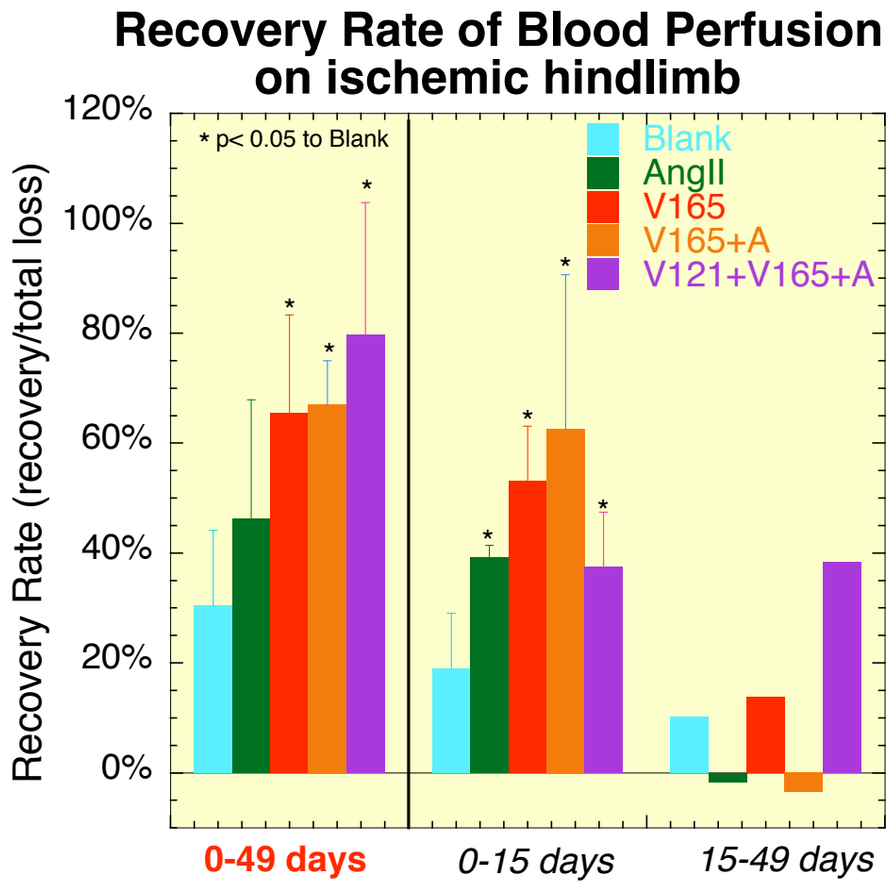
Angiogenesis *In vivo*: Mimicking Early Mechanisms





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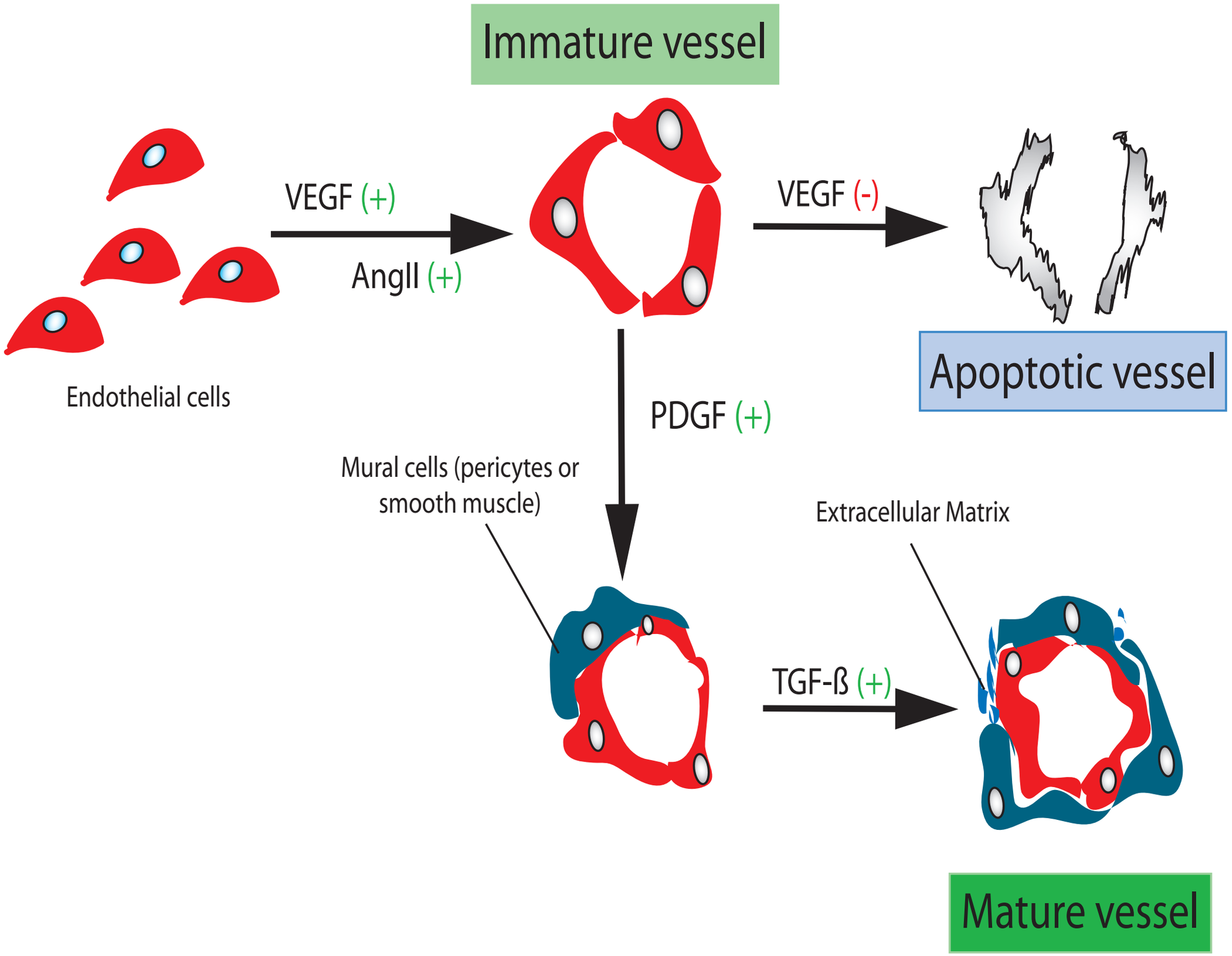
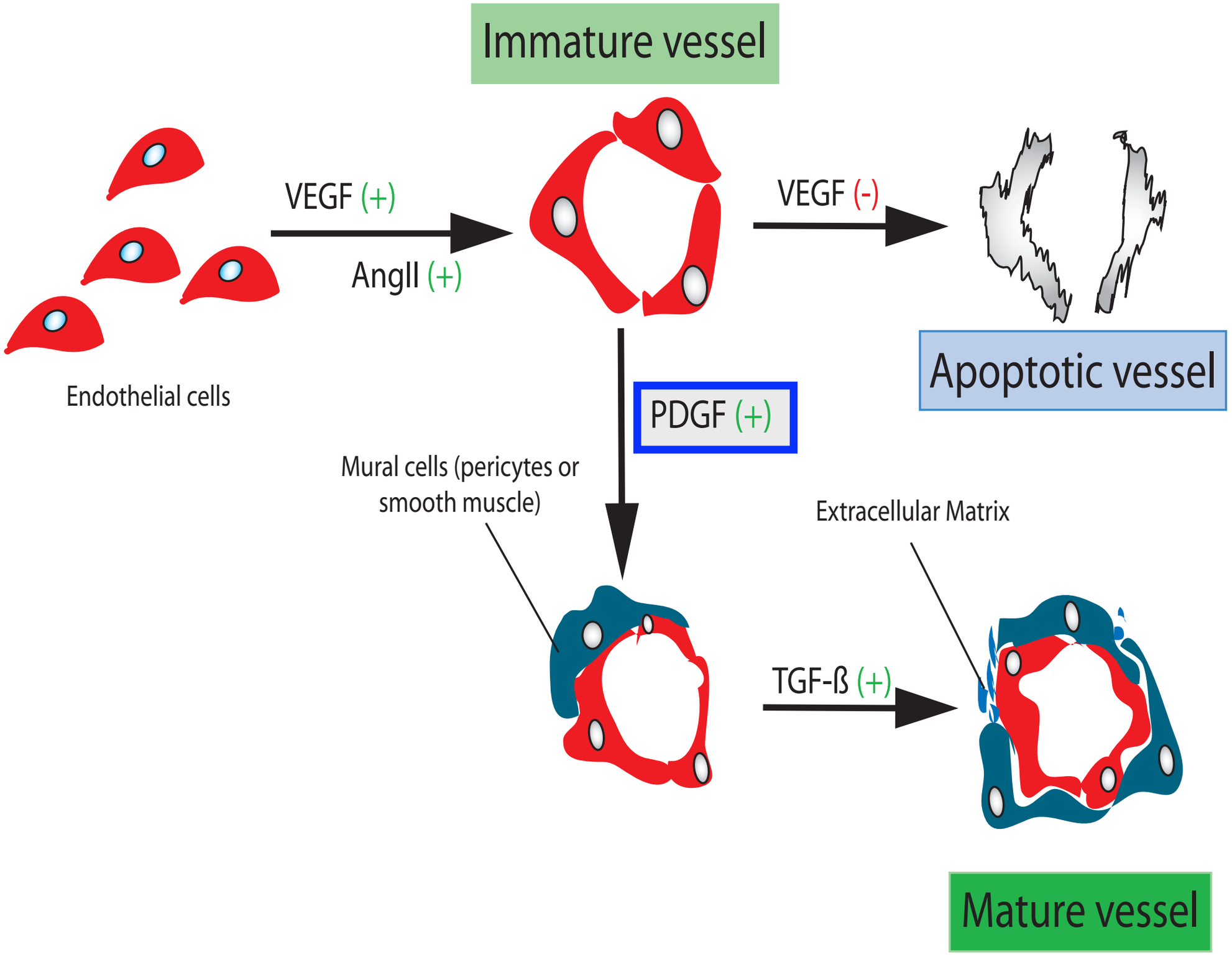
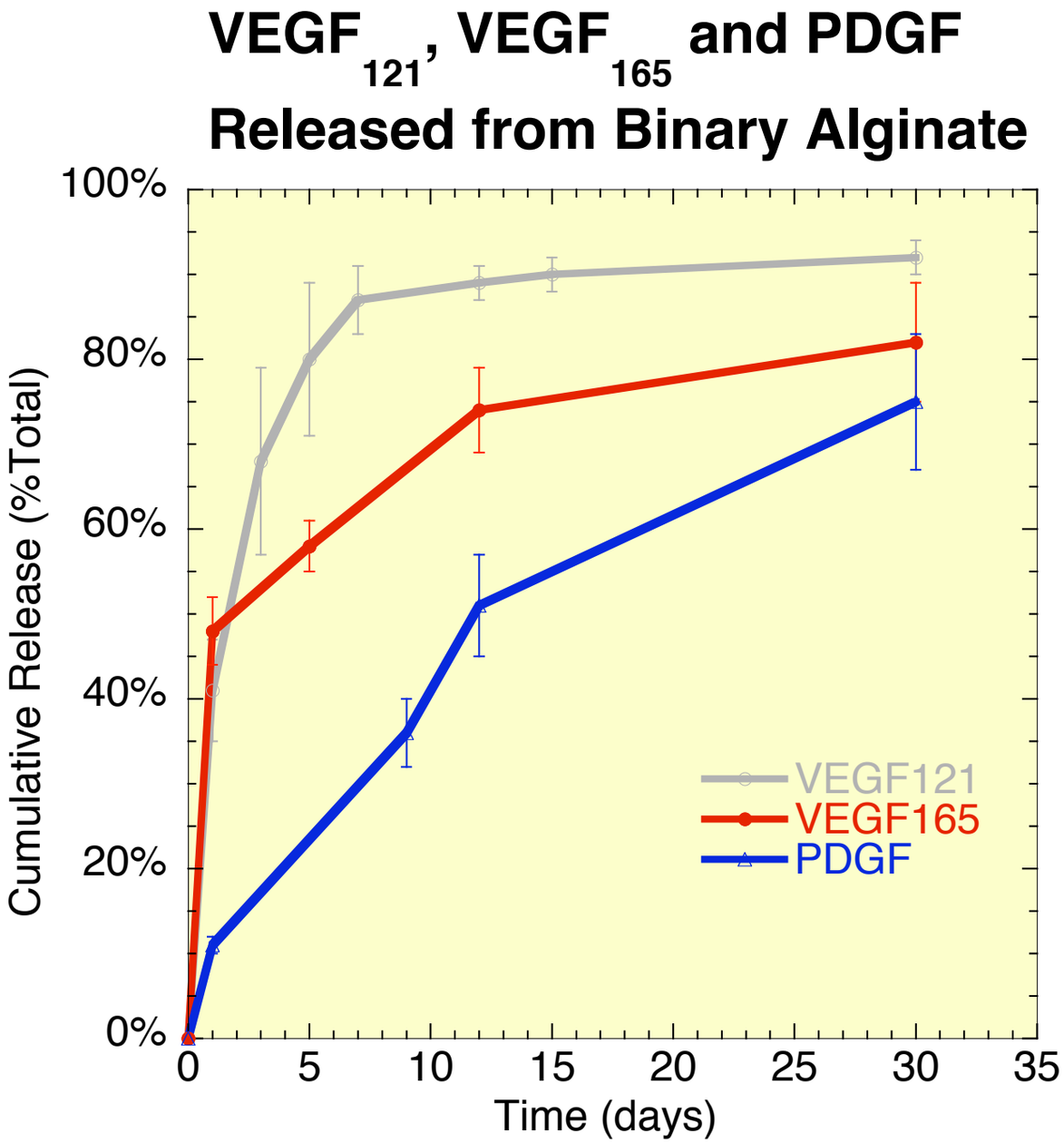
Angiogenesis: Multiple players...

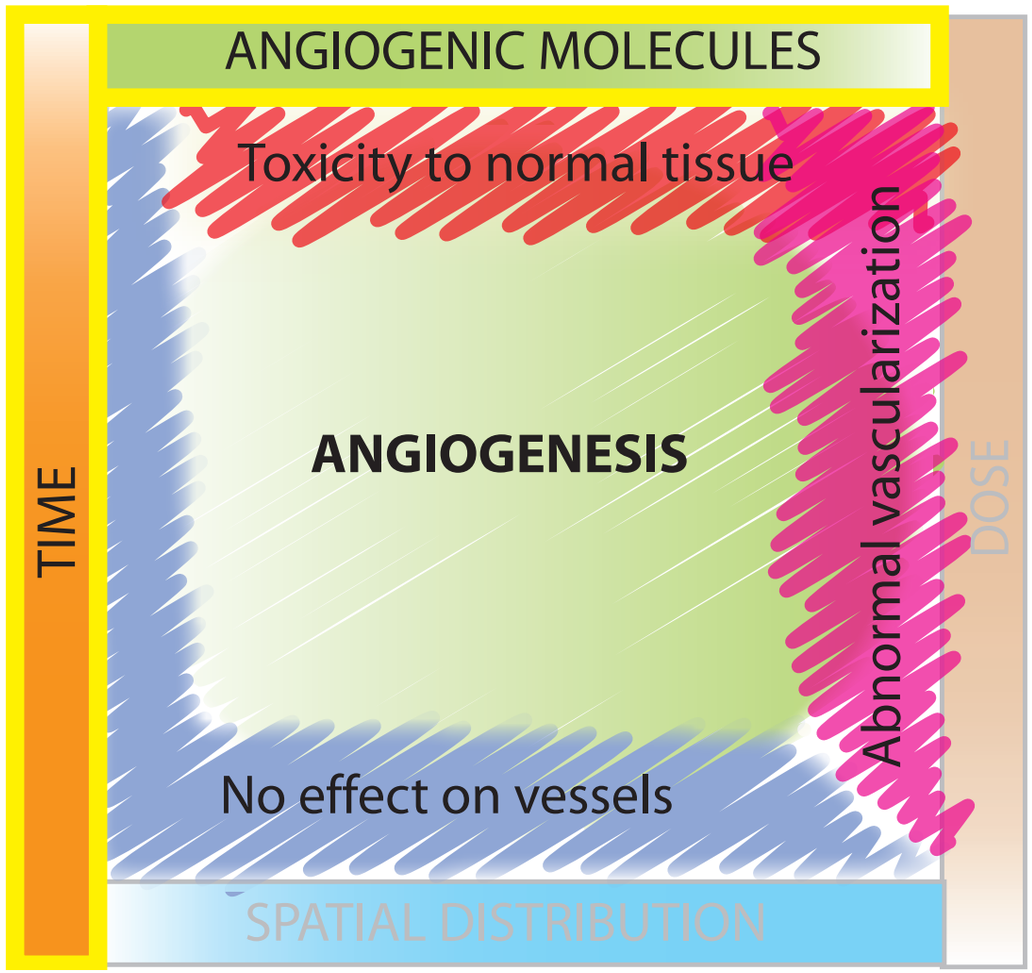


Angiogenesis: Maturation events...



Alginate: PDGF Release and Normalization *In vivo*





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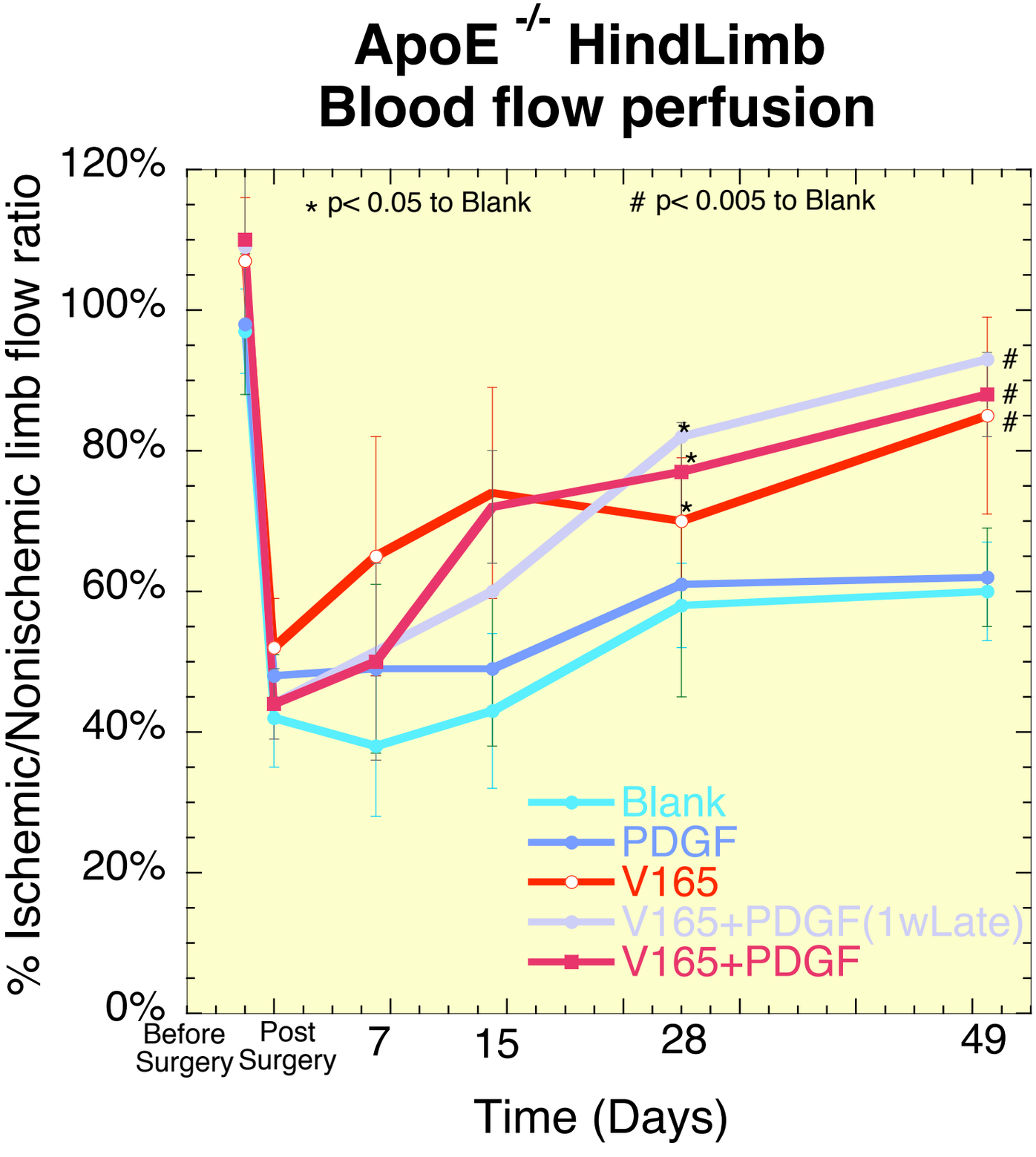
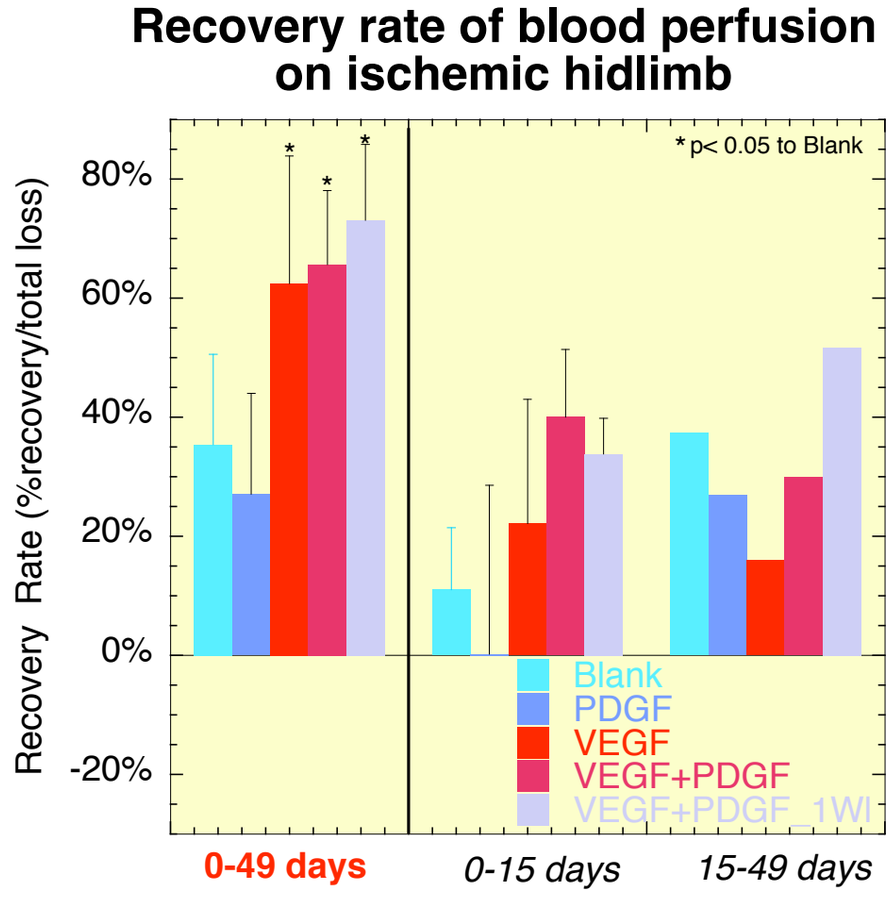
PDGF enhances perfusion at late time points





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Conclusions

3D *in vitro* sprouting assay confirmed that different isoforms of VEGF can cooperate in the organization of newly vascular networks

Development of a minimally invasive delivery vehicle that provides sustained and localized delivery of angiogenic molecules

Angiogenesis and perfusion can be improved by using binary alginate to locally deliver multiple factors

Delivery of VEGF alone significantly enhances reperfusion of ischemic hindlimbs by day 15

Multifactorial delivery of angiogenic agents is more effective than delivery of single factors

Future Work

Investigate the role of different VEGF isoforms in vivo

Investigate the potential of binary alginate as delivery vehicle of angiogenic agents in an ischemic heart

Explore the perspective of alginate as bifunctional vehicle for cells (Endothelial Progenitors cells-EPCs) and proteins delivery in an ischemic tissue

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Engineering *new* networks of blood vessels

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http://openwetware.org/wiki/Easilva

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