Engineering *new* networks of blood vessels

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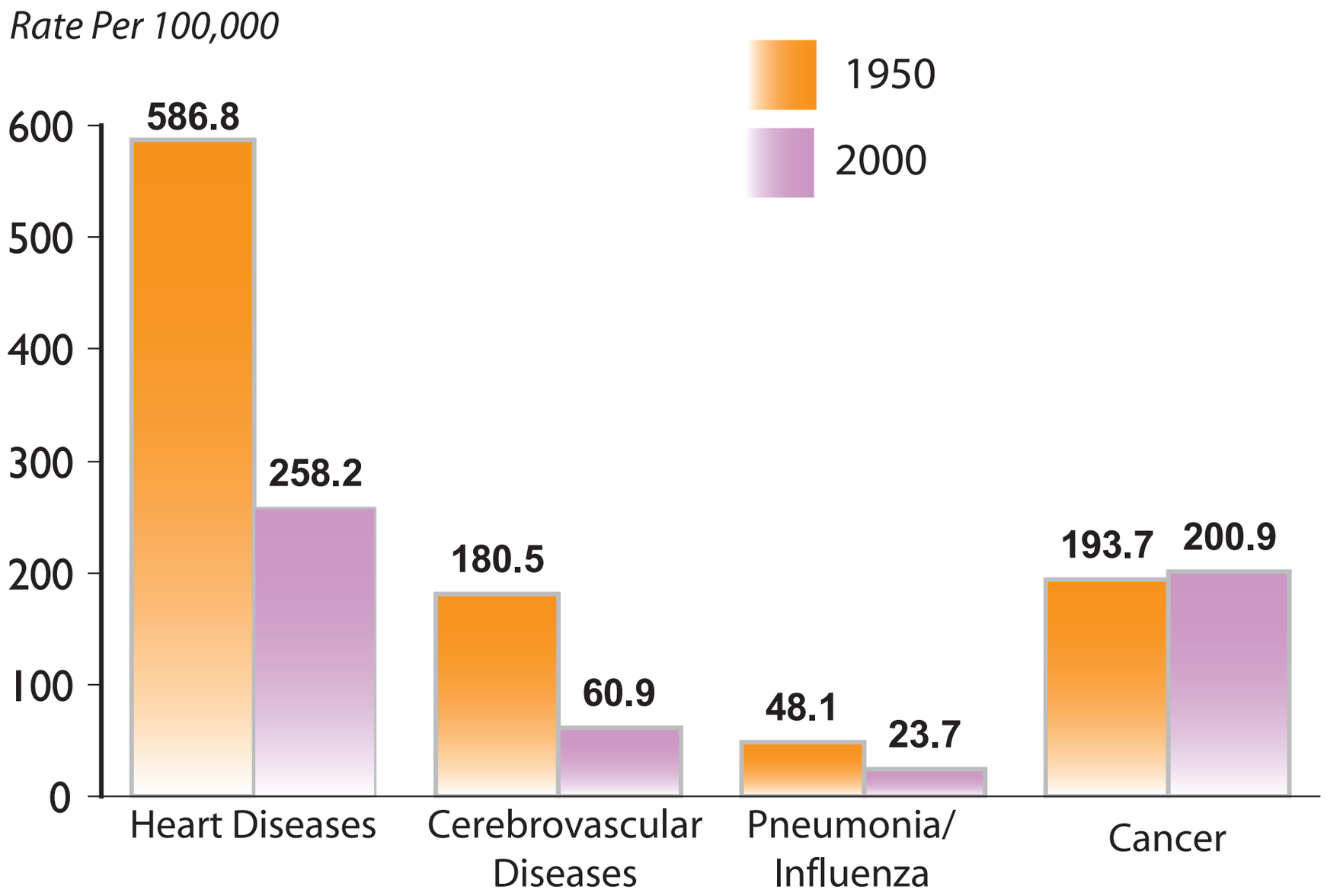
http://www.deas.harvard.edu/mooneylab/

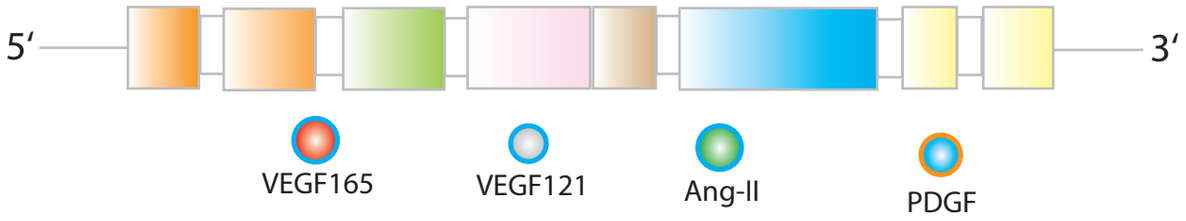
December 2005

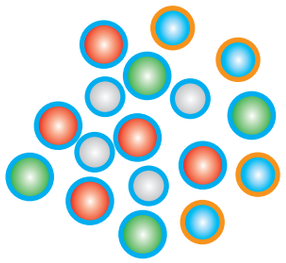
Change in the US Death Rates* by Cause, 1950 & 2000



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

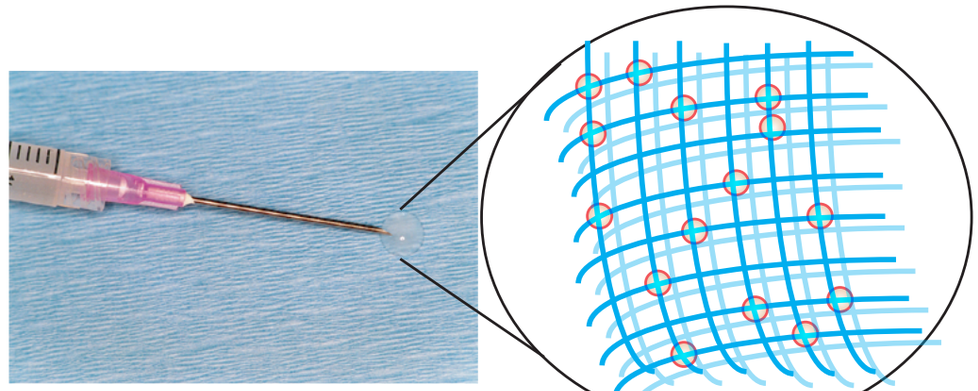
Vascular Endothelial Growth Factor (VEGF) gene

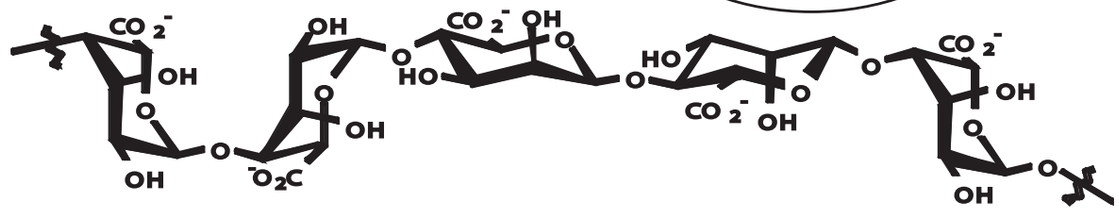


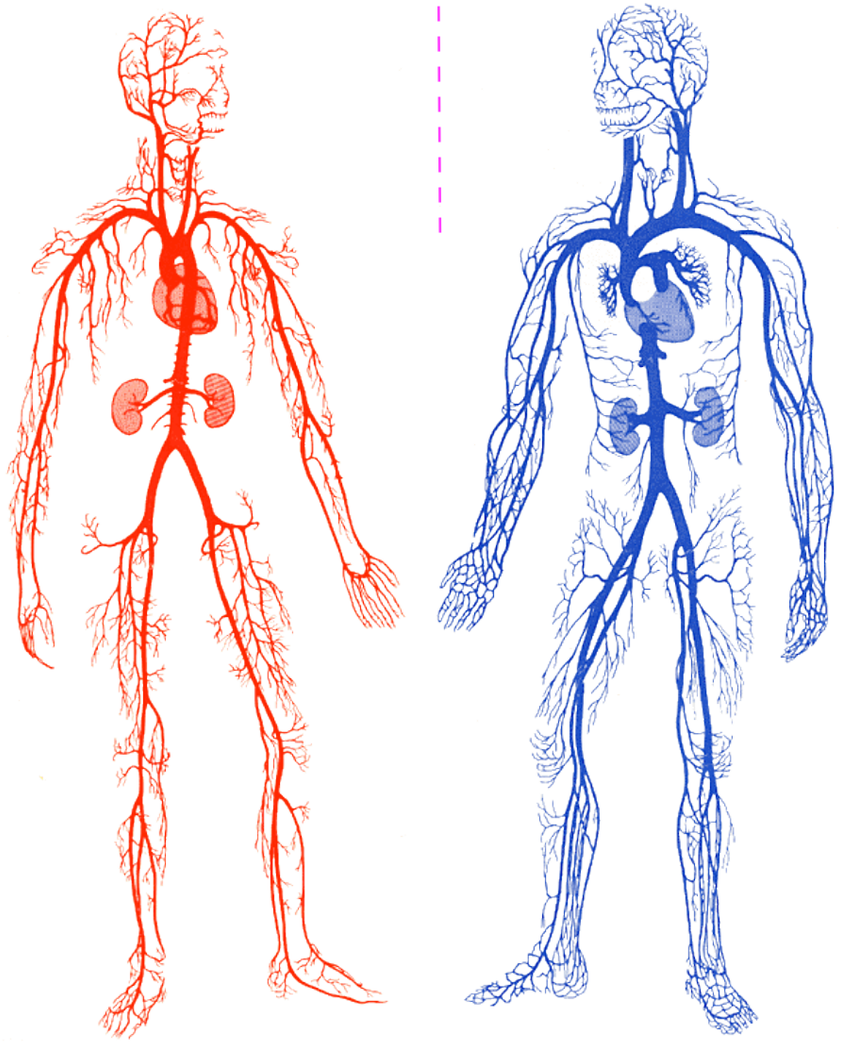


Angiogenic agents

Synthetic Extracellular Matrice







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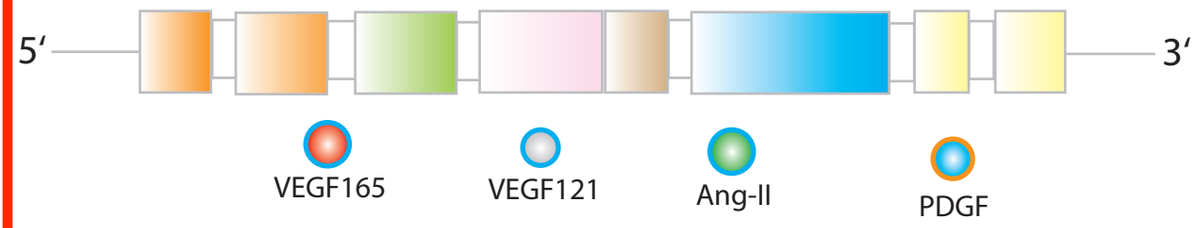

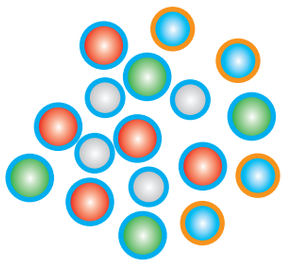

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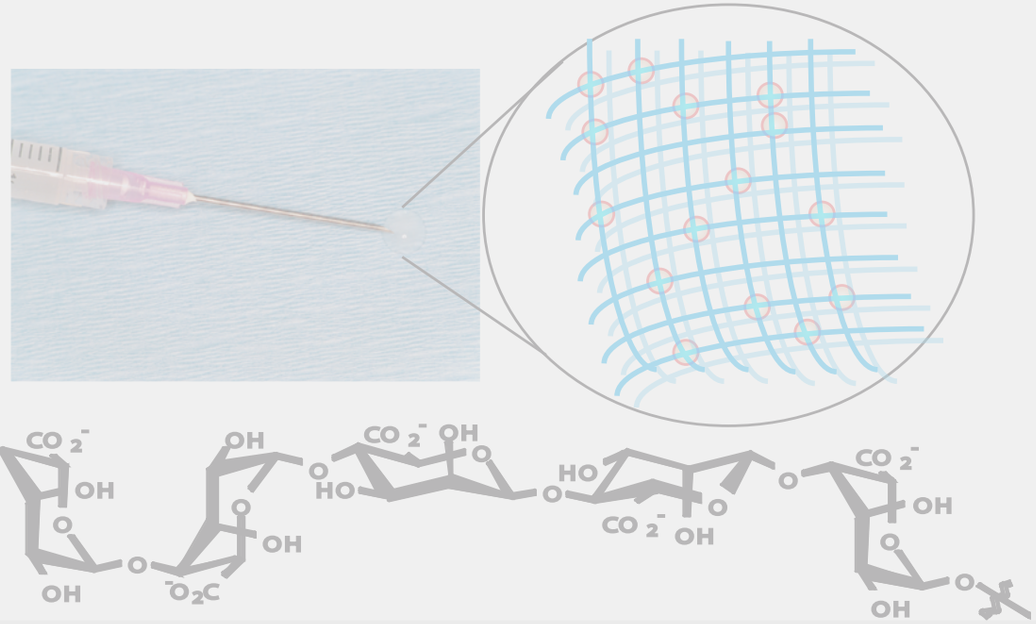

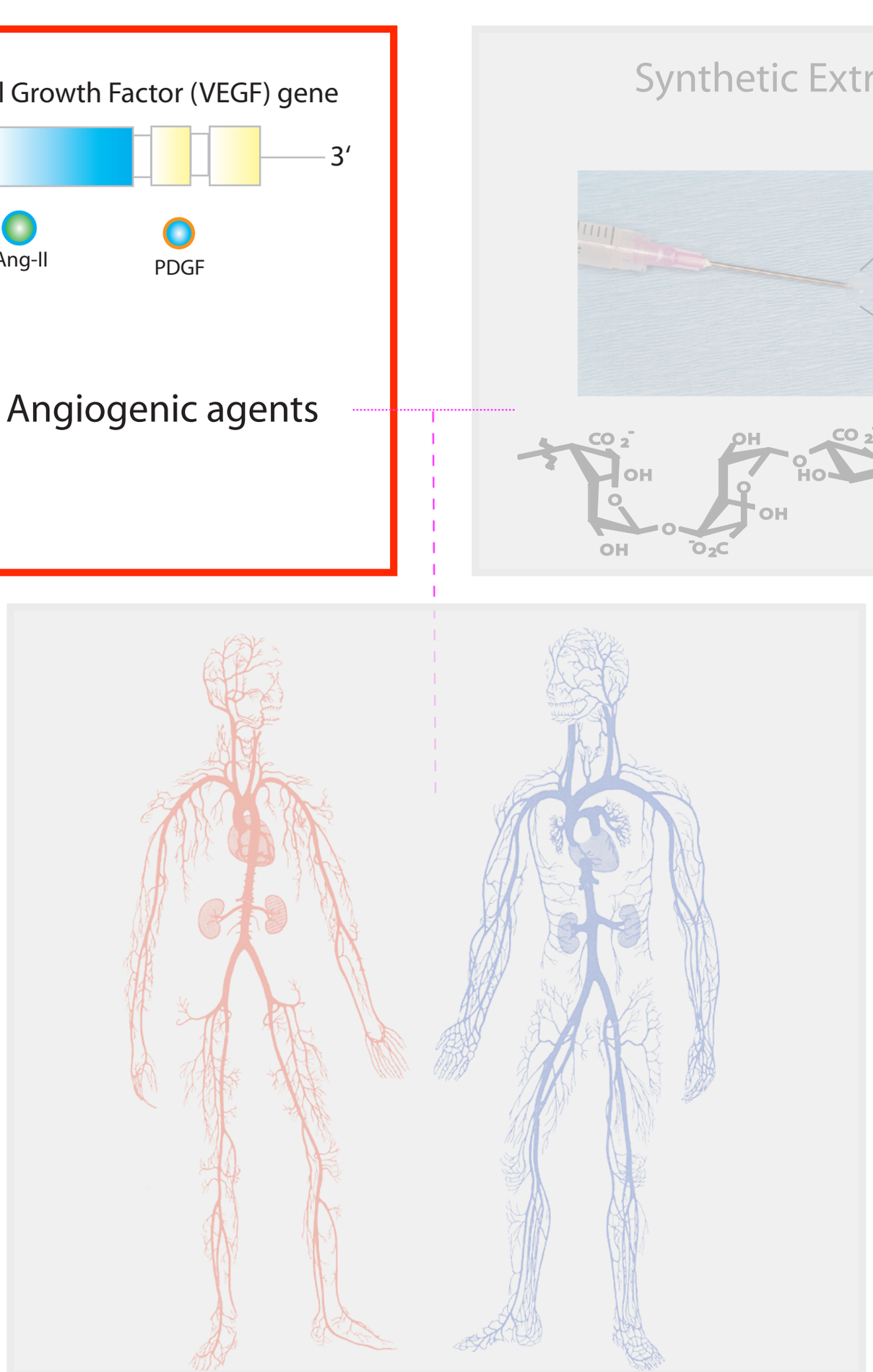

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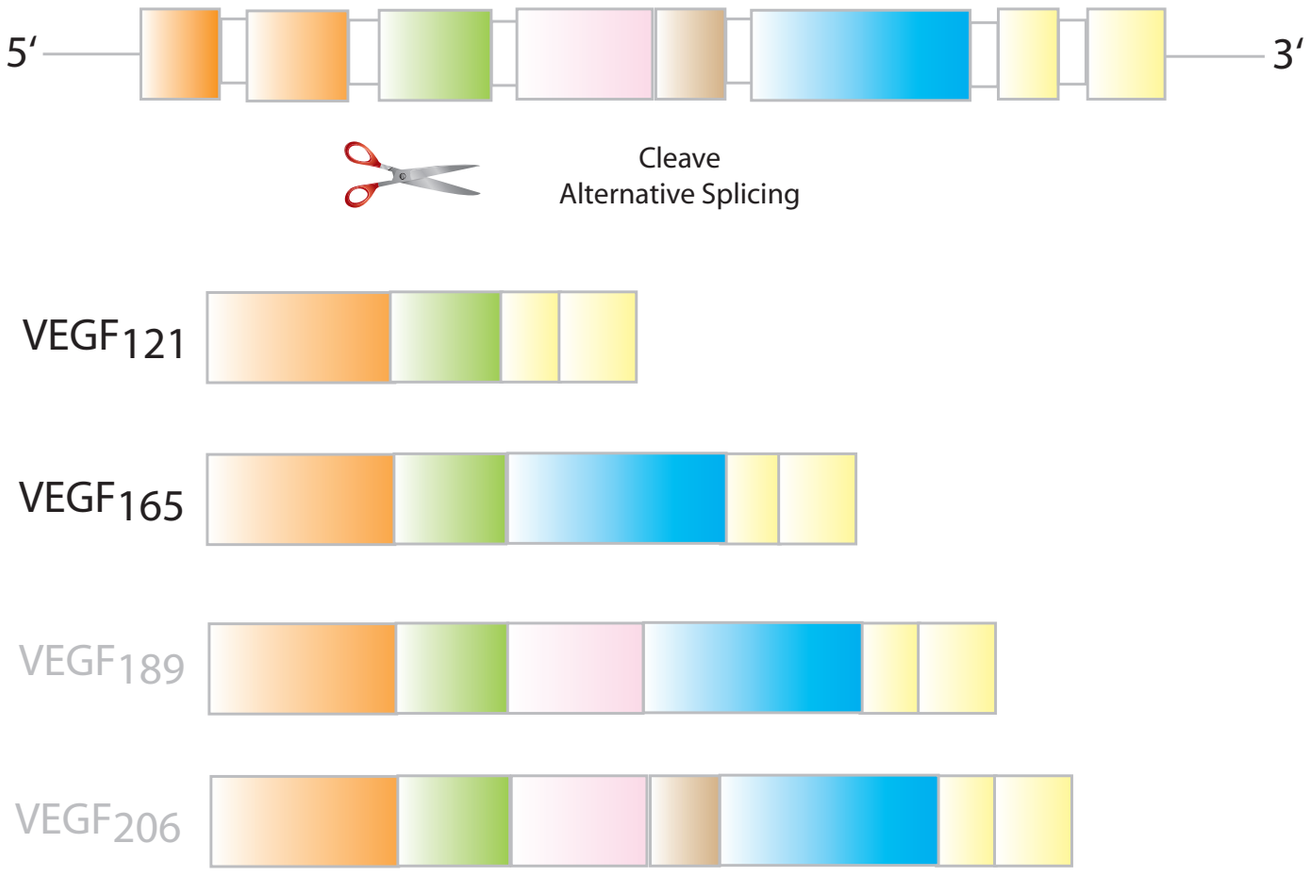
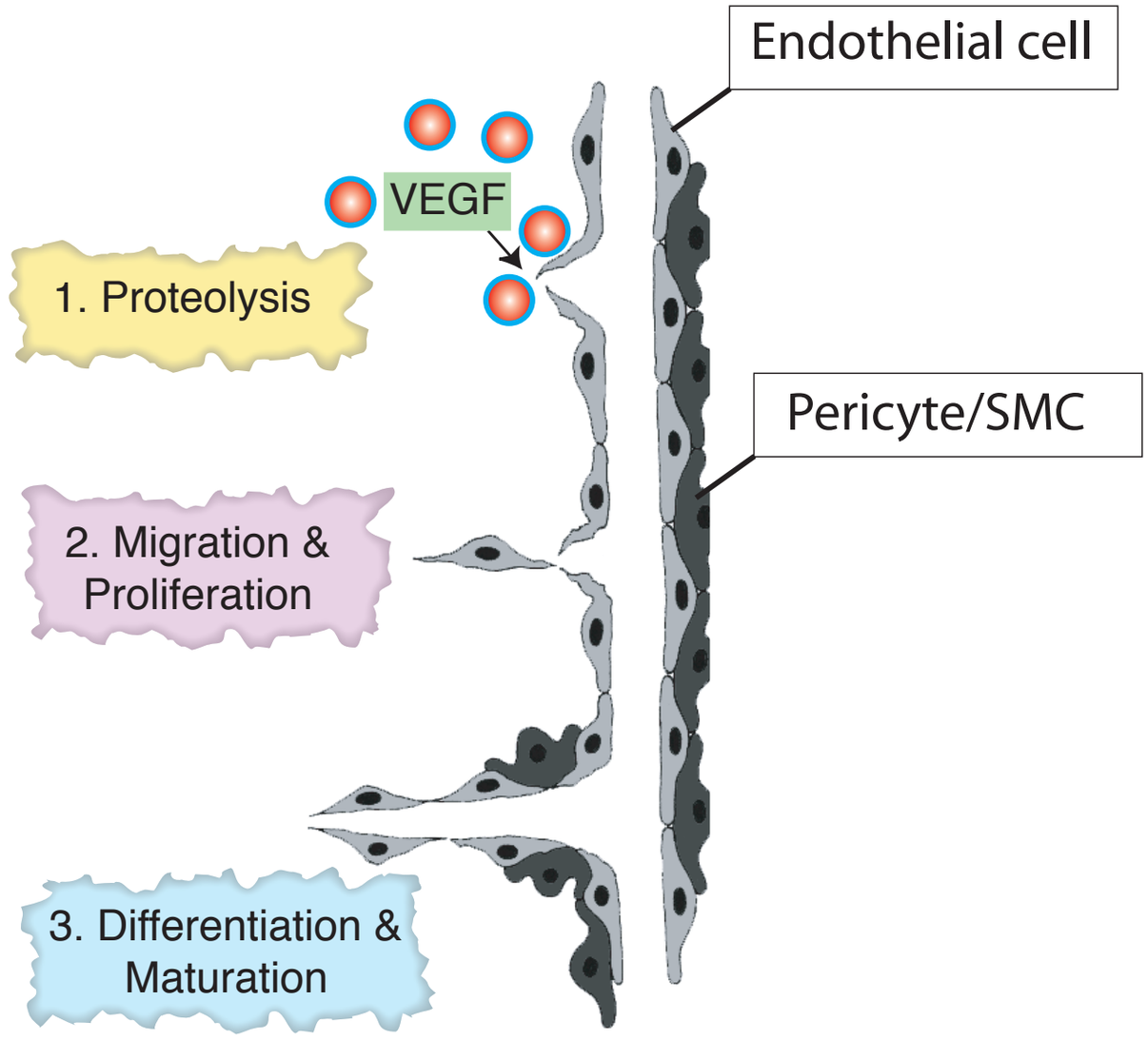
Angiogenesis and VEGF

Vascular Endothelial Growth Factor (VEGF) gene



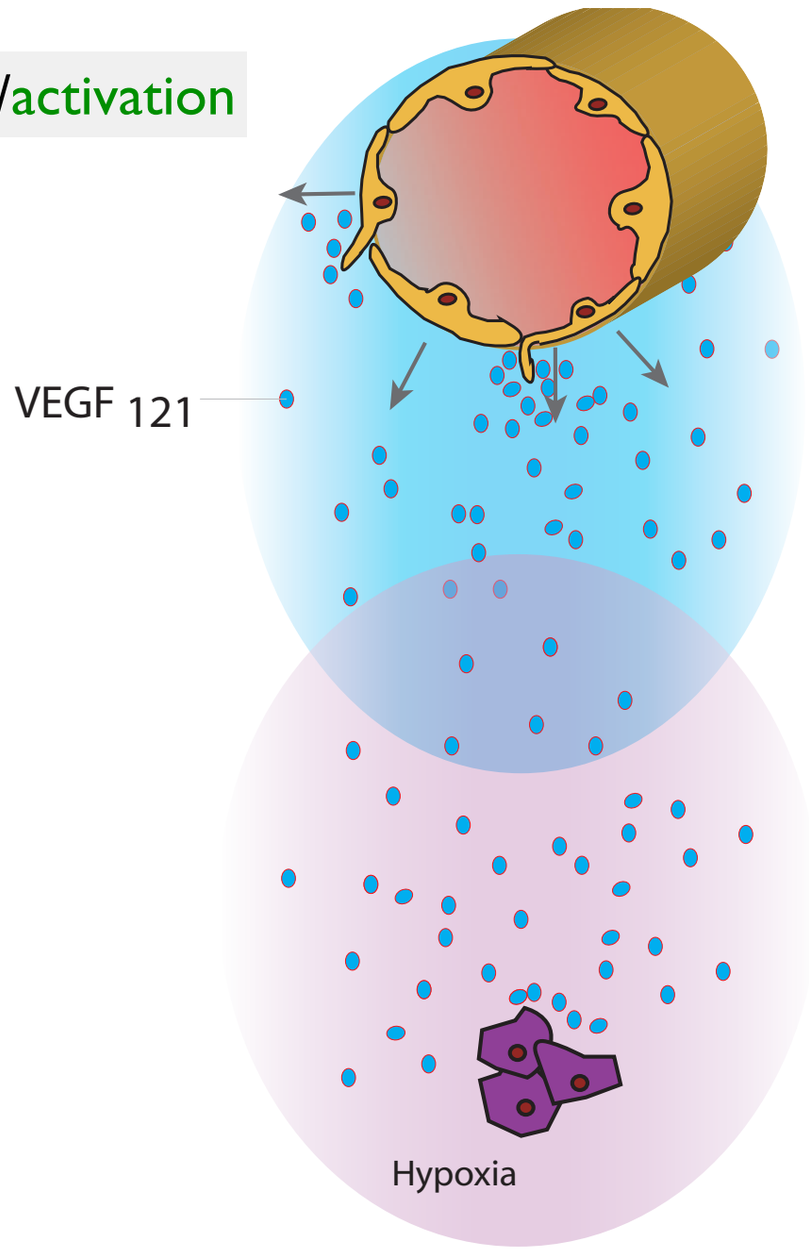
ANGIOGENESIS



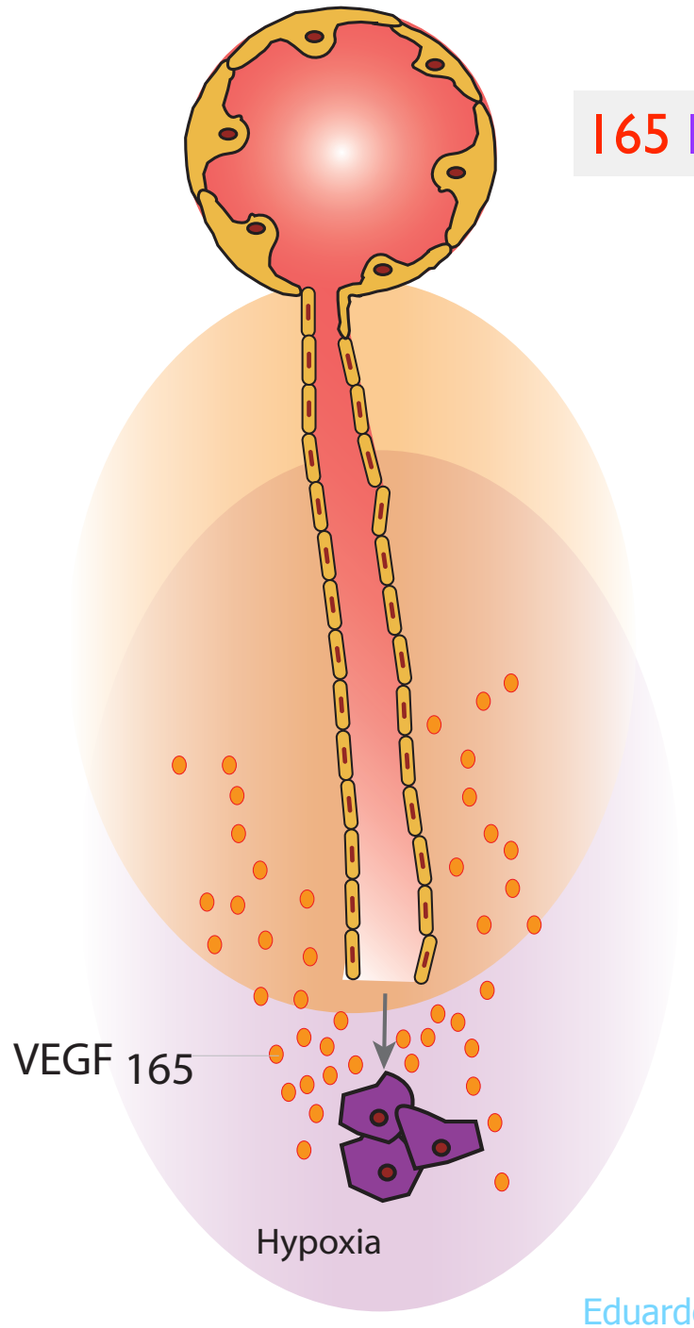
Hypothesis

Sustained and localized delivery of different VEGF isoforms 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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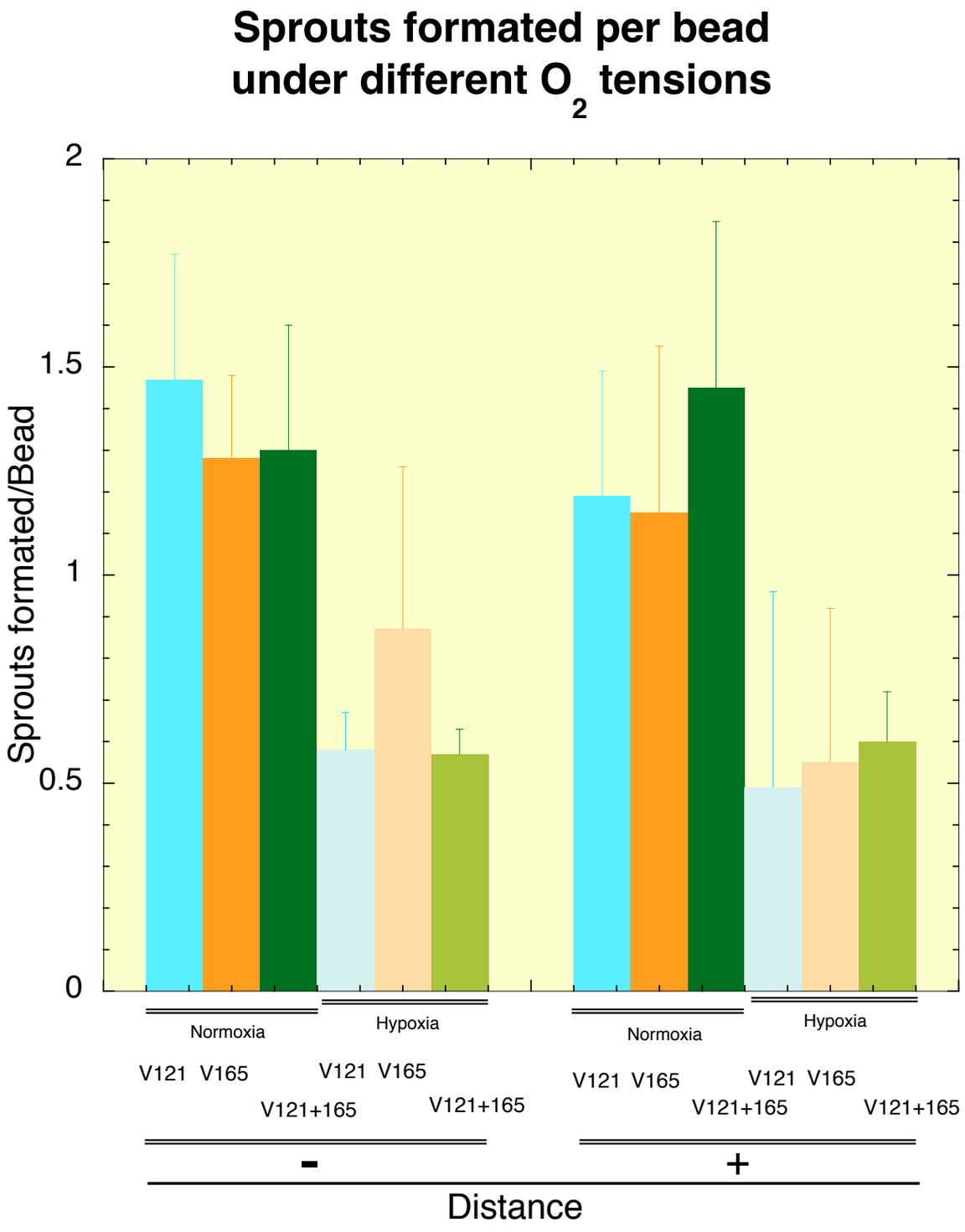
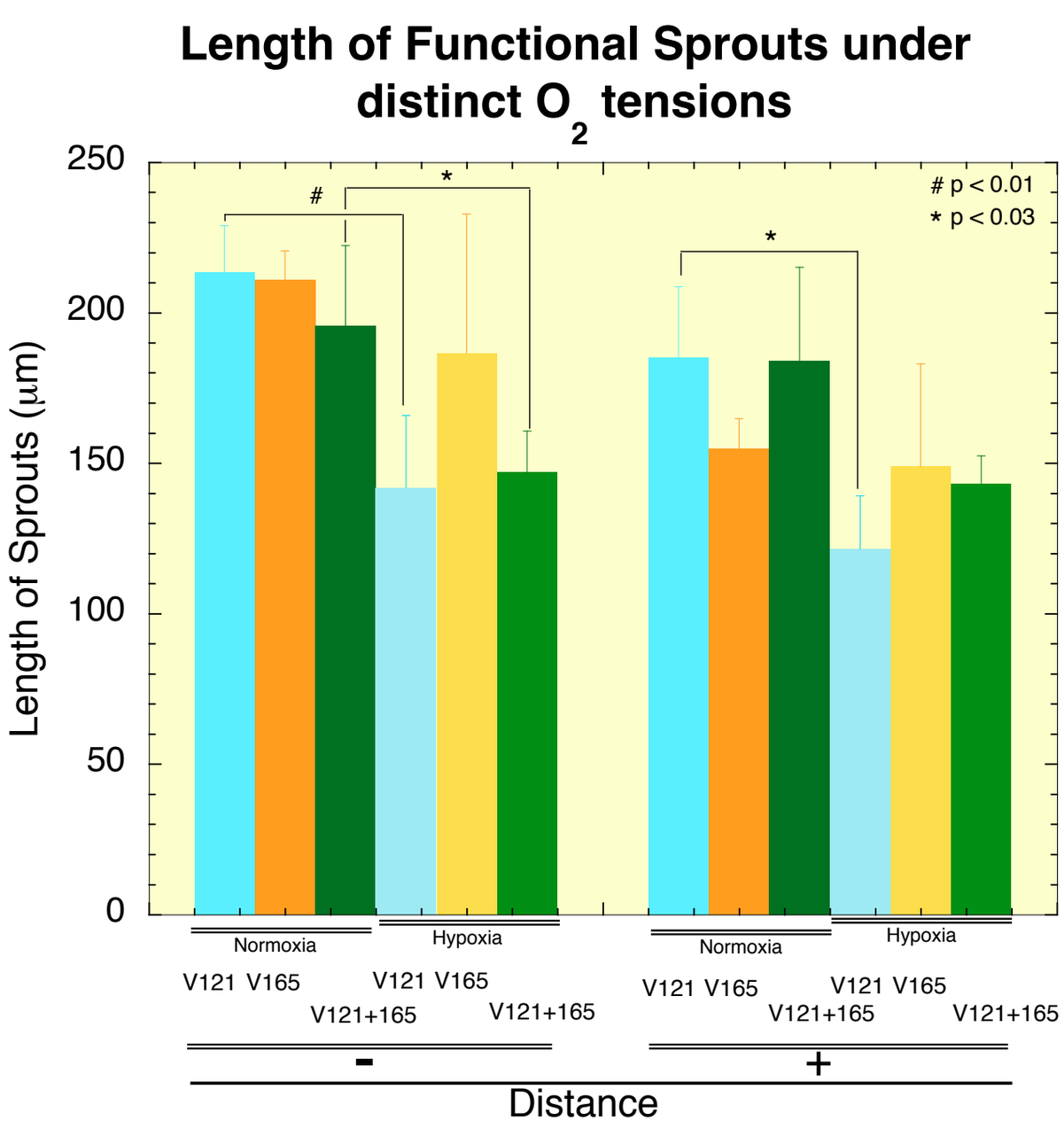
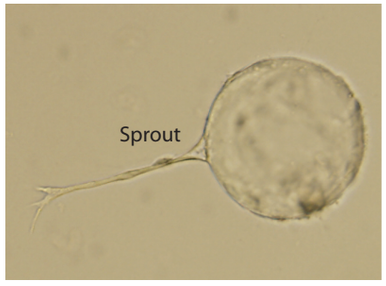
Distinct roles In Vitro?







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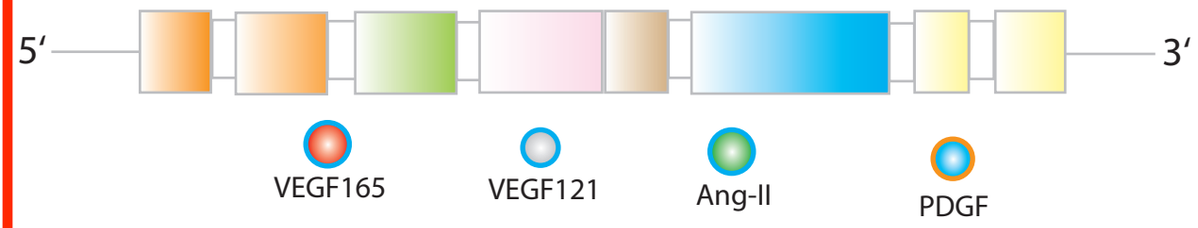
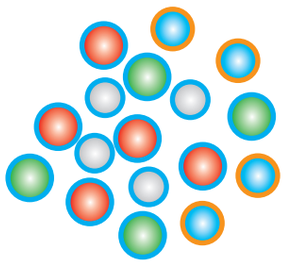
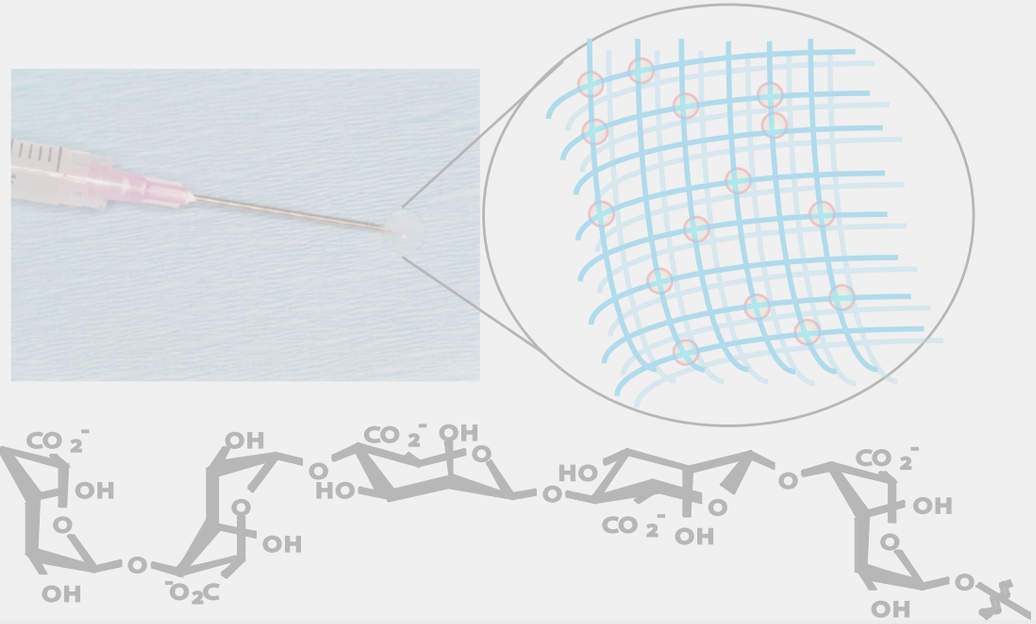
Vascular Endothelial Growth Factor (VEGF) gene

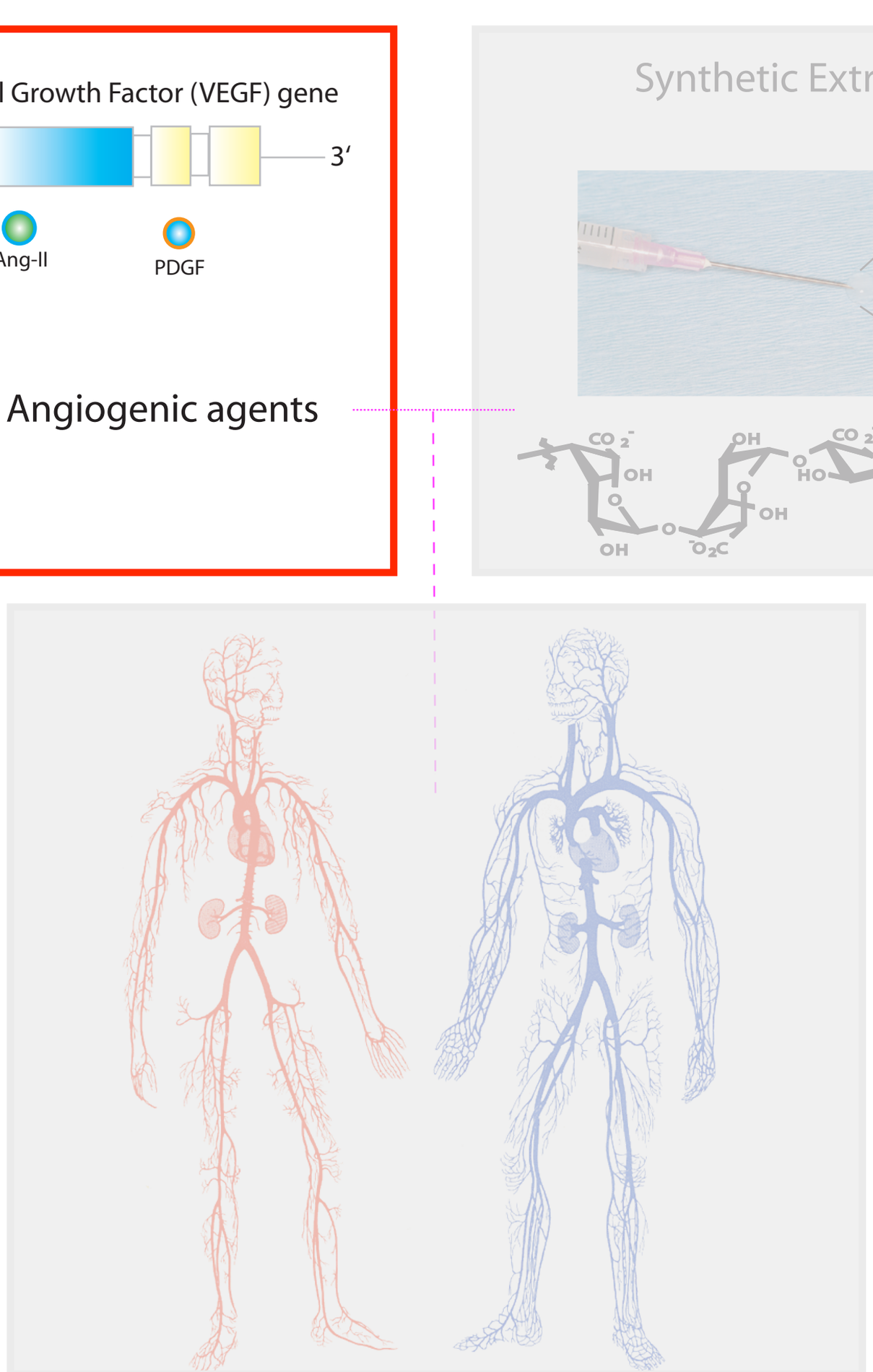




Angiogenic agents

Synthetic Extracellular Matrice





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5′ 3′

VEGF165 VEGF121 Ang-II PDGF

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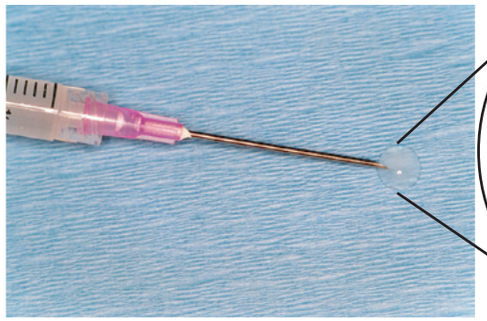

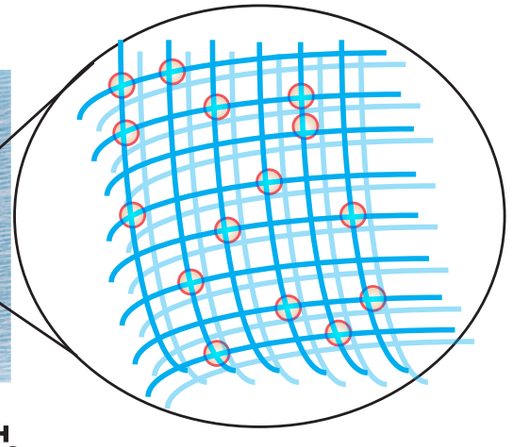

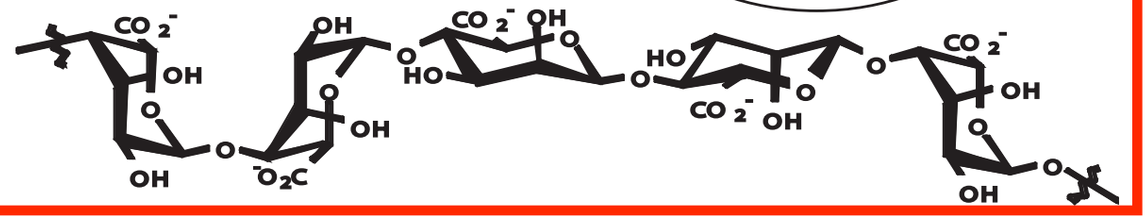

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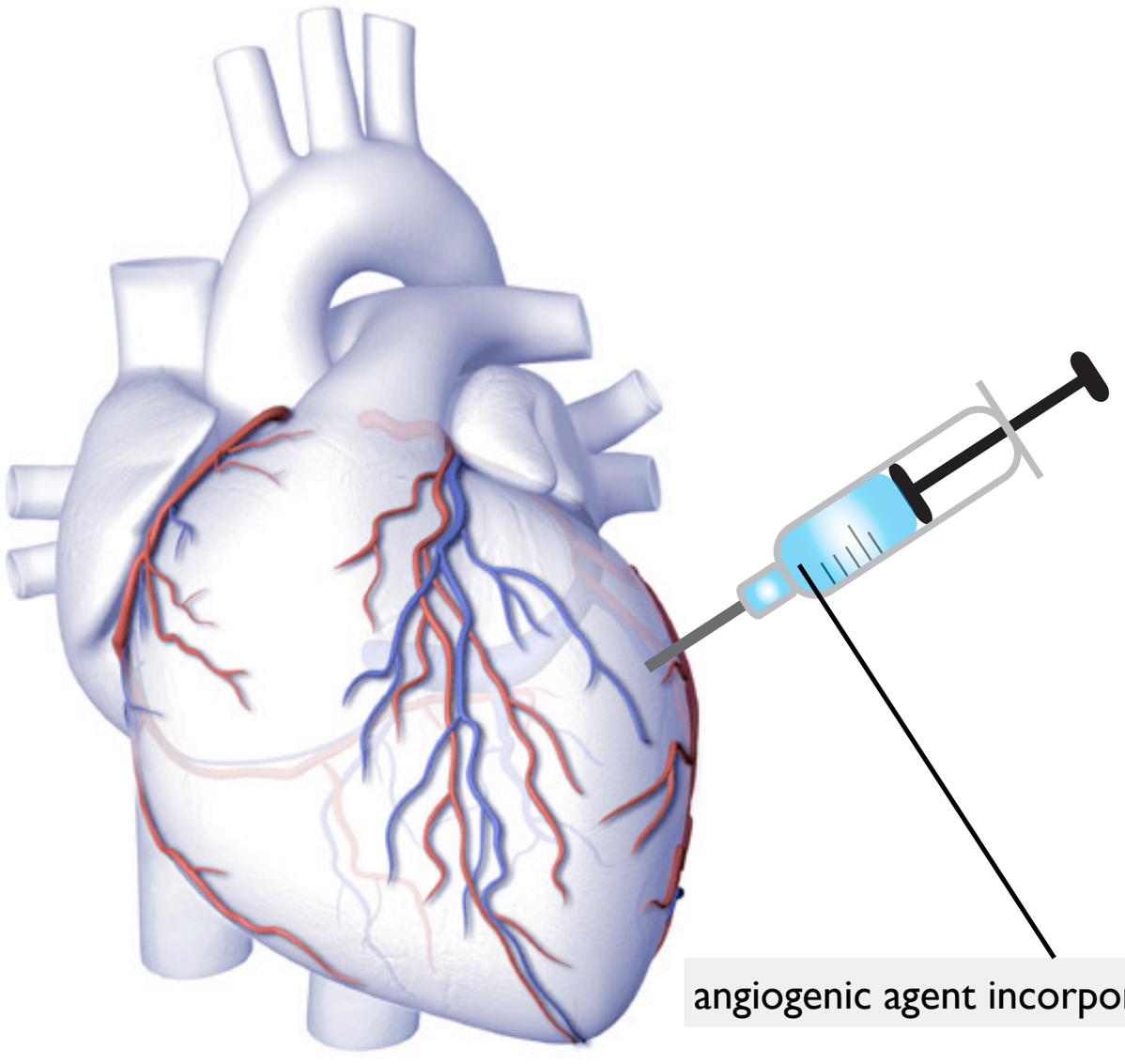
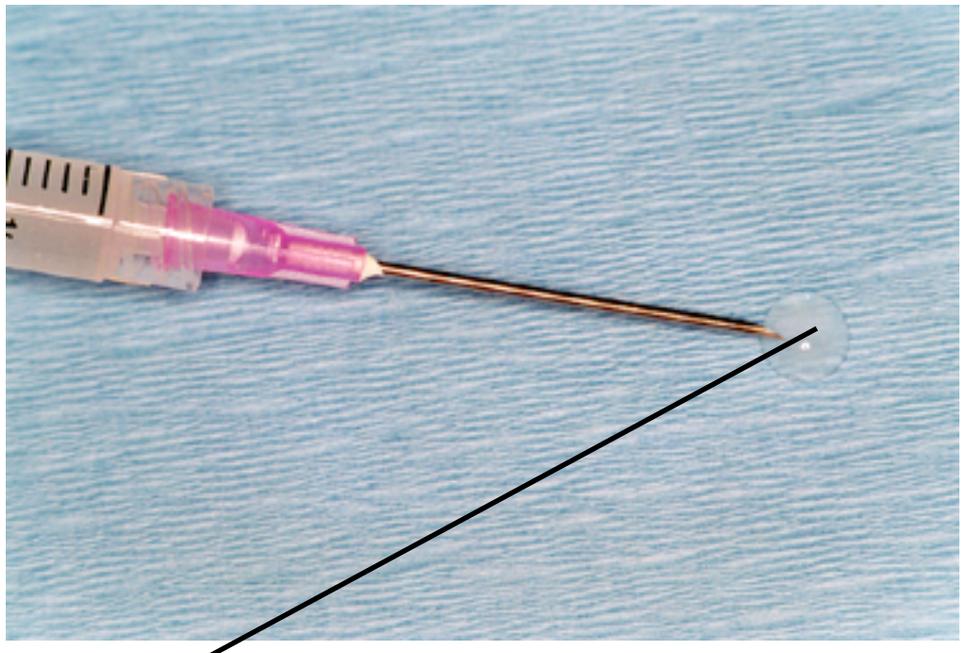
Engineering aim

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

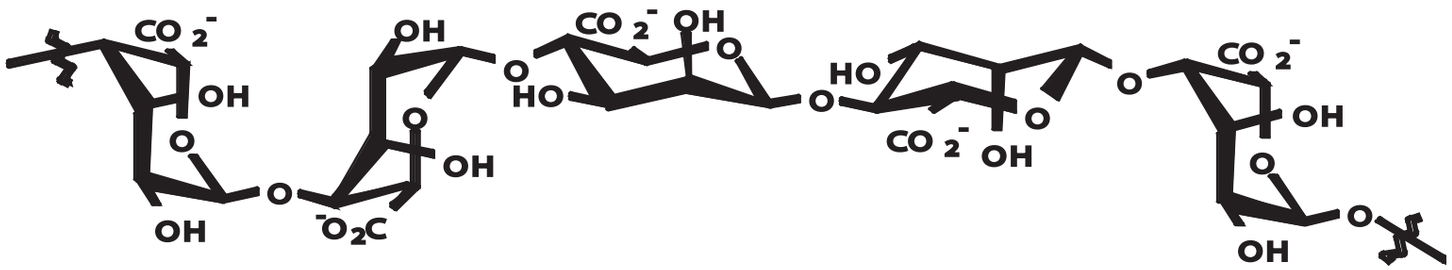




angiogenic agent incorporated in an injectable polymer

Polymeric System

ALGINATE



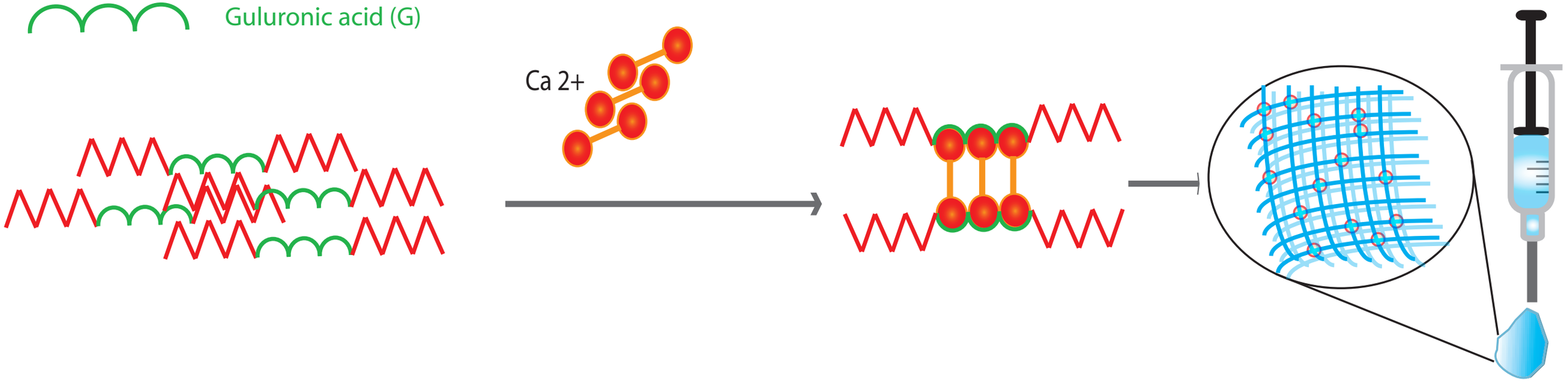
G G M M G

Mannuronic acid (M)

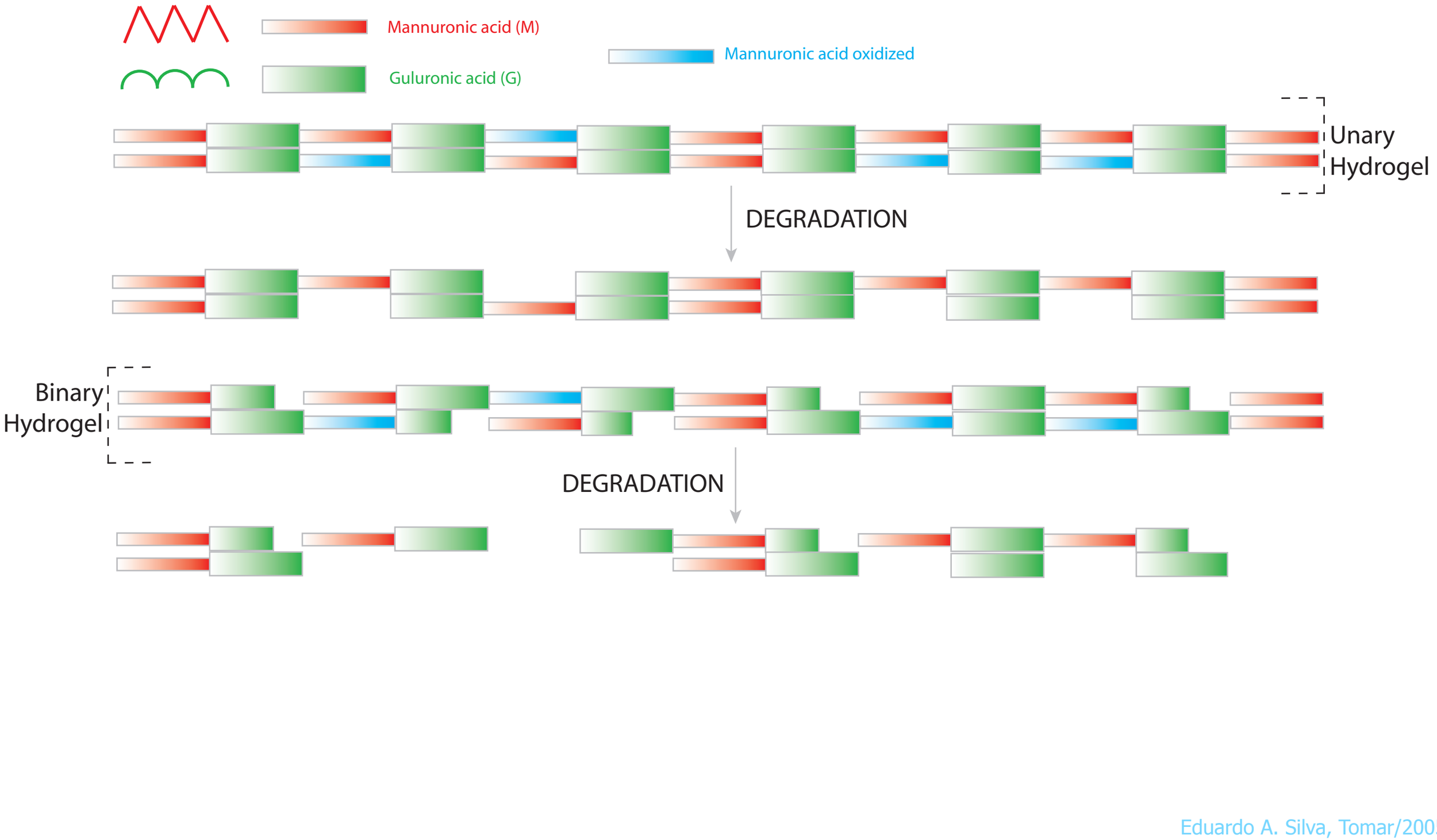
Guluronic acid (G)

Biocompatible
Drug/cell vehicle delivery
Non degradable

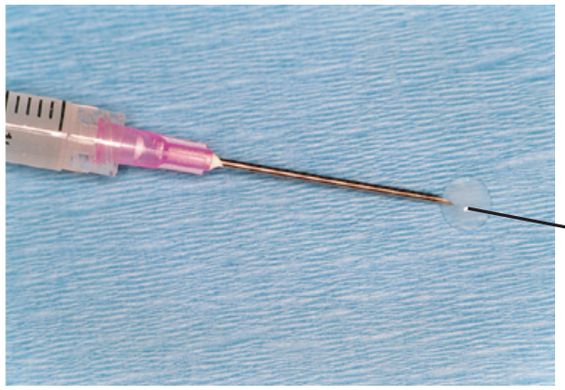
Alginate GEL



Alginate Modifications



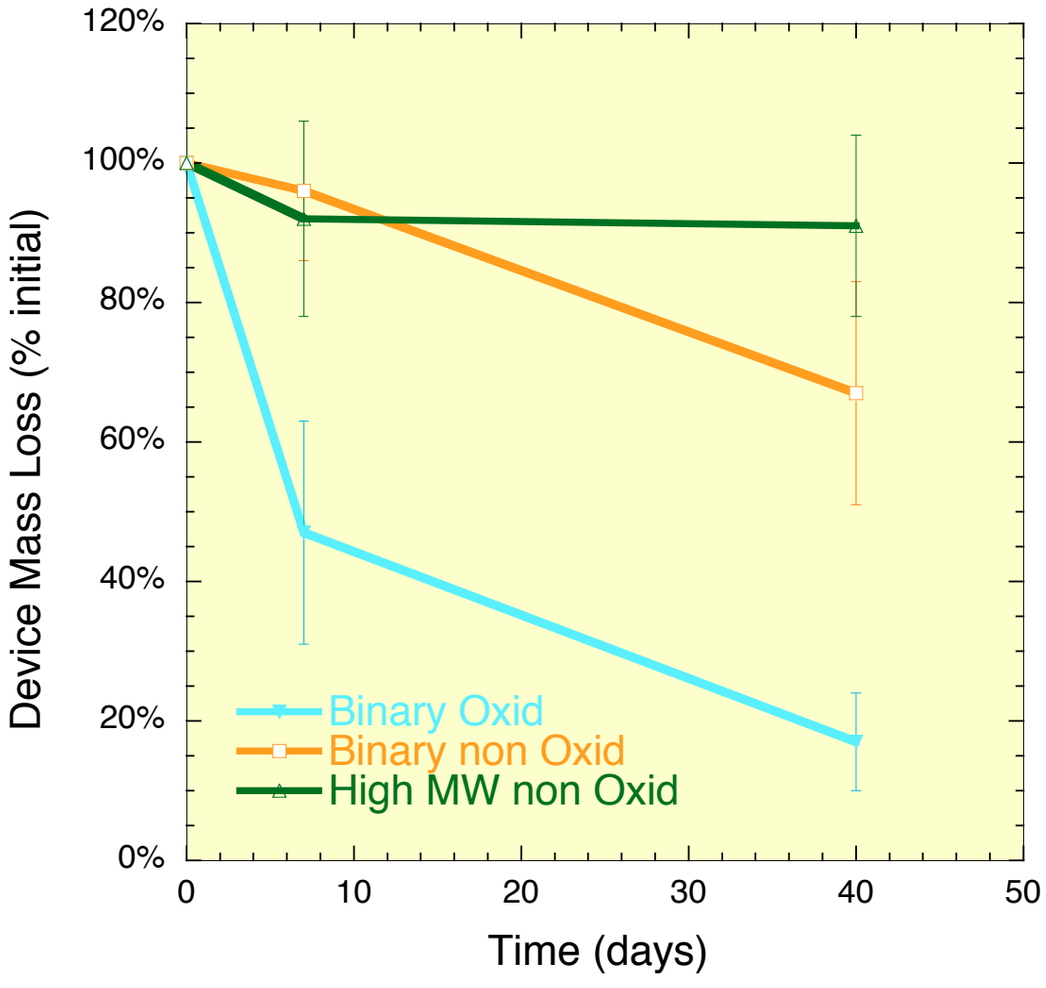
Alginate Properties



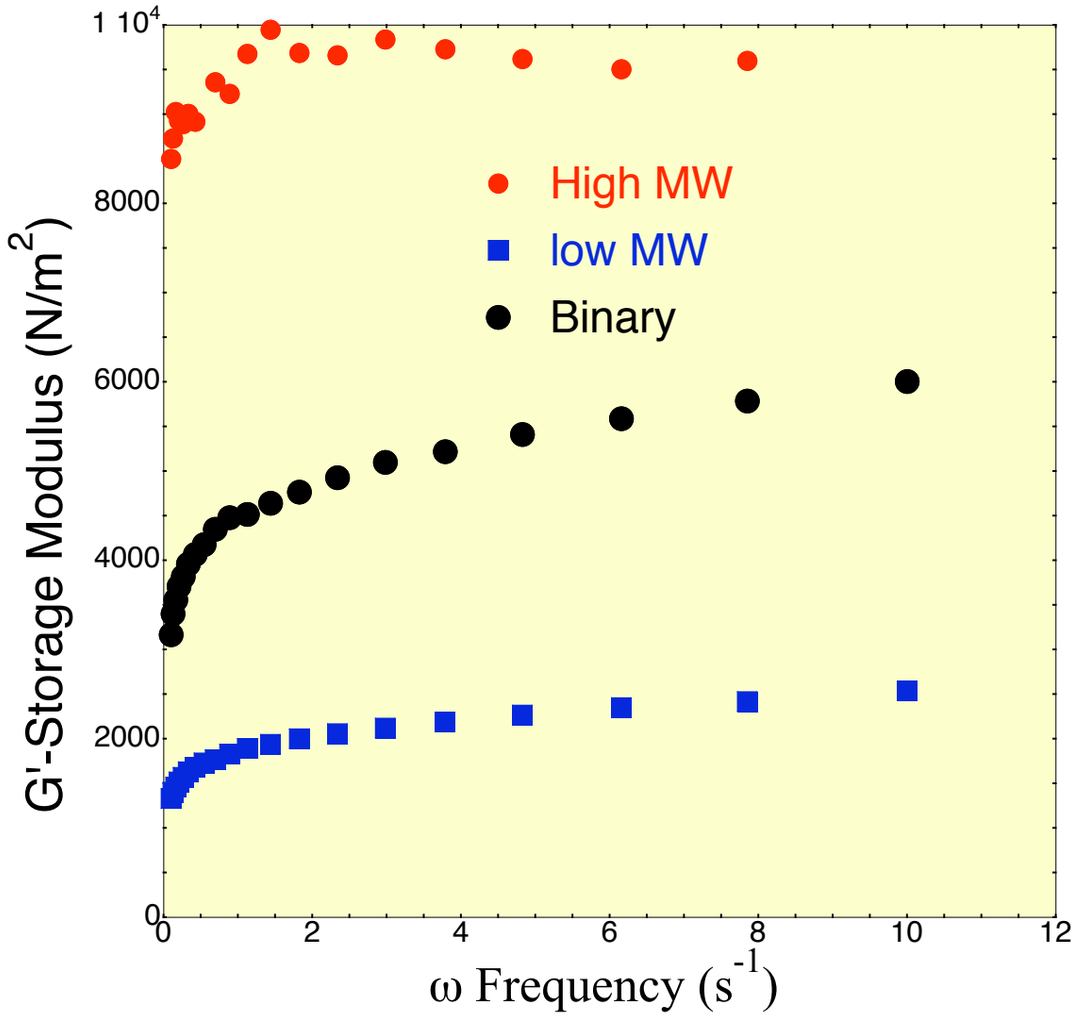
(Relative %)	Mw (Kg/mol)
High Molecular Weight (25%)	± 250
low Molecular Weight (75%)	± 50

Alginate Hydrogel
(Binary Molecular Weight Distribution)

Alginate Degradation In Vitro



Binary Alginate Viscoelastic behavior



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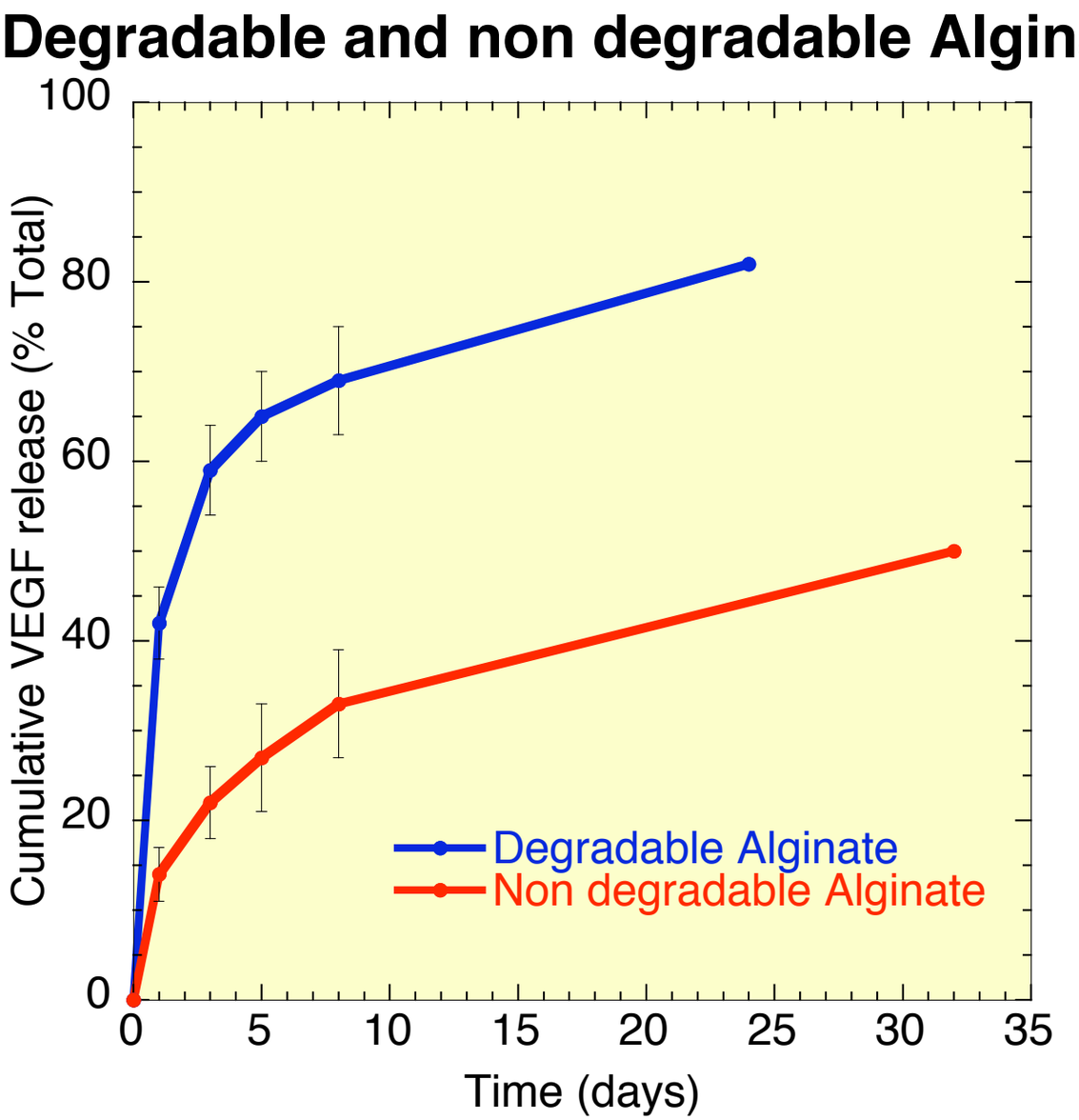
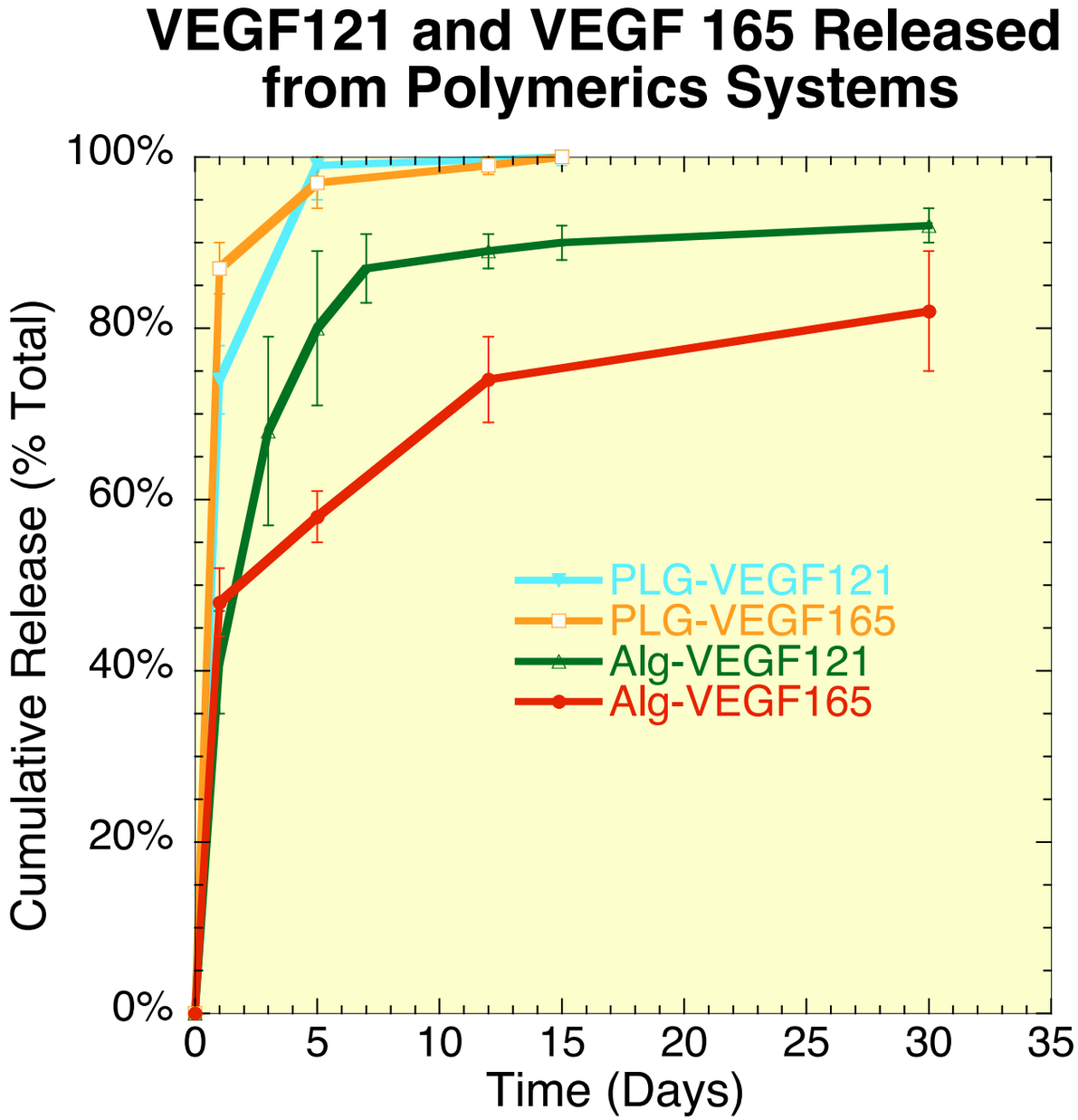
Alginate Releasing Properties





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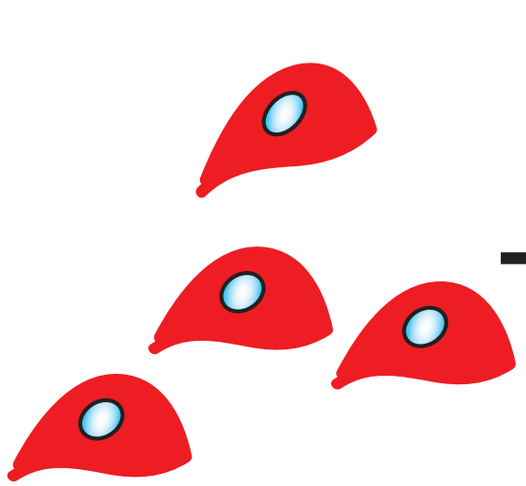
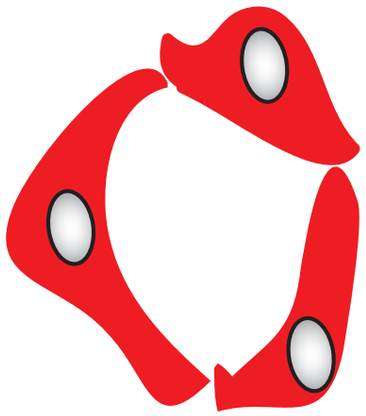
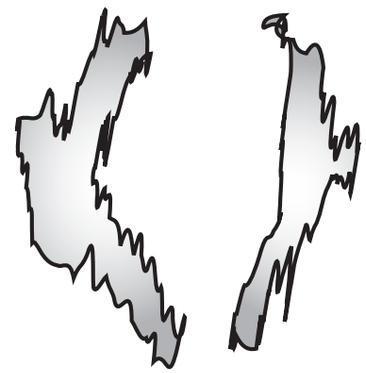
Immature vessel





VEGF (+)

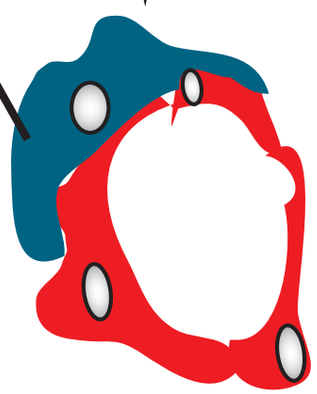


Apoptotic vessel

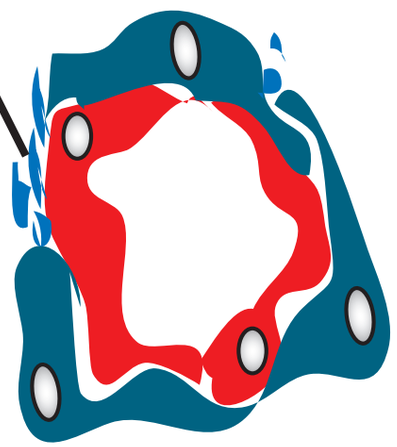
PDGF (+)

Mural cells (pericytes or smooth muscle)

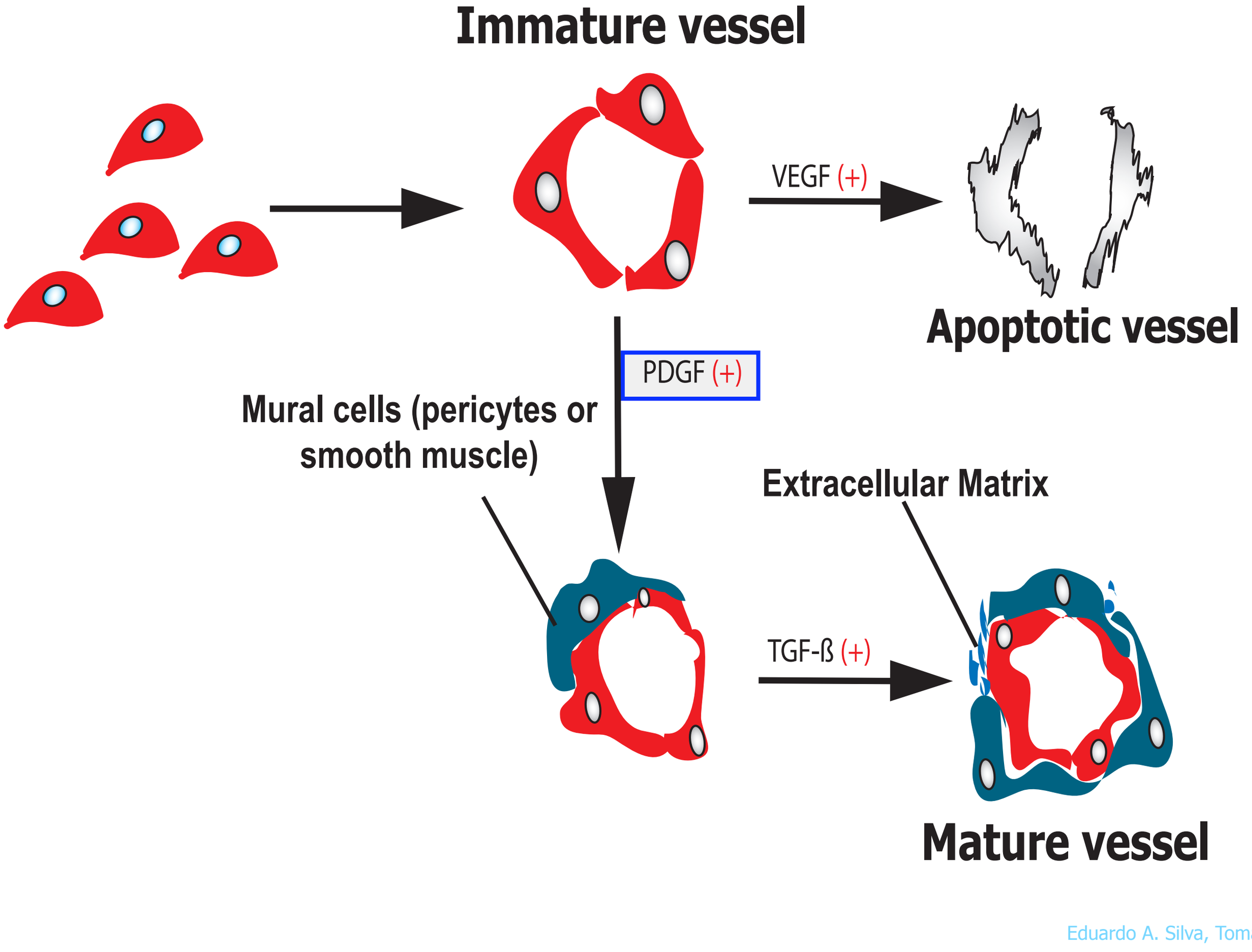
Extracellular Matrix



TGF-ß (+)



Mature vessel



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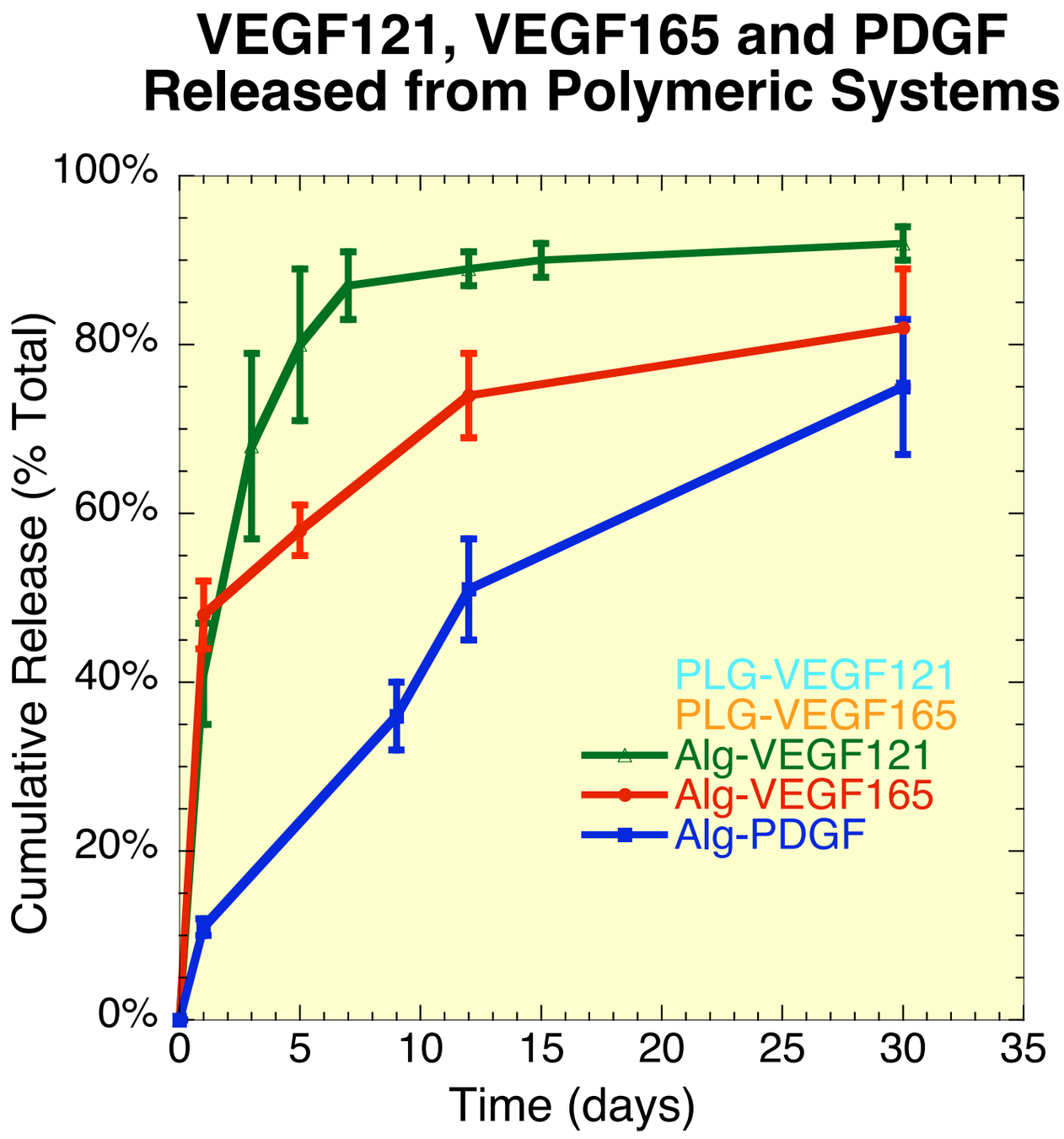
Alginate Releasing Properties



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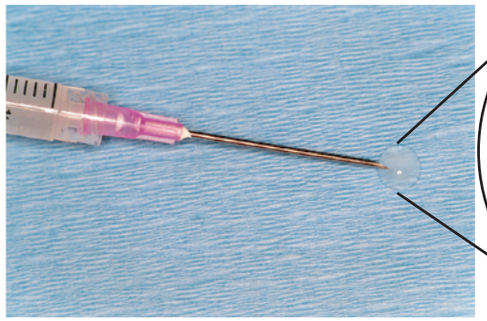

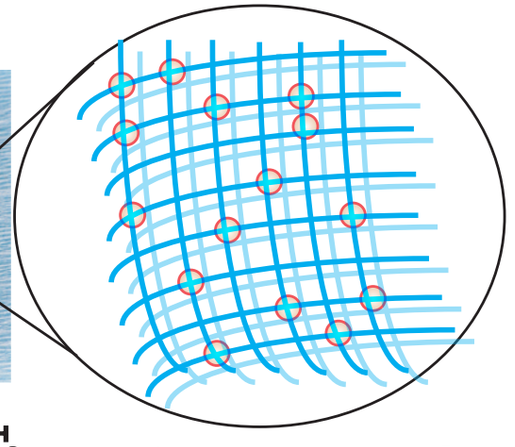

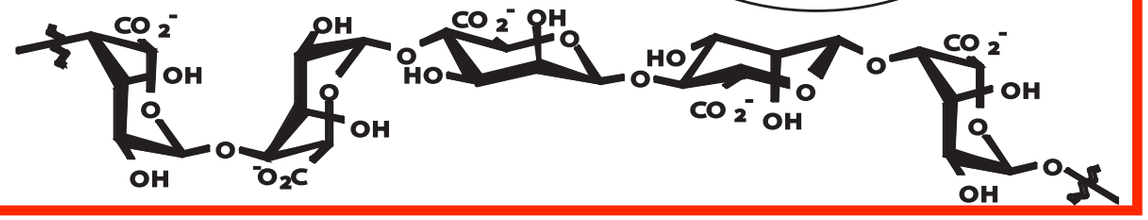

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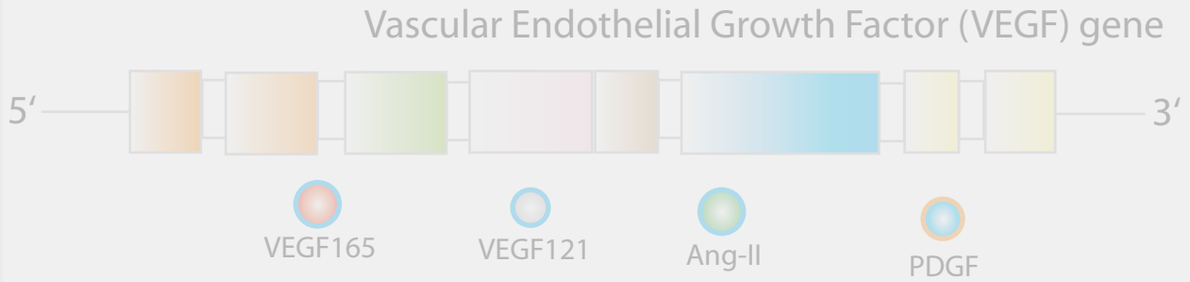

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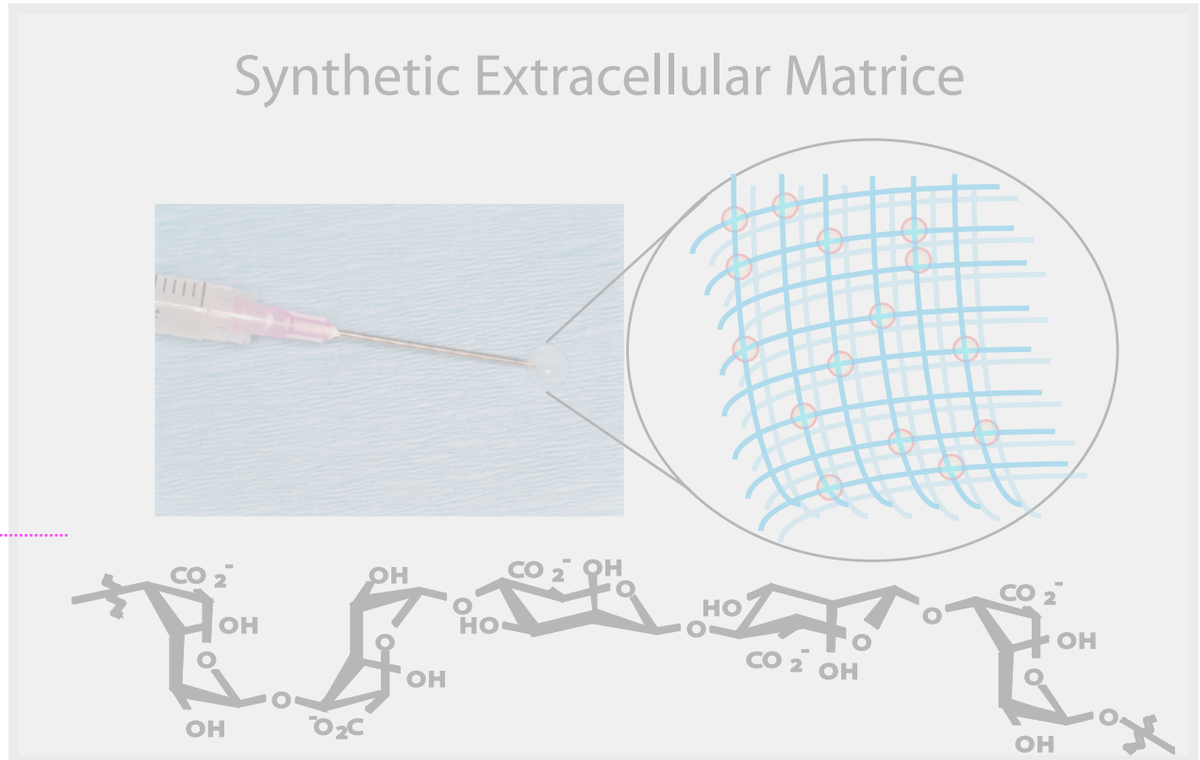
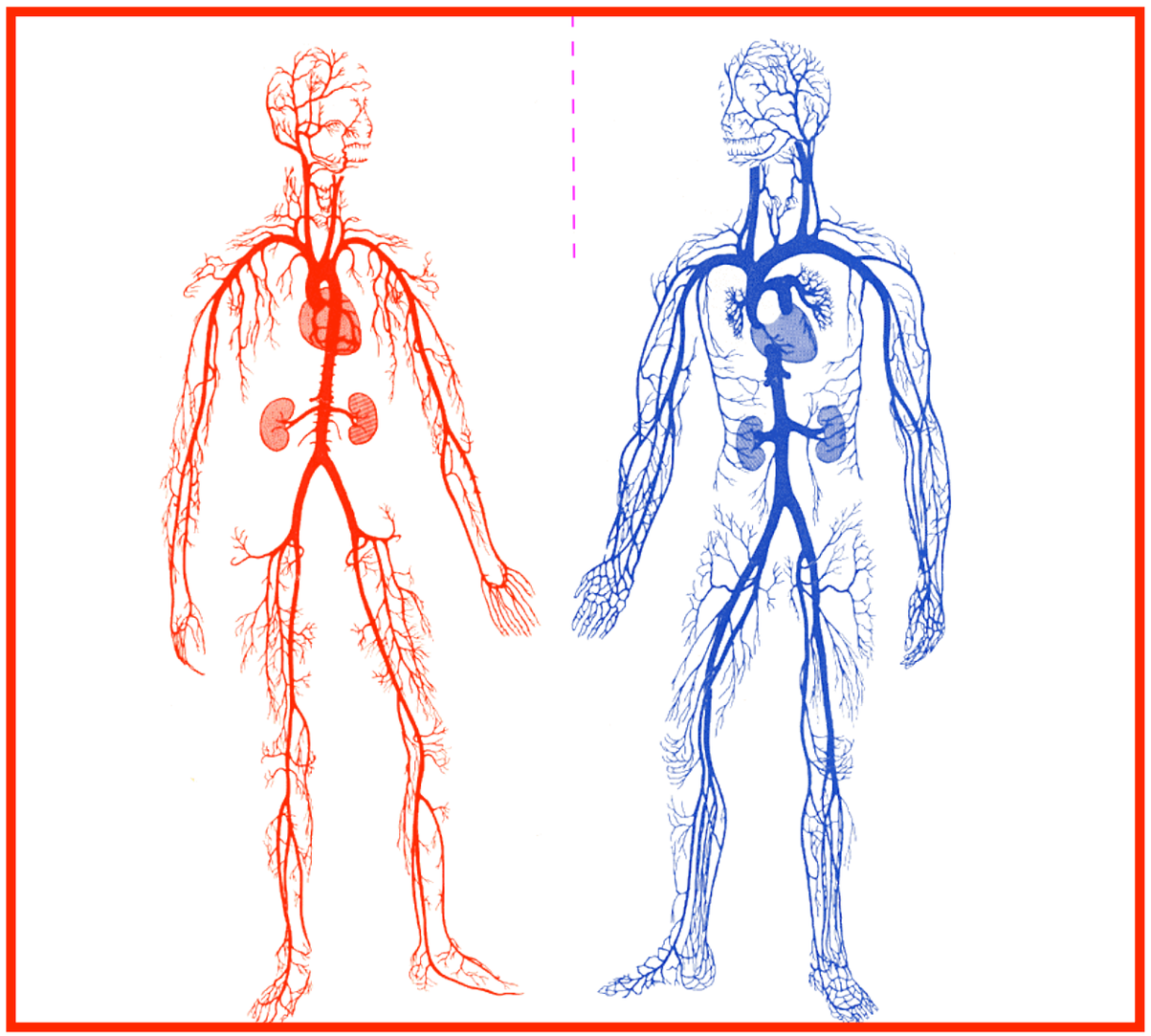
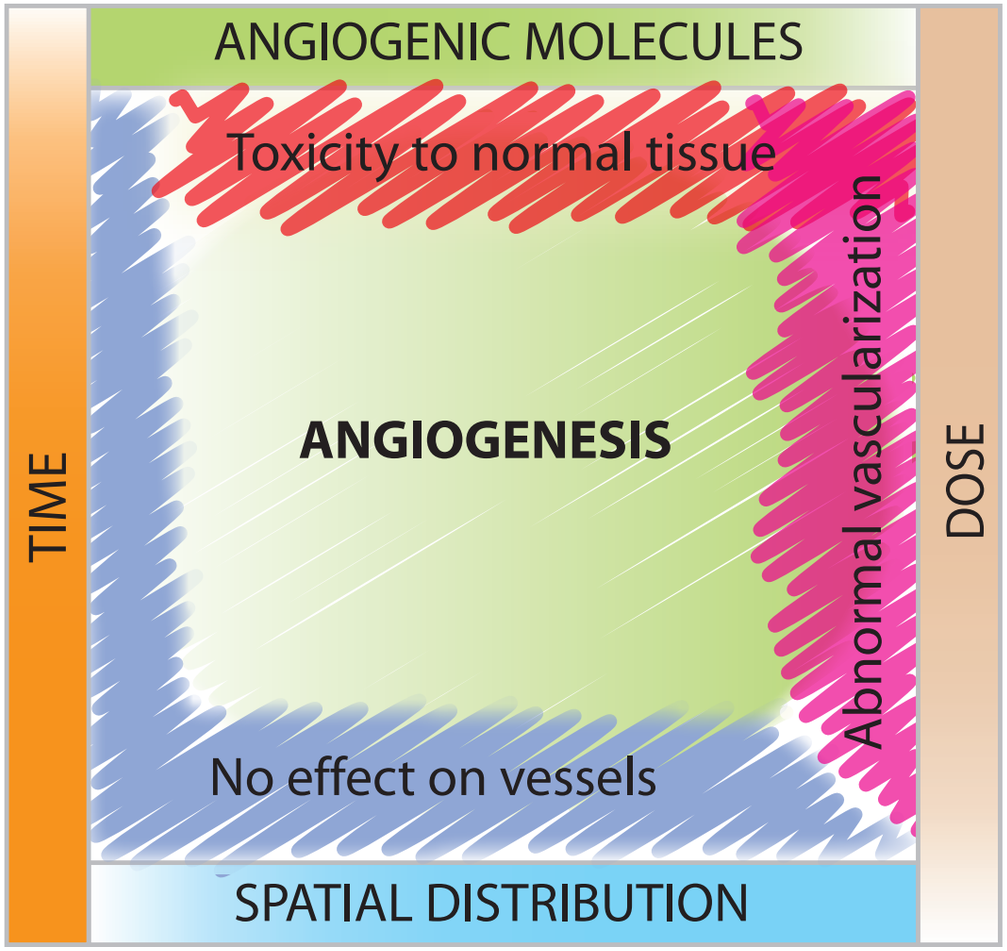
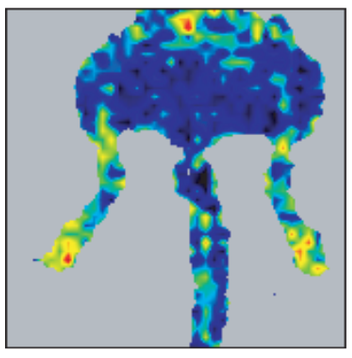




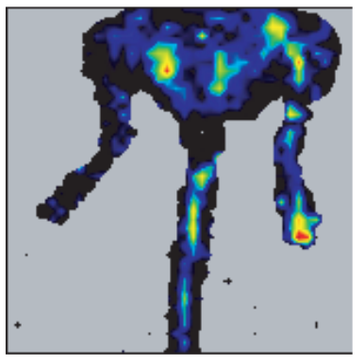


Laser Doppler Perfusion Imaging system (LDPI)

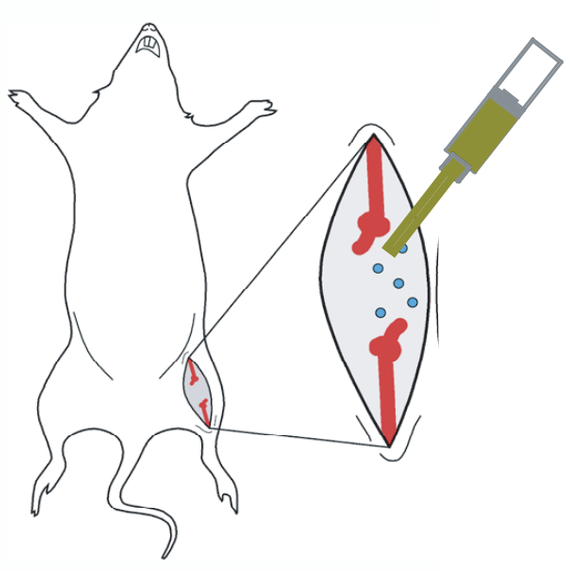
Before

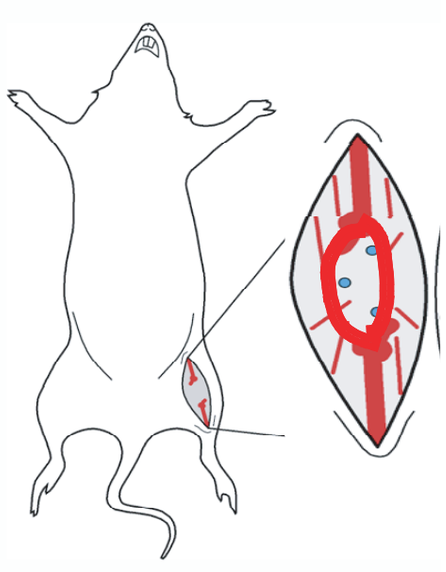


After



ApoE -/- Ischemic HindLimb Model





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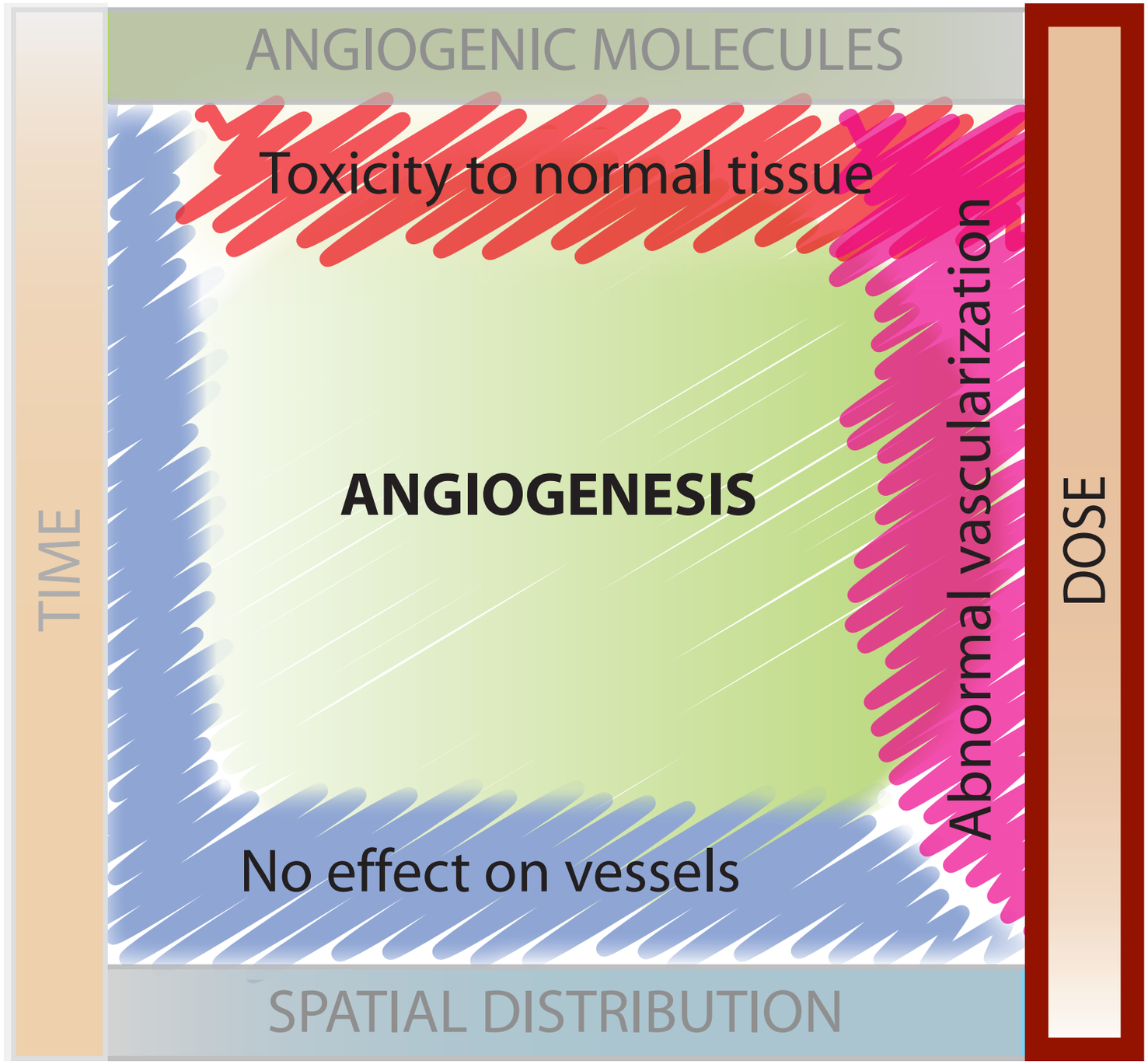
New Networks of blood vessels - In Vivo



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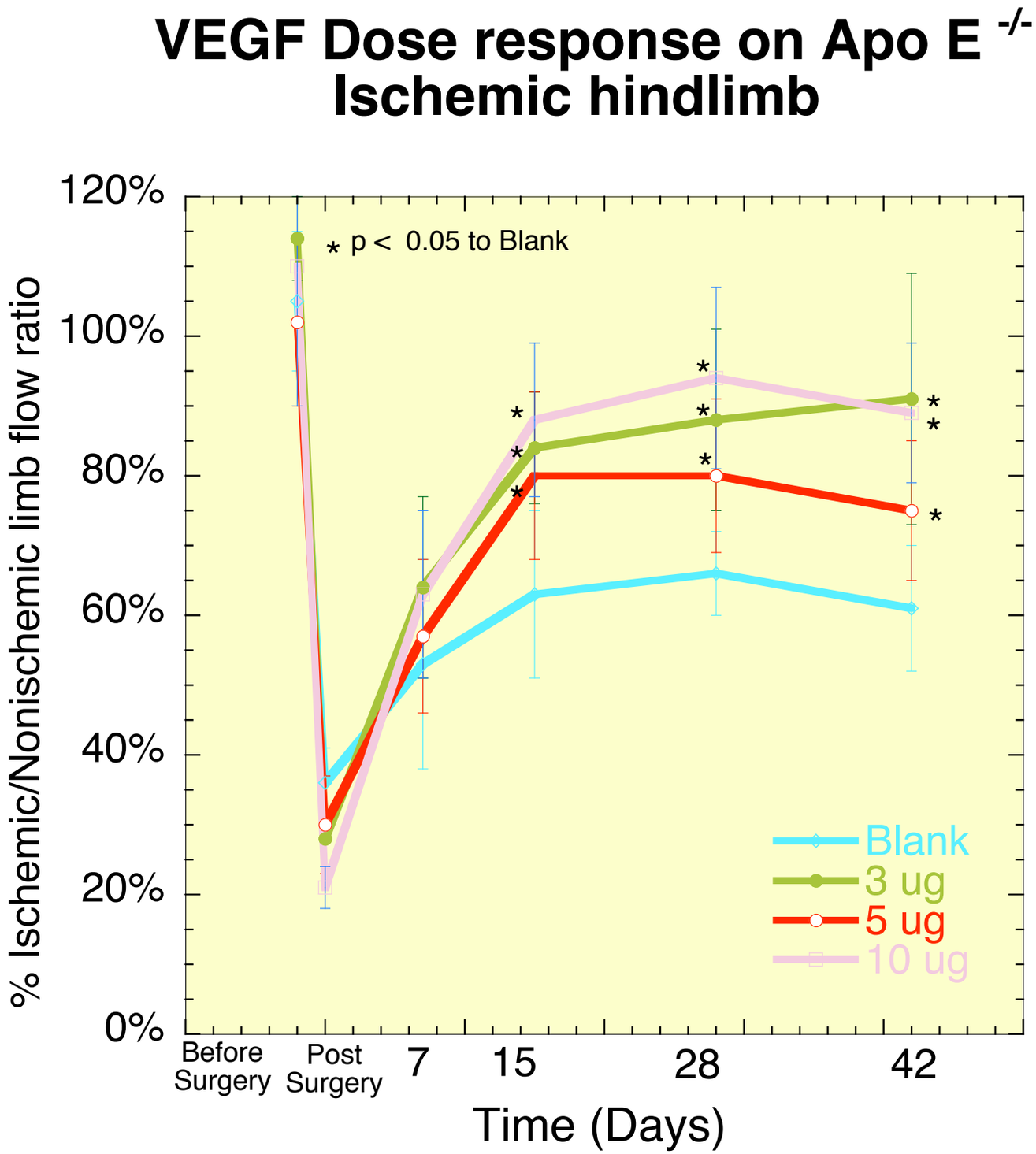

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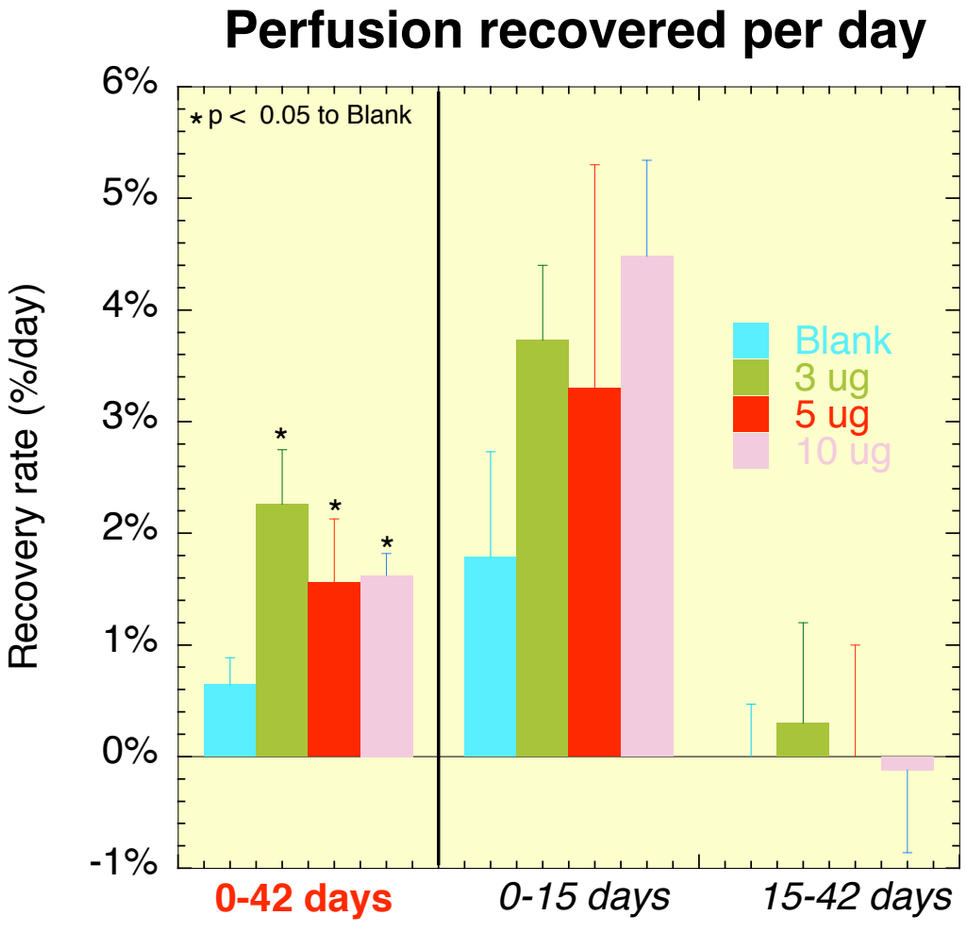

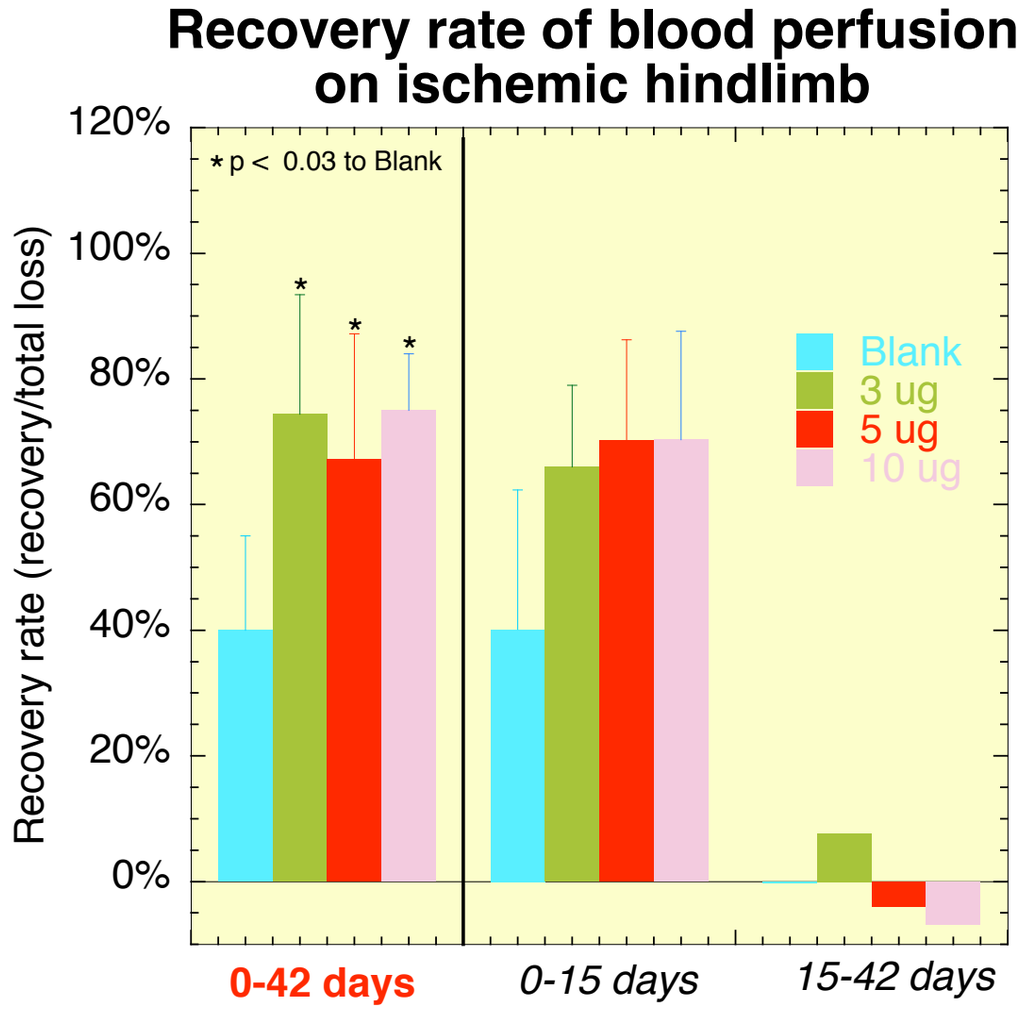

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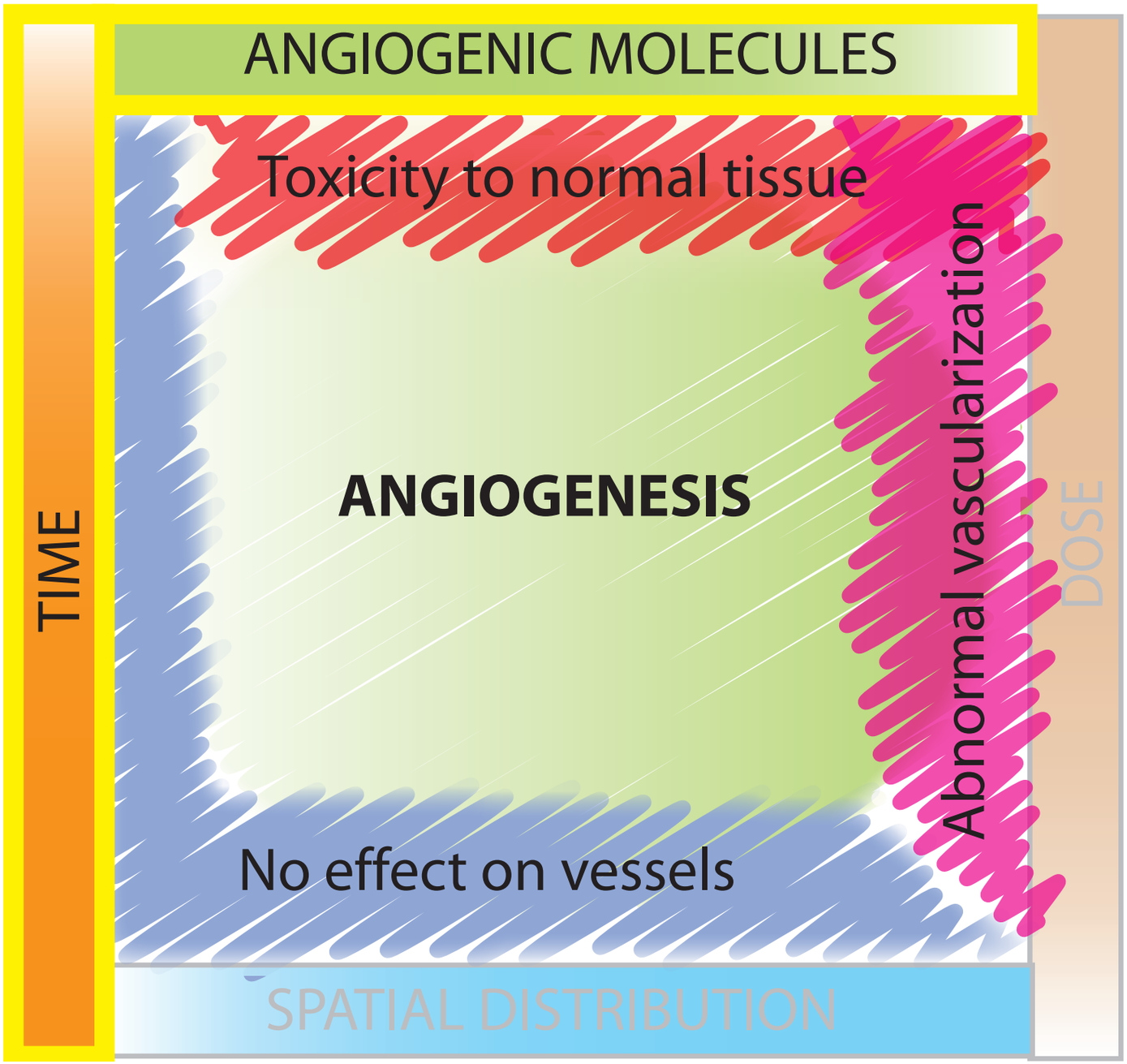

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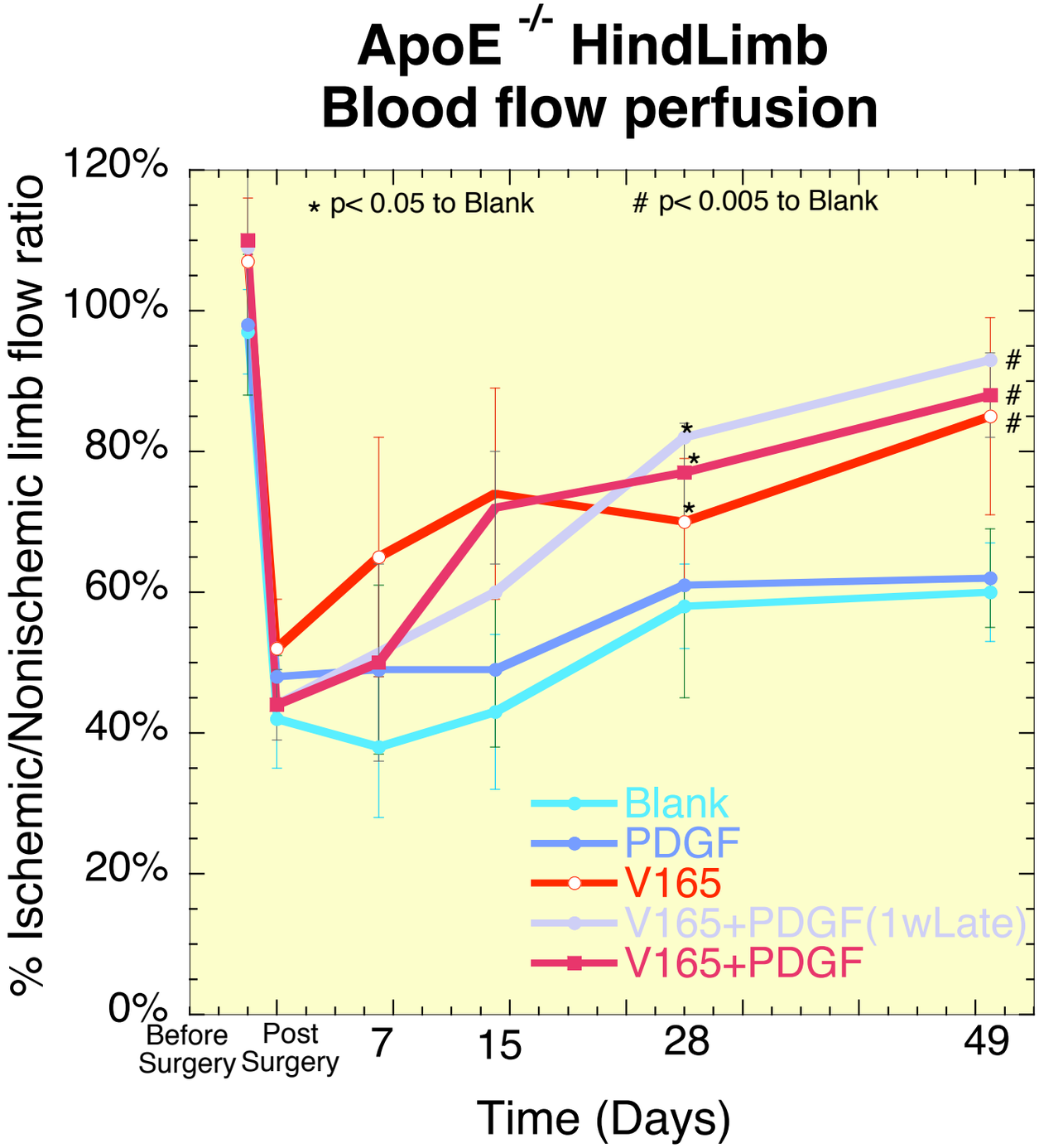
New Networks of blood vessels - In Vivo



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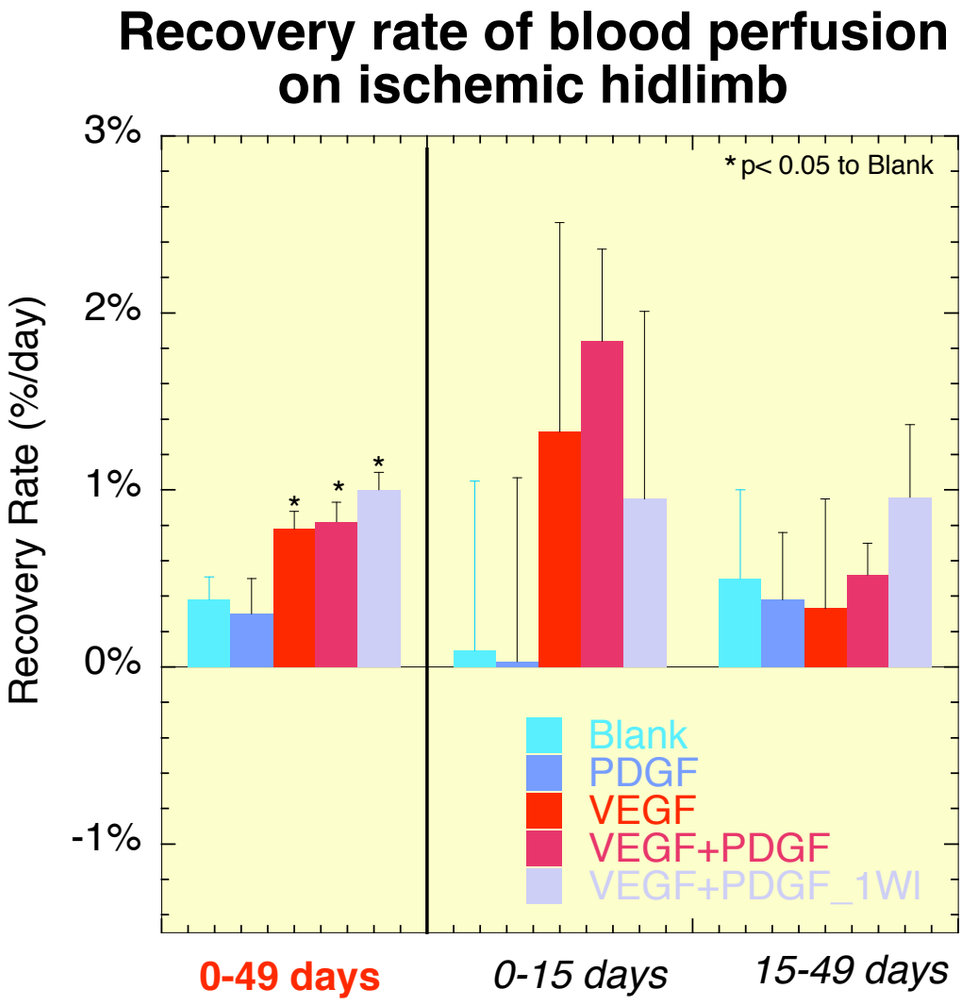
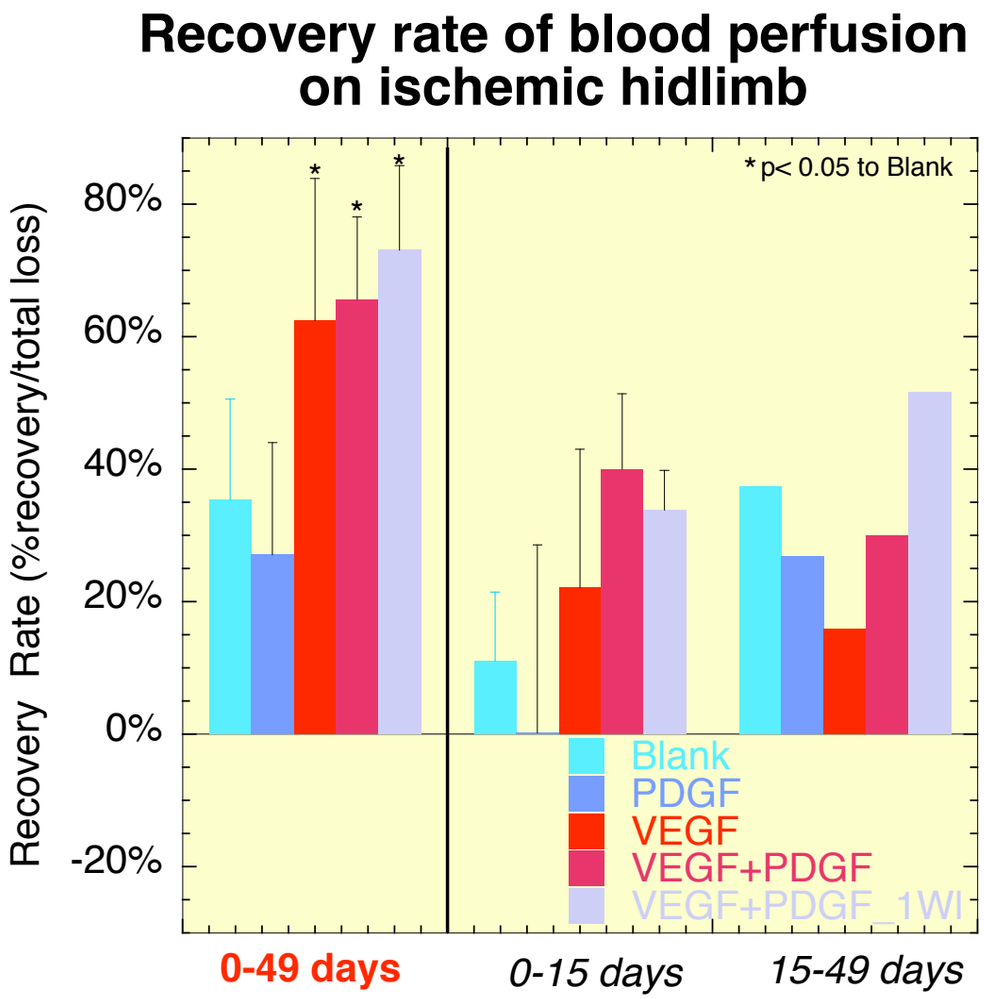
New Networks of blood vessels - In Vivo





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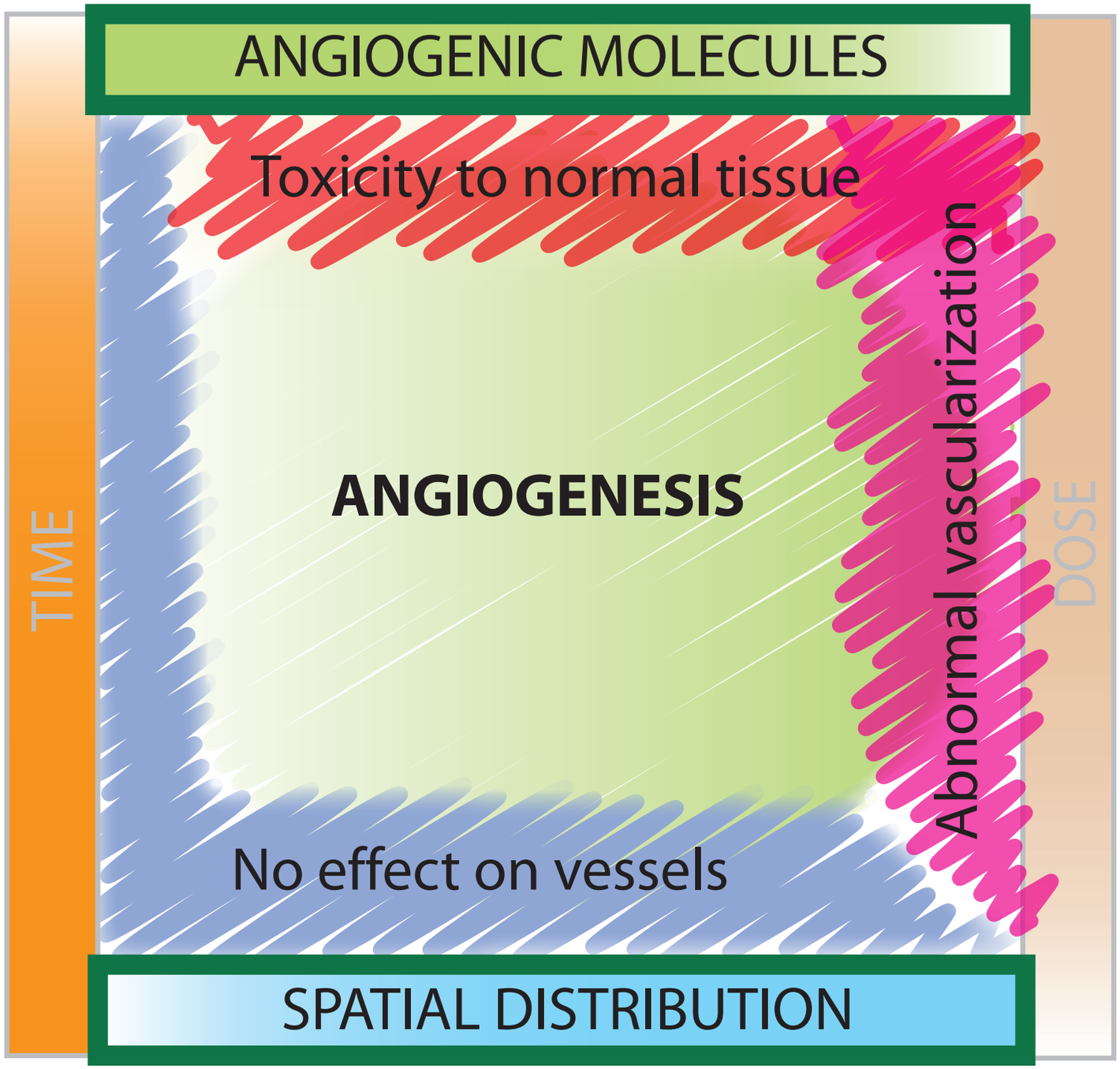

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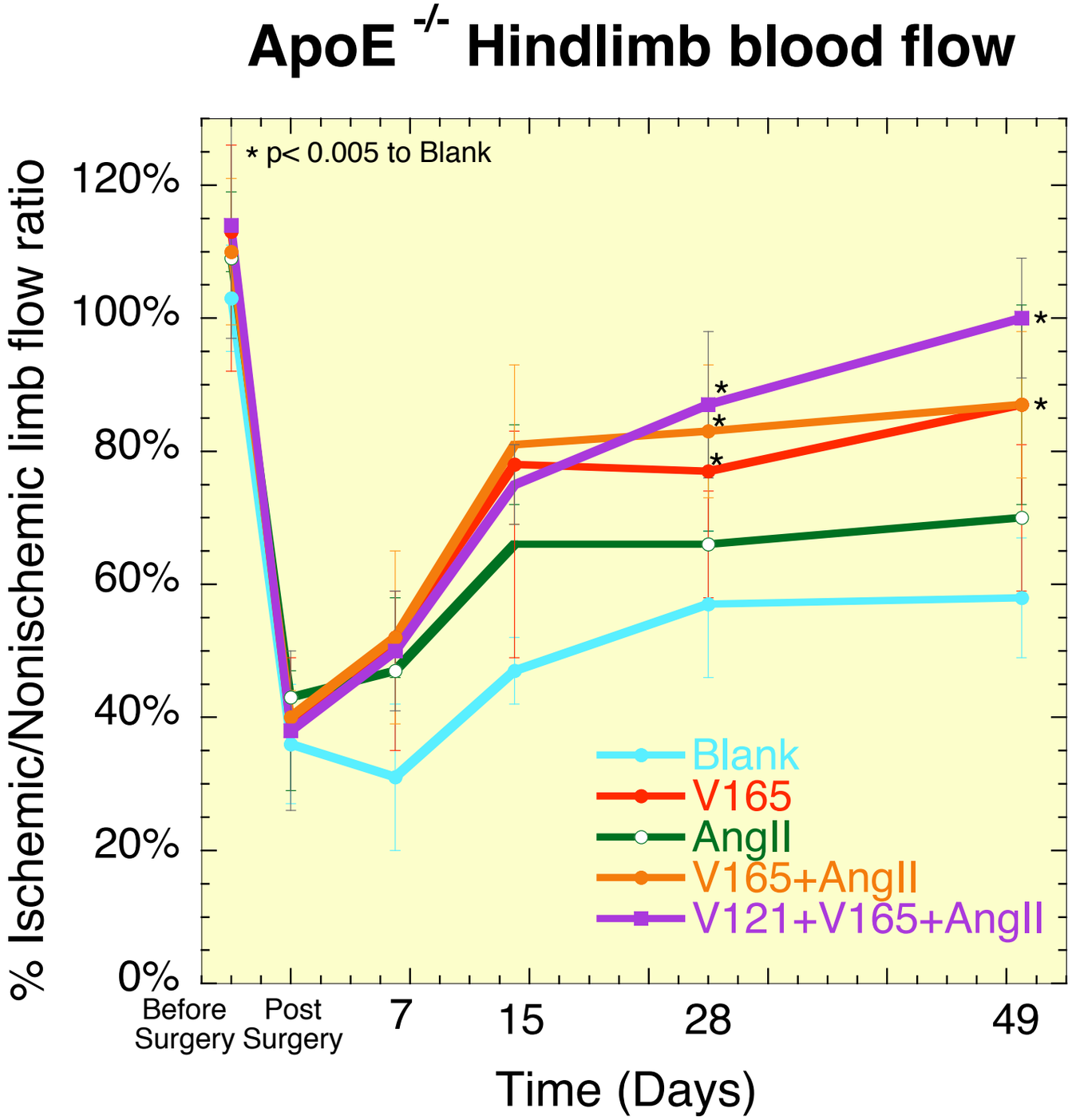

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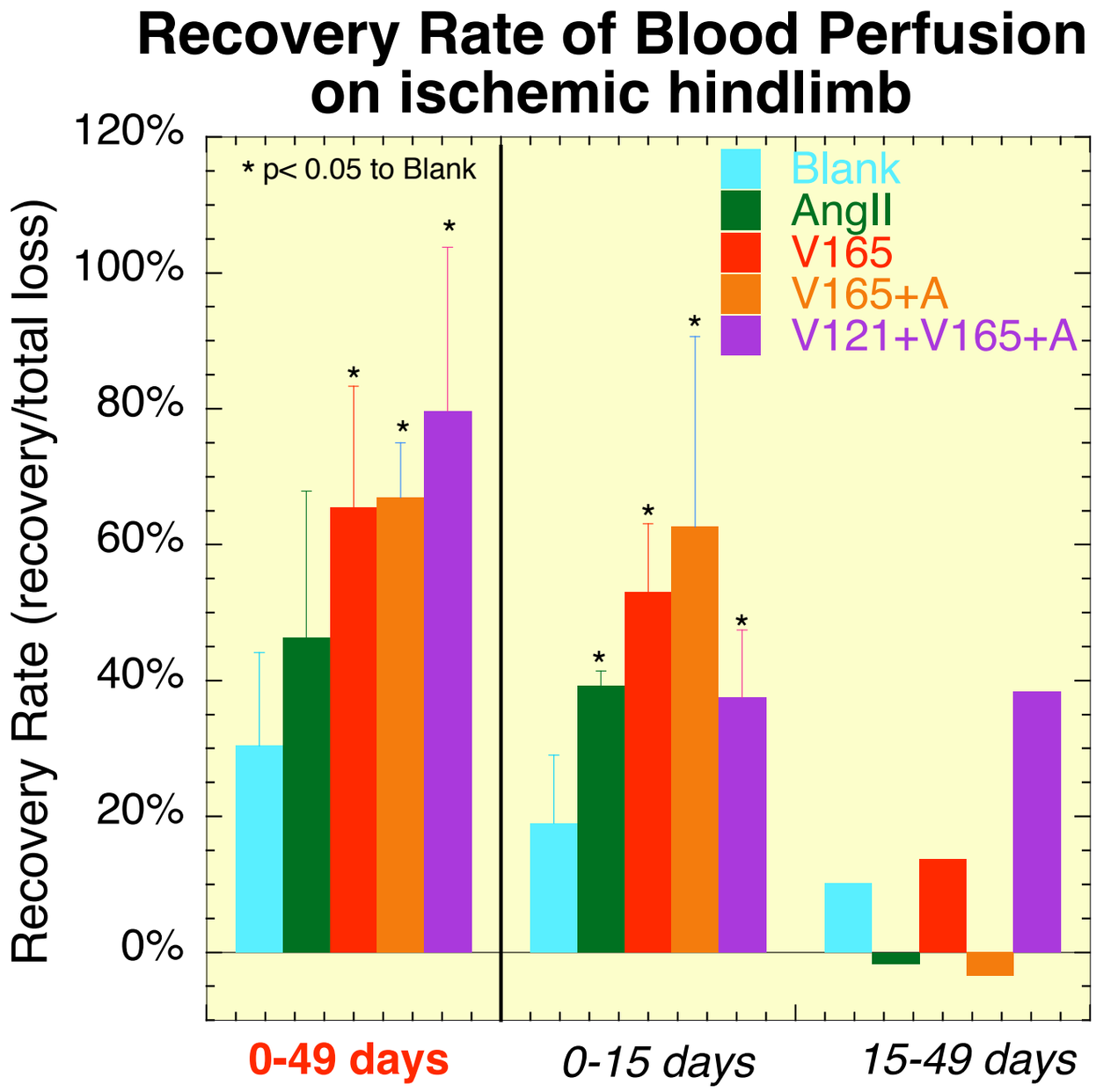

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Conclusions

Sustainable and controlled angiogenic molecules delivery can be achieved with binary alginate

Blood vessel formation and perfusion can be improved by using binary alginate as local multiple delivery vehicle

Multiple administered factor induce a fully functional network in a greater scale than single factor therapy

Future Work

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

Investigate the role of different VEGF isoforms In Vivo

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Engineering *new* networks of blood vessels

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