

Les Interactions Neurovasculaires Dans les Maladies de la Rétine

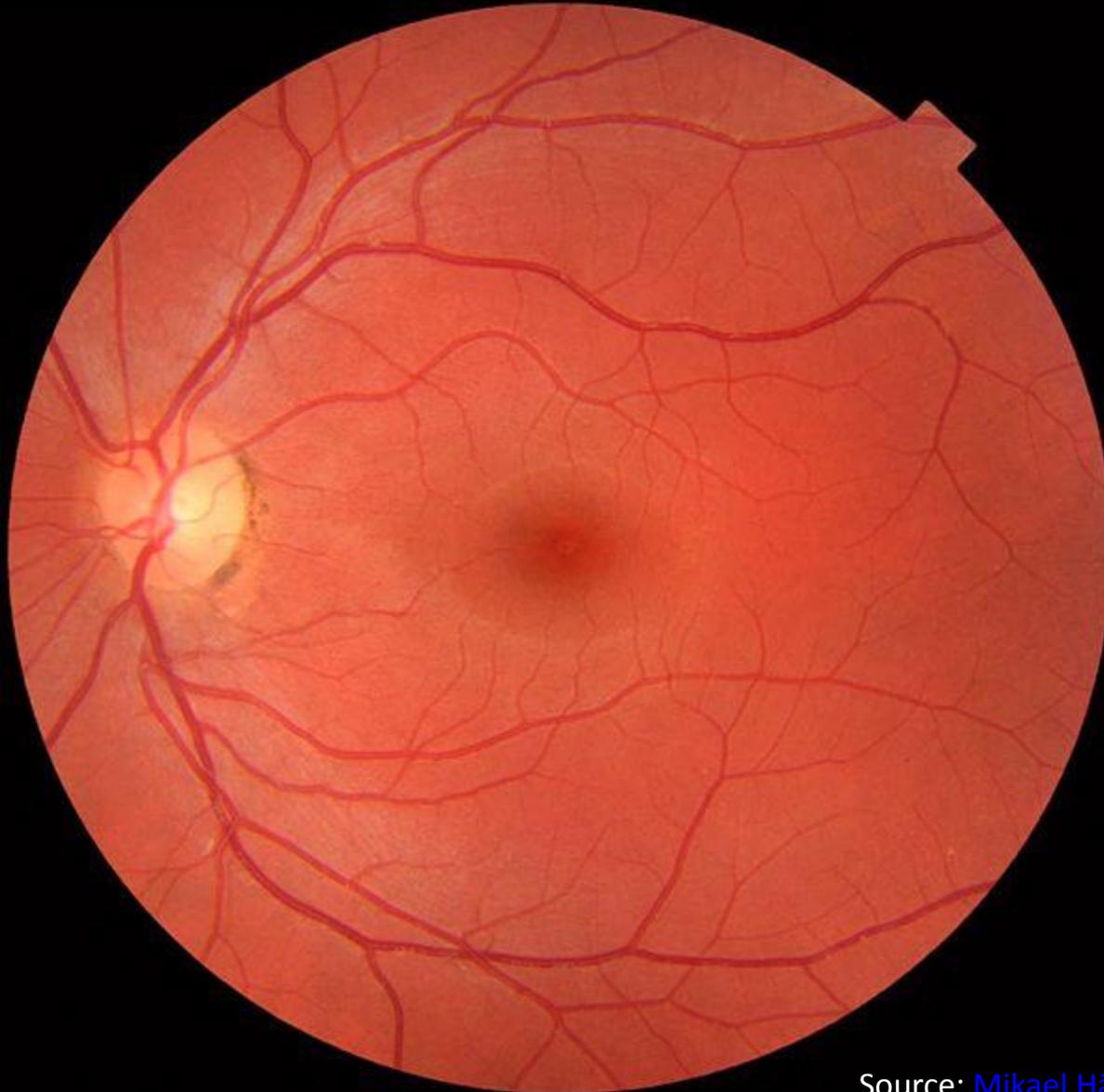
Assemblée Facultaire
Le 9 décembre 2015

Mike Przemyslaw Sapięha, PhD

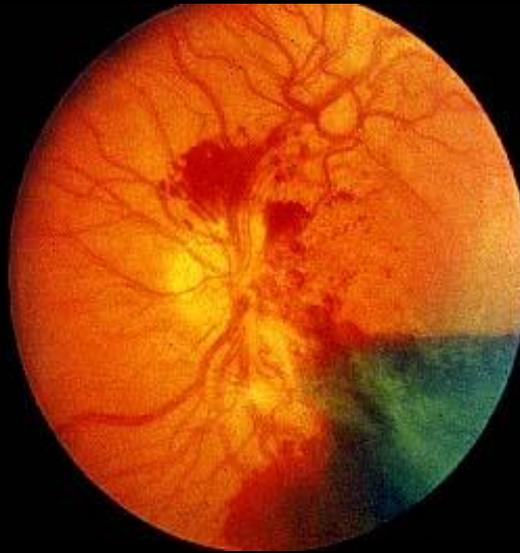
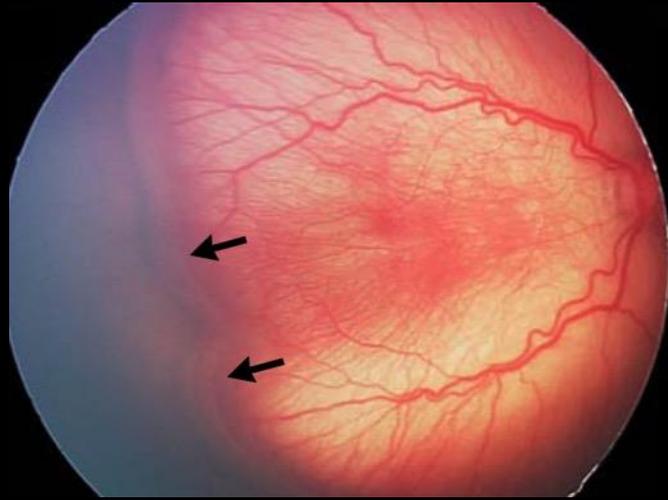
Département d'Ophtalmologie,

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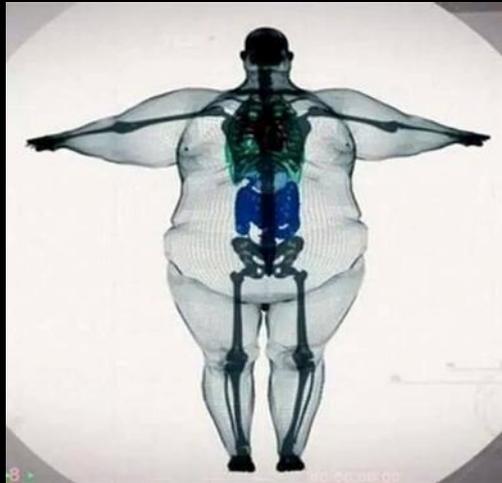
Rétine en santé



Maladies Vasculaires de la Rétine: Principales Causes de Cécité



Rétinopathie du prématuré

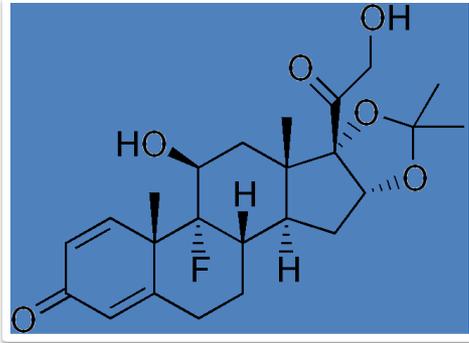


Rétinopathie diabétique

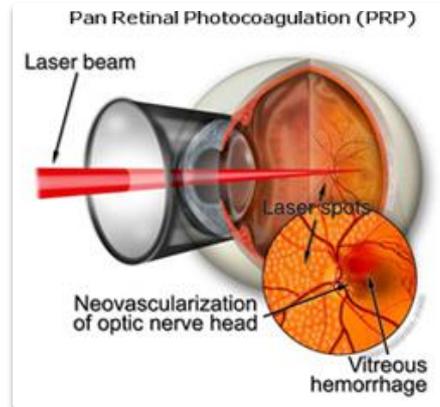


Dégénérescence maculaire
lié à l'âge

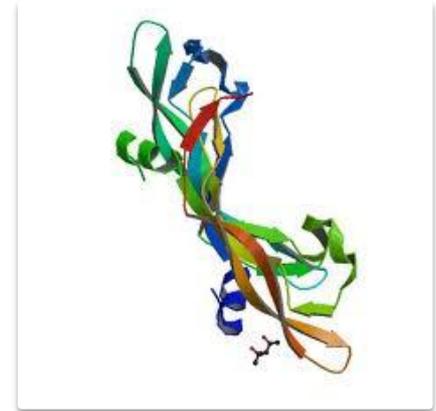
Exemples de traitements pour les complications vasculaires de la rétine



Corticosteroids
(Triamcinolone Acetonide)



Laser Photocoagulation



**Anti-VEGF
Therapy**

Effets Secondaires

- **↑ cataracts formation**
- **↑ intraocular pressure**

- **Partial vision loss (scotomas)**
- Laser Grid/focal for DME: excitation RPE: Liquid absorption
- Panretinal photocoagulation for Proliferative Retinopathies.

- **↑ neuronal toxicity, thromboembolia, and geographic atrophy with long-term use**

Nouvelle approche pour contrer les rétinopathies

Most salient clinical features of DR are of a microvascular nature

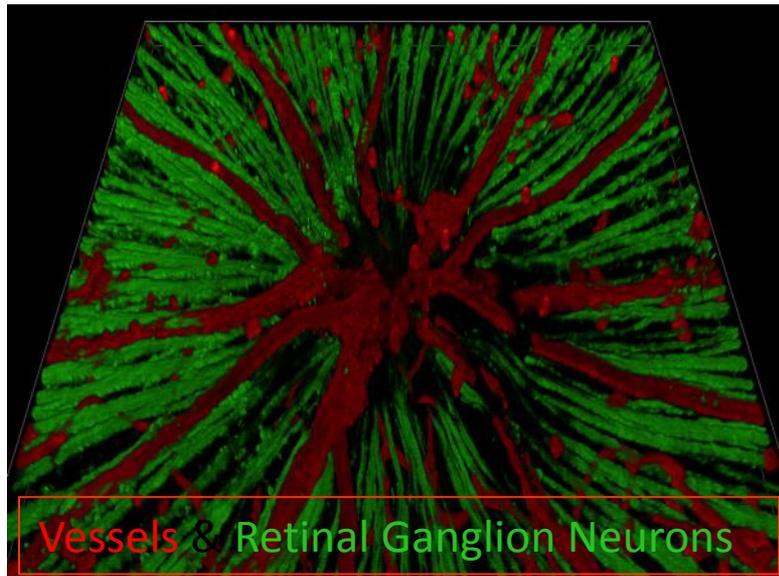


Current research: large focus on anti-VEGF therapy

Early changes in the NEURAL retina



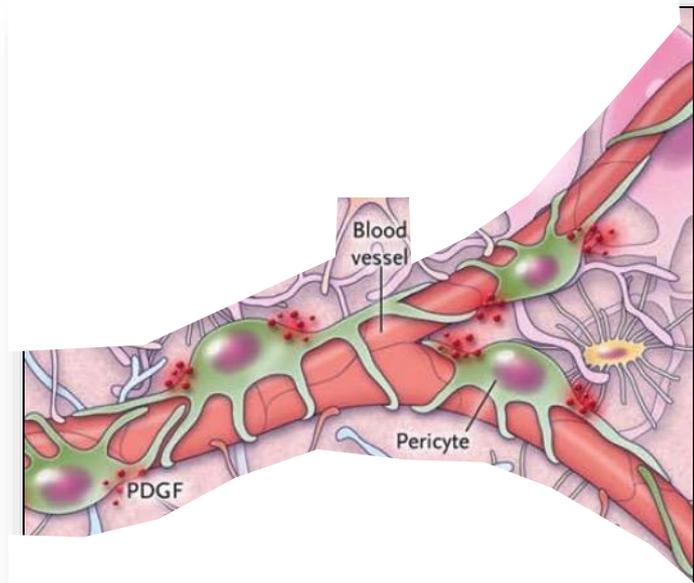
Neuro-vascular interplay in retinopathy



Vessels & Retinal Ganglion Neurons

Sapieha. Blood, 2012

The vascular unit

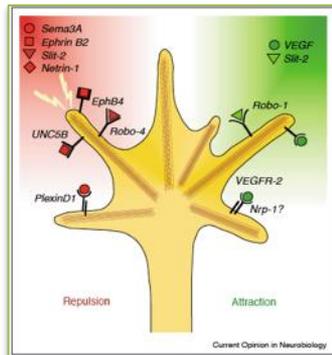
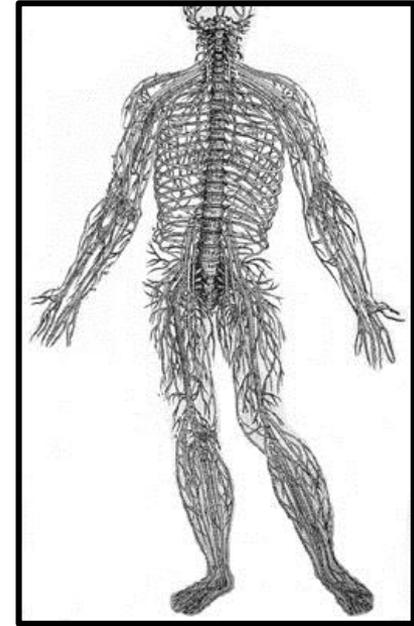
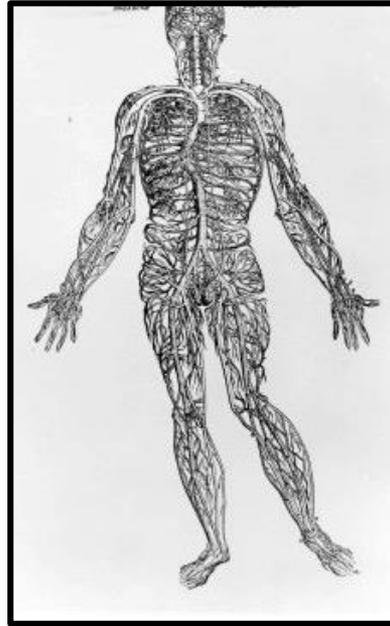


Antonetti *et al.*, N Engl J Med (2012)

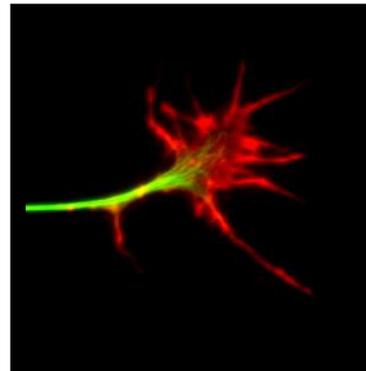
Les neurones et les vaisseaux: un guidage préservé



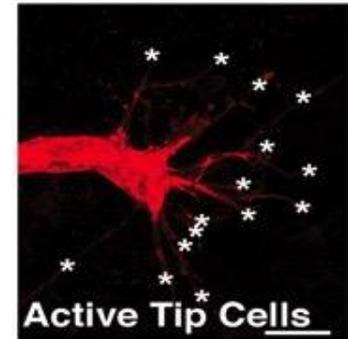
**ANDREAS VESALIUS
(1514-1564)**



Cellule nerveuse



Vaisseau sanguin



Les interactions neurovasculaires dans les rétinopathies

Cell Metabolism

Article

Neuronal ER Stress Impedes Myeloid-Cell-Induced Vascular Regeneration through IRE1 α Degradation of Netrin-1

François Binet,¹ Gaëlle Mawambo,² Nicholas Sitaras,¹ Nicolas Tetreault,⁴ Eric Lapalme,¹ Sandra Favret,¹ Agustin Cerani,² Dominique Leboeuf,³ Sophie Tremblay,¹ Flavio Rezende,¹ Aimee M. Juan,¹ Andreas Stahl,⁵ Jean-Sebastien Joyal,¹ Éric Milot,² Randal J. Kaufman,⁶ Martin Guimond,³ Timothy E. Kennedy,⁴ and Przemyslaw Sapieha^{1,2,4,*}



The Journal of Clinical Investigation

RESEARCH ARTICLE

Neuropilin-1 mediates myeloid cell chemoattraction and influences retinal neuroimmune crosstalk

Agnieszka Dejda,^{1,2} Gaëlle Mawambo,¹ Agustin Cerani,¹ Khalil Miloudi,³ Zhuo Shao,¹ Jean-Francois Daudelin,⁴ Salix Boulet,⁴ Malika Oubaha,³ Felix Beaudoin,¹ Naoufal Akla,² Sullivan Henriques,² Catherine Menard,¹ Andreas Stahl,⁵ Jean-Sébastien Delisle,⁴ Flavio A. Rezende,² Nathalie Labrecque,⁴ and Przemyslaw Sapieha^{1,2,3}

blood

2011 117: 6024-6035
Prepublished online February 25, 2011;
doi:10.1182/blood-2010-10-311589

Ischemic neurons prevent vascular regeneration of neural tissue by secreting semaphorin 3A

Jean-Sébastien Joyal, Nicholas Sitaras, François Binet, Jose Carlos Rivera, Andreas Stahl, Karine Zaniolo, Zhuo Shao, Anna Polosa, Tang Zhu, David Hamel, Mikheil Djavari, Dario Kunik, Jean-Claude Honoré, Emilie Picard, Alexandra Zabejda, Daya R. Varma, Gilles Hickson, Joseph Mancini, Michael Klagsbrun, Santiago Costantino, Christian Beauséjour, Pierre Lachapelle, Lois E. H. Smith, Sylvain Chemtob and Przemyslaw Sapieha

Cell Metabolism

Article

Neuron-Derived Semaphorin 3A Is an Early Inducer of Vascular Permeability in Diabetic Retinopathy via Neuropilin-1

Agustin Cerani,^{1,2,4} Nicolas Tetreault,^{2,3,4} Catherine Menard,^{2,4} Eric Lapalme,¹ Chintan Patel,¹ Nicholas Sitaras,¹ Felix Beaudoin,² Dominique Leboeuf,² Vincent De Guire,² François Binet,¹ Agnieszka Dejda,² Flavio A. Rezende,¹ Khalil Miloudi,³ and Przemyslaw Sapieha^{1,2,3,*}



Cell Metabolism

ER Stress and Angiogenesis



blood

Eyeing central neurons in vascular growth and reparative angiogenesis

Przemyslaw Sapieha^{1,2}

¹Department of Ophthalmology & Biochemistry, Maisonneuve-Rosemont Hospital Research Centre, University of Montreal, Montreal, QC; and ²Department of Neurology-Neurosurgery, McGill University, Montreal, QC

François Binet¹ and Przemyslaw Sapieha^{1,2,*}

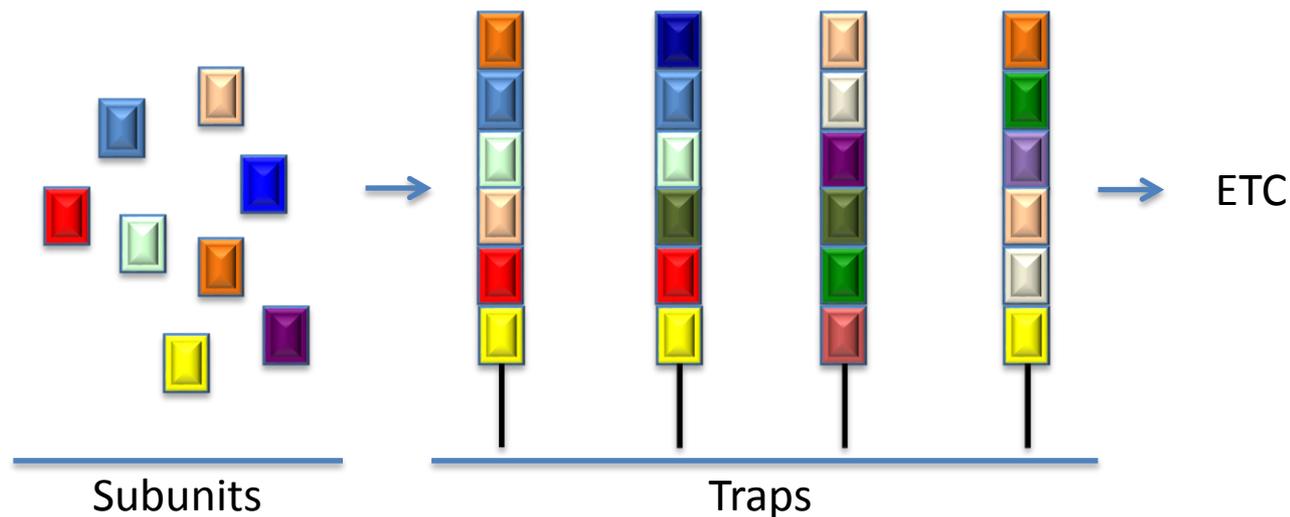
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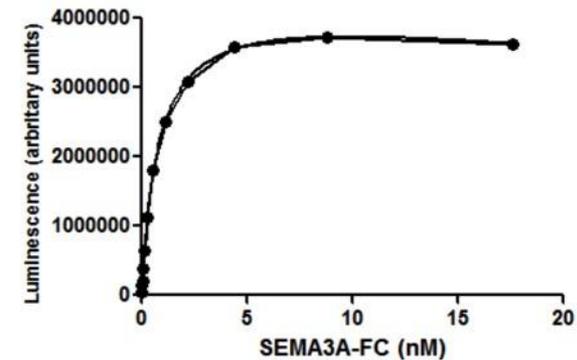
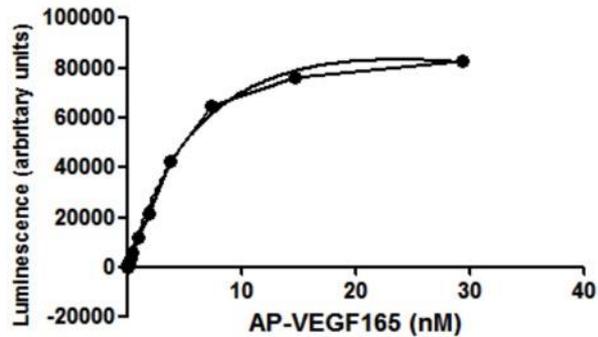
*Correspondence: mike.sapieha@umontreal.ca

Modulation thérapeutique des molécules de guidage neuronal

- 1- We have generated over 20 different TRAPS with various binding affinities for SEMA3A and VEGF165 and are testing efficacy in various models of retinal pathological retinal angiogenesis.
- 2- Our trap technology is highly modular and hence we can customize binding affinities towards different ligands.
- 3- We have already designed and produced several nM inhibitors for SEMA3A and/or VEGF with potent in vivo efficacy.

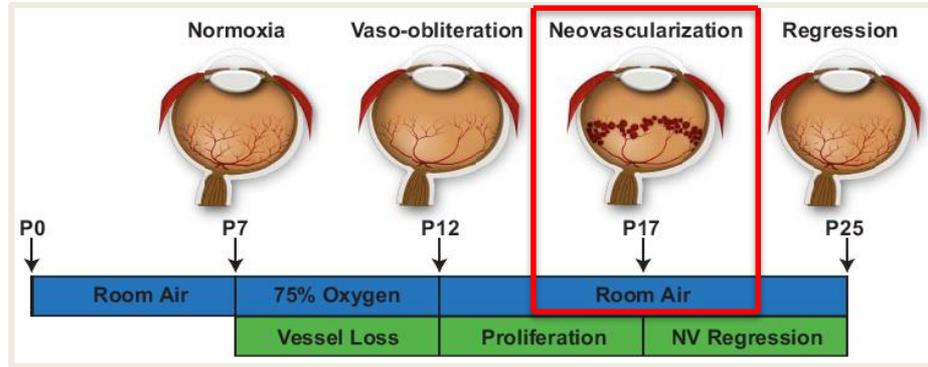


Kd pour les SEMA-TRAPS

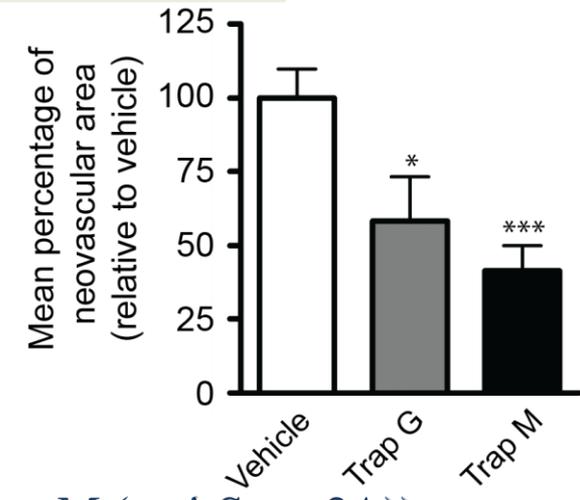
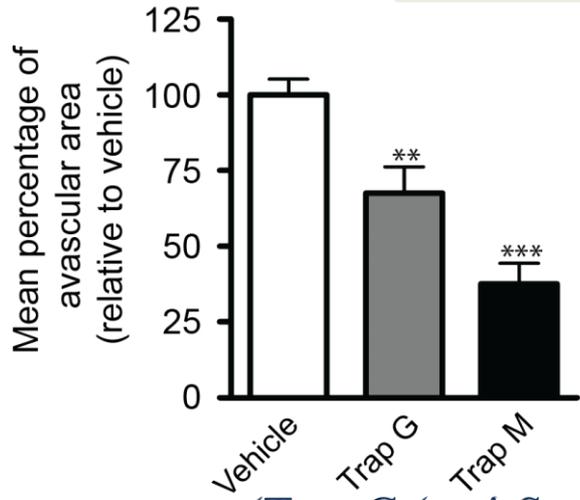


| Trap | SEMA3A-FC binding (nM) | AP-VEGF165 binding (nM) |
|------|------------------------|-------------------------|
| G | 0.8 | 6.75 |
| M | 0.95 | 20.13 |
| R | 6.15 | ND |
| W | 1.14 | 20.73 |
| Z | 4.44 | 66.96 |
| AB | ND | 29.51 |
| AC | 4 | No binding |

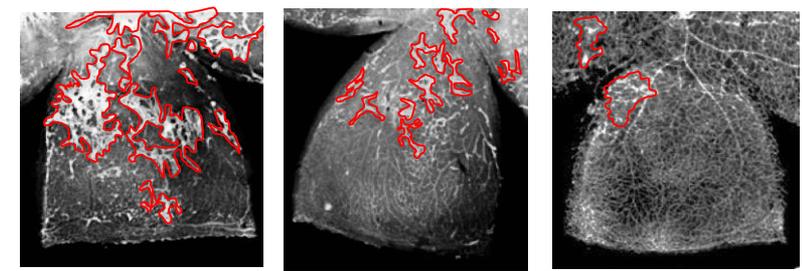
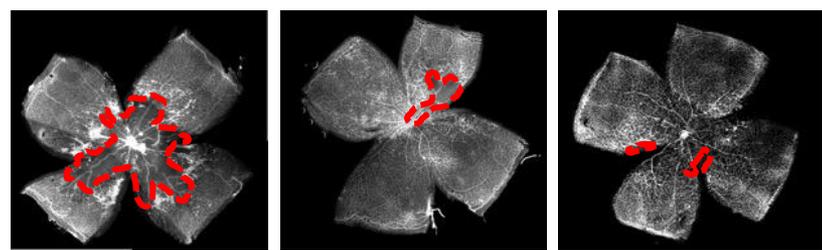
Les SEMA-TRAPs accélèrent la régénération vasculaire et inhibe l'angiogénese pathologique.



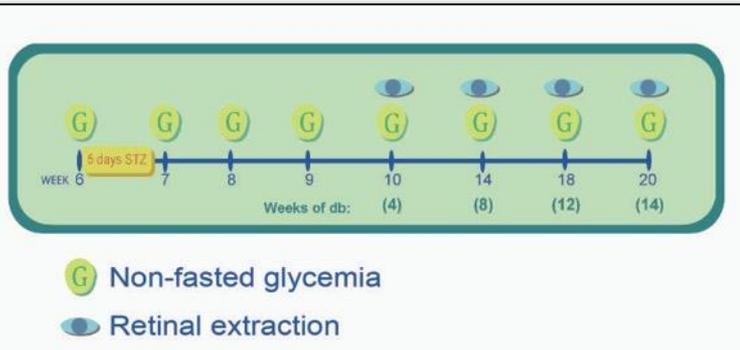
Stahl et al. IOVS. 2010



(Trap G (anti-Sema and anti-VEGF vs Trap M (anti-Sema3A))

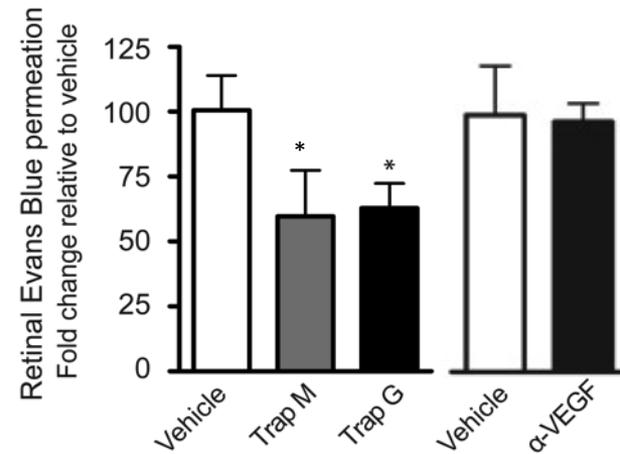
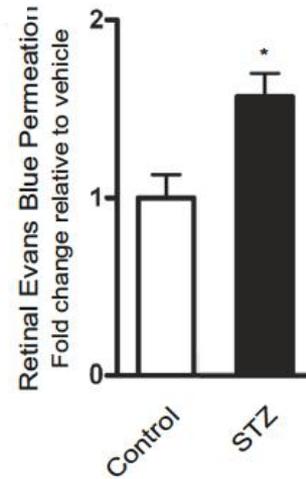
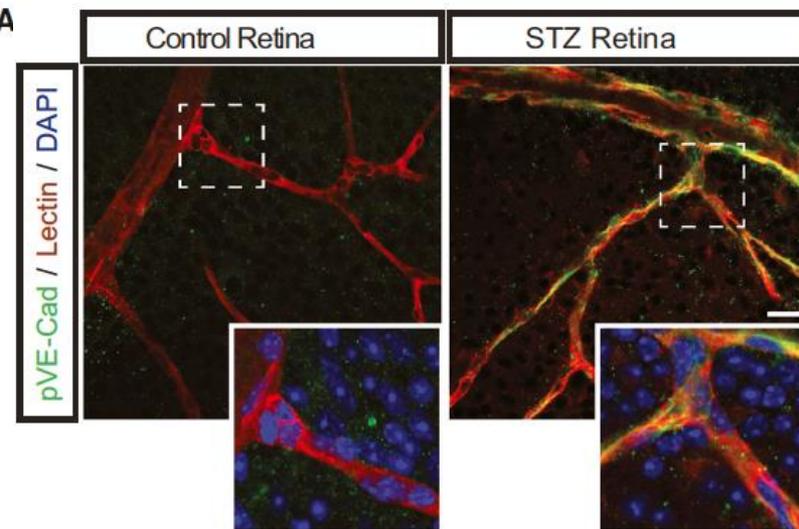


Les SEMA-TRAPs réduisent l'œdème rétinien



0.5ug/ul injected intravitreally at 6 & 7 week post STZ.

Assessment of retinal barrier function at 8 weeks.



Remerciements

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