CASEY EYE Institute
OHSU

Retinal Research Update

2018 Ophthalmic Medical Technology Program
Joe Simonett, MD

Overview

- Anti-VEGF: History and Data
- Data on the complications of intravitreal injection
- Research on emerging technologies for rare diseases

"Pure retinal neovascularization is directly related to a tissue state of relative retinal anoxia. Under such circumstances, an unknown **factor x** develops in this tissue and stimulates new vessel formation."

Wise GN. Retinal neovascularization. Trans Am Ophthalmol Soc. 1956;54:729-826.

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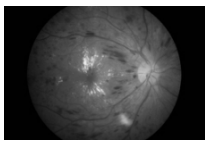

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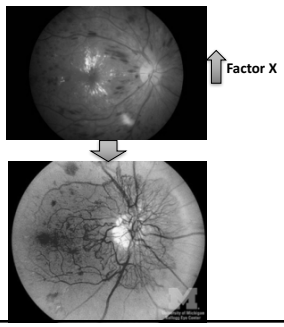

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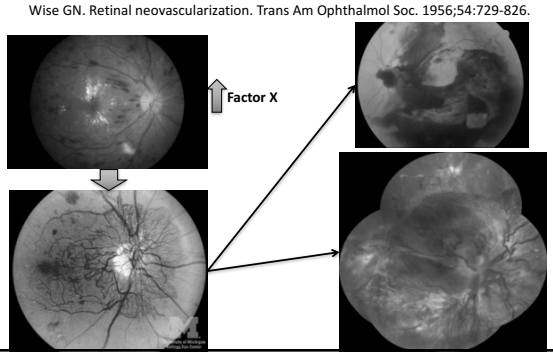
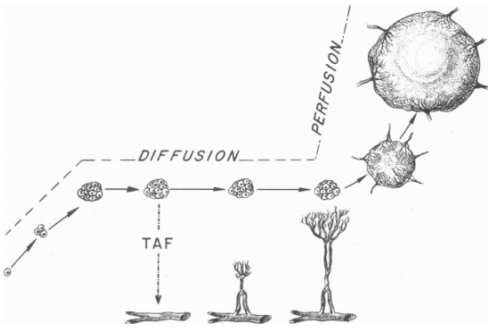


Illustration of the Concept That Most Solid Tumors May Exist Early as Tiny Cell Populations Living by Simple Diffusion in the Extracellular Space (Further Growth Requires Vascularization, and the Tumor Then Maintains Itself by Perfusion).



Folkman J. N Engl J Med 1971;285:1182-1186.

Science AAAS December 1989

REPORTS
Vascular endothelial growth factor is a secreted angiogenic mitogen
DW Leung, G Cachianes, WJ Kuang, DV Goeddel, N Ferrara
Department of Molecular Biology, Genetech, South San Francisco, CA 94080.

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PJ Keck, SD Hauser, G Krivi, K Sanzo, T Warren, J Feder, DT Connolly
+ See all authors and affiliations

Induced angiogenesis

Induced vascular permeability

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Induced angiogenesis

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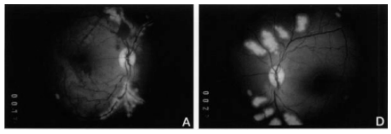
VEGF

Vascular Endothelial Growth Factor/Vascular Permeability Factor Is Temporally and Spatially Correlated with Ocular Angiogenesis in a Primate Model Joan W. Miller et al. 1994



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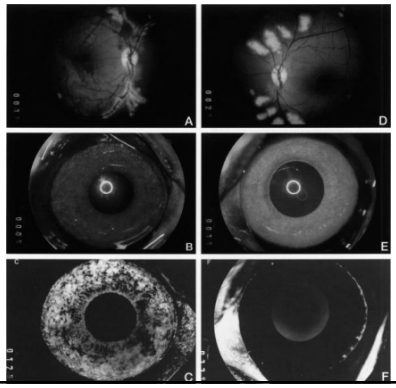

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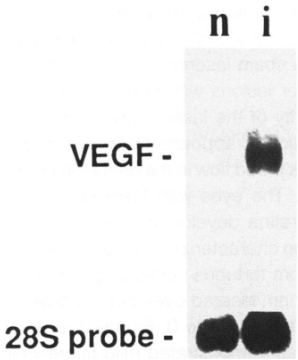
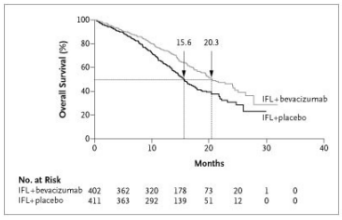


The NEW ENGLAND JOURNAL of MEDICINE

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., et al.

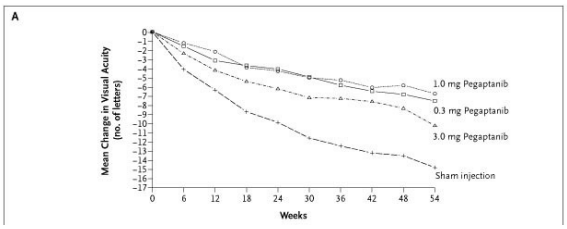


FDA approval in February 2004

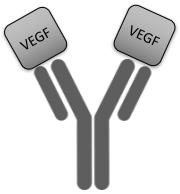
The NEW ENGLAND JOURNAL of MEDICINE

Pegaptanib for Neovascular Age-Related Macular Degeneration

Evangelos S. Gragoudas, M.D., Anthony P. Adamis, M.D., Emmett T. Cunningham, Jr., M.D., Ph.D., M.P.H., Matthew Feinsod, M.D., and David R. Guyer, M.D. for the VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group



FDA approval in December 2004



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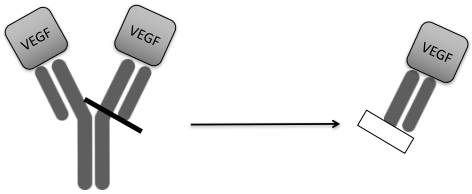
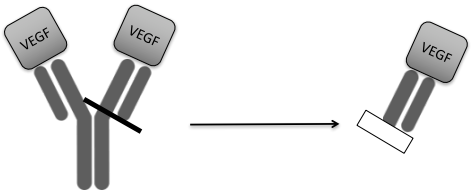
Bevacizuman (Avastin)



Bevacizuman (Avastin) Ranibizumab (Lucentis)



Bevacizuman (Avastin) Ranibizumab (Lucentis)

↓

Phase 3 clinical trials MARINA and ANCHOR

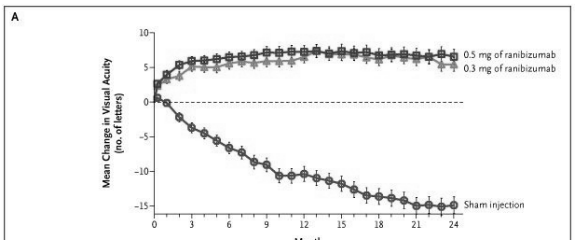
↓

FDA approved in 2006

The NEW ENGLAND JOURNAL of MEDICINE

Ranibizumab for Neovascular Age-Related Macular Degeneration

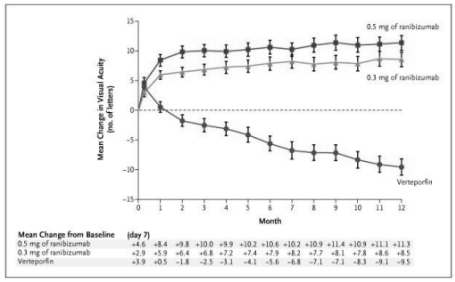
Philip J. Rosenfeld, M.D., Ph.D., David M. Brown, M.D., Jeffrey S. Heier, M.D., David S. Boyer, M.D., Peter K. Kaiser, M.D., Carol Y. Chung, Ph.D., and Robert Y. Kim, M.D. for the MARINA Study Group*



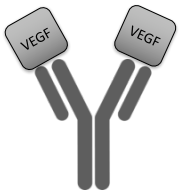
The NEW ENGLAND JOURNAL of MEDICINE

Ranibizumab versus Verteporfin for Neovascular Age-Related Macular Degeneration

David M. Brown, M.D., Peter K. Kaiser, M.D., Mark Michels, M.D., Gisele Soubrane, M.D., Jeffrey S. Heier, M.D., Robert Y. Kim, M.D., Judy P. Sy, Ph.D., and Susan Schneider, M.D. for the ANCHOR Study Group*



Mean Change from Baseline	(day 7)												
0.5 mg of ranibizumab	+4.6	+8.4	+9.8	+10.0	+9.9	+10.2	+10.6	+10.2	+10.9	+11.4	+10.9	+11.1	+11.3
0.3 mg of ranibizumab	+2.9	+5.9	+6.4	+6.8	+7.2	+7.4	+7.9	+8.2	+7.7	+8.1	+7.8	+8.6	+8.5
Verteporfin	+3.9	+0.5	−1.8	−2.5	−3.1	−4.1	−5.6	−6.8	−7.1	−7.1	−8.3	−9.1	−9.5



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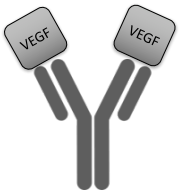

← Too big?? - Nope

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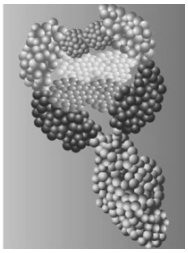


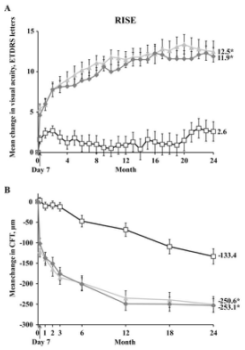
← VEGF receptor protein

← Human antibody portion

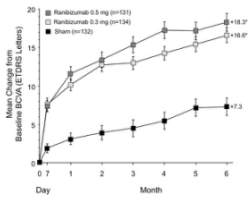
Aflibercept (Eylea)

-Higher VEGF binding affinity
-Improved pharmacokinetics in the vitreous
VIEW trial → Q2 month dosing

Macular edema in diabetes



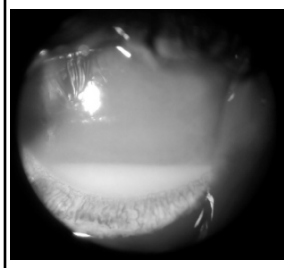
Macular edema in vein occlusions



Complications of intravitreal injections

- Damage to intraocular structures (trauma to lens or retina)
- IOP spike
- Corneal abrasion
- Sub-conjunctival hemorrhage
- Reflux of drug
- And…

Endophthalmitis



- Most feared complication, by patient and providers
- Risk ranges 0.019% to 0.056% per injection
  - Higher cumulative risk
- 5,000 intravitreal injections per year prior to 2001, 2,500,000 in 2014

Culture Proven Endophthalmitis after Intravitreal Injection: A 10-Year Analysis

Joseph M. Simonett, Austin Igelman, Stanford C. Taylor, J. Peter Campbell, Thomas S. Hwang, Phoebe Lin, Andreas K. Lauer, Christina J. Flaxel

35 cases of culture-positive endophthalmitis associated with IVI

- Visual acuity ranged from 20/60 to NLP (63% HM or worse)
- Average time of presentation 3.8 days after injection (~10% of patients presented on post-injection day #1)
- ~50% of patients had 20/200 or better at last follow up

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Joseph M. Simonett, Austin Igelman, Stanford C. Taylor, J. Peter Campbell, Thomas S. Hwang, Phoebe Lin, Andreas K. Lauer, Christina J. Flaxel

Bacterial isolate	N (%Total)
Coagulase-negative *staphylococcus*	20 (57.1)
S. epidermidis	8 (22.9)
S. lugdunensis	2 (5.7)
Unspecified species	10 (28.6)
Staphylococcus aureus	3 (8.6)
Streptococcus species	9 (25.7)
S. mitis	6 (17.1)
S. pneumoniae	1 (2.9)
S. salivarius	1 (2.9)
Unspecified species	1 (2.9)
Enterococcus Faecalis	2 (5.7)
Haemophilus influenza	1 (2.9)

	Bacteria associated with oral or respiratory flora	Other bacteria	p-value
Days from IVI to presentation	2.0 ± 0.6	4.61 ± 4.6	**<0.001**
Presenting visual acuity HM or worse	90.0% (9)	59.1% (12)	**0.038**
Underwent PPV	81.8% (9)	25.0% (6)	**0.002**
Visual acuity HM or worse at one month	66.7% (6)	16.7% (3)	**0.009**
Visual acuity HM or worse at last available visit	77.8% (7)	16.7% (3)	**0.002**

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Streptococcus spe	
S.	
S.	
S.	
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Enterococcus Fae	
Haemophilus infl	

	Bacteria associated with oral or respiratory flora	Other bacteria	p-value
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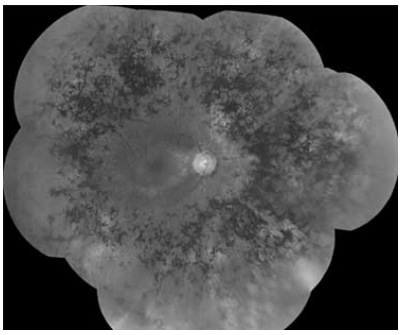
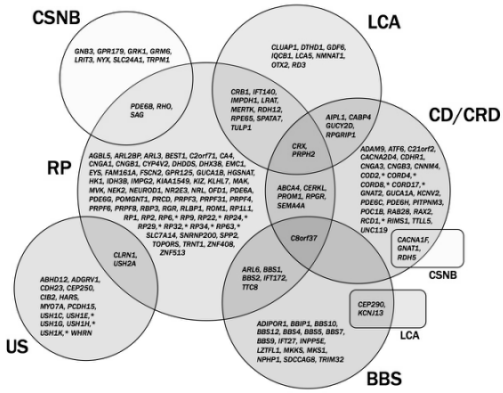
	81.8% (9)	25.0% (6)	**0.002**
d or worse	66.7% (6)	16.7% (3)	**0.009**
d or worse visit	77.8% (7)	16.7% (3)	**0.002**

New treatments for rare diseases

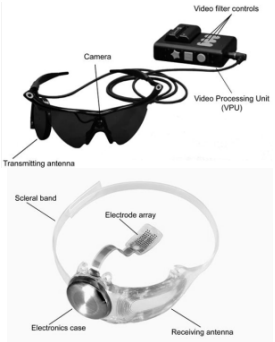


New treatments for rare diseases



New treatments for rare diseases

Retinal Prosthesis



New treatments for rare diseases

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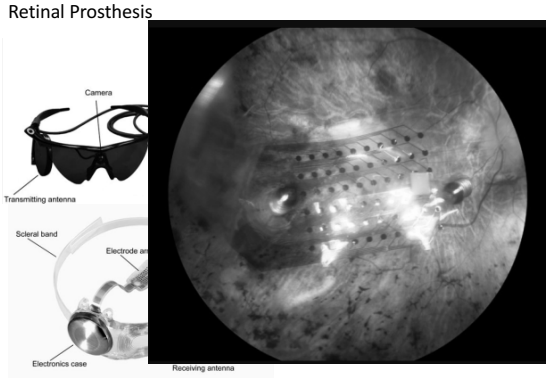
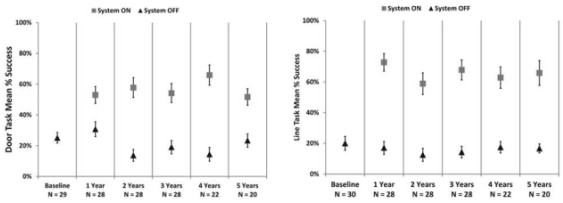


New treatments for rare diseases

Retinal Prosthesis



Locating a door

Following a white line

Cruz et al. 2016

New treatments for rare diseases

Gene Therapy

The NEW ENGLAND JOURNAL of MEDICINE

Safety and Efficacy of Gene Transfer for Leber's Congenital Amaurosis

Albert M. Maguire, M.D., Francesca Simonelli, M.D., Eric A. Pierce, M.D., Ph.D., Edward N. Pugh, Jr., Ph.D., Federico Mingozzi, Ph.D., Jeannette Bennicelli, Ph.D., Sandro Banfi, M.D., Kathleen A. Marshall, C.O.T., Francesco Testa, M.D., Enrico M. Surace, D.V.M., Settimio Rossi, M.D., Arkady Lyubarsky, Ph.D., Valder R. Arruda, M.D., Barbara Konkle, M.D., Edwin Stone, M.D., Ph.D., Junwei Sun, M.S., Jonathan Jacobs, Ph.D., Lou Dell'Osso, Ph.D., Richard Hertle, M.D., Jian-xing Ma, M.D., Ph.D., T. Michael Redmond, Ph.D., Xiaosong Zhu, M.D., Bernd Hauck, Ph.D., Olga Zelenaia, Ph.D., Kenneth S. Shindler, M.D., Ph.D., Maureen G. Maguire, Ph.D., J. Fraser Wright, Ph.D., Nicholas J. Volpe, M.D., Jennifer Wellman McDonnell, M.S., Alberto Auricchio, M.D., Katherine A. High, M.D., and Jean Bennett, M.D., Ph.D.
N Engl J Med 2008; 358:2240-2248 | May 22, 2008 | DOI: 10.1056/NEJMoa0802315

Effect of Gene Therapy on Visual Function in Leber's Congenital Amaurosis

James W.B. Bainbridge, Ph.D., F.R.C.Ophth., Alexander J. Smith, Ph.D., Susie S. Barker, Ph.D., Scott Robbie, M.R.C.Ophth., Robert Henderson, M.R.C.Ophth., Kamaljit Balaggan, M.R.C.Ophth., Ananth Viswanathan, M.D., F.R.C.Ophth., Graham E. Holder, Ph.D., Andrew Stockman, Ph.D., Nick Tyler, Ph.D., Simon Petersen-Jones, Ph.D., Shomi S. Bhattacharya, Ph.D., Adrian J. Thrasher, Ph.D., M.R.C.P., F.R.C.P., Fred W. Fitzke, Ph.D., Barrie J. Carter, Ph.D., Gary S. Rubin, Ph.D., Anthony T. Moore, F.R.C.Ophth., and Robin R. Ali, Ph.D.
N Engl J Med 2008; 358:2231-2239 | May 22, 2008 | DOI: 10.1056/NEJMoa0802268

HUMAN GENE THERAPY

Treatment of Leber Congenital Amaurosis Due to *RPE65* Mutations by Ocular Subretinal Injection of Adeno-Associated Virus Gene Vector: Short-Term Results of a Phase I Trial

William W. Hauswirth,[1,2] Tomas S. Aleman,[3] Shalesh Kaushal,[1] Artur V. Cideciyan,[3] Sharon B. Schwartz,[3] Lili Wang,[4] Thomas J. Conlon,[1] Sanford L. Boye,[1] Terence R. Flotte,[5] Barry J. Byrne,[1,2] and Samuel G. Jacobson[3]

New treatments for rare diseases

Gene Therapy

THE LANCET

Volume 390, Issue 10097, 26 August–1 September 2017, Pages 849-860

Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with *RPE65*-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial

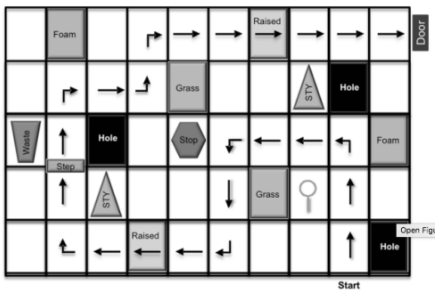
Dr Prof Stephen Russell MD [a], Prof Jean Bennett MD [b], Jennifer A Wellman MS [f], Daniel C Chung DO [f], Zi-Fan Yu ScD [g], Amy Tillman MS [g], Janet Wittes PhD [g], Julie Pappas BA [h], Okan Elci PhD [h], Sarah McCague BA [i], Dominique Cross MPH [i], Kathleen A Marshall COT [i], Jean Walshire AAS [i], Taylor L Kehoe BS [i], Hannah Reichert BS [i], Maria Davis BA [i], Leslie Raffini MD [k], Lindsey A George MD [k] … Prof Albert M Maguire MD [b]

- 31 patients randomized 2:1 to sub-retinal injection of AAV vector carrying WT RPE65 to the subretinal space

New treatments for rare diseases

Gene Therapy

Multi-lumen mobility testing

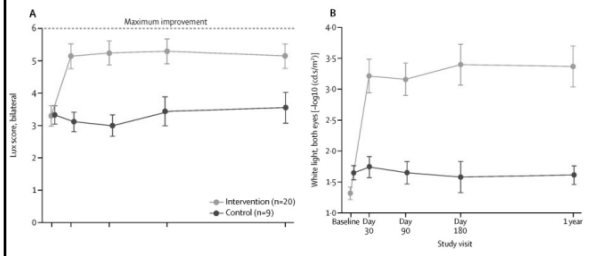


- 9 Standard illumination levels with obstacle rearrangement before each test

Chung et al. 2017

New treatments for rare diseases

Gene Therapy



Russell et al. 2017

References

1. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285(21):1182-6.
2. Leung DW, Cachianes G, Kuang WJ, Goeddel DV, Ferrara N. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science. 1989;246(4935):1306-9.
3. Keck PJ, Hauser SD, Krivi G, et al. Vascular permeability factor, an endothelial cell mitogen related to PDGF. Science. 1989;246(4935):1309-12.
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