

Gene Therapy for Retinal Disease



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Massachusetts Eye & Ear Infirmary
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Harvard Medical School
Boston, MA

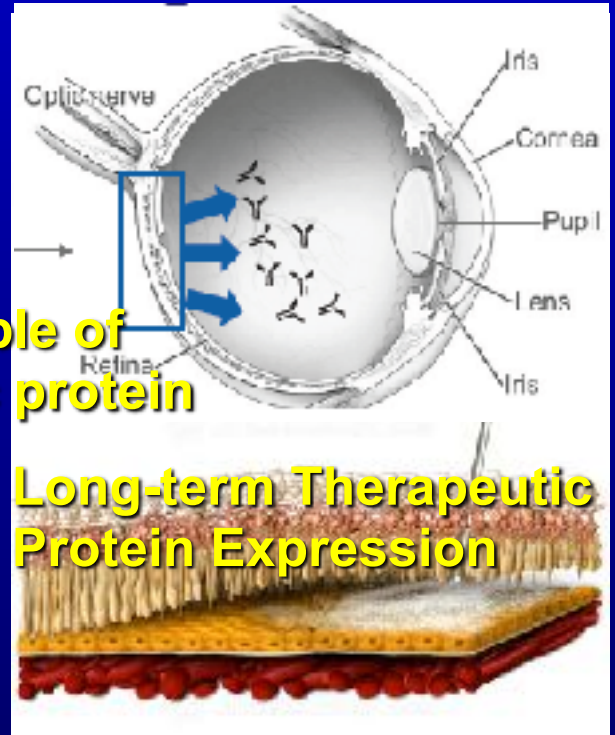


Gene Therapy



**Adeno-Associated
Virus**

**Functional gene capable of
producing therapeutic protein**



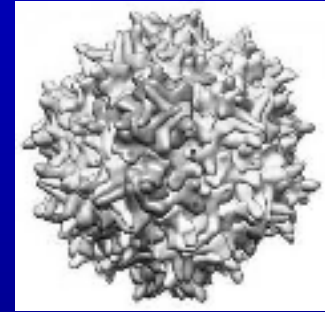
**Long-term Therapeutic
Protein Expression**

Subretinal Injection

**DNA containing
functional gene**

Gene Therapy

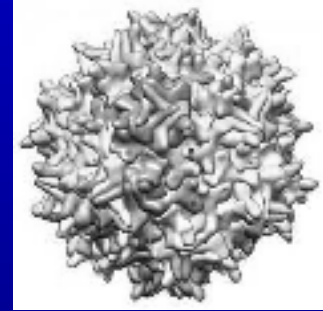
- **Adenovirus-Associated Vector (AAV)**
 - Contains no viral genes
 - minimizes adverse event possibilities



Gene Therapy

- **Adenovirus-Associated Vector (AAV)**

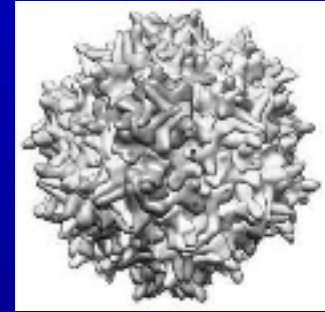
- Contains no viral genes
 - minimizes adverse event possibilities
- Does not alter patient's existing DNA
 - extra-chromosomal episome: circular DNA in nucleus
 - in contrast to lentiviral vectors which insert genes into patient's DNA



Gene Therapy

- **Adenovirus-Associated Vector (AAV)**

- Contains no viral genes
 - minimizes adverse event possibilities
- Can carry gene sequences up to 4,000 base pairs
 - 90% of human genes have coding sequences < 3,000 base pairs



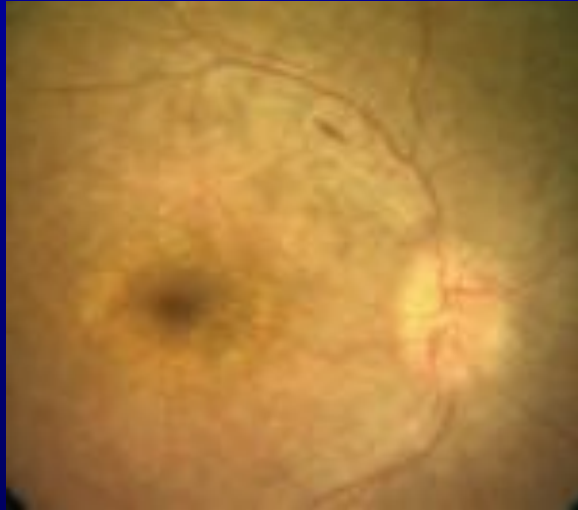
Gene Therapy

- **Leber's Congenital Amaurosis**
 - inherited retinal degeneration
 - blindness at birth, early childhood, or adolescence



Gene Therapy

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 - inherited retinal degeneration
 - blindness at birth, early childhood, or adolescence



**oculo-digital
sign**

Gene Therapy

- **Leber's Congenital Amaurosis**
 - inherited retinal degeneration
 - blindness at birth, early childhood, or adolescence



Gene Therapy

- **Leber's Congenital Amaurosis**

- caused by mutations in ~20 different genes

- one form is LCA2 (6% of all cases)

- mutations in RPE65 gene

- RPE65 protein essential for phototransduction (isomerase)

- converts *all-trans* retinyl ester to *11-cis* retinol so visual cycle can begin again

Gene Therapy

- **Leber's Congenital Amaurosis**
 - caused by mutations in ~20 different genes
 - one form is LCA2 (6% of all cases)
 - mutations in RPE65 gene
 - RPE65 protein essential for phototransduction
 - preclinical work
 - mouse and dog models



Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics
 - first 3 patients treated, subretinal injection

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 M. Fugh, Jr., Ph.D., Federico Mingozzi, Ph.D., Jeannette Bennicelli, Ph.D.,
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Nicholas J. Volpe, M.D., Jennifer Wellman, M.D., M.S., Alberto Auricchio, M.D.,
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Gene Therapy

- **Leber's Congenital Amaurosis:** navigation using untreated eye

SUPPLEMENTARY VIDEO 1A

Maguire et al

"Treatment of Leber Congenital Amaurosis due to RPE65 Mutations
in Children and Adults using Adeno-Associated Virus (AAV)-mediated
Gene Delivery

**CH09, day 90,
Navigation using untreated eye**

Gene Therapy

- **Leber's Congenital Amaurosis:** navigation using treated eye

SUPPLEMENTARY VIDEO 1B

Maguire et al

"Treatment of Leber Congenital Amaurosis due to RPE65 Mutations
in Children and Adults using Adeno-Associated Virus (AAV)-mediated
Gene Delivery

**CH09, day 90,
Navigation using treated eye**

Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics
 - two phase 1 studies
 - first 3 unilateral patients

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Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics
 - two phase 1 studies
 - first 3 unilateral patients
 - additional 12 unilateral patients

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Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial

Albert M. Maguire*, Katherine A. High*, Allison Auricchio, J. Fraser Wright, Eric A. Pierce, Francesca Testa, Federico Mingozzi, Jeannette Bencicelli, Sandro Hanf, Yung Settimio Rossi, Kathleen A. Marshall, Susan Banfi, Daniel F. Chung, Jessica P. Morgan, Bernd Hauck, Olga Zelenaia, Giovanni De Lella, Emilio Frasca, Christopher B. Wolfe, Edwin Stone, Kenneth S. Shindler, Nicholas J. Volpe, Edwin M. Stone, Corrado Aronni, Kristylye J. Borzick, T. Michael Redmond, Edwin Stone, Junwei Sun, Jennifer Wellman McDonnell, Bert P. Laro, Francesca Simonelli, Jean Bennett

Gene Therapy

- **Leber's Congenital Amaurosis**

- Spark Therapeutics

- two phase 1 studies
 - first 3 unilateral patients
 - additional 12 unilateral patients
- one phase 3 study
 - 20 bilaterally treated patients, 9 controls

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

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

Stephen Tocsi, Joe Bennett, Joseph A. Wilmer, Daniel Chung, Z. Yan, Amy T. Hines, Jonathan Lyubarsky, Oksana Serdyuk, Kenneth S. Shindler, Yung Settimio Rossi, Daniel F. Chung, Edwin Stone, Mark Fuchs, Michael J. Heckler, George F. Vitek, Bernd Hauck, Corrado Aron, Giovanni De Tullio, Jeffrey Fowler, Edwin Stone, Nicholas Volpe, Kristofor J. Bonkly, Christopher, Björk Eriksson, Elizabeth S. Shindler, Nicholas Volpe, Edwin Stone, Junwei Sun, Jennifer Wellman McDonnell, Bert Flanig, Francesca Simonelli, Jean Bennett, Albert M. Maguire

Gene Therapy

- **Leber's Congenital Amaurosis**

- Spark Therapeutics

- two phase 1 studies
 - first 3 unilateral patients
 - additional 12 unilateral patients
- one phase 3 study
 - 20 bilaterally treated patients, 9 controls
 - 11 fellow eyes of phase 1 patients

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 Bencicelli, Ph.D., Sandro Hanf, 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., Maurson 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.

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Safety and durability of effect of contralateral-eye administration of AAV2 gene therapy in patients with childhood-onset blindness caused by RPE65 mutations: a follow-on phase 1 trial

Jean Bennett, Jennifer Williams, Katherine A. High, Daniel Chung, Zhenyu Any, Ting Tang, Jonathan Lyubarsky, Jonathan Jacobs, Katherine A. High, Edwin Stone, Daniel F. Chung, Jerrisa P. Morgan, Bernd Hauck, Olga Zelenaia, Giovanni De Tullio, Arkady Lyubarsky, Jonathan Jacobs, Richard Hertle, Valder R. Arruda, Barbara Konkle, Edwin Stone, M.D., Ph.D., Nicholas J. Volpe, Edwin M. Stone, Fernando Arrascaaga, Katherine A. High, T. Michael Redmond, Edwin Stone, Junwei Sun, Jennifer Wellman McDonnell, Bert P. Laro, Francesca Simonelli, Jean Bennett

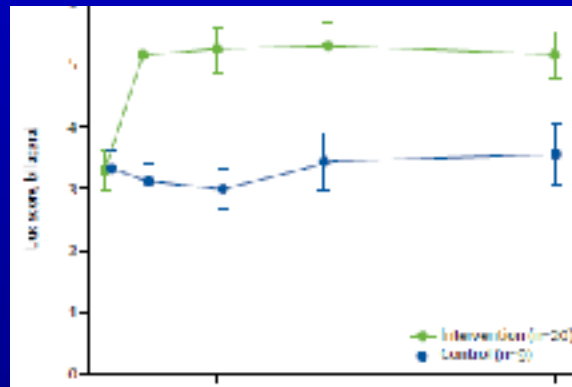
Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics

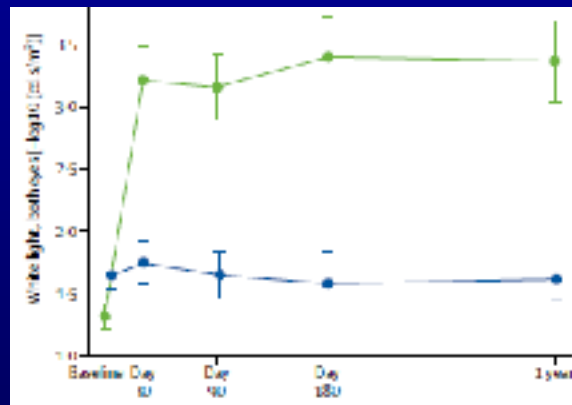
Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial

Stephen Tsiang, Joe Swartz, Joseph A Wilson, David C Chung, Di Yan, Amy Tam, Jennifer Pappas, Brandon Smith, Marissa Koenig, et al. *Lancet* 2017; 390: 1209-1217. doi:10.1016/S0140-6736(17)31730-9

**multi-luminance
mobility test (MLMT)**



**full-field light
sensitivity test (FST)**



Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics
 - FDA approval Dec 2017 (first ever!)

Gene Therapy

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 - Spark Therapeutics
 - FDA approval Dec 2017 (first ever!)
 - Luxturna (voretigene neparvovec)



Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics
 - FDA approval Dec 2017 (first ever!)
 - Luxturna (voretigene neparvovec)
 - \$425,000/eye = \$850,000
 - outcomes-based rebates



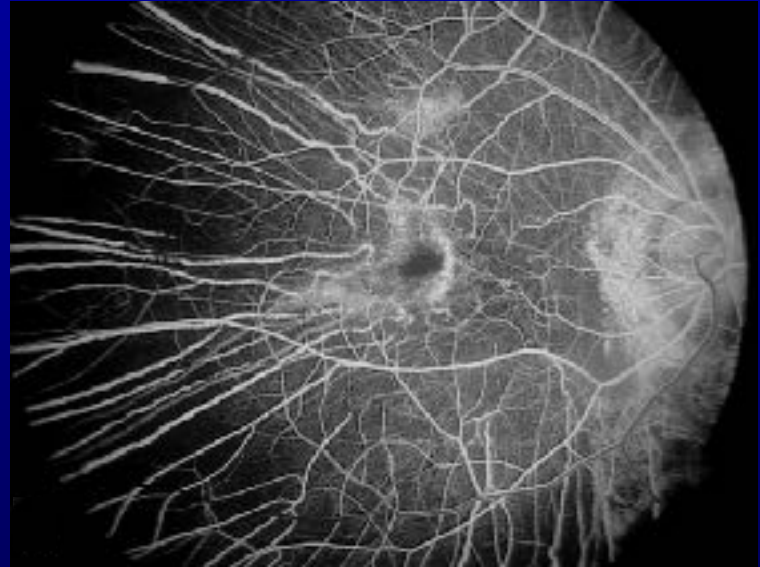
Gene Therapy

- **Leber's Congenital Amaurosis**
 - Spark Therapeutics
 - FDA approval Dec 2017 (first ever!)
 - Luxturna (voretigene neparvovec)
 - \$425,000/eye = \$850,000
 - outcomes-based rebates
 - 7 eye centers in US



Gene Therapy

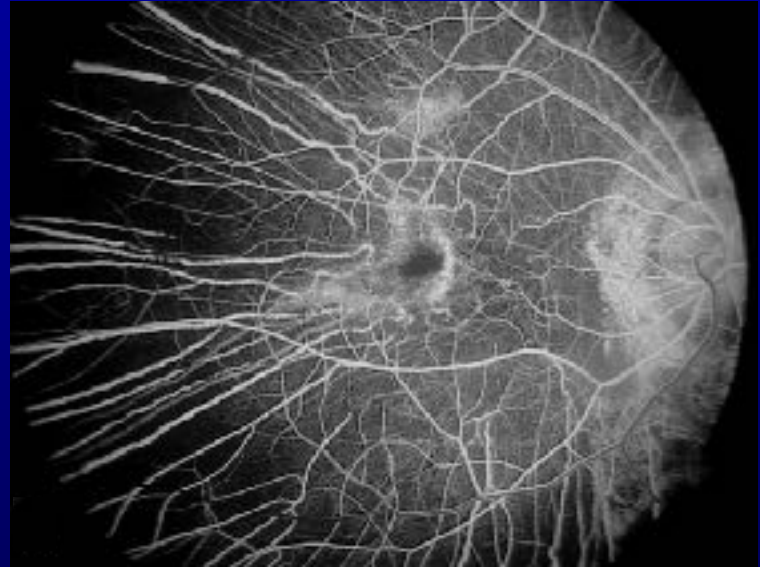
- **Choroideremia**
 - X-linked recessive
 - CHM gene, REP-1 protein



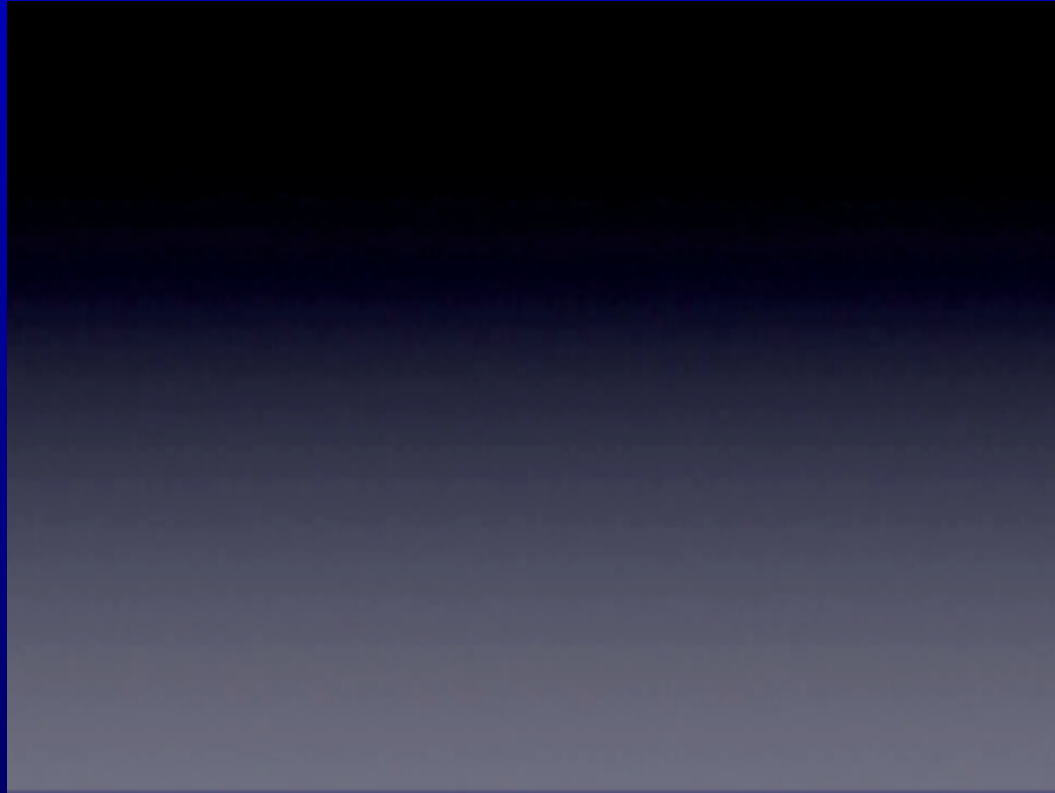
Gene Therapy

- **Choroideremia**

- Spark Therapeutics: fully enrolled phase 1/2 study



Gene Therapy: Choroideremia



Clinical Trial NCT02341807. www.clinicaltrials.gov.

Gene Therapy

- **Choroideremia**
 - Spark Therapeutics: fully enrolled phase 1/2 study

Gene Therapy

- **Choroideremia**

- Spark Therapeutics: fully enrolled phase 1/2 study
- Nightstar: completed phase 1/2 study, enrolling phase 3

Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial

Rubal F Marfan, Minkas Gougeon, Akar P Barooni, Charles F Culkin, Lijun Ishimaru, Fan Senguan, K Ross Clark, Malharaj Doray, Hans PM Enders, Lamele C M Black, Andrew J Farag, Visvan M Gnanasekaran, Andrew F Webster, Miguel C Saotua

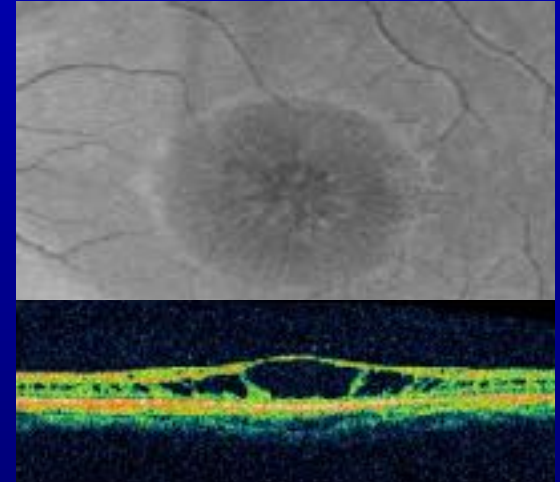
Visual Acuity after Retinal Gene Therapy for Choroideremia

Gene Therapy

- **AGTC**
 - Applied Genetic Technologies Corporation

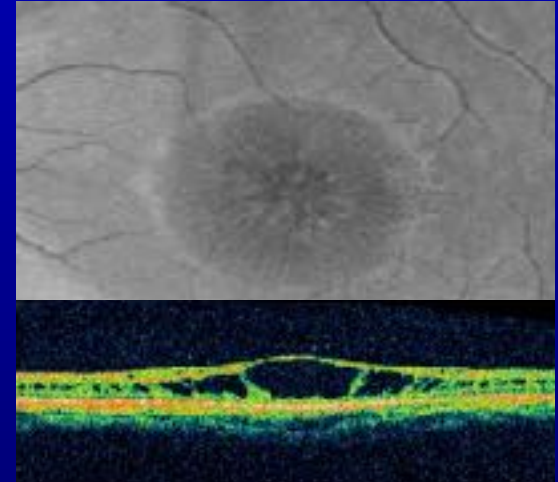
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - **X-linked Juvenile Retinoschisis (XLRS)**
 - RS1 gene: retinoschisin



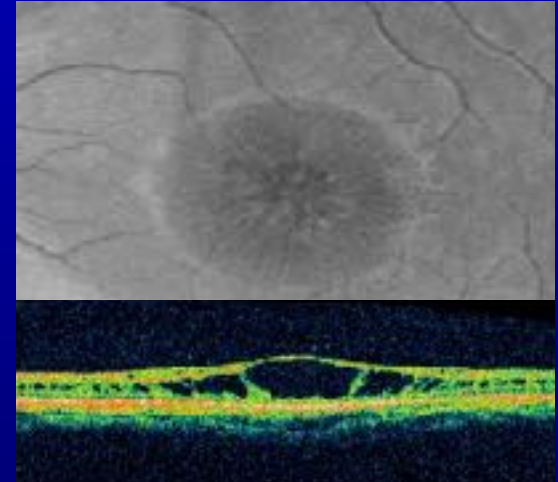
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - **X-linked Juvenile Retinoschisis (XLRS)**
 - RS1 gene: retinoschisin
 - intravitreal injection
 - risk of inflammation



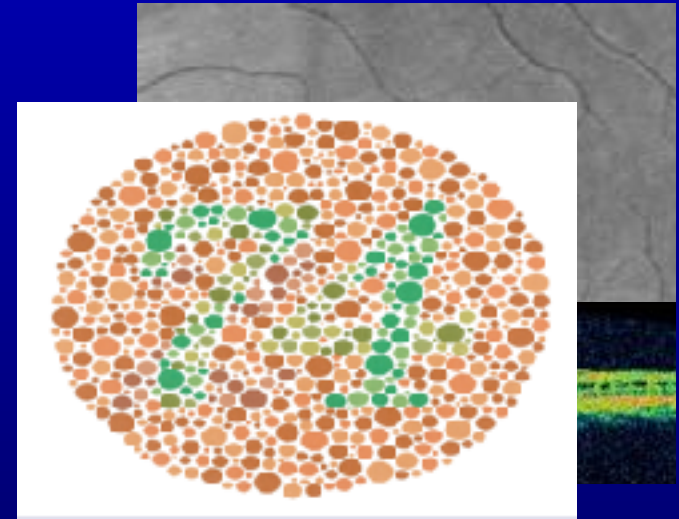
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - **X-linked Juvenile Retinoschisis (XLRS)**
 - RS1 gene: retinoschisin
 - intravitreal injection
 - risk of inflammation
 - phase 1/2
 - ~8 patients so far



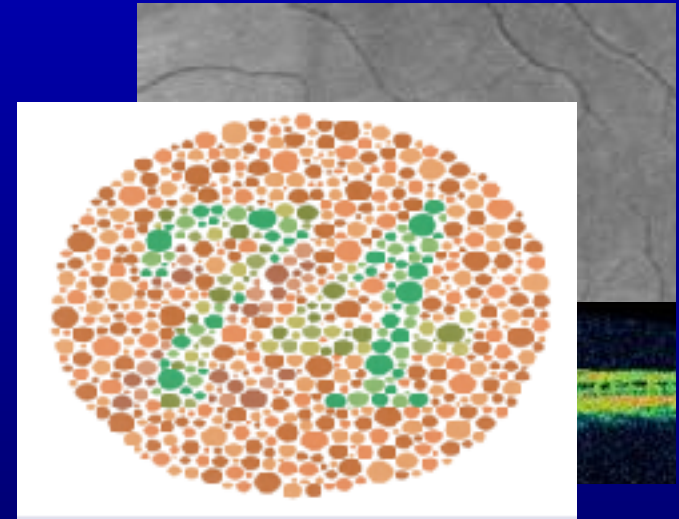
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - X-linked Juvenile Retinoschisis (XLRS)
 - **Achromatopsia (ACHM)**
 - color blindness, photophobia



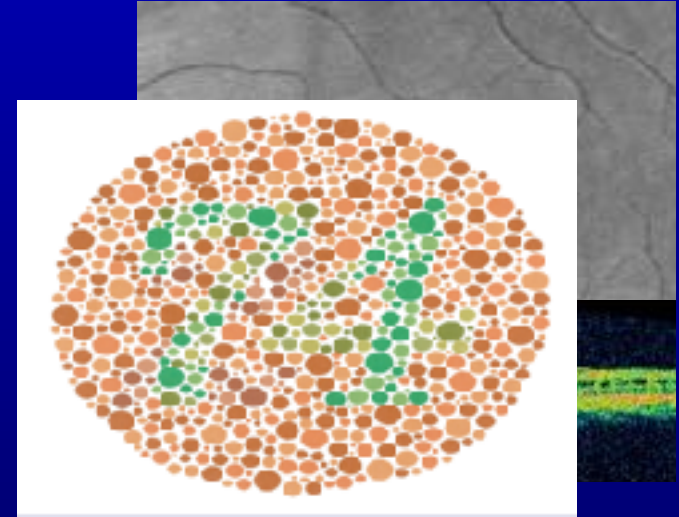
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - X-linked Juvenile Retinoschisis (XLRS)
 - **Achromatopsia (ACHM)**
 - color blindness, photophobia
 - subretinal injection



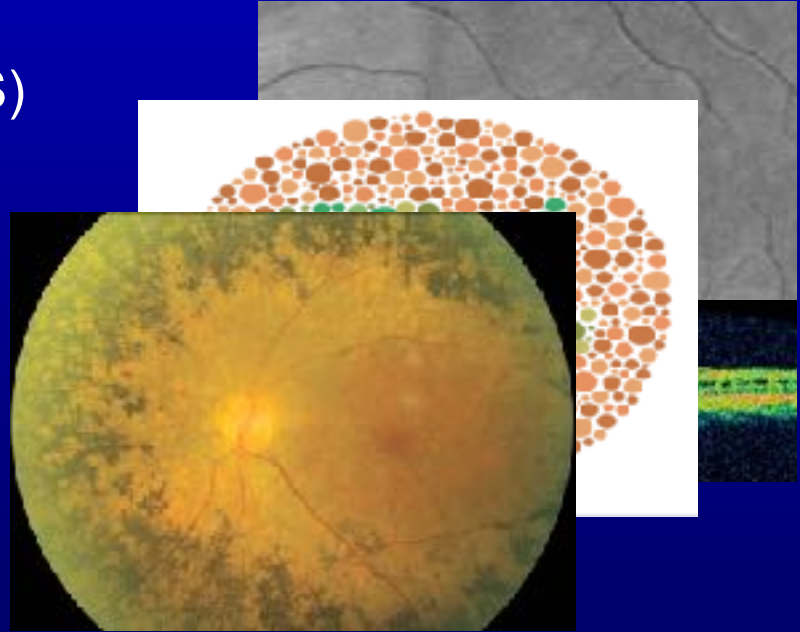
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - X-linked Juvenile Retinoschisis (XLRS)
 - **Achromatopsia (ACHM)**
 - color blindness, photophobia
 - subretinal injection
 - phase 1/2
 - just started



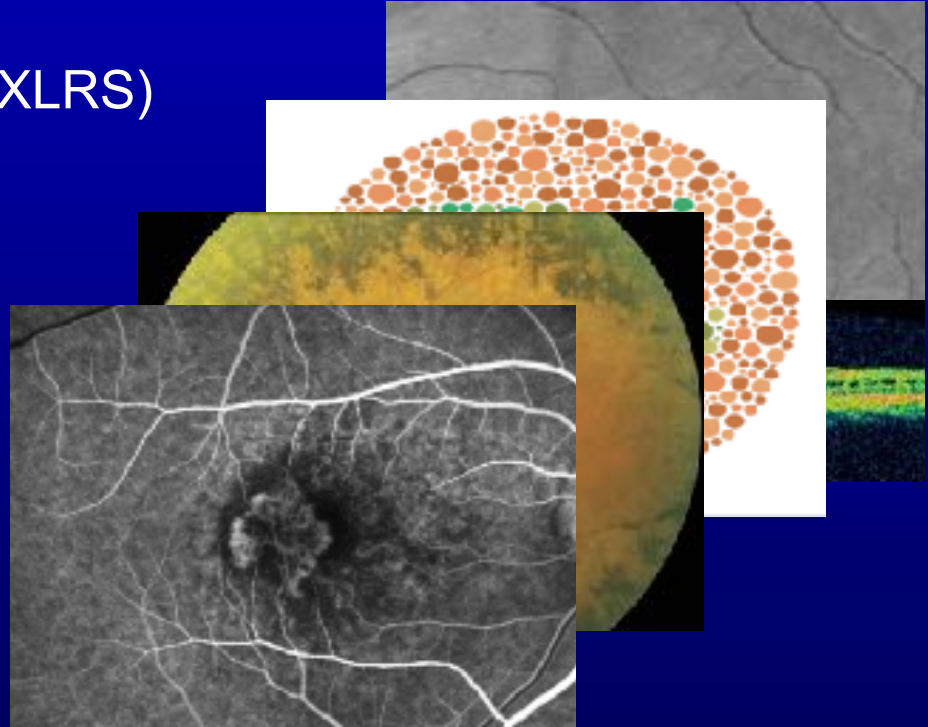
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - X-linked Juvenile Retinoschisis (XLRS)
 - Achromatopsia (ACHM)
 - **X-linked RP**
 - 10% of RP cases



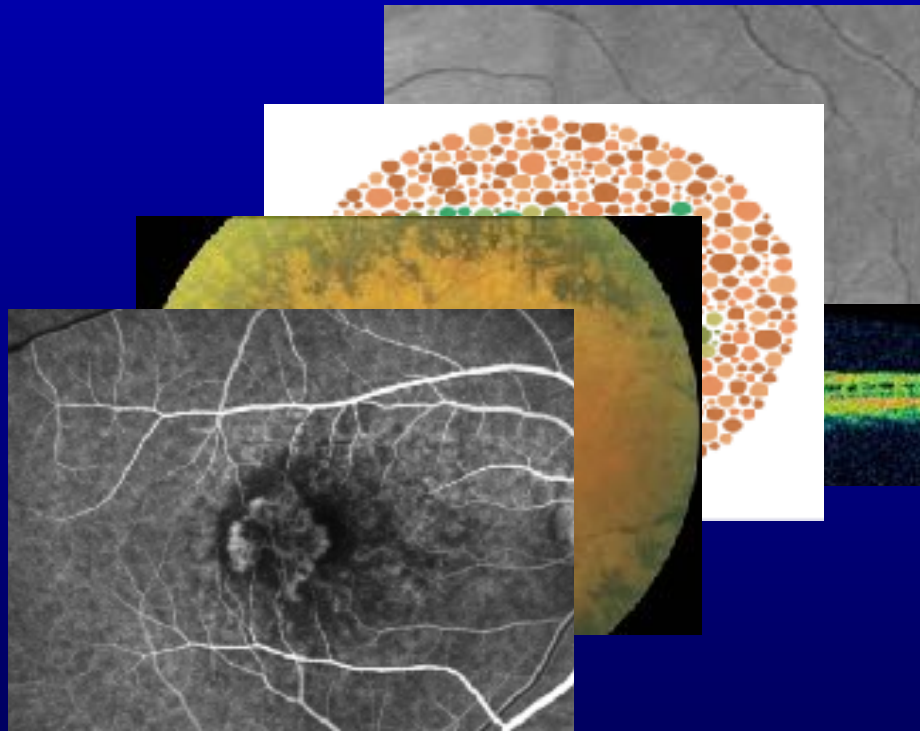
Gene Therapy

- AGTC (Applied Genetic Technologies Corporation)
 - X-linked Juvenile Retinoschisis (XLRS)
 - Achromatopsia (ACHM)
 - X-linked RP
 - **Wet AMD**

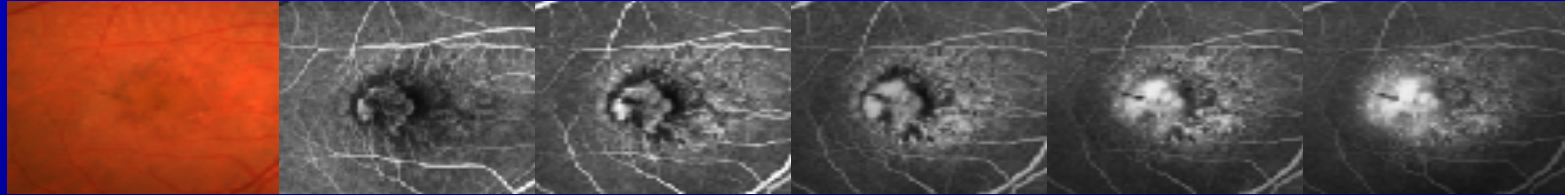


Gene Therapy

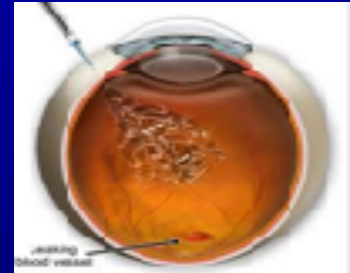
- AGTC (Applied Genetic Technologies Corporation)
 - collaboration with Biogen
 - up to \$1 billion



Wet AMD

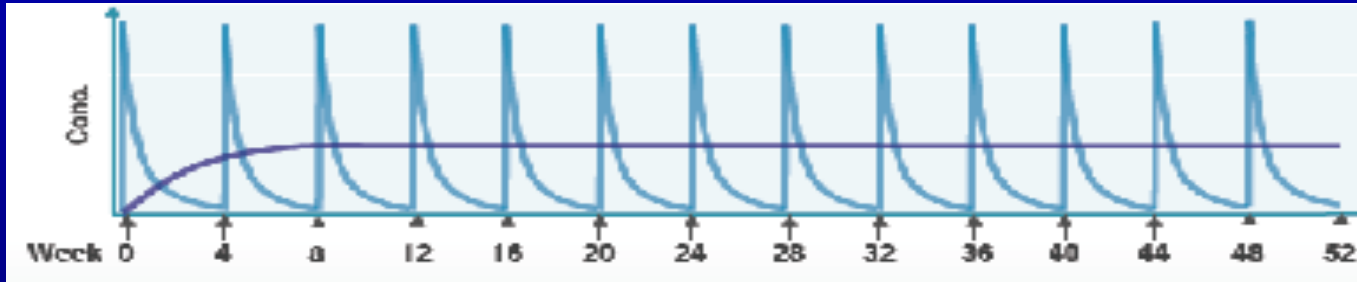


- Bevacizumab
- Ranibizumab
- Aflibercept



Gene Therapy

- Anti-VEGF



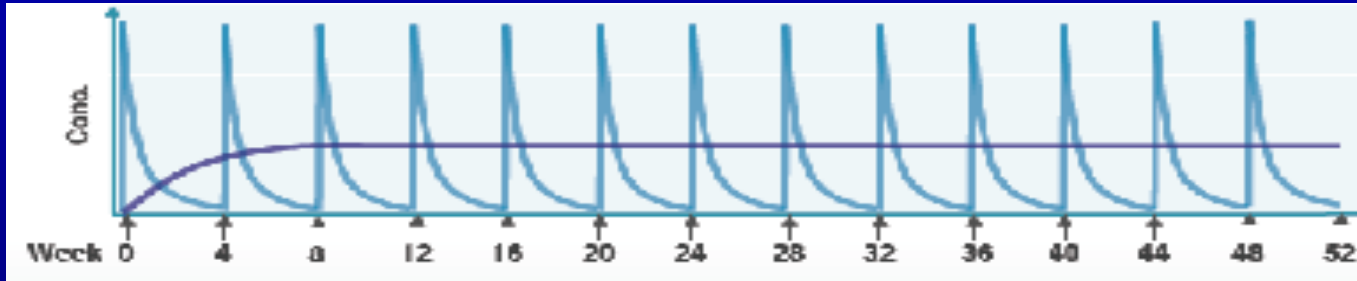
pulse delivery



Gene Therapy

- Anti-VEGF

sustained delivery



pulse delivery

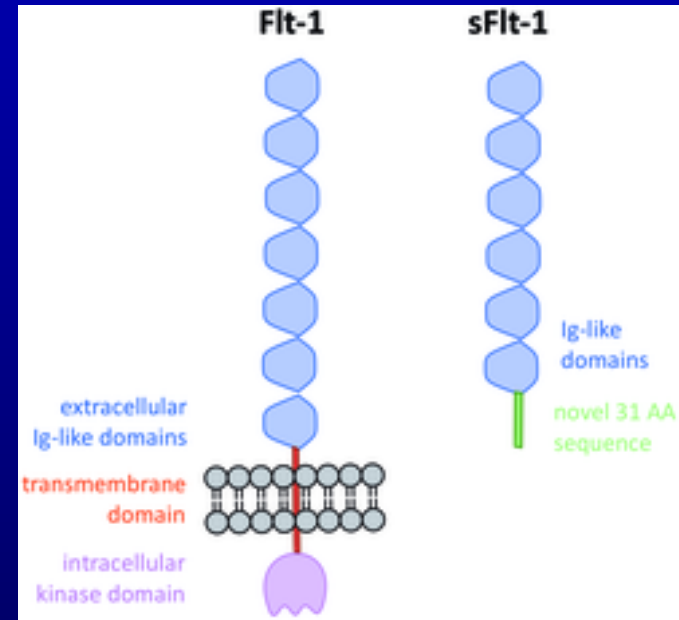
Gene Therapy

- **Wet AMD**

- Avalanche Biotechnologies

- **sFLT-1 gene**

- natural binding affinity to VEGF
- truncated form of VEGF receptor
- anti-VEGF



Gene Therapy

- **Wet AMD**

- Avalanche Biotechnologies

- **sFLT-1 gene**

- phase 1

- subretinal injection in 8 eyes

- results encouraging (safe, suggestion of efficacy)

Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a phase 1 randomised clinical trial

Elizabeth F. Shekoy, Christa-Magdalena Ansel, Megan Matharu, Willem, Marlyn Alvarado, Lisa M. Pardo, Michael Schwartz, Mark Williams, J. Hassan, W. Holmgren, Marissa A. Dagnall, David J. Lamb

Gene Therapy

- **Wet AMD**

- Avalanche Biotechnologies

- **sFLT-1 gene**
- phase 2a
- subretinal injection in 32 eyes
 - safe but no efficacy

Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a phase 1 randomised clinical trial

Elizabeth P. Rakoczy^{a,b,c}, Chooi-May Lai^{a,c}, Aaron L. Magno^a, Matthew L. Wilkins, Martyn A. French, Cora M. Fierce, Steven D. Schwartz, Mark S. Blumenkranz, Elizabeth P. Rakoczy, Mark S. Blumenkranz, Elizabeth P. Rakoczy, Cora M. Fierce, Steven D. Schwartz

Phase 2a Randomized Clinical Trial: Safety and Post Hoc Analysis of Subretinal rAAV.sFLT-1 for Wet Age-related Macular Degeneration

Ian J. Constable^{a,b,c}, Cora M. Fierce^a, Chooi-May Lai^{a,c}, Aaron L. Magno^a, Mariapia A. Degli-Esposti, Martyn A. French^{d,e}, Ian L. McAllister^{a,b,c}, Steve Butler^f, Samuel B. Barone^f, Steven D. Schwartz^g, Mark S. Blumenkranz^h, Elizabeth P. Rakoczy^{a,c,g}

Gene Therapy

- **Wet AMD**
 - Avalanche Biotechnologies
 - **sFLT-1 gene**
 - phase 2a
 - phase 2b cancelled

Gene therapy with recombinant adeno-associated vectors for neovascular age-related macular degeneration: 1 year follow-up of a phase 1 randomised clinical trial

Elizabeth P. Rakoczy^{a,b,c}, Chooi-May Lai^{a,c}, Aaron L. Magno^a, Matthew J. Wilkins, Martyn A. French, Cora M. Fierce, Steven D. Schwartz, Mark S. Blumenkranz, Elizabeth P. Rakoczy, Ian J. Constable

Phase 2a Randomized Clinical Trial: Safety and Post Hoc Analysis of Subretinal rAAV.sFLT-1 for Wet Age-related Macular Degeneration

Ian J. Constable^{a,b,c}, Cora M. Fierce^a, Chooi-May Lai^{a,c}, Aaron L. Magno^a, Mariapia A. Degli-Esposti, Martyn A. French^{d,e}, Ian L. McAllister^{a,b,c}, Steve Butler^f, Samuel B. Barone^f, Steven D. Schwartz^g, Mark S. Blumenkranz^h, Elizabeth P. Rakoczy^{a,c,g}

Gene Therapy

- **Wet AMD**
 - Avalanche Biotechnologies
 - **sFLT-1 gene**
 - phase 2a
 - phase 2b cancelled
 - Avalanche merged with Annapurna Therapeutics to create a new company called Adverum Biotechnologies

Gene Therapy

- **Wet AMD**
 - Adverum
 - preclinical study in primates
 - sustained expression >6 months
 - awaiting 12 month efficacy data



Gene Therapy

- **X-linked Juvenile Retinoschisis**
 - Adverum
 - collaboration with Regeneron

Gene Therapy

- **X-linked Juvenile Retinoschisis**
 - Adverum
 - collaboration with Regeneron
- **Other Inherited Retinal Diseases (non-disclosed)**
 - Adverum
 - collaboration with Editas

Gene Therapy

- **Wet AMD**
 - Sanofi-Genzyme
 - sFLT-1
 - intravitreal injection

Gene Therapy

- **Wet AMD**
 - Sanofi-Genzyme
 - sFLT-1
 - intravitreal injection
 - phase 1
 - 19 eyes

Intravitreal injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial

Jeffrey S Haler, Saleema Khavari, Shilpa Desai, Pravin Dugel, Shailesh Kaushal, Jeng-H Cheng, Cheryl D'Alzono, Annie Fumit, Susan Richards, Annig Le Halpern, John Connolly, Samuel C Wadsworth, Rajpal Varma, Ronald Buggage, Abraham Scaria, Peter A Campochiare

Gene Therapy

- **Wet AMD**

- Sanofi-Genzyme

- sFLT-1
- intravitreal injection
- marginal results
 - safe
 - efficacy: biologic activity in only 4 of 11 expected responders

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Gene Therapy

- **Wet AMD**

- Sanofi-Genzyme

- sFLT-1
- intravitreal injection
- marginal results
 - safe
 - efficacy: biologic activity in only 4 of 11 expected responders
 - » patients developed antibodies to AAV2

Intravitreal injection of AAV2-sFLT01 in patients with advanced neovascular age-related macular degeneration: a phase 1, open-label trial

Jeffrey S Haler, Saleema Khavari, Shilpa Desai, Pravin Dugel, Shailesh Kaushal, Jeng-H Cheng, Cheryl D'Alonzo, Annie Fumita, Susan Richards, Annig Le Halpern, John Connolly, Samuel C. Wadsworth, Rajpal Varma, Ronald Buggage, Abraham Scaria, Peter A. Campochiare

Gene Therapy

- **Wet AMD**
 - Regenxbio
 - anti-VEGF fab

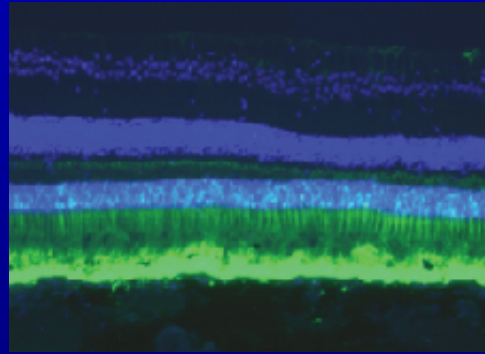
Gene Therapy

- **Wet AMD**

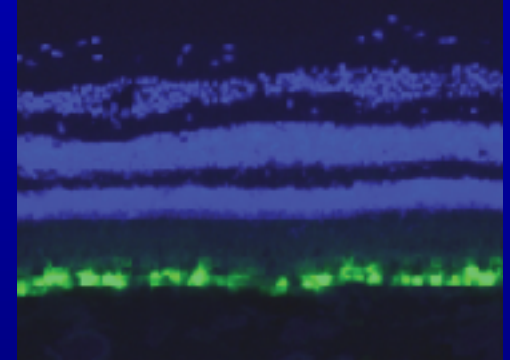
- Regenxbio

- anti-VEGF fab
- AAV8
- subretinal injection

AAV8



AAV2



more efficient gene
delivery to the RPE

Gene Therapy

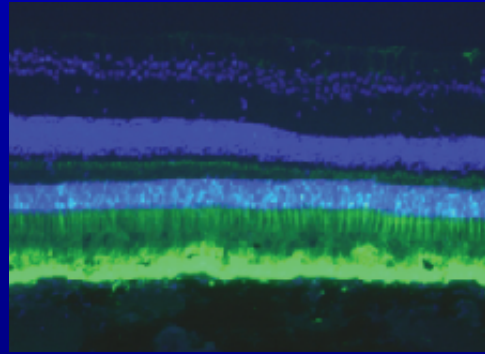
- **Wet AMD**

- Regenxbio

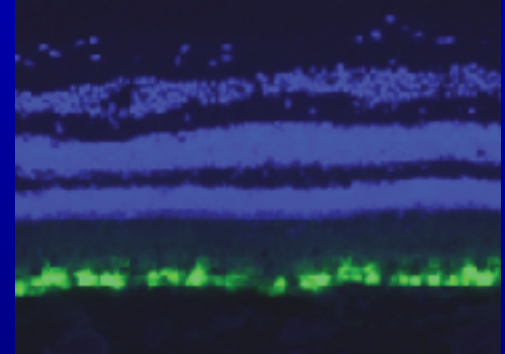
- anti-VEGF fab
- AAV8
- subretinal injection
- phase 1

- 3 cohorts, 6 patients each

AAV8



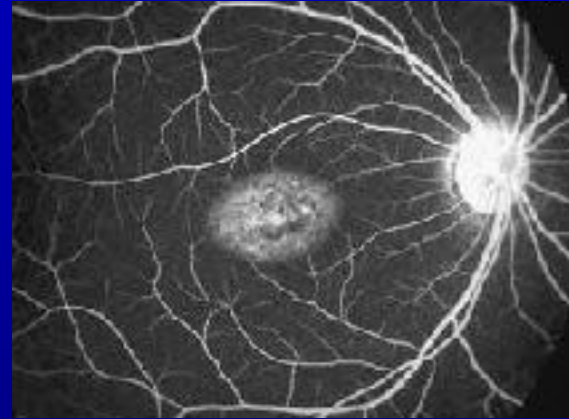
AAV2



more efficient gene delivery to the RPE

Gene Therapy

- **Stargardt Disease**
 - Sanofi-Genzyme
 - Oxford BioMedica
 - ABCA4 gene (7,000 base pairs)
 - lentivirus
 - phase 1/2a



Gene Therapy

- **Stargardt Disease**

- Sanofi-Genzyme
- Oxford BioMedica
 - phase 1/2a



- **RP with Usher type 1B**

- Sanofi-Genzyme
- phase 1/2a



Gene Therapy Summary

- **Monogenic Diseases**

- Leber's Congenital Amaurosis
- Choroideremia
- X-Linked Juvenile Retinoschisis
- Achromatopsia
- X-Linked RP
- Stargardt Disease
- RP with Usher type 1B

- **Wet AMD**

- **Corporations**

- Spark Therapeutics
- Nightstar
- AGTC
- Avalanche / Adverum
- Sanofi-Genzyme
- Regenxbio

Gene Therapy Leber's Congenital Amaurosis



Gene Therapy

Leber's Congenital Amaurosis

**Jack could see in the dark last night.
And he was able to ride his bicycle!**