Cone Targeted Gene Therapy: Animal Models
Which cone disease?

- Targets only cones
- Genetics are well established
- Animal model mimics human disease
- Clear clinical assay for therapy
Phototransduction

Cone genes causing foveal function loss

3 genes causing Achromatopsia

CNGA3

CNGB3

GNAT2
Phototransduction

Cone genes causing foveal function loss

3 genes causing Achromatopsia

- CNGA3
- CNGB3
- GNAT2

X-linked color blindness

Phototransduction

Cone genes causing foveal function loss

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CNGA3

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X-linked color blindness

Blue Cone Monochromacy

Phototransduction

Cone genes causing foveal function loss

3 genes causing Achromatopsia

CNGA3

CNGB3

GNAT2

X-linked color blindness

Blue Cone Monochromacy

Mouse model for GNAT2 Achromatopsia


AAV5-PR2.1-mGnat2

Is useful vision restored?
Mouse model for GNAT2 Achromatopsia


AAV5-PR2.1-mGnat2

Treatment effects

Cone ERG ~100% of normal
Cone structure ~normal
Visual Acuity

Visual Acuity (cycles / degree)

- Untreated Cpf3 Eyes
- Treated Cpf3 Eyes
- Wild Type Eyes

Visual Acuity

Visual Acuity (cycles / degree)

- Untreated Cpf13 Eyes
- Treated Cpf13 Eyes
- Wild Type Eyes

Can other genetic forms of Achromatopsia and other species with Achromatopsia be treated?
Phototransduction

Achromatopsia Genes

X-linked color blindness
Blue Cone Monochromacy

CNGA3

CNGB3
Dog model for CNGB3 Achromatopsia


AAV5-PR2.1-hCngb3

Treatment effects

Cone ERG ~10% of normal, but 50% in Tx area
Cone structure ~normal in Tx area
> 3 year persistence
Dog model for CNGB3 Achromatopsia


AAV5-PR2.1-hCngb3

Behavioral Effects?
Dog Movie
Visually guided maze test for dogs (n=6)

Visually guided maze test for dogs (n=6)

Phototransduction

Cone genes causing foveal function loss

3 genes causing Achromatopsia

CNGA3

CNGB3

GNAT2

X-linked color blindness
Blue Cone Monochromacy

Sheep model for CNGA3 Achromatopsia

Edward Averbukh; Ron Ofri; Elisha Gootwine; Raaya Ezra-Elia; Hen H. Honig; Alexander Rosov ; Esther Yamin; Alexey Obolensky; William W. Hauswirth; Eyal Banin ARVO (2013)

AAV5-PR2.1-\textit{hCnga3}

Treatment effects

Cone ERG $\sim30\%$ of normal, but $\sim100\%$ in Tx area

Cone structure ?
Sheep model for CNGA3 Achromatopsia

Edward Averbukh; Ron Ofri; Elisha Gootwine; Raaya Ezra-Elia; Hen H. Honig; Alexander Rosov; Esther Yamin; Alexey Obolensky; William W. Hauswirth; Eyal Banin
ARVO (2013)

AAV5-PR2.1-hCnga3

Behavioral Effects?
Visually guided maze test at 6 Mos. postTx

ARVO (2013)
Visually guided maze test at 6 Mos. postTx
Visually guided maze test at 6 Mos. postTx

N = 6

ARVO (2013)
Phototransduction

Cone genes causing foveal blindness

X-linked color blindness
Blue Cone Monochromacy

3 genes causing Achromatopsia

CNGA3
CNGB3
GNAT2

Mouse Model of BCM

The thyroid hormone receptor KO mouse (THrβ KO) has no detectible M-opsin, no recordable M-cone response to red light and a normal S-cone function. It is therefore a mouse model of BCM.

AAV8-IRBP/GNAT2-rat M-opsin

M-cone function (photopic red ERG)
Are M-cones restored in treated THβ KO mice?

M-opsin cones are Red

S-opsin cones are Green
THrβ KO mouse treatment effect – retinal whole mounts

45% of cones have M-opsin

M-cones are red
All cones are Green

24% of cones have M-opsin

0% of cones Have M-opsin
Phototransduction

Cone genes causing foveal blindness

3 genes causing Achromatopsia

X-linked color blindness
Blue Cone Monochromacy

Primate model of human red color blindness

Color Vision Testing Apparatus

Cambridge Colour Test

The color vision threshold defines how saturated each hue must be to distinguish it from gray.
Gene Therapy for X-Linked Color Blindness (Protanopy)


**AAV5-PR2.1-hR-Ops**

**Treatment effect**

Gain of ~normal red light ERG response (but only in treated area)
Squirrel Monkey #1 Thresholds

490nm (protan confusion $\lambda$)

550nm (normal response $\lambda$)

Nature (2009)
Gene therapy treated RPE65 LCA patients only start using the treated part of their retina after ~one year.

Nature (2009)
Why develop a treatment for red color blindness?

Blue Cone Monochromacy patients are missing both R-Ops and G-Ops. They have clinical symptoms very similar to Achromats.
# Cone Targeted Gene Therapy

<table>
<thead>
<tr>
<th>Species</th>
<th>Disease</th>
<th>Gene</th>
<th>Cone ERG</th>
<th>Vision</th>
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<tbody>
<tr>
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<td>Achromo.</td>
<td>gnat2</td>
<td>normal</td>
<td>~normal</td>
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<td>Dog</td>
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<tr>
<td>Sheep</td>
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<td>M-opsin</td>
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<td>Mouse</td>
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<tr>
<td>Monkey</td>
<td>Protanopia</td>
<td>L-opsin</td>
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<td>~normal</td>
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</table>
What’s next for cone targeted gene therapy?

- Recently funded NEI R24 for B3 Achm. IND/clin. trial
- Corporate support for B3 and A3 Achm. to parallel R24
Astronomic Adaptive Optics
Retinal Adaptive Optics
A New Adaptive Optics Technology

Conventional AO | Split-detector AO
---|---
Control

ACHM

Achromatopsia Patients

OCT Images

Conventional AO

Split Detector AO
