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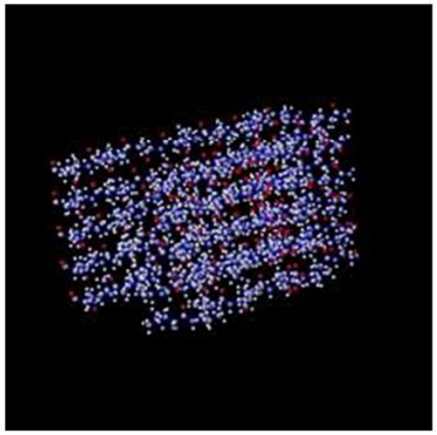
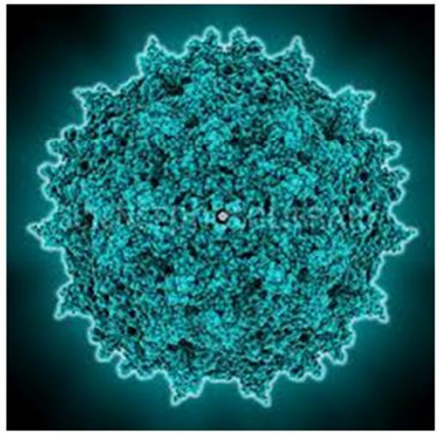
Toward the intra-ocular delivery of anti-amyloid antibody for dry AMD

Ruslan Grishanin, Ph.D.

RINAT

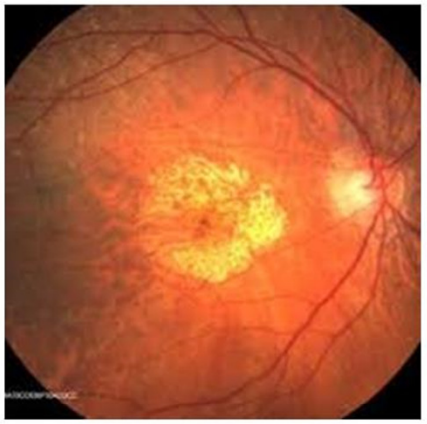
A Pfizer Research Unit

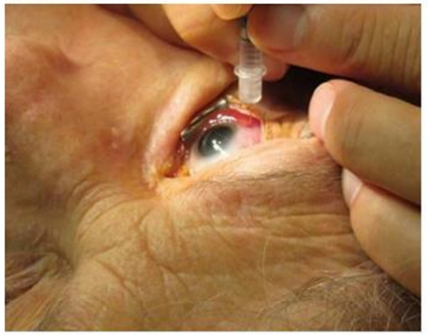




Age-Related Macular Degeneration: Significant Unmet Medical Need

Demographic/Prevalence Data





- **1.8 million** Americans 40 years and older have advanced AMD.
- **3.8%** of Americans aged 50 to 59 years have either intermediate or advanced AMD. By age 70 to 79 years, this increases to **14.4%**. Overall, today **7.3 million** people with intermediate AMD are at substantial risk for vision loss.
- By 2020 there will be **2.95 million** individuals with advanced AMD.
- There has been much focus and subsequent success generating treatments targeted at wet age-related macular degeneration.
- Minimizing the treatment burden and enhancing treatment efficacy remain unmet needs in therapy for this chronic disease.

There are no treatments available to fight dry AMD and to prevent its development into neovascular form or into geographic atrophy.

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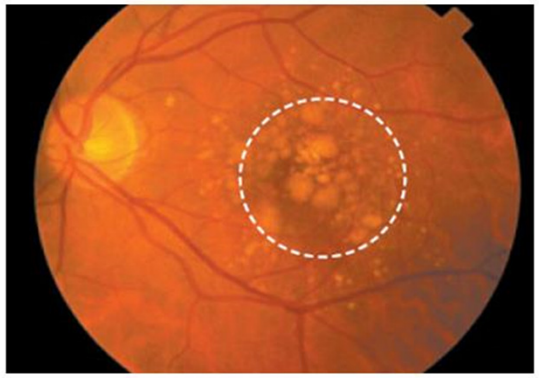
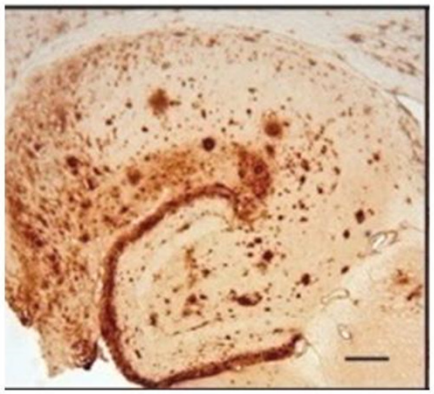
Amyloid deposits have been found to accumulate in the drusen of AMD

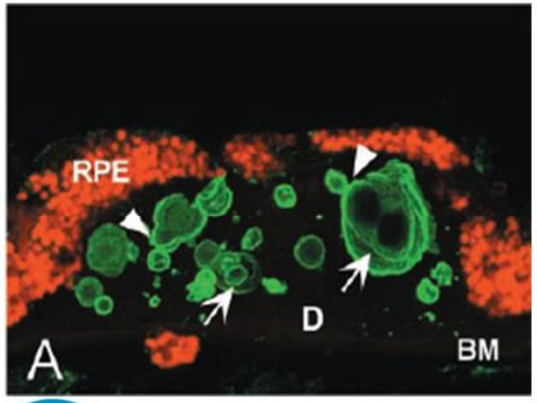
Aβ localized in the Alzheimer's disease brain



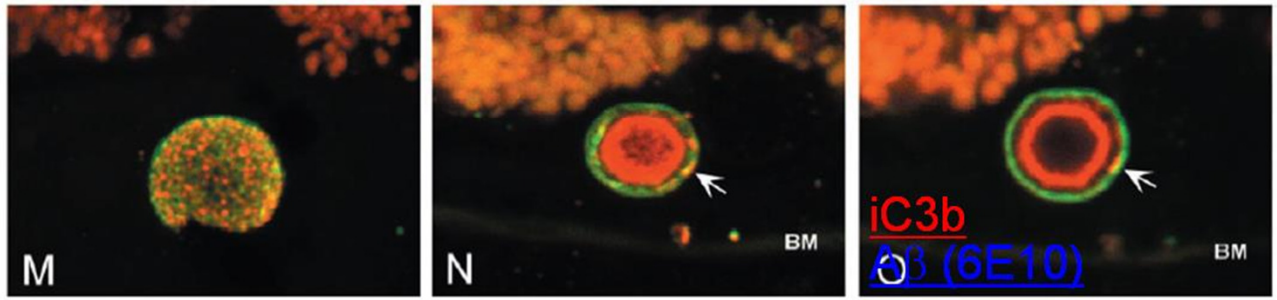


- Drusen are the hallmark of dry AMD pathology.
- Aβ deposits are found in drusen.
- Aβ deposits in drusen may be associated with the complement activation and inflammation.

Aβ is a component of drusen in eyes with AMD



Aβ localized in close vicinity of complement activation products in AMD drusen



Johnson et al. PNAS, 2002, 99:11830

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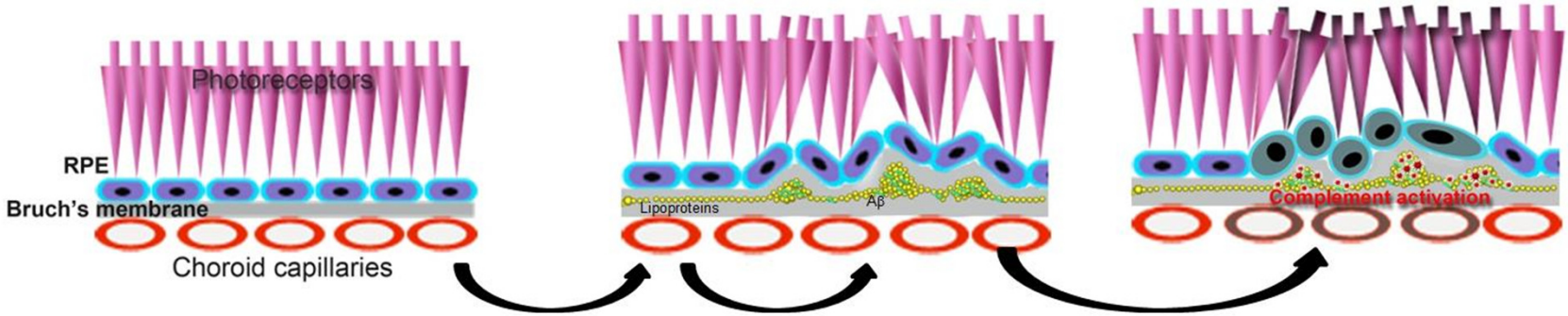
POTENTIAL MECHANISM OF Aβ INVOLVEMENT IN AMD



Potential involvement of Aβ in the inflammatory process and AMD pathology provides rationale for the clinical development of Aβ antibody for the dry AMD treatment

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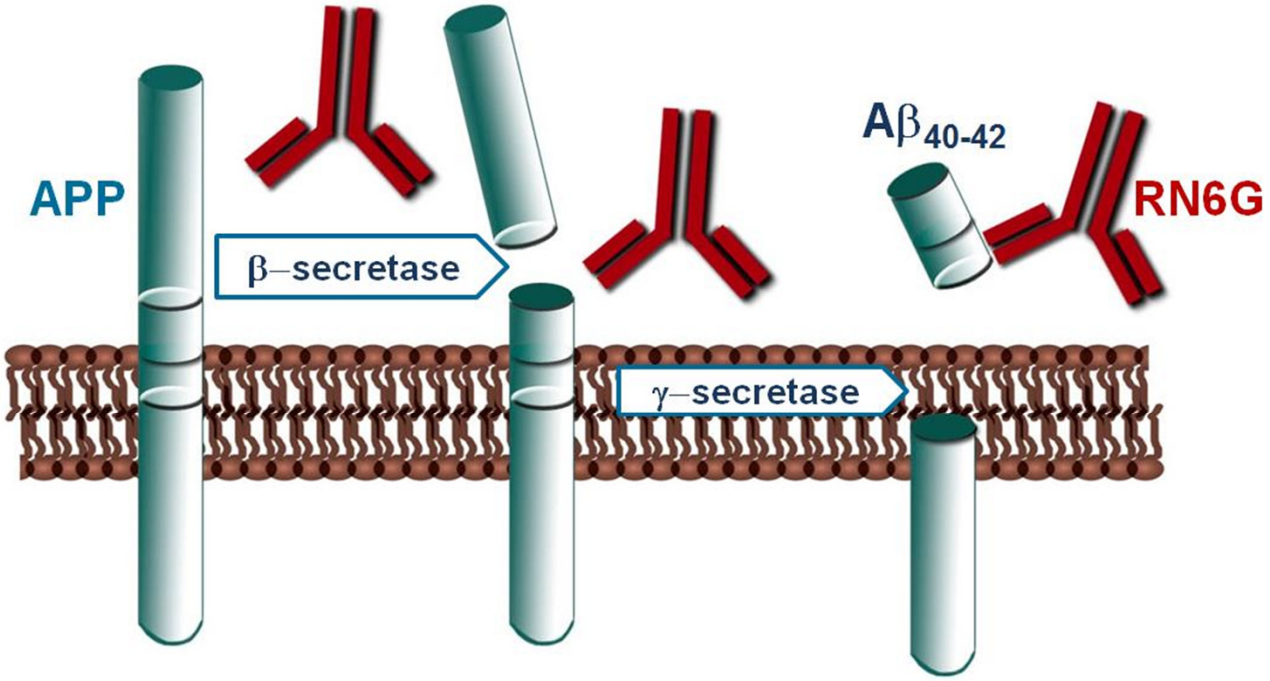
Pfizer's RN6G antibody capable of recognizing both Aβ40 and Aβ42 cytotoxic peptides but not APP



- RN6G epitope in APP is hidden in the lipid bi-layer and in-accessible for the antibody.
- RN6G recognizes and binds to $A\beta_{40-42}$ released from the membrane.
- RN6G Fc domain is engineered not to engage complement and Fcγ receptors of the immune cells.

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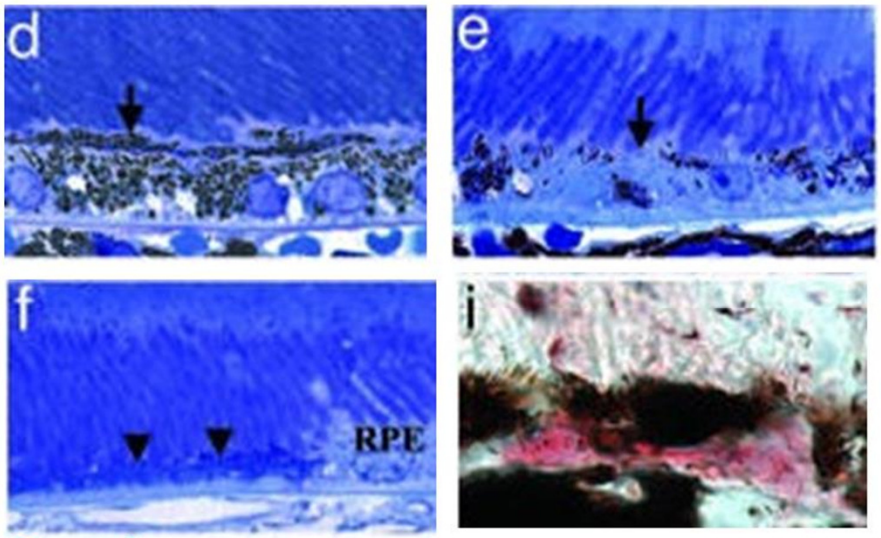
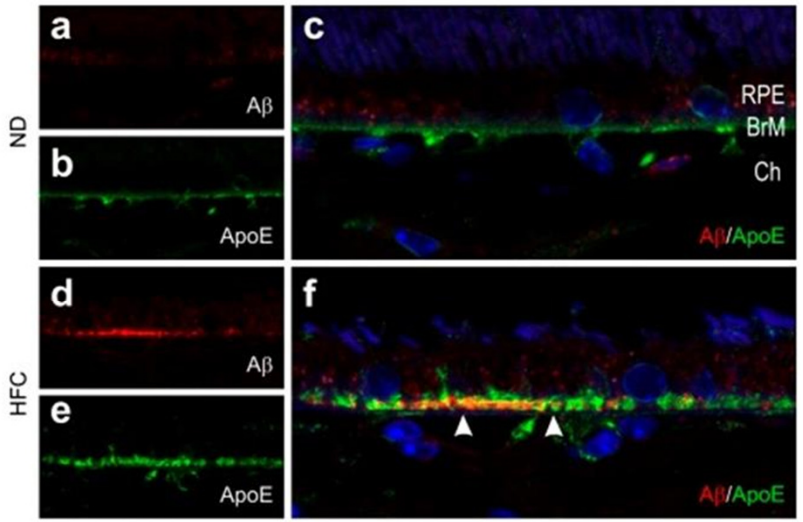
High fat/High cholesterol APOE4/APOE4 knock-in mouse model of dry AMD

- Advanced age (> 60 weeks)
- *APOE4* gene knock-in
- High fat and cholesterol (HF-C) diet for 8 weeks
- Anatomical change - RPE abnormalty
- Functional change - ERG deficits

RPE changes in the AMD model mice



Subretinal Aβ deposition in the AMD model mice



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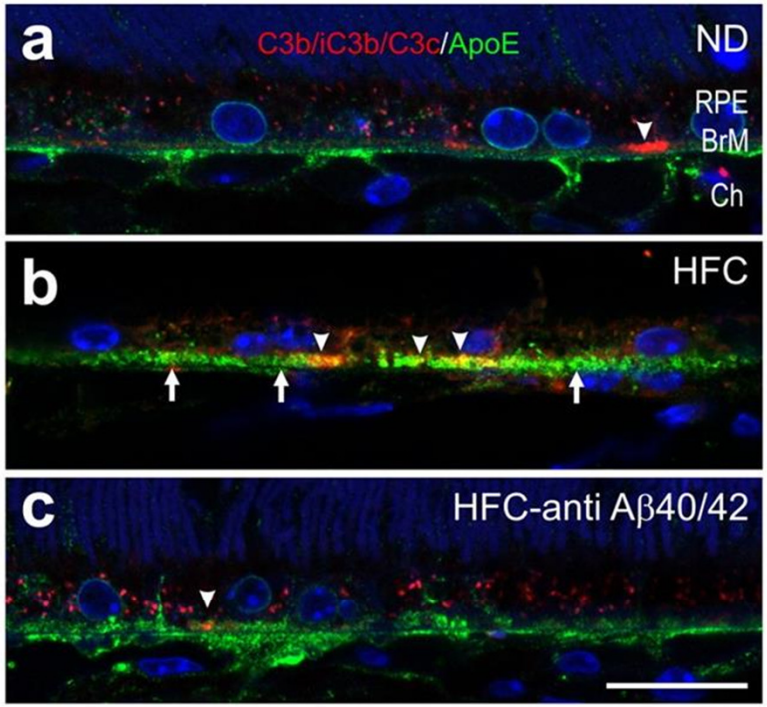
Malek et al, 2005; Ding et al, 2008,

Aβ antibody suppresses RPE inflammation and RPE pathology in the animal model of dry AMD

RN6G suppresses complement activation *in vivo* in the linear deposits in the mouse AMD model



Collaboration with Lincoln Johnson (UCSB), Catherine Bowes Rickman (Duke University), *Ding et al PNAS 2011.*

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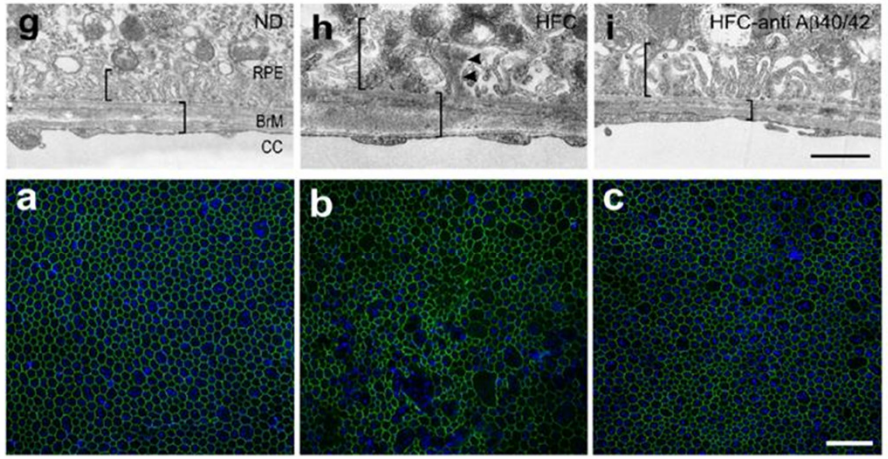
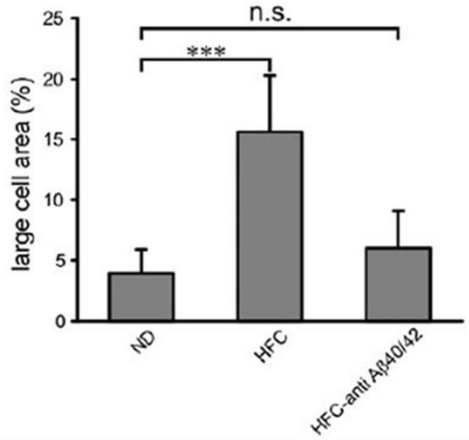
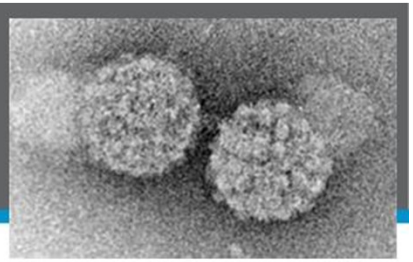
RN6G suppresses basal deposit formation and RPE cell loss and cell-size expansion





Amyloid β antibody delivery by the "gene therapy" approach



- Recent Phase 1 clinical trials have demonstrated excellent safety profile of RN6G.
- However, systemic or intravitreal delivery of antibody for the chronic and initially asymptomatic disease will impose significant burden on healthcare system and patients. Development of chronic delivery modalities for biologicals is essential.
- AAV-mediated gene delivery to the eye has been successfully explored as a potential long-term therapeutic delivery system.
    - RPE65 for Leber Congenital Amaurosis (Applied Genetic Technologies Corp)
    - sFlt1 for wet AMD (Avalanche Biotechnologies, Inc)
- Sustained elimination of amyloid β from retina could be achieved by the antibody expression in the eye.
- Technical problem: low packaging capacity of AAV-based vectors.

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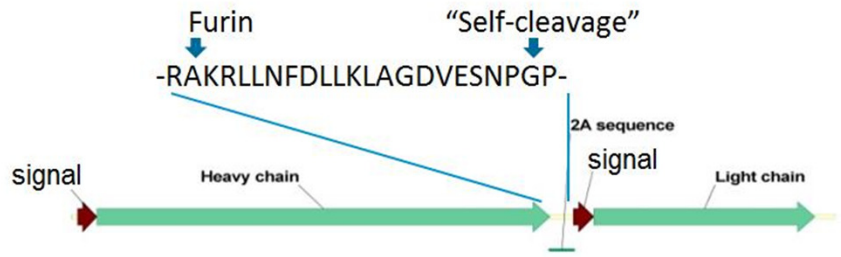
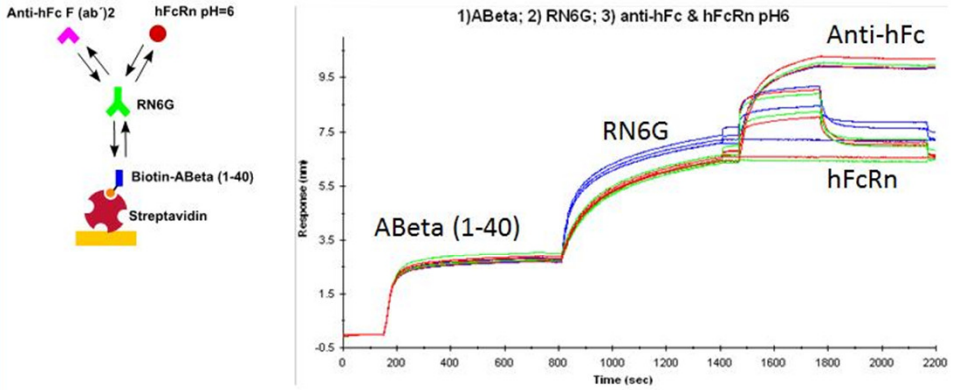
RN6G designed as a "polyprotein" expressed as full length IgG with the un-altered properties

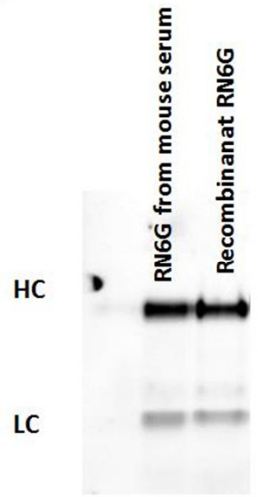


Analysis of interactions of RN6G expressed from monocistronic cassette as self-processing polyprotein



Legend: **blue: RN6G-V1 polyprotein; red: RN6G; green: RN6G**

Expression of RN6G from monocistronic cassette in vivo



HIGHLIGHTS

a. **RN6G is effectively produced from monocistronic polyprotein cassette.**
b. **As an antibody it is structurally identical to the original RN6G.**
c. **Binds amyloid-beta equally to the "original" RN6G.**
d. **Retains Fc-properties**

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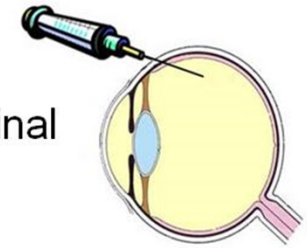
RN6G delivered to mouse eye intravitreally or subretinally, is expressed in the distinct retinal compartments

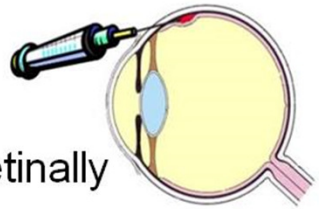
AAV2.2-RN6G

Effectively transduces inner retinal cells if delivered IVT



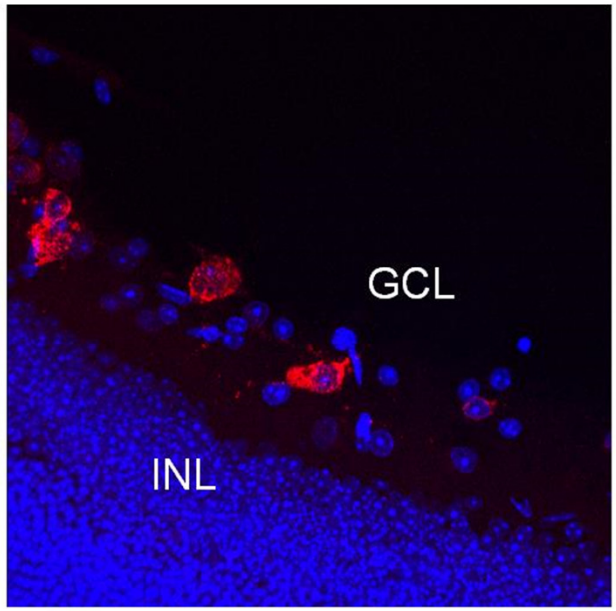
AAV2.5-RN6G

Effectively transduces outer retina/RPE if delivered subretinally



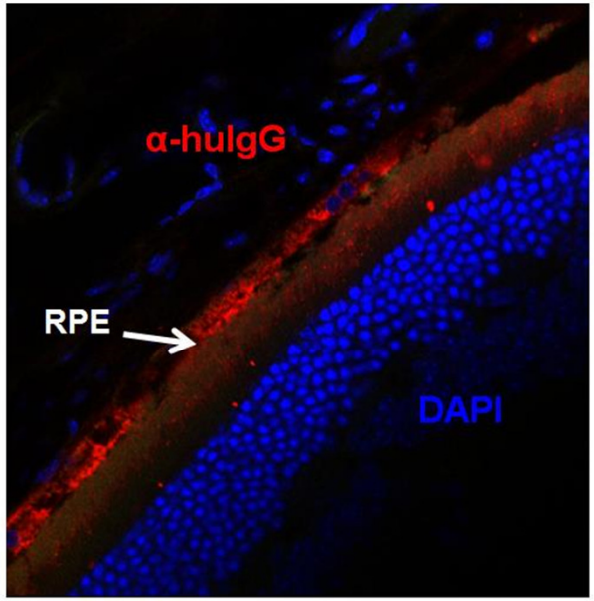
Intravitreal vector delivery, RN6G localization in retina

Red = Alexa568-goat-anti-human IgG (H+L)



Subretinal vector delivery, RN6G localization in retina

Red = Alexa568-goat-anti-human IgG (H+L)



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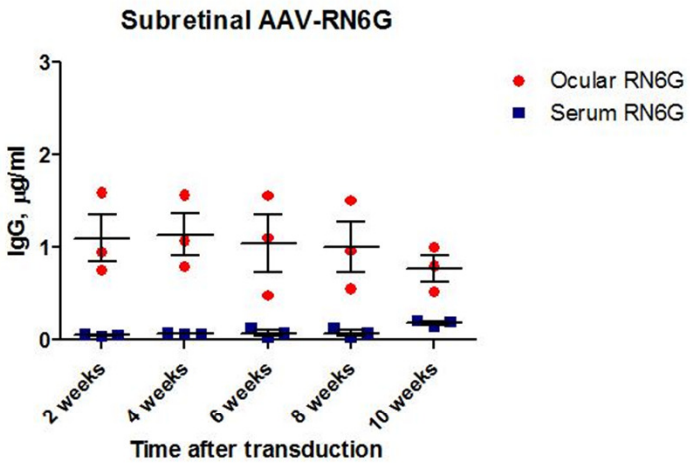
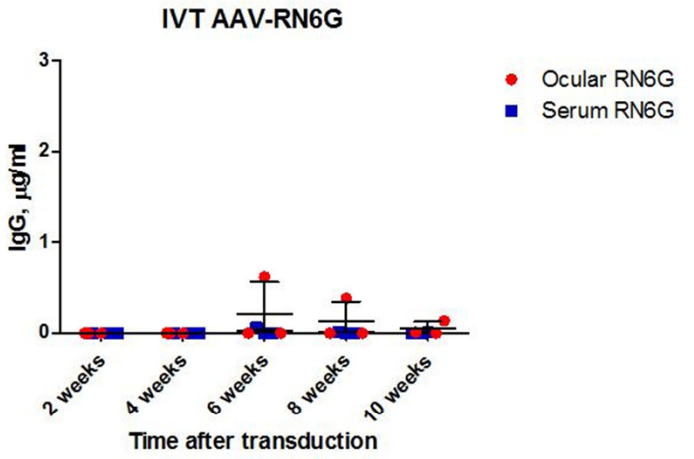
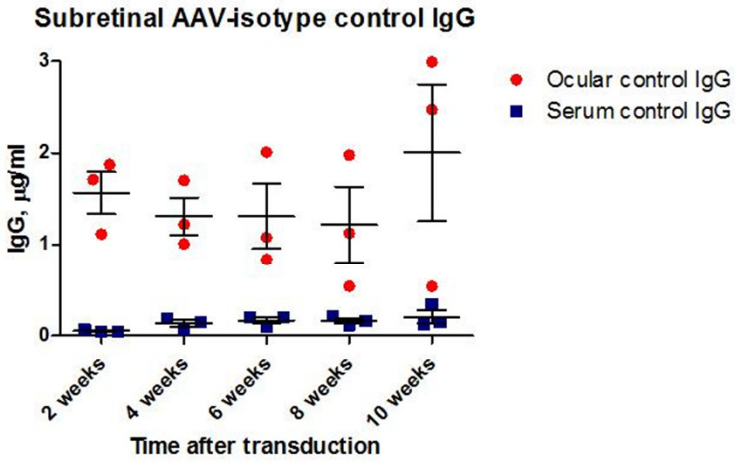
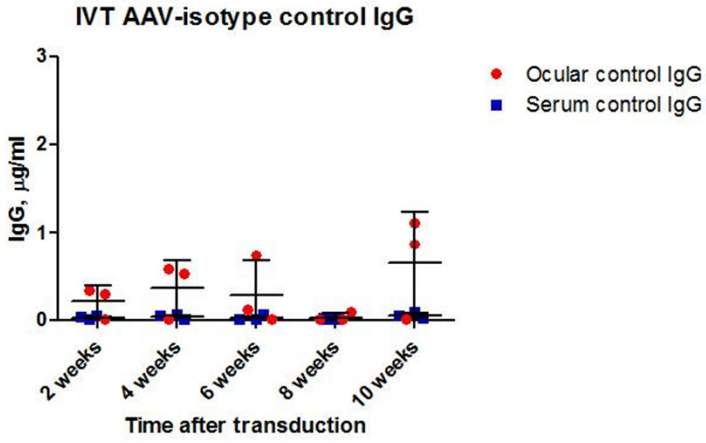
Delivery of AAV-IgG to RPE results in the sustained expression of antibody in the eye with low systemic exposure









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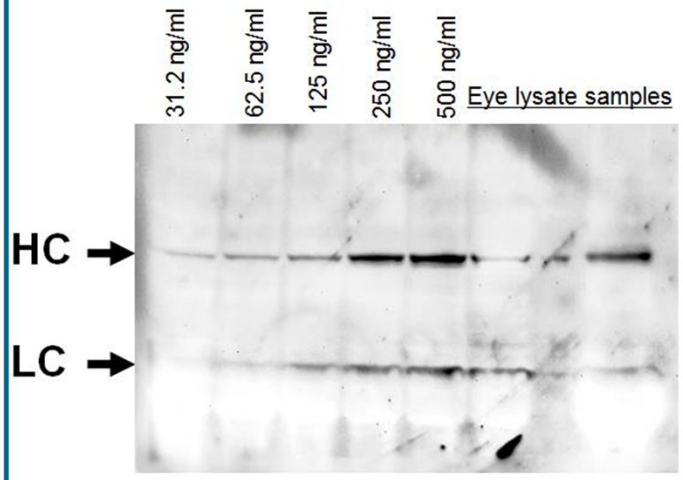
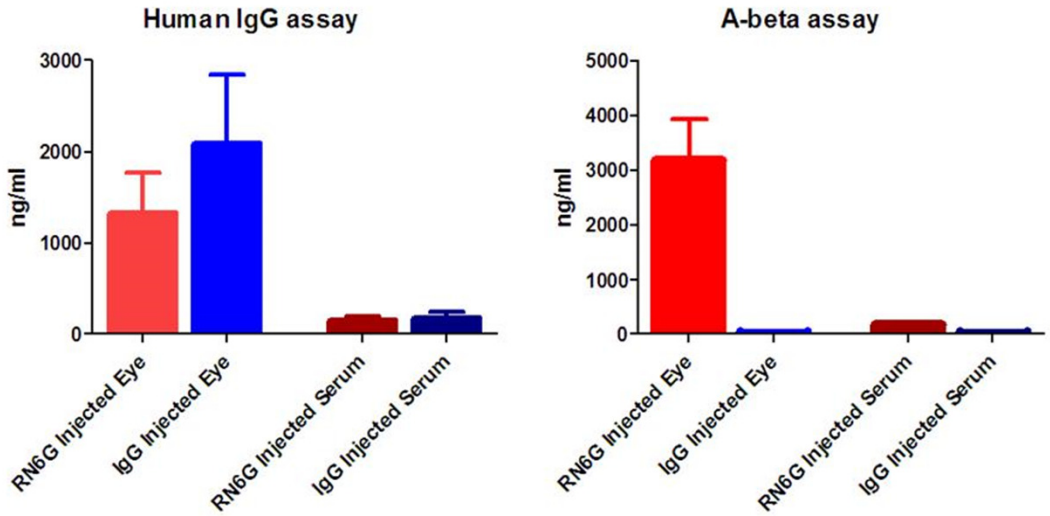
Full length RN6G Expressed in the RPE in vivo retains amyloid-β-binding activity

Expression of RN6G in the mouse eye assessed by Western blot



Detection of antigen-binding activity of RN6G expressed in the mouse eye by amyloid-beta ELISA



Levels of active RN6G measured by $A\beta_{1-40}$ ELISA approximates to a concentration detected by human IgG ELISA

AAV-mediated delivery of polyprotein cassette of full length RN6G may provide long-term passive immunization of the eye against pathogenic protein

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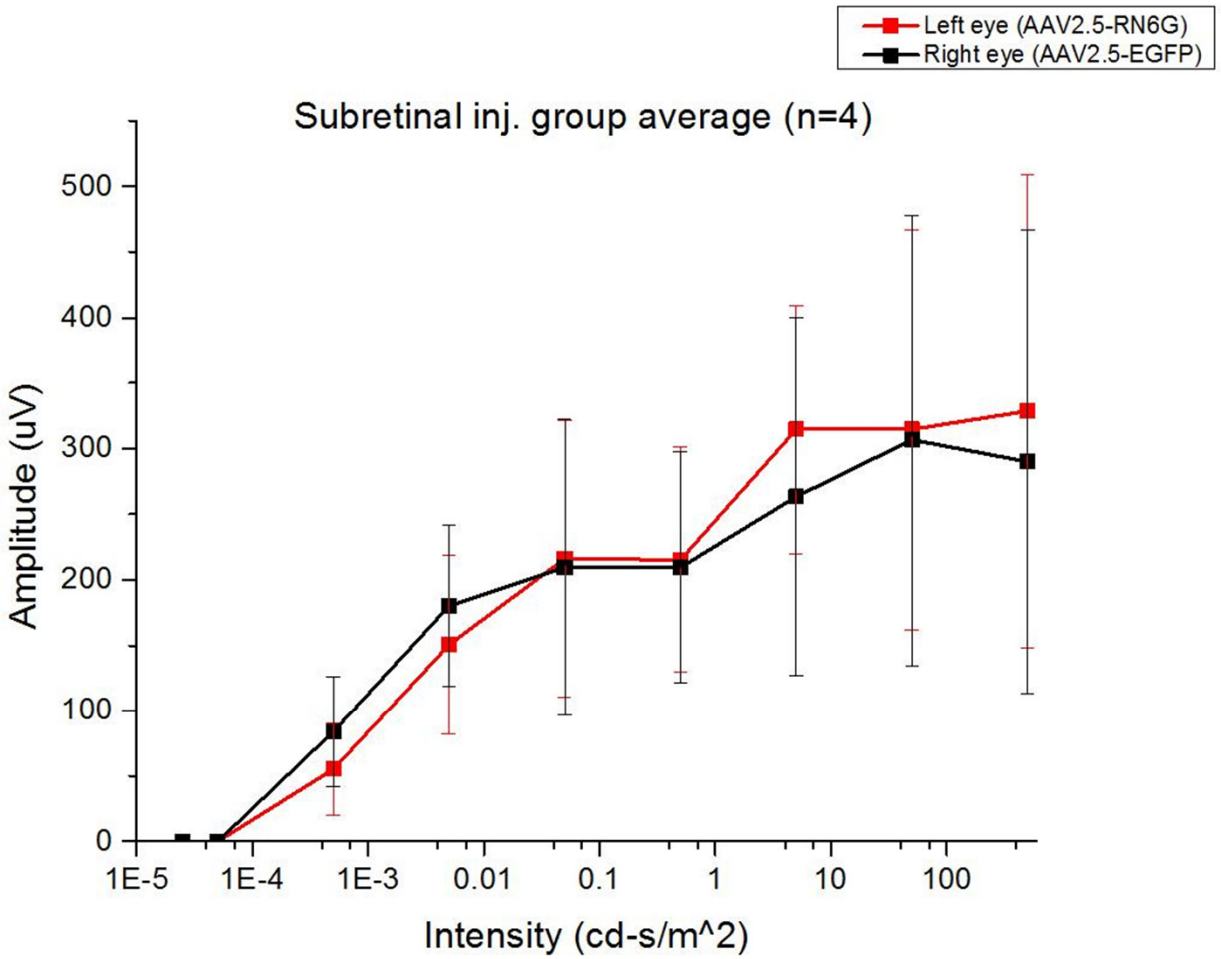
Expression of full length amyloid β antibody in RPE does not affect function of outer retina

Effect of retina transduction with AAV2.5-RN6G or AAV2.5-GFP on scotopic ERG B-wave



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Summary

- Amyloid β is a potential therapeutic target for the treatment of dry AMD.
- Full-length therapeutic anti-amyloid β IgG can be successfully delivered to the retina via rAAV vector.
- After subretinal delivery, full length pharmacologically active RN6G is stably expressed in RPE.
- Intraocular levels of the antibody are significantly higher than its serum levels. Intraretinal expression of RN6G does not impair retinal function measured by the electroretinogram.
- Since full length IgGs are stable molecules with low immunogenicity, the technology can provide a safe and effective way for the continuous delivery of therapeutic antibodies to treat chronic retinal degenerative diseases, if proven safe and effective in humans.

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Acknowledgement

Pfizer team

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Cathy Bowes Rickman
Jindong Ding
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UCSB

Lincoln Johnson

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