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Gene and Molecular Therapy; An Industry view

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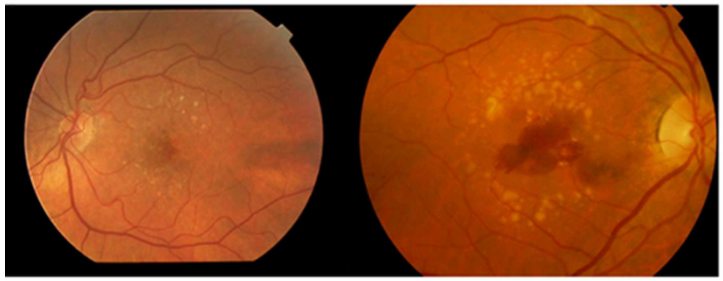
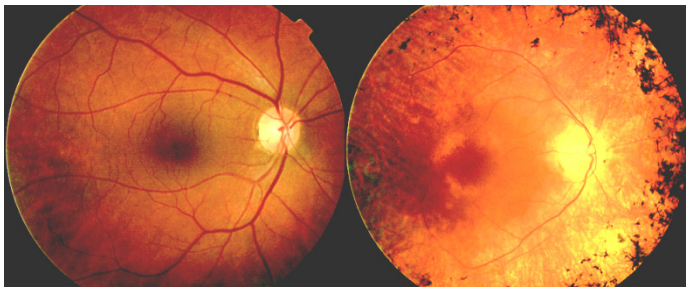
EU Regulatory Workshop – Ophthalmology – Clinical Development and Scientific Advice, 27th October 2011

Of the almost 200 million world-wide cases of visual handicap, degenerative retinopathies figure prominently. Preventive therapies are currently limited, or in many cases non-existent

Age-related macular degeneration

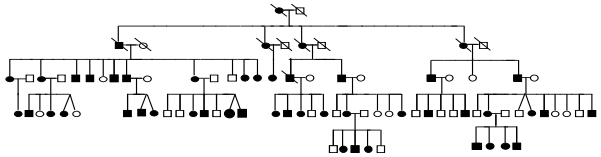


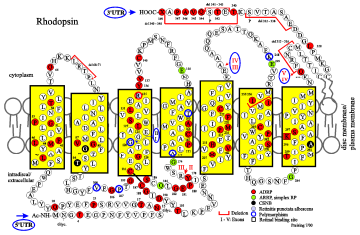
Retinitis pigmentosa



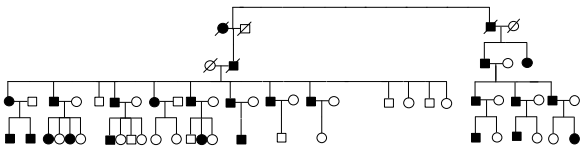
Retinitis pigmentosa

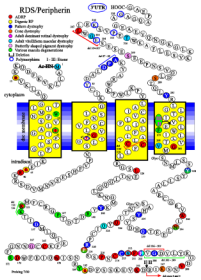
The most prevalent cause of registered visual handicap among those of working age - possibly the most genetically heterogeneous of any hereditary condition for which molecular pathologies have been explored



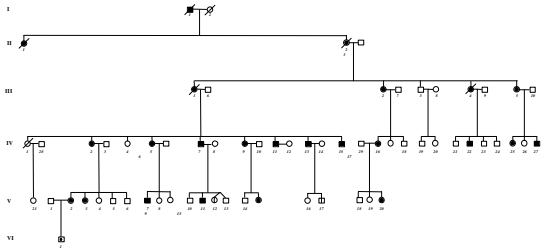


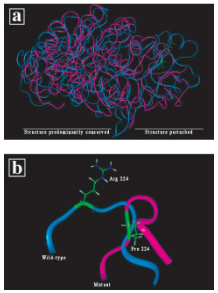
1989: Rhodopsin, 3q





RDS-peripherin, 6p1991





Inosine monophosphate Dehydrogenase 1, 7q, 1993

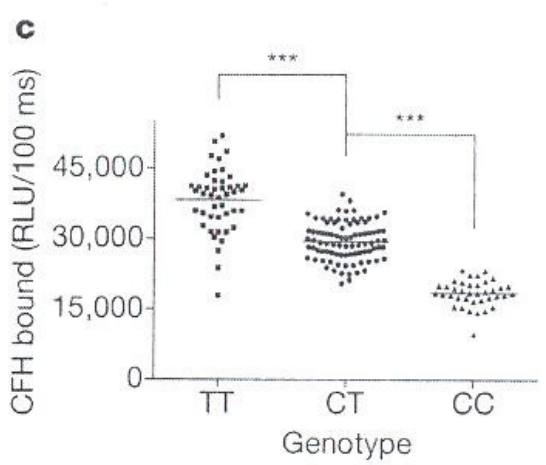
Current situation: RP/LCA/syndromic forms of retinopathy: 202 loci – 161 genes. Probably as many more remain to be identified.

Age-related macular degeneration

Multifactorial

Risk factors identified in genes encoding components of the complement cascades. CFH risk allele 402H, now known to have reduced capacity to sequester MDA, a pro-inflammatory product of lipid peroxidation.

Weissman et al., Nature 478 (2011) 76-81



Therapies:

Dry (non-exudative) form: no current means of therapeutic intervention.

Wet (exudative) form: Monoclonal antibody targeting VEGF (Lucentis) requires regular (monthly) invasive intra-ocular inoculation with risk of vision loss. No endpoints for treatment have been established

The challenge

"To design and validate gene and molecular therapies for degenerative retinal diseases that are applicable to a broad range of molecular pathologies"

Neuronal Barrier Modulation

A new non-invasive technology for systemic drug treatment of degenerative retinopathies

Pre-emptive systemic molecular therapy for early-stage age-related macular degeneration and Retinitis pigmentosa

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The Problem

- 98% of drugs with established potential for treating neurological diseases do not easily diffuse across the BBB or iBRB.

- Systemic delivery of such compounds is either impractical or highly inefficient.

- Poor penetration of these compounds is as a result not only of the low rates of diffusion across tight junctions but also the presence of P-glycoprotein efflux pump activity and a range of specific efflux receptors present in the microvascular endothelium

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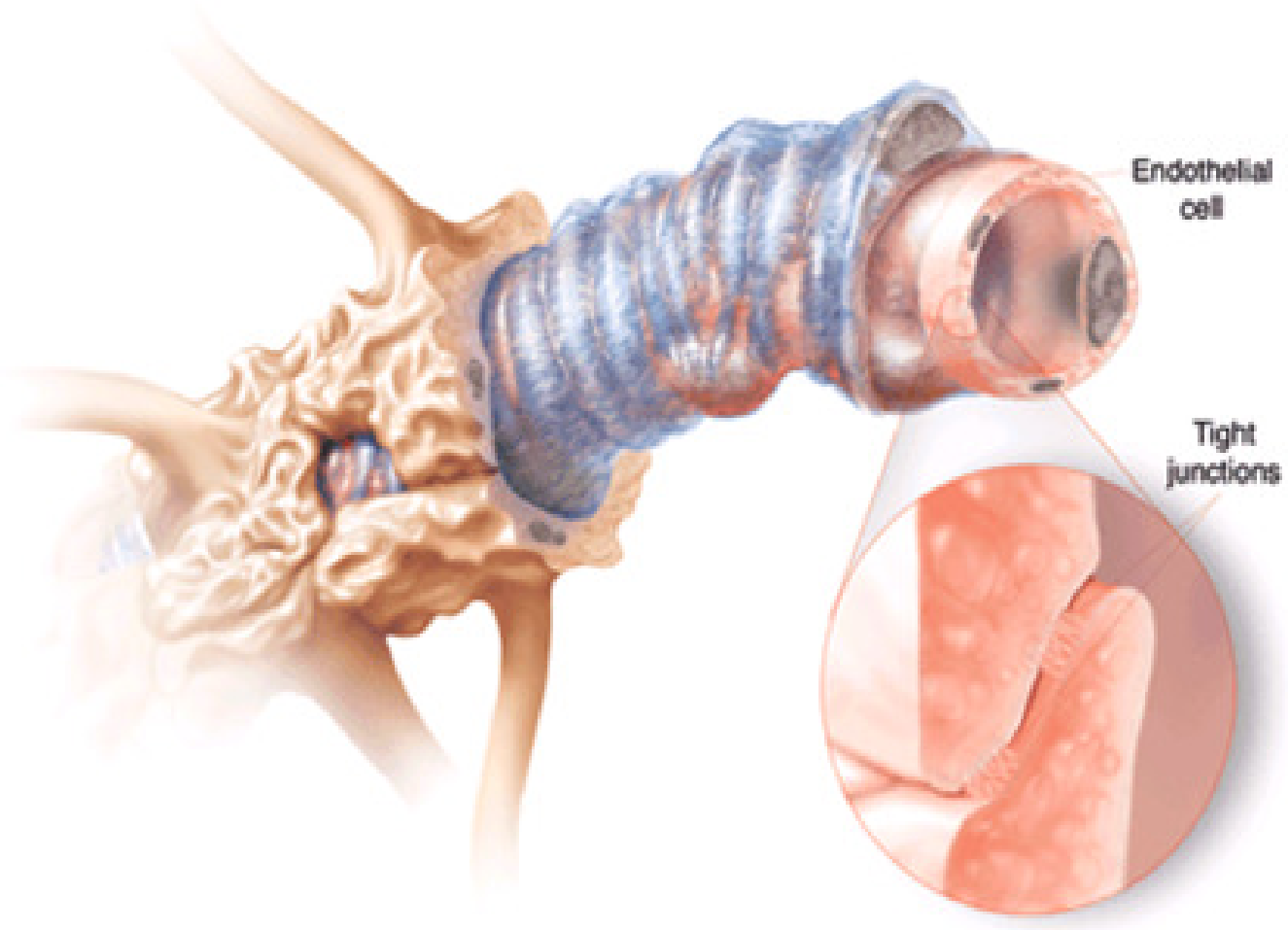

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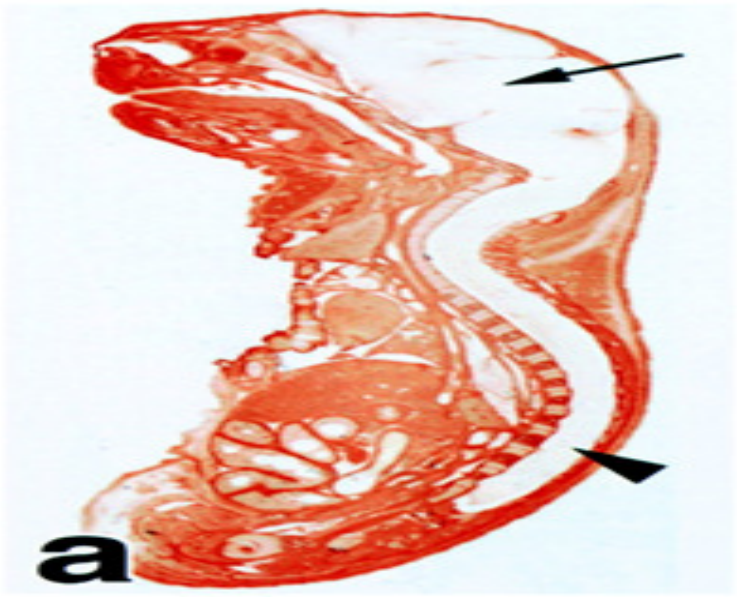
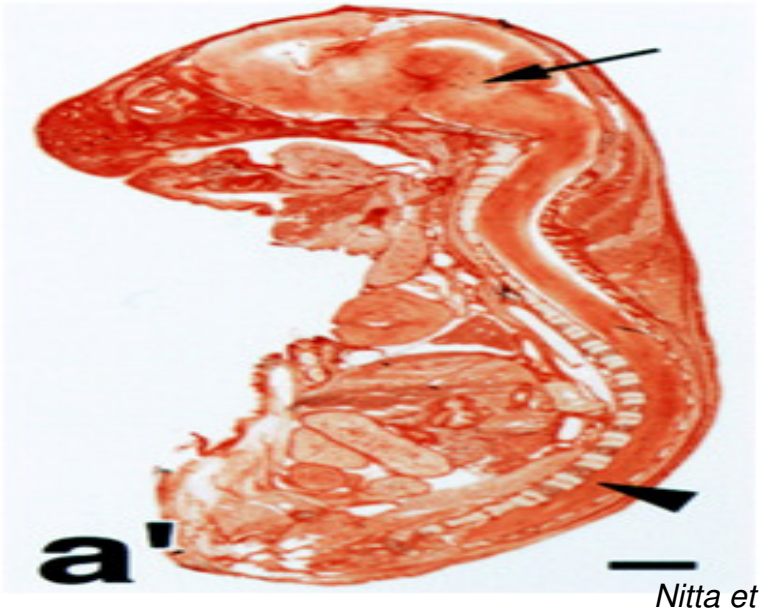
Abbott et al., 2006

Claudin-5

- 23 kDa tight junction protein

- In 2003, claudin-5 knockout mice were reported to show a size-selective BBB to molecules below 800 Daltons





Nitta et al., 2003

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Retinal Disease Models

- Age-Related Macular degeneration (AMD): Major sight threatening disease in developed countries

- Current therapies are limited and invasive- Direct and regular intraocular injection of antibodies targeting VEGF. No end-point has been established for treatment.

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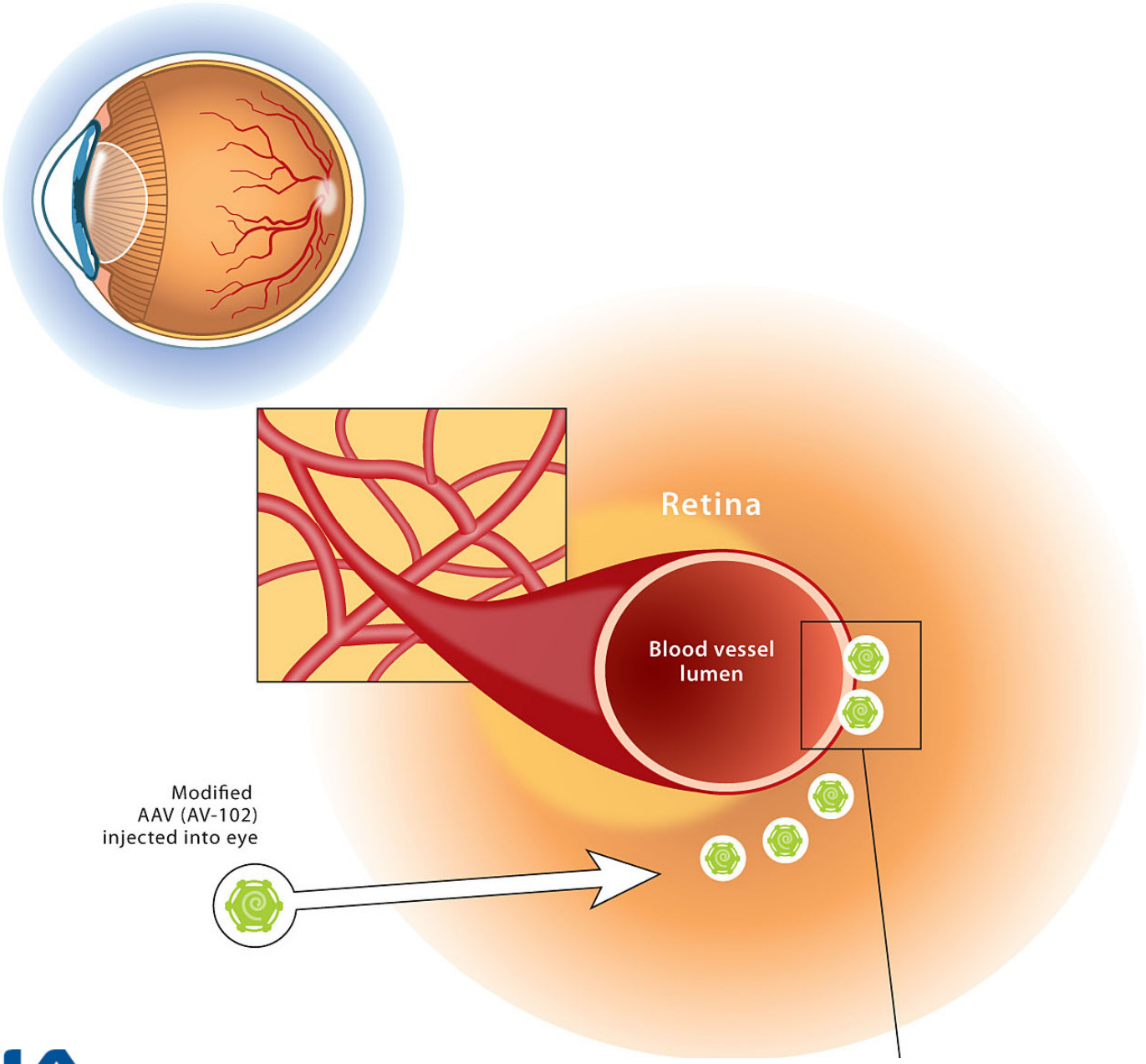

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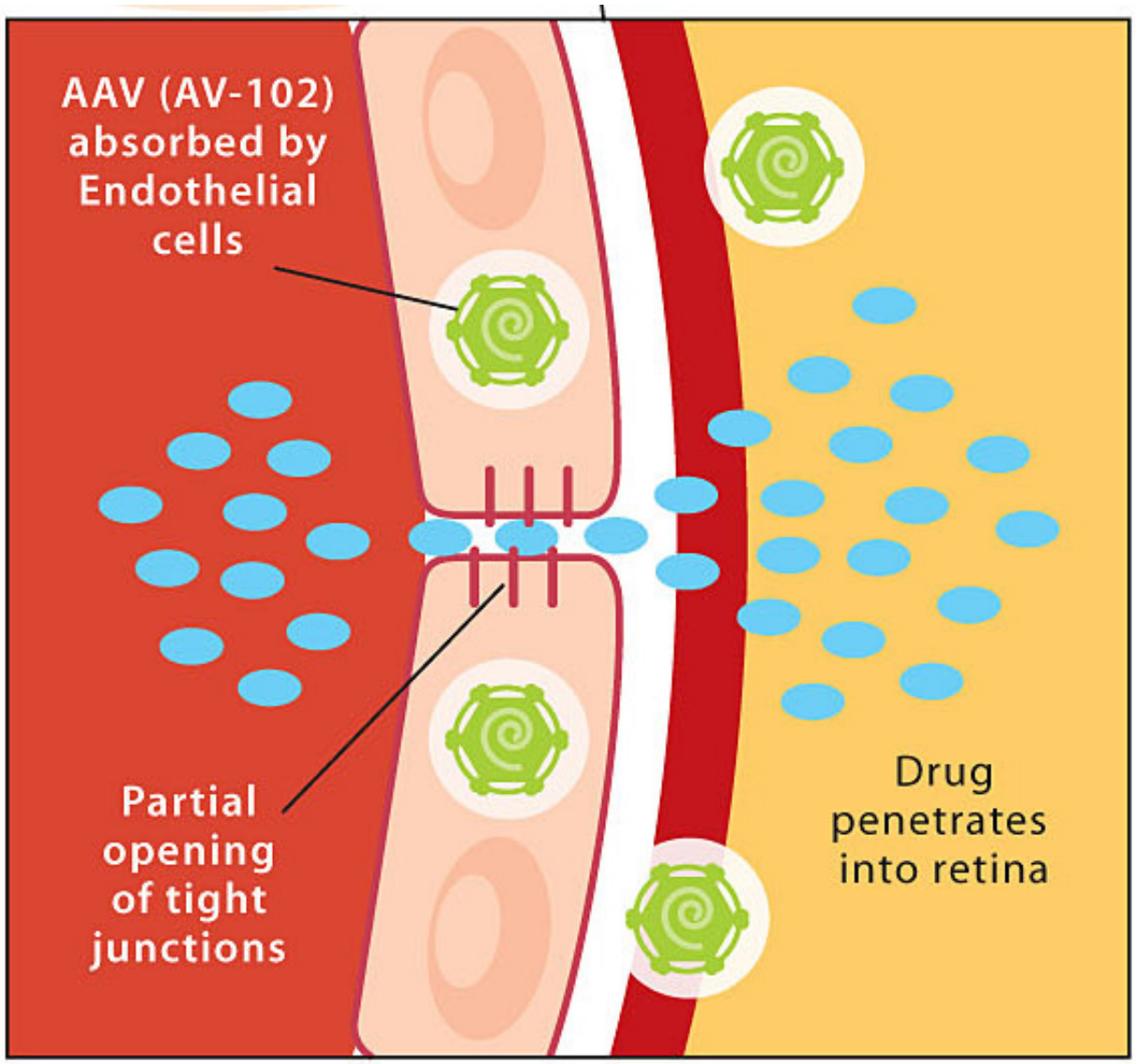

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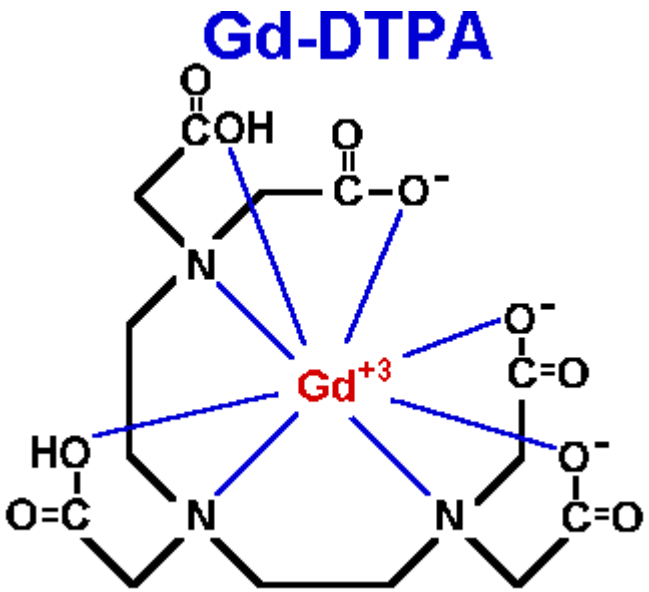
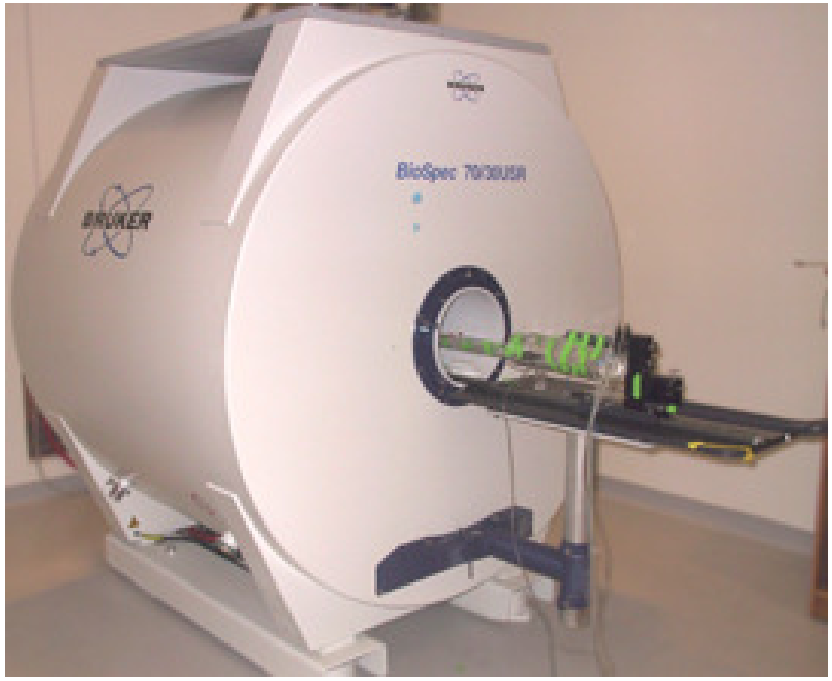
Magnetic Resonance Imaging (MRI)

Permeability experiments using Gadolinium-diethyenetriamine-penta-acetic acid injection



Gd-DTPA has a MW of 742 Daltons



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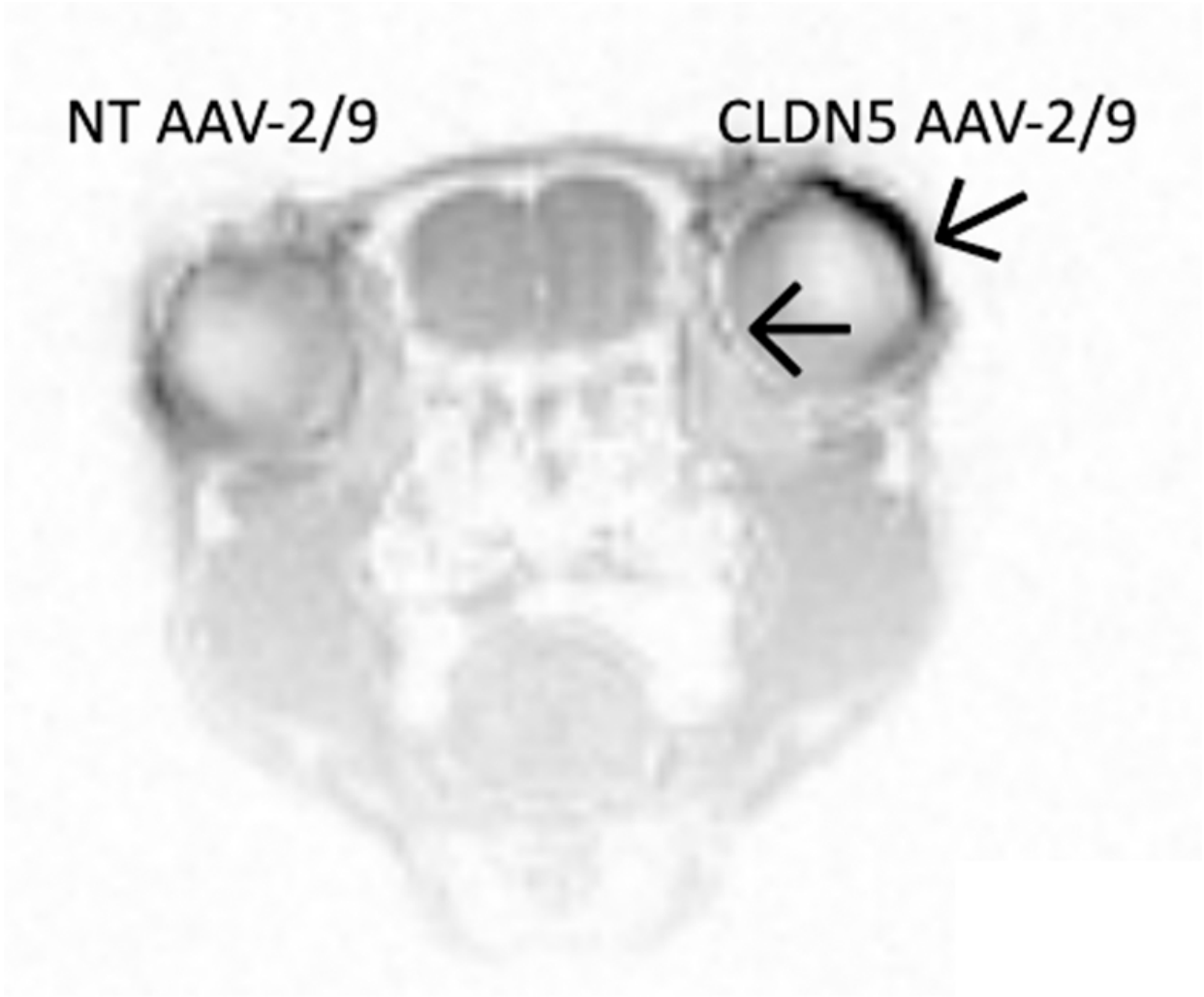
Ocular drug delivery by barrier modulation



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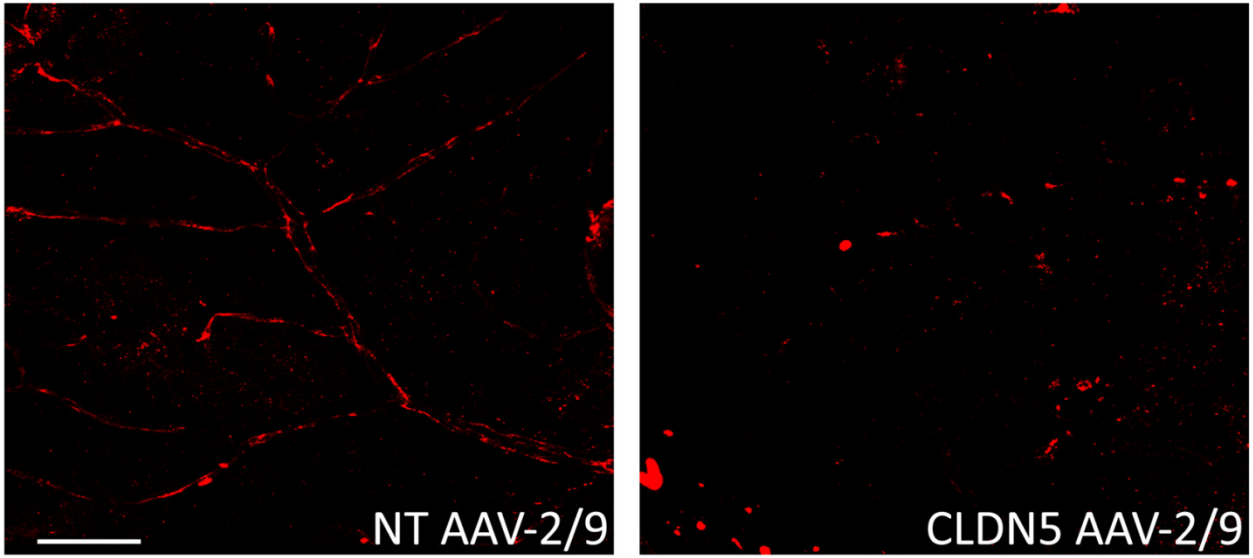

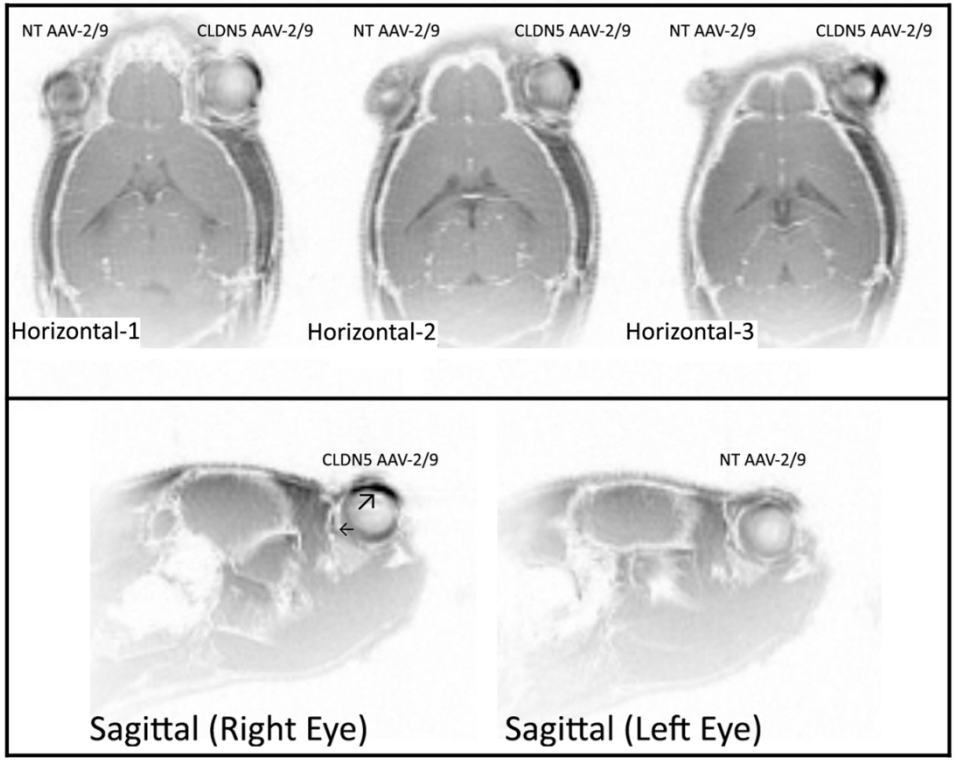

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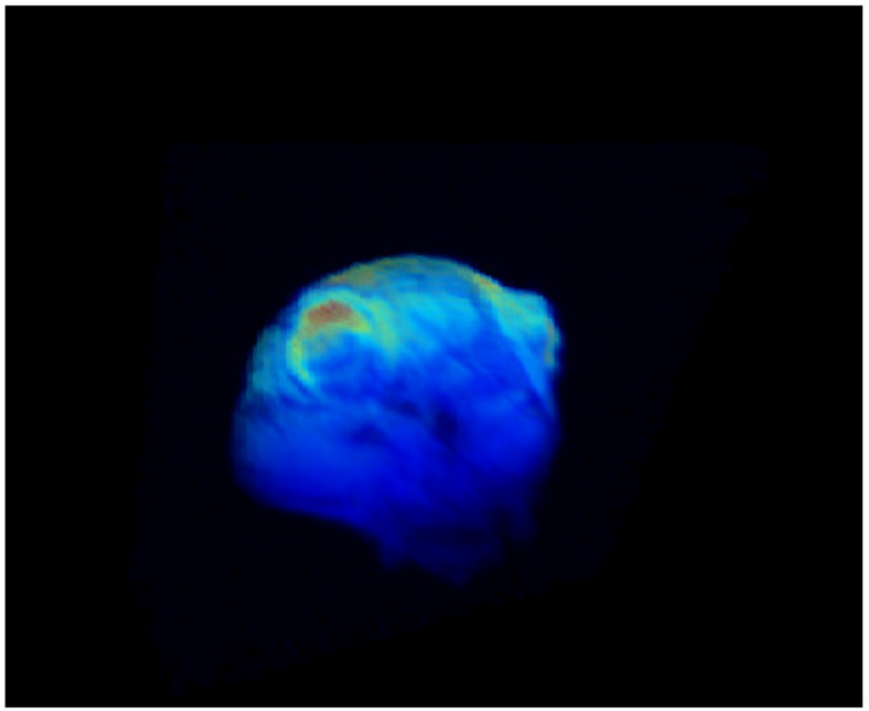

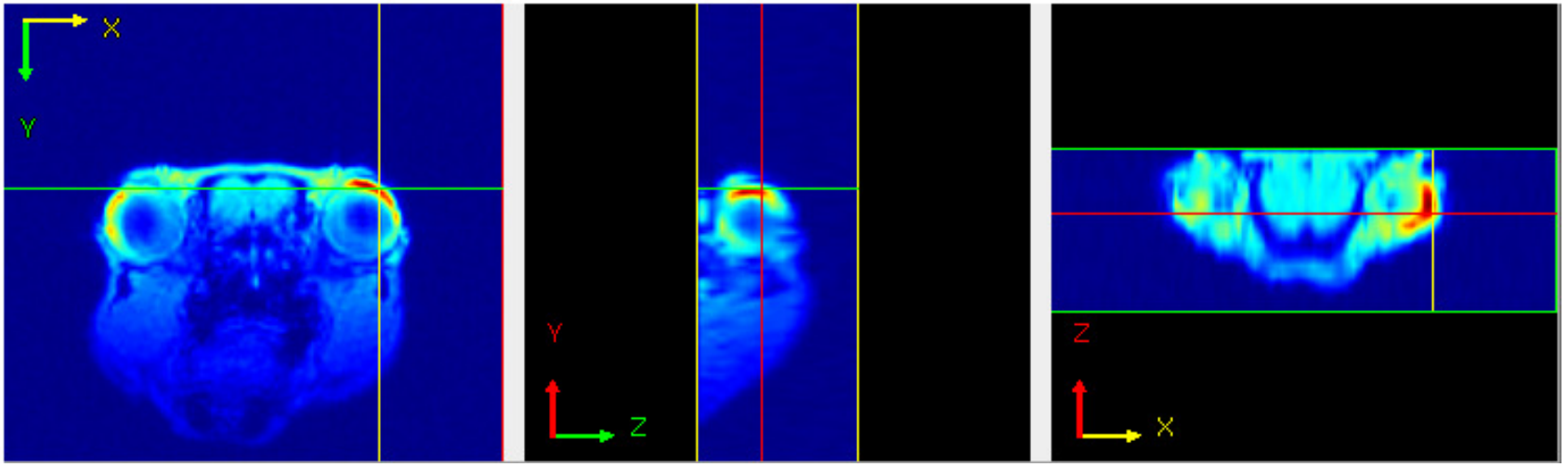

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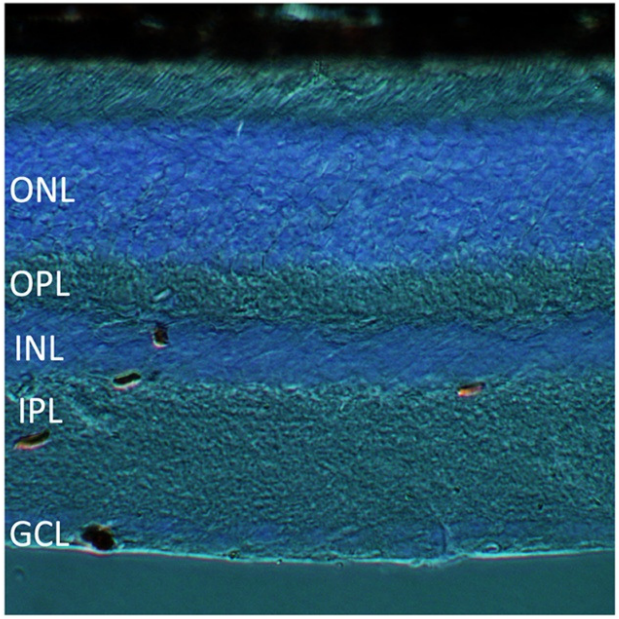
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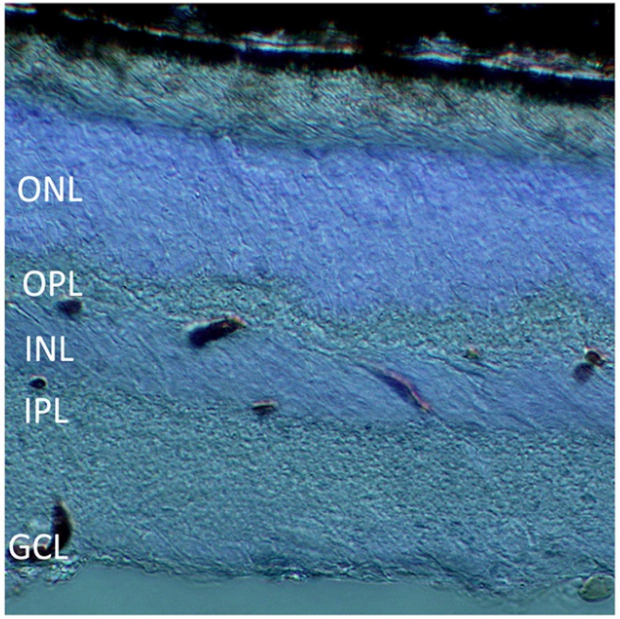
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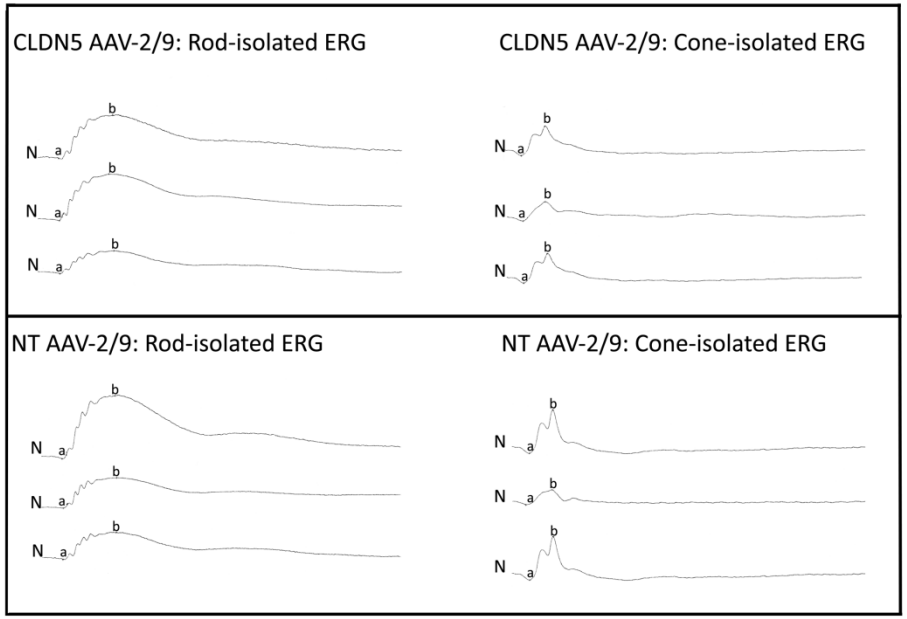
CLDN5 AAV-2/9: Rod-isolated ERG
CLDN5 AAV-2/9: Cone-isolated ERG
NT AAV-2/9: Rod-isolated ERG
NT AAV-2/9: Cone-isolated ERG
N
a
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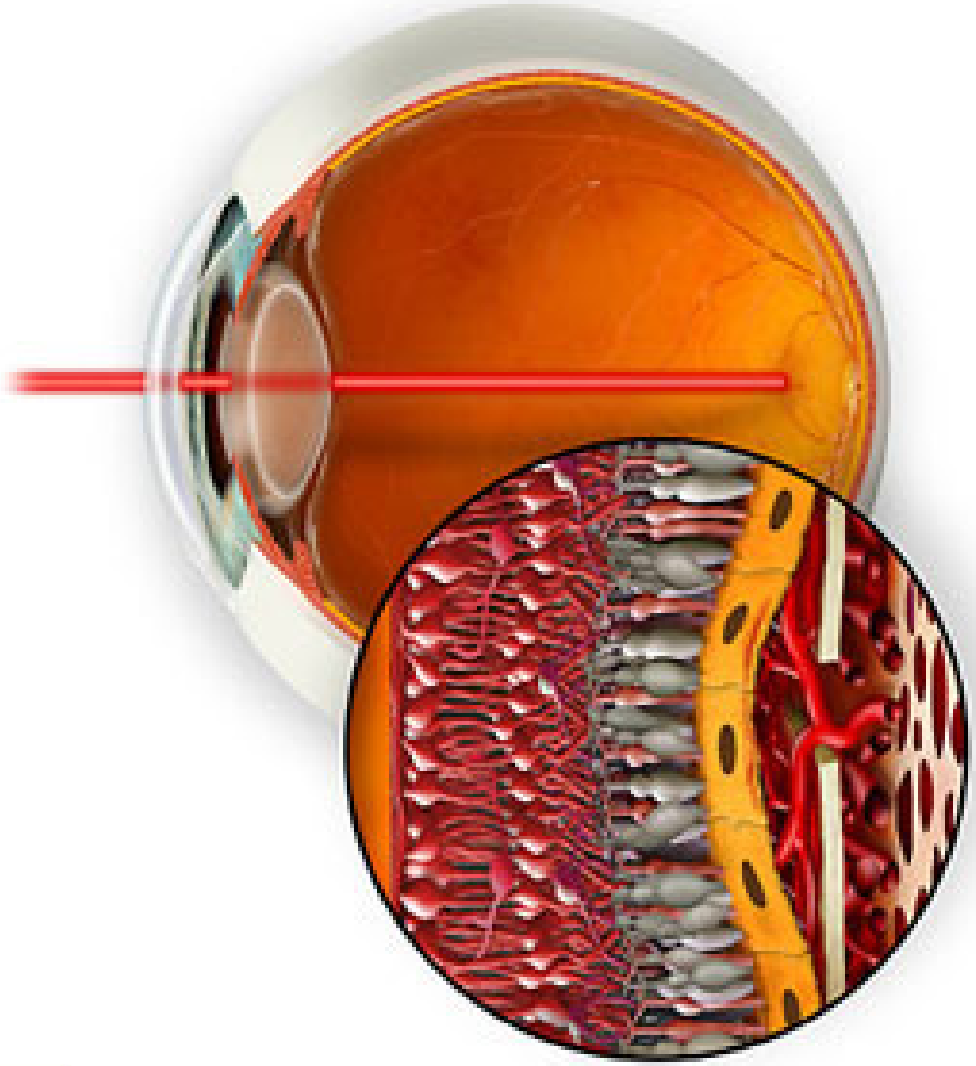
Laser induced Choroidal neovascularisation



Combination therapy

Administered Doxycycline in drinking water for 2 weeks while receiving 2 I.P injections of VEGF receptor antagonist **Sunitinib malate (532 Da)**

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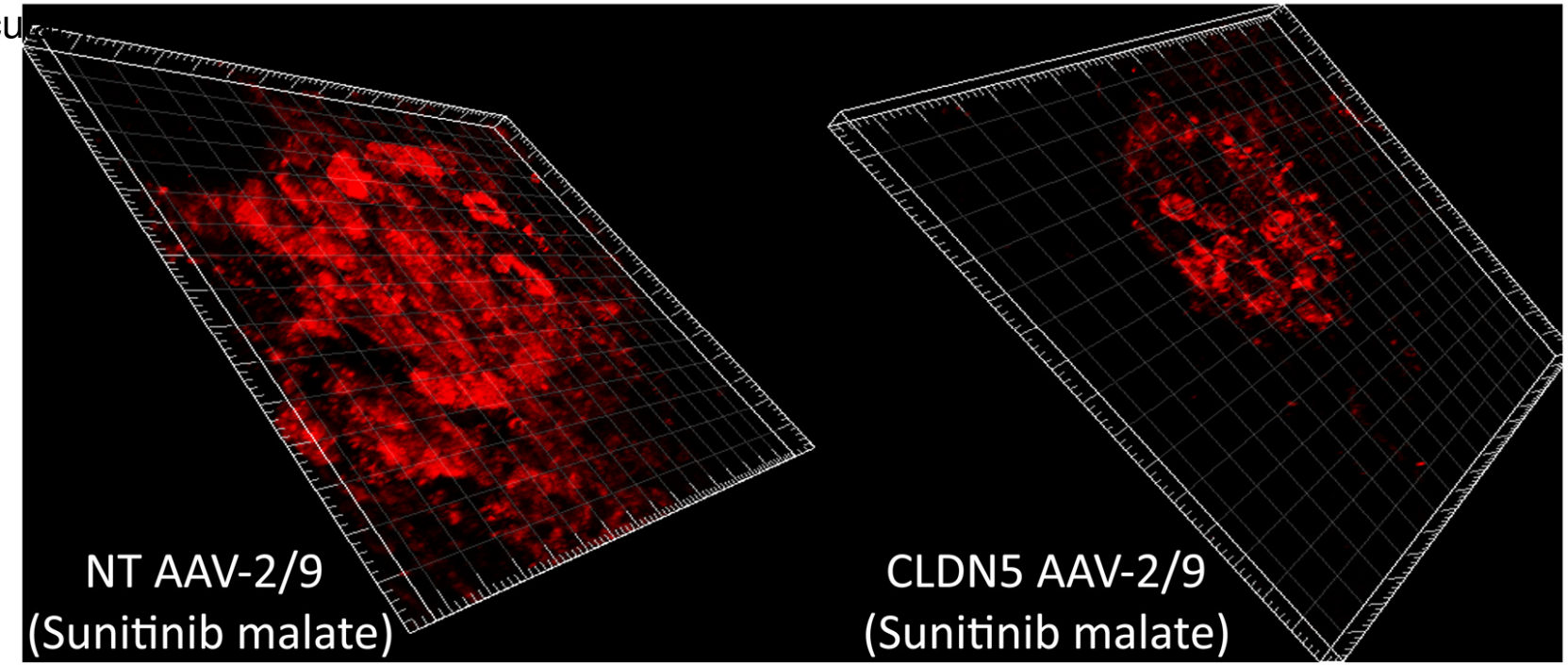
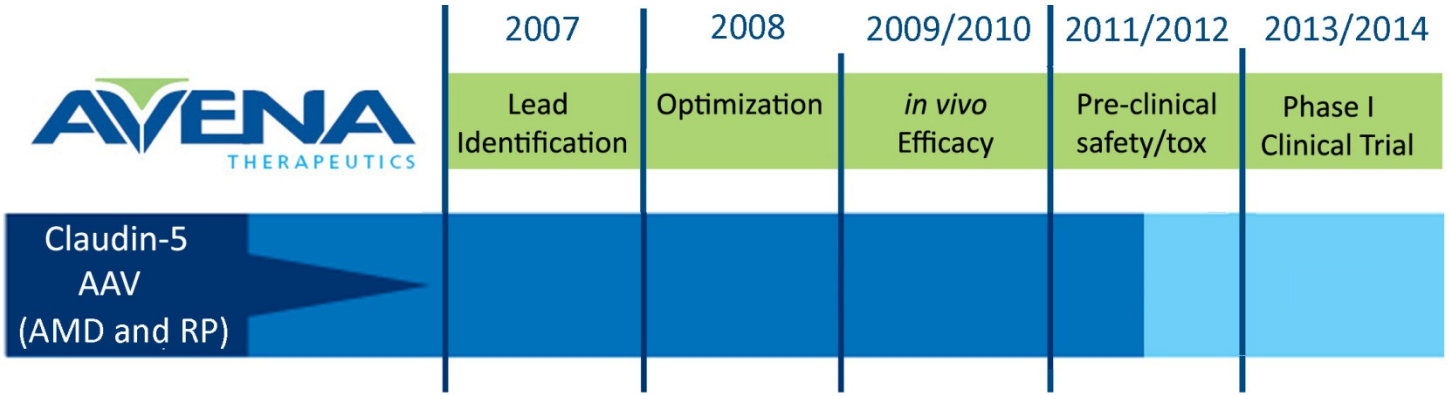
"The rationale was not to develop an RNAi therapeutic agent per se, but to use RNAi to allow the application of conventional drugs for treating diseases of the brain, CNS or eye".

[Professor John Rossi, commenting on the technology of Neuronal Barrier Modulation, EMBO Molecu





End-points in different phases

-Costs involved in pre-clinical safety/toxicology studies are extensive

-With wet AMD, what is the end-point and efficacy readout?

Duration of clinical trials

-Barrier modulation is preventative as opposed to a “cure”

-Is Safety/toxicology enough?

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The Ocular Genetics Unit at TCD

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Dr. Paul Kenna
Prof Jane Farrar
Ms Anh Nguyen
Mr Finnian Hanrahan
Mr James Keaney
Ms Ema Ozaki

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