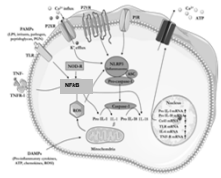
Ocular Therapeutics Conference 2020

Alternative drugs to anti-VEGF agents



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THE UNIVERSITY OF AUCKLAND NEW ZEALAND

Commercial Relationships

Speaker Disclosure: Colin Green

Founder Scientist **CoDaTherapeutics (NZ) Ltd**

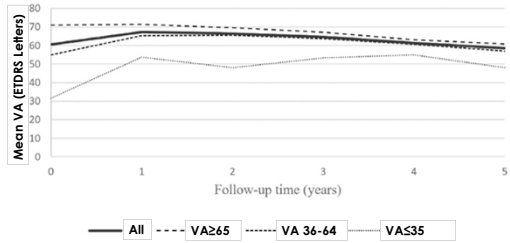
Founder Scientist **OcuNexus Therapeutics, Inc. USA**

Stockholder **OcuNexus Therapeutics, Inc. USA**

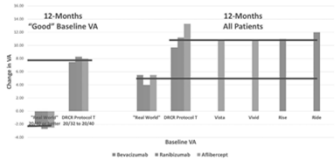
Inventor on 280+ patents (**31 patent families**) related to the regulation of connexin channels

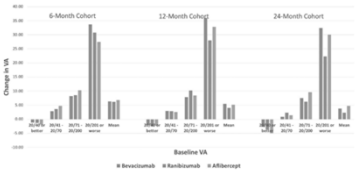
OcuNexus

The Anti-VEGF paradox in Treating Wet AMD



DME treatment in the real world doesn't match randomized clinical trials





Anti-VEGFs are the mainstay of ocular chronic disease treatments

New variations / combinations and better delivery offer increased chance of success

BUT:

- **>50% of patients don't improve BCVA after anti-VEGF**
- **10% don't respond to the treatment at all**
- **No treatment for dry AMD / Geographic atrophy**
- **We're only treating a late stage sign of disease**
- **Anti-VEGF cannot distinguish between bad and good blood vessels**
- **VEGF is just one cytokine upregulated in the vitreous of AMD/DR Patients**
  (others include IL-1, IL-6, IL-8, TNF- and MCP)
  – we're not shutting down the disease

The Current State of Play

Several new therapies have failed to deliver as expected:

Fovista (Ophthotech) (anti-PDGF and anti-VEGF combination)
Squalamine -Lucentis® (Ohr)

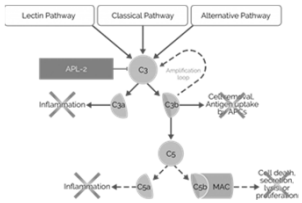
Complement Pathway factors
Lampalizumab (Genentech / Roche) (Complement Factor C5)
LFG316 (Novartis) (Complement Factor C5)

But hope remains?

- OPT-302 (Opthea) (VEGFR-3 or "Trap" molecule blocking VEGF-C and VEGF-D in combination with Lucentis® / VEGF-A inhibitor)
  Mean BCVA (week 24) gain of +3.4 letters (p=0.0107),compared to Sham + Ranibizumab
- Angiotensin II receptor type 1 (AT1R) blocker (Losartan, Candesartan) for Diabetic Retinopathy

- **Complement Pathway inhibitors are not exhausted**
- **Inflammasome pathway inhibitors remain untried**

APL-2 (Apellis) (Complement Factor C3) - Pegcetacoplan



Reduces GA spread - bimonthly or monthly injections

29% reduction in the growth of GA lesion area in the monthly treatment group (p=0.008)
20% reduction in the EOM treatment group (p=0.067) - compared to the pooled sham group.

Effect was more pronounced in the last six months of treatment, with observed reductions of 45% (p=0.0004) and 33% (p=0.009) for APL-2 monthly and EOM, respectively, compared to sham.

BUT -

- ***Benefit stops upon withdrawal of treatment = injections for life***
- ***20.9% 'conversion' to Wet AMD (versus 1.2% in shams***)

Inflammasome Pathway of the Innate Immune System

Inflammasome Signal 1 Priming

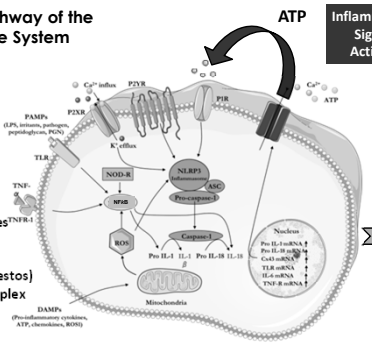
Pathogens
- **Pathogens**
- **Peptidoglycans**
- **LPS**

Danger signs
- **Inflammatory cytokines (TNF, IL-1 ….)**
- **Chemokines**

Crystals (silica, urate, asbestos)
- **Membrane attack complex (MAC)**

ATP

Inflammasome Signal 2 Activator



IL-1β
IL-18
TNFα
IL-6
IL-8
MCP1
iCAM
VEGF

Inflazome

(Dublin but opening office in Brisbane for Australian clinical trials)
- Two drugs targeting same site as MCC950 currently in Phase 1 safety trials
  - Inzomelid (blood brain barrier permeable)
  - Somalix

Canacinumab (Novartis) – IL-1β blocker
Rare autoimmune conditions and to reduce further heart attacks or stroke

Been shown to stop progression of retinal neovascularization, stabilize VA and mildly reduce retinal edema in PDR patients
No change in neovascularization in diabetic retinopathy
Possible effects on diabetic macular edema

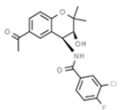
Anakinra - interleukin-1 (IL-1) receptor antagonist

OcuNexus - Xiflam

World Leader – Only Inflammasome targeting company at Phase II
Agreement with GSK for Xiflam Information Brochure, toxicity, carcinogenicity, human safety data
1 year ahead of the pack
Once daily **ORAL** tablet

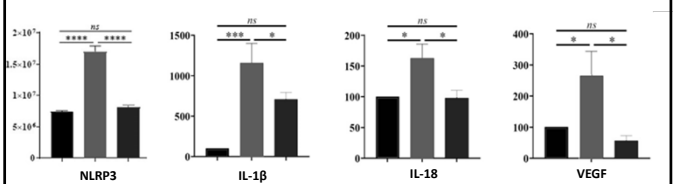
GA/DME/DR
Xiflam
(oral small molecule)
Stage: Phase 2B

- **Blocks hemichannel opening / reduces ATP release**
- **Once daily ORAL availability targeting ….**
- **Diabetic Eye Disease including DME, DR**
- **Dry (GA) and Wet AMD**
- **T_{max} 0.5 – 3 hrs, terminal half life 24 – 40 hrs**
- **No accumulation**
- **Safe – Used in over 1000 patients (as treatment for migraine)**



Xiflam shuts down the inflammasome pathway in the human retina

(Diabetic Retinopathy - Human Cadaver Retinas)



Tissues analysed using quantitative immunohistochemistry

Medium (cytokine secretion) analysed using Luminex cytokine bead array

- **Basal**
- **Glucose + Cytokines**
- **Glucose + Cytokines + Xiflam**

+ proven efficacious in animal models of GA and DR

For Anti-VEGF alternatives watch especially:
- **Apellis (Complement Factor C3 inhibitor)**
- **Inflazome (Inzomelid)**
- **OcuNexus (Xiflam)**