Fighting Blindness with 3D-NET "Drug Discovery & Development of Novel Eye Therapeutics"

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Background On Eye Disease

Blindness and visual impairment[1]

- **P**ermeability
- **A**ngiogenesis
- **I**nflamation
- **N**eurodegeneration

Diabetic retinopaty (DR)- 135mill.
Diabetic Macular Oedema (DMO)-21 mill.
Age-related Macular Degeneration (AMD)-20-25 mill
Opacity, Inflammation and/or Neovascularisation of the cornea

3D-NET[2]
Drug Discovery & Development of Novel Eye Therapeutics

What is 3D-NET[2]?

A new research consortium of industry and academic partners focusing on discovery & development of novel eye therapeutics to halt or reverse blindness. 3D-NET is funded through a €1.8 million Marie Curie Industry-Academia Pathways and Partnerships (IAPP) award from the EU Seventh Framework Programme (612218/3D-NET).

INDUSTRY

KALVISTA:
- Compounds
- In Vitro Screen Models (HCS)
- Drug development/ commercialization

RENASCi:
- STZ model of diabetes
- CNS techniques and Drug Physiology

Gadea[3]:
- Compounds
- Chemical Synthesis and Optimisation (SAR)
- Drug development/ commercialization

ACADEMIA

UCD[4]:
- Knowledge of eye biology and disease
- Compounds
- In vivo screens and efficacy/safety assays for ocular drugs
- In vivo models of ocular disease

UVA:
- Knowledge of eye biology and disease
- In vitro/ ex vivo/ in vivo models of ocular disease
- Contact with Patients

What we want to achieve ?

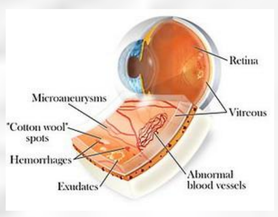
- Grow our expertise/our business.
- Enhance our ability to discover and develop ocular drugs.
- Enhance our industry-to-academia interaction.
- Enhance the career development of our researchers.
- Comprehend the route to spin-out, commercial success.
- Acquire new technical expertise.
- Collaborate with industry/academia to fill skills gaps.
- Publications & Patents

Discovery & development of small molecules that show novel antiangiogenic efficacy in the eye (WP1), reduce ocular inflamation or retinal vasculature permeability (WP2) and/or show "cell protective" activity in the eye (WP3)

Strategy:
Phenotype-base Drug Discovery And Development

Discovery Of Novel Small Molecules That Show Antiangiogenic Efficacy In The Eye (WP1)

The problem
Aberrant blood vessels



Current treatment
Intravitreal injection

Future
Eye drops

Aim
Uncover safer, more efficacious therapies for ocular neovascularisation and oedema

3D-NET
UCD-Gadea Collaboration
IP agreement
Transfer of knowledge (ToK)

gadea

Random Libraries And Target Compounds

-Design and Synthesis of new analogues
- Structure-Activity Relationship (SAR)
-ADME properties modifications

H2L

Lead Optimization

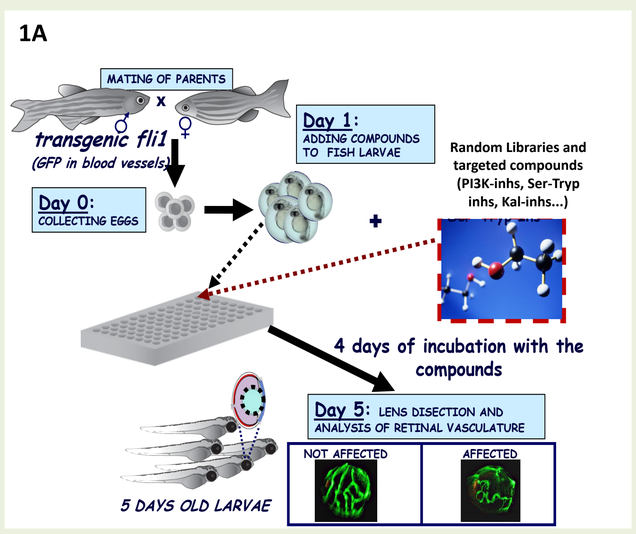
UCD Ireland's global university

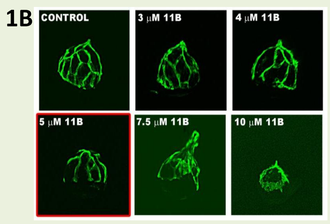
In vivo Drug Discovery

Hit Validation In Human Cell Lines

NEW ANTIANGIOGENIC DRUG

- ✓Antiangiogenic activity
- ✓Safety
- ✓Efficacy
- ✓ADME properties
- ✓Self-administer eye drops
- ✓Mechanism of action different to VEGF
- ✓Low cost treatment
- ✓IP generation





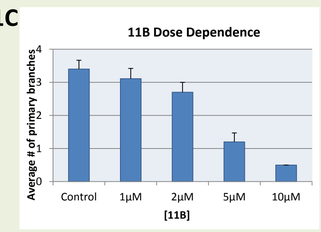
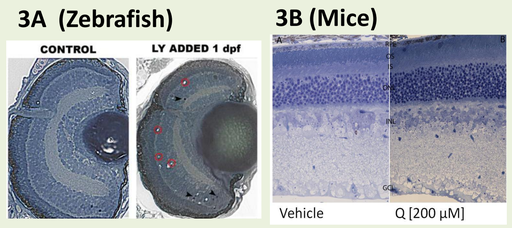


Figure 1.- (A) Scheme of the screen of small molecules inhibiting development angiogenesis in zebrafish. (B) Epi-fluorescent imagines of dissected zebrafish lenses with different concentration of compound 11B. (C) Graph of the average number of primary branches of hyaloid vasculature.

Mechanism of Action (MoA)

Safety and Efficacy:
- Zebrafish
-Preclinical Mouse Models
-Human Tissues
- Optokinetic Response

Computational Assisted Drug Design



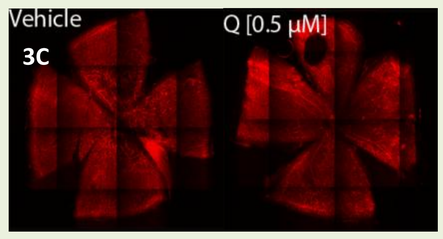


Figure 2.- (A) Histological section on Zebrafish eyes (B) Light micrographs of [200 μM] drug-treated retina (RHS) and vehicle (LHS) in adult mice (c) Angiogenesis inhibition in a mouse ocular neovascularisation model. (Hyposia/Normoxia treatment of P7 C57BL/6J mice-invitreally treatment of Q and vehicule).

References

[1]a)*N. Engl. J. Med.*, **2008**, *358*, 2606-2617; b)*N. Engl. J. Med.* **2004**, *350*, 48-58;c)*Nature Reviews Drug Discovery,* **2012**,*11*, 541-559;d) *Nature*, **2005**, *438*, 967-974;e)*Discov. Med.*, **2013**, *15*, 291-299
[2] http://www.ucd.ie/3dnet/; https://www.linkedin.com/groups/3DNET-5189321; https://twitter.com/3dnetconsortium; https://www.facebook.com/3DNETConsortium
[3] http://www.gadea.com/en/
[4]a) http://www.ucd.ie/sbbs/sbbsstaff/academicstaff/bkennedy/ b) Patent number: **US2013289066** c) Patent number: **WO2014012889**

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