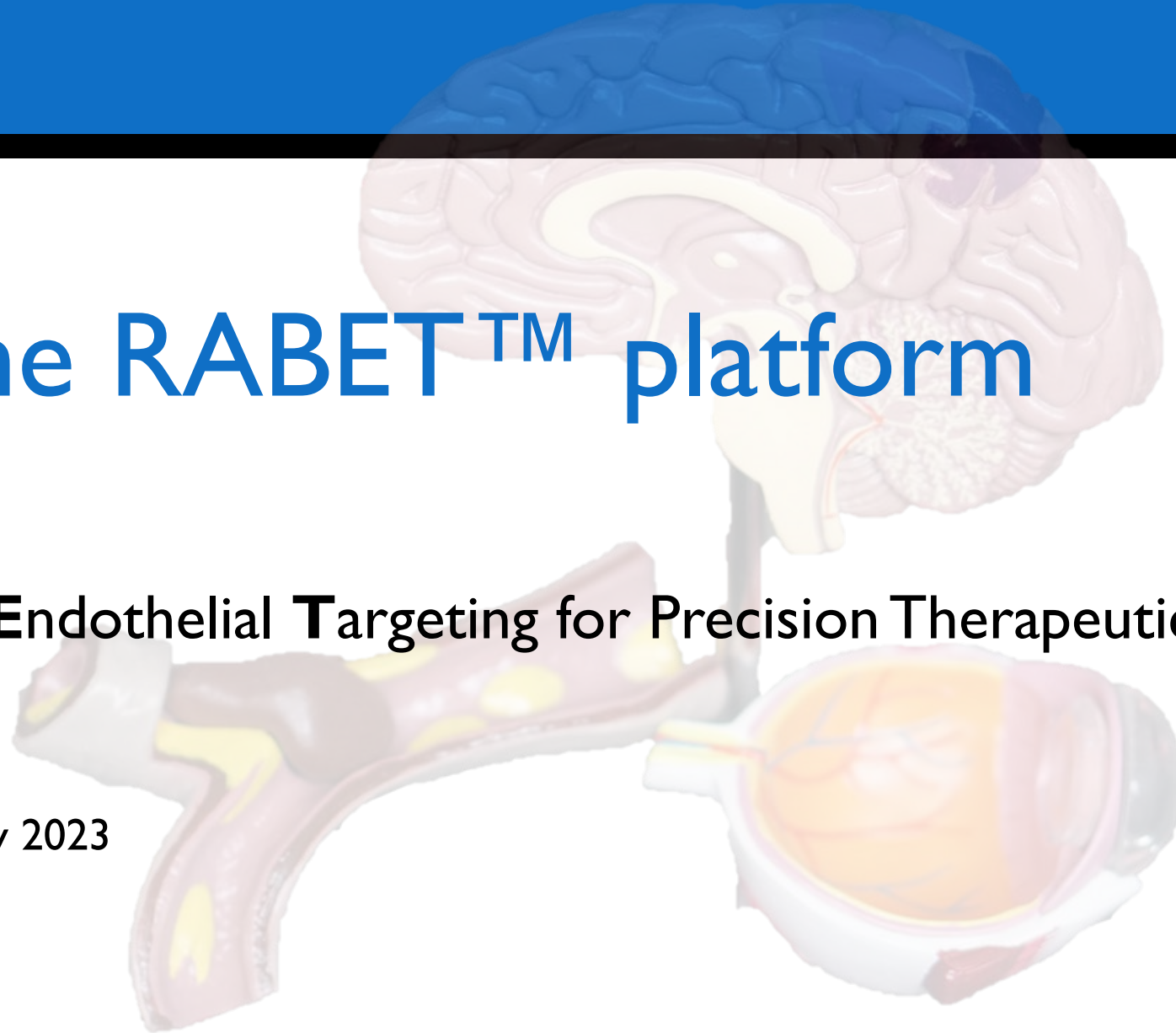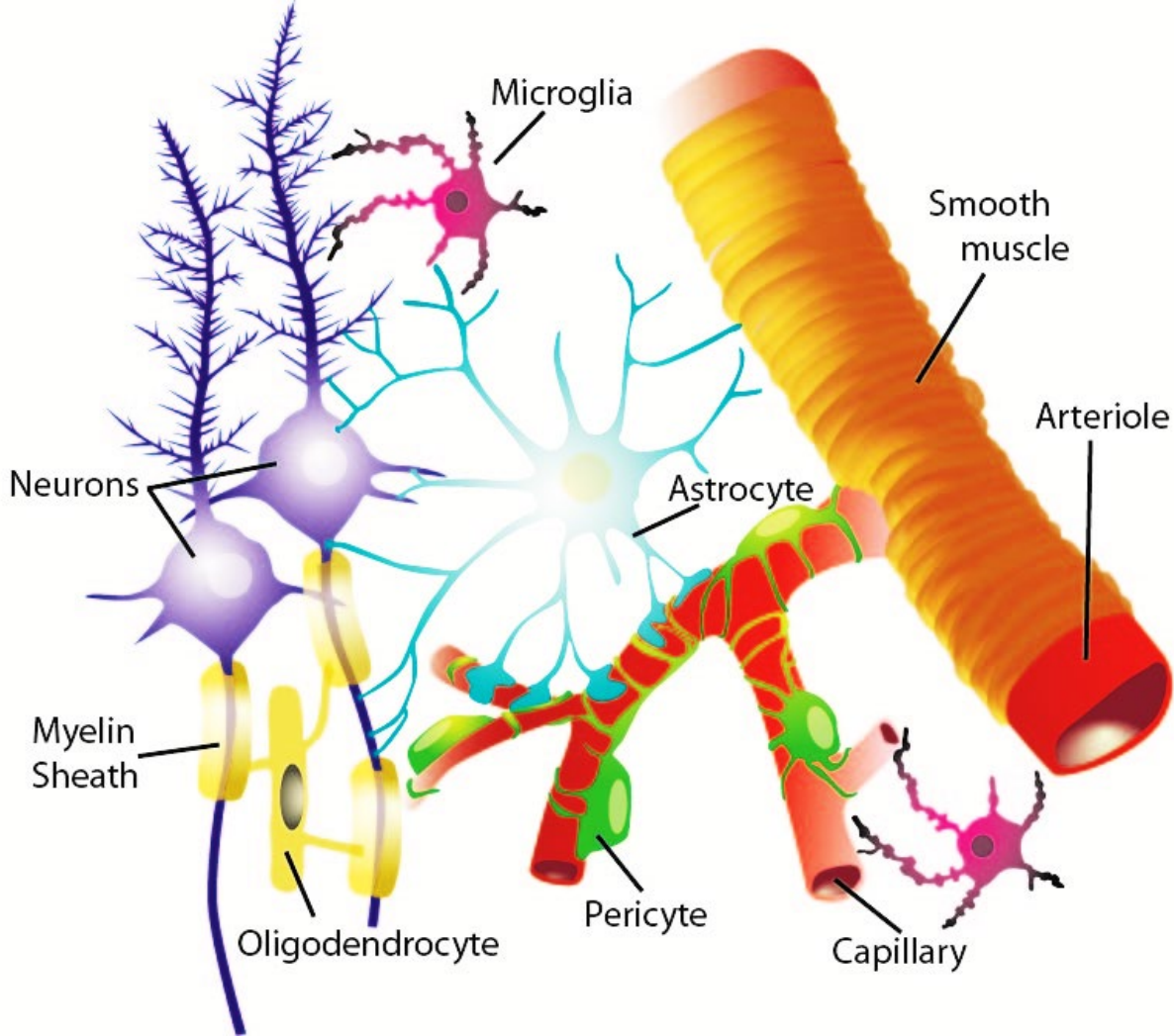# Building the RABET™ platform

**R**etinal **A**nd **B**rain **E**ndothelial **T**argeting for Precision Therapeutics
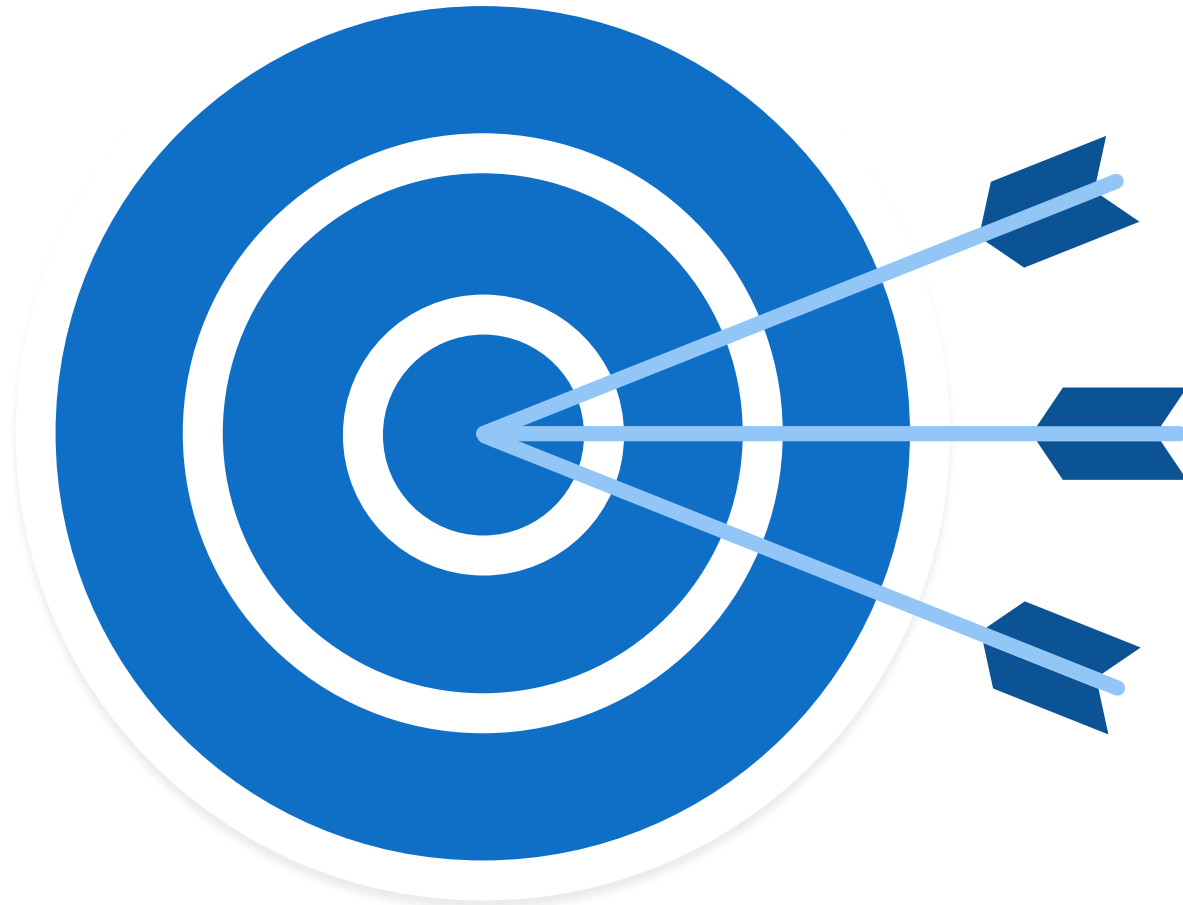
Yale Innovation Summit May 2023

# Disease mechanisms are cell-type specific, yet therapies are rarely targeted to affected cells

# Cell-type precision targeting would open up novel therapeutic modalities

**Benefits of precision targeting**

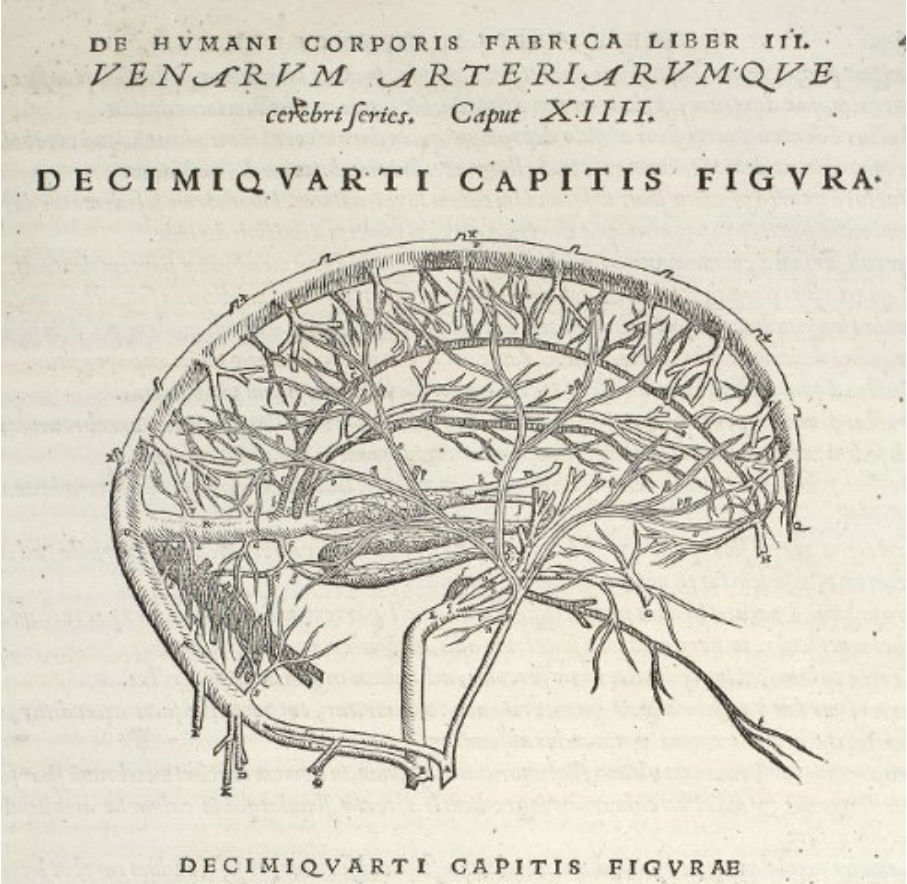Improved **treatment efficacy** by targeting mainly the affected cells
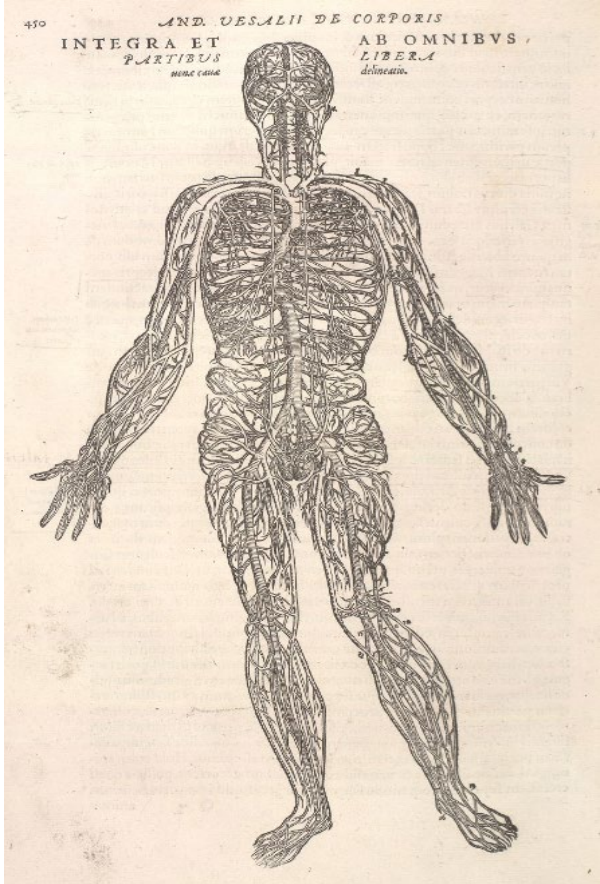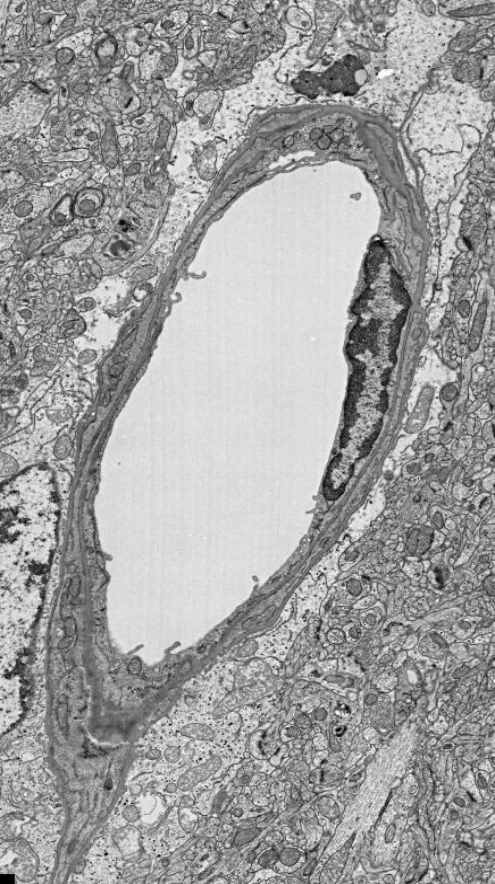
Improved **treatment tolerability** by sparing unaffected cells and organs

Broadened **treatment possibilities** by using drugs that would not be feasible for non-targeted delivery

# Endothelial cells are affected in brain and retina disorders but cannot be selectively targeted
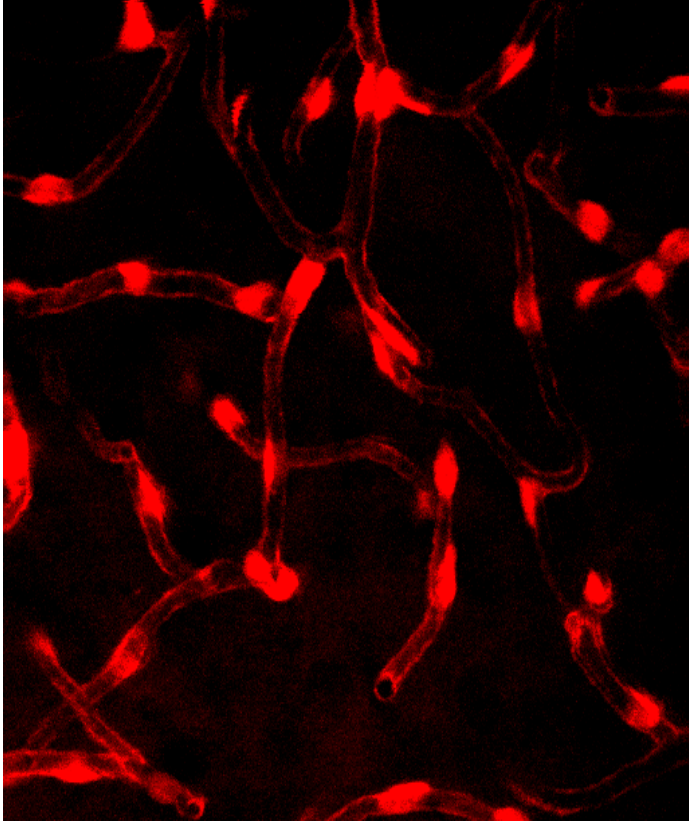
# RABET™ molecules that specifically target endothelial cells of the retina and brain
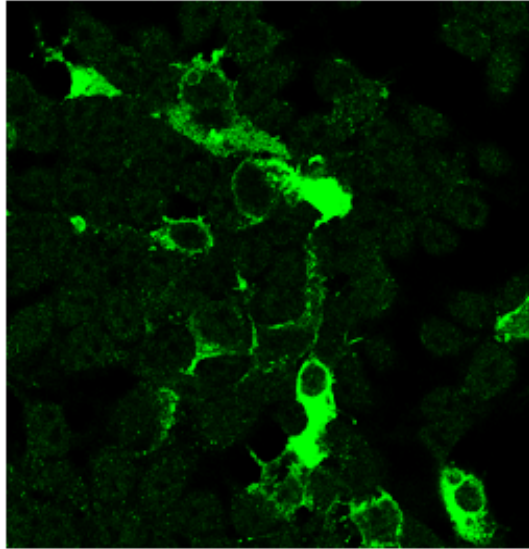
### Retina endothelium targeting
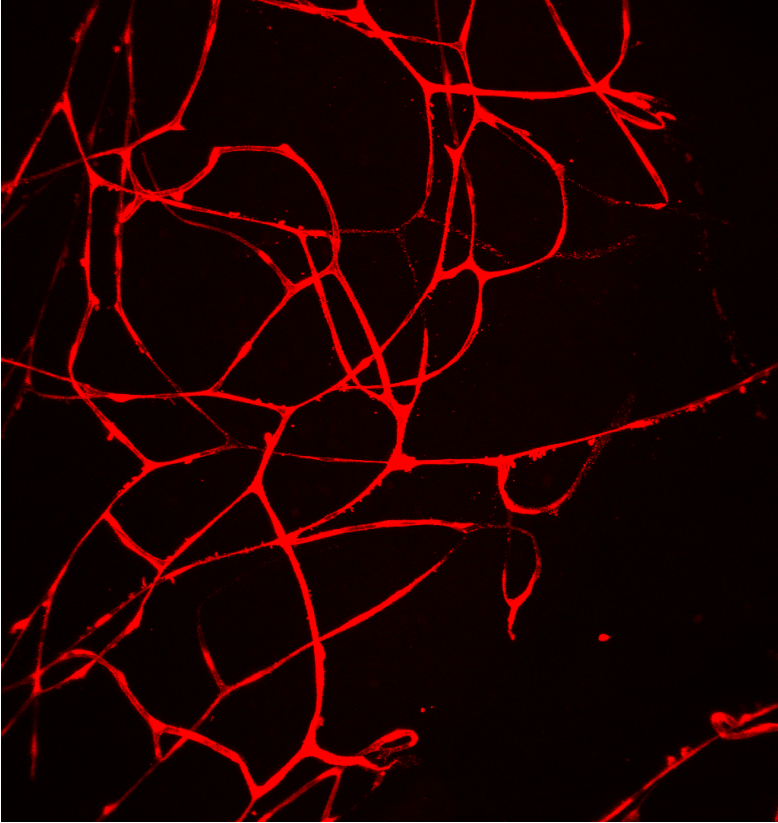
### Brain endothelium targeting

# The RABET™ mechanism of action is fully understood

HEK293 cells
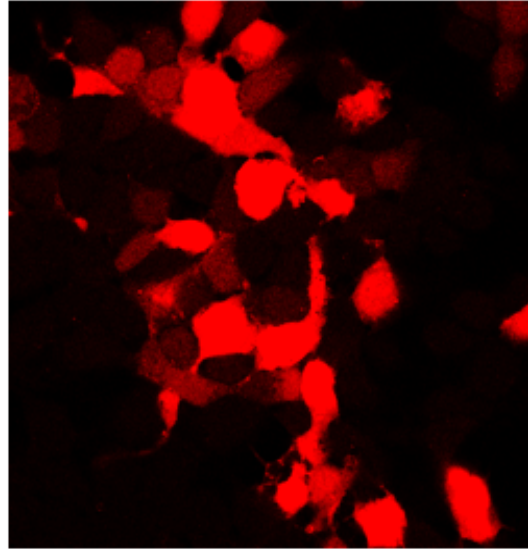


MoA protein          RABET™ molecule          Nuclei
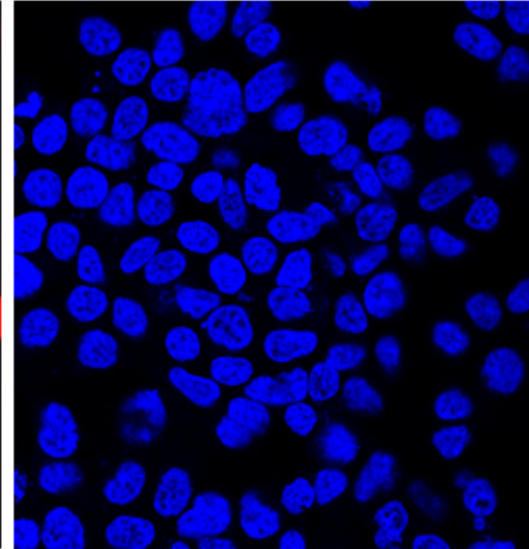
## Additional Experiments

- In vivo mouse over-expression and knockout experiments confirm MoA protein specificity

- Transfection of MoA human orthologue leads to RABET™ uptake in vitro and in vivo

# The RABET™ mechanism of action is conserved from mouse to human



| MoA Protein | Retina | | Brain | |
|---|---|---|---|---|
| | Endothelium | RPE | Endothelium | Oligodendrocytes |
| | ✓ | ✓ | ✓ | ✓ |

# Proof of Concept: RABET-Rx conjugates retain the pharmacological activity of Rx molecule

## RABET-Colchicine conjugate
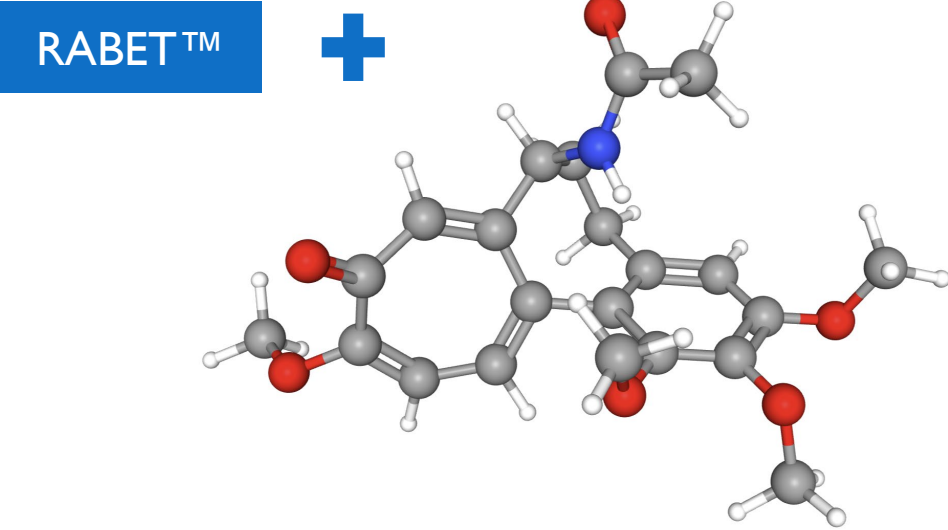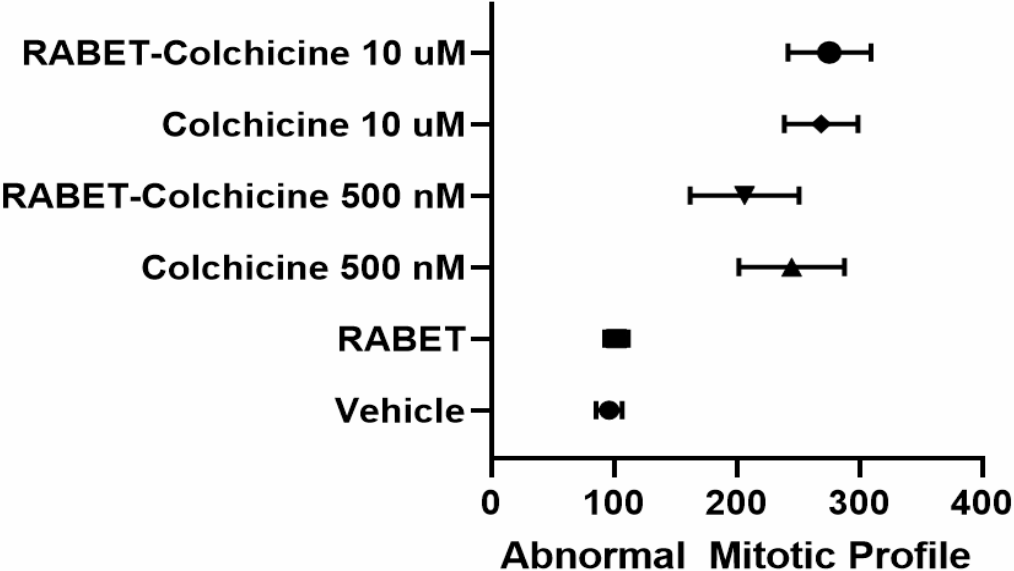
# The RABET™ platform is fluorescent and chemically tractable, facilitating structure activity relationship assessments of leads *in vitro* and *in vivo*

## RABET
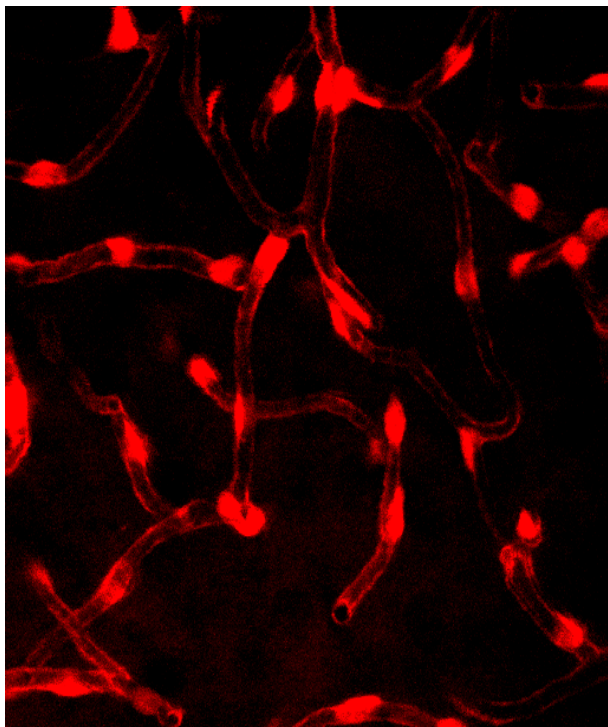
## RABET-Colchicine
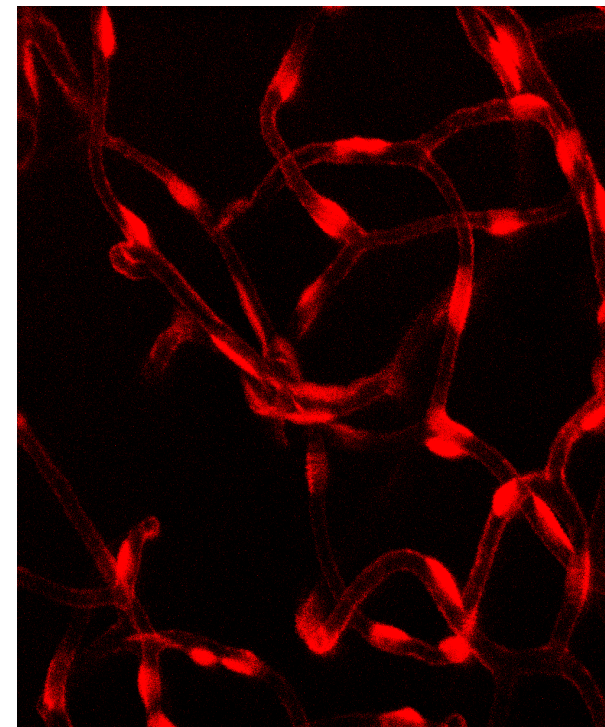


▶ **Conjugates tested up to 2kD in molecular weight**

# RABET-Rx conjugates reduce the off-target effects of Rx drugs

Colchicine

RABET-Colchicine

Subcutaneous injections for 10 days (40 µM) after fur clipping

Colchicine is well known to affect rapidly dividing cells like hair follicles

# Initial list of indications that may benefit from a RABET-Rx treatment

*NON-EXHAUSTIVE*

## Retinal indications

| Disease categories | Target indications |
|---|---|
| **Common diseases** | Age-related macular degeneration (AMD) |
| | Diabetic retinopathy |
| **Rare diseases** | Retinitis Pigmentosa |
| | Posterior uveitis |
| | Ischemic retinal vasculitis |

## Brain indications

| Disease categories | Target indications |
|---|---|
| **Neurodegenerative disease** | Vascular dementia |
| | Multiple Systems Atrophy |
| | Progressive Supranuclear Palsy |
| | Neuromyelitis Optica |
| | Multiple sclerosis |
| **Neurovascular diseases** | Hereditary cerebral cavernous malformations |
| | Brain vasculitis |
| | Stroke* |

▶ **Provisional patents filed for composition and uses of the RABET platform**

# AMD offers advantages as the indication for RABET-Rx PoC studies

| # | Retinal indication | US market size ($)* | Disease mechanism understood | Animal models available | Clear regulatory pathway |
|---|---|---|---|---|---|
| 1 | **Wet AMD** | ~10Bn[1] | ✓ | ✓ | ✓ |

*Market size for 2021/2022
1. https://www.datamintelligence.com/research-report/age-related-macular-degeneration-market

✓ Confirmed

# Age-related macular degeneration is driven by both endothelial and RPE pathology
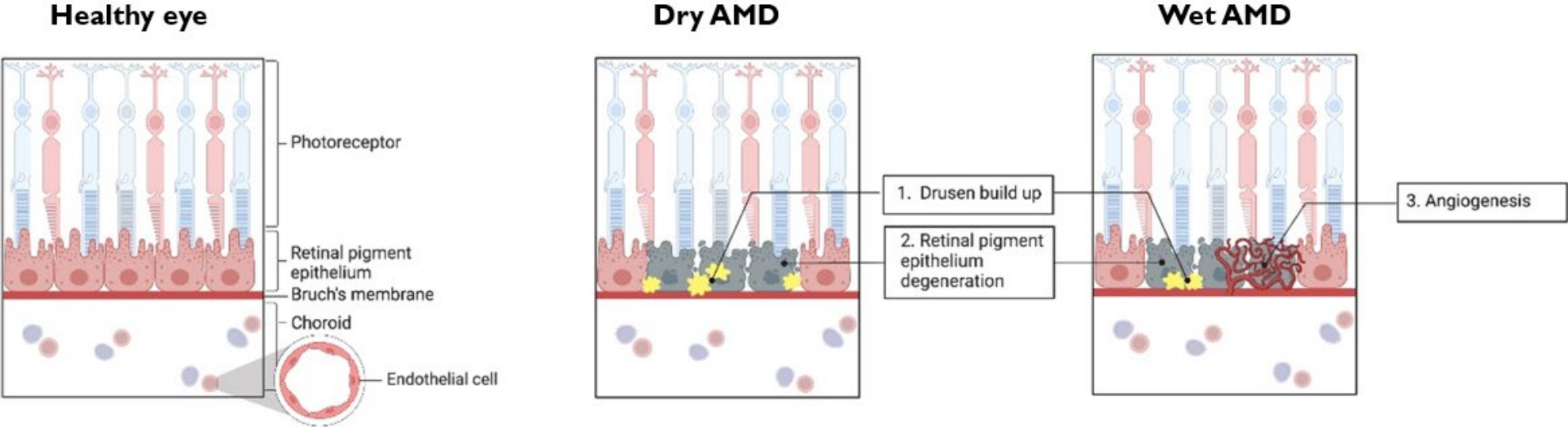
# A rigorous search identified a class of drugs for RABET™ proof-of-concept in AMD

## Anti-angiogenic + anti-inflammatory drugs for potential conjugation with RABET™



**Drug classes**

- *COX-2 inhibitors*
- *BTK inhibitors*
- *CE3 UL stimulants*
- *JAK inhibitors*
- *Other drug classes*

32   12   3   1

**JAK inhibitors**

1. Drug classes with **either** anti-angiogenic or anti-inflammatory activity

2. Drug classes with **both** anti-angiogenic and anti-inflammatory activity

3. Drugs classes with **low promiscuity** and relatively **good safety profile**

4. Drug class with **relatively high level of available knowledge**[1] about the drug class

1. Based on number of approved drugs in the class

# Number of identified drug classes

# RABET-Rx can synergize with and address challenges with existing treatments for AMD

| Current wAMD treatments | RABET-based solutions |
|---|---|
| Poor sustained efficacy | Drug with more than 1 mechanism of action (angiogenesis and inflammation) |
| IVT injection risks | Formulate and administer orally/topically? |
| Poor compliance due to fear of injections | Formulate and administer orally |
| No standard admin frequency | Standardize (daily) administration |
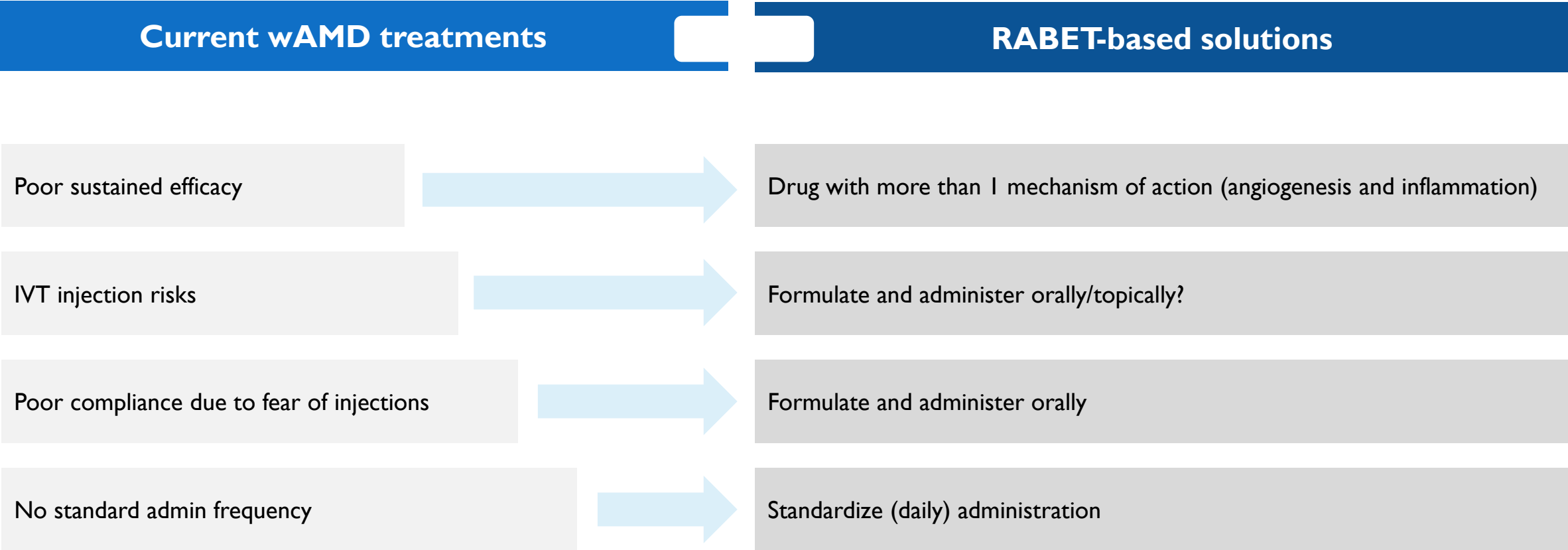
Platform development trajectory and funding strategy

# Looking forward to connecting with interested prospective collaborators or investors

Series A funding

Seed funding

**Key platform studies** 0

**Chemistry** 1

**Tolerability and Specificity** 2

**Efficacy & PK/route of admin** 3

**Lead selection & Pre-IND studies through Ph1b/Ph2a*** 4

Progress point          Completed

# The Team

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# Let's build the RABET™ platform for Precision Therapeutics

# Thank you

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