Building the RABET™ platform

Retinal And Brain Endothelial Targeting for Precision Therapeutics

December 2022
There is no known way to target endothelial cells in the eye or brain
The RABET™ platform for Precision Delivery

RABET™ are orally bioavailable molecules targeting retina and brain endothelial cells

Retinal labelling by RABET™ molecule

Features of the RABET™ platform for RABET-Rx application

1. High specificity
   Targeted delivery of medicines to retina and brain endothelial cells.

2. Oral bioavailability
   Convenient administration for patients

3. Low Mol. Wt.
   Carrier molecule for targeted delivery.

4. Fluorescence
   Visibility of molecules in early dev.

RABET-Rx is the conjugate of RABET™ and a drug
The RABET™ mechanism of action (MoA) is understood and conserved in humans.

**RABET™ MoA is a membrane protein**

- **MoA protein**
- **RABET™ molecule**
- **Nuclei**

**Interspecies homology for RABET™ MoA**

There is >75% homology across species for RABET™:
- *Homo sapiens* (humans)
- *Macaca mulatta* (Rhesus monkey)
- *Sus scrofa* (pig)
- *Rattus* (rat)
- *Mus musculus* (house mouse)

**Mouse over-expression and knockout experiments confirm MoA protein specificity**

**Transfection of human protein orthologue leads to robust RABET™ molecule uptake**

**The RABET™ molecule has a similar affinity for mouse and human mechanisms of cellular entry**
The RABET™ platform is flexible for structure activity relationship (*in vitro* SAR) and *in vivo* assessments of leads

**RABET**

**RABET-Rx**

*RABET-Rx* retains the precision of the RABET™ molecule and the potency (DNS) of the Rx drug.
Retinal And Brain Endothelial Targeting indications to benefit from Precision Delivery

A list of indications\(^\text{^\textsuperscript{a}}\) with retinal or brain endothelial cell mechanisms have been identified

<table>
<thead>
<tr>
<th>Disease categories</th>
<th>Target indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common diseases</strong></td>
<td>Wet AMD</td>
</tr>
<tr>
<td></td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td><strong>Rare diseases</strong></td>
<td>Posterior uveitis</td>
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<td><strong>Neurovascular diseases</strong></td>
<td>Hereditary cerebral cavernous malformations</td>
</tr>
<tr>
<td></td>
<td>Brain vasculitis</td>
</tr>
<tr>
<td></td>
<td>Stroke(^*)</td>
</tr>
<tr>
<td><strong>Neurodegenerative disease</strong></td>
<td>Vascular dementia</td>
</tr>
<tr>
<td></td>
<td>Alzheimer's disease</td>
</tr>
<tr>
<td><strong>Brain tumors</strong></td>
<td>Glioblastoma</td>
</tr>
<tr>
<td></td>
<td>Hemangioblastomas</td>
</tr>
<tr>
<td></td>
<td>Metastases</td>
</tr>
</tbody>
</table>

Retinal diseases have generally more advantages\(^*\)* for proof-of-concept studies

\(^*\)Indication that may benefit from targeted drug delivery to the retinal and brain endothelial cells

\(^*\)Cerebral edema, blood brain barrier and microvascular disruption after stroke

\(*\)Availability of rodent and non-human primate models, availability of assessment biomarkers etc.
Wet Age-related Macular Degeneration (Wet AMD) has been identified as the first-choice retinal indication for proof-of-concept studies.

### Retinal indication for proof-of-concept studies demonstrating the value of Precision Delivery

<table>
<thead>
<tr>
<th>#</th>
<th>Retinal indication</th>
<th>US market size ($)*</th>
<th>Disease mechanism understood</th>
<th>Animal models available</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wet AMD</td>
<td>~10Bn</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>#</th>
<th>RABET first choice indication in retinal disease</th>
<th>Global drug development</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ph 1</td>
</tr>
<tr>
<td>1</td>
<td>Wet AMD</td>
<td>18</td>
</tr>
</tbody>
</table>


- **RABET first choice indication**
- **Global drug development**
- **Non-targeted delivery**
- **Targeted delivery**
- **Oral medicine**
- **Non-oral medicine**

**Confirmed**

**Area of interest**
A rigorous search process was followed to identify an ideal class of drugs for RABET™ proof-of-concept in Wet AMD.

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

Selection of a drug class that could benefit from Precision Delivery

1. Based on number of approved drugs in the class

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

**Number of identified drug classes**
- 32
- 12
- 3
- 1

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

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

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

**Drug class with relatively high level of available knowledge about the drug class**

1. Based on number of approved drugs in the class
RABET™ proof-of-concept candidate RABET-Tofacitinib in Wet AMD – Bringing precision Tofacitinib to eye disease patients

RABET-Tofacitinib conjugate offers precision endothelial delivery of a dual-MOA (VEGFR/JAK) oral antagonist for Wet AMD

<table>
<thead>
<tr>
<th>Approved JAK inhibitors</th>
<th>Efficacy</th>
<th>Tolerability</th>
<th>Convenience</th>
</tr>
</thead>
<tbody>
<tr>
<td>#</td>
<td>Drug name</td>
<td>JAK1</td>
<td>JAK2</td>
</tr>
<tr>
<td>1</td>
<td>Tofacitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>2</td>
<td>Oclacitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>3</td>
<td>Baricitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>4</td>
<td>Ruxolitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>5</td>
<td>Peficitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>6</td>
<td>Upadacitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>7</td>
<td>Fedratinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>8</td>
<td>Delgocitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>9</td>
<td>Filgotinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>10</td>
<td>Abrocitinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>11</td>
<td>Pacritinib</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>12</td>
<td>Deucravacitinib</td>
<td>✓</td>
<td>✓</td>
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1. Anti-angiogenesis activity attributed more to JAK1 than the other JAK inhibitors
2. Anti-inflammatory activity is driven by JAK1/J3 inhibition

Selection process - the selected candidate should have anti-angiogenic and anti-inflammatory activity, relatively high potency plus a small enough molecular weight to allow for conjugation to the RABET molecule.

RD = retinal disease
Funding is required to answer gating questions for discovery, lead optimization and pre-IND activities for the first RABET-Rx product candidate.

**Gating questions and experiments**

1. **Chemistry & biodistribution**
   - Confirmation that oral administration of the RABET-Rx compound leads to delivery at the target cell types in the target organs
   - $100K

2. **Pharmacokinetics & dosing**
   - Dose optimization of 1 or more RABET-Rx compounds
   - Delivery of an anticipated effective dose to relevant destinations in selected disease models
   - $200K

3. **In vivo efficacy studies**
   - Results from RABET-Rx in vivo studies in retinal disease (e.g., Wet AMD)

4. **Lead selection & Pre-IND studies**
   - RABET-Rx lead compound
   - Pre-IND studies results
   - Pre-IND meeting with the FDA
   - $10 million

**Series A Funding**

- Blavatnik support
- Progress point
- Expected outcomes
- Funding
- Budget requirement

RABET-Rx is the conjugate of RABET™ and a drug molecule.
We have a dedicated team with a mix of complementary skills and capabilities to successfully launch the RABET™ platform

The launch team

Jaime Grutzendler, MD
Professor
Vice chair of research, Neurology
Depts of Neurology & Neuroscience
Yale University

Roshan Gunasekara, PhD
Assistant Professor
Dept of Neurology
Yale University

Emmanuel Aisabokhae, RPh, MBA
Blavatnik Fellow
Yale Ventures
Yale University
Let’s build the RABET™ platform for Precision Therapeutics

Thank you
Funding is required to answer gating questions for discovery, lead optimization and pre-IND activities for the first RABET-Rx product candidate.

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**Blavatnik support**

- Foundational experiments
- Target indication
- Drug candidate for conjugation

**Series A Funding**

- $200K
- $100K
- $10 million

RABET-Rx is the conjugate of RABET™ and a drug molecule.
Live imaging shows RABET™ molecules in mouse brain blood vessels after oral administration

Brain blood vessels - chow only

Brain blood vessels - chow + RABET™
RABET-Rx drug conjugate retains the potency of the Rx drug

Comparison of Potency

- RABET-Colchicine 10 uM
- Colchicine 10 uM
- RABET-Colchicine 500 nM
- Colchicine 500 nM
- RABET
- Vehicle

Abnormal Mitotic Profile
RABET foundational studies summary

The key scientific details underpinning the targeted delivery of RABET™ molecules into retinal and brain endothelial cells is fully understood

Summary from RABET™ foundational studies

- **Overexpression of MoA** is linked to increased entry into retina and brain endothelial cells (*in vitro data*)
- **Knock out of MoA** in mice is linked to disruption in cell entry (*in vivo data*)
- **Conservation** of the RABET mechanism of action from mouse to human is confirmed (*in vitro and in vivo data*)
- Limits of **cargo size** that can be carried into the retina and brain endothelial cells is determined (*in vivo data*)
- **Oral bioavailability of RABET molecules** is confirmed (*in vivo data*)
- **Selective entry of RABET and RABET-Rx molecules into retina and brain endothelial cells** is confirmed (*in vivo data*)
- **Preservation of precision by RABET-Rx conjugate** is confirmed (*in vivo data*)
- **Preservation of potency by RABET-Rx conjugate** is confirmed (*in vitro data*)

*For small molecules. Work ongoing for biological molecules*
Wet Age-related Macular Degeneration (Wet AMD) has been identified as the first-choice retinal indication for proof-of-concept studies

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<tr>
<td>2</td>
<td>Diabetic retinopathy</td>
<td>~7Bn²</td>
<td><img src="checkmark.png" alt="Checkmark" /></td>
<td><img src="checkmark.png" alt="Checkmark" /></td>
</tr>
<tr>
<td>3</td>
<td>Posterior uveitis</td>
<td>~0.09Bn³</td>
<td><img src="checkmark.png" alt="Checkmark" /></td>
<td><img src="checkmark.png" alt="Checkmark" /></td>
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**Common diseases**

**Rare diseases**

![Checkmark](checkmark.png) Confirmed

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¹Market size for 2021/2022

²For diabetic retinopathy, currently no model completely recapitulates the full pathophysiology of neuronal and vascular changes


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Retinal indication for proof-of-concept studies

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**Confidential**
A drug (tofacitinib) for RABET conjugation has been identified based on 4 key selection criteria

Selection criteria met by tofacitinib

1. **Approval status**
   - of the drug to be conjugated to RABET provides some assurance of safety and efficacy.

2. **Anti-angiogenic activity**
   - of the molecule addresses angiogenicity associated with Wet AMD.

3. **Molecule size**
   - that is low provides assurance that the conjugate with RABET will be able to successfully enter the retinal endothelial cells.

4. **Anti-inflammation**
   - potency ensures that the inflammation associated with Wet AMD is sufficiently treated.
Outline of gating questions and experiments to reach key inflection points in early development is clear

Gating questions and experiments

Key platform studies & decisions

- Foundational experiments
- Target indication
- Drug candidate for conjugation

Chemistry & biodistribution

- Confirmation that oral administration of the RABET-Rx compound leads to delivery at the target cell types in the target organs

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In vivo efficacy studies

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Lead selection & Pre-IND studies

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Blavatnik support

Series A funding

Progress point

Expected outcomes

Funding

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