Building the RABET™ platform

Retinal And Brain Endothelial Targeting 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
The RABET™ mechanism of action is fully understood

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

<table>
<thead>
<tr>
<th>MoA Protein</th>
<th>Retina</th>
<th>Brain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Endothelium</td>
<td>RPE</td>
</tr>
<tr>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Proof of Concept: RABET-Rx conjugates retain the pharmacological activity of Rx molecule

RABET-Colchicine conjugate

Comparison of Potency

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

Abnormal Mitotic Profile
The RABET™ platform is fluorescent and chemically tractable, facilitating structure activity relationship assessments of leads \textit{in vitro} and \textit{in vivo}.

\textbf{RABET}

\textbf{RABET-}Colchicine

\textbf{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

**Retinal indications**

<table>
<thead>
<tr>
<th>Disease categories</th>
<th>Target indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common diseases</td>
<td>Age-related macular degeneration (AMD)</td>
</tr>
<tr>
<td></td>
<td>Diabetic retinopathy</td>
</tr>
<tr>
<td>Rare diseases</td>
<td>Retinitis Pigmentosa</td>
</tr>
<tr>
<td></td>
<td>Posterior uveitis</td>
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<tr>
<td></td>
<td>Ischemic retinal vasculitis</td>
</tr>
</tbody>
</table>

**Brain indications**

<table>
<thead>
<tr>
<th>Disease categories</th>
<th>Target indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodegenerative disease</td>
<td>Vascular dementia</td>
</tr>
<tr>
<td></td>
<td>Multiple Systems Atrophy</td>
</tr>
<tr>
<td></td>
<td>Progressive Supranuclear Palsy</td>
</tr>
<tr>
<td></td>
<td>Neuromyelitis Optica</td>
</tr>
<tr>
<td></td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Neurovascular diseases</td>
<td>Hereditary cerebral cavernous malformations</td>
</tr>
<tr>
<td></td>
<td>Brain vasculitis</td>
</tr>
<tr>
<td></td>
<td>Stroke*</td>
</tr>
</tbody>
</table>

Provisional patents filed for composition and uses of the RABET platform
**AMD offers advantages as the indication for RABET-Rx PoC studies**

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

*Market size for 2021/2022
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

1. Based on number of approved drugs in the class

1. **COX-2 inhibitors**
2. **BTK inhibitors**
3. **CE3 UL stimulants**
4. **JAK inhibitors**
5. **Other drug classes**

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

- **JAK inhibitors**

32

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

12

Drugs classes with low promiscuity and relatively good safety profile

3

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

1

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1. Based on number of approved drugs in the class
**RABET-Rx** can synergize with and address challenges with existing treatments for AMD

<table>
<thead>
<tr>
<th><strong>Current wAMD treatments</strong></th>
<th><strong>RABET-based solutions</strong></th>
</tr>
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<tbody>
<tr>
<td>Poor sustained efficacy</td>
<td>Drug with more than 1 mechanism of action (angiogenesis and inflammation)</td>
</tr>
<tr>
<td>IVT injection risks</td>
<td>Formulate and administer orally/topically?</td>
</tr>
<tr>
<td>Poor compliance due to fear of injections</td>
<td>Formulate and administer orally</td>
</tr>
<tr>
<td>No standard admin frequency</td>
<td>Standardize (daily) administration</td>
</tr>
</tbody>
</table>
Looking forward to connecting with interested prospective collaborators or investors.

Platform development trajectory and funding strategy:

Key platform studies:
- Chemistry
- Tolerability and Specificity

Progress points:
- Completed

Steps:
1. Seed funding
2. Efficacy & PK/route of admin
3. Lead selection & Pre-IND studies through Ph1b/Ph2a
4. Series A funding
The Team

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Let’s build the RABET™ platform for Precision Therapeutics

Thank you

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