Alzheimer’s Disease: the Discovery of a Novel Phosphodiesterase 5 Inhibitor for its Cure.

Jole Fiorito, Ph.D.


“I thought elephants never forgot, but according to these results you have Alzheimer’s disease.”
Alzheimer's disease (AD) is the most common cause of dementia among people aged 65 and older;
• AD is a progressive neurodegenerative disorder that attacks neurons, resulting in loss of memory, thinking and language skills, and behavioral changes.
• It is estimated that as many as 5.1 million Americans may have Alzheimer's disease.
FDA approved drugs

Cholinesterase Inhibitors: Tacrine (Cognex)
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

NMDA Antagonist: Memantine (Namenda)

Current Targets for Drug Development

The NO cascade in learning and memory

**STRATEGY**

To Enhance Cell to Cell Communication

- Aβ down-regulates the NO/cGMP/CREB pathway
- Agents that enhance NO/cGMP/CREB signaling rescue Aβ-induced reduction of synaptic plasticity and memory

PDE5 Inhibitors

**STRATEGY**

To Enhance Cell to Cell Communication

Phosphodiesterase type 5 inhibitors (PDE5Is) increase cGMP level and ameliorate synaptic plasticity and memory

PDE5 Inhibitors

PDE5Is for the treatment of Erectile Dysfunction and Pulmonary Arterial Hypertension

GOALS

Novel PDE5Is which are optimized for AD:

- To identify compounds with high affinity and good selectivity for PDE5
- To identify new PDE5Is with good pharmacokinetic (PK) profile that cross blood brain Barrier (BBB)
- To identify new PDE5Is that rescue synaptic dysfunction and memory loss in a mouse model of AD
Based on the structure-activity relationship (SAR) analysis and given the high potency and selectivity, we have decided to use the quinoline scaffold as a template to develop the next generation of novel PDE5 inhibitors suitable for AD.
To identify compounds with high affinity and good selectivity for PDE5

<table>
<thead>
<tr>
<th>Compd</th>
<th>R8</th>
<th>PDE5 IC50 (nM)</th>
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<tbody>
<tr>
<td>7a</td>
<td></td>
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</tr>
<tr>
<td>7b</td>
<td>NMe₂</td>
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</tr>
<tr>
<td>7c</td>
<td>NH</td>
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<tr>
<td>7d</td>
<td>NH</td>
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<td>7e</td>
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<td>Sildenafil</td>
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To identify compounds with high affinity and good selectivity for PDE5

<table>
<thead>
<tr>
<th>Compd</th>
<th>PDE1</th>
<th>PDE2</th>
<th>PDE3</th>
<th>PDE4</th>
<th>PDE5</th>
<th>PDE6</th>
<th>PDE7</th>
<th>PDE8</th>
<th>PDE9</th>
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<tbody>
<tr>
<td>7a</td>
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<td></td>
<td>&gt;10^4</td>
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<td>1900</td>
<td>57000</td>
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<td>880</td>
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<td>61667</td>
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<td>&gt;10^4</td>
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Pharmacokinetics of 7a

To identify new PDE5Is with good PK profile that cross BBB

PK and BBB penetration capability of 7a was investigated. Plasma and brain concentrations were determined by the LC-MS/MS.

![Chemical Structure of 7a]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Brain</th>
<th>Plasma</th>
<th>Ratio*</th>
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</thead>
<tbody>
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<td>$T_{\text{max}}$ (h)</td>
<td>0.5</td>
<td>0.5</td>
<td>-</td>
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<tr>
<td>$C_{\text{max}}$ (ng/mL or ng/g)</td>
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<td>1022</td>
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<td>$\text{AUC}_{0-t}$ (ng∙h/mL or ng∙h/g)</td>
<td>418</td>
<td>1014</td>
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<tr>
<td>$\text{AUC}_{0-\infty}$ (ng∙h/mL or ng∙h/g)</td>
<td>420</td>
<td>1133</td>
<td>0.37</td>
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<tr>
<td>$T_{1/2}$ (h)</td>
<td>1.04</td>
<td>1.33</td>
<td>-</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>1.66</td>
<td>1.61</td>
<td>-</td>
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</table>
Long-Term Potentiation of 7a

3-month old APP/PS1 mice

- WT vehicle n=6
- APP/PS1 vehicle n=8
- WT 7a n=7
- APP/PS1 7a n=7

6-month old APP/PS1 mice

- WT vehicle n=7
- APP/PS1 vehicle n=8
- WT 7a n=11
- APP/PS1 7a n=8

fEPSP Slope (% of baseline)

Time (min)
In Vivo Studies of 7a

3-month old APP/PS1 mice

6-month old APP/PS1 mice
The chemical structure of our **lead compound** was modified in order to improve potency, selectivity, and PK parameters.

<table>
<thead>
<tr>
<th>Compds</th>
<th>PDE5A1 IC50 (nM)</th>
<th>PDE6C IC50 (nM)</th>
<th>Ratio PDE6/PDE5</th>
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<tbody>
<tr>
<td>JF5</td>
<td>21.6</td>
<td>ND</td>
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<tr>
<td>JF7</td>
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<td>JF8</td>
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<td>JF9</td>
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<td>JF11</td>
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<td>JF12</td>
<td>5.4</td>
<td>ND</td>
<td>-</td>
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<td>JF13</td>
<td>1.55</td>
<td>&gt;100</td>
<td>&gt;64.5</td>
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<tr>
<td>JF14</td>
<td>0.056</td>
<td>30.1</td>
<td>537.5</td>
</tr>
</tbody>
</table>
**Ex Vivo & In Vivo Studies of JF14**

2 day RAWM

- **Errors**
  - WT Vehicle (n=16)
  - WT JF14 3mg/kg (n=16)
  - APP/PS1 Vehicle (n=15)
  - APP/PS1 JF14 3mg/kg (n=15)

FC 24h Contextual

- **% Freezing**
  - WT Vehicle (n=16)
  - WT JF14 3mg/kg (n=16)
  - APP/PS1 Vehicle (n=15)
  - APP/PS1 JF14 3mg/kg (n=15)

LTP

- **fEPSP slope (% of baseline)**
  - WT + vehicle
  - WT + JF14
  - APP/PS1 + vehicle
  - APP/PS1 + JF14
• A strategy acting at the downstream level of amyloid-β might be beneficial against Alzheimer’s disease.

• We developed a lead compound inhibiting PDE5 that
  - is potent, selective, and crosses the BBB
  - rescues defects in synaptic function and memory

• Based on the structure of our lead compound, we are developing a pipeline of new PDE5Is to counteract Alzheimer’s disease.
Ottavio Arancio

• Agnieszka Staniszewski
• Faisal Saeed
• Hong Zhang
• Shijun Yan

Donald W. Landry

• Deng Shi-Xian
• Yan Feng
• Andrew Wasmuth

Q&A

“I call my invention ‘The Wheel’ but so far I’ve been unable to attract any venture capital”

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