Cyclin-Dependent Kinase Inhibitors as Cancer Therapeutics

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Emory OTT Breakfast Club
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Opportunity

• Novel, highly selective cyclin-dependent kinase (CDK) inhibitors

• CDKs belong to a group of protein kinases that are involved in a variety of cellular processes

• CDK7 an attractive target for drug development

• Pyrazolo[1,5-α]pyrimidine compounds that are useful for the selective inhibition of CDK7
CDK7 Regulates Cell Cycle Progression

Cell Proliferation
- Cancer
- Inflammation
- Atherosclerosis
- Immune diseases
CDK7 Selectivity of BS-181

<table>
<thead>
<tr>
<th>Kinase</th>
<th>Roscovitine IC₅₀ (µM)</th>
<th>BS-181 IC₅₀ (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK7</td>
<td>0.51</td>
<td><strong>0.021</strong></td>
</tr>
<tr>
<td>CDK2</td>
<td>0.1</td>
<td>0.88</td>
</tr>
<tr>
<td>CDK1</td>
<td>1.8</td>
<td>8.1</td>
</tr>
<tr>
<td>CDK4</td>
<td>15.3</td>
<td>33</td>
</tr>
<tr>
<td>CDK6</td>
<td>28</td>
<td>47</td>
</tr>
</tbody>
</table>

Comparative CDK7 Selectivity
- CDK7: **0.021**
- CDK2: 42X
- CDK1: 386X
- CDK4: 1571X
- CDK6: 2238X
BS-181 Inhibits Cell Growth and Promotes Apoptosis

Percentage of cells (n=3, +/- SEM)

BS-181 Concentration (µM)

- Apoptosis
- G1
- S-Phase
- G2/M
BS-181 Inhibits Growth of MCF-7 Tumors in Nude Mice

- **Relative Tumor Volume**
  - Control (N=11)
  - BS-181 10mg/kg/day (N=10)
  - BS-181 20mg/kg/day (N=13)
  - * p<0.05
  - ** p<0.01
  - *** p<0.001

- **Animal Weight (%) relative to Day 1**
  - Control (N=11)
  - BS-181 20mg/kg/day (N=13)
  - BS-181 10mg/kg/day (N=10)

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dose</th>
<th>Bioavailability</th>
<th>T1/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>IP</td>
<td>10mg/kg</td>
<td>37%</td>
<td>6.75hrs</td>
</tr>
<tr>
<td>Oral</td>
<td>10mg/kg</td>
<td>2%</td>
<td>1.15hrs</td>
</tr>
<tr>
<td>IV</td>
<td>10mg/kg</td>
<td>-</td>
<td>5.72hrs</td>
</tr>
</tbody>
</table>
Intellectual Property

• National stage applications pending
  • US, EPO, AU, and CA
  • July 2008 filing

• Claims address:
  • Novel compositions
  • Synthesis method
  • Methods of treatment
Summary and R&D Status

• CDK7 selective compound

• Refinements of BS-181 structure underway to increase bioavailability

• Cancer Research UK grant
  • £3m funding
  • Compound development
  • Clinical studies (Phase I trial)