CNPCANON 격려상

기적적 선택의 CDK7 억제물

• 첫 번째 선택의 CDK7 억제물로 동물의 in vivo 보다 효율성과 하단 nM 범위의 농도에서의 효능
• 시리즈 (CDK7 선택적 및 다중 CDK 모델링)에 대한 총 30 개의 액체주 및 저항성 확산성 활동

• 선택적 CDK7 억제물은 암 세포에 특정한 죽음적 응답을 유발시킵니다.
• 약물 효과와 선택적 및 in vitro ADME 프로필입니다.

OVERVIEW

THE OPPORTUNITY

CRT seeks a commercial partner for collaborative research and/or exclusive licensing for the further development of these CDK7 inhibitors. There is potential for "first in class" (CDK7-specific) therapies.

Cyclin-dependent kinases (CDKs) control two major biological processes in cells; cell cycle progression and gene transcription. Progression from the G1 to S phases of the cell cycle involves sequential phosphorylation of the Rb protein by cyclin D- and cyclin E-dependent kinases, CDK4, CDK6 and CDK2, which disrupts the Rb-mediated repression of the E2F-1 transcription factor to allow expression of genes required for S-phase transit. S-phase and G2-phase progression also requires CDK2 and CDK1 controls G2/M transition. CDK7 and CDK9 phosphorylate the C-terminal domain of the largest subunit of RNA polymerase II (PolII), a modification required for promoter release and transcription initiation by PolII. Moreover, phosphorylation of the cell cycle CDKs (including by CDK7) at a threonine residue in the activation segment (T-loop) is a key component of CDK activation. This phosphorylation is mediated by the CDK activating kinase (CAK), comprised of CDK7, cyclin H and the so-called accessory protein MAT1. It has been proposed that the activity of CDK7 in regulating cell cycle progression through phosphorylation of CDKs and its regulation of PolII activity helps to ensure that mRNAs encoding effectors of cell division are expressed at the right time in the cell cycle [1].

Deregulation of cell cycle progression is a universal characteristic of cancer, and the majority of human cancers have abnormalities in some component of CDK activity, frequently through elevated and/or inappropriate CDK activation. Hence there is considerable interest in the identification of CDK inhibitors as cancer therapeutics. Inhibition of the catalytic activity of CDK7 would be expected to inhibit cell cycle progression by blocking the phosphorylation of cell cycle CDKs, and would additionally inhibit transcription of effectors of cell division. CDK7 inhibition therefore represents an attractive strategy for an anti-tumour therapeutic. Small molecule inhibitors of CDK7 are anticipated to result in anti-proliferative and pro-apoptotic response.

POTENT AND SELECTIVE CDK7 INHIBITORS

The Imperial College Cancer Drug Design and Development Group, together with CRT, have identified several distinct CDK7 inhibitors. Two of these series have been progressed to lead optimization, including the CDK7 selective. Current data establish CDK7 selective compounds that inhibit CDK7 activity with low nM potency (Table 1), show excellent selectivity against a diverse panel of kinases and display drug-like physicochemical properties.

ABOUT CRT

CRT develops and commercialises exciting new discoveries in cancer research. We're the meeting point between academia and industry. Our deep understanding of both perspectives enables us to translate promising research into commercial propositions for the greatest patient benefit and maximum final return.

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Read more overleaf
In vitro ADME properties and in vivo pharmacokinetic profiles have been established for several of the compounds (Table 2). These assays show that:

- Several lead compounds inhibit the growth of a wide range of cancer cell lines (NCI60 panel) (Table 1)
- Growth inhibition is mediated by cell cycle arrest and apoptosis
- Inhibition of cell cycle by CDK7, PolII and Rb phosphorylation

Table 1: In vitro kinase inhibition and cell growth activities of Series Exemplifiers.

<table>
<thead>
<tr>
<th>Kinase (IC50nM)</th>
<th>Series Representative A (CDK7 Selective)</th>
<th>Series Representative B (Multi-CDK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDK1</td>
<td>1521</td>
<td>250</td>
</tr>
<tr>
<td>CDK2</td>
<td>578</td>
<td>3</td>
</tr>
<tr>
<td>CDK4</td>
<td>42000</td>
<td>20000</td>
</tr>
<tr>
<td>CDK5</td>
<td>9000</td>
<td>30</td>
</tr>
<tr>
<td>CDK6</td>
<td>32100</td>
<td>35000</td>
</tr>
<tr>
<td>CDK7</td>
<td>41</td>
<td>250</td>
</tr>
<tr>
<td>CDK9</td>
<td>1100</td>
<td>90</td>
</tr>
<tr>
<td>NC160 Cancer Cell Line Panel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (GI50μM)</td>
<td>0.31</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Table 2: Key properties of CDK7 specific lead series inhibitors (Series Representative A)

<table>
<thead>
<tr>
<th>CDK7 Chemical Matter</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selectivity vs. CDK2</td>
<td>x9 - x112</td>
</tr>
<tr>
<td>Solubility (μM)</td>
<td>&gt;100</td>
</tr>
<tr>
<td>Cell Activity (μM)</td>
<td>0.15 - 10</td>
</tr>
<tr>
<td>Plasma Protein Binding (%)</td>
<td>85 - 98</td>
</tr>
<tr>
<td>Bioavailability (% murine S.C.)</td>
<td>84 -110</td>
</tr>
<tr>
<td>Cytochrome P450 IC50 [μM]</td>
<td>7 - &gt;25</td>
</tr>
<tr>
<td>hERG Inhibition IC50 [μM]</td>
<td>8 - &gt;25</td>
</tr>
</tbody>
</table>

ANIMAL IN VIVO STUDIES USING CDK7 SELECTIVE INHIBITOR

Preliminary studies have been carried out using a CDK7 selective inhibitor (Series Representative A) and demonstrate that said compound is well tolerated in mice and can achieve significant tumour reduction (Figure 1). Oral administration results in inhibition of breast (MCF-7) and colorectal (HCT116) xenograft tumours, associated with inhibition of Rb phosphorylation in tumours (Figure 1).

ACADEMIC COLLABORATORS

The project is run by Prof Simak Ali, Prof Tony Barrett FRS FMedSci, Prof Charles Coombes FMedSci and Dr Matt Fuchter from the Imperial College Cancer Drug Design and Development Group and the Imperial College CRUK Cancer Centre.

REFERENCES


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Figure 1: Series Representative A inhibits MCF-7 tumour xenografts in a dose-dependent manner. The animals bearing tumours were randomized for treatment by oral gavage, with vehicle (5% DMSO in PBS; n = 12), 50 mg/kg bi-daily Series Representative A (n = 12) and 100 mg/kg CDK7 inhibitor (n = 13). Asterisks mark statistically significant differences in tumour growth (p<0.05) relative to the vehicle control. There was no significant change in body weight, compared with the vehicle control, over the course of the study.

Figure 2. Pharmacodynamic biomarker modulation with Series Representative A.