Novel Bax Activators as a New Class of Anti-cancer Drugs

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Opportunity

• Bax is a major proapoptotic protein which is required for cell death and functions as a tumor suppressor

• Bax presents an attractive target for drug development

• The first in class, potent and selective agonists of Bax with nanomolar activity

• Significantly less apoptotic effect on normal cells as compared to cancer cells, indicating selectivity for tumor cells
Apoptosis Signaling

Death Signals

Mitochondrion

Pro-apoptosis signal

Bax Activator

Bak/Bax

Bcl2

Bcl-X(L)

Apoptosome complex

Executioner caspases-3, 6, 7

Apoptosis

Anti-apoptosis signals
Development

300,000 compounds  \rightarrow  36 compounds  \rightarrow  3 compounds  \rightarrow  1 compound

NCI library screening

Highest affinity for Bax

Potently induce apoptosis in cancer cells

SMBA1 – Small Molecule Bax Activator

25 analogs

First generation SMBA analogs
SMBA analog suppress lung cancer cell growth and tumor growth

<table>
<thead>
<tr>
<th>Compound</th>
<th>SMBA1 (Parent)</th>
<th>CYD-2-11 (1st gen)</th>
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<td>IC50 (µM)</td>
<td>7.35</td>
<td>1.93</td>
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After treatment with SMBA1 or CYD-2-11:
- No weight loss
- Blood test normal
- No tissue toxicity
Improvement of Potency of SMBA by Structural Modification

- SMBA1: IC50: 7.35 μM
- SMBA CYD-2-11: IC50: 1.93 μM
- SMBA CYD-4-61: IC50: 0.026 μM
2nd generation analog CYD-4-61 with improved potency
2nd generation analog CYD-4-61 more potent than current therapies

CYD-4-61 potently suppresses the growth of various cisplatin resistant human lung cancer cells by 70% to 95% compared to ABT-737 and overcomes radioresistance
R&D Status and Intellectual Property

• Conduct further studies of 2\textsuperscript{nd} generation analog CYD-4-61
  • In-vivo mouse model of lung cancer
  • Pharmacokinetics and toxicity studies

• “BAX Agonist, Compositions, and Methods Related Thereto”
  • US provisional patent application (filed August 19\textsuperscript{th}, 2011)