Background

- A unique bicyclic peptide isolated as a fermentation product from Chromobacterium violaceum by Fujisawa Pharmaceuticals.
- Dropped by Fujisawa due to cardiotoxicity seen in preclinical toxicology studies.
- Selected as a compound of interest due to its unique structure and pattern of activity in the NCI 60 cell line screen.

In Vitro Studies

Depsipeptide is a novel histone deacetylase inhibitor that also induces p21 expression and apoptosis as illustrated in HUT78 cells by S. Bates et al., Medicine Branch, CCR, NCI.

Pharmacokinetic (PK) Studies

- Depsipeptide is rapidly eliminated from mouse, rat, and dog plasma with a t\textsubscript{1/2} of less than 30 minutes.
- Protein binding of depsipeptide is relatively high (82%–90%) for all species evaluated (mouse, rat, dog, and human).

Toxicology Studies

In Vitro Bone Marrow Assay

Potencies in nM for a 10-day exposure

<table>
<thead>
<tr>
<th>Species</th>
<th>IC\textsubscript{50}</th>
<th>IC\textsubscript{75}</th>
<th>IC\textsubscript{90}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>1.0</td>
<td>5.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Dog</td>
<td>0.35</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Human</td>
<td>0.030</td>
<td>1.5</td>
<td>6.0</td>
</tr>
</tbody>
</table>

Based on IC\textsubscript{50} values, human marrow is the most sensitive to the cytotoxic effects of depsipeptide. The dog will be a more appropriate species than mouse or rat for toxicity studies.

Mouse Efficacy vs. Toxicity Study

<table>
<thead>
<tr>
<th>Route</th>
<th>Schedule</th>
<th>Total Dose</th>
<th>Efficacy</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v.</td>
<td>Q4D x 3</td>
<td>15.9 mg/kg</td>
<td>10/10 CR</td>
<td>MTD</td>
</tr>
<tr>
<td>i.p.</td>
<td>D x 5</td>
<td>10.8 mg/kg</td>
<td>3/10 CR</td>
<td>LD40</td>
</tr>
<tr>
<td>i.p.</td>
<td>Q4D x 3</td>
<td>15.9 mg/kg</td>
<td>2/10 CR</td>
<td>LD20</td>
</tr>
<tr>
<td>i.p.</td>
<td>Q3H x 0, Q4D x 3</td>
<td>10.8 mg/kg</td>
<td>0/10</td>
<td>LD100</td>
</tr>
</tbody>
</table>

- Mice treated by i.v. with 10.8–24 mg/kg displayed local toxicity but no cardiac lesions.
- MTD was determined to be 15.9 mg/kg given once or twice weekly for 4 weeks.
- Based on the results of this study, the NCI decided to continue development.

Human Clinical Trial Experience

- Phase I—starting dose used was 1 mg/m\textsuperscript{2}, escalating to 24.9 mg/m\textsuperscript{2}.
- MTD was determined to be 18.7 mg/m\textsuperscript{2} administered i.v. over a 4-hour period, days 1 and 5 on a 21-day cycle.
- This trial noted 3 partial and 1 complete response in patients with cutaneous T-cell lymphoma and peripheral T-cell lymphoma, respectively.
- Hyperacetylation of histone was measurable in T cells isolated from patients.
- Phase II trials are in progress.

Depsipeptide


**National Cancer Institute Developmental Therapeutics Program**

**Mean Graphs**

**Developmental Therapeutics Program of the National Cancer Institute**