TGR-1202 SUPPRESSES ACUTE MYELOID LEUKEMIA (AML) AND ACUTE LYMPHOBASTIC LEUKEMIA (ALL) CELLS VIA SELECTIVE INHIBITION OF PI3K Kinase

Swaroop Vakkalanka1, Srikant Viswanadha2, Robert Niecestro3, Peter Sportelli2 and Michael Savona4

1Rhizen Pharmaceuticals S A, La Chaux-de-Fonds, Switzerland; 2Incogen Therapeutics Pvt. Ltd., Hyderabad, India; 3TG Therapeutics, Inc., New York, NY; 4Sarah Cannon Research Institute, Nashville, TN

Acute leukemia, characterized by the presence clonal hematopoietic cells in peripheral blood and bone marrow, and notable for an aggressive clinical course, comprises approximately 40% of newly diagnosed leukemias. Treatment for acute leukemias with multi-agent cytotoxic chemotherapy is usually associated with significant toxicity. Advances in therapy have been slow, and nearly all effective therapies lead to narrow suppression and toxicities associated with prolonged cytopenias.

TGR-1202 is a selective PI3K kinase inhibitor with several fold selectivity over the other PI3Ks isoforms as well as a 441-kinase panel. Specificity of the molecule was further corroborated in cell-based and Human Whole Blood assays. In vitro and in vivo xenograft studies demonstrated the therapeutic potential of the molecule in acute leukemia mediated via the PI3K pathway.

BACKGROUND

In vitro assays

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<thead>
<tr>
<th>Enzyme and Cell based Selectivity</th>
<th>PI3Kδ</th>
<th>PI3Kγ</th>
<th>PI3Kβ</th>
<th>PI3Kα</th>
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</thead>
<tbody>
<tr>
<td>Enzyme</td>
<td>22.23</td>
<td>&gt;1000</td>
<td>&gt;50</td>
<td>&gt;48</td>
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<tr>
<td>Cell based</td>
<td>24.27</td>
<td>&gt;1000</td>
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Table 1. Enzyme assay for inhibition of PI3Kδ and/or activity over other isoforms. Enzyme activity was determined using an in vitro PHK assay kit (Millipore, Billerica, MA) with modifications.

Cell based specifically PI3Kδ isoforms for select compounds. Concentration-response curves were determined for each compound.

Inhibition of Akt phosphorylation

Induction of Apoptosis

pAKT in Primary AML Cells

RESULTS

Anti-Tumor Effect of TGR-1202 in a Subcutaneous MOLT-4 Xenograft Model

Non-Clinical Pharmacokinetics of TGR-1202

CONCLUSIONS

- TGR-1202 is a potent and selective inhibitor of PI3Kδ producing:
  - A translational reduction in proliferation of antigen induced B-cells manifested by a reduction in CD19+ or CD45R+ cells
  - Reduction in pAKT, an effective biomarker in AML and ALL cell lines as well as cells derived from AML patients
  - Marked anti-tumor activity in a MOLT-4 subcutaneous xenograft mouse model

- TGR-1202 exhibited desirable pharmacological/ADME/PK properties along with an excellent safety profile in GLP-Tox studies

- A Phase I trial in patients with select hematologic malignancies is currently planned to open in early 2013