Inhibiting the Receptor Tyrosine Kinase-like Orphan Receptor 2 (ROR2) enzyme with small molecules for the treatment of cancer

Brett Rodgers¹, Michiru Nishita², William H. Bisson¹

¹Environmental and Molecular Toxicology, Oregon State University, Corvallis, OR 97331, USA.
²Physiology and Cell Biology, School of Medicine, Kobe University, Kobe 650-0017, Japan.

Abstract: Based on recent findings, our hypothesis is that the inhibition of the Receptor tyrosine kinase-like orphan receptor 2 (ROR2) enzyme can lead to tumor suppression.

ROR2 are trans-membrane proteins that are part of the receptor tyrosine kinase (RTK) family. ROR2 is generally not expressed in most normal adult tissues and represents a new target in the WNT signaling pathway. In order to test our hypothesis, we have developed a model using transiently transfected HEK-293T cells to screen for inhibition of ROR2-mediated downstream signaling. The inhibition of ROR2 activation, through canonical WNT pathway, will be studied by monitoring the level of activated ROR2-induced phosphorylation of G-protein coupled receptor Kinase 2 (GRK2) compared to untreated cells. The research proposed is significant because it will lead to novel lead compounds for multiple tumor types.

Introduction

• Studies indicate that in cancers driven by canonical Wnt signaling, ROR2 expression is increased.
• The elevated expression of ROR2 is correlated with tumor progression in multiple tumor types.
• Decreased ROR2 expression (siRNA) in melanoma suppresses cancer in mice.

Assay Development

Virtual Ligand Screening (VLS)

After VLS, a series of type I inhibitor candidates were selected for in vitro testing.

Conclusions

- An assay based on HEK293T cells was developed to detect ROR2-induced phosphorylation of downstream protein GRK2.
- Individual type I inhibitors and specific small molecule compounds libraries were selected for in vitro screenings.
- The best candidates will be tested for suppression of growth in a selected panel of ROR2+ cancer cell lines.

High Throughput Screening (HTS)

Figure 1: ROR2 expression in renal cell carcinoma (RCC) tissue. ROR2 is a transmembrane surface protein expressed (Wright et al. Oncogene 2009).

Table 1: ROR2+ human cancer cell lines.

<table>
<thead>
<tr>
<th>tissue</th>
<th>ROR2+ human cancer cell lines</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA-MB-453</td>
<td>breast Example of cell lines to be tested for suppression of growth.</td>
</tr>
<tr>
<td>HCT116</td>
<td>colon</td>
</tr>
<tr>
<td>786-0</td>
<td>kidney</td>
</tr>
</tbody>
</table>