Zuping Xia, J Stem Cell Res Ther 2014, 4:9
http://dx.doi.org/10.4172/2157-7633.S1.007

OMICS Group Conferences
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3rd International Conference and Exhibition on
Cell & Gene Therapy
October 27-29, 2014 Embassy Suites Las Vegas, USA

Development of sphingosine kinase inhibitors for cancer therapy

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It has become evident that cancers have complicated signaling survival pathways. Currently, the most effective treatment for cancer diseases commonly requires target multiple pathways. Sphingosine Kinase (SK) is one of the critical enzymes in spingolipid biosynthesis. So far there are two isoforms of SK discovered, SK1 and SK2. Although the similarity and differences between these two isoforms are still not quite clear, the convincing evidences have been shown that SK, especially SK1, is related to human diseases, such as cancer. SK1 has been revealed as an oncogene that is among the most commonly over-expressed oncogenes in human cancers. Furthermore, compared to the drug sensitive cancer cell lines, over-expression of SK has also been found to contribute to the drug resistance in many cancer chemotherapies. The cumulated evidence has strongly supported that SK is one of the potential druggable targets for cancer therapy. We have identified a few of SK inhibitors by screening a small molecule library. One of them stood out upon testing, namely 4-[4-(4-chlorophenyl)thiazol-2-ylamino] phenol (SKI-II). However, we found that SKI-II has a narrow therapeutic window, poor bioavailability and relatively unstable. In order to optimize this lead compound, we used three approaches and synthesized a series of SKI-II analogs. We have done primary evaluation of these compounds which will guide our further improvement of SK inhibitors for cancer therapy.

Biography

Zuping Xia obtained his PhD in Pharmaceutical Sciences (Medicinal Chemistry) from University of Alberta mentored by both Dr. Leonard Wiebe and Dr. Edward Knaus. He has completed his Postdoctoral training in Dr. Kenneth Brown Lab at Ohio University and in Dr. Charles Smith Lab at Penn State University. His major interests are in the drug discovery and ADME/PK studies. Presently, he is a Research Associate Professor and Director of NMR core at College of Pharmacy, Washington State University.

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