GLUT4 SELECTIVE INHIBITORS FOR CANCER THERAPY

Published date: July 12, 2018

Technology description

A novel drug compound that targets GLUT4 expression and glucose uptake in cancer cells.

BACKGROUND

Tumor cells, including those of the largely fatal plasma cell malignancy multiple myeloma (MM), exhibit elevated glucose uptake. Although the fundamental reliance of tumor cells on increased glucose catabolism for survival, proliferation and chemoresistance is well-established, there is still limited understanding of the cellular transporters responsible for glucose uptake. Cellular localization of the glucose transporter isoform 4 (GLUT4) varies in normal versus MM cells. Normally, GLUT4 localization at the plasma membrane (PM) is in response to insulin and exercise-stimulation, whereas MM cells exhibit increased constitutive expression at the PM. Furthermore, there is concomitant elevation of the anti-apoptotic protein, myeloid cell leukemia factor (MCL-1) with elevated glucose uptake by GLUT-4. Some studies also show that overexpression of MCL-1 promotes resistance of MM to a wide range of therapeutics, such as chemotherapy drugs.

ABSTRACT

A team of inventors has developed a highly selective GLUT-4 inhibitor that abrogates cell proliferation and chemoresistance more effectively in MM cell lines and patient samples than current MM therapeutics. Using GLUT4 homology models and virtual high-throughput screening, the inventors identified multiple series of novel GLUT4 antagonists. A series of initial hit-to-lead efforts were carried out to synthesize new analogs with improved potency and selectivity for GLUT4, and biological characterization studies of each compound in a variety of assays were performed. One lead compound (Compound 20) was found to be the most effective at inhibiting glucose uptake and GLUT-4-driven cell proliferation in MM. Importantly, lead compound 20 was used to show that inhibiting GLUT4 in MM results in a corresponding block in MCL-1 expression, which increases cell sensitivity to chemotherapy drugs such as, venetoclax and other therapeutic agents such as, dexamethasone and melphalan. Selective pharmacological inhibition of GLUT4 may therefore represent a novel strategy for the treatment and resensitization of MM and other cancers to therapeutic agents.

Publications

Wei C, Bajpai R, Sharma H, Heitmeier M, Jain AD, Matulis SM, Nooka AK, Mishra RK, Hruz PW, Schiltz GE and Shanmugam M (2017) Development of GLUT4-selective antagonists for multiple myeloma therapy. Eur J Med Chem. 139: 573-586.

Application area

Therapeutic drug for various cancers including MM

Advantages

More effective than current MM treatments
New mechanism of action targeting glucose uptake in cancer cells

Institution

Northwestern University

Inventors

Malathy Shanmugam
Paul Hruz
Gary Schiltz
Rama Mishra

联系我们

叶先生

电 话：021-65679356
手 机：13414935137

邮 箱：yeyingsheng@zf-ym.com