Aminopyrimidine-based kinase inhibitors for treatment of cancer

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Technology description

BACKGROUND

Acute myeloid leukemia (AML) is a cancer of the blood that is characterized by the rapid growth of abnormal white blood cells that build up in the bone marrow and disrupts the production of normal blood cells. Current treatments for AML include chemotherapy with targeted drug therapy and in some cases a bone marrow transplant. Even with these treatments, the 5-year survival prognosis for AML is low (~27%). As such, there is an urgent need for the development of innovative new approaches for the treatment of AML.

ABSTRACT

Northwestern researchers have identified a unique methodology to kill AML cells, involving targeting of an enzyme in the cell called Mnk. Blocking this enzyme previously showed in potent antileukemic effects against AML precursors in bone marrows from patients with AML and in an AML mouse models. Moreover, targeting this enzyme potentiates the antileukemic effects of chemotherapeutic agents used for the treatment of AML. Using a molecular modeling-based high throughput screen, a new series of compounds that act as Mnk inhibitors were identified. Further optimization of this series into a set of potent has led to novel compounds that inhibit Mnk activity.

Publications

Kosciuczuk EM, Saleiro D, Kroczynska B, Beauchamp EM, Eckerdt F, Blyth GT, Abedin SM, Giles FJ, Altman JK, Platanias LC (2016) Merestinib blocks Mnk kinase activity in acute myeloid leukemia progenitors and exhibits antileukemic effects in vitro and in vivo. Blood. 128, 410-414. doi: http://dx.doi.org/10.1182/blood-2016-02-698704 .

Bell JB, Eckerdt FD, Alley K, Magnusson LP, Hussain H, Bi Y, Arslan AD, Clymer J, Alvarez AA, Goldman S, Cheng SY, Nakano I, Horbinski C, Davuluri RV, David James C, Platanias LC (2016) MNK inhibition disrupts mesenchymal glioma stem cells and prolongs survival in a mouse model of glioblastoma. Molecular Cancer Research 14, 984-993. doi: http://dx.doi.org/10.1158/1541-7786.MCR-16-0172 .

Application area

• Cancer, including leukemias, breast, and brain

• Neurological disorders including autism, alzheimer's Disease, and fragile X Syndrome

Advantages

• Existing Mnk inhibitors have either modest potency, are non-selective for this kinase, or display significant toxicity
• Our compounds are very potent inhibitors of Mnk kinase and possess drug-like properties and selectivity suitable for a potential therapeutic

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