Compositions and Methods using RNA Splicing Modulation to Selectively Impair Leukemic Cancer Stem Cells

Published date: March 23, 2017

Technology description

Researchers from UC San Diego usedcomparative spliceisoform profiling of FACS-purified hematopoietic progenitors and whole transcriptome analyses, to identify unique splicing signatures that distinguishesnormal human HSC and progenitor cell aging from AML and MDS progenitors.The diagnostic potential is validated by confirmation that a novel pharmacological spliceosome modulatorydrug (see FD-895 and 17s-FD-895)disrupted AML leukemia stem cell (LSC) maintenance.Furthermore, normal versus malignant aging splice isoform switching signatures may be exploited in companion diagnostics to evaluate the efficacy of splicing modulators or other LSC-targeted agents.

The advancing age of the US population and increasing exposure to chemotherapy (for other malignancies) has resulted in increased rates of myelodysplastic syndrome (MDS). Following on the heels of MDS is progression to therapy-resistant acute myeloid leukemia (AML), which is predicted to rise significantly over the next few decades. The heterogeneity of molecular abnormalities in therapy-resistant secondary acute myeloid leukemia (sAML) combined with a paucity of effective treatment options has resulted in high relapse-related mortality rates. In addition to approved therapies, many experimental agents also target epigenetic regulators of gene expression in clinical trials for sAML. However, most of these agents fail to improve patient survival, suggesting that epigenetic modifier therapies may reduce leukemic burden but may not effectively target a subpopulation of therapy-resistant leukemia stem cells that drive relapse. Hence, there is a critical need for developing clinical candidates with different modes of action.Recent studies implicate the spliceosome as a therapeutic vulnerability in solid tumors.

Related Materials

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Adamia, S., et al. A genome-wide aberrant RNA splicing in patients with acute myeloid leukemia identifies novel potential disease markers and therapeutic targets. Clin Cancer Res 20, 1135-1145

(2014).
Mandel, A.L., Jones, B.D., La Clair, J.J. & Burkart, M.D. A synthetic entry to pladienolide B and FD-895. Bioorg Med Chem Lett 17, 5159-5164 (2007).
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Related Technologies

Synthetic Anticancer Polyketide Compounds

Application area

AML stem cell signatures may enable diagnostic and prognostic assessment of disease risk, patient stratification, and response to therapy. In addition, this technology enables the identification of splicemodulating drugs (as validated withFD-895 and 17s-FD-895)as that maydisrupt AML leukemia stem cell (LSC) maintenanceby promoting intron retention and altering splicing of AML-associated/ pro-survival transcripts.

Advantages

Splice isoform signatures distinguish normal and malignant progenitor cell aging
Pro-survival splice isoform switching is a feature of secondary AML LSC
Splice isoform biomarkers provide diagnostic and therapeutic targets for AML
Spliceosome modulators impair AML LSC maintenance in humanized pre-clinical models

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