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

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## BACKGROUND

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.

## TECHNOLOGY DESCRIPTION

Researchers from UC San Diego used comparative splice isoform profiling of FACS-purified hematopoietic progenitors and whole transcriptome analyses, to identify unique splicing signatures that distinguishes normal human HSC and progenitor cell aging from AML and MDS progenitors. The diagnostic potential is validated by confirmation that a novel pharmacological spliceosome modulatory drug (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.

## APPLICATIONS

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 splice modulating drugs (as validated with FD-895 and 17s-FD-895) as that may disrupt AML leukemia stem cell (LSC) maintenance by 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

## STATE OF DEVELOPMENT

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### OTHER INFORMATION

**KEYWORDS**

AML. MDS, sAML, HSC, LSC, leukemia, splicesome, transcriptome analyses

**CATEGORIZED AS**

- **Medical**
  - Disease: Cancer
  - Research Tools
  - Therapeutics
- **Research Tools**
  - Other

**RELATED CASES**

2016-033-0, 2012-262-0

Pre-clinical studies identified a predictive splice isoform biomarker for sAML and the anti-tumor activity of novel compositions of matter were demonstrated in vitro and in vivo (in a mouse model of AML). Splice modulatory compounds were validated toward this MOA by using a splicing reporter and PCR assays.

## INTELLECTUAL PROPERTY INFO

Worldwide rights available for pending patents available under confidentiality. A published, US patent on composition of matter is described at "Synthetic Anticancer Polyketide Compounds".

## PATENT STATUS

| Country | Type | Number | Dated | Case |
|---|---|---|---|---|
| United States Of America | Issued Patent | 10,675,267 | 06/09/2020 | 2016-033 |
| United States Of America | Issued Patent | 9,604,973 | 03/28/2017 | 2012-262 |
| Patent Cooperation Treaty | Published Application | 2017053887 | 03/30/2017 | 2016-033 |

## RELATED MATERIALS


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## RELATED TECHNOLOGIES

- Synthetic Anticancer Polyketide Compounds


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