

17S-FD-895: An Improved Synthetic Splice Modulator mirroring FD-895

Tech ID: 28845 / UC Case 2016-131-0

BACKGROUND

The spliceosome, the cellular splicing machinery, regulates RNA splicing of messenger RNA precursors (pre-mRNAs) into maturation of protein coding RNAs. Recurrent mutations and copy number changes in genes encoding spliceosomal proteins and splicing regulatory factors have tumor promoting or suppressive functions in hematological malignancies, as well as some other cancers.

Over the past 10 years, a list of natural products, including FD-895, pladienolide B, herboxidiene, and spliceostatin A, have been identified as spliceosome modulators. They have been shown to have anti-cancer effect *in vitro* and *in vivo* models. However, these compounds demonstrate poor metabolic stability and short half-lives *in vivo*, excluding them from entering clinical evaluation. This invention, 17S-FD-895, is an analog of FD-895 and was synthesized through the combination of total synthesis and synthetic methods, demonstrating improved stability and on-target effect. This new spliceosome targeting compound was evaluated in different secondary acute myeloid leukemia models and showed potent efficacy in inhibition of acute myeloid leukemia (AML) LSC and disruption of AML maintenance *in vitro* and in mouse xenograft models (Crews et al. 2016). The study by Crews et al. indicates the pivotal role of spliceosome in secondary acute myeloid leukemia and the therapeutic potential of targeting leukemia stem cells in this subtype of AML often unresponsive to current therapy.

TECHNOLOGY DESCRIPTION

Researchers from UC San Diego have designed a stable splice modulator with improved pharmacological properties. This new analog, described herein as FDGLY, provides several benefits over the known natural product based splice modulators including spliceostatins, pladienolides, and herboxidiene, as well as the current synthetic derivatives approaching or reached IND status including 17S-FD-895, E7107 or 6-deoxypladienolide B.

FDGLY is a fully-synthetic spliceosome modulator that mirrors the structural features of FD-895. While FD-895 displays poor pharmacological stability (a factor common to nearly all semi-synthetic or synthetically-derived splice modulators to date), FDGLY displays improved stability in pharmacological buffers, plasma, cell lysates and animal models.

APPLICATIONS

FDGLY can be potentially used as a therapeutic agent in clinical use against cancer, as well as an agent to potentiate the effects of known cancer agents. An additional use would be for research, as a molecular probe to modulate splicing.

ADVANTAGES

FDGLY offers the following improvements over known splicing modulators:

- ▶ Improved stability: unlike most of the natural product and synthetic derivatives designed to date FDGLY is bench stable.
- ▶ Easier synthetic preparation: the core unit of FDGLY is prepared from D-glucose streamlining the synthetic preparation.
- ▶ Potent activity in mammalian cell models: properties can be tuned to deliver unique splicing modulatory patterns.

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OTHER INFORMATION

KEYWORDS

therapeutic agent, cancer, RNA
splicing, spliceosome modulator, FD-895, FDGLY

CATEGORIZED AS

- ▶ **Medical**
 - ▶ Disease: Cancer
 - ▶ Research Tools
 - ▶ Therapeutics
- ▶ **Research Tools**
 - ▶ Reagents

RELATED CASES

2016-131-0

- ▶ Readily addressed medicinal chemical optimization: the use of D-glucose has allowed analog developed to rapidly proceed using other carbohydrate building blocks.
- ▶ The potential for targeting the splicing of specific genes: the carbohydrate motif allows this derivative, unlike any analog to date, to be subjected to detailed optimization of activity that targets specific genes.

STATE OF DEVELOPMENT

The synthesis of FDGLY has been completed and is currently being used in cell and animal models to complete pharmacological and activity studies. In addition, medicinal chemical efforts are being explored for translation into the clinic for the treatment of cancer. The use of FDGLY is being used to potentiate already known chemotherapeutic agents by using FDGLY to reduce the levels of the proteins targeted by known chemotherapeutics within targeted tumor cells.

INTELLECTUAL PROPERTY INFO

A provisional patent has been submitted and the technology is available to license.

RELATED MATERIALS

- ▶ Crews LA, Balaian L, Delos Santos NP, Leu HS, Court AC, Lazzari E, Sadarangani A, Zipeto MA, La Clair JJ, Villa R, Kulidjian A, Storb R, Morris SR, Ball ED, Burkart MD, Jamieson CHM. RNA Splicing Modulation Selectively Impairs Leukemia Stem Cell Maintenance in Secondary Human AML. *Cell Stem Cell*. 2016 Nov 3;19(5):599-612. - 11/03/2016
- ▶ Dhar S, La Clair JJ, León B, Hammons JC, Yu Z, Kashyap MK, Castro JE, Burkart MD. A Carbohydrate-Derived Splice Modulator. *J Am Chem Soc*. 2016 Apr 20;138(15):5063-8. - 04/20/2016

PATENT STATUS

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Patent Cooperation Treaty	Published Application	2017156454	09/14/2017	2016-131

Additional Patent Pending

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