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ELONGATION FACTOR 1-ALPHA INHIBITORS FOR THE TREATMENT OF MULTIPLE MYELOMA / MYC-DRIVEN CANCERS

Tech ID: 32686 / UC Case 2020-149-0

TECHNOLOGY DESCRIPTION

Persistent activation of MYC via genomic translocation or amplification, or via upstream oncogenic signals, underlies the pathogenesis of many aggressive cancers. Myc is still an undruggable oncogene and new therapies that target Myc oncogenic addiction are urgently needed. The translation machinery is a major downstream target of MYC oncogenic activity. Although there are several approved drugs and drug candidates that target translation initiation (including rapamycin, omacetaxine, and zotatifin), targeting the elongation phase of translation is a new, wide-open frontier for cancer drug discovery. Results by UCSF investigators indicate that translation elongation is highly regulated in cancer and represents a selective vulnerability in MYC-driven tumors.

UCSF investigators have designed and synthesized SR-A3, an optimized small-molecule modulator of translation elongation, and believe that SR-A3 has the potential to be a preclinical development candidate for specific cancers. With exceptional potency and a long drug-target residence time, SR-A3 directly modulates the eukaryotic elongation factor-1-alpha (eEF1A), a GTPase that delivers aminoacyl-tRNAs to elongating ribosomes. At low doses, SR-A3 selectively stabilizes an eEF1A/ribosome complex and elicits robust antitumor effects in mice without significantly affecting global protein synthesis.

While exhibiting a similar mechanism of action to another on-market drug for the treatment of relapsed/refractory multiple myeloma (e.g., Plitidepsin, a structurally unrelated eEF1A inhibitor), SR-A3 is structurally simpler and may address current dose-limiting toxicity challenges.

APPLICATION

For the treatment of cancer, including relapsed and refractory multiple myeloma, other hematological tumors, and potentially solid tumors

ADVANTAGES

- · SR-A3 has the potential to serve as a "best-in-class" drug
 - o Similar mechanism of action to plitdepsin (approved in Australia for the treatment of multiple myeloma), but with potential to exhibit superior efficacy (decreased toxicity, greater therapeutic index)
- Experimental data reveal long residence time and extended duration of action, along with greater anti-tumor efficacy (when compared to other known ternatin analogs) following in vivo administration

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INVENTORS

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OTHER INFORMATION

KEYWORDS

cancer, small molecule,

MYC, therapeutic, multiple

myeloma

CATEGORIZED AS

- Medical
 - Disease: Cancer
 - Therapeutics

RELATED CASES

2020-149-0

LOOKING FOR PARTNERS

To develop and commercialize the technology for patient benefit.

STAGE OF DEVELOPMENT

Pre-clinical

- synthesized and compared with other analogs in cell culture assays
- obtained high-resolution structure of SR-A3 bound to eEF1A/ribosome complex, facilitating the design of new analogs
- evaluated for acute toxicity in mice, maximum tolerated dose established
- preliminary data demonstrating antitumor activity in mice
- in vivo animal experiments (xenograft models) ongoing

DATA AVAILABILITY

Under NDA

RELATED MATERIALS

- ➤ Synthesis and single-molecule imaging reveal stereospecific enhancement of binding kinetics by the antitumor eEF1A antagonist SR-A3. Nature Chemistry. 2022 Sep 19;14:1443-50.
- ▶ mRNA decoding in human is kinetically and structurally distinct from bacteria. Nature. 2023 May;617:200-207.

PATENT STATUS

Country	Туре	Number	Dated	Case
European Patent Office	Published Application	EP4100007	12/12/2022	2020-149

Additional Patents Pending

OTHER INFORMATION

Pending US (17/760,090) and Foreign Applications (AU/CA/CN/EP/JP)

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