Small Molecule Inhibitors of IRE1 for Unfolded Protein Response (UPR)-Dependent Diseases

Tech ID: 22325 / UC Case 2009-147-0

INVENTION NOVELTY

Novel small molecules that effectively inhibit IRE1, an enzyme critical for the activation of the unfolded protein response (UPR), providing a new method for therapeutic intervention in UPR-dependent diseases, such as cancer, inflammatory disease, autoimmune disease, and neurodegeneration.

VALUE PROPOSITION

Cellular stress can lead to the accumulation of unfolded/misfolded proteins in the endoplasmic reticulum (ER). IRE1 is an ER-resident enzyme that acts as a sensor of unfolded proteins in the ER and activates the UPR which involves the production of effector proteins that influence protein synthesis, protein folding, and post-translational processing in order to alleviate cellular stress. Therefore, UPR activity is a key to the pathogenesis of many diseases. To date, however, inhibition of the UPR has not been possible. The presented invention is novel small molecules that inhibit human IRE1 and thus allow for new avenues of therapeutic intervention in a broad spectrum of UPR-dependent diseases.

Advantages

- Potent inhibitors of IRE1
- Broad claims to methods targeting the key enzyme upstream of the UPR

TECHNOLOGY DESCRIPTION

UCSF investigators have developed novel pharmacological compounds that inhibit human IRE1 activity, thus allowing the modulation of UPR. These drug-like inhibitors of IRE1 further describes decreasing IRE1-mediated UPR activity as a novel avenue of therapeutic intervention in cancer (e.g. Multiple Myeloma, breast cancer), inflammatory disease (e.g. XBP1-linked Crohn's disease), and autoimmune disease (e.g. Diabetes mellitus Type I). In addition, the lead compound shows strong mouse xenograft tumor growth inhibition with no apparent toxicity at doses below 50mg/kg.

LOOKING FOR PARTNERS

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OTHER INFORMATION

KEYWORDS

Ire1, Small Molecule, Inhibitors, Therapeutics, Unfolded protein response (UPR), Inflammatory Disease, Cancer, Autoimmune Disease, Neurodegeneration

CATEGORIZED AS

- **Medical**
  - Disease: Cancer
  - Disease: Central Nervous System
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2009-147-0, 2009-038-0

To develop and commercialize the technology as an effective therapeutic in cancers, inflammatory disease, and autoimmune diseases.

STATE OF DEVELOPMENT

Pre-Clinical

DATA AVAILABILITY

Under CDA / NDA

RELATED MATERIALS

- Korennykh AV, Egea PF, Korostelev AA, Finer-Moore J, Zhang C, Shokat KM, Stroud RM, Walter P. Nature. 2009 Feb 5;457(7230):687-93. Epub 2008 Dec 14. PMID: 19079236.
- Mendez, A. S., Alfaro, J., Morales-Soto, M. A., Dar, A. C., McCullagh, E., Gotthardt, K., ... & Bernales, S. (2015). Endoplasmic reticulum stress-independent activation of unfolded protein response kinases by a small molecule ATP-mimic. Elife, 4, e05434.

PATENT STATUS

Country	Type	Number	Dated	Case
United States Of America	Issued Patent	8,980,899	03/17/2015	2009-147

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