Cleveland Clinic Innovations

PRODUCT
Small molecule that inhibits protein disulfide isomerase (PDI) blocking a key survival mechanism for multiple myeloma cells

INDICATION
Multiple myeloma, other cancers associated with endoplasmic reticulum stress

VALUE PROPOSITION
- Improvement in clinical benefit over standard-of-care as a standalone or combination therapy in multiple myeloma
- First-in-class orally bioavailable irreversible PDI inhibitor

DEVELOPMENT STAGE
Preclinical candidate with demonstrated in vivo efficacy

INTELLECTUAL PROPERTY
EP 4203894 (pending/published)
US 18/023,087 (pending/published)

PUBLICATION
Hasipek, Metis et al. "Therapeutic Targeting of Protein Disulfide Isomerase PDIA1 in Multiple Myeloma." Cancers vol. 13,11 2649. 28 May. 2021.

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IDF#2018-155

Small Molecule Modulators of ER Stress Response for Multiple Myeloma

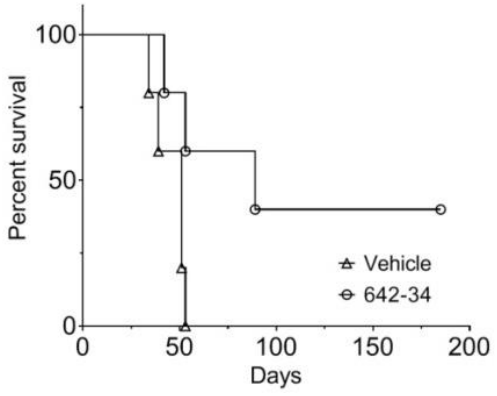
Babal Kant Jha, Jaroslaw Maciejewski, et al.
Cleveland Clinic Lerner Research Institute

UNMET NEED
Multiple myeloma (MM) is a cancer of antibody producing plasma cells with a five-year survival rate of ~50%. In the United States there are approximately 35,000 new MM diagnoses per year. Current standard of care beyond chemo/radiation is a combination therapy consisting of an immune modulator and proteasome inhibitor. Treatment success is limited with ~13,000 deaths reported on a yearly basis in the US. In instances of refractory MM, it has become clear that a blockade of the folding mechanism of proteins taken in by the ER, thereby reducing ER stress and misfolded protein accumulation, demonstrates promising therapeutic translation.

At present, there is a significant unmet need for novel therapeutics that specifically address the underlying mechanisms of refractory / drug resistant MM.

SOLUTION
Researchers at Cleveland Clinic have developed small molecule compounds that inhibit protein disulfide isomerase (PDI), an enzyme that catalyzes disulfide bond formation and rearrangement. This resident endoplasmic reticulum (ER) enzyme is required for proper folding of nascent antibodies produced by activated plasma cells and is upregulated in multiple myeloma providing a potential path for escaping ER stress.. By inhibiting PDI, multiple myeloma cells lose a key mechanism for mitigating ER stress leading to cell death.

Project is at preclinical candidate stage and will proceed into early IND-enabling studies including small animal PK/PD, metabolic ID, biodistribution / elimination, safety pharmacology and preliminary toxicology. Efficacy studies of produced compounds demonstrate inhibition of PDI1, PDI3, and PDI4 with bioavailability as an oral formulation in mice.



Proof of concept study in 5TGM1-luc/C57BL/KaLwRij mouse models of myeloma demonstrated improved survival in experimental group receiving PDI inhibitor candidate