Weill Cornell Medicine

Artemisinin-Proteasome Inhibitor Conjugates for the Treatment of Multiple Myeloma

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Background & Unmet Need

- Worldwide, there are ~86 K new multiple myeloma (MM) patients and ~63 K related deaths each year
- Proteasome inhibitor drugs are standard of care for the treatment of MM, but only have a response rate of ~25% when used as single agents
- Almost all MM patients using proteasome inhibitor treatment will relapse due to a variety of resistance pathways, including mutations in the proteasome subunit 19S
- Artemisinin and its analogues are clinically used to treat Malaria, but may also be promising cancer therapeutics as they demonstrate potent antineoplastic activity
- **Unmet Need:** Improved proteasome inhibitors for multiple myeloma and other cancers which overcome resistance mechanisms

Technology Overview

- **The Technology:** Artemisinin and proteasome inhibitor hybrids (Artezomibs, ATZs) for treatment of human cancers, including multiple myeloma
- The inventors have designed a series of Artezomibs, wherein Artemisinin analog *Artesunate* is conjugated to a proteasome inhibitor via a linker
- Artemisinin is known to cause degradation of Ferritin, which may in turn cause Ferroptosis, an iron-dependent programed cell death
- The longer, peptide-based proteasome inhibitors may overcome the resistance conferred via the mutations in proteasome subunits
- **PoC Data:** Proteasome inhibition assays demonstrated inhibitory activity of the Artezomibs against a variety of proteasome subunits
- Artezomibs demonstrated cytotoxicity against a panel of multiple myeloma cell lines, including MM.1S, CAG, and RPMI8226

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Patents:
PCT Application Filed
US Application Filed
EP Application Filed

Publications:
Zhan et al. *Cell Chem Biol.* 2023.

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Technology Applications

- Treatment of multiple myeloma, either alone or in combination with other proteasome inhibitors
- Therapeutic for other cancers susceptible to proteasome inhibition, such as pancreatic, head and neck cancer, and non small cell lung carcinoma

Technology Advantages

- Artezomibs can be tailored to inhibit one or more proteasome subunits
- Artezomibs show high potency *in vitro*
- Therapeutic activity of each moiety is preserved

Supporting Data / Figures

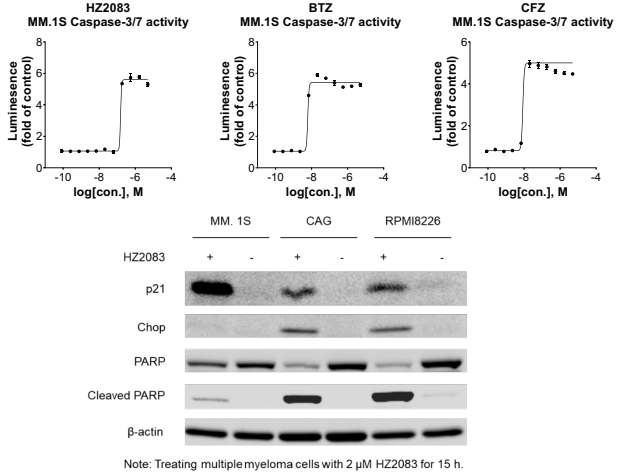

Figure 1: Artezomib induces apoptosis in multiple myeloma cells. **Top:** Treatment with HZ2083 increased Caspase-3/7 activity (associated with apoptosis) in an MM cell line comparable to clinically available proteasome inhibitor drugs. **Bottom:** Treatment with HZ2083 increased apoptosis-associated factors such as cleaved PARP, Chop, and p21.

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