Reversible Small Molecule Immunoproteasome Inhibitors for the Treatment of Multiple Diseases and Disorders

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Autoimmune & Inflammatory Diseases - Significant Unmet Medical Need

- More than 80 autoimmune diseases (Type I diabetes, rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, etc) affect more than 23.5 million Americans, \( \frac{3}{4} \) of them women
- 250,000 new diagnoses each year
- Most are treatable, but presently incurable
- Costing over $120 billion annually
Human 20s Proteasomes and Inhibitors

- Expressed in all cells
- Essential
- Regulates cell cycle, immune surveillance through degradation
- Intertwined with phosphorylation

- Expressed in immune cells, cells at the inflammation sites, all cells under stimulation of interferon-γ
- Non-essential: triple knockout mice immunocompetent
- Antigen presentation, cytokine regulation

- Bortezomib & Carfilzomib inhibit both constitutive and immunoproteasomes
- Bortezomib shows efficacy in lupus, kidney transplant patients, but long-term use prohibitive due to toxicity
Reversible Small Molecule Immunoproteasome Inhibitors

- Highly potent – $10^{-12}$ M IC50s
- Highly selective – ~ 18,000-fold
- Reversible inhibition
- Stable in plasma
- Non-cytotoxic & no acute toxicity in mice
In vivo Efficacy in TNBS-IBD and Triple Negative Breast Cancer

TNBS – Induced Acute Inflammatory Bowel Disease

4T1 Triple Negative Breast Cancer
Contact & More Information

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