



Targeting Proteasomes in Cancer and Infectious Disease: A Parallel Strategy to Treat Malignancies and Microbes

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Essential core pathways of cellular biology are preserved throughout evolution, highlighting the importance of these pathways for both bacteria and human cancer cells alike. Cell viability requires a proper balance between protein synthesis and degradation in order to maintain integrity of the proteome. Proteasomes are highly intricate, tightly regulated multisubunit complexes that are critical to achieve protein homeostasis (proteostasis) through the selective degradation of misfolded, redundant and damaged proteins. Proteasomes function as the catalytic core of the ubiquitin-proteasome pathway (UPP) which regulates a myriad of essential processes including growth, survival, differentiation, drug resistance and apoptosis. Proteasomes recognize and degrade proteins that have been marked by covalently attached poly-ubiquitin chains. Deregulation of the UPP has emerged as an essential etiology of many prominent diseases, including cancer. Proteasome inhibitors selectively target cancer cells, including those resistant to chemotherapy, while sparing healthy cells. Proteasome inhibition has emerged as a transformative anti-myeloma strategy that has extended survival for certain patient populations from 3 to 8 years. The structural architecture and functional activity of proteasomes is conserved from *Archaea* to humans to support the concept that proteasomes are actionable targets that can be inhibited in pathogenic organisms to improve the treatment of infectious diseases. Proteasomes have an essential role during all stages of the parasite life cycle and features that distinguish proteasomes in pathogens from human forms have been revealed. Advancement of inhibitors that target *Plasmodium* and *Mycobacterial* proteasomes is a means to improve treatment of malaria and tuberculosis. In addition, PIs may also synergize with current frontline agents support as resistance to conventional drugs continues to increase. The proteasome represents a highly promising, actionable target to combat infectious diseases that devastate lives and livelihoods around the globe.

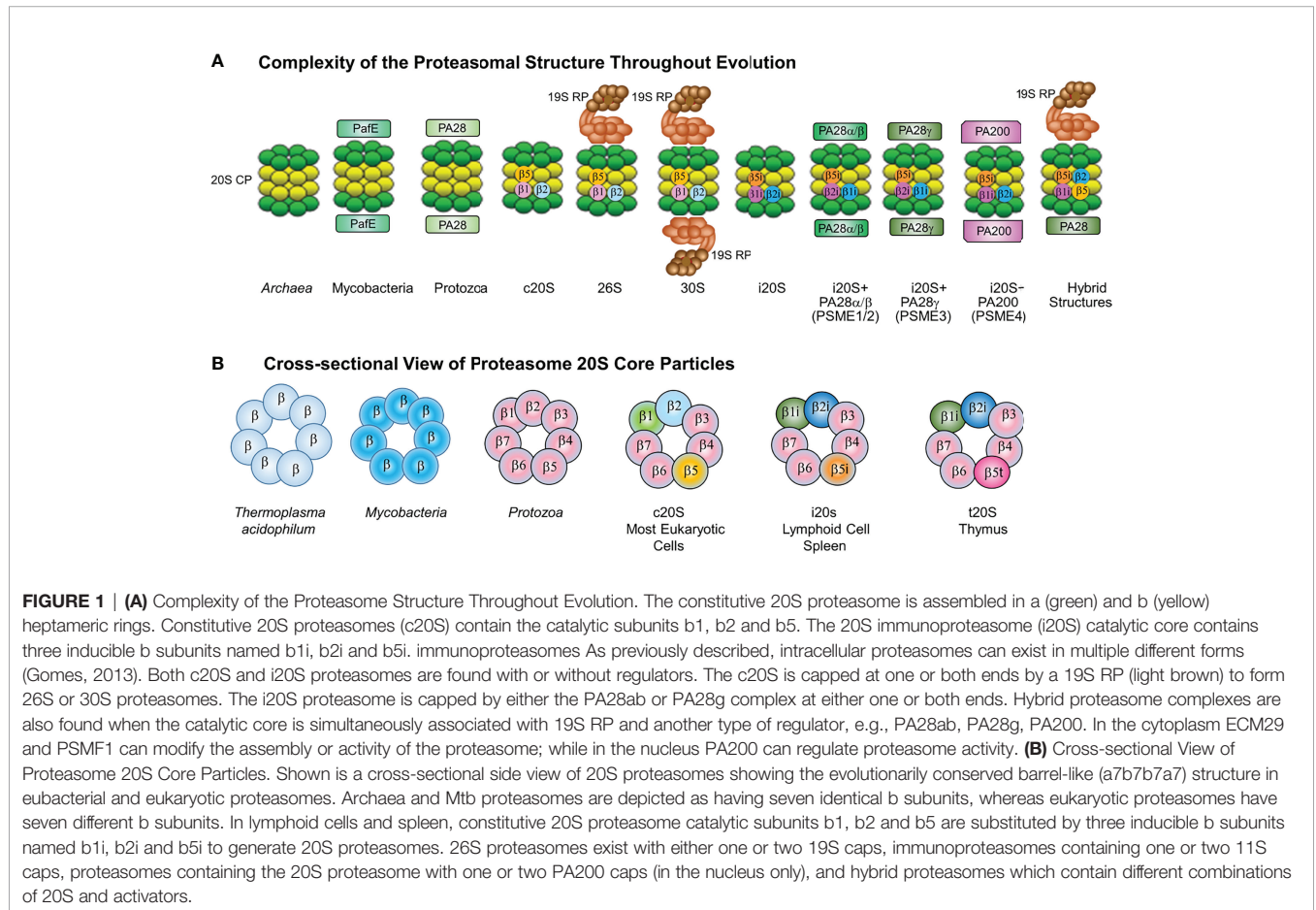
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OVERVIEW OF PROTEASOME COMPLEXES

Protein homeostasis (proteostasis) is pivotal for cell viability and is governed by precisely regulated processes that balance protein synthesis and degradation (Cromm and Crews, 2017). Cells utilize protein clearance mechanisms, e.g., the ubiquitin (Ub)-proteasome pathway (UPP), autophagy, and aggresomes, to regulate essential biological processes, eliminate misfolded, unfolded, denatured and redundant proteins and modulate the levels of regulatory proteins that govern cell cycle progression and the circadian rhythm (Kopito, 2000; Ciechanover, 2005; Finley, 2009; Dikic, 2017). The UPP is responsible for the majority of protein degradation within eukaryotic cells (Finley, 2009). Protein substrates are marked for turnover through covalent linkage of poly-Ub chains (Ciechanover, 2005). Ubiquitinated substrates are recognized by a 26S (~2.5MDa) ATP+Ub-dependent complex that hydrolyzes substrates into peptides and recycles free Ub. Eukaryotic cells contain high molecular weight (HMW), cylindrical ribonucleoprotein particles (RNPs) composed of a family of proteins with molecular masses of 19-36 kilodaltons. Numerous groups had described a non-lysosomal, multicatalytic proteinase (MCP) that exhibited peptide-hydrolyzing activity at neutral-alkaline pH against N-blocked tripeptide substrates with an Arg, Phe or

Glu residue adjacent to 4-MCA or 2-naphthylamide leaving groups (Wilk and Orlowski, 1980; Wilk and Orlowski, 1983; Dahlmann et al., 1983; Ray and Harris, 1985). Subsequently, Falkenberg et al. demonstrated by using electron microscopy, western blotting, RNA analysis and proteinase assays, that the RNPs and MCPs were structurally and immunologically-related entities (Falkenberg et al., 1988). Later studies showed that the 20S MCP - *the proteasome* - is in fact incorporated into the 26S ATP+Ub-dependent proteasome complex (Eytan et al., 1989; Driscoll and Goldberg, 1990). The 26S proteasome complex is assembled in an ATP-dependent manner by capping the 20S catalytic core particle (CP) at either or both ends with 19S regulatory particles (RP) that confer ATP and Ub-dependence (Figure 1).

Proteasomes are conserved from *Archaea* to humans, are found within the cytoplasm and nucleus and all forms observed thus far contain a 20S CP (Groll et al., 1997; Voges et al., 1999; Maupin-Furlow, 2012). In contrast to the 26S complex, the 20S proteasome can recognize and degrade unfolded or unstructured protein substrates in a Ub-independent manner (Driscoll and Goldberg, 1989; Matthews et al., 1989). The constitutive 20S proteasome (c20S) CP is arranged as 4 stacked heptameric rings in an $\alpha\beta\alpha\beta\alpha\beta\alpha\beta$ barrel-shaped manner (Groll et al., 1997; Voges et al., 1999; Ciechanover, 2005; Finley, 2009; Maupin-Furlow, 2012). The 2 distal rings are identical and contain 7 different α



subunits, whereas the 2 central rings contain 7 different β subunits, of which $\beta 1$, $\beta 2$, and $\beta 5$ exert catalytic activities. Proteasomes are a family of N-terminal hydrolases and each catalytic subunit has been ascribed a typical activity profile. The $\beta 1$ subunit cleaves predominantly after acidic amino acids (caspase-like activity), $\beta 2$ cleaves after basic residues (trypsin-like activity), and the $\beta 5$ subunit after hydrophobic amino acids (chymotrypsin-like/ChT-like) (Dahlmann et al., 1989; Dick et al., 1998; Gallastegui and Groll, 2010). Proteasomal hydrolysis of intracellular proteins also generates peptides that function as antigens bound to the major histocompatibility complex (MHC) class I molecule. In lymphoid cells and cells exposed to IFN- γ , the $\beta 1$, $\beta 2$, and $\beta 5$ subunits within c20S proteasomes are replaced by their inducible counterparts $\beta 1i$, $\beta 2i$, and $\beta 5i$, leading to immunoproteasome (i20S) formation (Brown et al., 1991; Driscoll and Finley, 1992; Kloetzel, 2001). i20S proteasomes exhibit catalytic activities distinct from c20S proteasomes, with lower caspase-like and greater ChT-like activity (Driscoll et al., 1993). Presentation of MHC class I antigens is favored in cells that harbor i20S proteasomes to shape the repertoire of immunodominant epitopes.

TARGETING THE PROTEASOME IN CANCER TREATMENT

Proteasomal inhibition leads to the accumulation of Ub-protein conjugated proteins that triggers endoplasmic reticulum (ER) stress, activates the unfolded protein response (UPR) and culminates in cell death. PIs are validated, safe and effective anti-cancer drugs (Orlowski and Kuhn, 2008; Dick and Fleming, 2010; Kisselev et al., 2012; Fricker, 2020). Bortezomib (Millennium-Takeda) is a boronate dipeptide aldehyde and first FDA-approved PI for MM. Bortezomib acts predominantly on the proteasomal ChT-L activity and displays potent inhibitory activity against the $\beta 1i$ ($IC_{50} = 5.5$ nM), $\beta 5c$ ($IC_{50} = 7$ nM) and $\beta 5i$ ($IC_{50} = 3.3$ nM) subunits (Table 1). However, dose-dependent peripheral neuropathy may limit clinical utility. In addition, bortezomib has limited activity against solid tumors since adequate dosing cannot be reached to overcome poor tissue penetration and rapid clearance from peripheral blood (Orlowski and Kuhn, 2008; Dick and Fleming, 2010; Kisselev et al., 2012; Fricker, 2020).

Second-generation proteasome inhibitors (PIs) were developed to overcome bortezomib resistance as well as improved efficacy and safety and convenient methods of administration (Kisselev et al., 2012; Fricker, 2020). Carfilzomib (Onyx/Amgen) is derived from epoxomicin, – a tetrapeptide epoxyketone natural product isolated from *Actinomyces* (Kuhn et al., 2007; Huber and Groll, 2012; Kisselev et al., 2012; Herndon et al., 2013; Park et al., 2018; Fricker, 2020; Jayaweera et al., 2021). Carfilzomib is FDA-approved as a single agent for treatment of refractory MM, specifically those who had received >2 prior lines of therapy and have progressed on or within 60 days of completion of their last therapy (Kuhn et al., 2007; Herndon et al., 2013; Park et al., 2018). The oral PI ixazomib (Millennium-Takeda) is a peptide boronic acid, approved in combination with lenalidomide and

dexamethasone, for MM patients who have received >1 prior therapy (Kumar et al., 2014; Moreau et al., 2016; Al-Salama et al., 2017). In adults with relapsed and/or refractory (RR)MM who previously had received 1-3 therapies, progression-free survival (PFS) was significantly prolonged in those who received ixazomib. A significantly longer time to progression and favorable hazard ratios for PFS were seen across all subgroups, including those with high risk cytogenetics.

PROTEASOMES IN AUTOINFLAMMATORY SYNDROMES AND NEURODEVELOPMENTAL DISORDERS

Proteasomes are conserved throughout evolution dating back to *Archaea* because of the fundamental role in maintaining protein homeostasis. It therefore follows that proteasome mutations, while clinically rare, when detected would be associated with profound morbidity. Indeed, the proteasome-associated autoinflammatory syndromes (PRAAS) represent a spectrum of inherited autoinflammatory conditions first described in 1939 with characteristic skin findings, recurrent fevers, and joint contractures (Agarwal et al., 2010; Kitamura et al., 2011; Brehm and Kruger, 2015; Brehm et al., 2016). Related syndromes have been subsequently described, including Chronic atypical neutrophilic dermatoses with lipodystrophy and elevated temperature (CANDLE) syndrome, Nakajo-Nishimura syndrome, and Japanese autoinflammatory syndrome with lipodystrophy (McDermott et al., 2015). Mutations in the proteasome-immunoproteasome system drive the pathophysiology of these syndromes. Several groups independently described homozygous loss of function mutations in *PSMB8* that inhibit incorporation of the $\beta 5i$ into the 20S proteasome. The lack of *PSMB8* lead to ineffective response to IFN- γ induced oxidative stress, promoting sustained activation of IFN- γ and MAPK signaling driving chronic inflammation. Additional proteasome mutations have been linked to these syndromes including mutations in *PSMG2/PAC2-Proteasome assembly chaperones* (De Jesus et al., 2019). Management is challenging, involving chronic immune suppression with steroids and Janus Kinase inhibitors with allograft stem cell transplantation providing more durable clinical response (Sanchez et al., 2018; De Jesus et al., 2019; Verhoeven et al., 2022). These syndromes provide clinical evidence of the profound importance of proteasome function in cellular function and regulation of inflammatory responses.

The intracellular and extracellular accumulation of aggregated protein are linked to many diseases, including a number of proteinopathies, ageing-related neurodegeneration and systemic amyloidosis (Kopito, 2000; Olzmann et al., 2008). Cells avoid accumulating potentially toxic aggregates by mechanisms including the suppression of aggregate formation by molecular chaperones and the degradation of misfolded proteins by proteasomes. Importantly, proteasome inhibition drives formation of intracellular inclusions known as the aggresome, protein aggregates that tend to be refractory to proteolysis and to accumulate in inclusion bodies (Kawaguchi et al., 2003). Aggresome

TABLE 1 | Fda-approved and investigational proteasomal inhibitors for the treatment of human disease.

DISEASE	STRUCTURE	STATUS	ACTIVE SITE	DISEASE TARGET/ DISEASE MODEL
ONCOLOGY				
Bortezomib (Orlowski and Kuhn, 2008; Dick and Fleming, 2010; Kisselev et al., 2012; Fricker, 2020)	Dipeptidyl boronate	FDA-Approval	$\beta 5 > \beta 1 > \beta 2$	MM, MCL, DLBCL
		RRMM (2003) MM (2007) Previously untreated MM (2008) SC injection for all approved indications (2012) MCL- with at least one prior tx (2007)		
Carfilzomib (Kuhn et al., 2007; Huber and Groll, 2012; Herndon et al., 2013; Park et al., 2018; Jayaweera et al., 2021)	Tetrapeptide epoxyketone	FDA-Approval	$\beta 5 > \beta 1 > \beta 2$	MM
		Advanced MM (2012) Relapsed MM (2015) RRMM (2016)		
Ixazomib (Kumar et al., 2014; Al-Salama et al., 2017)	Dipeptidyl boronate, oral	FDA-Approval	$\beta 5 > \beta 1 > \beta 2$	Oral agent, MM
		RRMM (2015)		
Marizomib (Huber and Groll, 2012; Park et al., 2018; Fricker, 2020)	β -lactone	FDA orphan status	$\beta 5 > \beta 2 > \beta 1$	MM, crosses BBB
(Salinosporamide A, NPI-0052)		MM (2013)		
Delanzomib (Huber and Groll, 2012; Park et al., 2018; Fricker, 2020)	C-terminal boronic acid peptide (phenylpyridine)		$\beta 5 > \beta 1 > \beta 2$	MM
ONX-0912 (Johnson et al., 2017; Schmidt et al., 2018; Xi et al., 2019)		Orphan status	$\beta 5 > \beta 1 > \beta 2$	MM, WM
(Oprozomib, PR-047)	oral	NCT02072863		
Lactacystin (Orlowski and Kuhn, 2008; Dick and Fleming, 2010; Kisselev et al., 2012; Fricker, 2020)	β -lactone	Pre-clinical	$\beta 5 > \beta 1 > \beta 2$	Cancers, MM
TMC-95A, B, C, D (Koguchi et al., 2000)	<i>Apiospora</i> broth	Pre-clinical	$\beta 5 > \beta 1 > \beta 2$	TMC-95A and diastereomers (B-D) exhibited cytotoxicity against human HCT-116 colon
AUTOIMMUNE DISEASES				
ONX-0914 (Kuhn et al., 2007; Huber and Groll, 2012; Herndon et al., 2013; Johnson et al., 2017; Park et al., 2018; Schmidt et al., 2018; Xi et al., 2019; Jayaweera et al., 2021)	Tripeptide Epoxyketone	Investigational	$\beta 5 i > \beta 1 i > \beta 2 i$	Experimental/murine autoimmune, rheumatoid arthritis, encephalomyelitis, inflammatory bowel disease, and GVHD models
(PR-957)				
KZR-504 (Johnson et al., 2017; Xi et al., 2019)	Dipeptide Epoxyketone	Investigational	$\beta 1 i > \beta 5 i > \beta 2$	RA, SLE
KZR-616 (Johnson et al., 2017; Xi et al., 2019)	Tetrapeptide Epoxyketone	NCT03393013	$\beta 5 i > \beta 1 i > \beta 2 i$	SLE with and without Lupus Nephritis
		NCT04033926 NCT04039477		Polymyositis or Dermatomyositis Active Autoimmune Hemolytic Anemia or ITP
TUBERCULOSIS				
GL5 (Totaro et al., 2017)	Oxathiazole-2-one derivative	Pre-clinical	$\beta 5$	Mtb20S-selective Kills non-replicating Mtb under NO stress Selective suicide substrate inhibitor of Mtb 20S OG proteasomes Cyclocarbonylates active site Thr >1,000-fold more effective against Mtb than human proteasomes

(Continued)

TABLE 1 | Continued

DISEASE	STRUCTURE	STATUS	ACTIVE SITE	DISEASE TARGET/ DISEASE MODEL
HT1171 (Totaro et al., 2017)	Oxathiazole-2-one derivative	Pre-clinical	β5	Mtb20S-selective Kills non-replicating Mtb under NO stress Selective suicide substrate inhibitor of Mtb 20S OG proteasomes Cyclocarbonylates the active site Thr >1,000-fold more effective against Mtb than human proteasomes
HT1171 (Totaro et al., 2017)	Oxathiazole-2-one derivative	Pre-clinical	β5	Mtb20S-selective Kills non-replicating Mtb under NO stress Selective suicide substrate inhibitor of Mtb 20S OG proteasomes Cyclocarbonylates the active site Thr >1,000-fold more effective against Mtb than human proteasomes
Fellutamide B (Lin et al., 2010)	Lipopeptide aldehyde	Pre-clinical	β5	Inhibits wild type (Mtb20SWT) and open-gate mutant (Mtb20SOG) Mtb proteasomes Inhibits Mtb proteasome through one-step mechanism, inhibits hu20S proteasome through two-step mechanism
Syringolin (Totaro et al., 2017) Analogues A/B	Natural products Macrocyclic lactam attached to an exocyclic dipeptide urea	Pre-clinical	β5	Species selective, bioactive Mtb inhibitors 74-fold > selectivity for Mtb > hu20S proteasomes
DPLG2 (Lin et al., 2013)	Phenylimidazole-based, N, C-Capped dipeptide	Pre-clinical	β5	Cell-permeable, covalent, irreversible 4,667-fold selective for Mtb proteasomes over human c20S and 3,647-fold over i20S proteasomes Cell-permeable, kill non-replicating Mtb under nitrosative stress
B6 (Zhan et al., 2019)	Phenylimidazole peptidomimetic	Pre-clinical	β5	>12,500-fold selective for Mtb proteasomes than human c20S and i20S proteasomes
TDI5575 (Zhang and Lin, 2021)	Macrocyclic Peptides	Translational	β5ic>β5c>β2i, β2c, β1i, β1c	Kills non-replicating Mtb under NO stress Induces accumulation of pupylated proteins Stable in plasma
MALARIA				
Artemisinins (Bridgford et al., 2018)	Natural bioactive sesquiterpene lactone containing an unusual endoperoxide	First-line treatment for uncomplicated <i>P. falciparum</i> malaria		Upregulation of the UPR Inhibits proteasome function Fast-acting against intraerythrocytic asexual blood-stage malaria Short half-life <i>in vivo</i>
Artesunate (Dondorp et al., 2010)	1,2,4-trioxane ring Semi-synthetic Lactol derivative	FDA-approved (IV) for severe malaria in adults and children		
Artemether (Esu et al., 2019)	Semi-synthetic Lactol derivative		β5>β1>>β2	Multi-pronged assault on protein homeostasis Activates ER stress, toxic accumulation of poly-Ub- proteins, kills parasites
WLW-vs (Stokes et al., 2019)	Peptide vinyl sulfones Irreversible	Pre-clinical	β2-selective	Plasmodium-selective, attenuate parasite growth <i>in vivo</i> in murine models
TDI-8304 (Zhan et al., 2021)	Macrocyclic peptide	Pre-clinical	β5	Species-selective Reduces parasitemia in humanized <i>P. falciparum</i> - infected mouse
PW28 (Tschan et al., 2013)	Peptido sulfonyl fluoride (Cbz-LLLL-VF)	Pre-clinical		Malaria
Carmaphycin B	Natural product			

(Continued)

TABLE 1 | Continued

DISEASE	STRUCTURE	STATUS	ACTIVE SITE	DISEASE TARGET/ DISEASE MODEL
analog 18 (LaMonte et al., 2017)	N-hexanoyl tripeptide, α,β -epoxyketone	Pre-clinical	$\beta 5$	Inhibit $\beta 5$ activity, blood-stage and gametocidal antimalarial activity
OZ439 (Charman et al., 2011) (Artefenomel)	Synthetic ozonide Artemisinin pharmacophore	Phase 2 trial		Good safety profile that clears parasitemia rapidly in both <i>P. falciparum</i> and <i>P. vivax</i> malaria
MPI-5 (Xie et al., 2021)	Amino-amide boronate	Pre-clinical		Selective, potent anti-malarial activity across the parasite lifecycle, fast-acting, species selective over human proteasome, high selectivity for Pf cultures Oral availability, efficacy in SCID mouse model
MPI-13 (Xie et al., 2021)	Amino-amide boronate	Pre-clinical		Selective, potent anti-malarial activity across the parasite lifecycle, fast-acting, species selective over human proteasome, high selectivity for Pf cultures Oral availability, efficacy in SCID mouse model
PROTOZOA				
GNF5343 (Khare et al., 2016)	Azabenzoxazole	Investigational	$\beta 5$	Inhibits kinetoplastid proteasome and growth Potent anti- <i>L. donovani</i> and anti- <i>T. brucei</i> activity for the treatment of <i>Leishmania</i> , Chagas disease, and Sleeping sickness
GNF6702 (101)	Azabenzoxazole	Investigational	$\beta 5$	Optimization of GNF5343. Reduced risk of toxicity, improved selectivity over mammalian cell growth inhibition, low clearance, acceptable bioavailability and a 400-fold increase in potency against intra-macrophage <i>L. donovani</i> compared with GNF5343

formation is a general response of cells which occurs when the capacity of the proteasome is exceeded by the production of aggregation-prone misfolded proteins. Aggresomes represents an important crossroads of the UPS and the unfolded protein response and are thought to be sequestered into autophagosomes before they are cleared by the lysosome. Large protein aggregates are unable to pass through the 20S proteasome, and increased protein aggregates can further proteasome inhibition, promoting a vicious cycle in neurodegenerative diseases, however proteasomes have been shown to co-localize with aggresomes. Hao and colleagues showed that Poh1, a proteasomal deubiquitinating enzyme, generates free K63-linked Ub chains that promote histone deacetylase 6 (HDAC6)-mediated aggresome clearance (Hao et al., 2013). HDAC6 has become a target for drug development to treat myeloma due to its major contribution in oncogenic cell transformation and overcomes resistance to PIs (Hideshima et al., 2016).

Proteasome Inhibitors to Treat Multiple Myeloma

MM is described by expansion of clonal plasma cells that reside within bone marrow (BM), monoclonal protein detected in blood and/or urine, and end-organ dysfunction (Hideshima et al., 2001; Hideshima et al., 2007; Palumbo and Anderson, 2011; Munshi et al., 2017; Rajkumar, 2020; van de Donk et al., 2021). MM accounts for approximately 13% of all hematologic malignancies and is the second most common blood cancer in high-income and Western countries (Hideshima et al., 2007). The annual age-adjusted incidence is ~7.1 cases/100,000 persons in the U.S. with 34,920 new cases in 2021 and ~0.8% of all adults diagnosed with MM during their lifetime. Hideshima et al. demonstrated that bortezomib directly blocks myeloma proliferation, promotes

killing of MM cell lines and freshly isolated patient MM cells and overcomes interleukin (IL)-6-mediated drug resistance (Moscvin et al., 2021). Bortezomib also reduces MM growth by impairing adherence to BMSCs and reducing their NF- κ B-dependent upregulation of IL-6 secretion. Bortezomib disrupts paracrine signaling which reduces the proliferation and growth signaling of residual adherent MM cells. These results demonstrated that bortezomib directly acts on MM cells and disrupts BMSC-dependent pro-tumorigenic events within the BM milieu (Kumar and Rajkumar, 2008; Moscvin et al., 2021).

Perturbations in intracellular protein homeostasis including the accumulation of ubiquitinated proteins is accompanied by a type I interferon (IFN) signature (Ebstein et al. 2019) Under sterile conditions, the unfolded protein response (UPR), typically initiated in response to an accumulation of unfolded and/or misfolded proteins in the endoplasmic reticulum (ER), i.e., ER stress response, triggers type I IFN. Since PRAAS are caused by inherited and/or *de novo* loss-of-function mutations in genes encoding proteasome subunits, e.g., *PSMB8*, *PSMB9*, *PSMB7*, *PSMA3*, or proteasome assembly factors including *POMP* and *PSMG2*, respectively (Poli et al., 2018; De Jesus et al., 2019). The recent observation that the UPR is engaged in subjects carrying *POMP* mutations strongly suggests a possible implication in the cause-and-effect relationship between proteasome impairment and interferonopathy onset. Proteasome inhibition is similarly associated with an induction of ER stress. Studencka-Turski et al. proposed a model where proteasome inhibition inhibits subsequent retro-translocation of misfolded ER proteins (Studencka-Turski et al., 2019). The buildup of these misfolded proteins activates all three cellular sensors of ER stress including Activation transcription factor 6 (ATF6), protein kinase R-like ER

kinase and inositol-requiring protein 1- α (IRE-1 α). They subsequently link IRE-1 α activity to the type I IFN response. The ERAD pathway is primarily defined as an ER-localized UPS that ensures the proteasome-mediated degradation of misfolded proteins trafficking in the ER (Liu and Kaufman, 2003; Schroder and Kaufman, 2005; Hetz et al., 2015). Damaged proteins and/or proteins aberrantly modified are transported from the ER lumen back to the cytosol by retro-translocation prior to subsequent ubiquitination and membrane extraction for degradation by proteasomes. Nearly ~30% of all proteins are synthesized at the ER by the secretory pathway and, as such, potential ERAD substrates make ERAD a reliable sensor to alarm cells to decreased ability to degrade proteins. The type-I IFN response also plays a key role in the efficacy of bortezomib in MM therapy. Gulla and colleagues demonstrated that bortezomib treatment modulates the immunosuppressive microenvironment in MM patients, promoting type-I IFN signaling through a cGAS/STING-mediated pathway (Gulla et al., 2021).

The immunoproteasome is classically associated with presentation of antigenic peptides presented by MHC class I molecules due to its higher cleavage activity after hydrophobic residues, but this hydrophobic processivity has important implications for antigen repertoire. Indeed, Chapiro et al. addressed this issue by analyzing processing of three clinically relevant antigens, showing that the gp100₂₀₈₋₂₁₇ and peptide tyrosinase₃₆₉₋₃₇₇ antigens are destroyed secondary to cleavage after an internal hydrophobic residue, while the peptide MAGE-C2₃₃₆₋₃₄₄ is destroyed by the constitutive proteasome due to cleavage after an acidic residue (Chapiro et al., 2006). Thus, the balance of constitutive and immunoproteasomes together play a key role in the antigen repertoire.

Proteasome Inhibitors to Treat Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a subtype of Non-Hodgkin's Lymphoma (NHL) which has a relatively poor prognosis, despite numerous cytotoxic chemotherapy options (Cheah et al., 2016). Bortezomib, initially approved for patients with RRMM, is also approved for RR MCL (Holkova and Grant, 2012). Robak et al. investigated whether switching bortezomib for vincristine in frontline therapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) improved outcome in newly diagnosed ND MCL patients (Robak et al., 2015). Bortezomib, rituximab, cyclophosphamide, doxorubicin and prednisone was more effective than R-CHOP for ND MCL but at the cost of increased hematologic toxicity.

Proteasome Inhibitors to Treat Diffuse Large B Cell Lymphoma

While the survival rate of DLBCL has significantly improved, many patients do not achieve CR or relapse, especially those diagnosed with the activated B cell-like (ABC) subtype. Bortezomib exhibits activity in DLBCL, especially the ABC DLBCL. A meta-analysis compared the efficacy and adverse events in bortezomib-containing regimens with standard R-CHOP treatment. Compared to R-CHOP, the bortezomib-

containing regimen did not prolong survival of ABC DLBCL patients and those who received bortezomib had greater risk of peripheral neuropathy (Dunleavy et al., 2009; Lin et al., 2018).

HIV+ patients exhibit much higher risk of developing DLBCL than an HIV- patient. These lymphomas are often associated with Epstein Barr Virus (EBV) and Human Herpes Virus 8 (HHV8) infection. Reid et al. postulated adding bortezomib to rituximab, ifosfamide, carboplatin and etoposide salvage therapy could activate latent viral infections and improve lymphoma control. Their regimen exhibits a 77% response rate and 57% 1-year survival, outperforming historic controls associated with increased viral titers of EBV and HIV was undetectable throughout the study. This regimen is recommended *per* NCCN guidelines for RR DLBCL in HIV+ patients with grade 2B evidence (Reid et al., 2018).

Proteasome Inhibitors to Treat Relapsed/Refractory Idiopathic Multicentric Castleman's

Treatment of RR idiopathic Multicentric Castleman's disease (RR iMCD) remains challenging and often has a poor prognosis (Cabot et al., 1954). Zhang et al. evaluated a bortezomib-cyclophosphamide-dexamethasone (BCD) as a regimen in 24 RR iMCD patients (Zhang et al., 2020). The estimated 1-year PFS and OS were 79% and 92%, respectively, and BCD was a safe, effective option in RR iMCD.

TARGETING PROTEASOMES TO TREAT INFECTIOUS DISEASE

Archaea are single celled organisms now recognized as a third domain of life (Eme et al., 2017). Molecular and genetic evidence suggests that *Eukarya* are related to *Archaea* and indicate that eukaryotes descend from *Archaea* (Eme et al., 2017). Like eukaryotes, *Archaea* are thought to use the proteasome as a primary system for energy-dependent protein degradation (Löwe et al., 2015; Eme et al., 2017; Majumder et al., 2019). Proteasomes from *Archaea* are highly related, but distinct, from eukaryotic forms in their structural organization and functional activities. While proteasomes perform critical functions in bacteria, they are not as absolutely essential as in *Archaea* and eukaryotes. Taken together, accumulating evidence indicate that proteasomal inhibition can affect the pathogenicity of select microbial pathogens. Therefore, it is reasonable that pharmacologic inhibition of proteasomes in organisms less evolutionarily developed than humans may represent a novel therapeutic approach to improve the treatment of infectious diseases caused by protozoans and bacteria.

Proteasome Inhibitors to Treat Malaria

Malaria ranks as one of the greatest global health problems and each year *P. falciparum* malaria infects >200 million individuals and causes >400,000 deaths (Phillips et al., 2017; World Health Organization, 2020). *Plasmodium* parasites,

which are spread to humans through the bites of infected female *Anopheles* mosquitoes, causes the acute, febrile illness malaria. At least 5 species cause malaria in humans. *P. falciparum*, most prevalent in Africa and *P. vivax*, dominant outside of sub-Saharan Africa, pose the greatest threat to humans (Phillips et al., 2017; World Health Organization, 2020; Bergmann et al., 2021). Current antimalarial control relies on artemisinin-based combination therapies (ACTs) which have a cure failure rate of ~50% in portions of Southeast Asia (Van de Pluijijm et al., 2019). Zani et al., 2014 Identification of novel actionable targets, active against all parasite life cycle stages and that prevent and/or overcome drug resistance remains an unmet need.

The *Plasmodium* proteasome represents a novel, actionable, therapeutic target to improve malaria treatment and disease prevention (<https://www.who.int/publications/digital/global-tuberculosis-report-2021>; Li et al., 2012; Li et al., 2014; Dogovski et al., 2015; Li et al., 2016; Ng et al., 2017; Kirkman et al., 2018; Krishnan and Williamson, 2018; Xie et al., 2018; Yoo et al., 2018; Van de Pluijijm et al., 2019; Bergmann et al., 2021; Zhan et al., 2021). The proteasome is essential throughout the *Plasmodium* life cycle as parasites quickly adapt to a new host and undergo morphologic changes during asexual replication and sexual differentiation. Because of the high replication rate during the erythrocytic stage of parasites, protein quality control is critical for *P. falciparum* survival. Inhibiting the *P. falciparum* proteasome represents a drug target that may improve current treatment and avoid overcome ACT-resistance. *Plasmodium* harbor 3 types of protease complexes: a eukaryotic (26S) cytoplasmic and nuclear proteasome, a prokaryotic mitochondrial proteasome homologous to ClpQ, and a caseinolytic, apicoplast ClpP protease (Krishnan and Williamson, 2018).

Structural information obtained for the *P. falciparum* proteasomal complex renewed efforts to generate and validate new PIs as well as to re-examine the previously studied PI classes, namely; dipeptidyl boronic acids, α,β -epoxyketones, β -lactones, peptide aldehydes, vinyl sulfones and cyclic peptides (**Table 1**). Compounds representative of each PI class were evaluated using proteasomes from *Plasmodium* (Li et al., 2012; Li et al., 2014; Dogovski et al., 2015; Li et al., 2016; Ng et al., 2017; Kirkman et al., 2018; Krishnan and Williamson, 2018; Xie et al., 2018; Yoo et al., 2018; Van de Pluijijm et al., 2019; Zhan et al., 2021). Li et al. screened a library of 670 carfilzomib-based analogs to detect those that selectively cytotoxic to parasites (Li et al., 2012). The authors identified PR3, which *in vitro* significantly killed the parasite but displayed dramatically reduced toxicity against the host. Parasite-specific toxicity was not due to selective targeting of *Plasmodium* proteasomes over host proteasomes, but rather, attributed to lack of efficacy against a human proteasome subunit. PR3 was later shown to significantly reduce the parasite load in *P. berghei*-infected mice in the absence of host toxicity. The results validated the proteasome as a viable anti-malarial drug target. Li et al. then employed active site specific probes to explore the *Plasmodium* proteasome. They demonstrated that PIs

often do not exhibit the same subunit-targeting profiles for host and parasite proteasomes (Li et al., 2014). *Plasmodium* parasites undergoing schizogony, a biologic phenomenon not present in human cell types, are highly sensitive to selective inhibition of proteasomal Ch-T-like activity. However, not all stages of the parasite are equally PI-sensitive. Most significant parasite killing results were obtained from co-inhibition of multiple *Plasmodium* proteasome catalytic subunits.

Dogovski et al. performed a kinetic analysis to compare drug responses of K13 wild-type and mutant isolates of *P. falciparum*, sourced from the Cambodian Pailin province (Dogovski et al., 2015). The authors determined that artemisinin slows parasite proliferation and induces Ub-protein conjugate levels. Interestingly, drug-resistant parasites exhibited a lower amount of Ub-conjugates as well as delayed onset of death. Carfilzomib strongly synergized with artemisinin activity against both sensitive and resistant parasites and synergy was observed against *P. berghei in vivo*. Kirkman et al. identified inhibitors with improved selectivity for the malarial proteasome $\beta 5$ subunit over each active subunit of human proteasomes (Kirkman et al., 2018). The agents killed *Plasmodium* at all stage of the life cycle and interacted synergistically with both artemisinin and a $\beta 2$ subunit inhibitor. Yoo et al. found that an optimized electrophilic warhead was needed to enable high selectivity and that toxicity was dictated by the extent of co-inhibition of human $\beta 2$ and $\beta 5$ catalytic subunits (Kaiser et al., 2007). The authors identified compounds with >3 orders of magnitude selectivity for *Plasmodium* proteasomes that were optimized for high potency, selectivity, solubility, metabolic stability and oral bioavailability (Yoo et al., 2018). Li et al. employed a substrate profiling technique to detect specificity differences between *P. falciparum* and human proteasomes. They designed inhibitory molecules based upon amino-acid preferences specific to the parasite proteasome, and found that these compounds preferentially inhibited the $\beta 2$ -subunit (Li et al., 2016). They employed cryo-electron microscopy and single-particle analysis at a resolution of 3.6 Å to determine the structure of the inhibitor bound-*P. falciparum* 20S proteasome. Results revealed an unusually open *P. falciparum* $\beta 2$ active site and revealed information to describe the architecture of the active-site as well as information to better refine inhibitor design. Xie et al. characterized potent, specific, amino-amide boronates that inhibited the *P. falciparum* 20S proteasome (Pf20S) $\beta 5$ active site and demonstrated rapid antimalarial activity (Xie et al., 2018). These boronates selectively impaired *P. falciparum* growth compared to human cells and showed significant potency against *P. falciparum* and *P. vivax* field isolates. The compounds also displayed oral efficacy in a murine model of *P. falciparum* malaria. Zhan et al. developed a noncovalent, macrocyclic peptide inhibitor of the malarial proteasome with high species selectivity and favorable pharmacokinetics. The compound specifically inhibited the Pf20S $\beta 5$ catalytic subunit, killed artemisinin-sensitive and -resistant *P. falciparum* isolates *in vitro* and reduced parasitemia in a murine model of *P. falciparum* (Zhan et al., 2021).

As reported by Ng et al., recent advances have lead agents that specifically target the *Plasmodium* proteasome to demonstrate

that targeting the UPP and other non-proteasomal protein clearance pathways to disrupt proteostasis is an attractive avenue to combat drug resistance (Ng et al., 2017).

Proteasome Inhibitors to Treat Bacterial Infections

Mycobacterium tuberculosis (Mtb), a highly lethal bacteria, is the focus of numerous active pharmaceutical development programs. The estimated incidence of TB suggests that ~10 million people fell ill with disease in 2020 (<https://www.who.int/publications/digital/global-tuberculosis-report-2021>). The global number of TB deaths increased between 2019 and 2020 from ~1.2 million to 1.3 million among HIV-negative people and from 209,000 to 214,000 among the HIV-positive (<https://www.who.int/publications/digital/global-tuberculosis-report-2021>). While the disease can be managed, many individuals develop drug resistance after attempting the first line of drug therapy- rifampicin, pyrazinamide, isoniazid, and ethambutol (<https://www.who.int/publications/digital/global-tuberculosis-report-2021>). Unfortunately, many TB patients do not have access to the care needed to maintain these treatments and two forms of drug resistant TB exist, multi-drug resistant TB described as resistance to rifampin and isoniazid, and extensive drug resistant TB described as disease refractory to rifampin and isoniazid, any fluoroquinolone, and one or more second-line drug.

Mtb require a functioning proteasome to elicit disease and encode a proteasome that is necessary for fatal effects in mice. Lin et al. sought to develop *Mtb*-selective PIs and identified oxathiazol-2-one compounds (Lin et al., 2009). These agents are cytotoxic to non-replicating Mtb and act as suicide-substrate inhibitors of *Mtb* proteasomes by cyclocarbonylating the active site Thr. A high-throughput, natural compound library screen detected fellutamide B, a lipopeptide aldehyde, as a potent inhibitor of *Mtb* proteasomal activity (Lin et al., 2010). An *in vitro* screen of ~20,000 compounds detected 2 oxathiazol-2-one compounds, GL5 and HT1171, which effectively inhibit *Mtb* proteasomes (Totaro et al., 2017). Using a model of nitroxidative stress that induces a pathologically relevant state of dormancy, GL5 and HT1171 also generated concentration-dependent *Mtb* death, whereas there was no apparent cell death in mammalian cell lines at comparable or higher concentrations. Kinetics experiments showed that GL5 and HT1171 were >1,000-fold more effective against *Mtb* proteasomes than human proteasomes to support species-specific selectivity. Using a molecular docking and simulation approach, Tyagi et al. screened a small molecule library from Medicines for Malaria Venture against the proteasome (Tyagi et al., 2022). They identified MMV019838 and MMV687146 which actively interacted with the catalytic domain of *Mtb* proteasomes and inhibited *Mtb* growth *in vitro*. Furthermore, their studies demonstrated strong and stable interaction of these molecules with *Mtb* proteasomes compared to that observed with human proteasomes.

Proteasome Inhibitors to Treat Other Parasitic Infections

Proteasomes have been isolated and studied in *Giardia*, *Entamoeba*, *Leishmania*, *Trypanosoma*, *Plasmodium* and *Toxoplasma* spp.; all

protozoan parasites of medical importance (Robertson, 1999; Shaw et al., 2000; De Diego et al., 2001; Makioka et al., 2002; Paugam et al., 2003; Khare et al., 2016). Lactacystin demonstrates wide-ranging activity *in vitro* blocking the growth of *Entamoeba histolytica* and *E. invadens* (Makioka et al., 2002; Paugam et al., 2003). In *L. mexicana*, the proteasome regulates the cell cycle and is essential for growth (Robertson, 1999). Surprisingly, lactacystin did not inhibit the *Leishmania* proteasome *in situ*. The proteasome has also been explored in the causative agent of Chagas disease, *Trypanosoma cruzi* (De Diego et al., 2001). GNF6702 is a selective inhibitor of the kinetoplastid proteasome, demonstrated unprecedented *in vivo* efficacy, cleared parasites from mice in 3 infection models and was well-tolerated (Khare et al., 2016). Importantly, GNF6702 did not inhibit the mammalian proteasome (Khare et al., 2016). Proteasomes are also active within the intracellular pathogen *Toxoplasma* during development and replication, representing another setting for PI therapy (Shaw et al., 2000).

CONCLUSIONS AND PERSPECTIVES

Features of the UPP are conserved throughout evolution from *Archaea* to humans. The proteasome represents an essential component of cellular biology and is a clinically validated, actionable target that can be pharmacologically modulated to treat human diseases. FDA-approved PIs have significantly improve the quality-of-life and overall survival of those afflicted with MM. Plasma cells are antibody-producing factories that synthesize and secrete vast amounts of immunoglobulins, and hence, are highly dependent on mechanisms that maintain proteostasis. Pharmacologic blockade of the UPP highlights the hypersensitivity of MM cells to agents that disrupt the delicate balance of protein synthesis and degradation. Similarly, that same rationale has been applied for the off-label use of proteasome and immunoproteasome inhibitors to target plasma cells that contribute to antibody-mediated rejection that precludes organ transplantation and autoimmune diseases (Johnson et al., 2017; Woodle et al., 2017; Schmidt et al., 2018; Xi et al., 2019; Woodle et al., 2020). KZR-616 is a first-in-class selective inhibitor of the immunoproteasome, which is active in >15 autoimmune disease models, including murine models of systemic lupus erythematosus (SLE) and lupus nephritis (LN) (Muchamuel et al., 2018; Xi et al., 2019). Selective inhibition of the immunoproteasome modulates both innate and adaptive immune effector cells, resulting in reduced inflammatory T helper cell subsets (Th1 and Th17), increased T regs, and decreased plasma cells and autoantibodies.

More effective drugs are urgently needed to treat parasitic diseases that persist as global health threats and leading causes of death, especially in the developing world. Proteasomes contained within pathogenic organisms possess a structural architecture and Ch-T-like active sites similar to that described in eukaryotic forms that are readily accessible and sensitive to pharmacologic inhibition. However, agents intended to target proteasomes in pathogenic microbes must spare human proteasomes to prevent unwanted toxicity and immunosuppression. Moreover, drug

resistance inevitably emerges during the course of treatment in MM patients through a multitude of molecular mechanisms (Driscoll and Brailey, 2017; Bo Kim, 2021). PIs that target malaria and Tb may potentially have a greater value for the treatment of patients that have developed resistance to current, standard-of-care agents. Since malaria and Tb affect individuals in the developing world, often children and those of child-bearing age, PIs to treat these diseases need to be not only orally bioavailable, cost-effective and curative following a short treatment course but also safe and non-teratogenic as well. As witnessed by advances over the past two decades in oncology, PIs offer potential as transformative agents in the treatment of infectious diseases in the upfront setting or when standard-of-care agents are ineffective and drug-resistant disease has emerged.

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AUTHOR CONTRIBUTIONS

JD, JI-H and EM developed the concept for the article, prepared the figure and table, wrote and edited the review. Each author made a substantial contribution to the manuscript and approved the final version. All authors contributed to the article and approved the submitted version.

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