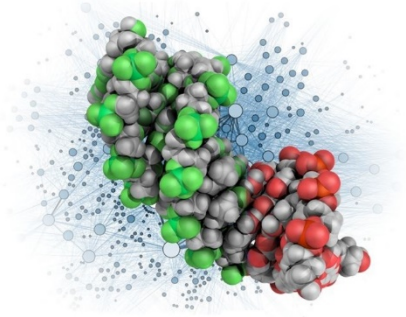

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Mapping the conformational and structural regulators involved in the inhibition of the human 20S proteasome inhibitors

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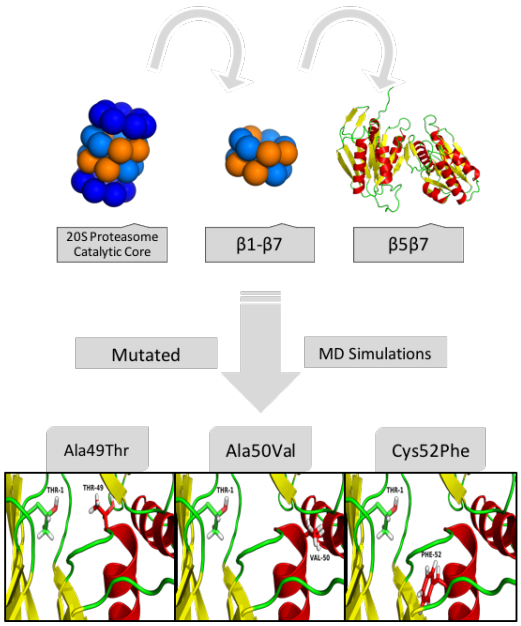
Graphical Abstract *(mandatory)*



Abstract. *(mandatory)*

The Ubiquitin Proteasome Pathway (UPP) plays a pivotal role in intracellular protein degradation and turnover in eukaryotic cells.[1] Therefore, modulation of the UPP emerged as a rational therapeutic approach in cancer, neurodegenerative diseases (Alzheimer, Parkinson), inflammatory pathologies (arthritis, psoriasis, asthma, colitis), organ transplant, infective diseases (malaria), among others.[2]

During the last two decades academia and pharmaceutical industry made huge efforts to develop natural and synthetic proteasome inhibitors (PI). In 2003 FDA approved the pioneering dipeptidyl boronic acid derivative PI bortezomib for the treatment of refractory multiple myeloma (MM) and subsequently frontline therapy for MM. However, despite the enormous potential of PI, their use is still limited to certain types of blood cancer and shows severe side effects, dose limiting toxicity, peripheral neuropathy, limited activity in solid tumour and innate or acquired drug resistance.[3]

In this work, we have used Molecular Dynamics (MD) simulations to perform the first conformational and structural characterization of the human native 20S proteasome structure[4]. We focused our analysis on the three catalytic subunits well known for their proteolytic activity (β1, β2 and β5) and we further extended our study to additional MD simulations of three different point mutations in the β5 catalytic subunit, with recognized importance in PI's resistance: Ala49Thr, Ala50Val and Cys52Phe. Hopefully, our studies will be able to shed the light on the structural key determinants that regulate the observed PI's resistance in

	the different mutations, and ultimately use the acquired knowledge in the development of new alternative and efficient proteasome inhibitors.

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