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cancer biology phd program

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MAIN FIELDS OF RESEARCH; ABSTRACT

Multiple Myeloma (MM) is a clonal disease of plasma cells that accounts for more than 10% of all hematological malignancies. In MM, plasma cells accumulate in the bone marrow and secrete high amount of monoclonal immunoglobulin that can be clinically detected in the serum and urine of patients. The outcome of MM patients has been significantly improved with the introduction of Bortezomib (Btz), the first proteasome inhibitor (PI) approved by FDA since 2003. PI-based new treatment regimens prolonged the overall survival of MM patients from 3 to 4 up to 7 to 8 years [1, 2]. The proteasome is a barrel shaped protein complex, consisting of three active subunits with substrate specific enzymatic activity: β1, β2 and β5 (caspase-like, trypsin-like, chymotrypsin-like activity), which ensures protein turnover and homeostasis in the cell. The degree of cytotoxicity of PI varies with the degree of co-inhibition of proteasome subunits β1, β2, β5 for constitutive and β1i, β2i and β5i for immunoproteasome. Btz is a backbone of current myeloma therapy. However, myeloma therapy is not curative in the majority of cases, and most patients still die from relapsed-refractory myeloma that is no longer responsive to proteasome inhibition. Thus, Btz resistance (either as primary resistance or as secondary, acquired resistance) is an eminent clinical problem. Efficacy of approved drugs in this population (Pomalidomide or Carfilzomib, (Cfz), a next-generation, irreversible PI) is only in the 20-30% range. The biology of proteasome inhibitor resistance is poorly understood and further improvements in the use of PI as cancer treatment are needed.
In cooperation with the group of prof. Herman Overkleeft from University of Leiden (Leiden Institute of Chemistry, Bio-organic Synthesis), our group has developed a unique tool for analysis of the activity of proteasome β-subunits, based on activity based fluorescent probes (ABP). These probes, tagged with fluorochromes selectively bind to the active side of the β-subunits, thereby visualizing the activity of the individual proteasome subunits. In combination with adapted MM cells to proteasome inhibitors (resistant cell lines AMOaBtz, AMOaCfz) and the use of high throughput "OMICS" methods (gene expression profiling, proteomics and metabolomics) we try to understand, describe and overcome the acquired resistance to proteasome inhibitors.
My project is in particular focused on: 1) the comparison of currently clinically available proteasome inhibitors and defining the most potent pattern of inhibition 2) deeper characterization of the metabolism based resistance to PI 3) Carfilzomib resistance based on ABCB-efflux pump upregulation and possibilities based on clinically relevant and available drugs

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