Therapeutic Applications of Small Molecule Proteasome Activation

Hematologic malignancies are comprised of multiple subtypes including, multiple myeloma (MM), mantle cell lymphoma (MCL), acute myeloid leukemia (AML), histiocytic neoplasms, non-Hodgkin lymphoma, Hodgkin lymphoma, and many others. The current front-line therapies for MM and MCL include the proteasome inhibitors, bortezomib or carfilzomib. These drugs elicit their anti-cancer activity by blocking protein degradation, resulting in the toxic accumulation of redundant proteins. Despite the FDA approval of these new drugs, patients still have a poor prognosis, with a 5-year survival of 30-50%. Moreover, nearly all patients (>98%) relapse, with survival at that stage often < 1 year. Mechanistically different therapies are urgently needed.

We are exploring a new chemotherapeutic approach that, instead of inhibiting protein degradation, enhances protein degradation. The approach specifically targets amplified cancer driving proteins, and translates well in a range of cancer cells (including bortezomib resistant cells), *in vivo* MM xenografts, and appears to be extremely well tolerated in mice and dogs. In collaboration with Prof. Vilma Yuzbasiyan-Gurkan at MSU's College of Veterinary Medicine, we are now initiating a canine clinical study in companion animals with naturally occurring cancers to validate and de-risk this new therapeutic strategy.