Novel biologically-based therapies for Waldenstrom's Macroglobulinemia (WM).

C.S. Mitsiades, N. Mitsiades, S.P. Treon, K.C. Anderson.
Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

Despite recent progress in its therapeutic management, WM remains an incurable B-cell malignancy and the development of novel treatment strategies is urgently needed. To address this need, we have embarked on the characterization of a series of targeted approaches against WM. This clinically-oriented research effort has built on our experience on bed-to-bedside translational studies for multiple myeloma (MM) and have allowed us to identify a constellation of novel classes of anti-WM, such as the proteasome inhibitor PS-341; the ansamycins family of inhibitors (e.g. geldanamycin and its analogs) of the hsp90 molecular chaperone; the histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA); the thiazolidinedione group of PPAR-γ agonists (e.g. ciglitazone or rosiglitazone); the inhibitors of the HMG-CoA enzyme (e.g. lovastatin). Pre-clinical data from our ex vivo studies show that these classes of agents induce growth arrest and apoptosis of WM cells (including both the WM-WSU cell line, as well as tumor cells freshly isolated from WM patients). To gain insight into the molecular mechanisms of action of these agents, we have characterized the transcriptomic and proteomic profiling of the signaling state of WM-WSU cells treated with members of the respective classes of agents. These studies, coupled with bio-informatic analyses and confirmatory mechanistic studies, have allowed us to document a series of overlapping molecular features of some of these classes of agents (e.g. effect of proteasome inhibitors and hsp90 inhibitors on NF-κB activity, decreased expression of inhibitors of apoptosis (IAPs) upon treatment with proteasome inhibitors, hsp90 inhibitors and thiazolidinediones, et.c.). On the other hand, distinct molecular sequelae induced by some agents (e.g. hsp90 inhibitor-induced depletion of intracellular levels of several kinases implicated in growth/survival cascades, multi-factorial impact of SAHA on gene expression profiling et.c.) suggest that novel therapeutic strategies for WM can be designed to include combinations of these agents, to simultaneously target multiple levels of diverse pathways important for tumor cell growth and survival, and thus maximize the pro-apoptotic activities of these agents and/or neutralize protective responses of WM against their effects. These molecular studies are therefore providing the framework for rational design of the next generation of combination therapies for WM.