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**Novel biologically based therapies for Waldenstrom's macroglobulinemia.**

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Waldenstrom's macroglobulinemia (WM) remains an incurable B-cell malignancy, necessitating urgent development of novel treatment strategies. Building on our experience on bed-to-bedside translational studies for multiple myeloma (mm), we identified a constellation of novel classes of anti-WM agents, including the proteasome inhibitor PS-341; the ansamycin family of inhibitors (eg, geldanamycin and its analogues) of the heat-shock protein 90 (hsp90) molecular chaperone; histone deacetylase inhibitors, such as suberoylanilide hydroxamic acid (SAHA); and the thiazolidinedione group of peroxisome proliferator-activated receptor-gamma (PPAR-gamma) agonists (eg, ciglitazone or rosiglitazone). Our preclinical data show that these classes of agents induce growth arrest and apoptosis of WM cells, at concentrations relevant to those achieved in previous clinical uses of these drugs, and 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 provide a framework for rational design of the next generation of combination therapies for WM. Copyright 2003 Elsevier Inc. All rights reserved.