Does Myeloma Have an Achilles Heel?

Kenneth C. Anderson, M.D. Dana-Farber Cancer Institute and Harvard Medical School

Identification of novel targets and validation of novel agents in models of multiple myeloma (MM) in the bone marrow (BM) have translated to clinical trials and FDA approval of immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies (MoAbs) and histone deacetylase(HDAC) inhibitors. Scientifically-informed combination therapies have achieved high rates of durable responses, and 3 to 4 fold prolongation of survival. We are targeting 3 Achilles heels in MM to further progress. Firstis targeting the ubiquitin proteasome cascade with new next-generation chymotryptic PI (carfilzomiband ixazomib) and chymotrypic, tryptic and caspase-like PI (marizomib). To overcome PI resistance in MM, b-AP15 targets upstream deubiquitylating enzymes (DUBs) USP14/UCHL5 upstream of the proteasome. We have developed HDAC6 selective inhibitor of the alternative aggresomal degradation pathway,which achieves responses in relapsed refractory MMin combination with either PI or IMiDs.Finally, we are synthesizing degronimidsto activate ubiquitin 3 ligases and degradation of selective substrates. The second Achilles heel is overcoming immune suppression in MM. IMiDs directly trigger MM cell apoptosis, abrogate adhesion to the BM, modulate cytokines, and inhibit angiogenesis; as well as augment T cell, NK cell, and NK-T cell function, while downregulating T regs. They increaseADCC and clinical activity of MoAbs(elotuzumab, daratubumab, and SAR650984)and immunotoxin (indatuximabravtansine). MM cells and accessory cells (myeloid derived suppressor cells MDSCs and plasmacytoid dendritic cells pDCs) express PD-L1, whereas immune effector T and NK cells express PD-1. Anti-PD-1 Ab and anti-PD-L1 induce autologous effector cell MM cytotoxicity, which is enhanced by IMiDs.HDAC6 inhibitor also augments autologous MM cytotoxicity and adds to MoAb and PD-L1Ab. Finally, peptide-and cell-based vaccine strategies can induce anti-MM immunity and are being evaluated in smoldering MM to block progression and to treat minimal residual disease posttransplant, respectively. Specific immune responses to vaccination can be enhanced by lenalidomide and/or checkpoint inhibition; and HDAC6 inhibitor augments autologous memory cytotoxic T cells. Combinations of immune approaches therefore have great promise.Finally, our genomic/epigenomic studies have identified extensive and complex DNA damage and no predominant mutations, with ongoing DNA damage underlying development of drug resistance and relapse. Multiple clones are present from the outset, with clonal evolution in multiple patterns underlying relapse. The third Achilles heel is targeting the biologic consequences of these biologic abnormalities. We identified a subset of MMwith decreased YAP1 copy number which survives despite high levels of constitutive and ongoing DNA damage, since YAP1 does not bind nuclear ABL1 and trigger downstream apoptosis; conversely, knockdown of STK4 upregulates YAP1 and P73-mediated apoptosis.A subset of MM with cMyc amplification and adverse prognosis has high levels of replicative stress and reactive oxygen species; combining therapeutic agents to block ATR with agents to induce ROS triggers synergistic apoptosis.Finally, KDM3A, a Jumonji C-domain containing histone demethylase, is elevated and essential for MM cell survival, and that KDM3 inhibition blocks KDM3A-KLF2-IRF4autoregulatory loop. Targetting these vulnerabilities offers therapeutic strategies to improve patient outcome even further.