IMS-IL-4 **Progress toward Identification and Development of Therapeutics in Protein Homeostasis**

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The Ubiquitin Proteasome System (UPS) is essential for maintaining cellular protein homeostasis (PH) in eukaryotic cells. The UPS mediates the degradation of key regulatory proteins involved in a diverse range of critical cellular functions such as repair of DNA damage, cell cycle, and apoptosis. Furthermore, the UPS along with autophagy clears the cell of potentially harmful mis-folded or aggregated proteins. Defects in the UPS result in up-regulation of response mechanisms to endoplasmic reticulum (ER) stress such as the Unfolded Protein Response (UPR). The discovery of bortezomib, an inhibitor of the proteasome, has demonstrated that cancer cells have the potential to be more dependent on a fully functional UPS than normal cells. The dependency of certain cancers on the UPS and overall protein homeostasis has made this an attractive area for novel targets and therapeutic intervention. Over the last decade, we been conducting research on several nodes involved in maintaining PH. Pevonedistat (MLN4924) is an inhibitor of the Nedd8 Activating Enzyme (NAE), which regulates a branch of the UPS, is currently in a phase 1b trial in combination with azacitidine. Most recently, Takeda has commenced a phase 1 trial in solid cancer with MLN7243, an inhibitor of the Ubiquitin Activating Enzyme (UAE), a master regulator of protein ubiquitination. In this presentation, we will describe our progress toward the identification of new agents in PH with diverse mechanisms of action and the potential to address a broad range of malignancies.