P006 Identification of novel inhibitors of deubiquitinating enzymes

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Dysregulation of DUBs has been implicated in a wide range of pathologies including cancer, neurodegeneration, and viral infection. Progenra has developed a novel assay to measure the proteolytic cleavage of ubiquitin or UBL (ubiquitin like protein) conjugates such as SUMO, NEDD8 or ISG15 by isopeptidases. More than 100 isopeptidases have been reported in the literature and we have tested many of these in the Progenra platform. Utilizing our proprietary assay we have screened a library of small molecules to identify inhibitors of the therapeutically relevant DUBs USP2a and USP7. Hits from these screens have been profiled in a number of secondary assays, focusing on selectivity against other DUBs, and cell-based assays designed to identify and profile compounds for preclinical development. The lead compounds are being developed as clinical candidates for novel therapeutics targeting USP2a and USP7. In addition to the compounds in preclinical development, a number of small molecules were found to be inappropriate for further development, but have potential as tool compounds aiding the dissection of the complex ubiquitin-proteaseome system. We will discuss data leading to the discovery of these compounds and give examples of how the compounds may be used broadly as research tools.