

Inhibitors of Ubiquitin-Specific Protease, the other side of the mountain

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Deregulations of the ubiquitin/proteasome system have been implicated in the pathogenesis of many human diseases, including cancer. The approval of the proteasome inhibitor Velcade[®] establishes this system as a valid target in cancer therapy. A promising alternative to targeting the proteasome itself would be to interact at the level of the upstream, ubiquitin conjugation/deconjugation system to generate more specific, less toxic anticancer agents.

A genome-wide RNAi screen of human Ubiquitin-specific proteases (USP) for cancer-relevant phenotypes identified a few USP as potent regulators of cell cycle, proliferation and/or survival of cancer cells. These thiol proteases mediate the specific removal and processing of ubiquitin from substrate proteins by cleaving isopeptidic bonds involving the C-terminus of ubiquitin. We developed advanced HTRF[®]-based substrates and assays to screen for inhibitors of USPs and identify the first drug-like small molecule inhibitors of this novel class of tumor molecular target.

In addition to targeting the USP catalytic core, Hybrigenics takes advantage of its functional proteomic platform to identify interactions between USPs and their specific substrates and/or cofactors. These interactions are then functionally validated and eventually screened for small molecule inhibitors using dedicated HTS-compatible, HTRF[®] assays.

In this field and in others, we developed a validation pipeline for protein-protein interaction using HTRF[®]-based biochemical assays. This validation process is also a direct entry point for assay optimisation and screening for small molecule inhibitors of protein-protein interaction.