“Development of Small-Molecule STAT6 Degraders”

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Signal transducers and activators of transcription (STAT) proteins are second messengers in the JAK/STAT signaling pathway. In normal cells, inactivated STATs are continuously shuttled between the cytoplasm and the nucleus. Activation of STATs occurs in the following manner. First, phosphorylation of a tyrosine residue on Janus-activated family kinases (JAK) occurs in response to the binding of cytokines, growth factors or hormones to a series of extracellular receptor proteins. Then, activated JAKs recruit and activate STATs via phosphorylation. The tyrosine phosphorylation of STATs in response to interleukin 4 (IL-4)/IL-13-stimulated receptor-tyrosine-kinase in the Janus kinase-mediated signaling results in subsequent STATs dimerization. Dimerized STATs accumulate in the nucleus, where they act as transcriptional transactivators. Among the STAT family members, the role of STAT6 in human cancers isn’t well understood. However, accumulating reports show that over-expressed STAT6 participates directly in tumorigenesis in prostate and colon cancers as well as lymphoma and leukemia. Furthermore, it was suggested that STAT6 plays a critical role in tumor invasion and metastasis. STAT6 is also indispensable for inflammatory responses mediated by IL-4 and IL-13.

Drug development targeting transcription factors, such as the STAT family members, remains challenging since they interact with other proteins through large interfaces that do not have well-defined pockets to bind small organic molecules at high affinities. However, a novel approach for inhibiting these proteins has emerged from a discovery made by the McMurray group. Although STATs lack conventional enzymatic activity, they contain functional domains such as Src homology domain 2 (SH2 domain). Binding of SH2 domain to phosphorylated tyrosine in STATs results in transcriptionally active homo- and hetero-dimers. McMurray and colleagues exploited this domain and reported phosphopeptide mimetics that potently disrupt the phosphorylated STAT6 proteins at low nanomolar concentrations. Nevertheless, efforts need to be made for further improvement in the potency and selectivity of inhibitors targeting STAT6.

One strategy to improve the efficacy and selectivity would be to use a technology called proteolysis targeting chimeras (PROTACs) that consists of two linked protein binding molecules, one capable of engaging an E3 ubiquitin ligase and the other to a target protein meant for degradation by the endogenous protein degradation machinery. Our long-term goal is to develop a highly potent and selective PROTAC molecule targeting STAT6. In this seminar, the preliminary work done in the past 6 months to test our idea will be presented.