CLASSICAL INHIBITORS VS. PROTACs TARGETING GALECTIN-8

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Galectin-8 (Gal-8), a tandem-repeat galectin, is involved in a number of physiological processes such as cell adhesion, proliferation, cell signalling, autophagy, and differentiation, as well as in a number of diseases, including fibrosis, cancer, and heart disease, making it a target of interest for highly selective and potent Gal-8 inhibitors [1]. These inhibitors follow a rather traditional principle of occupying one of the carbohydrate binding sites of Gal-8, which directly inhibits the protein's function by a competitive binding mechanism. The current issue with these classical Gal-8 inhibitors is their rather modest potency, with inhibitory or binding constants that mostly reach the low micromolar concentration range, although our group just revealed inhibitors that reach high nanomolar K_d values [2].
Proteolysis targeting chimeras (PROTACs) have recently emerged as small-molecule modalities that hijack the cell's degradation pathway (ubiquitin–proteasome system) to selectively induce degradation of a specific protein of interest [3]. Most importantly, they control the pathological effects of proteins by lowering their intracellular concentration rather than by classical inhibition, and as a consequence, PROTACs do not follow the classical dose-response pharmacodynamic effect. The current state-of-the-art in the design of PROTACs focuses mostly on intracellular proteins, yet Gal-8 (like many other galectins) exists both as an intracellular and an extracellular protein, which makes it a potential target for PROTACs-induced degradation. We have designed and synthesized a series of PROTACs designed to target Gal-8 and CRBN or VHL E3 ligases. These molecules were assayed for their Gal-8 and Gal-3 degradation in MD-MB-231 and HUVEC cell lines. PROTACs were further compared with classical inhibitors by using a tube formation assay [4] as a phenotypic assay to screen molecules for their anti-angiogenic effect. To the best of our knowledge, there is no PROTAC developed to trigger proteolysis of a protein that exists both in extracellular and intracellular space by depleting its intracellular pool. Therefore, this important question was addressed for the first time and the results of our work will be shared at EUROCARB22.

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