A Generic Approach to Cell-specific Induced Degradation of Intracellular Proteins

Today’s therapies are based on the direct binding of a drug to target proteins. For clinically relevant effects to manifest, drugs therefore need to bind a significant portion of target protein for extended periods of time. This is often limited by binding affinity as well as effective drug concentration at the site of action. A drastically different, event-based approach is represented by a novel class of drugs that, upon binding, result in the enzymatic destruction of their target protein. Such drugs can engage in multiple rounds of target destruction, finally alleviating the limiting paradigm of a one-to-one binding ratio. We therefore aim to create a novel platform enabling the rapid generation of degradation-inducing drug-like molecules against intracellular targets that have until now evaded drug discovery efforts.

These bispecific molecules (specific for both the target as well as a particular degrading enzyme) enable the specific destruction of a chosen intracellular protein through redirecting the cell’s own protein degradation machinery. One specificity is conferred by an antibody-like selected protein binder (DARPin) and is responsible for target binding, while the second is provided by a small molecule or peptide, capable of recruiting components of the cell’s protein degradation machinery. The use of antibody-like entities for target specificity represents a stark contrast to other approaches that are currently being considered elsewhere, as they are independent of the target presenting a binding site for small molecules (i.e., being ‘druggable’).

Date & time: Thursday, December 14, 2017 at 05:00 pm
Location: Lecture Hall Y44-H-05, UZH Irchel

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