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Main Fields Of Research; Abstract

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 in such occupancy-based mechanisms. 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 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'). In our approach, redirecting the system against a different target is possible through a facile exchange of the binder, giving the system a completely generic character. The second novelty lies in the unique fact that the employed binders are capable to be efficiently delivered to the cytosol in a cell-specific manner using bacterial import mechanisms recently developed in our laboratory.

To be able to improve the degradation strategy independent and in parallel to improving the uptake strategy, a custom microinjection setup, combined with high-content imaging techniques from the Center for Microscopy and Image Analysis (CMIA), is developed to, for the first time, accurately determine degradation rates as well as the system's catalytic character in living cancer cells. Only this novel detailed observation of such parameters will enable the full potential of protein engineering – the core competence of our laboratory – to be harnessed to rationally design this novel therapeutic approach.

Special Techniques And Equipment

Quantitative High-throughput live-cell fluorescence microscopy and subsequent efficient automated data analysis using CellProfiler, Matlab and R.