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Novel therapeutic strategies targeting the inside of cells

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We designed novel genetic approaches as well as fusion proteins providing a cell-specific delivery of intracellular regulators of immune activation. We present the world's first protein knockdown mouse, by the use of intrabodies, and regulated antigen peptide cross-presentation by Sec61 using intrabodies. Further, the E-selectin-specific ,"Sneaking Ligand" fusion protein inhibited NF-kB by interfering with endothelial IkB kinase 2 activity inside the cells *in vitro* and *in vivo*. The treatment drastically reduced the extravasation of inflammatory cells murine experimental peritonitis and significantly ameliorated the disease course in murine models of rheumatoid arthritis. Being able to access disease targets, which are not on the outside of the cell with biological, opens up a whole new area of therapeutic interventions. We present our different approaches how to achieve this. We hope to inspire the biologics engineering community to start thinking out of the box by opening doors to targets which so far could not be reached inside the cell, and to add extra punch or extra safety to biologics by targeting a combination of two disease specific features.

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