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Targeting proteins to engineer cell function

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Proteins are often the final executors of function. Because function is determined by many aspects that are specific to the protein level and cannot be studied by knockout at the gene- or RNA level, such as splice variants, post translational modifications, protein quantity and protein dynamics, more approaches are required that target proteins directly. Intracellular antibodies (intrabodies) can knock down functions by acting at the protein level and we present a new, generally applicable strategy based on intrabodies that allows gradual quantitative tuning of membrane-receptors or secreted proteins. We demonstrate knockdown at the protein level for five different targets in a standardized, comparable *in vitro* system. In the world's first transgenic intrabody mouse that we generated, the ablation of VCAM1 by an intracellular antibody resulted in aberrant localization of B cells in adult animals. Our transgenic mice showed a phenotype in adult mice, but were viable although genetic knockouts are lethal. In translational approaches, intracellular antibodies can in the future provide the advantage of a more targeted interference avoiding off-target effects in contrast to the systemic effect of classic antibody-therapy.