

Guest Editorial

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Protein engineering & design: hitting new heights

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Tailor-made proteins are playing a pivotal role in a plethora of different applications such as in biomedicine, in the chemical as well as food industry or in cosmetics. In a commonly used definition, the discipline ‘Protein Engineering’ describes the (more or less) targeted modification of already existing proteins, for instance, to enhance their biophysical or biochemical properties, whereas ‘Protein Design’ aims at generating artificial proteins displaying novel forms and functionalities. Presently engineered proteins affect the daily life of most of us – in fact with many of us often not even being aware of it. For example, engineered enzymes are exploited in order to process food or as ingredients in laundry detergents. A more obvious field in which protein engineering has made a tremendous impact is medicine. Many diagnostic reagents as well as the vast majority of biological therapeutics are engineered in one way or the other. A very prominent example of biomedical modalities are therapeutic antibodies. As of now, more than 100 antibodies have been approved by healthcare authorities. The vast majority – if not all – are artificially optimized molecules, for instance by humanization, by removal of sequence liabilities or by changes that improve the affinity for a cognate antigen. Furthermore, immunoglobulin-based derivatives that were engineered in a more sophisticated way are entering the clinical pipeline and the global market. Bispecific antibodies, for instance, bind two different antigens simultaneously thereby enabling to address the multifaceted nature of many diseases more adequately. Other approaches, such as antibody drug conjugates or prodrugs, aim at specifically activating the toxic properties of the therapeutic directly at the site of disease e.g. at the tumor tissue or the malignant cell to improve patient safety. Besides antibodies, also other protein-based molecules have proven to

be of utmost relevance regarding therapeutic or diagnostic applications. These include engineered enzymes or proteins that can be found in nature but that are optimized or tailor-made to fulfill a specific function. Within the past years the COVID-19 pandemic has shown that protein engineering is inevitable to understand this and other diseases but also to generate effective therapeutics and vaccines at an unprecedented pace. The recent developments in protein structure prediction and computational design promise to speed up these exciting developments even further. Therefore, we feel it is timely to place a special focus on this topic.

This Highlight Issue of *Biological Chemistry* is dedicated to novel trends in the field of Protein Engineering and Protein Design. Here, we provide a compilation of cutting-edge articles covering various aspects of tailor-made proteins ranging from antibody hit discovery via multispecific antibodies, antibody fusion proteins as well as prodrug approaches to antibody drug conjugates. Additionally, scaffold proteins, i.e. naturally occurring proteins engineered to comprise novel binding functionalities, as well as modular peptide binders as complementary modalities are discussed. The portfolio continues with insights on design principles for the generation of photo-controllable proteins. Finally, also the ongoing pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) found its way into this Highlight Issue. These excellent, peer-reviewed contributions nicely show the different approaches taken in the field and reflect the broad applicability of protein engineering and design.

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