The Impact of Protein Engineering on Modern Therapeutics

Michael Anderson[*]

Department of Biotechnology, University of Sydney, Sydney, Australia

DESCRIPTION

Protein engineering has become a powerful tool in therapeutic development, enabling the design of proteins with improved stability, specificity and activity. By modifying natural proteins or creating entirely new ones, scientists can address limitations of conventional drugs and expand treatment options for a wide range of diseases. One major application of protein engineering is the development of therapeutic enzymes. Enzyme replacement therapies are used to treat metabolic disorders caused by enzyme deficiencies. Engineering these proteins to resist degradation in the body or to function optimally at physiological conditions enhances their therapeutic effectiveness. For instance, engineered enzymes are being developed to treat lysosomal storage diseases by improving delivery to target tissues.

Monoclonal antibodies represent another success story of protein engineering. Through techniques such as affinity maturation and humanization, antibodies can be optimized for higher binding specificity and reduced immunogenicity. Antibody-based therapies are now widely used for cancer, autoimmune diseases and infectious conditions. Advances in antibody engineering have led to the development of bispecific antibodies that can bind two different targets simultaneously, broadening their therapeutic applications. Protein engineering also contributes to the design of novel drug delivery systems. Fusion proteins that combine therapeutic molecules with carrier domains can improve pharmacokinetics and target specificity. For example, antibody-drug conjugates deliver cytotoxic agents directly to cancer cells, sparing healthy tissues and reducing side effects.

Directed evolution, a technique that mimics natural selection in the laboratory, has revolutionized protein engineering. By generating large libraries of protein variants and selecting those with desired properties, researchers can evolve proteins with functions not found in nature. This approach has produced enzymes with industrial and medical applications, including proteins that degrade environmental toxins or catalyze new chemical reactions. Computational design is also transforming the field. Advances in structural biology and bioinformatics allow researchers to predict how amino acid changes will influence protein folding and function. Computer algorithms can design entirely new proteins with specific shapes and functions, opening avenues for creating synthetic molecules tailored to therapeutic needs. Challenges remain in ensuring that engineered proteins maintain stability, avoid immune reactions and can be produced at scale. However, continued progress in protein design and manufacturing technologies is addressing these issues. Regulatory frameworks are evolving to ensure safety and efficacy while supporting innovation.

Protein engineering has already delivered transformative therapies and its impact is set to grow as techniques become more sophisticated. By combining laboratory evolution, computational modeling and advanced screening methods, the future of protein-based therapeutics promises new solutions for diseases that remain difficult to treat with traditional approaches. An exciting frontier in protein engineering is de novo protein design, where proteins are created entirely from scratch rather than modified from natural templates. Unlike traditional engineering approaches that optimize existing proteins, de novo design enables researchers to build proteins with novel structures and functions that do not exist in nature. This approach opens up vast possibilities for creating therapeutic proteins that are optimized for stability, specificity and manufacturability from the ground up. One compelling application of de novo design is the development of new protein scaffolds that serve as alternatives to antibodies. These synthetic scaffolds, such as DARPins (designed ankyrin repeat proteins) or affibodies, can be engineered to bind specific targets with high affinity, similar to antibodies, but are smaller, more stable and easier to produce. Their compact size and robustness make them attractive for applications in cancer therapy, diagnostics and even targeted drug delivery. Additionally, de novo-designed proteins can be tailored to evade immune detection, making them especially promising for chronic diseases where repeated dosing is required.

The integration of synthetic biology with protein engineering further amplifies therapeutic potential. Synthetic biology aims to redesign existing biological systems or create entirely new ones

Correspondence to: Michael Anderson, Department of Biotechnology, University of Sydney, Sydney, Australia, E-mail: michael.anderson@sydneybio.au

using standardized genetic parts. In the context of therapeutics, this means engineering living cells often human or microbial to act as "smart" drug factories or delivery vehicles. For instance, engineered bacteria have been programmed to detect tumor microenvironments and release therapeutic proteins locally, reducing systemic side effects. Similarly, synthetic circuits within engineered immune cells like CAR-T cells can be fine-tuned using protein engineering to better control activation, persistence and tumor targeting. Protein switches, for example, can be designed to activate or deactivate in response to specific molecular signals, adding a layer of control and safety to cell-based therapies.

Moreover, engineered proteins are finding use in immunomodulation, where they are designed to either boost immune activity (e.g., for cancer) or suppress it (e.g., for autoimmune diseases). Cytokines, which are signaling proteins used by immune cells, can be modified to enhance their half-life, reduce toxicity, or improve receptor selectivity. These engineered cytokines are currently being tested in clinical trials for a range of immune-mediated conditions. Looking ahead, the fusion of artificial intelligence with protein engineering is expected to drastically accelerate the discovery of therapeutic proteins. Tools like Alpha Fold have already revolutionized protein structure prediction, enabling scientists to design and test therapeutic candidates with unprecedented speed and accuracy. As protein engineering continues to intersect with synthetic biology, AI and gene editing, its role in shaping the future of medicine will only grow stronger.