Targeted Biologics: The New Frontier for Precision Therapy

Functionalized antibodies, protein substitution, supplementation therapies, and enzyme-based therapeutics are protein-based approaches for the treatment and cure of human genetic and acquired diseases. Gene editing and RNA-based therapeutics, including siRNAs, microRNAs, and antisense oligonucleotides (ASOs), target the machinery that produces disease-associated proteins. Protein-based and RNA-based products are collectively referred to as biologics. This Thematic Issue opens a novel specialized section of Current Medicinal Chemistry focused on targeted biologics at various stages of discovery, preclinical and clinical development. We hope it might encourage the advancement of this field by stimulating researchers to share their results.

Within this issue, readers will find papers discussing the use of replacement proteins therapeutics, with two examples provided. Alpha-1-antitrypsin and C-1 inhibitor (or C1-esterase inhibitor) both belong to the family of serpins and are indicated for the treatment of conditions that result from pathologically low levels or non-functional variants. Alpha-1-antitrypsin is a small protein that inhibits the catalytic action of elastase, a proteolytic enzyme. When the action of elastase is not properly counterbalanced by alpha-1-antitrypsin in the lung, pulmonary emphysema develops. Alpha-1-antitrypsin was approved more than thirty years ago and is used for the treatment of Alpha-1-antitrypsin deficiency. The paper by Bianchera et al. [1] reports on issues associated with alpha-1-antitrypsin production from either animal sources or heterologous expression, focusing on existing and novel protein formulations and delivery strategies.

The C-1 inhibitor is involved in a regulatory network of complement, contact, coagulation, fibrinolytic systems and functions as an anti-inflammatory agent in circulation. C-1 inhibitor is used as a prophylactic or acute treatment in Hereditary Angioedema (HAE), which is a rare genetic disease. The paper by Karnaukhova et al. [4] provides an overview of the biochemical properties of C-1 inhibitor, its role in HAE, recent progress in therapeutic strategies for this disease treatment, as well as potential applications for sepsis, endotoxin shock, antibody-mediated rejection following kidney transplantation, and severe systemic abnormalities related to COVID-19.

During the Vietnam War in the late 1960s, the United States started searching for blood substitutes, such as modified hemoglobin or perfluorocarbon solutions, to replace transfusions when blood was unavailable. Since then, many attempts have been carried out, including the development of chemically and/or genetically modified hemoglobins designed to mimic red blood cells. The paper by Sakai et al. [7] summarizes the intense activities carried out predominantly in Japan towards the development of hemoglobin-containing liposomes. Issues associated with lipids purity, hemoglobin purification, and stability towards oxidation are presented and discussed.

There are many pathophysiologic aberrations associated with genetic variants of hemoglobin, often caused by single amino acid substitutions. One such example is the single amino acid Glu-Val substitution at position 6 of the beta chains, leading to sickle cell disease. Hydroxyurea is a mainstay of sickle cell disease therapy to increase the percentage of fetal hemoglobin. Novel marketed therapeutics are based on compounds either interacting directly with hemoglobin to modulate oxygen binding or altering water-controlling pump systems. Alternative and more recently proposed approaches are based on hematopoietic stem cell transplantation and gene therapy platforms. These approaches are reviewed by Garg et al. [3] which discuss advances in precision therapy for sickle cell disease and the preclinical and clinical advances in autologous hematopoietic stem cell gene therapy.

Breathing is a fundamental function for all living systems. It is made possible in both animals and humans by the presence of pulmonary surfactant, a complex mixture of lipids and proteins secreted into the alveolar lumen. Its role is the maintenance of lung homeostasis to avoid alveolar collapse. In addition, pulmonary surfactant provides a barrier against inhaled pathogens. An insufficient amount of surfactant or its functional inactivation is associated with lung pathologies, including neonatal respiratory distress syndrome. Pioselli et al. [6] reviewed the current state of pulmonary surfactant mimetics in development for replacement therapy. Presently, there are lifesaving products in this class approved for worldwide use in premature infants. Because novel proteins being studied in developmental stages are typically extracted from porcine sources, the production strategies for tailored surfactant proteins by recombinant technologies are being refined. Further, pulmonary surfactants are attractive candidates for synergistic and carrier molecules that enhance the treatment of a variety of respiratory diseases.
Enzymes are biomolecules that catalyze an impressive variety of chemical reactions. A key feature of an enzyme is its specificity for specific substrates. Therefore, it is not surprising that enzymes have been attractive for carrying out selective therapeutic actions. There are two main medicinal strategies based on enzymes: i) supplementation and ii) replacement. Cioni et al. [2] focused on a range of disorders where the supplementation of enzymes to patients provides the basis for therapeutic interventions, including clotting disorders, cystic fibrosis, lactose intolerance, collagen-based disorders, and cancers. Enzymes for therapeutic indications are increasing as a result of advancements in genetic engineering techniques. Typical examples are asparaginase and methionine gamma-lyase, used in cancer therapy to degrade either asparagine or methionine, respectively. The rationale is based on the vital need for these amino acids by cancer cells. Depletion of these amino acids in the cellular environment slows or prevents cancer cell growth, potentiating the efficacy of traditional chemotherapies. Because enzymes are very “fragile” biomolecules, novel strategies are being employed to optimize their stability and delivery. Enzyme replacement therapy is also the focus of the paper by Marchetti et al. [5]. Genetic deficiencies of a specific enzyme can lead to the accumulation of its substrates and toxic effects. For example, Gaucher and Fabry diseases are the first rare genetic lysosomal storage disorders for the treatment of which enzymes were successfully delivered. In these examples, enzymes were initially obtained from animal sources, then produced using recombinant technology with chemical modifications or genetic variants to enhance and extend their activity.

This first issue of the Targeted Biologics represents a small sampling of successful applications of biologics. We are confident that Current Medicinal Chemistry readers will find these examples intellectually stimulating and allow the journal to advance exciting concepts in Biologics for targeted therapy.

REFERENCES


