

# Small peptides for inhibition of central component of immunity: the complement system

**KEYWORDS:** Small peptides, complement immunotherapy, inflammatory diseases, autoimmune diseases, aging disorders.

## INTRODUCTION

The complement system plays a pivotal role in innate and adaptive immune responses (1). It consists of a number of proteins that interact to recognize and kill pathogens or abnormal cells in the body (1). The complement cascade can be activated through three major pathways: classical, lectin, and alternative pathways that converge on complement C3 (1). It leads to the principal effects of complement activation: opsonization, inflammation, immune activation, and formation of the membrane attack complex. The major effectors are i) C3b, an C3 active fragment which tags cell surfaces for removal from tissues or the bloodstream, ii) C3a and C5a anaphylatoxins that recruit inflammatory cells, influence T- and B-cell phenotypes and functions, and modulate the pro-inflammatory microenvironment, and iii) the membrane attack complex that lyse targeted surfaces (1). Excessive or uncontrolled complement activation, either due to an aging immune system or underlying genetic mutations in complement proteins can lead to a wide range of life-threatening or debilitating disorders (2). Such as the inflammatory chronic diseases associated with aging such as chronic obstructive pulmonary disease (COPD), (3) Alzheimer's disease (4), and age-related macular degeneration (AMD) (5), in addition to many autoimmune diseases (5) such as multiple sclerosis; and rare diseases (5) such as paroxysmal nocturnal hemoglobinuria (PNH).

## THERAPEUTIC APPROACH FOR COMPLEMENT IMMUNOTHERAPY

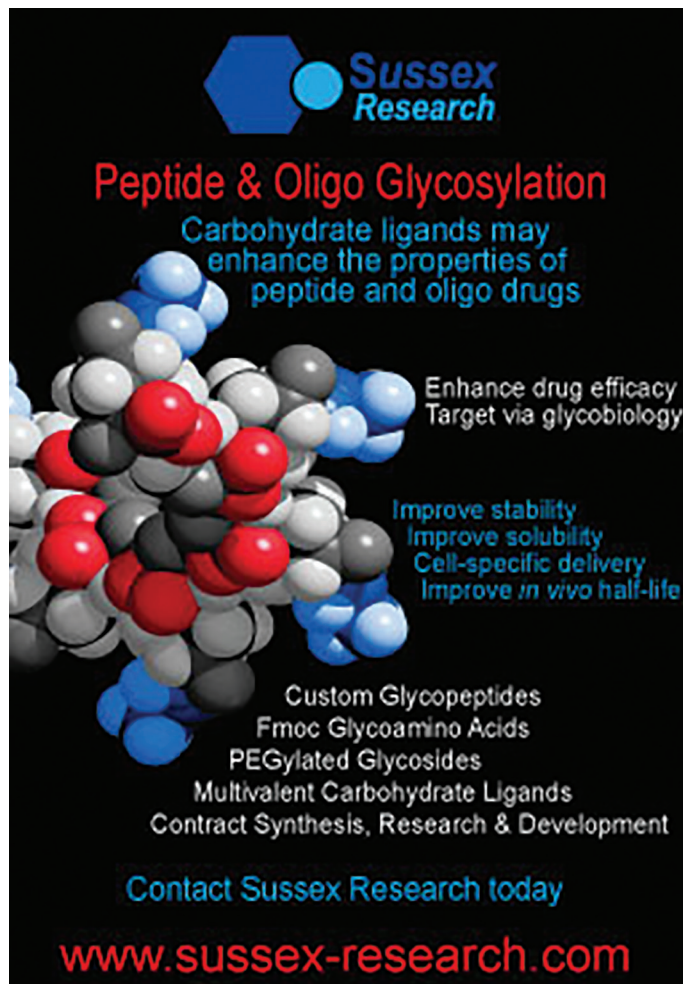
While the complement system has been known to be a major player in many diseases for decades, development of complement-inhibiting drugs has been a challenge with the first FDA-approval in 2007 (6). Since then, a number of complement inhibitors targeting different points in the pathways have entered the clinic (7), including mainly large proteins and antibodies. Although few peptides have been advanced to clinical trials, they represent an attractive approach due to their lower manufacturing cost, ease of delivery, and immunogenicity compared to large proteins and antibodies. Small molecules inhibitors of the complement systems have been developed decades ago and suffered from a lack of selectivity (e.g. many of them cross-reacted with proteins within the coagulation pathway) but peptides have the potential to combine the advantages of highly specific inhibition and ease of formulation and delivery. Peptides are also usually associated with good safety, tolerability, and efficacy. As a result, a number of peptidic complement inhibitors are now making their way into the clinic. The cyclic hexapeptide PMX53 developed by Teva Pharmaceutical inhibits C5a receptor which has the potential to control the inflammatory state of some diseases. The small peptide RA101495 developed by RA Pharmaceuticals, inhibits C5 cleavage and is being developed as a subcutaneous treatment for PNH. Apellis Pharmaceuticals is taking a broader inhibitory approach by targeting C3, the central protein of the complement cascade. APL-1 is an analog of the 13 amino-acid cyclic peptide compstatin (8). C3 inhibition has remained elusive in part because of the very high C3 level in circulation (~6 µM). The stakes are high as inhibition at C3 level may effectively control these diseases by preventing the entire complement cascade and may potentially correct the underlying immunological dysfunction by reprogramming the local immune microenvironment responsible for the autoimmunity and pro-inflammatory mechanisms in these conditions (9). Large proteins or antibodies would require too high of a dose, and smaller molecules don't have the potency, the half-life or the specificity required, so a small peptide like APL-1 might combine the right properties to become a successful treatment.

## CONCLUSION

As the activation of the complement system is a core pathogenic process associated with so many important diseases with large unmet clinical need, peptide-inhibitors of complement have the potential to have a significant impact in improving the quality of life of a broad diversity of patients suffering from these multiple conditions, but remain to reach the market.

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