# Future Prospects of Biologic Therapies for Immunologic Diseases

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**KEYWORDS**

• Asthma • Atopic dermatitis • Biologic • Churg-Strauss syndrome
• Hemophagocytic lymphohistiocytosis • Immune dysregulation • Immunodeficiency
• Mastocytosis

**KEY POINTS**

- Currently used or in-development biologic therapies have unexplored potential in treating various allergic and immunologic disorders.
- There is a substantial need for newer biologic therapies targeting specific disease pathways.
- Biologic therapies represent not only an innovative approach but also a substantial advance to disease management in the twenty-first century.

## INTRODUCTION

Although biologic therapies like insulin have been used for nearly a century, improvements in recombinant technology and production techniques have led to an explosion of biologic therapies over the past 2 decades. Biologic therapies are currently used for

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treating many disease conditions in humans as either an adjunct to conventional therapy or a sole therapeutic intervention. Several of these biologic agents are available on the market in the United States and are approved by the US Food and Drug Administration (FDA) for specific indications.

Outside of approved indications, the use of certain biologics to treat immunologic disease is supported by case series or small studies. In other instances, potential therapeutic benefit may merely be inferred from animal studies or knowledge of the mechanisms of action. The goal of this review is to explore future potential therapeutic use for currently available biologic therapies, based solely on the mechanism of action of the specific agent considered. The pathophysiologic targets and disease states described herein do not represent an exhaustive list. Rather, they represent a selection of potential therapies that may prove useful for the treatment of specific conditions in the near future.

## THERAPIES TARGETING CYTOKINES OR CYTOKINE RECEPTORS

Cytokines are soluble low-molecular-weight proteins that mediate communication between immune cells. As such, they are critically linked to the pathophysiology of immunologic disease.[1] Although there is some degree of overlap in the function of certain cytokines, in general, these proteins function in a predefined circuit. That is, release of given cytokine from a specific cell source will trigger a specific effector function by the receiving cell (**Table 1**). This makes cytokines an attractive target for therapeutic intervention, for neutralization of a particular cytokine may, in theory, abate a specific disease process without causing wholesale immunosuppression.[1,2]

### *Tocilizumab: Anti-Interleukin-6 Receptor Antibody*

Interleukin-6 (IL-6) and the IL-6 receptor (IL-6R) were discovered by Tadamitsu Kishimoto in Japan in the 1980s. IL-6 binds to and forms a complex with IL-6R and another cell membrane protein, gp130. Formation of this complex results in the activation of the Jak/STAT pathway through gp130. Two forms of the IL-6R subunit can be found—membrane bound (mIL-6R) and soluble (sIL-6R).[3–5] Membrane anchoring of the IL-6R subunit is not required for signaling, and indeed signaling can occur when IL-6 forms a complex with sIL-6R and gp130. Signaling through soluble receptor is termed trans-signaling and may result in different functional outcomes.[3,5] Understanding of the role of these molecules in various inflammatory pathways has led to numerous clinical trials with therapeutic agents that interfere with their mechanism of action.

Tocilizumab (Actemra) is a recombinant humanized anti-human IL-6R monoclonal antibody of the immunoglobulin G1 (IgG1) subclass. It is currently approved by the FDA for use in moderate to severe rheumatoid arthritis, systemic juvenile idiopathic arthritis, and polyarticular juvenile idiopathic arthritis.

#### *Allergic asthma*

IL-6 appears to play a role in allergic asthma. Patients with allergic asthma have high serum levels of sIL-6R at baseline, which is increased approximately 24 hours after an allergen challenge compared with controls.[6] Allergen-induced airway inflammation, specifically with house dust mite and cockroach, has been shown to induce mixed granulocytic inflammation in the airway of mice.[7,8] One may postulate that blockage of IL-6R would result in controlling mixed granulocytic inflammation in allergic asthma, potentially leading to clinical benefit. In a mouse model of allergen-induced asthma, cockroach-induced airway inflammation was shown to be attenuated by intranasal

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