

# Executive Summary

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In healthy individuals, the mechanisms of immunity work efficiently to destroy microbes and store in memory the identity of dangerous pathogens for future reference. The system can break down in a number of ways, however, and this report addresses some of them. Rheumatoid arthritis, inflammatory bowel disease (Crohn's disease and ulcerative colitis), psoriasis, lupus, and multiple sclerosis are generally considered autoimmune diseases, conditions in which the immune system loses its ability to differentiate the self from the foreign and directs an attack against healthy cells and tissues. Asthma is viewed as an allergic disease, characterized by an overreaction by the immune system in response to seemingly harmless environmental antigens.

Chapter 1 provides a brief overview of the immune system and of the faulty response that occurs in autoimmune disease. Chapter 2 reviews each of the 6 conditions dealt with in this report, examining their symptoms and pathology, their presumed causes, their methods of diagnosis, and their epidemiology.

A recurrent theme in discussions of treatment options for autoimmune diseases is the inadequacy of the standard of care. Management and pharmacotherapy are seeing incremental improvements, but there are no cures, or even extraordinarily safe and effective treatments, within reach. Current therapy for all of these conditions is a lifelong proposition that entails alleviating symptoms and inflammation with nonspecific drugs, slowing disease progression with disease-modifying agents, and improving quality of life with lifestyle modifications such as exercise, all while contending with side effects and resistance to medications. Patients with asthma tend to fare well with the drugs currently available, although better treatment options with less potential for side effects are needed. Chapter 3 reviews the existing drug therapies for each of the 6 diseases covered in this report.

Autoimmune disorders and asthma have drawn a great deal of attention from the pharmaceutical industry. The most successful new approach to treating inflammatory diseases in the last decade has addressed the pro-inflammatory role of cytokines, notably tumor necrosis factor (TNF)-alpha, in these types of conditions. Three TNF-alpha blockers—Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab)—are now marketed for treating a range of autoimmune diseases, and they enjoy true blockbuster status, with aggregate sales topping \$9 billion in 2006. Nevertheless, the door remains open for improved therapeutics. Some patients do not respond to the TNF-alpha inhibitors; the effectiveness of the agents depends on long-term, even lifelong, administration; and they have been linked to tuberculosis, lymphoma, and other adverse effects. Several new biological agents have begun to carve their own niches in the massive edifice of the TNF-alpha blockers. Orenia (abatacept), a T-cell costimulation modulator, was approved for the treatment of rheumatoid arthritis in 2005; Rituxan (rituximab), an anti-CD20 antibody, for rheumatoid arthritis in 2006; and Tysabri (natalizumab), an adhesion molecule blocker, for multiple sclerosis in 2006 and Crohn's disease in 2008. The pharmaceutical industry is exhaustively exploring novel targets in the search for new drugs that will displace, or at least complement, the blockbusters. Chapter 4 discusses other pharmacological strategies being used by the industry in developing biological and small-molecule agents for these diseases. In addition to TNF family inhibitors, promising agents include inhibitors of interleukins and other cytokines, chemokine receptor antagonists, anti-inflammatory cytokines, compounds targeting T-cell and B-cell antigens, complement inhibitors, adhesion molecule blockers, protease inhibitors, and kinase inhibitors. The chapter also reviews the compounds that have failed in the clinic since 2002, offering clues as to the approaches that have so far not lived up to optimistic preliminary forecasts, for example, CCR2 receptor blockers and TACE (TNF-alpha-converting enzyme) inhibitors. The largest part of Chapter 4 is dedicated to surveys of the R&D picture for each of the 6 diseases individually. These comprise tables of the approximately 200 compounds in clinical development and discussions of particularly noteworthy drug candidates.