

Executive Summary

The cytokines are a family of naturally occurring proteins that serve as intracellular messengers and are involved in generating and regulating the immune system. Produced in response to infection and inflammation, they play an important role in all aspects of immunity, from induction of the innate immune response to generation of cytotoxic T cells to the development of antibodies.

This report thoroughly evaluates the field of cytokines as it relates to drug development. It begins with a description of cytokines and an explanation as to how they are classified, then proceeds to provide in-depth coverage of approved and experimental cytokines and cytokine inhibitors. The report focuses on the interleukins (ILs), the interferons (IFNs), the tumor necrosis factor (TNF) superfamily, transforming growth factor- β , the hematopoietic growth factors, and the chemokines, or chemotactic cytokines.

Because of their ubiquity and multifunctional nature, cytokines have drawn immense interest from the pharmaceutical industry over the last 2 decades. Great effort has been devoted to finding ways to reproduce their effects, or to block their activity, in the quest to create novel drugs for cancer, infectious diseases, inflammatory and immune disorders, and myelosuppression.

When cytokines first began to be discovered and characterized, they generated great hope among researchers who believed they could be the gateway to human control of the immune system. With the biotechnology revolution of the 1980s, which finally enabled the mass production of human proteins, these expectations could be put to the test. The result: recombinant forms of natural cytokines were among the early success stories of the biotech boom. Genetically engineered versions of IL-2, IFN- α and β , erythropoietin, and the colony-stimulating factors have now been available for years and remain profitable products for their manufacturers.

Overall, though, the attempt to use cytokines as therapeutics has met with mixed success. Some candidates have performed poorly when administered outside the context of their usual physiological networks and cascades. A number of prominent cytokines that attracted the early interest of the pharmaceutical industry—IL-1, IL-4, IL-6, IL-10, and TNF- α among them—were unable to replicate their innate biological activity and/or caused acute side effects in clinical trials. And even many of the approved drugs can cause serious adverse effects or are ineffective in certain patients. Today, one of the areas of greatest activity in the field is the effort to develop improved versions of existing drugs, second-generation agents that are superior in terms of their safety, activity, or method of delivery. This report examines the cytokine therapeutics already on the market and the numerous drugs and programs that represent efforts to improve upon them, as well as programs involving previously untapped or recently discovered cytokines.

The other major subset of cytokine therapeutics is cytokine inhibitors. While this area has not yielded as many approved products as the cytokines and cytokine variants, it has nevertheless paid dividends. The most successful new approach to treating inflammatory diseases in the last decade has addressed the proinflammatory role of TNF- α , with compounds that bind to the molecules or their receptors and thus avert the consequences of receptor ligation. The drugs Enbrel, Remicade, and Humira fall into this category and have been very effective in treating rheumatoid arthritis, Crohn's disease, psoriasis, and other autoimmune disorders. This specialty is by no means exhausted. A number of pharmaceutical companies are pursuing second-generation TNF- α inhibitors that they hope will improve upon some of the features of the approved agents. In addition, several of the lesser-known cytokines, such as IL-4 and -13, receptor activator of NF- κ B ligand (RANKL), and B-lymphocyte stimulator (BLyS), are the targets of promising drugs now in clinical trials. Chemokine antagonism is another emerging niche, with compounds in development for asthma and autoimmune diseases, HIV infection, and stem cell mobilization. This report surveys inhibitors of cytokines and chemokines, covering marketed drugs and active clinical, preclinical, and research programs.

All told, this report examines more than 200 drugs and research programs, ranging from cytokines to cytokine variants and agonists to cytokine inhibitors. It concludes by evaluating the market potential for cytokine-based therapeutics.