Cytokine Therapies and Inhibitors: A Vibrant Pipeline and Active Approved Market

Mark C. Via
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-\(\alpha\) 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-\(\alpha\), 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-\(\alpha\) 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-\(\kappa\)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.
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Under a 2001 agreement, MedImmune is collaborating with Genaera to develop MEDI-528, a humanized IL-9-neutralizing MAb for asthma and potentially other respiratory disorders, including COPD and cystic fibrosis. Over 2004-2005, MedImmune conducted a Phase I study to assess the safety, pharmacokinetics, and immunogenicity of the MAb, administered intravenously, in healthy volunteers. It also began a study of subcutaneous administration. The lead indication for the compound is symptomatic, moderate to severe persistent asthma.

**Interleukin-12 and -23**

Interleukin-12, along with IL-23 and IL-27, comprise a family of structurally related cytokines involved in the regulation of cell-mediated immunity and Th1-type inflammatory reactions. Inhibition of these cytokines has been suggested as a means of interfering with the pathogenesis of cell-mediated autoimmune diseases including MS, RA, and Crohn’s disease.

**CNTO 1275**

CNTO 1275 is an antibody to the IL-12/p40 and IL-23/p40 subunits that is in the pipeline at Centocor (part of Johnson & Johnson). In March 2006, Centocor began a 1,200-patient, Phase III trial in patients with moderate to severe plaque-type psoriasis. The MAb is being given subcutaneously at baseline and week 4 and then every 12 weeks thereafter for a year. In a 12-week Phase II trial reported in early 2006, a greater than 75% improvement in Psoriasis Area and Severity Index (PASI) score was observed in 52%, 59%, 67%, and 81% of subjects treated with a 50-mg dose, a 100-mg dose, 4 weekly 50-mg injections, or 4 weekly 100-mg injections of the drug, respectively, compared with 2% of subjects given placebo. CNTO 1275 is also in Phase II trials for MS, Crohn’s disease, and psoriatic arthritis.

**ABT-874**

Abbott’s human anti-IL-12 MAb, ABT-874 (formerly J695), is in trials for Crohn’s disease, MS, and psoriasis. In a completed Phase II trial, Crohn’s patients given the higher ABT-874 dose had significantly higher response and remission rates than those given placebo. After 19 weeks of therapy, 69% of patients in the high-dose group achieved a clinical response and 50% were in remission. Abbott licensed exclusive rights to intellectual property related to IL-12 or IL-12 receptor antibodies from PDL BioPharma (then Protein Design Labs) in December 2003.
STA-5326

Synta Pharmaceuticals is taking an alternative approach to reducing the overproduction of IL-12. Its oral small-molecule compound, STA-5326 (apilimod mesylate), inhibits transcription within cells to reduce the production and secretion of the cytokine. The compound was safe and dramatically reduced IL-12 production in Phase I trials, according to the company. In May 2005, Synta announced results from a Phase IIa study in active Crohn’s disease, which found that daily treatment led to clinically meaningful disease response and remission rates. In September 2005, the company began a 6-month, placebo-controlled, Phase IIb study of STA-5326 in Crohn’s, called SCORE (Study in Crohn’s Disease of the Oral IL-12/IL-23 Inhibitor STA-5326 for the Induction of Response and Remission). In May 2006, Synta initiated Phase IIa trials in RA and common variable immunodeficiency. The company decided not to pursue development for psoriasis after finding that though clinical activity was seen in Phase IIa and IIb trials, the primary endpoint of the Phase IIb study, significant improvement in skin clearing relative to placebo, was not achieved.

Anti-IL-23 Aptimers

In July 2006, Archemix and Elan entered into a collaboration to develop aptamer therapeutics targeting IL-23 for treating autoimmune inflammatory diseases. Archemix’s aptamers are single-stranded nucleic acids that bind targets in a similar manner as antibodies. They are stable and have high affinity and specificity and low immunogenicity, and unlike antibodies are synthesized chemically rather than biologically expressed, potentially making them less expensive to manufacture.

Interleukin-15

Produced by activated macrophages, among other cell types, IL-15 plays a role in the recruitment of inflammatory T cells involved in several autoimmune diseases, including RA.

AMG 714

AMG 714, formerly known as HuMax-IL15, is a human anti-IL-15 MAb originally developed by Genmab and licensed to Amgen in 2003. Amgen completed a Phase II study in patients with active RA who had previously failed treatment with at least 1 DMARD. According to data presented in May 2006, after receiving treatment every 2 weeks for 12 weeks, 54% of patients given the highest dose of AMG 714 achieved
an ACR 20 response, 29% achieved ACR 50, and 14% ACR 70. The primary efficacy endpoint was not met, though the results suggest that the drug may be effective in this population, according to Amgen. In March 2006, Amgen announced that it had reformulated the product in a more commercially viable cell line. It plans to begin Phase I trials of the new formulation in 2006. Preclinical studies of AMG 714 for psoriasis are under way.

CRB-15

In July 2003, Roche acquired worldwide development and commercialization rights to Cardion’s IL-15 cytokine receptor blocker, CRB-15, in exchange for an initial payment, milestone payments of up to $90 million, and royalties on sales. The compound is now in preclinical studies at Roche for RA and transplant rejection. CRB-15 was invented in the laboratory of Terry Strom at Beth Israel Deaconess Medical Center in Boston and acquired by Cardion in 2001 through its acquisition of Tolerance Pharmaceuticals. It is a recombinant fusion protein of point-mutated IL-15 and the constant region of murine IgG2a (Fcγ2a) that strongly binds the IL-15 receptor without triggering signaling events—the Fc portion is intended to marshal the components of the innate immune system to delete the targeted cells. In preclinical studies, CRB-15 both prevented the development of arthritis and blocked disease progression in mouse models of RA, with long-term effects even after a short treatment regimen. It also reduced production of other proinflammatory cytokines and reduced infiltration of lymphocytes, bone erosion, and cartilage destruction.47

Other Interleukins

Centocor Research

IL-16 is a chemotactic cytokine that has been linked to a number of infectious, immune-mediated, and autoimmune inflammatory disorders, including atopic dermatitis, irritable bowel syndrome, systemic lupus erythematosus (SLE), asthma, allergic rhinitis, neurodegenerative disorders, and viral infections. Scientists at Centocor are further exploring its role and mechanisms in this wide range of diseases.48

ZymoGenetics/Serono/Novo Nordisk Research

ZymoGenetics has taken an active role in investigating several newer interleukins for inflammation. The company discovered IL-31, whose expression, along with that of its receptor, is increased in atopic dermatitis, IBD, asthma, and psoriasis. It is working in collaboration
with Serono in the United States and has licensed ex-US rights to the
target to Serono (in Mexico and Canada) and Novo Nordisk (outside
North America). In February 2006, the 3 companies entered into a
joint development agreement to develop an anti-IL-31 antibody for
atopic dermatitis.

ZymoGenetics also discovered IL-20, a cytokine that stimulates
epidermal cell activity in the skin. IL-20 and 2 subunits of its receptor,
IL-20α and IL-20β, are highly expressed in human psoriatic skin, and
IL-20 is expressed in psoriatic lesions, making this complex a potential
target for psoriasis drugs. The company has licensed worldwide
development rights for IL-20 to Novo Nordisk. IL-22, like IL-20 a
member of the IL-10 family of cytokines, also plays a role in psoriasis by
signaling via the IL-22α receptor subunit. Both IL-22 and IL-22α are
upregulated in psoriatic lesions. ZymoGenetics outlicensed rights to
develop products based on the receptor to Serono in September 2004.

3.2. Interferon Inhibitors

Interferon α

IFN-α levels are elevated in patients with SLE and other autoimmune
diseases, and the cytokine has been established to play a role in disease
pathogenesis. In fact, when administered as a treatment for hepatitis C
virus infection (see Section 2.2), recombinant IFN-α can induce SLE
and autoimmune thyroid disease. Therefore, blocking this pathway
represents a target for intervention in lupus and related disorders.
Table 3.2. Interferon Inhibitors in Clinical Trials

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Type and Target</th>
<th>Indication</th>
<th>Status (most advanced)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedImmune; Medarex</td>
<td>MEDI-545</td>
<td>Human anti-IFN-α mAb</td>
<td>SLE</td>
<td>Phase I</td>
</tr>
<tr>
<td>PDL BioPharma; Biogen Idec</td>
<td>HuZAF (fontolizumab)</td>
<td>Humanized anti-IFN-γ mAb</td>
<td>CD, RA</td>
<td>Phase II</td>
</tr>
<tr>
<td>Advanced Biotherapy</td>
<td>Anti-IFN-γ Antibodies</td>
<td>Anti-IFN-γ Antibodies</td>
<td>RA, MS, psoriasis, psoriatic arthritis, corneal transplant rejection, alopecia areata, vitiligo, DEB, pemphigus vulgaris, type I diabetes, uveitis, genital herpes, AIDS</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Abbreviations: CD, Crohn’s disease; DEB, dystrophic epidermolysis bullosa; IFN, interferon; mAb, monoclonal antibody; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Source: CHI Advances Reports

**MEDI-545/MEDI-546**

In a deal announced in November 2004, Medarex and MedImmune are collaborating on the development of fully human MAbs targeting interferon α and the type 1 interferon receptor. The collaboration is initially focusing on 2 compounds, MEDI-545 (formerly MDX-1103) and MEDI-546 (formerly MDX-1333). MEDI-545, which targets IFN-α, entered a Phase I trial in patients with mild SLE in April 2006. MEDI-546 targets the type 1 interferon receptor and is in preclinical development. Under the terms of the agreement, Medarex received an upfront payment of $15 million, and MedImmune assumed responsibility for the continued development of the compounds. Prior to the start of pivotal studies, Medarex may elect to codevelop the drugs in return for the opportunity to copromote and receive a share of US commercial profits. Medarex will receive milestone payments and royalties. The MAbs are generated using Medarex’s UltiMAb Human Antibody Development System.
Interferon γ

IFN-γ is a prominent proinflammatory cytokine that is responsible for cell-mediated immunity. Blocking its activity can inhibit the development of Th1 cells and prevent the activation of macrophages, monocytes, and natural killer cells, making this a possible approach for treating autoimmune diseases.

HuZAF

HuZAF (fontolizumab) is PDL BioPharma’s humanized antibody that targets IFN-γ. In 2 Phase II trials in patients with moderate to severe Crohn’s disease that were completed in 2004, HuZAF did not meet the primary endpoint at study day 28 following a single intravenous administration. However, following a second intravenous dose, the MAb was significantly more active compared with placebo at several time points. A Phase II trial in RA was initiated in the first quarter of 2006. Stemming from an alliance formed in September 2005, PDL (formerly Protein Design Labs) is collaborating with Biogen Idec on the further development of the MAb.

Advanced Biotherapies’ Anti-IFN-γ Antibodies

Advanced Biotherapies is developing use-patented antibodies to interferon γ for the treatment of autoimmune diseases. In proof-of-concept trials conducted in Russia, it demonstrated that its investigational antibodies were promising in patients with MS, RA, psoriasis, corneal transplant rejection, alopecia areata, vitiligo, dystrophic epidermolysis bullosa, pemphigus vulgaris, type I diabetes, uveitis, and genital herpes. It also conducted follow-up double-blind, placebo-controlled trials in MS and RA, which resulted in significant responses following a 5-day treatment course for up to a year in MS patients and for a month in RA patients. Advanced Biotherapies has US patents on the use of anti-IFN-γ antibodies for a number of the autoimmune diseases cited, and on the use of antibodies against IFN-γ, IFN-α, and TNF-α for the treatment of AIDS. Any antibodies that reach the commercialization stage will be fully human or humanized. The company is seeking to establish collaborations with other companies to continue the development of its antibodies.