

Other T cells, known as cytotoxic, killer, or CD8⁺ T cells, attack and destroy infected cells. They bind to the MHC-peptide complexes on APCs, in conjunction with activated Th cells, and as a result become activated themselves. They then attach themselves to invading cells expressing the appropriate antigen and eliminate them with an injection of granules containing toxic chemicals. Natural killer cells have a function similar to that of cytotoxic T cells, except that they do not need to be triggered by a specific antigen; they target tumor cells and some infectious microbes.

B cells, which grow in the bone marrow, secrete antibodies, proteins specific for a single complementary antigen, that circulate in the blood and lymph streams and attach to foreign antigens, marking them for destruction by other components of the immune system. A given B cell is programmed to make only 1 particular antibody, which it does, with the assistance of Th cells, when it encounters its triggering antigen. Antibody binding also activates the complement system, a group of serum proteins that help to destroy foreign invaders.

1.2. Immune Dysfunction and Autoimmune Disease

The MHC proteins present on virtually every cell in the body are encoded by several HLA genes with a great number of alleles, resulting in a combination of molecules that renders individuals unique. T cells ordinarily do not respond to this distinctive arrangement of molecules, recognizing it as “self” and reacting only against peptides flagged as foreign. Autoimmune disease arises when the T cells treat self-antigens as foreign antigens and subject them to attack.

Autoimmune disease arises when the T cells treat self-antigens as foreign antigens and subject them to attack.

In the study of autoimmune disease, the most significant unanswered question is what possesses T cells to turn against their host. It is generally accepted that a combination of genetic susceptibility and environmental stimuli sets the stage for autoimmune disease. The different alleles of HLA, variations that individualize the host immune response to foreign agents, have long been known to contribute to susceptibility to autoimmunity. A more recent discovery was the protein tyrosine phosphatase 22 gene (PTPN22), which encodes a phosphatase that suppresses T-cell activation; a variant of the gene, PTPN22 620W, has been associated with an increased risk of lupus, rheumatoid arthritis, and other disorders. Another gene, the cytotoxic T-lymphocyte antigen-4 gene (CTLA4), regulates T-cell proliferation and is a susceptibility locus for lupus, multiple sclerosis, and rheumatoid arthritis, in addition to autoimmune thyroid diseases and type 1 diabetes.^{1,2} The existence of genes such as these that are common to multiple autoimmune disorders

Laboratory tests complement physical signs and symptoms in the diagnosis of RA. For instance, 70% of RA sufferers have RF in their blood, with increased levels of this marker correlated with more severe disease, and 90% have an elevated erythrocyte sedimentation rate, a measure of inflammation. RF is not especially specific for RA; it is also found in patients with other rheumatic diseases, Sjögren's syndrome, and sometimes osteoarthritis. However, its specificity for RA increases dramatically at high titers (96% for RF of ≥ 50 IU/ml), although its sensitivity is only in the range of 50% to 60%. A newer test, assessing antibodies to cyclic citrullinated peptides (CCPs), has high specificity, at least 95%, giving it a low false-positive rate against other types of inflammatory arthritis. Its sensitivity ranges up to 75% for established arthritis, but it is only 40% to 55% in early RA.²⁶ The anti-CCP assay can be used in conjunction with the RF assay to achieve a better degree of sensitivity for RA, 81.4% in one study.²⁷ An important finding is that a positive CCP test at the early stages of disease is predictive of the future development of erosive RA.²⁸ Despite the development of new assays in recent years, the diagnosis of RA remains imprecise, particularly in the early stages of the disease.

Despite the development of new assays in recent years, the diagnosis of RA remains imprecise, particularly in the early stages of the disease.

Epidemiology

Approximately 2.1 million people in the United States suffer from RA, with the worldwide prevalence estimated at between 0.5% and 1%.²⁹ The incidence in women is as much as 3 times higher than in men, and the disease most often appears in people between ages 25 and 55. Recent studies suggest that the incidence may be declining somewhat. The reason for this is unknown, but may be linked to changes in environmental influences or lifestyle.

2.2. Inflammatory Bowel Disease

Crohn's disease and ulcerative colitis (UC), which together are known as inflammatory bowel disease (IBD), are chronic inflammatory diseases of the gastrointestinal tract. Crohn's (also called ileitis or enteritis) can affect any part of the digestive system, although it usually occurs in the ileum, or lower part of the small intestine, and UC is characterized by crypt abscesses and ulcerations of the epithelial lining of the colon and rectum. In Crohn's, the inflammation extends throughout the entire thickness of the bowel wall (transmural), whereas in UC it is restricted to the superficial (mucosal) layers of the colon. Also, whereas UC affects a continuous stretch of the colon, intestine affected by Crohn's can feature healthy sections, called "skip" areas, interspersed with diseased portions. Both are autoimmune conditions, driven by the inappropriate activation of the mucosal immune system.

the association between these drugs (except for higher doses of Vioxx) and increased cardiovascular mortality.⁸⁹ Another COX-2 inhibitor, Novartis' Prexige (lumiracoxib), is available in several countries, but was withdrawn from markets including Australia and Canada in 2007 because of hepatic toxicity. The FDA issued a "not-approvable" letter for the use of Prexige in treating osteoarthritis pain in September 2007, requesting additional safety data. Experts recommend using COX-2 inhibitors with caution, although, beyond prescribing the drugs at the lowest possible dose and for the shortest possible duration, the precise nature of this caution has not yet been elucidated.

Corticosteroids

Oral or injectable corticosteroids such as methylprednisolone and prednisone are given to RA patients to reduce inflammation, usually when the disease flares up or is unresponsive to DMARDs or NSAIDs. Some physicians prescribe low-dose corticosteroids in the early stages of the disease so that patients will attain some benefit during the weeks before the slower-acting DMARDs have a chance to work; they then taper or withdraw the steroids. These drugs are able to slow disease progression but are accompanied by dose-dependent side effects, including osteoporosis, thinning of the skin, cataracts, hypertension, and weight gain.^{87,89}

The most frequently used first-line DMARD, due to its efficacy, favorable toxicity profile, and low cost, is methotrexate.

Synthetic DMARDs

DMARDs are medications that slow or stop disease progression. Although in the past their initiation was delayed because of concerns about toxicity, current practice is to begin DMARD therapy as soon as possible because of the potential for great benefit. It may take several weeks or months for these compounds to begin to have an effect.

Methotrexate

The most frequently used first-line DMARD, due to its efficacy, favorable toxicity profile, and low cost, is methotrexate. In fact, a testament to its primacy is the fact that the newer biological agents are typically labeled for use in patients who do not respond adequately to methotrexate. The drug's popularity seems to be well founded: An observational study showed that RA patients who have been treated with methotrexate have significantly lower mortality than those who have not.⁹⁰ If once-weekly oral administration, the standard of care, is ineffective, subcutaneous

3.5. Multiple Sclerosis

As with the other autoimmune diseases, there is no cure for multiple sclerosis (MS). The standard of care comprises a mix of older and newer drugs, and regular exercise and physical therapy can aid in preserving motor function. Many drugs are also used to treat specific symptoms of MS, such as spasticity, fatigue, bladder dysfunction, bowel dysfunction, and sexual dysfunction.

To assess the efficacy of treatments, clinicians use the Kurtzke Expanded Disability Status Scale (EDSS), which scores disability in 8 functional systems. Developed in the 1950s and refined in the 1980s, the EDSS has faced criticism on several fronts, most notably that it places too much emphasis on ambulation. A National Multiple Sclerosis Society task force convened in the 1990s to address these limitations and designed the Multiple Sclerosis Functional Composite (MSFC), a quantitative assessment instrument that measures leg function/ambulation, arm/hand function, and cognitive function. Quantification of magnetic resonance imaging (MRI) scans is also used to evaluate disease activity, but the presence of MS lesions does not correlate well with disability.

Corticosteroids

For decades, corticosteroids have been the conventional form of therapy for MS. High-dose methylprednisolone has been a standard treatment for relapses. Steroids can reduce the duration and severity of attacks but do not affect the course of the disease over time. Evidence suggests that these drugs offer more benefit for motor as opposed to sensory symptoms of MS. Corticosteroids are historically associated with adverse effects such as acne, weight gain, osteoporosis, seizures, and psychosis, and are thus not recommended for long-term use. However, pulse steroids—infusions for 3 to 4 days every 3 to 4 months even during periods of stable disease—may reduce disability and improve MRI parameters without increasing the risk of serious side effects.⁷⁴

The FDA has approved 6 drugs for MS since 1993, including 3 versions of interferon beta.

Disease-Modifying Agents

The FDA has approved 6 drugs for MS since 1993, including 3 versions of interferon beta. Generally, clinicians initiate therapy with interferon beta or Copaxone (glatiramer acetate) on making a diagnosis of MS with a relapsing course; the goal is that the treatment will begin to take effect before the disease can cause significant damage.

4.1. New Approaches to Inflammatory Diseases

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-alpha (TNF-alpha)—in these types of conditions, with compounds that bind to the molecules or their receptors and thus avert the consequences of receptor ligation. Drugs that have reached the market have generally taken 2 forms: monoclonal antibodies (mAbs), like Remicade (infliximab) and Humira (adalimumab), and soluble receptors, such as Enbrel (etanercept) (see Chapter 3). The following sections discuss other strategies being used by the pharmaceutical industry in developing both biological and small-molecule agents for these diseases, focusing on approaches that cut across a range of the disorders covered in this report. More detail about particularly noteworthy drug candidates for specific conditions can be found in Sections 4.3 to 4.8.

Tumor Necrosis Factor Family Inhibitors

Several of the more advanced cytokine-inhibiting compounds in the clinic are next-generation versions of the TNF blockers that are already available. UCB's (Brussels, Belgium) Cimzia (certolizumab pegol; formerly CDP870), a PEGylated humanized anti-TNF-alpha antibody fragment (Fab), is under review in the United States and European Union for CD and in the United States for RA. It is already available as a CD treatment in Switzerland. Centocor's (Horsham, PA) CNTO 148 (golimumab), a human anti-TNF-alpha mAb, is in Phase III trials for RA and IBD and Phase II for asthma. (See Section 4.3 for more details on both of these agents.)

Some other experimental drugs that target TNF have run into problems in the clinic. In April 2005, Serono had to discontinue a Phase III trial of onercept, its soluble TNF receptor type 1, for psoriasis after 2 patients in the study developed sepsis and 1 of them died. Further, response to the drug was inferior to that seen with other available therapies. Amgen (Thousand Oaks, CA) was developing a PEGylated version of the same compound, which it called pegsunercept, and advanced it to Phase II trials for RA, but the company withdrew it from its pipeline. AtheroGenics (Alpharetta, GA) discontinued development of AGIX-4207 in 2004 after a Phase II trial in RA failed to meet its primary endpoint. AGIX-4207 is a vascular protectant, a drug that modulates TNF-alpha by interfering with the generation of other inflammatory proteins. Despite encouraging results in a Phase II trial in RA, Isis Pharmaceuticals (Carlsbad, CA) terminated development of its anti-TNF-alpha antisense drug ISIS 104838 because of strong competition in the market. In addition, the Finnish firm Biotie Therapies licensed

4.2. Setbacks

Although many drug candidates for autoimmune and inflammatory disorders are performing very well in clinical trials and progressing toward regulatory approval, there have been a notable number of setbacks in the last several years. Table 4.1 highlights some of the projects that have encountered problems in clinical trials, ranging from those that progressed all the way to Phase III but then had to be abandoned because of lack of efficacy (e.g., Celltech Group's CDP571) to those that were scuttled for reasons of safety or poor pharmacokinetics in Phase I (e.g., Genzyme's [Cambridge, MA] GENZ-29155). It also highlights some novel classes of compounds that have so far not lived up to optimistic preliminary forecasts, for example, CCR2 receptor blockers and TACE inhibitors. While concern about the CDP571 setback may be mitigated somewhat by the success of Remicade and Humira, which are directed at the same target, the failure of these other studies to validate many alternative targets for autoimmune diseases only reinforces the fact that a better understanding of disease processes and mechanisms of drug action is required.

Table 4.1. Clinical Programs in Inflammatory Diseases Suspended Since 2002

Company	Drug Name	Type of Compound	Indication	Explanation
Abbott Laboratories	ABT-325	Human anti-IL-18 mAb	Autoimmune diseases	Entered Phase I in about 2004; no longer in clinical development
Abgenix	ABX-IL8	Human anti-IL-8 mAb	RA, psoriasis	Abandoned for RA in 2002 and psoriasis in 2003 after it failed to show treatment benefit in Phase II trials
Alexion Pharmaceuticals	Eculizumab	Humanized anticomplement C5 mAb	RA	No longer developing for RA, although positive results presented in 2004; drug is marketed for paroxysmal nocturnal hemoglobinuria
Amgen	AMG 487	CXCR3 receptor blocker	Psoriasis, RA	Developed by Tularik and ChemoCentryx; Tularik began Phase II trial for psoriasis in 2003 and planned Phase II trial for RA in 2004; removed from clinical development for inflammatory diseases after Amgen acquired Tularik in 2004
Amgen	AMG 548	p38 MAP kinase inhibitor	RA	Development suspended in Phase I in about 2004 due to liver enzyme elevations

Continued

Table 4.2. Drugs in Clinical Trials for Rheumatoid Arthritis (cont.)

Company	Drug Name	Status	Type of Compound
Vertex Pharmaceuticals	VX-702	Phase II	p38 MAP kinase inhibitor
VGX Pharmaceuticals (Blue Bell, PA)	VGX-1027	Phase I	NF- κ B inhibitor
XOMA	XOMA-052	Phase I	Humanized anti-IL-1 beta mAb
Wyeth	ERB-041 (prinabere1)	Phase II	Estrogen receptor-beta agonist
ZymoGenetics; Merck Serono	Atacicept (TACI-Ig)	Phase II	Soluble fusion protein linking TACI receptor to Fc portion of Ig

BAFF, B-cell activating factor; BLYS, B-lymphocyte stimulator; dAb, domain antibody; DHODH, dihydroorotate dehydrogenase; DMARD, disease-modifying antirheumatic drug; Fab, antibody fragment; Fc, fragment crystallizable; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; IGF, insulin-like growth factor; IL, interleukin; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; mAb, monoclonal antibody; MAP, mitogen-activated protein; M-CSF, macrophage colony-stimulating factor; mTOR, target of rapamycin (mammalian); NA, not available; NF- κ B, nuclear factor- κ B; RANKL, receptor activator of NF- κ B ligand; S1P, sphingosine-1-phosphate; TACI, transmembrane activator and CAML (calcium modulator and cyclophilin ligand) interactor; TNF, tumor necrosis factor; VAP, vascular adhesion protein.

Source: Insight Pharma Reports

TNF-alpha Inhibitors

UCB

Cimzia (certolizumab pegol; formerly CDP870) is a PEGylated, humanized anti-TNF-alpha antibody fragment (Fab) that Brussels-based UCB acquired in its 2004 merger with Celltech Group. UCB applied for approval of the compound for Crohn's disease in the United States in February 2006 and in Europe in April 2006. The FDA issued a complete response letter in December of that year requesting more information, and UCB announced in March 2007 that it would conduct an additional short-term trial to confirm the induction of clinical response in patients with moderate to severe, active Crohn's. The European Medicines Agency's Committee for Medicinal Products for Human Use adopted a negative opinion on the application in November 2007, which UCB plans to appeal. Cimzia was approved in Switzerland for treating CD in September 2007. UCB filed a BLA with the FDA for Cimzia for RA at the end of 2007. Pivotal Phase III trial results presented in February 2007 indicated that Cimzia plus methotrexate was significantly superior to methotrexate alone in preventing structural joint damage in moderate to severe RA. The drug is also in Phase II trials for psoriasis.