

Arthritis

The aging populations of developed countries are likely to present a growing market for arthritis therapies.

Arthritis (from the Greek word for joint) is a chronic multifactorial disease induced when the immune system attacks and begins degrading the body's joints. The disease knows no racial boundaries and comes in many forms, including calcific peri-arthritis, enteropathic arthritis, chronic, gouty, and hand osteoarthritis, hip and knee osteoarthritis, thumb, Jaccoud's, and juvenile osteoarthritis, oligoarthritis, polyarthritis, and peripheral, psoriatic, rheumatoid, and septic arthritis. Rheumatoid arthritis (RA) alone is estimated to affect 1% of the world's population and is twice as prevalent in women as in men.

In the US, arthritis and other rheumatic conditions affect about 43 million people, or about 15% of the population, at a total dis-

ease burden close to \$65 billion. Prescription sales of the various drugs used to control the disease are in excess of \$3.5 billion, growing at about 11% annually¹. With such a massive economic and societal burden, it is not surprising that arthritis is a disease in which there is a tremendous amount of research to find effective drugs that focus not only on the symptoms, but also on the causes themselves.

Historical perspective

Some of the most effective treatments against arthritis have been the anti-inflammatories known as glucocorticoids that have been in use for about 50 years². However, the disease itself began having its histological and molecular characteristics investigated systematically only from the mid-1960s onward. For

example, electron microscopic studies of tissues in RA began showing in detail the extent of tissue damage in joints, but also corollary effects such as angiopathies³. Serological analyses in the late 1960s focused on developing correlations between the disease and known macromolecules, such as the deficiency in γ 1-A-globulin that occurs sometimes in RA⁴. These analyses were complemented by studies that focused on the effects of medications used at the time, such as anti-inflammatories, on joint or synovial tissue⁵. At the same time, initial efforts toward hip surgery, including endoprosthesis, were also being developed⁶.

The early 1970s saw the development of cell cultures from rheumatic tissues that would later form the basis of in vitro assays

Table 1. Selected companies with arthritis R&D programs

Company	Program	Status
Abgenix (Fremont, CA)	Human Mab against IL-8	Phase I/II, 11/98
Aeterna Laboratories (Québec, PQ, Canada)	Angiogenesis inhibitor (AE-941) derivative for osteoarthritis and rheumatoid arthritis	Preclinical
Agouron (La Jolla, CA)	Selective matrix metalloprotease (MMP) inhibitor	Phase I, 9/96
Alexion (New Haven, CT)	Human Mab C5 inhibitor of the complement cascade	Phase II, 8/99
Amgen (Thousand Oaks, CA)	Oral tumor necrosis factor binding protein	Phase II, 1999
Anergen (Redwood City, CA)	MHC peptide compound	Phase I, 7/98
AnorMed (Langley, BC, Canada)	Azaspirane immunomodulators (Atiprimod)	Phase I
AutoImmune (Lexington, MA)	Synthetic type II collagen peptide (second-generation Colloral)	Preclinical
Axys Pharmaceuticals (S. San Francisco, CA)	Cathepsin as arthritis target	Lead
BASF BioResearch (Worcester, MA)	Anti-tumor necrosis factor α (TNF α) Mab	Phase III, 2/2000
Bayer (Leverkusen, Germany)	Humanized anti-TNF antibody	Phase I
Biogen (Cambridge, MA)	Recombinant human γ -interferon	Phase III
Biomatrix (Ridgefield, NJ)	Elastoviscous hylan biopolymer for osteoarthritis of the knee (Synvisc)	Market, 8/97
Boehringer Ingelheim (Ingelheim, Germany)	Gene therapy to neutralize IL-1 and IL-10	Phase I, 1999
Boston Life Sciences (Boston, MA)	Oral amiprilose HCl (a modified hexose, Therafectin)	PLA or NDA Filed, 6/98
Cambridge Antibody Technology (Cambridge, UK)	Anti-TNF α Mab	Phase III, 2/2000
Celgene (Warren, NJ)	Thalidomide (Thalomid, formally Synovir)	Phase II, 8/99
Cell Genesys (Foster City, CA)	Human anti-IL-8 antibody from mouse transgenics	Preclinical
Centocor (Malvern, PA)	Chimeric anti-TNF Mab (Remicade)	Market, 11/99
Chiron (Emeryville, CA)	Insulin-like growth factor (IGF)-1 and IL-2	Lead
Cortech (Denver, CO)	Orally bioavailable (neutrophil) elastase inhibitor	Lead
Cypress Bioscience (San Diego, CA)	Protein-A matrix plasma apheresis column (Prosorba)	Market, 4/99
DepoTech (San Diego, CA)	IGF-1 and IL-2 DepoFoam formulations	Lead
G.D. Searle & Co. (Skokie, IL)	OX-2 inhibitor celecoxib (Celebrex)	Market
Genta (San Diego, CA)	Oral controlled-release formulation of diclofenac (Voltaren)	IND Filed
IDEC Pharmaceuticals (San Diego, CA)	Second-generation anti-CD4 Mab	Phase I/II, 1997
Immune Response Corp. (Carlsbad, CA)	Vb3, 14 and 17 T-cell receptor therapeutic vaccine for RA	Phase I, 9/92
Immunes (Seattle, WA)	Soluble TNF receptor (Enbrel)	Market, 11/98
Inflazyme (Vancouver, BC, Canada)	Inflammatory cell activation inhibitor (Bispan)	Preclinical, 1999
Isis Pharmaceuticals (Carlsbad, CA)	Antisense intercellular cell adhesion molecule-1 inhibitor	Terminated
Kissei Pharmaceutical (Tokyo)	Oral small molecule inhibitor of p38 MAP Kinase	Phase II
Ono Pharmaceutical (Osaka, Japan)	Orally bioavailable neutrophil elastase inhibitor	Lead
Peptide Therapeutics (Cambridge, UK)	HSP-tetrapeptide to split IgA and α -antitrypsin	Phase II, 9/97
SmithKline Beecham (Philadelphia, PA)	Second-generation anti-CD4 Mab	Phase I/II, 1997
Supergen (San Ramon, CA)	IV pentostatin (small-molecule purine analog, Nipent)	Phase II

Source: Biovista (www.biovista.com)

used for drug discovery⁷, as well as the application of nonsteroid and non-anti-inflammatory drugs in RA treatment, such as therapy using gold suspensions, which is used even today⁸. Later came the initial characterizations of autoantibodies against ubiquitous tissue antigens in RA⁹, setting the stage for today's approaches that focus on inhibiting the immune autorecognition events that cause the disease. Also in the late 1970s, immunosuppressants such as cyclosporin-A began to be used for treatment.

Diagnostics based on bone density measurements began to be validated in the case of postmenopausal osteoarthritis in the mid-1980s¹⁰, heralding the growing importance of diagnostic monitoring that aims to begin treatment as early as possible. There were also increasing efforts to characterize the cytotoxic T-cell response in arthritis, based initially on correlations with viral infections, such as Epstein-Barr infection¹¹. In the past 15 years, there has been a veritable explosion in the number of treatment options available, based on an increasing understanding of some of the key symptoms of the disease. Most of these therapies, however, focus on addressing the symptoms, rather than the underlying causes, of the disease.

Current state

The market for arthritis drugs is huge; therefore, it is not surprising that many companies, including some of the largest pharmaceutical companies, have R&D programs aimed at characterizing the self-antigens involved in the disease, or key enzymes that participate in the inflammatory response, in an effort to develop new or better drugs. A selection of these companies and their efforts against arthritis are listed in Table 1.

Key to the development of current therapies is the characterization of the variety of self-antigens that are the focus of the immune response. This is the subject of concerted efforts by many academic and corporate groups. One example of a recent autoantigen implicated in the disease is leukocyte function-associated antigen (LFA-1) in treatment-resistant Lyme arthritis¹².

Reducing inflammation is the most commonly used treatment option in arthritis, and glucocorticosteroids, such as prednisolone and methylprednisolone, are some typical choices. However, there is still much that is uncertain about their real efficacy and tolerance profiles, even though they have been in use for some time¹³. For example, they often need to be used in combination with calcitriol or bisphosphonates to reduce the risk of developing osteoporosis, which may occur as a result of the long-term administration of glucocorticosteroids.

At present, a great deal of attention is being focused on nonsteroidal anti-inflammatory drugs (NSAIDs) based on inhibiting the cyclooxygenase (COX) enzymes. The two isoforms, COX-1 and COX-2, are central to the production of prostaglandins, produced in excess at sites of inflammation. COX-1 synthesizes prostaglandins that are involved in the regulation of normal cell activity, whereas COX-2 produces prostaglandins mainly where inflammation occurs. Thus, selective inhibition of COX-2 in particular is sufficient to limit inflammation significantly, and COX-2 inhibitors, such as G.D. Searle's Celebrex, are heavily prescribed. There are still some concerns about side effects arising from the inhibition

Arthritis is now a disease that is fought with many drugs. On the whole, these drugs treat inflammation as a symptom, but do not address the actual cause of the disease.

of a key enzyme in tissues and organs other than the ones affected by the disease, such as the kidney and the brain¹⁴.

Finally, there is emerging recognition that synovial tissues in arthritis may be under attack not just from antibodies or cytotoxic T-cells that recognize self-antigens, but also from the complement system. This critical molecular cascade goes awry in a number of conditions, including arthritis, and is the subject of intense R&D¹⁵.

Clinical progress

Arthritis is the subject of numerous clinical trials investigating new agents or ones already in use for side effects. For example, even though Celebrex (celecoxib) is prescribed, clinical trials are ongoing to refine its side-effect profile and determine additional uses. For example, a recent report describes the effects of the drug on the gastrointestinal mucosal surface, and on platelet function in comparison to naproxen, a COX-1 inhibiting NSAID¹⁶. The small-scale trials showed that no ulcers occurred in patients receiving celecoxib in comparison to 19% of patients who received naproxen. Also, there was no statistically significant effect on platelet aggregation or bleeding time with celecoxib, whereas such effects were observed with naproxen. The results of these trials confirm the advantage of COX-2 selectivity in terms of reducing side effects in arthritis treatment. Indeed, COX-2 is the target for several inhibitors, in addition to celecoxib, that are under development with

the goal of improving efficacy and reducing side effects¹⁷.

In addition to single-drug clinical trials focusing on new targets, there are other trials that aim to optimize current approaches, specifically comparing various regimens of combination therapy in arthritis. One recent trial involved 199 patients in a multicenter, randomized study with a two-year follow-up, comparing combination therapy (sulfasalazine, methotrexate, hydroxychloroquine, and prednisolone) with a single antirheumatic drug (sulfasalazine or methotrexate) with or without prednisolone, in early RA¹⁸. Here, combination therapy was found to be better in causing initial remission in at least a proportion of the patients studied.

Finally, other types of trials aim to determine the effects of antiarthritis drugs on various molecular responses, such as the production and subsequent effect of cytokines. For example, a recent trial linked the immune suppressive effect of dexamethasone on interleukin-10 (IL-10) production and on the type 1 (T1)/type 2 (T2) T-cell balance found in RA¹⁹. Dexamethasone therapy in RA patients leads to a rapid, clinically beneficial effect, and the upregulation of IL-10 production observed after administration may be involved in the prolonged clinical benefit. At the same time, there is an immunosuppressive effect accompanied by a relative shift toward T2-cell activity. Such results offer significant insights into the individual mechanisms that affect the progression and outcome of the disease.

Industry challenges

Arthritis is now a disease that is fought with many drugs. On the whole, these drugs treat inflammation as a symptom, but do not address the actual cause of the disease. Thus, the industry's main challenge is to tackle the cause head-on—a task that is complex and difficult. For example, exactly why does the immune system turn against the host it is supposed to protect? This question is at the heart of all autoimmune disease, of which arthritis is one.

Several hypotheses can offer some insight, and some interesting approaches are emerging that attempt to enhance our understanding of the underlying causes, thus helping to design better drugs. For example, recent work focuses on gene variations that themselves correlate with arthritis. A good example is the variation observed in the estrogen receptor gene that has been linked to the age of onset of RA in women, but not in men²⁰. This correlation potentially links the serum concentrations of estrogen and the actual timing of onset of the disease, offering a novel set of targets as well as potential reasons for why and how

DISEASES

the disease develops.

In addition to trying to get to the root cause of the disease, the industry faces the challenge of refining its understanding of the multiple molecular mechanisms involved. For example, in addition to COX-2 inhibitors, there is a great deal of excitement caused by the emerging importance of matrix metalloproteinases (MMPs) in the disease. Enzymes that degrade the extracellular matrix, MMPs are controlled normally by a set of tissue inhibitors that, if disrupted, will allow the enzymes to work unchecked, degrading the matrix and promoting not only arthritis, but also tumor growth and metastasis.

Increasing understanding of this process has led to the validation of MMPs as targets for the development of inhibitors and has prompted efforts aimed at finding out why the inhibitors went out of balance in the first place. With respect to MMP inhibitors, there has been considerable progress recently in obtaining three-dimensional structures of the enzymes alone and in combination with their inhibitors, which will help in the design of novel inhibitors with clinical potential²¹.

Future directions

Future efforts against arthritis will center on the identification of what causes the immune system go awry, and also the identification of candidate self-antigens targeted in arthritis. Ongoing research will be helped by animal studies and in vitro models of arthritis based on tissue culture of rheumatoid synovial fibroblasts. The latter are being used increasingly to study specific signal transduction mechanisms in the disease. It was found recently that once the thrombin receptor is activated in these cells, they subsequently produce interleukin-6 and granulocyte colony-stimulating factor, both of which lead to inflammation²². Any suppression in the production of inflammation-causing signals in joints could help alleviate the symptoms, thus offering new avenues for drug targeting.

In the future, increasing attention will be directed toward by-products of molecular events that have gone wrong in arthritis and on their synergistic effect in promoting the disease. A good example, nitric oxide, is produced in excess in rheumatoid tissues and is now being investigated for its effects in cartilage damage in arthritic joints²³. Another good example is tumor necrosis factor α (TNF α), an inflammation-promoting cytokine associated with multiple inflammatory events, including arthritis. Anti-TNF α therapies are the subject of intense research, and first-generation therapies are already on the market²⁴.

Although a lot is already known about certain molecular pathways involved in spe-

cific aspects of arthritis, as well as the effects of drugs, the future will see increased efforts to refine our understanding of the mode of action of new drugs. Hopefully, this will lead to the design of even better drugs with more specific benefits and fewer side effects. For example, a recent study reports on the novel actions of the NSAID aceclofenac, prescribed for rheumatoid arthritis and osteoarthritis. The study showed that the therapeutic effects of aceclofenac are due, to a certain degree, to a newly described chondroprotective effect of a metabolite of the drug, which suppresses promatrix metalloproteinase production and proteoglycan release and therefore reduces arthritic symptoms²⁵. This and other studies of this type on mode of action issues will no doubt

Increasing understanding of the molecular cascades involved are already producing significantly better drugs than in the past with increased selectivity and fewer side effects.

lead to optimized drug design efforts as well as to the validation of novel targets for de novo drug design, via the elucidation of specific pathways involved in the disease. Specific examples of novel targets for anti-arthritis drugs include vascular adhesion protein-1 (VAP-1), which mediates leukocyte-endothelial cell interactions and can also be used as a potential target for imaging inflammation itself²⁶, vascular endothelial growth factor (VEGF) isoforms and VEGF receptors, Flt-1, KDR and neuropilin-1, all of which are involved in angiogenesis which itself is central to the development of rheumatoid arthritis²⁷.

It should also be pointed out that diagnostic methods for arthritis continue to improve and evolve. For example, a recent study shows how synovial fluid has certain physical characteristics that enable the distinction between inflammatory and degenerative arthritis using non-invasive analysis by spin echo diffusion, which is an analytical method for determining flow characteristics and differences among viscous fluids. This observation can potentially lead to a better prediction of the nature of arthritis early on in patients who have inflamed joints²⁸.

Finally, the future will also see the increasing application of gene therapy as a front-line defense against the disease, aiming at long-term corrective treatment. A variety of genes that code for antiarthritic

proteins are under investigation, including IL-1Ra, IL-1sR, TNFsR, transforming growth factor β (TGF β), IL-13, Fas L, IL-10, and vIL-10, as are the vectors that will carry them to arthritic tissues²⁹. Already, two human arthritis gene therapy protocols are underway in the US and Germany, with ex vivo transfer of an IL-1Ra cDNA to the metacarpophalangeal joints of patients with RA.

Conclusions

Arthritis presents a major socioeconomic burden that has and will continue to attract major research and development efforts aimed at elucidating the basis of the disease as well as developing effective therapies. Increasing understanding of the molecular cascades involved are already producing significantly better drugs than in the past with increased selectivity and fewer side effects, and this will continue into the foreseeable future as arthritis is a multifactorial disease that is unlikely to be solved with a magic bullet-type approach.

Reprinted from *Nature Biotechnology* 17, 726–727 (1999).

1. Prevalence data and sales figures from TDR Data (www.tdrdata.com).
2. Kirwan, J.R. et al. *Rheumatology* 38, 100–102 (1999).
3. Branemark, P.I. et al. *Acta Orthop. Scand.* 40, 153–175 (1969).
4. Bernacka, K. et al. *Rheumatologia* 7, 207–211 (1969).
5. Branemark, P.I. et al. *Acta Orthop. Scand.* 40, 279–299 (1969).
6. Buchholz H.W. *Langenbecks Arch. Chir.* 325, 777–789 (1969).
7. Wedum, B.G. *Ann. Rheum. Dis.* 29, 516–523 (1970).
8. Fernandez-Herlihy, L. *Lahey Clin. Found. Bull.* 19, 124–128 (1970).
9. Palosuo, T. et al. *Clin. Immunol. Immunopathol.* 10, 355–364 (1978).
10. Nilas, L. et al. *Clin. Endocrinol.* 25, 711–720 (1986).
11. Gaston, J.S. et al. *Ann. Rheum. Dis.* 45, 932–936 (1986).
12. Gross, D.M. et al. *Science* 281, 703–706 (1998).
13. Laan, R.F. et al. *Rheumatology* 38, 6–12 (1999).
14. Golden, B.D. & Abramson S.B. *Rheum. Dis. Clin. North Am.* 25, 359–378 (1999).
15. Persidis, A. *Nature Biotechnol.* 16, 882–883 (1998).
16. Geis, G.S. *J. Rheumatol.* 56, 31–36 (1999).
17. Mandell, B.F. *Cleve. Clin. J. Med.* 66, 285–292 (1999).
18. Mottonen, T. et al. *Lancet* 353, 1568–1573 (1999).
19. Verhoef, C.M. et al. *Ann. Rheum. Dis.* 58, 49–54 (1999).
20. Ushiyama, T. et al. *Ann. Rheum. Dis.* 58, 7–10 (1999).
21. Bode, W. et al. *Cell. Mol. Life Sci.* 55, 639–652 (1999).
22. Shin, H. et al. *Ann. Rheum. Dis.* 58, 55–60 (1999).
23. Lotz, M. *Rheum. Dis. Clin. North Am.* 25, 269–282 (1999).
24. Wendling, D. & Toussiot, E. *Rev. Rheum. Engl. Ed.* 66, 187–191 (1999).
25. Akimoto, H. et al. *Eur. J. Pharmacol.* 401, 429–436 (2000).
26. Jaakkola, K. et al. *Am. J. Pathol.* 157, 463–471 (2000).
27. Ikeda, M. et al. *J. Pathol.* 191, 426–433 (2000).
28. Eustace, S. et al. *Skeletal Radiol.* 29, 320–323 (2000).
29. Evans, C.H. & Robbins, P.D. *Intern. Med.* 38, 233–239 (1999).