Editorial

As if its importance were not already clear, inappropriate inflammation is getting in on the act in a whole range of disease processes not previously thought to have an immunological component central to their pathogenesis. In osteoporosis, for example, it is now clear that the osteoclast cells, responsible for bone mineral resorption, are recruited from the circulating monocyte pool. In Alzheimer's disease, beneficial effects of non-steroidal, anti-inflammatory agents might suggest that immune system function participates in the neurodegenerative process. In heart diseases, the discovery of the role of chronic inflammation in destabilising the atherosclerotic plaque has led to a *gestaltshift* in the way the pathogenesis of the disease is viewed, and in our search for new therapeutic agents.

Add in the wide range of diseases where the central role of inappropriate inflammatory responses was already clear, from autoimmune conditions such as multiple sclerosis and rheumatoid arthritis to inflammatory bowel disease, psoriasis and asthma, and the list of diseases potentially amenable to treatment with anti-inflammatory drugs has become very long indeed.

Inherently, anti-inflammatory therapeutics tread a fine balance between efficacy and toxicity: in general, the more powerful the anti-inflammatory effects, the greater the associated side-effects. At one extreme, we have immunosuppressive agents (such as cyclosporin or rapamycin) which can completely inhibit inappropriate inflammation only at the cost of severely impairing the function of the entire immune system. Glucocorticoids (such as dexamethasone or hydrocortisone) offer a better trade-off in most circumstances, combining powerful anti-inflammatory activity with a side-effect profile that is significant but controllable (at least during acute treatment at lower doses). The non-steroidal, anti-inflammatory drugs (NSAIDs) such as aspirin, indomethacin or celecoxib are generally less powerful anti-inflammatory agents, in most cases blocking inflammatory cell activation, rather than leukocyte recruitment, but the side-effects are also proportionally less severe than steroids.

More recently, as the molecular cues which orchestrate leukocyte traffic both in the healthy immune system and during pathological inflammation have become clear, new hopes have been raised that we can design targeted anti-inflammatory drugs which abolish the pathogenic leukocyte recruitment, without interfering with the normal immune system function. The chemokine superfamily represents a particularly attractive target for such intervention, since this network of more than 50 ligands and 20 receptors plays a central role in the precise temporal and spatial control of leukocyte recruitment, moving specific subsets of leukocytes to particular addresses with exquisite accuracy. If the right combination of chemokine signals could be specifically blocked, it seems plausible that a particular undesirable inflammatory response could be attenuated, without causing widespread disruption to the rest of the immune system.

Given the obvious appeal of the target and the amount of research effort which has been spent, it is perhaps surprising that clinically useful chemokine inhibitors have not emerged before now. Chemokine receptors are members of G-protein coupled receptor (GPCR) superfamily, which have a good history as successful targets for the pharmaceutical industry. The long delay from the first emergence of the central importance of the chemokine family in the early 1990s, to the first clinical trials of chemokine inhibitors may, in fact, reflect the difficulty in finding chemokine receptor antagonists with sufficient selectivity (both compared with receptors for other chemokines and with bioactive amine receptors). Despite these difficulties, clinical studies with chemokine inhibitors are finally underway, and early results are encouraging, although there is still a long way to go before chemokine inhibitors can be considered a new class of anti-inflammatory drugs in man.

In this issue, the biology of chemokine receptor signalling which underpins attempts to design therapeutic inhibitors is extensively reviewed. There are also in depth reviews of two of the most advanced specific chemokine receptor antagonists (the CCR1 antagonist BX471 and the CXCR4 antagonist AMD3100), as well as the Broad-spectrum Chemokine Inhibitors (BSCIs) we have developed. A different approach to chemokine inhibition is the exploitation of ligand-binding proteins from various viruses which, like the BSCIs, can inhibit the signals from multiple chemokines simultaneously, and the properties of these viral chemokine binding proteins are presented. Finally, if chemokine inhibitors are to offer a substantial clinical benefit over and above existing therapeutic options, then they need to deliver their promising anti-inflammatory activity with a better side-effect profile than current drugs. The issue therefore concludes with an early insight into the limited toxicological information currently available for chemokine inhibition *in vivo*, and discusses its implications for the future development of this broad class of drugs.

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