MONOCLONAL antibodies (Mabs) have been used experimentally to immunomodulate human rheumatic disease since the mid–late 1980s [1]. Their ability to target specific cells and cytokines accurately has yielded encouraging results, but a number of factors limit their wider application. Thus, immunogenicity may dictate the duration of therapy even with fully humanized Mabs [2] and, for some Mab specificities, optimal therapeutic characteristics have yet to be defined. For example, a number of therapeutic CD4 Mabs have been administered to patients, but it is unclear which properties are associated with therapeutic benefit [3]. Furthermore, such knowledge would not necessarily make it easier to design and produce the perfect CD4 Mab: each candidate would have to be screened for the desired characteristics.

Immunoadhesins (IA) are a novel class of biological agent which may overcome some of the problems associated with Mabs. The term was coined by Capon et al. [4] for a fusion protein between part of a CD4 molecule and part of an immunoglobulin (Ig) molecule (Fig. 1). This particular therapeutic was designed to bind gp120 on HIV and thereby block viral entry into CD4+ lymphocytes. Its efficacy was limited by virus mutation, but it served as the forerunner of a series of similar constructs comprising extracellular portions of cell surface molecules fused to Ig constant (C) regions, usually the hinge, CH2 and CH3 domains. Within these soluble molecules, the ‘extracellular’ entity bound its natural ligand, whilst the C-region endowed a number of properties: it prolonged the circulating half-life; it enabled dimerization, thereby increasing avidity for ligand; and it provided the potential for effector function. Like Mabs, their modus operandi is to inhibit the interaction between natural receptor and ligand, but as their sequences derive from self-proteins they should be less immunogenic. Moreover, their interaction with ligand should faithfully reproduce natural stoichiometry, thus overcoming some of the uncertainties inherent in Mab design. This is well illustrated by a VCAM-1 IA (in this article, immunoadhesins are denoted as X-IA where X is the receptor from which the IA is derived) which binds α4β1 integrin and is anti-inflammatory in mice. Unlike α4β1 Mabs, the IA only binds the activated form of its ligand, providing exquisite specificity [5]. Finally, since most Mabs have low ligand affinities compared with receptor–ligand interactions, most IAs are many times more potent than their Mab counterparts. For example, an IA derived from the p55 TNFα receptor (p55TNFα-IA) was 100–10 000 times more potent at binding TNFα than TNFα Mabs [6].

IAs are simple to design and construct once the DNA sequence of the receptor is known, and consequently a large number have been produced and applied to animal models of autoimmunity. A promising example is CTLA4-Ig. CTLA4 is a molecule which is upregulated on activated T cells and binds the B7 family of ligands on antigen-presenting cells (APCs). CD28, a co-stimulatory molecule expressed on T cells, also interacts with B7 and this interaction is required for T-cell activation. As CTLA4 has a 10- to 20-fold higher affinity than CD28 for B7, CTLA4-Ig prevents the CD28–B7 interaction and inhibits T-cell activation. More significantly, antigen recognition by the T-cell receptor in the absence of CD28-mediated signalling can result in antigen-specific tolerance. Thus, CTLA4-Ig has been used to facilitate transplantation tolerance across complete MHC [7] and even xenenogeneic barriers [8]. It has also proved effective in numerous animal models of autoimmunity. Particularly impressive results were obtained in a model of systemic lupus erythematosus, where advanced and progressive disease was halted by a limited course of therapy [9]. In this model, only murine CTLA4-Ig was effective—the human version provoked a neutralizing anti-IA response.

Few clinical trials have yet been formally reported. In a small phase I study, a p75TNFα-IA appeared better than placebo at providing symptomatic relief in RA [10]. This was confirmed in a subsequent phase II double-blind, placebo-controlled trial involving 180 patients in which p75TNFα-IA (three dosing levels) or placebo was administered twice weekly for 3 months [11]. Efficacy was dose related, adverse effects were minimal and no antibodies to the biological reagent were detected. An IA derived from the p55 TNFα receptor has also been tested, but results are awaited. An interleukin-1 (IL-1) receptor IA reduced swelling when administered intra-articularly in RA [12], but a subsequent study of s.c. administration showed no benefit over placebo [13]. This IA was constructed from the type I IL-1 receptor which is now known to have higher affinity for the naturally occurring IL-1 receptor antagonist than for IL-1 itself and would not, therefore, be today’s natural choice for an IL1R-IA.

A number of unknowns remain to be investigated. Although theoretically non-immunogenic, there is a potential neoepitope where the two parts of the molecule join. Ig allotypes may also provoke immune responses [14], although anti-allotypic responses have not been documented with humanized Mabs. Substitution of a receptor’s intracellular component with an Ig C-region should not interfere significantly.
with affinity for ligand, but the concept will not work predictably for multi-chain molecules unless the ligand-binding domain can be identified and can be shown to function independently. Moreover, if the affinity of a surface receptor for its ligand is low, then it may not transform into an effective IA. Thus, a CD4 IA is unlikely to interfere with antigen recognition by CD4+ lymphocytes, in contrast to CD4 Mabs. Lastly, it is important to attempt to establish the pharmacodynamics of IA–ligand interactions prior to their administration to patients: as in the case of the Type I IL-1R, they may not always function as anticipated. The p75TNFr-IA binds TNFα, but then releases it again, and can function as a carrier as well as an antagonist. In this way, it resembles natural soluble TNFα receptors which augment TNFα action by preventing its spontaneous decay [15], and in a model of Gram-negative sepsis a p55 but not a p75 TNF-IA was protective despite equivalent affinities for TNFα [16]. Similarly, and despite promising results in RA [11], the p75TNFr-IA was associated with a dose-dependent worsening of outcome in patients with septic shock [17].

So where does this leave us with regard to human therapy? Overall, IAs do appear to possess certain merits when compared with Mabs, but there are exceptions. Cytotoxic Mabs will probably retain an advantage when target cell lysis is required, although this is now less fashionable for immunomodulation of autoimmunity. There will also remain specificities for which IAs are ineffective, such as the MHC/CD4 interaction. Therefore, in the future, Mabs and IAs may well exist side by side, and may even be used together. The combination of a p75TNF-IA and CD4 Mab has already been applied successfully in collagen-induced arthritis [18] and similar combinations are likely to be tested in human disease.

J. D. Isaacs
Rheumatology and Rehabilitation Research Unit, Leeds University Research School of Medicine and Department of Rheumatology, Old Home, Leeds General Infirmary, Great George Street, Leeds LS1 3EX

REFERENCES

TROPICAL RHEUMATOLOGY: CHALLENGE OF THE FUTURE

Australia increasingly focus on the molecular biology of inflammatory arthritis, manpower issues, and the delicate relationship between primary care physicians and consultant rheumatologists, vast areas of the globe do without such a beast (the rheumatologist). Africa, South America, India and Asia have vast populations, few tertiary services and even fewer rheumatologists. Initiatives through the International League of Associations for Rheumatology (ILAR) and some of the regional leagues have seen the development of a number of epidemiological studies on rheumatic diseases in a number of these countries [1, 2]. These initiatives include the establishment of fellowship training in clinical epidemiology and rheumatology, and the development of long-term links and supports for young rheumatologists from developing countries. Many conditions occurring in these countries are similar to rheumatological conditions seen in developed countries, but in some cases the expression of the disease is different, modified perhaps by genetic make-up, chronic immunostimulation from parasitic disease or the general immunosuppressive effects of poor nutrition and social deprivation [3, 4].

The challenges of rheumatology in tropical countries can be summarized as follows: different diseases or varying expressions of rheumatic diseases seen elsewhere; lack of expertise in the diagnosis of rheumatic diseases and in resources for investigation; few treatment facilities and limited pharmacological agents. Some rheumatic diseases are seen almost uniquely in the tropics and these are primarily associated with infection. Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) have declined dramatically in this century. They remain, however, a part of life in many countries, particularly in the tropics. For the acute episode, bed rest is important until signs of activity have subsided. Penicillin will eradicate the streptococci and salicylate will relieve pain. Penicillin should be given in therapeutic doses (oral penicillin V at 250 mg q.i.d. for 10 days or benzathine penicillin at 1.2 million units i.m.). Secondary prophylaxis with 3-4 weekly injections of benzathine penicillin should probably be continued until the age of 21 yr in the absence of heart disease or at least 30 yr in the presence of rheumatic heart disease [5]. Compliance with long-term prophylaxis requires significant organization and communication between health workers, family and community. Rheumatic fever is usually associated with overcrowding and poverty, and primary prophylaxis should be directed to schoolchildren with sore throats. However, many cases are seen with established RHD at their first visit without prior presentation with ARF and no history of preceding sore throat. Addressing the root issues of poverty and overcrowding is at the heart of primary prevention and, where this has been achieved, combined with a national anti-rheumatic programme as in North Vietnam, the incidence of the disease has decreased [6].

Other bacterial infections in tropical areas include osteoarticular brucellosis and leprosy. Brucellosis can give rise to peripheral articular pain, particularly in large joints, and is also associated with sacroilitis, spondylitis and osteomyelitis [7]. Arthritis is a common feature of leprosy and contributes to disability in a variety of ways, either by destructive arthritis (usually monoarthropathy) in the lepromatous type or as an inflammatory polyarthritis which resembles rheumatoid disease in reactional states.

A variety of musculoskeletal syndromes have been described and associated with numerous parasitic infections [9]. Helminths cause rheumatic complaints ranging from transient allergic reactions to severe polyarticular disease, with filariasis and schistosomiasis being notable examples [10, 11]. Arthritis is also associated with several protozoal infections, such as toxoplasmosis, Giardia, coccidia and Cryptosporidium.

Viral infections associated with alphaviruses of chikungunya, o’nyong-nyong, sindbis, Ross River,
may be caused by mosquitoes and commonly present as high fever with arthralgia-arthritis and a maculopapular or erythematous rash. Dengue, a related virus, causes intense back pain, pain in the long bones, periarticular pain, but no arthritis. Treatment is symptomatic and the vast majority settle relatively quickly. Visitors to endemic areas returning home may present with these virus- or parasite-related arthropathies and may cause diagnostic difficulties. A history of travel to the tropics should trigger a search for these exotic conditions.

The diagnostic challenge of acute arthritis in a tropical setting is compounded by limited investigational facilities and rheumatological services. Where these have been available, cases previously designated ‘undiifferentiated’ or ‘tropical’ arthritis have been reassigned to reactive arthritis, gonococcal or arboviral arthritis, or other specific infectious agents [13]. In certain parts of the world (such as Papua New Guinea), where there is a high population prevalence of HLA-B27, reactive arthritis is particularly common [14]. A rising prevalence of reactive arthritis and other spondyloarthopathies has been reported from parts of Africa in the wake of the HIV pandemic [15, 16]. This was least expected in a population where the prevalence of HLA-B27 is low. Since this antigen has been shown to be associated with HIV spondyloarthopathy in Caucasians, these apparent contradictions in the epidemiology of spondyloarthopathy appear to challenge the central role for HLA-B27 in these disorders. The development and testing of further hypotheses to account for these findings should follow. Early reports of HIV-associated spondyloarthopathy in Africans [15, 16] and a recent report from Thailand [17] describe a mainly oligoarthropathy with a good response to NSAIDs. In a recent prospective study of over 250 patients from Zambia, Njobvu et al. [18] (in this issue) found many patients with persistent, destructive arthritis requiring maximum doses of NSAIDs and demonstrated the beneficial effect of intra-articular corticosteroid injections. There is also accumulating evidence that sulphasalazine is efficacious and safe in severe HIV-associated arthritis [19, 20].

In many parts of sub-Saharan Africa, other musculoskeletal disorders associated with HIV infection have become a significant cause of morbidity. For example, the incidence of bone and joint tuberculosis has risen in parallel with the rising prevalence of HIV-related tuberculosis [21]. Bacterial infections are common and often quite severe, and there is increased susceptibility due to infection at fracture or operation sites and the sites of implants [22]. This adds to the many dilemmas in the management of HIV-infected patients with bone disease. Tropical (staphylococcal) pyomyositis, an endemic disease in the tropics, is being reported with increasing frequency in association with HIV infection in young adults. In such patients, the disease has been noted to be more aggressive and to include a much wider spectrum of causative organisms [23, 24]. This has also become true for haematogenous long bone osteomyelitis usually seen in children [22].

What can be done to bridge this gap between such a wealth of clinical material and a dearth of rheumatological experience? Ours is a ‘low tech’ discipline (compared to most these days) in which clinical skills and experience remain paramount. Elements may be taught at all levels of medical and para-medical practice with some expectation of benefit to patients. The ILAR initiatives mentioned above could be the catalyst to establishing new and re-establishing old medical links between developed and developing nations. These need not necessarily be grandiose schemes. Much can be achieved by an individual brief visit, or secondment. From the developing world and its peoples, we in turn may learn how better to husband our own resources, stifle the demand of minor ailments and perhaps, through appropriate research, explore the link between environmental and genetic factors in a variety of rheumatic disorders.

P. McGill, A. Adebajo,* P. D. Njobvu† and P. M. Brooks‡
Division of General Medicine, Stobhill NHS Trust, Glasgow, *Department of Rheumatology, Barnsley District General Hospital, Barnsley, †Department of Medicine, University Teaching Hospital, Lusaka, Zambia and ‡St Vincent’s Hospital, Sydney, Australia

REFERENCES