Editors' view

Biological therapies: a long way on
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Although biological therapies are often thought to be a recent phenomenon, with an explosion of such therapies having appeared in the last decade, their history dates back many centuries. Edward Jenner, noting in the late 1700s how milkmaids were generally immune to smallpox, formulated the hypothesis that their exposure to pus in cowpox blisters led to cross-immunity to the related disease smallpox. From this insight was eventually developed the first smallpox vaccine, and this whole process from observation to hypothesis to new therapy is an exemplar in the history of medical epidemiology. Blood transfusions have been used in medical practice since the early 19th century, although in those early days often with fatal results, and it was only with the discovery of human blood groups by Karl Landsteiner in 1901 that the practice became relatively safe. Both of these are examples of biological therapies, which can be defined as substances made by, or indeed consisting of, living cells and used for the treatment or prevention of disease.

Other than vaccines and blood derivatives, biological therapies today also comprise gene therapy products, cells and tissues for transplantation, recombinant nucleic acids (oligonucleotides), recombinant proteins (e.g. insulin, factor VIII for haemophilia, erythropoietin, growth hormone), cytokines, receptor constructs (fusion proteins) and monoclonal antibodies (MAbs) for the treatment of cancer and immune-mediated diseases. To one point of view, many biological therapies differ from 'traditional' (small molecule) drugs simply in being larger, whilst doing similar jobs. For example, infliximab and losartan both block specific (albeit different) receptors. However, unlike small molecule drugs, biological therapies may consist of complex mixtures of macromolecules, involve a highly complex manufacturing process (rendering them expensive), may be quite delicate and sensitive to heat and/or light and/or shaking, are not easily analyzable (hence concentrations are not easily measured) and usually have to be given parenterally. The advances that they have offered

relate partly to their high effectiveness in particular disease areas, often immune-mediated diseases, since biological therapies often target the immune system, and partly to their high degree of specificity as regards their primary therapeutic target. Thus their potential for off-target effects is less than that for small molecule drugs, although of course their high activity on the primary target can give rise to important adverse effects, including immunosuppression (for biological therapies targeting the immune system) and hence the potential for increased infections (including atypical infections) and possibly cancers.

This area has expanded rapidly in recent years, such that we are now at a point where novel biological therapies are making a substantial contribution to the number of new drugs approved. This issue of the Journal is devoted to some of the important recent advances in the field. This field is indeed very wide, and this is reflected by the variety of subject matter covered in the pages of this issue of the Journal; and of necessity is not encyclopaedic, but what we have attempted to do is to touch on topics of particular current interest and novelty.

One of the inherent dangers with biological therapies, and in particular those targeting the immune system, relates to the severity of adverse reactions that can arise; and this became all too evident in the now infamous phase 1 study of TGN1412 at Northwick Park, where the six healthy volunteers who first received the drug (an immunomodulatory CD28 'super-agonistic' MAb) all suffered a life-threatening cytokine storm. At the time this was not foreseen, although with the benefit of hindsight a number of factors should have sounded alarm bells. Here, Eastwood and colleagues [1] show that, using a solid phase assay, the degree of interleukin-2 (IL-2) release from human peripheral blood mononuclear cells, and in parallel the number of IL-2-producing CD4⁺ T-cells, is predictive of the severity of adverse response to a variety of therapeutically used MAbs, including TGN1412. Such an assay may

be useful in screening novel immunomodulator biological therapies in the future prior to first-in-human studies.

Notwithstanding the severity of the reaction to TGN1412, and the notoriety that subsequently surrounded that trial, many MABs have subsequently been developed and administered to humans, some first to healthy volunteers and others first to patients with the target disease. Tranter and colleagues [2] searched the literature and identified 70 completed MAB trials conducted in healthy volunteers; but in only one such trial, namely that of TGN1412, did life-threatening adverse events occur. The authors rightly conclude that the practice is safe, so long as the improvements in practice and governance of such trials that have been implemented since TGN1412 are carefully adhered to, and so long as special oversight is given to MABs that are first in class, target immune-competent cells or are capable of inducing cytokine release (thus having the potential to activate a catastrophic immune cascade).

T-cells play a number of pivotal roles in immune regulation and these are reviewed by Smethurst [3]. He advances the notion that things have moved on since TGN1412, and novel ways of manipulation of T-cell responses, both those that modify the patient's T-cells (e.g. chimeric antigen receptor modified T-cells) *in vivo* and those that modify them *ex vivo* with a view to subsequent re-infusion into the patient, offer the now realistic prospect of highly specific and efficacious therapies, especially for certain cancers.

An important goal in patients treated with immunotherapeutic agents is to assess those patients' immune responses to such agents. Ferbas and colleagues [4] developed a flow cytometric bead array and B-cell ELISPOT assays to measure immune response (both primary and secondary) to immunization with keyhole limpet hemocyanin (KLH), both in healthy subjects and patients with systemic lupus erythematosus. They show that these assays reliably measure anti-KLH B-cell responses, and this approach holds promise for investigators in the future to assess both the therapeutic response and possible safety aspects in trials of novel (or indeed already marketed) immunotherapeutic agents.

Advanced therapy medicinal products are agents for human therapeutic use based on gene therapy, somatic cell therapy or tissue engineering. Although these offer the prospect of major advances in the ability to treat a wide variety of diseases, they also pose particular regulatory challenges. These are reviewed by Jones and colleagues from the Medicines and Healthcare products Regulatory Agency [5].

Influenza remains a cause of much illness worldwide, as well as death in particularly vulnerable patients and with the occasional emergence of especially virulent strains. Immunization against influenza has posed particular problems, since new vaccines have to be developed with each new outbreak due to frequent mutations in the prevailing virus. Oxford [6] reports his group's work on identifying

CD4+ cells which are present in influenza-infected volunteers who appear resistant to developing influenza, and in turn establishing which peptides in the virus protein matrix and nucleoprotein react with these cells. He also propounds a possible strategy for testing and then licensing a 'universal' influenza vaccine based on these peptides, which involves immunizing healthy volunteers and challenging them with the virus (in quarantine), and subsequently recording their clinical signs and quantities of virus excreted as compared with unvaccinated controls.

A number of papers in this issue look at novel biological therapy-based approaches to specific disease areas. Chtarto and colleagues [7] describe the use of recombinant adeno-associated virus vectors as tools for therapeutic gene delivery to the central nervous system in a variety of chronic neurological diseases. Lee and colleagues [8] review novel developments in antibodies and target molecules being investigated in cancer therapy. On a related theme, Lambert [9] describes recent developments in antibody-drug conjugate technology, which offers the promise of targeted anti-tumour activity with reduced systemic adverse effects. Böni-Schnetzler and Donath [10] illustrate the central role of interleukin-1 β (IL-1 β) in islet inflammation in type 2 diabetes, and show how the IL-1 receptor antagonist IL1Ra has provided proof of concept that targeting this system can improve indices of glycaemia; they go on to discuss how longer acting IL-1 β blocking antibodies, currently being trialled in type 2 diabetes, may provide a novel treatment approach in this difficult disease. Crooke & Geary [11] review the properties of mipomersen, a novel second generation antisense oligonucleotide that targets apolipoprotein B and can provide effective cholesterol lowering in patients with both heterozygous and homozygous familial hypercholesterolaemia, even in those on otherwise maximal lipid-lowering therapy. In the context of asthma, whilst the overall results of trials of a number of specific biological therapies have been disappointing, it is increasingly clear that some patients respond dramatically and others much less so (if at all). Holgate [12] argues that the identification of novel biomarkers, coupled with strict and accurate phenotyping of these patients, will allow much better targeting of novel biological therapies, based on pathways rather than simply drug severity/refractoriness to other therapies.

Finally, Gould [13] provides a fascinating, and at the same time disturbing, prospect that gene therapy, now showing promise in a number of disease areas, may in the future provide a basis for 'gene doping' in sport. The precise nature of this could take a number of forms, for example delivery of genes encoding transcription factors, enzymes or small inhibitory RNAs and the possible targets could include mechanisms of oxygen delivery to the tissues, pathways of glucose metabolism or regulators of muscle mass. Detection of gene doping could be much more difficult than that of standard doping. Gene doping also would carry significant long-term health risks to the ath-

letes who choose to undergo this. Is this the way that sporting cheats of the future will go? Only time will tell.

The articles in this issue provide a fascinating overview of the state of the field in biological therapies, as well as some intriguing insights into their future. Although we have come a long way since Jenner's pioneering work in the biological therapy field, his approach is as valid now as it was back then.

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