Cell Therapies and Tissue Engineering

Background

Today, most drug therapies are based on small molecules; they, and new ones developed in the future, will continue to be widely used because they are relatively effective and easy to manufacture. But, many conditions, especially the chronic degenerative diseases of old age and some serious genetically pre-disposed conditions of the young, are poorly addressed, if at all, by existing drugs and surgical practices.

Biotechnology's techniques have opened up the prospect of a range of new therapies which may address some of these conditions. Protein based drugs, such as recombinant insulin, are of value in many conditions despite the problems of products that cannot be taken orally. Additionally, most protein-based products and many prospective antibody products suffer, like small molecules, from the need for regular administration of small doses, frequently for many years in the case of some essentially prophylactic products.

We believe that biotechnology will produce many new types of therapy in the future, some of which will make a permanent improvement to a patient's condition with only a single application or a short programme. They will achieve this by harnessing the exquisitely accurate and efficient mechanisms that nature has itself devised. We also believe that regulatory systems designed for the examination and approval of small molecule drugs, and adapted somewhat for biopharmaceuticals, are not yet attuned to the cell- and gene-based products that can now be envisaged, and which are beginning to enter clinical environments.

This position paper identifies some potential therapies based on Cell Therapies and Tissue Engineering and comments on the regulatory developments that may be needed to address them.

Possible Therapies

(NB this whole section - down to the next bold heading - will need to be made interesting and easy to read by designer tricks - possibly using boxes, hotlinks etc to minimise the apparent amount of text; as usual one needs words to show that we know what we are talking about and simplicity not to bore people)

Artificial organs using animal cells

Circe Biomedical pioneered the use of a bioartificial liver containing pig cells. The cells were kept separate from the patient's system using hollow fibre membranes that allowed the exchange of metabolites. The Circe product has been tested in clinical trials to maintain patients in acute liver failure while awaiting the arrival of a transplantable liver from a suitable donor; in some cases, the use of the device allowed the patient's liver to recover without the need for a transplant. Circe has also carried out development of a bioartificial pancreas. One of the beauties of such a system is that it delivers exactly the effect that is needed, no more and no less, exactly at the time that is needed, because of the ability of the cells to produce the necessary metabolites when and only when they are needed and in response to metabolic changes.

Xenotransplantation

Imutran, purchased by Novartis, was one of the first companies to attempt the creation of transgenic animals as a source for whole organs that could be implanted into humans without producing an immediate and massive immunological response. While some concern remains about the possibility of retroviral contamination there is no doubt that this is currently the technique most able to address a shortage of organs, the major issue in transplantation surgery.

Using Human Cells for Artificial Organs and Reconstructive Surgery

It is conceivable, in the longer term, that organs (hearts, kidneys and livers) will be grown on biocompatible frames using cells of the right type. This could be achieved using donor stem cells which are encouraged to differentiate in the correct way, or the patient's own cells de-differentiated to become capable of multiplying, and then re-differentiated, to colonise the frame and create a new organ. Where possible the autologous route is likely to be preferred because there would be no need for the immunosuppression that would usually be required with donor cells. Reconstructive surgery will undoubtedly benefit from these techniques but it will also be one route by which corrective genes and growth factors might be introduced into a patient.

Cloning

Current ethical considerations preclude the creation of whole cloned persons from adult cells for any purpose including creating one's own set of spare parts, although this might be technologically possible. Our view is that this would be an unacceptable step that would lead to probably insoluble moral dilemmas for patients, doctors and society in general.

Gene re-programming

Some serious chronic diseases result from single gene polymorphisms and some cancers arise from over-expression of single genes or closely related gene clusters. In principle, such genes, or their protein products, can be switched off or supplies of fresh "normal" genes can be given. Such gene therapy can lead to the patient expressing the normal protein products for the rest of their lives but, of course, their genetic gift to the next generation, through the germ cells, would be unaltered. At present, it is considered unacceptable to alter germ cells but it may be only a matter of time before it is regarded as more unethical to allow further generations to be damaged by readily correctable chronic conditions bequeathed by the parents.

Immune System Activation

Many cancers are able to evade the normal immune system control procedures because they are not different enough from the surrounding cells. Dendreon is one of several companies seeking improved therapies in this area. In such techniques the aim is to take certain cells from the patient (eg dendritic cells) and to add something to them so that when they are re-infused they present a very obvious challenge to the immune system; in tackling them the latter is alerted to the characteristics of the cancer cells and its ability to seek out and destroy the cancer is enhanced.

Neurological Re-construction

Many chronic conditions of mature people (Alzheimer's, Parkinson's) are degenerative. In addition, the acute results of trauma to the head, neck and back, can have major consequences on mobility, speech, memory and other functions. Some companies are addressing the possibility of using stem cells to replace lost functionality. Stem cells, whether embryonic or obtained from placental or foetal tissue, or from the de-differentiation of adult cells, can possibly be used in chronic and acute conditions. Because of the relatively immunologically privileged situation within the brain, foetal cells are well accepted and it appears likely that de-differentiated non-self cells could be successfully used for therapy, but this has not yet been demonstrated.

Regulatory Considerations

The safety and efficacy considerations applied by regulatory agencies to small molecule drugs are complex and demanding but the essentials of the process are widely understood; in other words, the questions that have to be answered are well known and generally agreed. In recent years, there has been considerable harmonisation of approach to data requirements and to the assessment of manufacture, quality, safety and efficacy through the ICH programme.

This is anything but the case in the context of the new types of therapies under discussion in this paper. Safety and efficacy will of course remain paramount but it is not completely clear what these terms mean in the context of a therapy based on living cells. We are still largely at the stage of "guidelines", "notes" and "points to consider". Moreover, standard practice, such as positive controls and double-blind trials for efficacy assessment, will often be impractical. And, some diseases for which orphan drugs will be used have insufficiently large populations for statistical significance to be assessed by standard methodologies.

In only a few countries has there been adequate preparation of the regulatory systems to the extent that it is clear about what questions have to be answered before a therapy can be approved, and which regulatory bodies should be approached. Indeed, in some countries there is no specific "competent authority" (one which has legal status and empowerment to make judgements on this type of product) and establishing one may be part of the political process. In the UK for example, the possibility of xenotransplantation identified the fact that the necessary capabilities lay outside the remit of any existing regulatory body; as a result UKXIRA was rapidly convened with some guidelines issued by the government. But, the new body was obliged to spend its first several months of existence trying to define the processes that it considered relevant to its task, with consequent delay to interested parties.

MRL Experience

Through working with several leading-edge companies in this field, our principal associates (Alan Williams, Meredith Lloyd-Evans and Richard Kruger) have a wealth of experience that is relevant to the development, evaluation, approval and commercial assessment of products of this type, both in North America and in the major countries of Western Europe. Alan and Meredith are based in Cambridge UK; the former focuses on strategic and commercial issues while the latter has in-depth experience of the existing and developing regulatory systems

(Meredith has also managed networks of EU-wide R&D co-workers in tissue engineering and biomaterials). Richard, based in the USA near Boston, has unparalleled experience of steering cell- and tissue-based products and hybrid medical devices through FDA, in industry and latterly as a consultant.

As a result, MRL is extremely well placed to assist companies with such novel therapies, even more so when they address regulatory and market issues, including reimbursement, in more than one jurisdiction. In this sense, Europe may seem unified but there are differences of procedure and philosophy between different countries that can surprise the unwary. MRL's aim is to protect its clients from the adverse impacts of such variations and smooth the path to market entry.

MRL at BIO 2002

MRL considers the forthcoming annual conference of BIO (in Toronto) to be an appropriate time for these issues to be aired. Accordingly, we have invited a prestigious panel of experts from the industrial and public sectors the USA and the UK to make presentations in a seminar entitled "Cell Products - The Science and the Regulation".