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OPINION
ON
THE STATE OF THE ART CONCERNING TISSUE ENGINEERING

Adopted by
The Scientific Committee on Medicinal Products and Medical Devices
On 1st. October 2001

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Purpose and Scope of Opinion

During 2000, the Scientific Committee on Medicinal Products and Medical Devices discussed emerging issues related to public health concerns associated with medical treatment, and developed a list of priority areas. One of the areas identified was tissue engineering. In view of the very rapid progress made in this subject during the preceding years, the imminence of commercialisation of tissue engineered products and the absence of specific regulatory mechanisms that deal with such products, a Working Group was established to consider all relevant aspects and report back to the Scientific Committee. This Opinion provides a description of the scope of tissue engineering and related products, a summary of the risk factors associated with the future use of tissue engineering techniques and a series of observations and recommendations concerning the desirability of regulatory intervention at the Community level.

Introduction and Background

During the last decade, there has been a considerable interest in the area of medicine that has come to be known as tissue engineering. There is, understandably, much confusion as to exactly what is tissue engineering. As noted below, several definitions of tissue engineering have evolved over the last few years and several texts have been produced which cover the principles of the subject. The broad concept, however, is fairly straightforward. For several decades, the ability to replace or regenerate damaged, diseased or otherwise compromised tissues or organs, or to replace or augment their function, has rested either with the use of totally synthetic medical devices or with the techniques of organ transplantation. Neither of these approaches is without difficulty. Inert implantable or extracorporeal medical devices can rarely replace adequately the structure and function of natural tissues and organs (Williams, 1999a), whilst problems of either logistics or immunology limit the application of transplantation (Gubernatis and Kliemt, 2000; First, 2001; Kappas et al, 2001). Changes to both of these approaches to reconstruction have been taking place in order to overcome or minimise the problems. With implantable devices, there has been a trend towards bioactive rather than inert materials (Hubbell, 1999), the incorporation of biologically or pharmacologically active agents in devices (Lundvall and Zetterstom, 2000; Farb et al, 2001), and also in the use of non-viable animal tissues (Simonpietri et al, 2000; Human and Zilla, 2001). With transplantation there have been major advances in the use of immune-suppression to minimise risks of rejection (Cattral et al, 2000; Dumont, 2001; Yu et al, 2001). Nevertheless, these issues still remain, and the associated deficiencies have led to the emergence of tissue engineering (Stock and Vacanti, 2001).

It is important in providing this opinion that the scope of tissue engineering is defined. This is not a trivial process since the subject is still emerging. It is far from clear how the various aspects of tissue engineering will develop over the next few years and there are inevitable overlaps with other treatment modalities.

There have been several attempts, by individuals and committees, to define the term tissue engineering itself. Some of these try to define the term in the context of the mutidisciplinarity of the approach, and some by the objectives of the subject. Examples that may be found in various reports, often unattributed, include:

The application of the principles and methods of engineering and the life sciences towards the fundamental understanding of structure/function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve functions.

Tissue engineering is the application of knowledge and expertise from a multidisciplinary field, to develop and manufacture therapeutic products that utilise the combination of matrix scaffolds with viable human cell systems, or cell responsive biomolecules derived from such cells, for the repair, restoration or regeneration of cells or tissue damaged by injury or disease.

Tissue engineering is the design, specification and fabrication of cells, biomaterials or biomolecules to restore or modify the biological functions of tissues.

One currently popular simple definition is:

Tissue engineering is the persuasion of the body to heal itself, through the delivery to the appropriate sites, of molecular signals, cells and supporting structures (Williams, 1999b).

In providing this opinion, no rigid definition is used since the area is not sufficiently developed for clear boundaries to be drawn between tissue engineering and certain other allied areas, and it is not intended to be dogmatic on inclusions and exclusions from the area. Instead the opinion is based on a statement of the scope of tissue engineering that is most widely ascribed to it, with an explanation of the boundaries with these other areas, such as transplantation and cell therapy.

In effect, tissue engineering is the regeneration of biological tissue through the use of cells, with the aid of supporting structures and/or biomolecules.

It is anticipated, however, that the need will arise in the very near future to produce a scientifically valid and legally sustainable definition of tissue engineering, and tissue engineered products, in order to underpin a regulatory framework and to provide a sound basis for demarcation between tissue engineered products on the one hand and medical devices, pharmaceutical products and cell therapy on the other.

In this respect, any medical technique which involves the isolation of cells from some appropriate donor and their delivery to the site of treatment with minimal manipulation should be regarded as a version of cell therapy and not tissue engineering. One important boundary as yet to be precisely defined refers to the

degree to which cell manipulation has to take place before cell therapy should be considered as tissue engineering. The opinion that is the subject of this document is based on the principle that in tissue engineering the cells involved in the treatment should be attached to or cultured within some supporting structure or matrix that has been designed to facilitate the regeneration of tissue, with structural or functional properties, by the cells. It is also likely, but not mandatory, for the combination of cells and matrices/scaffolds to be augmented by biomolecules, such as growth factors or angiogenic factors, that are able to enhance or accelerate cell function and tissue regeneration.

Tissue engineered products may be considered analogous to medical devices, but yet in many ways they are quite different. Similarly they may carry the same types of risks associated with pharmaceuticals or cell therapy products but again are very different in other respects. It is emphasised that new products and processes are rapidly evolving, clinical trials are already underway (Falabella et al, 2000, Kuroyanagi et al, 2001), patents are already granted (Pabst, 1999) and systems ready to be implemented, yet there is no specifically designed European-wide regulatory mechanism in place to provide a framework for the introduction of tissue engineering into clinical practice. Not only should this be considered from the standpoint of research and development within Europe but also from the perspective that many developments are taking place outside of Europe (principally in the USA and Japan). European governments will soon be faced with the task of making decisions on the importation of products from overseas and the granting of permission for their clinical use within Member States. It should also be borne in mind that regulatory frameworks and standards are already evolving elsewhere, especially in the USA (for example, Federal Register, 2001) and also in individual Member States (Wassenaar et al, 2001).

Examples of Tissue Engineering and Associated Products

In order to appreciate better the scope of tissue engineering, some examples of current and prospective approaches are provided.

With respect to the source of the cells, many of the early attempts at tissue engineered products involved autologous cells of the appropriate phenotype, that is cells derived from the patients themselves, which are grown in culture and re-implanted in the patient once having formed new tissue of the required type. Thus epithelial cells or combinations of keratinocytes and fibroblasts could be used as a source of tissue-engineered skin (Briscoe et al, 1999), chondrocytes for cartilage (Ochi et al, 2001), osteoblasts for bone (Davies, 2000) and so on. As an alternative, patient-derived stem cells obtained from bone marrow whose differentiation into the appropriate phenotype is controlled by the precise culture conditions, are under increasing attention (Fukuda, 2001). Stem cells derived allogeneically are also of importance, particularly with respect to fetal or embryonic stem cells (Kehat et al, 2001). In many circumstances, single cell sources may be insufficient. For example there may be insufficient opportunity for patient derived epidermal cells to generate the amount of skin necessary for the treatment of major burns, in which case they have to be co-cultured with non-patient derived cells (Nemecek and Dayan, 1999). The possibility of feeder xenogeneic cells has been raised in this context. Alternatively, a more complex tissue may require more than one cell type, both endothelial cells and smooth muscle cells

being required for a tissue engineered blood vessel for example (Nerem and Seliktar, 2001).

With respect to the supporting structure or matrix, a number of possibilities exist. Several approaches to tissue engineering involve the use of a biodegradable scaffold made from either a synthetic polymer such as polylactic acid (Ma and Choi, 2001) or from a natural biopolymer such as collagen or a polysaccharide (Lee et al, 2001). In such a product, cells are seeded within the scaffold or matrix, which may degrade or dissolve as the new tissue is formed (Ma and Zhang, 2001). In other situations, the scaffold can provide the basis for tissue regeneration in an ex vivo bioreactor (Busse et al, 1999), the newly regenerated tissue or organ being harvested from this reactor at the end of the process. In any of these situations, precise control over the cellular environment is essential, with the delivery as appropriate of the molecular signals provided by growth factors (Sakiyama-Elbert and Hubbell, 2000), angiogenic factors (Soker et al, 2000) and so on, and also of mechanical signals (Smith et al, 2001).

Most advances have been made with the simple two-dimensional structure of skin (LaFrance and Armstrong, 1999, Kuroyanagi et al, 2001) and relatively homogeneous structures such as cartilage (Sweigart and Athanasiou, 2001) and, to a lesser extent, bone (Fleming et al, 200), ligament (Woo et al, 1999) and tendon (Awad et al, 2000). Within the cardiovascular system, there are few truly tissue engineered products or processes available as yet, although arteries (Ratcliffe, 2000) and heart valves (Sodian et al, 2000) are all under development. Similarly there have been attempts to reconstruct the bladder and segments of the urinary tract (Atala, 1999). The regeneration of nerve tissue is a major priority (Hadlock et al, 2000). On the borderline between tissue engineering and cell therapy are techniques to re-establish tissue function, for example the use of Islets in the development of the 'bioartificial pancreas' (Gappa et al, 2001), and certain techniques to replace the dopamine producing function of brain cells in Parkinson's disease (Woerly, 2000; Emerich and Salzberg, 2001). Tissue engineering does not exclusively imply that structural tissues have to be generated within the body of the treated patient and it is possible for the functions of tissue to be developed in an extracorporeal device such as a cell-based liver perfusion column. It should be recognised that most of these developments are likely to involve animal cells rather than human cells, such that the principles and constraints of xenotransplantation (SCMPMD, 2001) will have to apply as well as those of tissue engineering.

Risk Factors in Tissue Engineering

The sourcing and handling of cells, their culture in bioreactors or within scaffolds, their subsequent preservation or storage and the re-implantation of the resulting tissue engineered product into the patient are all associated with risks. This opinion is concerned with the additional risks to patients associated with tissue engineered products. It is not concerned with risks of medical treatment in general, nor does it address exposure to risks of staff in tissue engineering laboratories or hospitals. It is recognised that such risks do exist, for example to nursing staff, but they should be addressed by the normal safety procedures in these institutions.

It should also be emphasised that tissue engineered products are likely to show much greater variability in composition and performance compared to medical devices and

pharmaceutical products, and this may need to be reflected in labelling requirements and product descriptions.

In view of the risks involved, it is assumed that the scientific principles and processes are validated in suitable animal models before clinical use.

The nature of these risks to patients, and aspects of risk management relating to them, are summarised below.

1. *Microbiological contamination associated with source materials, including the possibility of latent viruses, which may give rise to infectious diseases*. With patient derived cells this is largely a risk of re-infection. With the sourcing of cells from other humans, for example in the use of cadavers to provide material, the exclusion of certain types of donors will have to be considered. In addition, common biological contaminants such as chlamydia have to be considered. The archiving of source material will be important.

2. *Disease transmission*. When using allogeneic sources it will also be necessary to consider other disease states associated with the donor, including cancer, blood disorders and genetic diseases.

3. *Contamination associated with the production process*. Process-related microbiological contamination is considered to be much lower risk than with the source material and any such contamination should be relatively easily detected. Attention will have to be paid to the possibility of contamination from the personnel that process the cells. It is also possible for the contamination to be of non-biological origin, for example from airborne particulates. Minimisation of this risk will involve the establishment of standard operating procedures and quality systems, including the use of controlled environments.

4. *Risks associated with the delivery of un-wanted cells*. This risk will vary with the type of tissue and cell involved. The initial presence of a few percent fibroblasts in endothelium may result in a much larger fraction after culture, resulting in inappropriate tissue structure and function. Identification of the characteristics of the tissue and some assessment of performance may be necessary.

5. *The risks of mix-ups in the process, specifically when using autologous cells, and the risks of transposing products from one patient to another*. Maximum risk reduction will be achieved by the use of appropriate quality systems; risk reduction mechanisms should include labelling and the genetic characterisation of cells. The extent of the risk, and the need for risk management processes may vary from product to product.

6. *Risks associated with the modification of cells during the processes of cell amplification or differentiation, especially those involving genetic manipulation.*

7. *Risks inherently associated with the scaffold / matrix component*. These are likely to be similar to biological safety risks associated with medical devices. The safety evaluation, including the assessment of mutagenicity, should be carried out in a similar manner to that prescribed for devices. For biodegradable scaffolds, it will be necessary for extensive testing to be carried out over periods longer than the anticipated duration of the material within the device, since there may be latent periods for the induction of tissue changes associated with the generation and distribution of degradation products. Continued monitoring of the degradation profile by relevant non-invasive techniques should be undertaken in clinical trials since degradation kinetics in humans may not follow the profiles established experimentally in vitro or in vivo. The assessment of carcinogenicity and toxicity should take into account any systemic effects associated with the products of biodegradation.

8. *Risks associated with achievement of sterility of the final product, which may be a complex combination of cells and materials and biologically active agents*. It is necessary to achieve sterility without destroying the inherent function of the components or employing inappropriate levels of antibiotics in the final product. It is considered that process evaluation may be as important as product evaluation in the achievement and monitoring of sterility. Detailed assessment of the shelf life of tissue engineered products will be necessary.

9. *Risks associated with the potential toxicity of cryopreservatives, process additives and other residues*. Also included here is the possibility of adverse systemic effects arising from the use of pharmacologically active agents such as growth factors, whose function is intended to be localised within or around the tissue engineered product.

10. *Risks associated with the performance of the final product*. In many cases the product will be regenerated tissue, such as a heart valve or a blood vessel, which have to possess appropriate mechanical or physical properties. There are risks that the regenerative process may not yield tissue of adequate properties. For some products or processes, functional testing may be necessary to ensure performance, although it is recognised that this will not always be possible. The identification of acceptance criteria may be difficult and will have to be considered carefully. They may not become obvious until the clinical trial stage, but there should be an expectation that minimum requirements with respect to critical parameters will have to be established before clinical use.

11. *Unknown risks associated with the interaction between cells and scaffolds.* It is not known exactly how cells will behave when cultured and proliferated on an un-natural substrate. As far as possible the nature of such effects should be established during the pre-clinical testing.

12. *Patient specific responses, such as penicillin allergy or allergy to substances used during processing*. It will be necessary to consider patient history and possibly some testing. A well-defined history may lead to exclusion.

General Considerations

1. It is recognised that significant scientific advances are being made at the present time within the area of tissue engineering and it is likely that some of these will lead to marked improvements in medical treatment, either by providing better outcomes than can be achieved with currently available techniques or by making available treatments for diseases or conditions for which there are no current alternatives. However, the application of such scientific developments to clinical use carries several significant risks, including types of risk that have hitherto not been seen in health care. This situation requires careful analysis in terms of the risk – benefit equation and the need for formal control over the experimentation and clinical use.

2. Tissue engineering in general does not carry the same level of risk as seen with xenotransplantation, unless it specifically involves the use of animal cells, either as the cell source or during the production process. This is because the risks are confined to the patients themselves and not to the community at large, as may be the case when living, potentially infectious animal cells are used. It may also be argued that tissue engineering could be associated with less risk than is seen with conventional medical devices or medicinal products, since the latter are mass-produced and the hazards related to defective products or unforeseen mechanisms can affect thousands of patients. Tissue engineering is essentially a customised process, which, although involving some commercialised components, is directed towards individual patients, thereby, with a few exceptions, minimising the scale of the hazard.

3. On the other hand, tissue engineering, as with cell therapy, involves the manipulation of live cells and the interaction of these cells with substrates and biomolecules in unusual circumstances, leading to possibilities of contamination, process errors and as-yet unknown cell-substrate interactions that could have serious consequences. The analysis of risks and benefits has to take into account the fact that some applications carry very high risk (for example when associated with the functional performance of a tissue engineered artery, the failure of which is likely to be fatal) but which address immensely important clinical conditions, whilst others are aimed at non-life threatening conditions for which there are already adequate treatment methods and which carry little risk of serious adverse effects (for example tissue engineered devices for cosmetic surgery). In other words, both risks and benefits vary considerably. This suggests that the procedures for any regulation of tissue engineering may not have to be uniformly applied.

4. The ethical and logistical dimensions of any therapy involving cells have to be taken into account, especially in the context of the position of tissue engineering in relation to transplantation, xenotransplantation, and stem cell therapy. Tissue engineering involving autologous cells should be considered a medical therapy with minimal ethical considerations, since it is only the patients themselves who are involved, rather than human or animal donors, including fetal or embryo sources. However, it is obvious that reliance on patient-derived cells cannot be guaranteed for every application, since there

may not be sufficient time or the opportunity to develop the tissue engineered product from a sample of the patients own cells. In such cases, and especially in those situations where embryonic stem cells are used, the ethical considerations will be paramount and, probably being based upon established national or cultural aspects, will have to be developed further.

5. Aspects of ownership and intellectual property also arise with tissue engineered products if cells from any source other than the patient are involved. Some of these factors have yet to be discussed in a legal framework and could prove of significance in the long term. The impact of public concerns about ownership of tissues and organs post mortem and a widespread distrust of the commercialisation of tissues should not be underestimated.

6. In view of the significant risks to patients under certain circumstances, it is considered essential that some form of regulatory process is introduced on a European basis. It is fully recognised and accepted that regulatory processes should not inhibit or indeed interfere with scientific progress in this area, but at the very least, regulatory control should be exercised at the stage when tissue engineering enters clinical trial phases and/or involves a commercial process. Under some circumstances, it may be necessary for such control to be applied to the point at which a tissue engineered product or process is utilised in man for the first time. Although some aspects of complex tissue engineering processes may well be suitable for regulation under an existing European Directive, for example in relation to medicinal products, or medical devices, or clinical trials, it is unlikely that all aspects of tissue engineering can be encompassed by current legislation.

7. The majority of tissue engineering involves procedures that currently come within the sphere of competence of health care and scientific professionals, and no additional special qualifications or training would be required. However, in certain cases, highly sophisticated techniques will emerge, and maximum benefit and optimal safety will only be produced when exceptionally well trained and motivated staff are involved. It might also be anticipated that, in certain cases, a restriction in the nature of the scientific, commercial and clinical institutions or enterprises involved with the delivery of tissue engineering may be beneficial.

<u>Specific Recommendations</u>

1. Since no existing regulatory framework is available within Europe, the European Commission should establish a Tissue Engineering Regulatory Body that has oversight over the introduction of tissue engineered products and processes into the European Community. Such a regulatory body could be an entirely new organisation or be incorporated within an existing organisation. It should address issues of risk and benefit and should relate as far as possible to current standards and regulations that apply to the constituent aspects of tissue engineering. These include, but are not limited to, the standards for testing the biological safety of medical devices (International Standards Organisation, ISO 10993), standards for quality assurance systems (International Standards Organisation, ISO 9001 and ISO 13485), guidelines for clinical trials (European Union, 2001/20/EC), and regulatory procedures for

medical devices (European Union, 93/42/EEC) and pharmaceutical products (European Union, 65/65/EEC).

Recommendation 1.

In view of the significant risks associated with tissue engineering, the European Commission should propose the establishment of a Tissue Engineering Regulatory Body that has oversight over the introduction and monitoring of tissue engineered products and associated processes in the European Community.

2. Should this recommendation be accepted, the first action should be the development of a definition of tissue engineering that is scientifically rigorous but also of practical value in unambiguously defining the boundaries of the area that will be regulated in this way. It is proposed that such a definition should stipulate that tissue engineered products must involve both cells and supporting structures and that the presence of biomolecules is optional.

Recommendation 2.

The first task of such a regulatory body should be to establish scientifically rigorous definitions of tissue engineering products and processes that would provide a practical and unambiguous method of demarcation between tissue engineering and other therapies.

3. Because of the variation in the level of risk associated with tissue engineered products, the extent of regulatory control should also vary. This implies a type of classification of tissue engineered products. Since the level of risk is difficult to define at this stage, such categorisation should in the first instance be confined to situations of low risk and high risk.

Recommendation 3

In consideration of the wide range of risks inherent in tissue engineering, tissue engineered products and processes should be classified according to the level of risk to the patient. The process of categorisation needs to be developed but in the first instance this should be confined to levels of low risk and high risk.

4. In areas designated as high risk, which could include any product used for the replacement of tissues within the cardiovascular system, sensory organs, the central nervous system or major segments of the musculoskeletal system, regulatory control should be exercised over the first use in man of the product. This implies that a full

technical file be established for the process and/or product that is able to demonstrate an acceptable level of safety, and it should be a requirement that, as far as possible, evidence is provided of the equivalence or superiority over conventional therapies or devices. For low risk situations, which could include skin tissue, dental applications, and soft tissue replacement for cosmetic purposes, proof of principle in man could be permitted without significant governmental regulatory control. Such early stage clinical applications should be governed by local ethical committees, although there should always be the requirement that evidence is provided that tissue engineering would be expected to demonstrate effectiveness not achievable by existing treatment modalities.

Recommendation 4

The demarcation between high and low risk should primarily be based on the risk associated with the performance of the final product. In products or processes defined as of high risk, regulatory control should be exercised over the first use in man.

5. Whatever the application, clinical trials should be conducted according to procedures set out by the new Regulatory Body. This may be best achieved by an annex to the existing Clinical Trials Directive (European Union, 2001/20/EC).

Recommendation 5

Clinical trials of tissue engineered products and processes should be governed by the Clinical Trials Directive.

6. Similarly, whenever a tissue engineering process is commercialised, the placing of the process or product in the market place should be regulated. It is unlikely that this could be achieved solely through the declaration of conformance to quality assurance systems requirements, such as currently exists with medical devices, and a system distinct from the CE marking process through Notified Bodies would be necessary.

Recommendation 6

The Tissue Engineering Regulatory Body should establish a system for regulatory evaluation and approval that is different from the current procedures for medical devices.

7. However, a quality assurance systems approach is considered an essential component of any regulatory process. This should reflect best practice with the handling of cells and should encompass appropriate levels of traceability. Special emphasis should be given to situations in which different components of a tissue

engineered product, such as scaffolds, pharmaceuticals and cells from multiple sources, are obtained and incorporated into the product at the point of clinical use. Procedures for transport and storage should be established. Labelling of all components and products is of critical importance.

Recommendation 7

The regulatory process should incorporate quality assurance systems and should reflect best practice for all source materials and processes, with emphasis on traceability, transport, storage and labelling.

8. Any organisation or institution involved with a product or process that is in the high-risk category should be licensed or accredited in accordance with approved and relevant criteria.

Recommendation 8

Any organisation or institution involved with a tissue engineered product or process should be licensed or accredited in accordance with approved and relevant criteria

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