Tissue engineering: viable technologies seeking regulation – a Finnish perspective

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The progress made in understanding the differentiation of cells, the regeneration of tissues, the expansion and manipulation of cells *in vitro* and advances in the technology of biocompatible materials have raised hope in the capability to restore cellular and/or organ functions that have been lost as a result of injuries or other diseases. It is evident that the most ambitious goals will not be achieved without using living cells as the 'active substance' of future remedies. These products have been called 'cell therapy' products or 'tissue engineering' (TE) products. As cellular- and tissue-based products emerge, developers and regulators are concerned that the current regulatory framework and praxis for medical devices or medicinal products might not be adequate for all future cell-based therapies. Within the European Union (EU), current regulations include Directive 2001/83/EC (for some cell therapy products) and Directive 93/42/EEC modified with 2000/70/EC (for medical devices incorporating human plasma derivatives). In addition, there is a draft proposal for a directive of the European Parliament and the Council of the EU on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells – the 'Tissue directive' [1]. However, the classification of the wide range of products according to their origin (autologous, allogenic or xenogeneic) might prove difficult because an autologous or allogenic product could include xenogenic materials, tissues, cells, derivatives, engineered matrix or engineered organs. Many of the cell-based products will fall into the category of medicinal products and should be regulated accordingly. Current EU-legislation (Directive 93/42/EEC) directs that a product containing living human cells cannot be regulated as a medical device. Several EU member states have adopted variable national policies to fill the perceived gap between medical devices and medicinal products. As a result, the development of products to the common EU market is extremely difficult.

Recently, EuropaBio (http://www.europabio.org) called for the creation of a new EU regulation that is specific to cell and/or tissue engineered products, is outside medical device and medicinal product regulation and is based on the degree of manipulation and on primary mode of actions (a pharmacological, metabolic, immunological, physiological or systemic effect). Furthermore, recent proposals by the industry for regulation of cell-based therapies and related products encompasses different options: a decentralized procedure in which governmental or non-governmental Notified Bodies (NB) approve the product for all EU markets, a centralized procedure in which market authorization is granted by an agency, for example, the European Medicines Evaluation Agency (EMEA) and a compromise in which the decentralized route would apply, but the NB would be required to seek consultation from an expert committee and the final decision for market authorization would be granted by national authorities of EU member states [1]. The recent approach adopted by the FDA for regulation of human tissues, cells, and cellular- and tissue-based products provides an alternative approach [http://www.fda.gov/cber/tiss.htm (6 March 2003)]. The FDA has presented a unified, tiered approach in which the level of regulation is commensurate with the degree of risk. From the point of view of the developer, this approach increases the predictability of regulatory requirements and supports innovation [2]. In the proposed regulatory strategy for cellular therapy products, preparation of the products would be under current Good Tissue Practice (cGTP) guidelines for minimally manipulated products or current Good Manufacturing Practice (cGMP) guidelines for more than minimally manipulated products [3]. Within the EU, the future 'Tissue directive' will set uniform standards for quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, irrespective of the product classification. Additional requirements (GMP) will be applicable to products that are manipulated further.

As the regulation of cell-based and related therapies is currently in a state of turmoil in the EU, researchers and potential product developers in Finland, as in many other Northern European countries, are moving ahead without being able to anticipate future regulatory requirements. Thus, the aim of this article is to contribute to an

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insight for building a future regulatory framework within the EU, which would facilitate bringing safe, ethically acceptable and commercially viable products to the market without an unreasonable delay. Consequently, this communication addresses key issues and potential regulatory problems of cell-based and related therapies, including tissue engineering, as viewed by researchers in Finland. These views are also interpreted from a European regulatory point of view.

The present communication is based on data collected in 2003 from interviews with academics and authorities in Finland. In total, 18 experts were interviewed, of whom 13 were academics from different universities, four represented national authorities and one other expert was a specialist in commercialization of innovations. Although the number of interviewees was limited, those that were interviewed were carefully selected to represent local, internationally recognized scientists and other experts in the field. Interviews were conducted in a structured manner [4], but the experts were free to express their own insights. Following the responses to individual questions, the focus of the discussion moved to the interpretation of the pros and cons of various regulatory options[i].

Views and concerns of product developers and regulators

For a regulatory framework to be functional, it will be necessary to create a sustainable terminology and a scheme for classifying products into categories. Thus, the first issue that had to be addressed was to establish how interviewees interpreted the term 'tissue engineering'.

Is tissue engineering a sustainable term?

Defining tissue engineering is difficult. The majority of the interviewees had to dwell carefully on the question as to what exactly tissue engineering is and what it encompasses. The majority (nine out of 12) of the interviewees gave a broad definition for tissue engineering as including all cell-based products. A narrower definition restricted tissue engineering to products in which normal tissue has been processed and possibly connected to artificial material for the purpose of repairing an injury. In addition, many of those interviewed considered tissue engineering to include pure cell-based products, as well as products with a scaffold. Moreover, most of the interviewees felt that tissue engineering implicitly involves some form of stem cell technology.

The above results might be interpreted as indicating a need for a sustainable definition of tissue engineering for the legal basis of regulation. It is evident that the choice of a particular regulatory pathway will have a crucial impact on the development, approval, marketing, data protection and reimbursement of a cell-based product. Therefore, the definition of tissue engineering should enable the classification of products without a risk of different interpretations by different authorities.

The term 'tissue engineering' does not appear anywhere in the current harmonized EU legislation, whereas 'cell therapy' has been included in the clinical trials directive[ii], a communication of the EU Commission (Commission communication on the Community marketing authorization procedures for medicinal products, 98/C 229/03), the Annex I of Directive 2001/83/EC and the regulatory guidelines issued by the Committee of Proprietary Medicinal Products (CPMP) of the EMEA. These definitions of 'cell therapy' are not exactly the same but the following aspects are highlighted: use of living cells as starting material, significant manipulation *in vitro,* production on an industrial scale, a pharmacological, metabolic or immunological mode of action and the intended use for the diagnosis, treatment or prevention of diseases or for the restoration of a physiological function. Using these definitions, a wide range of autologous, allogenic and xenogeneic cell therapy products have been classified as medicinal products and are currently being developed according to the medicinal product legislation. Thus, the definition of a tissue engineering product should be based on scientific criteria that will make it possible to distinguish the tissue engineering products from medicinal products.

Should risk be a factor in a new regulatory path?

The majority of interviewees (ten out of 13) were of the opinion that existing legislation is not sufficient for covering all cell-based therapies and products and that there should be a new category and regulatory path for such products. The majority (five out of eight) of academics who expanded on this issue further divided these products into smaller subgroups. The subgroups were seen as a necessity for the adequate assessment of the specific risks involved with certain technologies. The risks associated with cell-based and related therapies and products were considered to be far larger than those of medicinal products or medical devices. The interviewees were also of the opinion that it was difficult to make comparisons between product categories because there is

[i] The regulatory comments are personal opinions of Pekka Kurki, who did not take part in or have access to any raw interview data. These comments do not necessarily reflect the position of any regulatory body.
[ii] Directive 2001/20/EC of the European Parliament and Council (4 April 2001) concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

heterogeneity within product classes. Thus, it was thought that future legislation should reflect this heterogeneity. Of the authorities interviewed, three saw a need for creating a new category and procedures, but one could not see any reason for taking such measures. With reference to classification as medical devices, four of the academics were of the opinion that some products (i.e. products without living cells) could be classified as medical devices. This route would lead to a less stringent regulation of the simpler and less risky products.

The main risks of cell-based and related therapies mentioned by interviewees included, transmission of infectious diseases, inflammation, carcinogenicity, immunity-related risks and risks associated with surgical procedures that involve the administration of the product. Evidently, even though interviewees have evaluated the field as being broad, possible risks reflected a rather narrow and consistent view. Interviewees considered risks associated with xenogeneic cell products to be considerable. Furthermore, in the literature, all types of xenogeneic cell products are associated with one or more significant problems, including hyperacute rejection, delayed rejection, cell-based immune rejection and risks for novel zoonoses [5]. The interviewees expressed limited confidence in the potential of xenogeneic cell products, although they did not wish to exclude them completely as potential future products.

Considering the agreement on the relatively high risk of TE products, it could be suggested that putative new legislation should be based on the same principles as those used for legislation of medicinal products. The risk cannot be judged in isolation from the benefit and quality or safety and efficacy (i.e. benefit and/or risk) that should be demonstrated before marketing authorization is granted. For safety reasons, look back and adverse event-reporting systems should be established and the conduct of clinical trials should be regulated. As a consequence, the development of TE products according to these principles will be difficult for small companies and hospital-based research groups. Furthermore, some autologous cell products will have difficulty in meeting the requirements for cell banking, uniform specifications and batch release testing.

Who should regulate products and how?

In the present survey, a clear majority of the interviewees called for an appropriate EU Community legal framework. Of this majority, eight out of 12 opted for a regulation that would cover the EU as widely as possible. However, seven of the interviewees that held this opinion also thought that issues relating to ethics and religion, with particular reference to stem cells, should be dealt with at the national level. This can be interpreted as a pragmatic approach that could facilitate consensus. The same approach, the creation of common standards while enabling national adjustments, has already been adopted in the blood directive 2002/98/EEC and has been proposed for the draft tissue directive (EEC; 50/2003). Unfortunately, common standards alone do not necessarily lead to uniform requirements in all EU member states, as has been seen in the medicinal product area. A centralized evaluation seems to be the only way to a common approach to TE products that provides for the access to the common EU market. There are several reasons why future product developers might be expected to support an EU-wide regulation. Clearly, markets for future products are worldwide and product developers would find it easier to apply a harmonized regulation. Some supporters of the member state-based regulation were concerned that a pan-European regulation restricts research, particularly on stem cells. There are fewer ethical and religious objections towards stem cell research in Northern Europe and a unified approach might impose unjustified restrictions on research and development.

Will stem cells drive the development of future therapies?

Although some of academics interviewed thought that stem cells will be the drivers of the next wave of innovative new treatments, others were concerned about their premature entry to the market. In this study, interviewees were not unanimous in their views on whether or not stem cell products should be more strictly legislated and supervised than other cell-based products. However, all agreed that product safety, particularly with reference to carcinogenicity and consistency of the manufacturing process, must be ensured through exhaustive long-term studies.

Interestingly, human embryonic stem cells (ES), which are the most controversial candidates from an ethical point of view, might be the best candidates to satisfy some of the future regulatory requirements [6]. Cells such as ES can be grown in large quantities under defined conditions and can be subjected to a range of tests that would not be feasible to perform for autologous cells (because of their limited supply). However, in the present study, adult stem cells were thought to be the more probable candidates for TE, although their ability to differentiate was considered to be more limited. It could be interpreted that favouring the use of adult stem cells is a consequence of the ethical problems associated with using ES cells. By contrast, many interviewees see the use of ES cells as offering so many advantages that it is thought these cells will become the main focus of research, provided that

ethical, religious and political issues can be resolved in the future.

The commercialization of embryonic stem cells was seen as one of the major ethical problems, even from a Northern European perspective. Another ethical issue discussed was the procurement of tissues (e.g. from areas in a military conflict and from poor countries for financial benefit) and the hazards of the possible surgical procedure needed for administration of the product to the patient. Although a few of the interviewees (three out of 16) intimated that the commercialization of stem cell-based therapies is not at all ethically acceptable, this was not an inflexible opinion of the interviewees. Limited reimbursement of the treatment with tissue engineering products might also create ethical problems for the health care system and financial problems for the companies. Overall, the interviewees expressed concern that only a small proportion of the population would have access to future tissue engineering products. Regardless of these concerns, the ethical problems were not seen as obstacles for high-quality scientific research, of which stem cells were considered to be an essential part. However, the commercialization of embryonic stem cell-based products is not currently possible in Finland or any other EU country. Thus, ethical issues must be resolved before commercially viable products can be developed.

The future

Most interviewees stated that some reasonably simple products will be launched in the next few years, but it will take 10–20 years before there are more sophisticated products on the market. Ethical issues were mentioned as the main obstacles in product development by six out of eight of the interviewees. Other concerns were regulatory and scientific aspects. Two academics had confidence in autologous products, three in a more diverse range of products and two stressed that autologous and diverse products will emerge. According to most interviewees, cell-based therapy will be an expensive treatment method that will increase health care expenditure. However, as these might offer the only treatment for many diseases, health care systems will need to adapt to future societal and ethical demands.

The majority of interviewees were optimistic about the future of cell-based and related therapies in Finland, but some believed that there can only be success in niche areas. Insufficient knowledge of developing a commercial product, the lack of sufficient co-operation between research groups and the incomplete knowledge of academics about regulatory procedures were seen as major challenges. These difficulties reflect the novelty of the field itself, as well as the lack of appropriate legislation and guidance. Furthermore, funding was considered to be insufficient. The hesitancy of investors to commit to financing cell-based and related therapies is a common problem within the biotech industry. Interestingly, interviewees considered the uncertainty of the future of regulatory procedures to have only a minor affect on financial prospects.

Evidently, regardless of considerable research efforts, Finnish groups appear to be still at the concept stage in the commercialization of their cell-based products, whereas competitors abroad are already running clinical trials with various autologous, allogenic and xenogeneic cell-therapy products. Some American and European companies are already marketing tissue engineered products.

Conclusions on product development and regulation – can a consensus be reached?

The majority of Finnish experts called for common standards for the EU area. However, common standards do not necessarily lead to uniform requirements in all EU member states. A centralized evaluation seems the only way to ensure a uniform assessment of TE products, a feature that is necessary for the access to the common EU market. Evidently, the existing regulation for cell-based and related therapies is not sufficient for covering all product categories. However, a new regulatory product category might not be the only solution. There is a general consensus that although some of the products do resemble medicinal products, others are compatible with medical devices. In addition, there is agreement in the importance of the risk of infections in the use of products containing living cells, particularly xenogeneic cells. Although the risks of TE products for patients are regarded as high, developers feel that the current legislation is not suitable for these products. From the regulatory point of view, this should lead to a legislation that would be at least as stringent as current legislation for medicinal products. Thus, a new tissue engineering directive would be feasible only for products for which the level of requirements can be more flexible and adjustable than that of a medicinal product. In any case, future regulatory requirements for TE products will probably not be stricter than the current requirements for medicinal products. Thus, research groups that are currently in the concept stage of the commercialization of cell-based products can safely develop products according to the principles applied for medicinal products. Developers should also be aware that although development of a medicinal product might be more costly, these products would be supported by scientific advice, by regulators, data protection and eligibility for reimbursement.

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References

1 Chignon, T. (2003) Regulation of human tissue/cell products in Europe. *Keynote Presentation, Regulatory Affairs Professional Services Discussion Forum: development and regulation of cell-based and related therapies* (20–21 March 2003, London, UK) (unpublished)
2 Warner, J. (2003) The status of regulation of cell therapy products by the US FDA. *Keynote Presentation, Regulatory Affairs Professional Services Discussion Forum: development and regulation of cell-based and related therapies* (20–21 March 2003, London, UK) (unpublished)
3 Gee, A.P. (2002) The impact of regulatory policy on the development of somatic cell therapies. *Transpl. Immunol.* 9, 295–300
4 Hirsjarvi, S. and Hurme, H. (2000) *Tutkimushaastattelu – Teemahaastattelun teoria ja käytäntö* (1st edn), Yliopistopaino
5 Persidis, A. (1999) Xenotransplantation. *Nat. Biotechnol.* 17, 205–206
6 Dove, A. (2002) Cell-based therapies go live. *Nat. Biotechnol.* 20, 339–343

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The analysis of tandem mass spectrometric datasets: high-throughput investigations require high-quality validation

As the various technologies involved in proteomic analyses have matured to become capable of rapidly generating high-quality data, recent studies have focussed on high-throughput, automated applications of these technologies. However, the quality of the output data must be considered. Given this, the timely review by Nesvizhskii and Aebersold [1] in a recent issue of *Drug Discovery Today* summarizes many of the key requirements for the statistical analysis and validation of the results of large-scale proteomic experiments [1].

One of the primary factors that requires consideration is the amount of information that is needed from the generated dataset. Studies carried out within our laboratory have indicated that extremely limited sequence data are sufficient for the identification of the gene from which peptide ion-fragmentation data derives, with a high degree of confidence in many cases (as in the so-called 'just-enough diagnostic information' approach [2]). Indeed, this approach has the advantage that the ion current of tandem mass spectrometry (MS–MS) spectra can be concentrated on a smaller number of fragment ions, thus increasing their abundance and, in cases where high-quality sequence databases are available, significantly increasing the confidence of the matched sequences identified by database searching.

Although decreasing the rate of false-positive peptide identification in database searching is clearly desirable, there is also a strong case to be made for allowing more minor sequence variations. This could enable peptides with high-interspecies identity to be matched to orthologues and errors in sequence databases and post-translational modifications to be more readily incorporated into searches.

Another requirement that many high-throughput proteomic strategies overlook is the biological significance of the data. In a typical MS–MS-based approach, peptides are selected for MS–MS based on their relative abundance. Clearly, the nature of many of the peptides selected using these criteria will be the products of housekeeping genes (i.e. proteins that are essential for cell function, but the levels of which fluctuate insignificantly). However, in the analysis of biological processes such genes are rarely informative. Hence, the preselection of ions having relative intensities that vary significantly between cells under different conditions would clearly give a more biologically relevant dataset. This type of strategy exploits the developed stable isotope methods, although inter- and intra-experimental variability require further investigation [3].

For proteomic data to be shared and compared between different laboratories, standardized criteria for the

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