


Forschungsergebnisse
aus dem Institut für Rechtsmedizin der Universität Hamburg
Herausgeber: Prof. Dr. med. Klaus Püschel
Band 31

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**Postmortale Gewebespende:
Quo vadis?**

STIFTUNG
EUROPÄISCHE 
GEWEBEBANKEN

Jahresband 2014/15

Verlag Dr. Kovač

New perspectives for tissue banking in Europe

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According to the survey of the European Commission over half million allografts have been distributed in Europe in 2013. These grafts have been produced by 1083 Tissue establishments. Despite these volume, the number of tissue establishments have been decreased over the past ten years. One of the reasons for this decrease is the increasing quality demands put upon the tissue banks by the European legislation on safety and quality of tissues and cells (EU Directive 2004/23 et.al.). These requirements forced the establishments to invest in infrastructure, staff, documentation and even ICT support. Those banks that have been able to manage these changes are nowadays officially licensed by the Competent Authorities. The remaining tissue banks have either closed down or merged to form one of the larger tissue establishments.

Despite these developments, the characteristics of tissue banks are still dominated by their origin, which is often based in local hospitals wards, and related to enthusiastic surgeons who have started their own tissue storage in the eighties or nineties of last century. They mainly supply their own hospital with a limited variety of products. Sometimes there is an association between these hospital banks and the regional blood banks. The full scale tissue banks however, where several types of tissues are processed on an large scale, are limited to one or a few per country ($\pm 25-30$ in Europe).

In general the current tissue banks can be characterized as follows:

- Small or medium scale enterprises, with limited number of staff often specialized in 1 type of tissue
- Closely linked to local hospitals and certain surgeons
- Limited or no capacity for research or product development
- Not for profit, but otherwise an unclear business model
- Financed in different ways, only partly depending on actual sales
- No marketing knowledge or capabilities
- Able to maintain GTP (Good Tissue Practice) levels, but not able to implement pharmaceutical production regulation
- Changes in the use of human allograft products

Due to aging of patients, development of new applications and the growth of health care consumption in newly industrialized countries, it is expected that the demand for tissue will increase further over the coming years. This can either be in the form of the traditional transplants, or as base material for new, bio technologically processed, tissue products. As a consequence the market for tissue is growing and will becoming more and more internationally orientated. This has a constant impact on the position of current tissue establishments. Furthermore, standards and regulations for production of allografts have become more demanding, due to the introduction of legislation (EU directives, FDA), and at the same time biotechnological research is increasing and is developing new type of products.

These developments in the use of human allografts induce significant changes in the traditional way tissue banks produces human allografts. Among others, the following trends can be distinguished:

- **Scarcity in Europe**

The availability of human donor materials is limited and banks in general have difficulty to keep up with the increasing demand. In Europe, donor referral programs have been established in many countries to fulfill the patient demands, but the total number of cadaveric donors for instance (estimated about 13.000 based on Eurocet survey) is insufficient to meet the demands for certain products like tendons, composite allografts, and heart valves. To bridge part of the gap, Europe still has extensive living donor programs (femoral heads and to a certain degree, domino hearts). However due to the high cost for processing and the small amount of tissue it renders, living donations are rather cost-inefficient. The increasing demand for grafts is otherwise met by substituting human allografts with synthetic tissue, prostheses or other non-human biologicals. Especially faced with unpredictable scarcities, surgeons may prefer synthetic materials, not per se because of the clinical outcome but more because the guaranteed availability.

- **Increasing availability of human tissue in the US and other parts of the world**

In the US, the banking community has acknowledged the growing demand for human allografts in an early stage. This has lead to implementation

of highly effective donor recruitment programs, which results in the recruitment of large number of donors (AATB annual survey). On the other hand the donor potential in Asia and the former East European countries has also the potential to surpass the European donation levels per head of the population.

- **Increase of import/export and strategic alliances**

The overproduction of some allografts in the US has led to a need for new distribution channels, which promoted strategic partnerships between traditional tissue establishments and commercial parties like distributors, medical devices companies and other parties active in the medical field. These new partnerships enable not only the set up of mutual marketing and sales strategies, but also provide funding for development of new products. Finally, alliances with European banks, EMEA banks and distributors have been built to export to Europe and newly industrialized countries, which do not have a fully developed system for donor retrieval and tissue banking yet.

- **Quality demands and product developments**

The demands for quality and safety of human allografts are imposed on the tissue banks by European legislation, but also by the medical field. Surgeons expect human grafts to meet the same standards as synthetics grafting material, especially in relation to patients' safety for infectious disease transmission. To meet these challenges the tissue banking community needs to increase their economy of scale. On the one hand biotechnical developments have opened a variety of opportunities for product development like (mesenchymal) stem cells, scaffolds, or combinations of bio and synthetic materials. To be able to participate in these new developments, traditional tissue banks are forced to collaborate with third parties, who are able to invest in product developments, or can contribute to their research efforts like academia and biotech companies.

- **Risk of losing autonomy and self reliance**

Because tissue banking becomes more and more dominated by the "commercial" approach of tissue industry (often US based), the independence of tissue banking in Europe may be at risk. Not only may

Europe fall behind in applying new technologies, the price setting and availability of tissue jeopardizes the current position of the European tissue banks. After all, many European countries have policies of non-remuneration and not-for-profit price levels installed, originating from their philosophy towards human donated material. This philosophy can be on strained terms with the industrial approach we see in other parts of the world.

Consequences for tissue banking in Europe

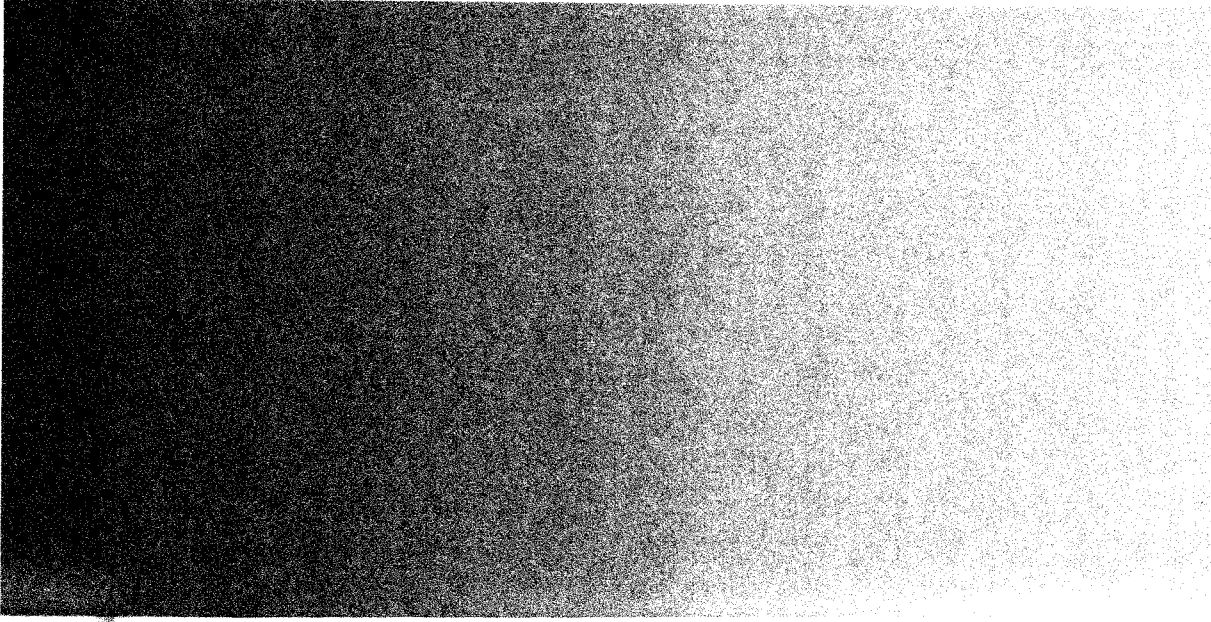
More small-scale hospital banks will close because of competition from tissue industry, the distributors of medical devices and cost reductions in hospitals. Their strong point: the affiliation with local surgeons and hospitals might be overshadowed by the pharmaceutical marketing strategies of large parties. Furthermore the price setting of allografts, despite the increase in quality requirements, will remain under pressure because of the marketing and export strategies of large tissue banks for outside Europe.

The size of tissue establishments has to increase, not only to be able to employ staff that is knowledgeable in the field of product developments, GMP environment and biotechnology, but also because a minimum throughput is required to guarantee efficient processing. For cadaveric processing for instance, a minimum number of post mortem donors is needed to maintain a cost-benefit balance for the exploitation of the processing lab, the training programs, validation studies and the quality systems.

This economy of scale can be achieved by collaboration or merge between tissue establishments, but it can also be realized by other cost effective strategic partnership(s) for instance with (for profit) processing facilities or joint ventures with industry and/or academia.

Future challenges to be met

With the developments in bio-engineering techniques and the expanding knowledge of the role of stem cells, new products will emerge, which are composed of the properties of the original tissue, combined with pharmaceutical, biological or medical devices additives. Traditional tissue products will gradually be transformed into products that are bio-engineered or modified from base material, stem cells and growth factors that can, for instance, be manufactured through recombinant techniques. Many of these products will be considered ATMPs (advanced therapy medicinal products) especially when living cells are added, or Medical Devices, in



case tissue is extensively manufactured but no living cells remain. For tissue banks it is essential for their future position, to keep in touch with these developments by forming partnerships with research institutes, biotechnology companies or universities that are active in this field. The banks can play an important role as supplier of some of the base material for these future products. The final manufacturing of these complex tissue products requires a pharmaceutical GMP environment including the expertise and capacity to produce on a more industrial scale.

The future developments in the treatment of patients who are in need of tissues will represent a constant change in the scenery of tissue banking. Only those banks that are able to adjust to these trends will be able to continue their role in the support of the medical professionals that are looking for the safest, cost-efficient and effective therapy.