VITAL TISSUE: A FRESH HUMAN TISSUE SUPPLY CHAIN TO ENABLE TRANSLATIONAL RESEARCH

RECOMMENDATIONS FOR THE SUSTAINABLE USE OF VITAL HUMAN TISSUE MATERIAL FOR (APPLIED) SCIENTIFIC RESEARCH AND TO REDUCE THE NEED FOR ANIMAL TESTING

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TNO innovation for life

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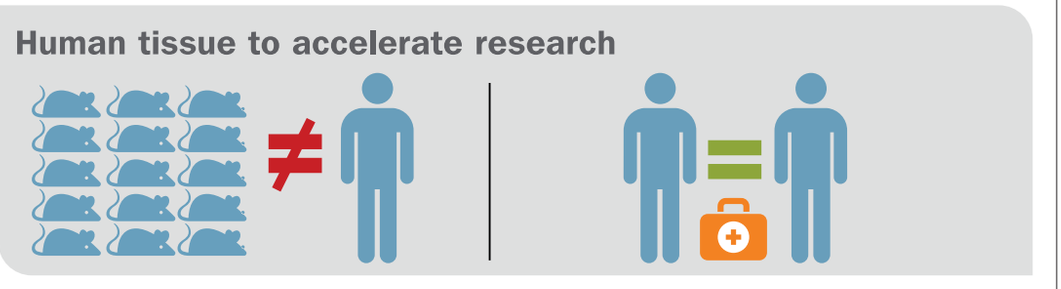
INTRODUCTION

In the Netherlands every year more than 500.000 (in 2015 528.159 registered[1]) animals are being used for scientific research, professional training and for testing safety and efficacy of products (including medicines). Before use in/for humans, animals or the environment, new products can only be marketed when acceptable safety standards have been met in validated toxicological and pharmacological models using animals and/or in vitro models.

Over a decade ago, the previous "Platform alternatives to animal testing" and the "Programmacommissie Alternatieven voor Dierproeven" of ZonMw[2] promoted research aimed to develop feasible alternatives for animal use in The Netherlands. ZonMw did a study on the use of human tissue material in scientific research in the Netherlands. From a survey in 1996[3], it was concluded that many researchers were in favor of using human tissue material, which could in some cases be used as an alternative for the use of animals in scientific research (e.g. ex vivo human skin instead of in vivo rodent skin absorption). Moreover, it was suggested that human tissue could provide better extrapolation of safety and efficacy outcomes to humans compared to outcomes obtained from immortalised cell lines and animal studies, thus increasing pre-clinical predictions.



In contrast to these outcomes, a survey in 1998[4] revealed that many research groups still did not use human tissues, although they believed that their research would benefit from it. The most important reason mentioned appeared to be: the limited availability and lack of supply of human tissues, the insecurity related to legal implications for the medical residents, consultant, surgeons and other suppliers. Additionally, researchers were also uncertain about ethical governance of the use of human tissues. Last but not least, also the infrastructure for the organisation of tissue banking appeared to raise many hurdles.

In 2001, the FMWV (Federatie van Medisch Wetenschappelijke Verenigingen) started with the definition of the Code Goed Gebruik[5] (Code of conduct for responsible use), a guideline for the proper use of human tissue for another purpose than for which it was originally removed. This code includes recommendations what should be arranged for proper use of human material especially for protection of the privacy of the donor, information transfer and how and when informed consent from the patient should be required, which has been revised in 2011[6]. According to this guideline, the responsible surgeon has to take care of this process by providing a coding system of the available medical records, which could be available as coded data for researchers. The donor should be informed about the nature of the scientific research the material will be used for, and should sign for agreement (informed consent). Although this approach will level legal and ethical hurdles, still the organisational and logistic problems need to be solved individually by all parties.

Starting in 2014, a new survey regarding the use of human material for (applied) scientific research as an alternative for animal use and in vitro animal cell systems was conducted in the Netherlands. Although several biobanks with human bio specimens are already operational in the Netherlands[7], none of them can provide fresh and vital, not frozen/non-preserved human tissue material nation-wide or even regional. Abroad however, there are some tissue banks which can commercially deliver fresh human material. Conventional biobanks are supported by networks and collaborations between (international) biobanks that provide information regarding EU guidelines, ethics and (preservation) technology.

Examples of such networks are the European Network of Research Tissue Banks (ENRTB), and the Biobanking and BioMolecular resources Research Infrastructure, the Netherlands (BBMRI-NL) that is promoting collaboration and standardisation between the clinical and population cohort biobanks in the Netherlands. Although not focusing on vital, fresh tissue, these initiatives provided a framework that sharpens the initiative to set up a human tissue supply chain providing scientific and applied research with vital, non-frozen human tissue material in the Netherlands.

To determine the need and interest for this initiative, we, a consortium of research institutes and some companies, have recently performed a qualitative survey amongst peers and eminent stakeholders, such as medical researchers, patients representatives and industry, by oral interviews and questionnaires. The first outcomes of the survey revealed that there is still a public interest and scientific need for fresh, vital human material to provide predictive models for translational research and at the same time contribute to the aim to replace animal testing. In this paper we first discuss the use of human material for scientific research in general. The governance structure of the human tissue supply chain will include stakeholders such as medical hospitals and donors (or their representatives such as patient organizations). The outcomes of the interviews with stakeholders will be discussed, followed by a presentation of our recommendations regarding a vital human tissue supply chain in the Netherlands.

HUMAN TISSUE FOR SCIENTIFIC AND APPLIED RESEARCH

Most biomedical scientific research is focused on enhancing knowledge on human physiology and pathology to improve health and quality of life. Animals are often used in scientific research e.g. for drug development as models for safety, pharmacokinetics and efficacy testing before administering the compounds to humans. Although humans and animals share similarities in general physiology, there are major species differences that can contribute to differences in responses to exogenous compounds e.g. the toxicity or efficacy of medication. These differences, at least partially, explain the adverse effects observed during drug development in the clinical phase, were a significant number of compounds are not tolerated by or even toxic to humans, whereas in the animals models this toxicity was not observed. In addition, there is an increasing amount of pressure from national and international goverments to reduce, refine or replace animals for scientific research and promote the search for alternatives.

The use of human tissue meets the scientific and ethical considerations regarding the use of animals for scientific research. Cohen & De Cock Buning[3] showed in 1996, followed by Meijer[4] in 1998 and Hauman[8] in 2003, that the use of human material for scientific research can significantly reduce the number of animals experiments. A survey amongst researches indicated that they consider the use of human material as an adequate alternative for certain animal experiments. In addition, the use of human material would make extrapolation to the human situation easier, and increases the efficiency of scientific research. One of the major objections indicated by researches was the variability between human donors compared to the animals used for scientific experiments. This could however also be considered as an advantage, since knowledge on variability is of great importance for the development of drugs and would permit to include materials from different types of patients (gender, age).
There are some profit organisations providing human materials and tissues (mostly frozen), but only very limited examples of not-for-profit organisations providing human material for scientific research have been established[9]. The European Network of Research Tissue Banks (ENRTB) has been established with the goal to coordinate the demand and supply of human tissue for scientific research[10].
The survey from 1998 indicated that the existence of such a biobank could be beneficial for the use of vital human tissue material for scientific research. As indicated before, several biobanks for human material exist in the Netherlands[7], but only providing conserved and/or frozen human tissue samples which can only be used for experiments requiring non-vital human material.

SURVEY 'FROM DONOR TO TEST RESULTS'

The survey was conducted by interviewing stakeholders using an introduction sheet and a questionnaire. The stakeholders included e.g. end-user both from academia and industries, biobank experts from multiple institutions, BBMRI-NL, Dutch Association for Plastic Surgery, pathologists and patient associations to represent the donors.

All interviewed stakeholders did see the potential and underlined the need for initiating a vital human tissue supply chain. An essential difference between a biobank and a supply chain is that a supply chain is not the storage of human material but only transport from a hospital to a research institute. As potential benefits from such a tissue supply chain, better access to vital human material and direct extrapolation of outcomes to humans was mentioned. Replacing the use of animals and animal materials is a great asset and political and public motivator for successful implementation and promotion of such an infrastructure.

A human tissue supply chain: supplementing the biobanks

A national organised human tissue supply chain can act more rapidly in response to national and regional demands, fulfilling the meeting the needs for vital human tissue, which cannot be provided by internationally operating banks abroad. Such a supply chain will not compete with current biobank-projects, since biobanks store mostly frozen tissue and cells relevant to study diseases represented in those samples. For non-diseased-tissue there might be competition with in-house research programs at academic hospitals. In addition, although multiple interviewed stakeholders stated that the quantity of human material potentially suitable for experiments is not an issue, access to the tissues might prove to be challenging. Currently, there is no national standardised procedure to inform patients, to obtain informed consent for further use, for preserving human tissue and include tissue in biobanks. The system that delivers fresh viable human tissue to researchers currently works on personal connections and interests of doctors, pathologists and scientists, and is governed by Standard Operating Procedures (SOPs) specifically designed for each academic hospital.

Transparency and donor participation

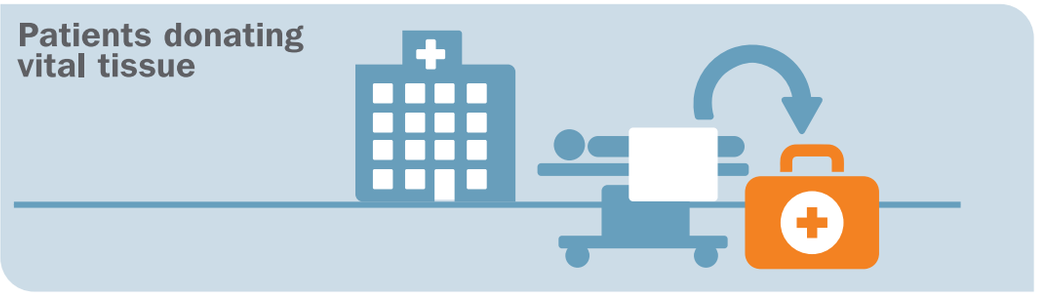
Biobanks depend heavily on public support, both for the willingness of donors to participate as well as for support in the ongoing policy discussion regarding privacy and data control[114]. An initiative regarding a vital human tissue supply chain will need a similar support. Despite the high confidence of the public in biobanks in the Netherlands, attitudes towards the use of tissue for research in an industrial setting should be approached very carefully.

Patients and donors wish to contribute to good research, not just for themselves but also even more for the next generations. Donors have ideas, concerns and preferences regarding the use and control of their tissues[12]. Ethical experts and lawyers now regularly face researchers and patient organisations in the discussions regarding privacy and legislation of commercialising human tissue for scientific research[13]. Often, donors attach importance to matters other than those stated by ethicists and legal experts, and generally attach less importance to extensive prior informed consent than to sufficient information, updates on research progress and long-term monitoring[14, 15].

Therefore, transparency is crucial for a national tissue supply chain to be successful, as is the support from relevant (groups of) clinicians. The involvement of patients or patient associations can provide public support and enhance transparency. In addition, it was stated that an independent (research) organisation should be responsible for coordination.

Supply of human material

There is an abundant potential supply of vital, non-frozen human tissue available at the academic and peripheral hospitals, depending on the type of human material. Skin, fat, blood(plasma) and uteri are examples of tissues that are often discarded after surgery, especially at peripheral hospitals. Human material that is less commonly available for scientific research after medical diagnostics are colon, liver and lung tissue, e.g. from tumor resections.



The implementation of the proposed tissue supply chain in the existing logistics of both academic and peripheral hospitals requires adaptations in their daily work. After surgery, the human tissue is transported to the appointed pathologist, and processed for diagnostics, in-house research, storage in biobanks or discarded. Within the first half hour upon arrival at the department of pathology, the tissue will be preserved by cryo or fixation techniques, typically resulting in non-vital fixed and frozen material.

RECOMMENDATIONS

Based on the survey and taking into account the results of the conducted studies, we recommend that both the needs and potential supply of vital, non-frozen human tissue for scientific research is large enough to start a feasibility study. A feasibility study to investigate whether a vital human tissue supply can be organised for researchers in (academic) institutes and industry, in a not-for-profit but sustainable way. This feasibility study should preferably be executed by relevant stakeholders, such as hospitals, patients organisations, researchers from academic andnon-academic organisations, IT and logistic companies and the government. Important issues that should be addressed: identifying and matching suppliers and users, quality control and tissue viability, logistics and transport, administration and order handling, legal and ethical implications, including informed consent, privacy and security. In addition, the development of business cases is needed to assess the feasibility of a national human tissue supply chain. Specific attention should be paid to peripheral hospitals as potential suppliers as they have an excess to human tissue, which is currently discarded since there is no request from scientific research for these tissues within these hospitals. Attention should be paid to transparency towards (potential) donors as well as to the benefits of participation for involved clinicians. Patients and patient associations should be involved in the governance of the organisation.

We believe that a vital human tissue supply chain is an unique approach to fulfill the unmet need for fresh human tissue in biomedical research. Therewith contribution to a better translation to humans and at the same time significantly contributing to the reduction of experimental animal use.

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