Conference Report

Improving the Availability of Human Tissues for Medical Research in the UK

In 20 October this year, the Safer Medicines Trust, Biopta and Asterand, hosted a discussion meeting at the House of Lords. The aim of this meeting was to examine whether it was possible to increase the supply of human tissues for medical research, with a view to improving the predictivity of preclinical studies on new medicines. The ultimate outcome is envisaged to be the delivery of safer and more-effective medicines to the market.

Bob Coleman, a pharmaceutical industry consultant, has championed the efforts of the Safer Medicines Trust to improve the safety of medicines. During his introductory presentation, Bob illustrated that foodstuffs such as chocolate would never have been marketed, if we had relied on rat or dog data. Similarly, David Bunton, of Biopta Ltd, indicated that the effects of some drugs, such as serotonin, are far more effective at inducing muscle contraction in arteries isolated from humans than in those isolated from dogs. This means that some products with real therapeutic benefits might never make it to the market, whilst others might be given at dangerously high doses.

Both Coleman and Bunton looked specifically at how drug development could be improved by using freshly isolated human tissues in studies. Iain Dougall, from AstraZeneca, went on to describe how local hospitals supply AstraZeneca with tissue for respiratory medicine research and development. Taking a slightly different approach, Kelly BéruBé, from Cardiff University, looked at how human tissues could supply a variety of cell types for reconstructing useful human models of the human respiratory system that, although not perfect representations of the human lung, are sufficiently similar to the human lung to be useful for the testing of new drugs. BéruBé's group has already managed to grow 'mini-lungs' for drug and chemical testing on plastic inserts in dishes that support the lung cells' growth at the interface between the nutrient broth, that the cells require for growth, and the air. This mimics the microenvironment experienced by cells in the lung. Even more realistically, the group are currently growing lung cells on the surface of gel beads which are half a millimetre in diameter, essentially producing a tiny 'inside-out' lung around each bead. The ultimate aim is to develop a chip on which thousands of microlungs (or, indeed, any organ) can be grown and then tested simultaneously.

There are a number of different sources of human cells and tissues from living donors, such as patients who have undergone surgical biopsies or cosmetic surgery, as well as post-partum stem-cell donations. However, despite the public perception that the surgical supply of tissues is plentiful, after the required portion of the surgically-removed tissue has been taken by the pathologist for analysis, the small amount of tissue remaining, and the fact that it is generally diseased tissue, is problematic. If human cells and tissues are to be used, healthy and diseased samples must be made widely-available and supplied consistently.

This is where the Safer Medicines Trust believes that efforts to improve the availability of non-transplantable tissues and organs from brain-stem dead but heart-beating donors, are key. These donors are likely to also supply better-quality organs than are available from cadaveric donors, which, although extremely valuable, cannot be used as a source of the tissues most sensitive to oxygen deprivation, such as neural tissues.

There is clearly a duty of care to ensure that the knowledge from studies on human tissues confers better tangible benefits to patient care, and it is clear from representations made by Jane Hair, of the Bio-repository NHS Greater Glasgow & Clyde (NHSGGC), that informed patients, when fully involved in the process of tissue acquisition, will consent more often than not. This is particularly true if the patients themselves can see the value of their donated tissue to medicine. More specifically, patients are more likely to consider donations, if they or patients suffering from the same disease are likely to derive a benefit from the analysis of their donated tissues. By incorporating an IT-driven system, it is hoped that fewer potential donors will be lost because they simply were not asked to consent to the research use of their tissues.

In line with this, there are a number of perceptions that need to be challenged before a shift in the legal framework that governs consenting and acquisition can be reformulated to make human cells and tissues more accessible for research. One is clarifying the role of the pathologist. It is increasingly commonplace for pathologists to lead translational research by using the tissues to answer questions which will, in turn, inform patient care. Chris Foster, a pathologist exonerated by the Redfern enquiry (the Alder Hey organs scandal report) indi-

cated that, for instance, one in three men diagnosed with prostate cancer have an aggressive form of the disease that requires immediate hormone treatment. However, this treatment carries a risk that almost all of the treated men will suffer a severely debilitating fracture of the pelvis within 10 years of the start of treatment. Giving this treatment to the remaining two out of every three men diagnosed with prostate cancer who do not have this aggressive form of the disease, will almost certainly mean that their quality of lives will be severely affected, or their life expectancy will be reduced. As such, if treatment can be delayed, by up to 15 years in some cases, then this will be beneficial for some patients. Those men who express a particular biomarker are now known to need immediate treatment, whilst those who do not are monitored until treatment is needed. Since these biomarkers were identified from translational research-based studies conducted by pathologists, it is clear that the pathologist plays a crucial role in improving clinical outcomes. This carries at least as much weight as the use of tissues in drug development. However, studying tissues from the deceased is perhaps more contentious than studying tissues from living donors.

Vivienne Parry, who chaired the Organ Donor Task Force, reminded the audience that the events at Alder Hey are still very much a fresh memory for many people, not least because of the associated 'cash-for-organs' scandal. The reality is that, although 90% of people claim to support organ donation, only 25% of the UK population are registered donors. There are deep rooted fears that organs will be harvested before death is confirmed, about mutilation, and that organs will not go to a 'good home'. The suggestion of an opt-out donation system triggered additional fears that, once you die, your body belongs to the state — a direct contravention of all we are led to believe by UK case law and human rights legislation.

What role, then, should the NHS play in nurturing a culture conducive to improving the supply of human tissues, and how far does this role conflict with its primary goal, if at all? Nurturing a culture of trust between the clinical team and the would-be donor is crucial, and this must operate at a level where clinical staff that regularly interact with patients are able to seek and record the consenting process. Pathologist Barry Gusterson, from the University of Glasgow, indicated that because young doctors have often never seen a diseased organ and are not trained to undertake post-mortem examinations, the number of patients being consented for post-mortem tissue sampling has fallen, despite the wealth of information that might be derived from such studies. This is a vicious circle of mistrust, leading to fewer bodies being left to research, resulting in restricted training, and thus resulting in fewer requests being made for posthumous donations. This problem must be tackled from within the NHS.

The timing of consent requests must also be considered, since asking the next-of-kin after the sudden loss of a loved one requires considerable skill and sensitivity. If the next-of-kin then veto a confirmed donor's wishes, these wishes will be respected, even though they have no legal foundation. Perhaps a system that operates along the same lines as that described by Dolores Baldasare, from the International Institute for the Advancement of Medicine (IIAM, USA), is needed, in order to encourage posthumous donations of organs and tissues for research within the UK. The IIAM liaises between the donor family, hospitals and researchers, and works with around 50 organ procurement organisations to provide tissues for research around the world. Its organ division receives around 9,000 referrals for non-transplantable organs from posthumous donors each year. UNOS (United Network for Organ Sharing) compliance requires that effective consent is acquired. Since the Uniform Anatomical Gift Act (UAGA) confers a legal right to a donated body for research, transplantation, education or therapy, would-be donors can consent simultaneously for these purposes. In the UK there is no equivalent legislation, and this means that non-transplantable organs are rarely consented for research or education.

One interesting point made by Baldasare is that the IIAM estimates that 61% of their clients are pharmaceutical and biotechnology companies, confirming that there is enormous commercial interest in using human organs and tissues for research and development. Hence, perhaps the idea that would-be donors are not well-enough informed to realise that pharmaceutical companies are not just out to make a profit, but are also the key drivers in delivering new treatments to the market/patients, is naïve. It is also, however, naïve to believe that pharmaceutical companies will drive forward a move toward the use of human organs and tissues whilst established animal models continue to tick the regulatory boxes and are not perceived to be fundamentally flawed.

It is for this reason that Coleman is of the opinion that using human tissues must not be merely desirable, but a regulatory requirement. Several of those present reiterated this sentiment, adding that improving access to posthumous tissue donations, although heavily reliant on nurturing a culture of trust between clinicians and the public, is our best chance of not only improving healthcare but also, as a consequence, reducing our untenable and unsustainable reliance on animal experiments.

This met with a degree of opposition from representatives from the Medicines and Healthcare products Regulatory Agency (MHRA), who believe

that animal models have their role in preclinical evaluation and will continue to do so for many years to come, particularly since models based on human cells and tissue-based models have their limitations. Just as animal models may not capture population-wide responses, or accurately depict what will happen in a human patient, no single organ — not even models such as the entire gastrointestinal tract which is used to examine the gut absorption of drugs (as previously described by Coleman) — is able to inform what happens in the whole patient.

Current drug development bottlenecks mean that the chances of marketing new medicines and keeping them on the market are diminishing. Many argue that this is because of our continued reliance on animal models in an age where medicines are becoming ever more sophisticated and human-specific. Yet regulators express considerable sceptism over whether many of the alternatives are capable of filling the gaps, should animal studies not be relied upon. When quizzed further, it is clear that some regulators, although willing to engage in retrospective evaluation of drug development approaches, feel under-resourced to do so. This is disappointing, as the retrospective evaluation of product dossiers several years after a product has been marketed, is capable of providing information as to those methods that are fit-for-purpose and, at the same time, might also help to weed out approaches that have poor clinical relevance. Only then can we hope to identify where the gaps exist in the specific preclinical testing needs of products, and begin to develop relevant paradigms for the efficacy and safety evaluation of new medical products.

Perhaps, in the words of Lord McColl of Dulwich, patient power is the key, and it is time we just got on with it.

A complete audio recording of the discussions that followed the formal presentations is available from the Safer Medicines Trust website (www.safermedicines.org/humantissues/).

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