**Strategy**

**Human tissues, preclinical drug safety assessment and the 3Rs**

Human functional tissues are increasingly being used to assess the safety of preclinical drug candidates. Human fresh tissues have long been considered the closest possible model of human pharmacology because they closely retain the tissue phenotype and can be used to measure a wide range of pharmacological responses. Moreover, there is considerable capacity to make better use of human tissues that are residual to surgery or transplant procedures: over 95% of patients are happy to donate surgical tissues to research and there are over 65,000 surgical procedures in England and Wales each year. This suggests that uptake of human tissues for research could make a significant impact on the 3Rs. Despite this, relatively little drug development is conducted using fresh human tissue because of the perceived logistical and ethical difficulties surrounding the availability of tissue and practicalities of experimental work. Overcoming the barriers to uptake of human tissue research remains a challenge but is supported here by clear evidence of the benefits of such an approach.

**What sources of human tissues are available for preclinical research?**

1. Tissues residual to surgery: tissues not required for diagnosis or which are generated by Tissue and organs from transplant procedures: organ donation rightly takes
2. Tissues and organs from transplant procedures: over 95% of patients are happy to donate surgical tissues to research and there are over 65,000 surgical procedures in England and Wales each year.
3. Tissues retrieved post-mortem: these human tissues are most often mixed or fixed and used in target discovery or identification.

**Human fresh tissue experimental techniques**

- **Tissue baths**: Wire myographs, Perfusion myographs, Ex vivo cultures
- **Using chambers**: Contraction/relaxation; nerve-muscle interactions
- **Perfusion myographs**: Bi-directional membrane transport; ion channels

**Example of a typical project in fresh tissues**

- Tissue transported immediately to laboratory
- For example, small blood vessels isolated from tissue sample
- The “living” tissues are exposed to drugs
- Cardiac safety

Ventricular trabeculae dissected from human heart samples, mounted in tissue baths and electrically paced for measurement of isometric force. Shown opposite is an example of the concentration-dependent coronary artery vasoconstriction caused by 5-hydroxytryptamine (5-HT) or ‘serotonin’.

**Vascular safety**

Intact, functional coronary arteries dissected from human heart samples, mounted on wire myographs for measurement of isometric force. Changes in blood flow and vascular tone can greatly affect cardiac function; even a brief reduction in coronary blood flow can induce dysfunction of the heart.

**Respiratory safety**

Current in vivo experiments for the assessment of drug-mediated changes in minute volume, tidal volume and respiratory rate may not reflect the most common causes of respiratory side-effects, which are often due to changes in airway resistance or compliance.

**Gastrointestinal safety**

Isolated mucosa from the small or large intestine mounted in Ussing chambers allows measurements of bi-directional ion transport. This can be a useful predictor of gastrointestinal adverse drug effects such as secretory diarrhoea.

**Summary**

Preclinical human tissue assays can be successfully used to help predict clinical adverse effects. Data generated may contribute to the determination of therapeutic index by correlating a measured biological effect with drug concentration in target or surrogate tissue. Whilst assays such as these do not completely replace existing safety tests, they can contribute to a platform of evidence that increases the probability of clinical success and reduces the risk that species differences will go undetected. The considerable untapped resource of residual tissues has the potential to contribute significantly to the 3Rs.

**References**

2. Defined as procedures involving “excisions or partial excisions” Hospital Episode Statistics, Admitted Patent Care 2011-12 in England.
3. A comparison of respiratory abnormalities identified in clinical trials Murphy, D.J. Regulatory Toxicology and Pharmacology (2014) 69, 135-140