Fresh, functional human tissues and the prediction of drug safety

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Strategy

Human tissues, preclinical drug safety assessment and the 3Rs

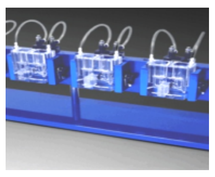
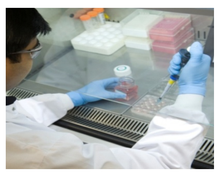
Human functional tissues are increasingly being used to assess the safety of preclinical drug candidates. Human fresh tissues have long been considered the closest possible model of human pharmacology because they closely retain the tissue phenotype and can be used to measure a wide range of pharmacological 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[1] and there are over 650,000 surgical procedures in England and Wales each year[2]. 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.

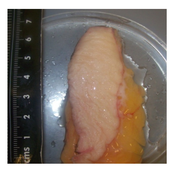
What sources of human tissues are available for preclinical research?

1. Tissues residual to surgery: tissues not required for diagnosis or which are generated by cosmetic procedures can be accessed rapidly and stored as fresh, fixed or frozen tissues.
2. Tissues and organs from transplant procedures: organ donation rightly takes precedence over research; however, many organs cannot be used in a transplant procedure and may be consented for use in medical research.
3. Tissues retrieved post-mortem: these human tissues are most often frozen or fixed and used in target discovery or identification.

Human fresh tissue experimental techniques

Tissue baths	Wire myographs	Ussing chambers	Perfusion myographs	*Ex vivo* cultures
				
Contraction/ relaxation; nerve-muscle interactions	Contraction/ relaxation	Bi-directional membrane transport; ion channels	Contraction/ Relaxation; vascular permeability (angioedema)	Test compound absorption and biomarker secretion; therapeutic index

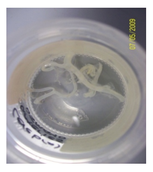
Example of a typical project in fresh tissues



Residual surgical tissue e.g. skin, lung, heart or gastrointestinal tissue

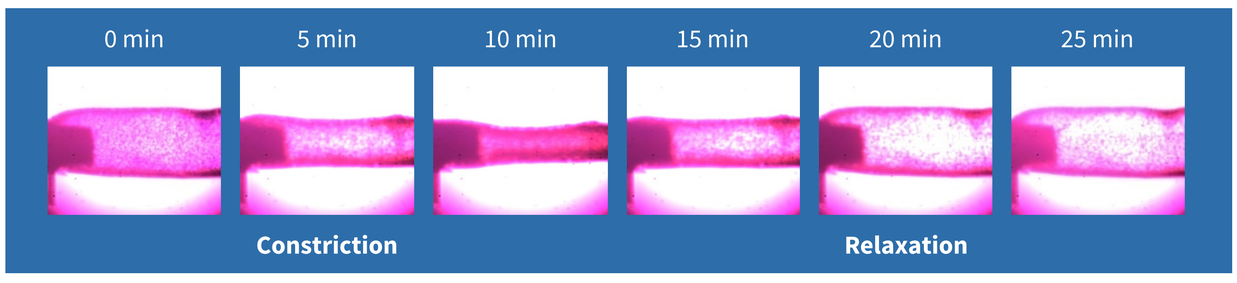
Tissue transported immediately to laboratory

Scientist isolates the tissues of interest



For example, small blood vessels isolated from tissue sample

The "living" tissues are exposed to drugs



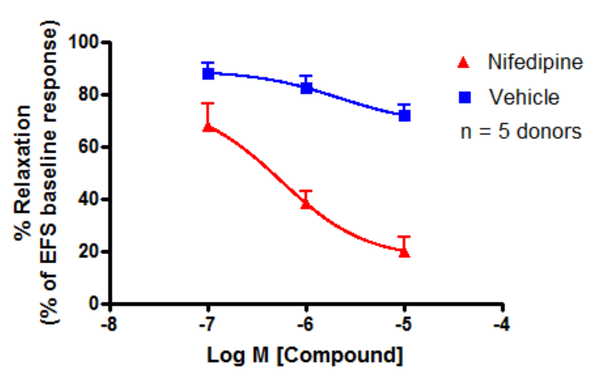
⬆ blood pressure ⬇ blood pressure

Cardiac safety

Ventricular trabeculae dissected from human heart samples, mounted in tissue baths and electrically paced for measurement of isometric force.

These functional human heart tissue preparations provide data on the inotropic and lusitropic effects of test compounds.

Shown opposite is an example of the concentration-dependent negative inotropic effect of nifedipine (a sodium channel blocker) on human ventricular trabeculae.

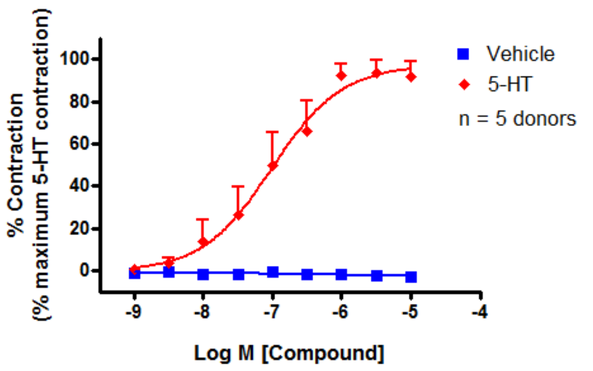


Vascular safety

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.

Shown opposite is an example of the concentration-dependent coronary artery vasoconstriction caused by 5-hydroxytryptamine ('5-HT' or 'serotonin').

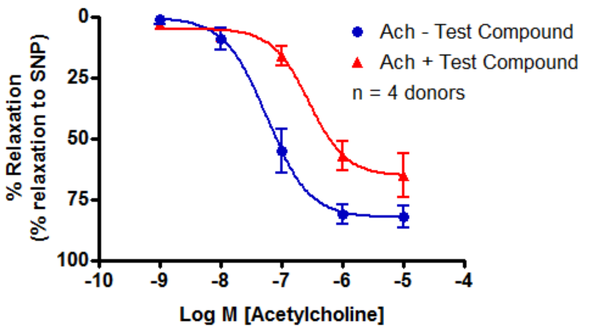


Small subcutaneous resistance arteries (approx. 200 µm diameter) were dissected from human skin samples and mounted on wire myographs for measurement of isometric force.

Subcutaneous arteries preparations provide data to help predict the influence of test compounds on human blood pressure.

In the example opposite, the test compound was shown to inhibit acetylcholine-mediated vasodilatation. In the clinic, a rise in patient blood pressure might be expected as a result.

This compound was also screened *in vivo* in rats and adverse blood pressure effects were not detected.

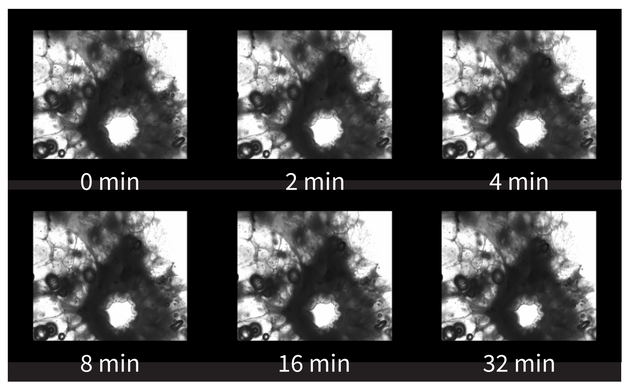


Respiratory safety

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[3].

Human isolated bronchi or precision-cut lung slices are an excellent model to assess the effects of test compounds on airway resistance.

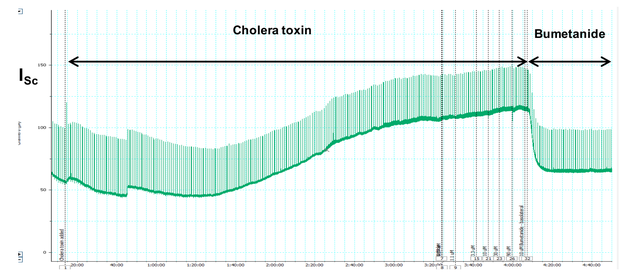
The image opposite shows the constriction observed to the muscarinic agonist carbachol over a period of 32 minutes, in a human precision-cut lung slice airway.



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.

The example data trace shows the effect of cholera toxin (known to cause diarrhoea) on short-circuit current passing across human isolated colon. Cholera toxin increases the secretion of chloride ions into the lumen of the gut, sodium ion follows, leading to the movement of water into the gut.



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

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