Fresh, functional human tissues and the prediction of drug safety

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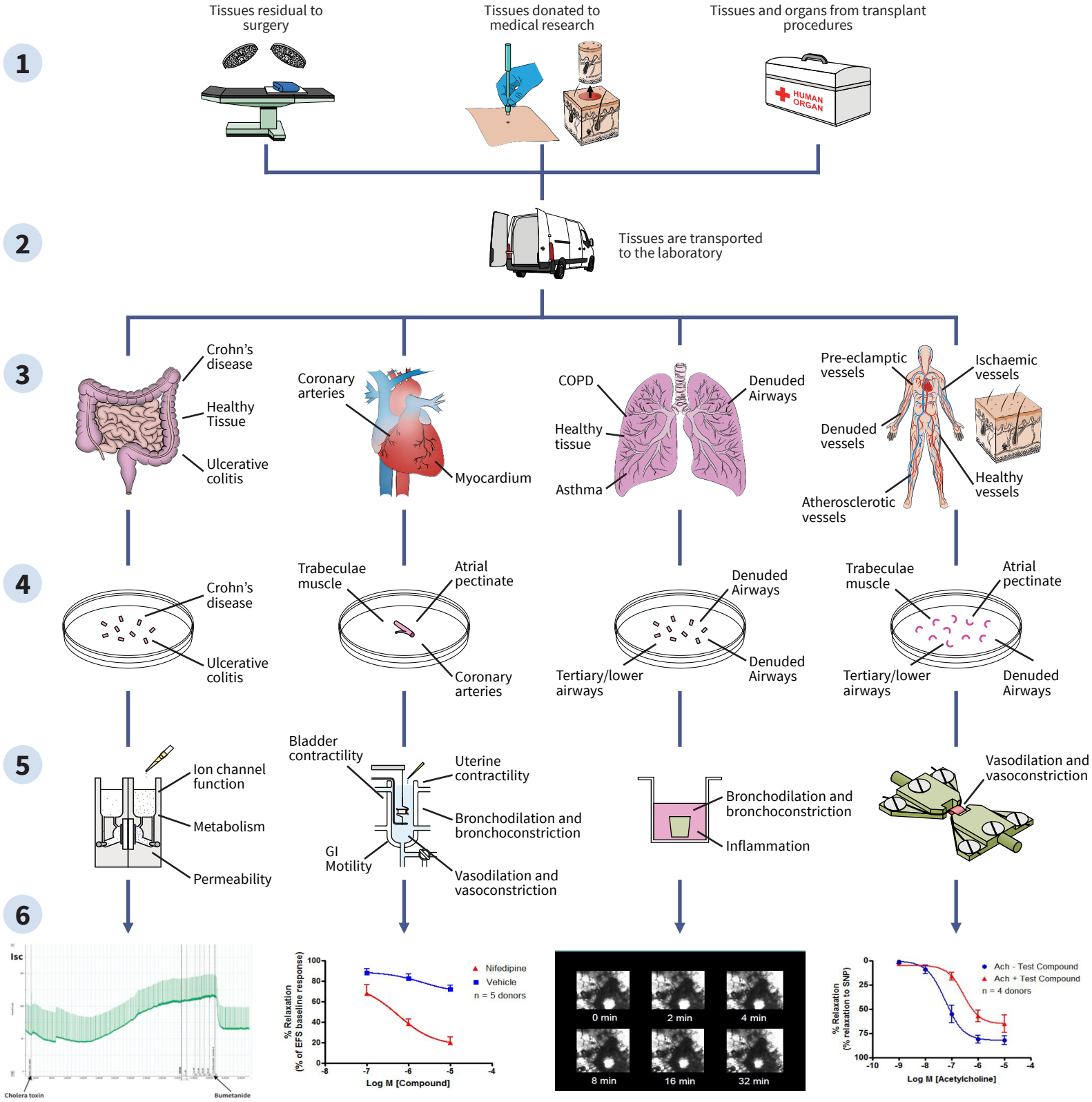
Human functional tissues are increasingly being used to assess the safety of preclinical drug candidates. These *ex vivo* assays have long been considered the closest possible model of human pharmacology because they retain tissue structure and phenotype. Human tissue models can be used to measure a wide range of pharmacological responses, and 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 the 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.

In this poster, we will explain the typical workflow of a human tissue project, from tissue procurement, experimentation, and endpoint analysis.



Gastrointestinal Safety

Isolated mucosa from the small or large intestine mounted in Ussing chambers allows measurements of bidirectional 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, and sodium ion follows, leading to the movement of water into the gut.

Cardiac Safety

Ventricular trabeculae dissected from human heart samples, mounted in tissue baths, and electrically paced during 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.

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

Vascular Safety

Small subcutaneous resistance arteries (approx. 200µm 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 vasodilation. 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.

Key

1. What sources of human tissues are available for preclinical research?

Tissues procured for *ex vivo* studies can be sourced from a variety of channels. Residual surgical tissue not required for diagnosis can be donated by patients for research purposes. For example, patients undergoing cosmetic procedures can donate excess skin samples for research. Living patients may also donate tissue biopsies or serum via specialised clinical sites. And while organ donation rightly takes precedence over research, organs that cannot be used in a transplant procedure may be consented for preclinical use.

2. How quickly should human tissues be transported to the laboratory?

To retain physiological function, donated tissues should be transported immediately to the laboratory for experimentation. Ideally, human tissue laboratories are open 24/7 to accept deliveries at any time.

3. Can diseased tissues be used to make human tissue models?

Yes, it can be useful to test compounds in tissues from a diseased patient to predict their therapeutic efficacy; it is possible to use disease specimens in *ex vivo* model systems. For example, gastrointestinal (GI) tissues from donors with inflammatory bowel disease (IBD) can be used to test the ant-inflammatory effect of experimental drugs. Airways from patients with COPD can be used to assess bronchoconstriction or dilation. And atherosclerotic subcutaneous blood vessels can help predict the effect of drug treatments in patients with cardiovascular disease (CVD).

4. What platform technologies are used to measure drug behaviour *ex vivo*?

The platform technologies used in human tissue research are well established, and have been employed by pharmacologists for decades. Ussing chambers can be used to measure changes in ion channel activity, or predict the oral bioavailability of compounds. Organ baths and wire myographs can be used to estimate changes in muscle tension or blood vessel and airway tone. And organo-culture models can determine changes in biomarker expression or airway tone.

5. What end points can be measured using human tissues?

Human tissue studies were traditionally used by pharmacologists to predict changes in muscle tone, and remain the gold standard for this endpoint. Yet today, there are many more experimental outcomes. For example, changes in inflammatory mediator expression, ion channel activity, and oral bioavailability can all be measured in human fresh tissue models.

6. Are there examples of data generated from human tissue studies?

We have provided some examples of data generated using human fresh tissues in this section of the poster. This will hopefully give you an idea of the wide range of endpoints that can be achieved in human tissues in different experimental platforms.

Summary

Preclinical human tissue assays can be successfully used to help predict clinical adverse effects. Data generated in human tissue can help predict drug behaviour by relating biological effect to patient phenotype. Whilst human tissue assays cannot fully replace existing safety tests, they can contribute to a platform of evidence that supports clinical success and eliminates species differences. And finally, the considerable untapped resource of residual tissues has the potential to contribute significantly to the 3Rs.

References

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