

Integrating Human Tissue Research into Drug Discovery and Development – Challenges, Approaches and Benefits

a report by

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Why Should We Consider Human *In Vitro* Testing?

Recent drug attrition statistics indicate that the biopharmaceutical industry is still finding it difficult to translate good ideas into safe, effective medicines. Although the target for new medicines is man, the methods employed to identify and validate suitable therapeutic targets and potential new medicines have historically been almost entirely non-human, and the ability of such methods to predict efficacy and safety in man has been demonstrably unreliable. Despite a growing appreciation of the value of human-based test methods, much pre-clinical efficacy and safety testing still relies extensively on the use of experimental animals. Furthermore, there is no clear indication that this situation is likely to change. If such non-human test methods remain central to drug

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discovery and development programmes, it is essential to understand how fit they are for their intended purpose. If the fit is poor, the compound will likely fail, or a promising new possibility may never see the light of day; therefore, anything that can be done to provide greater confidence in their utility should be done. Thus, the introduction of human *in vitro* data to validate (or otherwise) animal-based test methods will enable a more informed choice as to their use, and will likely greatly enhance the quality of resulting decision-making.

In some cases, there is no useful animal model for establishing proof-of-concept for efficacy. Cystic fibrosis (CF), an apparently unique human disease, results from the presence of a mutant form of the gene encoding the epithelial ion transporter: CF transmembrane regulator (CFTR). Although CF causes problems with epithelial function in organs throughout the body, it is its effects on the lung that are usually the cause of death. Attempts to develop a useful animal model have failed; even CFTR knockout mice fail to display the broncho-pulmonary symptoms that are so characteristic of human CF.

There are examples where the enthusiasm for the use of established, available animal models persists despite evidence of their unsuitability for purpose. Much contemporary research into new treatments for irritable bowel syndrome (IBS), a disorder of the human colon in which clinical studies have strongly implicated the involvement of 5-hydroxytryptamine

(5-HT), has focused on drugs that act at 5-HT₃ and 5-HT₄ receptors, because these receptors are implicated in animal studies. This is despite the fact that two marketed drugs acting at these receptors – the 5-HT₃ antagonist Lotronex and the 5-HT₄ partial agonist Zelmac – exhibit not only limited clinical efficacy, but also use-limiting side effects. There is also evidence that, unlike in experimental animals, the receptors mediating the excitatory effects of 5-HT in the human colon are of the 5-HT_{2B} subtype. Such failings do not condemn the use of animal model approaches as a whole, but do highlight their potential shortcomings and suggest that such models should be validated in terms of their human relevance before becoming accepted as predictive for man.

We do not intend to suggest that *in vitro* data alone can provide all the necessary information for clinical go/no-go decision-making; however, in light of the examples above, we believe that efforts should be directed towards human tissue studies *in vitro* in order to better understand the relevance of *in vivo* test systems. It must also be accepted that *in vitro* testing has its limitations, at least in part because isolated tissues can never fully represent the complex integrated biological systems operating *in vivo*. Indeed, there are examples of diseases for which efficacy and side effect testing can really be undertaken only *in vivo*, such as psychiatric

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disorders. In such cases, as with the choice of species for absorption, distribution, metabolism and excretion (ADME)/safety testing, research scientists have a responsibility to establish as far as possible the relevance of the model(s) chosen. This can be achieved in part by comparing the expression and function profiles of key targets and biochemical pathways in relevant human tissues with those in candidate animal models.

In order to make human *in vitro* testing available to the biopharmaceutical industry, Asterand has established XpressBANK and ProCURE, through which it provides human tissues as required for companies' research programmes, and PhaseZERO, through which it provides human tissue-based research services. These not only serve to aid the identification and validation of human native targets and biomarkers, but also contribute to an understanding of the action, disposition and safety of potential new medicines.

The Challenges

Despite the undoubted value of integrating human tissue approaches into drug discovery and development programmes, the acquisition of human tissues remains a significant challenge due largely to the many legal, ethical, logistical and practical issues that must be addressed in order to acquire them.

Typically, human tissues may be acquired for research use either following medically required surgery or organ donation, or *post mortem*. In the case of organ donation, their use for transplantation always takes priority over research, and in surgical cases the requirement of tissue samples for pathology and diagnosis always takes precedence over samples for research. Such prioritisation significantly reduces the availability for research. However, the public is generally willing to donate tissue to aid research for new medicines, and over the last 11 years Asterand has developed relationships with medical intermediaries to establish an extensive global network that allows us to access a wide range of human tissue types, ethically sourced and consented for research.

The logistics of working with human tissue also provide challenges. One cannot predict, and therefore cannot plan for, exactly when human tissues may be available. For tissues that are to be prepared for storage, for example snap-frozen or formalin-fixed for later use, this problem can be solved through good, established relationships with medical intermediaries trained in the use of specific tissue-processing standard operating procedures (SOPs). The frequency of availability and the logistics of access are most challenging for human fresh tissues, which for many applications must be processed for experimental use as quickly as

possible. Asterand has addressed this by establishing a 24/7 PhaseZERO research services platform whereby we are able to prepare in advance for our experimental work and be ready to perform the required studies as soon as fresh tissue becomes available.

A key challenge for human tissue research lies in the expectations of scientists themselves. The use of animal-based and recombinant animal and human test methods in drug discovery and development allows consistent, reproducible laboratory data to be generated quickly, allowing timely decision-making. This is not so with human-based test systems,

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whether *in vitro* or indeed *in vivo* (clinical), as humans are outbred in the extreme and have infinitely variable lifestyles, resulting in considerable variability in experimental outcomes. The levels of standardisation achievable in animal-based test systems are thus unrealistic when working with humans, and are also of course unrepresentative of the target patient population. Indeed, with advancing methods of identifying and developing personalised medicines, this variability in man can and will



The *human* approach to drug discovery and development

PhaseZERO
Empowering Human Drug Discovery

Human drug discovery services

- Gene expression & localization
- Protein localization
- Pharmacology
- ADMET

XpressBANK
Accelerate Your Discovery

Human biomaterials

- Frozen and fixed tissues
- Bio-fluids
- Cell lines
- RNA, DNA
- Primary cells

ProCURE
Your Needs. Our Network.

Custom procurement services

- Frozen and/or fixed tissues
- Fresh tissue in media
- Fresh or Frozen bio-fluids

THE BENEFITS

Validated native human targets , Early drug attrition, Advance promising compounds faster
Fewer development failures, Reduced development costs

Confidence For Clinical Success

undoubtedly be embraced and exploited. This inherent variability in human-based test systems demands well-designed *in vitro* experiments with sufficient numbers of donors, maximised human tissue sample quality and the availability of comprehensive donor and clinical data.

The Approaches

Asterand's global human tissue network for the procurement of ethically consented human tissues and biofluids for research underpins our core business: the provision of high-quality human tissues and research services to support the development of safe, effective new medicines for man. The combination of our existing biorepository (XpressBANK) and our ability to prospectively source (ProCURE) and perform a range of experimental work using human tissues to support target validation and compound profiling (PhaseZERO) provides the biopharmaceutical industry with a comprehensive solution to their human tissue research needs.

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Access to diseased tissues provides a great opportunity for identifying disease-related targets/biomarkers and investigating any disease-related differences in the pharmacology of new chemical entities (NCEs). In addition, access to a range of tissue types (organ systems) and formats (frozen, fixed, fresh) allows the integration of human tissue research across multiple therapeutic areas.

Ensuring that tissue is of the highest quality is achieved through a standardised approach to tissue collection with the application of appropriate quality control (QC) procedures, and for experimental work quality is assured through assay optimisation, careful donor selection and application of tissue viability controls.

The Benefits

The benefits of integrating human tissue research into drug discovery and development programmes are the confidence that it provides in the selection of the NCEs most likely to succeed in the clinic, and the ability to do this in the most financially efficient way.

Picking the Winners

The two key aspects of an NCE profile that must be satisfied before it can be submitted to clinical evaluation are efficacy and safety. Evidence of potential clinical effectiveness is the primary determinant for a drug company when deciding whether to take an NCE into the clinic; no company will commit the huge resources required to evaluate something that they feel is unlikely to work. On the other hand, the regulatory authorities are primarily concerned with safety, minimising the appearance of side effects or toxicity in the volunteer or patient population. Between these two decision-makers is the need for as much confidence as

possible before a clinical trial can begin. It is generating this confidence that is responsible for much of the cost and lost time in drug development programmes. Getting the drug into the clinic is only the start. The majority of new drugs that enter the clinical stage of development fail to become medicines. There are many reasons for this, including inadequate efficacy, unacceptable side effects and frank toxicity as the main contributors, all risks that may be reduced by appropriate human tissue studies earlier in a drug's development. Encouragingly, over recent years there has been an apparent decline in clinical drug attrition resulting from issues with pharmacokinetics, a change that we believe may owe something to the established application of human tissue-based approaches for optimising drug metabolism and pharmacokinetics (DMPK) parameters.

Fail Early, Fail Cheap

Accepting that most NCEs emerging from research programmes are destined to fail, it is better to identify failures as early as possible in order to concentrate valuable resources on potential winners. Even when a drug has made it to market, it is not necessarily out of the woods. The withdrawal of marketed drugs due to unexpected side effects is a major financial blow to any company. The antidiabetes drug Rezulin (troglitazone) was withdrawn in 2000 as a result of hepatotoxicity in some patients. In a subsequent published PhaseZERO study, troglitazone and two other compounds of the same class – rosiglitazone and pioglitazone – were tested for hepatotoxicity on human hepatocytes. Troglitazone demonstrated a very narrow therapeutic window when comparing the concentrations required to induce frank hepatotoxicity *in vitro* with the maximum blood concentrations in patients. This narrow window was not observed with rosiglitazone or pioglitazone. Early PhaseZERO profiling of troglitazone could have identified a high risk of liver toxicity and provided a means of identifying a safer compound of comparable efficacy.

Conclusions

The huge and ever-increasing cost of developing new drugs is no secret, with current estimates in the order of US\$1 billion being required to get a new drug to market; even then, a resulting medicine may not be a commercial success. Also no secret is the industry's staggering attrition rate, where in many cases hundreds of thousands of compounds are tested and abandoned simply to get one to the clinic. Anything that can

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help pick out the potential winners and losers at an earlier stage will have an impact on these measures of efficiency. Pre-clinical use of human tissues can provide valuable insight into the likely success or otherwise of a novel clinical candidate. Although human *in vitro* approaches will never provide all the answers, and are unlikely ever to totally replace whole animal studies, their appropriate and systematic use will result in more effective drug discovery and development programmes. With Asterand's human tissue supply network and expertise in the provision of human tissue-based services, human tissue research as a reliable and timely component of the industry's drug research and development programmes is now a reality. ■