



Human Tissue Research for Drug Discovery

Can this Type of Approach Help Improve Clinical Success?

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Recent drug-attribution statistics indicate that the biopharmaceutical industry is still finding it difficult to translate good ideas into safe, effective medicines. Although the target for most new medicines is man, the methods employed to identify and validate suitable therapeutic targets and potential new medicines have historically been almost entirely nonhuman. The ability of such methods to predict efficacy and safety for man has thus been unreliable.

Despite a growing appreciation of the value of human-based test methods, much preclinical efficacy and safety testing still relies on the use of experimental animals. There is no clear indication that this situation is likely to change.

If nonhuman test methods are to remain central to drug discovery and development, 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 possibility may never see the light of day.

There are many examples where the enthusiasm for the use of established, available animal models persists despite evidence of unsuitability. Much contemporary research into new treatments for irritable bowel syndrome 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

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receptors—Lotronex, a 5-HT₃ antagonist, and Zelmec, a 5-HT₄ partial agonist—exhibit not only limited clinical efficacy but also use-limiting side effects.

Such failings do not condemn the use of animal model approaches as a whole but highlight their potential shortcomings. Such models should thus be validated in terms of their human relevance before becoming accepted as predictive for man.

Informed Choice

The introduction of human in vitro data to validate animal-based test methods will enable a more informed choice as to their use and will likely enhance the quality of the resulting decision making.

In some cases, there is no useful animal model for establishing proof-of-concept for efficacy. Cystic fibrosis results from the presence of a mutant form of the gene encoding the epithelial ion transporter CFTR. Although cystic fibrosis causes problems with epithelial function in organs throughout the body, it is the effects on the lung that are usually the cause of death. Attempts to develop a useful animal model have failed. Even CFTR knockout mice do not display the broncho-pulmonary symptoms that are so characteristic of cystic fibrosis.



Asterand has established XpressBANK and ProCURE to provide human tissues for research programs, and PhaseZERO, through which it provides human tissue-based research services.

We do not intend to suggest that in vitro data alone can provide all the necessary information for clinical go/no-go decision making. In light of these examples, however, we believe that efforts should be directed toward human tissue studies in vitro 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 only be undertaken in vivo, such as psychiatric disorders. In such cases, as with the choice of species for ADME/safety testing, scientists have a responsibility to establish, as far as possible, the relevance of the model(s) chosen. This can in part be achieved by com-

paring profiles of expression and function of key targets and biochemical pathways in relevant human tissues with those in candidate animal models.

To make human in vitro testing available to the biopharmaceutical industry, Asterand (www.asterand.com) has established XpressBANK™ and ProCURE™, through which it provides human tissues for research programs, and PhaseZERO®, through which it provides human tissue-based research services. These not only 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.

For example, the antidiabetes drug Rezulin (troglitazone) was withdrawn from the commercial market 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 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.

Challenges

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

Typically human tissues may be acquired for research use either following medically required surgery, organ donation, or post-mortem. In terms of organ donation, their use for transplantation always takes priority over research. In surgical cases, the requirement of tissue samples for pathology and diagnosis always take precedence over samples for research. Such issues sig-

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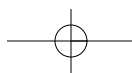


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nificantly reduce the availability for research.

Thankfully the public is generally willing to donate tissue to aid in research for new medicines. Over the last 11 years Asterand has developed relationships with medical intermediaries to establish a global network that allows it to access a range of human tissue types consented for ethically approved research.

The logistics of working with human tissue also provides challenges. One cannot predict and therefore plan for exactly when human tissues may be available. For tissues that are to be prepared for storage, such as snap-frozen or formalin-fixed for later use, this can be achieved through established relationships with medical intermediaries trained in the use of specific tissue-processing SOPs.

The frequency of availability and logistics of access are most challenging for fresh human tissues where, for many applications, they must be processed for experimental use as quickly as possible. Asterand has addressed this by establishing a 24/7 PhaseZERO research services platform whereby the company is able to prepare in advance for experimental work and be ready to perform the required studies as soon as fresh tissue becomes available.

Expectations

Another 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 allow consistent, reproducible laboratory data to be generated quickly, allowing timely decision making. This is not so with human-based test systems, whether in vitro or in vivo, as humans are outbred in the extreme and have infinitely variable lifestyles, resulting in considerable variability in experimental outcomes.

The levels of standardization achievable in animal-based test systems are thus unrealistic when working with humans and are also unrepresentative of the target patient population.

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

The combination of Asterand's existing biorepository (XpressBANK) as well as its ability to prospectively source (ProCURE) and to perform a range of experimental work using human tissues to support target validation and compound profiling (PhaseZERO) provides the biopharmaceutical industry with a solution to its human tissue research needs.

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

Asterand ensures its tissue quality

through a standardized approach to tissue collection with the application of appropriate QC procedures. For experimental work, quality is assured through assay optimization, careful donor selection, and application of tissue viability controls.

Benefits

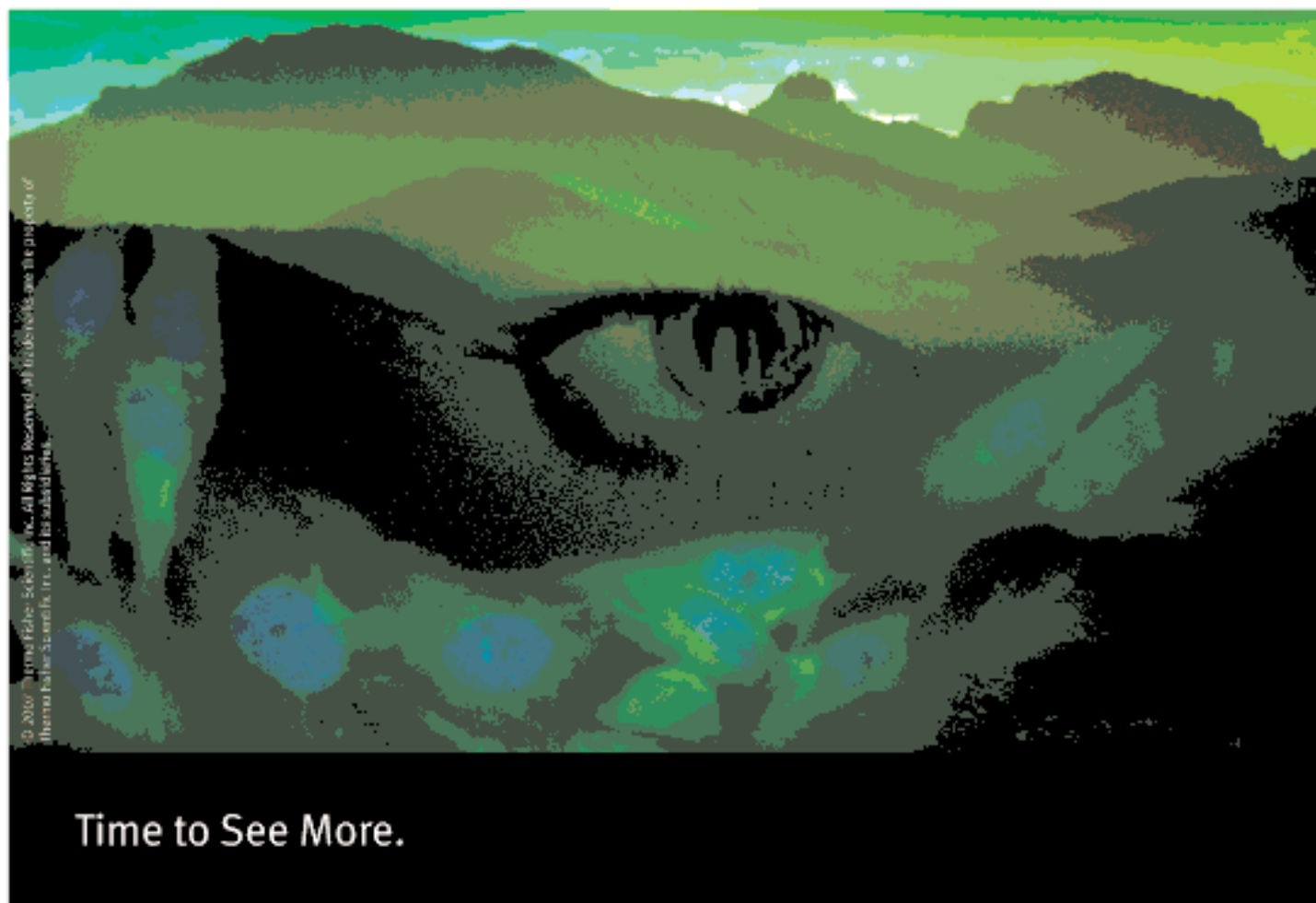
A benefit of integrating human tissue research into drug discovery and development is the confidence that it provides in the selection of the NCEs most likely to

succeed in the clinic.

The majority of new drugs that enter the clinical stage of development fail to become medicines. The reasons for this include inadequate efficacy, unacceptable side effects, and frank toxicity. These risks may be reduced by appropriate human tissue studies earlier in a drug's development. Encouragingly, over recent years there has been a 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 optimizing DMPK parameters.

Preclinical use of human tissues can provide valuable insight into the likely success or otherwise of clinical candidates. Although human in vitro approaches will never provide all the answers and are unlikely to ever totally replace whole animal studies, their appropriate and systematic use will result in more effective drug discovery and development programs. **GEN**



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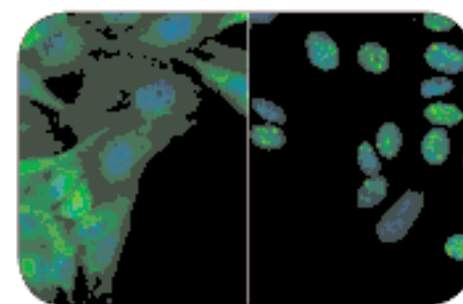
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