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The use of functional human tissues in drug development

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Abstract Fresh, functional human tissues have long been considered the closest possible model of human in vivo function and can be used to measure a wide range of pharmacological responses. Despite this, relatively little drug development is conducted using fresh human tissue because of the logistical and ethical difficulties surrounding the availability of tissue and practicalities of experimental work. Most tests of drug activity require a living test system comprising cells, tissues or whole organisms. In some instances, "living" (fresh) human tissues have the potential to reduce or replace animal tests through superior prediction of drug safety and efficacy. Before functional human tissue tests become a routine part of drug development, two factors must co-exist. Firstly, organisations such as Biopta must continue to create compelling evidence that human tissues are more predictive than alternative models; such evidence will drive demand from the pharmaceutical industry for human tissue-based tests. Secondly, the vast number of tissues and organs residual to surgery or unsuitable for transplant must be routinely consented for medical research and made available to all researchers in an equitable and timely manner. This requires a concerted effort throughout the NHS and consistent demand as well as financial support from researchers, particularly within industry. It is our view that the next 5–10 years will generate compelling evidence of the value of functional human tissue-based tests and recognition that more efficient use of residual or non-transplantable tissues and organs is an urgent priority for the development of new medicines.

Keywords Surgical tissues · Transplant · Drug safety · Pharmacodynamics · Pharmacokinetics

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Fresh, functional human tissues have long been considered the closest possible model of human in vivo function and can be used to measure a wide range of pharmacological responses. Despite this, relatively little drug development is conducted using fresh human tissue because of the logistical and ethical difficulties surrounding the availability of tissue and practicalities of experimental work. Most tests of drug activity require a living test system comprising cells, tissues or whole organisms; currently this mainly achieved using animal test systems, which do not always reflect human biology. In some instances, "living" (fresh) human tissues have the potential to reduce or replace animal tests by improving predictions of drug safety and efficacy. Intact tissues retain the three-dimensional structure that is essential to the normal behaviour of tissues; such cell-to-cell interactions are difficult to reproduce

through the use of alternative methods such as tissue engineering, even when primary human cells are used to reconstruct 3-D tissues. Both surgery and transplantation procedures create large numbers of residual tissues and organs which, if stored appropriately, can be used to model drug responses.

Before proceeding further, it should be noted that the use of fresh tissue complements the more common use of fixed/frozen human tissues, which is to determine the presence and location of a drug target. Such tests using fixed/frozen tissues provide no information on the pharmacology of a test drug; to achieve this, the tissue (and therefore the target and its downstream effectors) must be responsive to the drug and the response must mimic the in vivo response as closely as possible. It is only with functioning "living" tissue that pharmacodynamic (the magnitude or potency of drug responses) or pharmacokinetic (changes in absorption, distribution, metabolism and excretion with time) information may be generated.

If functional human tissues offer such promise, it is reasonable to ask whether sufficient human tissue is available to make a significant contribution to drug development. In England and Wales, upwards of 600,000 residual surgical tissues are generated each year, yet only a tiny fraction is made available to researchers. Clearly, not all of the tissue will be suitable for research and the primary concern must always be patient care and diagnosis; however, if 10 to 20% of this resource were made available it could generate between 50 to 100,000 experiments annually. This is still small in comparison to the number of animal tests conducted annually (between 3.5 and 4 million in the UK), but living human tissues are typically used late in the non-clinical development process where the number of compounds tested is relatively small.

Before functional human tissue tests become a routine part of drug development, two factors must therefore co-exist. Firstly, organisations such as Biopta must continue to create compelling evidence that human tissues are more predictive than alternative models; such evidence will drive demand from the pharmaceutical industry for human tissue-based tests. Secondly, the vast number of tissues and organs residual to surgery or unsuitable for transplant must be routinely consented for medical research and made available to all researchers in a fair, equitable and timely manner. This requires a concerted effort throughout the NHS and consistent demand as well as financial support from researchers, particularly within industry. It is our view that the next 5–10 years will generate compelling evidence of the value of functional human tissue-based tests, which in turn will drive more efficient processes for the distribution of ethically-obtained residual tissues and organs.