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Efficacy and safety of new medicines: a human focus

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Abstract The introduction of safe and effective new medicines is proving ever more difficult, a problem arguably due at least in part to over-reliance on experimental animal-based test systems. In light of the increasing awareness of the lack of predictiveness of such non-human approaches, the necessity to focus on human-based test methods is clear. There has been considerable progress in human in vivo (microdosing) and *in silico* approaches, primarily to identify ADMET issues, however, in vitro functional studies using human tissues are receiving inadequate attention. The potential scope of human tissue-based research is considerable, but much methodological development is required, which necessitates an increased willingness on the part of the Pharma industry to support it. This approach also requires considerably improved access to the cells and tissues themselves. While current acquisition is almost exclusively from surgery and *post mortem*, the range of tissue types, the quantity, quality and frequency of supply will remain inadequate to support human tissue as a key component of pre-clinical efficacy and safety testing. Additional routine access to non-transplantable tissues from organ donors for research purposes would be of inestimable value, but in order to realise this, true collaboration will be required between NHS, the Pharma and biotech industries, and the general public.

Keywords Heart-beating donors · Drug safety · TGN1412

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It is generally agreed that the pharma industry has a problem in bringing safe and effective new drugs to market. This may well be due, at least in part, to the over-reliance of the industry on using animals as human surrogates. Indeed, the most widely used animal species, rodents, dogs and non-human primates, have all been shown to be highly unreliable in their ability to predict drug behaviour in man. A comparison of the bioavailability of a range of drugs in man with that in these three species by Grass and Sinko (2002) demonstrated a very poor level of correlation. Furthermore, a retrospective study by Olson et al. (2000), showed that for some systems, the predictive value of animal studies to identify potential toxicity in human subjects performed little better than the spin of a coin. In the light of such low predictive power, it seems surprising that such store is set by animal safety data. To look at the situation from another angle, if evidence of animal tolerability was required before foodstuffs were deemed safe for human consumption, we would for example not have coffee, Brussels sprouts, avocados, orange juice, chocolate or onions, as all these and many others prove toxic when consumed by rats and/or dogs. And of course the

notorious Te Genero drug, TGN1412, that caused such devastating effects in human volunteers in its first exposure to man at Northwick Park (Suntharalingam et al. 2006) was extremely well-tolerated by non-human primates at doses 500-fold higher than those that nearly proved fatal to the unfortunate volunteers (Stebbings et al. 2007).

In their 2002 report on the use of primates, the Animal Procedures Committee argued that "the development and implementation of non-animal alternatives to replace the use of non-human primates must be accepted within industry and the international regulatory area as a high priority goal". This is a view supported by a number of critical publications, including that of Matthews (2008), who showed that the likelihood of animals predicting human clinical outcome was not significantly better than 50:50. So, if animals' performance in this regard is so poor, why do we continue to use them? There are a number of reasons, some of these relating simply to the way things have always been done, the insistence of the regulators for animal data, and the difficulty in finding an alternative.

The obvious alternative is to concentrate on human, rather than non-human, biology in pre-clinical testing. But how? The three approaches available are in vivo, *in silico* and in vitro. The former, involving early clinical testing with microdoses (i.e. doses some 100-fold lower than the lowest intended clinical dose) is now establishing itself, with growing evidence that it has predictive value (Lappin and Garner 2010). There is little doubt that if the early encouraging data are replicated, this approach will be increasingly used in future drug testing. Similarly, *in silico* testing, using computational approaches, is showing promise, and with many models already commercially available, its role in predicting drug behaviour in humans will grow. The area that is really being sorely neglected is the use of human in vitro techniques.

The value of the in vitro approach is nicely illustrated by TGN1412, where following its disastrous clinical trial, an in vitro method was rapidly developed that modelled the near-fatal cytokine storm experienced by the clinical volunteers (Findlay et al. 2010). Had this been developed and used before exposing human subjects to the drug, the trial would never have taken place. Surely the time has come for there to be a rigorous prospective evaluation of human-based approaches, not only in vivo and *in silico*, but critically also in vitro, as alternatives to the deeply flawed, animal-based approaches in current use in the identification of potential safety issues for new drugs in man.

While the attraction of human in vitro studies is in the wide range of functions that can be studied, it must be acknowledged that unless we improve radically our access to viable human tissues, such testing will represent a considerable bottleneck in pre-clinical drug testing programmes. At present in the UK we are limited almost exclusively to acquisition of tissues from surgery and *post mortem*. While tissue acquired from these sources is of considerable value, it is not enough. From these sources, we are limited in terms of the range of tissue types, the quantity that may be supplied, the quality and the frequency. These are issues that must be addressed if human tissue is ever to become a key component of pre-clinical efficacy and safety testing. The answer lies in access to tissues from heartbeating, brainstem dead organ donors.

But for human tissue research to become a key component of the drug testing paradigm, it must become a 'need to have', and that will only happen if it becomes a regulatory requirement. This will not happen until we can guarantee access to the tissues of the required range, of the appropriate condition, in sufficient quantity and with the necessary frequency. A collaboration between NHS Blood and Transplant and the pharma industry, together with buy-in by the general public to facilitate the availability and use of human tissue for research is essential to realise the full potential of a human-based approach to drug research and development.

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