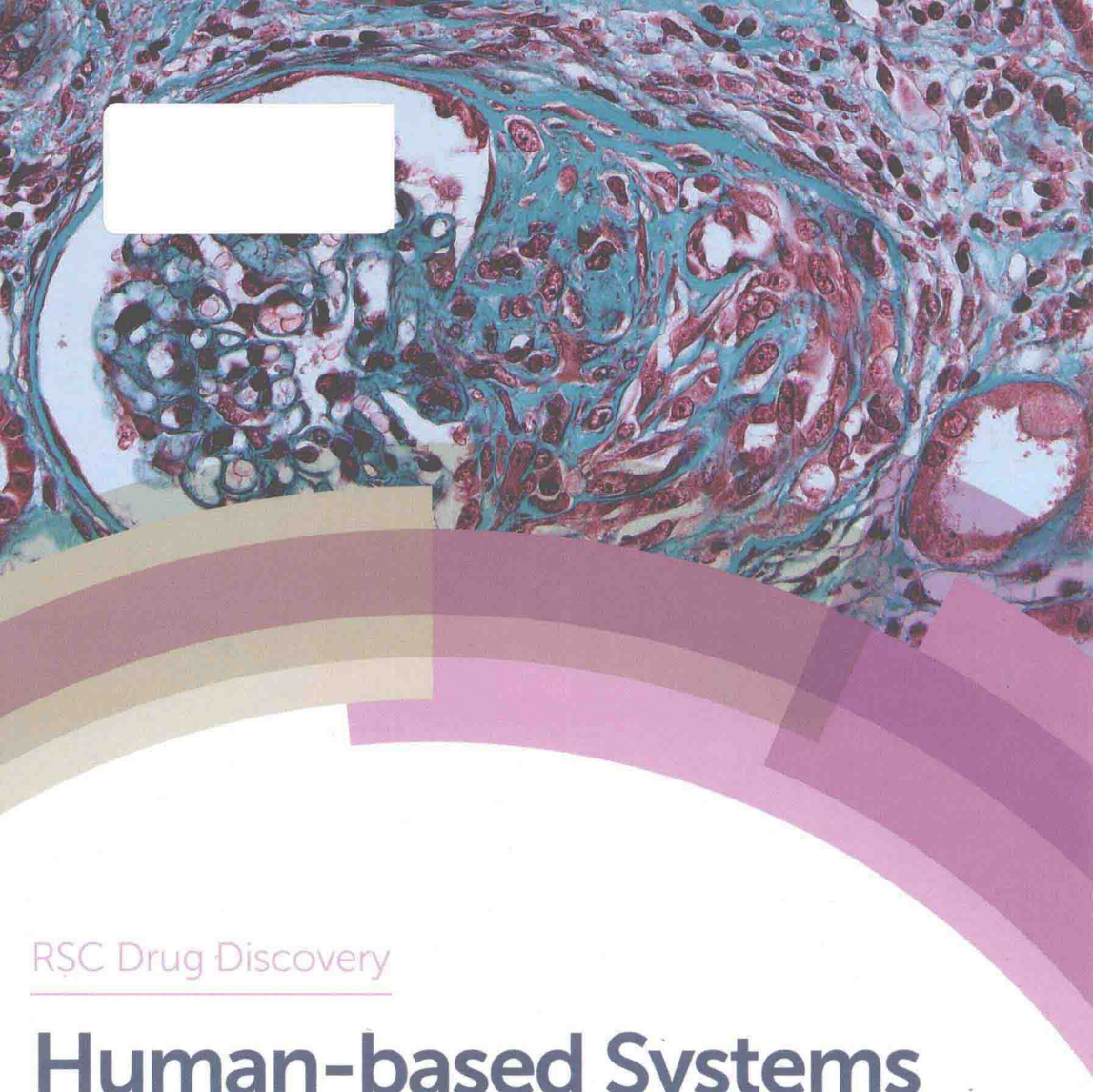

RSC Drug Discovery

Human-based Systems for Translational Research

Edited by Robert Coleman

ROYAL SOCIETY OF CHEMISTRY

Human-based Systems for Translational Research

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Preface

Experimental animals have been a mainstay in the discovery and development of new medicines for human diseases for over half a century, so why do we now need to consider the use of humanised systems?

Historically, the pharmaceutical industry has been hugely successful, bringing a wide range of powerful and effective medicines to the market. Medicines to treat a wide range of disorders for which there had previously been, at best, inadequate treatment have been discovered and added to the clinician's armamentarium. It seemed that nothing could stop the almost exponential increase in the pharmaceutical industry's output. However, the last two to three decades have seen a marked decline in the productivity of this once prolific industry,[1,2] the effects of which have been stark, leading to a complete restructuring of the sector. Unfortunately, however dramatic such restructuring has been, it has not resulted in the hoped for increases in output of new safe and effective medicines per unit investment.[3] Increasingly, when potential medicines developed using animal models are tested in human subjects, they are being found to fail for reasons of either lack of efficacy or associated use-limiting side effects and frank toxicity.

While lack of efficacy is of course a real problem, even more serious is the capacity of new medicines to do harm. In the early part of the 20th century, human medicines could be introduced onto the market with no legal requirement for the manufacturer to explore and report their safety profiles, but this changed following the Elixir sulfanilamide scandal. In 1937, a novel preparation of the antibacterial drug, sulfanilamide, was introduced to the US market, and was responsible for in excess of 100 fatalities.[4] This led to Congress passing the 1938 Food, Drug, and Cosmetic Act, requiring companies to present safety data obtained in experimental animals on any proposed new drug, and to submit the data for approval by the FDA before

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being allowed to proceed to market. And so the use of animals to identify potential human hazards became routine within the pharmaceutical industry. The idea of using animals as human surrogates was based on the physiological parallels between humans and other animals, particularly those most closely related in evolutionary terms, *i.e.* mammalian species. While this was a clearly rational approach, it did not totally resolve the issue, and this was most clearly demonstrated in the 1950s with the thalidomide disaster.[5] Thalidomide had been introduced as a mild sedative, particularly useful in reducing morning sickness in pregnancy, but was subsequently identified as the causative agent in the sudden explosion of cases of serious birth defects in the offspring of women who had been prescribed the drug. It is not that thalidomide had not been tested for side effects in experimental animals, it was simply the case that none had been performed on pregnant females to assess effects of the drug on the offspring, and interestingly, even if it had, because of species differences in this effect, the problem would probably not have been picked up. However, it was the thalidomide affair that consolidated the need for the rigorous safety evaluation of new potential medicines, and led to the increased use of animals as patient substitutes that persists to the present day.

As first-line testing for safety issues in human patients or volunteers was and remains ethically unacceptable, the logic behind using experimental animals on the basis of overall physiological similarity was uncontroversial. However, as time has passed, it has become increasingly clear that non-human species do not always respond to drugs in the same way as the humans that they are meant to represent, and their ability to reflect both clinical efficacy and safety issues has been shown to be highly variable, depending on particular drug type and disease target. Despite this, there has been a general acceptance by the medical establishment, the pharmaceutical industry and the regulators that overall, despite their shortcomings, they are doing a fair job, and with the lack of any obvious alternative, we have continued to rely on the animal-based status quo to assure the public of the safety of new medicines. But in the light of ever-increasing numbers of high-profile failures, including, but by no means restricted to, phen-fen,[6] various statins[7,8] and COX2 inhibitors,[9,10] this situation has become untenable, and it has become essential to do something to improve our ability to ensure the lack of safety problems with new medicines.

Much effort has been expended in exploring alternative approaches to new medicines R&D, and official organisations such as ECVAM (Europe) and ICCVAM (USA) have been established to determine their value. Unfortunately the output from these organisations is disappointingly low,[11] and relatively few alternatives have received the necessary level of validation required for regulatory authorities to accept these tests as viable contributors to preclinical safety testing. Furthermore, even in cases where tests have been approved for use in drug submissions, there remains the issue of persuading the pharmaceutical industry to abandon their established animal-based methods in favour of the validated alternative.

Although a rigorous validation process is applied to new technologies, it is a fact that few if any of the animal-based tests that form the basis of our current safety testing paradigm have themselves been subjected to such scrutiny; their value has been taken as a given, despite the wealth of evidence of their shortcomings. Indeed, if one looks for peer-reviewed publications providing support for the status quo, there is really only one, and that merely reports an overall modest (approximately 70%) concordance between toxicity seen in animal species and in human subjects.[12] In contrast, there is a wealth of publications providing data on the lack of value of animal data in identifying potential clinical safety issues.[13–16] Indeed, a recent publication has explored the value of dogs as predictors of human safety profiles using more sophisticated measures of predictive power (likelihood ratios) than simple concordance, and have concluded that while demonstration of toxicity can in some cases reflect toxicity in humans (in line with Olson's findings), absence of toxicity in dogs provides no useful indication of absence in man.[17]

If testing in animals is an unreliable indicator of potential clinical safety issues, then why are they still demanded and relied upon? A comprehensive answer to this question is outside the scope of this volume, but one key factor is the widespread belief that while flawed, they are superior to whatever else is available.[18] While there have long been proponents of a wider use of *in vitro* human systems, most moves in this direction have been rebuffed by claims that it is impossible to reflect the complexity of a whole integrated organism by looking at its parts in isolation, thus necessitating the use of animal surrogates. Such an attitude may be justified if there really are no viable alternatives available, *and* if the level of inaccuracy can be regarded as acceptable. For a long time, this attitude was (and in some quarters still is) the case, but technology moves on, and the seemingly impossible of yesterday becomes the possible of today, and the commonplace of tomorrow. With this in mind, together with the increasingly obvious inadequacies of the status quo, the exploration of human-based approaches seems unavoidable. Indeed, even the FDA, the primary regulatory authority in the USA, has come to this conclusion, stating on its website: "Consideration should be given to the use of appropriate *in vitro* alternative methods for safety evaluation. These methods, if accepted by all ICH regulatory authorities, can be used to replace current standard methods."[19]

It is fair to say that at this moment, we are not in a position to replace the current *in vivo* animal-based paradigm of assessing the potential safety and efficacy of new medicines with methods based on human *in vitro* models; there is much more work to do. However, we do now have greatly improved access to voluntarily donated viable human cells and tissues, an ever-increasing ability to generate a wide variety of tissue types from induced stem cells, and huge advances being made in a wide range of other technologies to apply to these materials, including those presented in this volume. With all this, we are now ready to perform proper evaluations of approaches which alone and in combination may offer superior means of establishing safety and efficacy of new medicines, consistent with 21st century science.

The purpose of this book therefore is not to present a list of established assays that can reliably identify the potential efficacies and safety issues associated with new medicines, but rather to illustrate what is currently possible in humanising medicines R&D, which with sufficient commitment of time, effort and imagination will provide a basis on which to establish more rational and reliable means of developing safe and effective drugs for the future than those on which we currently rely.

Robert Coleman

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