Drug Discovery and Development Tomorrow — Changing the Mindset

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Summary — Today's drug discovery and development paradigm is not working, and something needs to be done about it. There is good reason to believe that a move away from reliance on animal surrogates for human subjects in the Pharma Industry's R&D programmes could provide an important step forward. However, no serious move will be made in that direction until there is some hard evidence that it will be rewarded with improved productivity outcomes. The Safer Medicines Trust are proposing that a study be undertaken, involving a range of drugs that have been approved for human use, but have subsequently proved to have limitations in terms of safety and/or efficacy. The aim is to determine the efficiency of a battery of human-based test methods to identify a compound's safety and efficacy profiles, and to compare this with that of the more traditional, largely animal-based methods that were employed in their original development. Should such an approach prove more reliable, the authorities will be faced with important decisions relating to the role of human biological test data in regulatory submissions, while the Pharma Industry will be faced with the key logistical issue of how to acquire the human biomaterials necessary to make possible the routine application of such test methods.

Key words: *drug discovery and development, human focus, human tissues and organs, success rate.*

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Introduction

It is generally agreed that there is a problem in the ability of the Pharma Industry to introduce effective and safe new medicines to the market (1, 2). Despite ever-increasing R&D expenditure, a more thorough understanding of the molecular basis of disease, and the introduction and application of new technologies, new drugs continue to fail in terms of their clinical efficacy and/or safety profiles. The industry has now been in a state of continuous upheaval for more that a decade, ever restructuring itself in an attempt to find the answer to its productivity problems, apparently without any significantly positive outcome. It is clear that something needs to be done if the Pharma industry is to continue to exist as an entity responsible for the development of new and effective medicines for human disease.

Drug Discovery at Glaxo

I started my career in the Pharma Industry in 1965, when I joined Allen & Hanbury's, part of the Glaxo Group, as laboratory technician. My arrival there coincided with the discovery and development of salbutamol (marketed as Ventolin), the drug which opened the way to something of a 'Golden Age' for Glaxo. The company's successes were the direct result of the leadership and inspiration of Dr (now Sir) David Jack. It was Sir David, inspired by the example of his fellow Scot, Sir James Black, who instigated a move away from the largely empirical approach to drug discovery and development that had prevailed in the industry up to that time, by taking a more structured and more rational line, based in the main on an understanding of the targets at which drugs act (3). This approach led to the successful introduction, not only of Ventolin, but also of a whole series of important and well known drugs for a range of indications, including ranitidine (Zantac), beclomethasone (Becotide), labetalol (Trandate), cefuroxime (Ceftazidine), ondansetron (Xofran), sumatriptan (Imigran), fluticasone (Flixotide), and salmeterol (Serevent).

Despite the rationality of his approach, and the success that ensued, in one aspect Sir David could be regarded as having been lucky in achieving this prodigious output. Virtually all of the pre-clinical

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work that resulted in the discovery and development of these drugs was conducted on laboratory animals. And it proved successful. Salbutamol and salmeterol, for example, are bronchodilators, and are as effective in relaxing airways smooth muscle in guinea-pigs as they are in humans (4). Ranitidine inhibits gastric acid secretion in the rat as effectively as it does in man (5). In addition, in terms of their safety profiles, both these classes of drug proved to be relatively benign in both experimental animals and human subjects (6, 7).

Shortcomings of Animal-based Approaches

So the question arises, 'If the animal-based approach worked so well then, why is it proving to be so much less productive today?' — 'What has changed?' The answer, of course, is that nothing has changed, it is simply that experimental animals have always been unreliable in their predictive power for human efficacy and safety, providing useful information on some drug candidates, but not on others. Despite the impressive output from the Glaxo stable during the latter third of the 20th century, many other exciting programmes that were progressing at the same time came to nothing. Such failure was due, at least in part, to the failure of experiments on animals to predict outcomes in human patients. It may well be that the drug mechanisms for which animals can provide some useful prediction of potential efficacy and safety in man, have already been exploited, so the proportion for which they are less useful, or even frankly misleading, is increasing. There may, of course, be additional issues. For example, it may well be that the very ingenuity of experimental scientists in mimicking human diseases in animals blinds them to the fact that underlying the induced disorder is a non-human physiology. There is a wealth of evidence, in a wide range of physiological systems, that even closely related species can use quite different biochemical pathways to achieve the same biological end (8–12), and even within species, choice of strain can have a profound influence (9, 10, 13, 14).

Although the unreliability of tests in non-human species for predicting efficacy and safety in man is increasingly well accepted, it seems to have had limited impact on the enthusiasm of scientists for their use. Despite the wealth of information testifying to unreliability of the mouse and the sheep to accurately indicate which drugs are likely to be effective in human asthma (15, 16), researchers into respiratory medicines continue to use them (17, 18). To a degree, the mapping of the human and mouse genomes may be to blame; it seems that all the lessons painfully learned as to the unreliability of mice as human surrogates in drug discovery and development generally were forgotten as soon as we discovered the level of concordance between the human and murine genomes (19), despite the fact that similarity in gene sequence does not necessarily reflect similarity in expression, and therefore in function (20).

Human-based Approaches to Drug Discovery and Development

So, if animals can no longer be relied upon, what alternatives are there? I suggest that the answer, at least in principle, is startlingly simple: 'We should focus on the target species, i.e. humans'. There are many ways in which human biology can be accessed and exploited, not only through clinical studies on human volunteers and patients, whether these involve full clinical trials or highly focused micro-dosing studies, but also via studies on human cells, tissues and even organs *in vitro*. *In vitro* approaches are now available in abundance, and while these may involve studying the effects of novel agents on single cells or tissues in isolation, this is by no means an absolute limitation, and technologies are now becoming available for studying the effects of drugs on integrated systems *in vitro*. Alternatively, we can use humans indirectly by constructing *in silico* models based on the ever-increasing amount of human data available. There are, of course, systems that are too complex and/or intractable to lend themselves to a relatively simple *in vitro* approach, and where *in vivo* studies in non-human species seem the only way forward. In such cases, comparative studies in animal and human cells and tissues *in vitro* can prove invaluable for the identification of the most relevant animal species to employ in any particular disease modelling exercise.

A concern commonly expressed when discussing such approaches, is that they are too expensive and low-throughput to be useful to the Industry. I think that it is worth bearing in mind that there is nothing more expensive in drug discovery and development than getting the wrong answer. Also, while throughput may currently be a problem, this may merely represent a challenge to human ingenuity. There also seems to be an underlying concern that making any change is risky, and this appears to be particularly true in this case, where there is no guarantee that novel human-focused approaches will be any better than the animal-based approaches in current use.

It is for this reason that the Safer Medicines Trust and the Safer Medicines Campaign (21) are proposing the setting up of a study to answer this question. It is their intention that a range of drugs with established clinical profiles should be submitted to a battery of alternative human-focused

approaches, in order to establish directly their value in identifying the efficacy and safety profiles of the selected compounds, both in absolute terms, and also in comparison with the 'classical' methods that were originally employed during their development. Should the human-focused approaches prove more effective in profiling the strengths and weaknesses of the selected compounds, it will provide compelling evidence for a new, more powerful direction in tomorrow's drug development.

Who Should be Responsible?

The question arises, 'Who should be driving and, of course, funding such a human-focused approach?' In view of the fact that, in the UK, the National Health Service (NHS) needs improved medicines to enhance its provision of effective healthcare, and it is the Pharma Industry's role to provide those medicines, it seems logical that these two bodies should be responsible for providing the necessary resources. However, in reality, while some Pharma companies are indeed beginning to wake up to the necessity to move in this direction, some more enthusiastically than others, the main drivers have for some time been academics, charitable research groups and small biotech companies. These enthusiasts are all motivated by a keen desire to employ new, more reliable approaches to increase the human-focus of the R&D process, and thereby to enhance its ability to introduce safer, more effective drugs to the market. Unfortunately, they are all limited by funding constraints, relying on academic grants, venture capital funding, and some support from major Pharma companies, usually through the provision of services.

How to Proceed?

Of course, such human-focused approaches require human participants, as clinical volunteers or as donors of cells, tissue and organs, and the question arises 'How are these to be found?' Fortunately, humans are not scarce, and in general, they are willing to contribute, both in terms of volunteering to be clinical 'guinea-pigs' and in the donation of their organs, tissues and cells following surgery or *post mortem*. It is unclear why, to date, this resource has been so poorly tapped, particularly for the donation of viable tissues for direct pharmacological and toxicological evaluation.

Over 20 years ago, my colleague, Gordon Baxter, and I founded Pharmagene, the world's first company to attempt drug discovery and development work solely through the use of voluntarily donated human tissues and cells. At this time, the acquisition of the necessary human biomaterials was difficult, there being no clear legal or ethical guidelines through which to work, or indeed, much in the way of the necessary infrastructure in the NHS to enable such acquisition from would-be donors (22). This situation came to a head with the Alder Hey scandal, but what this did was to give the public a voice in stating that they did *not* object to donating material for research, simply that they *did* want to be asked. It also led to legislation in the form of the *Human Tissue Act 2004* (23) and the work of the Human Tissue Authority (24), which between them provided a legal, ethical and practical framework for the acquisition and use of human organs, tissues and cells (25). Despite this, in 2008, the acquisition of viable biomaterials for research purposes remains a considerable bottleneck.

Of course, the situation is not limited to the research community, and the Prime Minister, Gordon Brown, along with the Chief Medical Officer, Sir Liam Donaldson, and the British Medical Association have recently been reported as proposing the implementation of a policy of 'presumed consent' to improve the availability of human organs for transplant (26). However, consent may well not be the issue, but rather the lack of recovery teams at the sites of would-be donation (27). Without these, no amount of presumed consent will have any marked effect on the availability of transplantable organs. I would suggest that UK Transplant, the Pharma Industry and politicians need to work together, to make possible a system through which human biomaterials can be acquired, and then made available to assist in *all* aspects of human healthcare.

To conclude, the current paradigm for the delivery of novel, safe and effective medicines is not working, and an alternative, human-focused, approach has been suggested. It must be put to the test, and the fact that it requires human participation should not be regarded as a problem; it simply requires imagination and commitment from the relevant stakeholders.

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