Drug Discovery & Development Tomorrow – Changing the Mindset

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It is now generally accepted that there is a problem in the ability of the Pharma Industry to introduce safe, effective new drugs to the market, and that something needs to be done about it.

I started my career in the Pharma Industry in 1965, when I joined A&H, part of the Glaxo Group, as lab 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. This Golden Age was the direct result of the leadership and inspiration of the then Dr (now Sir) David Jack, who abandoned the rather empirical approach to drug discovery that had prevailed in the industry up to that time, and took a novel and rational line. 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 he could be regarded as having been lucky in this prodigious output of safe and effective medicines. Virtually all of the pre-clinical work that resulted in the discovery and development of these drugs was conducted on experimental animals; rats, guinea-pigs, cats, dogs, etc. And it proved successful. Salbutamol and salmeterol for example are bronchodilators, and are as effective in guinea-pigs as they are in humans. Ranitidine inhibits gastric acid secretion in the rat as effectively as it does in man. While in terms of their safety profiles, both classes of drug proved to be benign in animals and man.

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, but not for others. It may well be that many of those targets for which animals provide reliable information have already been exploited, and thus the proportion for which they are less useful is increasing.

Although the unreliability of animal prediction is increasingly well accepted, it seems to have limited impact on scientists' willingness to use them. 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, researchers into respiratory medicines steadfastly continue to use them. To a degree, the mapping of the human and mouse genomes is 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 human and murine genomes.

So, if animals can no longer be relied upon to do the job, what are we to do? The answer I believe is startlingly simple, 'we should focus on the target species, ie man'. There are many ways in which human biology can be accessed and exploited. Obviously, human biology may be accessed directly either through clinical studies on volunteers, or via studies on cells, tissues and even organs isolated from them.

Alternatively, we can use humans indirectly either by constructing *in silico* models based on the ever-increasing amount of human data available, or through undertaking comparative studies in animal and human cells and tissues to help us identify the most relevant animal model for *in vivo* studies, where *in vitro* approaches are simply inadequate to model *in vivo* complexity.

The question arises 'Who should be driving such a human-focused approach?' In my view, this is undoubtedly the Pharma Industry in cooperation with the NHS. They have the problem, and between them they have the wherewithal to find the answer. What is in fact the case is that while some Pharma companies are indeed waking up to the necessity to move in this direction, the main drivers have for some time been academics, charitable research groups and small biotechs, all of which have limited funding, and we are going to hear later from representatives from all of these sectors on the impressive advances that they have made in providing a human-focus to efficacy and safety determinations of novel medicines. I do not intend to suggest that today's contributors are the only groups doing such important work, and I would like to mention a couple of additional academic scientists who have impressed me with their achievements.

First is Dr Mark Williams at UEA, who has pioneered an *in vitro* preparation of functional human colonic crypts. Aberrant behaviour of cell in these crypts results in the development of polyps from which malignancies, and thus colo-rectal cancer develops. While most in the field are using mice, Dr Williams is looking where it matters.

Second is Prof Dan Stamer of U Arizona, who is working in glaucoma research, and has developed the methodology to study aqueous humour flow dynamics in human eye preparations *in vitro*. His results have proved not only to be highly predictive of activity in human patients, but also more predictive than *in vivo* studies in monkeys.

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. There is also always a concern that change is risky, particularly where there is no guarantee that novel human-focused approaches will be any better than the animal-based approaches in current use. That is why today's hosts, Safer Medicines Trust, are pressing to set up a study to answer this question. It is their intention to set up a study in which a range of drugs with established clinical profiles are submitted to a battery of alternative human-focused approaches, to see how they fare in identifying the efficacy and safety profiles of the selected compounds in comparison to the methods 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.

Such human-focused approaches of course 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 to donate organs, tissues and cells following surgery or *post mortem*. It is unclear why to date, this resource has been so poorly tapped into, particularly for the donation of viable tissues for pharmacological and toxicological evaluation.

Over 20 years ago, a 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 Health Service to enable such acquisition from would-be donors. This situation came to a head with the Alder Hey scandal, but what this did was firstly 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, and secondly it led to legislation in the form of the Human Tissue Act (2004) and the work of the Human Tissue Authority, which between them provided a legal, ethical and practical framework for the acquisition and use of human organs, tissues and cells. Despite this, in 2008 the acquisition of viable biomaterials for research purposes remains a considerable bottleneck.

The situation is of course not limited to the research community, and the Prime Minister, Gordon Brown, has recently championed the implementation of a policy of 'presumed consent' to improve the availability of human organs for transplant. However, consent may well not be the issue, but rather the lack of recovery teams at the sites of would-be donation. 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 can then be made available to assist in all aspects of human healthcare.

In summary, the current paradigm for the delivery of novel, safe and effective medicines is not working, and an alternative approach has been suggested. It must be put to the test. And finally, a human-focused approach requires human participation. I contend that this should not be regarded as a problem, and simply requires imagination and commitment from the relevant stakeholders.