

Translational Research – A Multidisciplinary Approach

Dear Editor,

Translational research aims to convert laboratory discoveries into therapeutic gains for patients – in oncology, drug development is a prime example. This multifaceted process is often complicated and requires huge investments in time, money and expertise. However, the reality remains that most laboratory discoveries fail to enter clinical practice and to quote two recent articles – “only 5% of all molecules identified in discovery make it to human trials ...”¹ and “the US Food and Drug Administration (FDA) stated that more than 80% of drugs entering (human trials) as Investigational New Drugs fail to get marketing approval, and the failure rate in phase III trials is estimated at approximately 50%. The cost of bringing a new drug to market ... is estimated at US\$0.8 to 1.7 billion and requires 8 to 10 years ...”² Despite access to huge resources, even pharmaceutical companies can ill afford to encounter major or repeated setbacks. Not surprisingly, those involved in drug development are constantly seeking to create a more streamlined, efficient and cost-effective process – as clinicians, we require drugs that are better, available faster and at lower costs for our patients.

The major dilemma however, is that drug development is becoming increasingly complex particularly in the current era of molecular targeting. In this model, biological targets are first identified by pathways analysis which is followed by in-vivo modelling, often in murine systems. Lead compound(s) are found against these targets (e.g., by chemical library screening), optimised (e.g., by combinatorial chemistry), an appropriate delivery / pharmaceutical vehicle is developed and compounds are validated in-vivo. It is also advantageous to develop relevant biomarkers prior to clinical testing. Potential drug toxicities, pharmacokinetic and pharmacodynamic properties and preliminary anti-tumour activity are elucidated in early phase I and II trials and progression to large phase III trials occurs if these results are satisfactory.

As molecular and genetic research reaches new levels of sophistication, the wealth of knowledge being generated is tremendous. To cope, various areas of scientific sub-specialisation are emerging such as bioinformatics³ which is crucial in the data management of transcriptomic and proteomic studies and in-vivo modelling which requires the input of specialist murine biologists and pathologists. Some novel approaches promise to reduce the time from bench to bedside such as in-vivo molecular imaging techniques^{4,5} utilising [¹¹C] Thymidine PET scanning and

biomarker development employing microarray technology.⁶ The obvious challenge then emerges – the collation and integration of a vast expanse of knowledge to promote translational research. In the pursuit of such collaboration, what role does the clinician play?

Collaborative Research

A collaborative model to draw together clinical and scientific disciplines has now been recognised as a priority by major research organisations. The US National Cancer Institute aims to “develop a seamless process for integrating discovery activities, accelerating the development of new interventions and ensuring the delivery of new evidence-based interventions for all cancers” – the 3D continuum.³ Through various frameworks, notably the Cancer Biomedical Informatics Grid (caBIG), it seeks to encourage global communication and resource sharing. The nascent UK equivalent, the National Cancer Research Institute (NCRI) Informatics Initiative, is similarly promoting the integration of basic science and clinical activity.⁷ Many advantages are envisaged including the incorporation of molecular applications into clinical studies, access to raw data for analyses, and the sharing of resources and expertise. Troubleshooting can be conducted more effectively, this being a potential cause of lengthy time delays in research. As clinicians we are already familiar with a similar model namely the multidisciplinary team approach which is commonplace and has been practiced in the hospital setting for many years.

The Clinician

Ultimately, the clinician has the pivotal responsibility of trialling these novel therapies in the clinic but there is a growing realisation of the importance of clinical input into the pre-clinical stages of pharmaceutical development. For the clinician to be able to engage the scientific community however, we have to literally learn to speak a new language. This may mean expanding traditional medical school education and professional training with structured laboratory-based training. In the UK, this has conventionally occurred at postgraduate level prior to completion of specialist training, whereby registrars undertake 2 to 3 years of full-time research leading to an MD or PhD degree. Integrated undergraduate systems, such as the MBBS-PhD programme,⁸ should also increase the pool of competent clinician-scientists. Compared to undertaking undergraduate doctoral research, some consider research pursued

at registrar level advantageous as it allows greater insight into the clinical applications of basic research, training in more up-to-date techniques and maintaining momentum for pursuing post-doctoral studies. Fresh MBBS-PhD graduates will have to complete demanding junior postings and contend with further specialist exams whilst maintaining the motivation for research in a constantly evolving field.

Within undergraduate education in the UK, there is also an increasing emphasis to nurture research ability and the medical curriculum now often incorporates clinical audit or research based assessments, self-directed learning modules to promote independent thought and integrated BSc degrees. For practising clinicians who do not wish to commit to an extensive period of laboratory study, they may find cross-specialty secondments invaluable for developing an eye for collaborative studies. Gaining experience in pharmaceuticals can offer a useful commercial perspective to drug development. A number of hospitals and research institutions organise both formal and informal multi-disciplinary research meetings to promote an exchange of knowledge and ideas between scientists and clinicians.

As translational research continues to surge ahead with new discoveries and technologies – a multi-disciplinary approach seems most expedient. The clinician undoubtedly, will continue to play a key role in this process.

Declaration

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