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editorial

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Translational medicines research

Traditionally, scientific research has been categorised as either fundamental or applied. Fundamental research is driven by scientific curiosity and does not necessarily have any obvious practical value, whereas applied research is designed to solve practical problems rather than to acquire knowledge for its own sake. Fundamental and applied researchers therefore occupy different worlds, possess distinct cultures and have different drivers. In the medical domain, this makes it difficult to translate fundamental research results into practical applications that enhance human health and well-being. To help bridge this gap, the concept of translational (or bench-to-bedside) research was proposed in 1968 and has led to the concept of translational medicines research (TMR) [1–3].

TMR is expanding and evolving very rapidly. Both the European Commission and the US National Institutes of Health have made translational research to develop new medicines a priority. They have funded a number of major initiatives in this area, including: (i) the Innovative Medicines Initiative (IMI); (ii) the National Centre for Advancement of Translational Sciences and (iii) the Critical Path Initiative [3]. National initiatives are also appearing. These include: (i) the Translational Research Partnerships at the National Institute of Health Research in England; (ii) the Life Sciences Wales Fund; (iii) the Scottish Translational Medicines Collaboration; and the numerous translational medicines research centres established in the People's Republic of China. In addition, translational research organisations and programmes have been established in many academic centres, non-government organisations, pharmaceutical companies and disease-related organisations, along with individual hospitals and academic health centres. The term 'translational research' is also becoming increasingly recognised and understood with the emergence of scientific journals dedicated to this area [4]. These include: (i) *Translational Medicine*; (ii) *The Journal of Translational Medicine*; (iii) *Translational Research*; (iv) *American Journal of Translational Research*; (v) *Science Translational Medicine* and (vi) *The Open Translational Medicine Journal*.

The essence of TMR is the efficient and effective conversion of biomedical knowledge into new medicines. It encompasses all research activity from fundamental biology to a marketed drug. The key aspects of this process are described below.

i. **Understanding the biological basis of human disorders**: Research that leads to the discovery of a tractable molecular target for drug discovery is a critical part of the process by which new medicines are discovered. This includes studies of *post-mortem* tissue, the human genome, experimental models of human disorders, knowledge of key pathways involved in disease expression and the effect of compounds on biological systems. Such studies form the basis of hypotheses to explain both the aetiology and the pathogenesis of human disorders. This then informs and directs strategies to discover and develop new medicines [5].

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ii. **Lead generation and optimisation**: Structural biology is making an increasingly important contribution to the process of lead generation, with the expression, purification, and crystallisation of protein targets. This helps describe the molecular features necessary for molecular recognition of a ligand, allowing *in silico* screening of millions of virtual compounds. It thus facilitates the identification of molecules (hits) that modulate the function of molecular targets. Once this stage is complete, these hits are transformed into high-content lead series and then 'drug-like' leads. These are then further optimised into candidate drugs, and subjected to a battery of tests to demonstrate that they are likely to be safe and effective in human studies. A critical part of this complex and iterative process is an understanding of the relationship between the three dimensional structure of a molecule and its biological activity, along with an appreciation of the pharmacokinetic–pharmacodynamic principles of exposure at the site of action [5–7].In addition to small molecule drugs, a number of biotechnological medicines (biologicals) are on the market. These include both recombinant proteins (e.g. erythropoietin, filgrastim and somatropin) and monoclonal antibodies (e.g. abciximab, bevacizumab and natalizumab). An emerging source of new medicines, particularly for the treatment of genetic disorders or infections, is antisense therapy. When the genetic sequence of a specific gene is known to cause a particular disorder, it is possible to synthesise a strand of nucleic acid (DNA, RNA or a chemical analogue) that will bind to the messenger RNA produced by that gene and thus inactivate it. Despite substantial research, only one antisense drug (Fomivirsen) has been approved by the U.S. Food and Drug Administration (FDA). For protein and nucleotide therapeutics, methods to improve the efficiency and effectiveness of production and reduce production costs would be an important contribution to TMR.

iii. **Clinical testing**: It has to comply with the standards of safety, quality and performance laid down by regulatory authorities, such as the FDA and the European Medicines Agency. Even so, there is still scope for improvement in the methods used. This includes the use of biomarkers to provide: (i) improved homogeneity of patient populations; (ii) surrogate measures of therapeutic efficacy; (iii) pharmacodynamic markers of drug candidate efficacy and (iv) surrogate measures of side-effect liability.

Traditionally, the pathway from discovery to market has been viewed as a series of linear stages driven by a single organisation: a fully integrated pharmaceutical company. However, this model is increasingly being replaced by a more collaborative approach in which multiple stakeholders interact in collaborative ecosystems [8]. The progression of drug candidates in these distributed ecosystems involves a succession of relationships between multiple stakeholders with distinct cultures and drivers. This new approach has led to the formation of translational research organisations in order to build relationships between the relevant parties and thus facilitate medicines research.

Academia is the major source of new knowledge of the biological basis of human disorders and often: (i) discovers new drug targets, (ii) establishes experimental models for use in drug discovery; (iii) discovers new biomarkers; (iv) discovers new drug candidates; (v) plays a key role in clinical trials, including experimental medicine and (vi) discovers new approaches for drug delivery. In addition, contract research organisations (particularly small to medium sized enterprises) are playing an increasing role in both medicinal and synthetic chemistry, drug candidate screening, ADMET studies, pharmaceutical formulation, biomarker discovery and use, experimental medicine, clinical trials and drug delivery.

The funding structures that support these ecosystems are also evolving and include new players that work alongside the classical venture capital-Pharma funding model. For example, not-for-profit organisations (NPOs) now play a vital role in TMR. Major players include: (i) the Bill and Melinda Gates Foundation; (ii) the Michael J. Fox Foundation; (iii) the Huntington's Disease Society of America; (iv) the Alzheimer's Drug Discovery Foundation; (v) EU-AIMS (autism research in Europe); (vi) the Breast Cancer Alliance and (vii) the Cystic Fibrosis Foundation (CFF). These NPOs now: (i) provide substantial funding for targeted research, (ii) help set research agendas, identify and engage research professionals, (iii) recruit patients from among their membership for clinical trials and (iv) establish collaborative relationships with industry. The effectiveness of this approach is well illustrated by the collaboration between CFF and Vertex Pharmaceuticals Inc., which led to a new oral medication for the treatment of cystic fibrosis (Ivacaftor) gaining FDA approval in 2012 [9].

In the UK, NPOs (medical charities) account for one-third of all public expenditure on medical and health research. However, the majority of these charities exclude medicines research companies from applying for funding. By doing so, they are rejecting the very organisations with the know-how and expertise to translate research into tangible patient benefit. Important exceptions are (i) Medical Research Council Technology; (ii) Cancer Research Technology (CRT) and (iii) the Wellcome Trust. These World-leading organisations illustrate what can be achieved outside of traditional pharmaceutical business constructs, particularly in early stage TMR. New public private partnerships are also evolving where risks and resources are shared among several participants. Examples include (i) the Division of Signal Transduction Therapy in Dundee; (ii) the Structural Genomics Consortium in Oxford; (iii) the collaboration between AstraZeneca (AZ) and the UK's Medical Research Council, which involves academic scientists using 22 AZ compounds to study a broad range of diseases; (iv) the Quebec Consortium for Drug Discovery in Canada, which funds and supports partnerships between academia and industry to develop tools and technologies that facilitate the drug discovery process, and (v) the Global Alliance of Leading Drug Discovery and Development Centres (GALDDC) that aims to strengthen international academic and not-for-profit TMRs. GALDDC consists of: (i) The Centre for Drug Research and Development (Canada), (ii) Lead Discovery Centre (Germany), (iii) The Scripps Research Institute, Scripps Florida (USA), (iv) The Centre for Drug Design and Discovery, KU Leuven R&D (Belgium), (v) MRCT (UK) and (vi) CRT (UK).

Over the last 60 years there have been major advances in: (i) our understanding of the biological basis of human disorders; (ii) the process and practise by which new medicines are discovered and developed and (iii) the technology to support medicines research.

And yet, the number of new drugs approved per billion US dollars spent on research and development has halved roughly every 9 years since 1950 and getting a drug to market now costs more than $1.3 billion. On top of this, there is: (i) increased competition from generic drugs; (ii) an increasing requirement to demonstrate superiority over generic drugs; (iii) an increasing downward pressure on drug pricing and (iv) more than a hundred billion dollars of revenue at risk as a consequence of patent expirations over the next 3 years [10]. One way Big Pharma is addressing these issues is by changing the way it does TMR. There is a clear move to work more collaboratively with other organisations to discover and develop new medicines, which entails sharing knowledge, intellectual property and information as freely as possible. Such 'open innovation' represents a compelling opportunity to improve the efficiency and effectiveness of medicines research. Examples include: (i) Pfizer's recent formation of Centres for Therapeutic Innovation that aims to conduct TMR through partnerships with Academia; (ii) GSK's support for the Tres Cantos Open Lab Foundation in Spain, the UK's first open innovation bioscience campus (http://www.stevenagecatalyst.com); (iii) Eli Lilly's Open Innovation Drug Discovery platform (http://openinnovation.lilly.com) and (iv) the 'Lead Factory', which is an IMI-supported public–private partnership that constitutes a pan-European consortium of 30 partners that includes Big Pharma, small and medium-sized enterprises and academia. These, and other TMR initiatives, reflect a new paradigm for medicines research that is based on open and integrated partnerships and wider stakeholder involvement. It has the potential to improve the efficiency and effectiveness by which new medicines are discovered and developed [3,8].

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