Accelerating the transition of clinical science to translational medicine

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The SARS-CoV-2 pandemic has shown the importance of medical research in responding to the urgent prevention and health needs to combat the devastating disease, COVID-19, that this β-coronavirus unleashed. Equally, it has demonstrated the importance of interdisciplinary working to translate scientific discovery into public and patient benefit. As we come to adjust to live with this new virus, it is important to look back and see what lessons we have learnt in the way scientific medical discoveries can be more effectively and rapidly moved into public benefit. Clinical Science has had a long and distinguished history with this Journal bearing the same name and being an important contributor to the rapidly increasing use of human pathobiological data to gain mechanistic understanding of disease mechanisms leading to new diagnostic tests and treatments. The recognition that many complex diseases engage multiple causal pathways that may vary from patient to patient, and at different times across the lifecourse, has led to the emergence of stratified or precision medicine in which the right treatment is given to the right patient at the right time and, in doing so, minimise ‘non-responders’ and off-target side effects. Applications of omics technologies, the digitalisation of biology and the applications of machine learning and artificial intelligence (AI) are accelerating disease insights at pace with translation of discoveries into new diagnostic tests and treatments. The future of clinical science, as it morphs into translational medicine, is now creating unique possibilities where even the most intractable diseases are now open to being conquered.

Having experienced the horrendous effects of the SARS-CoV-2 COVID-19 pandemic, it now seems timely to look back over this period to see how the medical scientific community has evolved to meet the demands this placed upon our healthcare and social systems and what lessons can be learnt for delivering medical research in the future. As this new virus spread across the world, what rapidly became clear was that the majority of healthcare systems were poorly prepared and that new ways of operating to treat those with COVID-19 illness and, at the same time, protect vulnerable people from being infected. Before exploring lessons learnt from this extraordinary experience, it is salutary to look on how translational medical research has emerged and reflected in the pages of the journal, Clinical Science.

My own first contact with Clinical Science, the official journal of the Medical Research Society (MRS) came in the early 1980s when I first embarked upon a research career in medicine. I was introduced to the MRS by my mentor Prof Jack Howell, a renowned respiratory physiologist, and founding Professor of Medicine at the new Medical School in Southampton, U.K. [1]. I recall the MRS meetings as the ‘hot bed’ of new medical concepts and Clinical Science was the instrument for their publication as full papers.

The MRS was formed following a report by a subcommittee of the U.K. Medical Research Council on the ‘Future Policy for the Promotion of Clinical Research’ [2]. The MRS was founded by Sir Thomas Lewis (a renowned cardiovascular disease specialist [3]) in 1930, ‘for the purpose of advancing knowledge of
the causes and processes of disease, by clinical or related experimental studies in man' and began with 18 ordinary members and 2 honorary members, Archibald Garrod and John Scott Haldane. The first meeting of the Society was held at University College Hospital on 24 October 1930. Indeed, it was Lewis who first coined the term 'Clinical Science' [4] and the journal bearing that name was launched in 1945 with Lewis as Editor-in-Chief [1]. In fact, Clinical Science evolved from a previous journal 'Heart: A Journal for the Study of the Circulation' (also known as 'Heart') was created in 1909 by Thomas Lewis and James Mackenzie (a Scottish cardiologist) to reflect the widening interests of the two founders.

With molecular medicine focusing more on the cellular and molecular phenomena and interventions rather than the previous conceptual and observational focus on patients and their organs, in 1973 Clinical Science was renamed Clinical Science and Molecular Medicine but in 1979 reverted back to Clinical Science [1] and then, in 2003, the journal owned jointly by the MRS and Biochemical Society came under the sole ownership of the Biochemical Society [5].

The MRS continued to hold regular research meetings until October 2011 when it merged with the Academy of Medical Sciences (AMS) [6]. The AMS still holds an annual Clinical Academics in Training Annual Conference (CATAC) which, like the original MRS, is designed as a cross-specialty event to bringing clinical academics together to present and discuss their work. A final step occurred in 2007 with the merger of the Novartis Foundation (previously the Ciba Foundation) with the AMS [7]. With deep roots in promoting medical science and research, the Ciba Foundation was founded in 1947 to enable world-class scientists to meet and discuss cutting-edge developments across a wide spectrum to promote international cooperation in medical and chemical research [8].

With its characteristic olive-green cover and ivory pages, Clinical Science became the publication outlet that connected the various speciality fields of medicine together using state of the art methodologies of the time for measuring physiological, metabolic, endocrine, immunological and pharmacological responses in health and disease. It was also the home of experimental medicine defined by the MRC as, ‘The investigation undertaken in humans, relating where appropriate to model systems, to identify mechanisms of pathophysiology or disease, or to demonstrate proof-of-concept evidence of the validity and importance of new discoveries or treatments’ [9]. As an example, Clinical Science published one of my earliest research career outputs in which regular high-dose use of inhaled β2-adrenoceptor agonists were shown to induce a state of adrenergic tolerance [10], and thereby provided one of several plausible explanations for the increased asthma deaths linked to overdependency on inhaled bronchodilators observed in the 1970–1990s [11]. However, it is noteworthy that it took until 2019 for the Global Initiative for Asthma (GINA) to no longer recommend regular short-acting β-agonists used alone in the treatment of asthma [12].

Medical research would be very different without models of health and disease. We use cells, tissues and animals to determine what healthy biological processes look like, how they change with disease, and to test new interventions. Traditionally, discoveries were made in models and then, once appropriate, tested as potential interventions in people. While cell and animal models will continue to be a cornerstone of medical research, increasingly there has been more emphasis on studying normal and diseased humans as the ‘model organism’. Over the last decade new tools have been developed that is allowing questions about the human body that we are used to asking of cells, insects and mammals. Just as genomics accelerated the emergence of molecular medicine, technological advances in the form of data science, non-invasive imaging and the digitalisation of biology have created the opportunity to interrogate biological complexities like never before [13]. Technologies ushered in by the human genome project, are now being used in the ‘omics’ fields of genomics, transcriptomics, proteomics and metabolomics to track the intricacies of disease mechanisms from blood or urine samples [14,15]. New imaging technologies such as hyperpolarised and functional magnetic resonance are giving us non-invasive access to the human body at detailed resolutions, allowing not only visualisation of structure, but also function.

These approaches have also changed the way novel therapeutics are discovered with a move away from studying organ-based diseases (or models thereof) to a more interconnected or systems approach. The previous dependency of the pharmaceutical industry on animal models of disease was fine when pharmacological mechanisms were shared across species, but what has become increasingly apparent is that ‘simple’ animal models translate poorly into complex diseases [16,17] accounting for a high proportion of the failure of preclinical animal models to predict clinical efficacy and safety. The problem is not helped by lack of rigour in the design of animal experiments (internal validity) and provides a powerful case for the for the need of science driven replacement, refinement and reduction in animals used in research. Indeed, the U.K. National Centre for the 3Rs (NC3Rs) [18] was founded in 2004 to do just that – fund research and early career development, support open innovation and commercialisation of 3Rs technologies, and to stimulate changes in policy, regulations, and practice. For example, the Experimental Design Assistant (EDA) is a free online tool from the NC3Rs, designed to guide researchers through the design of their experiments [19], and the recent update of the Animal Research: Reporting of In Vivo Experiments (ARRIVE) Guidelines, is a checklist
Figure 1. The pathway of stratified medicine research

This should not be considered a linear process from marker discovery to clinical impact. Each phase should interact iteratively and reciprocally with the others, and be informed by them in their design and interpretation, e.g., initial framing of the research question should consider clinical need and eventual impact; verification of markers may inform mechanistic understanding and further exploratory research etc. (reproduced from: The MRC Framework for the Development, Design and Analysis of Stratified Medicine Research (2018) https://mrc.ukri.org/publications/browse/mrc-framework-for-stratified-medicine/; accessed 20 August 2021).

of information to include in publications and grant proposals that include animal research [20]. Beyond issues relating to experimental design which can be modified, there is the added difficulty of external validity, i.e. the extent to which research findings derived in one setting, population or species can be reliably applied to other settings, populations and species – a situation that cannot be easily modified without major genetic manipulation [21]. Research approaches that are physiologically relevant to humans avoid the need for animals and thus eliminate the problem of animal/human species differences [22]. Increasingly, industry is moving towards a view that animals will only be used when there are no alternatives, e.g., the effects of a medicine or vaccine in a whole living body, or because the regulatory authorities require it.

A clearer understanding of the interacting pathways that translate into clinical disease patterns has opened up the field of personalised, stratified or precision medicine – the identification of key subgroups of patients within a heterogeneous disease population with differing mechanisms, risk or course of disease or particular responses to treatments [23] (Figure 1). Stratification can be used to improve mechanistic understanding of disease processes and enable the identification of new targets for treatments, develop biomarkers for disease risk, diagnosis, prognosis and response
to treatment and allow treatments to be developed, tested and applied in the most appropriate patient groups with the anticipated end result of ensuring that the right patient gets the right treatment at the right time [24]. Stratification of heterogeneous patient groups is possible through measurement of traits assessed through any number of modalities – genomic, epigenomic, metabolomics, proteomics, microbiomics, histological, imaging, clinical scores, behavioural/psychological assessment, demographic etc. Strata are increasingly able to be defined by multiple variables, measured through multiple modalities [24] (Figure 1). Precision medicine has now been generally adopted as the preferred terminology where the focus is on identifying which approaches will be effective for which patients based on genetic, environmental and lifestyle factors [25].

Technology development is playing a large part in advancing the delivery of precision medicine. This is especially so in the diagnosis of disease using molecular pathology approaches that seeks to describe and understand the origins and mechanisms of disease at the level of macromolecules (for example, DNA, RNA and protein) largely using patient samples [26]. Molecular pathology has been absolutely crucial in the fight against the SARS-CoV-2 pandemic through routine use of PCR and lateral flow testing, the former being of additional value in enabling detection of different virus variants as well as point-of-care and multiplex testing for differentiating COVID-19 from other respiratory infections [27]. A key aspect of the rapidly evolving discipline of molecular pathology is the greater diagnostic accuracy when diagnoses are based both on the morphological changes in tissues (anatomical pathology) and on molecular testing.

Molecular pathology approaches have been greatly enhanced by whole-genome sequencing as demonstrated by initiatives such as the 100,000 Genomes Project in rare diseases and cancer [28]. The project is deeply embedded in the U.K. National Health Service through The Genomics England Clinical Interpretation Partnership (GeCIP; 2500 clinicians and scientists from approximately 300 institutions in 24 countries) with researchers creating domains around particular conditions (respiratory, renal, endocrine etc), cancer types and research areas such as Machine Learning and Health Economics [29]. The partnership is integrated with the U.K. National Health Service (NHS) with the objective of improving the uptake of genotype and phenotype data in healthcare, and for producing a platform for interdisciplinary genomic research collaborations to improve the knowledge base for genetic disorders. In addition, a range of biotechnology/pharmaceutical companies have formed a pre-competitive industry trial, the Genomics Expert Network for Enterprises (GENE) Consortium to bring industry expertise involved in developing new medicines and diagnostics [30].

There have also been great strides in anatomical diagnostics. Non-invasive and minimally invasive imaging using ultrasound, nuclear, computed tomography, magnetic resonance, thermal and many other approaches have enabled greater diagnostic precision and lend itself to screening in susceptible individuals. Machine learning techniques, especially deep learning, an artificial intelligence (AI) function that is modelled on the workings of the human brain for processing data and creating patterns used in decision-making, have been successfully applied to general image recognitions [31]. Such techniques are now being applied to various histopathological images where it has already outperformed experienced pathologists for recognising histopathological images especially in the diagnosis of cancer [32].

These many advances in medicine made possible through digital biology and the process of biodigitisation are fundamentally about data – the collection of it, its storage, the modelling of it and its transfer into biological form [33,34]. While this brings with it issues such as data storage, custodianship, protection and other ethical considerations, there can be no doubt that collection, analysis and combination of data is the new frontier for medical research.

On 30 November 2020, DeepMind (a subsidiary of Google’s parent company Alphabet focusing on AI) – took a great step forward in its ability to predict the correct, three-dimensional structures of proteins based on their constituent, one-dimensional amino acid sequences. They generated a neural network-based machine learning model, AlphaFold, that incorporates physical and biological knowledge about protein structure, leveraging multi-sequence alignments, into the design of the deep learning algorithm [35]. They went on to use the updated AlphaFold2 computer network, comprising 128 machine learning processors to train the algorithm on 170000 experimentally determined protein structures in addition to large databases containing protein sequences of unknown structure [36]. What is so remarkable, beyond the sheer accuracy of AlphaFold2 in predicting 3D protein structures, is that it took only 48 h to obtain the 350000 protein predictions as compared with the slow pace of experimental structure determination. Paul Workman, Director of the Institute of Cancer Research in the U.K. [37], summarises the advance as ‘greatly benefiting fundamental research (understanding the structure and function of life), the biotechnology industry (engineering proteins as molecular machines and foods) and the discovery of new drugs . . . which allows researchers to understand which targets are relatively straightforward to develop drugs for and which ones will represent a major challenge’. Also in the field of cancer, the recent validation of GRAIL’s multicancer early detection test, Gallern™, which detects unique circulating, cancer-specific DNA sequences from 50 different types of cancer [38], is

In terms of human capability, what the SARS-CoV-2 pandemic has revealed is the remarkable ingenuity and ambition that medical scientists are capable of when emergence of a new disease demands rapid action whether the creation of safe and effective vaccines, new diagnostic tests, novel drugs or improved personal protective equipment. What has become abundantly clear for the efficient translation from discovery to clinical use is the absolute need of a skilled interdisciplinary research workforce and the appropriate localities and equipment to prosecute high-quality research for patient and public benefit. In U.K., the National Institute for Health Research (NIHR) Biomedical Research Centres [39] and related infrastructures have proven themselves many times over, especially in delivering high-quality clinical trials. The importance of patient-oriented research, as clinical science is now sometimes called, has never been more important, especially if some of the great achievements and processes produced during the SARS-CoV-2 pandemic can be transferred to other fields of medicine.

Clinical Science, as envisaged by Sir Thomas Lewis over 90 years ago, is not only thriving but has assumed unrivalled importance in a healthy modern society where translational medicine and evidence-based healthcare are becoming the norm [40,41].

Competing Interests
The author declares that there are no competing interests associated with the manuscript.

Abbreviations
AI, artificial intelligence; AMS, Academy of Medical Sciences; MRS, Medical Research Society; NC3Rs, U.K. National Centre for the 3Rs.

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