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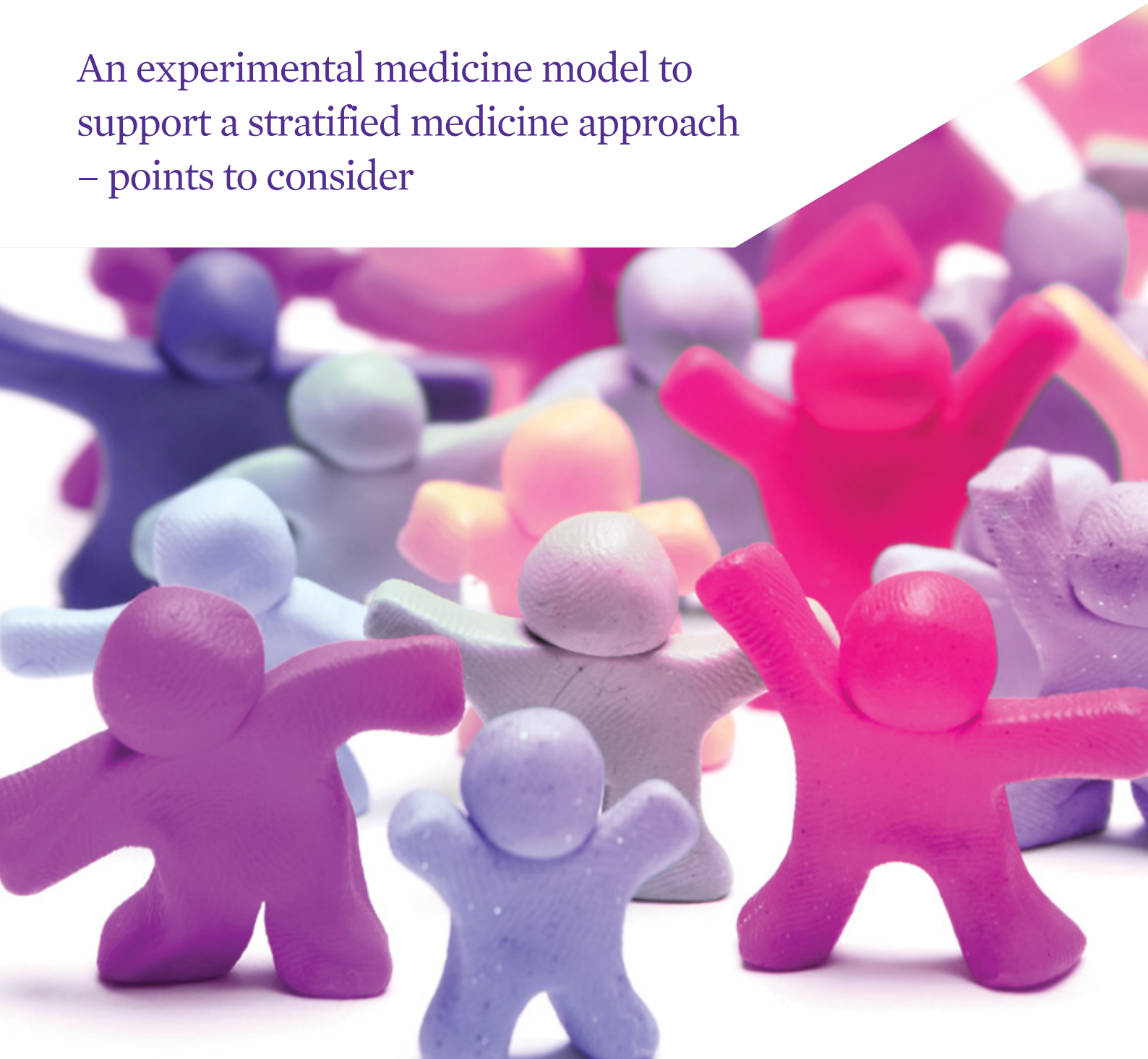
Bringing medicines to *life*

An experimental medicine model to support a stratified medicine approach – points to consider



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Abstract

This paper encourages researchers to use experimental models in health research to better understand the mechanism of action of potential new medicines and disease mechanisms, and to identify which patients can gain most benefit and/or experience fewer adverse reactions to a therapy – an approach referred to as stratified medicine. This paper highlights the extensive infrastructure established over the last few years to promote research partnerships in the UK between the NHS, academia and biopharmaceutical industry.

Introduction

Medical innovation focused on finding the patients who gain most benefit and/or experience fewer adverse reactions to a therapy can result in the delivery of new medicines that offer enhanced patient outcomes (efficacy and safety), improved adherence, reduced wastage, and facilitate earlier uptake and adoption through the clear 'value proposition' they present to payers[1]. This targeted approach is variously referred to as a 'personalised' or perhaps more informatively 'stratified' medicine approach. This review details how experimental medicine practice within the UK can support a stratified medicine approach in drug development, and increase the attractiveness of the UK as a place for exploratory development.

Delivery of stratified medicine within the UK can be best achieved through the creation of strong and integrated partnerships between the pharmaceutical and diagnostic industries, the NHS, the funders of exploratory academic biomedical science, and the various national and international regulatory bodies throughout the drug discovery and development process. In December 2011, the UK Government launched its Life Sciences Strategy, putting partnerships for health research as a priority for the discovery, development and commercialisation of medical innovations[2]. The development and execution of an integrated strategy in the area of stratification of disease to date has seen a growing commitment from stakeholders but this has focused in certain areas eg translational science[3]. There is now a need to formalise and embed this evolving culture of collaboration amongst all biomedical scientists, from academia, NHS, public sector research and the biopharmaceutical and diagnostic industries. This expansion and integration has to cover all aspects of delivering stratified medicines to patients and is vital to make the UK an attractive research and development environment. All avenues must connect and collaborate, and embrace private/public partnerships if we are to drive rapid progress in the adoption of disease stratification and personalised medicine.

1. Integration across the research and development pipeline

1.1 Preclinical studies

A stratified medicine approach can be applied at any stage in a medicine's discovery and development, but it is best planned early, ideally near the time of target discovery. This gives the best opportunity to generate the data to inform the critical decisions around the therapeutic potential of the target, including the indication for the medicine and the appropriate patient population.

Factors capable of delivering clinically meaningful stratification may be identified through a variety of approaches, including but not limited to studying the molecular pathways involved in the engagement of the target and their downstream consequences, as well as the molecular aetiology of the disease and phenotypic variance.

Examples of factors of stratification:

1. Understanding of the various phenotypes of the disease to identify sub-groups of patients
2. Understanding the target and its role in the disease and the disease phenotypes
3. Target biology and/or pathophysiology: validity of the target in humans who have the disease of interest (ie translation from pre-clinical to human)
4. Experimental model to investigate the pharmacodynamic effect of the drug in all patients or in patients with a defined phenotype or genotype of relevance to the target biology.

Pharmaceutical research collaborations that involve NHS and academia seem best placed to contribute to the understanding of phenotypes of diseases, and to involve patients early in research. In addition, bio-material samples provided by patients suffering from disease are invaluable for testing target biology or gaining pharmacokinetic or pharmacodynamic data. Large scale population biobanks (see section 2.3.4.) also offer an invaluable resource that can drive effective multi-stakeholder research collaborations on the understanding of the genetic and environmental determinants of health and disease.

1.2 Translation from preclinical to human biology and pharmacology

Early adoption of experimental medicine strategies allows for effective learning about target biology in healthy controls and patients. These Phase 0 non-intervention studies and Phase 1 experimental medicine studies can inform the choice of:

1. a relevant study population comprising subject believed most likely to demonstrate some biomarkers of efficacy in early phase clinical trials
2. relevant doses to test in Phase 1 trials
3. endpoints that are relevant to the biology and pathophysiology of the disease and the pharmacology of the molecule.

The outcome of the Phase 0/1 research and/or of the target biology in tissue samples may identify sub-groups of patients with different pharmacodynamic or safety potential outcomes. In turn, this can inform the choice of dose to give to patients for Phase 2 clinical trials, or the right study population for the Phase 2 studies.

For example, crizotinib is recognised as a highly effective therapy for patients with advanced non-small cell lung cancer (NSCLC) who have specific translocations of the anaplastic lymphoma kinase (ALK) gene (ALK-positive)[4]. ALK rearrangements as oncogenic drivers in NSCLC were identified during the early Phase 1 of crizotinib development. This provided a clear rationale for expanding

the dose escalation Phase 1 trial of crizotinib in patients with NSCLC who were ALK-positive[5]. The promising results generated clearly supported the conduct of Phase 2 clinical trials in patients whose disease was aetiologically specified through molecular diagnostic assay. As a result, the effect of treatment was not diluted out by the inclusion of patients who were unlikely to respond, and the development of crizotinib to the market has proved rapid.

1.3 Stratified medicine approach in later drug development

As a medicine progresses through to the later phases of development, Phases 3, 4 and post-launch, it can still be useful to pursue the identification of biomarkers for prospective selection of patients. Such approaches may help to identify a sub-group of patients responding better to the drug. Clearly such information can prove important to patients, the doctors who prescribe, and healthcare payers. In these later stages of medicine development, a biomarker for stratification may differ from biomarkers initially used to study the target biology, and may or may not be supported by experimental medicine models and early development practice.

An example of such a 'retrospective stratified medicine approach' unplanned in early development is provided by gefitinib. Gefitinib is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of the epidermal growth factor receptor – tyrosine kinase (EGFR-TK). The relevant mutations that offer modulation by the drug were only identified as significant to gefitinib response several years after the Phase 1 and Phase 2 clinical trials had been initiated. Nonetheless lifecycle studies examining the clinical use of these mutations as targeting companion diagnostics for gefitinib were carried out and in 2009, Mok et al[6] published the Phase 3 clinical trial that showed for the first time that the presence in the tumour of a mutation of the EGFR gene is a strong predictor of a better outcome for gefitinib treatment.

2. Opportunities within the UK to develop stratified medicines

The strategy of the UK Government is to promote public/private partnerships to deliver the best research in the UK. It has committed significant funding and infrastructure through several initiatives in the field of experimental and stratified medicine.

The following provides some highlights of UK stakeholders' commitment to public/private partnerships, not with the intention of being exhaustive, but to assist scientists in navigating the field of public research provision relating to stratified medicine in the UK. The scientists may also refer to a useful publication *Unlock your global business potential: UK stratified medicine* from UK Trade & Investment[7].

2.1 The Technology Strategy Board

The Technology Strategy Board (TSB)[8] is an agency established by the UK Government to support innovation across UK industry. Healthcare was prioritised as one of the key industries and in October 2010 the TSB launched the 'Stratified Medicines Innovation Platform"[9,10], specifically to help accelerate the rate of development and uptake of stratified medicines in the UK, for the benefit of patients, healthcare providers and business.

The Stratified Medicines Innovation Platform is a five-year partnership programme including the TSB and seven public/charity sector organisations who have agreed to work together and combine resources to accelerate research, development and, ultimately, uptake of stratified medicines in the UK. The partners are the TSB, the Medical Research Council, the Department of Health England, the Scottish Executive Health Directorate, Cancer Research UK (CRUK), Arthritis Research UK and the National Institute for Health and Clinical Excellence (NICE).

By way of example, in May 2011, seven projects were granted funding[11]. Including contributions from the project partners, the total value of the research and development will be over £7 million. The projects are led by AstraZeneca UK Ltd, GlaxoSmithKline (three projects), Ig Innovations Ltd, Janssen UK and Randox Laboratories Ltd.

Additional calls for research proposals are currently being developed and the TSB website (www.innovateuk.org/) provides further information and application details.

2.2 Medical Research Council

Stratified medicine is also one of the priority areas for the UK Medical Research Council (MRC). The MRC will commit £60 million to this area over the next four years. The MRC is currently inviting proposals from disease-focused consortia to stratify specific diseases by using the best science to select the best therapy for each patient and achieve the best outcome for each group. There are two MRC-ABPI consortia already established to aid understanding of disease/conditions of unmet need and better identification of targeted medicines (£11 million programme, launched October 2010)[12, 13]: one for rheumatoid arthritis and one for chronic obstructive pulmonary disease (COPD). A third consortium, MRC-ABPI Diabetes Stratification, is being established which will explore extreme responders to diabetes therapy and define clinical and molecular criteria for stratification[14, 15].

The established MRC-ABPI consortium for rheumatoid arthritis investigates responder/non-responder status for anti-TNF biological therapies, and aims to create an immunological toolkit (biomarker signature of acute disease progression to identify patients at risk), which will aid stratification.

The established MRC-ABPI COPD consortium investigates phenotypes in cohorts of patients, role of infection, tissue injury and repair, and co-morbidities.

Each formally managed consortium is integrated between academia and industry and has developed its work plan with industry to include deliverables and milestones. The ABPI member companies contribute expertise, database handling and informatics, assay development, trial data, existing cohorts and collections, etc.

The MRC website provides further information, including details of other partnerships between MRC and industry, and contact details: www.mrc.ac.uk/Ourresearch/MRCIndustry/Opportunitiesforcollaboration/index.htm.

2.3 National Institute of Health Research

In addition to funding health-related research through the MRC, the UK Government currently also funds health-related research through the National Institute for Health Research (NIHR). The NIHR commissions and funds NHS and public health research essential for delivering societal responsibilities in health services. Its role is to develop research evidence to support decision making by professionals, policy makers and patients, make this evidence available, and encourage its uptake and use. In the last three to five years it has had a focus on developing translational medicine and clinical trial infrastructure within the UK.

The Efficacy and Mechanism Evaluation programme, funded by both the MRC and NIHR, with contributions from the CSO in Scotland and NISCHR in Wales, has recently completed a call for commissioned studies in the field of stratified medicine focused on the development, understanding or use of diagnostic or predictive tests or algorithms.

2.3.1 UK Clinical Research Collaboration

The UK Clinical Research Collaboration (UKCRC) brings together the NHS, research funders, healthcare and pharmaceutical industries, regulatory bodies, Royal Colleges, patient groups and

academia. The aim of this forum is to work together to improve various aspects of the research environment. The details of the partners and the stakeholders, as well as the many achievements for facilitating clinical research in the UK can be seen on the UKCRC website (www.ukcrc.org/).

The NIHR Experimental Medicine Resource Finder, and the Model Agreements between sponsors and host institutions to be used without modification, exemplify enabling steps in the field of stratified medicine.

2.3.2 Biomedical Research Centres and Biomedical Research Units

In August 2011, funding from the Department of Health for biomedical research in NHS and university partnerships in the UK was renewed. Eleven Biomedical Research Centres (BRCs)[15] and 20 Biomedical Research Units (BRUs)[16] were awarded funding for five years, from April 2012, to support the recurrent costs of patient-focused research. The aim of the BRC funding is to translate fundamental biomedical research into clinical research that benefits patients and the BRCs are early adopters of new insights in technologies, techniques and treatments for improving health.

One of the criteria for selection of a BRC or a BRU is the strength of their strategic partnerships, including those with industry. Both the UK-based biopharmaceutical industry and the BRCs/BRUs are therefore strongly encouraged to engage in collaborations.

2.3.3 Translational Research Partnership

There are currently two NIHR Translational Research Partnerships (TRPs)[12, 17] as announced by ministers in October 2010 at the ABPI Conference. A TRP is a co-operative venture between research centres that have proven ability to deliver experimental medicine and translational research in specific disease areas. The two existing TRPs focus on

a) joint and related inflammatory diseases, including rheumatoid arthritis, osteoarthritis, synovitis, and

b) inflammatory respiratory disease, including asthma, allergy, COPD, cystic fibrosis, acute lung injury, respiratory infection.

These research co-operatives have committed to work with industry and leverage the NIHR Office for Clinical Research Infrastructure (NOCRI) as a single point of contact facilitating access to principal investigators and clinical academic centres of excellence. The biopharmaceutical company members of the ABPI have provided compounds into the pilot schemes of the TRPs. Building on this model, a Translational Research Collaboration in Dementia was recently established.

2.3.4 Biobanks

2.3.4.1 The UK Biobank

The UK Biobank Resource[18] is a resource for health research comprising of baseline data and samples collected from more than 500,000 people aged between 40 and 69 when they joined the project during 2006-10. The people have undergone measures, provided blood, urine and saliva samples for future analysis, detailed information about themselves and agreed to have their health followed. Researchers are encouraged to make use of the data and since 30 March 2012, all researchers, whether in universities, charities, government agencies or commercial companies, and whether based in the UK or abroad, can apply to use the data; the same application process and approval criteria apply to all.[3, 19] The UK Biobank is funded by the Wellcome Trust, Medical Research Council, Department of Health, Scottish Government, Welsh Government and the British Heart Foundation, with a budget of £25 million for years 2011-2016.

2.3.4.2 NIHR Bioresources

The Cambridge BioResource[20] is a resource of patients and healthy volunteers who are willing to be approached and invited to participate in local research studies investigating the links between

genes, the environment and common diseases. It is collaboration between the NIHR-funded Cambridge Biomedical Research Centre, the University of Cambridge, NHS Blood and Transplant and the Medical Research Council, with additional support from the MRC Cusrow Wadia Fund and the Milly Apthorp Charitable Trust.

Recently a similar National NIHR Bioresource[2, 21] has also been developed by the Oxford, Cambridge and London Biomedical Research Clusters and the Leicester Biomedical Research Unit to support companies and researchers in recruiting participants to undertake stratified studies. Initial funding of £2.5 million for the first year has been provided from the NIHR.

2.3.5 Clinical Practice Research Datalink service

The NIHR has partnered with the Medicines and Healthcare products Regulatory Agency (MHRA) to create the new Clinical Practice Research Datalink service (CPRD), launched in October 2011 and fully established since 1 April 2012[22, 23]. This is another enabling aspect of experimental medicine to support the stratified medicine approach, as CPRD will provide access to observational data for researchers (NHS, social care and others), interventional research services, formal, protocol-based research and governance. The NHS Health and Social Care Information Centre (HSCIC)[24] also provides complementary data extraction and linkage services, and health outcomes data for non-protocol research.

2.4 Genomic data

The 100K Genomes project run by Genomics England[25] will sequence the genomes of up to 100,000 patients within the next five years. When linked with other phenotypic data, it will be a valuable resource for stratified medicine.

3. Intellectual property

The majority of intellectual property (IP) associated with deliberately stratified drug development tends to be predicated on the compound used to treat the stratified group rather than the stratifying diagnostic per se. This reflects the well established practices surrounding the protection of IP associated with therapeutic agents. Nonetheless, whenever diagnostic tests are used to stratify the patient population, the diagnostic test itself (particularly manufactured reagents such as molecular diagnostic probes) may offer a route to protected IP that is separate from that of the compound itself. In particular, defensible IP arising from the use of an innovative selection factor identified outwith a drug development programme may represent significant commercial opportunity.

4. Sharing data

Sharing data from the research industry, academia and public partners could lead to optimum use of research samples and avoid duplication of research effort. Already, UK and European legislation, legal agreements and research governance exists to facilitate data sharing by ensuring effective protection of the individual participants' personal information.

Despite such safeguards, sharing data requires a mind shift for both industry and academia. There are real challenges, for example pooling data is sometimes compromised by different scoring systems in use by various collaborators. In the case of the stratifying factors, often the research use assays for the gene/target identification have been developed locally with a dedicated scoring system, then applied to locally held tissue and are reported in isolation. When collaborations are put in place it can transpire that discussion is needed about which testing platform is the most appropriate and agreement needs to be reached about whether results are comparable/poolable if different probes and scoring systems have been adopted.

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