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Translational research in the pharmaceutical industry: from bench to bedside

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Current developments in basic discovery sciences have not been mirrored by the same level of progress in understanding the clinical basis of disease and ultimately the development of novel effective therapies. This can be improved by applying translational research throughout the late-stage discovery and exploratory development stages of drug development. A bi-directional dialogue between research scientists and clinicians concerning the biology of mechanism of action and clinical basis for disease will deliver biomarkers that enable drug development decisions to be made earlier and with increased confidence. Thus, we can better exploit the many targets that have been discovered through the mapping of the genome and other breakthroughs in medical sciences, such as the polyomic technologies.

Making the case

Translational research describes a bi-directional sharing of knowledge and ideas by the scientific and clinical disciplines to develop biomarkers that reliably select the mechanisms that can lead to breakthrough therapeutics.

The vast majority of tested compounds do not progress from drug developers laboratories to patients' bedsides. Historically, 14% of the tested products entering Phase I trials eventually cleared the hurdle of gaining FDA approval and entered the market. Nowadays, the chance of success has reduced by almost half, to just 8% [1–4]. This high attrition rate has led to two inescapable consequences: fewer drug and biological submissions; and the development costs of these products reaching unprecedented levels. For example, the FDA filings of standard new medical entities decreased from 34 in 1995 to 12 in 2003. Original biological licence applications have declined from 33 in 1997 to 14 in 2003. At the same time, some estimate the cost of developing a single drug has increased from US$1.1 billion in 1995 to US$1.7 billion in 2002 [5–7].

In addition to the cost, the path to market for successful candidates is lengthy, often caused by the reliance on assessment methods that were not designed specifically to assess the early safety and efficacy of new medical interventions. As a measure of the economic consequences caused by this lack of foresight, the FDA estimates that just a 10% improvement in predicting a product's failure in clinical trials could save US$100 million in development costs per drug [2].

Somewhat of a paradox, in this paradigm where failure is many times more likely than success, is that the pharmaceutical industry, in its desire to convert a mechanism to a medicine, usually plans for success in exploratory development with many parallel investments designed to jump-start the process. Perhaps, then, it would better to plan more expediently. The pharmaceutical industry's R&D attrition is directly tied to its success in building confidence in the rationale (efficacy and differentiation) that underpins a given target, and equally in executing all programmes in a manner that would lead to accurate and cost-effective decision-making with respect to the target mechanism. Identifying the key attrition point for a novel drug candidate, and performing the 'killer experiment' as early and as cost-effectively as possible, becomes a key lever to address the drug productivity deficit. Because it is clear that most drug candidates will fail, exploratory drug development should have a primary and overarching focus on the plans and options that proceed to this point with minimum investment, based on an active reduction in the uncertainty around key risks – pharmacology, pharmacokinetic–pharmacodynamic (PK–PD) properties, safety, differentiation, and so on [8–11].

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Translational medicine and drug development application needs

The American Physiological Society (APS) has defined translational research as 'the transfer of knowledge gained from basic research to new and improved methods of preventing, diagnosing, or treating disease, as well as the transfer of clinical insights into hypotheses that can be tested and validated in the basic research laboratory' [12]. It is a two way process of iterative learning from experimentation [12]. Within the context of the biopharmaceutical drug industry, translational research constitutes the cross-line preclinical and clinical research strategies and experiments that bridge the scientific and operational gaps between *in vivo* research (lead generation) and early-stage clinical studies (proof of concept).

Translational research has two key elements and can be described as the thought process by which information is applied from different perspectives:

- From research to development it relates signals from animal studies that can predict the efficacy (confidence in rationale) and safety (confidence in safety) of compounds in early development (animal pharmacology and associated exposures describes PK–PD translation of PK–PD to humans, and animal disease model efficacy describes projected efficacious exposures translation of efficacy to clinical patients). Such correlates can be derived from mechanistic biomarkers. They can have, or turn out to have, poor correlation with disease but they measure the pharmacology of a compound in humans [13,14].
- The transition from development to research findings in humans and patients with diseases enables a clear understanding of the biology and pathophysiology, and so can trigger *in vitro* and animal experiments that better mimic the human and patient condition. This is, therefore, likely to enhance confidence in the appropriateness of the target and help in the dose selection for subsequent trials. These are referred to as disease-orientated biomarkers.

The integration of this bi-directional thought process can be extremely powerful. An example from bench to bedside includes xenograft testing for oncology; and in bedside to bench clinical experience an observation that has been translated back into a legitimate drug target and discovery effort, is the case of Viagra® (sildenafil citrate). So, effective translational research in drug development implies a required two-way dialogue and interaction between scientists in preclinical drug discovery and clinical developers, who understand the disease and its symptomatology, to take novel drugs and biologicals to volunteer and patient trials. With the application of translational research to exploratory drug development, it is often necessary to implement different early-phase clinical trial designs to validate new biological end-points, if the full potential of new biopharmaceutical agents is to be realized [15]. The 'proof of principle with mechanistic analysis' strategy, often adopted in the application of translational research in drug development, allows optimization of the therapy from the beginning of clinical drug development and provides important feedback to preclinical drug developers [16]. Examples include: the central nervous system (CNS) single photon emission computed tomography (SPECT) analysis of nicotinic agents in attention deficit and hyperactivity disorder (ADHD); the use of γ-secretase inhibitor in Alzheimer's disease; building confidence in the scientific approach before starting a lengthy trial; developing plasma and cerebrospinal fluid markers for enzyme inhibition in Phase I; measuring neuronal activity [glucose uptake by fluorodeoxyglucose positron emission tomography (FDG-PET)]; and creating beneficial cognitive models [functional magnetic resonance imaging (fMRI) of hippocampal and cortical activity to evaluate spatial memory]. In oncology, examples of the benefit of translational medicine include defining which patients respond to targeted therapy by identifying cell lines with appropriately activated oncogene, identifying tumour subtypes encompassing a drug-responsive signature, and profiling tumours on low-density array to identify potential responders.

- Phase I is no longer just about establishing PKs and/or maximum tolerated dose, but rather an essential part of early clinical development where important decisions on the future development of a drug can be made. The emphasis is on the application of mechanistic biomarkers in early phase clinical trials to maximize the chances of obtaining clinical data to make sound go–no-go decisions [13,17,18]. Every first Phase II trial must be a valid test of the drug target. It requires a fundamental understanding of the required level of pharmacological activity from preclinical work. This translates to humans as go–no-go decision criteria for proof of mechanism (POM). To that end, it is crucial to prove that the compound safely expresses adequate pharmacology in Phase I, and one should only start Phase II if POM is achieved. In turn, Phase II results validate the drug target and enable data-driven programme decisions to predict late-phase success. Several examples exist wherein this determination of POM is pivotal in defining go–no-go criteria. For example: obesity programmes (food intake and energy balance); ADHD (cognitive effects and functional imaging); osteoporosis (bone biomarkers); psychotherapeutic programmes (PET receptor occupancy); oncology programmes [angiogenesis biomarkers (dynamic contrast-enhanced MRI, vessel density), tyrosine kinase inhibition (target phosphorylation), tumor response (FDG-PET)]; and atherosclerosis (lipids and inflammation biomarkers).

Successful implementation of translational research, to link preclinical data with clinical outcomes, can provide several essential benefits to the drug development programme. These include increased confidence in the rationale at earlier points in the research and development process, more confidence in the efficacy or safety of an unprecedented approach, the ability to determine earlier whether an approach can be differentiated from existing therapies, and the ability to construct a suitable PK–PD model to allow more precise dose-selection for Phase IIb. It is reasonable to believe that these strategies could improve drug candidate survival and overall productivity.

Precedented mechanisms to treat existing diseases will enable incremental, but often important, improvements on existing therapies. Many indications are now treated with relatively efficacious and well-tolerated medications, so it is difficult to produce new therapies that can be differentiated from existing treatments. Therefore, new medicines with small incremental improvements are becoming harder, commercially, to bring to market. The institutional payers are becoming increasingly resistant to such approaches and reimbursement is a challenging dilemma [19,20]. Many European countries and managed care organizations in the

USA are devising new mechanisms, such as reference pricing, to limit pharmaceutical expenditure [21,22]. In this way, the next wave of breakthrough medications will come either from unprecedented mechanisms that carry a high attrition risk or from more precedented mechanisms, where the risk of achieving sufficient differentiation in clinical end-points might result in high attrition. Activities that increase confidence in the rationale of these targets early in research and development would help to significantly improve the efficiency and productivity of the process and, crucially, increase the chance of success in late Phase II and III. Therefore, investment in clinical target validation, using suitable probe drugs or compounds, is necessary to gain key efficacy or safety data for some of these unprecedented targets.

The fundamental bottleneck in drug discovery is not the validation of a target, but the validation of a disease model itself. It is now a realization within the R&D industry that *in vivo* research is essential to validate the therapeutic utility of drug candidates as early as possible [23]. Validation of a model not only requires a detailed understanding of the underlying scientific assumptions, but also evidence of a good correlation between the observed model disease phenotype and the human disease condition. Congruence between disease models and human disease is ultimately a question of ontology. Is it possible to derive accurate disease models if the human disease itself is a composite of multiple aetiologies? Clinical target validation involves the use of probes that have the desired pharmacology to test novel hypotheses in indications where those mechanisms have no clinical precedence for efficacy. Clinical probes can be obtained from a variety of sources, such as: (i) existing agents used for their alternative pharmacological effects; (ii) through combinations of existing agents; (iii) drug development candidates that are developmentally flawed but have evidence of pharmacological activity in humans; (iv) synthetic human biochemicals and hormones; and (v) biologicals. At present, only a minority of unprecedented mechanisms can be tested in this way (because the prevailing modality of drug development is still to develop drug candidates on the presumption that they will be ultimately successful – but this could prove a valuable process to increase clinical confidence for the rationale behind developing therapeutics directed against new targets. Translational researchers could facilitate such a process by identifying discovery projects that have low confidence with respect to the rationale and safety, searching for suitable drugs or probe compounds to use in the studies, defining the clinical hypothesis to be tested and ensuring appropriate study design. Additionally, they should agree what impact results from such a study would have on discovery efforts in that area and analyze the molecular correlation between human disease and *in vivo* models.

As has been pointed out by Mankoff *et al.* [24], hypothesis-driven research alone cannot meet the needs of translational research:

> This is because hypotheses derived from complex experimental models often simply do not translate to human pathology. It has been suggested that discovery-driven research should be promoted in the context of translational medicine and should be better referred to as ''reality-driven'' research underlining the concept that direct human observation may direct to the study of hypotheses relevant to human reality!

This is a future concept where medicine might be developed as an observational art. At present, most disease classification is not as a result of fulfilling molecular criteria, but rather based on an accumulation of symptoms that occur commonly together in patients or through histopathological observations.

Practically, however, reality-driven research in humans faces obstacles of its own. First, communication between basic and clinical scientists is rare and sporadic. Few meetings are devoted primarily to bringing the two entities together to promote a mutually beneficial exchange. Therefore, translational research should involve the coordination of preclinical and clinical studies, which should allow true alignment between the disciplines and the realization of increased productivity. It should involve a free exchange of ideas, as well as a focused, unified and coordinated approach to core translational research activities. Translational drug investigators need to draw on the expertise of various discovery, preclinical safety and clinical groups. To that end, it is crucial in drug development to have dedicated translational groups to implement translational research strategy at the therapeutic and project levels. Such groups include discovery biologists, members of preclinical and clinical safety sciences, clinical pharmacologists and experimental medicine experts. They must be familiar with regulatory, statistical and administrative issues related to clinical investigation and have expertise in the basic science underlying new technologies or pharmacological agents in a particular therapeutic area. Sustaining a vigorous rate of transfer of basic findings into clinical application requires a stable and well-trained cadre of 'translational' drug investigators to patrol the borders of the basic–clinical interface [25]. These investigators need to be recruited, educated and continuously kept up-to-date in scientific techniques – as well as becoming active members of functional translational research groups. Effective two-way communication between research and other development colleagues in translational, planning and operational groups will allow efficient translation of pharmacology into the clinic, leading to greater candidate yield.

Technical advances to aid translational research

Innovation in medicine is best driven by an understanding of disease processes. Current advances in technology are important tools that help us to understand these pathways. The pharmaceutical industry's efforts in translational research are increasingly focused on activities that can enhance the ability to translate the scientific promise of new mechanisms to clinical applications.

Polyomics

Revolutionary progress in basic research, such as human genomics, together with the sequencing of the genome of many of the commonly-used laboratory species, provides an important opportunity to understand the comparative determinants of efficacy, toxicity and adverse reactions [26,27]. Indeed, the scientific advances in genomics and other emerging technologies, such as proteomics, biochips, signal transduction and toxicogenomics, provide the biopharmaceutical industry with a real opportunity to improve and innovate the discovery and

exploratory development processes and the links between discovery and development. In other words, truly to fulfil the promise that translational research can deliver.

Polyomics can be defined as the integration and mining of information-rich datasets (obtained through analysis of preclinical and clinical specimens using technologies with the aim of improving discovery) with the development and use of novel therapeutic agents. A recent example is a monoclonal antibody that targets the overexpression of HER2 protein in certain breast cancer patients, Herceptin™ (trastuzumab). Approximately 20–25% breast cancer patients are HER2-positive and respond well to treatment with Herceptin™, compared with HER2-negative patients [28]. It is based on a variety of platform technologies, which have been developed throughout the last decade, offering the opportunity to 'industrialize' the generation of biomedical data. Through the application of such polyomics, which include genomics, transcriptomics, peptidomics, proteomics and metabonomics, drug development will occupy an even more pivotal role, because many more drug candidates will be generated in the years ahead compared with the present. Although each of these technologies has been heralded as the answer to industry's productivity challenges, each technology offers complementary views on – and approaches to – the underlying biological and pathological processes being examined. It is only with a much greater in-depth understanding of the basic attributes of the individual technologies, for example, sensitivity and signal-to-noise ratio and the application of epidemiological and mathematical tools, that the power of these technologies will be unlocked. The impact of polyomics and the potential for pharmaceutical drug development to respond appropriately can be considered at three levels: (i) increased understanding of disease aetiology, and target identification and validation; (ii) improved decision-making during the development process and (iii) the identification of diagnostic tests to improve prescribing precision by identifying subjects likely to have a poor response or an adverse event before starting therapy.

The application of the above technologies generates large quantities of biological data, which will alter as a result of the disease state and severity and pharmacological interventions. There is already evidence that these tools can be used to detect specific changes that predict disease prognosis and drug response [29,30]. However, each technology examines different components of the biological system under study. As a result, it is widely expected that integration of the information derived from all the technologies will produce a synergistic increase over the sum of their individual value. This integration requires appropriate biomedical, informatics, data management, and statistical and mathematical resource. To this end, biosimulation is crucial in the integration and interrogation of the dynamics of biological systems, thereby affording analysis and prediction of system behaviour [31]. The increasing emphasis on validated biomarker development, the growing use of these technologies within the biopharmaceutical industry and the increasing use of Biobank strategies (which specifically aim to obtain matched sample sets for genetic, transcription, proteomic and metabolomic analyses) makes the development of integrated data capture, storage and analysis system crucial. A cohesive integrated strategy to implement these technologies offers the potential to create a holistic systems biology approach to truly harness the power of these technologies [31–34].

Biomarkers

Biomarkers are quantitative measures of biological effects that provide informative links between mechanism of action and clinical effectiveness [35]. For this reason, thoughtful and proactive use of biomarkers can improve the mechanistic information generated in drug development. This would allow a better understanding of sources of variation and the correlation between discovery, preclinical and clinical information. Biomarker use can actively reduce the uncertainty around key risks in the drug development cycle (pharmacology, PK–PD, toxicology and safety, and so on). Through the incorporation of appropriately validated biomarkers, one can expect better clinical study designs, in more suitably defined populations, with endpoints yielding improved labelling and marketing information. Biomarkers move us closer to realizing the goals of personalized medicine. Their ability to deliver improved preclinical screening, diagnosis, disease staging and monitoring of treatment better enables clinicians to determine the most appropriate drug for an individual patient at a given stage of disease or treatment. Achieving this will require further development and refinement of novel ways to measure complex biological signals. Crucially, the relationship between biomarker response and efficacy in preclinical models must be understood to establish the degree of biomarker signal associated with the desired outcome. The biomarker signal must be quantitative and reflect activity of the compound in the tissue of interest, which is relevant to the indication. For this reason, in some cases, the study must be carried out in the target population. The biomarker response should be evaluated over a wide range of doses and exposures in single and/or multiple dose studies and also include sampling times that provide an understanding of the relationship between time of dosing (exposure) to biomarker response.

Optimizing selection of Phase II dose and regimen using biomarkers in Phase I clinical trails has several important considerations. Biomarker signals (of both desirable and undesirable pharmacological activity) that are safe and are indicative of efficacy must be established. These can come from preclinical models, from studies of the biomarker in patients with various levels of disease activity and from the comparison of the biomarker signal in patients and normal subjects. Detailed knowledge of biomarker responses associated with efficacy, such as whether intermittent high levels of pharmacological activity or constant levels of pharmacological activity are preferred. Time relationships between biomarker signals and PK must be understood – the biomarker signal might not be synchronous in time to the pharmacokinetic exposure data (hysteresis). Some direct pharmacological effects might not be rapidly reversible or might have irreversible downstream effects on the disease. The doses selected should result in clearly separated levels of pharmacological activity based on biomarker data and exposure-response modelling [13,34–36].

The use of biomarkers in Phase I to help compounds through Phase II is an important benefit but selection of a threshold level of pharmacological activity, which is required to initiate Phase II, has the inherent risk of discontinuing development after Phase I if the amount of pharmacological activity at the maximum tolerated dose is less than an agreed threshold. A false-negative decision at this stage is serious because it could lead to the

loss of a good compound and possibly the discontinuation of a programme owing to an incorrect conclusion about the efficacy or safety of the mechanism. Setting biomarker criteria for Phase II should therefore be data-driven. This requires an understanding of the relationship between biomarker signal and efficacy in pre-clinical animal models, the relationship between biomarker signal and disease activity from human data and the relationship between biomarker signal and disease activity from previous Phase II studies with similar compounds. The minimally acceptable signal must be defined before generating biomarker data in Phase I. Waiting for the data and then deciding on acceptable criteria is poor practice. A high business impact for false termination leads to pressure to be reasonably conservative in setting decision criteria for proof of nonviability (PONV) decisions in Phase II. If there is clear precedence for the predictive power of the biomarker, then decision criteria can be more stringent and a higher biomarker signal threshold is appropriate. If there is no clear precedence, then one should set a low biomarker threshold for PONV. If the uncertainty for acceptable biomarker activity is large, then the PONV threshold should be set low and the POM thresholds should be set high.

The application of biomarkers in the drug development process will translate into benefits including increased probability of programme success and reduced cycle times, matching patients with therapy, faster optimization of therapy, improved compliance with therapy, reduced complications of therapy and disease, reduced drug development costs, reduced healthcare costs and, ultimately, reduced societal healthcare burden. However, this vision will only be achieved if the right approach to optimization of biomarker investment, performance and application is taken – which is a core deliverable of translational research.

One of the key roles of translational research is to develop and validate novel methodologies that are able to define proof of concept and guide dose selection in indications where large outpatient trials would otherwise be needed. Biomarkers, as outlined above, are one such aid, allowing sound decisions to be made as early as possible, both in development and in terms of differentiating mechanisms of action to give the maximum amount of information at Phase IIb. This position is reinforced by the growing importance of alternative clinical indications discovery, clinical target validation and the recent emergence of approaches using biologically active targets and pharmacologically active doses. All of these paradigms would be much easier to implement if valid biomarkers existed.

Conclusion

Translational research can enhance many aspects of the pharmaceutical business. The efficient use of predictive technology and new techniques could ensure the timely removal of poor compounds and facilitate the identification and acceleration of good compounds that fulfil a medical need, as well as those that are based on a better clinical profile that will deliver the label the clinician and patient needs. In this way, translational research will bring increased confidence in the rationale(s) supporting the mechanistic approaches at a much earlier point in the research and development process. Increased confidence in the mechanism of an unprecedented approach, coupled with an earlier ability to determine whether it can be differentiated from existing therapies, together with the ability to construct PK–PD models, will allow more precise dose selection for Phase IIb. It is reasonable to assume that these strategies will improve drug candidate survival and overall productivity of the drug development process.

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