A focus on translational medicine is necessary to close the innovation gap in pharmaceutical medicine

“Translational medicine is essential to deliver the progress of basic science into the clinic and to more reliably predict therapeutic efficacy.”

Keywords: early development strategies • personalized healthcare • pharmaceutical R&D productivity • progress in biomedical research • translational medicine

The advances in life sciences – including genomics, proteomics and metabolomics – made in the last two decades are breathtaking. This progress in basic research has, however, not (yet) fully reached clinical practice and has not (yet) delivered the hoped for benefits for patients. The human genome has proven to be more complex and – at least so far – much less amenable to functional analysis and therapeutic intervention than most scientists had anticipated 13 years ago, when the International Human Genome Sequencing Consortium announced the draft of the complete genome [1]. There is little doubt, however, that the dramatic evolution in biomedical research will eventually change the practice of medicine. Scientific and healthcare communities such as the European Science Foundation [2] or the Genomic Alliance for Global Health [3] and other national initiatives are developing policies, education and infrastructures that will enable this change in healthcare.

Obviously, these evolutions offer promising opportunities for pharmaceutical companies. As described in multiple articles the industry has suffered from a loss in R&D productivity over the last decade [7,12–14]. This trend has not changed and Pharma is still struggling to apply the insights from the molecular sciences to improve its performance. According to a study released this year by Deloitte and Thomson Reuters, the average internal rate of return from pharmaceutical R&D fell to around 4.8% in 2013 from 7.2% last year and 10.5% in 2010. Over the same 4-year period, the average cost of developing new medicines rose 18% to US$1.3 billion [4].

Despite all rational analysis and changes in process design, pharmaceutical R&D, still today, remains a trial-and-error process. Finding novel drugs with meaningful additional clinical benefit is increasingly difficult and liable to uncertainty and high attrition during the development process. It has become clear that identifying ways to run R&D most effectively, rather than as fast as possible, is the primary business imperative. The frequency of R&D reorganizations has significantly increased, and they have become more wide ranging and more focused on cutting costs. It is questionable whether further mega mergers will address the R&D productivity challenges and several analyses indicate that size of an organization does not matter for productivity [5,6]. In fact, smaller R&D units are more agile and more efficient.

The success of organizational changes is often difficult to assess. A key mistake made is the use of milestones as performance metrics. The number of ‘leads generated’, ‘GLP tox programs’ or ‘entry-into-human studies’ initiated become surrogate performance goals to meet. The experience with such metrics in larger R&D organizations is that they almost always can be met. They are, however, not necessarily related to tangible productivity. Unlike production goals, the quality of deliverables in R&D is much more dependent on subjective judgment. Quantitative surrogate metrics may even provide wrong incentives, since it is not sufficient to reward only success to reach a next milestone but it
is equally important to promote incentives for stopping unpromising candidates as early as rationally feasible. Ringel et al. correlated factors with success and failures in drug development. They analyzed a database of 842 molecules with known full development outcome [6]. The two metrics that correlated most with an R&D organization’s success were indicators of scientific acumen and indicators of good judgment and decision-making. There were no significant differences among most therapeutic areas with the exception of neurosciences and infectious diseases: neuroscience research has been notoriously difficult, while infectious disease research benefits from predictive preclinical model systems. Interestingly, the decisiveness of the company to make early discontinuation decisions correlated most strongly with R&D success.

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Enhancing the probability of success before entering large, costly Phase III trials is the biggest driver to improve R&D productivity. Reducing late-stage failures has significantly higher impact than enhancing speed or reducing costs of development phases [7]. High-quality translational medicine capabilities, and assessing and selecting programs early are therefore key for effective R&D organizations. These capabilities need to be trained and developed more systematically in both academia and the pharmaceutical industry. Education programs and schools should be jointly established and funded: clinical researchers, who can collaborate effectively with discovery scientists, with modeling and trial simulation experts, and with other key disciplines, are essential to leverage the biomedical progress for better therapies for patients.

The aim of translational medicine in pharmaceutical R&D is to generate an iterative increase in knowledge about the relationship between molecular intervention and disease pathophysiology. The identification, profiling and validation of biomarkers are required to determine patient subpopulations and to assess efficacy and safety. While traditional R&D takes 5–7 years from high-throughput screening to get clinical readouts (typically only in Phase II), the focus of translational medicine is to identify the key questions upfront and to test them in humans as early as it is safe and practicable to do so. Only when confidence in the clinical relevance of the compound has been established, further development activities, such as in technical development, along with larger investments should be made. This strategy requires a shift in mindset, since inevitably more time will be used in early development and delays compared with ‘fully front-loaded strategies’ will occur. The translational clinical plan has always to be tailored, has to take into account competitor projects, and should focus on answering the key development questions upfront [8]. The development of vemurafenib, a \textit{BRAF} kinase inhibitor, is a case study, illustrating the successful translation of molecular science into clinical benefit for patients with metastatic melanoma. Vemurafenib was developed with a companion cobas® 4800 (Roche Molecular Diagnostics, CA, USA) \textit{BRAF} mutation test to identify the subpopulation of patients with mutated \textit{BRAF} [9]. While Phase I took 2.5 years to establish efficacy in the appropriate patient population, as well as to address formulation challenges, confirmatory Phase II and III could be successfully completed in 2 years, based on the strong early development data. In Roche (Basel, Switzerland), the focus on translational medicine was introduced in 2007 and within 4 years, success rates in Phase II doubled compared to the industry peer reference value of 22% (KMR, IL, USA) and reached 50%. In line with a focus on early efficacy exploration and selection, most programs included patients in the first studies and subsequently attrition rates in Phase I increased, allowing however earlier and more cost-effective selection and higher success rates in Phase II.

Translational science is core to enable personalized healthcare (PHC). While the terminology ‘personalized’ may suggest individually tailored therapies, the principle of PHC is rather to allow a better prediction of the individuals’ predisposition to disease and response to treatment, while reducing the risks and expenditure associated with treating patients with inappropriate drugs. To enable translational medicine and PHC, companies have to invest in a better understanding of the molecular mechanisms and pathophysiology of diseases. The objective must be to investigate the disease variability arising from different etiologies and to identify relevant biomarkers. To link the molecular patterns to phenotypes, large collections of well-characterized samples from clinically phenotyped individuals and good quality biobanks need to be established. To stratify patients into clinical trials distinct diagnostic tools may need to be developed, such as in the \textit{BRAF} case [9]. Since statistical correlations between genomics and molecular patterns or phenotypes neither provide causality nor mechanistically explain particular conditions, the benefit/risk of such targeted interventions need to be confirmed in clinical studies.

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agendas define how medicine evolves. The ability to better distinguish what makes one person respond differently to a therapy from another is at the center of this shift to more predictable, more reliable outcomes. While prescription drugs only account for about 10% of healthcare expenditures, payers see rising drug costs as a more important business challenge than nondrug costs [10]. Payers and patients are much more critical about the value of new medicines and are not willing to pay for costly products that do not provide tangible medical value and quality of life benefits compared with established treatments. Not surprisingly, the call to reward the actual performance of the product, that is pay for the added value compared with established and competitor products.

In conclusion, companies who will be successful and deliver clinically value-adding innovative products have to have strong translational medicine capabilities, as core to their R&D. Translational medicine is essential to deliver the progress of basic science into the clinic and to more reliably predict therapeutic efficacy. The discipline needs to be further developed in the academic, as well as in the pharmaceutical R&D environment. High competence in this field will not only enhance success rates, the main driver for R&D productivity, but enable more tailored medicines that will deliver the needed outcome benefits for patients.

Financial & competing interests disclosure

The author is employed by F. Hoffmann-La Roche Ltd, Basel, Switzerland. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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