Expanding precompetitive space

Developing collaborative approaches to provide greater confidence in the validity of novel drug targets may have a key role in reducing clinical attrition in the long term.

Following the sequencing of the human genome a decade ago, it was hoped that a wealth of novel therapeutic targets was on the horizon. However, although there have been a few notable genomics-based medical breakthroughs, particularly in oncology, such as the recent approval of the kinase inhibitor crizotinib (see page 897) for patients with lung cancer who possess a fusion gene that encodes an oncogenic kinase — reported only 4 years ago — most other therapeutic areas have not yet seen such success.

In part, this lack of demonstrated clinical success so far reflects the fact that the time needed to move from target identification to pivotal clinical trials is typically substantially longer than that seen for crizotinib, which benefited from the prior availability of a suitable compound to clinically test the target hypothesis and the rapid pace of clinical development that is possible in oncology. Nevertheless, there has not been a lack of genomic studies suggesting starting points for target identification in other therapeutic areas, and indeed the pool of such information has grown dramatically in recent years with the advent of genome-wide association studies (GWAS). However, the number of genomics-based therapeutic targets that could be viewed as sufficiently validated for companies to even consider initiating drug discovery programmes around them is a small proportion of the overall pool.

The probable consequences of the pursuit of insufficiently validated targets are apparent in data on attrition in Phase II trials. A recent report[1] noted that Phase II success rates for new development projects fell from 28% (2006–2007) to 18% (2008–2009), and that ~50% of the failures from 2008 to 2010 were due to lack of efficacy — an outcome in which the initial target hypothesis is likely to have been a key factor. Furthermore, an analysis of the productivity challenges in pharmaceutical research and development (R&D) has indicated that Phase II success rates have the greatest impact on the overall cost, with a change of ~10% in either the positive or negative direction (from a baseline of 34%) for Phase II success rates affecting the capitalized cost per drug launch by ~US$400 million[2].

The conclusion from such data that better target selection is crucial to reducing costly late-stage attrition is not surprising, but there are currently a far larger number of potential starting points for target identification, especially derived from GWAS, than any single company could hope to investigate and validate effectively alone. However, it now seems that recognition of this issue is driving the development of a potential solution: expansion of 'precompetitive space' into target identification and validation. In November, the US National Institutes of Health convened a special workshop bringing together leaders from industry and academia to discuss the formation of a precompetitive consortium focused on validating potential therapeutic targets (see http://bit.ly/tsU0Er). Even more ambitiously, another initiative known as Arch2POCM, announced earlier this year, is seeking to achieve proof of concept for agents that modulate new targets in Phase II trials in a precompetitive environment[3].

Among the potential advantages for precompetitive target validation by public–private partnerships (PPPs) is that it harnesses complementary strengths of academic and industrial research, and so might provide a greater return on government investment than developing R&D capabilities in academia in areas that industry is already strong in, such as medicinal chemistry. The costs are also small compared with those associated with later stages of drug development. Furthermore, even a relatively small number of more effectively validated new targets could provide a substantial opportunity for the industry overall to gain sufficient return on the major investments needed in drug development. Indeed, over the past three decades, on average only around four drugs per year modulating new targets in the human genome have made it to market[4].

Although there are major challenges for precompetitive PPPs, such as dealing with intellectual property and achieving efficient management, there is now considerable experience with these issues from established PPPs — such as the Innovative Medicines Initiative[5] — which have so far focused on other areas of drug discovery and development, such as biomarker identification and drug safety. If the lessons from such initiatives can be applied, expanding the precompetitive space into target validation could provide a key opportunity to begin to address the long-standing challenge of improving R&D productivity.

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