Can Emerging Drug Classes Improve R&D Productivity?

Christoph Meier, Sarah Cairns-Smith, Ulrik Schulze
For decades, pharmaceutical R&D productivity has been declining [1]. As a result, returns on R&D investment have reached a point at which a large proportion of drug discovery programs are unprofitable [2]. We estimate that across the industry, the internal rate of return (IRR) of small-molecule R&D is only 7 percent, less than the industry’s long-term cost of capital of 8–10 percent, while the IRR on biologics R&D investment is 13 percent. This has led many companies to increase biologics investments and pare back on investments in small molecules.

There are many new drug modalities emerging (e.g. antisense therapies, cell therapy, gene therapy, etc.). Interestingly, we are now seeing the emergence of a category of drugs that combines features of small molecules and biologics. Given the different rates of return of small molecules and biologics, an important question for R&D productivity is which parent they most resemble. Here we review some of these emerging drug classes – antibody–drug conjugates (ADCs), and small-molecule inhibitors of protein–protein interactions (SMIPPs) – and address this question.

**Antibody-drug conjugates (ADCs).** ADCs, which are produced by chemically linking a potent small molecule cytotoxin to a monoclonal antibody, have become one of today’s most dynamic drug classes. After overcoming initial technical issues with efficacy and product stability (e.g. [3]), substantial numbers of ADCs have recently entered clinical trials: e.g. in 2005 only seven ADCs were in clinical development, while by 2012 that number has grown to 34 [4]. Worldwide sales of ADC drugs are forecast to reach $2.5 billion per year by 2018, mainly in oncology indications [5]. In the long term, ADCs could become a dominant form of targeted cancer therapy.

ADCs function by combining the cytotoxic effects of oncology therapies with the cell-targeting abilities of monoclonal antibodies. Our analysis shows that bringing together two such well-understood mechanisms is achieving high success rates: latest-generation ADCs (those that have been in development between 2005 and 2012) have a success rate of 79 percent in phase I clinical trials, compared to 54 percent for all new molecular entities (NMEs) [6]. The high phase I success rates also suggest that the stability and toxicity issues, which plagued earlier generations of ADCs, have largely been addressed. In phase II clinical trials the ADC success rate was 50 percent, compared to 34 percent for all NMEs [6]. The number of ADCs was too small to reliably calculate
success probabilities in the phase III clinical trials, but initial observations indicate that latest-generation ADCs may perform similarly to or better than other drug classes. Based on these findings, we estimate an IRR of 11 percent for the research and development of ADCs involving newly discovered antibodies, and 15 percent for ADCs based on pre-existing antibodies. For ADCs expected to reach blockbuster status, such as Roche’s breast cancer drug Kadcyla/T-DM1 (an ADC based on the Herceptin antibody), the IRR can be substantially higher.

Given such favorable returns, ADCs are attractive not just for pharmaceutical companies but also for other investors. For example, Celtic Therapeutics, a private equity fund, recently established ADC Therapeutics, a start-up focusing on the development of ADCs and other drug conjugates [7]. This highlights the maturity of today’s ADC technology and underscores the paradigm of combining small molecule and biological drugs.

**Small-molecule inhibitors of protein–protein interactions (SMIPPIs).** Protein–protein interactions are responsible for a large number of disease mechanisms [8]. Some of these interactions have been successfully targeted with biologics (e.g., cytokine-receptor interactions); however, biologics typically require administration by injection. In contrast, targeting protein–protein interactions with small molecules opens up a broader array of indications with the added convenience of oral delivery. Historically, because of the size of the binding surfaces involved, very few protein–protein interactions were successfully targeted with small molecules and feasibility was considered uncertain [9]. However, over the past decade it has become clear that protein–protein interactions can be effectively disrupted by targeting specific ‘hot spots’ on the protein surface, which are often compact enough to be spanned by a small molecule. This approach, together with improvements in medicinal chemistry and screening technology, has allowed a number of protein–protein interactions to be targeted with small molecules [10]. Examples included chemokine receptor interactions (e.g., Pfizer’s Selzentry), integrin interactions (e.g., SARcode’s Lifitegrast), and the p53-MDM2 interaction (e.g., Roche’s RG7112). At present over 15 SMIPPIs are in clinical development, and worldwide sales are forecast to reach over $800 million per year by 2018 [5]. In the longer term, SMIPPIs could take substantial market share in therapeutic areas currently treated with biologics, e.g. autoimmune diseases and oncology indications.

It has previously been noted that SMIPPI discovery differs from conventional small-molecule R&D in that it has much higher upfront chemical risk, but that biological risk can be minimized through target selection [8]. Our analysis confirms this hypothesis: while very few SMIPPIs have made it to clinical trials, those that do have a high chance of success. In phase I, latest-generation SMIPPIs (those that have been in development between 2005 and 2012) have an 82 percent probability of success, compared to 54 percent for all NMEs [6]. In phase II the probability of success is 57 percent, versus 34 percent for all NMEs [6]. Phase III success probabilities for SMIPPIs cannot yet be determined due to small sample size. However, given the strong biological validation of many protein–protein interactions, we believe it is reasonable to expect a success rate that is comparable to or better than that of other NMEs. Based on these observations, we estimate that R&D on SMIPPIs has an IRR of 12 percent or higher. For SMIPPIs with clinical validation (e.g., from an antibody against the same target) the IRR may be substantially greater. This suggests that SMIPPI R&D is more attractive than conventional small-molecule R&D.

The potential of SMIPPIs has now been recognized by pharmaceutical companies. In 2012 alone, there were at least six major licensing and collaboration agreements with a total deal volume of over $60 million in upfront fees, and with milestone and royalty commitments of over $1 billion – a strong indication of the attractiveness of SMIPPIs.

**Implications for pharmaceutical companies.** Our analysis has several lessons for pharmaceutical companies that are deciding where to invest. First, new drug classes and associated technologies can substantially affect R&D productivity and return on R&D investment. Smart technology selection, therefore, represents a key productivity lever. Furthermore, technologies that shift risk in a favorable direction – e.g. from late stage to early stage, as in the case of SMIPPIs – can substantially affect productivity and return on investment. Second, beyond the marvel of technology, we note a recurring element underlying the success of biologics, as well as the promise of ADCs and SMIPPIs: these drug classes rest on simple target hypotheses that address relatively well-understood biology. For example, the notion of combining two drug entities (antibody + cytotoxic) to make a drug with more therapeutic ‘firepower’ (ADC) is conceptually simple yet highly successful in disease contexts that require effective cell killing, such as oncology. In a similar manner, SMIPPIs can target well understood biological interactions and thus explore simple and fundamental biological hypotheses. We believe that the high clinical success rates of ADCs and SMIPPIs strongly support the simplicity paradigm – the importance of a clear, strong disease biology hypothesis. Finally, we observe that new technologies usually take a long time to mature and be reduced to practice. For example, the conceptual underpinning of ADCs dates back to the early 20th century, yet it took decades of research and many false starts before ADCs could finally begin to fulfill the potential we see in them today. The challenge for the pharmaceutical industry, therefore, is to find those simple ideas whose time has come.

**Funding disclosure**

This study was supported by The Boston Consulting Group.

**References**


4 Citeline database – excludes antibody-radioisotope conjugates and fusion protein toxins.


7 Celtic Therapeutics Launches $50M Antibody Drug Conjugates Development Company with 10 ADC Development Programs (Reuters – March 26, 2012).


**C. Meier**  
*Boston Consulting Group, 20 Manchester Square, London W1U 3PZ, UK*

**S. Cairns-Smith**  
*Boston Consulting Group, Exchange Place, 31st Floor, Boston, MA 02109, USA*

---

**U. Schulze***  
*Boston Consulting Group, Münstergasse 2, Zürich 8001, Switzerland*

*Corresponding author:  
email: Meier.Christoph@bcg.com (C. Meier), Cairns-Smith.Sarah@bcg.com (S. Cairns-Smith), Schulze.Ulrik@bcg.com (U. Schulze)