FROM THE ANALYST'S COUCH

Does size matter in R&D productivity? If not, what does?

Freudian couch, Steve Hellerstein/Alamy

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It is commonly thought that small companies have higher research and development (R&D) productivity compared with larger companies because they are less bureaucratic and more entrepreneurial. Indeed, some analysts have even proposed that large companies exit research altogether. The problem with this argument is that it has little empirical foundation. Several high-quality analyses comparing the track record of smaller biotechnology companies with established pharmaceutical companies have concluded that company size is not an indicator of success in terms of R&D productivity[1,2].

In the analysis presented here, we at The Boston Consulting Group examined 842 molecules over the past decade from 419 companies, and again found no correlation between company size and the likelihood of R&D success. But if size does not matter, what does?

Analysis of successes versus failures

We analysed 842 individual molecules from 2002 to 2011 with a known full development outcome. Out of these 842 molecules, 205 achieved regulatory approval and 637 failed in Phase II trials or later. Each molecule was analysed on up to 18 attributes for correlation with success or failure. Some of these attributes are characteristics of the molecule itself (for example, molecular mass); some are of the pathway and indication targeted (for example, target family and therapeutic area); and some are of the company developing the molecule (for example, the size of its R&D budget). For a detailed description of our methodology, see Supplementary information S1 (box).

Before reviewing the factors that do show a significant correlation, we consider those attributes with no observed relationship (FIG. 1). First, company size (measured by R&D spend) is non-significant. Our data set of 842 molecules covers 419 companies that originated the molecules. Out of these 419 companies, 265 were publicly owned and 154 were privately owned. For the publicly owned companies, 28 spent more than US$1 billion annually on R&D, 28 spent between $200 million and $1 billion and 209 spent less than $200 million. There are no significant differences in success rates among any of the groups of companies, confirming what other researchers before us have found using other methodologies. We also found no significant differences in success rates that were due to the location of the company headquarters, the market size of the targeted indication, the therapeutic area (with some important exceptions discussed below) or the target family.

FIGURE 2 depicts those attributes that do have a significant relationship with success. In our view, all of these factors are proxy metrics that are indicative of scientific acumen or good judgment. Although it is a matter of interpretation how closely these proxy metrics reflect these two factors, what is not is that these metrics significantly correlate with success.

The first three metrics in FIG. 2 measure the scientific track record of the company (from 2001 to 2003) in terms of publications per US dollar of R&D expenditure, patents per dollar of R&D expenditure and the number of times the publications were cited by others. There was ▸

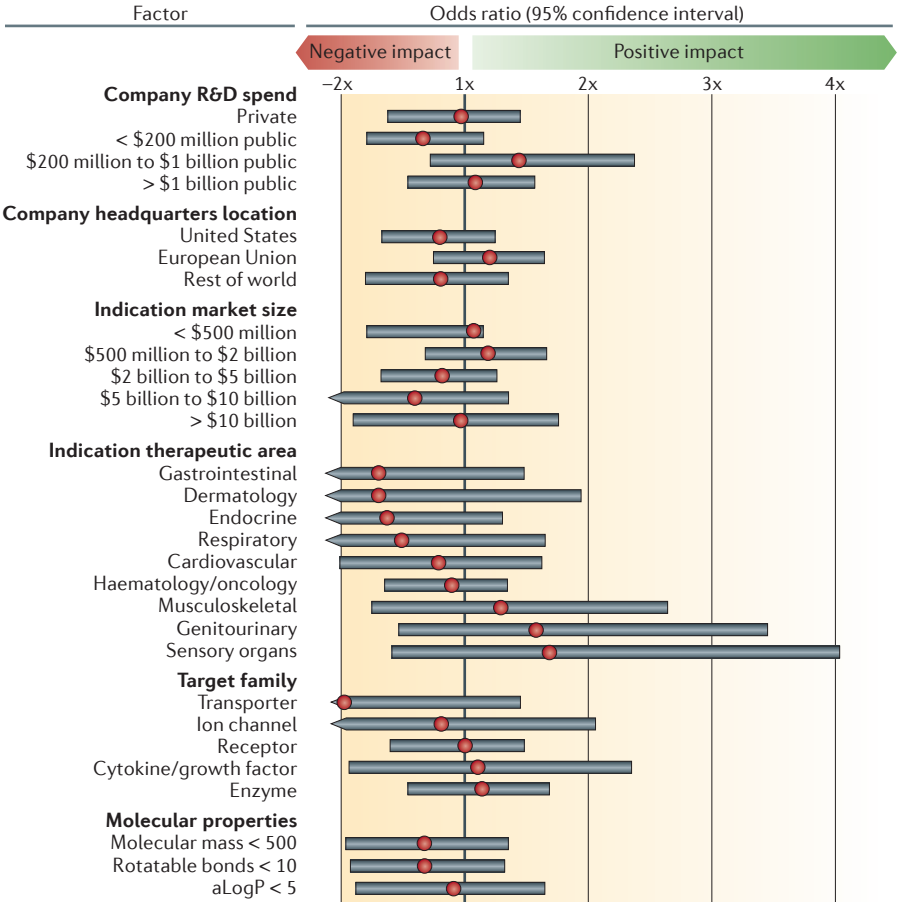

Figure 1 | **Factors not correlated with success or failure in drug development.** These factors have no statistically significant relationship with success or failure in our data set of 842 molecules. At an odds ratio of 1, the factor is equally frequent among successes and failures. As the odds ratio increases, the factor is more common among successes, and as it decreases, more common among failures. Red dots denote the point estimate for the odds ratio, and horizontal grey lines denote the 95% confidence intervals. Where the confidence interval crosses odds ratio = 1 (as is true for all the factors in this figure), the null hypothesis cannot be rejected. For details of the data set and analysis, see Supplementary information S1 (box). R&D, research and development.

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a significant correlation between these factors and success of the molecule (from 2004 to 2011). There was also a significant correlation with success when the company has a major R&D facility present in a science hub — a factor that we believe improves scientific acumen by providing better access to internal talent and to networks for collaboration.

As a last example of the importance of scientific acumen, although we found no significant differences among most therapeutic areas, there are two outliers: neuroscience and infectious disease. Neuroscience has been a notoriously difficult therapeutic area, and a key factor in the lack of success in this area is widely thought to be the lack of effective models in which to test theories about the mechanisms of disease, and thereby deepen scientific understanding. By contrast, in the infectious disease area, model systems (such as *in vitro* screens against the pathogen) are often highly predictive, and scientific clarity has enabled rapid iterative testing and improved understanding of the targets involved.

In addition to factors we categorize as evidence of scientific acumen, we also found significant correlation with factors that we consider to be evidence of good judgment. These include the company historically having an R&D leader with a long tenure, which could be an indicator of greater experience and other aspects of exercising good judgment. Surprisingly, we even found that more frequent use of phrases such as 'return on investment' and 'decision-making' in company-related articles (for example, discussing the company's investment plans) correlated with company success. Moreover, the strongest single correlator with success (odds ratio 3.9) was having a high termination rate in preclinical/Phase I stages. This indicates that companies have an early idea of which assets are likely to succeed, and that the companies most willing to face the hard decisions about which assets to terminate do better than companies that let assets linger.

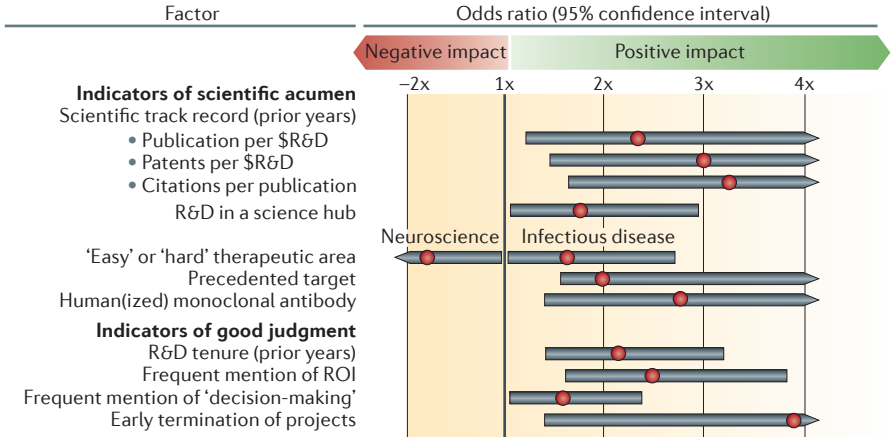

Figure 2 | **Factors correlated with success or failure in drug development.** These factors (laid out as in FIG. 1) have a statistically significant relationship with success or failure in our data set of 842 molecules. For details of the data set and analysis, see Supplementary information S1 (box). R&D, research and development; ROI, return on investment.

Seeking truth, not progression

A major obstacle that we see to achieving greater R&D productivity is the likelihood that many low-viability compounds are knowingly being progressed to advanced phases of development. We estimate that 90% of industry R&D expenditures now go into molecules that never reach the market. In this context, making the right decision on what to progress to late-stage clinical trials is paramount in driving productivity. Indeed, researchers from Pfizer recently published a powerful analysis showing that two-thirds of the company's Phase I assets that were progressed could have been predicted to be likely failures on the basis of available data[3]. We have seen similar data privately as part of our work with many other companies.

Why are so many such molecules being advanced across the industry? Here, a behavioural perspective could provide insight. There is a strong bias in most R&D organizations to engage in what we call 'progression-seeking' behaviour. Although it is common knowledge that most R&D projects will fail, when we talk to R&D teams in industry, most state that their asset is going to be one of the successes. Positive data tends to go unquestioned, whereas negative data is parsed, re-analysed, and, in many cases, explained away. Anecdotes of successful molecules saved from oblivion often feed this dynamic. Moreover, because it is uncertain which assets will fail, the temptation is to continue working on them. This reaction is not surprising when one considers that personal success for team members is often tied closely to project progression: it can affect job security, influence within the organization and the ability to pursue one's passion. In this organizational context, progression-seeking behaviour is entirely rational.

We have seen success in changing this outlook by changing the organizational context of R&D teams so that 'truth-seeking' rather than progression-seeking becomes a more rational behaviour for individuals and teams. Teams are rewarded (in terms of job security, organizational status, compensation, and so on) not for progressing their asset but rather for revealing the scientific truth about the asset as accurately and efficiently as possible. Governance is likewise characterized by an emphasis on return on investment and a culture of enterprise value creation. There is enormous untapped potential in designing the right organizational context to drive these desired behaviours[4]. Indeed, it is factors such as these — great science and an organization tuned to rewarding the right behaviours — not structural factors such as company size that will ultimately drive renewed R&D productivity.

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Competing financial interests
The authors declare competing interests: see Web version for details.

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