Should scientific innovation be managed?

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Pharmaceutical companies in recent years have turned to rigorous project and portfolio management [1], in an attempt to increase the number of product launches and reduce R&D costs. This has resulted in a flurry of benchmarking activities [2–4], best practices initiatives, outsourcing [5,6], and the formulation of overly ambitious business goals [1].

Initially limited to drug development, these activities are now entering research laboratories to increase productivity [4,6]. Not surprisingly, the outcry among researchers is profound – science must not be bridled; productivity cannot be prescribed. By contrast, driven by financial imperatives, top management insists that their laboratories meet productivity goals. To the business strategist, the world of science seems to allow individualists to roam free of any accountability, deliverables or restrictions. It seems incomprehensible that outcomes cannot be guaranteed, that science cannot be scheduled. In turn, the scientist trying to come up with a new disease treatment oscillates between passion and frustration when once again the experiment fails. In his experience, good experimental design and luck, not prescriptive business goals, determine success. Portfolio management or strategy is viewed with scepticism at best, and with outright indignation at worst.

This divide between the camps is widening in an environment where mergers and acquisitions [1,7] provide what in-house scientists seem unable to deliver [8] – new products and thus the survival of the organization. In this scenario it is easy to blame the opposite party rather than reaching out to understand the other world; to combine the best of both and thus achieve the unthinkable – increasing the predictability of delivery from pharmaceutical research.

How does innovation happen: is innovation cause or effect?

This is a key question if we want to shape a future R&D environment where innovation is more likely to happen. The pharmaceutical industry has been enormously innovative over the past few decades, evidenced by the launches of major drug classes such as histamine receptor antagonists, angiotensin converting enzyme (ACE) inhibitors, β-adrenoceptor antagonists, β-adrenoceptor agonists, statins, and cyclooxygenase inhibitors, to name but a few. But how did this happen? Has the pharmaceutical industry decided to innovate (i.e. innovation is the effect) and thereby created an environment in which scientists succeed? And what did this environment look like? If innovation is the effect of creating the right environment, then science can indeed be managed. Or is the opposite true: innovation being the cause, something that happens by chance through a few talented individuals, such as the likes of Sir James Black [9], and the entire industry grew around these hot spots of success? If this is true, then business planning becomes unpredictable.

The question seems academic. Pharmaceutical research has a track record of delivery and billions of dollars are invested in research. Surely, productivity demands and the creation of the right environment have driven innovation and created today's industry. Unfortunately, the obvious is not necessarily correct. The long cycle-times in the pharmaceutical industry, which can be over 15 years from conception to product launch [10], separate cause and effect. Investments made today will bear fruit in 15 years time or even later. Consequently, the products which were delivered over the past 10 years, and which made the industry what it is, were the result of scientific research from 15–25 years ago. Do we really understand the environment for researchers as far back as that? Corporate myths talk of complete scientific freedom, of hiring the brightest kids from university. Whether such corporate myths are true is another matter.

Also, we need to understand what is meant by innovation, because innovation comes in two guises, both of equal importance, both equally difficult to achieve and both 'innovative', yet conceptually entirely different (Fig. 1):

1. Non-linear, quantum leap innovation, which is unexpected and unpredictable, where the future goal is unclear or non-existent (such as the discovery of totally new therapeutic drug classes that are currently not linked to disease mechanisms); and
2. Linear, 'logical' innovation, based on incremental improvements, dedicated to reaching superior, well-defined goals (such as aiming to improve on existing therapies by discovering safer or better drugs within the same therapeutic class).

How to manage non-linear innovation

The authors consider non-linear innovation as the quantum leap to generate

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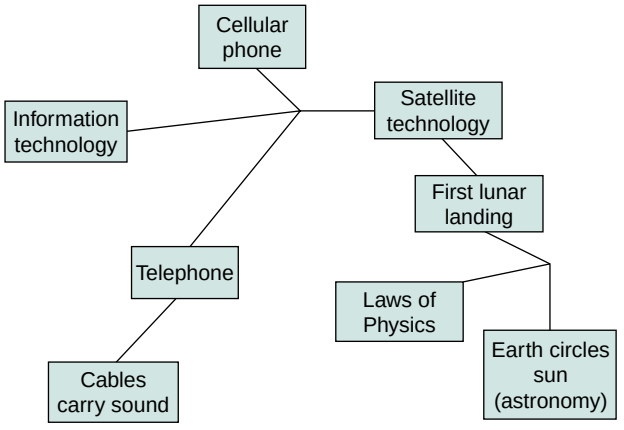

Figure 1. Simplified example of the interplay between quantum and incremental innovations, allowing the branching out of new tracks which interconnect at the point of quantum innovations.

something new, inconceiveable by linear deduction. This type of innovation is unpredictable, at the time of conception there was no goal to aim for, no foundation on which to base logical deduction. The very fact that a future state can be conceived means that the innovation is not of the quantum type.

Non-linear innovation is rare, might need unbridled minds, nurtured in an environment of limited management control and delivery dates [11] so that serendipitous events can be generated, observed and responded to. Demanding success in these circumstances is likely to cause demotivation, if not worse [11]. A perfect example of such 'non-linear' innovation would be the discovery of penicillin. Sir Alexander Fleming did not go out to discover agents that killed bacteria, rather, in 1928 when he was working on the influenza virus, he happened to observe the stunted growth of staphylococcus cultures around 'infections' of mold. How many other researchers before him must have thrown out such 'contaminated' samples? John Tyndall in 1875 and Andre Gratia in 1925 both described the antibacterial properties of mold. Fleming was the one who – by drawing novel conclusions from a discovery – recognized the importance of his discovery and made the leap from linear reality to non-linear innovation. In doing so, he was responsible for opening the gate for the discovery of diverse antibiotics, via the linear route of innovation.

Thus, we postulate that non-linear innovation requires serendipity, an unforeseen event, from which the innovator observes and derives his or her leap of imagination. These innovations allow the tracks of 'reality' to branch (Fig. 1) – they prepare the way for incremental innovation.

Incremental innovation

It is rare that the first drug against a new disease harbours all the properties that makes it a favourite of doctors and patients; flaws can limit its use. To reach the ideal, another 10–15 years of fierce competition is needed, which brings forth innovation based on optimization, in an attempt to improve metabolism and side effects. Here, the scientific approach is one of stealth, teamwork and gradual improvement, moving inch by inch towards a pre-set goal line. That is not to say it is totally predictable, but it is manageable.

An example from the world of technology would be incremental innovations such as the telephone and cellular phones, which are derived from a series of successive increments based on the initial discovery that cables carry sound.

An interesting case of how quantum leap innovation could in fact itself be divided into 'base' innovation and 'goal-based' innovation is the discovery of jet engines. The base discovery in this case is Sir Isaac Newton's law of force and counterforce. This was followed by Sir Frank Whittle's 'goal-based' innovation, constituting a quantum leap, because it was not considered possible to design a plane based on jet engines. Thus, the initial base innovation (e.g. Newton's work on gravity and force) has provided the substrate for occasional, self-managed, goal-based quantum leaps (quantum physics, jet engine, and so on). They were then followed by incremental innovations and improvements that had a clear future state at the outset (such as modern aircrafts).

The aircraft jet engine designed by Whittle and the cargo hull designed by Howard Hughes were both requisite steps to lay the foundation for the design of modern fighter and passenger aircraft. Before Whittle proved jet propulsion with the Gloster plane, aircraft relied on piston-engine driven propellers, which allowed only limited speed. A generation of engineers building on Whittle's discovery has resulted in the world of commercial jets. While Whittle propelled aviation into new realms, Hughes pursued a parallel road with his flying boats, generating the biggest aircraft ever built, and paving the way for the jumbo jets.

Pharmaceutical innovation was cause *and* effect

Leaving base innovations to one side, because they are the rarest of events, it seems likely that today's pharmaceutical industry was created by a self-propagating mix of innovators who made a quantum jump, via a self-managed drive to seek an explanation for chance discoveries. These serendipitous achievements provided the foundations on which the industry based its growth via incremental innovation and improvements. Improvements were achieved via project teams dedicated to drug optimization that had a clear view of where

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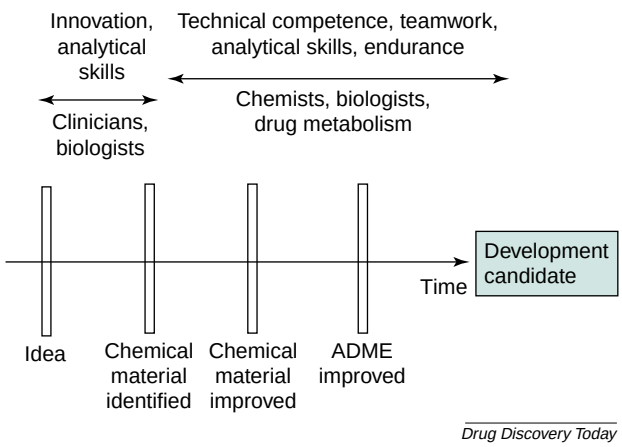

Figure 2. Simplified schematic diagram of a project over time (described by the horizontal arrow) going through key steps and gates (depicted by vertical rectangles) during the drug discovery process, to deliver a development candidate. Thin arrows at the top of the graph indicate differential skill/resource requirements.

they were heading, and were tightly managed.

Both types of innovation are needed if the business is to survive. However, the challenge is to disentangle the two, and to ensure that both are given the best chance of success. For quantum innovations, this could be done by identifying those individuals who might come up with quantum leaps, providing them with the facilities to do their research within broad boundaries, while leaving them undisturbed by productivity goals and timelines set by top management. Such innovators might be distinguishable by an innate aptitude to spot serendipitous events, and a prepared mind that exploits discontinuities through self-management. Although probably not totally applicable to the divide in innovation types described in this paper, Kirton's work on cognitive styles [12,13], which resulted in a scoring framework, could provide some guidance to managers of scientists. These scores could help to identify the extreme end of the innovation spectrum, which is likely to contain individuals with potential for making quantum leap discoveries, even though it will not be able to point to any one individual with certainty.

Those scientists, whose ability lie in incremental improvement, should be managed via defined business strategies, achievable goals, and transparent decision-making processes. The challenge for management is to manage the 'right' tracks, identifying early where they might interconnect.

Managing scientific innovation

Scientific innovation of the incremental kind, can and must be managed. However, the traditional project management approach is unlikely to meet a warm reception. Few scientists acknowledge the difference between the two types of innovation and most will make a case to be involved in both. Thus, much education must go ahead of any attempt to manage scientists to schedules. There are two major types of management that need to be applied to pharmaceutical research: project management and portfolio management. Both must be adapted to the research environment if they are to succeed.

Managing incremental innovation via discovery project management

Drug discovery is an iterative and risky process and therefore project management needs to take a soft approach, accepting ambiguity, frequent project failures, slippage and resource over- or underspend. Scientists will not take kindly to having their 'spare time' scheduled for another project. Despite this, scheduling is feasible, within wide margins, and a reasonable assessment of resource requirements should be made based on the type of project in question. This requires project managers who understand the science of the project – or scientists who can project manage. Unfortunately, such individuals are still quite rare. Figure 2 describes key steps in the drug discovery process that can be used to create gates through which projects must pass. This type of project management can only be applied to incremental innovation (drug optimization). The gates depicted in Figure 2 are examples of project management milestones. They not only generate the opportunity to schedule, measure and adjust (i.e. control), but also indicate clearly where the divide between incremental and quantum innovation and their respective requisite skills sets occur: namely between the idea and the 'chemical material identified' stage. The identification and acceptance of these key steps and gates throughout the organization generates a powerful substrate for resource planning, risk analysis, productivity forecasting and decision-making. The world of drug discovery has become a managed process.

Discovery portfolio management of incremental projects

The totality of all drug discovery projects at their various stages in the process forms the basis for portfolio management. Good portfolio management should ask the following key questions:

- Does the portfolio contain the right projects?
- Is risk sufficiently balanced?
- Does the portfolio have the right shape for sustainable productivity?
- Can this portfolio deliver the required productivity?
- Are resources deployed where they have most impact?
- When should we start or stop certain projects and what should the decision be based on?

The answers to these questions will drive management actions – productivity can be forecast and actively managed.

The full potential of portfolio management can only be harnessed if control comes from top management, who must have the courage to take decisive action, because the most difficult thing in research is knowing when to stop or what not to start. If these conditions are met, then productivity goals can be put into context, organizational expectations can be managed, and shortfalls can be adjusted. This creates a more secure environment and the emotional distress of working on ill-fated projects is reduced. Modelling how the portfolio will evolve (forecasting of expected output), based on performance analysis (metrics of historical performance and output) allows comparison with management expectations and leads to more realistic productivity goals. In parallel, decision support systems need to be employed to structure decision-making and quantify management preferences to define the types of programmes that should enter such a portfolio.

Figure 3 shows an example of portfolio management, based on forecasts (probability of reaching the next step in the research process). For every 10 new ideas, only X% will pass the first gate within a certain time period. The % survival will be subject to the type of projects that constitute these 10 ideas. The same applies to the next steps in the process. Thus, the projects 'thin out' over time. The resultant productivity (Z candidates) can thus be forecast. This also provides the opportunity to work back from a desired productivity to yield the ideal portfolio. Needless to say that resource requirements can be layered on top of such a forecasting tool.

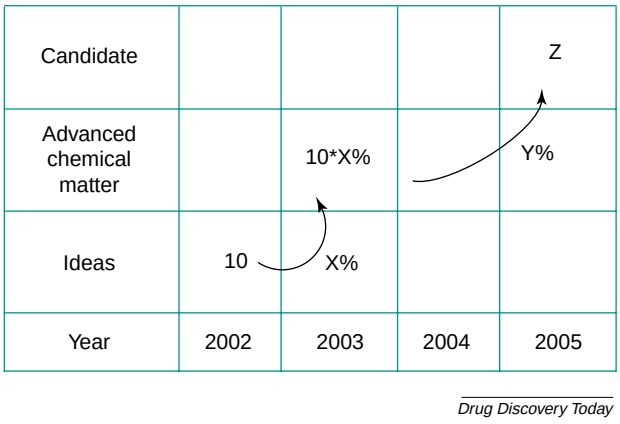

Figure 3. Portfolio management tool. Ten ideas in 2002 will have an X% chance to reach the next stage (advanced chemical matter) in 2003. If X = 50%, then five advanced chemicals would result ($10 \times 0.5 = 5$). These, in turn, move to 'Candidate' stage with a probability of Y%, yielding Z number of candidates.

Conclusion

Managing innovative scientists is a challenging task, especially in light of the current demands on pharmaceutical productivity. Yet, the authors firmly believe that innovation can and should be managed. However, conventional recipes of using consultants and standardized management tools have little scope to impact positively on scientific staff or, indeed, discovery. This places the responsibility firmly with management and in-house strategic planning. They have to come up with sustainable business solutions, based on scientific practicalities, and the capabilities of their staff. The first step for them is to acknowledge and communicate that pharmaceutical innovation comes in two different guises, each of which requiring unique skills from scientists, but also from those who manage them. To achieve ultimate success demands a departure from the open-ended messages to 'increase productivity'. Rather, it needs portfolio managers who understand the science – and the scientists – but also have a keen sense for what the business needs, and who can bring together disparate disciplines, so that the portfolio that is being managed has depth and quality. There is a place for project and portfolio management in discovery, but it needs to be handled sensitively, engaging staff, and adapting it to a research environment where productivity forecasts bear an uncanny resemblance to weather forecasts.

In no other area is the need to harness diversity greater than in drug discovery. Therefore, it is of vital importance to allow scientists to make best use of their skills. This means managing diverse people with differing skills against differing expectations to encourage unique contributions [14,15]. In other words: let the innovators innovate and the drug hunters optimize drugs and reward each for their unique achievements.

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Predicting novel proteins and their interactions

Different experimental and computational approaches are experiencing significant interest in the hunt for new proteins as potential therapeutic targets. Two contributions in the recent *Information Biotechnology* supplement to *Drug Discovery Today* focus on *in silico* identification of target proteins [1] and the study of protein interaction networks [2]. In addition, an excellent analysis of currently available yeast protein interaction data has recently been published in *Nature* [3]. Taken together, these reports highlight the potential of such approaches for target discovery.

The *in silico* approach to target identification is largely based on (increasingly sophisticated) detection of sequence homology, both at the DNA and protein level [1]. Typically, genome sequences are scanned for detectable similarity to protein domains of known target families or superfamilies (such G-protein-coupled receptors or protein kinases). By contrast, the basic idea of protein–protein interaction analysis is to identify novel proteins that interact with partners implicated in disease states or cellular networks involving disease-related proteins [2]. Computer methods applied in this context generally do not predict protein–protein interactions directly but attempt to establish functional relationships between proteins, which are thought to often involve actual binding events. Essentially, these methods are based on the analysis of gene fusion and proximity or orthology and phylogenetic profiles and have thus far mostly relied on the comparison of prokaryotic genomes.

Recently, von Mering *et al*. have compared protein–protein interactions in yeast identified by, or inferred from, different high-throughput technologies [3]. Some of their data are summarized in Figure 1. A total of ~80,000 yeast protein interactions have been detected, to date. The number of interactions identified by different methods ranges

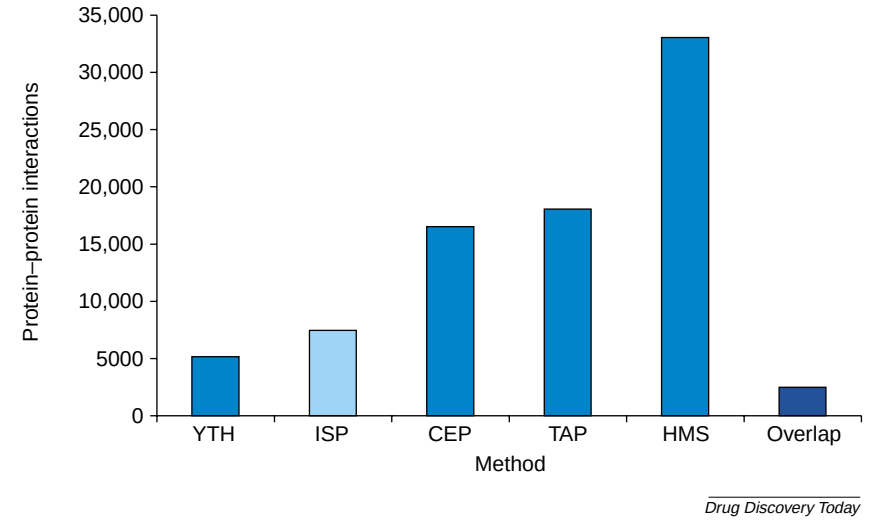

Figure 1. Protein–protein interactions in yeast determined by different high-throughput methods. Abbreviations: YTH, yeast-two-hybrid; ISP, *in silico* predictions; CEP, correlated expression profiling (mRNA arrays); TAP, tandem affinity purification; HMS, high-performance mass spectrometry. 'Overlap' is defined here as the number of interactions identified by more than one method. Data were taken from reference [3].

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