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Drug discovery management, small is still beautiful: Why a number of companies get it wrong

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This review provides an account of why more companies involved in drug discovery fail than succeed at releasing the creative energy of gifted scientists, whose invention of new drugs they rely upon to remain at the forefront of the biopharma industry. Initiatives aimed at improving output of new chemical entities often have the opposite effect from that intended and scientists become demotivated. Those with drive, vision and enthusiasm may move to smaller companies to rediscover the spirit of discovery. Some executives fail to understand the psyche of researchers; an applied understanding of the intrinsic motivation of scientists would improve research performance. Entities that focus on smaller autonomous units and sound ethical values will discover the most innovative and successful new drugs.

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Lars Knutsen began his research career at Glaxo, Ware, UK after his MA in Chemistry at Oxford. At Glaxo he completed his PhD in C-Nucleoside Medicinal Chemistry, joining Novo Nordisk in 1986. There, he led two CNS projects, identifying anticonvulsant GABA uptake inhibitor Tiagabine™ and NNC 21-0136, an adenosine agonist stroke drug candidate. At Vernalis, UK 1997–2001 he initiated two projects leading to clinically investigated drugs, adenosine A_{2A} antagonist V2006/BIIB014 for Parkinson's Disease and a CB_1 antagonist. Lars then joined Ionix Pharmaceuticals, a pain-focused Biotech in Cambridge, UK as Director of Chemistry, moving to Cephalon's US Medicinal Chemistry group as the company's first Distinguished Scientist in late 2005, where he invented CEP-26401, a novel histamine H_3 antagonist. Lars lectures widely on drug discovery, and has published 45 papers, holds 25 patents and is an Adjunct Professor at Drexel University College of Medicine. He runs Discovery Pharma LLC, a drug R&D consulting company in West Chester, PA, USA (www.discoverypharm.com).

One of the turning points of my career in drug discovery came when overhearing a dinner table conversation at a Gordon Conference relating to drug research. These conferences (http://www.grc.org/conferences.aspx, accessed April, 2011) are a superb place for scientists to interact. Two former colleagues from a pharma company were reflecting on the events of the past year when one had left the 'secure' larger company to pursue his science in a venture capital (VC)-financed biotech. 'Don't you worry about job security?' was the question. The answer was, 'I have been so mistreated by management in Big Pharma in the past that job security is no longer an issue for me'.

When making the move from Big Pharma into the world of biotech after 18 years in larger companies, a former colleague, Dr Jim Piggott, then at Zymogenetics in Seattle, suggested that I would thrive on the energising atmosphere of a biotechnology company. 'When something good happens in the lab then everybody knows about it. If those companies can be successfully financed, they are great places to practice the science of drug discovery'. What Jim told me then was an important insight into the world of biotech, but also an insight into how scientists are motivated. My epiphany continued as I transitioned to practice drug discovery from larger company environments to smaller biotech companies, and observed what motivated my colleagues.

Issues with motivation in drug discovery

A 2007 article in *Drug Discovery Today* addressed what is seen as a crisis of morale in drug discovery [1]. The author, Joost Uitdehaag, described a situation of pessimism, low perceived self-esteem of

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those engaged in this profession and the consequent lack of attractiveness of the career role of 'Drug Hunter' for highly qualified graduates entering this field of applied science. Uitdehaag in many ways hit the nail on the head with his observations, and correctly described the state of mind for many drug researchers, but his suggested solution was to adopt a series of personal behaviours summarized as a 'warrior mentality'. Since that important article was published, there have been further ructions in the pharmaceutical world, with widespread downsizings, mergers and the closure of research labs, including a current trend to transfer research resources to the emerging economies of India and China.

The premise of this current article is that, however well-girded individuals might be in terms of a robust self-image and positive mentality, a working environment that is at odds with their needs, often misunderstanding the mindset of scientists, is really the root cause of cynicism and lack of motivation of researchers. The motivation of scientists who need to utilize a diverse range of skillsets to succeed is a crucial factor in the performance of drug discovery organizations, where there is a long time span before a hypothesis can be tested in humans, and a high probability of overall project failure.

There has been serious concern about the downturn in numbers of approved drugs since 1996 [2,3]. Productivity, measured in terms of either investigative new drug applications (INDs) or new drug applications (NDAs), is inconsistent with growing investments being made in pharmaceutical R&D (Fig. 1) [3]. Although extensive analysis has taken place to identify reasons behind these lower numbers [4,5], only relatively few observers have addressed hostile working environments for researchers as a possible explanation for reduced industry output. However, there are some voices out there.

One senior industry figure, Pedro Cuatrecasas, suggested that reduced productivity in the drug industry is caused mainly by corporate policies that discourage innovation. This is compounded by various consequences of mega-mergers, the obsession for blockbuster drugs, the shift of control of research from scientists to marketers, a need for rapid sales growth and the discontinuation of development compounds for nontechnical reasons [6]. Cuatrecasas considers that the top management tier at most corporations does not understand the complexities of science, its mode of conduct or objectives, and, thus, tends to run these already highly regulated companies in ways that stifle creativity and innovation.

A description of the legendary Drug Hunter, Paul Janssen, and his people-centred approach suggests that a leadership style like Janssen's offers a competitive advantage over more-hierarchical systems, providing improved chances of success. Recalling his time working with Janssen, Paul Lewi reflects wisely that causes of declining productivity in drug discovery are often attributed to difficulties in finding new drug targets, stricter regulatory requirements and huge development costs. Less regularly mentioned is the stifling hierarchical organization of research in many compa-

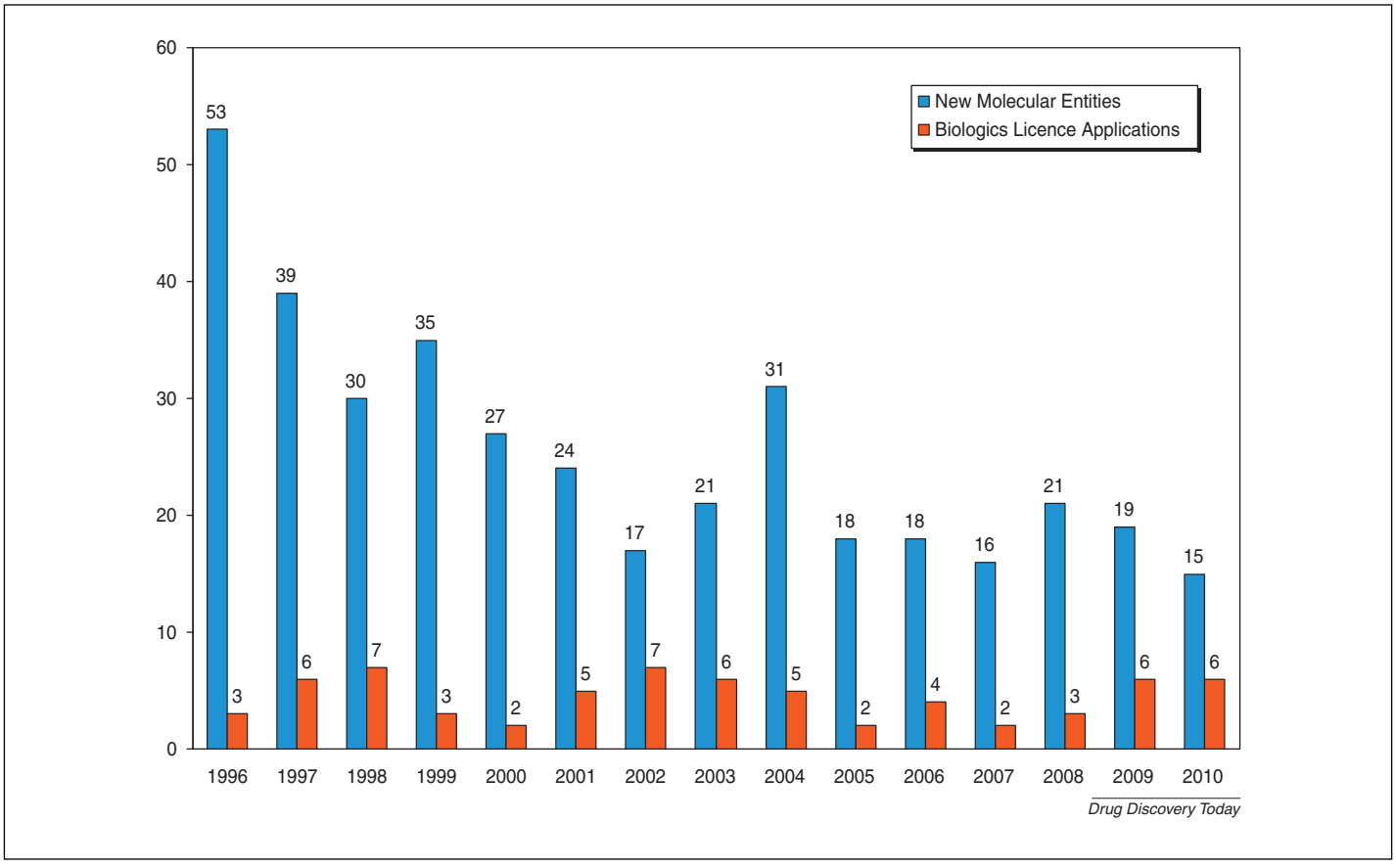

FIGURE 1

US Food and Drug Administration drug approvals since 1996. Number of new molecular entities and biologics licence applications approved by the FDA's Center for Drug Evaluation and Research, by year.

nies and the reluctance to provide freedom for competent and daring researchers to excel in their chosen field [6,7]. Janssen managed to provide a remarkable working environment that stimulated invention, providing 79 drugs in 40 years, an outstanding output [8,9].

If gifted researchers are repeatedly prevented from exercising their creative genius and are effectively demotivated in their working environment they will either become cynical and uninspired, losing their 'warrior mentality' [1], or vote with their feet, changing career path or moving to companies that they feel will attempt to meet their needs by providing a work environment that more readily stimulates inventions. This premise leads to three questions:

i. Can effective drug discovery thrive in modern working environments?
ii. What are the characteristics of environments that stimulate excellence among researchers and result in outstanding pipelines of drug candidates and creation of shareholder value?
iii. How are working environments responsive to the needs of researchers created and sustained?

Can drug discovery thrive in modern working environments?

'Feeding the monster' – issues facing large Big Pharma

Humankind has reaped extraordinary benefits from the pharmacological revolution of the 20th century [10] when teams of chemists and biologists worked together in drug discovery environments to provide a steady stream of new drugs, thereby revolutionising medicine. The seemingly inevitable 'merger mania' taking place over the past two decades has provided the pharma industry with some truly heavyweight companies. Whenever potential mergers are mooted, the benefits in terms of improved R&D pipelines, extermination of duplicated functions and higher sales-force numbers are perceived as the prime motivations behind the new enlarged entity. These combined companies were seen by analysts and investors as the locomotives pulling the pharma industry onwards and upwards. However, the number of drugs produced by increasing R&D investment has declined sharply during the past two decades (Fig. 1) [2,3], as we are reminded by several observers including Bernard Munos [4].

Once behemoth pharma companies have been created there is a phenomenon known as 'feeding the monster'. A company with a turnover of, for example, US$50 billion p.a. would need at least one potential blockbuster drug launch each year to grow its business by even a few percent. To reach more-desirable growth rates large pharmaceutical companies need to produce an average of 2–3 new molecular entities (NMEs) per year to meet growth objectives, so the fact that none even approach this output level [3] despite predictive statements is very concerning. Companies rarely ever launch more than one drug per year [4].

For several reasons – notably a diminution in the number of new druggable targets [2,10] and, by some analyses, the advent of target-based drug discovery [11], seeking a 'magic bullet' [12] and other factors, such as risk averse regulators – blockbuster drugs are becoming much harder to come by. Discomfort has been felt by some of the majors in recent years, such as Johnson & Johnson, Merck, Pfizer and AstraZeneca. Strategies to unearth blockbusters are 'not working', says biochemist Alfred Alberts, who helped invent Mevacor®, the first statin, as well as its successor Zocor® at Merck [13].

These companies, many of which had a very good reputation as an employer, have made major efforts in reducing their fixed costs, but could have unwittingly destroyed exactly what is required to build a viable drug discovery platform by undermining the motivation of highly capable and creative scientists. I have personally worked in drug discovery in companies involved in some of these mergers and, although some merged entities claim successes, the perception of staff working for them is that they are employed in corporate giants whose senior management appears increasingly remote and impervious.

Many mergers involve one company seeking an improved drug pipeline by acquiring another; eliminating research sites in the process, laying-off staff and deleting projects. In many cases, a retrospective analysis reveals the total elimination of one well-functioning pharma company by another, which, a few years later, ends up as a similar-sized company with a few extra assets. Some of the eliminated companies include household names like Warner Lambert/Parke Davis, Burroughs Wellcome, Beecham and Rhone-Poulenc, as well as more recently Wyeth and Schering Plough.

Human capital in knowledge-based companies

The concept of 'human capital', whereby companies invest in and value their staff to promote excellence and loyalty, as well as seeing their employees as a major asset not to be disposed of lightly, has been superseded by job insecurity. In a more ideal world, employees engaged in inventive science would be able to trust their employers, buying into the notion of working hard and dedicating themselves and their inventions to the benefit of the company with their trust being rewarded. Unfortunately, that trust has often been seen as misplaced.

The new metrics and working environment of the information age demand that human capital comes to the fore. The western world is generally no longer making 'widgets' to drive our economies, we are increasingly a knowledge- and information-based economy where the goal is to capture the creativity of the human mind *via* new technologies, building on new discoveries. The pharma/biotech industry is at the cutting edge of the knowledge economy.

However, many companies are still structurally aligned to the manufacturing era, with military-style command systems that can fail to capture the contribution of people [14]. 'Scientists are a unique breed' [15] and these creative people, who are often unconventional thinkers and on whose innovation and insights much of the new economy depends, can feel trapped in a depersonalized, controlling machine. A level of senior management conservatism expressed in real life situations, such as in a mid-western pharma company where a scientist was sent home to change clothes after attending a meeting wearing the wrong colour suit; when staff are told to cut their hair or are informed that they will not get promoted wearing the wrong colour tie, forces deadening conformity, which can extinguish the spark of drug discovery. Rigid corporate values, directed at the non-scientific part of the organization and used to measure performance, are inappropriate for the diverse and free-thinking natures of many of

the innovation-generating scientists; rigidity tends to be absent in smaller biotechs.

The best inventors are unconventional thinkers. Cuatrecasas agrees that the industry needs to overhaul or restructure the current system for drug discovery. 'Today's pharmaceutical companies are dinosaurs. They are anachronisms trying to do today what they did in past eras rather than adapting to the realities of this era.' [14] Creativity is a crucial element in sparking pharma innovation and is seen as a function of three components: expertise, creative thinking and motivation [16]. Many managers act as if expertise is the only requirement – but the other requirements must not be ignored.

The question of leadership and motivation in knowledge-intensive companies was analysed by Mads Øvlisen, a truly inspiring industry leader and the former CEO of Novo Nordisk, in a presentation at the Copenhagen Business School. Øvlisen emphasized that full utilization of the potential of human capital in every organization is key to creating sustainable advantage. 'That means we need to reflect on the type of leadership style that is needed to push this initiative. The vision of the company needs to be made known to the employees. The core values of the organization should guide the behaviour of the employees. Furthermore, the employees need to be given the resources of time, money and – equally important – knowledge to stretch their imagination' (http://uk.cbs.dk/videreuddannelse/nyheder/leadership_in_knowledge_intensive_companies_by_mads_oevlisen, accessed April, 2011).

Although measuring the value of human capital is low on most companies' agendas, Novo Nordisk adopted 'People Metrics/Indicators'. Data on the employees, including their employment details and satisfaction levels, are collected, aiming to capture information on issues relating to leadership and innovation, diversity and internationalization to identify trends and targets. Moreover, organizational audits are conducted to evaluate if staff have the necessary skills and are organized in a proper manner to implement strategies and plans. Personally, I learnt a lot through management training modules at Novo Nordisk, which were inspired by principles of ethical management [17] and as managers we were all encouraged to read the book. No company is perfect but Novo had some exemplary principles.

The fragility of drug discovery

Anyone who has worked in a top-performing drug discovery unit understands how fragile such organizations are, because productivity in terms of pipelines of new drugs can be disrupted fairly quickly; momentum can take ten years to build up yet can be destroyed very quickly. One senior manager at Glaxo, Barry Price, whom I found particularly inspiring, suggested that 'The best discoveries are made in secure environments'. Gifted scientists can take risks if they feel they have the time, permission and space to develop their thoughts and ideas, liberated from short-term thinking. Although great urgency in research projects is obviously required, if scientists are asked to function in inherently driven, insecure and frenetic environments, where they cannot reflect on data, innovative discoveries are often just not made.

In companies that either have recently merged or are subject to rumours of closure, secure environments are an illusion; employees do not know if their particular research site is the next one to have a line crossed through it at the perceived whim of corporate management – drug discoverers know they should be regarded as forming a profit center rather than as a cost center. When companies merge, pipelines of new drugs are inevitably interrupted, and a key message of this article regards the spirit of drug discovery and how it can be re-established after it has been disrupted or lost.

One consequence of mergers is that the organization is in limbo as the new merged structure is established. So, owing to uncertainty, there is a tendency for R&D to become paralysed as scientists keep their heads below the metaphorical parapet. This obviously stifles innovation, which is recoverable if the new organization is given time and stability to gel and new working relationships can be established. However, in many companies, mergers continue apace, so that scientists adopt a permanent 'keep your head down' culture – a real source of decreased innovation.

What is not often appreciated is the potential for egos to be a motivating force behind mergers and creation of mega-companies. One CEO could have the aspiration to be in charge of the world's largest pharmaceutical company, so a merger might be based upon naked ambition. Ambition might, however, not be the only motivator because, in some cases, vengeance could be a more sinister motive. I served for many years in one company where it gradually became clear that a whole division was being dismantled because of a history of enmity between two vice presidents (VPs), one of whom had recently been head-hunted away from the company. Once the VP in question had departed, the new VP of R&D set about dismantling everything that had been painstakingly built up by the previous incumbent. This had a disastrous effect on the motivation of the scientists and therefore on the later output of the company in question, which subsequently abandoned small-molecule R&D after >20 years of engagement.

Alternatively, one merger/acquisition partner will find that they have a poor clinical pipeline because that part of the company has been neglected or is underperforming because of a range of factors. In these cases researchers can become aware that management has been looking for a strategic fit in a future merger partner rather than investing in novel internal projects and research strategies.

One factor driving the mega-mergers of the past decade is the increased cost of drug development and the risk of failure at the 11th hour. If a company, regardless of size, experiences too many late-stage clinical failures then its whole future is at risk; when the cost of drug development is at least US$800 million per approved NME [18], recently updated to US$1800 million with new underlying assumptions by Paul *et al.* [5]. What is usually never addressed is that the seeds of many clinical failures are evident in the earlier drug discovery phase, where optimization of salient drug features takes place by teams of scientists working to a very tight schedule. The selection of drug candidates emerging from research has become much more complex in recent years because so much more information on a potential drug is available in the preclinical phase, providing a later pay-back in quality. The entry into preclinical development is now a crucial cusp in the progress of any drug candidate. The analysis by David Brown [11], ex-GlaxoSmithKline (GSK), outlines some reasons for failure of drugs:

- The chosen target mechanism fails in animal or clinical studies.
- There could be either total failure to find a lead that can be optimized or 'hits' are selected as leads that later prove non-druggable.

- The final drug candidate selected from the lead series fails to pass regulatory toxicology requirements at the IND stage.
- Adverse events or poor pharmacokinetics are observed in clinical trials that were not predicted by animal studies.
- Failure to demonstrate the efficacy expected from animal studies or results from earlier smaller clinical trials.

Because many of these factors can be evident at the time of preclinical candidate selection, transition of a high quality compounds from research into preclinical development is the key to success. Providing an outstanding drug discovery environment where such candidates are progressed, despite potential pitfalls analysing the vast available data volume [10], must be a priority for any entity wishing to be successful. This might, however, not be a focus during a merger of pharma companies. In my experience, some drug candidates have progressed primarily to trigger annual bonus payments for senior management, which certainly will not address the pharma industry's long-term woes.

No matter how the mega-companies evolved, we now have a series of giant pharmaceutical companies, which are worldwide players and their human capital is dispensed with at will. Recent downsizings where staff at whole pharmaceutical research sites are terminated, and only selected people are hired back only to be let go a year or two later, is symptomatic of a lack of understanding of what is required to drive creativity in drug discovery and how long it takes to build up momentum in this endeavour. Scientific creativity cannot be switched on or off at will, and is not stimulated by hiring here and firing there. It is appreciated that researchers need to return loyalty to their companies but other strategies, such as temporary wage cuts for all staff, funding local start-ups for exiting senior staff or setting up new public–private partnerships, can be alternatives to traditional downsizing.

The culture of mega-companies often means that constructive criticism is resisted internally [6] and 'whistle-blowers' are treated with contempt, even though ethical standards in these companies should be extremely high, given the total honesty, openness and transparency required by regulatory authorities such as the FDA.

To key industry figures, such as Jürgen Drews, it is evident that attitudes driving Big Pharma are unsupportive of science and innovation [12]. Those working environments described herein, which neglect human capital, can exist in some pharmaceutical companies and tend not, in my experience, to bring out the best in researchers. Many features of modern corporate culture in pharma environments thwart high-performing drug discovery units.

What are the characteristics of environments that stimulate excellence among researchers and result in outstanding pipelines of drug candidates and creation of shareholder value?

The roots of good research

There are some companies and research sites where excellent, inventive drug discovery has prospered. One can name a few, for example: Janssen, Merck Frosst, Gilead, and Glaxo (Ware).

What are the common features that make these drug discovery sites successful? The insights I have been fortunate enough to pick up in >25 years in drug discovery suggest that there are four common features of high-performing drug discovery organizations:

- Visionary and inspirational leadership
- Passionate project managers
- Human-scale organizations, where teams of scientists interact freely
- Positive working environments, understanding the psyche and intrinsic motivation of researchers

BOX 1

Intrinsic versus extrinsic motivation

Intrinsic motivation is defined as coming from within, whereas extrinsic motivation comes from external factors. These notions have recently been revisited in an excellent book entitled 'Drive – The Surprising Truth About What Motivates Us' by Daniel Pink [26] and have also been reviewed in a drug research context [16]. Scientists are almost universally intrinsically motivated, and this type of motivation is characterized by the following: seeking to overcome challenges inherent in their work, wanting the respect of their peers, a basic curiosity-driven approach to work and seeking a relatively secure, collegial atmosphere. A level of autonomy is also a prerequisite for inventions to happen. Extrinsic motivators such as large bonuses, personalized parking spaces, expanded pension schemes, the Jaguar in the driveway, tend not to top the list of motivators of gifted scientists, as long as they work without undue financial stress and see the fruits of their endeavours being taken seriously. Money does not necessarily stop people from being creative, but in many situations it does not help. Industry leaders should know that incentives affecting intrinsic motivation will yield more immediate results [16].

Pink [26] suggests three characteristics of intrinsic motivation:

Autonomy – the desire to direct our own lives

Mastery – the urge to get better and better at something that matters

Purpose – the yearning to do what we do in the service of something larger than ourselves.

Tensions can arise in the Pharma industry when decisions are made by VPs who are almost always extrinsically motivated, with type A personalities. There is a tendency to treat everyone else in the company as having the same personality type, a misunderstanding of what makes scientists tick. Type A skillsets are typically found in sales environments, and I have observed serious tensions in companies led by extrinsically motivated CEOs with sales and marketing backgrounds. They have learned a *modus operandi* where those who fail to achieve sales targets are fired, because these financial goals are relatively easy to measure. When these 'hire and fire' habits are translated into R&D settings, tensions arise when scientists, who are working on very difficult projects, with nuanced performance measures in an environment where their efforts might not be properly understood by senior management, are threatened with dismissal. Scientists who have overcome adversity in their scientific endeavours become more effective problem-solvers, and will be more likely to achieve creative success by persevering through difficult problems [16]. If a work environment does not value and recognize this, researchers will move elsewhere to try to create an environment where the spirit of discovery can thrive. Senior managers who are extrinsically motivated tend to propose solutions to organizational problems based on new extrinsic motivators, rather than trying to understand the finer points of intrinsic motivation. Companies involved in drug discovery ignore intrinsic motivation at their peril; this is suggested to be one underlying reason for the recent contractions in Big Pharma.

Visionary and inspirational leadership

The unfortunate impression given is that many senior managers in the pharma industry do not have a strong understanding of what really motivates researchers (Box 1). Many top managers appear as

if the financial bottom line is the only goal of the organization. There are so many other motivators, such as patient benefit, creating new products and fulfilling lives for staff and gaining their commitment, and building a successful company that is a sought after place to work.

Should money be the sole goal of every company? Mads Øvlisen, retired CEO of Novo Nordisk, emphasized to his staff that money is not the goal, but a way of measuring the progress of the company. He was quoted in 1992 as saying, 'It is not this company's goal just to make money. Novo's goal is to make some very special products based on its biotechnological background; products that improve the way people live and work. It is to be able to finance this aim that making money is important. Unless we earn money that allows us to plough money into research and new plants then we are not going to be able to finance this thing.' (http://www.icis.com/Articles/1992/10/19/13695/novos-approach-takes-it-to-the-top.html, accessed April, 2011).

Improved patient care, ultimate customer benefit and making a difference to the world are important motivators. Companies obviously need to make money, but get the customer service and products right and positive net cash flow will follow. One of my formative experiences in drug discovery was during a Phase II clinical trial of Gabitril™, a drug I worked on at Novo Nordisk, when the mother of a boy who had suffered terribly from seizures telephoned the company in tears to share that this was the first time in years that her son had been seizure-free. That sort of motivation is completely unrelated to finance.

Some scientists such as Craig Smith, the co-inventor with Raymond Goodwin of the rheumatoid arthritis drug Enbrel®, suggested that company management increasingly favours, 'the short-term developmental route', rather than investing in more-speculative projects [13]; these researchers eventually voted with their feet. Leadership that instils vision to drug discovery, emphasizes human capital, sets a strategy, challenges and communicates it to scientists, as well as emphasising intrinsic motivation and teamwork rather than solely the financial bottom line is likely to provide a successful pipeline of drugs for development.

Passionate project managers

Most projects leading to clinically investigated or marketed drugs succeed because there is someone in the organization who is passionate about the progress of the compound. These people are often the project leaders, who might not realize it but have the characteristics of a drug hunter, described by Williams as having 'elements of passion, scientific competence, objectivity and drug discovery experience that differentiate the Drug Hunter' [18]. Such leaders love the science, show passion in their desire to win, have the resilience to soldier on in the face of multiple setbacks and genuinely care about members of their teams. These inspiring people must be identified, protected and supported [15].

Such people are either implicitly assumed as present or treated as irrelevant despite knowledge that individuals are key to success. This has led to a situation where much of current biomedical research could be considered ephemeral and routine, in many ways reflecting the comments of deceased Nobel Laureate Sir James Black who described the current approach to research in terms of a need for, 'intense concentration and relentless commitment', to drive the iterative drug discovery process [9]. Black also noted a lack of focused commitment, of a pervasive trend of researchers giving up on difficult problems, 'research people get tired and want to quit when the breaks are not coming', instead of transferring their energies from one unsolved problem to another. The history of major breakthroughs in drug discovery [13] shows how the true drug hunter has the persistence and intrinsic motivation to drive forward new discoveries.

Human-scale organizations, where teams of scientists interact freely

Smaller research organizations might be able to adopt Janssen's approach as described above [7–9] more easily than larger companies that arise through mergers and acquisitions. This could be particularly true for the 'younger' biotechnology companies. Nevertheless, the concept worked well at the height of productivity of Janssen Research, when the laboratory had expanded to >500 scientists, technicians and administrative staff. At this stage the laboratory had crystallized around key activities guided by competent and trusted scientists whom Janssen referred to as '*primus inter pares*'.

Positive working environments, understanding the psyche of researchers

An account of a twelve-month lead optimization programme by medicinal chemists Simon Macdonald and Paul Smith from GSK illustrates how urgency and tight timelines can be combined with compassionate treatment of scientists under stress. Aside from an efficiently executed scientific strategy, three key messages are apparent [19].

In describing the evolution of this stressful project, the authors suggest that, because this was an unusual experience for them, they responded slowly to providing sufficient levels of psychological support to the scientists. As happens in pressurized situations, some relationships buckled under the strain. Debate over particular scientific issues could become vehicles for venting frustration and differing personal philosophies. Ultimately, however, it was found that training in coping with stress and working as a team acted as pressure-release valves, providing techniques for handling strains. On completion of the project, the team spent two weeks exclusively reviewing what had and what had not been successful. They had never done this before, despite most of the group having been in medicinal chemistry for over ten years, and it was found to be one of the most influential exercises they had ever been involved in.

The article also provides a valuable insight into intrinsic motivation: most chemists have genuine interest in science and frequently conduct personal projects that managers turn a blind eye to. Reward for achieving the project goal could, therefore, include time and/or resources to pursue the chemist's own research interests; in other words, a form of sabbatical. Although on the surface this appears temporarily to decrease resource levels, substantial benefits emerge. These are well documented and include refreshing the scientist's creativity, allowing people the necessary time to recharge their batteries after working to aggressive deadlines and the potential for gaining new spin-off science and products.

In the working environment inspired by Paul Janssen it was found that success, however, was not obtained without sacrifice. Life as a scientist or inventor can be demanding, not only on the

individual but also on partners and children, because continuous strain causes personal and familial problems. When they arose, Janssen did have a great concern and understanding for these situations and he was always supportive when his collaborators went through life's difficulties. Apart from being an inventor of medicines he was also a physician and humanist. He was to his staff a *pater familias* – demanding, fair and caring [7] – much preferable to hiring and firing.

Overall, my view is that researchers respond to:

- Human-sized organizations with a level of autonomy
- An environment where their unique skills and aptitudes are valued and appreciated
- An impression of stability so that plans can be made and executed
- Extreme teamwork – a feature of effective teams
- Incentive schemes that value intrinsic motivation
- An environment that values scientific creativity above politics
- An environment where line management exists to serve projects, challenging but driving effective project management
- Staff who are not one-dimensional and have balance in their lives.

How are working environments responsive to the needs of researchers created and sustained?

What are the characteristics of working environments that stimulate excellence in research and result in excellent pipelines of drug candidates and creation of shareholder value? Providing 'human-sized' organizations that capture the creativity of researchers and understand their psyche, especially their intrinsic motivation, is the key. Human-sized is a maximum of a few hundred people where everybody knows each other's names, reflecting the spirit of 'small is beautiful'. Having the right organization in place will also increase the likelihood of providing a robust conceptual setting that will stimulate rather than hinder identifying new drugs. Over the past decade or so drug discovery projects have been categorized into distinct phases; previously a project was not as easily defined. These phases are:

- Target ID and validation
- Hit ID (especially relevant to HTS projects)
- Hit-to-lead
- Lead optimization
- Candidate nomination
- Entry of drug candidate(s) into preclinical development

In many ways, the advent of these project phases and associated definitions has provided welcome order to drug discovery projects. They also, however, provide senior management with ready categories or pigeonholes for each project, which can be good and bad.

Using management metrics, each phase of a project is typically time-lined, which in itself can provide unrealistic expectations of projects elaborating difficult targets [2]. In reality, projects tend to hover on the borderlines between these defined phases. All projects are in constant flux and some projects even appear to move backwards. If, for example, a lead series does not provide a drug candidate and fails to 'deliver the goods' the project moves back into the hit-to-lead phase. Even in the most successful companies, where scientists are well-motivated and drug discovery management is supportive and responsive, only ~30% of projects provide drug candidates. A discouraging statistic is that overall the industry norm sees only ~1 in 50 projects leading to marketed drugs [20].

However, if a lack of understanding of drug discovery and the psyche of researchers is prevalent in an organization, project leaders and their teams could find that reporting of negative data, or lack of progress against objectives, is received with derision, and a culture of healthy openness and scientific honesty will suffer. Projects take many years of dedication and, without that, several blockbuster drugs such as the antipsychotic Risperdal® would simply not have been developed, according to its inventor Ludo Kennis, now retired from Janssen. He said that nowadays, 'management people give us a certain period of time to find a new compound. . .you cannot spend ten years on something for which you do not know the outcome' [13].

I was hired into one company that had funded in-house research for over two decades without coming up with an internally invented marketed drug. The company, which prospered on in-licensed drugs and novel formulations, decided to expand R&D and brought in new talent in an attempt to remedy the situation it was in. The new researchers duly arrived, became engaged in new teams and set about the hard work of identifying new drug candidates for IND-enabling studies and clinical development. However, the strategy was doomed to failure because the senior management of the company in question appeared not to have addressed the reasons for past failures, and any process of constructive self-criticism was lacking. Inherent features of the company had resulted in poor research performance, such as:

- An inability to set a strategy and stay with it
- Lack of team-building
- A blame culture and frequent staff changes – hiring and firing
- Senior management focusing on short-term bonuses rather than building true value, and apparently lacking desirable self-criticism
- Sociopathic behaviours (defined by not caring what is done to other people) and a lack of honesty in the organization

Some companies demonstrate extreme urgency to discover drugs, which can unfortunately be self-destructive – metaphorically 'killing the goose that lays the golden egg'. These companies set up what I term as an 'invent it by next Tuesday' syndrome, where instead of providing a measured and thoughtful environment, with urgency, where inventions are nurtured and therefore more likely to happen, a metaphorical gun is held to the head of researchers who could wilt under the pressure. This is typified in very short reporting periods, rather than giving teams, for example, a period of six months' resources and some stability to attempt to build value in projects. Urgency in research is very important; but excess long-term stress disrupts higher brain function and results in a loss of inventiveness and processing of key information among scientists.

Whereas exposure to acute stress tends appears to facilitate memory formation and consolidation, long-term stress or chronic exposure to stress hormones such as glucocorticoids impairs cognitive performance and higher brain function [21]. Research settings characterized by serious long-term stress will therefore destroy the creative process of drug design. Unfortunately many corporations tend to do what corporations are perceived to do – looking after their own and shareholders' interests, and each layer in the food chain 'beats up' on the layer below to provide its

BOX 2

Drug discovery 1995

DD 1995 at Novo Nordisk was a revolution in organizational change in what are often conservative drug companies. It was orchestrated at the Danish R&D base by VP of CNS Drug Discovery Tage Honoré and Anthropologist Gert Egger, two of the best analytical minds in the Pharma industry. It effectively empowered project leaders and virtually removed negative influences of line management from a large drug discovery group. This unit was entirely project-driven, with the following key features:

- A group of directors, one for each scientific area, was assembled, covering *In Vivo* Biology, Biochemistry, *In Vitro* Pharmacology and Medicinal Chemistry, to form a drug discovery management team (DDMT), reporting in to the VP of Drug Discovery, Tage Honoré.
- Aside from the DDMT, the only managers were project leaders who, on their own initiative, selected one person from DDMT to be their mentor and boss. Scientists took initiative to be recruited into projects based on project description, but could also be recruited by project leaders.
- By definition, the project leaders had temporary positions, depending on the project cycle. DDMT assigned project leaders, often the originators of a project. When projects came to an end, the project managers moved back to the pool of regular scientists in the company, looking to start new projects.
- The project leaders made up a project management team (PMT) that made resource recommendations for the entire portfolio to DDMT. The Chairman of the PMT, Malcolm Sheardown, provided a link to DDMT to assess the overall needs of projects and resources available.
- The most capable project leaders who initiated and ran successful projects would be reappointed to lead new projects: 'the cream would rise to the top'.
- Success was defined as timely termination of difficult or slow-moving projects as well as identifying drug candidates for development.
- One key principle is that the role of line management is to provide an environment where drug discovery projects prosper. As observed repeatedly by Nobel Laureate James Black, line managers are nice people, but can slow research down by insisting in being involved in the minutiae of projects, which is strictly the role of project teams.
- The idea of this project-driven organization was to free up the project leaders to drive forward their projects, without constant interference from line managers who could have been building their own 'kingdoms'.
- In my view, DD 1995 was an outstanding example of an information-age organization, not the old 'widget-focused structure' discussed above, and the instigators Tage Honoré and Gert Eggers deserve great credit for this model.
- Unfortunately even in a relatively forward-thinking company such as Novo Nordisk, these changes were seen as being too radical and the system was dismantled during the next of many company reorganizations, despite a demonstrated increase in productivity. The cycle was completed when, in 2006, this otherwise well-respected company abandoned small-molecule drug discovery after investing in it for >20 years.

bonuses. Such hierarchical systems are not conducive to drug discovery, and companies that are bastions of control cannot bring out the best in free-thinking inventors. However, I am encouraged by the management commitment in companies such as Novo Nordisk and BiogenIdec that provide their research teams six months between major project review cycles. Project teams can then plan and move forward knowing that their resources, in terms of both people and finance, will not be taken away for at least this period. To a project leader, this is infinitely preferable to constant threats of resource changes and project closure.

In a real sense, discoveries and inventions by definition cannot easily be time-lined, because they are new and nobody has been in that particular territory before. Obviously, speed in drug discovery is very important but managers who define overly tight timelines should also expend their energies on providing a terrific creative and entrepreneurial environment, valuing analytical skills and intrinsic motivation of scientists, so that researchers have a higher likelihood of making discoveries. Strict timelines can lead to lack of innovation and poor-quality science focused on generating 'good' (i.e. supporting) data, not always good science, and ignoring 'bad' data. The goal is to gain greater understanding alongside achieving a particular goal. To quote one former colleague, 'all they are interested in is a number', referring to the code number for a prospective drug candidate.

Inventions are much more likely to happen in an environment where an innovative, measured culture exists and, if scheduled, they are in a sense no longer inventions. In drug development, as opposed to discovery, projects can be accurately time-lined, because we know for example how long a one-month toxicology study with analysis and write-up time will take. If research is too tightly controlled it ceases being research; and, rather like the wave-particle duality of the electron, once it is defined and measured it is no longer there. Although all projects should show a sense of urgency, the 'invent it by next Tuesday' syndrome of an extreme type A culture has negative consequences.

Drug discovery thrives on a level of 'managed chaos' – where creativity, innovative ways of doing things and the intrinsic motivation of researchers prospers and are rewarded in a not-overly-structured environment. An IBM mantra states, 'good management is to bring order where there is too much chaos, and chaos where there is too much order'. The flat organization built by Paul Janssen lacked formal priorities, deliverables and deadlines [7]. Because so many drugs are invented serendipitously [13], there has to be the time and energy available to observe and conclude from puzzling data. Serendipity, or 'making your own luck' as I would prefer to call it, was behind the discovery of Penicillin, Viagra®, Acyclovir®, Zidovudine® and a host of other major drugs. Over-organization of research tends to lessen the chances of serendipity.

To quote the gifted ex-Pfizer researcher Simon Campbell, 'drug discovery requires passion, commitment and often serendipity – it's not a mechanical event, it's not numbers-driven, it's a personal experience! Pasteur's famous dictum states that, 'chance only favours the prepared mind', you need to be able to see what other people are doing and how you can apply it yourself. Very often that was the secret of our success.' [22]

Concluding remarks

In conclusion, the premise of this article is that drug discovery environments in many pharma companies fail to release the creative energy of gifted scientists – whose invention of new drugs they rely upon to remain at the forefront of the industry. The

settings for research efforts have degraded to a level where top quality science and a painstaking approach to research are no longer valued, and there is a sole focus on the bottom line. A renewed focus on individuality, a firm commitment to science and the way it unfolds, the motivation of scientists, and cultural and ethical standards that are derived from those of medicine itself [23] need to be re-established. The alternative is that an industry downsizing and failing in many metrics will suffer further losses in output, performance, staff and prestige.

Multiple factors are involved in improving the output of the pharma industry, including the evolution of a less risk-averse FDA, recovering from the regulatory 'squeeze' after several drug withdrawals. Christopher Milne from the Tufts University Center for the Study of Drug Development suggests, 'Many people could not wait for the past decade to go away; I think the next one will be better – a more productive and efficient decade.' [24]

Senior management in drug discovery needs to re-establish values of respect, true innovation and integrity, realizing that primarily focusing on the need of patients rather than totally on the bottom line is paramount in rebuilding this dynamic, knowledge-based industry. These values, a spirit of true invention and a respect for intrinsic motivation that drives inventors are, in my view, more likely to be found within smaller drug discovery units [22]. To quote a later article by Uitdehaag, 'Research organizations need to deliver high value output, even if this means that output is irregular. They need to discover novel protocols and therefore to give their researchers maximum freedom to operate. This results in a flat organization, a collective of research groups in which management functions as a sort of home base' [25], as in the model described in Box 2. It is my hope that this present article will help initiate a wave of change that will help to re-establish the sound science of drug discovery in environments where it has not prospered.

The message is plain and clear: ignore quality science, the needs of inventive scientists and the need to build a terrific entrepreneurial environment, as described herein, and pharma companies will continue to stifle research and suffer further degradation of their drug pipelines.

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