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The future of discovery chemistry: *quo vadis*? Academic to industrial – the maturation of medicinal chemistry to chemical biology

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At Roche, we set out to think about the future role of medicinal chemistry in drug discovery in a project involving both Roche internal stakeholders and external experts in drug discovery chemistry. To derive a coherent strategy, selected scientists were asked to take extreme positions and to derive two orthogonal strategic options: chemistry as the traditional mainstream science and chemistry as the central entrepreneurial science. We believe today's role of medicinal chemistry in industry has remained too narrow. To provide the innovation that industry requires, medicinal chemistry must play its part and diversify at pace with our increasing understanding of chemical biology and network pharmacology.

Introduction

The discipline of chemical biology has now been around for more than a decade, as witnessed by several scientific journals, such as the *Journal of Chemical Biology*, *Nature Chemical Biology* and *ACS Chemical Biology*, to name a few. But regardless of its history and origin, the field of chemical biology, defined here as both the use of chemistry to advance a molecular understanding of biology and the harnessing of biology to advance chemistry (http://www.rsc.org/ScienceAndTechnology/Policy/Bulletins/Issue3/Chemicalbiology.asp), has not taken broad hold in those organizations that could really benefit from its advances, large pharmaceutical companies. Indeed, today, medicinal chemistry remains the main discipline of chemistry practised in the pharmaceutical industry and, unfortunately, it has acquired something of a bad reputation in drug discovery. Medicinal chemistry is often referred to as a 'mature science' evoking images of the grandfather of drug discovery – geriatric, slow and even grumpy. In this article, we outline a chain of thoughts that concludes that chemistry has a wider part to play in innovative drug discovery than it is currently permitted by industry to have. The application of chemical biology, blurring the boundaries between chemistry and biology, within industry holds the promise of delivering innovation in healthcare that reaches far beyond the limitations of traditional medicinal chemistry.

At Roche, we set out to think about the future role of medicinal chemistry in drug discovery in a project involving both Roche internal stakeholders and 19 external experts in drug discovery chemistry. We held exploratory interviews to assemble views on such topics as the organization of discovery chemistry in pharmaceutical companies, the level of innovation apparent, current challenges and what would constitute scientific breakthroughs, as well as the likely future of discovery chemistry given the challenges faced by the industry in general. The external experts were leaders of R&D or chemistry departments in big pharmaceutical companies (12), independent chemistry consultants and academics (4) and peer-reviewed scientific journal publishers (3). The interviews were not designed to gain quantitative insight into the performance of discovery chemistry but were a discussion of personal opinions of the *status quo* and potential *quo vadis*.

Here, we reflect on our findings from these discussions, describe our approach to thinking

 1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2010.02.002

about the strategy for discovery chemistry going forward and opine on the opportunities that might lie ahead for discovery chemistry as it truly evolves into chemical biology.

Status quo

Although there are two distinct ways that Big Pharma companies organize discovery chemistry, central chemistry and therapeutic area (TA) alignment, neither was seen as better than the other by the experts we spoke to. In the former structure, all chemists are aligned and report to a chemistry site head who, in turn, reports to a global chemistry head. In a therapeutically aligned organization, a chemistry site head reports to a TA chemistry head who, in turn, reports to a TA head. The relative success of each organizational structure will depend on the culture of the organization in question. There is an increased risk of having chemistry play a supporting part in the central chemistry model, and organizations counteract this through leadership that is inclusive and that involves the complete cross-functional team in decision making, regardless of reporting lines. In the TA alignment model, there is stronger involvement in and ownership of drug discovery projects but a weaker network between chemists across TAs and a higher risk of slow adoption of best practices.

The greatest tension in discovery research in Big Pharma companies, however, seems to result not from how companies are organized but rather from the competing goals of efficiency and innovation. Key levers for encouraging (and discouraging) specific behaviours are the metrics used to reward performance. The metrics currently used in discovery in Big Pharma could be considered 'efficiency' metrics and are based on the achievement of project-related milestones, such as reaching decision gates. Other metrics include the number of development candidates or leads produced, the time taken to advance candidates through the pipeline and the incremental change in value of the portfolio over time. Although these metrics can be easy to measure, their effect on encouraging innovation is considered low [1]. In fact, they might actively discourage some forms of innovation. We would argue that the problem is not the volume of compounds being produced and the number of projects in the early discovery research phase but rather the quality of those compounds and the diversity of approaches taken.

We believe that given the challenges expected to face the Pharma industry in the next five to ten years and beyond, a significant investment in innovation is the only way forward for proprietary pharmaceutical drug discovery and development. The increasing cost pressure put on healthcare systems (and, therefore, the industry), the widespread encouragement of generic use by payers, heightening regulatory hurdles and the potential to address currently unmet medical needs and specific patient populations as biological science matures must drive the industry to innovate. Regulatory authorities will proactively approve innovative treatments that can truly change health care options for patients. Consequently, we believe that the *status quo* is not an option for the future of discovery chemistry in the Pharma industry.

Taking extreme positions

To derive a coherent strategy for discovery chemistry at Roche, selected scientists were asked to take extreme positions and to derive strategic options. Using this line of thinking, two orthogonal main options were explored: chemistry as the traditional mainstream science and chemistry as the central entrepreneurial science (Table 1).

Chemistry as the traditional mainstream science

In this option, scientists were asked to consider a strategy for chemistry in which current chemistry is leveraged to the full but is kept on the traditional tracks of medicinal chemistry. Efficiency remains the focus of performance and, as such, innovation is likely to be incremental and activities remain within the defined limits of the current approaches and therapeutic interests of the organization. Small molecules were defined as organic molecules of synthetic or biological origin with molecular weight of 1000 g/mol or less, in most cases less than 500 g/mol.

The key opportunities for chemistry to deliver new medicines to patients here were oral bioavailability, clinical differentiation and the potential of applying more holistic polypharmacology approaches, also using phenotypic screening systems [2]. It was hypothesized that small molecules will remain the only therapeutic option for oral delivery, which will be particularly important as large developing economies with limited cold supply chain capabilities experience high growth in consumption of pharmaceuticals. There are also specific therapeutic opportunities for differentiated small molecules where large molecules are facing serious challenges to perform; for example, targets within the CNS and intracellular targets in general. Finally, the application of polypharmacology [3], the designed ability of a small molecule to interact

TABLE 1

Taking extreme positions[a]

Chemistry as...	The traditional mainstream science	The central entrepreneurial science
...**Characteristics**	The practise of medicinal chemistry within the limits of current approaches	'Blue sky' or fundamental research
	Efficiency remains the focus of performance	Discovery chemists are innovators and fully leverage their potential to reinvent pharmaceutical R&D
	Innovation is likely to be incremental	Broadened scientific competencies are required, and the interface with biology is crucial
...**Opportunities to deliver better medicines to patients**	Oral bioavailability	Delivery of nonpermeable molecules and macromolecules into cytoplasm and cell nucleus
	Clinical differentiation	Molecules that regulate gene expression
	Oligo-pharmacology	Molecules that direct cellular self-renewal, pluripotency and stem cell differentiation
	Phenotypic screening approaches	
	Further improved safety profiles based on improved *in vitro* and *in silico* tools	
...**Outcomes**	Small-molecule therapeutics: organic molecules of synthetic or biological origin with molecular weight of less than 500–1000 g/mol	New therapeutic modalities combining design and synthesis of molecules with the increased knowledge of chemical biology

[a] To derive a coherent strategy for Research Chemistry at Roche, selected scientists were asked to take extreme positions and to derive strategic options. Two positions were explored.

with multiple targets, is largely within the realm of a small-molecule drug.

There is no doubt that small molecules have intrinsic advantages, such as oral bioavailability and broad accessibility of all cellular compartments, consistent manufacturing processes, a low cost of goods, and a reliable and predictable patent situation. It is well documented in the literature [4], however, that unfavourable molecular properties can be correlated with target promiscuity and an increased risk of off-target activities leading to toxic adverse effects. Consequently, if discovery chemists succeed in designing small molecules with a polar surface area $>75A^2$, log D < 3, ligand efficiency >0.5 and a daily human dose of less than 10 mg, then the risk for off-target side-effects would be very much minimized. To state the obvious, such rules and criteria for successes need to be used in a meaningful manner and with appropriate care.

With respect to personalized healthcare, discovery chemistry is optimally positioned to design and deliver tailor-made molecules using rapid and close iterative design and characterization cycles, *in vitro* and *in silico*. Individual isoforms of targeted proteins in certain patient populations may serve as a simple example that may benefit from a well-organized small-molecule discovery platform with rapid feedback loops from early clinical research back to molecular design and the medicinal chemistry bench.

In addition, an improvement to current practise in this traditional approach would be to move away from single pharmacology targets and to apply discovery chemistry to more holistic and phenotypic screening approaches. For example, cellular assay systems that resemble the disease-like state of a particular medical condition could be used, rather than applying assay formats using recombinant cells and single-target pharmacology as the primary read-out mechanism.

An excellent example of a molecule arising from the traditional approach and exerting dual pharmacology is the peroxisome proliferator-activated receptor α/γ coagonist Aleglitazar [5]. At a rather low daily dose of 150 μg per patient and with a strong cardioprotective safety profile, Aleglitazar represents an innovative antidiabetic treatment option designed for diabetic patients at risk of cardiovascular complications [6].

Chemistry as the central entrepreneurial science

In this option, chemistry has the freedom to pursue experimental work that, in part, could be considered 'blue sky' or fundamental research, but within a defined set of organizational goals. Discovery chemists are not limited to using innovative methods but are encouraged to pursue innovative goals. Discovery chemists are scientifically broad innovators who propose and work on all targets for existing and novel therapeutic modalities. As a central enabling science, however, discovery chemistry fully leverages its potential to reinvent pharmaceutical R&D. The most significant research results will influence society because they will revolutionize healthcare options. To achieve this, broadened scientific competencies are required from chemists and the interface with biology becomes even more crucial to success. The decision regarding the best approach to a specific target, large or small molecule, is made as data are generated.

Viewing chemistry as an entrepreneurial science offers the potential for a step change in value creation for patients, payers and the industry through the development of what we term 'new therapeutic modalities'. Three examples of what we mean by this are given below and describe innovations resulting from this approach.

Example 1. Delivery of nonpermeable molecules and macromolecules into cytoplasm and the cell nucleus [7]. In this research scheme, active and passive transport mechanisms, endo- and transcytosis, artificial viruses, and cell-penetrating peptide motifs must be studied in greater detail. This example encompasses intracellular delivery of polar small molecules, peptides, proteins, and DNA and RNA. If successful, the approach would fully enable therapeutic siRNA application in its broadest sense.

Example 2. Molecules that regulate gene expression [8]. In this approach, researchers investigate mRNA, rRNA and tRNA as drug targets for the alteration of gene transcription in the nucleus and of gene translation in the initiation, elongation and termination phase of the protein biosynthesis. Besides antibiotic therapeutics, the whole research area has been neglected by medicinal chemistry in the past, although it offers a unique opportunity for the design and discovery of new therapeutic modalities that have the potential to cure diseases, in particular in those cases in which the misprocessing of a protein during protein biosynthesis or the protein itself is causing the disease (such as cystic fibrosis or Alzheimer's disease).

Example 3. Molecules that direct cellular self-renewal, pluripotency and stem cell differentiation [9]. Regenerative medicine could become the future standard treatment for many diseases 20 years from now. For example, if we had an oral treatment that would enable differentiation of implanted stem cells into functional insulin-secreting beta cells, neuronal glia cells, fully functional cardiomyocytes and hepatocytes, then such treatment modalities would revolutionize health care options for patients with severe life-threatening and devastating chronic diseases.

A historical comparison to research in material science might serve to illustrate the powerful potential of this scenario. In the late 1920s, the most important scientific breakthrough for DuPont was the result of such fundamental research (http://www2.dupont.com/DuPont_Home/en_US/index.html). The head of research noted: 'We are including in the budget for 1927 an item of $20,000 to cover what may be called, for want of a better name, pure science or fundamental research work. . .the sort of work we refer to. . .has the object of establishing or discovering new scientific facts.' The chemistry research team around the chemist Dr Wallace Hume Carothers developed the understanding of radical polymerization and established the basic principles for condensation polymerization. The efforts led to the invention and commercialization of nylon in 1938, which marked the beginning of the modern materials revolution. Neoprene, a synthetic rubber, was designed by the same group in 1933.

Another important element for successful discovery chemistry – regardless of the approaches taken – is based on effective knowledge sharing and improved *in silico* prediction tools. Organizations that have learned to effectively manage knowledge sharing from molecular design all the way up to clinical safety and efficacy will become most successful in future. In addition to strong multi-dimensional optimization capabilities *in vitro*, *in silico* tools must be constantly improved based on accumulating internal and external knowledge. If we had powerful substructure searchable knowledge databases that would enable chemists to map chemical substructures to complex molecular functions, such as network pharmacology [10], *in vivo* efficacy, safety and tolerability, then such *in silico* tools would enable chemists to rapidly design and synthesize constantly improved molecules. Equally important, the use of such *in silico* tools must also consider the latest technology developments of interactive user computer interfaces, such as interactive touchscreen surfaces, where large sets of molecular structures can be visualized and rapidly sorted with respect to their biological functions and properties.

Both options – chemistry as the traditional mainstream science and chemistry as the central

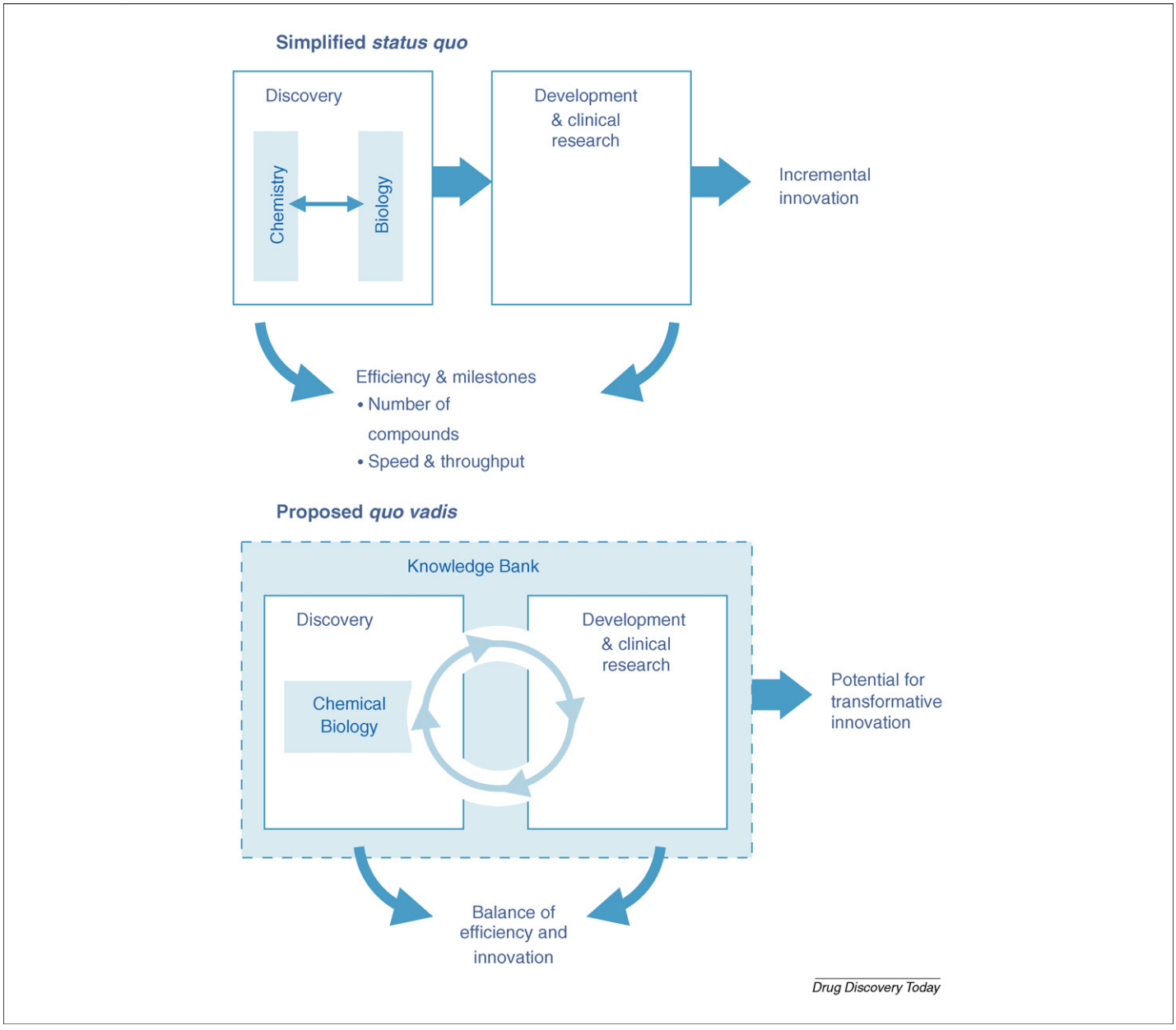

FIGURE 1

entrepreneurial science – can be made to be mutually exclusive through an exercise of thought. But in reality, it is the proper balance between efficiency and innovation that industry requires to bring valuable medicines to patients in the future. Therefore, we support a broadening of the discipline of medicinal chemistry to chemical biology, which could result in a paradigm shift for the pharmaceutical industry (Fig. 1).

Concluding remarks

We believe today's role of medicinal chemistry in industry has remained too narrow. To provide the innovation that industry requires, medicinal chemistry must play its part and diversify at pace with our increasing understanding of chemical biology and network pharmacology. To foster innovation, we must enable smaller discovery research teams composed of the most gifted and curious scientists that are able to reach across the boundaries of scientific disciplines and create organizational structures that support the right focus, whether efficiency or innovation, at the right time during discovery research. Research teams must have direct interfaces to all scientific disciplines involved in pharmaceutical research and development, as well as to experts in the field, whether they are internal or external to the organization. Short feedback loops with clinical teams must be created to ensure rapid improvement of these new approaches, and such dedicated groups must have the freedom to operate and to conduct research with relevance to the improvement of healthcare. Research teams will need to be relieved from milestone pressure and rewarded in a manner that recognizes their contribution to innovation. Following this approach, chemists with a broadened horizon towards chemical biology will have a crucial and central role in truly advancing this research field for improved treatment options for patients.

The United Nations General Assembly with its resolution 63/209 has declared that year 2011 will become the International Year of Chemistry – a most timely decision to remind us that chemistry is indeed a central science.

Acknowledgements

The essential contributions of the project team members Bodo Baumeister, Simona Ceccarelli, Tobias Gabriel, Nicholas Huby, Yan Lou, Matthias Steger and David Wadsworth were highly appreciated. The authors acknowledge the Steering Committee members of this project, Hans-Joachim Böhm, Nader Fotouhi and Steve Arlington, for their trust, dedicated support and guidance.

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