Morphochem: breeding small molecules

Lutz Weber

Morphochem integrates innovative chemistry with bio- and chemoinformatics and the post-genomic biology tools of drug discovery. The company has built a highly efficient drug discovery engine, leveraging the ideas of chemical genomics and applying Nature's principles of evolution towards the parallel and high-speed discovery and optimization of small molecules into novel drug candidates.

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▼ Morphochem's vision is to bridge the gap between genomics-driven new biology and the creation of small-molecule drug candidates. The company has introduced evolutionary drug discovery technologies to breed small molecules for new drug targets, creating a powerful drug discovery engine for chemistry-driven target validation and the discovery of novel therapeutics. The use of small molecules as enabling tools for functional genomics translates into a novel process that uniquely integrates chemistry and genomics at the front of the drug discovery process. The urgent need for validated, drugable targets, as well as for small-molecule drug candidates, are addressed in parallel by this 'front-loaded' chemical genomics process (Fig. 1).

History of Morphochem – the space of chemistry

Morphochem was started as a spin-out from the Technical University of Munich by Alexander Dömling and Wolfgang Richter in 1996, with the aim to commercialize multi-component reaction (MCR) chemistry. In contrast to classical chemistry, MCRs use more than just two starting materials in one reaction step. Morphochem chemists have shown that up to seven different starting materials can be used at a time to yield highly complex chemical structures in only one step, demonstrating that MCR chemistry is the most efficient way towards the fastest assembly of novel small molecules [1].

The chemical space that is accessible to MCR chemistry appears to be unlimited: using commercially available starting materials only, one MCR could potentially deliver up to 10^{20} individual products. Morphochem has increased the repertoire of MCR reactions and corresponding building blocks dramatically. Today, more than 300 different, mostly unexploited MCRs are known, giving rise to a novel, huge space of chemical diversity [2]. This specific and broad knowledge of MCR principles provided the foundation for Morphochem. To leverage the potential of its MCR chemistry expertise for the novel chemical genomics drug discovery paradigm, the company received venture capital financing in 1998.

Artificial evolution – breeding small molecules

Finding molecules that bind and modulate specifically one protein out of the full protein complement of a cell, thereby exerting desired functions like induction or repression of gene expression, or reversals or induction of a specific phenotype, represents a tremendous challenge. The idea behind Morphochem's repertoire of proprietary technologies is that they mimic and apply Nature's evolutionary principles to identify and create molecules from its huge MCR chemistry space. The company's artificial evolution process uses heuristic optimization procedures as neuronal networks and genetic algorithms in which small synthetic molecules are described by *in silico* genes, in the same way as DNA encodes for proteins [3,4]. The rapid, overnight synthesis of molecules through MCR chemistry, combined with a quick determination of their biochemical and biophysical characteristics, enables the synthesis of molecules that have a higher probability of success in development, to

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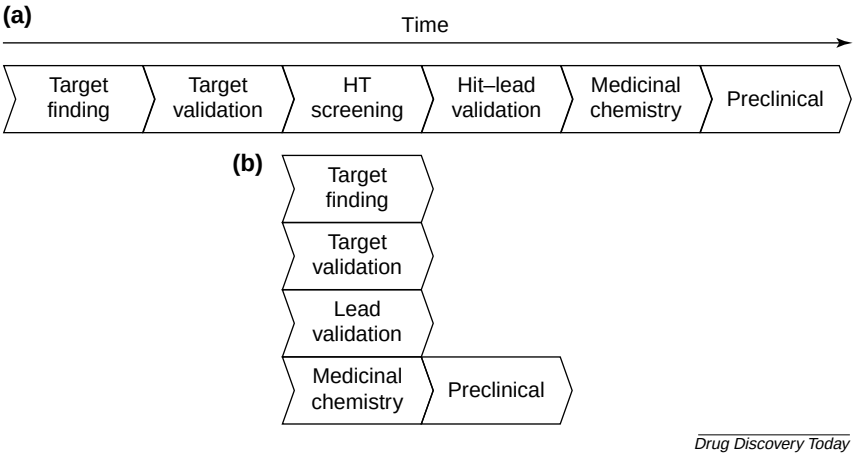

Figure 1. (a) Today's sequential drug discovery process of milestones and **(b)** the front-loaded chemical genomics drug discovery process that combines chemistry with pharmacology and genomics and informatics in tight feedback cycles.

be produced in a short timeframe; that is, days versus weeks or months, as is found in classical approaches. The automated breeding of improved molecules over multiple generations provides an opportunity for identifying and optimizing drug candidates more efficiently. Ultimately, we envisage a co-evolutionary drug discovery process in which small molecules enable the validation of novel drug targets, but which are also improved by parallel biological feedback loops into highly potent and selective new drug candidates.

Integrating complementary biology – chemical genomics

As a matching counterpart to the MCR chemistry, complementary biology was put in place, and an industrialized process was built around the concept of chemical genomics. The acquisition of SMT, a Princeton-based US biotech company, in March 2000, added a rich repertoire of protein–protein interaction screening technologies and cell-based assays. These assays provide rapid reporter-gene-based read-outs for a variety of signaling pathways and physiologically relevant protein interactions for Morphochem's chemical genomics approach, introducing the 'molecular breeding' concept for small molecules.

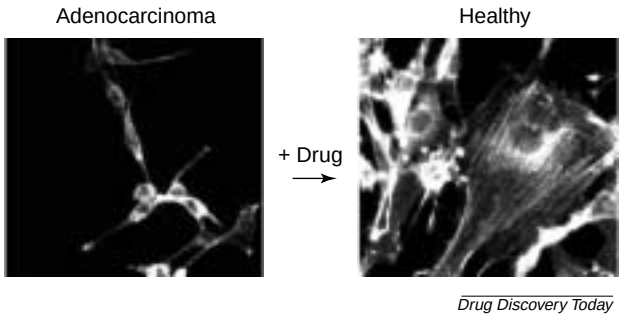

Figure 2. Chemical genomics, schematically exemplified by Morphochem's pancreatic cancer program. Cells isolated from pancreatic cancer tissue show a phenotype with a poorly formed cytoskeleton. Screening of Morphochem compound libraries resulted in compounds that are able to revert the oncogenic phenotype on a cellular level. Parallel screening with protein–protein interaction technologies, such as yeast two-hybrid systems, revealed that active molecules modulate the interaction of the oncogene *Ras* with its effector, the *Raf* protein, validating this interaction as a viable drug target.

An important milestone in the development of Morphochem was the recruitment of a distinguished, pharma-experienced team around Wolfgang Keck together with the creation of a research site in Basel, Switzerland. This team pioneered the application of genomics to antimicrobial drug discovery and added further complementary technologies to Morphochem's chemical genomics repertoire, including a core expertise in transcriptional analysis, thus enabling the complex responses of biological systems to compounds to be unravelled. Furthermore, a biostructural research unit, including x-ray crystallography and high-throughput docking, generates information on molecular interactions and conformations of the ligand–target complexes, which is fed back into the automated evolutionary optimization process. Using its unique knowledge base in the anti-infective disease area, the company has now built a balanced portfolio of anti-infective projects.

Proof-of-concept and contributions to the value chain of drug discovery

The classical drug discovery process starts by selecting a biological target and then identifying a specific molecule in a sequential process, hoping (often without success) that such a molecule will, in later stages of the process, exhibit the desired pharmacological effect. By contrast, chemical genomics selects

Box 1. Key personnel at Morphochem

Executive management position	Current position	Former position
Lutz Weber	Chief Executive Officer	Vice Director for New Technologies at Roche, Basel
Thomas Loeser	Chief Financial Officer	Small Cap Network, Munich (Germany) and Boston (MA, USA)
Werner Schiebler	Chief Business Officer	Director, Technology Licensing and Alliance, Aventis Pharma
Wolfgang Richter	Intellectual Property and Human Resources	Founder
Wolfgang Keck	Head, Switzerland	Vice Director for Anti-infectives at Roche, Basel
Eric Eastman	Head, US	Chief Technical Officer of GeneLogic

Scientific Advisory Board

Ivar Ugi, Technical University, Munich (Germany); Sir Jack Baldwin, Oxford University, Oxford (UK); Ludger Wessjohann, Leibniz Institute for Plant Biochemistry, Halle (Germany); Victor Snieckus, Queens University, Kingston (Ontario, Canada); Alfred Wittinghofer, Max Planck Institute, Dortmund (Germany); Erica Golemis, Fox Chase Cancer Center, Philadelphia (PA, USA); Armin Kessler, formerly COO, Roche, Basel (Switzerland); Karl-Heinz Büchel, formerly Managing Director, Bayer, Leverkusen (Germany); Richard Woychik, Lynx Therapeutics, Hayward (CA, USA); and Gerhard Höfle, GBF, Braunschweig (Germany).

for molecules that show pharmacological efficacy from the beginning, such as through changing phenotypes of cell lines, identifying the molecular pathways later or in parallel. In a first proof-of-concept for Morphochem's chemical genomics approach, molecules were identified that revert the oncogenic phenotype of constitutively activated ras cell lines (Fig. 2). At the same time, it could be shown that these molecules modulate the binding of the oncogene *Ras* with its downstream partner *Raf*. Our current research combines protein–protein-binding screening technologies like two-hybrid systems with protein crystallography, providing the input for optimization of these novel mode-of-action, potential anti-cancer drug candidates. This example illustrates that it is not only possible to rapidly identify novel drugable biological targets, but also molecules that are efficacious in functional screens, thus increasing the likelihood of success of drug discovery.

In another proof-of-concept experiment, Morphochem's automated evolutionary drug discovery process, which encompasses genetic algorithm-driven synthesis-on-demand and multiplexed biological screening, was used against two biological targets in parallel. Only ten rounds of synthesis and screening were needed to create both active and selective molecules for both targets. Today, Morphochem is expanding this parallel process for up to ten biological targets at a time.

Collaborations

Morphochem has succeeded in the assembly of a continuum of expertise and has already built many steps of its industrialized chemical genomics-driven discovery process. The approach has been validated through successful alliances, which include research and success-driven milestone payments as well as royalties on marketed products. In one example, Aventis Pharma was provided with a library of small synthetic molecules within six months that mimic the activity of a synthetically difficult-to-access natural product that was used to validate an innovative target in diabetes. Today, Morphochem is also collaborating with Aventis in the field of novel anti-infective drugs.

To build and expand its own technology platform further, Morphochem is assembling a collaborative network with researchers from universities and institutions (Fox Chase Cancer Center in Philadelphia, PA, USA; UCLA in Los Angeles, CA, USA; Institute of the Biochemistry of Plants in Halle, Germany; and University of Barcelona, Spain), as well as biotech companies (Synt:em, Sosei, Sequenom, Automated Cell and Migragen).

Overall, Morphochem is looking forward to:

- Enabling strategic partners to improve significantly their drug candidate discovery capabilities, through a more effective, parallel and industrialized drug discovery process that delivers molecules with a higher likelihood of success in later development.
- Developing its own pipeline of novel small-molecule drug candidates, specifically in the fields of infectious diseases and cancer. In both areas, molecules have been generated that are now evaluated in animal experiments. These molecules will provide a richness of partnering and development opportunities.

The company currently has 130 employees, with 60 in Munich (Germany), 40 in Basel (Switzerland) and 30 in its Monmouth Junction US research site (NJ, USA) (Box 1). The company's supervisory board is chaired by Helmut Schühsler, Managing Partner of the company's lead investor, TVM. Other key investors include Alta Berkeley, Alta Partners California, Merlin Biosciences, Nomura, WestLB Panmure and Life Science Partners. Since its launch in 1998, the company has raised more than €70 million in four different private equity financing rounds and is currently preparing itself for an initial public offering within the next 12–18 months.

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