# Perspectives of Computer-Aided Drug Design

**Prof. Dr. Alexander Hillisch, Bayer Pharma AG**

**Working with models, namely three-dimensional illustrations of reality, is an integral part of any industrial design process. However, can we also use 'design' in relation to drug research? What is our understanding of these techniques today?**

Anyone wishing to build a new kitchen will generally start planning with a pencil, a ruler and paper. However, the representational form of a two-dimensional plan has its limitations. In the past, the desire for structured, three-dimensional illustrations of reality frequently induced the committed DIY enthusiast to create intricate wooden or cardboard models crafted in meticulous detail. Today, we are able to 'click' together that dream kitchen in just a few minutes on a PC, observe it with astounding reality from all sides using 3D imagery, and also reject and revise any drafts we dislike. Working with models enables problems to be recognised at an early stage before actual realisation and facilitates better planning and more efficient work in general. As a result, computer-aided design (CAD) is now an indispensable part of industries such as car manufacturing, aircraft construction and shipbuilding, to name but a few. In this respect, skilled crafts and planning have not been replaced, but rather have been enhanced by material- and time-saving computer methods.

**What is the significance of CAD within the realm of drug research? Can industrial design, as depicted above, actually be transferred to drug discovery?**

The drug discovery process has always been dominated by 'trial and error'. Due to the lack of precise knowledge of molecular interaction in the human organism, thoughts of rational drug design have long been all but impossible. Drugs were discovered purely empirical, using natural products and screening approaches and optimized through the synthesis and testing of a large number of structure variations. Stimulated by advancements in molecular biology, protein production and x-ray crystallography as well as initial successes in structure-based drug design, at the start of the 1990s several advocates of this discipline were predicting that drug research would be heavily dominated by a rational approach in the near future. Ultimately, these predictions could not be realised in such a short space of time and consequently led to massive investment in other technologies, such as combinatorial chemistry and high-throughput screening. If we compare today's knowledge of molecular targets with that of 20 years ago, it is now clear how unrealistic these perceptions were. In 1990, the EMBL Bank held around 35,000 nucleotide sequences, today it holds over 250 million. In 1990, 450 protein crystal structures were stored in the Protein Data Bank (PDB), today the figure is

around 78,000. In 2012, for example, the ChEMBL database contained around 10 million bioactivity data for 1.2 million different compounds on 9,000 target proteins.

## So what have we learnt from all this data? Has our approach to drug discovery changed?

The testing of large substance libraries continues to represent an important pillar of lead structure identification. Today, however, coincidence is being aided ever-more frequently by the targeted design of compounds. Given the structurally well-understood target protein families, we are able to combine different parts of compounds on a computer screen, alter or supplement these in consideration of the synthetic feasiblility and subsequently draft proposals for entirely new active compounds. We call this 'protein structure-based de novo design'. Following synthesis and testing of the compounds, the approach delivered several new lead structures and a development compound in our hands. In contrast to the past, using our computer designs we not only consider the active substance's binding affinity to the target protein, but also aspects such as absorption by the body, metabolism and toxicity of the compounds. We have derived rules based on the many test results from earlier drug discovery projects and formulated these into computer programs, which now enable us to predict pharmacokinetic aspects in some measure. To this end, the design of new compounds is occurring against a background of close coordination between medicinal and computational chemists. Unfortunately, this highly targeted, design-oriented method does not succeed with all projects, with the result that 'trial and error' will remain an important element of drug discovery. At present, we still do not understand the complex molecular interactions in physiology to the same extent as, for example, is the case for the physics of fluid dynamics in aircraft construction. Nevertheless, I believe our approach in drug research is far more targeted today and that methods promoting such an approach will continue to gain significantly in importance. Enhanced programs to predict the binding affinities of compounds on target proteins or anti-targets, quicker access to available experimental data for the generation of knowledge, and the close networking of medicinal chemistry, computational chemistry, biophysics, pharmacology and pharmacokinetics are just some of the success factors that will improve the efficiency of drug discovery through design.

■ **alexander.hillisch@bayer.com**

**Alexander Hillisch,** was born in 1971 and studied pharmacy at the University of Vienna. He conducted his Ph.D. thesis at the Institute of Molecular Biotechnology (IMB), Jena in the area of biophysics and molecular modeling. In 1998, he completed his doctorate in biochemistry with Prof. Peter Schuster and joined EnTec GmbH Hamburg/Jena, a subsidiary of Schering AG, where he developed the department of 'Structural bioinformatics and drug design' and directed drug discovery projects on women's health and oncology indications. In 2003, he transferred to medicinal chemistry as the department head of 'Computational Chemistry' at Bayer HealthCare AG, Wuppertal. Together with his team, he supports early drug discovery in cardiovascular, oncology and ophthalmology. He was appointed honorary professor by the University of Cologne in 2010 and is co-author of 36 publications, 35 patents and 2 books.