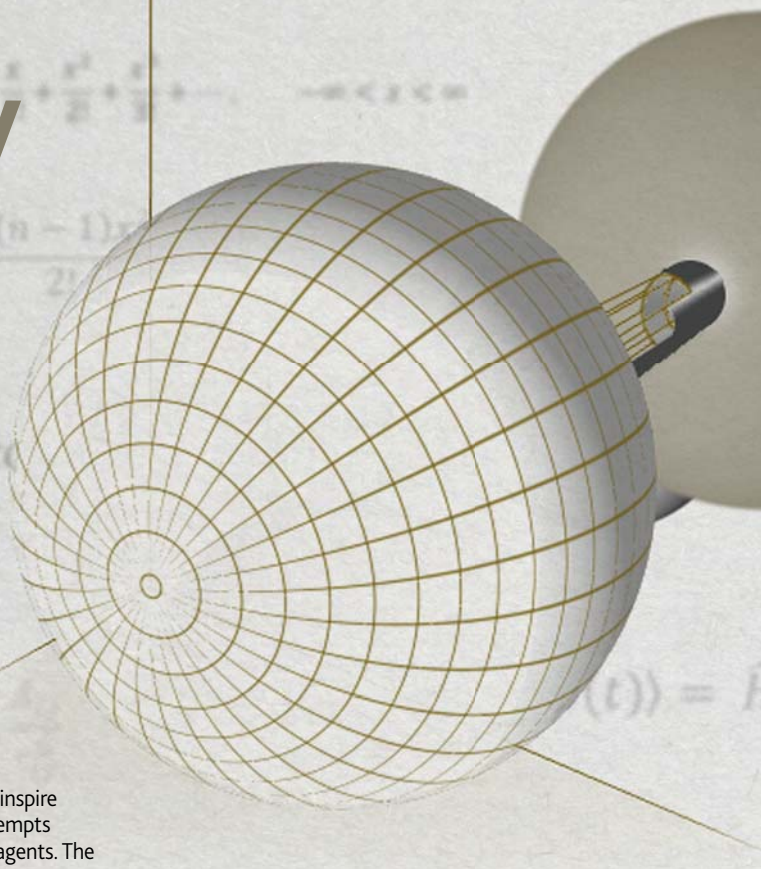
DR GISBERT SCHNEIDER

New era of drug discovery

ILLUSTRATIONS BY
MAX PILLONG, ETH ZÜRICH



Dr Gisbert Schneider is Full Professor of Computer-Assisted Drug Design at ETH Zürich. Here, he discusses his involvement in work that could revolutionise the process of drug creation

Firstly, could you briefly describe the main objectives of the project and explain what is meant by '*de novo*' molecule design?

Innovative bioactive agents fuel sustained drug discovery and the development of new medicines. A driving role in this setting is performed by leading-edge concepts in computer-assisted molecular design, by providing access to a virtually infinite source of novel drug-like compounds and guiding experimental screening campaigns. '*De novo*' design is a fancy term meaning the computer-based construction of innovative molecules. In our projects we try to mimic a medicinal chemist's way of coming up with ideas for novel bioactive compounds. The ultimate goal is to discover innovative, easily synthesisable chemical entities exhibiting a desired biological or pharmacological activity profile with minimal side effects. While this might sound like science fiction, we have come a long way in realising this challenging project since the early attempts dating back to the 1990s.

How is your own computer program distinct from others? Has your team been able to access molecules that chemists have been unable to see before?

We have developed a suite of algorithms and software tools that are meant to support and inspire medicinal chemists in their attempts to design innovative bioactive agents. The most important feature is to stimulate chemists by suggesting attractive compounds that can actually be synthesised with limited experimental effort. The great advantage of using computers is their speed of sieving through virtually billions of drug-like compounds and picking the most promising ones. Our software not only inspects approximately 8 million known and readily available compounds, but also accesses a virtually infinite space of molecules that can be constructed by known rules of chemistry.

Who will the computer program be available to, and where are you hoping to see its applications?

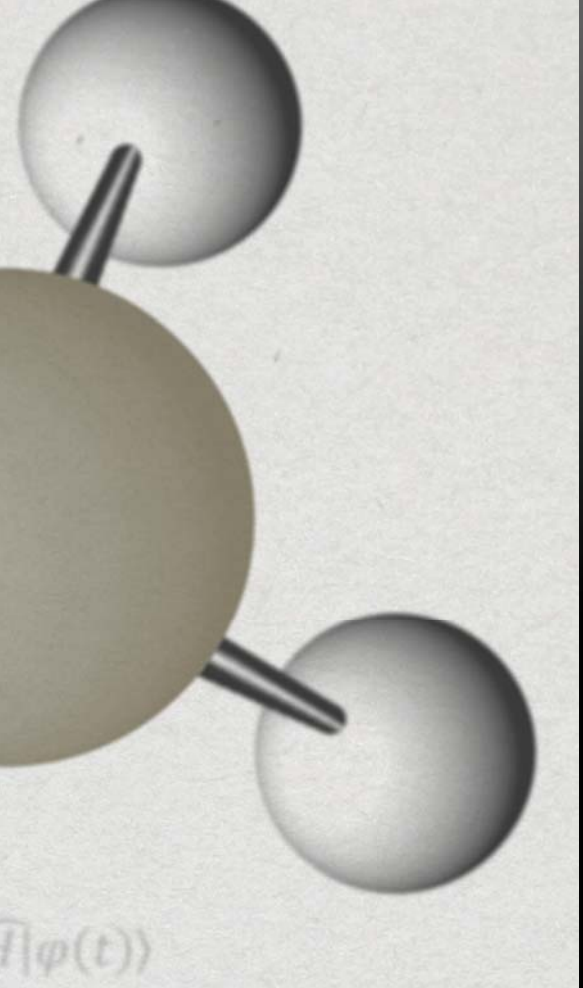
Our computer programs are research tools – we're not a software company. The main aim is to come up with new ideas for computer-assisted molecular design, implement prototype software and provide the proof-of-concept for its applicability in medicinal chemistry. For selected programs, interested scientists in academia and industry have the possibility to obtain a license from ETH Zürich. We are constantly updating and improving our software implementations, and plan to provide new versions as we make progress. Often, we develop our software in direct cooperation with partners from the pharmaceutical industry. This way, both partners learn from each other and product-focused scientific research is facilitated.

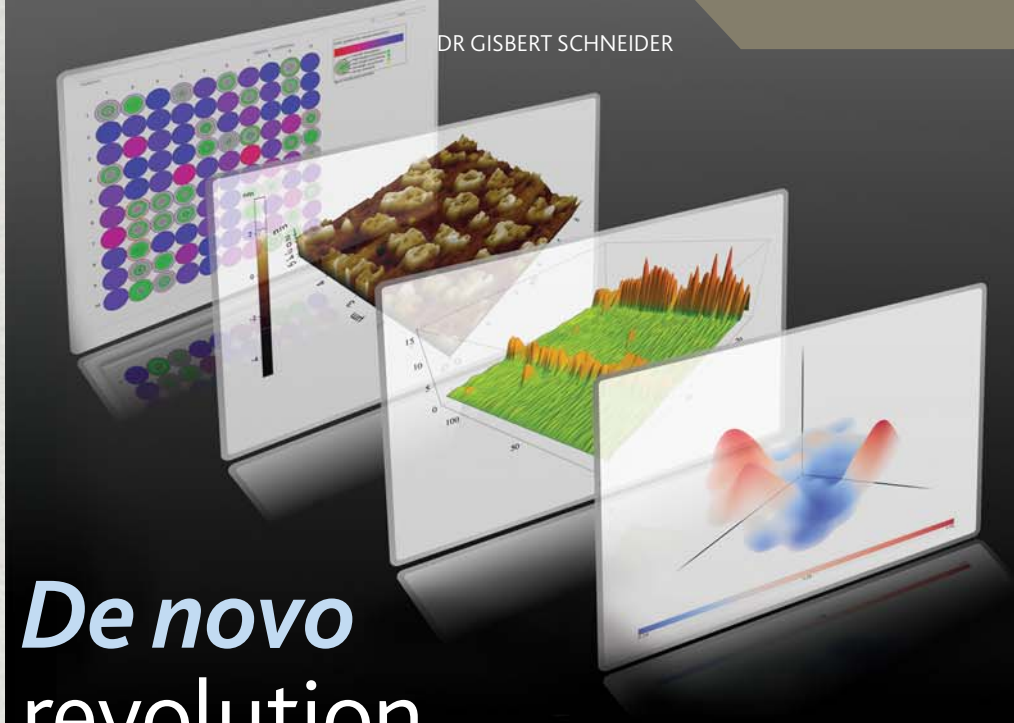
What led you to make the discovery of a pharmaceutically-active molecule which can disable the excessive production of an immune system messenger substance? How could this knowledge help patients with autoimmune disease?

Some autoimmune disorders are characterised by excessive production of interferon. We have applied our virtual screening technology to find a small compound that binds to interferon-alpha and blocks the interaction with the interferon receptor. As a consequence, a disease-associated signal cascade is suspended. The new substance is the first example of a small molecule exhibiting such properties. We consider this finding as a first step towards the discovery and development of innovative immune-modulatory drugs.

Could you elaborate on the *de novo* Design Of Genuine Structures (DOGS) software?

DOGS is a tool for chemical 'scaffold-hopping', producing isofunctional but structurally-diverse new chemotypes. This property renders *de novo* design methods like DOGS premier computer-based techniques for idea generation in medicinal chemistry. Some of our original designs are in advanced development.





De novo revolution

Researchers from the Institute of Pharmaceutical Sciences at **ETH Zürich** are pioneering new methods for creating pharmaceutically active compounds from scratch using sophisticated computational techniques

THE 20TH CENTURY was the age of the medicinal compound. The world saw a whole cornucopia of new drugs come in to existence for the very first time, but over recent years development has slowed and even fallen into decline. In 2010, *Science* reported that AstraZeneca were pulling out of drug discovery in the entire field of neuroscience, including blockbuster areas they dominated in the 1990s such as pain and depression. GlaxoSmithKline soon followed suit, ending their drug discovery work in such important areas as schizophrenia, bipolar disorder, depression and anxiety. A comprehensive report delivered by Thomson Reuters last year declared we are now at the end of an era in terms of traditional drug discovery; after decades of growth, the drug industry entered decline in 2008 and has not yet recovered. R&D costs continue to rise while the blockbuster patents that bring in major revenue streams are now beginning to expire. For an industry with discovery in its DNA, this amounts to a major crisis. Since the 1990s, a sea change has been approaching that has the potential to shake the foundations of the way that new drugs come to fruition. Now, the tide is approaching and if a group of Zurich-based researchers are correct, it may soon be upon us.

BREAKING TRADITION

In the past, drug discovery was largely serendipitous; discoveries ranging from penicillin and chlorpromazine to lithium and even lysergic acid diethylamide (LSD) came into being largely by accident. More recently, technologies such as high-throughput screening (HTS) and fragment-based approaches have become the norm, but in many areas where progress is badly needed, development has hit a brick wall. The latest innovations in the field of drug discovery revolve around a central aim of using machine learning to identify new, never before seen chemical structures using a '*de novo*' design. Professor Gisbert Schneider outlined the concept in a perspective in *Nature Reviews in Drug Discovery* in 2010 titled 'Virtual screening: an endless staircase?'. The *de novo* term is a play on *in vivo* biology – experiments that take place inside living organisms – which in turn lead to *'in silico'* testing – experimentation in a virtual environment. *De novo* design is the creation of new compounds virtually using computational chemistry. The hope at this stage is that *de novo* approaches will be particularly valuable for hit-and-lead discovery.

NEW LANDSCAPES

Schneider leads a new interdisciplinary working group based at ETH Zürich that focuses on *de novo* drug design research and combines expertise from pharmaceutical chemistry and computer sciences. The group employs machine learning for hit-and-lead structure identification through virtual screening. Part of this work revolves around the construction of 'adaptive fitness landscapes'. It is already possible to profile the chemical properties of biochemical assays, however the Swiss team now aims to create new drugs differently by virtually assembling molecular building-blocks, guided by multi-objective 'fitness functions' that help navigate in chemical space towards regions of desired bioactivity.

To conclude, what is next for the computer program? Are you looking to develop this further, or turn your hand to a new research area?

For us, software development is a means to problem solving. Our interdisciplinary approach includes algorithm and software engineering in tight combination with chemical synthesis and biochemical testing. The central idea of our work is to combine smart computer algorithms, so-called autonomous systems, with medicinal chemistry and biological testing. This unique connection of chemical and biological space by using pattern recognition techniques has already resulted in several new drug targets and compounds combating life-threatening bacterial and viral infection.

Looking to the future, we envisage a seamless amalgamation of cutting-edge concepts in computational drug design and machine-learning methods with miniaturised lab-on-a-chip systems to explore opportunities for pharmaceutical research. Also, judging from current trends, next-generation drugs will be designed to be active on several receptors in parallel, and not just single-target orientated. This multi-dimensional view of biological and chemical systems is an ideal substrate for computer-based *de novo* drug design.

INTELLIGENCE

DESIGNING MOLECULES *DE NOVO*

OBJECTIVES

To develop and combine smart computer algorithms with medicinal chemistry and biological testing to discover new compounds for combating life-threatening diseases.

KEY COLLABORATORS

Dr Karl-Heinz Baringhaus, Sanofi-Aventis, Germany

Dr Edgar Jacoby, Novartis, Switzerland

Dr Jan Kriegl, Boehringer-Ingelheim, Germany

Dr Zoe Waibler, Paul-Ehrlich Institute, Germany

Professor Dr Silja Wessler, Paris-Lodron University of Salzburg, Austria

FUNDING

ETH Zürich • Swiss National Science Foundation Deutsche Forschungsgemeinschaft • European Commission Marie Curie Actions • Opo-Foundation Zürich • Industrial partnerships

CONTACT

Professor Dr Gisbert Schneider
Principal investigator

Eidgenössische Technische Hochschule (ETH)
Department of Chemistry and Applied Biosciences
Institute of Pharmaceutical Sciences
Wolfgang-Pauli-Str. 10
CH-8093 Zürich
Switzerland

T +41 44 633 73 27
E gisbert.schneider@pharma.ethz.ch

www.modlab.ethz.ch

PROFESSOR GISBERT SCHNEIDER studied biochemistry and computer science at the Free University of Berlin, Germany, where he received his doctoral degree in 1994. He joined Roche Pharmaceuticals in Basel, Switzerland, where he headed the Cheminformatics group until 2001. He received his Habilitation and Venia Legendi in biochemistry and bioinformatics from the University of Freiburg, Germany. From 2002-09 he was Full Professor of Chem- and Bioinformatics at Goethe-University Frankfurt, Germany. In 2010, Schneider joined ETH Zürich, Switzerland, as a Full Professor of Computer-Assisted Drug Design.

This presents colossal opportunities for drug development. Theoretically the number of organic molecules that could possibly be synthesised is estimated to exceed 10^{60}. This number is so extraordinarily great that any uncoordinated expansive exploration would be impossible. A traditional HTS campaign would only involve around a couple of million chemical compounds, a drop in the ocean in comparison to the sheer number of compounds theoretically available using *de novo* design. Schneider proposes to begin searching using what he calls a 'negative approach' by local optimisation tactics; this involves eliminating molecules that have known adverse properties or features, as opposed to initially seeking out molecules with positive characteristics and then working back.

RECENT SUCCESSES

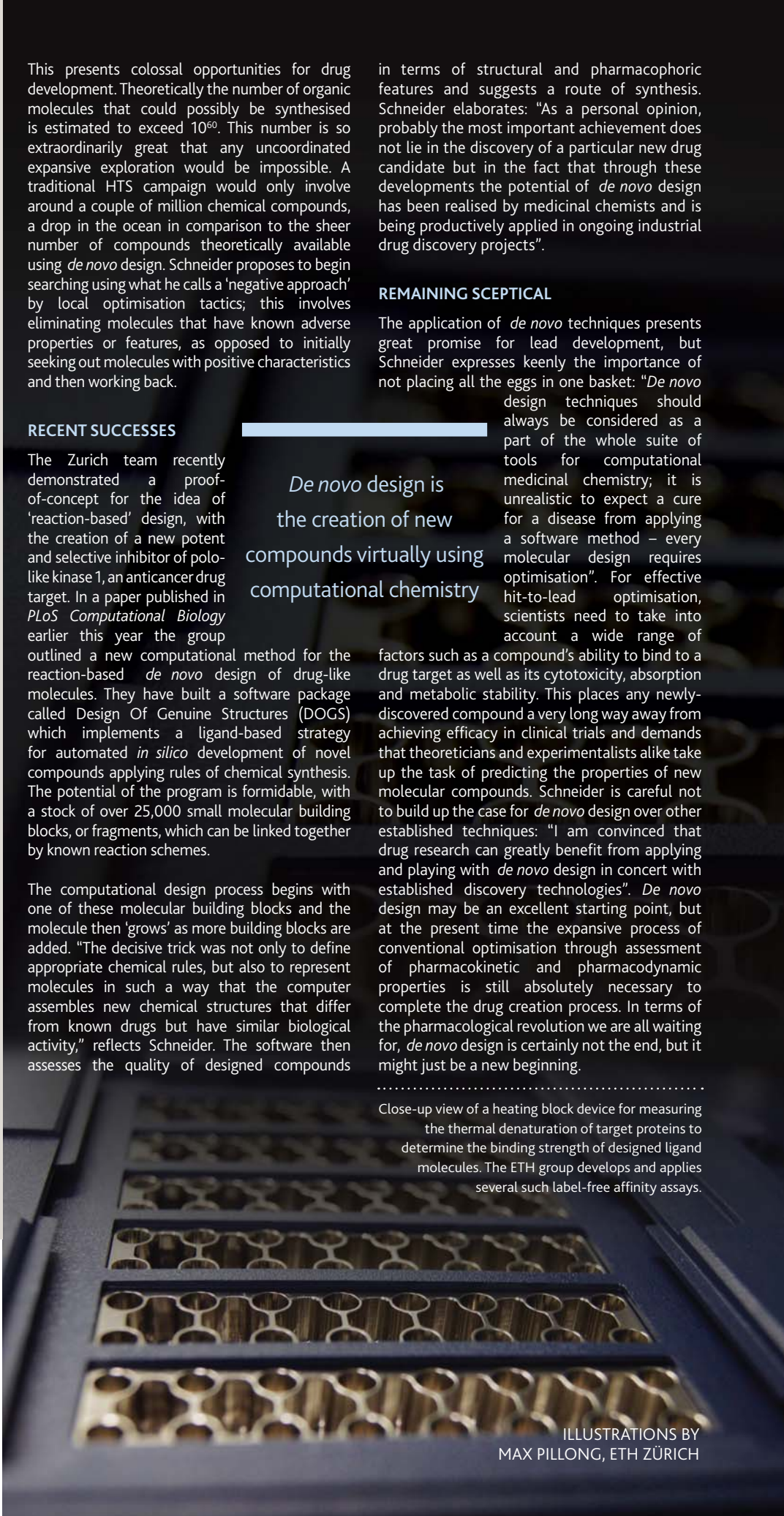
The Zurich team recently demonstrated a proof-of-concept for the idea of 'reaction-based' design, with the creation of a new potent and selective inhibitor of polo-like kinase 1, an anticancer drug target. In a paper published in *PLoS Computational Biology* earlier this year the group outlined a new computational method for the reaction-based *de novo* design of drug-like molecules. They have built a software package called Design Of Genuine Structures (DOGS) which implements a ligand-based strategy for automated *in silico* development of novel compounds applying rules of chemical synthesis. The potential of the program is formidable, with a stock of over 25,000 small molecular building blocks, or fragments, which can be linked together by known reaction schemes.

> *De novo* design is the creation of new compounds virtually using computational chemistry

The computational design process begins with one of these molecular building blocks and the molecule then 'grows' as more building blocks are added. "The decisive trick was not only to define appropriate chemical rules, but also to represent molecules in such a way that the computer assembles new chemical structures that differ from known drugs but have similar biological activity," reflects Schneider. The software then assesses the quality of designed compounds in terms of structural and pharmacophoric features and suggests a route of synthesis. Schneider elaborates: "As a personal opinion, probably the most important achievement does not lie in the discovery of a particular new drug candidate but in the fact that through these developments the potential of *de novo* design has been realised by medicinal chemists and is being productively applied in ongoing industrial drug discovery projects".

REMAINING SCEPTICAL

The application of *de novo* techniques presents great promise for lead development, but Schneider expresses keenly the importance of not placing all the eggs in one basket: "*De novo* design techniques should always be considered as a part of the whole suite of tools for computational medicinal chemistry; it is unrealistic to expect a cure for a disease from applying a software method – every molecular design requires optimisation". For effective hit-to-lead optimisation, scientists need to take into account a wide range of factors such as a compound's ability to bind to a drug target as well as its cytotoxicity, absorption and metabolic stability. This places any newly-discovered compound a very long way away from achieving efficacy in clinical trials and demands that theoreticians and experimentalists alike take up the task of predicting the properties of new molecular compounds. Schneider is careful not to build up the case for *de novo* design over other established techniques: "I am convinced that drug research can greatly benefit from applying and playing with *de novo* design in concert with established discovery technologies". *De novo* design may be an excellent starting point, but at the present time the expansive process of conventional optimisation through assessment of pharmacokinetic and pharmacodynamic properties is still absolutely necessary to complete the drug creation process. In terms of the pharmacological revolution we are all waiting for, *de novo* design is certainly not the end, but it might just be a new beginning.



Close-up view of a heating block device for measuring the thermal denaturation of target proteins to determine the binding strength of designed ligand molecules. The ETH group develops and applies several such label-free affinity assays.

ILLUSTRATIONS BY MAX PILLONG, ETH ZÜRICH

IPW Institute of Pharmaceutical Sciences

ETH Eidgenössische Technische Hochschule Zürich Swiss Federal Institute of Technology Zurich