Healthcare industry BW

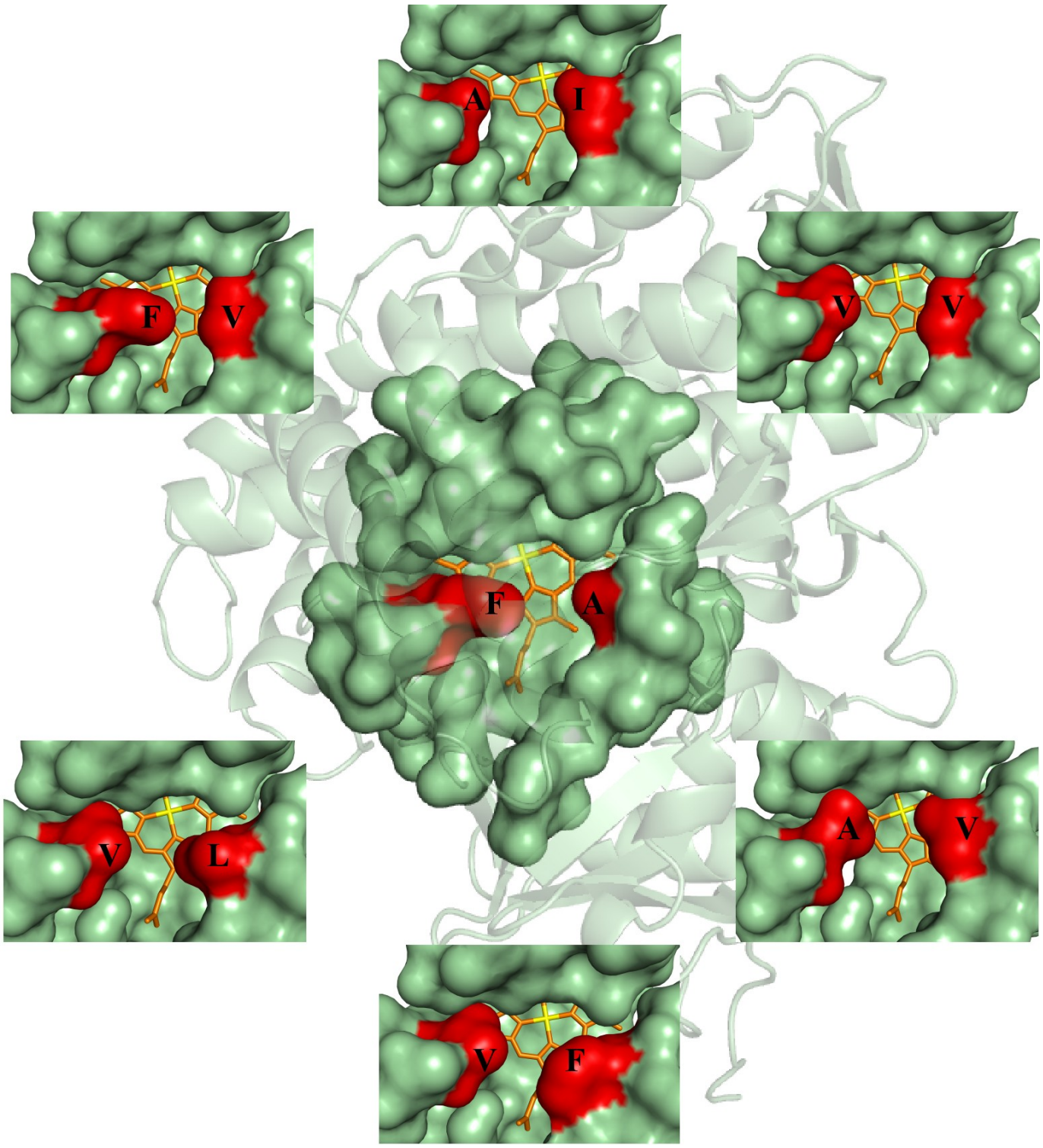
Molecular design made to measure and the requirements

Biomolecules such as peptides and nucleic acids can nowadays be synthesised relatively quickly and inexpensively. In addition, great progress has been made in the development of methods enabling the directed mutagenesis in microorganisms. These two developments have boosted the design of new, and the reorganisation of known, molecules. Moreover, these help in the utilisation of certain molecule functions in research and in the industrial production of substances and active agents. Molecular design has also become an important process in medicine and environmental technology.

Subtle sterical changes in the three-dimensional structure of a molecule can have far-reaching consequences for one or several of the molecule's functions. The shape of molecules is not only determined genetically, but is also determined through their environment wherein the chemical environment and physical conditions, such as pressure and temperature, are important parameters. Moreover, other molecules can affect the structure of a biomolecule, for example in order to enhance, attenuate or completely inhibit a molecule's particular function. In this process, the interplay of influences and interactions can be extraordinarily complex.

Even if a molecule's structure and all environmental parameters are known, it is still possible to modulate its function, since biomolecules are dynamic and because the movement of their constituents underlies certain degrees of freedom. The molecular oscillations can be so strong as to enable the binding pockets of proteins to close or open. Even if a molecule is present in its 'proper' three-dimensional structure, this does not necessarily mean that a potential binding partner can in any case come into contact with it.

These associations already reveal the challenges faced by designers of new molecules. A huge amount of data needs to be acquired in order to be able to describe all the natural states of a molecule and its interactions with other molecules. Such a huge amount of data can only be acquired with the help of modern bioinformatics, which is a field that has been growing in importance in recent years. For example, researchers at the Centre for Bioinformatics at the University of Tübingen are developing special software programmes that enable the discovery of new pharmaceutically active molecules or modify known active agents so that they can be oriented to specific research questions. These software programmes are used to model and simulate certain situations and conditions based on existing knowledge. The "BALL" software package developed by the researchers from Tübingen is available free of charge to interested scientists. The bioinformaticians from Tübingen are already working towards "Second Life" in order to enable experts from all around the world to work simultaneously with a virtual 3D molecule.



Access to the catalytically active haem group (yellow) in a bacterial monooxygenase enzyme can be modified by introducing mutations into the two "hotspots" (red). The shape of the binding site in six highly selective mutants differs from the binding site of the naturally occurring enzyme (centre). Fig.: Seifert A, Vomund S, Grohmann K, Kriening S, Urlacher VB, Laschat S, Pleiss J: Rational design of a minimal and highly enriched CYP102A1 mutant library with improved regio-, stereo- and chemoselectivity. ChemBioChem. 2009. 10: 853-861. Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced with permission.

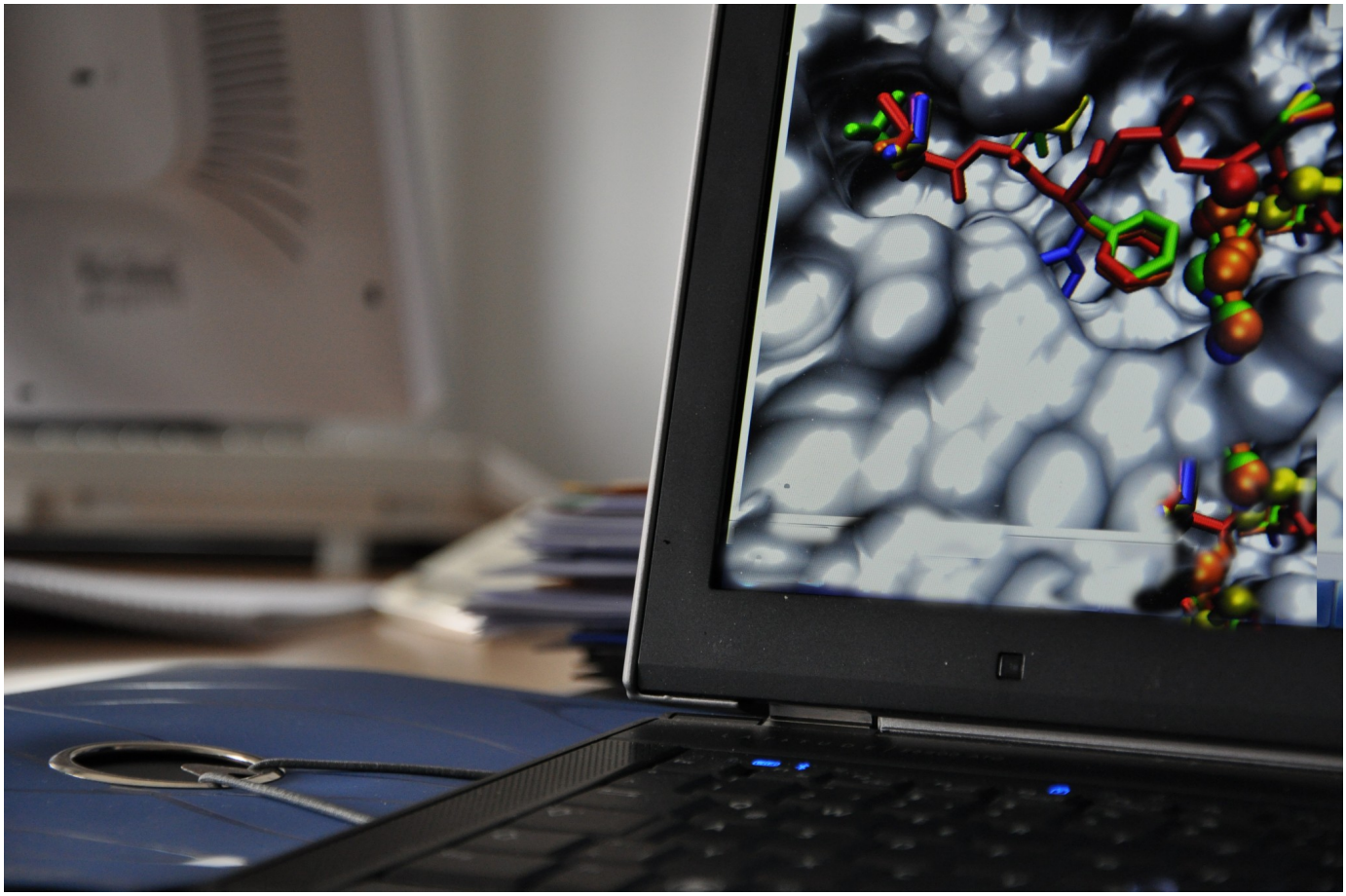
"Virtual Screening" reduces the design efforts considerably

Computers are also required to design new and optimised enzymes that are used in industrial production and the production of pharmaceuticals, such as biocatalysts. For example, researchers at the Institute of Technical Biochemistry at the University of Stuttgart optimise substrate binding

pockets on the computer in order to increase an enzyme's selectivity for certain substrates. Subsequently, enzyme modifications are modelled in silico in order to design enzymes that highly selectively produce only one stereoisomer of a certain product.

The "Molecular and Cellular Modelling" group at EML Research gGmbH in Heidelberg has been dealing with macromolecules since 2000. The group is mainly focused on proteins and develops computer-assisted methods to predict and simulate biomolecular interactions.

Hardness test in the laboratory



Virtual screening has become an important method in computer-based drug research.

Whether the researchers design a medical compound or a biocatalyst, all molecular designs that have stood their test in virtual simulations need to be tested on a small scale in the laboratory before they are ready for application. The scientists are often faced with surprising discoveries. Not all new or modified molecules stand a hardness test in the laboratory. If a newly designed molecule does not work as expected, it will once again be tested in a virtual environment. This is not as bad as it may sound, because the scientists usually have several suitable candidates available that were previously selected based on database searches.

The researchers can specifically look for molecules or molecule fragments in 3D databases containing structural data that fit into a certain reaction site in a target molecule or are complementary with it and have the sought-after sterical and electrochemical properties. 'Virtual screening' is gaining in importance as the knowledge about molecules and their functional principles increases. Virtual screening helps to limit the number of active molecules that need to be tested in the laboratory to between 50 and 1,000.

Structural data are often obtained from the analysis of X-ray diffraction patterns resulting from the irradiation of crystallised molecules. X-ray diffraction patterns help to determine the exact positions of the atoms and deduce the duration and angle of binding. However, not all proteins can be crystallised easily, which is also why other methods are used to elucidate the proteins' structure. NMR spectroscopy, a specialty of the "NMR Core Facility" at the University of Constance, provides an alternative and complementation to other methods. The nuclear magnetic resonance spectroscope produces a broad range of information about the chemical connections of the molecules analysed and about their interactions with their molecular environment.

De novo molecular design – in the footsteps of evolution

Sometimes, mathematical algorithms are used to imitate evolutionary developments and thereby enable the de novo design of biomolecules for use as medical compounds. These mathematical algorithms involve sequential cycles of accidental mutagenesis and selection. The recombination of genes can also be reproduced with computers.

The non-evolutionary de novo design does not necessarily involve the new combination of atoms. If possible, known structural fragments of different length are combined. In the case of medical compounds, the crystal structure of a target molecule serves as reference structure. Care needs to be taken that the new molecule fits spatially into the crystal structure of the target molecule and that it interacts specifically with the target structure.

Molecular design is not always only used for the search for new active compounds or the optimisation of a certain reaction. A group of researchers led by Prof. Dr. Willi Bannwarth from the Institute of Organic Chemistry and Biochemistry at the University of Freiburg deals with the expansion of the genetic code in order to introduce non-natural amino acids at specific protein positions. One of the researchers' goals is to evaluate the site and efficiency of expression by analysing the reaction of the non-natural amino acids with a fluorescent dye.

Combining and testing

Combinatorial chemistry is a procedure that for many decades has been used to design new molecules. Moreover, it has been gradually optimised. The chemical residues of a molecule's backbone are altered or newly combined. The method is based on solid-phase synthesis in which the starting molecule is bound to a resin and exposed to an excess of certain binding partners in different solutions. Depending on the protocol used, this leads to a broad range of new compounds that are collected in compound libraries. In the laboratory, sometimes also with the help of computers, molecules with the sought-after characteristics are subsequently selected from the compounds contained in such libraries. High-throughput screening is an important tool to identify novel chemical entities.

Dossier

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