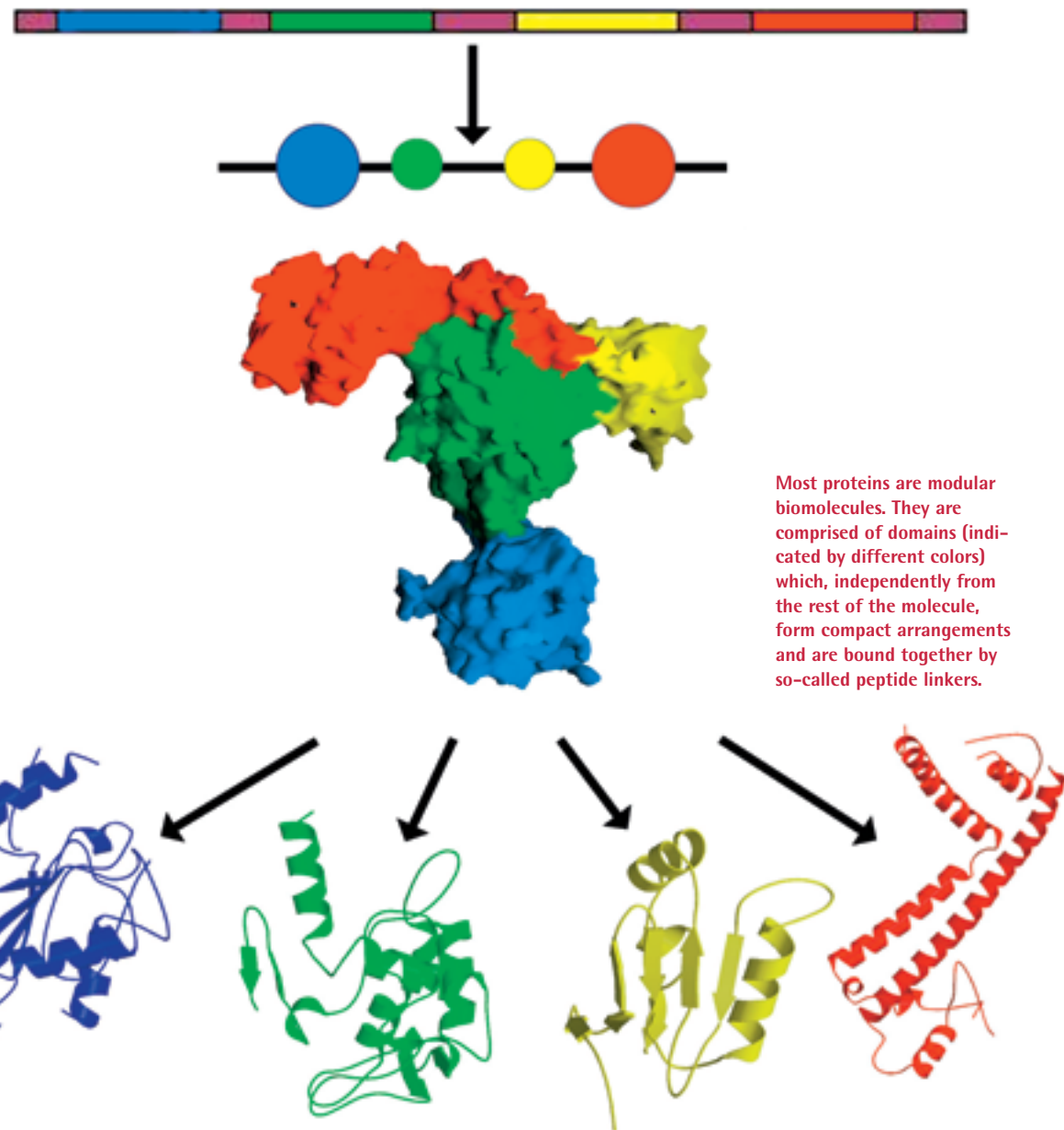


Making New Drugs from Old Recipes

In the search for pharmaceuticals, the orientation, if possible, is based on natural models – on molecules that control biochemical processes in animals and plants. The group of scientists headed by **HERBERT WALDMANN**, Director at the **MAX PLANCK INSTITUTE FOR MOLECULAR PHYSIOLOGY** in Dortmund, draw inspiration from such evolutionally proven structures, using them as “blueprints” for developing new drugs.



If I want to develop new biological-ly or medicinally active compounds, I must aim to hit the galaxy rather than stumble around in intergalactic space.” The person saying this is neither a medic nor an astronomer, but first and foremost an organic chemist and, since 1999, Director at the Max Planck Institute for Molecular Physiology in Dortmund. And when he says this, Herbert Waldmann criticizes a fundamental credo of pharmaceutical research of the last ten years: by using a robot, a “compound library” can be synthesized in a very short time – sometimes in just a few days.

Such a compound library may contain more than a million different compounds that more or less originate according to chemical feasibility. Using similarly computer-controlled high-throughput screening systems, the library for new medical drugs is searched – substances that, for example, block a receptor, resulting in the rise or fall of blood pressure. According to theory, if the libraries are large enough, new drugs can be found with this method relatively quickly and inexpensively. “In reality, this rarely works,” says Waldmann. Hardly any drug that has entered the market in the last few years has been discovered through this approach.

In fact, despite huge advances in molecular biology and technology, the yield of new pharmaceuticals seems to have been particularly lean in the last ten years. “It has merely been shown that the molecules from conventional, combinatorially derived libraries are seldom biologically relevant,” stresses Waldmann. “And that is precisely what we want to change.”

That is why the Dortmund chemist and his colleagues began a few years ago to synthesize small molecule libraries based on biologically active natural substances and molecules that resemble natural substances. The researchers define natural substances as chemical compounds with low molecular weight that are produced by living organisms. Instead of relying on the “law of numbers,” as in conventional combinatorial chemistry, the scientists invest a healthy portion of gray matter in both the choice of their starting molecule and in steering the reactions. They definitely do not exclusively enlist simple chemical reactions that are easy to automate, but develop complex transformations that allow natural substance synthesis on solid supports – an essential technique in modern drug research.

SEARCHING FOR CLUES IN THE CHEMICAL UNIVERSE

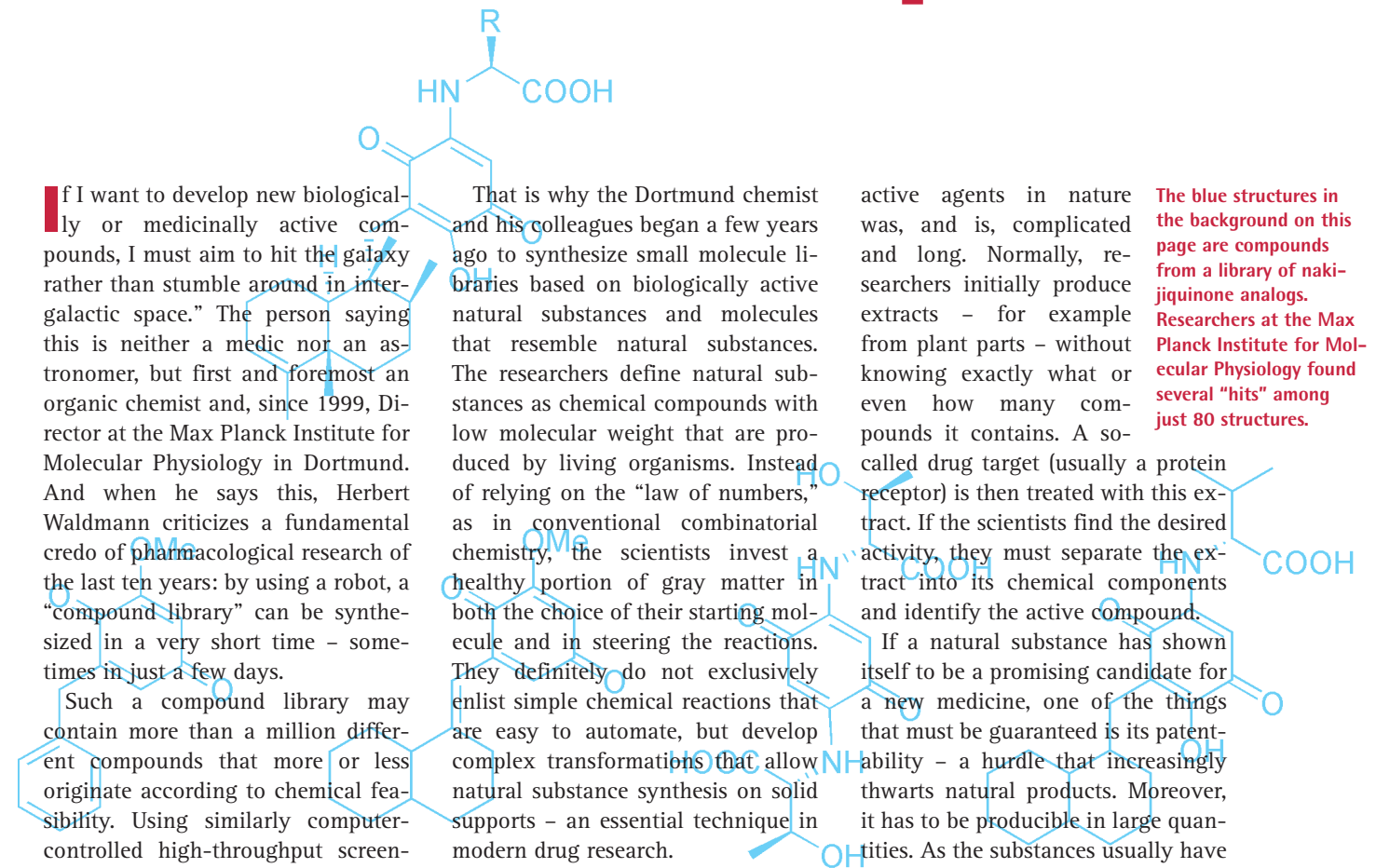
Herbert Waldmann calls the results of this method “natural compound-driven substance library development.” He adds: “All this is, of course, considerably more complex and takes longer than conventional combinatorial chemistry, but the process delivers higher quality and relevance – and our hit rates are also significantly higher.”

More than half of all the pharmaceuticals available today are natural compounds, natural compound derivatives or developments stimulated by natural compounds; in fact, in the case of antibiotics and anti-cancer drugs, the figure is closer to three quarters of all preparations. This suggests a general “comeback” for natural compounds in drug development. However, the search for new

active agents in nature was, and is, complicated and long. Normally, researchers initially produce extracts – for example from plant parts – without knowing exactly what or even how many compounds it contains. A so-called drug target (usually a protein receptor) is then treated with this extract. If the scientists find the desired activity, they must separate the extract into its chemical components and identify the active compound.

If a natural substance has shown itself to be a promising candidate for a new medicine, one of the things that must be guaranteed is its patentability – a hurdle that increasingly thwarts natural products. Moreover, it has to be producible in large quantities. As the substances usually have a complex structure, this implies the development of complicated multi-step synthesis procedures.

The blue structures in the background on this page are compounds from a library of naki-jiquinone analogs. Researchers at the Max Planck Institute for Molecular Physiology found several “hits” among just 80 structures.



Clear strategy: In contrast to traditional combinatorial chemistry, Herbert Waldmann and his colleagues take a targeted approach to compiling their libraries.

PHOTOS: FALK SIEBAND / GRAPHICS: MPI FOR MOLECULAR PHYSIOLOGY



The Dortmund scientists are developing new and complex procedures for synthesizing natural substances on solid supports.

Which is why, at the beginning of the 1990s, the arrival of computers and synthesis robots in pharmaceutical labs was celebrated as a huge achievement. Combinatorial chemistry was faster and cheaper than natural substance synthesis. And speed was now also essential for a completely different reason: molecular biologists were identifying new target receptors at breathtaking rates – and chemists were expected to keep pace in synthesizing new lead compounds. Yet the new robots could cope with only comparatively simple chemical reactions, and therefore produced relatively simple, small molecules. As a result, they embodied only a tiny part of the “chemical universe.” Specialists coined this term to define a multi-dimensional spatial structure with a coordinate system made up of chemical properties, where each molecule – according to its structure and properties – represents one point.

Hardly surprising in this context is the result of a study conducted and published by the Bayer company in 1999. The study compared natural compounds with synthetically produced substances and found that natural compounds have, on average, a higher molecular weight, fewer hydrogen, halogen and sulfur atoms, and instead, more oxygen atoms. In addition, they have a more complex spatial structure and possess, for example, more ring structures and chiral centers (for example,

carbon atoms bonded to four different atoms or atom groups).

Compound libraries that reflect as many properties of natural products as possible should be more biologically relevant and consequently more medically useful. This assumption spurred Herbert Waldmann and his team to try out new methods to develop combinatorial libraries. “Natural compounds are substances that have already proven their biological worth,” stresses Waldmann, “and this fact should definitely be taken advantage of.” After all, organisms do not produce natural compounds without a reason. On the contrary: in the course of evolution, they are selected and optimized to fulfill important physiological tasks – mostly to specifically interact with particular protein receptors.

Medications fulfill precisely the same task in the human body. They accumulate, in an ideal case selectively, at protein-binding sites and so activate or block particular metabolic processes. Since, in this sense, they are based on the same active principle, it is not surprising that penicillin, for example, which is produced by mold, functions in humans as an antibiotic, or that morphine, which is found in plants, works as a painkiller. These substances meet proteins with matching binding sites in other organisms – and lock onto them there.

NATURE RELIES ON VERSATILITY

The age-old observation that many natural products not only bind to their original target protein, but also to human proteins can now be explained by scientists at a molecular level. They have found that most proteins are modular biomolecules made up of individual domains – three-dimensional elements that resemble a sphere, a barrel or a loop, as well as other forms. For example, while there are several hundred thousand different human proteins,

researchers now estimate that only about one thousand different folding types exist for domain families. Consequently, similar domains turn up in different proteins. “When things are produced that can be used over and over again, that is efficient,” comments Waldmann. “Furthermore, there is good reason for favoring certain three-dimensional structures: they are physically very stable.” Interestingly, similar domains can be constructed from similar amino acid sequences (the building blocks of every protein), although this is not necessarily inevitable.

All this opens up new opportunities in the search for new active compounds in medicine. For example, if an inhibitor, or opponent, is known for a protein with a particular domain, then there is at least a valid suspicion that it – or slightly altered analogs – may inhibit other proteins that contain the same or a very similar domain. That is why the Dortmund-based Max Planck scientists are investigating a particular kinase called HER-2/Neu receptor tyrosine kinase; this enzyme is produced in unusually high amounts in more than a third of all primary breast, ovarian and stomach tumors. As yet, scientists know of only one group of substances, the nakijiquinones, that occur naturally and inhibit this kinase.

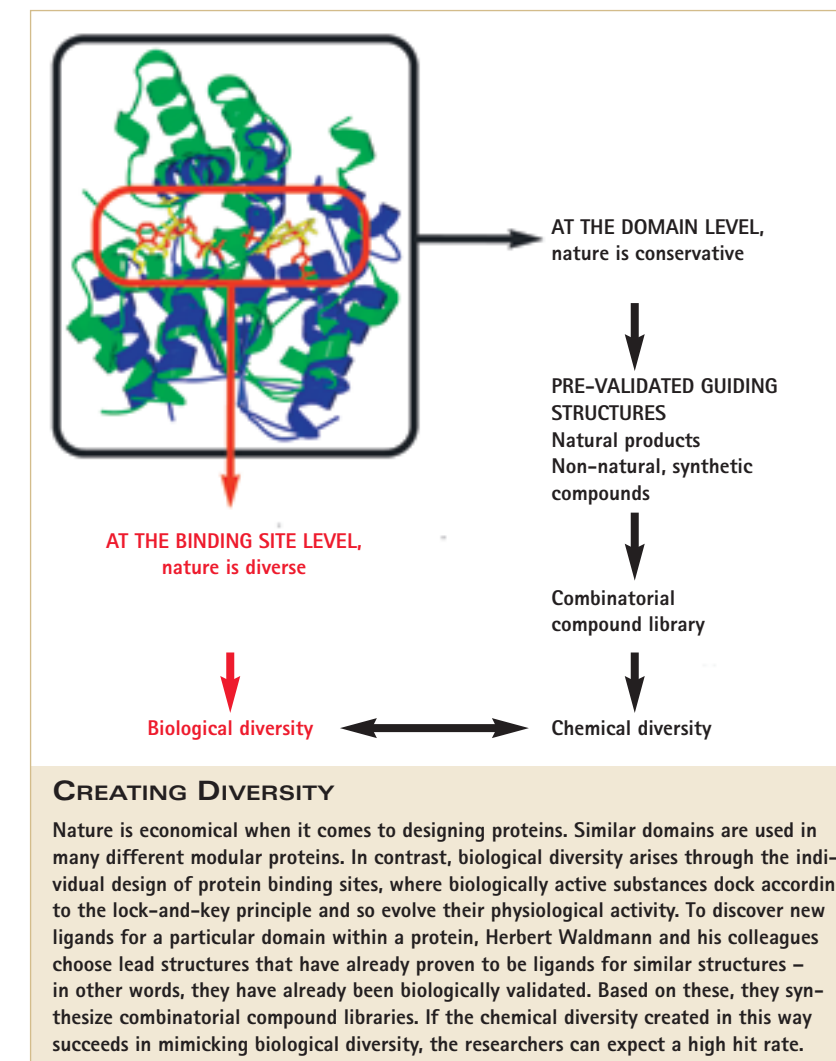
Using the basic nakijiquinone structure as the starting point, researchers synthesized a compound library of around 80 analogs and subsequently tested whether these compounds inhibited a further, similarly medically relevant group of receptor kinases for which there is as yet no suitable inhibitor. The result was amazing: although none of the naturally occurring nakijiquinones affected the enzymes analyzed, the comparatively tiny library produced several analogs with significant activity. The scientists even succeeded in selectively inhibiting a kinase that plays a significant role in blood ves-

sel formation and thus in cancer growth. “If we had tested only natural substances, we would never have found this new inhibitor type,” says Herbert Waldmann. “This means that compound libraries do, in fact, have to be created, but they don’t necessarily have to be very large.”

While, in this case, Waldmann and his colleagues developed other kinase ligands from known kinase inhibitors, the method also functions with enzymes that catalyze different reactions – assuming, of course, that they possess the same domains. For example, the Dortmund researchers took the basic structure of a naturally occurring phosphatase inhibitor and developed a compound library with around 250 analogs. Among these, they found 10 compounds that inhibit dehydrogenase or esterase. “Based on 3-D data, we knew that the enzymes were made up of similar domains, even though they catalyze different reactions. So far, we have been able to show five times that the method also works in such cases,” says Waldmann.

Ideally, therefore, when searching for new ligands, the scientists require information only about the particular protein’s domain architecture, not about its function. This structural data is anything but easy to determine with conventional methods. “However, advances in bioinformatics are ensuring that we can figure out more and more protein domains from the amino acid sequence data alone,” says Herbert Waldmann.

The chemist also wants to use bioinformatics for a completely different project. He is convinced that nature works rationally, and not only in the creation of protein domains: “We suspect that basic types similarly exist among small molecules with biological activity, and that natural substances are built up according to the conservation principle to some extent.” Using computer analyses, Waldmann wants to



search for such basic types. “According to the latest information, the majority of all proteins exhibit only about a thousand folding types. Working on the principle of analogy, we want to determine how many basic structures are needed to categorize, for example, 90 percent of all natural substances.”

CHEMISTS AND BIOLOGISTS AS LIBRARIANS

These structures would then be ideal starting points for combinatorial libraries that should provide – at least in theory – a wealth of new biologically active substances, and perhaps even medicinal agents. “Our current goal is to build up 20 different libraries, each with 500 analogs

based on the basic structure of natural substances,” explains Waldmann. His group has already synthesized the first few.

The fact that chemists and biologists have doubts about the success of their projects now and then does not dampen the ambitious chemist’s plans. “We will not be in a position to solve every biological or medical problem with our libraries,” Waldmann willingly admits. Rather, there will be systems where the scientists will be successful and others where they will not be. “However, it will be exciting to see what the ratio between these two cases turns out to be,” says the scientist, with a smile that leaves no doubt as to how he assesses the situation. UTE HÄNSLER