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New construction kit for designing new proteins

Protein building blocks with well-defined properties that can be assembled into new molecules with desired structures and functions are highly sought after in biotechnology and medicine. Birte Höcker, a biologist at the Max Planck Institute for Developmental Biology in Tübingen, is currently working on this in a project she calls "Protein Lego".

Dr. Birte Höcker's "Protein Lego" study was recently granted a European Research Council Consolidator Grant.
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What if you could take protein fragments with known structures and capabilities, and recombine them at will into new functional units such as enzymes, drugs or biosensors? This is the dream of protein biochemistry that could become reality in the not-too-distant future. Or at least that is what Dr. Birte Höcker from the Max Planck Institute for Developmental Biology in Tübingen believes.

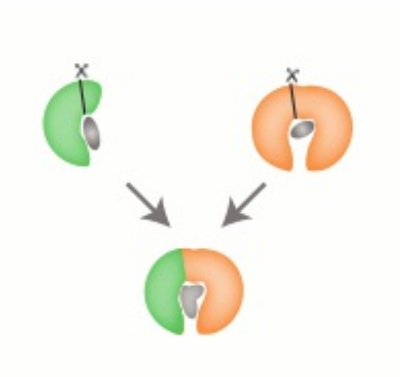
Her "Protein Lego" project has been awarded an ERC (European Research Council) Consolidator Grant that will provide her with around two million euros for a period of five years. Supported by three doctoral students and one technical assistant, Höcker is aiming to use the time and money to develop a functional protein construction kit.

The particularity about Höcker's building blocks is that they will need to be as small as possible. Rather than using complete functional domains, she is seeking to recombine small protein fragments into functional proteins as if she were building a construction kit. The key to this is a database-based research of protein evolution across the animal, plant and microbe kingdoms.

"We are analysing individual amino acid sequences to identify highly conserved areas. We have already identified several highly conserved sequences in completely different domains. I think that these are the units that evolution has used as building blocks for creating the wide diversity of proteins," explained the researcher.

Evolutionary trees of proteins are therefore a fast track to perfecting protein design. If the evolutionary trees reveal the repeated appearance of certain amino acid sequences in a large number of branches, such sequences, it is assumed, could be functionally and/or structurally relevant even in very different proteins. Höcker is hoping to identify these fragments and use them for her construction kit. This cannot be done without bioinformatics or the establishment of a database where information about all protein fragments is stored. This database is an important linchpin of the whole project and the researchers are therefore working hard to develop it.

Birte Höcker worked on computer-based protein design while she was doing her postdoctoral research in the USA, which makes things a lot easier now. "I was also involved in the development of software programmes, so I was well-versed in the subject. So now I am able to do this kind of research independently," said the biologist.



Schematic representation showing how the combination of fragment building blocks makes it possible to design proteins with new functions.

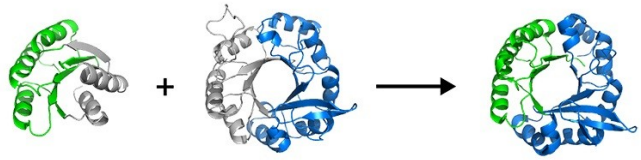
Protein Lego only works with the help of computers

However, Höcker is not just hoping to establish a comparative database with as many structural fragments as possible. She also wants to make the database available to everybody, which is why it has to have a web-based design. In addition, the researchers are continually switching between laboratory work and computers, as all theoretical findings need to be confirmed experimentally. This means that it must be proven in the laboratory that the fragments can be recombined into new proteins with the desired functions. The Protein Lego project is therefore specifically focused on recombining and optimising fragments virtually and in practice. "An important question, for example, is whether certain protein folds are accidentally similar or whether they are actually related to one another and have already been used as building blocks as the different proteins evolved," says Höcker.

Höcker's Protein Lego approach differs fundamentally from the principle of directed evolution, which is a popular method in protein engineering. Directed evolution is a method that evolves proteins towards a defined goal. The method starts off by subjecting a gene to numerous rounds of mutagenesis, and then selecting mutants with the desired function. However, directed evolution is not what Höcker is ultimately seeking: "We want to use a computer-based approach to create starting points for new and efficient enzymes much more quickly than evolution is able to do."

Learning from evolution: the relationship of sequence, structure and function

On the level of basic research, Höcker hopes that her work will also contribute to finding out why



A new protein can be designed from the fragments of two different protein folds (green and blue), first in silico and then in the laboratory.

proteins fold the way they do. "I would like to understand how the sequence determines the structure," said Höcker. The database will connect all structural knowledge and additional important information. It will reveal the fragments that interact with each other and the underlying functional options. For example, her research might show why a specific building block combination is a suitable binding site for other molecules.

"I want to achieve three levels of complexity. First, I have the plan to build stable structures, second, I then hope to derive a function. Third, I would like to produce combinations. We will have to find out on a case-by-case basis how much fine-tuning is necessary," said Höcker well aware that this may lead to unexpected combinations. The more complex a protein is, the greater the possibility that unexpected constellations can arise. As is always the case, the whole can be more than the sum of its parts. But it is precisely this complexity that the project aims to study.

Article

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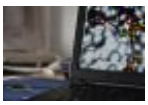

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