Light and peptides: New method diversifies natural building blocks of life

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Sunlight experiment. The reactions can be performed using the light from the sun in a simple glass flask. Credit: J. Waser/EPFL

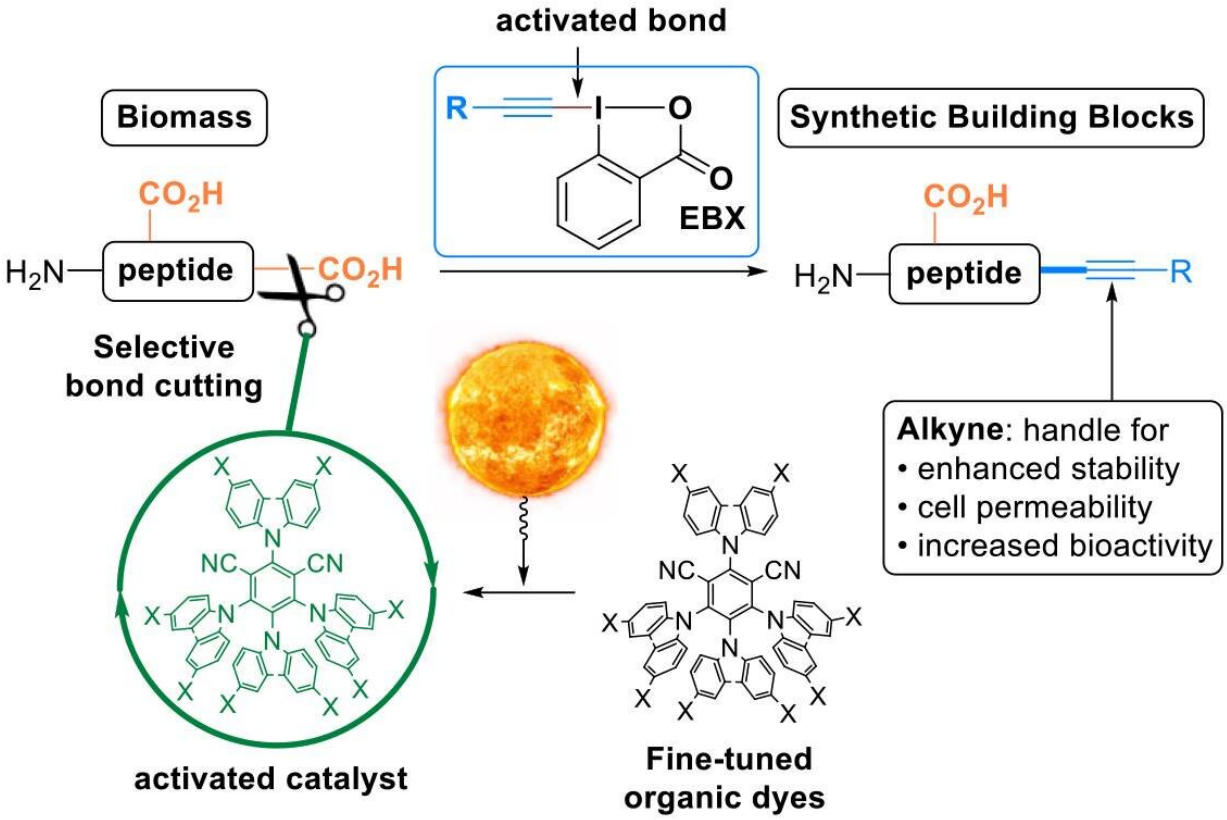
Discovering new biological targets is a critical part of our ongoing battle against diseases. Over the years, scientists have made impressive progress towards the understanding of biological systems, constantly identifying novel targets. The structural diversity of these targets requires a broad range of different therapeutic agents.

"Small synthetic molecules are still key players, but biomolecules such as peptides, proteins and oligonucleotides have become an important area of research," says Professor Jérôme Waser, director of EPFL's Laboratory of Catalysis and Organic Synthesis. Peptides are particularly interesting, with about 140 evaluated in clinical trials in 2015. However, peptides often are not stable in the blood and cannot permeate cells well, both of which diminish their potential use as drugs.

One solution to overcome these difficulties is chemically modifying the natural structure of peptides, a process called "functionalization". In chemistry, a molecule is "functionalized" by adding chemical groups to it, thus endowing it with new functions, capabilities, or properties, such as enhanced stability in the human body. However, functionalization of peptides is difficult, due to their complex structure.

"The main reason is the lack of selectivity when you try to modify a peptide: it contains many positions that react with chemicals, resulting in useless mixtures," explains Waser. "Therefore, methods enabling selective functionalization of a single position in peptides are actively sought-after to access more efficient ant stable peptide-based drugs."

This is what Waser's lab has now achieved, using "EBX reagents" – a class of very reactive organic compounds developed by the group and now commercially available. Using those reagents, the researchers converted the C-terminal carboxylic acid of peptides into a carbon-carbon triple bond – an alkyne (in chemical jargon a "decarboxylative alkynylation"). The alkyne moiety is a very valuable functional group that can be used to further modify the peptides. It has been used extensively in drug discovery, material sciences and chemical biology.



Bridging the natural and the synthetic world in one step: Modification of peptides using organic dyes excited with visible-light and EBX reagents. Credit: J. Waser/EPFL

Peptides do not spontaneously react with EBX reagents, so the scientists had to use a catalyst. In order to activate it, the researchers turned to light or, in more technical terms, "photoredox catalysis": visible light is absorbed by the catalyst, which then selectively activates one bond in the reacting molecules. "Using light as a renewable energy source to perform organic reactions allows a temporal and spatial resolution with very mild reaction conditions," says Waser.

The researchers made two innovations: First, they designed novel fine-

tuned organic dyes as photoredox catalysts. This was important as light-mediated reactions are based usually on rare, toxic and expensive transition metal catalysts.

Second, the researchers achieved this first "decarboxylative alkynylation" on native peptides. This is an especially attractive one-step transformation of a natural compound into a synthetic derivative as it offers a platform for modifying the physical and chemical properties of the peptide through a single, easy to perform manipulation (all the "ingredients" just need to be mixed up and let to stand in natural light).

The method can be used with almost all amino acids present on the peptides, while maintaining complete selectivity towards the C-terminal position over the peptide side-chains.

With their new method, the scientists were also able to obtain derivatives from the valuable bioactive peptide GRGDNP that blocks cells from attaching to fibronectin, an important process in the vasodilatation of blood vessels, which could be very useful in the study of cardiovascular disease.

More information: Marion Garreau et al. C-Terminal Bioconjugation of Peptides through Photoredox Catalyzed Decarboxylative Alkynylation, *Angewandte Chemie International Edition* (2019). DOI: 10.1002/anie.201901922

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