Researchers develop a method to examine millions of potential self-produced drug candidates in one go

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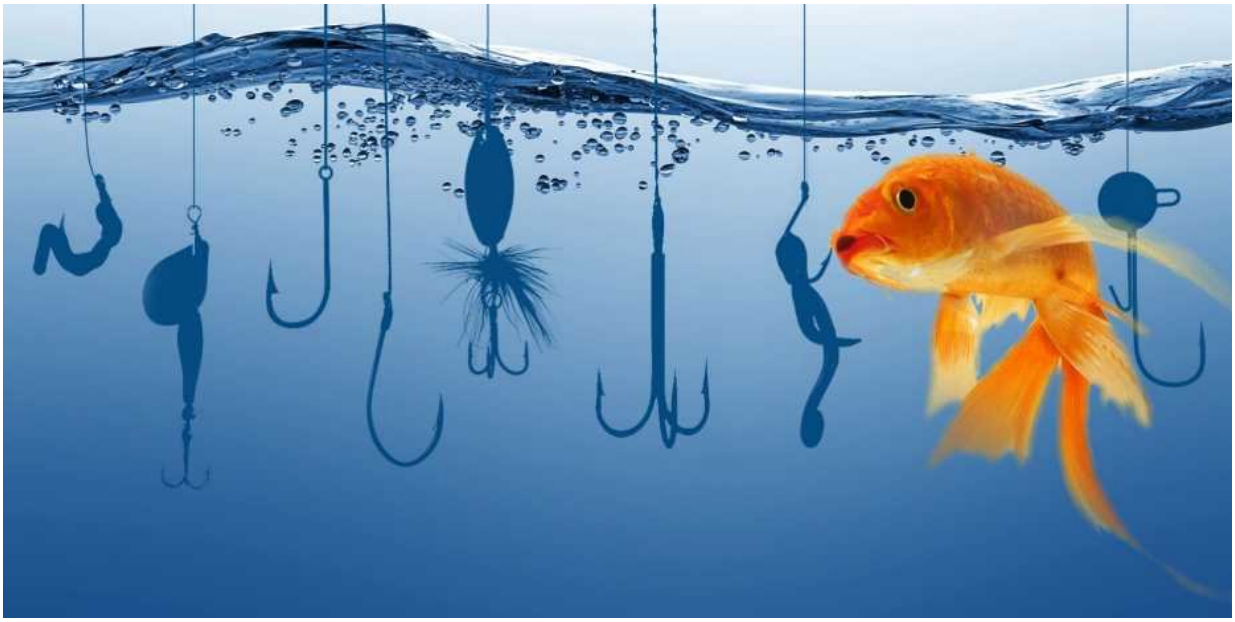

With a large collection of "fishhooks", ETH chemists are trying to catch the fish in a highly specific way, i.e. a molecular target. Credit: ETH Zurich / Morris Köchle

Searching for new drugs is like fishing in the dark: the prospect of catching something is very uncertain, and it requires patience, skill and – of course – money. ETH researchers led by Dario Neri have developed a new screening method that speeds up the search for drugs, making it

cheaper and more efficient, as they reported in the journal *Nature Chemistry*.

At the centre of the method is a new DNA-encoded chemical library (DECL) that contains 35 million different drug candidates. Such collections are nothing new, but the structure and scope of the substances contained in this one are something special.

Stable basic structure, varied attachments

Each of the drug candidates contained in the collection consists of a stable ring-shaped basic structure borrowed from the work of Manfred Mutter from the University of Lausanne. The chemists then attached three different small molecules to one side of each ring. "Together, they form a kind of highly-specific fish hook that can bind onto a protein if its form perfectly matches the protein's structure," says Jörg Scheuermann, who is currently finishing his habilitation thesis on DNA-encoded chemical libraries in Dario Neri's group. The researchers used hundreds of such molecules, combining them in various ways to create a library of 35 million different "fish hooks."

The researchers encoded the blueprint of the three molecules in three short DNA sequences, in which the DNA was chemically tied to the reverse of the basic structure. This artificial piece of genetic material works like a barcode, which the scientists can use to identify each fish hook individually.

Thirty-five million fish hooks tested at once

With their chemical collection, the researchers could then start fishing: to find out if a target protein would be caught on one of the "fish hooks," the researchers put the collection of all 35 million compounds in a

reaction vessel containing the protein on a carrier. After a certain amount of time, the researchers washed the chemical collection away. All the drug candidates that did not bind to the protein were thereby removed; the ones that "stuck" to the protein remained in the sample, and could then be identified via their DNA barcodes. In this way, the researchers were able to very quickly test the whole collection for potential matches in one go.

The ETH researchers led by Dario Neri and Jörg Scheuermann have already been working on DECLs for years. The foundations for the principle of DNA-encoding were first laid by the Scripps researchers Richard Lerner and Nobel Prize winner Sidney Brenner at the beginning of the 1990s, but the idea was not converted into practice for a decade. ETH Professor Neri and his colleague David Liu from Harvard University took up the idea again at the beginning of the 2000s. Seven years later, the researchers presented the first such DNA-encoded chemical collection containing more than a million candidates (as reported by ETH Life).

Closer to antigen-antibody interaction

DECL technology has caught on in the pharmaceutical industry in recent years, not least because it is inexpensive as well as highly efficient. "The design of our DECL is based on the fact that we wanted to generate a new molecule form that would be functionally equivalent to an antibody reduced to its minimum size, and therefore accessible via chemical synthesis," says Scheuermann. "By using molecules that possess three or more chemical hooks, we come closer to antigen-antibody interactions."

One potential treatment approach could involve linking a cytotoxin to a specific protein binder (as a small-molecule drug conjugate or SMDC). This would then use the protein to recognise a foreign or tumour cell, attach to it and release the toxin in a high local concentration, which

would cause the death of the tumour cell. Previously, this strategy has been implemented with antibodies as antibody-drug conjugates (ADC). "However, as antibodies are relatively large, they were not able to penetrate tumour tissue well; small molecules should be able to accomplish this better," explains Scheuermann. The researchers were recently able to test this research on the new kinds of DECLS and the new treatment concept as part of the SNF Sinergia project "Drugs of the future."

More information: Yizhou Li et al. Versatile protein recognition by the encoded display of multiple chemical elements on a constant macrocyclic scaffold, *Nature Chemistry* (2018). DOI: 10.1038/s41557-018-0017-8

Dario Neri et al. DNA-Encoded Chemical Libraries: A Selection System Based On Endowing Organic Compounds with Amplifiable Information, *Annual Review of Biochemistry* (2018). DOI: 10.1146/annurev-biochem-062917-012550

Samuele Cazzamalli et al. Chemically Defined Antibody– and Small Molecule–Drug Conjugates for in Vivo Tumor Targeting Applications: A Comparative Analysis, *Journal of the American Chemical Society* (2018). DOI: 10.1021/jacs.7b13361

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