New technique for developing drugs to treat serious illnesses

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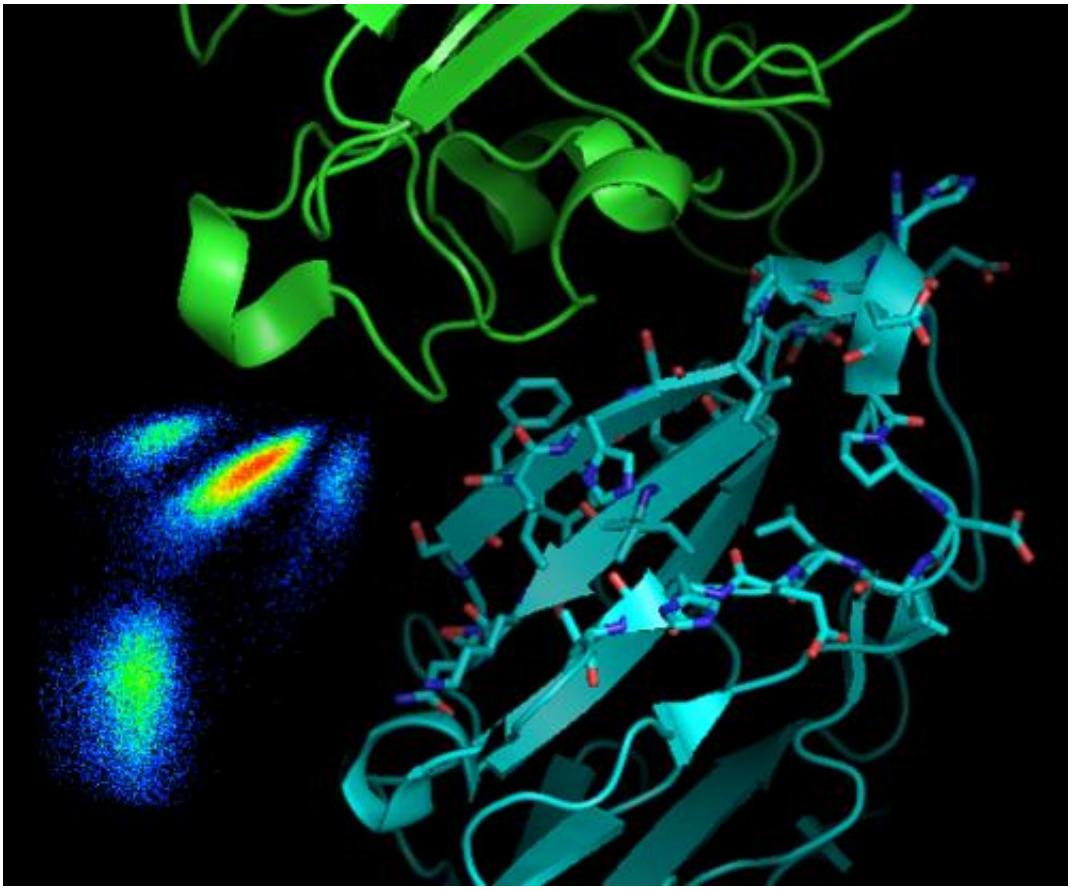

The image shows a flow cytometer plot of sub-populations of cells expressing variants of the target protein created in the process of evolving the ligand trap. The structure of the binding interface being evolved is also depicted. Credit: WA Barton et al 2006 *Nat. Struct. Mol. Biol.* 13 524-532.

An international team of researchers led by the University of Leicester has "harnessed the power of evolution" to create a new drug for possible use against heart disease, inflammation and other illnesses.

Researchers in the Department of Cardiovascular Sciences and Department of Biochemistry at the University of Leicester, together with colleagues in Cambridge, the USA and Italy, have employed a new technique to create protein-based drugs.

According to Professor Nick Brindle, the lead researcher: "This technique harnesses the power of evolution to engineer specific functions into a protein, such as the ability to neutralise a toxin or to activate healing.

"This involves making a particular cell type generate millions of different variants of our protein, selecting the variants that have improved properties and then repeating the cycle until the protein has been changed to a form with the exact properties we want."

To show how the method works, the group took a protein normally found in the body and evolved it into a form that can block a molecule involved in blood vessel growth and inflammation.

This new protein, called a ligand-trap, is now being developed as a potential therapeutic for treating heart disease, inflammation and other illnesses.

Said Professor Brindle: "The idea that you can evolve proteins into forms that do what you want is not new, but it has been very difficult to do this for many of the complex proteins that we want to use as drugs or for other applications.

"This new approach promises to make engineering of such proteins not

only possible but relatively easy. In addition to medicine, these specifically evolved 'designer proteins' have a wide range of applications in the chemical, pharmaceutical, and agricultural industries.

"This is a big step forward. We are hoping that, over the next five years or so, this new protein can be developed into a form that could be used to treat inflammation and other conditions."

The work, being published in the *Journal of Biological Chemistry*, was funded by the Biotechnology and Biological Sciences Research Council (BBSRC), MRC and the Wellcome Trust. The Leicester team collaborated principally with Dr Julian Sale at the MRC Laboratory of Molecular Biology in Cambridge, with additional input from Dr Hiroshi Arakawa in Italy and Dr Jean-Marie Buerstedde at Yale.

Professor Brindle said: "We are really excited about getting this technique to work and are already using it to make other new molecules that we think will be useful to people. It was a real bonus for us to be able to evolve the ligand trap using the technique as this trap targets a molecule that is involved in a whole range of health problems."

Provided by University of Leicester