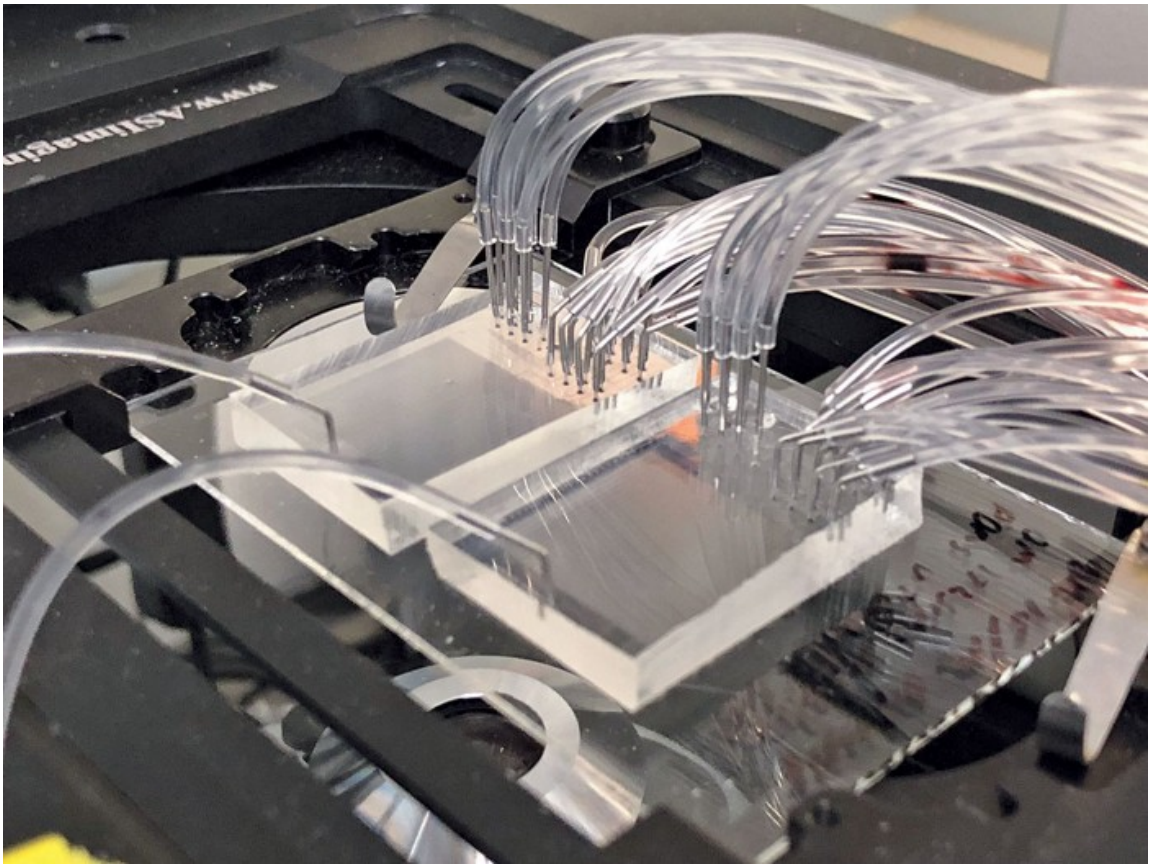
MICROFLUIDICS

High-throughput enzymology

Microfluidic device makes, purifies, and assays 1,500 different mutants at the same time

by ***Laura Howes***

July 26, 2021 | A version of this story appeared in **Volume 99, Issue 27**



Credit: Craig Markin

These microfluidic devices, each the size of a small microscope slide, can make 1,500 enzymatic mutants and then assay them.

Machine learning can now predict how a protein might fold, and chemists have uncovered how many enzymes work their catalytic magic, but enzymologist Daniel Herschlag saw the need to develop methods for large-scale studies of how the sequence of individual amino acids in proteins affects their function. So the Stanford University researcher teamed up with Stanford microfluidics expert Polly Fordyce to develop a high-throughput tool for studying enzymatic activity. They built a microfluidic device the size of a microscope slide that simultaneously makes up to 1,500 different variants of an enzyme before purifying them and performing characterization experiments (*Science* 2021, DOI: **10.1126/science.abf8761**). To test this setup, the team created 1,036 different mutants of PafA, an alkaline phosphatase enzyme. Over multiple rounds of experiments, the researchers assembled physical data such as substrate specificity, catalytic constants, and inhibition rates for each version of the enzyme created. These parameters helped the Stanford team to understand which amino acids in PafA contribute to the enzyme's activity, even if they were far away from the active site. Fordyce says the device will allow

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enzymologists to quickly create and characterize any enzyme as long as they can design in vivo fluorescent assays for it. That means the device should help researchers explore how naturally occurring enzymes with distinct amino acid sequences differ, how to tweak enzymes designed in the lab to improve their activity, and uncover drug targets.

Chemical & Engineering News
ISSN 0009-2347

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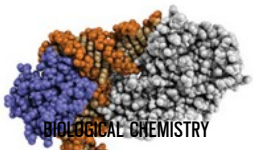

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