A Machine That Spits Out Peptides

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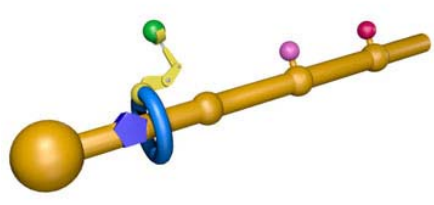
A ribosome-inspired molecular machine for building peptides has been introduced. How does it work? Find out...

Simple motors and switches have dominated the world of molecular machinery for years, but now a more advanced model is poised to take over. For the first time using synthetic materials, scientists have created an artificial ribosome-inspired molecular machine that can string amino acids together into a chain.

"We've made a molecular machine that's able to build other molecules. You just set the machine up and let it stitch things together," said David Leigh, an organic chemist at the University of Manchester, UK and author of a paper published today in *Science* that describes the machine (1). "That's quite a complex process; it shows we can now design molecular-sized machines that will do complicated tasks."



Leigh and his team designed a tiny synthetic thread just a few nanometers long, studded with three amino acids. Around the thread they looped a molecular ring with a tiny reactive arm. Source: Leigh

Previously, scientists have built both synthetic molecular machines that performed mechanical work and biological molecular machines—made from DNA, proteins, or other biomolecules—that performed simple functions. But none of these machines has performed a task as complex as those that occur naturally in cells such as building proteins from amino acids using a messenger RNA (mRNA) code, the main function of the ribosome.

Leigh and his team designed a tiny synthetic thread just a few nanometers long, and covalently attached three amino acids. Around the thread they looped a molecular ring with a tiny reactive arm.

Then the researchers turned their machine on. Through random Brownian motion, the ring bumped into the first amino acid on the thread. It stayed there until its reactive arm picked up the amino acid through native chemical ligation and deposited it at a specific site on the reactive arm called the peptide elongation site.

With the barrier of that first amino acid removed, the ring moved along the thread to the next amino acid where it once again paused. Its arm then picked up this amino acid and linked it to the first one. It repeated this process for the third amino acid as well, forming a peptide.

"Since the ring can only meet the building blocks in the order they appear on the track, that gives the synthesis sequence integrity," says Leigh.

In the experiment, the scientists ran 1018 of these tiny machines in parallel, isolating milligrams of the peptide at the end of the 36-hour operation. Using tandem mass spectrometry, the team confirmed the peptide sequence.

Although reporting the formation of a three amino acid peptide in the paper, Leigh's group has since used the machine to create a four amino acid peptide in other experiments. Now his lab is working towards linking even more amino acids together with the goal of building a complete protein.

When comparing the machine to a natural ribosome, Leigh said that their molecule is "still much simpler" and "doesn't do the same job in anywhere near as sophisticated a fashion."

But in the end, Leigh believes these machines will have applications in chemical and pharmaceutical manufacturing. "If we can come up with molecular factories where molecules actually make themselves using molecular machines, that's bound to have, in the long-term, great benefits in terms of efficiency and effectiveness," says Leigh.

References

1. Lewandowski, B., G. De Bo, J.W. Ward, M. Papmeyer, S. Kuschel, M.J. Aldegunde, P.M.E. Gramlich, D. Heckmann, S.M. Goldup, D.M. D'Souza, A.E. Fernandes, and D.A. Leigh. 2013. Sequence-specific peptide synthesis by an artificial small-molecule machine. Science 339:189-193.

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