Paving the way for new peptide-based therapeutics with novel method of phage display

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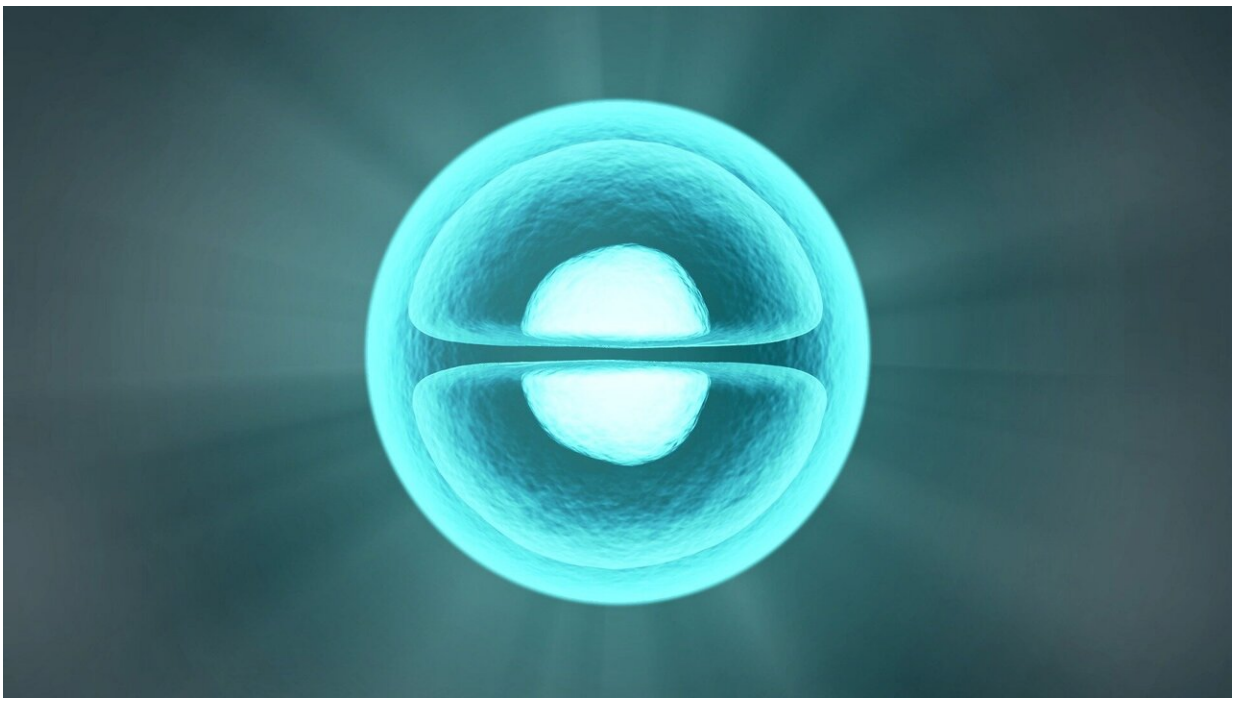

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Chemists at Texas A&M University are taking a p[h]age from bacteria's playbook in order to beat viruses at their own game and develop new drugs to fight cancer and a host of other human diseases in the process.

For decades, scientists have relied on phage display—a technique used to identify novel peptide ligands, or peptides that bind to other proteins or molecules—as a versatile tool in a variety of applications ranging from drug discovery to materials science. A team led by Texas A&M chemist and 2018 Texas A&M Presidential Impact Fellow Dr. Wenshe R. Liu has learned a new trick from an old master, bacteria, successfully harnessing its ability to make short peptides containing noncanonical amino acids (ncAAs) that equip them with special properties, such as enzyme degradation resistance and targeted protein binding capabilities.

Using a clever strategy to "trick" the system so that only viruses containing peptides with ncAAs are capable of reproducing, the Liu research group has found a way to stack the phage display library construction deck, effectively expanding the genetic code of bacteriophages and paving the way for new peptide-based therapeutics. Their findings were published Friday (March 13) in the journal *Nature Communications*.

"Utilizing unnatural amino acids, we greatly expand the utility of phage display for identifying new peptide therapeutics," Liu said.

Phage display is one of several tools that scientist rely on to find new peptides with potential use as drugs to treat diseases, explains 2018 Texas A&M chemistry Ph.D. graduate Dr. Jeffery M. Tharp, a postdoctoral associate at Yale University and lead author on the team's paper, the third thus far representing his thesis work at Texas A&M. In addition, it is one of the first from the Texas A&M Drug Discovery Laboratory, founded by Liu and fellow Texas A&M chemists in 2018.

"Phage display uses viruses, or phages, to 'fish out' specific peptides from a pool of millions of different peptide variants; however, it is very difficult to use this technique to find peptides containing ncAAs," Tharp added. "In our paper, we developed a new method of phage display that

allows for easy retrieval of potential peptide drugs containing diverse ncAAs. In addition, we used our new technique to identify novel peptides containing ncAAs that are very strong inhibitors of sirtuin 2—an enzyme that is involved in regulating human lifespan and is a promising drug target for the treatment of human cancers."

The Liu group collaborated with the Laboratory for Molecular Simulation (LMS), including Texas A&M chemistry Ph.D. candidate and LMS interim manager Andreas Ehnbom and Texas A&M High Performance Research Computing Associate Director Dr. Lisa M. Pérez, who performed the molecular dynamics simulations that enabled the team to understand the selectivity involved for specific peptides.

"The beauty of this work, at least in my mind, is that it crosses multiple disciplines of chemistry—synthetic chemistry, chemical biology and computations," Ehnbom said.

Tharp notes that the founders of phage display were awarded the 2018 Nobel Prize in Chemistry in recognition of the technique's versatility, relative ease of use and effectiveness across myriad disciplines. In combination with the resulting new molecules, he predicts the Liu group's new method will be similarly useful for all applications of phage display.

"This technique allows ncAAs with unique structures to be incorporated into the phage peptides, which can help identify more potent peptide drugs," Tharp added. "In addition, we can include reactive ncAAs into the phage peptides, which can potentially be used to make better materials and drug delivery systems."

Tharp says the team will continue to use their new phage display technique to search for other peptides containing ncAAs that inhibit enzymes related to human disease while continuing to develop other

methods that expand its utility.

More information: Jeffery M. Tharp et al, An amber obligate active site-directed ligand evolution technique for phage display, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15057-7

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