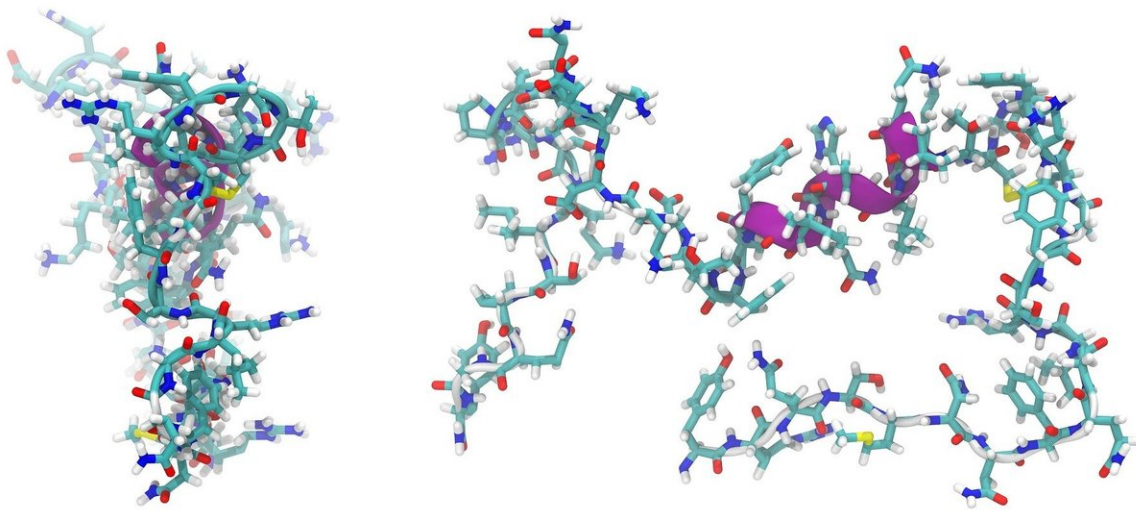


# Researchers show 'encrypted' peptides could be wellspring of natural antibiotics

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While biologists and chemists race to develop new antibiotics to combat constantly mutating bacteria, predicted to lead to 10 million deaths by 2050, engineers are approaching the problem through a different lens: finding naturally occurring antibiotics in the human genome.

The billions of base pairs in the genome are essentially one long string of code that contains the instructions for making all of the molecules the body needs. The most basic of these molecules are amino acids, the

building blocks for [peptides](#), which in turn combine to form proteins. However, there is still much to learn about how—and where—a particular set of instructions are encoded.

Now, bringing a computer science approach to a life science problem, an interdisciplinary team of Penn researchers have used a carefully designed algorithm to discover a new suite of antimicrobial peptides, hiding deep within this code.

The study, published in *Nature Biomedical Engineering*, was led by Cesar de la Fuente, Presidential Assistant Professor in Bioengineering, Microbiology, Psychiatry, and Chemical and Biomolecular Engineering, spanning both Penn Engineering and Penn Medicine, and his postdocs Marcelo Torres and Marcelo Melo. Collaborators Orlando Crescenzi and Eugenio Notomista of the University of Naples Federico II also contributed to this work.

"The human body is a treasure trove of information, a biological dataset. By using the right tools, we can mine for answers to some of the most challenging questions," says de la Fuente. "We use the word 'encrypted' to describe the [antimicrobial peptides](#) we found because they are hidden within larger proteins that seem to have no connection to the immune system, the area where we expect to find this function."

Antimicrobial peptides (AMPs) are small, naturally occurring molecules, produced by almost every living organism. Because of their ability to defend the body from infection, identifying new AMPs has been an active area of research, but traditional search methods, mostly based on chemical intuition and experimentation, have limited the discovery of peptide antibiotics beyond conventional AMPs.

"In this study, we applied a new way of using AI for antibiotic discovery in previously unrecognized places. What better place to start than by

exploring our very own biological information, the collection of genes and proteins that make us who we are," says de la Fuente.

The researchers' approach started with the physiochemical characteristics all AMPs have in common: They are 8 to 50 amino acids in length, positively charged, and possess both hydrophobic and hydrophilic parts. This new method operates like a search function to identify peptides with antimicrobial properties in genomes and proteomes.

"Imagine you want to find a specific word in a huge Word document such as an encyclopedia. You would simply use the search function, set the parameters for the text you are looking for, and the algorithm would rapidly highlight all of the areas in the document that match," says de la Fuente. "That's essentially the approach we took when searching for [new antibiotics](#). We knew the sort of molecules we were looking for, and utilized the algorithm to act like a search function to find them throughout the human body".

The algorithm searched the proteome, the complete set of proteins in the body, and returned 43,000 peptides of 8 to 50 [amino acids](#) in length, many of which were found in a new region of the proteome all together. This wide scope of potential antimicrobials was then filtered to 2,603 peptides based on their fitness function inclusive of all the parameters.

To validate the antimicrobial properties of these algorithm-derived peptides, 55 were synthesized and exposed to eight different pathogens including *E. coli* and bacteria that cause staph infection and pneumonia.

"We found that 63.6% of these 55 encrypted peptides displayed antimicrobial activity," says de la Fuente. "Interestingly, these peptides not only fought off infection by some of the most harmful bacteria in the world, they also targeted gut and skin commensal organisms that are

beneficial to us. We speculate that this could be indicative of a microbiota modulating role that these peptides may possess as well."

The team also tested the ability of the peptides to act synergistically and found that cocktails of peptides derived from the same biogeographic area within the body were able to potentiate their individual ability to fight off infection by 100-fold.

"This synergistic effect is likely already happening in our bodies," says de la Fuente. "Some of the peptides discovered by our algorithm exhibited antimicrobial activity at levels that are physiologically relevant. These molecules are found throughout the body, including the immune system. A surprising finding was that these peptides were not only encoded in the [immune system](#) but were also found in the digestive, circulatory, and nervous systems, for example, indicating that fighting off infections caused by invading organisms may be a more holistic approach than previously thought."

When tested *in vivo* in relevant preclinical mouse models, these peptides again proved to fend off infection, decreasing the bacterial load by three orders of magnitude, an ability on par with known potent antibiotics and AMPs. Additionally, using these peptides as antibiotics in the mouse models did not lead to any signs of toxicity.

As one of the main concerns of antibiotic discovery, bacterial resistance was the next challenge the researchers addressed.

"Because these encrypted peptides have potential to be applied as natural antibiotics, we need to understand how they influence the mutation of bacteria to understand if they will promote resistance," says de la Fuente. "What we found was that these encrypted molecules attack bacteria by permeating their outer membranes, an integral organelle for survival. This more damaging membrane permeation would require a great

amount of energy and multiple generations of mutations to create resistance in bacteria, indicating that these newly discovered peptides are good candidates for sustainable antibiotics."

By understanding that certain proteins under certain circumstances can be cleaved to secrete encrypted peptides, we can improve our understanding of the [human body](#)'s ability to naturally protect itself against infection while conserving energy at the genomic level, where one gene encodes for one protein, which can perform many useful functions beyond its initial physiological role.

"This work highlights that every organism is a dataset of code to which AI can be applied to find relevant molecules," says de la Fuente. "This tool can potentially be applied to 'omes' other than the genome and proteome, such as the transcriptome and metabolome, to quickly and thoroughly search a wide range of places for those molecules, whether they be antimicrobial, anti-cancer or anti-viral, opening new doors in many areas of drug discovery and molecular research."

**More information:** Cesar de la Fuente-Nunez, Mining for encrypted peptide antibiotics in the human proteome, *Nature Biomedical Engineering* (2021). [DOI: 10.1038/s41551-021-00801-1](https://doi.org/10.1038/s41551-021-00801-1).  
[www.nature.com/articles/s41551-021-00801-1](https://www.nature.com/articles/s41551-021-00801-1)

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