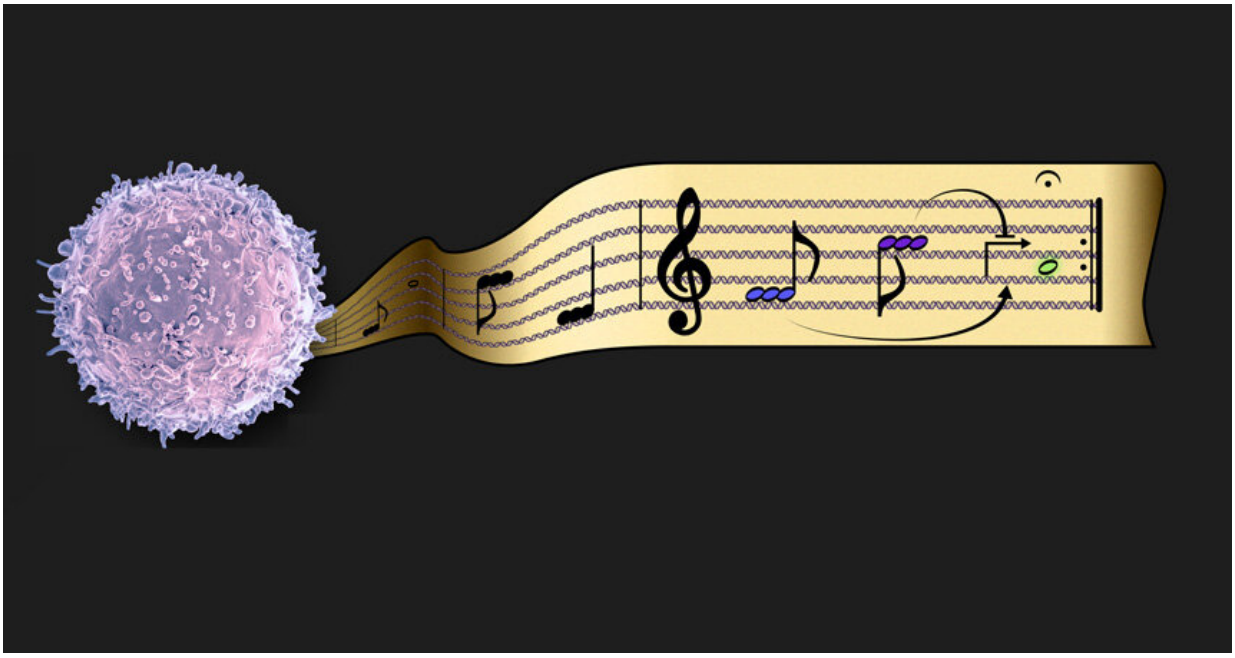
New platform for composing genetic programs in mammalian cells

February 7 2020



Credit: Joshua Leonard, Hailey Edelstein, Patrick Donahue, and Joe Muldoon, Northwestern University. Cell image by NIAID/NIH, used and modified under Creative Commons 2.0 license. DNA brush by James Hedberg, used and modified under CC0.

A new synthetic biology toolkit developed at Northwestern University will help researchers design mammalian cells with new functionalities.

The toolkit, called the Composable Mammalian Elements of

Transcription (COMET), includes an ensemble of synthetic transcription factors and promoters that enable the design and tuning of gene expression programs in a way not previously possible. The result could be new therapies for difficult-to-treat diseases, like cancer.

"Our long-term goal is enabling bioengineers to build customizable cell-based therapies and boiling a design goal down into a genetic program requires suitable biological parts. Building this COMET toolkit was an important step towards enabling us to truly design new functions in mammalian cells," said Josh Leonard, associate professor of chemical and biological engineering at Northwestern University's McCormick School of Engineering, who led the research. He is also a member of Northwestern's Center for Synthetic Biology.

The results were published February 7 in the journal *Nature Communications*.

Creating new technology to tune cells

Synthetic biology researchers look to reprogram cells by changing their DNA to give them new functionality. While researchers have had success reprogramming the DNA of bacteria cells to create new therapeutics and chemicals, mammalian cells currently are more difficult to modify because of their complicated underlying biology.

Powerful tools like CRISPR-Cas9 can edit single genes within these cells, but those tools do not allow researchers to readily create more nuanced, sophisticated functionality that requires introducing and often finetuning novel genetic networks.

Leonard and his team are interested in developing cell-based therapies—like reprogrammed cells that find tumors in the body and treat cancer at the sites of disease—but realized that they needed to

develop a toolkit to construct many of the functionalities that could be most useful. Recent advances in the field have paved the way for identifying desirable therapeutic functions, even within the context of such a complicated system, and the key challenge was figuring out how to modify a cell to carry out those tasks.

"The therapies we develop require sophisticated technologies," said Patrick Donahue, a graduate student in Leonard's lab and first author of the paper. "There was an opportunity to develop one such technology to expand the functions we can implement in a mammalian cell. So, as I was starting my Ph.D., we sat down and asked, 'What characteristics would we want in a transcription engineering toolkit?'"

A new library to advance the field

The group then worked to develop a library of promoters and transcription factors—which copy DNA into RNA—that enable the design and tuning of gene expression. The authors characterized these components and how they work together in order to enable precise tuning of gene expression levels. They also developed a mathematical model that explains how the system works.

"For a synthetic biology technology, having a mathematical model is essential for enabling reusable and predictable modules that other researches can apply and expand upon. We model this principle in the COMET system," said Neda Bagheri, who collaborated with Leonard. Bagheri is associate adjunct professor of chemical and biological engineering at Northwestern and a Distinguished Washington Research Foundation Investigator at the University of Washington Seattle.

Now, Leonard and his team are working to use the platform to build biological systems that can carry out sophisticated functions, like delivering therapies directly to tumors. That involves programming a cell

to be able to evaluate its environment to determine whether tissue is healthy or cancerous.

A key mission for the group is making this new technology readily available to other groups, so that others can both expand COMET and use it to further research across multiple fields. The prepublication paper on bioRxiv has already received much attention, and the biological parts will be distributed as a kit by Addgene.

"COMET will enable researchers to test hypotheses that weren't otherwise possible to test, helping us both build useful biotechnologies and improve our understanding of complicated processes, like immune function or development. In emerging technical fields like synthetic biology, creating technology platforms is vital for sparking innovation. We're excited to see what COMET will enable our community to do next," Leonard said.

More information: Patrick S. Donahue et al, The COMET toolkit for composing customizable genetic programs in mammalian cells, *Nature Communications* (2020). DOI: 10.1038/s41467-019-14147-5

Provided by Northwestern University