# Discovery

Research at Princeton 2018-2019

PRINCETON UNIVERSITY

# Finding meaning
## among the junk

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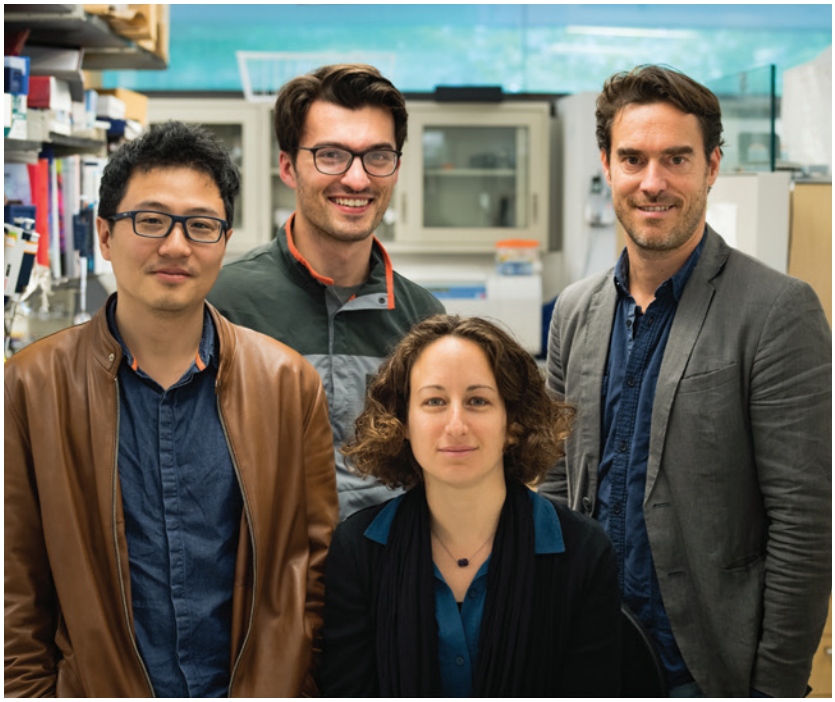

Thomas Gregor and his team are exploring how pieces of DNA once thought of as junk are involved in the regulation of other genes. From left: Hongtao Chen, Lev Barinov, Michal Levo and Thomas Gregor.

Genes make up only about 10 percent of the human genome. The other 90 percent? Once called "junk DNA," researchers now know that this genetic material contains on-off switches that can activate genes. But how these segments, called enhancers, find and activate a target gene in the crowded environment of a cell's nucleus is not well understood.

Researchers have now filmed the enhancers as they find, connect and activate genes in living cells. The study was published in the journal *Nature Genetics* in July 2018 by an international team led by Thomas Gregor, an associate professor of physics and the Lewis-Sigler Institute for Integrative Genomics.

The malfunction of gene activation causes the development of many diseases, including cancer.

"The key to curing such conditions is our ability to elucidate underlying mechanisms," Gregor said. "The goal is to use these rules to regulate and re-engineer the programs underlying development and disease processes."

Since enhancers are sometimes located far from the gene they regulate, researchers have been puzzled by how the two segments find each other. Previous studies conducted on non-living cells provided only snapshots that omitted important details.

In the new study, researchers used imaging techniques developed at Princeton to track the position of an enhancer and its target gene while simultaneously monitoring the gene's activity in living fly embryos. Hongtao Chen, an associate research scholar and lead author on the study, attached fluorescent tags to the enhancer and its target gene. He also attached a separate fluorescent tagging system to the target gene that lights up when the gene is activated.

Video of the cells let researchers observe how two regions of DNA interact with each other, said Michal Levo, a postdoctoral research fellow. "We can monitor in real time where the enhancer and the gene are physically located and simultaneously measure the gene's activity in an attempt to relate these processes," she said.

The researchers found that physical contact between the enhancer and gene is necessary to activate transcription, the first step in reading the genetic instructions. The enhancers stay connected to the gene the entire time it is active. When the enhancer disconnects, gene activity stops.

Their observations contradict a favored hypothesis known as the "hit-and-run model," which suggested that the enhancer does not need to stay attached to the gene during transcription.

The team discovered that sometimes the enhancer and gene met and connected but gene activation did not occur, a finding they plan to explore further.

The study, which included work by Princeton graduate student Lev Barinov and collaborators at Thomas Jefferson University, was funded by the National Institutes of Health and the National Science Foundation.

**–By Kevin McElwee**