More tricks with next-generation DNA sequencing: DNA barcodes gone wild

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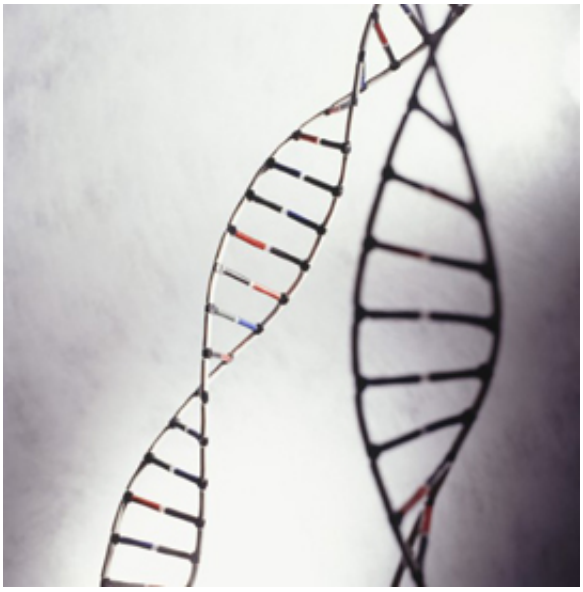

Credit: NIH

A team of researchers at Sinai Health System's Lunenfeld-Tanenbaum Research Institute (LTRI) and University of Toronto's Donnelly Centre has developed a new technology that can stitch together DNA barcodes inside a cell to simultaneously search amongst millions of protein pairs for protein interactions. The paper will be published today in the journal *Molecular Systems Biology*.

In recent years, DNA barcoding has enabled scientists to carry out highly parallel experiments, in which many different types of cells can be tested

in the same tube. This has been further enabled by next-generation DNA sequencing which can efficiently count barcodes and 'read out' the results. However, the number of experiments that can be combined in the same tube has been limited to the number of barcoded cell types. Allowing barcodes to fuse together inside cells means scientists can now break that barrier. The new technology results in a 10-fold increased rate of discovery for the same price.

"Using DNA barcodes for multiplex experiments has been an extremely powerful technology," said Frederick (Fritz) Roth, senior author on the study who is cross-appointed at Lunenfeld-Tanenbaum Research Institute and Donnelly Centre, and is also a Canada Excellence Research Chair and Senior Fellow of the Canadian Institute for Advanced Research. "However it has been one-dimensional, in the sense that we only got to read one experiment per barcode. By combining barcodes inside cells, we can dramatically increase the number of experiments we can combine together in a single test tube"

In a widely-used method called Yeast Two Hybrid (Y2H), yeast cells carrying a 'bait' protein are mated with yeast cells carrying a 'prey' protein. The Y2H system is rigged so that only cells in which bait and prey proteins stick together can survive and this allows scientists to see which proteins associate with which other proteins. Dr. Roth's team named their new technology Barcode Fusion Genetics-Yeast Two Hybrid (BFG-Y2H). In BFG-Y2H, cells carrying thousands of 'bait' and 'prey' proteins are mated together in the same culture. Says Roth, "To ensure that every protein pair is tested for interaction, the process ensures that every cell type mates with every other cell type. It's like Spring Break in Miami."

The authors say that the BFG-Y2H method's novelty is that the cells are programmed to connect DNA barcodes from bait and prey cells together into a single 'fused barcode.' Next-generation DNA sequencing methods

can then be applied to detect fused barcodes that correspond to the combinations of bait and prey proteins that stuck together and enabled their cell to survive.

Proteins, working alone or in larger assemblies, are the machinery that carries out many of the operations of a cell. The authors say that more efficient technologies for mapping protein interactions could expand researchers' understanding of how our cells work, and reveal protein interactions that only occur under certain environmental conditions.

Nozomu Yachie of the University of Tokyo, one of the paper's lead authors, notes that "millions of protein pairs can be tested for interaction in a single flask, so that dozens of conditions could be tested in parallel by one researcher in as little as two weeks in the lab."

Evangelia Petsalaki of the LTRI, also a lead author, notes that "the ultimate goal is to generate a '3D video' of the protein interaction network map rather than a static picture. Our BFG-Y2H method will accelerate our understanding of gene functions and human disease by efficiently generating more information-rich protein interaction maps."

The paper, entitled "Pooled-matrix protein interaction screens using Barcode Fusion Genetics" appeared April 22, 2016 in the journal *Molecular Systems Biology* (article 12: 863).

More information: *Molecular Systems Biology*, msb.embopress.org/cgi/doi/10.15252/msb.20156660

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