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Cover Story

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Treating Complex Diseases with Expansion Technology

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Expansion technology is a step forward in efforts to treat complex diseases and in cancer and Alzheimer's research. The technology has been developed by researchers from Bar-Ilan University, Harvard University and the Massachusetts Institute of Technology (MIT). HealthManagement.org spoke to Dr Shahar Alon, of Bar-Ilan University's Faculty of Engineering, Multidisciplinary Brain Research Center and Institute of Nanotechnology and Advanced Materials to learn more about this novel technology and the role it can play in future.

Can you explain the concept of expansion technology and its application in diagnosing and treating complex diseases like cancer and Alzheimer's?

The concept is simple – instead of extracting RNA molecules from tissues and then quantifying them, we quantify RNA molecules inside tissues. Therefore we obtain the location of RNA molecules within the tissue. This spatial information is known to be important for learning and memory in brain tissues, and likely to be important in diseases such as Alzheimer's and cancer.

Building this technology took years of work. The main difficulty was the fact that tissues are very dense, and therefore mapping RNA in their original location is a complicated task. We solve this difficulty by physically expanding the tissues. This creates room inside the tissues and allows us to reach RNA molecules deep inside them.

When you say this technology can map tissues with nanoscale resolution, what does that mean exactly?

It means that this technology allows to pinpoint RNA not only to individual cells inside tissues, but also into subcellular regions. One key example is the synapses that connects neurons in the brain. These synapses are very small and can be seen only with nanoscale resolution (only termed 'super-resolution'). With this new technology, we map RNA inside synapses.

Does this method target genes?

This method can work in two ways: untargeted - meaning that the users don't need to pick specific targets in advance, therefore allowing unexpected discoveries; and targeted, meaning that specific genes (usually between 50-300 genes) are targeted. The targeted method allows high detection yield – meaning that roughly 50% of individual RNA molecules within a cell are detected.

Molecules from a tissue of a healthy individual can be compared to that of a diseased one, possibly revealing the cause of disease. How accurate do you think that would be? What advantages does that offer over the diagnostic tools/strategies that are already available?

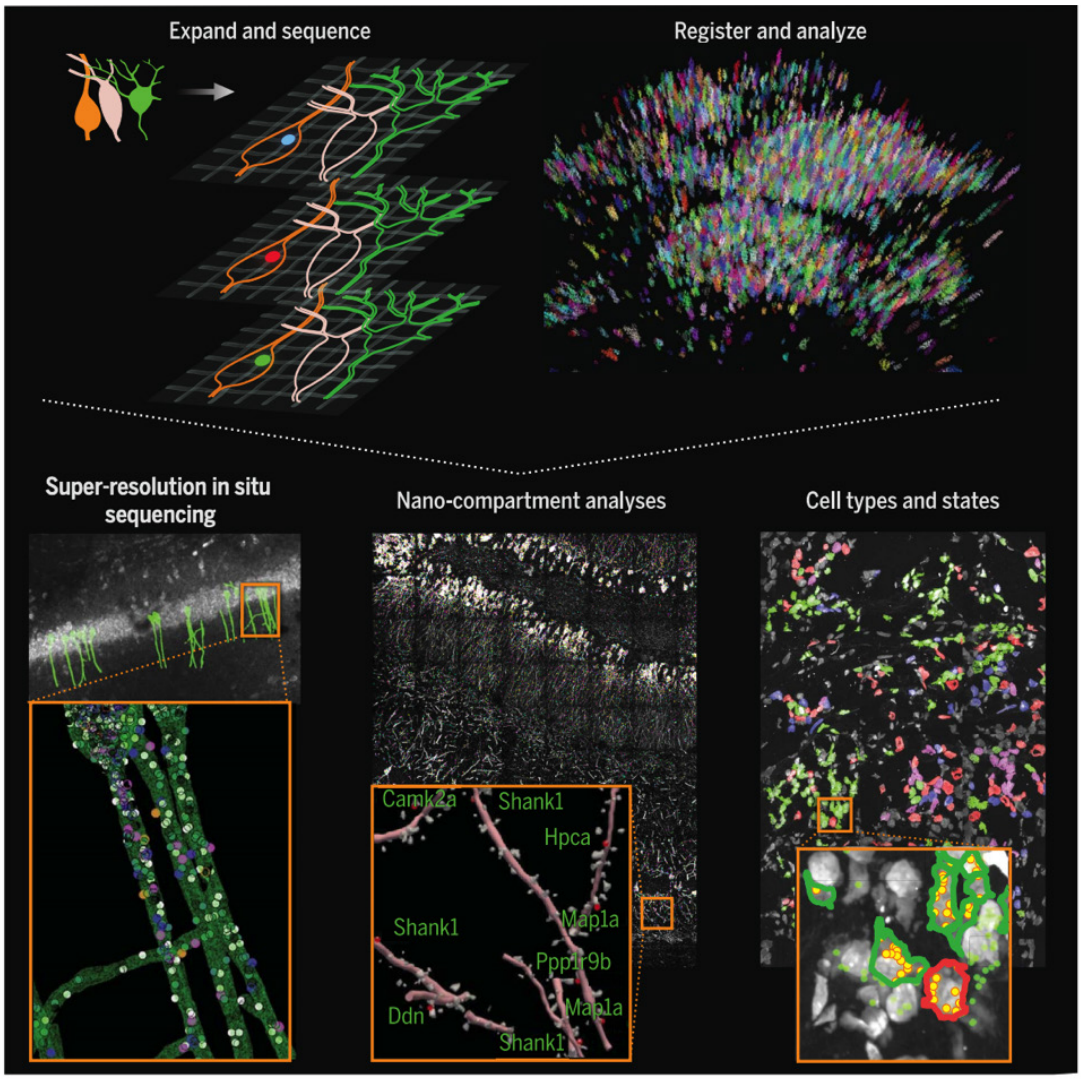
Regarding accuracy, we compared our technology to standard RNA sequencing technology and found it to be very accurate. Still, the main advantage is the ability to see aspects of the tissue that were not seen before, namely the 3D location of millions of individual RNA molecules. It remains to be seen how important this information is in studying disease.

Expansion technology has the potential to create complete molecular maps of tissues. How close are you to achieving that and do you think there are experts with the capability to read those maps?

The technology can create complete molecular maps of small tissues, say a small cancer biopsy. However, we are only in the beginning of building the capability to read those maps. This effort will require new computer vision, machine learning, and artificial intelligence tools.

Moving forward, how do you see expansion technology contributing towards cancer research and improved cancer treatment and management?

Expansion sequencing is one technology in the new field of spatial genomics – studying genes in their original location in space. I anticipate that this new field will allow new



In situ sequencing of physically expanded specimens enables multiplexed mapping of RNAs at nanoscale, subcellular resolution throughout intact tissues. (Top) Schematics of physical expansion and in situ sequencing (left) and image analysis (right). (Bottom) Characterization of nanoscale transcriptomic compartmentalization in mouse hippocampal neuron dendrites and spines (left and middle) and maps of cell types and states in a metastatic human breast cancer biopsy (right).

Image credit: Alon et al., Science 371, 481 (2021)

understanding in cancer research. Indeed, Nature Methods just declared this field as the technological breakthrough of the year.

What is your outlook about expansion technology and the overall goals of this project?

These are exciting times for us. After years of developing this new technology we can finally utilise it in the study of complex diseases. In our lab in Bar-Ilan University we study eye diseases, Alzheimer's, and many other applications.

Building of this new technology required a large multidisciplinary effort. This includes researchers from MIT, Harvard and other centres around the world.

Conflict of Interest

None. ■

REFERENCES

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