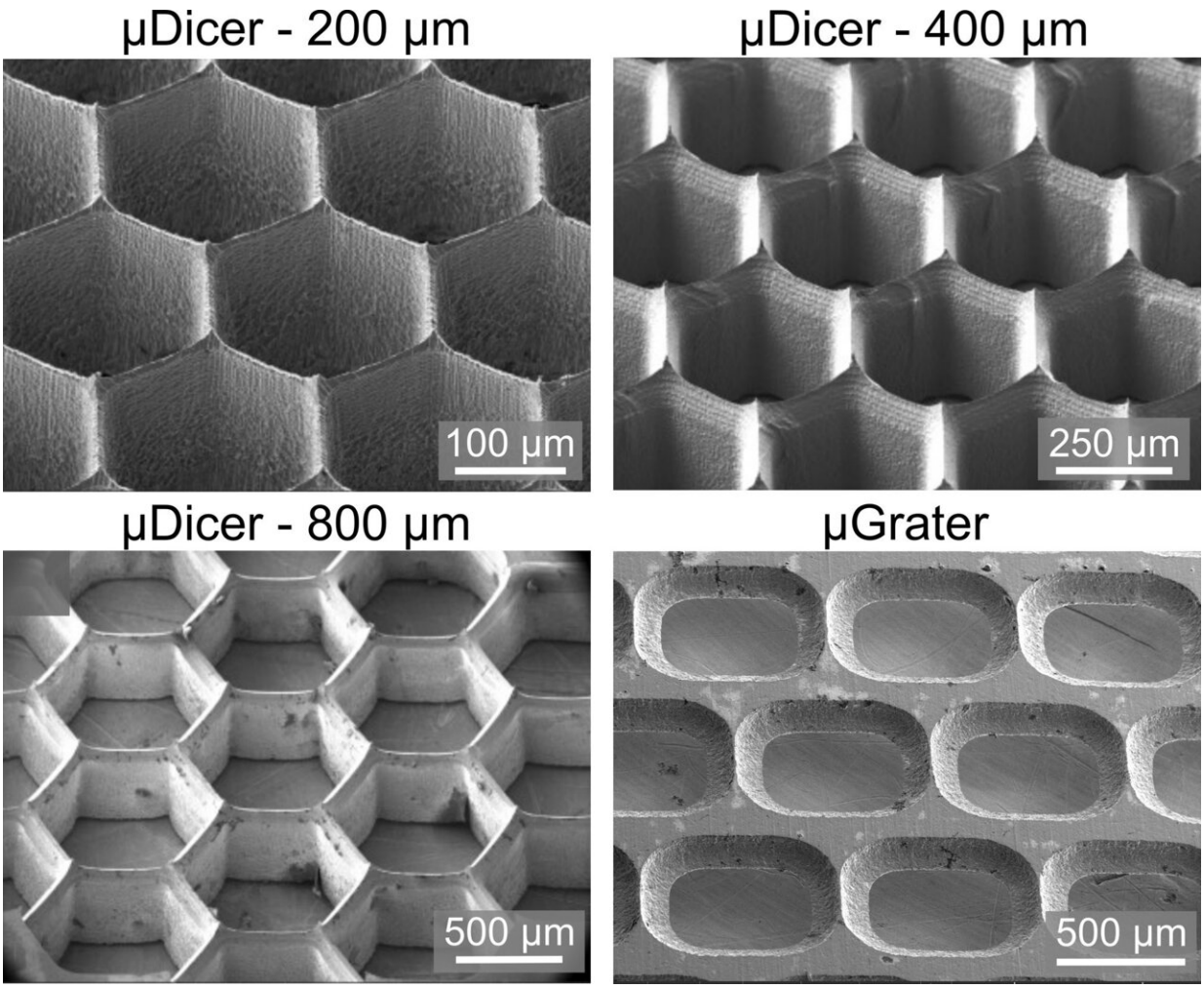
New precision tools make quick work of tumor dissection

September 10 2024, by Andrew Myers



Scanning microscopy images of the microDicer (blade spacings 200 µm, 400 µm, and 800 µm, respectively) and microGrater. Credit: Seth Cordts and Saisneha Koppaka

As fascinating as it is to work in a modern biology lab, in many cases a lot of repetitive, detailed work is necessary before the research can start. For example, cancer researchers are now capable of using hundreds or even thousands of small, lab-grown tumor samples—known as organoids—to test multiple cancer therapies, including immunotherapies, at once.

To produce organoids, researchers often need to mince a fresh tumor into small pieces by hand, using scissors to snip, snip, snip the specimen down to submillimeter size. This dissection work is tedious and yet often done by skilled—and usually overqualified—graduate students or research scientists.

Those days of drudgery may soon be past as researchers at the Stanford School of Engineering have developed two new tools that accelerate the precision cutting of tumor samples into submillimeter-scale organoids. Introducing: the microDicer (μDicer) and the microGrater (μGrater).

The inventors believe these tools, not unlike familiar utensils used in kitchens everywhere to dice vegetables or grate cheese, will allow researchers to improve the consistency and quality of samples, which have a direct impact on the quality of the data from downstream experiments such as measurements of drug response.

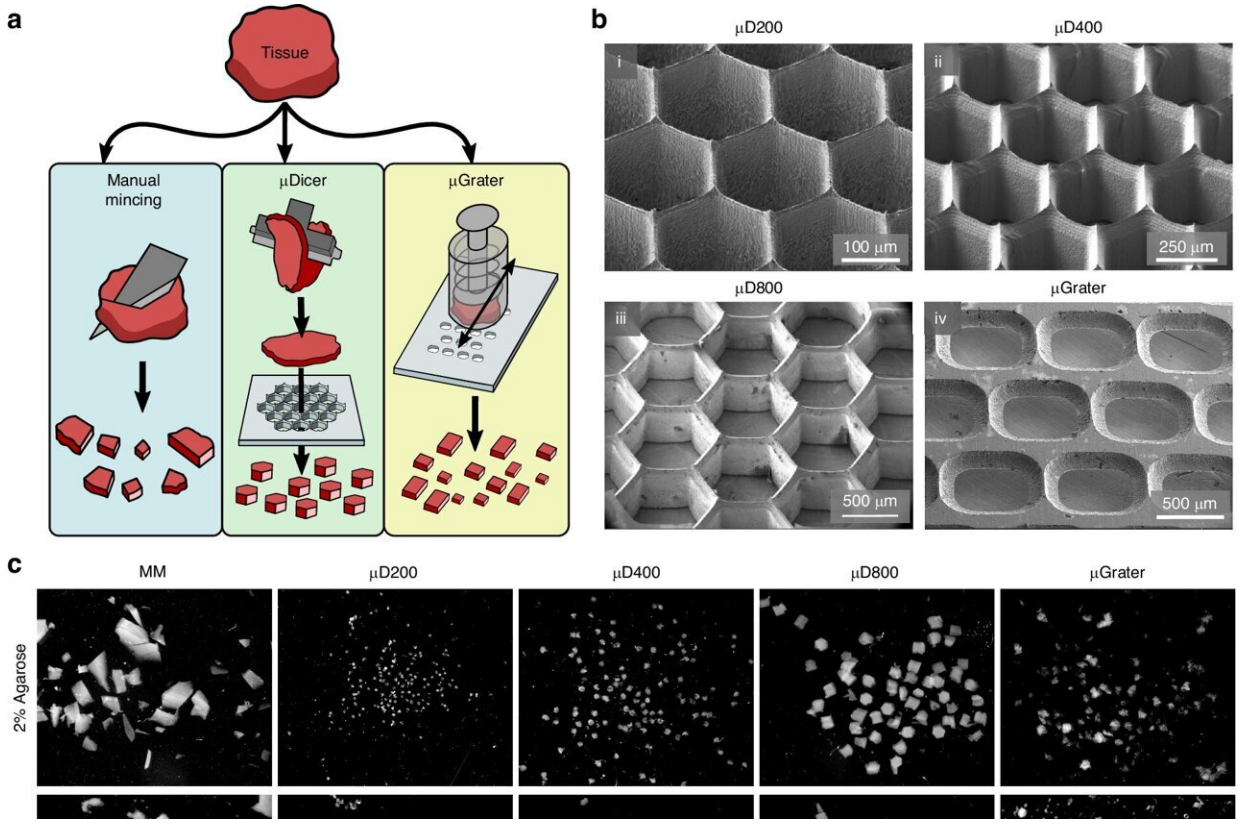
"Our collaborator and co-author Calvin Kuo, co-lead of the Cancer Biology Program at the Stanford Cancer Center, has shown that in cancer immunotherapy research, maintaining the spatial relationships between groups of tumor cells and immune cells that have already infiltrated the tumor—as opposed to working with individual cells—is really important for accuracy in testing drugs and immunotherapies. Our tools help researchers more efficiently create organoids that maintain those relationships," says Sindy Tang, an associate professor of mechanical engineering and senior author of a new study describing the

microDicer and the microGrater.

The work appears*Microsystems & Nanoengineering*.

"These new tools will speed up the manual lab work, but their utility goes beyond that obvious advantage," Tang added. "These tools produce uniform sized organoids and the blades can be varied to whatever size the researcher requires."

Having precise control over organoid size allows researchers to ask the question whether there is a "perfect" organoid size. If the organoid is too small, it may not retain the original properties of the tumor as it existed in the body. If the organoid is too big, however, it may die due to the difficulty of oxygen and nutrients getting through to the interior tumor cells.



Overview of the μDicer and μGrater devices and initial testing with 2% agarose and porcine kidney tissue. Credit: *Microsystems & Nanoengineering* (2024). DOI: 10.1038/s41378-024-00756-8

Precise blades

Tang and her team fashioned the blades of the microDicer in silicon using micromachining tools of classical computer chipmaking. The blade patterns are etched into silicon using a reactive plasma. The blades of the microGrater are made of stainless steel.

The microDicer's blade looks like a mesh of vertical, interlocking hexagons, resembling a honeycomb with sharpened edges. To use the microDicer, a researcher shaves off thin layers of tissue that are then pressed through the microDicer's honeycomb mesh to produce precise, uniform tumor samples.

The microGrater's array of blades, on the other hand, boasts a series of neat, rounded rectangles a bit more than half a millimeter long; the edges of each rounded rectangle are beveled to form the blades that shave off precise organoids as the tissue is moved back and forth across the grater.

Future promise

The tumor samples Tang and her colleagues are studying are grown in lab mice and are a good model of human tumors. The ultimate goal is a sort of bespoke, personalized cancer therapy in which samples are gathered from a specific patient to test which immunotherapies will work best for them. By standardizing the process flow and organoid sizes

in a way that manual mincing cannot, these new tools can expedite approval from regulatory agencies, like the FDA, for broader use, Tang says.

Her most recent work building upon these technologies will look to identify the ideal size for organoids across different tissue types. It is possible that different cancers and tissues have different dimensional requirements, a parameter that the flexibility of Tang's tools should help address. She can fine-tune the blades to make organoids of pretty much any size between a few hundred micrometers and a millimeter. Furthermore, she is now investigating how the shape of the blades affects the fidelity of the cuts. The physics of cutting soft biological tissues is a difficult problem and not well understood.

Once Tang had the idea for the microDicer, she turned the prototyping process into a graduate-level product design class, titled "Advanced Micro and Nano Fabrication Laboratory," taught by Roger Howe and Jonathan Fan. In that class, Ph.D. students learned to make micro-scale devices in a hands-on, project-based environment in the Stanford Nanofabrication Facility. Several of Tang's students are co-authors on the paper.

The microDicer and microGrater are not Tang's first mechanical tools for biological purposes. She made headlines a few years back with another tool—a cellular guillotine—able to split individual cells in two to study how single cells heal. That invention drew considerable interest from other biology labs inquiring about the possibility of cutting tissues, which motivated the development of the microDicer and microGrater. She is now evaluating ways to disseminate the tools to the research community, including the possibility of bringing the tools to market.

More information: Seth C. Cordts et al, Microdissection tools to generate organoids for modeling the tumor immune microenvironment,

Microsystems & Nanoengineering (2024). DOI: 10.1038/s41378-024-00756-8