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Hydrogel uses biology and light to release proteins on demand, advancing hopes for synthetic tissues

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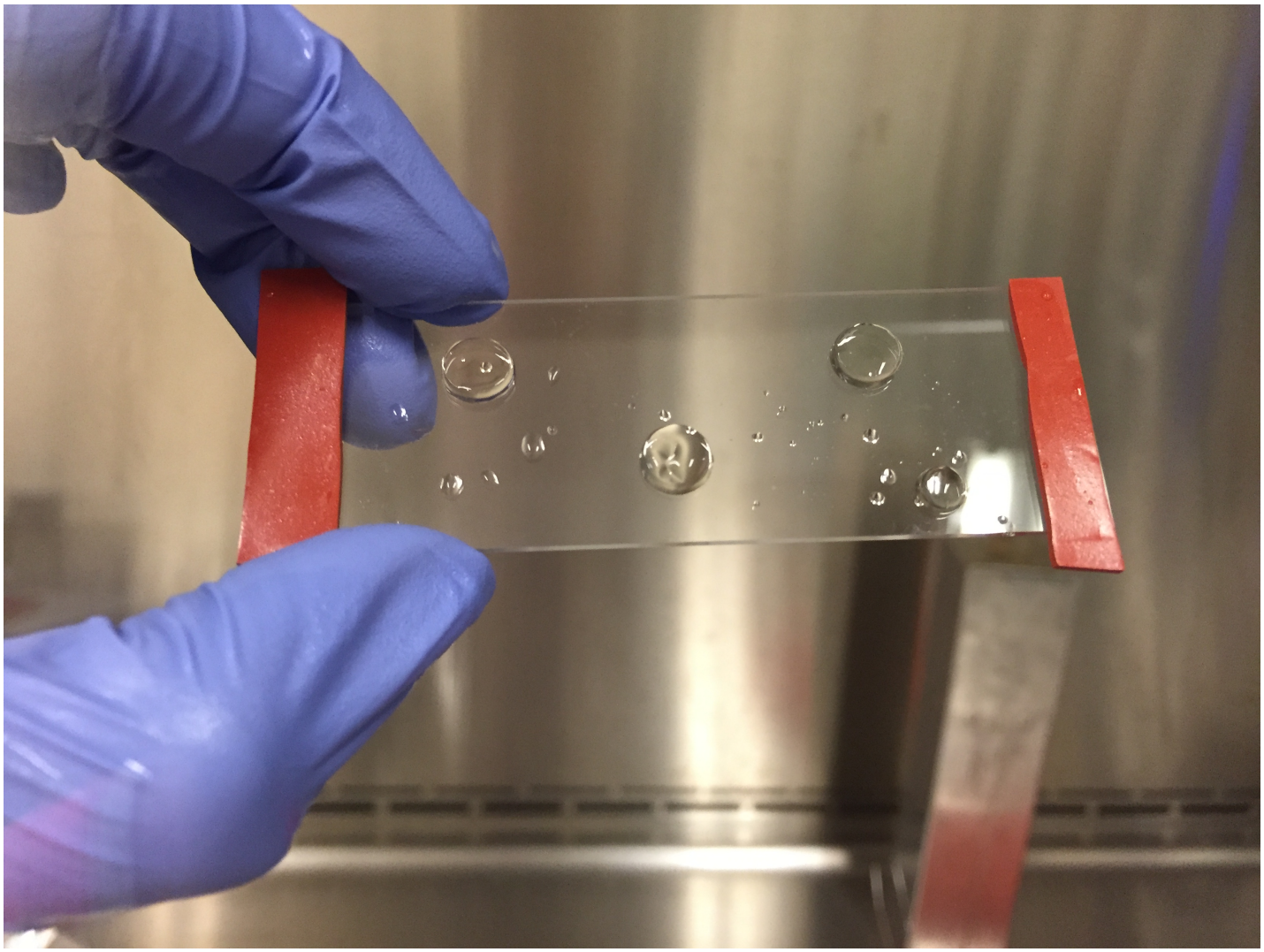

(http://blog.pnas.org/wp-content/uploads/2019/10/IMG_2064.jpg)

A novel type of clear hydrogel offers a new way to release proteins through a material. Image credit: Cole DeForest.

A wiggly cylinder of protein, hydrogel, and human cells, about the size of a wristwatch battery, could one day serve as a building block for synthetic tissues. The implications could be big for biological research and even organ transplants, according to a recent study (https://pubs.acs.org/doi/10.1021/jacs.9b07239) that reported the creation of the gelatinous cylinder. The work brings researchers a step closer to fabricating tissues as complex as the human heart, or concocting implants that release medicine on demand.

The material's power stems from its ability to release working proteins in different patterns throughout a group of cells embedded in hydrogel, explains paper coauthor and University of Washington chemical engineer Cole DeForest in Seattle. That task has been a longstanding challenge for bioengineers attempting to design these cutting edge materials.

The material is essentially a scaffolding of polymer mesh studded with human cells, like grapes in a Jell-O mold. Proteins appear throughout the material too, stitched to the scaffolding. If and when the stitching frays, the proteins fall off the scaffolding and into the cells, where they can affect cellular processes. Bioengineers want to control when and where the stitching breaks, effectively deciding which proteins get into which cells, and when.

Previous types of stitching consisted of two pieces, DeForest explains. One was a chemical handle that bound to an amino acid on the protein. The other was a light-sensitive molecule that grabbed the chemical handle on one side, and the polymer scaffolding on the other, leashing the protein to the material's matrix. When exposed to light, the light-sensitive molecule broke in two, releasing the protein and handle into a nearby cell.

But the old chemical handle wasn't specific enough to a single protein binding site, DeForest explains. If it bound the wrong site, it rendered the protein nonfunctional.

The key innovation in this new material, published in the *Journal of the American Chemical Society*, is a novel kind of stitching that tethers the protein to the hydrogel scaffolding. As with previous approaches, it's made of several pieces, including a chemical handle and a molecule that breaks in response to light. But in this case, the chemical handle is perfectly specific to just one nonrepeating amino acid sequence, ensuring that the handle doesn't disrupt the protein's function.

The light-sensitive molecule in this novel stitching is a recently-engineered light-cleavable protein (https://www.nature.com/articles/nmeth.4222) , which researchers could easily grow in their labs without expertise in small-molecule synthesis—a hindrance for some other approaches.

Using this new approach, DeForest's team patterned a hydrogel with proteins that promote cell growth. Then the researchers exposed the material to light. As planned, the light selectively released the proteins in the desired pattern, encouraging some cells in the material to grow, but not others. Bioengineer Eben Alsberg at the University of Illinois at Chicago called the recent research "an elegant new strategy for tethering proteins to hydrogels," noting that the new work has overcome key challenges in the field.

In the future, materials that release proteins on demand could be implanted under the skin and designed to release medications, such as insulin, in response to a targeted flash of light, DeForest says. Transplanting synthetic organs could also become more feasible, as the ability to spatially control cell development is a step toward fabricating tissues with the same complexity as real tissues. Making a synthetic heart for organ transplant is "a tall order" today, DeForest says, "and kind of the holy grail of this approach."

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