Nontoxic underwater adhesive could bring new surgical glue

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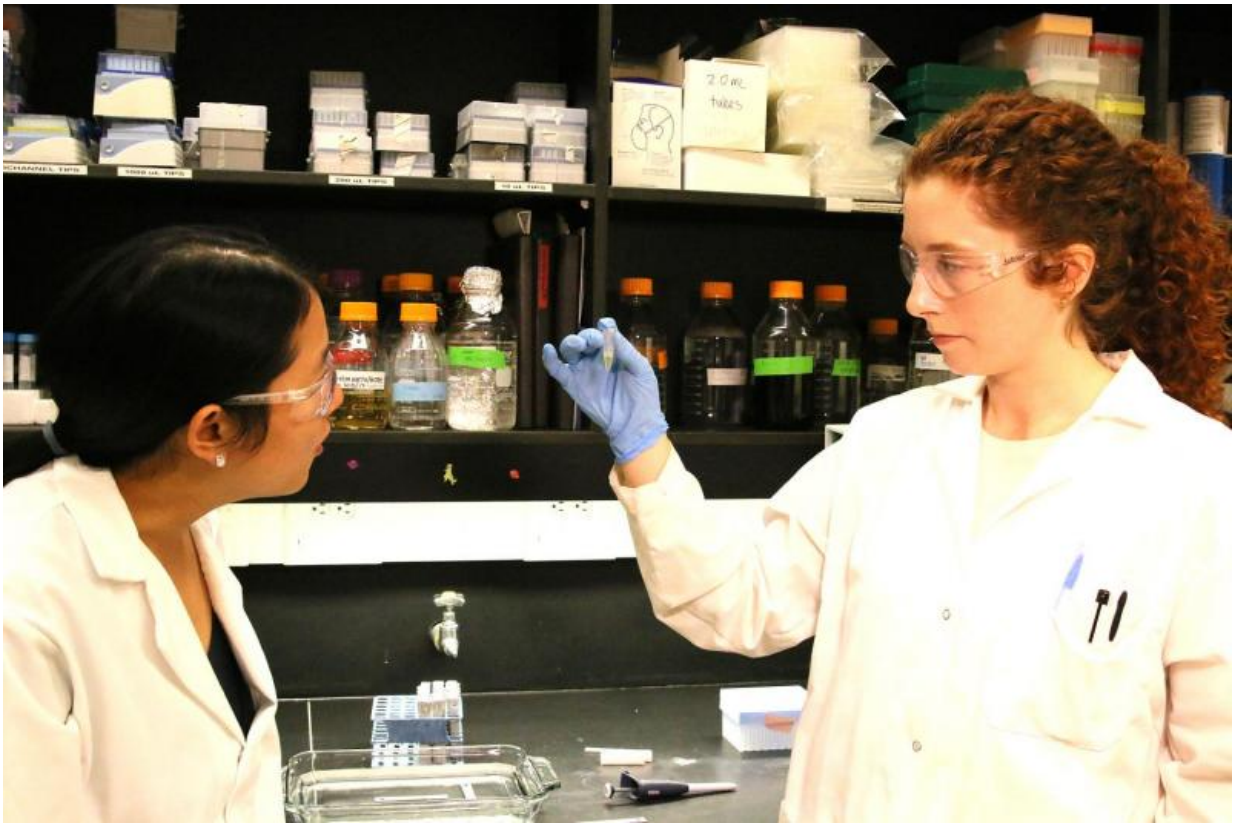

Purdue University associate professor Julie Liu, at left, and doctoral student Sydney Hollingshead, prepare to test a new protein-based adhesive underwater. Credit: Purdue University image/Erin Easterling

A nontoxic glue modeled after adhesive proteins produced by mussels

and other creatures has been found to out-perform commercially available products, pointing toward potential surgical glues to replace sutures and staples.

More than 230 million major surgeries are performed worldwide each year, and over 12 million traumatic wounds are treated in the United States alone. About 60 percent of these wounds are closed using mechanical methods such as sutures and staples.

"Sutures and staples have several disadvantages relative to adhesives, including patient discomfort, higher risk of infection and the inherent damage to surrounding healthy tissue," said Julie Liu, an associate professor of chemical engineering and biomedical engineering at Purdue University.

Most adhesives do not work well in moist environments because water interferes with the adhesion process. While developing adhesives that overcome this problem is challenging, glues for medical applications must meet an additional requirement: they must be nontoxic and biocompatible, as well.

"Current biomedical adhesive technologies do not meet these needs," she said. "We designed a bioinspired protein system that shows promise to achieve biocompatible underwater adhesion coupled with environmentally responsive behavior that is 'smart,' meaning it can be tuned to suit a specific application."

In efforts to develop better alternatives, researchers have been inspired by natural glues. Specifically, underwater application and bonding has been demonstrated with materials based on organisms such as sandcastle worms and mussels. Both produce proteins containing the amino acid 3,4- dihydroxyphenylalanine, or DOPA, which has been shown to provide adhesion strength, even in wet environments.

Research findings were detailed in a research paper published in April in *Biomaterials*. The paper was authored by graduate student M. Jane Brennan; undergraduate Bridget F. Kilbride; Jonathan Wilker, a professor of chemistry and materials engineering; and Liu.

Current FDA-approved adhesives and sealants face several challenges: many exhibit toxic characteristics, some can only be applied topically because they degrade into carcinogenic products; some are derived from blood sources and carry the potential for blood-borne pathogen transmission such as hepatitis and HIV; and others cause inflammation and irritation.

"More important, however, is that most of these adhesives do not possess sufficient adhesion in an excessively wet environment and are not approved for application in wound closure," Liu said. "In fact, many of these materials specifically advise to dry the application area as much as possible."

The Purdue researchers created a new adhesive material called ELY16, an "elastin-like polypeptide," or ELP. It contains elastin, a highly elastic protein found in connective tissue, and tyrosine, an amino acid. The ELY16 was modified by adding the enzyme tyrosinase, converting tyrosine into the adhesive DOPA molecule and forming mELY16.

Both ELY16 and mELY16 are not toxic to cells and work well under dry conditions. Modification with DOPA increases adhesion strength in highly humid conditions. Moreover, the modified version is "tunable" to varying environmental conditions and might be engineered to match the properties of different tissue types.

"To our knowledge, mELY16 provides the strongest bonds of any engineered protein when used completely underwater, and its high yields make it more viable for commercial application compared to natural

adhesive proteins," she said. "So it shows great potential to be a new smart underwater adhesive."

The adhesive also has outstanding biocompatibility due to the use of human elastin.

"Our goal was to mimic the type of adhesion that mussel adhesive proteins have, and much other work has focused on the DOPA molecule as being critical to that adhesion," said Liu. "We found that when the adhesive materials were exposed to large amounts of moisture, proteins containing DOPA had a much higher adhesion strength compared to unconverted proteins containing only tyrosine. So, DOPA conferred much stronger adhesion in wet environments."

Testing the adhesive in a highly humid environment is important to determine how well the adhesive will perform and cure in the presence of moisture in biomedical applications.

The research showed mELY16 outperformed commercial adhesives including an FDA-approved sealant.

"Compared to this sealant, our proteins with DOPA have significantly higher adhesion strengths," Liu said.

Elastin-like polypeptides have the innate ability to "coacervate," which causes them to separate into "two liquid phases," one denser and more protein-rich than the other, mimicking the adhesion mechanism used by sandcastle worms.

The elastin provides this coacervation property, which makes possible an easy way to apply the adhesive under water. It's also a flexible naturally occurring protein found in tissues, and it has been shown that elastin-like polypeptides can be "crosslinked," or strengthened to change stiffness to

mimic soft tissues.

"This elastin-like polypeptide can be produced in high yields from Escherichia coli and can 'coacervate' in response to environmental factors such as temperature, pH, and salinity," she said. "Because the protein will coacervate in a warm liquid bath, a dense protein-rich phase forms. This protein-rich phase contains our adhesive material in concentrated form, and because it is denser than water, it does not disperse."

The researchers tested the polymer with mouse cells called NIH/3T3 fibroblasts. These cells are often used in research to assess toxicity by examining how well cells survive and grow when exposed to new materials. To test for biocompatibility, the researchers measured the viability of NIH/3T3 fibroblasts cultured for 48 hours directly on a layer of ELY16, mELY16, and a control. In all groups, viability was greater than 95 percent.

Future research will include work to optimize the formulation of the adhesive and perform tests with natural materials.

"We started our tests with aluminum substrates because it is easier to achieve reproducible results using aluminum," Liu said. "However, if we are interested in biomedical applications, we need to test substrates that are more similar to soft tissues in the body, and these substrates are more challenging to work with."

More information: M. Jane Brennan et al. A bioinspired elastin-based protein for a cytocompatible underwater adhesive, *Biomaterials* (2017). DOI: 10.1016/j.biomaterials.2017.01.034

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