Novel nanogels hold promise for improved drug delivery to cancer patients

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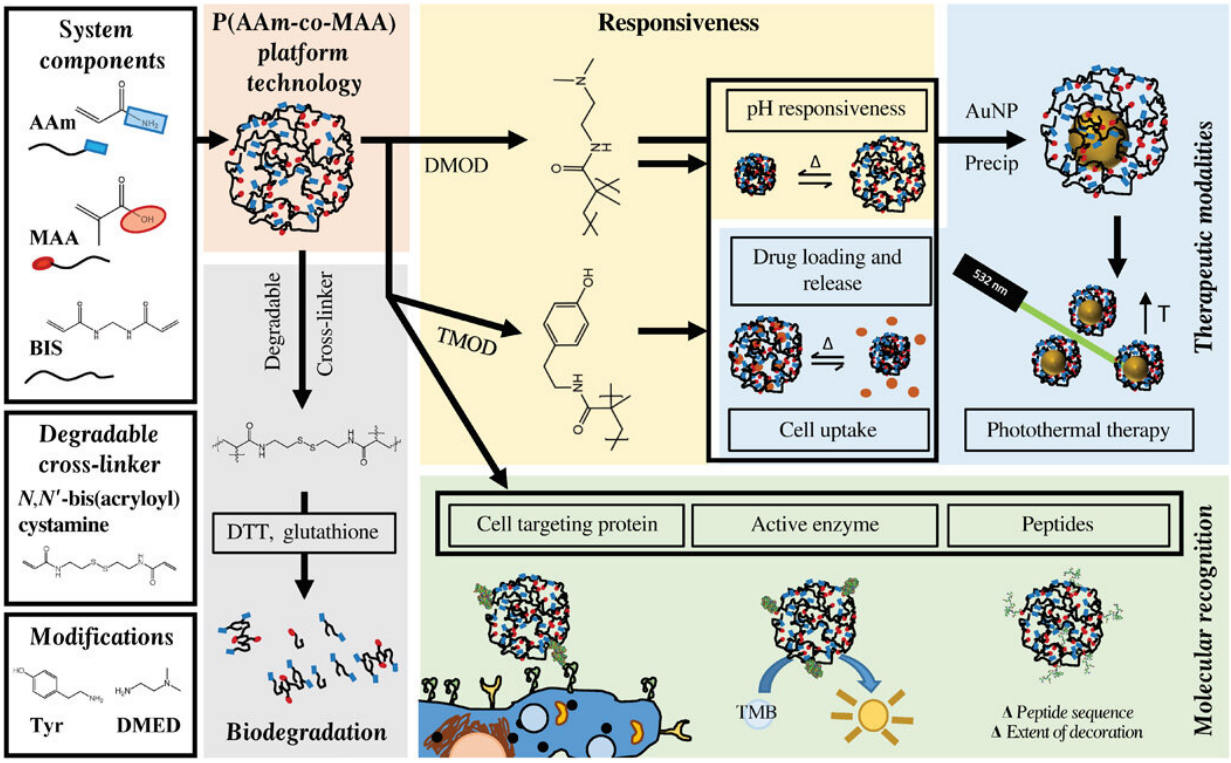

Overview of the P(AAm-co-MAA) nanogel platform and the use of its derivatives for precision medicine applications. Nanoscale networks of acrylamide (AAm) and methacrylic acid (MAA), cross-linked with methylenebisacrylamide (BIS) or its degradable disulfide analog [N,N′-bis(acryloyl)cystamine], were synthesized by inverse emulsion polymerization and modified via carbodiimide chemistry with tyramine (Tyr), N,N-dimethylethylenediamine (DMED), proteins, or peptides. In an additional post-synthesis step, gold nanoparticles (AuNP) were precipitated within DMED-modified (DMOD) nanogels. Here, we document the synthesis and modification

of this nanogel platform and demonstrate the impact of nanogels' modification on their ability to respond to the pH environment, load and release a model cationic drug, target cells, act as a functional enzyme, and transduce green light for photothermal therapy. Because of its tunability and the variety of therapeutic modalities enabled, we believe that this platform is suitable for precision medicine applications. DTT, dithiothreitol; TMB, 3,3′,5,5′-tetramethylbenzidine. Credit: *Science Advances* (2019). DOI: 10.1126/sciadv.aax7946

Researchers at The University of Texas at Austin have developed new guidelines for fabricating nanoscale gel materials, or nanogels, that can deliver numerous therapeutic treatments to treat cancer in a precise manner. In addition to enabling the delivery of drugs in response to tumors, their nanogels can target malignant cells (or biomarkers), degrade into nontoxic components and execute multiple clinical functions.

The most important characteristic of the engineering researchers' nanogels is their ability to be chemically modified or "decorated" with many bioactive molecules. These modifications give the decorated nanogels more diverse physical and chemical properties than any other existing technique, despite their identical origin. Such systems, which have the potential of being tailored to specific diseases or even individual patients, could be a useful tool for oncologists in the future.

In a study published in the latest issue of *Science Advances*, researchers in the Department of Biomedical Engineering and the McKetta Department of Chemical Engineering in the Cockrell School of Engineering outline the development of these multipurpose nanogels for cancer treatment. Following a series of chemical modifications, the nanogels are capable of performing the following simultaneously or in sequence: loading and releasing drugs, responding to unique pH environments, identifying biomarkers, converting light into therapeutic

heating and exhibiting degradation characteristics.

The research team, led by drug delivery pioneer Nicholas Peppas, a professor in the departments of biomedical engineering and chemical engineering, the UT College of Pharmacy and the Dell Medical School, conducted the study over four years at UT's Institute for Biomaterials, Drug Delivery & Regenerative Medicine, which Peppas directs.

They synthesized and purified nanogels containing carboxylic acids, chemical functional groups that are common in natural biological molecules. These functional groups allowed the researchers to modify, or chemically couple, the nanogels to bioactive molecules, such as small molecules, peptides and proteins. A combination of modifications was needed to tailor the nanogels for targeted and environmentally sensitive drug delivery.

"One way to think of our nanogel is like a blank canvas," said John Clegg, who was a Ph.D. candidate in the Cockrell School when he worked on the study and is currently a postdoctoral fellow at Harvard University. "Untouched, a blank canvas is nothing more than some wood and fabric. Likewise, the nanogel is a simple structure (made of polymer-joining agents and water). When it is modified, or decorated, with different bioactive groups, it retains the activity of each added group. So, the system can be quite simple or quite sophisticated."

The team's modular approach—combining many useful parts into a single, greater whole—is frequently applied to other engineering systems, including but not limited to robotics and manufacturing. The Texas Engineering researchers have applied similar logic, except on the nanoscale, to develop their nanogels.

The researchers indicate their work could also serve as a blueprint for "precision medicine" approaches. In precision medicine, a patient is

treated with finely tuned doses of targeted therapeutics, prescribed in amounts that correspond to the known characteristics of a patient and the disease that are identified in diagnostic tests.

"If nanoparticle carriers like our nanogels are to be useful for precision medicine applications, they will need to be adaptable enough to match each patient's needs," Clegg said. "We believe that our approach, where a base nanogel is adapted to the unique characteristics of an individual patient and facilitates multiple therapeutic modalities, is advantageous in comparison to developing many separate platforms, which each deliver a single therapy."

The researchers believe that their study can serve as a practical guide and proof of concept for scientists who are developing nanoscale materials for precision medicine applications.

More information: "Synthetic networks with tunable responsiveness, biodegradation, and molecular recognition for precision medicine applications" *Science Advances* (2019). DOI: 10.1126/sciadv.aax7946 , advances.sciencemag.org/content/5/9/eaax7946

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