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News and opinions

Gold nanosensors make simple work of disease detection

Cordelia Sealy

Tiny clusters of gold atoms are widely used as contrast agents for biomedical imaging but now researchers from the UK and USA have harnessed the catalytic activity of these particles to create a simple color change urine test for disease diagnosis [Loynachan and Soleimany et al., *Nature Nanotechnology* **14** (2019) 883, https://doi.org/10.1038/s41565-019-0527-6].

“The goal of this work was to develop a simple and sensitive diagnostic for cancer that could be used outside of hospital settings – regardless of the local resources available,” explains Molly M. Stevens of Imperial College London, lead author of the study with Sangeeta N. Bhatia of Massachusetts Institute of Technology.

Cancer and infectious diseases produce biological cues, including specific types of enzyme, which show elevated levels in the body. The new approach relies on tying tiny gold nanoclusters onto proteins cores using linker molecules that are broken – or cleaved – by these enzymes. If a tumor is present in the body, elevated levels of specific enzymes will cleave the gold nanoclusters from their protein core. The gold nanoclusters will then be cleared through the kidneys and into the urine where they can be detected via a catalyzed color-change reaction with hydrogen peroxide and a chemical substrate (Fig. 1).

The approach hinges on the ability to synthesize enzyme-responsive catalytic nanoparticles small enough to be cleared into the urine (i.e. less than 5 nm in diameter) that retain their catalytic activity even after exposure to the physiological environment in the body.

“The ‘aha’ moment came right at the beginning when the labs of Molly Stevens and Sangeeta Bhatia joined forces to combine our catalytic nanoparticle amplification and *in vivo* enzyme activity sensing technologies,” says Colleen N. Loynachan, first author of the study.

The nanoclusters, which are just 2 nm in diameter, are synthesized using a simple one-pot method that produces gold cores protected by peptide sequences. The synthesis method can be tailored to produce nanoclusters with functional enzyme-responsive ligands on the surface.

“The gold nanoclusters have several properties critical for sensor stability and functionality,” points out Loynachan. “The particles are small enough to be renal clearable (< 5 nm), stable in physiological environments (e.g. serum and urine), have robust catalytic activity, and present enzyme-responsive ligands on their surface.”

The development of nanoparticles that are stable in the complex environment of the body is a significant advance. Proteins in blood and serum readily stick to nanoparticles, encouraging coalescence into larger aggregates and affecting clearance from the body. That these nanoclusters are unaffected by the physiological environment and retain their catalytic activity when released into the urine is novel, say the researchers.

“[This] is an exciting first demonstration of engineering catalytic nanomaterials for disease detection,” says Ava P. Soleimany, co-first author of the study. “By designing versions of our sensors that can be cut by different enzymes, we could apply this color-based test to detect a range of conditions.”

The researchers are particularly interested in developing tests for infectious diseases and drug-resistant infections. For some diseases, where a more quantitative measure of biomarkers are needed beyond a simple yes/no response, Loynachan suggests that a standard curve and color scale would need to be developed.

“We are actively developing this system for detection of other disease-associated enzymes, and are also making key advancements to the delivery system and further optimizing the catalytic properties of our nanomaterials to improve both sensitivity and specificity of our sensors,” says Soleimany. “However, there’s still a lot of optimization and testing needed before the technology can move beyond the lab.”

E-mail address: cordelia.sealy@googlemail.com

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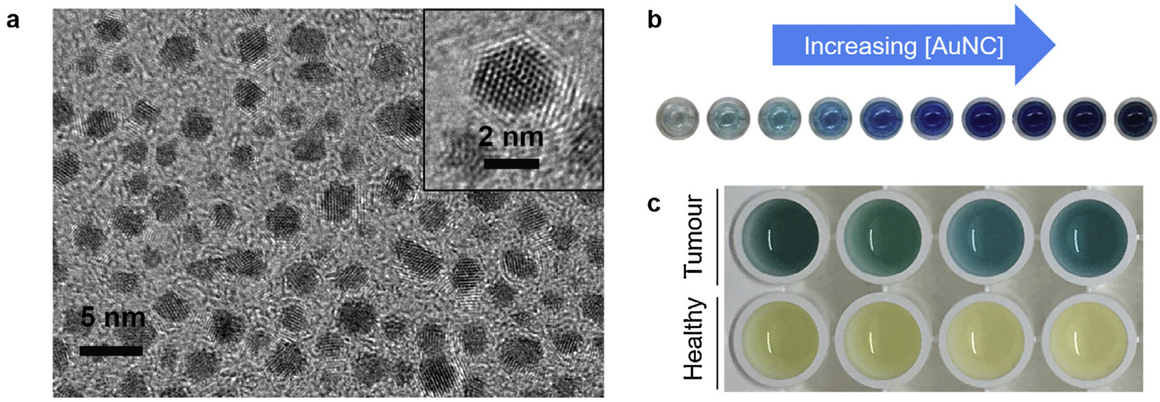

Fig. 1. (a) Transmission electron micrograph image of ultrasmall catalytic gold nanoclusters (AuNCs). (b) Picture of varying concentrations of AuNCs in the presence of a chromogenic substrate and hydrogen peroxide, where the intensity of the blue colored dye increases with increasing AuNC concentration. (c) Photograph of representative examples of colorimetric assay on urine samples from tumor-bearing (top) and healthy (bottom) mice injected with nanosensors.

Although Jie Zheng, Professor of Chemistry and Biochemistry at The University of Texas at Dallas, believes the approach is a novel and promising one, he agrees that there are some remaining challenges in the clinical translation of the researchers' approach.

"The novelty of this work is that by integrating renal clearance and catalytic activity of ultrasmall gold nanoparticles together, the protease nanosensors can respond to matrix metalloproteinases (MMPs) in tumor microenvironments at high sensitivity, making tumors to be readily detectable through a simple color change in the urine."

However, he points out this particular enzyme is also highly expressed in other diseases as well as cancer.

"Increasing the specificity of this technology for tumor detection is one of key issues," he says. "In addition, there are many other physiological processes in the body that might also reduce the detection specificity by inducing nonspecific disassembly of these renal clearable gold nanoparticle-based nanosensors."