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Nanoparticle Self-Assembly Triggered by Tumor-Associated Enzyme

There is a growing recognition among cancer researchers that the most accurate methods for detecting early-stage cancer will require the development of sensitive assays that can identify simultaneously multiple biomarkers associated with malignant cells. Now, using sets of nanoparticles designed to aggregate in response to finding more cancer biomarkers, a team of researchers funded by the Alliance for Nanotechnology in Cancer has developed a multiplexed analytical system that could detect cancer using standard magnetic resonance imaging (MRI).

Sangeeta Bhatia, M.D., Ph.D., a joint member of the Centers for Cancer Nanotechnology (CCNE) based at both the [University of California, San Diego](#) (UCSD) and [MIT-Harvard](#), and Michael Sailor, Ph.D., a member of the UCSD CCNE, led the research team that developed what it calls a logic-based nanoparticulate system for detecting multiple cancer biomarkers. The researchers published their results in the *Journal of the American Chemical Society*.

The investigators built their system using superparamagnetic nanoparticles that they first coated with either avidin or biotin, two biomolecules that bind to one another with legendary specificity and avidity. Then, to keep these nanoparticles from binding to each other through their new biotin or avidin coatings, the investigators added one of two different protein-polymer constructions. Both constructions consisted of a short segment of protein linked to a long stretch of poly(ethylene glycol) (PEG); in one case, the protein segment was a substrate for an enzyme known as MMP2, in the other case, the protein was a substrate for the enzyme MMP7. MMP2 is overexpressed in many types of cancer, particularly metastatic disease, whereas MMP7 may be involved in the early stages of breast cancer development. Tests showed that only these specific enzymes were able to cleave their specific protein substrates, releasing the PEG layer from the nanoparticles.

To assay for the presence of both MMP2 and MMP7, both types of nanoparticles are combined in the same reaction tube. When a test mixture containing both enzymes is added to the pair, the enzymes remove the protective PEG coatings from both types of nanoparticles, allowing them to self-assemble through their avidin and biotin coatings. The self-assembled nanoparticles produce a 30 percent boost in MRI signal intensity. In contrast, the researchers observed no signal enhancement when the test solution contained only MMP2 or MMP7 but not both. The investigators call this nanoparticle pair a logical AND - it only produces an MRI signal boost when both enzymes are present - and they note that they can create such an AND system using any pair of linker proteins that would act as substrates for any pair of enzymes.

Next, the investigators created a logical OR system, one that would produce an MRI signal boost when either MMP2 or MMP7 are present. To build this system, the researchers created a single protein-PEG construct consisting of both MMP2- and MMP7-susceptible sequences and attached it to the biotin-containing nanoparticle, while leaving the avidin-coated nanoparticle unmodified. When combined, the two types of nanoparticles self-assembled when either of the two enzymes was present in a test solution.

This work, which was supported by the National Cancer Institute's Alliance for Nanotechnology in Cancer, is detailed in the paper "Nanoparticle self-assembly gated by logical proteolytic triggers." This paper was published online in advance of print publication. An abstract of this paper is available through PubMed.

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