Nanoparticles and Mini-NMR point the way to personalized cancer therapy

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(PhysOrg.com) -- With the advent of targeted drug therapy for treating cancer, it has become clear that an important predictor of success of these therapies is whether such a drug is reaching its target in the patient. The bottom-line measure of success is survival, but having some rapid measure of drug targeting would enable oncologists to make early changes in therapy if the amount of drug reaching its intended target was insufficient to kill a tumor.

Ralph Weissleder and his colleagues at the Harvard Medical School may have developed just what oncologists ordered. Using magnetic nanoparticles as a sensitive readout of drug targeting, and a miniaturized nuclear magnetic resonance (NMR) instrument, Weissleder's team created a novel system for directly measuring both target expression and drug binding in a small number of tumor cells obtained via needle biopsy . This new technique has the potential to provide real-time results at the time of biopsy. Weissleder is the co-principal investigator of the MIT-Harvard Center for Cancer Nanotechnology Excellence.

Reporting its work in the journal *ACS Nano*, the Harvard team showed that they could use their system to measure how effective so-called PARP inhibitors are at binding to their intended target, the protein poly(ADP-ribose) polymerase (PARP). Several PARP inhibitors are moving through clinical trials for the treatment of breast and ovarian cancers. The researchers note, though, that their system is broadly applicable to most any type of drug that must bind to a specific molecular target.

The key component of this specific assay system is a dextran-coated, cross-linked iron oxide (CLIO) nanoparticle linked to a small molecule inhibitor of PARP. Once the investigators prepared this construct, they tested it on five different tumor cell lines that produce varying levels of PARP. After mixing the nanoparticles with the cells, levels of PARP expression were measured using a miniaturized NMR instrument about the size of a cell phone. The results, obtained from as few as 1500 cells, matched those obtained using standard protein expression technologies.

Next, the investigators tested their system to see if it could determine target binding for five different commercially available PARP inhibitors. Again, the results, obtained in less than 90 minutes and from 10,000 cells, matched those obtained using other, more elaborate, time-consuming, and far less sensitive standard technologies.

With these results in hand, Weissleder's team measured drug targeting in live cells and blood samples. From samples as small as 1500 cells, the investigators found that their system could detect differences in PARP expression and drug binding across different tumor types. The results, wrote the researchers, "suggest the potential for a future 'treatment index,' where patients with high drug-binding efficacy would receive lower therapeutic doses, while patients with low drug-binding efficacy would require higher doses or be candidates to receive alternative drugs." The investigators are already at work on a second-generation system that would require even fewer, or even single, cells that might enable clinicians to identify the development of rare drug resistant cells.

This work, which is detailed in a paper titled, "Nanoparticle-Mediated Measurement of Target-Drug Binding in Cancer Cells," was supported in part by the NCI Alliance for Nanotechnology in Cancer, a comprehensive initiative designed to accelerate the application of nanotechnology to the prevention, diagnosis, and treatment of cancer. An abstract of this paper is available at the journal's website.

More information: View Abstract

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