



## Multifunctional nanodevice reverses drug resistance

Multidrug resistance in cancer cells is most commonly due to the expression of energy-dependent drug transporters that are able to efflux a variety of structurally and functionally unrelated drugs. Reporting in *PNAS*, João Conde and colleagues now present an implantable nanogold-containing hydrogel that can sense and silence multidrug resistance genes prior to drug release, and that reports on these events by emitting fluorescence.

The gold nanoparticles in the hydrogel were studded with ‘nanobeacons’ consisting of thiol-DNA hairpins that were labelled with a near-infrared (NIR) dye, as well as DNA oligonucleotides labelled with a quencher. When in the hairpin configuration, the proximity of the NIR dye to the quencher leads to fluorescence quenching. However, when the DNA of the hairpin hybridizes to a complementary mRNA sequence, the resulting conformational

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reorganization restores fluorescence, thereby providing a readout for target engagement. The nanobeacons were loaded with 5-fluorouracil (5-FU), a widely used nucleoside analogue chemotherapeutic drug. 5-FU wedges between the bases along the double-stranded part of the hairpin and is released within target cells when the nanobeacon hairpin opens.

The hairpins can be designed to bind to any mRNA sequence, leading to its degradation (that is, an mRNA knockdown), at the same time as acting as on/off switches that induce both drug delivery and fluorescence emission in response to the detection of a particular mRNA. In order to combine drug resistance reversal with drug delivery, the authors designed nanobeacons that were complementary to multidrug resistance protein 1 (MRP1), an energy-dependent efflux pump that is upregulated frequently in cancer cells.

The nanobeacons were tested in a 5-FU-resistant triple-negative breast cancer cell line (MDA-MB-231) that was engineered to express luciferase. 5-FU-loaded nanobeacons that were complementary to luciferase, nonsense nanobeacons and various nanobeacons without 5-FU were used as controls. Fluorescence indicated binding — there was no fluorescence detected for nonsense nanobeacons. Cell viability assays showed that the constructs without 5-FU and the nonsense constructs with 5-FU did not induce any cell death. Anti-luciferase constructs that released 5-FU induced limited cell death, whereas anti-MRP1 nanobeacons reversed drug resistance and killed the cells efficiently.

For *in vivo* experiments, anti-MRP1 and control nanoparticles were embedded in a hydrogel, and injected next to tumours in an orthotopic MDA-MB-231-xenograft breast cancer model. The hydrogel allowed for efficacious local release of the nanoparticles and prevented their accumulation in the liver (a common problem with systemic nanoparticle administration). There were no signs of inflammation at the surgical site or weight loss. Compared with control constructs or treatment with free drug, anti-MRP1 nanobeacons achieved more than 90% tumour reduction by 2 weeks after injection.

The authors point out that this system can be designed to detect and inhibit any gene of interest, followed by the delivery of any choice of intercalated drug — thereby serving as a theranostic as well as a universal gene therapy and drug delivery vehicle for cancer therapy.

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**ORIGINAL RESEARCH PAPER** Conde, J. et al. Implantable hydrogel embedded dark-gold nanoswitch as a theranostic probe to sense and overcome cancer multidrug resistance. *Proc. Natl Acad. Sci. USA* 112, E1278–E1287 (2015)