

Bio Focus

Targeted drug delivery, again and again

A major aim in biomaterials research is to develop improved strategies for delivering therapeutic drugs to injury- and disease-affected tissues in an efficient, effective, and safe manner. This goal is particularly important in the realm of cancer therapy, where targeted delivery of drugs to diseased cells could minimize toxicity to healthy tissues and thus reduce the detrimental side effects of chemotherapy. Improved targeted drug delivery, in turn, calls for new materials-based strategies, where solid structures offer unique advantages for integration with the body and for the mediation of transport processes. For example, polymer gels can be used as controllable drug-eluting systems. The polymer is first decorated with a small-molecule drug through chemical cross-linking. The drug gradually leaches from the polymer at a rate determined by the type and extent of cross-linking employed, and by the solution environment of the drug-polymer complex. Implanting

these polymer complexes directly into a diseased tissue thereby provides site-specific drug dosing. While this approach has been explored in several biomedical contexts, previous applications of the strategy have suffered from a single-use-only limitation. Once the material implant has exhausted its store of drugs, the remaining polymer is rendered therapeutically useless, possibly calling for surgery to remove the structure or to refill it with a fresh supply of drugs. A new report by Y. Brudno of Harvard University and colleagues, however, offers an alternate and easier strategy for resetting the delivery system, as summarized neatly in the title of their contribution to the September 2 issue of *Proceedings of the National Academy of Sciences*, “Refilling drug delivery depots through the blood” (DOI: 10.1073/pnas.1413027111; p. 12722).

The main concept advanced by this report is the use of drug-carrying polymer strands (or drug payloads) that are introduced into the bloodstream in a relatively noninvasive manner, such as through intravenous injection. Once in the body, the payloads selectively attach

to a previously implanted drug-eluting polymer gel source, thereby refilling the source’s drug stores as needed.

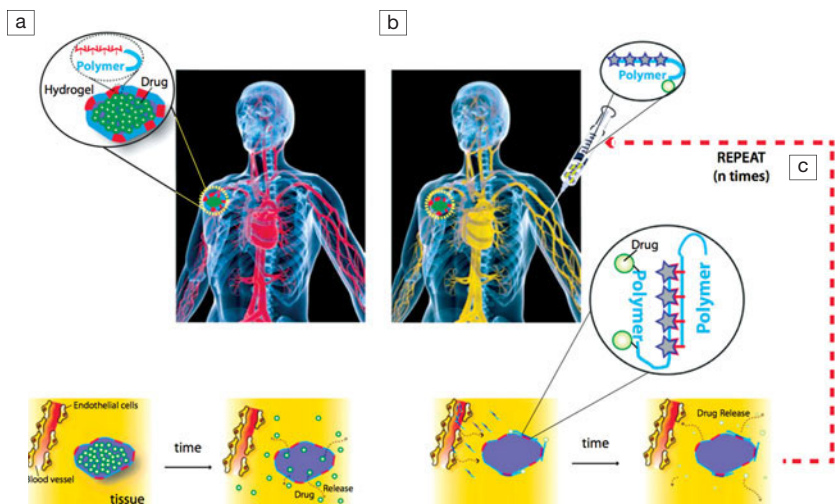
The research group demonstrated the concept by treating cancer-affected mice with an alginate hydrogel infused with doxorubicin (a chemotherapeutic), which was implanted into the tumor. Doxorubicin-coated alginate strands were subsequently injected intravenously to periodically refill the hydrogel. To enable selective attachment, the alginate was additionally modified with short DNA strands, where the DNA sequence associated with the gel implant was complementary to the DNA sequence associated with the injected alginate strands. This system of addressing the payload to the implanted gel relies on several mechanisms that can be further optimized, such as the stability of the linked DNA and the circulation behavior of the alginate strands, which (in addition to binding to their target gel) can also accumulate nonspecifically in tissues such as the liver and kidneys.

Despite these challenges, the researchers demonstrate that their new refilling approach yields significant results. Alginate strands carrying complementary DNA bind to the target gel in fivefold greater quantities than control strands with noncomplementary DNA.

Most importantly, only in mice subjected to the full refilling strategy were tumors found to shrink over a seven-week treatment schedule. Controls involving injection of just the drug or the drug-modified alginate carrying a DNA homing sequence incapable of binding to the gel saw tumor size increase over the same treatment period.

The results show that blood-based drug refilling holds great promise as a noninvasive route for effective disease treatment, and the approach could be adapted to a variety of future drug delivery devices and disease treatment therapies.

Lukmaan A. Bawazer



Schematic overview of the drug depot refilling strategy. Reproduced with permission from *Proc. Natl. Acad. Sci. U.S.A.* **111** (35) (2014), DOI: 10.1073/pnas.1413027111; p. 12722.

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