targeting mechanism. Researchers inject an alginate hydrogel modified with bioorthogonal handles (tetrazines) at the site where a drug is needed, and then add a pro-drug that carries complementary handles (for example, trans-cyclooctene modified doxorubicin). The pro-drug is stable and almost inactive in the body, until it comes into contact with the hydrogel, at which point the bioorthogonal reaction frees the drug. This reduces off-target exposure and enables very high local dosing of the drug.

The company has used the method to deliver doxorubicin in mice with soft tissue sarcoma grafts and found that it causes substantially lower side effects and greater efficacy than treatment with doxorubicin alone. Similar experiments in mice using an antibiotic pro-drug showed that the hydrogel contained enough bioorthogonal handles to activate the antibiotic even after repeated doses. "That's because the amount of binding agent you have on the material is so much larger than the dose you're providing," explains Jose M. Mejia Oneto, President and CEO of Shasqi.

Unciti-Broceta hopes that the launch of first clinical trials of in vivo bioorthogonal chemistry will generate more interest in this multidisciplinary field. Meanwhile, specialist companies are now providing the starting reagents needed for bioorthogonal chemistry, making it more accessible for those unfamiliar with organic synthesis. "The feeling is that the community is really growing," Unciti-Broceta says, "and it's helping to create a lot of new collaborations." ❐

Mark Peplow
Cambridge, UK

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PODCAST

First Rounders: Cigall Kadoch

Cigall Kadoch is a co-founder of Foghorn Therapeutics and an assistant professor at the Dana-Farber Cancer Institute, where she runs the Kadoch lab. In her talk with *Nature Biotechnology*, she discusses launching Foghorn, how geography affects biotech success, and the link between interior design and scientific rigor.
https://www.nature.com/nbt/podcast

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