Radionuclide therapy with accumulated nanobots reduces bladder tumor size in vivo

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Enzyme-powered nanoparticles, known as nanobots, have emerged as a promising approach for performing tasks at the nanoscale, ranging from targeted drug delivery to precision medicine. Among these, urease-powered nanobots have shown improved diffusion and 3D navigation within biological environments[1] and drug delivery efficacy[2,3], compared to non-motile nanoparticles. The propulsion mechanism of these urease-powered nanobots, driven by urea (a readily available substance in the body), makes them particularly well-suited for potential applications in treating bladder cancer. Current treatments for this disease involve intravesical drug administration, which has shown good survival rates but limited therapeutic efficacy. Several factors, such as the sedimentation of therapeutic agents and the continuous addition of fresh urine, hinder the even diffusion of drugs throughout the entire bladder volume. Moreover, poor retention in the bladder and low penetration in the target site may leave certain subregions untreated, potentially leading to recurrence. To address these unresolved medical challenges, nanobots have emerged as a viable solution. In this context, our study demonstrates an enhanced accumulation of radiolabeled urease-powered nanobots within bladder tumors using an orthotopic murine model. Furthermore, we provide evidence that intravesically administered radio-iodinated nanobots exhibit a radionuclide therapeutic effect, resulting in significant tumor size reductions of approximately 90% when compared with non-treated mice. These promising results firmly position nanobots as highly efficient nanosystems for bladder cancer therapy.

References

[1] Hortelao, A. C.; Simó, C.; Guix, M.; Guallar-Garrido, S.; Julián, E.; Vilela, D.; Rejc, L.; Ramos-Cabrer, P.; Cossío, U.; Gómez-Vallejo, V.; Patiño, T.; Llop, J.; Sánchez, S. Swarming Behavior and in Vivo Monitoring of Enzymatic Nanomotors within the Bladder. *Sci. Robot.* **2021**, *6* (52), eabd2823. https://doi.org/10.1126/scirobotics.abd2823.

[2] Llopis-Lorente, A.; Garciá-Fernández, A.; Murillo-Cremaes, N.; Hortelaõ, A. C.; Patinõ, T.; Villalonga, R.; Sancenón, F.; Martínez-Máñez, R.; Sánchez, S. Enzyme-Powered Gated Mesoporous Silica Nanomotors for on-Command Intracellular Payload Delivery. *ACS Nano* **2019**, *13* (10), 12171–12183. https://doi.org/10.1021/acsnano.9b06706.

[3] Hortelão, A. C.; Patiño, T.; Perez-Jiménez, A.; Blanco, À.; Sánchez, S. Enzyme-Powered Nanobots Enhance Anticancer Drug Delivery. *Adv. Funct. Mater.* **2018**, *28* (25), 1–10. https://doi.org/10.1002/adfm.201705086.

Figures

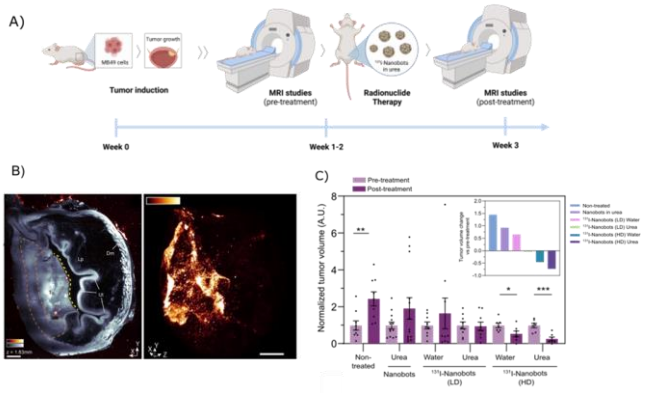

Figure 1. Nanobots penetrate and reduce bladder tumors size. A) Schematic representation of the radionuclide therapy studies. B) Left: Plane in the center of the bladder showing autofluorescence (grey) and scattered light-sheet (sLS) signal. Right: Maximum intensity projection of sLS signal inside the bladder. C) Normalized tumor volume obtained by MRI pre- and post-treatment. LD denotes low dose and HD high dose of ^{131}I.