Starving Tumor to Death by DNA Nanorobots

Reported by YAN Fusheng

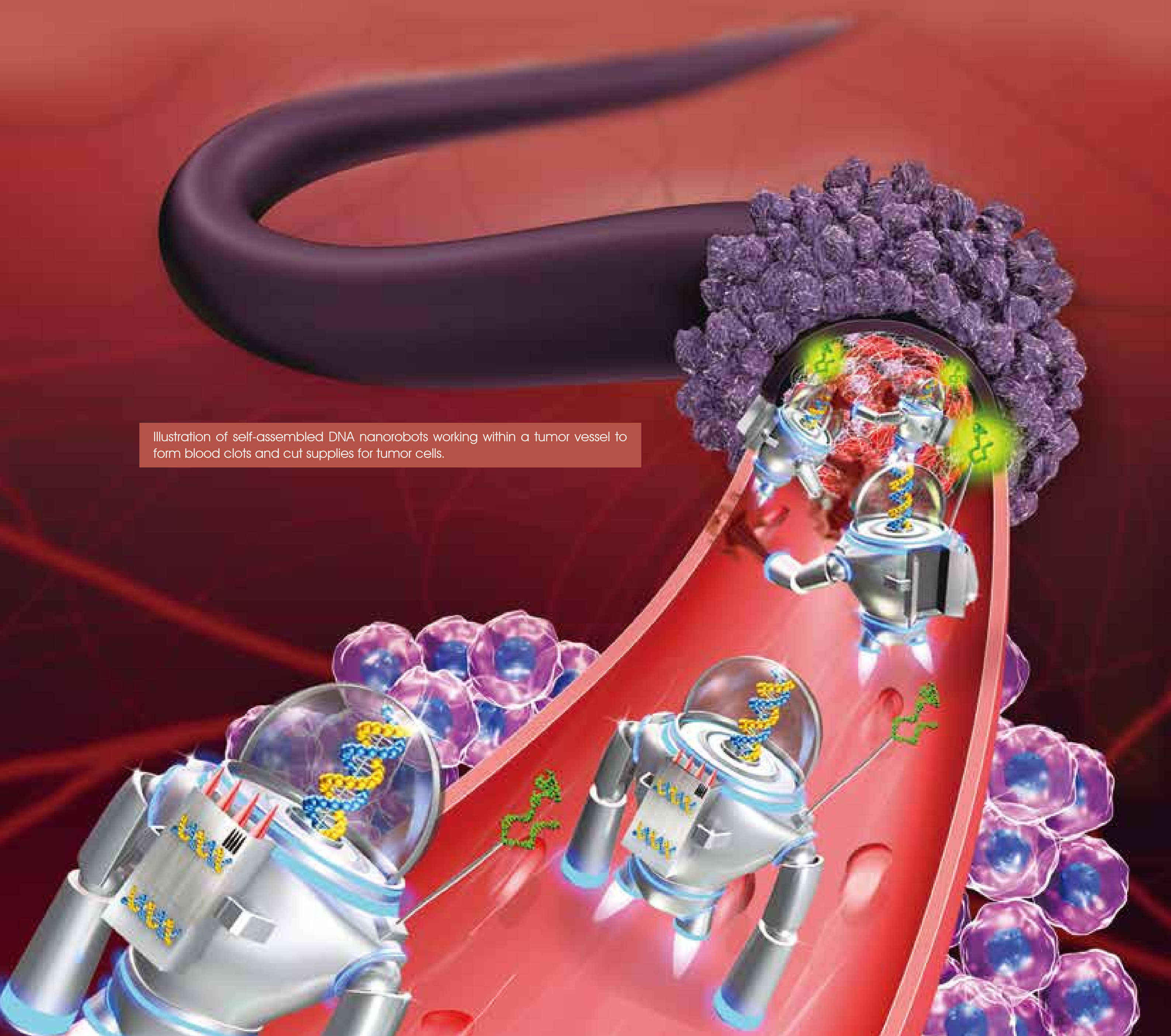
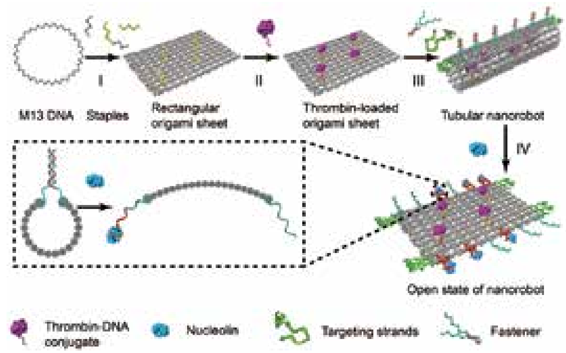


Illustration of self-assembled DNA nanorobots working within a tumor vessel to form blood clots and cut supplies for tumor cells.

Scientists have long been seeking to spontaneously spot and cure human diseases by using smart nanorobots. In February 2018, a kind of DNA origami-based nanorobots for cancer therapy was devised by a combined team jointly led by Profs. NIE Guangjun, DING Baoquan and ZHAO Yuliang from the **CAS National Center for Nanoscience and Technology (NCNST) based in Beijing, China** and Prof. YAN Hao from Arizona State University, USA. Once introduced into the circulation, these nanorobots can deliver thrombin – an enzyme that causes blood clotting – precisely to tumor-associated blood vessels, trigger clotting at the tumor site to cut off blood supply to the tumor cells, and starve them to death.

These nanorobots consist of three functional parts: DNA origami nanostructure, thrombin and DNA aptamer (see figure *Right*). DNA origami is a type of folding DNA with a precise nanoscale shape or pattern, which are usually folded from a long single-stranded scaffold DNA (M13 genomic DNA in this case) with hundreds of short helper DNA strands (the staples). In this design, DNA origami, in the shape of a rectangular raft, is loaded with thrombin, an enzyme that causes blood clotting. DNA aptamer is a short single-stranded DNA that can bind to a certain target. In this case, it binds to nucleolin, a tumor biomarker highly expressed within the tumor environment. DNA aptamers are used in the design of targeting strands and fasteners (figure *Right*). The targeting strands are anchored at the ends of DNA tubes for the navigation of nanorobots; the fasteners suture and lock the origami raft into a tube to form the smart nanorobots.

Highlighted in this design is the automatic mechanism inherent to the DNA functional parts that makes the nanorobots "smart". When the nanorobots are initially injected into the blood circulation, the thrombin molecules are encapsulated within the origami tubes, and thus are prevented from causing blood clots. The targeting strands allow the nanorobots to better navigate into the blood vessels at the tumor site. Once the nanorobots enter these tumor-associated vessels, they will unfold themselves upon recognizing and docking nucleolin – a surface marker that is highly expressed on the surface of actively proliferating tumor vascular endothelial cells – through the fasteners.



Design of the smart DNA Nanorobot. DNA origami, in the shape of a rectangular raft, is loaded with thrombin, an enzyme that causes blood clotting. The origami raft is sutured into a tube by the fasteners. One of the fasteners is zoomed in, indicating how the smart DNA nanorobot unfolds itself upon recognizing and docking onto nucleolin, a surface protein that highly expressed on tumor-associated endothelial cells. (Credit: NCNST)

Upon unfolding, the loaded thrombins set to work, building up blockage by catalyzing the formation of blood clots. This smart feature of stimuli-responsive reconfiguration of nanorobots ensures that clotting only occurs at the tumor site, not at the site of normal tissues, where they could cause damages.

These DNA nanorobots have demonstrated the ability to shrink various tumors in mice models, and are safe to use in miniature pigs without eliciting systematic blood clots and detrimental immune responses, confirmed the researchers.

Though its clinical relevance remains to be tested in humans, this work sets a paradigm for designing smart nanorobots for tumor infarction therapies. One setback, however, is that the short helper DNA strands (the staples) require to be artificially synthesized and do not come cheap; meanwhile, a large number of these DNA strands are required to build one single nanorobot, which ultimately adds up the costs.

To advance DNA nanorobots for human use, scientists still need to figure out how to reduce the costs for both the DNA chemical synthesis and the production of DNA nanostructures with high purity, stated the researchers in another review paper.

References

1. Suping Li, Qiao Jiang, Shaoli Liu, Yinlong Zhang, Yanhua Tian, Chen Song, Jing Wang, Yiguo Zou, Gregory J. Anderson, Jing-Yan Han, Yung Chang, Yan Liu, Chen Zhang, Liang Chen, Guangbiao Zhou, **Guangjun Nie***, **Hao Yan***, **Baoquan Ding***, **Yuliang Zhao***, A DNA Nanorobot Functions as a Cancer Therapeutic in Response to a Molecular Trigger In Vivo. *Nature biotechnology* 36, 258 (Published: February 12, 2018). doi: 10.1038/nbt.4071.

2. Suping Li, Qiao Jiang, **Baoquan Ding***, **Guangjun Nie***, Anticancer Activities of Tumor-Killing Nanorobots. *Trends in biotechnology*, (Published: February 27, 2019). doi: 10.1016/j.tibtech.2019.01.010.