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CANCER IMMUNOTHERAPY

T cells tackle tumours

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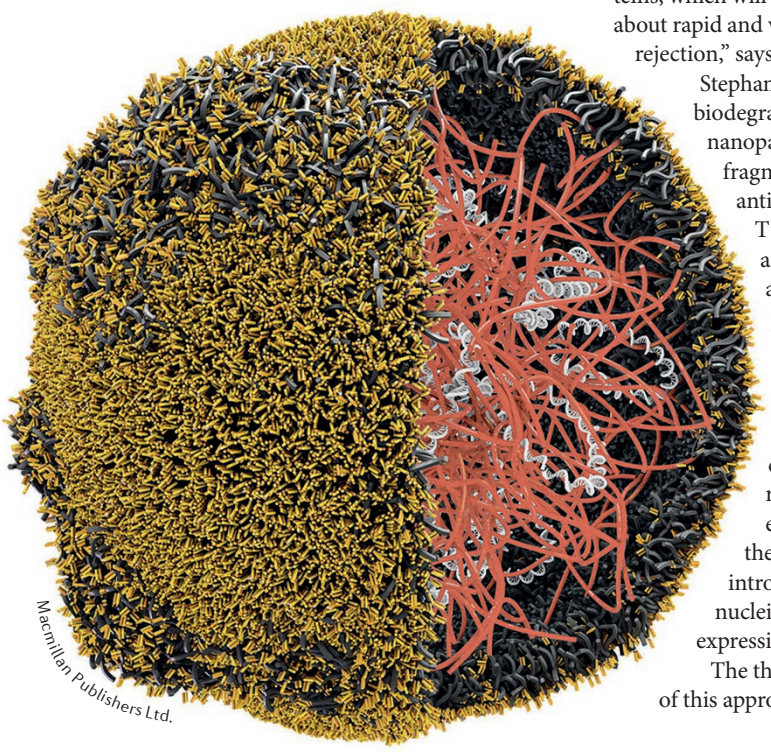
Systemically injected synthetic nanoparticles can direct T cells to recognize specific receptors on cancer cells and cause cancer cell death *in vivo*, report Matthias Stephan and colleagues in *Nature Nanotechnology*.

Using targeted T cell therapies to treat cancer has the potential to be a more precise arsenal against the disease compared with chemotherapy and radiotherapy. However, conventional methods for this cancer immunotherapy approach require patient-derived T cells to be modified with genes and increased in number *ex vivo* before reinfusion into the patient. This leads to costly manufacturing steps and limits the number of patients who can receive treatment because of the need for specialist centres.

Now, Matthias Stephan and colleagues report a nanoparticle-based delivery system that can introduce plasmid DNA encoding leukaemia-specific receptors into the nuclei of T cells *in vivo*. The nanoparticles can programme T cells to recognize cancer cells in sufficient quantities to show long-term remission in a leukaemia mouse model. "We demonstrate that T cells circulating in the blood can be genetically reconfigured by targeted, gene-bearing nanoparticles to express receptors that bind specifically to tumour proteins, which will enable them to bring about rapid and vigorous tumour rejection," says Stephan.



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Stephan and colleagues use biodegradable polymeric nanoparticles coated with fragments of anti-CD3 antibodies to target T lymphocytes. These antibody fragments allow the nanoparticles to enter the cells through endocytosis. The plasmid DNA encoded with leukaemia-specific chimeric antigen receptors (CARs) encapsulated in these nanocarriers is introduced to the T cell nuclei, and persistent CAR expression is observed.

The therapeutic efficacy of this approach — in terms of cancer regression — is similar to the efficacy of using conventional infusions of T cells that have been modified and expanded *ex vivo*. However, an 'off-the-shelf' nanoparticle system that circumvents the need for T cells to be isolated and then reinfused at a later time has clear practical advantages.

The challenge now is to translate this technology into a clinical setting. In addition, the researchers aim to use different targeting ligands to direct nanocarriers to other immune cells, including phagocytes, natural killer cells, invariant natural killer T cells, or even synergistic cell combinations, with the end goal of attacking cancer cells.

There is also considerable scope for treating different cancers with this nanoparticle system in the future. "Many new cancer-recognizing receptors are cloned each year, so we believe this system will yield a conceptual framework that eventually produces a repertoire of nanoparticle-based drugs for cancer patients," explains Stephan.

"Besides CARs, we are adapting this technology to reprogramme host T cells with cloned high-affinity T cell receptors specific for various viral antigens," says Stephan. "Thus, the results of our study could also provide groundwork for developing a new strategy to treat infectious diseases, such as HIV or hepatitis."

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ORIGINAL ARTICLE Smith, T. T. *et al. In situ* programming of leukaemia-specific T cells using synthetic DNA nanocarriers. *Nat. Nanotechnol.* http://dx.doi.org/10.1038/nnano.2017.57 (2017)

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