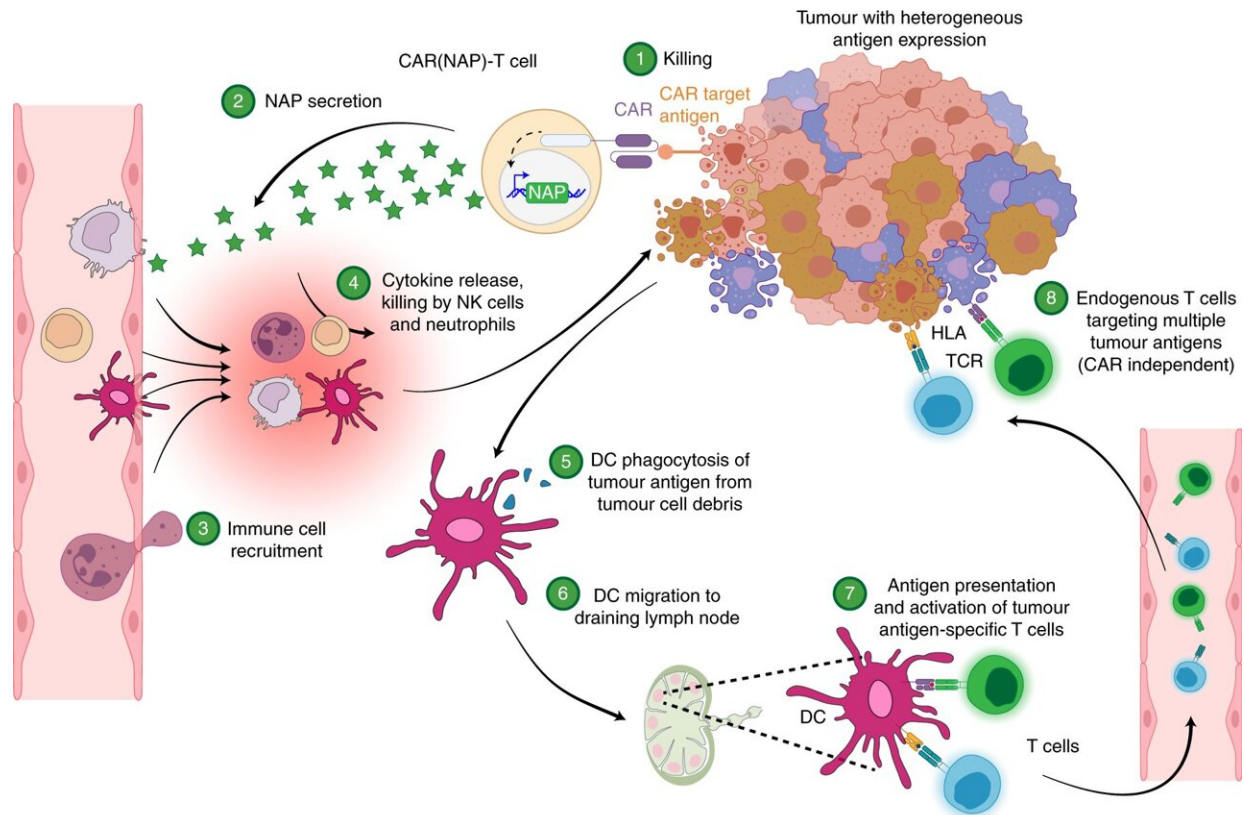


Armed CAR-T cells to better fight cancer

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Proposed mode of action of CAR(NAP) T-cell therapy. CAR(NAP) T cells are CAR T cells armed with NAP, an immune activator derived from *H. pylori*. Within a solid tumor, heterogeneity in antigen expression makes it difficult to eradicate all tumor cells with conventional CAR T cells. CAR(NAP) T cells secrete NAP during killing of tumor cells (Steps 1 and 2). NAP works as a chemoattractant, recruiting innate immune cells, such as neutrophils and NK cells, and activates them to directly kill tumor cells independent of whether they express the CAR target or not (Steps 3 and 4). NAP also recruits monocytes and DCs, and activates them to secrete pro-inflammatory cytokines that directly counteract the hostile tumor microenvironment and strengthen the function of

CAR(NAP) T cells. Immature DCs can phagocytose cell debris from dying tumor cells (Step 5). During this process, the DCs mature and migrate to a draining lymph node (Step 6) where they degrade the tumor cell debris and present peptides, including tumor-associated antigens, on the human leukocyte antigen (HLA) molecules to naive T cells. T cells with matching T-cell receptors (TCRs) recognize tumor-associated antigen epitopes and become activated (Step 7). The newly activated T cells recirculate back to the tumor site and kill the tumor cells through TCR-mediated recognition, which is independent of the antigen targeted by the CAR (Step 8). Therefore, this technology can counteract heterogeneity in antigen expression within solid tumors. Credit: *Nature Biomedical Engineering* (2022). DOI: 10.1038/s41551-022-00875-5

Immunotherapy is increasingly becoming a successful way to treat cancer. Researchers at Uppsala University have now developed armed CAR-T cells that reinforce the immune defense against cancer and that could increase the possibilities to successfully treat solid tumors. The study has been published in the journal *Nature Biomedical Engineering*.

The use of immunotherapy to treat cancer is increasing and genetically modified immune cells called CAR-T cells are efficacious for treating [blood cancer](#). Unfortunately, their efficiency is impaired in [solid tumors](#) due to local immune suppression in the tumor.

To avoid this problem, the Uppsala researchers have armed CAR-T cells by introducing a gene that encodes the immune stimulatory protein NAP (neutrophil-activating protein) from the bacteria *Helicobacter pylori*. When NAP is released from the CAR-T cells this creates a proinflammatory environment which directly combats the immunosuppressive microenvironment in solid tumors and strengthens the function of the CAR-T cells.

"We believe that this new technology to arm CAR-T cells has the

potential to completely change CAR-T cell treatment. NAP, secreted from the armed CAR-T cells can revert the tumors from immunologically 'cold' to 'hot.' In addition, NAP can also recruit other types of [immune cells](#) that can attack the tumor cells that are not recognized by the CAR-T cells," says Di Yu, researcher at the Department of Immunology, Genetics and Pathology, who has led the study together with Professor Magnus Essand at the same department.

To investigate the effect of CAR(NAP)-T cells, the researchers treated mice with different types of tumors and saw that tumor growth was reduced. The survival also increased compared to when CAR-T cells without NAP were used. The researchers also studied human CAR(NAP)-T cells in in vitro experiments and found that they had a better immunostimulatory capacity than conventional human CAR-T cells.

"We have a strong tradition with CAR-T cell treatment of [cancer](#) in Uppsala, with Gunilla Enblad and Angelica Loskog treating the first patients in Europe back in 2014. Two academic trials, with in total 39 treated patients, have been performed at Uppsala University Hospital. Based on the strong results in our *Nature Biomedical Engineering* paper, we are now planning for a clinical trial with our new armed CAR-T cells. We hope to treat the first patient by the end of this year," says Magnus Essand.

More information: Chuan Jin et al, CAR T cells expressing a bacterial virulence factor trigger potent bystander antitumour responses in solid cancers, *Nature Biomedical Engineering* (2022). [DOI: 10.1038/s41551-022-00875-5](https://doi.org/10.1038/s41551-022-00875-5)

Provided by Uppsala University

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