KILLCANCER Project

Nanobody-targeted photodynamic therapy to kill cancer

Current cancer therapies often fail to cure patients. Ideally, a cancer therapy should locally eradicate the cancer and should be capable of activating the immune system to create a memory and protect from recurrences.

Photodynamic therapy (PDT) is a treatment approach in which cancer cells are killed with compounds, named photosensitisers, that are activated locally through light exposure. Either the photosensitiser or the light alone are harmless, but when combined these can create toxicity and damage cells containing the photosensitiser.

Current protocols in the clinic start with the injection of a solution of photosensitiser into the bloodstream, allowing its distribution throughout the body. Two to four days later, the photosensitiser has been eliminated from normal cells, but is retained in cancer cells. At that point, the tumour is exposed to laser light of a specific wavelength. This activates the photosensitiser, which leads to the production of toxic reactive oxygen species that destroy cancer cells. Importantly, PDT has been described to activate the immune system, which could protect patients from recurrences. However, current PDT is only partly cancer specific and patients remain sensitive to light for several weeks after treatment.

Over the years, efforts have been made to improve cancer specificity of PDT, for instance by using antibodies to target the photosensitisers to cancer cells. Although this has been a significant improvement, and is currently being investigated in clinical trials, further advancements are still possible. Preclinical studies have shown that the antibody-photosensitiser conjugates are relatively large to penetrate and distribute homogeneously through tumours, preventing them from completely eradicating the cancer. Antibodies also circulate in the bloodstream for several days, which delays light application and makes the photosensitivity a remaining issue.

To solve all these issues, Dr. Oliveira has been developing since 2012 a new form of targeted PDT, using nanobodies to target the photosensitiser to cancer cells. Nanobodies are small antibody fragments derived from a particular class of antibodies that exist in camelids. Nanobodies are roughly ten times smaller than conventional antibodies, and because of this small size: 1. nanobodies accumulate in tumours within 1-2 hours after intravenous administration, 2. they distribute very well through a tumour mass, and 3. they are rapidly eliminated, if not associated or bound to cells. Thus, nanobody-targeted PDT enables the application of light shortly after administration of the nanobody-photosensitiser conjugate. Unlike the most traditional photosensitisers, the one use in this new approach is water soluble, so it does not stick randomly to every cell it encounters, but needs the nanobody to make it stick to the tumour cells.

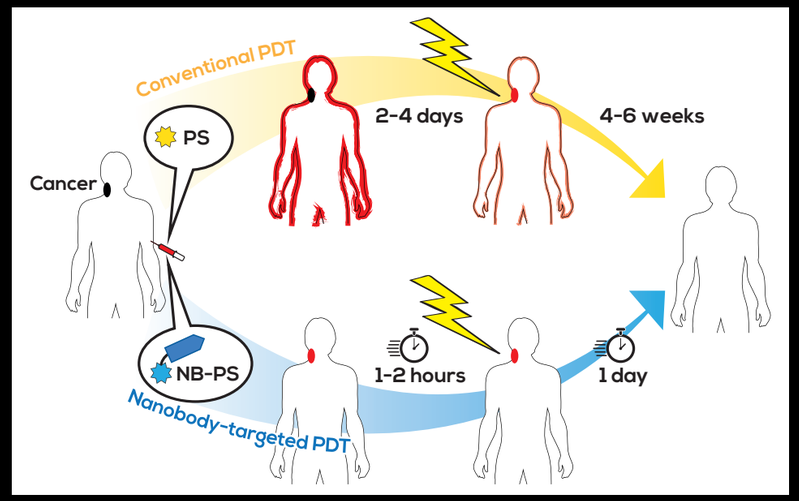

Figure 1. Schematic representation of conventional photodynamic therapy (PDT) and of what can be expected from the nanobody-targeted PDT. (PS: photosensitiser; NB-PS: nanobody-photosensitiser conjugate)

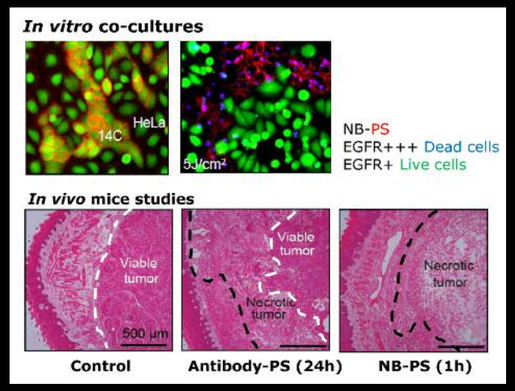

Figure 2. Nanobody-targeted PDT is selective to cells with overexpression of the tumour marker (e.g. EGFR), whereas normal cells remain alive. Proof of principle in vivo study showing extensive tumour damage when nanobody-targeted PDT is applied, while areas of viable tumour are visible after antibody-targeted PDT. (Illumination time post injection is indicated)

One of the great advantages of PDT is that the toxicity is only created where light is applied, thus it is not harmful to the patient's healthy tissues. By rendering the accumulation of the photosensitiser even more cancer-specific, using nanobodies, the chances of side-effects are even lower. This makes targeted PDT an excellent alternative for patients with tumours in places that are too risky to operate on, for example in the head and neck regions, because of the collateral damage that could occur. The second main advantage of PDT is that it can activate the patient's immune system, possibly inducing long-term protection against the recurrence of the cancer.

Studies in vitro and in vivo show that nanobody-photosensitiser conjugates bind rapidly and specifically to the cancer cells, distribute homogeneously throughout the tumour, and after illumination lead to approximately 90% tumour damage. These conjugates can also be traced in the body though optical imaging, to help and guide the application of PDT.

Since July 2016, within the KILLCANCER project, efforts have been made to better understand the mechanism of nanobody-targeted PDT, its potential to induce tumour regression in vivo, and its capacity to trigger the immune system. Encouraging results have been obtained and scientific publications are in preparation. In addition, efforts have been made with cell lines from other species, in an attempt to move into the veterinary clinic for testing of this new treatment in companion animals with spontaneously developing cancers.

KILLCANCER will scientifically advance the field of targeted PDT, by providing essential information on its mechanism of action and the feasibility of this approach to treat human cancer patients, to ultimately improve current cancer treatment.

The KILLCANCER team. Left to right: postdoc Yingxin Yu, PhD student Vida Mashayekhi, Sabrina Oliveira and PhD student Irati Beltrán Hernández

KILLCANCER
NANOBODY TARGETED PHOTODYNAMIC THERAPY TO KILL CANCER

PROJECT SUMMARY

KILLCANCER aims to better understand and to advance a new form of targeted photodynamic therapy, a cancer therapy that is local, cancer specific, and may induce long-term protection through activation of the immune system. This new form makes use of nanobodies to render the therapy more effective and cancer specific.

PROJECT PARTNERS

Important partners in this project are the Science Faculty and the Veterinary Faculty of Utrecht University, the Utrecht and Leiden University Medical Centers, and the Erasmus Medical Center in Rotterdam. These ensure the clinical relevance of our studies and will contribute to a faster translation to the clinic.

PROJECT LEAD PROFILE

Dr Oliveira is an Assistant Professor at Utrecht University, with a shared position between the department of Biology and the department of Pharmaceutical Sciences. Her research group is named Molecular Targeted Therapies and focuses on improving current therapies by making these more target-specific using nanobodies.

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