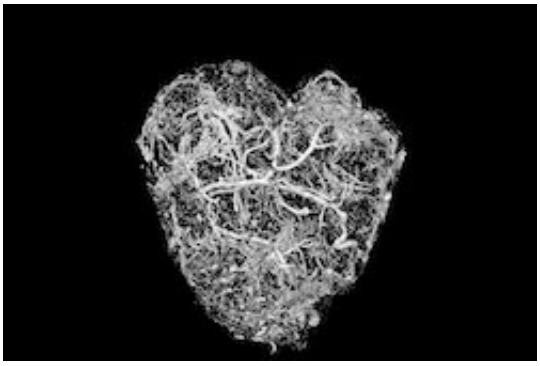
New tools to boost the delivery of drugs to cancer tumours

May 2 2018



Credit: Prof Dr Twan Lanmers

The treatment of cancer tumours is made complex by their microenvironment and the abnormalities of the blood vessels sustaining them. The EU-funded NeoNaNo project has developed methods to improve drug delivery to tumours and improve the efficacy of anticancer therapy.

Drug delivery to tumours is difficult. The blood vessels they depend on are abnormally structured, heterogeneously distributed and relatively poorly perfused, so transporting the drugs is challenging. Once the drugs have been delivered, the dense and hostile tumour microenvironment makes it hard to target them precisely.

The NeoNaNo (Neoadjuvant Nanomedicines for vascular

Normalization) project worked to establish whether, by pre-treating tumours with anti-inflammatory nanomedicines, they could improve drug delivery to the areas in which they are most needed. The project evaluated the potential of pre-treating tumours with anti-inflammatory nanomedicines to prime the tumour vasculature for more efficient drug and oxygen delivery, thereby improving the efficacy of subsequently administered chemo- and radiotherapy.

Both pharmacological (liposomal dexamethasone, anti-CCL2 agents, macrophage-modulating proteins) and physical combination treatments (sonoporation) were evaluated as means of enhancing the delivery and efficacy of both standard chemotherapeutic drugs (

Surmounting the challenge

"The first stage of establishing a more effective treatment for cancer tumours is to get a clear idea of the structure of the tumour," explained Professor Twan Lammers, the project's principal investigator. "We then needed to accurately visualise and quantify drug delivery within that structure."

In the first half of the project, NeoNaNo optimised in vivo and ex vivo contrast-enhanced micro-computed tomography (CT) to improve quantitative 3-D analyses on the vascular network in tumours.

To establish how well the delivered drug was distributed and to see if there was build-up in the tumour, the team also harnessed hybrid computed tomography, fluorescence molecular tomography (CT-FMT). This permitted them to non-invasively and quantitatively assess the biodistribution and target site accumulation of nanomedicine formulations.

Using these visualisation techniques NeoNaNo went on to assess the

impact of vascular normalisation on tumour blood vessels, on drug delivery to tumours, and on the therapeutic efficacy of nanomedicine-based combination therapies.

Boosting the efficacy of drug delivery systems

"We found that we were able to lower the collagen content in tumours by using liposomal dexamethasone. This helped with the accumulation and penetration of drugs," says Prof. Lammers, based at the University of Aachen, Germany.

The project's research showed drug delivery systems (DDS) also benefited from the inhibition of CCL2-dependent macrophage infiltration, which had the added advantage of attenuating pathological angiogenesis. Finally, by using a combination of ultrasound and microbubbles, the project showed it was possible to open up blood vessels in tumours, and in the brain, enhancing DDS extravasation and penetration.

Translating findings into results

These findings add to the tools that clinicians can draw on to pre-treat tumours to make them more susceptible to the traditional approaches of chemo- and radio-therapies.

Their results showed that pharmacological and physical priming, such as broadly applicable ultrasound protocols to enhance drug delivery to, and into, tumours, can improve tumour-targeted drug delivery. Priming may also help to improve the efficacy of systemic (nano-) chemotherapeutic interventions.

Liposomal dexamethasone is now being evaluated in a first, in-man

clinical trial at the Center for Clinical and Translational Research in Aachen for the treatment of multiple myeloma.

"Our EU funding through NeoNaNo has fostered the development of tumour-targeted combination therapies," says Lammers. "Through NeoNaNo, relevant steps were taken to further the pharmaceutical and clinical development of a novel liposomal corticosteroid formulation, which may have multiple advantages when applied in combination with other drugs in patients suffering from multiple myeloma."

Provided by CORDIS