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AREA OF EXPERTISE:	Tumor Immunology
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DISSERTATION TITLE: *Activation of antitumor M1 macrophages for cancer immunotherapy.*

The last few years have seen the arrival of new effective cancer therapies which is directed at the immune system rather than the cancer cells directly. One type of cancer immunotherapies is the so-called checkpoint inhibitors, which function by releasing a break on the immune response against cancer cells. Although resulting in impressive results, certain patients remain unresponsive and new strategies for immunotherapies are needed.

In her PhD project, Elisabeth Müller has been searching for a switch that could get a part of the body's immune cells started fighting cancer cells. She has found several new molecular combinations that are able to activate antitumor functions of macrophages in vitro. Her findings may result in the development of better strategies for delivering active drugs specifically to the macrophages in tumors. Such strategies include the use of viral vectors that specifically infect tumor cells and drugs that are encapsulated into nanoparticles. Once tested and confirmed in vivo, activation of antitumor macrophages could be an important treatment strategy for patients that do not respond sufficiently to checkpoint inhibitors, or in combination with therapeutic cancer vaccines which are not effective as monotherapy.

Elisabeth Müller and her colleagues were able to find several compounds, called TLR agonists that activate macrophages when combined with the protein interferon-γ (IFN-γ). These macrophages produce a toxic compound called nitric oxide and prevent cancer cells from growing in vitro. However, it has previously been proven difficult to treat patients with effective doses of IFN-γ without causing harmful side effects. This thesis describes a new way to deliver IFN-γ to the tumor only using viral vectors that specifically infect cancer cells. Upon infection, the cancer cells are programmed to produce and secrete IFN-γ, before later

dying. The IFN-γ produced was able to activate antitumor macrophages when combined with TLR agonists. These viral vectors will be tested in vivo for their ability to infect cancer cells in growing tumors and activate a macrophage-mediated antitumor immune response.

In her last paper, Elisabeth Müller and colleagues discovered that two other proteins, IFN-α and IFN-β, can activate macrophages in a similar way as IFN-γ. As macrophages can produce their own IFN-α and IFN-β, this opens up for new ways to make macrophages inhibit cancer cell growth. Müller replaced these proteins altogether with a combination of two TLR agonists, one of which made the macrophages produce IFN-α and IFN-β. This TLR agonist, poly(I:C), also was encapsulated into highly effective nanoparticles, which are taken up specifically by macrophages. Such nanoparticles have the potential to improve the accuracy of drug delivery to tumors and will be tested in animal models in the future.