Modulation of STAT3-mediated tumor-associated tolerance mechanisms using IL-2 functionalized hydroxyethyl starch (HES) nanocapsules

Marie-Luise Frey[1], Matthias P. Domogalla[2], Sarah Christmann[1], Svenja Morsbach[1], Kerstin Steinbrink[2] and Katharina Landfester[1]

[1] *Max-Planck-Institute for Polymer Research, 55128 Mainz, Germany*
[2] *Department of Dermatology, University Medical Center Mainz, Johannes Gutenberg-University Mainz, 55099 Mainz, Germany*

Since immunotherapy has proven to be a successful method for cancer treatment, combining it with nanotechnology is the next step in modern medicine. Nonetheless, tumor-associated tolerance mechanisms are able to promote tumor growth and still represent a big challenge in anti-cancer therapies [1]. The human immune system consists of many different cell types whose regulation is extraordinarily complex. Using the cytokine IL-2, T-cells can specifically be activated and their growth and differentiation can be stimulated. Since the exact amount of IL-2 plays an important role for addressing different T-cell subsets, hydroxyethyl starch (HES)-based nanocapsules are used as carriers for a controlled delivery to the immune cells [2]. These nanocapsules with defined size are prepared in an inverse miniemulsion process and are further functionalized by introducing dibenzocyclooctyne (DBCO) groups for copper-free click chemistry. By inserting an azide group into IL-2, the protein was covalently bind to the nanocapsule surface [2]. Flow cytometry and laser scanning microscopy experiments showed increased binding and uptake of these surface modified HES-nanocapsules by human activated T-cells, which indicates that the biological activity of the cytokine can be maintained. By reducing the amount of IL-2 on the capsule surface, a dose-dependency could be shown, while in contrast, however, a dose-independent uptake by regulatory T-cells (Treg) could be highlighted. Since regulatory T-cells (Treg) are involved in STAT3-mediated tolerance mechanisms, the controlled delivery of encapsulated STAT3-inhibitors could represent one example of the intervention into such a tumor-associated tolerance mechanism.

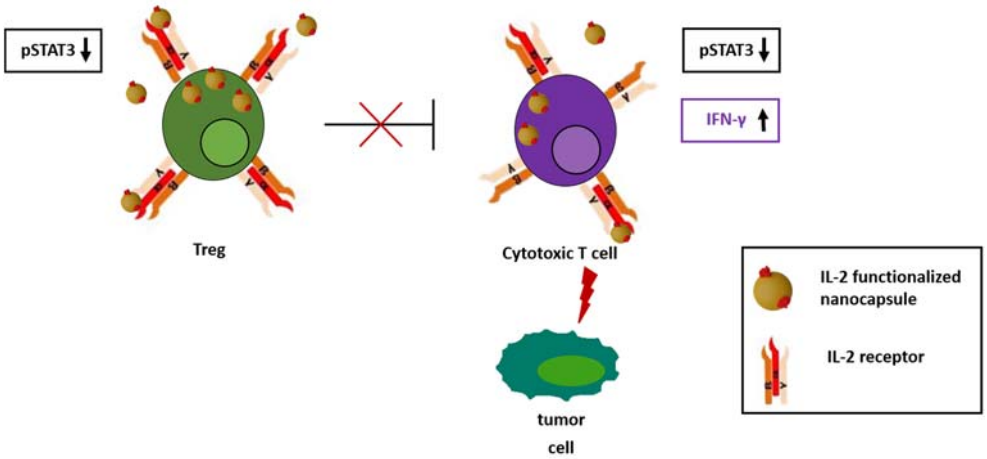

Figure 1. IL-2 functionalized nanocapsules could inhibit Treg cells and lead to tumor elimination.

[1] A. J. Adler, *Current Cancer Drug Targets* **7**, (2007), 3-14.
[2] S. U. Frick, M. P. Domogalla, G. Baier, F. R. Wurm, V. Mailänder, K. Landfester, K. Steinbrink, *ACS Nano* **10**, (2016), 9216-9226.

Acknowledgement: The authors acknowledge funding from SFB 1066 and the MPG.