Cancer immunotherapy aims to support the immune system in destroying tumors. Optimizing its effectiveness represents a major opportunity and unmet need.

The second messenger cyclic adenosine monophosphate (cAMP)(1) is used by all cell types and life forms to regulate metabolic activity and gene expression. In the immune system, disease-induced or pharmacological sustained elevation of cAMP levels dampen the function of all immune cell types.(2)

Christian Becker

Tobias Bopp

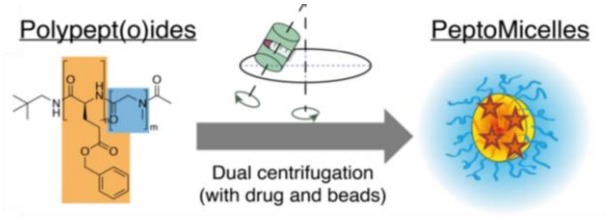
In 2006 Tobias and I started to investigate the immunosuppressive function of regulatory T cells (Treg) in mice and humans. We discovered, that Treg, unlike other T cells, accumulate increased intracellular amounts of cAMP and require it for the regulation of other immune cells.(3) Building on this observation, we were later able to show that Interferon-α, used for adjuvant therapy of melanoma, interferes with the cAMP formation in Treg, inactivating their suppressive activity.(4)

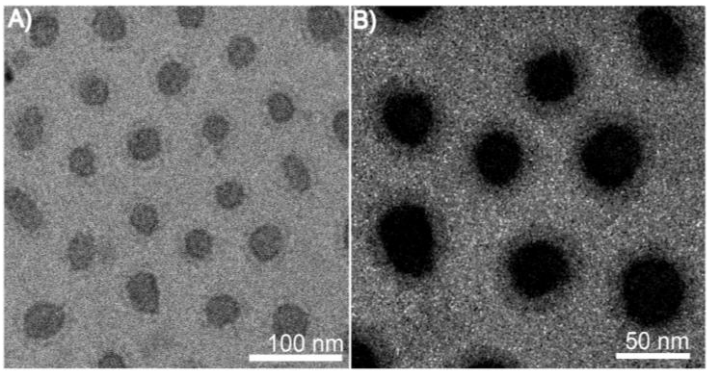
Excitingly, melanomas also appear to have elevated intracellular cAMP levels and these appear to promote metastasis, drug resistance and suppress immune responses against the tumor.(5-7) Investigating the origin of cAMP in melanoma, we found elevated levels of cAMP not only in melanoma cells and Treg, but also in tumor infiltrating macrophages (TAM). Following up on this observation, we showed that melanomas trigger increased cAMP formation in macrophages by acidifying their microenvironment, preventing them from targeting the tumor.(8)

Because of the pathway's involvement in virtually all physiological processes, it should not be interfered with systemically.

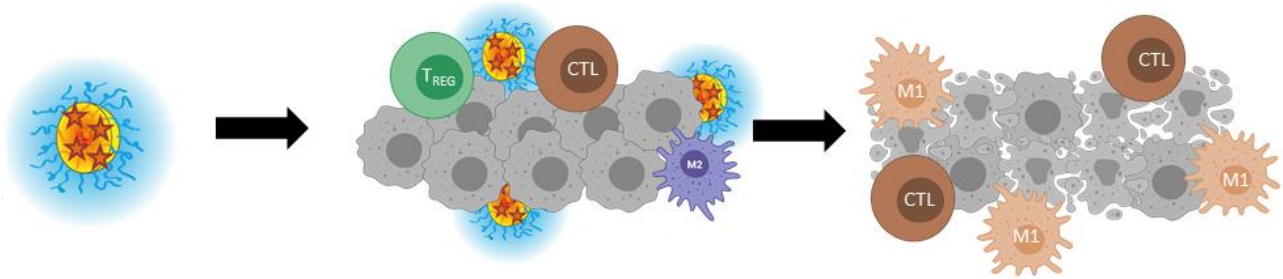
Matthias Barz

We therefore looked for a way to target it in tumor tissue, and so in 2017 we teamed up with Matthias Barz as part of a Collaborative Research Center SFB 1066 "Nanodimensional Polymer Therapeutics for Tumor Therapy" https://sfb1066.de/ project to explore the use of nanoparticles to interfere with cAMP formation in melanoma.





By the use of polymer micelles(9) and peritumoral injections we were able to restrict the effects of the adenylate cyclase inhibitor MDL 12330A to the tumor microenvironment and achieved a sustain release over prolonged times lowering cAMP levels locally at the tumor site. The use of amphiphilic block copolymers based on endogenous amino acids, namely polypept(o)ides (polypeptides-block-polypeptoid copolymers),(10-12) for the formulation of the drug avoided any detectable toxicity at the applied therapeutic doses.



Together, we have now shown that polymeric nanoparticles releasing an AC inhibitor in tumor tissue can be used to arrest melanoma growth.
We hope to have found a new approach for the therapy of melanoma and are developing it further towards systemic applicable therapies.

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