**Creation of immunosuppressive exosomes for the induction of antigen-specific tolerance**

DESCRIPTION FOR THE GENERAL PUBLIC

The immune system fights against cancer cells which can be recognized and destroyed by various mechanisms. Only after all the mechanisms of host immune defence have been overcome or in other words, the immune system is suppressed, a tumor is able to develop. A major player in the fight against cancer is the cytotoxic T cell which is able to destroy cancer cells. Interestingly, the cancerôs escape from the destruction by cytotoxic T cells is antigen specific: cancer induced tolerance does not suppress the immune system systematically, but shuts down the specific immune reaction to cancer cells. Cancer cells communicate their immunosuppressive activity in several different ways. One of them uses exosomes which are released by cancer cells and taken up by immune cells. Exosomes are biological nanoparticles generated intracellularly and released into the circulation. Exosomes function in intercellular communication through the exchange of proteins, functional mRNA and microRNA (miRNA) that can reprogram recipient cells. Cancer cell-derived exosomes contribute to cancer immunosuppression partially through reprogramming of antigen presenting cells which are converted into repressor cells.

In the current project, we propose to copy the strategy used by cancer cells to **create immunosuppressive exosomes able to shut down unwanted immune reactions**. A potentially harmful activation of the immune system occurs for instance during transplant rejections or autoimmune diseases. The overall idea is that exosomes are collected from donor cells (e.g. transplanted organ or tissue affected by auto-immune attacks) and manipulated in vitro to equip them with tolerogenic capacities. They should be e.g. loaded with miRNAs capable of inhibiting the expression of co-receptor proteins necessary for the efficient activation of immune responses. The lack of such co-receptors concomitant with intact antigen recognition will induce antigen-specific immunosuppression. The modified exosomes are then transferred into the patient where they are taken up by dendritic cells and induce their tolerogenic character.

For the project, in vitro studies are planned to elucidate the feasibility of such an approach. Exosomes isolated from cell cultures of normal cells will be loaded with siRNAs through electroporation. Dendritic cells, which occupy the key position deciding about immune stimulation or repression, will take up these exosomes and should acquire an inhibitory character. The co-receptor expression, maturation status and suppressive activity of exosome-treated dendritic cells will be analyzed. The suggested procedure should generate a powerful agent suitable for **antigen-specific** down-modulation of immune responses. In contrast to general immunosuppression through immunosuppressive drugs, which is currently applied after transplantation, the application of tolerogenic exosomes should be free from adverse side reactions. This is the first time that the usage of exosomes is suggested. The development of an antigen-specific natural approach for tolerance induction would provide the perfect tool to treat autoimmune diseases and to decrease rejection rates after organ transplantation.