KoRS-CB-NTU Joint PhD Programme in Chemical Biology

Project Summary

Our laboratory has developed and characterized biodegradable poly(D,L-lactide-*co*-glycolide) microspheres (PLGA-MS) as T cell vaccines against infectious diseases and cancer for many years. Protein or peptide antigens can be microencapsulated together with toll-like receptor (TLR) ligands into PLGA-MS (1), which are released from the MS over 30 days in aqueous solutions or in tissues. PLGA-MS are taken up by macrophages and dendritic cells (2, 3) which efficiently present the encapsulated antigen on MHC class I and II molecules (4, 5). In vivo application of PLGA-MS in mice enables long lasting cytotoxic and helper T cell responses which are strong enough to eliminate even large tumor masses (6, 7).

While we have thoroughly optimized the loading of PLGA-MS with TLR ligands and antigens, we have not yet tried to specifically target PLGA-MS to those subtypes of DC which are most effective in eliciting cytotoxic T cell responses. In this project we want to cooperate with the group of Prof. Valentin Wittmann (Dept. of Chemistry, Konstanz University) to develop PLGA-MS which are specifically targeted to mannose receptor positive DC. To this aim an activated mannose will be ether linked to the terminal hydroxy group of PLGA with lower molecular weight (commercially available at 2kD and 4 kD). The resulting mannose bearing polymers will be co-encapsulated with the so far used 14 kD PLGA polymer as well as ovalbumin as model antigen and CpG oligonucleotides as TLR ligands. Such mannose containing MS will then be compared to conventional MS in vitro with respect to their release kinetics, their uptake kinetics into DC, their ability to mature DC, and their efficiency to feed antigens into the MHC I and II presentation pathways.

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After the achievement of this aim, the Ph.D. student will travel to the laboratory of Prof. Karjalainen at NTU to test the strength of cytotoxic and helper T cell responses elicited by mannose containing as compared to conventional MS. To test, which DC and macrophage subpopulations are required to elicit these T cell responses, the different DTR transgenic mice recently generated by Profs. Karjalainen and Ruedl, which lack the respective antigen presenting cells, will be vaccinated with conventional and mannose containing MS and the T cell responses will be quantitatively assessed. Finally, it will be investigated at the NTU whether stronger T cell responses will result in the faster and more potent elimination of tumors.

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