Abstract Title: Development of frameshift peptide antigen based vaccine for cancer prevention in Lynch syndrome patients

Author Name: Prof. Matthias Kloor, Deputy Medical Director

Author Institute: Department of Applied Tumor Biology, Institute of Pathology, Heidelberg University Hospital, Heidelberg, Germany

Abstract: Lynch syndrome is caused by heterozygous germ line mutations of the DNA mismatch repair (MMR) genes. During life, somatic mutation events (second hits) lead to loss of MMR function in multiple crypts within the colonic mucosa. From thousands of such MMR-deficient crypt foci, however, only a very small part develops into clinically manifest cancers. These cancers are mostly diploid, but characterized by the microsatellite instability (MSI) phenotype, i.e. the accumulation of numerous insertion/deletion mutations at repetitive microsatellite sequences. Mutations affecting microsatellites in genes coding for tumor suppressor genes promote MSI tumor development in Lynch syndrome. Using a bioinformatics-based model, we have predicted a set of coding microsatellite mutations with likely driver function in Lynch syndrome. These mutations also lead to shifts of the translational reading frame and to the generation of MMR deficiency-related frameshift peptides (FSPs). The well-defined pattern of MMR deficiency-induced mutations and neoantigens has wide-ranging implications on the clinical course of the disease: as exactly the same mutations recurrently occur in exactly the same tumor suppressor genes, Lynch syndrome cancers share a small and predictable set of highly immunogenic FSP neoantigens. Immune responses against these FSP neoantigens can already be detected in tumor-free Lynch syndrome mutation carriers, suggesting that there is a lifelong interaction between the immune system and emerging precancerous cell clones. We have developed an FSP-based vaccine for cancer prevention in Lynch syndrome and obtained effectiveness data in a pre-clinical model. In addition, we successfully concluded a first-in-human clinical phase I/IIa trial demonstrating the safety and feasibility of the approach. The presentation will summarize the current status of the development and outline challenges and planned next steps towards the translation of cancer-preventive vaccines into the clinical reality.

Area of expertise: Hereditary cancer, Lynch syndrome, tumor immunology, cancer evolution, cancer prevention