High-risk HPV type 16 is the most oncogenic virus type that cause cervical, vulvar and head and neck cancer. Therapeutic vaccination with a set of 13 overlapping synthetic long peptides (SLP) covering the entire sequences of the E6 and E7 oncoproteins of HPV16 resulted in complete or partial regression of premalignant lesions in >50% of women presenting with premalignant HPV16-positive vulvar intraepithelial neoplasia (VIN) (Kenter et al. NEJM 2009). In preclinical mouse models TLR ligand-peptide conjugates performed better as therapeutic vaccines than long peptides mixed with the same TLR ligands. Notably, covalent attachment of TLR ligands to synthetic long peptides allows superior Dendritic cell (DC) targeting with antigen and DC activation \textit{in vitro} and \textit{in vivo}, resulting in superior T cell priming and tumor control in these animal models. Subsequently D Filippov and colleagues developed a proprietary TLR1/2 ligand, based on knowledge of the crystal structure of its interaction with the TLR1/2 receptor.

In 2013 we will conduct a phase I/II toxicity/immunogenicity clinical trial in HPV16-positive head and neck cancer patients with a vaccine formulation consisting of synthetic long peptides conjugated to the improved TLR-ligand. Two peptides were selected from the set of 13 HPV16 SLP based on immunogenicity in vaccinated patients in previous trials. When these novel TLR ligand-HPV peptide conjugates were functionally tested \textit{in vitro}, they both induced significant mouse and human DC maturation, as determined by IL-12 production and the upregulation of co-stimulatory molecules and other activation markers. Moreover, as determined by specific T-cell proliferation and cytokine production, the epitopes present in the peptides of both conjugates were much more efficiently recognized by HPV-specific human T-cell clones derived from VIN patients in comparison to mixtures of SLP and the same TLR ligand. Taken together, these results provide a solid basis for the further clinical development of proprietary TLRLigand-SLP conjugates.