Peptide-based vaccination is an immunotherapeutic strategy for cancer treatment involving administration of patients with immunogenic peptides derived from tumor antigens. The ability of a peptide cancer vaccine to elicit a strong immune response is determined by several factors, including the peptide’s affinity for MHC complexes, the antigen’s immunogenicity, and the presence of T cell clones (naive or memory) able to recognize the antigen. One of the factors influencing T cell repertoire development is the peptide:MHC complexity. We present a pre-existing cross-reactive heterologous memory T cell immunity selected by the gut microbiota can be activated by OncoMimics™ peptides and drive an efficient T cell immune response against Tumor-Associated Antigens (TAAs).

General CONCEPT and METHOD

**RESULTS**

Selected microbiota-derived OncoMimics™ peptides induce cross-reactive immune responses against human TAA peptides in HLA-A.02 humanized mice

**CONCLUSIONS**

Many studies support the link between microbiome and clinical response in cancer patients treated with targeted immunotherapies or with specific chemotherapeutic agents. Results obtained by Enterome and collaborators show that the innovative method presented here allows identification of gut microbiota-derived peptides presented on HLA and showing molecular memory with human tumor antigens. These peptides termed OncoMimics™ can elicit a strong immune response in HLA-A.02 humanized mice and drive the expansion of a significant pool of cytotoxic CD8 T cell cross-reactive against tumor antigens and cancer cells. Importantly, our data show that OncoMimics™ peptide-specific CD8 T cells are naturally present in human peripheral blood and are included in effector/memory compartments suggesting that they could have been guided by the gut microbiota. Our results also show that such T cell clones can be expanded in vitro and display a cytotoxic response against Tumor-Associated Antigens peptides. Thus, capitalizing on these T cells to target Tumor-Associated Antigens that are by themselves poorly immunogenic could harness, alone or in combination with immune checkpoint blockade, the cytotoxic immune response against a variety of cancers. In conclusion, Enterome has developed an innovative, microbiome-based approach for the discovery of therapeutic multipeptide cancer immunotherapies/vaccines. Two vaccine candidates are now being tested in 3 independent clinical trials (Glioblastoma, Adenral cancers, B-lymphomas).