ABSTRACT

Background: The current challenge in developing effective cancer vaccines is the accurate prediction of epitopes that induce CD8+ cytotoxic T-cell responses. Recent technological advances have enabled development of patient-specific therapeutic vaccines. However, in these vaccines only about 10-20% of the predicted neoepitopes induced CD8+ T-cell responses in patients. To overcome this limitation, we developed PASCal for improved selection of 10-peptide pools derived from predicted HLA-epitope pairs.

Method: PASCal operates by 3 modules: (1) a validated epitope database containing 10-peptide pools derived from 1300 tumor antigens and HLA Class I and II molecules covering the HLA genotypes of 26,000 subjects. (2) Expression frequency-based shared tumor antigen database established for 10 indications based on >68,000 tumor biopsies. (3) Algorithm for the identification of immunogenic peptides by the selection of personal epitopes (PEPIs) binding to 23 autologous HLA alleles. Using PASCal, personal 20mer peptide pools were designed for 3 PEPIs -epitope pairs derived from 1300 tumor antigens and optimized for CRC population.

Results: Personalized cancer vaccines containing PEPIs from 12 disease specific tumor-antigens most frequently expressed in the patients' disease. T-cell responses were induced by 100% of peptides. An average of 11/12 PEPIs induced CD8+ T-cell responses and 12/13 induced CD4+ T-cell responses in each patient. Pre-existing antigen specific T2-cell reactivities were detectable against 25% of vaccine antigens (consistent with the expression of the target vaccine antigens by the patient's tumor), the others were indeed de novo. Both CD8- and CD4+ T-cell responses were polyclonal, as evidenced by secretion of multiple cytokines determined by ELISPOT and Intracellular Cytokine Staining (ICS).

Conclusion: We used the largest validated database of tumor epitopes reported to-date along with an algorithm successfully selecting immunogenic peptides to develop personalized cancer vaccines. PASCal outperformed immunogenicity of personalized neoantigen vaccines and induced unprecedented immune responses in cancer patients.

PERSONAL EPITOPES (PEPIs)

PEPI is an epitope restricted by ≥2 autologous HLA of the individual capable to mount T cell response against the cell expressing the same PEPI.

PASCAL TECHNOLOGY

Key step: selection of validated Personal EPItopes (PEPIs) specific to the patient's HLA-genotype, not only to individual alleles.

PERI VALIDATION

Analytical validation – prediction of HLA-epitope binding was determined with an established Reference Standard containing HLA-epitope pairs derived by experimental methods (direct binding assays) reported immunogenicity of personalized mutation-based vaccines and induced peptide-specific immune responses for PT1 and PT2.

PERFECT VACCINATION

Memory CD8+ T cell responses were detected 14 months (436 days) after last vaccination against 4 tumor antigens Effecter (Ex-vivo) CD8+ T cell responses were detected 135 days (4.5 months) after last vaccination

SUMMARY

• PASCal is a new platform for
- the design of true immunogenic peptides - clinically validated
- target selection without the need for tumor biopsy - confirmed by measured immunogenicity responses
- 19 cancer indications – including the ones with low mutational burden
- PEPIs outperform reported immunogenicity of personalized mutation-based neoantigen vaccines and induced unprecedented immune responses in cancer patients.

References: Töke ER et al, JCO, 37, 2019 (suppl abstr #1025) Tóke ER et al, JCO, 37, 2019 (suppl abstr #1030) Tóke ER et al, JCO, 37, 2019 (suppl abstr #1031) Tóke ER et al, JCO, 37, 2019 (suppl abstr #1032) Treos Bio Zrt., Veszprém, Hungary; The Interdisciplinary Oncology Center Munich, Germany; #1181PD

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