IDENTIFICATION OF FREQUENTLY PRESENTED NON-MUTATED TUMOR-SPECIFIC IMMUNOGENS FOR THE DEVELOPMENT OF BOTH OFF-THE-SHELF AND PERSONALIZED VACCINES WITHOUT NEED FOR TUMOR BIOPSY

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Background Vaccines have little chance of destroying heterogeneous tumor cells since they rarely induce polyclonal T-cell responses against the tumor. The main challenge is the accurate identification of tumor targets recognizable by T cells. Presently, 6–8% of neoepitopes selected based on the patients' tumor biopsies are confirmed as real T cell targets.^{1 2}. To overcome this limitation, we developed a computational platform called Personal Antigen Selection Calculator (PASCAL) that identifies frequently presented immunogenic peptide sequences built on HLA-genetics and tumor profile of thousands of real individuals.³ Here we show the performance of PASCAL for the identification of both shared and personalized tumor targets in metastatic colorectal cancer (mCRC) and breast cancer subjects.

Methods Expression frequency of the tumor-specific antigens (TSAs) ranked in PASCAL's database (based on 7,548 CRC specimen) was compared to the RNA-sequencing data of CRC tumors obtained from TCGA. Using PASCAL, 12 shared PEPs (epitopes restricted to at least 3 HLA class I alleles of a subject from an in silico cohort) derived from 7 TSAs were selected as frequent targets (calculated probability: average 2.5 [95%CI 2.4–2.8] TSAs/patient). Spontaneous immune responses against each of the twelve 9mer peptides were determined by ELISpot using PBMCs of 10 mCRC subjects who participated in the OBERTO-101 study.⁴ PEPs selected for a breast cancer subject based on her HLA genotype were also tested.

Results Each of the 106 tumors analyzed expressed at least 13, average 15 of the 20 top-ranked TSAs in PASCAL's database confirming their prevalence in CRC. 7/10 subjects had spontaneous CD8+ T-cell responses against at least one peptide selected with PASCAL. Each peptide (12/12) was recognized by at least one patient. Patients' T-cells reacted with average 3.6/12 (30%) peptides confirming the expression of average 2.8 [95%CI 1.0–4.6] TSAs (n=10). After HLA-matching, among the subjects for whom we could select at least 4 PEPs (average 5) from the list of 12 peptides (n=6), average 2.5 (50%) peptides were positive. Of the 12 PEPs selected with PASCAL for a breast cancer subject, we detected spontaneous T-cell responses against 9 PEPs, indicating that at least 75% of the selected peptides were present in the subject's tumor and were recognized by T-cells.

Conclusions PASCAL platform accommodates both tumor- and patient heterogeneity and identifies non-mutated tumor targets that may trigger polyclonal cytotoxic T-cell responses. It is a rapid tool for the design of both off-the-shelf and personalized cancer vaccines negating the need for tumor biopsy.

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