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ORAL ABSTRACTS

654.MGUS, AMYLOIDOSIS AND OTHER NON-MYELOMA PLASMA CELL DYSCRASIAS: CLINICAL AND EPIDEMIOLOGICAL

Early Intervention and Favorable Biologic Effects of Personalized Neoantigen Vaccines on the Tumor Immune Microenvironment in Smoldering Waldenstrom Macroglobulinemia

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Lymphoplasmacytic lymphoma (LPL) is an incurable low-grade B-cell lymphoma, characterized by the presence of clonal tumor cells infiltrating the bone marrow. Despite a cumulative risk of progression, there is no approved therapy for patients in the asymptomatic phase. We conducted a first-in-human clinical trial of a novel individualized therapeutic DNA idiotype neoantigen vaccine as an early intervention in nine patients with untreated asymptomatic LPL. The vaccine platform encoded the autologous LPL-derived Ig single chain variable fragment fused to human chemokine CCL20 (macrophage inflammatory protein-3, MIP-3a), which was designed to trigger T-cell immunity by targeting delivery of the expressed fusion protein to antigen presenting cells. The vaccine was well tolerated with no dose limiting toxicities. One patient achieved a minor response, and all remaining patients experienced stable disease, with median time to disease progression of 61+ months, which compares favorably to median time to progression of 3.9 years in published series.

Direct interrogation of the tumor microenvironment by single-cell transcriptome analysis revealed explanations for lack of more robust objective clinical responses. Comparing paired pre- and post- vaccine bone marrow samples, we observed a striking dichotomous pattern of significantly reduced numbers of clonal tumor cells, identified by their unique BCR sequences, and downregulation of genes involved in signaling pathways critical for B-cell survival among the mature B cells subpopulation post-vaccine in the majority of patients, but no change in clonally related plasma cell-like clusters of any patient (Figure 1). Downregulation of HLA molecule expression suggested intrinsic resistance by tumor plasma cell subpopulations and cell-cell interaction analyses predicted paradoxical upregulation of IGF signaling post vaccine by plasma cell, but not mature B-cell subpopulations, suggesting a potential mechanism of acquired resistance.

Vaccine therapy induced dynamic changes in bone marrow T-cells, including upregulation of signaling pathways involved in T-cell activation, expansion of T-cell clonotypes (Figure 2), increased T-cell clonal diversity, and functional tumor idiotype-specific cytokine production, with little change in co-inhibitory pathways or Treg.

Vaccine therapy also globally altered cell-cell communication networks across various bone marrow cell types. CellChat analysis inferred significant downregulation of signaling pathways post-vaccine that likely directly promote growth of LPL cells, such as APRIL and IL-6 which are known to promote B- or plasma cell survival. Other pathways were reduced post-vaccine, such as RESISTIN, which has a known role in supporting proliferation of solid cancers. A role for RESISTIN in supporting LPL has not been previously inferred, but it has been reported to induce multidrug resistance in multiple myeloma. Bioinformatic analysis also identified a predominant role for myeloid cells in the tumor microenvironment as a source of vaccine-induced, downregulated pro-tumoral signaling to LPL cells. The pathways affected were primarily associated with monocytic, rather than granulocytic or dendritic cell subpopulations, particularly non-classical $CD14^{-}CD16^{+}$ monocytes, and to a lesser extent

classical CD14 $^{+}$CD16 $^{-}$ monocytes . Recent reports indicate that an increased pro-inflammatory myeloid signature is an early step in the development of LPL and in monoclonal gammopathy of undetermined significance.
Taken together, these results suggest that this prototype neoantigen vaccine favorably perturbed the tumor immune microenvironment, resulting in reduction of clonal tumor mature B-cell, but not plasma cell subpopulations. Future functional studies of the pathways affected are needed to confirm mechanisms of resistance elucidated and to design combination strategies to circumvent them. Such strategies could include adding IFN gamma or epigenetic drugs, designed to increase HLA molecule expression on plasma cell-like LPL subpopulations and combining neoantigen vaccines with agents that specifically target plasma cells or pathways known to promote their growth, such as IGF-1 receptor inhibitors. Finally, our data suggest that combinations of these vaccines with myeloid cell checkpoint blockade may be worthwhile.

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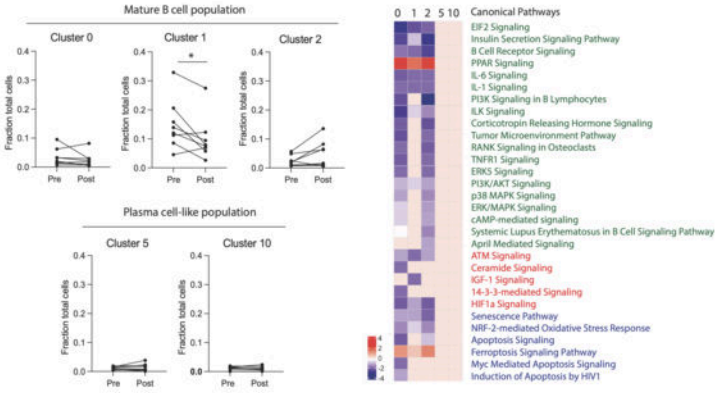

Fig 1. Vaccine-associated reduction of LPL B-cell but not plasma cell-like subpopulations in the bone marrow tumor microenvironment. Cell frequencies by total B-lineage cluster of mature B cell phenotype and plasma cell-like phenotype for each patient in paired pre- and post-vaccine bone marrow samples (left). Statistical analysis was performed using a two-sided t-test. *P≤0.05, **P≤0.01, and ***P≤0.001. Ingenuity Pathway Analysis (Qiagen IPA) based on differentially expressed genes of pooled data for all patients post vs. pre vaccination (adjusted log p-value >1.3) of canonical pathways contrasting tumor mature B-cell (0-2) and plasma cell-like clusters (5 and 10), respectively (right).

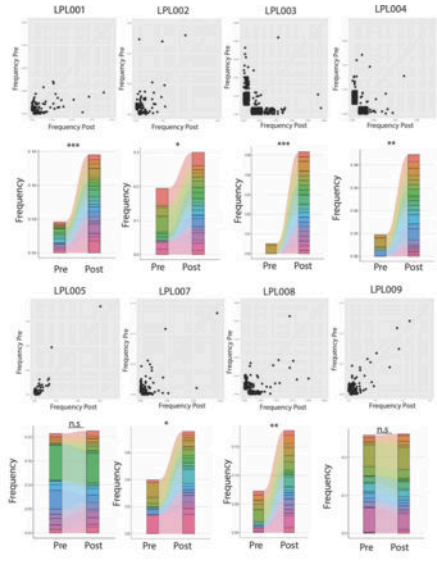

Fig 2. Paired single cell TCR-seq reveals T-cell clonal expansion in the tumor microenvironment following vaccine treatment. Scatterplots of TCR clonotype frequencies pre-vaccine (y-axis) and post-vaccine (x-axis) for each patient (top) and corresponding frequencies of the 20 most prevalent T-cell clonotypes identified within the post-vaccination T-cell repertoire, compared with their matching clonotype pre-vaccine (bottom). Statistical analysis of paired data from each patient was performed using a two-sided t-test. *P≤0.05, **P≤0.01, and ***P≤0.001. n.s., not significant.

Figure 1

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