MICROFLUIDICS CELL SQUEEZING ENABLES HUMAN PBMC AS DRIVERS OF ANTIGEN-SPECIFIC CD8 T RESPONSES ACROSS WIDE RANGE OF ANTIGENS FOR DIVERSE CLINICAL APPLICATIONS

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Background: Antigen-specific CD8+ T cell activity is critical for mounting an effective immune response in a wide range of indications, including immune-oncology and infectious diseases.

Methods: To elicit antigen-specific CD8+ T cell activity, we used microfluidics cell squeezing (Cell Squeeze®) to deliver antigens directly to the cytosol of antigen presenting cells (APCs). Direct cytosolic delivery bypasses the need for cross-presentation and efficiently loads antigen into the major histocompatibility complex class I (MHC-I) pathway. The Cell Squeeze® platform is generally agnostic to cell type and material. Therefore, not only does microfluidic squeezing enable cell subsets within human peripheral blood mononuclear cells (PBMCs) to function as unconventional APCs, but it also enables us to efficiently investigate a wide range of antigens including whole protein, peptides, and mRNA. This ‘plug and play’ nature of the platform allows for broad application in multiple disease areas.

Results: In human cells, we demonstrated that microfluidic squeezing of PBMCs enables effective delivery to the major cell subsets including T cells, B cells, NK cells and monocytes. Delivery of CMV and HPV16 synthetic long peptides (SLPs) resulted in robust in vitro responses of both CD8+ T cell clones and patient-derived memory populations. To broaden the impact of our PBMC-based cell therapy approach, we investigated several other antigens relevant to other disease areas. Additional materials delivered via squeezing and demonstrated antigen presentation include neoantigens, M1 Influenza mRNA, and pp65 SLP. Cell Squeeze® platform is simple to use and amenable to scale up. We demonstrated that delivery and viability for research scale process (~2 × 10^6 cells) is equivalent to delivery and viability of PBMCs processed at manufacturing scale (~1 × 10^6 cells).

Conclusions: Microfluidic cell squeezing of human PBMCs with antigenic material can be tailored to produce APCs that drive robust CD8+ T cell response against targets across multiple disease areas and has been scaled up for clinical use. SQZ-PBMC-HPV are currently under clinical evaluation for treatment of HPV16+ tumors.

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MICROFLUIDICS CELL SQUEEZING ENABLES POTENT CELLULAR VACCINES IN MURINE MODELS THROUGH DIRECT CYTOSOLIC LOADING AND DIRECT CD8 T CELL PRIMING

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Background: The presentation of sufficient antigen on major histocompatibility complex class I (MHC-I) is essential to prime CD8+ T cells.

Methods: To achieve efficient MHC-I presentation, we used microfluidics cell squeezing (Cell Squeeze®) to deliver antigens directly to the cytosol of antigen presenting cells (APCs), bypassing the need for cross-presentation. In addition to facilitating priming by professional APCs, this approach enables lymphocytic subsets within peripheral blood mononuclear cells (PBMCs) to function as unconventional APCs in mouse preclinical models.

Results: We demonstrated that microfluidic cell squeezing delivers cargo to major cell populations within splenocytes (T cells, B cells, NK cells, and monocytes) and that protein, peptide, or mRNA antigens are rapidly processed and presented. In vivo, squeezed splenocytes directly presented antigen to CD8+ T cells. In the TC-1 tumor model for HPV+ cancers, squeezed splenocytes completely protect mice when administered prophylactically, protecting 15/15 animals from primary challenge and 11/15 animals from tumor re-challenge. Following therapeutic administration, squeezed splenocytes significantly improved median survival time to 56 days from 28 days, as observed with untreated controls. Immunization can also be combined with chemotherapy to further enhance therapeutic efficacy, improving median survival to over 100 days compared to 81 days with SQZ monotherapy or 32 days with chemotherapy alone. When tumor infiltrating lymphocytes (TILs) were analyzed following therapeutic immunization, squeezed splenocyte immunization elicited a significant influx of antigen specific CD8+ T cells: with SQZ treatment, ~87% of tumor-infiltrating CD8 T cells were antigen-specific, as measured by an E7-tetramer stain, while only ~33.6% and ~1.15% of infiltrating CD8 T cells were specific for E7 with subcutaneous peptide vaccination and no treatment, respectively.

Conclusions: Through the direct cytosolic delivery of antigen, we have engineered unfractionated PBMCs to function as potent APCs. This strategy generates potent antigen-specific CD8+ T cell responses in mouse models. Taken together, these findings support the potential of SQZ-PBMCs as an effective antigen-specific vaccination strategy against cancer. SQZ-PBMC-HPV is currently under clinical evaluation for HPV16+ tumor indications.

Ethics Approval: All methods were performed in accordance with relevant guidelines and regulations; Animal studies were approved by the Institutional Animal Care and Use Committee (IACUC) at SQZ Biotechnologies, using the recommendations from the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health and the Office of Laboratory Animals. All activities were also conducted in accordance with Public Health Service (PHS) Policy on Humane Use and Care of Laboratory Animals.

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PRECLINICAL STUDIES SUPPORT THERAPEUTIC APPLICATION OF THE LEUKEMIC CELL-BASED CANCER RELAPSE VACCINE DCP-001 IN OVARIAN CANCER

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Background: Ovarian cancer (OC) is the gynecological malignancy with the highest mortality due to the late diagnosis of