SELECTIVE INFILTRATION OF ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) MEDIATING IMMUNE CELLS IN RESPONSE TO TREATMENT IN A HUMAN TUMOR HISTO-CULTURE PLATFORM

¹Satish Sankaran, ¹Nandini Pal Basak*, ¹Sindhu Govindan, ²BV Prakash, ³BV Manjula, ⁴MS Ganesh, ⁴Amritha Prabha, ¹Kowshik Jaganathan, ¹K Vasanth, ¹K Gowri Shankar, ¹A Manimaran, ¹M Rajashekar, ¹Ritu Malhotra, ¹M Oliyarsi, ¹Rachita Rao. ¹Farcast BioSciences Pvt Ltd, Bangalore, India; ²Sri Lakshmi Multi Speciality Hospital, Bangalore, India; ³Bangalore Baptist Hospital, Bangalore, India; ⁴Vydehi Multi Speciality Hospital, Bangalore, India

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Background A 3D histo-culture platform provides a near native Tumor immune Micro-Environment (TiME), making it best suited for evaluating response to immunotherapy drugs. Farcast™ TiME is a human 3D tumor histo-culture platform that preserves TiME and maintains functional fidelity of intratumoral immune cells (IIC). In this study we investigated the utility of this platform in demonstrating treatment induced Antibody-Dependent Cellular Cytotoxicity (ADCC) mechanism driven by IICs alone versus co-culture with autologous peripheral blood immune cells.

Methods Head and neck squamous cell carcinoma tissue samples (n=5) along with matched blood from consented patients were used in this study. All Peripheral Blood Nucleated Cells (PBNCs) including lymphocytes, monocytes, NK cells and neutrophils were isolated and stained with a tracking dye to distinguish them from IICs. Tumor tissues were processed to generate explants, treated with 184 µg/ml Cetuximab (anti-EGFR) or vehicle control, and cultured with or without PBNCs for 72 hrs. Response was evaluated using flow cytometry and cytokine release assay.

Results Amount of infiltrated autologous PBNCs showed a strong negative correlation (R2=0.98) with the amount of IICs in the absence of drug treatment. The proportions of infiltrated immune cell sub-populations were similar to the composition of PBNCs added in culture. Cetuximab treatment, however, led to enhanced infiltration of the effector cells for ADCC driven tumor killing, namely NK cells, macrophages, neutrophils, and cytotoxic T cells (CTLs). Notably the unique infiltration pattern of effector cell populations observed in each sample was reflected in the secretion of specific cytokine/chemokines associated with that cell population. NK cell increase (fold change: 1.6 ± 0.8) was observed in all samples with a concomitant increase in MCP-1 secretion (fold change: 1.7 ± 0.9). Granzyme-B expressing NK cells increased (>1.7 fold) in a subset of samples. Samples showing increase in neutrophil infiltration exhibited increased MMP9 secretion, involved in neutrophil infiltration via stromal remodeling. Sample with highest increase in infiltration of CD16+ Monocyte/Macrophages (>2.4 fold) showed maximum increase in Granzyme-B secretion with respect to the untreated arm. Increase in fold secretion (>1.4) of CXCL9/CXCL10 was associated with the sample that showed highest fold increase of Granzyme-B expressing CTL in comparison to untreated arm. IICs alone were not sufficient in eliciting optimal ADCC response.

Conclusions The study demonstrated ADCC response in the explant/PBNC co-culture platform leading to specific infiltration of effector sub-populations. Farcast™ TiME thus provides a unique platform to explore for heterologous adoptive cell and CAR-T therapies that involve immune cell infiltration.

Ethics Approval All samples included in the study were approved by institutional review boards of the centers providing the samples.