ADOPTIVELY TRANSFERRED TH17 CELLS COOPERATE WITH HOST B CELLS TO MEDIATE ROBUST IMMUNITY TO TUMORS

Anna Cole*, Hannah Knochelmann, Amalia Rivera-Reyes, Aubrey Smith, Megan Wyatt, Guillermo Rangel Rivera, Jeremy Boss, Gregory Lesinski, Chrystal Paulos. Emory University, Atlanta, GA, USA; Medical University of South Carolina, Charleston, SC, USA; University of Colorado, Aurora, CO, USA; Orange Grove Bio, Cincinnati, OH, USA

Background Adoptive T cell transfer therapy mediates potent immunity in some patients with aggressive malignancies, but many individuals do not respond, or may relapse. One reason for therapy failure is due to lack of T cell persistence. To overcome this problem, we aimed to generate a cell product that will lead to long term antitumor immunity in aggressive models. Accordingly, our team reported that a subset of CD4+ T cells termed Th17 cells, persist long term and can eradicate solid tumors when infused into mice. However, how Th17 cells mediate tumor immunity is unclear.

Methods To model Th17 cell adoptive T cell transfer therapy, we use a transgenic mouse model in which CD4+ cells express a T cell receptor (TCR) that recognizes tyrosinase-related protein 1 (TRP-1) expressed on melanoma, and polarized naïve CD4+ T cell to Th17 cells. These cells are infused into mice bearing B16F10 melanoma tumors that received non-myeloablative lymphodepleting total body irradiation. Tumor growth is measured over time or tumors, spleen, and lymph nodes are analyzed 12 days post cell transfer.

Results To understand how Th17 cells elicit robust antitumor activity, we performed an unbiased analysis of RNA transcripts on tumor-draining lymph nodes of mice treated with Th17 cells. Surprisingly, we found that mice infused with anti-tumor Th17 cells have increased transcripts associated with B cells, and factors that trigger B cell maturation, antibody-secretion, and enhanced antigen presentation. Furthermore, host B cells, but not CD8+ T cells, were surprisingly critical in sustaining long-term immunity, as their depletion significantly impaired survival. B cells enhance Th17 cell persistence and promote their differentiation into IFN-γ producers and away from regulatory IL-10 production. Th17 cells induce B cell activation and maturation in an IL-21-dependent manner, causing the production of class switched antibodies which can alone partially protect against tumor challenge. Finally, we found that IL-21, ICOS, and IFN-γ are required for this antitumor response as inhibition of any of these three abrogates durable tumor immunity.

Conclusions Altogether, this suggests a cooperative relationship between transferred Th17 cells and host B cells in mediating long term tumor immunity. Our novel findings highlight Th17 cell therapy as a way to harness both T and B cell responses against cancer. Ongoing experiments will further determine the mechanism of how B cells collaborate with Th17 cells to mediate superior antitumor activity.

Acknowledgements We would like to acknowledge Emory University, The Winship Cancer Institute, and the Pediatrics/Winship Flow Cytometry Core.

Ethics Approval All animal procedures were approved by the Institutional Animal Care and Use Committee of Emory University, protocol number 201900225.