Dario Vignali, PhD
Vice Chair and Professor
Immunology
Inhibitory Mechanisms in the Tumor Microenvironment

Dario AA Vignali, PhD is the Frank Dixon Chair in Cancer Immunology, Vice Chair and Professor of Immunology in the Immunology Department, University of Pittsburgh School of Medicine. He is also Associate Director for Scientific Strategy, co-leader of the Cancer Immunology and Immunotherapy Program and co-director of the Tumor Microenvironment Center in the UPMC Hillman Cancer Center. He received his PhD in 1988 from the London School of Hygiene & Tropical Medicine, University of London, where he studied immunity to Schistosoma mansoni. He then held two post-doctoral positions from 1988-1993, first at the Institute for Immunology and Genetics, German Cancer Research Center, Heidelberg, Germany, with Prof. Gunter Hammerling, and then at the Department of Biochemistry and Molecular Biology, Harvard University, Cambridge, Massachusetts, USA, with Prof. Jack Strominger. He then started his own independent research program in the Department of Immunology, St. Jude Children's Research Hospital, Memphis, Tennessee, rising to the rank of Vice Chair and Member (Full Professor equivalent). After nearly 21 years at St Jude he moved to Pittsburgh in July 2014. His research focuses on molecular and cellular aspects of negative regulatory immune mechanisms including regulatory T cells, inhibitory receptors, and inhibitory cytokines. His lab was instrumental in uncovering the role of LAG3 in mouse models of cancer, tolerance, autoimmunity and immune regulation. His lab discovered the inhibitory cytokine IL35 and the NRP1:SEMA4A axis, which are key regulators of intratumoral Treg stability and function. His current research extensively uses systems immunology approaches to understand transcriptional regulation of effector T cell exhaustion and regulatory T cell function and fate in murine models of cancer and autoimmunity, and numerous human tumors. He has been a Highly Cited Researcher (top 1% by citations; Clarivate Analytics) for the last five years (2016-2020) and has published over 195 papers with over 37 as senior or co-author in high impact journals (IF>10). He has a strong record of extramural funding, which currently includes an NIH P01 and four R01 grants. His innovative, discovery-based research has led to 15 patent awards (11 in the US) and 11 pending patent applications worldwide, and he is a co-founding scientist of several companies (Potenza Therapeutics [sold to Astellas], Tizona Therapeutics [sold to Gilead], Novasenta). Lastly, he is Director of the Cancer Immunology Training Program (NCI T32), and has trained, or currently training, 46

postdoctoral research or clinical fellows and 14 graduate students, with several successfully obtaining extramural fellowships (14 total), emphasizing his commitment to train the next generation of immunologists.

Abstract: Immunotherapies targeting the PD1/PDL1 pathway have had a major impact on cancer treatment. However, only a proportion of patients respond, and an even smaller proportion exhibit a long-term, durable cure. Several mechanisms of resistance and potential combinatorial approaches will be discussed. Many cancer patients do not develop a durable response to current standard of care immunotherapies despite substantial advances in targeting immune IRs (IRs). A potentially important and unappreciated compounding issue, which may serve as a dominant resistance mechanism, is the inherent systemic immune dysfunction that is often associated with advanced cancer. Although this has been described for decades, primary mechanisms and drivers remain unknown. Lack of response to IR blockade therapy and increased disease burden has been associated with circulating, peripheral $CD8^+$ T cell exhaustion, which is defined by poor T cell function linked to increased IR expression (eg: PD1, LAG3, neuropilin-1 [NRP1]). LAG3 is the third IR to be targeted in the clinic, consequently garnering considerable interest and scrutiny. However, persistent antigen exposure in the tumor microenvironment results in sustained PD1/LAG3 expression, contributing to a state of exhaustion manifest in impaired proliferation and cytokine production. However, the striking synergy between LAG3 and PD1 observed in multiple settings. There are now at least 10 LAG3-targeted therapies in the clinic with many more in preclinical development, emphasizing the broad interest in LAG3. Lastly, regulatory T cells (T_{regs}) inhibit beneficial anti-tumor responses. T_{reg} depletion enhances tumor rejection in animal models and the clinic but also leads to substantial adverse events. Thus, approaches have been sought to target Tregs in tumors while limiting systemic autoimmune and inflammatory manifestations. For instance, interleukin-35 (IL35) is a T_{reg}-secreted cytokine known to inhibit effector T cell proliferation and mediate infectious tolerance via induction of suppressive IL35-producing induced T_{regs}, iTr35. Using antibody-mediated neutralization, T_{reg}-restricted deletion of Ebi3 and novel reporter mice, we have shown that IL35 facilitated tumor growth by limiting anti-tumor immunity in transplantable and genetically-induced murine models of melanoma and lung carcinoma. These findings reveal the previously unappreciated importance of IL35 in limiting anti-tumor immunity and present IL35 as a potential therapeutic target in cancer. Alternatively, we have shown that the immune cell surface ligand semaphorin-4a (Sema4a) on conventional T cells and DCs, and the T_{reg}-restricted receptor NRP1 interact to potentiate T_{reg} function. Mice with a T_{reg}-restricted deletion of Nrp1 exhibit limited tumor-induced tolerance and thus substantial resistance to tumors, yet do not develop any autoimmune manifestations. Thus, NRP1 ligation maintains T_{reg} stability and function in highly inflammatory sites but is dispensable for the maintenance of immune homeostasis, highlighting NRP1 as a potential immunotherapeutic target in cancer.