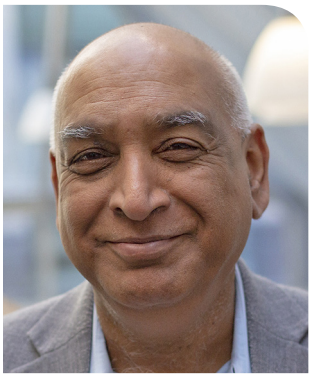
Shiv Pillai, MD, PhD



Pillai Laboratory

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The Pillai laboratory asks questions about the biology of the immune system and susceptibility to disease. Some of these questions are 1) can we manipulate the immune system to treat autoimmunity and cancer and to increase immunological memory? 2) can we understand how genetics and the environment affect lymphoid clones to drive common diseases? and 3) can this latter information be used to better understand and develop new therapies for inflammatory human diseases such as COVID-19, systemic sclerosis and IgG4-related disease? We have discovered an underlying basis for why natural infection will not lead to herd immunity in COVID-19, emphasizing the need for vaccination. Our earlier discovery of the role of an enzyme called Btk in the activation of B cells has contributed to the generation of Btk inhibitors that are effective in B cell malignancies and in trials of autoimmunity. One of the pathways we are currently studying suggests new approaches for the treatment of autoimmune disorders.

Pathogenesis of Inflammatory diseases (NIAID Autoimmune Center of Excellence at MGH)

In studies on COVID-19 we have described the underlying reason for the defect in humoral immunity by interrogating immune activation processes in lymph nodes, spleen and the blood. We have shown that a block in the final stage of T follicular helper cell differentiation leads to the collapse of germinal centers and accounts for the lack of durable immunity. A detailed understanding of adaptive immune changes in the lung in COVID-19 has also been obtained. In systemic sclerosis and IgG4-related disease we have shown that apoptosis of specific cell types in each disease, induced by cytotoxic T cells, is a prelude to fibrosis.

Studies on murine and human B and T cell biology

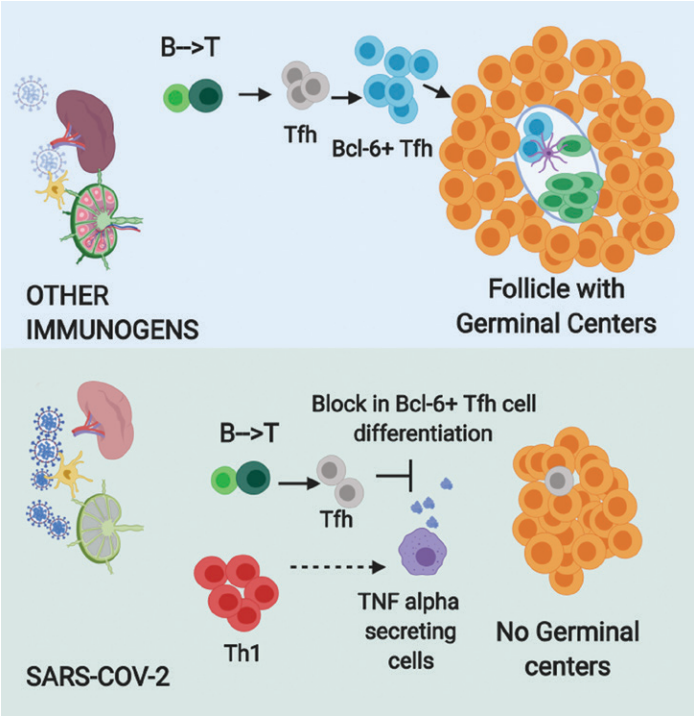
We are using a number of single cell transcriptomic, epigenetic and genetic approaches to examine the heterogeneity and development of selected murine and human B and T cells, as well as the molecular bases of the processes of T-B collaboration and germinal center formation.

DNA methylation, B cell self-renewal and chronic lymphocytic leukemia

We have long been interested in cell fate decisions in B cell development and in the development of self-renewing B cell subsets. The roles of DNMT3a in B-1a B cell self-renewal and of specific methylation events in chronic lymphocytic leukemia are being investigated. The contributions of DNA methylation and demethylation to the biology of CD4+ CTL and TFH cells are also being investigated.

Studies on Human CTLA4 and NFκB1 mutations and early B cell development

The underlying mechanism for the human B cell developmental defect in individuals with CTLA4 and NFκB1 mutations has been



A model for the humoral immune defect in COVID-19.

studied helping us to better understand how regulatory T cells can influence early B cell development and humoral autoimmunity.

Selected Publications:

Mahajan VS, Mattoo H, Sun N, Viswanadham V, Yuen GJ, Allard-Chamard H, Ahmad M, Murphy SJH, Cariappa A, Tuncay Y, **Pillai S**. B1a and B2 cells are characterized by distinct CpG modification states at DNMT3A-maintained enhancers. *Nat Commun.* 2021 Apr 13;12(1):2208.

Kaneko N, Kuo HH, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, Piechocka-Trocha A,...Lingwood D, Schmidt AG, Lichterfeld M, Walker BD, Yu XG, Padera RF Jr, **Pillai S**; Massachusetts Consortium on Pathogen Readiness Specimen Working Group. Loss of Bcl-6-Expressing T Follicular Helper Cells and Germinal Centers in COVID-19. *Cell*. 2020 Oct 1;183(1):143-157.e13.

Maehara T*, Kaneko N*, Perugino CA*, Mattoo H, Kers J, Allard-Chamard H, Mahajan VS, Liu H, Murphy SJ, Ghebremichael M, Fox D, Payne AS, Lafyatis R, Stone JH, Khanna D, **Pillai S**. Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis. *J Clin Invest.* 2020 May 1;130(5):2451-2464.

Perugino CA, Kaneko N, Maehara T, Mattoo H,...Nakamura S, Yosef N, Stone JH, **Pillai S**. CD4+ and CD8+ cytotoxic T lymphocytes may induce mesenchymal cell apoptosis in IgG4-related disease. *J Allergy Clin Immunol*. 2020 May 30:S0091-6749(20)30741-7.

Farmer JR, Allard-Chamard H, Sun N, Ahmad M,...Ghebremichael M, Shalek AK, Batista F, Gerszten R, **Pillai S**. Induction of metabolic quiescence defines the transitional to follicular B cell switch. *Sci Signal*. 2019 Oct 22;12(604):eaaw5573.

Della-Torre E, Rigamonti E, Perugino C, Baghai-Sain S, Sun N, Kaneko N, Maehara T, Rovati L, Ponzoni M, Milani R, Lanzillotta M, Mahajan V, Mattoo H, Molineris I, Deshpande V, Stone JH, Falconi M, Manfredi AA, **Pillai S**. B lymphocytes directly contribute to tissue fibrosis in patients with IgG4-related disease. *J Allergy Clin Immunol*. 2020 Mar;145(3):968-981.e14.

*Denotes equal contribution