KOREA-US

# Frontiers in Health and Life Sciences

2025. 11. 6(Thu) - 7(Fri)

Four Seasons Hotel, Grandballroom(3F)

## Curriculum Vitae

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| **Name** | **First Name** | Arlene | **Last Name** | Sharpe |
| **Country** | United States of America | | |  |
| **Affiliation** | Harvard Medical School | | | |

| **Educational Background** | | | |
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| 1975 | BA | Biochemistry and Molecular Biology | Harvard University, Cambridge, MA |
| 1981 | PhD | Microbiology and Molecular Genetics | Harvard University, Cambridge, MA |
| 1982 | MD | Medicine | Harvard Medical School, Boston, MA |

| **Professional Career** | |
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| 2023-Present | Kolokotrones University Professor, Harvard University |
| 2023-Present | Vice-Director, Gene Lay Institute of Immunology & Inflammation, BWH, MGH, HMS |
| 2019-Present | Member, Broad Institute |
| 2018-Present | Chair, Department of Immunology, HMS |
| 2015-Present | Leader, Cancer Immunology Program, DF/HCC |
| 2003-Present | Professor of Pathology, BWH |


**Research Field**

1. **Defining the functions of the B7-1 and B7-2 pathway in T cell activation and tolerance.**
Our studies of B7-1 deficient mice provided the first *in vivo* evidence for the existence of alternative CTLA4 counter-receptors. As a result, a second CTLA4 counter-receptor, B7-2, was cloned. Our studies revealed that B7-2 is the major early activating costimulator for initiating immune responses. The discovery of B7-2 led us to compare B7-1 and B7-2 functions. We found that B7-1 and B7-2 have critical, overlapping roles in germinal center formation and Ig class switching *in vivo*, and both contribute to T helper cell differentiation. In the mouse model of Multiple Sclerosis, experimental autoimmune encephalomyelitis (EAE), we found that B7-1 and B7-2 have critical overlapping roles not only in the initial activation and expansion of self-reactive T cells, but also in the effector phase of encephalitogenic T cell activation within the central nervous system. The role for B7-1/B7-2 costimulation during the effector phase of autoimmune disease had not been appreciated previously. These findings inspired development of pathway antagonists to block pathogenic T cell responses.

2. **Defining the critical inhibitory functions of CTLA-4 in vivo.**
Our studies with CTLA-4 deficient mice revealed the critical function inhibitory function for CTLA-4, and a previously unsuspected means by which costimulation can regulate responses, showing that costimulation can have both positive and negative regulatory roles. The phenotype of the CTLA-4 deficient mouse strain suggested a critical role for CTLA-4 in regulating T cell tolerance. We demonstrated an essential role for CTLA-4 in regulating the induction of anergy *in vivo.* More recently, we generated CTLA-4 conditionally deficient mice and used them to dissect CTLA-4 function CD4+ FoxP3- T cells and regulatory cells (Tfr).

3. **Defining the role of PD-1 and its ligands in regulating T cell activation, tolerance and exhaustion.**
Our studies first demonstrated that PD-L1 and PD-L2 can inhibit T cell proliferation and cytokine production *in vitro*. We determined that the PD-1:PD-L pathway exerts critical inhibitory functions in T cell activation, tolerance, chronic viral infections and tumors. We also showed that PD-L1 is expressed on tumors. We demonstrated that this pathway controls multiple tolerance checkpoints that prevent autoimmunity. We also identified a novel role for PD-L1 on non-hematopoietic cells in regulating self-reactive T cells. In collaboration with the laboratories of Drs. Rafi Ahmed and Gordon Freeman, we discovered that the PD-1:PD-L1 pathway contributes directly to T cell exhaustion and lack of viral control during chronic LCMV infection. These studies revealed the therapeutic potential for this pathway for treating T cell exhaustion and have translated into clinical trials and cancer immunotherapy. We are currently investigating other coinhibitory pathways and their interplay with the PD-1 pathway in tolerance, infection and cancer.

4. **Defining the functions of T follicular regulatory cells (Tfr).**
Tfr cells are a recently discovered Treg subset that inhibits humoral immunity. We have developed methods to determine mechanisms of Tfr cell suppression, and found that Tfr cells can prevent activation of both Tfh and B cells. By separating analyzing Tfh and Tfr cells, we determined that Tfr cell differentiation is restrained by PD-1 and CTLA-4. We also found that PD-1 inhibits Tfr suppressive function, while CTLA-4 is a mediator of Tfr suppressive capacity.

5. **Defining novel regulators of immunity using in vivo CRISPR screens.**
We have developed a system for perturbation of genes in immune cells *in vivo* using CRISPR-Cas9. This system expands the breadth of immune lineages that can be edited including naïve T and B cells, macrophages and dendritic cells, and enables in vivo pooled screens to discover immunoregulatory genes and knockout individual genes to characterize their function.


**Papers, Books, etc. presented or published by your name**

**Complete List of Published Work in MyBibliography:**
https://www.ncbi.nlm.nih.gov/myncbi/arlene.sharpe.1/bibliography/public/

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2. Tivol EA, et al. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. Immunity. 1995 Nov;3(5):541-7.
3. Latchman Y, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. Nat Immunol. 2001 Mar;2(3):261-8.
4. Keir ME, et al. Tissue expression of PD-L1 mediates peripheral T cell tolerance. J Exp Med. 2006 Apr 17;203(4):883-95.
5. Sage PT, et al. The receptor PD-1 controls follicular regulatory T cells in the lymph nodes and blood. Nat Immunol. 2013 Feb;14(2):152-61.
6. Sage PT, et al. Defective TFH Cell Function and Increased TFR Cells Contribute to Defective Antibody Production in Aging. Cell Rep. 2015 Jul 14;12(2):163-71.
7. LaFleur MW, et al. A CRISPR-Cas9 delivery system for in vivo screening of genes in the immune system. Nat Commun. 2019 Apr 10;10(1):1668.
8. LaFleur MW, et al. PTPN2 regulates the generation of exhausted CD8$^{+}$ T cell subpopulations and restrains tumor immunity. Nat Immunol. 2019 Oct;20(10):1335-1347.
9. Ringel, et al. Obesity Shapes Metabolism in the Tumor Microenvironment to Suppress Anti-Tumor Immunity. Cell. 2020 Dec 23;183(7):1848-1866.e26.
10. Pauken KE, et al. Single-cell analyses identify circulating anti-tumor CD8 T cells and markers for their enrichment. J Exp Med. 2021 Apr 5;218(4):e20200920.
11. Rowe JH, et al. Formate supplementation enhances anti-tumor CD8+ T cell fitness and efficacy of PD-1 blockade. Cancer Discovery 2023 13 (12):2566-2583.
12. LaFleur MW, et al. X-CHIME enables combinatorial, inducible, lineage-specific and sequential knockout of genes in the immune system. Nat Immunol. 2024 Jan;25(1):178-188.