• **Name:** Suzanne L. Topalian

• **Current Position & Affiliation:** Bloomberg-Kimmel Professor of Cancer Immunotherapy; Professor of Surgery and Oncology, Johns Hopkins University School of Medicine; Director, Melanoma Program, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; Associate Director, Johns Hopkins Bloomberg~Kimmel Institute for Cancer Immunotherapy

• **Country:** USA

• Educational Background:

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Wellesley College, Wellesley, MA	BA	1975	English
Tufts University School of Medicine, Boston, MA	MD	1979	Medicine
Thomas Jefferson Univ. Hosp., Philadelphia, PA	Residency	1979-1985	General Surgery
Children's Hosp. of Philadelphia, Philadelphia, PA	Fellowship	1982-1983	Pediatric Sur. Research
National Cancer Institute, NIH, Bethesda, MD	Fellowship	1985-1989	Surgical Oncology

• Professional Experience:

- 2018-present: Bloomberg-Kimmel Professor of Cancer Immunotherapy, Johns Hopkins University School of Medicine, Baltimore, MD
- 2016-present: Associate Director, Bloomberg~Kimmel Institute for Cancer Immunotherapy, Baltimore, MD
- 2006-present: Director, Melanoma Program, Kimmel Cancer Center at Johns Hopkins, Baltimore, MD
- 2006-present: Professor, Surgery and Oncology, Johns Hopkins Univ. Sch. of Med., Baltimore, MD
- 1989-2006: Senior Investigator, Surgery Branch, National Cancer Institute, NIH, Bethesda, MD

• Professional Organizations:

- 2020-2023: Member, Board of Directors, American Association for Cancer Research (AACR;elected position)
- 2014-pres.: Member, Board of Directors, Melanoma Research Alliance
- 2013-2016: Member, Board of Directors, Society for the Immunotherapy of Cancer (SITC; elected position)

- 2013-pres.: Chair, Scientific Advisory Panel, Melanoma Research Alliance
- 2012-pres.: Member, Regulatory Science and Policy Task Force, AACR
- 2009-2013: Chief Science Officer, Melanoma Research Alliance
- 2008-2010: Clinical Review Committee, Kimmel Cancer Center at Johns Hopkins University SOM
- 2008-2009: Chair, Grant Review Committee, Melanoma Research Alliance
- 2007-2009: Awards Committee of the Research Council, Kimmel Cancer Center at Johns Hopkins
- 2005-2006: Steering Committee, Vaccine Working Group, NCI, NIH
- 2001-2006: Clinical Review Panel, NCI, NIH
- 2000-2001: Promotions and Tenure Review Committee, NCI, NI

• Main Scientific Publications:

1. As a postdoctoral fellow, I devised laboratory and clinical methods enabling the earliest trials of adoptive T cell transfer therapy, which are still in use today. Human tumor infiltrating lymphocytes (TILs) with anti- tumor specificity were successfully cultured for the first time on an automated preparative scale. Functional characterization revealed that TILs could recognize uniquely mutated as well as shared non-mutated tumor antigens. These fundamentals laid the groundwork for the molecular identification of tumor antigens and clinical applications in recombinant vaccines and genetically engineered TCR-transduced T cells.

a. Topalian SL, Solomon D, Avis, FP, Chang AE, Freerksen DL, Linehan WM, Lotze MT, Robertson CN, Seipp CA, Simon P, Simpson CG, and Rosenberg SA. Immunotherapy of patients with advanced cancer using tumor infiltrating lymphocytes and recombinant interleukin-2: A pilot study. J Clin Oncol 1988; 6:839-53.
b. Rosenberg SA, Packard B, Aebersold PM, Solomon D, Topalian SL, Toy ST, Simon P, Lotze MT, Yang JC, Seipp CA, Simpson C, Carter C, Bock S, Schwartzentruber D, Wei JP, White DE. Immunotherapy of patients with metastatic melanoma using tumor infiltrating lymphocytes and interleukin-2: Preliminary report. N Engl J Med 1988; 319:1676-1680.
c. Topalian SL, Solomon D, and Rosenberg SA. Tumor-specific cytolysis by lymphocytes infiltrating human melanomas. J Immunol 1989; 142:3714-25.
d. Hom SS, Topalian SL, Simonis T, Mancini M, Rosenberg SA: Common expression of melanoma tumor-associated antigens recognized by human tumor infiltrating lymphocytes: Analysis by HLA restriction. J Immunother 1991; 10:153-164.

2. Using CD8+ melanoma-specific TILs as functional probes, I collaborated to identify shared non-mutated tumor antigens and their derivative epitopes, which were used to develop cancer vaccines formulated as synthetic peptides, recombinant proteins, or recombinant viral vectors. I was a PI or co-investigator on NCI clinical trials of these vaccines. My laboratory developed correlative assays to monitor the clinical effects of cancer vaccines. However, monotherapy with vaccines based exclusively on shared CD8-recognized MHC I-restricted epitopes was found to have limited clinical impact.

a. Kawakami Y, Eliyahu S, Delgado CH, Robbins PF, Rivoltini L, Topalian SL, Miki T, Rosenberg SA. Cloning of the gene coding for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. Proc Natl Acad Sci USA 1994; 91:3515-3519.
b. Robbins PF, El-Gamil M, Li Y, Topalian SL, Rivoltini L, Sakaguchi K, Appella E, Kawakami Y, Rosenberg SA. Cloning of a new gene recognized by melanoma-specific HLA-A24 restricted tumor infiltrating lymphocytes. J Immunol 1995; 154:5944-5950.
c. Housseau F, Lindsey KR, Oberholtzer SD, Gonzales MI, Boutin P, Moorthy AK, Shankara S, Roberts BL, Topalian SL. Quantitative real-time RT-PCR as a method for monitoring T lymphocyte reactivity to full length tyrosinase protein in vaccinated melanoma patients. J

Immunol Methods 2002; 266:87-103.

d. Lindsey KR, Gritz L, Sherry R, Abati A, Fetsch PA, Goldfeder LC, Gonzales MI, Zinnack KA, Rogers-Freezer L, Haworth L, Mavroukakis SA, White DE, Steinberg SM, Restifo NP, Panicali DL, Rosenberg SA, Topalian SL. Evaluation of prime/boost regimens using recombinant poxvirus/tyrosinase vaccines for the treatment of patients with metastatic melanoma. Clin Cancer Res 2006; 12:2526-2537.

3. In seminal work, I characterized the importance of CD4+ T cells in human anti-tumor immunity and developed methods for identifying MHC II-restricted tumor antigens and derivative immunogenic epitopes. TCRs from CD4+ tumor-specific TILs were cloned, and in collaboration with Dr. Roy Mariuzza at the University of Maryland, structural and biophysical interactions in TCR-peptide-MHC complexes were defined for the first time with human MHC II-restricted tumor antigens. These studies revealed that mutant tumor antigen ("neoantigen") complexes, anticipated to participate in high-affinity interactions, instead resembled self antigens with weak binding characteristics. This suggested that generating specific immunity against mutant tumor antigens would not be sufficient to mediate tumor elimination.

a. Topalian SL, Rivoltini L, Mancini M, Markus NR, Robbins PF, Kawakami Y, and Rosenberg SA. Human CD4+ T cells specifically recognize a shared melanoma-associated antigen encoded by the tyrosinase gene. Proc Natl Acad Sci USA 1994; 91:9461-5.

b. Pieper R, Christian R, Gonzales MI, Nishimura MI, Gupta G, Settlage RE, Shabanowitz J, Rosenberg SA, Hunt DF, Topalian SL. Biochemical identification of a mutated human melanoma antigen recognized by CD4+ T cells. J Exp Med 1999; 189:757-765.

c. Wang R-F, Wang X, Atwood AC, Topalian SL, and Rosenberg SA. Cloning genes encoding MHC class II-restricted antigens: Mutated CDC27 as a tumor antigen. Science 1999;1351-4.

d. Deng L, Langley R, Brown PH, Xu G, Teng L, Gonzales MI, Nishimura MI, Topalian SL*, Mariuzza RA*. Structural basis for recognition of mutant self by a tumor-specific, MHC class II-restricted TCR. Nature Immunol 2007; 8:398-408. *co-corresponding author

4. Endogenous anti-tumor immunity is hampered by suppressive pathways termed "immune checkpoints". I have focused on the PD-1/PD-L1 pathway as a target for cancer therapy. Collaborating with Medarex Inc. and later with Bristol-Myers Squibb which acquired Medarex, we designed and executed the first clinical trials to test the potential for PD-1 blockade to reverse local tumor immune suppression and mediate the regression of advanced cancers. In the earliest trials, activity was observed in several cancer types including melanoma, kidney, colon, and lung cancer, indicating that blocking a single checkpoint pathway could have broad activity. At the same time, our correlative laboratory studies guided further clinical development by demonstrating the prolonged pharmacodynamics of anti-PD-1 and anti-PD-L1, and by providing the first evidence for an association between tumor cell expression of the ligand PD-L1, and the likelihood of response to PD-1 receptor blockade. These early findings attracted multiple pharmaceutical companies into this research space and catalyzed further biomarker development and FDA approvals. Since 2014, the FDA has approved the use of 6 different anti-PD-1/PD-L1 drugs in 17 individual cancer types, plus the genetically-defined categories of solid tumors with DNA mismatch repair deficiency (MSI- high) or high tumor mutational burden (TMB ≥10/Mb). More recently, I have collaborated to innovate the application of anti-PD-(L)1 in earlier disease settings (neoadjuvant, or pre-surgical therapy), which holds promise for extending relapse-free survival after surgery.

a. Brahmer JR, Drake CG, Wollner I, Powderly J, Picus J, Sharfman W, Stankevich E, Pons A, Salay TM, McMiller TL, Gilson MM, Wang C, Selby M, Taube JM, Anders R, Chen L, Korman AJ, Pardoll DM, Lowy I, and Topalian SL. A phase I study of single-agent anti-PD-1 (MDX-1106) in refractory solid tumors: Safety, clinical activity, pharmacodynamics and immunological correlates. J Clin Oncol 2010; 28:3167-75. PMC4834717.

b. Topalian SL, Hodi FS, Brahmer JR, et al. (30 authors). Safety, activity, and immune correlates

of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366:2443-54. PMC3544539.

c. Ngheim PT*, Bhatia S, Lipson EJ,.....,Topalian SL*, Cheever MA (31 authors). PD-1 blockade with pembrolizumab in advanced Merkel-cell carcinoma. N Engl J Med 2016; 374:2542-2552.

a. PMC4927341. *co-corresponding author

d. Forde P, Chaft J, Smith K, …Topalian SL, Brahmer J, Pardoll D (35 authors). Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018; 378:1976-1986. PMC6223617.

5. Our studies established the "adaptive immune resistance" hypothesis explaining tumor PD-L1 expression as a response to immune attack and interferon-gamma-mediated inflammation. Ongoing work aims to develop multi-factorial biomarkers of response/resistance to PD-1 blockade. In melanoma and other cancers, PD-L1 expression was found to be associated with an inflammatory microenvironment expressing other immune inhibitory molecules, such as IL-10 and LAG-3. Therapies combining anti-PD-1 with distinct checkpoint blockers are under evaluation in the clinic.

a. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, Chen S, Klein AP, Pardoll DM, Topalian SL,* Chen L.* Co-localization of inflammatory response with B7-H1 [PD-L1] expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Science Transl Med 2012; 4:127ra37. PMC3568523. *co-corresponding author

b. Lipson EJ, Vincent JG, Loyo M, Kagohara LT, Luber BS, Wang H, Xu H, Nayar SK, Wang TS, Sidransky D, Anders RA, Topalian SL*, Taube JM*. PD-L1 expression in the Merkel cell carcinoma microenvironment: Association with inflammation, Merkel cell polyomavirus and overall survival. Cancer Immunol Res, 2013; 1:54-63. PMC3548952. *co-corresponding author

c. Taube JM*, Klein A, Brahmer JR, Xu H, Pan X, Kim JH, Chen L, Pardoll DM, Topalian SL*, Anders RA. Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy. Clin Cancer Res 2014; 20:5064-74. PMC4185001. *co- corresponding author.

d. Taube JM, Young GD, McMiller TL, Chen S, Salas JT, Pritchard TS, Xu H, Meeker AK, Fan J, Cheadle C, Berger AE, Pardoll DM, Topalian SL. Differential expression of immune-regulatory genes associated with PD-L1 display in melanoma: implications for PD-1 pathway blockade. Clin Cancer Res 2015; 21:3969-76. PMC4558237.