BIOGRAPHICAL SKETCH

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NAME: Jedd David Wolchok

eRA COMMONS USER NAME (credential, e.g., agency login): wolchokj

POSITION TITLE: Chief, Melanoma and Immunotherapeutics Service; Member and Attending Physician

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Princeton University, Princeton, NJ	BA	06/87	Molecular Biology
New York University, New York, NY	MS	01/91	Microbiology
New York University, New York, NY	PhD	5/93	Microbiology
New York University, New York, NY	MD	5/94	Medicine

A. Personal Statement

My clinical experience has been focused on the development and investigation of novel immunotherapeutic approaches to the treatment of cancer. I initiated a program in xenogeneic DNA vaccination at Memorial Sloan-Kettering and followed the translational pathway from initial mouse studies through on-site GMP manufacturing and eventually leading phase I trials. As part of this endeavor, in collaboration with Drs. Alan Houghton, James Allison, Lloyd Old, I established the Ludwig Center for Cancer Immunotherapy, which serves as the core facility for clinical immune monitoring at MSKCC (now co-led with Dr. Alexander Rudensky). This facility employs a full-time staff dedicated to conduct validated immunologic assays and has emerged as a true leader in the field for identifying biomarkers for the activity of T cell checkpoint blockade. My clinical research efforts have led to the FDA approval of the CTLA-4 blocking antibody ipilimumab and, recently, the PD-1 blocking antibodies pembrolizumab and nivolumab for metastatic melanoma. Most recently, a trial of combined CTLA-4 + PD-1 blockade led by me has shown a high rate of rapidly emerging responses in melanomas. This work has led to recently completed Phase 2 and 3 trials of the combination in melanoma that have further validated the exceptional response rate. Additionally, the success of CTLA-4 + PD-1 blockade in melanomas have prompted promising development of this combination in several other cancer types, including non-small cell lung cancer in particular. In addition, I supervise an R01-funded basic science laboratory focused on investigating novel immunotherapeutic agents and combination approaches in pre-clinical mouse models. In 2011, I established the Immunotherapeutics Clinical Core, a specialized Phase 1-2 outpatient unit at MSKCC that is focused on the conduct of novel immunotherapy trials, with a specific emphasis on translational biomarker identification..

B. Positions and Employment

1994-1994 Intern in Internal Medicine, New York University Medical Center/Bellevue Hospital
1995-1996 Resident in Internal Medicine, New York University Medical Center/Bellevue Hospital
1996-2000 Medical Oncology/Hematology Fellow, Memorial Sloan-Kettering Cancer Center (MSKCC)
1997-1998 Chief Fellow, Medical Oncology/Hematology, MSKCC
2000-2004 Clinical Assistant Attending Physician, MSKCC and Instructor, Weill Medical College
2004-present Assistant Professor of Medicine, Weill Medical College of Cornell University
2006-present Associate Attending Physician, MSKCC, 1275 York Avenue, New York, NY 10065
2006-present Associate Director, Ludwig Center for Cancer Immunotherapy, MSKCC
2006-present Director, Immunotherapy Clinical Trials, Dept of Medicine, MSKCC
2009-present Assistant Member, Ludwig Institute for Cancer Research, LTD, NewYork, NY
2011-present Director, Cancer Vaccine Collaborative
2011-present Associate Chairman, Immunotherapeutics, MSKCC, 1275 Avenue, NY, NY 10065

2014-present Chief, Melanoma & Immunotherapeutics Service
2014-present Attending Physician, Memorial Sloan Kettering Cancer Center
2014-present Member, Memorial Sloan Kettering Cancer Center
2014-present Professor of Medicine, Weill Medical College of Cornell University
2015-present Member, Ludwig Institute for Cancer Research, LTD, New York, NY

Honors

1994 Friedland Award for Excellence in Internal Medicine (NYU)
1998-1999 Clinical Scholars Research Award, MSKCC
1999-2001 CaPCURE Research Award
2000 AACR/Aventis Young Investigator Scholar Award
2000 ASCO Merit Award
2003 Damon Runyon-Lilly Clinical Investigator Award
2004 NYU School of Medicine- Julia Zelmanovich Young Alumni Award
2006 Keystone Symposium Poster Contest Winner
2010 Melanoma Research Foundation – Humanitarian Award
2012 Melanoma International Foundation – Doctor of the Year
2013 Hematology/Oncology Fellows Teaching Award
2013 The Lloyd J. Old Chair for Clinical Investigation
2013 Puccini Foundation Shared Cancers Shared Cures Visionary Award
2014 AACR Richard and Hinda Rosenthal Memorial Award
2014 Giant of Cancer Care in Melanoma Award
2014 The Alexander Bodini Foundation Prize for Scientific Excellence in Medicine
2015 Melvin L. and Dr. Sylvia F. Griem Lectureship & Award Recipient

C. Contribution to Science

1. Combination Immunotherapy

A major effort during the past three years of my career has been the exploration of combined CTLA-4 and PD-1 blockade in clinical trials and biomarker studies. My team led a phase 1 trial of ipilimumab and nivolumab in patients with melanoma, showing an unprecedented 53% response rate in patients treated with optimal doses and 88% 2-year survival (Wolchok et al, NEJM, 2013). Led by my team at MSKCC, Phase 2 and 3 trials comparing the combination with monotherapy have just been completed, enrolling over 1000 patients worldwide in just over 1 year. The Phase 2 study was recently published (Postow et al, NEJM 2015), validating the remarkable efficacy of ipilimumab + nivolumab, and confirming the improved response rate compared to ipilimumab (59% vs 11%). The Phase 3 study followed just thereafter (Larkin et al, NEJM 2015), again demonstrating substantial responses rates and progression-free survival with the combination that exceeded PD-1 or CTLA-4 monotherapy. Importantly, sustained responses to combination therapy occurred irrespective tumor cell expression of PD-L1. Thus, the provision of the combination may allow for more patients to respond not only because of different effects on immune cell populations but also because of treatment-related changes in the microenvironment that permit patients to overcome the 'hurdle' of the PD-L1 biomarker. This collective body of work may change the standard of care in melanoma and has already led to similar investigations in other cancers. The success of combined CTLA-4 and PD-1 pathway blockade has given rise to other combinatorial investigations. My group has published (Holmgaard et al) on the significant therapeutic potential of blocking indoleamine dioxygenase (IDO) in combination with CTLA-4.

a) **J. D. Wolchok**, H. Kluger, M. K. Callahan, M. A. Postow, N. A. Rizvi, A. M. Lesokhin, N. H. Segal, C. E. Ariyan, R. A. Gordon, K. Reed, M. M. Burke, A. Caldwell, S. A. Kronenberg, B. U. Agunwamba, X. Zhang, I. Lowy, H. D. Inzunza, W. Feely, C. E. Horak, Q. Hong, A. J. Korman, J. M. Wigginton, A. Gupta, M. Sznol, Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med* **369**, 122-133 (2013). PMID 23724867
b) M. A. Postow, J. Chesney, A. C. Pavlick, C. Robert, K. Grossmann, D. McDermott, G. P. Linette, N. Meyer, J. K. Giguere, S. S. Agarwala, M. Shaheen, M. S. Ernstoff, D. Minor, A. K. Salama, M. Taylor, P. A. Ott, L. M. Rollin, C. Horak, P. Gagnier, **J. D. Wolchok**, F. S. Hodi, Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. *N Engl J Med*, 372:2006-2017 (2015) PMID 25891304
c) J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.J. Grob, C.L. Cowey, C.D. Lao, D. Schadendorf, R. Dummer, M. Smylie, P. Rutkowski, P.F. Ferrucci, A. Hill, J. Wagstaff, M.S. Carlino, J.B. Haanen, M. Maio, I. Marquez-Rodas, G.A. McArthur, P.A. Ascierto, G.V. Long, M.K. Callahan, M.A. Postow, K. Grossmann, M. Sznol, B. Dreno, L. Bastholt, A. Yang, L.M. Rollin, C. Horak, F.S. Hodi, and J.D.

Wolchok, Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* **373**, 23-34 (2015). PMID 26027431

d) R. B. Holmgaard, D. Zamarin, D. H. Munn, **J. D. Wolchok**, J. P. Allison, Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4. *The Journal of Experimental Medicine* **210**, 1389-1402 (2013). PMID 23752227

2. Predictive Biomarkers

We discovered that patients with pre-existing antibody responses to cancer testis antigens (NY-ESO-1) had a higher likelihood of responding to ipilimumab than patients without such baseline immunity. During the past two years, we spent considerable resources to analyze the relationship between clinical response to CTLA-4 blockade with ipilimumab and the mutational and neo-epitope landscape of an individual patient's tumor. In collaboration with cancer geneticist Tim Chan and his team, we recently described that in melanoma patients treated with ipilimumab durable response is associated with the number and quality of non-synonymous 'passenger' mutations in their tumor (Snyder et al, NEJM, 2014). We have also investigated the impact of the genomic landscape on response to PD-1 blockade in patients with lung cancers (Rizvi, Hellmann, et al, Science 2015), where nonsynonymous mutation burden, neoantigen burden, and the molecular signature of smoking highly correlated with response to pembrolizumab. In both studies, we identified neoantigen specific T cell responses in the peripheral blood in a few cases, highlighting the feasibility of using exome sequencing and in vitro methods including MHC multimers and intracellular cytokine staining to functionally validate targets of response to T cell checkpoint blockade. Understanding the molecular determinants of response to immunotherapies represents a paradigm shift in our examination of predictive biomarkers.

a) A. Snyder, V. Makarov, T. Merghoub, J. Yuan, J. M. Zaretsky, A. Desrichard, L. A. Walsh, M. A. Postow, P. Wong, T. S. Ho, T. J. Hollmann, C. Bruggeman, K. Kannan, Y. Li, C. Elipenahli, C. Liu, C. T. Harbison, L. Wang, A. Ribas, **J. D. Wolchok**, T. A. Chan, Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med* **371**, 2189-2199 (2014). PMID 25409260

b) N. A. Rizvi, M. D. Hellmann, A. Snyder, P. Kvistborg, V. Makarov, J. J. Havel, W. Lee, J. Yuan, P. Wong, T. S. Ho, M. L. Miller, N. Rekhtman, A. L. Moreira, F. Ibrahim, C. Bruggeman, B. Gasmi, R. Zappasodi, Y. Maeda, C. Sander, E. B. Garon, T. Merghoub, **J. D. Wolchok**, T. N. Schumacher, T. A. Chan, Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*, **348**(6230); 124-128 (2015). PMID 25765070

c) M. A. Postow, M. K. Callahan, C. A. Barker, Y. Yamada, J. Yuan, S. Kitano, Z. Mu, T. Rasalan, M. Adamow, E. Ritter, C. Sedrak, A. A. Jungbluth, R. Chua, A. S. Yang, R. A. Roman, S. Rosner, B. Benson, J. P. Allison, A. M. Lesokhin, S. Gnjatic, **J. D. Wolchok**, Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med* **366**, 925-931 (2012). PMCID: PMC3345206

3. Lessons from CTLA-4 Blockade: Clinical Investigations

I led 10 clinical trials using the CTLA-4 blocking antibody, ipilimumab, at MSKCC, including serving as overall study chair for the randomized phase III trial in patients with previously untreated metastatic melanoma. This study and another that I led at MSKCC showed that ipilimumab was the first drug to extend overall survival in patients with metastatic melanoma and led to the US FDA approval of ipilimumab. As these trials were ongoing, it became clear that conventional imaging-based endpoints were insufficient to capture the full clinical activity of ipilimumab. This heterogeneity in response kinetics presented a significant challenge to drug development. In collaboration with other colleagues in the field, I proposed a new response criteria, termed the immune related response criteria, which represent a major change in the way in which immunotherapeutic cancer drugs are evaluated and are currently being used in numerous clinical trials.

a) **J. D. Wolchok**, A. Hoos, S. O'Day, J. S. Weber, O. Hamid, C. Lebbe, M. Maio, M. Binder, O. Bohnsack, G. Nichol, R. Humphrey, F. S. Hodi, Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clinical Cancer Research.* **15**, 7412-7420 (2009). PMID 19934295

b) C. Robert, L. Thomas, I. Bondarenko, S. O'Day, D. J. M, C. Garbe, C. Lebbe, J. F. Baurain, A. Testori, J. J. Grob, N. Davidson, J. Richards, M. Maio, A. Hauschild, W. H. Miller, Jr., P. Gascon, M. Lotem, K. Harmankaya, R. Ibrahim, S. Francis, T. T. Chen, R. Humphrey, A. Hoos, **J. D. Wolchok**, Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* **364**, 2517-2526 (2011). PMID 21639810

c) F. S. Hodi, S. J. O'Day, D. F. McDermott, R. W. Weber, J. A. Sosman, J. B. Haanen, R. Gonzalez, C. Robert, D. Schadendorf, J. C. Hassel, W. Akerley, A. J. van den Eertwegh, J. Lutzky, P. Lorigan, J. M. Vaubel, G. P. Linette, D. Hogg, C. H. Ottensmeier, C. Lebbe, C. Peschel, I. Quirt, J. I. Clark, **J. D.**

Wolchok, J. S. Weber, J. Tian, M. J. Yellin, G. M. Nichol, A. Hoos, W. J. Urba, Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* **363**, 711-723 (2010). PMID 20525992

4. Maximizing Immunotherapy Efficacy with Molecularly Targeted Therapy and Oncolytic Viruses

The therapeutic success shown with small molecules targeting oncogenic 'driver' pathways has logically given rise to the concept of combining those with immunotherapy to introduce durability to the responses seen. In the first of these efforts, we found (Callahan et al, NEJM 2012), that BRAF inhibitors have a dose-dependent paradoxical activating effect on lymphocytes, while MEK inhibitors have a time-dependent inhibitory effect. Our group also had an important publication in 2014 (Zamarin et al, STM 2014) regarding the ability of Newcastle Disease Virus (NDV) to mediate immune infiltration of a tumor remote from the site of injection, via a Type I IFN-dependent mechanism. We are working on identifying recombinant NDV constructs encoding cytokines or agonist agents, which can then be further combined with immune modulating antibodies. A related project is exploring the ability of attenuated poxvirus constructs to mediate systemic immunity and an oncolytic effect.

a) M. K. Callahan, R. Rampal, J. J. Harding, V. M. Klimek, Y. R. Chung, T. Merghoub, **J. D. Wolchok**, D. B. Solit, N. Rosen, O. Abdel-Wahab, R. L. Levine, P. B. Chapman, Progression of RAS-mutant leukemia during RAF inhibitor treatment. *N Engl J Med* **367**, 2316-2321 (2012); published online EpubDec 13 (10.1056/NEJMoa1208958). PMID 23134356

b) D. Zamarin, R. B. Holmgaard, S. K. Subudhi, J. S. Park, M. Mansour, P. Palese, T. Merghoub, **J. D. Wolchok**, J. P. Allison, Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. *Science Translational Medicine* **6**, 226ra232 (2014). PMCID: PMC4106918

5. Pre-Clinical Laboratory Research to Examine New Immunotherapy Targets

Our preclinical studies concentrate on modulation of the glucocorticoid induced TNF-receptor (GITR) and OX40 pathways. GITR is expressed on activated effector T cells and regulatory T cells (Treg). We have shown that an agonist antibody to GITR acts both as a potent adjuvant for cancer vaccines as well as inducing a significant therapeutic effect against established tumors when administered alone. Our studies using an agonist antibody to OX40, another TNF receptor superfamily member presented on activated T cells, are similarly directed toward a mechanistic understanding of how this agent mediates significant regressions of large established tumors in mice. We have shown that while an OX40 agonist antibody has little effect on B16 melanoma tumors, combining it with modest doses of cyclophosphamide results in rapid and durable regression. A unique mechanism involving activation-induced cell death of Treg cells within the tumor, revealed by our work (Hirschhorn-Cymerman et al, J. Exp. Med, 2009 and 2012), shows the induction of a novel directly cytolytic phenotype in antigen-specific (transgenic) CD4 cells by the combination of OX40 agonist antibody and cyclophosphamide.

a) D. A. Schaer, S. Budhu, C. Liu, C. Bryson, N. Malandro, A. Cohen, H. Zhong, X. Yang, A. N. Houghton, T. Merghoub, **J. D. Wolchok**, GITR pathway activation abrogates tumor immune suppression through loss of regulatory T cell lineage stability. *Cancer Immunology Research* **1**, 320-331 (2013); published online EpubNov (10.1158/2326-6066.CIR-13-0086). PMCID: PMC3885345

b) D. Hirschhorn-Cymerman, S. Budhu, S. Kitano, C. Liu, F. Zhao, H. Zhong, A. M. Lesokhin, F. Avogadri-Connors, J. Yuan, Y. Li, A. N. Houghton, T. Merghoub, **J. D. Wolchok**, Induction of tumoricidal function in CD4+ T cells is associated with concomitant memory and terminally differentiated phenotype. *The Journal of Experimental Medicine* **209**, 2113-2126 (2012). PMID 23008334

Complete List of Published Work:
http://www.ncbi.nlm.nih.gov/sites/myncbi/jedd.wolchok.1/bibliography/44806992/public/?sort=date&direction=ascending

D. Ongoing Research Support

5R01 CA56821-18 (PI: Wolchok) 04/1/2016 - 03/31/2021
NIH/NCI
Immunity to Melanoma Differentiation Antigens
The major goal of this grant is to rationally examine combinations of active and passive immunotherapies in transplantable and spontaneous mouse models of melanoma.
Role: PI

2 R25 CA020449-34 (PI: Wolchok) NIH/NCI 08/01/2011 - 07/31/2016
Summer research experiences for medical students supervised by faculty mentors

The MSKCC Summer Student Fellowship Program helps address two significant challenges in the field of oncology. First, the program will help increase the number of oncologists to serve the aging population -- an accomplishment which will help ameliorate the 36% shortage of oncologists projected by the American Society of Clinical Oncology to occur by 2020. Second, the program provides opportunities for students from minority communities underrepresented in the sciences to participate in the research end. Role: PI

Industry-Partnered Team Science Award 06/01/2013-05/31/2016
Melanoma Research Alliance
Immune checkpoint inhibitor therapy with anti-CTLA-4 and anti-PD1: Human tumor microenvironment assessment for therapeutic target discovery, disease biomarkers and treatment of resistant disease.
This project is an in-depth investigation of the immunologic effects of combined CTLA-4 and PD-1 blockade in patients with melanoma and comparison with monotherapy studies. Role:PI

Harry J Lloyd (PI: Wolchok) 07/1/2014 - 06/30/2016
Tumor Mutational Landscape and Response to Checkpoint Blockade in Metastatic Melanoma
The goal of this project aims to determine the tumor genetic factors that may impact response to immune therapy. Role: PI

GC225051 (PI: Rudin) Role: Institutional Principal 07/1/2015 - 06/30/2018
Stand up to Cancer-American Cancer Society Lung Cancer Dream Team
Targeting KRAS Mutant Lung Cancers
Our proposed research ambitiously sets as its goal improving outcomes for lung cancer patients with a specific mutation, called KRAS, that is notoriously difficult to treat. For decades, patients with this type of lung cancer h ave done poorly on standard lung cancer therapies. In this proposal, researchers from top Cancer Centers across the country

Completed

5 R01 CA138738-05 (PI: Brentjens) 03/01/2009 - 01/31/2015
NIH/NCI
Adoptive Immunotherapy of Cancer with IL-12 Secreting Tumor-Targeted T Cells
Patient T cells may be genetically modified to target tumor through the introduction of genes
Encoding chimeric antigen recepters (CARS) specific to tumor associated antigens. Role: Consultant

P01 CA59350-13A1 (PI–Sadelain) 05/01/2011-04/30/2012
NIH/NCI
MSKCC Cancer Gene Therapy Program
Project 3: Genetic approaches to immune adjuvants (PI: Wolchok since 10/01/07). Role: PI Project 3

Team Science Award (Wolchok) 10/01/2009-09/30/2012
Melanoma Research Alliance
Defining the Importance of Immunity to NY-ESO-1 in Melanoma. Role: PI

Immunotherapy Dream Team (PI: Allison, MSKCC Principal: Wolchok) 3/1/2014-2/28/2015
Stand Up to Cancer AACR/CRI
Immunologic Checkpoint Blockade and Adoptive Cell Transfer in Cancer Therapy
The goal of this multi-center effort is the identification of mechanistic biomarkers for checkpoint blocking antibodies for a variety of malignancies, as well as novel approaches to the use of adoptive T cell therapy. Role: Institutional Principal