BIOGRAPHICAL SKETCH

NAME: Zarour, Hassane M.

eRA COMMONS USER NAME: zarourhm

POSITION TITLE: Professor of Medicine, Immunology and Dermatology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
School of Medicine, University of Marseille, France	MD	05/1979	Medicine
School of Medicine, University of Marseille, France	Resident	05/1986	Dermatology
School of Medicine, University of Marseille, France	Assistant Professor	05/1991	Dermatology
Ludwig Institute for Cancer Research, Brussels, Belgium	Research Fellow	07/1996	Tumor Immunology

A. Personal Statement

I am a Cancer Immunologist with a long-lasting interest in cancer immunotherapies, cancer vaccines and human T cell immunology. As an independent investigator, my research that focuses on immunotherapies of melanoma, T cell responses to melanoma antigens and on the mechanisms of melanoma-induced T cell dysfunction has been funded since 2002 by NIH/NCI RO1 grants as well as awards/contracts from the Cancer Research Institute, New-York and pharmaceutical industries. I have made seminal contributions in the field of human cancer immunology, identifying multiple novel tumor antigen-specific CD4 epitopes, and determining the role of the novel inhibitory receptor pathways Tim-3 and TIGIT in impeding T cell responses to melanoma. These findings have been translated into multiple first-in-human clinical trials in melanoma and other solid tumors, including cancer vaccines comprised of CD4 epitopes and adjuvants (CPG) and third generation immune checkpoint blockades with anti-Tim-3 or anti-TIGIT antibodies together with anti-PD-1 antibodies at HCC and other cancer centers in the US. Most recently, I have initiated translational studies evaluating the role of the gut microbiome in regulating clinical responses to PD-1 blockade in melanoma, including a first-in-human clinical trial to evaluate the safety and efficacy of fecal microbiota transplant (FMT) obtained from long-term PD-1 responder patients and pembrolizumab in PD-1 refractory melanoma patients. As a co-leader of the of the Cancer Immunology and Immunotherapy Program (CIIP), I will contribute to its mission, and together with basic and clinical investigators, foster the translation of novel laboratory findings into novel immunotherapy of cancers.

1. Chauvin JM, Pagliano O, Fourcade J, Sun Z, Hong Wang, Cindy Sanders, Kirkwood JM, Chen TT, Maurer M, Korman A.J, Zarour HM. TIGIT and PD-1 impair tumor antigen-specific CD8$^+$ T cells in melanoma patients. J Clin Invest. 2015 May 125(5):2046-58. PMCID: PMC4463210.
2. Fourcade J, Sun Z, Pagliano O, Chauvin JM, Sander C, Janjic B, Tarhini AA, Tawbi HA, Kirkwood JM, Moschos S, Wang H, Guillaume P, Luescher IF, Krieg A, Anderson AC, Kuchroo VK, Zarour HM. PD-1 and Tim-3 regulate the expansion of tumor antigen-specific CD8$^+$ T cells induced by melanoma vaccines. Cancer Res. 2014 15;74(4):1045-55. PMCID: PMC3952491.
3. Fourcade J, Sun Z, Benallaoua M, Guillaume P, Luescher IF, Sander C, Kirkwood JM, Kuchroo V, Zarour HM. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8$^+$ T cell dysfunction in melanoma patients. J Exp Med. 2010 27;207(10):2175-86. PMCID: PMC2947081
4. Zarour HM, Kirkwood JM, Kierstead LS, Herr W, Brusic V, Singluff CL, Sidney J, Sette A and Storkus WJ. Melan-A/MART-1 (51-73) represents an immunogenic HLA-DR4-restricted epitope recognized by melanoma-reactive CD4($^+$) T cells. Proc Natl Acad Sci U S A, 2000, 4:97: 400-405 PMID: 10618430; PMCID: PMC26675

B. Positions and Honors

Positions and Employment

1986-1991	Resident in Internal Medicine and Dermatology, University of Marseille, Medical School, France
1991-1993	Clinical Assistant Professor of Dermatology, Melanoma Center, Hospital Sainte-Marguerite, Marseille, France
1993-1995	Research Fellow at the Ludwig Institute for Cancer Research, Brussels, Belgium
1995-1997	Attending Physician, Dermatology, Hospital de Chambery, France
1997-1999	Research Associate, Department of Medicine and Melanoma and Skin Cancer Program, University of Pittsburgh Cancer Institute (UPCI), Pittsburgh, PA
2000-2002	Research Assistant Professor, Department of Medicine and Melanoma and Skin Cancer Program, University of Pittsburgh, Pittsburgh, PA
2002-2008	Assistant Professor, Department of Medicine, Immunology and Dermatology, University of Pittsburgh, Pittsburgh, PA
2008-2013	Associate Professor, Department of Medicine and Immunology and Dermatology, University of Pittsburgh, Pittsburgh, PA
2013-	Professor, Department of Medicine and Immunology and Dermatology, University of Pittsburgh, Pittsburgh, PA

Other Experience and Professional Memberships

1993	Training Award, Association pour la Recherche sur le Cancer, France
1994	Training Award, INSERM, France
1995	Training Award, Conseil Regional PACA, France
1999	Competitive Medical Research Fund (CMRF), University of Pittsburgh Medical Center
2000	American Association of Immunology (AAI)
2000	Eastern Cooperative Oncology Group (ECOG)
2000	American Association for Cancer Research (AACR)
2000	Member of the Cancer Vaccine Collaborative, Cancer Research Institute, New-York
2004	American Society of Clinical Oncology (ASCO)
2005	International Society of Biological Therapy of Cancer (iSBTc)
2005	NIH peer-review committees: Physiology and Pathobiology Fellowships, Oncology Fellowships, Diversity Fellowships and Experimental Therapeutics SBIR, adhoc reviewer
2010	Team Science Recognition Award, International Society for Biological Therapies of Cancer
2011	Co-leader of the Cancer Immunotherapy Trial Network (CITN) at the University of Pittsburgh
2014	Member, Department of Medicine Appointments and Promotions Committee
2014	Co-Leader, Melanoma Program, UPMC Hillman Cancer Center Pittsburgh, PA
2018	Co-Leader, Cancer Immunology and Immunotherapy Program, UPMC Hillman Cancer Center, Pittsburgh, PA
2019	Member of the Tenured Faculty Promotions and Appointments Committee, School of Medicine
2019	James W. and Frances G. McGlothlin Chair in Melanoma Immunotherapy Research
2019	External reviewer, Clinical/Translational Science study section, Intramural Research Program (IRP), Ohio State University Comprehensive Cancer Center

C. Contributions to Science

1. **The identification of novel MHC class II epitopes derived from tumor antigens.**

Because $CD4^+$ T cell play a critical role in the persistence and function of $CD8^+$ T cells, we reasoned that cancer vaccines with T-helper epitopes may contribute to increase the immunogenicity of MHC class I peptides in patients with advanced melanoma. My laboratory has developed successfully the approach to identify T-helper epitopes derived from a number of human tumor antigens and capable of stimulation antigen-specific $CD4^+$ T cells in patients with advanced cancer. Interestingly, we have identified a number of “promiscuous” MHC class epitopes that can bind to the most common HLA DR class II molecules and stimulate $CD4^+$ T cells in the majority of patients. Our findings have allowed the fine dissection of antigen-specific $CD4^+$ T cells in patients with cancer with the development of novel MHC class II tetramers. They also have allowed the identification of spontaneous antigen-specific $CD4^+$ Tregs in patients with advanced melanoma.

a. Mandic M, Castelli F, Janjic B, Almunia C, Andrade P, Gillet D, Brusic V, Kirkwood JM, Maillere B, Zarour HM. One NY-ESO-1-derived epitope that promiscuously binds to multiple HLA-DR and HLA-DP4 molecules and stimulates autologous $CD4^+$ T cells from patients with NY-ESO-1-expressing melanoma. J Immunol. 2005 Feb 1;174(3):1751-9. PMID: 15661941.

b. Mandic M, Almunia C, Vicel S, Gillet D, Janjic B, Coval K, Maillere B, Kirkwood JM, Zarour HM. The alternative open reading frame of LAGE-1 gives rise to multiple promiscuous HLA-DR-restricted epitopes recognized by T-helper 1-type tumor-reactive $CD4^+$ T cells. Cancer Res. 2003 Oct 1;63(19):6506-15. PMID: 14559844.

c. Zarour HM, Maillere B, Brusic V, Coval K, Williams E, Pouvelle-Moratille S, Castelli F, Land S, Bennouna J, Logan T, Kirkwood JM. NY-ESO-1 119-143 is a promiscuous major histocompatibility complex class II T-helper epitope recognized by Th1- and Th2-type tumor-reactive $CD4^+$ T cells. Cancer Res. 2002 Jan 1;62(1):213-8. PMID: 11782380.

d. Zarour HM, Kirkwood JM, Kierstead LS, Herr W, Brusic V, Singluff CL, Sidney J, Sette A and Storkus WJ. Melan-A/MART-1 (51-73) represents an immunogenic HLA-DR4-restricted epitope recognized by melanoma-reactive $CD4(^+)$ T cells. Proc Natl Acad Sci USA. 2000 Jan 4:97(1):400-05. PMCID: PMC26675.

2. **Novel Immunotherapies of melanoma.** Following the successful identifications of multiple promiscuous T-helper epitopes from tumor antigens, we have performed two first-in-human clinical trials with peptides and adjuvants. In particular, we have successfully performed two pilot trials with MHC class I and MHC class II epitopes derived from the cancer/testis antigen NY-ESO-1 in combination with CPG in patients with advanced melanoma. We have first demonstrated the capability of CPG to stimulate potent and ex vivo detectable $CD8^+$ T cell responses to NY-ESO-1. We have also shown that that melanoma vaccines with T-helper epitopes increase the expansion and functions of vaccine-induced $CD8^+$ T cells, supporting the potency of the approach. We have also performed the first-in-human clinical trial with pembrolizumab and low-dose Peginterferon to enhance the immunogenicity and efficacy of PD-1 blockade in melanoma.

a. Davar D, Wang H, Chauvin JM, Pagliano O, Fourcade JJ, Ka M, Menna C, Rose A, Sander C, Borhani AA, Karunamurthy A, Tarhini AA, Tawbi HA, Zhao Q, Moreno BH, Ebbinghaus S, Ibrahim N, Kirkwood JM, Zarour HM. Phase Ib/II Study of Pembrolizumab and Pegylated-Interferon Alfa-2b in Advanced Melanoma. J Clin Oncol 2018 Oct 25:JCO1800632 [Epub ahead of print] PMID:30359157

b. Fourcade J, Sun Z, Pagliano O, Chauvin JM, Sander C, Janjic B, Tarhini AA, Tawbi HA, Kirkwood JM, Moschos S, Wang H, Guillaume P, Luescher IF, Krieg A, Anderson AC, Kuchroo VK, Zarour HM. PD-1 and Tim-3 regulate the expansion of tumor antigen-specific $CD8^+$ T cells induced by melanoma vaccines. Cancer Res. 2014 Feb 15;74(4):1045-55. PMCID: PMC3952491.

c. Fourcade J, Kudela P, Andrade Filho PA, Janjic B, Land SR, Sander C, Krieg A, Donnenberg A, Shen H, Kirkwood JM, Zarour HM. Immunization with analogue peptide in combination with CpG and montanide expands tumor antigen-specific $CD8^+$ T cells in melanoma patients. J Immunother. 2008 Oct;31(8):781-91. PMCID: PMC3901357.

3. **The studies of the mechanisms of melanoma-induced T cell dysfunction including the role of the inhibitory receptor (IR) PD-1, Tim-3, BTLA and TIGIT pathways**. We have reported the upregulation of multiple IRs by tumor antigen-specific $CD8^+$T cells in human melanoma, including PD-1, Tim-3, BTLA and TIGIT. These studies have led to the identification of $CD8^+$T cell subsets present in the tumor microenvironment and exhibiting variable levels of T cell dysfunction. Interestingly, we have also shown that PD-1 and TIM-3 can also be upregulated upon T cell activation by vaccine-induced $CD8^+$ T cells and that dual PD-1/Tim-3 blockade can further increase the expansion and function of vaccine-induced $CD8^+$ T cells. Such data strongly support the implementation of combinatorial cancer vaccines with MHC class I and class II epitopes and dual PD-1/Tim-3 blockade. Most recently, we have shown the role of the TIGIT/CD226 axis in regulting the $CD4^+$Treg functions in melanoma. Collectively, our findings serve as rationale for multiple ongoing first-in-human clinical trials with dual PD-1/Tim-3 blockade (Novartis, Tesaro), and dual PD-1/TIGIT blockade (BMS) in patients with solid tumors, including melanoma.

a. Fourcade J, Sun Z, Chauvin JM, Ka M, Davar D, Pagliano O, Wang H, Saada S, Menna C, Amin R, Sander C, Kirkwood JM, Korman AJ, Zarour HM. CD226 opposes TIGIT to disrupt Tregs in melanoma. JCI Insight. 2018 Jul 25;3(14). pii: 121157. doi: 10.1172/jci.insight.121157. [Epub ahead of print] PMID: 30046006

b. Chauvin JM, Pagliano O, Fourcade J, Sun Z , Hong Wang, Cindy Sanders, Kirkwood JM, Chen TT, Maurer M, Korman A.J, Zarour HM. TGIT and PD-1 impair tumor antigen-specific $CD8^+$ T cells in melanoma patients. J Clin Invest. 2015 May 125(5):2046-58. PMCID: PMC4463210.

c. Fourcade J, Sun Z, Pagliano O, Guillaume P, Luescher IF, Sander C, Kirkwood JM, Olive D, Kuchroo V, Zarour HM. CD8(+) T cells specific for tumor antigens can be rendered dysfunctional by the tumor microenvironment through upregulation of the inhibitory receptors BTLA and PD-1. Cancer Res. 2012 15;72(4):887-96. PMCID: PMC3288235.

d. Fourcade J, Sun Z, Benallaoua M, Guillaume P, Luescher IF, Sander C, Kirkwood JM, Kuchroo V, Zarour HM. Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific $CD8^+$ T cell dysfunction in melanoma patients. J Exp Med. 2010 Sep 27;207(10):2175-86. PMCID: PMC2947081.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/pubmed/?term=zarour+H

D. Research Support

ACTIVE

R01 CA228181-01 06/01/18-05/31/23 1.80 Calendar
NIH/NCI $221,886 Direct
"Targeting TIGIT and PD-1 in Melanoma".
The information derived from the outlined studies will serve as rationale for the development of novel therapeutic strategies to reverse tumor-induced T cell dysfunction in patients with advanced melanoma and increase the likelihood of clinical benefits.

R01 CA222203-01 06/01/18-05/31/23 1.80 Calendar
NIH/NCI $307,571 Direct
"Fecal Microbiota Transplant and PD-1 blockade in Melanoma"
We propose to identify the gut microbiota from PD1 responder melanoma patients capable of promoting immunological and clinical responses to PD1 blockade. We will also test, in the context of a novel clinical trial, whether transplant of fecal microbiota combined with PD1 blockade converts PD1 non-responders into PD1 responder melanoma patients.

P30 CA047904-29 (Ferris) 08/01/15-07/31/20 0.60 Calendar
NIH $12,105 Direct
"Cancer Center Support Grant"
The CCSG supports 12 scientific research programs, including the Melanoma Program and 15 shared facilities at the University of Pittsburgh Cancer Institute (UPCI), a NCI-designated comprehensive cancer center. The Cancer Center focuses on cancer research, education, and care. Together with Dr. Kirkwood, Dr. Zarour is co-leader of the Melanoma Program.

Research Agreement (Zarour) 03/07/17-12/31/19 1.20 Calendar
Tesaro, Inc. $174,265 Direct
"Targeting PD-1 and Tim-3 with novel monoclonal antibodies to reverse tumor-induced T cell dysfunction"
The goal of this project is to target PD-1 and Tim-3 to reverse tumor-induced T-cell dysfunction.

BMS - CA020-002 Study (Zarour) 09/27/17-09/26/20 1.20 Calendar
Bristol-Myers-Squibb $210,775 Direct
"Correlative Studies of Antitumor Immune Responses and the Gut Microbiome of the TIGIT"

BMS correlative studies.

Research Agreement 04/25/18-10/24/19 0.60 Calendar
ImCheck Therapeutics $72,945 Direct
"Targeting PD-1 and BTLA with novel monoclonal antibodies to reverse tumor-induced T cell dysfunction"
To investigate the role of BTLA blockade alone (5 mAbs) or in combination with PD-1 blockade (1 mAb) adaptive and innate responses to cancer including the proliferation and cytokine (IFN-□, TNF, IL-2) production of NY-ESO1-specific $CD8^+$ T cells isolated from patients with advanced melanoma (8 patients) and $CD8^+$ and $CD4^+$TILs isolated from melanoma.

ITTC IPA 2019 No.6 01/01/18-01/01/20 0.60 Calendar
UPMC $169,408 Direct
"TDI ITTC"

Trial #17-034 (Davar) 10/9/17-2/22/28 0.60 Calendar
Merck – MISP #55482 $754,180 (total)
"Phase II Feasibility Study of Fecal Microbiota Transplant (FMT) in Advanced Melanoma Patients Not Responding to PD-1 blockade at 12 weeks"

Trial #17-169 (Davar) 7/25/18-12/31/23 0.60 Calendar
Checkmate $799,560 (total)
"Neoadjuvant Phase II Study of TLR9 Agonist CMP-001 in Combination with Nivolumab in Stage III B/C/D Melanoma Patients with Clinically Apparent Lymph Node Disease"

PENDING

Clinical Research Agreement (Zarour) 10/01/19-08/31/20 0.60 Calendar
Checkmate (SRA445) $368,755 Direct
"Single cell RNAseq studies of therapy with intratumoral CMP001 and Nivolumab in melanoma patients"

OVERLAP

None