OMB No. 0925-0001 and 0925-0002 (Rev. 10/15 Approved Through 10/31/2018)

BIOGRAPHICAL SKETCH

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NAME: **DuPage, Michel J.**

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

POSITION TITLE: Assistant Professor

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.)

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| --- | --- | --- | --- |
| INSTITUTION AND LOCATION | DEGREE  *(if applicable)* | Completion Date MM/YYYY | FIELD OF STUDY |
|  |  |  |  |
| University of California, Berkeley (CA) | B.A. | 05/2000 | Genetics |
| Massachusetts Institute of Technology, Cambridge (MA) | Ph.D. | 01/2011 | Cancer Biology |
| University of California, San Francisco (CA) | Postdoc | 06/2016 | Immunology |
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A. Personal Statement

The aim of my research is to identify and target the mechanisms controlling Treg reprogramming, establishing a new paradigm for modulating immune responses to treat cancer and autoimmune disease. As a Ph.D. candidate with Tyler Jacks at MIT, I pioneered the investigation of immune responses to cancer in the laboratory. As a result of my initial efforts, the laboratory since expanded research in this area to 4 postdocs and 4 Ph.D. candidates. By recapitulating many of the physiologic attributes of the human disease, my studies revealed the context-dependent nature of immune-tumor interactions. Most importantly, my research was at the forefront of a transformation in thinking about the importance of tumor-specific neo-antigens both in the process of cancer immunoediting, as well as for cancer immunotherapy. As a postdoctoral fellow with Jeff Bluestone at UCSF,I spearheaded the investigation of epigenetic control of regulatory T cell (Treg) stability and function in the laboratory. My research revealed how key extracellular cues sensed in the microenvironment impinge on Treg homeostasis. By combining my experiences investigating T cell responses to cancer with my work identifying epigenetic contributions to the functional stability of Tregs, I am uniquely positioned to study how Treg homeostasis within distinct tissue microenvironments is altered by, and influences, immune-based disease.

B. Positions and Honors

| ACTIVITY/OCCUPATION | BEGINNING DATE (mm/yy) | ENDING DATE (mm/yy) | FIELD | INSTITUTION/COMPANY | SUPERVISOR/ EMPLOYER |
| --- | --- | --- | --- | --- | --- |
| Research Associate  Research Associate | 06/1999  09/2000 | 09/1999  06/2003 | Genetics  Immunology | University of California,  Berkeley  Genentech, So. San Francisco (CA) | Thomas W. Cline  Andrew C. Chan |
| Postdoctoral Fellow  Principal Investigator  Assistant Professor | 06/2011  07/2016  07/2017 | 06/2016  06/2017  Current | Immunology  Cancer Immunotherapy  Immunology & Pathogenesis | University of California, San Francisco  Parker Institute for Cancer Immunotherapy, UCSF  University of California, Berkeley | Jeffrey A. Bluestone  Lewis Lanier, Dept. of Microbiology & Immunology  David Drubin, Dept. of Molecular & Cell Biology |

Academic and Professional Honors

1996 – 2000 Robert C. Byrd Honors Scholarship recipient

1997 – 2000 Golden Key National Honor Society

2000 – pres. Phi Beta Kappa Society

1999 – 2000 Honors Undergraduate Research in Molecular and Cell Biology

2000 Outstanding Scholar (1st in class) of the Department of Molecular and Cell Biology, UC Berkeley

2003 – 2004 Dupont MIT Alliance Fellow

2006 – 2007 Margaret A. Cunningham Immune Mechanisms in Cancer Fellowship

2011 – 2013 Ruth L. Kirschstein Institutional National Research Service Award (T32)

2013 – 2016 Helen Hay Whitney Foundation Postdoctoral Fellow

2016 – 2017 Parker Institute for Cancer Immunotherapy Fellow

C. Contribution to Science

1. Much of what is understood about immune surveillance of cancer has come from comparing susceptibility to transplantable or carcinogen-induced cancer models in normal versus various immuno-compromised strains of mice. As a PhD candidate, I overcame many of the obstacles of transplantable and carcinogen-induced models of cancer by generating autochthonous, genetically engineered mouse models (GEMMs) of cancer that could be induced to express or lack model tumor-specific neo-antigens (TSAs) to investigate the consequences of immune-tumor interactions in the pathophysiology of distinct forms of cancer. My work resulted in two key discoveries for the field of cancer immunoediting – the process by which immune cells protect the host from the development of cancer or drive the outgrowth of tumor cells with decreased sensitivity to immune attack. First, oncogene-driven, autochthonous sarcomas undergo immunoediting in a manner similar to carcinogen-driven tumors if they express model TSAs. Immunoediting occurs via loss of TSA or MHCI expression. Second, sarcomas induced without potent TSAs are significantly less immunogenic, even when they develop in the absence of the adaptive immune system. Therefore, my work revealed that recognition of TSAs by lymphocytes is a critical determinant of immunoediting and that tumor immunogenicity is not a universal characteristic of all cancers. My work was transformative because it provided the first experimental system to unify the apparently conflicting results obtained using either carcinogen-induced or genetically engineered mouse models of cancer by identifying TSAs as the critical determinants that invoke adaptive immunosurveillance and immunoediting. Finally, by comparing T cell responses in TSA-expressing models of lung adenocarcinomas and sarcomas, I discovered that in contrast to sarcomas, endogenous T cell responses to lung tumors are less productive and are incapable of driving antigen loss; thus uncovering a considerable degree of heterogeneity in T cell responses depending on the type of cancer and the environmental context.
2. Cheung AF, **DuPage M**, Dong HK, Chen J, Jacks T. Regulated expression of a tumor-associated antigen reveals multiple levels of T-cell tolerance in a mouse model of lung cancer. *Cancer Res.* (2008) 68:9459-68.
3. **DuPage M**, CheungAF, MazumdarC, WinslowMM, Bronson R, Schmidt LM, CrowleyD, ChenJ, Jacks T. Endogenous T cell responses to antigens expressed in lung adenocarcinomas delay malignant tumor progression. *Cancer Cell* (2011) 19: 72-85.
4. **DuPage M**, Mazumdar C, Schmidt LM, Cheung AF, Jacks T. Expression of tumour-specific antigens underlies cancer immunoediting. *Nature* (2012) 482: 405.
5. **DuPage M**, Jacks T. Genetically engineered mouse models of cancer reveal new insights about the antitumor immune response. *Curr Opin Immunol.* (2013) 25:192-9.
6. To elucidate the role of T cell responses to genetically engineered mouse models (GEMMs) of cancer, I created multi-functional lentiviral vectors that allowed for the induction of next-generation GEM tumor models that express neo-antigens. The use of lentiviruses was a technological advancement essential for many discoveries from the laboratory and the entire GEMM field because it provided a new paradigm for rapidly introducing key cDNAs, shRNAs, or CRISPR/Cas9 into multiple autochthonous cancer models.
7. **DuPage M**, Dooley AL, Jacks T. Conditional mouse lung cancer models using adenoviral or lentiviral delivery of Cre recombinase. *Nat Protoc.* (2009) 4: 1064-72.
8. Winslow MM, Dayton TL, Verhaak R, Kim-Kiselak C, Snyder EL, Feldser DM, Hubbard D, **DuPage M**, Whittaker CA, Hoersch S, Yoon S, Crowley D, Bronson RT, Chiang DY, Meyerson M, Jacks T. Suppression of lung adenocarcinoma progression by Nkx2-1. *Nature* (2011) 473: 101-104.
9. Joshi NS, Akama-Garren EH, Lu Y, Lee DY, Chang GP, Li A, **DuPage M**, Tammela T, Kerper NR, Farago AF, Robbins R, Crowley DM, Bronson RT, Jacks T. Regulatory T cells in tumor-associated tertiary lymphoid structures suppress anti-tumor T cell responses. *Immunity* (2015) 43: 579-590.
10. While the role of the polycomb genes in maintaining cellular fate decisions during development is established, their role in maintaining the identity of mature, differentiated cells after cellular activation is less clear. As a postdoctoral fellow, I identified Ezh2 as an epigenetic modifier induced by CD28 co-stimulation, thus connecting an established extracellular cue required for Treg maintenance with an epigenetic regulator of cell identity. Mice with Ezh2-deficient Treg cells fail to maintain immune tolerance, develop multi-organ autoimmunity, and are incapable of resolving inflammation in CNS tissues upon acute induction of autoimmunity (EAE). Ezh2-deficiency selectively disrupts Tregs after activation, severely compromising the Foxp3-dependent gene expression program and Treg lineage stability. Thus, Ezh2 coordinates cellular activation and the maintenance of cellular identity by directly responding to extracellular cues that drive proliferation (CD28 co-stimulation) and functioning with lineage specifying transcription factors (Foxp3) to reinforce the cells’ transcriptional program. In the context of the adaptive immune system, where the activation and expansion of subsets of cells with unique specificities is essential, epigenetic regulation of the fidelity of cell identity is paramount. This is especially important in the context of inflamed tissues where activated Treg cells must preserve their core gene expression program in the face of a complex milieu of extracellular cues. In addition to environmental cues from the CD28 receptor, Treg homeostasis and stability requires environmental sensing of the IL-2 cytokine, which is enhanced in Tregs by the constitutive expression of the high affinity IL-2 receptor alpha chain (CD25). Importantly, in mice and patients with autoimmune disease, responding Tregs in inflamed tissues commonly exhibit defects in IL-2 responsiveness, often due to reduced expression of CD25. IL-2 engagement of its receptor triggers the activation of two major signaling nodes – the STAT5 and phoshoinositide 3-kinase (PI3K) pathways. While STAT5 activity is essential for Treg maintenance, Tregs, in opposition to effector T cells, do not trigger strong activation of PI3K or the downstream kinase Akt. I generated mice with Treg-specific deletion of PTEN (a lipid phosphatase that opposes the activity of PI3K) and revealed that the uncontrolled activation of PI3K severely compromised Treg function and lineage stability. Treg instability was due in part to the down-regulation of CD25 expression in response to elevated Akt activation. In addition, PTEN-deficient Tregs exhibited an altered metabolic state more similar to effector T cells. My results revealed that Tregs utilize PTEN to finely control the balance of PI3K and STAT5 signaling in response to IL-2, an essential cytokine sensed in their microenvironment. All together, these findings bear high translational relevance, as small molecule drugs targeting Ezh2 and PI3K/Akt pathways are being tested in clinical trials as anti-cancer agents, creating tremendous potential for repurposing such drugs to simultaneously modulate immune cells in the tumor microenvironment. Importantly, my ongoing work has revealed that mice with Ezh2 deficient Tregs are more resistant to the development of transplantable tumors, supporting the potential for Ezh2 inhibition to treat cancers by acting directly on tumors as well as on the immune microenvironment.
11. Huynh A, **DuPage M**, Priyadharshini B, Sage PT, Quiros J, Borges CM, Townamchai N, Gerriets VA, Rathmell JC, Sharpe AH, Bluestone JA, Turka LA. Control of PI(3) kinase in Treg cells maintains homeostasis and lineage stability. *Nat Immunol* (2015) 16: 188-96.

b. **DuPage M**, Chopra G, Quiros J, Rosenthal WL, Morar MM, Holohan D, Zhang R, Turka L, Marson A,

Bluestone JA. The chromatin-modifying enzyme Ezh2 is critical for the maintenance of regulatory T cell identity after activation. *Immunity* (2015) 42: 227-238.

c. **DuPage M**, Bluestone JA. Harnessing the plasticity of CD4+ T cells to treat immune-mediated disease.

*Nat Rev Immunol* (2016) doi: 10.1038/nri.2015.18. [Epub ahead of print].

**Complete List of Published Work in MyBibliography**

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1HMNmEHlLD65G/bibliography/49721635/public/?sort=date&direction=ascending>

**D. Additional Information: Research Support and/or Scholastic Performance**

## Ongoing Research Support

Parker Institute for Cancer Immunotherapy, UCSF DuPage/Spitzer (PI) 07/01/17-06/30/18

Harnessing mass cytometry to monitor the dynamics of T cell clonotype and phenotype in cancer progression and immunotherapy

The goal of this research is to adapt the mass cytometry platform to link T cell specificity to the functional, phenotype and anatomic location of tumor-reactive T cells during tumor progression and after immunotherapy.

Role: Co-investigator

## Completed Research Support

Parker Institute for Cancer Immunotherapy, UCSF DuPage (PI) 07/01/16-06/30/17

Epigenetic control of regulatory T cell function in cancer and autoimmunity

The goal of this research is to identify and characterize key epigenetic mechanisms governing immune cell function in cancer, and target the pathways to selectively enhance the immune response against cancer while mitigating autoimmunity.

Role: PI

Helen Hay Whitney Foundation DuPage (PI) 05/01/13-04/30/16

Temporal dissection of Ezh2 activity in regulatory T cell plasticity and function

The goal of this research fellowship is to examine how Ezh2 activity controls the fate and plasticity of Tregs during different stages of Treg development and function.

Role: PI