BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: To-Ha Thai

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

POSITION TITLE: Instructor in Pathology

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
Univ of CA at Los Angeles, Los Angeles, CA	B.A.	06/90	Bacteriology
CA State Univ at Los Angeles, Los Angeles, CA	M.Sc. Honors	06/91	Molecular Virology
Univ of Alabama at Birmingham, Birmingham, AL	Ph.D.	12/04	Immunology
Immune Disease Institute, Harvard Medical School, Boston, MA	Postdoctoral Fellow	04/11	Immunology
Beth Israel Deaconess Medical Center, Department of Medicine, Boston, MA	Senior Fellow	04/14	Immunology

A. Personal Statement

My long-standing interest is to understand molecular mechanisms governing lymphocyte development and functions in an adaptive immune response. Under the guidance of Drs. John F. Kearney and Max D. Cooper at the University of Alabama at Birmingham, my scientific career began in the bone marrow characterizing the gene terminal deoxynucleotidyl transferase (*Dntt*) involved in the diversification of both T-cell and B-cell receptors during lymphocyte development. While at UAB, I uncovered an unexpected function of the long isoform of terminal deoxynucleotidyl transferase (TdT). I showed that this isoform has intrinsic 3' to 5' exonuclease activity suggesting that this enzyme may be involved in the trimming of the coding joins during V(D)J recombination.

After completing my Ph.D., my focus expanded to studying the genetic regulation of lymphocyte effector function. I joined Dr. Klaus Rajewsky's laboratory at the Immune Disease Institute, Harvard Medical School. There I began to unravel the role of a new class of gene regulators, micro-RNAs (miRNAs) in regulating lymphocyte effector function by generating both the knock-out and knock-in mice of the evolutionary conserved miR-155. Using these mice, I showed that miR-155 controls the mammalian immune system, specifically by regulating T helper function and the germinal center reaction to produce an optimal T-cell dependent antibody response. This was the first report of a miRNA regulating the immune response in mammals.

With the completion of my postdoctoral fellowship, I joined Harvard Medical School as an Instructor at Beth Israel Deaconess Medical Center. As a continuation of my effort to understand how miR-155 affects the immune response, I identified the heterochromatin protein 1γ (*Cbx3*/HP1γ) as a potential target. As implied by its name, *Cbx3*/HP1γ is involved in chromatin remodeling.

My results demonstrate for the first time that *Cbx3*/HP1γ has an essential, non-redundant function in the regulation of the adaptive immune response. I discover that *Cbx3*/HP1γ positively controls GC and high-affinity antibody responses to T-dependent antigens. It does so by restricting $CD8^+$ T-cell effector capacity, mainly the production of perforin, granzyme B and IFN-γ. Haploinsufficiency of *Cbx3*/HP1γ results in the enhanced production of perforin, granzyme B and IFN-γ by mutant $CD8^+$ effector T cells, which are more superior in killing tumor cells compared to control cells.

My long-term goals are to continue to discover means to manipulate the adaptive immune system to identify novel mechanisms for the discovery of novel therapeutic targets to treat immune-related disorders and solid tumors.

My strong background in genetic, molecular and biochemical approaches to examine gene regulation, my specific experience with gene targeting, and a record of productivity and supervision place me in a strong position to succeed in achieving my goals.
Because of two serious illnesses, my transition from postdoctoral fellow to independent faculty takes a detour thus longer than the traditional path.

1. **Thai, T.H.**, Calado, D.P., Casola, S., Ansel, K.M., Xiao, C.C., Xue, Y., Murphy, A., Frendewey, D., Valenzuela, D., Kutok, J.L., Schmidt-Supprian, M., Rajewsky, N., Yancopoulos, G., Rao, A., and Rajewsky, K. Regulation of the germinal center response by microRNA-155. Science. 316, 604-608 (2007). PMID:17463289.
2. ***Thai, T.H.**, Patterson, H.C., Pham, D.H., Kis-Toth, K., Kaminski, D.A., Tsokos, G.C. (*corresponding author). Deletion of microRNA-155 reduces autoantibody responses and alleviates lupus-like disease in the Fas (lpr) mouse. Proc. Natl. Acad. Sci. USA. 110, 20194-20199 (2013). PMID: 24282294. PMCID: PMC3864325.
3. Ha, N., Pham, D-H., Shahsafaei, A., Naruse, C., Asano, M., **Thai, T.H.** HP-1γ controls high-affinity antibody response to T-dependent antigens. Front. Immunol. 5, 271 doi:10.3389/fimmu.2014.00271 (2014). PMID: 21971082.
4. Sun, M., Ha, N., Pham, D-H., Frederick, M., Sharma, B., Naruse, C., Asano, M., Pipkin, M.E., George, R.E., **Thai, T.H.** *Cbx3*/HP1γ deficiency confers enhanced tumor-killing capacity on $CD8^+$ T cells. Sci. Rep. 7, 42888; doi: 10.1038/srep42888 (2017).

B. Positions and Honors

Positions and Employment

2005-2011 Research Fellow, Immunology, Immune Disease Institute, Harvard Medical School
2011-2014 Senior Fellow, Department of Medicine, Beth Israel Deaconess Medical Center
2014-present Instructor in Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School

Other Experience and Professional Memberships

1990-1991 Teaching Assistant, California State University at Los Angeles, Los Angeles, CA
1992-1995 Senior Scientist, Sandoz Pharmaceuticals, NJ

Honors

1991 Outstanding Graduate Student Presentation, American Society of Microbiology
1997 Outstanding Graduate Research Oral Presentation-2nd place, Microbiology, University of Alabama at Birmingham, Birmingham, AL
1998 Outstanding Graduate Research Oral Presentation-1st place, Microbiology, University of Alabama at Birmingham, Birmingham, AL
2002 The John R. Durant Award for Excellence in Cancer Research, The Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, AL
2004 Postdoctoral Research Services Fellowship, National Institute of Health
2006 Outstanding Poster Presentation Award, CBR Institute for Biomedical Research
2007 Award for excellence in poster presentation, Immune Disease Institute Research

C. Contributions to Science

1. Findings derived from my graduate work expand our understanding of antigen receptor diversification. I show for the first time that, *in vitro* and *in vivo*, TdTL is a 3' → 5' exonuclease catalyzing the deletion of nucleotides at coding joins. Diversity in the antigen-binding region of immunoglobulin (Ig) heavy (H) and light (L) chains and T cell receptors (TCRs) results from the combinatorial rearrangements of the variable (V_H+ V_L), diversity (D_H) and joining (J_{H+L}) gene segments by a process known as V(D)J recombination, which occurs at specific stages of B and T cell development. The short splice variant of mouse terminal deoxynucleotidyl transferase (TdTS) catalyzes the addition of nontemplated nucleotides (N addition) at the coding joins of B-cell and T-cell antigen receptor genes. However, the activity and function of the long isoform of TdT (TdTL) have not been determined. Therefore, my results show that the two TdT isoforms may act in concert to preserve the integrity of the variable region of antigen receptors while generating diversity. The generation of optimal antigen receptors is crucial for the development of lymphoid cells thus the eradication of infections and tumors.

a. **Thai, T.H.**, Purugganan, M.M., Roth, D.B., and Kearney, J.F. Distinct and opposite diversifying activities of terminal transferase splice variants. Nat. Immunol. 3, 457-462 (2002). [This article was featured on the cover of this issue]. PMID: 11938351.
b. **Thai, T.H.**, and Kearney, J.F. Distinct and opposite activities of human terminal deoxynucleotidyl transferase splice variants. J. Immunol. 173, 4009-4019 (2004). PMID: 15356150.
c. **Thai, T.H.** and Kearney, J.F. Isoforms of terminal deoxynucleotidyltransferase: developmental aspects and function. Adv. Immunol. 86, 113-136 (2005). PMID: 15705420.

2. My subsequent work shows for the first time that microRNAs (miRNAs) can control the adaptive immune response thus contributing to our understanding and appreciation of the complexity of the adaptive immune response. MicroRNAs are small RNA species involved in biological control at multiple levels. Using genetic deletion and transgenic approaches, I show that the evolutionarily conserved microRNA-155 (miR-155) has an important role in the mammalian immune system, specifically in regulating T helper cell function and the germinal center reaction to produce an optimal T-cell-dependent antibody response. MiR-155 exerts this control, at least in part, by regulating cytokine production. These results also suggest that individual microRNAs can exert critical control over mammalian differentiation processes *in vivo*. Dysregulation of miR-155 expression could have a profound impact on immune disorders and control of tumor growth.
   a. **Thai, T.H.**, Calado, D.P., Casola, S., Ansel, K.M., Xiao, C.C., Xue, Y., Murphy, A., Frendewey, D., Valenzuela, D., Kutok, J.L., Schmidt-Supprian, M., Rajewsky, N., Yancopoulos, G., Rao, A., and Rajewsky, K. Regulation of the germinal center response by microRNA-155. Science. 316, 604-608 (2007). PMID:17463289.
   b. *Lu, L-F., ***Thai, T.H.**, Calado, D.P., Chaudhry, A., Kubo, M., Tanak, K., Loeb, G.B., Lee, H., Yoshimura, A., Rajewsky, K., and Rudensky, A.Y. (*equal contributing authors). Foxp3-dependent microRNA-155 confers competitive fitness to regulatory T cells through targeting SOCS1. Immunity. 30, 80-91 (2009). PMCID: PMC 2654249.
   c. Zhang, Y., Roccaro, A.M., Rombaoa, C., Flores, L., Obad, S., Fernandes, S.M., Sacco, A., Liu, Y., Ngo, H., Quang, P., Azab, A.K., Azab, F., Maiso, P., Reagan, M., Brown, J.R., ***Thai, T.H.**, *Kauppinen, S., *Ghobrial I.M. (*equal contributing authors). LNA-mediated anti-microRNA-155 silencing in low-grade B cell lymphomas. Blood. 120, 1678-86 (2012). PMID: 22797699.
   d. ¶**Thai, T.H.**, Patterson, H.C., Pham, D.H., Kis-Toth, K., Kaminski, D.A., Tsokos, G.C. (¶corresponding author). Deletion of microRNA-155 reduces autoantibody responses and alleviates lupus-like disease in the Fas (lpr) mouse. Proc. Natl. Acad. Sci. USA. 110, 20194-20199 (2013). PMID: 24282294. PMCID: PMC3864325.

3. As a continuation of my effort to understand how miR-155 affects the immune response, I identified the heterochromatin protein 1γ (*Cbx3*/HP1γ) as a potential target. As implied by its name, *Cbx3*/HP1γ is involved in chromatin remodeling. My results demonstrate for the first time that *Cbx3*/HP1γ has an essential, non-redundant function in the regulation of the adaptive immune response. I discover that *Cbx3*/HP1γ positively controls the germinal center and high-affinity antibody responses to T-dependent antigens. It does so by restricting $CD8^+$ T-cell effector capacity, mainly the production of perforin, granzyme B and IFN-γ. Haploinsufficiency of *Cbx3*/HP1γ results in the enhanced production of these effector molecules by mutant $CD8^+$ effector T cells. More importantly, adoptive T-cell therapy using *Cbx3*/HP1γ $CD8^+$ T cells into tumor-bearing animals drastically reduces tumor cell growth.
   a. Ha, N., Pham, D-H., Shahsafaei, A., Naruse, C., Asano, M., **Thai, T.H.** HP-1γ controls high-affinity antibody response to T-dependent antigens. Front. Immunol. 5, 271 doi:10.3389/fimmu.2014.00271 (2014). PMID: 21971082.
   b. Sun, M., Ha, N., Pham, D-H., Frederick, M., Sharma, B., Naruse, C., Asano, M., Pipkin, M.E., George, R.E., **Thai, T.H.** *Cbx3*/HP1γ deficiency confers enhanced tumor-killing capacity on $CD8^+$ T cells. Sci. Rep. 7, 42888; doi: 10.1038/srep42888 (2017).
   c. Le, T.P. and **Thai, T.H.** The state of cellular adoptive immunotherapy for neuroblastoma and other pediatric solid tumors. Front. Immunol. 8, 1640 doi: 10.3389/fimmu.2017.01640 (2017).

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/toha.thai.1/bibliograpahy/47864586/public/?sort=date&direction=ascending

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

Current Support

NIH/NCI 1R21 CA198263-01A1 Thai (PI) 04/01/16-03/31/18
"*Cbx3*/HP1γ deficiency confers anti-tumor immunity"
The goal of this proposal is to generate compelling data showing we can enhance the effector function of the adaptive immune system through manipulation of *Cbx3*/HP1γ levels to control **melanoma** tumor growth *in vivo*.

The Mayer Family Fund Thai (PI) 04/01/14-present
"Understanding the role of *Cbx3*/HP1γ and epigenetic modifications in immunopathologies"
The goal of this proposal is to study the interplay between *cbx-3*/HP-1γ and epigenetic modifications in the adaptive immune response and immune related diseases.

Completed Support

NIH/NIAID R56 AI099012-01 Thai (PI) 04/01/12-03/31/14
"Regulation of chromatin modifications by miRNAs to control cytokine expression"
This proposal seeks to study the novel role of miR-155 in the expression and function of the histone modifier *Cbx3*/HP1γ in immune cells.

Friends for Life Neuroblastoma Research Program Thai (PI) 01/01/15-12/31/16
"Function of the Histone Reader *Cbx3*/HP1γ in the Anti-Neuroblastoma Response"
The goal of this application is to generate compelling preliminary data demonstrating the effects of *Cbx3*/HP1γ deficiency on anti-neuroblastoma immunity in mice.