

2006

## OR.107. TIM-1 Plays a Crucial Role in the Expansion of Autopathogenic T-Cells and Regulation of Autoimmunity [abstract only]

Sheng Xioa

*Harvard Medical School*

Nader Najafian

*Harvard Medical School*

Jay Reddy

*University of Nebraska - Lincoln, jayreddy@unl.edu*

Monica Albin


*Harvard Medical School*

Chen Zhu

*Harvard Medical School*

*See next page for additional authors*

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Xioa, Sheng; Najafian, Nader; Reddy, Jay; Albin, Monica; Zhu, Chen; Anderson, Ana; Zhang, Zheng; Gutierrez, Cristina; Sobel, Raymond; Umetsu, Dale; Yagita, Hideo; Akiba, Hisaya; Sayegh, Mohamed; DeKruyff, Rosemarie; and Kuchroo, Vijay K., "OR.107. TIM-1 Plays a Crucial Role in the Expansion of Autopathogenic T-Cells and Regulation of Autoimmunity [abstract only]" (2006). *Jay Reddy Publications*. 16.

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**Authors**

Sheng Xioa, Nader Najafian, Jay Reddy, Monica Albin, Chen Zhu, Ana Anderson, Zheng Zhang, Cristina Gutierrez, Raymond Sobel, Dale Umetsu, Hideo Yagita, Hisaya Akiba, Mohamed Sayegh, Rosemarie DeKruyff, and Vijay K. Kuchroo

Federation of Clinical Immunology Societies

Abstracts

Thematic Symposium 3202: Controlling Inflammatory Reactions  
Sunday, June 4

OR.107. TIM-1 Plays a Crucial Role in the Expansion of Autopathogenic T-Cells and Regulation of Autoimmunity

Sheng Xiao,<sup>1</sup> Nader Najafian,<sup>2</sup> Jay Reddy,<sup>1,6</sup> Monica Albin,<sup>2</sup> Chen Zhu,<sup>1</sup> Ana Anderson,<sup>1</sup> Zheng Zhang,<sup>1</sup> Cristina Gutierrez,<sup>1</sup> Raymond Sobel,<sup>3</sup> Dale Umetsu,<sup>4</sup> Hideo Yagita,<sup>5</sup> Hisaya Akiba,<sup>5</sup> Mohamed Sayegh,<sup>2</sup> Rosemarie DeKruyff,<sup>4</sup> Samia Khoury,<sup>1</sup> Vijay Kuchroo<sup>1</sup>

<sup>1</sup>Center for Neurologic Diseases, Brigham and Womens Hospital, Harvard Medical School, Boston, Massachusetts

<sup>2</sup>Transplantation Research Center, Brigham and Womens Hospital and Childrens Hospital Boston, Harvard Medical School, Boston, Massachusetts

<sup>3</sup>Department of Pathology, Stanford University School of Medicine, Stanford, California

<sup>4</sup>Division of Immunology, Childrens Hospital, Harvard Medical School, Boston, Massachusetts

<sup>5</sup>Department of Molecular Immunology, Tokyo Medical and Dental University, Tokyo, Japan

<sup>6</sup>Affiliation 2009-: University of Nebraska-Lincoln, Lincoln, Nebraska, USA

T-cell immunoglobulin and mucin (TIM) family Members are differentially expressed on Th1 and Th2 cells. Polymorphisms of TIM-1 have been associated with susceptibility to asthma; however, its role in regulating autoimmunity has not been studied. Here, we have used an agonistic anti-TIM-1 antibody (Ab, Clone 3B3) which has previously been shown to costimulate T-cell activation and expansion, to analyze the role of TIM-1 in the development and regulation of experimental autoimmune encephalomyelitis (EAE). Treatment with 3B3 dramatically enhances the severity of

EAE as well as the frequency of encephalitogenic CD4<sup>+</sup> T-cells and the production of IFN- $\gamma$  and IL-17 by these cells. Furthermore, administration of 3B3 breaks self-tolerance and induces EAE in the disease resistant B10.S strain. We have utilized another anti-TIM-1 Ab (RMT1-10) that does not costimulate T-cell activation in vitro. In contrast to 3B3, treatment with RMT1-10 inhibits the development of EAE and reduces the frequency of encephalitogenic CD4<sup>+</sup> T-cells with a commensurate decrease in the production of IFN- $\gamma$  and IL-17. Treatment with RMT1-10 causes CD4<sup>+</sup> T-cells to produce more IL-4 and IL-10. We provide evidence that both 3B3 and RMT1-10 bind to the same epitope in the Ig domain of TIM-1, but the binding affinity of 3B3 is much higher than that of RMT1-10. These data suggest that TIM-1 engagement with the agonistic Ab, along with TcR ligation, costimulates T-cell expansion with pro-inflammatory IFN- $\gamma$  and IL-17 production resulting in the breakdown of self-tolerance and development of autoimmunity, whereas blocking anti-TIM-1 Ab causes a decrease in the autopathogenic Th1/Th17 responses. This study demonstrates that TIM-1 is a key cell surface molecule that regulates effector T-cell response and depending on how the molecule is engaged, autoimmune responses can be either enhanced or inhibited in vivo.