

## Professor Wenwei Tu (涂文偉)

MBBS & MMSc (China), Ph.D. (HKU)

### Professor

Department of Paediatrics and Adolescent Medicine,  
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The University of Hong Kong

### Specialty

Viral Immunology & Transplantation Immunology

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## RESEARCH

*TRANSLATIONAL IMMUNOLOGY* emphasizing on discovering and translating the novel discoveries in the field of immunology to the delivery of effective immunological solutions for human diseases is my long-standing interest.

**Humanized Mouse Model:** My laboratory has established the humanized mice with complete human immune system. Using humanized mice, we have successfully established different disease models, such as virus infection, tumors, graft-versus-host disease (GVHD), allograft transplantation and lung fibrosis models. Now we are focusing on establishment of different autoimmune disease models in humanized mice.

**Viral Immunology:** To understand cellular and molecular basis involved in the host immune responses to influenza viruses and Epstein-Barr virus (EBV) and develop novel antiviral strategies. We have report for the first time that the small-for-gestational-age and preterm neonates have impaired antiviral activity of V $\gamma$ 9V $\delta$ 2-T and NK cells against influenza virus. By targeting human  $\gamma\delta$ -T cell immunity, we have further discovered novel strategies to treat human and avian influenza diseases and control EBV-induced tumors. Now we are studying the roles of  $\gamma\delta$ -T and NK cells in immune surveillance of influenza virus and EBV infections.

**Transplantation Immunology:** To understand the basic processes that control T-cell-mediated inflammation and tolerance. We have developed the novel methods to generate antigen-specific CD4 and CD8 regulatory T cells (Tregs). We also confirmed that ex vivo-generated human CD8 Tregs can control graft-versus-host disease (GVHD) in an allo-specific manner while leaving graft versus tumor and general immune responses intact in humanized mice. We are now focusing on translating these basic studies into the development of new therapies for GVHD, organ transplantation and autoimmune diseases.

### Selected publications (\* Corresponding author)

1. **Tu W\*** and Zheng J. Chapter 10. Application of Humanized Mice in Immunological Research. In: Maria Cristina Cuturi and Ignacio Anegón (eds.), *Suppression and Regulation of Immune Responses: Methods and Protocols, Volume II, Methods in Molecular Biology*, vol. 1371, DOI 10.1007/978-1-4939-3139-2\_10, © Springer Science+Business Media New York 2016
2. Chen Q, Wen K, Lv A, Liu M, Ni K, Xiang Z, Liu Y, **Tu W\***. Human V $\gamma$ 9V $\delta$ 2-T cells synergize CD4<sup>+</sup> Tfh cells to produce influenza virus-specific antibody. *Frontiers in Immunology*, 04 April 2018 | <https://doi.org/10.3389/fimmu.2018.00599>.

3. Xiang Z and **Tu W\***. Dual face of V $\gamma$ 9V $\delta$ 2-T cells in tumor immunology: anti- versus pro-tumoral activities, *Frontiers in Immunology*, 2017 Aug 28;8:1041. doi: 10.3389/fimmu.2017.01041. eCollection 2017.
4. Liu Y, Zheng J, Liu Y, Wen L, Huang L, Xiang Z, Lam KT, Lv A, Mao H, Lau YL, **Tu W\***. Uncompromised NK cell activation is essential for virus-specific CTL activity during acute influenza virus infection. *Cell Mol Immunol*. 2017 Apr 17. doi: 10.1038/cmi.2017.10.
5. Chen Q, Liu Y, Lu A, Ni K, Xiang Z, Wen K, **Tu W\***. Influenza virus infection exacerbates experimental autoimmune encephalomyelitis disease by promoting type I T cells infiltration into central nervous system. *J Autoimmun*. 2017 Feb;77:1-10. doi: 10.1016/j.jaut.2016.10.006.
6. Wu Y, **Tu W\***, Lam KT, Chow KH, Ho PL, Guan Y, Peiris JS, Lau YL. Lethal co-infection of influenza virus and *Streptococcus pneumoniae* lowers antibody response to influenza virus in lung, and reduces germinal center B cells, T follicular helper cells and plasma cells in mediastinal lymph node. *Journal of Virology*. 2015 Feb;89(4):2013-23. doi: 10.1128/JVI.02455-14.
7. Xiang Z, Liu Y, Zheng J, Liu M, Lv A, Gao Y, Hu H, Lam KT, Chan GC, Yang Y, Chen H, Tsao GS, Bonneville M, Lau YL, **Tu W\***. Targeted activation of human V $\gamma$ 9V $\delta$ 2-T cells controls Epstein-Barr virus-induced B cell lymphoproliferative disease. *Cancer Cell* 2014 Oct 13;26(4):565-576. doi: 10.1016/j.ccr.2014.07.026.
8. Li J, Li H, Mo H, Yu M, Feng T, Yang F, Fan Y, Lu Q, Shen C, Yin Z, Mao M, **Tu W\***. Impaired NK cell antiviral cytokine response against influenza virus in small-for-gestational-age neonates. *Cellular and Molecular Immunology* 2013 Sep;10(5):437-43. doi: 10.1038/cmi.2013.31.
9. Zheng J, Liu Y, Liu M, Xiang Z, Lam KT, Lewis DB, Lau YL, **Tu W\***. Human CD8 regulatory T cells inhibit graft-versus-host disease and preserve general immunity in humanized mice. *Science Translational Medicine* 2013 Jan 16;5(168):168ra9.
10. Zheng J, Liu Y, Lau YL and **Tu W\***. Gammadelta-T Cells: unpolished sword in human antiviral Immunity. *Cellular and Molecular Immunology*, 2013 Jan;10(1):50-7.
11. Qin G, Liu Y, Zheng J, Ng IH, Peiris JSM, Lau YL and **Tu W\***. Phenotypic and functional characterization of human  $\gamma\delta$  T cell subsets in response to influenza A viruses. *Journal of Infectious Diseases*. 2012 Jun;205(11):1646-53.
12. Mao H, Yang W, Lee PPW, Ho MHK, Yang J, Zeng S, Chong CY, Lee TL, **Tu W\***, Lau YL. Exome Sequencing Identifies Novel Compound Heterozygous Mutations in *Interleukin-10 Receptor A* in a Neonatal-Onset Crohn's Disease Patient. *Genes and Immunity* 2012 Jul;13(5):437-42.
13. Qin G, Liu Y, Zheng J, Ng IH, Xiang Z, Lam KT, Mao H, Li H, Peiris JSM, Lau YL and **Tu W\***. Type-1 responses of human V $\gamma$ 9V $\delta$ 2 T cells to influenza A viruses. *Journal of Virology*. 2011 oct; 85(19):10109-16
14. **Tu W\***, Zheng J, Liu Y, Sia SF, Liu M, Qin G, Ng IHY, Lam KT, Peiris JSM, and Lau YL. The aminobisphosphonate pamidronate controls influenza pathogenesis by expanding a gammadelta T cell population in humanized mice. *Journal of Experimental Medicine*. 2011 Jul 4; 208(7):1511-22.
15. **Tu W\***, Mao H, Zheng J, Liu Y, Chiu SS, Qin G, Chan PL, Lam KT, Guan J, Zhang L, Guan Y, Yuen KY, Peiris JSM and Lau YL. Cytotoxic T Lymphocytes Established by Seasonal Human Influenza Cross-react against 2009 Pandemic H1N1 Influenza Virus. *Journal of Virology*. 2010 Jul;84(13):6527-35.
16. Mao H, **Tu W\***, Qin G, Law HKW, Sia SF, Chan PL, Liu Y, Lam KT, Zheng J, Peiris JSM and Lau YL. Influenza virus directly infects human natural killer cells and induces cell apoptosis. *Journal of Virology*. 2009 Sep;83(18):9215-22.
17. Zheng J, Liu Y, Qin G, Chan PL, Mao H, Lewis DB, Lau YL and **Tu W\***. Efficient induction and expansion of human alloantigen-specific CD8 regulatory T cells from naive precursors by CD40-activated B cells. *Journal of Immunology* 2009 Sep 15;183(6):3742-50.
18. Qin G, Mao H, Zheng J, Sia FS, Liu Y, Peiris JSM, Lau YL and **Tu W\***. Phosphoantigen-expanded gammadelta T

cells display potent cytotoxicity against human and avian influenza virus-infected monocyte-derived macrophages. *Journal of Infectious Diseases* 2009 Sep 15;200(6):858-65.

19. **Tu W\***, Lau YL, Zheng J, Liu Y, Chan PL, Mao H, Dionis K, Schneider P, and Lewis DB. Efficient generation of human alloantigen-specific CD4<sup>+</sup> regulatory T cells from naïve precursors by CD40-activated B cells. *Blood*. 2008;112(6):2554-62.
20. **Tu W**, Potena L, Stepick-Biek P, Liu L, Dionis KY, Luikart H, Fearon WF, Holmes TH, Chin C, Cooke JP, Valantine HA, Mocarski ES, Lewis DB. T-Cell Immunity to Subclinical Cytomegalovirus Infection Reduces Cardiac Allograft Disease. *Circulation*. 2006 Oct; 114(15): 1608-15.

#### **Research Grants (External)**

1. Costimulatory effect of 4-1BB signal in the antitumor activity of human gammadelta-T cells against EBV-induced lymphoproliferative disease. **(RGC/GRF - \$1,232,899/2017)PI**
2. Role of costimulatory molecule CD137 in the antiviral activity of human gammadelta-T cells against influenza virus. **(RGC/GRF - \$1,022,409/2015)PI**
3. Viral, host and environmental determinants of influenza virus transmission and pathogenesis. [[UGC/Theme-based Research Scheme \(TRS\)](#) - \$75,060,000 /2014]/Co-PI.
4. Human gammadelta-T cell-mediated virus-specific immune regulation during influenza virus infection. **(RGC/GRF - \$701,839/ 2014)PI**
5. The role of NLRP3 inflammasome in the induction of protective Th1 and Th17 immune response towards *Penicillium marneffei*. **(RGC/GRF - \$973,024 / 2014)CI**
6. Center for Nasopharyngeal Carcinoma Research, 2<sup>nd</sup> phase. ([UGC/Areas of Excellence \(AoE\)](#), - \$40,250,000M, 2014-2017)CI.
7. Role of human gammadelta-T cells in the generation of influenza virus-specific antibody. **(RGC/GRF - \$1,125,842/ 2013)PI**
8. Antiviral activity of human gammadelta-T cells against Enterovirus 71. **(HMRF-\$1,000,000/ 2013)PI**
9. The effects of BTK mutation on TLR3-mediated type I IFN response against poliovirus infection in X-linked agammaglobulinemia. **(RGC/GRF - \$684,166/ 2013)CI**
10. Human lung local immunity to influenza virus - role of lung antibody and resident memory T cells. **(RGC/GRF - \$692,826/ 2013)CI**
11. Roles of SIRT1 deacetylase in human T-cell leukemia virus type I transcription and leukemogenesis. **(RGC/GRF - \$822,731/ 2013)CI**
12. Molecular Mechanisms of Innate Immunity. **(Croucher Foundation - \$100,000/2012)CI**.
13. Induction of tolerance by alloantigen-specific regulatory T cells in humanized mice and non-human primates. **(NSFC/RGC Joint Research Scheme - HK\$819,366 + RMB450,000/ 2011)PI**.
14. Antiviral Activity of Human gammadelta-T Cells against Epstein-Barr Virus Infection. **(RGC/GRF - \$1,173,000/ 2011)PI**.
15. Immune Evasion of Natural Killer Cells by Influenza Virus in Vivo **(Research Fund for the Control of Infectious Diseases - \$989,490/ 2011)PI**.
16. Role of influenza hemagglutinin glycoprotein in activation of dendritic cells and induction of effective immune response through C-type lectin receptors **(RGC/GRF - \$591,600/ 2010)CI**.
17. Pathogenesis of human swine influenza virus and *Streptococcus pneumoniae* infection co-infection. **(Research Fund for the Control of Infectious Diseases - \$730,000/ 2009)CI**.
18. Rotavirus Vaccine Programme **(Hong Kong Society for the Relief of Disabled Children - \$3,036,000/ 2009)Co-PI**.

19. Pneumococcal Vaccine Programme. (**Hong Kong Society for the Relief of Disabled Children** - \$668,000/2009)/**Co-PI**.
20. Case-control study of Sichuan and Hong Kong children with melamine associated renal stones – renal ultrasounds and urinary IL-8 and MCP-1. (**Melamine Incident-funded Project** - \$523,124/2009)/**CI**.
21. RFCID commissioned grant for avian influenza infection. (**Research Fund for the Control of Infectious Diseases** - \$5,000,000/2009)/**CI**.
22. The Role of Natural Killer Cells in the Pathogenesis of Avian Influenza Virus Infection. (**RGC/GRF** - \$377,365/2008)/**PI**.
23. Immune responses to influenza viruses in the patients with X-linked agammaglobulinemia. (**RGC/GRF** - \$718,773/2008)/**CI**.
24. Control of Pandemic and Inter-Pandemic Influenza. (**UGC/[Areas of Excellence \(AoE\)](#)**, - \$76,000,000/2008)/**CI**.
25. Immune defense of human gammadelta-T Cells against influenza A viruses. (**RGC/GRF** - \$740,731/2007)/ **PI**.
26. Humanized mouse as a model to study the antiviral activity of human gammadelta-T cells against human and avian influenza A viruses in vivo. (**Research Fund for the Control of Infectious Diseases** - \$789,648/2007)/**PI**.
27. A comparison study of humoral and cellular immune responses in very young infants after intradermal versus intramuscular injection of influenza vaccine. (**RGC/GRF** - \$670,717/2007)/**CI**.

## Patents

### Patent granted:

1. Method to induce and expand therapeutic alloantigen-specific human regulatory T cells in large-scale (US patent: US8658159B2)
2. Method to induce and expand therapeutic alloantigen-specific human regulatory T cells in large-scale (European Patent: 2300602)
3. 大规模诱导和扩增治疗性同种异体抗原特异性的人调节性T细胞的方法。(China patent: 200980125228.0)
4. Patent Cooperation Treaty: Methods to generation of human alloantigen-specific CD4 regulatory T cells. (PCT/CN2009/000484).
5. Human CD8 regulatory T cells inhibit graft-versus-host disease and preserve general immunity (US patent: 61/927.046).

### Patents are filed and pending for grant

6. Biophosphonate Compounds and Gamma Delta T Cell-Mediated Therapy for Treating Epstein-Barr Virus Associated Disorders (US patent: 62/036,487).

## Awards

- 2015: Outstanding Research Output Award, LKS Faculty of Medicine, HKU.
- 2004: The **second class prize** of “*The Progress of Science and Technology*” was awarded by the Ministry of Education of the People’s Republic of China for the study on “Neonatal Immune Functions”.
- 2002: Travel award for Federation of Clinical Immunology Societies, USA
- 2002: The **second class prize** of “*The Progress of Science and Technology*” was awarded by Chongqing Municipal Government for the study on “Developmental Immune Dysfunctions”.
- 2001: Dean Fellowship, Stanford University
- 2000: Dean Fellowship, Stanford University
- 1998: The **third class prize** of “*The Progress of Science and Technology*” was awarded by Chongqing Municipal Government for the study on “The immunoregulatory role of Chinese herb *Astragalus membranaceus*”.

*and its clinical significance”.*

- 1997: The **first class prize** of “*The Progress of Science and Technology*” was awarded by Chongqing Municipal Government for the study on “T lymphocyte dysfunction and clinical diseases”.
- 1994: The **second class prize** of “*The Progress of Science and Technology*” was awarded by Sichuan Province Government for the study on “The role of T cells and their cytokines in immunoglobulin isotype switching and their clinical significance”.

### **Editorship or editorial board membership of scholarly journals**

- 2015-: Guest editor for PLOS Pathogens.
- 2015-: Member of Editorial Board, *Frontiers in Immunology*
- 2013-: Member of Editorial Board. *Virologica Sinica*.
- 2012-: Member of Editorial Board. *Dataset Papers in Medicine* (Hindawi Publish Corporation).
- 2012-: Member of Editorial Board. *Scientifica* (Hindawi Publish Corporation).
- 2010-: Member of Editorial Board. *Cellular and Molecular Immunology* (Nature Publishing Group)
- 2008-: Member of Editorial Board. *Journal of Pediatric Pharmacology*.
- 2007-: Member of Editorial Board. *Chinese Journal of Paediatrics*

### **Leadership in Professional Society**

- Council member Chinese NSFC Board of Medical Research (2018)
- Chair Symposium at Primary and acquired Immunodeficiency 2016 World Life Science Congress, Beijing (2016)
- Members Expert group responsible for drafting the chapters of the Immunology Research and Development for Chinese NSFC **13<sup>th</sup>-5 Years Strategy Plan** (2014).
- President Hong Kong Society of Immunology (2012-2014).
- President Hong Kong Society of Flow Cytometry (2010-2011)
- Council member Paediatric Infectious Disease Committee, Chinese Medical Association. (2010- )
- Member Evaluation Committee for Chang Jiang Scholars, Ministry of Education of the People’s Republic of China, China (2009- )
- Chair Viral Infection Symposium at 13<sup>th</sup> Asian Pacific Congress of Pediatrics (2009)
- Council member Chinese National Pediatric Virology Group (2008- )
- Council member Hong Kong Society of Immunology (2008- )
- Council member Paediatric Immunology Committee, Chinese Medical Association (2007-2010)

### **Teaching**

6 MPhil students (5 graduated), 10 PhD students (7 graduated)