FYSS

04/12-04/13

Formosa Immunology 2019 Spring School and Symposium

Frontier of Emerging Concepts in Immunology

Venue:

Biomedical Research Building 1F,Chang Gung Memorial Hospital,Linkou

Organizer

Chang Gung Memorial Hospital

Chang Gung University

Taiwan Oncology Society

The Chinese Society of Immunology

Co-organizer

National Yang-Ming University

National Taiwan University

Genomics Research Center, Academia Sinica

About FISS

The field of immunology is one of the fastest growing disciplines in biomedical research. Immunology comprises a multifaceted research agenda that has roots in the clinical challenges of host defense against infection, transplantation, autoimmunity, tumor immunology, and allergy. To date, it also becomes clear that outside the traditional immunological diseases, dysregulation of immune responses is associated with the development of many metabolic disorders and neurodegenerative diseases. These exciting findings in basic immunology research provide momentum in clinical immunology research that offers substantial therapeutic promise and brought novel interventions for the treatment of many human diseases.

In the past decade, researchers in Taiwan have made several outstanding discoveries and breakthroughs in both basic and clinical immunology. Multiple institutes in Taiwan, including Chang Gung University, Chang Gung Memorial Hospital System, have devoted an enormous effort to nurture and support fundamental and clinical research of immunology. However, as the subject of immunology becomes more complex, it is imperative to train the next generation of immunologists to stay at the forefront of their respective lines of research in this ever-evolving field. Moreover, it is also well recognized that multidisciplinary collaborations both locally and internationally become increasingly important to deal with the massive data sets acquired by ever-advancing technology. In light of this, several Taiwanese immunologists from Chang Gung University/Hospital System as well as many other research institutes and universities at home and abroad have worked together to organize this first-ever immunology spring school and symposium, ***Formosa Immunology Spring School and Symposium (FISS) - Emerging Concepts in Immunology.*** The goals of this event are to foster biomedical research for our next generation and to provide a platform to bridge local scientists with world-renowned immunologists.

FISS, is a five-day event that will be held in Taiwan on April 9-13, 2019. Having 10 world-class immunology experts along with top Taiwanese researchers, this event will provide a comprehensive overview of both basic concepts and cutting-edge knowledge in immunology. Specifically, for the first three days, the Spring School offers a combination of lectures from the guest faculty and poster/oral presentation sessions from the 30 selected students, which allow intellectual interaction covering the current challenges and/or issues of broad topics of immunology research. The entire event will end with a one-and-half day symposium in which the invited international and

Taiwanese faculty will present and share their exciting on-going research work. We look forward to seeing the best young scientists from Taiwan to participate in the program. The selection process for the students is highly competitive. It is expected that the selected students to be highly motivated to actively participate in all the program activities during this intensive five-day event.

We genuinely believe that the **FISS** is the excellent opportunity for young students, postdocs and physician scientists in Taiwan to broaden their horizons in immunology research and to have the chance to present their work and interact with leading scientists within the field. It is our hope that this event will encourage local scientists to tackle the challenges ahead of us and to bring top-notch researchers together for fruitful scientific interactions. Ultimately, we believe this effort will inspire new generations of Taiwanese researchers and generate great momentum to move biomedical research in Taiwan forward.

- FISS Team

Organization Committee

Chair

Dr. Chang-Fu Kuo (郭昶甫), Professor, Chang Gung Memorial Hospital

Co-Chair

Dr. Cheng-Lung Ku (顧正崙), Associate Professor, Chang Gung University

Committee

Dr. Nien-Jung Chen (陳念榮), Associate Professor, National Yang-Ming University

Dr. Sze-Ting Chen (陳斯婷), Assistant Professor, National Yang-Ming University

Dr. Ping-Chih Ho (何秉智), Assistant Professor, University of Lausanne, Switzerland

Dr. Chia-Lin Hsu (徐嘉琳), Associate Professor, National Yang-Ming University

Dr. Stanley Huang (黃景政), Assistant Professor, Case Western Reserve University, USA

Dr. Ming-Ling Kuo (郭敏玲), Professor, Chang Gung University

Dr. Chien-Kuo Lee (李建國), Professor, National Taiwan University

Dr. Wan-Lin Lo (駱宛琳), Postdoc scholar, University of California San Francisco, USA

Dr. Ching-Lan Lu (路景蘭), Instructor, The Rockefeller University

Dr. Li-Fan Lu (呂理帆), Associate Professor, University of California San Diego, USA

Dr. Chia-Ning Shen (沈家寧), Associate Research Fellow, Academia Sinica

Dr. Chia-Rui Shen (沈家瑞), Professor, Chang Gung University

Dr. Wen-Yi Tseng (曾文逸), Assistant Professor, Chang Gung Memorial Hospital

Dr. Muh-Hwa Yang (楊慕華), Professor, National Yang-Ming University

Dr. Huang-Yu Yang (楊皇煜), Associate Professor, Chang Gung Memorial Hospital

Advisory Committee

Dr. Fu-Tong Liu (劉扶東), Distinguished Research Fellow, Academia Sinica

Dr. Ming-Zong Lai (賴明宗), Distinguished Research Fellow, Academia Sinica

Day 1: 2019/04/12

Time	Topic / Speaker / Moderator*
11:00-13:30	***Registration***
13:30-13:40	**Opening** **Wen-Jin Cherng**, Chairman of Steering Committee, Chang Gung Memorial Hospital
13:40-13:55	Distinguished Guest’ s Remark **Dar-Bin Shieh**, Deputy Minister, Ministry of Science and Technology **Fu-Tong Liu**, Corresponding Research Fellow and Vice President, Academia Sinica **Chia-Chu Pao**, President, Chang Gung University
13:55-14:00	Committee Chair **Chang-Fu Kuo**, Director, Department of Medical Research and Development, Linkou Chang Gung Memorial Hospital
14:00-15:00	**Keynote Seminar:** Toward a genetic theory of childhood infectious diseases **Jean-Laurent Casanova**, Professor, The Rockefeller University, USA *Jacob See-Tong Pang, Vice-Superintendent, Linkou Chang Gung Memorial Hospital
15:00-15:45	The critical role of myeloid lectin in the pathogenesis of viral infections **Shie-Liang Hsieh**, Professor, Academia Sinica, Taiwan *Cheng-Lung Ku, Associate Professor, Chang Gung University
15:45-16:15	*Break & Group Photo*
16:15-17:00	Microglial autophagy and metabolic fitness in Alzheimer’s disease **Marco Colonna**, Professor, Washington University School of Medicine, USA *Tzu-Chen Yen, Professor, Chang Gung Memorial Hospital
17:00-17:30	Focus on the inbetweener: Regulation of group 2 innate lymphoid cells in asthma **Ya-Jen Chang**, Assistant Research Fellow, Academia Sinica, Taiwan *Chia-Rui Shen, Professor, Chang Gung University
17:30-18:15	Development and function of innate-like alpha beta T cells **Mitch Kronenberg**, President, La Jolla Institute for Allergy and Immunology, USA *Chin-Yen Lin, Professor, Chang Gung Memorial Hospital
18:15-19:15	*Welcome Reception for Immunology Symposium*
19:00-21:00	*Conference Banquet (By invitation)*

Day 2: 2019/04/13

Time	Topic / Speaker / Moderator*
08:00-08:30	***Registration***
08:30-09:15	Immune-modulating approaches to cancer therapy: focusing on combinations **Jedd Wolchok**, Professor, Memorial Sloan-Kettering Cancer Center, USA *Chyong-Huey Lai, Vice-Superintendent, Linkou Chang Gung Memorial Hospital
09:15-09:45	Dynamic interplay between tumor cells and macrophages during cancer progression **Muh-Hwa Yang**, Professor/Vice President, National Yang Ming University, Taiwan "MSD sponsored symposia" *Wen-Hung Chung, Professor, Chang Gung Memorial Hospital
9:45-10:30	Tumor-derived extracellular vesicles **Michele De Palma**, Associate professor, Ecole Polytechnique Federale de Lausanne, Switzerland *John Wen-Cheng Chang, Director, Taiwan Society of Immunotherapy of Cancer
10:30-11:00	*Break*
11:00-11:30	Metabolic perspective of trained immunity **Shih-Chin (James) Cheng**, Assistant Professor, National Tsing Hua University, Taiwan *Stanley Huang, Assistant Professor, Case Western Reserve University
11:30-12:15	A long noncoding RNA in the *Cd8* locus controls functional differentiation of CD4 T cells **Hilde Cheroutre**, Professor/Head, La Jolla Institute for Allergy and Immunology, USA *Jing-Long Huang, Vice-Superintendent, Linkou Chang Gung Memorial Hospital
12:15-13:30	*Lunch*
13:30-14:15	New Insights into Mechanisms involved in TCR Ligand Discrimination **Arthur Weiss**, Professor, University of California San Francisco, USA *Shue-Fen Luo, Professor, Chang Gung Memorial Hospital
14:15-14:45	Regulation of dendritic cell development by type I IFN signaling pathway **Chien-Kuo Lee**, Professor/Director, National Taiwan University, Taiwan *Ping-Chih Ho, Assistant Professor, University of Lausanne
14:45-15:30	Self tolerance: new thoughts on an old issue **Jonathan Sprent**, Professor, Garvan Institute of Medical Research, Australia *Wei-Chen Lee, Professor, Chang Gung Memorial Hospital
15:30-16:00	*Break*
16:00-16:45	Cytokine communication in inflammation: The T cell-phagocyte interface **Burkhard Becher,** Professor, University of Zurich, Switzerland *Ming-Ling Kuo, Dean of Research and Development, Chang Gung University
16:45-17:15	Glutamine modulates the balance of Th17 and Treg by metabolic and epigenetic change **Huang-Yu Yang**, Associate Professor, Chang Gung Memorial Hospital, Taiwan *Li-Fan Lu, Associate Professor, University of California, San Diego
17:15-18:00	Epigenetic and transcriptional mechanisms of cellular memory **Alexander Rudensky**, Professor, Memorial Sloan-Kettering Cancer Center, USA *Jenn-Haung Lai, Professor, Chang Gung Memorial Hospital
18:00-18:30	**Award Ceremony & Closing** **Jacob See-Tong Pang**, Vice-Superintendent, Linkou Chang Gung Memorial Hospital **Chang-Fu Kuo**, Director, Department of Medical Research and Development, Linkou Chang Gung Memorial Hospital

Curriculum Vitae

Jean-Laurent Casanova, M.D., Ph.D.

Investigator, Howard Hughes Medical Institute

Professor

The Rockefeller University, USA

E-mail: jean-laurent.casanova@rockefeller.edu

Highest Education

Ph.D., Paris Pierre & Marie Curie University, France

M.D., Paris Descartes University, France

Honor and Awards

2018 Distinguished Service Award, Clinical Immunology Society

2017 AAI-Steinman Award for Human Immunology Research

2016 Inserm *Grand Prix*

2015 National Academy of Medicine

2014 Robert Koch Prize

2012 Milstein Award

2012 Ilse and Helmut Wachter Foundation Award

2011 InBev Baillet-Latour Health Prize

2008 Richard Lounsbery Award

2004 Professor Lucien Dautrebande Pathophysiology Foundation Prize

Selected Publications

- Zhang, S.Y. et al. Inborn errors of RNA lariat metabolism in humans with brainstem viral infection. *Cell,* 172, 952-965 (2018).
- Israel, L. et al. Human adaptive immunity rescues an inborn error of innate immunity. *Cell,* 168, 789–800 (2017).
- Okada, S. et al. Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic *RORC* mutations. *Science,* 349, 606–613 (2015).
- Zhang, X. et al. Human intracellular ISG15 prevents interferon-α/β over-amplification and auto-inflammation. *Nature,* 517, 89–93 (2015).
- Ciancanelli, M.J. et al. Life-threatening influenza and impaired interferon amplification in human IRF7 deficiency. *Science,* 348, 448–453 (2015).

Toward a genetic theory of childhood infectious diseases

Abstract

The hypothesis that inborn errors of immunity underlie infectious diseases is gaining experimental support. However, the apparent modes of inheritance of predisposition or resistance differ considerably between diseases and between studies. A coherent genetic architecture of infectious diseases is lacking. We suggest here that life-threatening infectious diseases in childhood, occurring in the course of primary infection, result mostly from individually rare but collectively diverse single-gene variations of variable clinical penetrance, whereas the genetic component of predisposition to secondary or reactivation infections in adults is more complex. This model is consistent with (i) the high incidence of most infectious diseases in early childhood, followed by a steady decline, (ii) theoretical modeling of the impact of monogenic or polygenic predisposition on the incidence distribution of infectious diseases before reproductive age, (iii) available molecular evidence from both monogenic and complex genetics of infectious diseases in children and adults, (iv) current knowledge of immunity to primary and secondary or latent infections, (v) the state of the art in the clinical genetics of non-infectious pediatric and adult diseases, and (vi) evolutionary data for the genes underlying single-gene and complex disease risk. With the recent advent of new-generation deep resequencing, this model of single-gene variations underlying severe pediatric infectious diseases is experimentally testable.

Curriculum Vitae

Shie-Liang Hsieh, M.D., Ph.D.

Distinguished Research Fellow

Genomics Research Center, Academia Sinica, Taiwan

E-mail: slhsieh@gate.sinica.edu.tw

Highest Education

Ph.D., Department of Biochemistry, University of Oxford, UK

M.D., National Yang-Ming University School of Medicine, Taipei, Taiwan

Honors and Awards

2013 8th Session TienTe Lee Award

2012 National Chair Professor Award

2010 Outstanding Researcher Award from the National Science Council

2009 Long-Term Award from Acer Foundation

2009 Academic Achievement Award, Ministry of Education

2009 Academic Achievement Award, Ministry of Education

2009 Outstanding Immunology Scholar Award, The Chinese Society of Immunology

Selected Publications

- Tsai, HW. et al. Decoy receptor 3 promotes cell adhesion and enhances endometriosis development. *The Journal of Pathology* 244(2), 189-202 (2018).
- Chen, ST. et al. CLEC5A is a Critical Receptor in Innate Immunity against Listeria Infection. *Nature Communications* 8, 299 (2017).
- Wu, MF. et al. CLEC5A is critical for dengue virus-induced inflammasome activation in human macrophages. *Blood* 121(1), 95-106 (2013).
- Chen, ST. et al. CLEC5A regulates Japanese encephalitis virus-induced neuroinflammation and lethality. *PLoS Pathogen 8*(4), e1002655 (2012).
- Chen, ST. et al. et al. CLEC5A is critical for dengue-virus-induced lethal disease. *Nature 453*(7195), 672-676 (2012).

The critical role of myeloid lectins in the pathogenesis of viral infections

Abstract

Platelet-leukocyte interaction amplifies inflammatory reactions, but underlying mechanism is still unclear. CLEC5A (C-type lectin domain family 5, member A) is a spleen tyrosine kinase-coupled C-type lectin receptor (Syk-CLR) abundantly expressed in leukocytes, and acts as a pattern recognition receptor to members of flaviviruses (including dengue virus, Japanese encephalitis virus, Zika virus) and type A influenza viruses (IAVs, including H1N1, H5N1, and H7N9). Recently, we further found that CLEC5A associated with TLR2, and CLEC5A/TLR2 heterocomplex was co-activated by bacteria. The present study is to further investigate the role of CLEC5A/TLR2 in the pathogenesis of dengue virus- and H5N1-induced systemic inflammation and lethality, and test the possibility to attenuate inflammation and reduce lethality via blockade of CLEC5A/TLR2. To address this question, wild type and knockout mice (*clec5a*$^{-/-}$, *tlr2*$^{-/-}$, *clec5a* $^{-/-}$/*tlr2*$^{-/-}$) were incubated with DV and H5N1 IAV, respectively, in the presence or absence of platelets. The harvested EVs were used to induce neutrophil extracellular traps (NET) formation and proinflammatory cytokine release. We further compared the susceptibility of *clec5a*$^{-/-}$, *tlr2*$^{-/-}$, *clec5a* $^{-/-}$/*tlr2*$^{-/-}$ mice to DV- and IAV-induced inflammation and lethality in mice model. We found that Viruses-induced EVs (exosomes and microvesicles) were capable of enhancing NET formation and proinflammatory cytokine release via CLEC5A and TLR2. In addition, antagonistic anti-CLEC5A and anti-TLR2 mAbs attenuated systemic inflammation and reduced lethality. Thus, bi-specific antagonistic mAb against CLEC5A and TLR2 is a promising therapeutic agent to protect host from virus-induced severe inflammation and lethality.

Keywords: C-type lectin (CLEC), flaviviruses, NETs, platelets, extracellular vesicles (EVs)

Curriculum Vitae

Marco Colonna, M.D.

Professor

Washington University School of Medicine, St. Louis, USA

E-mail: mcolonna@wustl.edu

Highest Education

M.D., University of Parma, Italy

Honor and Awards

2014 Ceppellini Lecture, European Federation for Immunogenetics, Stockholm, Sweden

2011 European Federation of Immunological Societies Lecture Award, Riccione, Italy

2003 Member of the American Society of Clinical Investigators (ASCI)

Selected Publications

- Collins, PL. et al. Gene Regulatory Programs Conferring Phenotypic Identities to Human NK Cells. *Cell* 176(1-2), 348-360. e12 (2019).
- Barrow, AD. et al. Natural Killer Cells Control Tumor Growth by Sensing a Growth Factor. *Cell* 72, 534-548 (2018).
- Cervantes-Barragan, L. et al. *Lactobacillus reuteri* induces gut intraepithelial $CD4^+$ $CD8\alpha\alpha^+$ T cells. *Science* 357, 806-810 (2017).
- Ulland, TK. et al. TREM2 Maintains Microglial Metabolic Fitness in Alzheimer's Disease. *Cell* 170, 649-663 (2017).
- Koues, OI. et al. Distinct Gene Regulatory Pathways for Human Innate versus Adaptive Lymphoid Cells. *Cell* 165, 1134-1146 (2016).

Microglial autophagy and metabolic fitness in Alzheimer's disease

Abstract

Elevated risk of developing Alzheimer's disease (AD) is associated with hypomorphic variants of a surface receptor called triggering receptor expressed on myeloid cells 2 (TREM2). My laboratory originally cloned TREM2 and demonstrated that it is required for microglial responses to amyloid-β (Aβ) plaques, including proliferation, survival, clustering and phagocytosis (1,2). How TREM2 promotes such diverse responses was unknown. Recently, we found that microglia in AD patients carrying TREM2 risk variants and TREM2-deficient mice with AD-like pathology have abundant autophagic vesicles, as do TREM2-deficient macrophages under growth factor limitation or endoplasmic reticulum (ER) stress (3). Combined metabolomics and RNA-seq linked this anomalous autophagy to defective mTOR signaling, which affects ATP levels and biosynthetic pathways. Thus, TREM2 is required to sustain the increased metabolic demands of microglia during responses to Aβ plaques, while defective mTOR signaling in TREM2-deficient microglia is associated with a compensatory increase of autophagy *in vitro* and *in vivo* in AD.

Our studies show that, while increased autophagy may be beneficial in reducing inflammation and Aβ load in the short-term, a defect in mTOR signaling is detrimental and severely impairs microglia fitness and capacity to respond to Aβ accumulation in the long-term (3). Moreover, autophagy and metabolic derailment can be offset *in vitro* through creatine analogs that can supply ATP. Dietary creatine analogs can temper autophagy, restore microglial clustering around plaques, and decrease plaque-adjacent neuronal dystrophy in TREM2-deficient mice with Aβ pathology. Thus, TREM2 enables microglial responses during AD by sustaining cellular energetic, biosynthetic metabolism and preventing prolonged autophagy.

References

1. Wang et al, TREM2 lipid sensing sustains the microglial response in an Alzheimer's disease model. *Cell* 2015.
2. Wang et al, TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. *JEM* 2016.
3. Ulland, Song et al, TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell* 2017.

Curriculum Vitae

Ya-Jen Chang, Ph.D.

Assistant Research Fellow

Institute of Biomedical Sciences, Academia Sinica, Taiwan

E-mail: yajchang@ibms.sinica.edu.tw

Highest Education

Ph.D., Pharmacology, National Taiwan University, Taiwan

Honors and Awards

2018 Outstanding Research Award (Allergy) from the Chinese Society of Immunology

2016 MOST outstanding Young Investigator Grant

2015 Young Scientists 2015, selected by the InterAcademy Partnership (IAP)/Global Young Academy (GYA)

2015 The 3rd Annual Excellence in Creativity Award for Young Scholar from The Foundation for the Advancement of Outstanding Scholarship

2015 The 23rd Annual Top Ten Distinguished Young Woman

2015 Academia Sinica Career Development Award

Selected Publications

- Thio, CL. et al. TLR9-dependent interferon production prevents group 2 innate lymphoid cell-driven airway hyperreactivity. *J Allergy Clin Immunol*. In press (2019).
- Thio, CL. et al. Regulation of type 2 innate lymphoid cell–dependent airway hyperreactivity by butyrate. *J Allergy Clin Immunol.* 142(6), 1867-1883.e12 (2018).
- Chen, WY. et al. IL-33/ST2 axis mediates hyperplasia of intrarenal urothelium in obstructive renal injury. *Experimental & Molecular Medicine* 50(4), 1-11 (2018).
- Albacker, LA*., Chaudhary, V*., Chang, YJ*., Kim, HY*. et al. Invariant natural killer T cells recognize a fungal glycosphingolipid that can induce airway hyperreactivity. *Nature Medicine* 19(10), 1297-1304 (2013). *co-first author
- Chang, YJ. et al. Innate lymphoid cells mediate influenza-induced asthma independent of adaptive immunity. *Nature Immunology* 12(7):631-638 (2011)

Focus on the inbetweener: Regulation of group 2 innate lymphoid cells in asthma.

Abstract

Asthma is a disease of the airway characterized by airway hyperreactivity (AHR) and inflammation. Despite being a heterogeneous disease, allergen-induced allergic asthma remains the most prevalent form, affecting most children and approximately 50% of adults. Recent studies have identified group 2 innate lymphoid cells (ILC2s) as a critical immune component in driving allergic asthma development. ILC2s are activated by epithelial-derived cytokines such as interleukin (IL)-33, IL-25, and thymic stromal lymphopoietin (TSLP), leading to the rapid production of copious amounts of type 2 cytokines IL-13, IL-5 and IL-9. ILC2-derived IL-13 and IL-5 have been shown to induce AHR and airway eosinophilia under various environmental stimuli, including fungal allergen *Alternaria alternata* and house dust mites (HDM). Moreover, ILC2s have been implicated in severe, steroid-resistant asthma triggered by fungal sensitization. Hence, understanding the biology of ILC2s and identifying molecules that can modulate ILC2 function is pertinent for therapeutic advancements in asthma. In recent decades, studies have shown that interactions between microbes and their host can modulate host immunity by either triggering or suppressing host immune response. Microbial metabolites such as short chain fatty acids (SCFAs) possess beneficial immunomodulatory effects during chronic asthma mediated by T cells. However, their roles in regulating ILC2s remain unclear. In this talk, I will present our recent work on investigating the role of SCFAs in the regulation of ILC2 function. We showed that butyrate, but not acetate or propionate, inhibited cytokine production by murine ILC2s. Systemic and local administration of butyrate significantly ameliorated ILC2-driven AHR and airway inflammation in mice. Mechanistically, butyrate inhibited ILC2 proliferation and GATA3 expression through histone deacetylase inhibition independently of G-coupled protein receptor (GPR41) and GPR43. Importantly, butyrate also reduced cytokine production in human ILC2s. Collectively, these findings revealed important regulatory mechanisms to counteract ILC2-driven airway inflammation, which may pave way for the development of new therapeutics to prevent or treat ILC2-dependent asthma.

Curriculum Vitae

Mitch Kronenberg, Ph.D.

President and Chief Scientific Officer
La Jolla Institute for Allergy and Immunology

E-mail: mitch@lji.org

Highest Education

Ph.D., California Institute of Technology, USA

Honor and Awards

2016 American Association of Immunologists Distinguished Service Award

2016 Most Admired CEO (large nonprofit category) awarded by the San Diego Business Journal

2015 Fellow of American Association for the Advancement of Science (AAAS)

2007 Institute for Scientific Information (ISI) Highly Cited Scientist

2006 NIH NIAID Merit (R37) Award

2002 Burroughs Wellcome Fund Visiting Professor in Basic Biomedical Sciences (Harvard University)

2000 Roy and Robert Kroc Distinguished Professor in Medicine and Immunology, UC Davis

Selected Publications

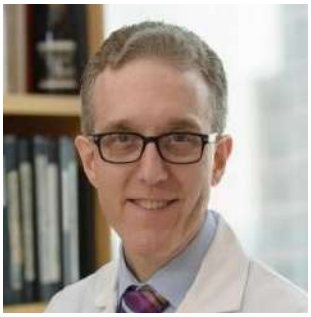
- Chandra, S. et al. Mrp1 is involved in lipid presentation and iNKT cell activation by Streptococcus pneumoniae. *Nature Communications* 9(1), 4279 (2018).
- Hartmann, N1. Kronenberg, M. Cancer immunity thwarted by the microbiome. *Science* 360(6391), 858-859 (2018).
- Engel, I. et al. Innate-like functions of natural killer T cell subsets result from highly divergent gene programs. *Nature Immunology* 17, 728-739 (2016).
- Chandra, S. et al. A new mouse strain for the analysis of invariant NKT cell function. *Nature Immunology* 16, 799-800 (2015).
- Shui, J.-W. et al. HVEM signaling at mucosal barriers provides host defense against pathogenic bacteria. *Nature* 488, 222-225 (2012).

Development and function of innate-like αβ T cells

Abstract

Mammals have two populations of highly conserved TCR $\alpha\beta^+$ T lymphocytes, NKT cells and MAIT cells, which are strikingly different from most T lymphocytes. These cells recognize antigens rather than peptides, lipids in the case of NKT cells and riboflavin metabolites in the case of MAIT cells, and they make rapid cytokine responses similar to innate immune cells. Functional subsets of these cells NKT cells and MAIT cells that are analogous to T helper subsets develop in the thymus, and we have analyzed the chromatin landscape and transcriptome of these subsets to gain insights into their development, function, tissue localization and the dynamic changes that occur after antigen exposure. One factor influencing NKT cell subset differentiation is TCR avidity. We will present data from recent studies providing insights into how subsets of NKT cells provide protection during bacterial infections and how they contribute to lessen damage in arthritis pathogenesis.

Curriculum Vitae



Jedd Wolchok, M.D., Ph.D.

Director, Parker Institute for Cancer Immunotherapy at Memorial Sloan Kettering Cancer Center;
Associate Director
Ludwig Center for Cancer Immunotherapy

E-mail: wolchokj@mskcc.org

Highest Education

Ph.D., New York University, New York, USA
M.D., New York University, New York, USA

Honor and Awards

2017 RCCS Monsey Medical Devotion Award
2015 Melvin L. and Dr. Sylvia F. Griem Lectureship & Award Recipient
2014 The Alexander Bodini Foundation Prize for Scientific Excellence in Medicine
2014 AACR Richard and Hinda Rosenthal Memorial Award
2014 Giant of Cancer Care in Melanoma Award

Selected Publications

- Hodi, FS. Et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *The Lancet Oncology* 19(11), 1480-1492 (2018).
- Zappasodi, R. et al. Non-conventional Inhibitory $CD4^{+}Foxp3^{-}PD\text{-}1^{hi}$ T Cells as a Biomarker of Immune Checkpoint Blockade Activity. *Cancer Cell* 34(4):691 (2018).
- Zappasodi R, Merghoub T, Wolchok JD. Emerging Concepts for Immune Checkpoint Blockade-Based Combination Therapies. *Cancer Cell* 33(4):581-598 (2018).
- Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science* 359(6382), 1350-1355 (2018).
- Hellmann, MD. et al. Genomic Features of Response to Combination Immunotherapy in Patients with Advanced Non-Small-Cell Lung Cancer. *Cancer cell* 33(5), 843-852.e4 (2018).

Immune-Modulating Approaches to Cancer Therapy: Focusing on Combinations

Abstract

Given the activity noted with both CTLA-4 or PD-1 blockade, clinical trials are now investigating combination checkpoint blockade. The most mature data with a combination of ipilimumab + nivolumab in melanoma showed a response rate of 60% in the context of increased, yet manageable toxicity. Such responses are generally durable, even when treatment was stopped early for toxicity. Unlike in studies of PD-1 blockade monotherapy, there was no significant difference in clinical activity based on tumor expression of PD-L1. This approach has gained regulatory approval for metastatic melanoma and is in late stage clinical trials for other malignancies. Attention is being paid to the reasons underlying the efficacy of checkpoint blockade in certain malignancies. One hypothesis has been that cancers having a high mutational load may be more amenable to immune modulation by virtue of the larger number of potential neo-epitopes present, fostering baseline immune recognition that can then be potentiated by checkpoint blockade. We have found that melanoma patients having long term clinical activity with ipilimumab have a significantly greater median number of non-synonymous passenger mutations, compared with patients who do not respond or those who have only short-term regression. Strategies to enhance baseline immune reactivity are therefore necessary to investigate as means to improve the impact of checkpoint blockade on a broad spectrum of cancers. The presence of suppressive myeloid cells in the tumor microenvironment also is emerging as a mechanism of resistance to the anti-tumor activity for checkpoint blockade. Strategies to overcome this include inhibition of CSF-1R signaling, IDO activity and selective suppression of PI3K-γ.

Curriculum Vitae

Muh-Hwa Yang, M.D., Ph.D.

Professor/Vice President

National Yang-Ming University, Taiwan

E-mail: mhyang2@vghtpe.gov.tw

Highest Education

Ph.D., National Yang-Ming University, Taiwan

M.D., National Yang-Ming University, Taiwan

Honors and Awards

2018 MOST outstanding research award (2013-2015, 2016-2018)

2017 Distinguished Thesis, Taipei Veterans General Hospital (2009, 2011, 2013-2015)

2015 Dr. Chien-Tien Hsu Memorial Award for Outstanding Cancer Research, Taiwan Oncology Society

2015 Scientific paper award, Y.Z. Hsu Scientific and Technology Memorial Foundation

2015 Outstanding Immunology Scholar Award, The Chinese Society of Immunology (Taiwan)

2011 Award for Junior Research Investigators, Academia Sinica

Selected Publications

- Hwang, WL. et al. Snail-induced claudin-11 prompts collective migration for tumour progression. *Nature Cell Biology* 21, 251-262 (2019).
- Lee CC. et al. Macrophage-secreted interleukin-35 regulates cancer cell plasticity to facilitate metastatic colonization. *Nature Communications* 9(1), 3763 (2018).
- Pan YR. et al. STAT3-coordinated migration facilitates the dissemination of diffuse large B-cell lymphomas. *Nature Communications* 9(1), 3696 (2018).
- Hsu, DS. et al. Acetylation of Snail modulates the cytokinome of cancer cells to enhance the recruitment of macrophages. *Cancer Cell* 26, 534-548 (2014).
- Hwang, WL. et al. MicroRNA-146a directs the symmetrical division of Snail-dominant colorectal cancer stem cells. *Nature Cell Biology* 16, 268-280 (2014).

Dynamic interplay between tumor cells and macrophages during cancer progression

Abstract

Remodeling of tumor microenvironments is a critical process for facilitating tumor progression and metastatic colonization, and infiltration of the host immune cells is the key event during tumor microenvironments (TME) remodeling. Tumor-associated macrophages (TAMs) are one of the most abundant types of host immune cells in the TME that expedite tumor growth, angiogenesis, immune evasion, and remodeling of the extracellular matrix to facilitate cancer metastasis. We previously showed that acetylation of the epithelial-mesenchymal transition (EMT) transcriptional factor induces the expression of several key cytokine genes including *TNFA*, *CCL2*, and *CCL5*, which act cooperatively to promote the recruitment of TAMs. We recently further found that Snail-expressing cancer cells promotes M2 polarization of TAMs through delivering of miR-21-abundant exosomes. Furthermore, we demonstrate that TAMs secrete interleukin-35 (IL-35) to facilitate metastatic colonization through activation of JAK2-STAT6-GATA3 signaling in cancer cells to reverse EMT at metastatic sites. Neutralization of IL-35 or knockout of IL-35 in macrophages reduces metastatic colonization. In summary, our findings suggest that the dynamic interplay between TAMs and cancer cells at either primary or metastatic tumors is crucial for cancer progression.

Curriculum Vitae

Michele De Palma, Ph.D.

Associate professor

Ecole Polytechnique Federale de Lausanne (EPFL), Switzerland

E-mail: michele.depalma@epfl.ch

Highest Education

Ph.D., University of Turin Medical School, Italy

Honor and Awards

2017 Robert Wenner Prize for Cancer Research

2016 European Research Council (ERC) Consolidator grant

2013 AAAS Wachtel Cancer Research Award (Honorable Mention)

2013 Leenaards Prize

2012 Anna Fuller Prize

2009 European Research Council (ERC) Starting grant

2007 Young Investigator Award, European Society of Gene Therapy (ESGT)

2004-06 Post-doctoral fellowship, Italian Association for Cancer Research (AIRC)

2001 & 2003 Excellence in Research Award, American Society of Gene Therapy (ASGT)

Selected Publications

- Keklikoglou, I. et al. Chemotherapy elicits pro-metastatic extracellular vesicles in breast cancer models. *Nature Cell Biology* 21, 190-202 (2019).
- Neubert, NJ. et al. T cell-induced CSF1 promotes melanoma resistance to PD1 blockade. *Science Translational Medicine* 10(436), pii: eaan3311 (2018).
- Keklikoglou, I. et al. Periostin limits tumor response to VEGFA inhibition. *Cell Reports* 22(10), 2530-2540 (2018).
- Squadrito, M.L. et al. EVIR: Chimeric receptors that enhance dendritic cell cross-dressing with tumor antigens. *Nature Methods* 15, 183-186 (2018).
- Schmittnaegel, M. et al. Dual angiopoietin-2 and VEGFA inhibition elicits antitumor immunity that is enhanced by PD-1 checkpoint blockade. *Science Translational Medicine* 12, 9(385), pii: eaak9670 (2017).

Tumor-derived extracellular vesicles

Abstract

Increasing data indicate that primary tumors release extracellular vesicles (EVs) that modulate cancer biology and progression both locally in the tumor microenvironment and remotely in pre-metastatic niches. Notably, both cancer cells and tumor-associated cells of host origin, such as macrophages, release EVs. We recently showed that two classes of cytotoxic drugs broadly employed in pre-operative (neoadjuvant) breast cancer therapy, taxanes and anthracyclines, elicit breast cancer cell-derived EVs with enhanced pro-metastatic capacity. Chemotherapy-elicited EVs enhance metastasis through annexin-A6, an EV-associated protein that promotes *Ccl2* transcription and $CCR2^{+}$ monocyte expansion in the lung pre-metastatic niche to facilitate monocyte-dependent breast cancer metastasis. Our unpublished data also indicate that, besides cancer cells, tumor-associated macrophages (TAMs) are an important source of tumor-derived EVs. We therefore developed methodology for the direct isolation, quantification, and proteomic and lipidomic analysis of TAM-derived EVs. While portraying some similarities with EVs of *in vitro*-polarized macrophages, TAM-derived EVs present distinctive molecular profiles that may impinge on the regulation of lipid metabolism and inflammatory signaling in the tumor microenvironment. In the symposium, I will present data on various aspects of EV biology that are relevant to cancer immunology, progression, and therapy.

Curriculum Vitae

Shih-Chin (James) Cheng, Ph.D.

Assistant Professor

National Tsing-Hua University, Taiwan

E-mail: jamescheng@life.nthu.edu.tw

Highest Education

Ph.D., University Medical Center Nijmegen, the Netherlands

Honors and Awards

2018 NTHU Young Faculty Research Award

2018 NHRI Career Development Grant

2017 MOST outstanding young investigator grant

2016 MOST special outstanding talent award

2015 Veni laureate of Dutch Research Council

Selected Publications

- Cheng, SC. et al. Broad defects in the energy metabolism of leukocytes underlie immunoparalysis in sepsis. *Nature Immunology* 17(4), 406-413 (2016).
- Cheng, SC. et al. mTOR- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity. *Science* 345(6204), 1250684 (2014).
- Kumar V*, Cheng SC*. et al. Immunochip SNP array identifies novel genetic variants conferring susceptibility to candidaemia. *Nature Communications* 5, 4675 (2014). *co-first author
- Oosting M, Cheng SC. et al. Human TLR10 is an anti-inflammatory pattern-recognition receptor. *Proc. Natl. Acad. Sci. USA* 111(42), E4478-4484. (2014).
- Cheng, SC. et al. The dectin-1/inflammasome/Th17 pathway discriminates between invasion and colonization with *Candida albicans*. *Journal of Leukocyte Biology* 90(2), 357-366 (2011).

Metabolic perspective of trained immunity

Abstract

Immune memory is previously considered as an exclusively feature of adaptive immunity due to the presence of antigen-specific memory. However, recent advances reveal the adaptive feature of innate immune memory in both natural killer cells and monocytes/macrophages. Trained immunity is reported as the property allowing innate immune cells to respond more rapidly when they reencounter pathogens. As opposed to the adaptive immune memory which requires specific antigen to recall the memory response, trained immunity incorporates the epigenetic modification enabling innate immune cell to respond to secondary stimulation in an antigen-nonspecific manner. In addition to the change of the epigenetic change of the trained immunity, we further identified the glucose metabolism is rewired from oxidative phosphorylation toward glycolysis-prone state in trained immunity. Furthermore, we also identified fumarate as the key metabolite which bridges the metabolic rewiring and epigenetic change in the trained immunity.

Curriculum Vitae

Hilde Cheroutre, Ph.D.

Professor/Head, Division of Developmental Immunology

La Joll Institute for Allergy and Immunology, USA

E-mail: hilde@lji.org

Highest Education

Ph.D., Max−State University of Ghent, Belgium

Honor and Awards

NATO Postdoctoral Fellowship (Awarded Twice)

Markey Foundation Postdoctoral Fellowship

University of California, Los Angeles Tumor Cell Biology Training Grant

Cancer Research Coordinating Committee (C.R.C.C.) Fellowship

UCSD Warren Foundation Celiac Disease Grant

NIH Director's Pioneer Award Recipient 2009

Selected Publications

- Larange, A., Cheroutre, H. Retinoic Acid and Retinoic Acid Receptors as Pleiotropic Modulators of the Immune System. *Annu Rev Immunol* 34, 369-394 (2016).
- Mayans, S. et al. αβT Cell Receptors Expressed by CD4(-)CD8αβ(-) Intraepithelial T Cells Drive Their Fate into a Unique Lineage with Unusual MHC Reactivities. *Immunity* 41(2), 207-218 (2014).
- Mucida, D. et al. Transcriptional reprogramming of mature CD4(+) helper T cells generates distinct MHC class II-restricted cytotoxic T lymphocytes. *Nat Immunol* PMID: 23334788 (2013).
- Huang, Y. et al. Mucosal memory $CD8^+$ T cells are selected in the periphery by an MHC class I molecule. *Nat Immunol* 12(11), 1086-1095 (2011).
- Mucida, D. et al. Retinoic acid can directly promote TGF-beta-mediated Foxp3(+) Treg cell conversion of naïve T cells. *Immunity* 30(4), 471-472 (2009).

A long noncoding RNA in the *Cd8* locus controls functional differentiation of CD4 T cells

Abstract

The expression of key transcription factors drives CD4 T cells to develop into functional T helper (Th) subsets, each characterized by secretion of particular cytokines. This process is critical for normal immune function. CD4 T cells can also reprogram to cytotoxic T lymphocytes (CTL), but the key transcriptional mechanism that controls this process has not been defined. Cytokine TGFβ, an important regulator of CD4 Th subset differentiation induces the master transcription factor, FOXP3 in induced regulatory T cells (iTreg) or RORγt in IL-17-secreting T cells (Th17 cells). TGFβ is also important for the CD4 CTL differentiation, characterized by T-BET and RUNX3 expression, whereas *Foxp3* and *Rorc* genes are repressed in these cells. Here, we identify a long noncoding RNA transcribed from the *Cd8* locus (*Cd8*LncRNA), as critical for the coordinated expression and function of T-BET and RUNX3, combined with *Foxp3* and *Rorc* suppression, in CD4 CTL. These findings define *Cd8*LncRNA as a master controller of the helper versus cytotoxic gene expression profile in differentiating CD4 effector T cells. The action of this LncRNA adds another mode of regulation of CD4 T cell function and expands the opportunity to define new drug targets for the treatment of cancers and immune diseases.

Curriculum Vitae

Arthur Weiss, M.D., Ph.D.

Investigator, Howard Hughes Medical Institute

Professor

University of California San Francisco, USA

E-mail: Arthur.Weiss@ucsf.edu

Highest Education

Ph.D., University of Chicago, USA

Honor and Awards

2017 EMBO associate member

2016 Ephraim P. Engleman Memorial Lecture, American College of Rheumatology

2016 NIH Merit Award

2012 UCSF Lifetime Achievement in Mentoring Award

2012 Lifetime Achievement Award, AAI

2004 Member of National Academy of Sciences

2004 Member of Institute of Medicine

2002 Thermo Fisher Meritorious Career Award

Selected Publications

- Lo, W.L. et al. Lck promotes Zap70-dependent LAT phosphorylation by bridging Zap70 to LAT. *Nature Immunology* 19, 733-741 (2018).
- Shang, W. et al. Genome-wide CRISPR screen identifies FAM49B as a key regulator of actin dynamics and T cell activation. *Proc. Natl. Acad. Sci. USA.* 115(17), E4051-E4060 (2018).
- Au-Yeung, B.B. et al. ZAP-70 in Signaling, Biology, and Disease. *Annual Review of Immunology* 36, 127-156 (2017).
- Courtney, A.H. et al. A phosphosite within the SH2 domain of LcK regulates its activation by CD45. *Molecular Cell* 67(3), 498-511 (2017).
- Skrzypczynska, K.M. et al. Positive regulation of Lyn kinase by CD148 is required for B cell receptor signaling in B1 but not B2 B cells. *Immunity* 45(6), 1232-1244 (2016).

New Insights into Mechanisms involved in TCR Ligand Discrimination

Abstract

The T cell antigen receptor (TCR) must recognize and discriminate self peptide-MHC (pMHC) from agonist pMHC. It must do so with high accuracy and sensitivity to initiate appropriate immune responses and to avoid autoimmunity. Recent studies in our lab have identified two critical mechanisms that play roles in TCR ligand discrimination.

The first mechanism involves a phosphorylation site in the LAT adaptor that is involved in the recruitment of phospholipase C γ1 (PLCγ1) where it is activated by the Itk kinase. Activation of PLCγ1 leads to the TCR-induced calcium increase and activation of PKC and the Ras/MAPK pathways which are critical for T cell activation. Evolution has selected the PLCγ1 recruitment site to be a kinetically poor but an important phosphorylation site for Zap70 in mammals. The slow phosphorylation of this site in mammals appears to have been selected in order to impose a time delay required for appropriate ligand discrimination.

The second mechanism involves the regulation of Lck activity by the opposing actions of the cytoplasmic kinase Csk and the receptor-like tyrosine phosphatase CD45. An appropriate level of Lck activity is required for appropriate ligand recognition. High levels of CD45 are required both for the activation of Lck and to restrain cells from inappropriate activation by weak pMHC ligands.

Curriculum Vitae

Chien-Kuo Lee, Ph.D.

Professor/Director,

Graduate Institute of Immunology at National Taiwan University, Taiwan

E-mail: leeck@ntu.edu.tw

Highest Education

Ph.D., New York University School of Medicine, USA

Honor and Awards

2017 Tsungming Tu Memorial Lecture Award (杜聰明博士紀念演講獎)

2017 Travel award, ICIS annual meeting

2016 The outstanding research award (three-time grant awardee) from NHRI

2014 The 12th YZ Hsu Scientific Paper Award (有庠科技論文獎)

2012 Travel award, ISICR annual Meeting

2011 Travel award, ISICR annual Meeting

1999-2000 Fellowship for Arthritis Research Campaign, UK

Selected Publications

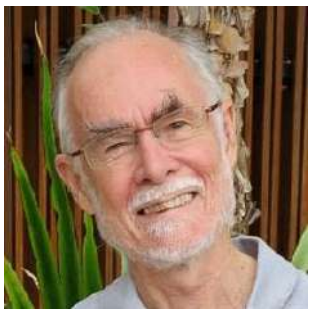
- Tsai, MH., Lee, CK. STAT3 Cooperates With Phospholipid Scramblase 2 to Suppress Type I Interferon Response. *Frontiers Immunology* 9, 1886 (2018).
- Chen, TT. et al. STAT1 regulates marginal zone B cell differentiation in response to inflammation and infection with blood-borne bacteria. *J. Exp. Med.* 213(13), 3025-3039 (2016).
- Chen, YL. et al. Efficient Generation of Plasmacytoid Dendritic Cell from Common Lymphoid Progenitors by Flt3 Ligand. *PLoS One* 10(8), e0135217 (2015).
- Chen, YL. et al. A type I IFN/Flt3 ligand axis augments plasmacytoid dendritic cell development from common lymphoid progenitors. *J. Exp. Med.* 210, 2515-2522 (2013).
- Wang, WB. et al. STAT3 negatively regulates type I IFN-mediated antiviral response. *J. Immunol.*187(5), 2578-2585 (2011).

Regulation of dendritic cell development by type I IFN signaling pathway

Abstract

Dendritic cells (DCs), including plasmacytoid DCs (pDCs) and conventional DCs (cDCs) play essential roles in regulating the immune response. During infections and inflammation, pDCs are the most potent type I interferon (IFN-I)-producing cells. However, the developmental origin of pDCs and the signals dictating pDC generation remain incompletely understood. Previously we reported a synergistic role for IFN-I and Flt3 ligand (FL) in pDC development from common lymphoid progenitors (CLPs) at steady state. Here, we demonstrated that the administration of R848, a TLR7 agonist, dramatically altered the developmental program by enhancing cDC production at the expense of pDC *in vitro* and *in vivo*. The ratio of cDC1 to cDC2 also decreased upon TLR stimulation. More importantly, ex vivo DC development from CLPs of mice previously treated with R848 also favored cDC generation even though R848 is omitted in the culture condition. Coculture of WT and *Myd88*$^{-/-}$ CLPs showed that the effect was dependent on primary and secondary signaling events downstream of TLR7. The mechanism of TLR7-dependent enhancement of cDC generation is mainly through STAT1 and partially through IFN-I signaling pathway. In sum, these findings reveal that DC developmental program from their CLPs is very dynamic during steady state and inflammation. Moreover, we define a novel function of STAT1 and IFN-I signaling in TLR-mediated reprogramming of DC development.

Curriculum Vitae



Jonathan Sprent, Ph.D.

Professor

Garvan Institute of Medical Research, Australia

E-mail: j.sprent@garvan.org.au

Highest Education

Ph.D., (Immunology) Walter and Eliza Hall Institute, Melbourne, Australia

Honor and Awards

2017 Member of National Academy of Sciences

2010 Achievement Award NHMRC

2006 Honorary Member of British Society of Immunology

2006 Fellow of the Australian Academy

1998 Fellow of the Royal Society

1995 J. Allyn Taylor International Prize in Medicine

Selected Publications

- Yi, J. et al. Unregulated antigen-presenting cell activation by T cells breaks self tolerance. *Proc. Natl. Acad. Sci. USA* 116(3), 1007-1016 (2018).
- Cho JH, Sprent J. TCR tuning of T cell subsets. *Immunological Reviews* 283(1), 129-137 (2018).
- Sprent J. T cell-B cell collaboration. *Nature Reviews Immunology* 17(9), 532 (2017).
- Vazquez-Lombardi, R. et al. Potent antitumour activity of interleukin-2-Fc fusion proteins requires Fc-mediated depletion of regulatory T-cells. *Nature Communications* 8, 15373 (2017).
- Cho, JH. et al. CD45-mediated control of TCR tuning in naïve and memory CD8+ T cells. *Nature Communications* 7, 13373. (2016).

Self tolerance: new thoughts on an old issue

Abstract

Thymic selection is known to generate a repertoire of mature T cells with low but significant reactivity to self MHC/peptide ligands, recognition of these ligands being important for keeping naïve T cells alive; overt T cell recognition of self ligands is avoided by a combination of negative selection in the thymus and suppression by $Foxp3^+$ T regulatory cells (Tregs). Studies with Foxp3.DTR mice have shown that acute removal of Tregs leads to prominent lymphadenopathy and autoimmune disease, though whether this disease is directed to self antigens or foreign antigens is unclear. Based on studies on Foxp3.DTR and Rag-deficient mice raised in an antigen-free environment, I will discuss how removal of Tregs allows a subset of high-affinity T cells to become overtly reactive to self ligands, both *in vivo* and *in vitro*.

Curriculum Vitae

Burkhard Becher, Ph.D.

Professor and Co-Chair of the Inst. of Experimental Immunology, University of Zurich, Switzerland

E-mail: becher@immunology.uzh.ch

Highest Education

Ph.D., Institute for Molecular Genetics, Faculty of Mathematics and Natural Sciences, University of Cologne, Germany & the Dept. of Neuroimmunology, McGill University, Montreal, Canada

Honor and Awards

2010 Prof. Max Cloëtta Award

2008 Biogen Dompè MS-Research Prize

2008 Robert Bing Prize

2004 Sobek Junior Research Award

2002 Harry Weaver Scholar of the National Multiple Sclerosis Society

1999 Fellowship Award National Multiple Sclerosis Society

Selected Publications

- Becher, B. Waisman A and Lu LF. Conditional Gene-Targeting in Mice: Problems and Solutions. *Immunity* 48(5), 835-836 (2018).
- Mrdjen, D. et al. High-Dimensional Single-Cell Mapping of Central Nervous System Immune Cells Reveals Distinct Myeloid Subsets in Health, Aging, and Disease. *Immunity* 48(2), 380-395 e6 (2018).
- Krieg, C. et al. High dimensional single cell analysis predicts response to anti-PD-1 immunotherapy. *Nature Medicine* 24(2), 144-153 (2018).
- Becher B, Spath S and Goverman J. Cytokine networks in neuroinflammation. *Nature Reviews Immunology* 17(1), 49-59 (2017).
- Becher B, Tugues S and Greter M. GM-CSF: From Growth Factor to Central Mediator of Tissue Inflammation. *Immunity* 45(5), 963-73 (2016).

Cytokine communication in inflammation: The T cell - phagocyte interface

Abstract

Whereas T cells are generally thought of as mediators of tissue damage in chronic tissue inflammation, the cellular infiltrate is always dominated by myeloid cells. The granulocyte-macrophage colony-stimulating factor (GM-CSF) was initially classified as a hematopoietic growth factor. However, unlike its close relatives macrophage CSF (M-CSF) and granulocyte CSF (G-CSF), the majority of myeloid cells do not require GM-CSF for steady-state myelopoiesis. Instead, in inflammation, GM-CSF serves as a communication conduit between tissue-invading lymphocytes and myeloid cells. Even though lymphocytes are in all likelihood the instigators of chronic inflammatory disease, GM-CSF-activated phagocytes are well equipped to cause tissue damage. The pivotal role of GM-CSF at the T cell:myeloid cell interface might shift our attention toward studying the function of the myeloid compartment in immunopathology and targeting specifically the crosstalk between T cells and myeloid cells through GM-CSF holds promise for the development of therapeutics to combat chronic tissue inflammation. I will discuss how GM-CSF licenses phagocytes to initiate tissue damage in chronic inflammatory diseases and present new tools for tracing and fate-mapping of GM-CSF expressing cells and their role in tissue inflammation in vivo.

Curriculum Vitae

Huang-Yu Yang, M.D., Ph.D.

Associate Professor

Department of Medicine at Chang Gung Memorial Hospital, Taiwan

E-mail: hyyang01@gmail.com

Highest Education

Ph.D., Johns Hopkins School of Medicine, USA

M.D., Taipei Medical University, Taiwan

Honor and Awards

2018 The Chinese Society of Immunology

2017 Annual Meeting of Taiwan Society of Nephrology

2017 AAI Early Career Faculty Travel Grant

2016 AAI Travel Award for ICI

2016 International Congress of Immunology

Selected Publications

- Yang, HY. et al. The MicroRNA miR-17 modulates regulatory T cell activity by targeting Foxp3 Co-regulators. *Immunity* 45(1), 83-93 (2016).
- Yang, HY. et al. Overlooked Risk for Chronic Kidney Disease after Leptospiral Infection: A Population-based Survey and Epidemiological Cohort Evidence. *PLoS Negl Trop Dis* 9(10), e0004105 (2015).
- Wu, CY., Yang, LH., Yang, HY. et al. Enhanced cancer radiotherapy through immunosuppressive stromal cell destruction in tumors. *Clin Cancer Res*. 20(3), 644-657 (2014).
- Chen, Z., Barbi, J., Bu, S., Yang, HY. et al. The ubiquitin ligase stub1 negatively modulates regulatory T cell suppressive activity by promoting degradation of the transcription factor foxp3. *Immunity* 39(2), 272-285 (2013).
- Yang, HY. et al. Control of T(H)17/T(reg) Balance by Hypoxia-Inducible Factor 1. Cell 146(5), 772-784 (2011).

Glutamine modulates the balance of Th17 and Treg by metabolic and epigenetic change

Abstract

Bioenergetic and biosynthetic demands of T cells increase drastically during T cell activation. Thus, T cell fate and function is closely related to nutrient uptake and utilization. Glutaminolysis is one such process crucial for effector T cell activation. However, information on how amino acid deficiency impacts immune balance is lacking. Here we report the semi-essential amino acid glutamine's critical role in controlling the balance between Th17 and Treg. Upon Th17 polarization, amino acids are taken up by the cell, and glutamine and glutamate account for the majority of the amino acids. Glutamine deprivation prevents Th17 polarization despite the upregulation of the master transcription factors, RoRγt and STAT3, which is compatible with the observed chromatin modification, including histone H3 lysine 4 trimethylation (H3K4me3), histone H3 lysine 27 acetylation (H3K27ac), and histone H3 lysine 27 trimethylation (H3K27me3). Succinate induced by glutamine drives HIF-1α stabilization and IL-17 production. Furthermore, cell-permeable diethylsuccinate partially rescues Th17 polarization under glutamine deprivation. In addition, glutamine-free condition favors the $Foxp3^{+}$ $IL17^{-}$ population through H3K4me3, H3K27ac modification and demethylation of FOXP3 gene. REDOX homeostasis pathway and fatty acid utilization are associated with the glutamine-free condition. Moreover, in the glutamine-free medium, antioxidants N-acetyl-cysteine (NAC) and glutathione (GSH) increase IL17 and decrease Foxp3 expression. Thus, these findings highlight the critical role of glutamine in T cell fate determination through a metabolic–epigenetic axis and suggest that metabolic modulation could ameliorate certain T cell-related autoimmune diseases.

Curriculum Vitae

Alexander Rudensky, Ph.D.

Investigator, Howard Hughes Medical Institute
Chair of Immunology Program, SKI
Director of Ludwig Center at MSK
Memorial Sloan Kettering Cancer Center

E-mail: rudenska@mskcc.org

Highest Education

Ph.D., Gabrichevsky Research Institute of Epidemiology and Microbiology, Moscow

Honor and Awards

2018 Vilcek Prize in Biomedical Science
2017 Crafoord Prize, the Royal Swedish Academy of Sciences
2015 Member of the National Academy of Medicine
2015 Member of the American Academy of Arts and Sciences
2015 Coley Award in Basic Immunology, Cancer Research Institute
2015 Thomson Reuters Citation Laureate
2012 Member of the National Academy of Sciences
2009 Merit Award, National Institutes of Health

Selected Publications

- Azizi, E. et al. Single-Cell Map of Diverse Immune Phenotypes in the Breast Tumor Microenvironment. *Cell* 174(5), 1293-1308 (2018).
- Levine, AG. et al. Stability and function of regulatory T cells expressing the transcription factor T-bet. *Nature* 546, 421-425 (2017).
- Chinen, T. et al. An essential role for the IL-2 receptor in T_{reg} cell function. *Nat Immunol* 17(11), 1322-1333 (2016).
- van der Veeken, J. et al. Memory of Inflammation in Regulatory T Cells. Memory of Inflammation in Regulatory T Cells. *Cell* 166(4), 977-990 (2016).
- Gasteiger, G. et al. Tissue residency of innate lymphoid cells in lymphoid and non-lymphoid organs. *Science* 350, 981-985 (2015).

Epigenetic and Transcriptional Mechanisms of Cellular Memory

Abstract

Stable changes in chromatin states and gene expression in cells of the immune system form the basis for memory of infections and other challenges. Here, we used naturally occurring *cis*-regulatory variation in wild-derived inbred mouse strains to explore the mechanisms underlying long-lasting vs. transient gene regulation in CD8 T cells responding to acute viral infection. Stably responsive DNA elements were characterized by dramatic and congruent chromatin remodeling events affecting multiple neighboring sites, and required distinct transcription factor binding motifs for their accessibility. Specifically, we found that cooperative recruitment of T-box and Runx family transcription factors to shared targets mediated stable chromatin remodeling upon T cell activation. Our observations provide new insights into the molecular mechanisms driving virus-specific CD8 T cell responses, and suggest a general mechanism for the formation of epigenetic memory applicable to other immune and non-immune cells.

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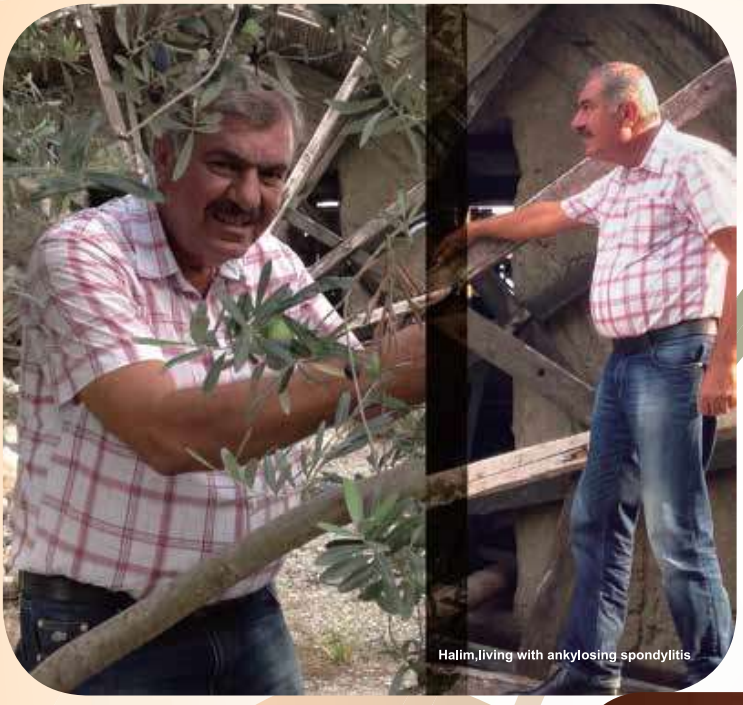

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【適應症】適用於對疾病緩解型抗風濕性藥物（即 DMARDs，包括 methotrexate）無適當療效之成人活動性類風濕性關節炎。也適用於先前未使用 methotrexate 治療之成人中度至重度活動性類風濕性關節炎，這些病人的 X 光檢查顯示，本品可以減緩疾病造成的關節結構性受損。亦適用於 methotrexate 治療無效或無法耐受的 2 歲以上兒童及青少年的活動性多關節幼年型慢性關節炎。尚未對不足 2 歲的兒童進行試驗。適用於對疾病緩解型抗風濕性藥物無療效之成人活動性與進行性乾癬性關節炎。治療活動性僵直性脊椎炎。適用於對其他全身性治療（包括 cyclosporine、methotrexate 或光化療法【PUVA】）無效、有禁忌或無法耐受之中度至重度乾癬成人病人。適用於對其他全身性治療或光化療法無法有效控制或無法耐受之 6 歲以上兒童及青少年的重度乾癬。【用法用量】恩博的治療應在有經驗的專科醫師監督下進行對類風濕性關節炎、乾癬性關節炎、僵直性脊椎炎、乾癬或幼年乾癬之診斷及治療。類風濕性關節炎，恩博的建議劑量為每次 25 毫克，每週二次。亦可以每週給予一次 50 毫克的方式治療，同樣具有可靠的療效與安全性。乾癬性關節炎與僵直性脊椎炎：恩博的建議劑量為 25 毫克，每週二次。也可以每週給予一次 50 毫克的方式治療。乾癬：恩博的建議劑量為 25 毫克，每週二次，但亦可每週給予一次 50 毫克的方式治療。亦可選擇先以每週兩次給予 50 毫克，持續給予達 12 週後，再調整為 25 毫克，每週二次，或每週給予一次 50 毫克的方式治療。應持續（最多 24 週）恩博的治療以達到症狀緩解。若病人使用 12 週後對藥物沒有反應則應停藥。如以恩博再度治療，應謹慎上述之用法用量治療。其劑量應為 25 毫克，每週兩次，但亦可每週給予一次 50 毫克的方式治療。特殊族群：孕婦：此劑型的恩博為單一次使用針劑，是用於體重 62.5 公斤或以上的病人。另有凍晶注射劑小瓶（調配後濃度為 25 毫克/毫升），適用於所需劑量小於 25 毫克的病人使用。活動性多關節幼年型慢性關節炎（2 歲以上）：投與 0.4 毫克/公斤的劑量（每次最大劑量為 25 毫克），每週二次，皮下注射，劑量間之投藥間隔為 3-4 天；或 0.8 毫克/公斤的劑量（每次最大劑量為 50 毫克），每週一次。病人在使用四個月後沒反應則應考慮停藥。針對 2 到 3 歲的兒童沒有進行正式的臨床試驗。然而從紀錄中病人有限的安全性資料說明在每週每公斤使用皮下注射 0.8 毫克的 2 到 3 歲兒童之安全性是相似於四歲以上的兒童和成年人。恩博並不適用於未滿 2 歲的活動性多關節幼年型慢性關節炎。幼年乾癬（6 歲以上）：投與 0.8 毫克/公斤的劑量（每次最大劑量為 50 毫克），每週一次，至多 24 週。如果病人使用 12 週後對藥物沒有反應，則應停藥。如以恩博再度治療，應謹慎上述之用法用量治療。其劑量應為 0.8 毫克/公斤的劑量（每次最大劑量為 50 毫克），每週一次。恩博並不適用於未滿 6 歲的幼年乾癬。老年人：無需調整劑量。用法用量與 18-64 歲成人相同。腎衰及肝損功能受損病人：無需調整劑量。

【警語與注意事項】在開始接受恩博治療前、治療期間及治療後，都應為病人進行感染症的篩選。如果病人發生嚴重的感染，應中止恩博治療。所有病人在接受恩博治療前都應先進行活躍型與非活躍型（潛伏性）結核病的篩檢。恩博禁止使用於活躍型結核病人；非活躍型（潛伏性結核病人）則應在開始恩博療程前，先接受經衛生主管機關認可的抗結核病藥物治療，以控制其非活躍型結核病。在開始以恩博治療前，應先接受 B 型肝炎篩檢。有 C 型肝炎病史的病人使用恩博時應小心。如果發生任何過敏反應，應立刻中止恩博的治療並給予適當處置。對於曾罹患惡性腫瘤病人考慮使用 TNF 拮抗劑或罹癌病人當考慮使用時應小心。對於有充血性心臟衰竭的病人，醫師應小心使用恩博。

PP-ENB-TWN-0148-201810

仿單版本：版本：SPC 20171204-2 本藥限由醫師使用

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台北總公司
新北市251淡水區中正東路二段177號
TEL:(02)2809-7979 FAX:(02)2809-7676
www.pfizer.com.tw

台中辦事處
台中市408公益路二段51號10樓A室
TEL:(04)2328-2818 FAX:(04)2320-5438

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【適應症與用途】類風濕性關節炎：XELJANZ XR 適用於治療患有中至重度活動性類風濕性關節炎且對methotrexate無法產生適當治療反應或無法耐受methotrexate之成人病人。本品可用於單一療法或與methotrexate或其他非生物性的疾病緩解型抗風濕藥物(DMARDs)合併使用。**乾癬性關節炎**：XELJANZ XR 與非生物性的疾病緩解型抗風濕藥物(DMARDs)合併使用，適用於治療患有活動性乾癬性關節炎且對methotrexate 或其他疾病緩解型抗風濕性藥物（DMARDs）無法產生適當治療反應或無法耐受之成人病人。使用限制：本品不建議與生物性的疾病及緩解型抗風濕性藥物DMARDs或與強效免疫抑制劑(如azathioprine與cyclosporine)合併使用。【劑量與用法】XELJANZ XR 為口服給藥，建議劑量為11 毫克每日一次，可與食物併服，亦可不與食物併服。【劑型與含量】XELJANZ XR為11毫克tofacitinib (相當於17.77毫克tofacitinib citrate)錠劑：粉紅色、橢圓形、持續性藥效膜衣錠，錠劑環帶一端讀有一小孔，錠劑另一面印有「JKI 11」字樣。【警語】嚴重感染 病人使用XELJANZ XR 治療時，發生可能導致住院或死亡之嚴重感染症的風險會升高。發生這些感染症的病人大部份都曾同時使用免疫抑制劑(如methotrexate)或皮質類固醇。如果發生嚴重的感染症，應暫時停用 XELJANZ XR，直到感染獲得控制。曾見於報告的感染症包括：活動性結核病，可能會伴隨出現肺臟疾病或肺外疾病。病人在接受 XELJANZ XR 治療之前與治療期間都應接受潛伏性結核病的檢查。潛伏性感染的治療應在使用XELJANZ XR 之前即開始進行。侵入性黴菌感染症，包括隱球菌病和肺囊蟲病。罹患侵入性黴菌感染症的病人可能會出現瀰漫性(而非局部性)的疾病表現。伺機性病原體所引起的細菌性感染、病毒性感染、包括帶狀皰疹及其它感染症。對患有慢性或復發性感染症的病人，在開始治療前應審慎評估使用 XELJANZ XR 治療的風險與效益。 在使用 XELJANZ XR 治療期間與治療之後，應密切監視病人是否出現感染的徵兆與症狀，包括開始治療前在潛伏性結核病感染檢驗中呈陰性反應的病人是否發生結核病 [參見仿單警語和注意事項(5.1)]。 惡性腫瘤 在使用XELJANZ治療的病人中，曾觀察到發生淋巴瘤與其它惡性腫瘤的病例。在接受XELJANZ治療並同時使用免疫抑制藥物的腎臟移植病人中，曾觀察到Epstein Barr病毒相關性移植後淋巴增生疾病的發生率升高的現象。【副作用】最常見於報告的嚴重感染症包括肺炎、蜂窩性組織炎、帶狀皰疹、尿道感染、憩室炎與闌尾炎。

(仿單編號 USPI 201712-2；細節請參閱完整處方資訊)

Pfizer Limited
輝瑞大藥廠股份有限公司

台北總公司
新北市251淡水區中正東路二段177號
TEL:(02)2809-7979 FAX:(02)2809-7676
www.pfizer.com.tw

台中辦事處
台中市408公益路二段51號10樓A室
TEL:(04)2328-2818 FAX:(04)2320-5438

高雄辦事處
高雄市802苓雅區四維三路6號16樓A室
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僅限醫療專業人士參閱

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TW1712754128

Roche

莫須瘤® 注射劑 MabThera® Solution for IV Infusion

類風溼性關節炎

與 methotrexate 併用，適用於治療曾接受一種 (含) 以上之腫瘤壞死因子(TNF) 抑制療法治療但效果不彰，或無法耐受的活動性類風濕性關節炎成人患者。

莫須瘤 (MabThera) 與 methotrexate 併用，經 X 光檢查已證實可減緩關節結構受損的進展。

肉芽腫性血管炎 (GPA)(Wegener's 肉芽腫症) 及顯微多發性血管炎 (MPA)

莫須瘤 (MabThera) 與葡萄糖皮質素 (glucocorticoids) 併用，適用於治療成人之肉芽腫性血管炎 (GPA，亦稱為韋格納肉芽腫症) 及顯微多發性血管炎 (MPA)。

羅氏大藥廠股份有限公司
台北市信義區松仁路100號40樓
電話：(02)27153111

03-17-MABT-02-AD

衛署菌疫輸字第000928號
北市衛藥廣字第106040218號
本藥限由醫師使用．詳細資料備索
使用前詳閱說明書警語及注意事項

MABTHERA®
RITUXIMAB
B CELL THERAPY. SEROPOSITIVE RESULTS.

適應症

1. **黑色素細胞瘤**

   治療無法切除或轉移性黑色素瘤患者；

2. **非小細胞肺癌**

   單獨使用，用於第一線治療經確效之試驗檢測出腫瘤高度表現PD-L1 (tumor proportion score (TPS) ≥ 50%)的轉移非小細胞肺癌患者，患者不具有EGFR或ALK腫瘤基因異常者。
   單獨使用，治療接受含鉑化學治療後疾病惡化且其經確效之試驗檢測出腫瘤高度表現PD-L1 (tumor proportion score ≥ 50%)的晚期非小細胞肺癌患者，患者若具有EGFR或ALK腫瘤基因異常者，則須經EGFR或ALK抑制劑治療後出現疾病惡化現象。
   與pemetrexed及carboplatin併用，做為轉移性，不具有EGFR或ALK腫瘤基因異常之非鱗狀非小細胞肺癌的第一線治療藥物。此適應症是以腫瘤療效反應率與無惡化存活期為基礎，獲得加速核准。此適應症的後續審查核准可能要視療效確認試驗中之臨床效益的確認結果與陳述內容而定。

3. **典型何杰金氏淋巴瘤**

   治療罹患頑固性或先前至少已接受三種治療仍復發之典型何杰金氏淋巴瘤的患者。此適應症是以腫瘤療效反應率與療效反應持久性為基礎，獲得加速核准。此適應症的後續審查核准可能要視療效確認試驗中之臨床效益的確認結果與陳述內容而定。

4. **頭頸部鱗狀細胞癌**

   治療在使用含鉑化學治療期間或治療後出現疾病惡化的復發或轉移性頭頸部鱗狀細胞癌 (HNSCC)的患者。
   本項適應症係依據腫整體反應率及治療反應持續時間獲得加速核准。適應症的持續核准須要 後續確認性試驗(confirmatory trial)證明確實達到臨床效益。

5. **泌尿道上皮癌**

   治療接受含鉑化學治療期間或治療後出現疾病惡化現象的局部晚期或轉移性泌尿道上皮癌患者。
   治療不適合接受cisplatin化學療法的局部晚期或轉移性泌尿道上皮癌患者。適應症係依據腫瘤整體反應率及反應持續時間加速核准，此適應症仍須執行確認性試驗以證明其臨床效益。

禁忌症

無。

警告及注意事項

合併感染B型或C型肝炎患者
本藥品黑色素瘤及非小細胞肺癌之臨床試驗皆排除B型或C型肝炎患者(包括無症狀帶原者)，本藥品對於該族群之安全性仍未知，因此目前尚無足夠資料用以建議本藥品使用於合併感染B型或C型肝炎患者。

免疫媒介性肺炎(Immune-Mediated Pneumonitis)
KEYTRUDA可能會造成免疫媒介性肺炎，包括死亡案例。應監視患者是否出現肺炎的徵兆與症狀。

免疫媒介性結腸炎(Immune-Mediated Colitis)
KEYTRUDA可能會造成免疫媒介性結腸炎。應監視患者是否出現結腸炎的徵兆與症狀。

免疫媒介性肝炎(Immune-Mediated Hepatitis)
KEYTRUDA可能會造成免疫媒介性肝炎。應監測患者的肝功能是否發生變化。

免疫媒介性內分泌病變(Immune-Mediated Endocrinopathies)
腦下垂體炎(Hypophysitis)
KEYTRUDA可能會造成腦下垂體炎。應監視患者是否出現腦下垂體炎的徵兆與症狀(包括腦下垂體功能低下和腎上腺功能不足)。

甲狀腺病變(Thyroid Disorders)
KEYTRUDA可能會造成甲狀腺失調，包括甲狀腺機能亢進、甲狀腺機能低下及甲狀腺炎。應監測患者的甲狀腺功能是否發生變化(開始治療時、治療期間(定期)、以及臨床評估顯示有必要時)，以及是否出現甲狀腺失調的臨床徵兆與症狀。

第1型糖尿病(Type 1 Diabetes mellitus)
KEYTRUDA可能會造成第1型糖尿病，包括糖尿病酮酸中毒。應監測患者是否出現高血糖或糖尿病的其他徵兆與症狀。

免疫媒介性腎炎與腎功能不全(Immune-Mediated Nephritis and Renal Dysfunction)
KEYTRUDA可能會造成免疫媒介性腎炎。應監測患者的腎功能是否發生變化。

免疫媒介性皮膚不良反應(Immune-Mediated Skin Adverse Reactions)
可能發生免疫媒介性皮疹，包含SJS、TEN(有些為死亡案例)、剝落性皮膚炎以及大皰性類天皰瘡。疑似發生嚴重皮膚反應時，應進行監控並排除其他導因。如果出現SJS或TEN的徵兆或症狀，即停用KEYTRUDA，併轉介至專門科室進行評估及治療。一旦確診為SJS或TEN，即永久停用KEYTRUDA。

其他免疫媒介性不良反應(Other Immune-Mediated Adverse Reactions)
KEYTRUDA可能會造成其他臨床上重要的免疫媒介性不良反應。免疫媒介性不良反應可影響多種身體系統同時發生。
疑似發生免疫媒介性不良反應時，一定要進行適當的評估，以確定病因或排除其他導因。應依據不良反應的嚴重程度，暫時停用KEYTRUDA及投予皮質類固醇。

輸注相關反應(Infusion-Related Reactions)
KEYTRUDA可能會造成重度或危及生命的輸注相關反應。應監測患者是否發生輸注相關反應的徵兆與症狀，包含寒顫、畏寒、呼吸喘鳴聲、搔癢、潮紅、皮疹、低血壓、低血氧症及發燒。

接受異體造血幹細胞移植之併發症(complications of allogeneic HSCT)
KEYTRUDA治療前接受異體造血幹細胞移植
在過去曾接受過異體造血幹細胞移植(HSCT)的病患中，曾有在接受KEYTRUDA治療後發生移植物對抗宿主疾病(GVHD)的案例。

KEYTRUDA治療後接受異體造血幹細胞移植之併發症
包括死亡案例的免疫媒介性併發症曾發生於接受KEYTRUDA治療後進行異體造血幹細胞移植(HSCT)的患者。

胚胎胎兒毒性
根據其作用機制，對孕婦投予KEYTRUDA會造成胎兒傷害。如果在懷孕期間使用本品，或患者在使用本品期間懷孕，應告知患者本品對胎兒造成傷害的可能性。應囑咐具生育能力的女性患者，在使用KEYTRUDA治療期間應採取高度有效的避孕措施，在使用最後一劑KEYTRUDA之後亦應繼續避孕4個月。

其他仿單內容，處方前請詳閱藥品仿單說明書。

MSD
美商默沙東藥廠股份有限公司台灣分公司
台北市信義路五段106號12樓
電話(02)6631-6000

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衛部菌疫輸字第001025號
北市衛藥廣字第107060412號

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OPDIVO™ (nivolumab)

適應症

無法切除或轉移性黑色素瘤
OPDIVO單一療法或併用ipilimumab適用於治療無法切除或轉移性黑色素瘤病人

非小細胞肺癌
適用於接受含鉑化學治療時或之後疾病惡化的晚期鱗狀非小細胞肺癌(Squamous NSCLC)病人。
適用接受含鉑化學治療時或之後疾病惡化且其腫瘤表現PD-L1(IHC PD-L1 expression ≥ 5%)的晚期非鱗狀非小細胞肺癌(Non-Squamous NSCLC)病人，病人若具有EGFR或ALK腫瘤基因異常者，則須經EGFR或ALK抑制劑治療後出現疾病惡化現象。

腎細胞癌
適用於先前經抗血管新生療法治療(anti-angiogenic therapy)的晚期腎細胞癌病人。

頭頸部鱗狀細胞癌
適用於接受含鉑化學治療時或之後疾病惡化的復發或轉移性頭頸部鱗狀細胞癌(SCCHN)病人。

典型何杰金氏淋巴瘤
適用於治療接受自體造血幹細胞移植(HSCT)與移植後brentuximab vedotin復發或惡化的典型何杰金氏淋巴瘤病人。

泌尿道上皮癌
適用於治療接受含鉑療法期間或之後惡化的局部晚期無法切除或轉移性泌尿上皮道癌病人。

無法切除的晚期或復發性胃癌
適用於治療先前經兩種或兩種以上化學治療的晚期或復發性胃癌或胃食道癌(Gastroesophageal Junction, GEJ)的病人。

肝細胞癌
適用於先前經sorafenib治療的肝細胞癌(HCC)病人。

[用法] OPDIVO的建議劑量為3 mg/kg連續靜脈輸注60分鐘，每2週一次，直到疾病惡化或出現無法接受之毒性為止。合併使用時，OPDIVO的建議劑量為1 mg/kg靜脈輸注60分鐘後，隨後同一天給予ipilimumab，每3週給予，共4次劑量。後續OPDIVO單一療法的建議劑量為3 mg/kg，連續靜脈輸注60分鐘，每2週一次，直到疾病惡化或出現無法接受之毒性為止。[禁忌症] 無。[警語及注意事項] • 使用OPDIVO治療有可能發生定義為需要以皮質類固醇治療且無明顯其他病因之免疫媒介性肺炎(曾通報死亡病例)、免疫媒介性結腸炎、免疫媒介性肝炎、免疫媒介性腎功能不全或腎炎(肌酸酐≥第2級升高)、免疫媒介性皮疹(包括SJS及TEN，曾有致死病例)、免疫媒介性腦炎、免疫媒介性內分泌病變如腦下垂體炎、腎上腺功能不全、自體免疫甲狀腺疾病及第1型糖尿病。• 應監測病人的肺炎、結腸炎、腦下垂體炎及腎上腺功能不全徵兆及症狀，甲狀腺功能及高血糖。應監測病人是否發生皮疹。病人應於治療前及治療期間定期監測肝功能是否異常、是否有血清肌酸酐濃度上升。出現SJS或TEN之徵兆及症狀時，應暫時停用OPDIVO，並將病人轉介至專科進行評估及治療。應評估病人的神經學症狀。應密集追蹤病人移植相關併發症的早期症狀。• 其他免疫媒介性不良反應：在OPDIVO作為單一藥物或併用Ipilimumab治療的臨床試驗中，曾出現下列具臨床意義的免疫媒介性不良反應：心肌炎、橫紋肌溶解症、肌炎、葡萄膜炎、虹膜炎、胰臟炎、腺部及外展神經輕癱(paresis)、髓鞘脫失(demyelination)、風濕性多發性肌痛、自體免疫神經病變、急性多發性神經炎(Guillain-Barré syndrome)、腦下垂體功能低下症、全身發炎反應症候群、胃炎、十二指腸炎、類肉瘤病(sarcoidosis)、組織細胞壞死性淋巴炎(菊地氏病)(Kikuchi lymphadenitis)、運動功能障礙、血管炎及肌無力症。• 輸注反應：接受OPDIVO治療病人其嚴重輸注反應的發生率小於1.0%。• OPVIDO治療後之異體造血幹細胞移植(HSCT)併發症：在使用OPDIVO後進行異體HSCT之病人曾發生併發症，包括致死事件。[懷孕及胚胎毒性] 應告知孕婦OPDIVO對胎兒的潛在風險。應告知具有生育能力的婦女在接受OPDIVO治療期間至OPDIVO最後一劑用藥後至少5個月內，需採取有效的避孕措施。[授乳] 目前尚不清楚OPDIVO是否會分泌至人體乳汁中。應告知婦女在OPDIVO治療期間停止哺乳。[嚴重不良反應] • 試驗CA209037中為腹痛、低血鈉症、AST增加及脂肪酶增加。• 試驗CA209067中為腹瀉、結腸炎及發熱。• 試驗CA209017中為怒性腫瘤惡化、肺炎、發熱與高血鈣症。• 試驗CA209057中為肺炎、肺栓塞、呼吸困難、肋膜積水及呼吸衰竭。• 試驗CA209025中急性腎臟損傷、肋膜積水、肺炎、腹瀉及高血鈣症。• 試驗CA209141中為肺炎、呼吸困難、呼吸衰竭、呼吸道感染及敗血症。• 試驗CA209205及CA209039中為輸注相關反應、肺炎(pneumonia)、肋膜積水、發熱、皮疹及肺炎(pneumonitis)。• 試驗CA209275中為泌尿道感染、敗血症、腹瀉、小腸阻塞與整體生理健康衰退。• 試驗CA209040中觀察到之毒性數據與其他癌症大致相似，除了較高發生率的轉胺酶及膽紅素升高。[不良反應] • 試驗CA209037中為皮疹。試驗CA209067中為疲倦、皮疹、腹瀉、噁心。試驗CA209017中為呼吸困難、咳嗽、疲倦、與食慾降低。試驗CA209057中為疲倦、肌肉骨骼疼痛、咳嗽、食慾減退和便秘。試驗CA209025中為虛弱狀態、咳嗽、噁心、皮疹、呼吸困難、腹瀉、便秘、食慾降低、背痛及關節痛。試驗CA209141中為咳嗽、呼吸困難。試驗CA209205及CA209039中為皮疹、肌肉骨骼疼痛、搔癢、噁心、關節痛及周邊神經病變。試驗CA209275中為疲倦、肌肉骨骼疼痛、噁心與食慾減退。試驗ONO-4538-12中發生率≥5%的為搔癢、腹瀉、皮疹、及疲倦。

ONO PHARMA TAIWAN
臺北市信義區松高路1號7樓之3
NV-040318-AD-01

【本藥限由醫師使用】
衛部菌疫輸字第001013號　北市衛藥廣字第107040322號
【僅限醫藥專業人員參考，處方藥物請參考衛生福利部核准仿單說明書】

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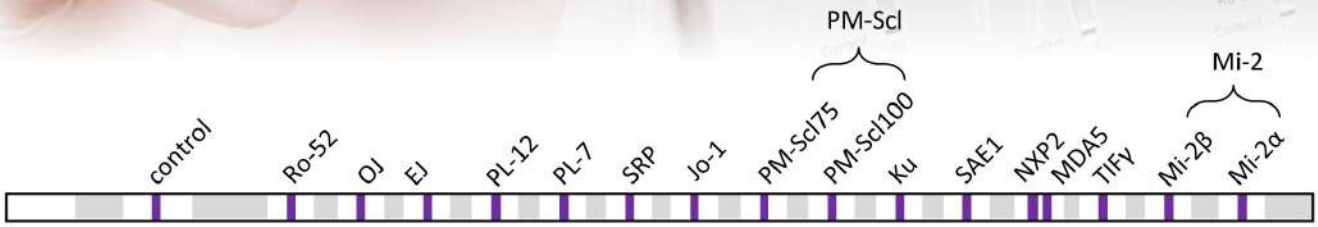
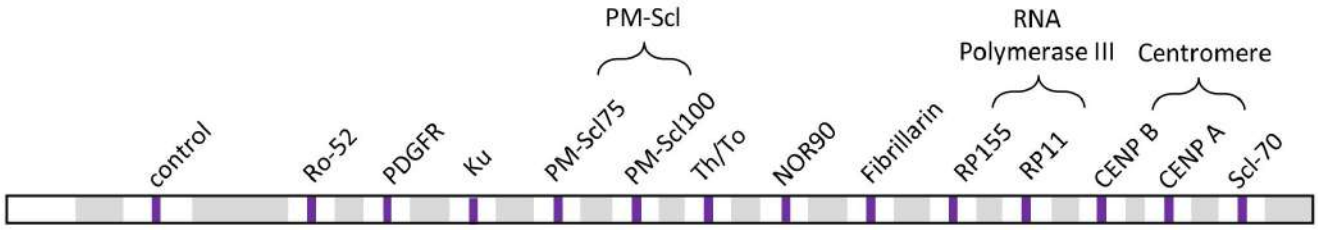
1506TW18PR01982-01

EUROLINE Immunoblot



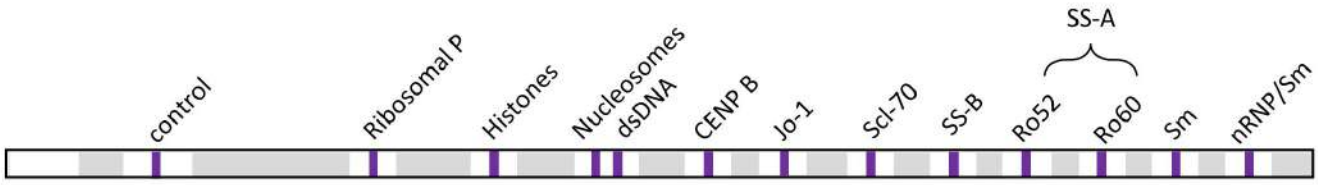
Autoimmune Inflammatory Myopathies

Order no. DL 1530-1601-4 G



Systemic Sclerosis (Nucleoli) Profile

Order no. DL 1532-1601 G



ANA Profile

Order no. DL 1590-1601-8 G

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golimumab

潰瘍性結腸炎 類風濕性關節炎 僵直性脊椎炎 乾癬性關節炎

一月一劑，藥效持續

欣普尼注射液
SimponiTM (Golimumab) Solution for Injection冷藏貯存於2ºC至8ºC
限由醫師使用
[適應症]
●類風濕性關節炎：欣普尼SIMPONITM與methotrexate併用適用於治療中至重度活動性類風濕性關節炎成人患者。
●乾癬性關節炎：欣普尼SIMPONITM單獨使用或與methotrexate併用適用於治療對疾病修飾性抗風濕藥物(DMARDs)無效之活動性乾癬性關節炎成人患者。
●僵直性脊椎炎：欣普尼SIMPONITM適用於治療活動性僵直性脊椎炎成人患者。
●潰瘍性結腸炎: 欣普尼SIMPONI適用於對於皮質類固醇和6-mercaptopurine (6-MP)或azathioprine (AZA)等傳統治療無效、或對這種療法不耐受或有醫療禁忌之中度至嚴重活動性潰瘍性結腸炎成人病患。
[禁忌]
●對本藥品主成份或任何一賦型劑過敏者。
●活動性肺結核(active tuberculosis)或其他嚴重感染者，如敗血症及伺機性感染。
●中度或重度心衰竭者(NYHA class III/IV)
[劑量與用法]
類風濕性關節炎、乾癬性關節炎及僵直性脊椎炎:
欣普尼SIMPONITM的投藥療程為每月一次以皮下注射方式投予50毫克。
對類風濕性關節炎(RA)病人，應採取欣普尼SIMPONITM合併methotrexate的方式治療，對乾癬性關節炎(PsA)或僵直性脊椎炎(AS)病人，則可單獨使用欣普尼SIMPONITM或合併投予methotrexate或其他非生物性的疾病修飾性抗風濕藥物(DMARDs)。對RA、PsA或AS病人，在使用欣普尼SIMPONITM治療期間，或可繼續使用皮質類固醇、非生物性DMARDs及(或)NSAIDs類的藥物。
中度至嚴重活動性潰瘍性結腸炎:
體重小於80公斤的病患-
第0週皮下注射200毫克，第2週注射100毫克，然後每4週注射50毫克。
體重大於或等於80公斤的病患-
第0週皮下注射200毫克，第2週注射100毫克，然後每4週注射100毫克。
[警語]
接受欣普尼SIMPONI治療的病人會增加發生嚴重感染 (包括多種器官系統和部位) 的風險，並導致住院或死亡。如果病人發生嚴重感染、伺機性感染或敗血症，即應停用欣普尼SIMPONI。
在開始使用欣普尼SIMPONI治療之前，應對病人進行結核病危險因子的評估，並檢查是否患有潛伏性感染症，在治療期間亦應定期進行檢查。
如果患者病人發生嚴重的全身性疾病，並且曾在黴菌病流行地區居住或旅行，在鑑別診斷中應考慮可能為侵入性黴菌感染症。
對慢性B型肝炎帶原者(即表面抗原陽性的病人)，使用TNF阻斷劑(包括欣普尼SIMPONI)可能會誘使B型肝炎病毒(HBV)再度活化。病人在開始使用TNF阻斷劑(包括欣普尼SIMPONI)之前，應先進行B型肝炎病毒(HBV)感染檢測。
在開始使用欣普尼SIMPONI治療之前應先進行C型肝炎篩檢。
在接受TNF阻斷劑(欣普尼SIMPONI也屬於此類藥物)治療的兒童、青少年與年輕成人中(開始治療的年齡≦18歲)，曾有發生惡性腫瘤(甚至造成死亡)的報告。
曾有在使用TNF阻斷劑(包括欣普尼SIMPONI)期間充血性心臟衰竭(CHF)出現惡化現象與新發生CHF的病例報告。
曾有少數使用TNF阻斷劑(欣普尼SIMPONI也屬於此類藥物)而發生新的中樞神經系統髓鞘脫失性疾病(包括多發性硬化症(MS))或造成既有髓鞘脫失性疾病症狀惡化，以及發生周邊髓鞘脫失性疾病(包括Guillain-Barré症候群)的病例。
使用TNF阻斷劑(包含欣普尼SIMPONI)可能會導致抗核抗體(antinuclear antibodies, ANA)的形成，而有很少的案例會發展成狼瘡樣症候群(lupus-like syndrome)。如果病人在使用欣普尼SIMPONI後發生疑似狼瘡樣症候群的症狀，應停止欣普尼SIMPONI的治療。
接受TNF阻斷劑治療的病人曾有發生全血球減少症、白血球減少症、嗜中性白血球減少症、再生不能性貧血及血小板減少症的報告。
接受欣普尼SIMPONI治療的病人可以接種活性疫苗以外之疫苗。
在上市後的使用經驗中，曾有在投予欣普尼SIMPONI後發生嚴重全身性過敏反應(包括過敏性反應)的報告。
[不良反應]
於臨床試驗中常見: 感染症、髓鞘脫失性疾病、肝臟酵素升高、自體免疫疾病與自體抗體、注射部位反應、免疫生成性等。
在欣普尼SIMPONI獲得核准後的使用期間曾發現下列不良反應:
嚴重全身性過敏反應(包括過敏性反應) 、肉狀瘤病 、黑色素瘤 、Merkel細胞癌、間質性肺病、 皮膚剝落、疹、大皰性皮膚反應。
[其他不良反應請詳見仿單]

USPI_May2018_1802

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使用前詳閱說明書警語及注意事項

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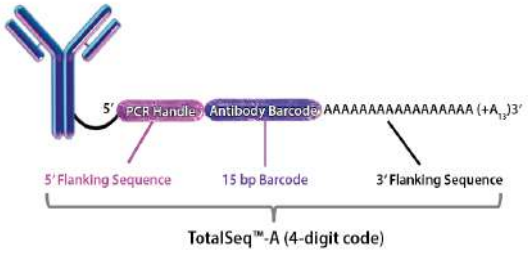
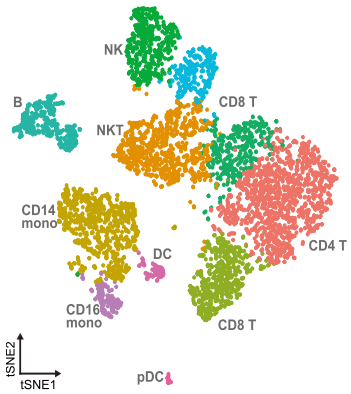
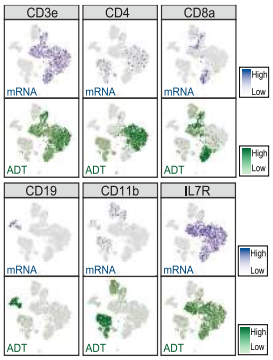
Nadia (Dolomite Bio), Droplet-based Home brew systems







Clustering of 5,000 CITE-seq single-cell expression profiles of PBMCs reveals distinct cell populations based on transcriptome analysis. The top panel shows global gene expression relationships among all cells, and major cell types separated based on gene expression as indicated. The bottom panels show mRNA (blue) and corresponding Antibody-Derived Tag (ADT, green) signal.

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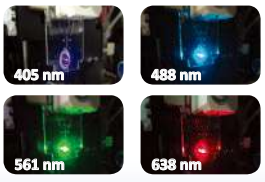
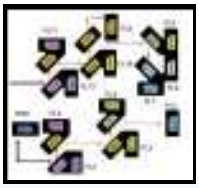
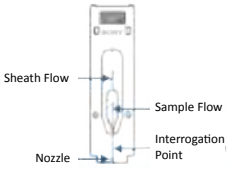



12色螢光濾片組合

簡易載入分選晶片



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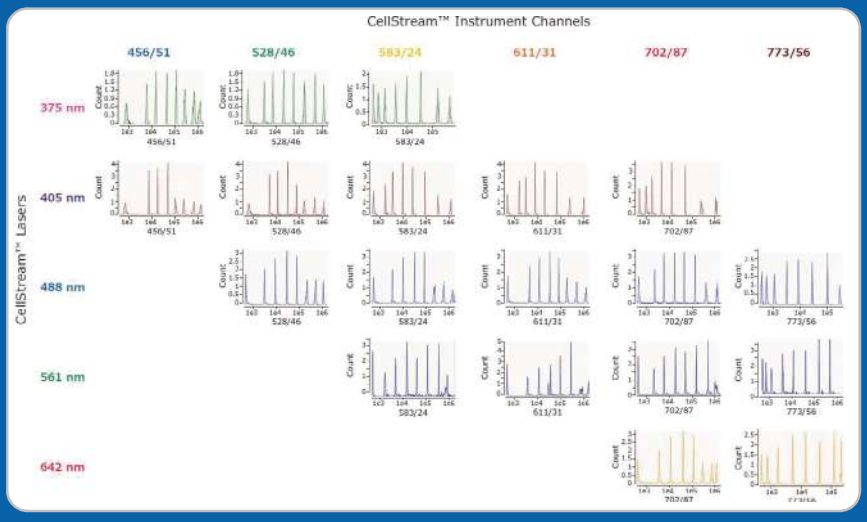
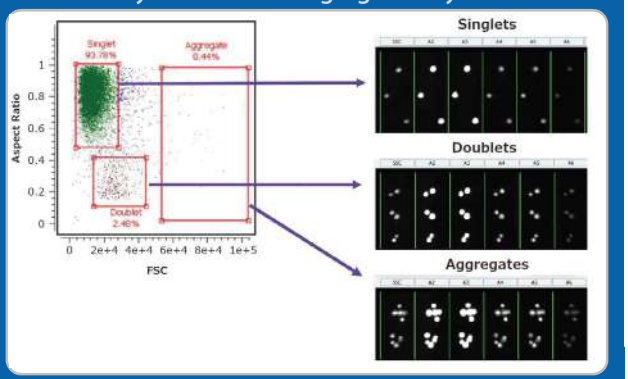
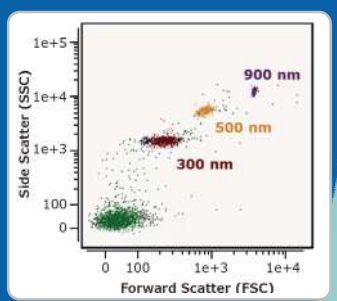


Real-time Event Gallery
- Provides verification of suspected populations
- Aids in troubleshooting
- Unlike any other non-imaging flow cytometer





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Spring School

王亮晴 Lian-Chin Wang

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