出國報告（出國類別：參加國際會議）

自體免疫暨癌症之免疫調控

服務機關：國立中正大學生科系

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派赴國家：加拿大

出國期間：106年3月26日至3月30日

報告日期：106 年 4 月 26 日

摘要:

本次出國主要參加國際學術研討會議，主題是: 自體免疫暨癌症之免疫調控 (Immune Regulation in Autoimmune and Cancer)。此會議日期為今年 3 月 26 日至 30 日，在加拿大舉行。本次會議討論的主題為自體免疫疾病以及腫瘤這兩類疾病之免疫調控機轉以及其應用。由於免疫系統中許多造成自體免疫的機轉已有一些瞭解，在腫瘤環境中的免疫抑制機轉近來也有一些進展，對於發展治療的方式有許多的貢獻，但仍有許多機制不甚明瞭，因此這次會議包含這兩方面的內容；也討論基礎研究以及最新的臨床試驗進展，透過這次會議的交流，對於基礎以及臨床治療有更多討論，使得治療上遇見的問題可以激發更多的基礎研究，透過更多基礎研究，對於形成疾病的原因的探究，期望能夠對與疾病的治療有更多的幫助。

目錄

一、 目的:

本次出國主要參加國際學術會議，會議名稱: Immune Regulation in Autoimmunity and Cancer (自體免疫暨癌症之免疫調控)，會議主題主要探討自體免疫疾病以及癌症的免疫反應以及其調控的機轉，藉此機會學習這方面最新的進展以及目前研究的趨勢和方向。我也有一海報發表最近實驗室的成果，題目是: Expression of Helios in gastric tumor cells predict better survival in gastric cancer patients (Helios 表現在胃癌細胞在胃癌病人有較好的存活率)。

二、 參加會議經過:

會議日期為今年3月26日至30日，26日由嘉義搭乘高鐵至桃園站，再搭機場捷運至桃園機場，抵達機場時由於已在網路上報到，所以想說可以不用這麼早去報到，但手上行李還是需要拖運，因此雖然飛機是11:55的飛機，10點多還是先行報到。到了長榮櫃檯，才知道去加拿大在今年初已經需要辦理簽證，但是我們這次沒有先辦，正在想是不是已經出不了國沒法去開會時，櫃檯告訴我們在隔壁不遠處可以辦理網路上的簽證，但櫃檯11:10會關櫃檯，所以必須在此之前取得簽證，一連串的意外使得我們非常緊張，還好及時辦完，可以順利的拿到簽證，坐上飛往加拿大的飛機。在經歷將近12個小時的飛行之後，抵達溫哥華，但會場在惠斯勒(Whistler)，尚須坐2.5小時的巴士才能到開會附近的旅館，真是漫長的旅程! 抵達旅館已是當地時間晚上，盥洗完也累了，雖然和台灣有時差但還是早早睡覺以準備明天一早8點的開會!

27日議程邀請唐獎得主James P. Allison演講，主題為: Immune checkpoints and cancer immunotherapy (免疫檢查點與腫瘤免疫治療)：介紹近期使用抑制免疫抑制的抗體在腫瘤治療的使用與其優缺點，由於仍有許多機制不十分明白，因此也介紹目前對於這方面最新的研究進展。目前通過美國食品藥物管理局核可使用的免疫檢查點抑制劑共有兩類: 其中一種即是講者所研究的重點，由於臨床上目前的許多試驗結果約有兩到三成的腫瘤轉移病患使用這類藥物有很好的抗腫瘤效果，並且由最初的研究:黑色素細胞癌(是白種人最易罹患的一種皮膚癌)，目前已有許多臨床試驗正在進行其他癌症的測試。然而科學家們也在尋找對其他七至八成失敗的病人其他的

治療方式:包括合併其他已有的方式如化療、小分子藥物或其他方式等。目前已有許多臨床試驗正在進行中；並且有許多臨床研究也在積極分析這些臨床上收集的數據，期望對這些藥物以及疾病的交互作用有更多了解。其中干擾素或其受體(interferon gamma and the receptor)若有缺陷，則臨床試驗結果顯示對這些藥物的反應不佳。

第二天的議題則是代謝反應對於T細胞生理和功能的影響。近期的研究顯示糖的濃度以及其代謝與T細胞的反應有關，若葡萄糖濃度過低(<0.3mM)則CD28 所傳遞的訊息將受到大幅的影響。此影響分子與粒線體的功能有關。此外體內各離子的濃度不僅跟體液的平衡，也與免疫反應有關。近期的研究顯示淋巴結各不同部位其鈉離子濃度各有不同，且與其功能有關。因此免疫系統也與水分和代謝有密切關係。此外攝食過多的鹽會導致自體免疫疾病的發生，其發生的機制與T細胞族群有關。

29日的主題則是各樣的免疫細胞與自體免疫以及腫瘤的關係。包括先天免疫系統中的巨噬細胞，自然殺手細胞，和樹突狀細胞；以及後天免疫細胞的B和T細胞，在腫瘤環境以及自體免疫疾病的各樣角色以及調控。由於腫瘤細胞和免疫系統的交互作用牽涉許多不同細胞，包含各式腫瘤細胞以及不同的免疫細胞，還有這些細胞交互作用後所產生各種的微環境，因此在不同腫瘤有不同的狀態。而不同腫瘤的階段也會反映不同的免疫型式，因此這是一個複雜的環境，須針對許多不同條件進行分析以及探討。

30日則是討論T細胞中的TH17細胞在自體免疫疾病的各樣調控，以及目前新的藥物在臨床試驗的最新進展，使得許多的自體免疫疾病有更多更有效果的藥物，可

以治療這些複雜的疾病。並且因著科學研究的進展，這10年間從發現、定義這個細胞族群到有臨床的用藥治療許多相關的疾病，許多科學研究的進展造福許多的病人，也更了解疾病的機轉。相信不久的將來，將有更多自體免疫疾病可以有效的控制，而腫瘤這個疾病也可以得到更有效的治療，甚至痊癒。

三、與會心得:

近年來因為免疫學的進步，對許多相關的免疫機轉已有相當多深入的研究，然而因為免疫細胞種類繁多，又與各類組織和其他非免疫細胞有許多交互作用，並且其所分泌的細胞激素所形成的微環境，這中間有許多龐大的資料，且是千一髮而動全局。然而由於科學的進步，目前可以做到單一細胞定序(single cell sequencing)，這次的會議有許多的報告也是分析在各樣的免疫環境中(特別是腫瘤環境)的單細胞定序。由於這樣的分析會產生非常龐大的資料，因此目前這類的研究除了瞭角生物的操作，也需要資料分析以及軟體程式的應用，因此生物資訊的相關領域也是這類研究所不可少的，統和這些資料的分析之後，尚須回到生物的現象，做出一個有意義的解釋，便於了解所分析的資料如何解釋生物現象。因此況領域的合作，人才的整合是這類研究所不可少的。

四、建議:

近年在生物醫學界有個希望是腫瘤能夠治癒，突破以前的方式，希望它不再是一個不治之症。最近的醫學進步使用免疫治療，也看到許多令人興奮的消息，有些反應良好的腫瘤轉移病人，甚至長達 10 年的存活率，截至文章發表病人依然沒有再復發。因此，腫瘤的免疫治療在科學的進步之下，應是未來一個十分具潛力的發展方向。個人認為參加此研討會對本身相關研究及教學工作有很大之助益;相信藉由研討會之新知可協助瞭解最新之知識及方向,進而對研究產生更好的想法與作法。

五、攜回資料名稱及內容

名稱:

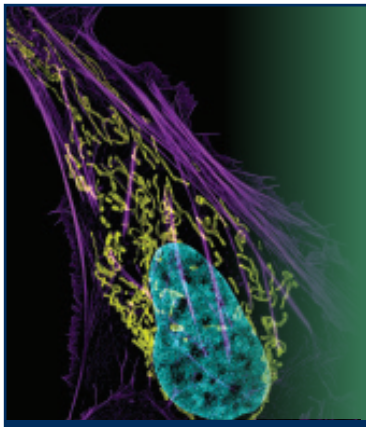
Immune Regulation in Autoimmunity and Cancer (D1)　“Program Book”

內容: 大會議程、及摘要。

六、附件:

參加會議摘要:

Chronic inflammation has been indicated with tumor developments. The interaction with tumor cell and immunity usually contributes to establish a cancer-induced immune tolerance. Gastric cancer is initially asymptomatic and is often diagnosed at late stage or has been metastasis or progress to an advanced or even terminal stage. In our recent study, we found that regulatory T cell immunosuppressive functions in gastric tumor patients were significantly increased. Helios belongs to Ikaros family proteins, a kind of zinc finger transcription factors, is expressed in Tcells especially in regulatory T cells, forced expression of Helios enhanced the suppressive function in foxp3+CD4+Tcells. Strikingly, we found that not only tumor infiltrated lymphocytes were expressed with Helios, the gastric tumor cells and adjacent normal cells also positive staining with Helios. Kaplan Meier survival analysis revealed significantly better median overall survival in high Helios expression group than low Helios expression group. Helicobacter pylori (HP) infection is the most important risk factor for gastric malignancies. Among HP positive infected gastric cancer patients, high Helios expression group showed a significant better survival than low Helios expression group. Kaplan-Meier survival analysis revealed high Helios expression is a significant better prognostic factor of median overall survival than low Helios expression in advanced gastric cancer patients but not in early cancer stage patients. In conclusion, our present study revealed a novel aspect of Helios expression in gastric cancer, the Helios expression was an independent factor of survival in advanced gastric cancer patients, high Helios expression is a significant better prognostic factor of median overall survival than low Helios expression.



Immune Regulation in Autoimmunity and Cancer

March 26–30, 2017 | Whistler Conference Centre | Whistler, British Columbia | Canada

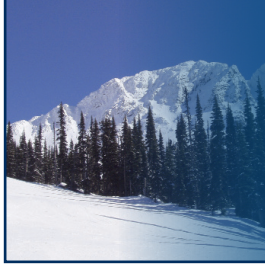
Scientific Organizers:
David A. Hafler, Yale University School of Medicine, USA
Vijay K. Kuchroo, Brigham and Women's Hospital, Harvard Medical School, USA
Jane L. Grogan, Genentech, Inc., USA

While the importance of innate and adaptive immunity has been clear in the pathogenesis of human autoimmune disease resulting in a multitude of immune-based therapeutic approaches, the realization is now apparent that understanding immune evasion by cancer is central in developing curative treatments. This meeting will explore and contrast the underlying immune mechanisms resulting in autoimmunity and tumor evasion. The meeting is innovative in bringing together basic immunologists investigating mechanisms of tolerance with scientists exploring immune mechanisms of autoimmunity and cancer in both patients and experimental models. Thus, this Keystone Symposia meeting will cover the pathways in immunity and tolerance that lead to loss of immunological control, dysregulated immune responses and chronic inflammatory disease or tumor evasion. Presentations will include consideration of preclinical and clinical aspects of a diverse number of autoimmune and inflammatory diseases and cancer. Conference participants engaged in preclinical, translational and clinical research will hopefully engage in continuing conversations and collaborations which, over the long-term, will provide greater insights into the human immune response and allow us to reassess and further explore pathways that are driving autoimmune disease yet in opposition, lead to tumor evasion. Understanding checkpoints in autoimmunity and immune cell tolerance is important for delivering therapies to patients with autoimmune disease and cancer, and this meeting will provide a platform for the cross-pollination of clinical experience and experimental research. Attendees will have learned about the impact of targeted immune-based therapeutics on clinical outcome and, consequently, be able to widen their research scope accordingly.

Session Topics:

- Tissue Micro-Immune Environments in Tumors and Autoimmune Tissue Inflammation
- Basic Mechanisms of T Cell Tolerance
- Metabolic Regulation of T Cell Function in Cancer and Autoimmunity
- Effector T Cell Dysfunction: Surface Receptors in Autoimmunity vs. Cancer
- Innate Regulation of Autoimmunity and Cancer
- B Cell Regulation of Autoimmunity
- 10 Years of Discovery of Th17 Cell. From Bench to Bedside
- Systems Biology Approaches to Understanding Tolerance in Cancer and Autoimmunity

Scholarship Application & Discounted Abstract Deadline: November 29, 2016
Abstract Deadline: January 10, 2017
Discounted Registration Deadline: January 25, 2017



Note: Scholarships are available for graduate students and postdoctoral fellows and are awarded based on the abstract submitted.

Upper image courtesy of: The Web site of the National Cancer Institute (http://www.cancer.gov).

Meeting Hashtag: #KSimmreg
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Abstract & Scholarship Deadline: November 29, 2016 / Abstract Deadline: January 10, 2017 / Discounted Registration Deadline: January 25, 2017

SUNDAY, MARCH 26

Arrival and Registration

MONDAY, MARCH 27

Welcome and Keynote Address

*__David A. Hafler__, Yale University School of Medicine, USA

__James P. Allison__, University of Texas MD Anderson Cancer Center, USA
Cancer Immunotherapy

Tissue Micro-Immune Environments in Tumors and Autoimmune Tissue Inflammation

__Padmanee Sharma__, University of Texas MD Anderson Cancer Center, USA
From the Clinic to the Lab: Investigating Response and Resistance Mechanisms to Immune Checkpoint Therapy

__Jennifer L. Gommerman__, University of Toronto, Canada
Compartmentalization of B Cells During CNS Inflammation

*__Jane L. Grogan__, Genentech, Inc., USA
Immunoregulatory Roles of TIGIT and PVR-nectin Family in Tumors

__Abigail E. Overacre__, University of Pittsburgh, USA
Short Talk: Interferon-gamma drives Treg Functional Instability thereby Promoting Anti-Tumor Immunity

Workshop 1: Effector T Cells

*__Thomas Korn__, Technical University Munich, Germany

*__Jane L. Grogan__, Genentech, Inc., USA

__June-Yong Lee__, New York University School of Medicine, USA
Systemic and Local Functions of Serum Amyloid A (SAA) in Th17 Cell Pathogenicity

__Jinju Lee__, Kyoto University Graduate School of Medicine, Japan
Regulation of Th17 Expansion by PGE2-EP2/EP4 Signaling and its Clinical Implication

__Pradip Nair__, Biocon Research Limited, India
T Cell Activation and Differentiation to Th17 Cells is Modulated by a CD6 Domain 1 Antibody Itolizumab

__Patricia Castillo__, University of Pittsburgh, USA
Disrupted Enteric Th17 Signaling Exacerbates Autoimmune Inflammation

__Michael Waterfield__, University of California, San Francisco, USA
Characterization of a Novel Epigenetic Regulator Required for Th17 Differentiation

__Mark S. Sundrud__, The Scripps Research Institute, USA
The Xenobiotic Transporter Mdr1 Permits T Cell Adaptation to Mucosa-Associated Bile Acids in the Ileum

__Geoffrey Alexander Smith__, University of California, San Francisco, USA
IL-2RB Receptor Levels Tune T-Cell IL-2 Responses by Altering Signaling Dynamics in Different T Cell Subsets

__Peter A. Morawski__, NIAID, National Institutes of Health, USA
Brain Infiltrating CD8+ T Cells in Lupus-Prone Mice

Basic Mechanisms of T Cell Tolerance

*__Jeffrey A. Bluestone__, University of California, San Francisco, USA
Treg Biology and Treatment in Autoimmune Diseases and Cancer

__David A. Hafler__, Yale University School of Medicine, USA
IFNgamma Identifies Dysfunctional Regulatory T Cells in Autoimmunity and Cancer

__Alexander Y. Rudensky__, HHMI/Memorial Sloan Kettering Cancer Center, USA
Regulatory T Cells in Cancer

Poster Session 1

TUESDAY, MARCH 28

Metabolic Regulation of T Cell Function in Cancer and Autoimmunity

*__Erika L. Pearce__, Max Planck Institute of Immunobiology and Epigenetics, Germany
How Metabolism Influences CD8 Cells in Cancer

__Douglas R. Green__, St. Jude Children's Research Hospital, USA
Cell Death and Resuscitation: To the Edge of Necroptosis and Back

__Jens Titze__, Vanderbilt University, USA
Rethinking Sodium Metabolism

__Tomokazu Sumida__, Yale School of Medicine, USA
Short Talk: Beta-catenin Links High Salt and Proinflammatory Signature in Treg

__Seungho Lee__, Yonsei University, South Korea
Short Talk: Exploration of Tumor Microenvironment and Metabolism using Tumor Infiltrating Lymphocytes and FDG-PET CT

Workshop 2: Tregs in Autoimmunity and Cancer

*__Alexander Y. Rudensky__, HHMI/Memorial Sloan Kettering Cancer Center, USA

*__Ana Carrizosa Anderson__, Harvard Medical School, USA

__Liliana Elisa Lucca__, Yale University, USA
PD-1 Marks Dysfunctional Regulatory T Cells in Malignant Gliomas

__Maran L. Sprouse__, Baylor College of Medicine, USA
High CD5 Expression is a Marker of Functional Regulatory T Cells in Autoimmunity

__Catherine Konopacki__, Memorial Sloan Kettering Cancer Center, USA
Foxp1 Is a Foxp3 Binding Partner that Contributes to Regulatory T Cell Stability and Function

__Allison L. Bayer__, University of Miami School of Medicine, USA
Immunomodulation Requirements for Treg Immunotherapy for Autoimmune Diabetes

__Danbee Ha__, Osaka University, Japan
ADCC-Mediated in vitro Depletion of Human Treg Cells by Anti-CTLA-4 mAb Enhances CD8+ T Cell Responses against Self/Tumor Antigens

__David Bauche__, Merck, USA
Foxp3+ Regulatory T Cells Prevent from ILC3-Driven Colitis

__Wenxian Fu__, University of California, San Diego, USA
A Tissue-Resident Macrophage Specific Coinhibitory Molecule Promotes Regulatory T Cell Differentiation and Stability

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Dana Catherine Gilmore, University of Chicago, USA
Identification of Natural Peptide Epitopes Recognized by Regulatory T Cells

Effector T Cell Dysfunction: Surface Receptors in Autoimmunity vs. Cancer

*__Arlene H. Sharpe__, Harvard Medical School, USA
Role of Coinhibitory Receptors in Controlling Effector T Cells

E. John Wherry, University of Pennsylvania, USA
Molecular Basis of T Cell Exhaustion: Insights for Immunotherapy

Ana Carrizosa Anderson, Harvard Medical School, USA
T Cell Dysfunction: From Co-Inhibitory Receptors to Molecular Programs

Christopher E. Rudd, University of Montreal, Canada
Short Talk: A Next Generation Approach using Small Molecules to Inhibit PD-1 Transcription Is as Effective as Anti-PD-1/PL1 Biologics in Immunotherapy

Poster Session 2

WEDNESDAY, MARCH 29

Innate Regulation of Autoimmunity and Cancer

Nina Bhardwaj, Icahn School of Medicine at Mount Sinai, USA
Role of Dendritic Cells and NK Cells in Mediating Anti-Tumor Responses

Federica Sallusto, University of Italian Switzerland, Switzerland
Autoreactive T Cells in Narcoleptic Patients

*__Carla V. Rothlin__, Yale University, USA
Innate Immune Checkpoints in Anti-Tumor Immunity

Mark J. Smyth, QIMR Berghofer Medical Research Institute, Australia
Barriers to NK Cell Control of Cancer

Keiji Hirota, Institute for Frontier Life and Medical Sciences, Kyoto University, Japan
Short Talk: An Inflammatory Cellular Network of Autoimmune Th17 Cells, GM-CSF-Producing ILCs and Synoviocytes in the Development of Autoimmune Arthritis

Workshop 3: T Cell Tolerance, Exhaustion and Dysfunction in Autoimmunity and Cancer

*__Kenneth Smith__, University of Cambridge, UK

Rachel S. Friedman, National Jewish Health and University of Colorado, Denver, USA
MerTK Mediates T Cell Tolerance in the Pancreatic Islets during Type 1 Diabetes

Yemsratch T. Akalu, Yale University School of Medicine, USA
An eMERging Target in Cancer Immunotherapy

Rachael Bashford-Rogers, University of Cambridge, UK
Using High-Throughput Sequencing to Reveal Insights into the Relationship between B-Cell Repertoire, Phenotype and Function in Health, Cancer and Autoimmune Disease

David M. Sansom, University College London Medical School, UK
CTLA-4 Mutations from Patients with Immune Dysregulation Syndromes Inform our Understanding of CTLA-4 Function

Jennifer Lori Blanchfield, Emory University, USA
MOG-Specific Tolerance Mechanisms Limit Autoimmune Demyelinating Disease following Bacterial Delivery of MOG Epitope

John R. Sedy, Sanford Burnham Prebys Medical Discovery Institute, USA
Cancer Mutations Targeting TNFRSF14 alter Microenvironment Checkpoint Interactions to Limit Tumor Clearance by Cytotoxic Cells

Greg M. Delgoffe, University of Pittsburgh, USA
Defects in Mitochondrial Biogenesis and Oxidative Function Underlie Tumor-Infiltrating T Dysfunction

B Cell Regulation of Autoimmunity

*__Antonio Lanzavecchia__, Institute for Research in Biomedicine, Switzerland
Mechanisms of Antibody Diversification

Kenneth Smith, University of Cambridge, UK
Predicting and Explaining the Future: A New Biology of Clinical Outcome in Autoimmunity?

Alicia Gonzalez-Martin, The Scripps Research Institute, USA
Short Talk: MicroRNA Control of B Cell Tolerance and Autoimmunity

Bonnie Huang, NHGRI, National Institutes of Health, USA
Short Talk: Dissecting T Follicular Helper Cell Development in vivo using CRISPR

Poster Session 3

THURSDAY, MARCH 30

Ten Years of Discovery of Th17 Cells: From Bench to Bedside

*__Vijay K. Kuchroo__, Brigham and Women's Hospital, Harvard Medical School, USA
Transcriptional Networks in Development of Th17 Cells

Dan R. Littman, HHMI, New York University School of Medicine, USA
Th17 Cells in the Gut Homoeostasis

Thomas Korn, Technical University Munich, Germany
Trans-presentation of IL-6 by Dendritic Cells - A Novel Mode of IL-6 Signaling – Is Required for the Priming of Pathogenic TH17 Cells in vivo

Daniel J. Cua, Merck Research Laboratories, USA
The IL-23-Th17 Immune Axis: From Mechanisms to Therapeutic Testing

Dhavalkumar D. Patel, Novartis Institutes for BioMedical Research, Switzerland
Therapeutic Targeting of Th17 Cells in Autoimmune Diseases

Systems Biology Approaches to Understanding Tolerance in Cancer and Autoimmunity

*__Frank Oliver Nestle__, Sanofi, USA
Deciphering the Rules of Engagement of Tissue Immunity

Alex Marson, University of California, San Francisco, USA
Decoding T Cell Circuitry

Meromit Singer, Broad Institute, USA
Short Talk: Identification and Validation of a Gene Module Specific for T Cell Dysfunction in Tumor via Population and Single-Cell Transcriptomics

Meeting Wrap-Up: Outcomes and Future Directions (Organizers)

Sponsored by Abide Therapeutics Inc., BioLegend, Inc., Genentech, Inc., Juno Therapeutics, MorphoSys AG, OncoMed Pharmaceuticals, Inc., Pfizer Inc. and Roche. This activity was supported by an educational grant from Celgene Corporation.

FRIDAY, MARCH 31

Departure