EuroSciCon

DAY 1

Scientific Tracks & Abstracts

15th International Conference on

Immunology

July 05-07, 2018 Vienna, Austria

DAY 1

JULY 05-06, 2018

Sessions

Immunotherapy and Vaccine | Diagnostic Immunology | Allergies and Hypersensitivities | Immunotoxicology | Immune Tolerance | Tumor Immunology | Autoimmune disease | Immuno Genomics | Nutritional Immunology | Clinical Immunology | Cancer Immunothrapy | Reproductive Immunology

Session Chair
Gilbert Glady
European Bio Immune(G)ene Medicine, France

Session Co-Chair
Nataliya M Kushnir
Institute of Integrative Immunology, Berkeley, USA

Session Introduction

Title: Foxp3 expression in iTreg cells is stabilized by C/EBP in inflammatory environments
Rho H. Seong, Seoul National University, South Korea

Title: Macromolecular nano immunoconjugates targeting checkpoint inhibitors CTLA-4 and PD-1 for treatment of breast cancer
Eggehard Holler, Cedars-Sinai Medical Centre , USA

Title: New hypotheses for the maintenance of peripheral T-cell tolerance.
Kim Varming, Aalborg University Hospital, Denmark

Title: Combination immunotherapy enhanced anti-tumor activities of XBP1, CD138 and CS1 antigens-specific CD8+ cytotoxic T lymphocytes against multiple myeloma and solid tumors.
Jooeun Bae, Dana-Farber Cancer Institute, Harvard Medical School, USA

Title: Unsaturated Squalene Content in Emulsion Vaccine Adjuvants Plays a Crucial Role in ROS-Mediated Antigen Uptake and Cellular Immunity
Ming-Hsi Huang, National Health Research Institutes , Taiwan

Title: Stratification of Patients with Primary Immunodeficiency Diseases: Relevance to Etiology and Therapy
Mariam Ali Al-Nesf Al-Mansouri, Hamad Medical Corporation, Qatar

Title: Ellagic acid modulates the expression of vaginal innate immune mediators
Wipawee Nittayananta, Thammasat University, Thailand

Title: Obesogenic environment inflammation-related insulin resistance
Paulo mendes, University Cruzeiro do Sul, Brazil

Title: Role of dietary fiber in immune modulation by short chain fatty acids
Jefferson Bitencourt Borges, University Cruzeiro do Sul, Brazil

Title: The role of glycosphingolipids in immune tolerance of pregnancy
John Yu, Chang Gung Memorial Hospital, Taiwan

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Rho H Seong et al., Insights Allergy Asthma Bronchitis 2018, Volume: 4
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FOXP3 EXPRESSION IN ITREG CELLS IS STABILIZED BY C/EBP IN INFLAMMATORY ENVIRONMENTS

Rho H Seong, Sung-Kyu Lee, Jieun Kim, Hyungyu Min and Kyungsoo Park

Seoul National University, Korea

Proper control of immune responses by Foxp3$^+$ regulatory T cells at inflamed sites is crucial for the prevention of immunopathology. TGF-β induced Foxp3+ regulatory T (iTreg) cells are generated in inflammatory environments as well as in steady state conditions. Inflammatory cytokines such as IFN-γ and IL-4 have an antagonistic effect on iTreg cell conversion. However, it is not known how naive CD4$^+$ T cells overcome the inhibitory environment in inflamed sites to differentiate into iTreg cells. Here, we show that CCAAT/Enhancer-binding protein (C/EBP) functions as a safeguard that enhances iTreg generation by dampening the inhibitory effect of IFN-γ and IL-4 on Foxp3 expression. We found that C/EBPβ is induced by retinoic acid and binds to the methyl-CRE sequence in the *Foxp3* TSDR to sustain its expression. C/EBPβ-transduced iTreg cells showed more potent suppressive activity in mouse disease models for experimental autoimmune encephalitis. We also found that C/EBPβ-transduced human iTreg cells exhibited more enhanced suppressor function in *in vitro* suppression assay. These results establish C/EBP as a new molecular target for stabilizing iTreg cells in inflammatory environments.

Biography

Rho H Seong has completed his PhD from Stanford University and Post-doctoral studies from Stanford University School of Medicine. He is the Director of Institute of Molecular Biology and Genetics, Seoul National University. He has published more than 90 papers in reputed journals and has served as an Editor-In-Chief of *Molecules and Cells*.

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MACROMOLECULAR NANO IMMUNOCONJUGATES TARGETING CHECKPOINT INHIBITORS CTLA-4 AND PD-1 FOR TREATMENT OF BREAST CANCER

Eggehard Holler[1,2], Anna Galstyan[1], Antonella Chiechi[1], Alexander V Ljubimov[1], Tao Sun[1], Ekaterina Shatalova[1], Keith L Black[1], Hui Ding[1] and Julia Y Ljubimova[1]

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Breast cancer (BC) is the most diagnosed malignancy and the second cause of cancer death in women in the United States. It is estimated that 252,710 new cases of BC will be diagnosed in 2017 and 40,610 women are projected to die from breast cancer in the US. Human epidermal growth factor receptor *HER2/neu* overexpression is found in 25-30% of human BCs and correlates with high aggression, high risk of relapse, high rate of metastasis, and poor survival. We have developed novel nano immune conjugate (NIC) versions with single conjugated anti-mouse CTLA-4 mAb (a-msCTLA-4) and anti-PD-1mAb (a-PD-1). The NIC activities were tested in BALB/c mice bearing subcutaneous (sc) syngeneic murine mammary carcinoma cells D2F2. This cell line is the parental line of the D2F2/E2 that expresses human HER2. Tumor growth was significantly inhibited when treated with NIC's containing a-CTLA-4 and tumour targeting anti-mouse TfR mAb (a-msTfR) compared to free a-CTLA-4. Inhibition was accompanied by reduced levels of CD4+FOXP3+ Tregs that are also targets of a-CTLA-4. Anti-PD-1 treatment was performed with animals carrying primary HER2+ D2F2/E2 sc tumours using the NIC P/a-msTfR/a-PD-1. Serum cytokine IL10, and especially IL-12, were significantly enhanced in comparison with treatment of a-pD-1 alone, and increased further during treatment with NIC P/a-msTfR/a-PD-1/AON c-Myc. In all cases, size of sc D2F2/E2 breast cancer was significantly reduced. The expression of IL-12 and IL-10 was also induced in mouse sera treated with free a-pD-1. Interestingly, NIC with AON to c-Myc induced higher cytokine expression. It is expected that a much stronger anti-tumour activity is observed for co-administration and/or codelivery of the antibodies and antisense drugs.

Conclusion: Treatment of HER2 breast cancer with nano immune conjugates increased significantly client survival.

Biography

Eggehard Holler, PhD, is Professor of Neurosurgery and Biomedical Sciences, and Director of Syntheses at Nanomedicine Research Centre, Department of Neurosurgery, Cedars-Sinai Medical Centre, Los Angeles, USA. He has completed his PhD from University of Regensburg, DE and has Postdoctoral appointments at Cornell and Berkeley. He was Professor of Biochemistry at University of Regensburg until 2005, and since 2008, he is Research Scientist and Professor at Cedars-Sinai Medical Centre, USA. He has served at several international universities as Visiting Professor, published more than 150 papers and was Interims Director of Institute of Biophysical Chemistry at Regensburg.

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NEW HYPOTHESES FOR THE MAINTENANCE OF PERIPHERAL T-CELL TOLERANCE

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According to the traditional models for peripheral T-cell tolerance, T-cells and regulatory T-cells (Tregs) have to be bound to MHC on the same antigen presenting cell (dendritic cell), whereby the Tregs downregulate the non-Tregs. Here, I will discuss new models/hypotheses where Tregs regulate non-Tregs directly in an antigen specific way, and I will further discuss how extracellular microvesicles may play a role in keeping the Tregs active. In modern immunotherapy, we use different biological drugs to combat cancer and autoimmune diseases. Unfortunately, these treatments attack the immune system in a very wide way and therefore they have some potential serious side effects. A nice goal for "immunologists" could be to develop antigen-specific modulators for cancer and autoimmune diseases. New models of the immune system will lead us in that direction.

Biography

Kim Varming is a Medical Specialist in Clinical Immunology. Since 2003 he has been the Medical Director for the department of Clinical Immunology at Aalborg University Hospital. He is a Board Member in The Danish Society for Clinical Immunology and in the Organization of Transfusion Centers in Denmark. He has published more than 60 papers in Peer Reviewed journals. His main research areas are General Immunology, Extracellular Vesicles and Cellular cancer-immunotherapy.

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Jooeun Bae et al., Insights Allergy Asthma Bronchitis 2018, Volume: 4
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COMBINATION IMMUNOTHERAPY ENHANCED ANTI-TUMOR ACTIVITIES OF XBP1, CD138 AND CS1 ANTIGENS-SPECIFIC CD8+ CYTOTOXIC T LYMPHOCYTES AGAINST MULTIPLE MYELOMA AND SOLID TUMORS

Jooeun Bae, Teru Hideshima, Nikhil Munshi and Kenneth Anderson

Dana-Farber Cancer Institute, Harvard Medical School, USA

Background: A recently completed Phase I/2a trials using a HLA-A2 XBP1, CD138 and CS1 multipeptide vaccine in smoldering multiple myeloma (SMM) patients demonstrated induction of antigen-specific CD8+ memory CTL. The antigens-specific Th1 type responses were further enhanced in the patients in combination with lenalidomide, as evidenced by increased Tetramer+ CTL and functional immune responses. Beyond myeloma, the multipeptide vaccine is in clinical trial to treat the patients with triple negative breast cancer by overexpression of the antigens in various solid tumours.

Objective: To expand therapeutic opportunities beyond HLA-A2 specificity, we have identified novel immunogenic peptides to HLA-A24 molecule, which is the second most dominant MHC Class I molecule in North America and the most frequent MHC Class I molecule in Asia.

Findings: Individual HLA-A24 peptides, XBP1 $UN_{185-193}$ (I S P W I L A V L), XBP1 $SP_{223-231}$ (V Y P E G P S S L), $CD138_{265-273}$ (I F A V C L V G F) and $CS1_{240-248}$ (L F V L G L F L W), induced the antigens-specific CTL with anti-tumour immune responses against both MM and solid tumours in an HLA-A24 restricted manner. CTL phenotypic characterization revealed the upregulation of immune costimulatory (OX40, GITR) and checkpoint antigens (PD1, CTLA, LAG3, TIM3). Peptide-specific CTL treated with clinical grade anti-OX40 or anti-PD1 displayed enhanced cytotoxicity and Th1 cytokines production to tumour cells. Furthermore, the central memory ($CD45RO^+CCR7^+$) CTL subset demonstrated enhanced functional activities to the respective tumour cells, with the highest increases induced by the OX40 stimulation or PD1 inhibition.

Significance: These results highlight the potential therapeutic application of a cocktail of HLA-A24 XBP1/CD138/CS1 peptides to evoke the antigens-specific CTL with a broad spectrum of responses against tumor and provide the framework for a combination immunotherapy with multipeptide vaccination and immune agonist or checkpoint inhibitor to inhibit immune suppression and enhance tumor-specific memory CTL activities in cancer patients.

Biography

Jooeun Bae has completed her PhD from Virginia Polytechnic Institute and State University and Postdoctoral studies from Harvard Medical School (Boston, MA) and Rush University Medical Center (Chicago, IL). She worked as an Assistant Professor at Rush University Medical Center, Senior Research Scientist at Cell Genesys Inc. (San Francisco, CA) and currently working as an Instructor at Dana-Farber Cancer Institute, Harvard Medical School. Her expertise has been Cancer Immunology and Immunotherapy, focused on discovery and development of cancer vaccine, which are currently in multiple clinical trials. She has published more than 22 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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UNSATURATED SQUALENE CONTENT IN EMULSION VACCINE ADJUVANTS PLAYS A CRUCIAL ROLE IN ROS-MEDIATED ANTIGEN UPTAKE AND CELLULAR IMMUNITY

Chung-Hsiung Huang, Chiung-Yi Huang and Ming-Hsi Huang
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In the context of vaccine immunogenicity, it is important to evaluate whether co-culturing candidate adjuvants can promote antigen uptake by antigen-presenting cells and lead to enhance vaccination feasibility. Here, we explored mechanistic reasoning toward embracing the interface between the physicochemical and biological signatures for core oil selection in vaccine immunogenicity. Our results showed that treatment of dendritic cells (DCs) and splenocytes with a squalene-based emulsion (referred as SqE) induced reactive oxidative species (ROS) production and resulted in an increase in apoptotic and necrotic cells in a concentration- and time-dependent manner. Furthermore, DCs co-cultured with cellular debris of SqE-pretreated splenocytes resulted in a higher level of ovalbumin (OVA) antigen uptake by DCs than those co-cultured with untreated splenocytes. Interestingly, the potency was rather attenuated when splenocytes pretreated with a typical ROS inhibitor, N-acetyl-cysteine. Notably, SqE possesses a high impact on eliciting ROS-mediated antigen uptake compared with a squalane-based emulsion (SqA). Concordantly, immunogenicity studies have shown that SqE is better able than SqA to activate antigen-presenting cells, and to enhance antigen-specific T-cell immunity. Accordingly, our results highlight the importance of unsaturated squalene core oil in the adjuvant activity of emulsions and offer insight into the design and development of vaccine adjuvants.

Biography

Ming-Hsi Huang obtained his PhD degree in 2004 in Materials Chemistry from University Montpellier I in France. He worked as a Postdoctoral fellow and an Assistant Investigator in Vaccine Research and Development Centre of NHRI. Currently, he is an Associate Investigator in NIIDV of NHRI, Taiwan. He has published more than 30 SCI journal articles, 1 book chapter, and granted 5 patents.

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STRATIFICATION OF PATIENTS WITH PRIMARY IMMUNODEFICIENCY DISEASES: RELEVANCE TO ETIOLOGY AND THERAPY

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Humoral immunodeficiencies are the commonest category of primary immunodeficiency disease and are characterized by variable degrees of recurrent infection, malignancy, allergy, and autoimmunity, ranging from almost absence of all serum immunoglobulin classes and also B cells to selective antibody deficiency and normal serum immunoglobulin. The 2017 international union of immunodeficiency societies (IUIS) classification differentiates between nine subgroups. Stratifying the patients based on clinical and blood biomarkers is needed to improve patients' care. Retrospective data analysis was done for 48 cases (different immunodeficiency disorders) followed in adult allergy and immunology unit, Hamad Medical Corporation over the last ten years. 27 cases with humoral immunodeficiency analyzed for IUIS classification, the inflammatory markers, the age of maturation at presentation, and associated micronutrients levels. Vitamin D was low in most of the cases. CRP was not statistically significant, but the mean and median is observationally higher in patients with bronchiectasis. CRP mean in bronchiectasis, other complications (arthritis, malignancy, and allergy) and no complications cases are 58±63.2, 9.3±6.12 and 5 and median= 21 (3.3-167), 6 (5-19) and 5 respectively (P=0.075). Age of presentation to health service is not an indicator of the presence of multiple comorbidity or severe outcome. Patients presented with pediatric age group have more incidence of bronchiectasis. Gender and smoking are not associated with increased rate of complications in this cohort (P>0.05). The current IUIS classification is limited regarding the continuity of care, despite being fundamental in the diagnosis and classifying the diseases. Long-term continuous evaluation and monitoring are needed in the care of patients with primary immunodeficiency for any evolving complications, and the guidelines in this area are scanty. Meaningful stratification may lead to better understanding of the etiology of the diseases, as well as help tailor effective therapy.

Biography

Al-Nesf MA has completed her MD from Sultan Qaboos University, Sultanate of Oman in 1999 and Arab Board of Medical Specialization in 2005 in Medicine. She finished speciality training in Pulmonary Medicine and in the Allergy and Clinical Immunology fellowships from 2005-2009. She is the Head of Allergy and Immunology Section, Hamad Medical Corporation, Qatar since 2016. Currently, she is advancing her academic career by studying the degree of Cellular and Molecular Medicine (MSc) (R) in the Faculty of Biomedical Science at the University of Bristol, UK. She has published more than six papers in reputed journals and multiple abstracts.

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ELLAGIC ACID MODULATES THE EXPRESSION OF VAGINAL INNATE IMMUNE MEDIATORS

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Objective: To investigate the *in vitro* effects of ellagic acid on vaginal innate immunity.

Methods: Vaginal epithelial cell culture was performed in the presence or absence of ellagic acid. Expression of human hBD2 and SLPI was determined at both transcriptional and translational levels. In addition, expression of various cytokines and chemokines including IL-2, IL-4, IL-6, IL-8, IL-10, CCL-2, CCL-5, TNF- α, IL-1β, and IFN-γ were investigated using Luminex assay. Cytotoxicity of ellagic was also determined using MTT assay.

Results: The expression of hBD2 mRNA was significantly increased at both transcriptional and translational levels in response to ellagic acid ($p<0.05$). SLPI mRNA expression was significantly increased in the presence of ellagic acid. The expression of IL-2 was induced in response to ellagic acid in a dose-dependent manner. In contrast, no changes in the expression of other cytokines/chemokines were observed. No cytotoxicity of ellagic acid was noted on vaginal epithelial cells.

Conclusions: We conclude that vaginal epithelial cells can recognize a plant-derived compound. Innate immune factors produced by vaginal epithelial cells are differentially expressed in response to ellagic acid. Thus, plant-derived compounds such as ellagic acid may be useful to be developed as an immunomodulatory agent to improve vaginal health.

Biography

Wipawee Nittayananta has obtained her Doctoral degree from Freie Universitaet Berlin, Germany and completed her PhD from the University of Washington, USA. She has published more than 40 papers in reputed journals and has been serving as an Editorial Board Member of repute.

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OBESOGENIC ENVIRONMENT INFLAMMATION-RELATED INSULIN RESISTANCE

Mendes P[1], Bitencourt, J B[1] and Heibel A B[2]

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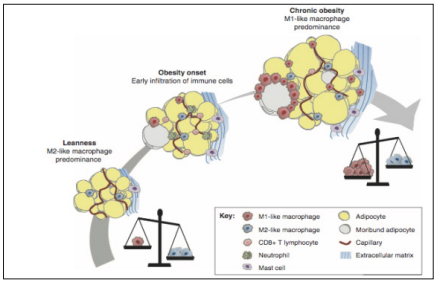
[2]Universidade de Brasília, Brazil

Obesity has been reaching alarming levels in the past ten years. Moreover, WHO already consider such pandemic event as worthy of concern due to the expansive costs do human and public health. Among with the malignant consequences related to a chronic obesogenic condition, insulin resistance takes place. One of the main manifestations of this clinical condition is due to a low-grade systemic inflammation, where adipocytes keep being stimulated to hypertrophy and hyperplasia by lipoprotein lipase action, triggered by the constant hyperinsulinemic environment. Research shows that structural changes can generate hypoxia, activating thus the hypoxia-inducible factor 1 (HIF-1) and culminate in the M1 macrophage polarization. Notably, these leukocytes can produce and secrete tumor necrosis factor alpha (TNF-1 α), interleukin-12 and interleukin-1β. TNF-α in particular can trigger insulin receptor (IR) action and self-phosphorylate it in serine residues, instead tyrosine residues. Since IR belongs to tyrosine-kinase class, an inadequate phosphorylation can make it inefficient by generating an inappropriate response. Data suggests that this self-phosphorylation is crucial to the following intracellular reactions mediated by PDK and PKC, resulting thus in Glucose Transporter 2 and 4 (GLUT-2 4) releases from its vesicle and active transportation to cell cytoplasm. Furthermore, the constant stimulation and phosphorylation in serine residues, promoted by TNF-1 α release by M1 macrophages induced by adipocyte growth and accretion can lead to insulin resistance among low-grade inflammation.



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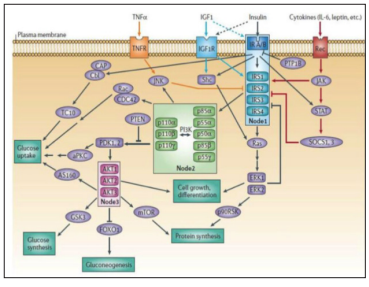

Elise Dalmas, Karine Cle'ment and Miche`le Guerre-Millo. Defining macrophage phenotype and function in adipose tissue. Trends in Immunology, July 2011, Vol. 32, No. 7, 307-314

Biography

Paulo Mendes is a Nutritionist, graduated from the University Center of Brasília. He has Specialization in Exercise Physiology from the University of Brasília and Postgraduated in Functional Clinical Nutrition from University Cruzeiro do Sul and Positive Vitality Functional Nutrition Center. He works in clinical, sports, professional and recreational athletes, functional nutritional services, as well as teaching classes, lectures and workshops.

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ROLE OF DIETARY FIBER IN IMMUNE MODULATION BY SHORT CHAIN FATTY ACIDS

Jefferson Bitencourt[1], Paulo Mendes[1] and Lucas Salgado[2]

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In the last 50 years the population has been affected by chronic non-transmissible diseases (CND's) whose chronic low-grade inflammatory base is well elucidated. In addition, it is observed that CND's are strongly associated with the western dietary pattern, and that adjuvant to these diseases there are presence of gastrointestinal symptoms. It is a characteristic of the Western diet, the low fiber intake due to the reduced consumption of unprocessed or minimally processed foods of plant origin. In this context, the role of dietary or supplementary fibers on immune regulation is known, especially when they are metabolized by probiotic bacteria, and converted to short chain fatty acids (SCFA's). Among SCFA's, butyrate has the greatest impact on the maintenance of intestinal selective permeability in two ways: when it is metabolized by the intestinal L-cell, it stimulates the release of GLP-2 (Glucagon Like Peptide 2), responsible for the maintenance of tight junctions; and by the stimulation of G protein receptors (GPRC), butyrate appears able to signal the NACHT, LRR and PYD domains-containing protein 3 (NALP3) pathway involved in the inflammasome system, stimulating the production of IL-18, therefore improving epithelial integrity. Other SFCA's such as acetate promote the differentiation of goblet cells as well as increase mucus production. The role of these bacterial metabolites on the stimulation of IgA production by B lymphocytes and in the promotion of T_{reg} cell stimulation is also evidenced, resulting in a higher immunological tolerance to food antigens. T_{reg} cells, when metabolizing butyrate, produce IL-10, which plays local anti-inflammatory effect. Finally, these SFCA's shows an anti-inflammatory potential by inhibiting the production of NF-kb, TNF, IL-6 and Interferon in macrophages. Thus, it is necessary improve the intake of fiber-rich foods aiming to reduce chronic low-grade inflammation which is one of the major culprits of CND's.

Biography

Jefferson holds a degree in Nutrition from the University of Brasília (2013). Currently, he is a Nutritionist - GENES Nutrition Consulting. He has an experience in Nutrition, with emphasis in Nutrition Biochemistry. He holds a Postgraduate degree in Functional Clinical Nutrition from the VP - Nutrition Consulting (2016) and is currently pursuing a Postgraduate degree in Sports Nutrition and Exercise Physiology from UFG and Clinical Nutrition Applied to Pathologies Based on Orthomolecular Practice. He is a Professor of Post-graduation in VP Functional Nutrition since 2017.

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THE ROLE OF GLYCOSPHINGOLIPIDS IN IMMUNE TOLERANCE OF PREGNANCY

John Yu

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[2]Institute of Cellular and Organismic Biology, Academia Sinica, Taiwan

The overall objectives of our studies are to interrogate the roles of pregnancy-associated glycosphingolipids (GSLs) in immune tolerance of pregnancy, and exploit their potential immune modulatory activities. Although it was demonstrated that one of the most prevalent tumor associated GSLs (Globo H ceramide) acts as an immune checkpoint to suppress T and B lymphocytes, and as an angiogenic factor to promote tumor growth in tumor microenvironment, very little is known about the role of this and other GSLs in pregnancy. An analogy to the immune suppressive milieu of the host microenvironment in tumor tissues is the immune tolerance of pregnancy. A deeper understanding of the events and the key regulators involved in the establishment of a healthy embryo implantation remains a goal only incompletely realized. We expect that GSLs mediated transfer from human microvilli, trophoblasts, or stromal mesenchymal stem cells from either maternal chorio-decidua or fetal origin, could be incorporated into immune cells and that certain GSLs may facilitate immune tolerance, leading to successful implantation of embryo. Specifically, we employ the new technology platforms, state of the art mass spec. facility, as well as expertise in reproductive medicine and tumor immunology, to explore an innovative concept concerning the embryo/endometrium crosstalk. In addition, similar mechanistic investigation of the immune checkpoint and angiogenesis activities will be carried out for uterine tissues and compared. Through such endeavours, our studies will likely provide a roadmap for heretofore un-chartered territory of research regarding the involvement of GSLs in early embryogenesis and the key regulators involved in the establishment of a healthy pregnancy.

Biography

John Yu is distinguished Chair Professor/Director at Institute of Stem Cell/Translational Cancer Research, CGMH. He is also distinguished Visiting Research Fellow at Institute of Cellular and Organismic Biology, Academia Sinica, and was the Director for the same Institute (2002-2009). He is the founding President for Taiwan Society for Stem Cell Research. He was elected to serve in many ISSCR Committees USA, the Steering Committee of Asia-Pacific Stem Cell Network, and advisor for Stem Cell Biology, Kumamoto Univ. He was Director of Exp. Hematology (1998-2002) at Scripps Research Institute, USA. He received an established Investigatorship Award from American Heart Assoc. and many other awards.

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DAY 1

Workshop

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DEVELOPING NEW TB VACCINE STRATEGIES TO TAKE AIM AT UNNATURAL MUCOSAL IMMUNITY

Zhou Xing
McMaster University, Canada

Mycobacterium tuberculosis **(Mtb) has evolved with robust mechanisms to counter host defence mechanisms, and the world is still facing TB epidemics despite decades of use of BCG vaccine and antibiotics. New TB vaccines are needed. In spite of major progress made in developing TB vaccine strategies with a dozen novel vaccines currently in the clinical pipeline, we still do not have an effective TB vaccine. This raises the question whether any major breakthroughs can be achieved without making a departure from the current strategy which creates a state of near-natural immunity, imitating the natural immunity developed after Mtb infection. Mounting new evidence suggests that an effective new strategy ought to induce a state of all-around unnatural immunity consisting of trained innate immunity, tissue resident memory T cells, and anti-Mtb surface antibodies in the respiratory mucosa. We will present the current state of knowledge and progress.**

Biography

Zhou Xing was trained in Medicine and Anatomic Pathology in China, and subsequently completed his PhD in Immunology at McMaster University, Canada. Since 2007, he has been Full Professor at McMaster Immunology Research Centre of McMaster University. He is an author of up to 175 peer-reviewed publications.

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DAY 2

Scientific Tracks & Abstracts

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DAY 2

JULY 06-07, 2018

Sessions

Clinical Immunology | Immune Tolerance | Allergies and Hypersensitivities | Diagnostic Immunology | Immunotoxicology | Neuroimmunology | Immunotherapy and Vaccine | Microbial Immunology | Tumor Immunology | Cellular Immunology

Session Chair
John Yu
Chang Gung Memorial Hospital, Taiwan

Session Co-Chair
Yaffa Mizrachi Nebenzahl
Ben Gurion University of the Negev, Israel

Session Introduction

Title: **Immunostimulating activity of bio-polymers isolated from Taxus cuspidata and a bacterial strain Rhizobium massiliae**
Jae Kweon Park, Gachon University, Republic of Korea

Title: **Delivery of checkpoint inhibitors with nano immunoconjugates for activation of local brain tumor immune system for glioma treatment**
Julia Ljubimova, Cedars-Sinai Medical Centre USA

Title: **Valvular Interstitial Cell Innate Immunity in the Pathobiology of Calcific Aortic Valve Disease**
Xianzhong Meng, University of Colorado Denver, USA

Title: **Influence of bacteriophages on the immune system – comparative study**
Andrzej Siwicki, University of Warmia and Mazury in Olsztyn, Poland

Title: **Immunomics technologies using protein and peptide microarrays – for antibody profiling**
Andreas Weinhäusel, Austrian Institute of Technology, Molecular Diagnostics, Vienna, Austria

Title: **Trauma-induced X-linked white blood cell selection contributes to a sex-biased innate immune response in humans**
Zoltan Spolarics, Rutgers-New Jersey Medical School, USA

Title: **Hydrogen Peroxide Triggers a Dual Signaling Axis To Selectively Suppress CXCL11/CXCR3 – activated Human T Lymphocyte Migration**
Stephen G Ward, University of Bath, UK

Title: **Immunosuppressive Effect of Tolerogenic Dendritic Cells on Mice Skin Allograft Pulsed by Liver X Receptor Agonist and The Potential Mechanism**
Haiyan Xu, Third Affiliated Hospital of Soochow University, China

Title: **Immunological characterisation of vaccines based on Generalised Modules for Membrane Antigens (GMMA)**
Francesca Mancini, Glaxo Vaccines Institute For Global Health (GVGH), Italy

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IMMUNOSTIMULATING ACTIVITY OF BIO-POLYMERS ISOLATED FROM TAXUS CUSPIDATA AND A BACTERIAL STRAIN RHIZOBIUM MASSILIAE

Jae Kweon Park, You Jin Hwang and Dae Young Kim

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The aim of this study is to investigate the isolation and characterization of biochemical properties of water-soluble extracellular polysaccharides (WSP) isolated from a novel bacterial strain *Rhizobium massiliae* CA-1 and polyhydric alcohol (PAL) isolated from *Taxus cuspidata*, respectively. The primary monosaccharide composition of the WSP and PAL was determined to be glucose by HPAEC. Interestingly, no significant amount of any other sugars was observed, however, glycerol and xylitol were identified as the main sugar alcohols in PAL. We evaluated immunomodulatory effects of WSP and PAL on RAW 264.7 macrophage activation. The results showed that the WSP and PAL dose-dependently induced the release of the pro-inflammatory cytokines such as TNF-α and IL-6, respectively. Furthermore, treatment of RAW 264.7 cells with PAL for 24 h remarkably increased the phosphorylation levels of ERK, p38 and JNK in a dose-dependent manner, whereas the total protein levels of ERK (t-ERK), p38 (t-p38) and JNK (t-JNK) remained unchanged. In addition, WSP induced nitric oxide synthase (iNOS) expression and increased the production of nitric oxide (NO). Intriguingly, WSP remarkably increased the mRNA expression of Toll-like receptor-2 (TLR-2) and the phosphorylation of MAPKs (ERK, JNK and p38) in RAW 264.7 cells. Furthermore, our results clearly demonstrate that PAL stimulates the immune response in RAW 264.7 cells through the activation of MAPKs (ERK, p38 and JNK) signaling pathway. To the best of our knowledge, this is the first study to demonstrate the primary structure and immune-stimulating activities of PAL from the fruit of *T.cuspidata*. In addition, WSP activates macrophages to secrete pro-inflammatory cytokines and induces iNOS expression via the activation of the TLR-2/MAPKs signaling pathways. Conclusively, we suggest that WSP of *R. massiliae* CA-1 and PAL of *T. cuspidata* can be a new immunomodulatory biopolymers enhancing the early innate immunity. Further studies of other potent biopolymers such as chitosan and beta-glucan are under-going.

Biography

Jae Kweon Park has completed his PhD from Shimane University in 1998, Japan, Postdoctoral and Research Associate studies from The Johns Hopkins University, McGill University and University of Rochester (1998~2007). He is currently working as Professor of the Gachon Univeristy from 2011, Korea. He has published more than 50 papers in reputed journals and has been serving as an Editorial Board Member of the *Journal of Chitin and Chitosan*, Korea.

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DELIVERY OF CHECKPOINT INHIBITORS WITH NANO IMMUNOCONJUGATES FOR ACTIVATION OF LOCAL BRAIN TUMOR IMMUNE SYSTEM FOR GLIOMA TREATMENT

Julia Y Ljubimova[1], Anna Galstyan[1], Antonella Chiechi[1], Ekaterina Shatalova[1], Tao Sun[1], Vladimir A Ljubimov, Keith L Black[1], Hui Ding[1] and Eggehard Holler[1,2]

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Check point antibody CTLA-4 and PD-1 act on regulatory T cells (Treg) to remove their suppression of cytotoxic T lymphocytes (CTL) that start attacking the tumor. However, treatment of gliomas with combination of these antibodies was not successful because as other antibodies they do not cross the blood brain barrier (BBB). Upon this treatment, only systemic immune response was activated. The technology we had developed is focused on engineering and preclinical testing of such nanoimmunotherapeutics to treat brain cancers which activated both systemic and local brain tumor immune systems. Synthesis of immuno-nanoconjugates: immuno-nanoconjugates (INC) crossing BBB, P/PEG/msTfR/anti-CTLA-4 and P/PEG/msTfR/anti-PD-1 were synthesized. They are based on natural polymer, poly β (L-malic acid) (P), and contain anti-transferrin receptor antibody (MsTfR). Physico-chemical, pharmaceutical, and toxicological parameters of INCs were determined. Brain tumor treatment: syngeneic GL261 glioma cells (20,000) were intracranially inoculated into C57/BL mice. Six treatment groups were injected with either PBS, anti-PD-1 and anti-CTLA-4 as a control, or polymer-conjugated anti-PD-1(P/PD-1), anti-CTLA-4 (P/CTLA-4) or a combination of polymers with antibodies, (P/CTLA-4 + P/PD-1) at 10 mg/kg, 5 times I V. Immuno-nanoconjugates P/CTLA-4 and P/PD-1 significantly improved survival of brain tumor-bearing mice compared to free anti-CTLA-4 and anti-PD-1 ($p<0.04$ and $p<0.004$, respectively). The combination P/CTLA-4 + P/PD-1 showed the highest survival efficacy compared with CTLA-4, PD-1, and PBS groups ($p<0.001$, $p<0.04$, and $p<0.0001$, respectively). Flow cytometry analysis of T cell population in the brain tumor revealed reduction of the total number of CD4+ T-cells in animals treated with P/PD-1 and combination P/CTLA-4 + P/PD-1. The fraction of Tregs (CD4+FOXP3+) was also reduced by all polymer conjugates compared to free antibodies. Activation of CD8+ T-cells (CD8+IFNγ+ and CD8+CD69+) was increased by polymer-conjugated anti-CTLA-4/PD-1 and combination therapy. Animals treated with polymer-conjugated anti-PD-1 and combination treatment showed significant decrease in PD-1 expression by CD8+ cells compared to controls. Multiplex assay to measure cytokine response to treatment demonstrated significant increase in the expression of IL-1β, IL-2, IL-10, TNFα, IL-6, IL-12, and IFNγ in the brain and serum after combination therapy.

Conclusion: **Brain tumor treatment with immuno-nanoconjugates that can cross BBB significantly increased animal survival.**

Biography

Julia Y Ljubimova is Professor of Neurosurgery and Biomedical Sciences, and Director of Nanomedicine Research Center, Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, USA. She has been working in clinical and basic cancer research during her entire career. Her major scientific discoveries are: 1) The cancer biomarkers as tools for developing new nanomedicine imaging agents and drugs against primary and metastatic tumors and 2) The development of nano imaging and therapeutic agents that are crossing multiple biological barriers including blood brain barrier (BBB). Nano immunology and nano toxicology are novel important subjects of the fight against tumors and inflammation, which are currently studied in the Nanomedicine Research Center. Her research is supported by National Institutes of Health/National Cancer Institute, private and industry grants. She is the author of over 100 publications, reviews and book chapters as well as an inventor on twelve issued patents, and patent applications.

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VALVULAR INTERSTITIAL CELL INNATE IMMUNITY IN THE PATHOBIOLOGY OF CALCIFIC AORTIC VALVE DISEASE

Xianzhong Meng, Lihua Ao and David A Fullerton
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Calcific aortic valve disease (CAVD) is one of the most prevalent cardiovascular diseases in the elderly and is becoming an increasingly important health issue with the emerging longevity. Chronic inflammation and progressive calcification of the aortic valve leaflets cause valvular dysfunction and heart failure. Currently, pharmacological intervention of CAVD progression is unavailable and the interaction between the pro-inflammatory and pro-osteogenic mechanisms in aortic valve calcification is poorly understood. Aortic valve interstitial cells (AVICs) are actively involved in valvular calcification. Our studies found that human AVICs express osteogenic proteins (including BMP-2 and TGF-β1) in response to stimulation of Toll-like receptor (TLR) 2, 3 or 4. Further, the TLR-mediated osteogenic response in human AVICs leads to pro-osteogenic reprogramming characterized by the expression of Runx2 and alkaline phosphatase, and formation of calcium deposits. These studies uncovered a novel mechanistic role of the AVIC innate immunity in aortic valve calcification. Our recent work identified several endogenous factors that can elicit the osteogenic responses in human AVICs through TLRs, including oxidized low-density lipoprotein, biglycan and matrilin 2. While these endogenous factors utilize distinct TLRs, they induce the osteogenic responses through common signalling pathways, mainly the NF-κB and ERK1/2 pathways. Our findings demonstrate that damage-associated molecular patterns are capable of inducing the osteogenic responses in human AVICs and that the innate immune receptors have novel functions in modulating the osteogenic responses in human aortic valve cells. These findings suggest that AVIC TLRs may play an important role in the pathogenesis of CAVD and that modulation of the common signalling pathways utilized by TLRs may have therapeutic potential for suppression of CAVD progression.

Biography

Xianzhong Meng has been graduated from Harbin Medical University, Harbin, China in 1978. He received MS in 1981 and PhD in 1985 from the same university. He then received Postdoctoral training at Cleveland Clinic, Cleveland, USA. He became an Investigator in the Cardiothoracic Inflammtion Research Laboratory, Department of Surgery, University of Colorado Denver in 1990. He is currently a Tenured Professor in the Department of Surgery and the Director of Cardiothoracic Inflammation Research Program at University of Colorado Denver. His current research focusses on the impact of aging on myocardial ischemia/reperfusion injury and the molecular mechanism of heart valve calcification. His research is supported continuously by NIH grants. He is the author/co-author of over 160 papers published in peer-reviewed journals, and he has given over 100 presentations, invited lectures and seminars in universities, professional societies, and international conferences.

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INFLUENCE OF BACTERIOPHAGES ON THE IMMUNE SYSTEM: A COMPARATIVE STUDY

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Bacteriophages are ubiquitous, specific viruses. They attack sensitive bacteria. Elements of their capsids bind to specific molecules on the target host surface. Bacteria that do not have such a receptor can't be attacked. Their use as therapeutics of infectious diseases of animals and people refers to the times before antibiotic therapy. The ability of phages to kill bacterial cells is the basis of the idea of using them as therapeutic agents. Innate immunity is rarely discussed in terms of phage therapy. New research has demonstrated that the host immune response is an important factor in the effectiveness of phage therapy. In recent years, there have been reports about the interaction of bacteriophages with the immune system. It mainly concern people. Our studies have demonstrated the immunomodulatory effect of bacteriophages on lower vertebrates.

Biography

Andrzej K Siwicki is Head of Department, Microbiology and Clinical Immunology, Faculty of Veterinary Medicine, University of Warmia and Mazury; Department of Pathology and Immunology, IFI in Olsztyn, Poland. He is the author of over 500 original papers in reputed journals and about 200 scientific communications (index-h 32, index of citation: 4502). His fields of interest are modulation of defence mechanisms and protection against diseases by natural and synthetic products in animals, influence of pollutants on the cell-mediated immunity and restoration of immunity after suppression induced by xenobiotics. He developed a new possibility in the comparative immunotoxicology for control of effect of xenobiotics and pharmaceutical products on the defence mechanisms and protection against diseases. He attended scientific missions in USA, Japan, France and Israel, was a Co-ordinator of USDA and FAO projects and he is Professor conferring of 14 PhDs and 4 DScs.

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IMMUNOMICS TECHNOLOGIES USING PROTEIN AND PEPTIDE MICROARRAYS – FOR ANTIBODY PROFILING

Andreas Weinhausel, Regina Soldo, Peter Hettegger, Silvia Schonthaler, Lisa Milchram, Ronald Kulovics, Manuela Hofner, Christa Noehammer, Stephan Pabinger and Klemens Vierlinger

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An individual's antibody profile or immunome is stable over years but can change in respect to pathological changes as well as these changes can be triggered by vaccination/ immunization or different therapeutic intervention. Antibody profiling on high density protein and peptide arrays has been shown to elucidate pathophysiological alterations in various indications like auto-immune, cancerous, and neurological disease, as well as in allergy and infectious disease. Protein-arrays are usually generated using recombinant expression, and have limited flexibility – but can be customized when proteins are available. Peptide-arrays can be easily customized to present proteins deduced from sequences, without the need of protein-expression. We have setup immunomics discovery technologies using protein- and peptide-microarrays (presenting 32000 spots or up to 6 million peptides, respectively) as well as targeted multiplexed technologies for validation of findings. These are all customizable and affordable even when discovery studies are done with a small number of samples. In line with the different technologies we have established and optimized bioinformatics and laboratory methods and can provide complete workflows from design, experimental setup and sample analysis till data-analysis. This is also true when we have lower multiplexed technologies available providing targeted micro-arrays (presenting hundreds-thousands antigens) as well as bead-arrays in an up to 500-plexed format for marker-refinement and confirmation. For broader validation and clinical studies we have both micro- and bead-array technologies established for analyzing large series of samples in 96-well microtiter-plates in medium-plexed assays. We have established and optimized different methods and combined these to a full workflow for providing modules as well as the entire pipeline for antibody-based analysis and diagnostics, which can be conducted with 10µl amounts of serum or plasma as well as using other body fluids like saliva.

Biography

Andreas Weinhausel is a Biotechnologist and Specialist in Human Genetics. He has more than 20 years' experience in Molecular Diagnostics. He has worked at the Children's Cancer Research Institute, Vienna (1995-2004); he is specialized in Human Molecular Genetics Diagnostics of Syndromal and Hereditary Neoplastic Disease. Since 2004, he has been working in the Molecular Diagnostics unit at the AIT-Austrian Institute of Technology and his focus is on DNA-methylation and protein biomarker development for cancerous and other systemic human disease using omics discovery and high throughput validation technologies. He is also an Associate Professor for Molecular Biology at the University of Natural Resources and Applied Life Sciences, Vienna.

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TRAUMA-INDUCED X-LINKED WHITE BLOOD CELL SELECTION CONTRIBUTES TO A SEX-BIASED INNATE IMMUNE RESPONSE IN HUMANS

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Sex-related disparities in the immune response manifesting female disadvantage in autoimmune diseases whereas improved outcomes over males following injuries and infections are well known. Whereas the role of sex hormones in modulating the immune response is well accepted, the potential contribution of X chromosome (ChrX)-related sex differences in the context of common genetic polymorphisms has not been well investigated. The fact that females carry two parental ChrXs whereas males carry only one suggests sex differences in the load of common polymorphic alleles. Furthermore, random ChrX inactivation, which is unique to females, results in cellular mosaicism for the expression of X-linked polymorphic alleles, possibly causing additional sex-related differences in cellular variability. Thus, we tested whether ChrX mosaicism manifests skewed white blood cell responses following injuries in humans. Serial blood samples were analysed for ChrX inactivation-ratios (XCI-R) testing methylation at the polymorphic HUMARA locus in neutrophils and lymphocytes from female trauma patients (n=99). About a third of the patients presented trauma-induced change in XCI-R of 30% or greater over initial during the hospital course. XCI-R changes correlated with the severity of trauma, ventilator support and pneumonia. XCI-R kinetics of neutrophils and lymphocytes indicated that more marked changes occurred during the earlier phases of injury or at the onset of post-injury complications like sepsis or pneumonia. During the recovery phase, XCI-R tended to return to initial values similar to that found at admission. The findings indicate that during the innate immune response, female patients may manifest acute and reversible immune cell selection through subtle phenotypic differences driven by respective polymorphic parental ChrXs. X-linked cellular mosaicism in females with variable responsiveness to dynamically changing pathophysiological conditions, together with an apparent lack of this mechanism in males, implies differences in immuno-modulatory mechanisms, which may contribute to sex-based outcome differences in the critically ill.

Biography

Zoltan Spolarics has received his MD from the Semmelweis Medical University in 1980 and PhD degree from the Hungarian Academy of Sciences in 1989. He had postdoctoral trainings at Semmelweis Biochemistry Institute and later in the USA at the Medical College of Virginia, Richmond VA then Louisiana State University Medical Center, New Orleans LA. Since 1993, he is a principal investigator at Rutgers-New Jersey Medical School, Newark NJ, USA where he leads NIH-sponsored studies investigating various aspects of the innate immune response. He published over 80 peer-reviewed papers in reputed journals, has been serving on NIH scientific review panels and journal editorial boards, Shock and Critical Care Medicine.

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HYDROGEN PEROXIDE TRIGGERS A DUAL SIGNALING AXIS TO SELECTIVELY SUPPRESS CXCL11/CXCR3 –ACTIVATED HUMAN T LYMPHOCYTE MIGRATION

Jennifer A Ball[1], Will Wood[2] and Stephen G Ward[1]

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Reactive oxygen species (ROS) are known to influence the outcome of T cell responses. Depending on concentration, exposure time, and microenvironment, the effects of ROS on T cells can be very distinct and affect a variety of physiological events, including cell proliferation, host defense, differentiation, apoptosis, senescence, and activation of growth-related signaling pathways. T cells can produce low levels of H_2O_2 upon TCR and chemokine stimulation, which have been shown to facilitate T cell activation. Additionally, T lymphocytes also express NADPH oxidase enzymes NOX_2 and DUOX1 that catalyze the reduction of molecular oxygen to generate superoxide O_2, which can dismute to generate ROS species. These ROS participate in host defense by killing or damaging invading microbes. Additionally, in several human pathologies, including cancer and a variety of auto- immune disorders, high levels of pro-oxidants are known to induce T lymphocyte hypo responsiveness. H_2O_2 is an early danger cue required for innate immune cell recruitment to wounds, but little is known about the effect of H_2O_2 on migration of human adaptive immune cells to sites of inflammation. However, oxidative stress is known to impair T cell activity, induce actin stiffness, and inhibit cell polarization. In this study, we show that H_2O_2 selectively impedes chemokinesis and chemotaxis of previously activated human T cells to CXCL11, but not other chemokines. This deficiency in migration is due to a reduction in inflammatory chemokine receptor CXCR3 surface expression and cellular activation of lipid phosphatase SHIP-1. Moreover, pharmacological evidence indicates that H_2O_2 acts via a Src kinase to activate the lipid phosphatase SHIP-1, a negative regulator of PI3K signaling. Thus, while H_2O_2 can function as an early recruitment trigger for innate immune cells, it appears to operate as an inhibitor of T lymphocyte immune adaptive responses that are not required until later in the repair process.

Biography

Stephen Ward is Head of Pharmacy and Pharmacology at the University of Bath and has held several personal fellowships and received funding from the Wellcome Trust, MRC, BBSRC and Royal Society. He has published over 110 primary research articles and reviews in the field of Inflammatory Cell Biology and has supervised over 35 PhD students. This research has often involved close collaboration with industry that has enhanced student training by allowing them to spend time in industrial laboratories.

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IMMUNOSUPPRESSIVE EFFECT OF TOLEROGENIC DENDRITIC CELLS ON MICE SKIN ALLOGRAFT PULSED BY LIVER X RECEPTOR AGONIST AND THE POTENTIAL MECHANISM

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In the previous studies, we found that dendritic cells induced from mice bone marrow cells pulsed by liver X receptor agonist (T0901317) showed tolerogenic characteristics. To further investigate the suppressive effect of T-tDCs, mice skin transplantation model was applied. T-tDCs were tested by flow cytometric assay and mixed lymphocyte reaction. Then T-tDCs were stained by CM-DiL and injected into mice by caudal vein. At day -1, -3, -5, -7, peripheral blood, spleens, lymph nodes, kidneys, livers and skin were collected for observing the distribution of T-tDCs. C57BL/6 mice were recipients, BALB/c mice were donors and mice flap transplantation model were established. Total 5 groups were set up, high dose treated group (CM-DiL-tDC, 5×10^7, HD-group), median treated group (1×10^7, MD-group), low dose treated group (2×10^6, LD-group), CsA-group, and PS-group, respectively and 6 mice were in each group. The corresponding concentration of CM-DiL-tDC cells was injected to mice by caydal vein at day-1 and day-8 after transplantation of three different dose treated groups. The status of allograft rejection was evaluated at day-8, -9, -11, and -14 of one mouse in each group. At day-14, all mice were sacrificed. Blood sampling, serum, spleens, skin flap grafts, livers, kidneys and axillary and inguinal lymph nodes were all collected for detection. TGF-β1 and IL-10 in tissues were detected by IHC; CD4 and FoxP3 expression in tissues were detected by confocal. Results indicated that, CM-DiL-tDC could be found at day -5,-7 in PB, every day in spleens and livers, only day-5 in lymph nodes, day-3,-5,-7 in skins, and no detection in kidney. Compared with PS-group, rejection scores at day-9,-11 and -13 in CsA group, rejection score of HD-group significantly decreased ($P < 0.05$), respectively. And TGF-β1 expression in CsA-group, HD-group and LD-group significantly increased, compared with PS-group ($P<0.05$, $P<0.01$, respectively); IL-10 expression in CsA-group, HD-group, MD-group and LD-group all significantly increased, compared with PS-group (all $P < 0.01$), and IL-10 expression in HD-group even much higher than that in CsA group. Much more CD4+ FoxP3+ cells were found in skin allograft tissues of HD-group at day-9, -11 and -13 after transplantation. It could be concluded that local production of TGF-β1 and IL-10, and the induction of Tregs should be the fundamental way of T-tDC during its suppressive function.

Biography

Haiyan Xu has devoted herself on relative study of kidney transplantation, including rejection, opportunistic viral infection and induction of immune tolerance, since she got PhD. Taking B cell activating factor (BAFF) as the research breakthrough point, she found BAFF signalling system involve in the progression of renal allograft rejection and blockade of BAFF signalling should become the potential anti-rejection options; BAFF signalling crosstalk with HCMV/TLR9 in renal transplant recipients, which would decrease the long-term outcome of renal allograft, and mouse DC induced by liver X receptor agonist show immunosuppressive effect, which differ from natural tolerance DC.

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IMMUNOLOGICAL CHARACTERISATION OF VACCINES BASED ON GENERALISED MODULES FOR MEMBRANE ANTIGENS (GMMA)

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GSK Vaccines Institute for Global Health (GVGH) aims to develop affordable vaccines to fight neglected bacterial diseases prevalently affecting developing countries. GMMA (generalized module for membrane antigens) are outer membrane blebs naturally released from Gram-negative bacteria, genetically modified to induce hyper-blebbing and reduce the endotoxic activity of lipopolysaccharides. We have developed a panel of immuno-assays to assure full characterization of GMMA based vaccines. Such methods have been used in pre-clinical studies and are important to support GMMA clinical testing. Immunogenicity of sera is assessed by ELISA, while functionality of antibodies is characterized through a newly developed high-throughput luminescence-based serum bactericidal assay (L-SBA), able to detect surviving bacteria by measuring their ATP. L-SBA considerably shortens assay time, facilitates data acquisition and analysis, and reduces the operator dependency, avoiding the plating and counting of CFUs. We showed, both in pre-clinical and clinical studies that GMMA based vaccines targeting different pathogens such as *Shigella, Salmonella* or *N. meningitidis* are highly immunogenic. In animal studies, GMMA elicited higher functional antibody responses against key vaccine candidate antigens, whether these are polysaccharide or protein moieties, compared with corresponding purified antigens delivered as glycoconjugate vaccines (for polysaccharide antigens, e.g. O-antigen of *Salmonella*) or recombinant formulations (for protein antigens, e.g. factor H binding protein of meningococcus). This could be the result of efficient antigen presentation to the immune system, the adjuvanting effect of GMMA, which changes the IgG profile or a combination of both effects. S. *sonnei* GMMA have been already tested in clinical trials, showing to be well tolerated and immunogenic in European adults and endemic populations. With good immunogenicity, low cost, and ability to induce functional antibodies, GMMA technology is potentially attractive for development of vaccines against bacteria of global health significance.

Biography

Francesca Mancini has completed her PhD from Padova University and Post-doctoral studies from Novartis Vaccines and Florence University. She is a Scientist at Glaxo Vaccines Institute for Global Health (GVGH), an organization that operates in order to develop effective and affordable vaccines against neglected infectious diseases, such as typhoid fever, shigellosis and streptococcal disease (and relevant complications). She has published 10 papers in reputed journals.

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