# FOCIS 2011-Advanced Course in Basic & Clinical Immunology

## A Brief Report

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The Advanced Course in Basic and Clinical Immunology organized by the Federation of Clinical Immunology Societies (FOCIS) was held on March 2 to 6, 2011 at the FireSky Resort & Spa, Scottsdale, Arizona. The meeting chairpersons were Dr. Andrew Lichtman, (Brigham and Women's Hospital) and Dr. Abul K. Abbas (University of California, San Francisco). This course brought together a diverse group of scientists working in the fields of basic and clinical immunology and explored how immunology can be used most effectively to impact the clinical response to human diseases. The course was introduced by Dr. Andrew Lichtmann and the keynote address was given by Dr. Abul Abbas who discussed the clinical immunology and FOCIS.

The idea and concept of the FOCIS course involving interrelationships between fields sharing clinical immunology expertise is a better way to integrate science to improve knowledge of immunology. Course delegates represented a diverse group of professionals who attended this course to enhance their understanding of immunology. Invited speakers were experts in basic and clinical immunology. Major highlights or topics in this Advanced course were cellular and molecular immunology, including innate immunity, B cells, T cells, dendritic cells, cytokines and mucosal immunity; autoimmune, allergic and an immunodeficiency disease, as well as new advances in interventional clinical immunology and the molecular and genetic basis of immunologically mediated diseases. All lecturers encouraged interactions with the attendees through questions and discussions during lecture time. Since the course attracted clinicians and immunologists from all over the world, participants gained a global perspective on the cutting edge of basic and clinical immunology.

## Day 1

### Innate immunity: Dr. Kenneth Rock, University of Massachusetts Medical School

The scientific session was opened by Dr. Kenneth Rock who gave an overview of the innate immune system, a front-line defense system providing a non-specific response to pathogens in all plant and animals. Dr. Rock also discussed that unlike the adaptive immune response, the innate immune system does not generate memory or protective immunity. There was a discussion about an essential part of the mammalian innate immune system that is the function of NK cells that recognize and destroy cells infected with intracellular pathogens, including viruses, parasites, and bacteria. Along with him, the group of attendees explored the innate immunity

by discussing one of its important responses that is inflammation, inflammatory mediators, and mechanism of inflammation. He also gave a clear view about the various innate immune receptors; the most important is the TLRs (Toll-Like receptors). We get an in-depth knowledge of the innate immune system and how it has evolved mechanisms to sense injury (external or internal).

**Antigen Presentation and Dendritic Cells: Dr. Yong-Jun Liu, University of Texas, M.D. Anderson Cancer Center**

There is a great deal of interest in dendritic cells (DCs) and how DCs might be exploited as a form of immunotherapy. A detailed insight into the clear picture of DCs was given by Dr. Yong-Jun Liu. Dr. Liu discussed in detail about the DCs, their generation, major DCs susbsets, and molecular basis of DC functional plasticity. DCs are being studied as adjuvants for vaccines or as a direct therapy to induce immunity against cancer. He highlighted the role of DCs in innate and adaptive immunity. DCs loaded with tumor lysates, tumor antigen-derived peptides, MHC class I restricted peptides, or whole protein have all been shown to generate anti-cancer immune responses and activity, including in some cases the ability to induce complete regression of existing tumor. Thus, there is a great desire to test these strategies and use tumor-antigen bearing DCs as a vaccine in humans and Yong-Jun Liu. The exciting discussions demonstrated the utility of DCs in the generation and activation of immune response against various diseases.

**Leukocyte Migration: Dr. Ulrich von Andrian, Harvard Medical School**

Dr. Ulrich von Andrian discussed about a critical feature of the immune system that is leukocyte migration which is the ability of leukocytes to leave the blood-stream and migrate into tissues and essential in eliminating infectious pathogens and allowing leukocyte accumulation at sites of injury, infection or inflammation. Lymphocytes continuously recirculate between tissues, lymphoid organs and blood, whereas neutrophils or monocytes lack this capacity. Migration of various leukocyte subpopulations into tissues is regulated by specific combinations of adhesion receptors and chemoattractants which direct them into tissues. Selectins initiate leukocyte attachment along vascular endothelium by mediating leukocyte rolling along inflamed endothelium. He also emphasized that leukocyte migration is an important mechanism in the pathogenesis of inflammatory diseases, the regulation of hematopoiesis and homeostasis. This reaction is also involved in the pathogenesis of atherosclerosis, reperfusion injuries and malignant cell metastasis. He also had gone through the importance of leukocyte migration inhibitors that may have therapeutic potential against inflammation and associated diseases. Systematic and in-depth scientific investigations have dissected and delineated the complex, but fascinating, molecular mechanisms involved in this cellular behavior. He concluded the exciting discussions by stating that this knowledge should facilitate the research and development of effective medicines for treatment of inflammation.

**T cell Activation and Costimulation: Dr. Abul Abbas, University of California**

The immune system has the remarkable ability to defend against diverse microbial pathogens and yet not to respond to self. T cells are key mediators of the immune response, and their activation is tightly regulated to prevent autoreactivity. The processes of T-cell activation and self-tolerance are therefore potential targets for manipulation by drugs. Dr. Abul Abbas explained a clear concept of T cell activation and role of costimulatory molecules. Co-stimulation is believed to be critical for optimal induction of T cell responses. He also emphasized on the two signal requirement for T cell activation and therapeutic targeting of molecules involved in T cell responses. The immunological synapse proved to be a stimulating concept, particularly he discussed on the similarity of intercellular communication controlling disparate biological processes. He also clarified some of the underlying molecular mechanisms and functions of the immunological synapse. Optimal T-cell activation requires engagement of the TCR (signal one) and a costimulatory signal (signal two). He discussed that the second signal is dependent on soluble factors such as IL-2 or the ligation of cell surface molecules and most T-cell surface costimulatory molecules are members of the immunoglobulin and TNF superfamilies and are important components of the immunologic synapse. Finally, the physiological relevance of costimulatory molecules in T cell activation and its consequences for immunotherapy are discussed by Dr. Abbas.

## Day 2

**Cytokines and T cell Subsets: Dr. Andrew Lichtman, Brigham & Women's Hospital**

Dr. Andrew Lichtman formed an emerging picture that in response to infection, immunocytes express a finely balanced and tightly regulated pattern of cytokines, which promote the most effective immunity against the infecting agent. As our knowledge about the pathological processes that underlie many diseases develops, there has been a huge increase in the identification of new therapeutic targets, which, in turn, has led to an expanding array of biologic drugs aimed to a large part at altering the balance of cytokines in disease. Dr. Lichtmann discussed that cytokines are exemplary of translational research, where important advances in basic science are quickly translated into new therapies for clinical practice. Whilst many of the inflammatory processes and cytokine abnormalities are common to disparate diseases, the original trigger and the factors dictating disease expression may be very different. He talked about the common final pathway leading to tissue destruction and many drugs which were originally designed to combat the symptoms of diseases are now being harnessed to treat diverse conditions.

**B cell Activation and Regulation: Dr. Shiv Pillai, Massachusetts General Hospital**

Dr. Shiv Pillai outlined the concepts about the B cells as a critical component of the adaptive immune system that provides both specific and long-lasting protection from a tremendously diverse range of potential pathogens. The importance of these effector cells in enhancing an individual's survival requires that the processes underlying B cell activation be both highly coordinated and precisely regulated. He detailed the identification of the important mediators and characterization of signaling pathways involved in the B cells activation and formed an essential foundation for developing our understanding of how humoral immune responses are initiated. Throughout he highlighted the emerging and important role of the B cell cytoskeleton in regulating B cell activation in vivo. In conclusion, he described the latest therapeutic strategies targeting B cells and effector antibodies.

**NK and NKT Cells: Dr. Lewis Lanier, University of California**

Dr. Lewis Lanier provided a detailed description of the importance of Natural Killer (NK) and NKT cells in innate immunity and the influence these cells have on the adaptive immune response. NK cells are functionally characterized by their ability to kill certain tumor cells without prior sensitization and to produce pro-inflammatory cytokines, especially interferon gamma (IFNγ), following activation. A unique subset of T cells, designated NKT cells, express the NK1.1 marker, as well as other typical NK receptors and upon stimulation through their TCR, rapidly produce substantial amounts of cytokines especially IL4. He discussed that NK cells constitute the first line of host defense against invading pathogens and recent advances in understanding NK cell biology have opened new avenues for boosting innate and adaptive immune responses in. Further, he added that unlike NK cells, NKT cells develop in the thymus and express a rearranged TCR. In contrast to typical T cells, NKT cells respond to antigen presented by the atypical MHC Class I molecule, CD1D, and express intermediate levels of TCR. In addition, NKT cells are either $CD4^+$ or $CD4^-CD8^-$, in contrast to typical $CD8^+$ Class I restricted T cells. He also emphasized that NK and NKT cells modulate immune responses by secreting a variety of cytokines and chemokines. He concluded that NK and NKT cells are essential not only for defense against pathogens, but also for the initiation of adaptive immune responses and in regulating autoimmune responses.

**Tolerance and Immune Regulation: Dr. Abul Abbas, University of California**

Immunological tolerance guards against spurious immune responses to body constituents. Tolerance encompasses a network of mechanisms: central and peripheral, cell-autonomous and cell-interactive. Our understanding of these mechanisms had improved greatly by Dr. Abul Abbas who reflected new insights into the processes underlying human immune diseases. He also discussed that the understanding of the cellular and molecular regulation of immunological tolerance is of fundamental importance in basic immunology. It is also of major significance in

the clinic, as we pursue mechanisms that underlie the breaking of self –tolerance in various autoimmune disorders and design strategies to restore tolerance to self-antigens. To conclude he described that there has been considerable progress in understanding how sets of gene products coordinate self tolerance mechanisms and how failure of these controls can predispose to autoimmune diseases.

**Lessons Learned from Immunodeficiency Diseases: Dr. Mary Ellen Conley, St. Jude Children's Research Hospital**

Worldwide, the most common causes of increased susceptibility to infection are malnutrition and infection. Dr. Mary Ellen Conley described the heterogeneous group of disorders that result in an increased susceptibility to infection and also the genes responsible for over 150 different immunodeficiencies which have been identified in the last 20 years. She gave a brief description of the systems of immune defense; adaptive and innate immune system. She detailed the highly variable immunodeficiencies stating that most immunodeficiencies result in susceptibility to specific infections rather than global susceptibility and infection with a specific organism may result in a different set of clinical signs and symptoms in immunodeficient patients compared to controls.

## Day 3

**Allergic Disease: Dr. Stephen Galli, Stanford University**

Allergies are the result of inappropriate immune responses to normally harmless substances. Dr. Stephen Galli gave overview explaining that allergy problems are now not restricted to seasons and regions, with people often allergic to numerous environmental allergens and experiencing multiple symptoms associated with a range of conditions including allergic asthma, allergic rhinitis, food allergies, and dermatological problems. He also discussed the recent escalation of allergic diseases which may be attributable in part to environmental factors: people are now exposed to a multitude of substances, both natural and man-made, that would have been alien just a few decades ago. A plethora of new indoor and outdoor pollutants may also play a role in the duration of allergies, with today's allergy patients suffering for longer. He then explored the celllular and molecular mechanisms involved in asthma and allergic diseases, from basic immunology to the treatment of patients. He described important early events in our understanding of mast cells & their possible functions in allergic reactions. In conclusion, he showed the significant impact of allergic diseases on the lives of patients and their families demonstrating that allergic diseases are an increasingly important problem for the people worldwide.

**New and Emerging Therapies: Dr. Scott Plevy, University of North Carolina**

Dr. Scott Plevy initiated the discussion with the history of immunotherapy and rise of biopharmaceutical market sectors delineating with its development strategies. He described monoclonal antibodies as the fastest growing class of human therapeutics.

In addition to cancer, antibody therapeutics are being developed to treat infectious diseases, cardiovascular disease, eye disorders, allergies and autoimmune diseases. He staged the recombinant monoclonal antibodies in the center of the biotech industry and also showed the continuing considerable appetite for antibody therapeutics. He gave a conclusion that despite the proliferation of immunotherapies, there are still unmet medical needs.

**Transplantation: Dr. Jonathan Maltzman, University of Pennsylvania**

Thousands of transplants of organs, tissues, and cells are performed throughout the world annually. The major barrier to organ, tissue, and cell transplantation in humans is the immune response to the graft or, the immune response of the graft against the recipient which was discussed in detail by Dr. Jonathan Maltzman. His talk lead to a discussion on the indications and problems associated with transplantation. He moved further describing immunosuppression which has improved graft survival but leaves the patient susceptible to infectious complications, of which pulmonary infections are the leading cause of morbidity and mortality. He defined transplant tolerance in immunologic and clinical terms as a state of antigen-specific T cell unresponsiveness. Advances in transplantation continue to be hindered by infection and rejection. The optimal immunosuppressive regimen maintains graft function, minimizing rejection while limiting the potential for infection. Because transplant patients tolerate established infection poorly, prevention is of paramount importance. He described that the future of transplantation lies in the ability to more selectively create immune tolerance of the graft while preserving the patient's ability to mount an immune response to infection.

**Mucosal Immunity: Dr. Richard Blumberg, Brigham & Women's Hospital**

The immune system, associated with mucosal surfaces covering the largest area of the body (200–300 $m^2$), evolved mechanisms discriminating between harmless antigens and commensal microorganisms and dangerous pathogens. Dr. Richard Blumberg discussed mucosa-associated lymphoid tissues (MALT), which together form the largest mammalian lymphoid organ system and represents a highly compartmentalized immunological system that functions essentially independent from the systemic immune apparatus. He described the methodological advances of recent years that allowed more intense study of mucosal immune responses and also led to growing interest in trying to better understand the specific features of mucosal as compared with systemic immunity. He emphasized and concluded that understanding the regulation of immune responses on mucosal surfaces may be the key to targeted manipulation of pathological responses in allergic and other chronic diseases.

## Autoimmunity: Dr. Mark Anderson, University of California

Dr. Mark Anderson brought the concept of autoimmunity and autoimmune disorders where the immune system attacks self tissues. The perplexing issue of what allows the immune system to attack self tissues which is a continuing focus of research was discussed in detail by Dr. Anderson. In the past, autoimmune diseases have been studied on the basis of the organ affected, but in recent years the focus has switched to a more cross-disciplinary approach with a view to provide a better understanding of the common mechanisms underlying the pathogenesis of these diseases. He gave a clear view of better understanding of the molecules involved in immune responses which in turn help in the identification of many potential targets for the treatment of autoimmune diseases. He described various autoimmune diseases major causes of morbidity and mortality throughout the world. Many of these diseases tend to be difficult or impossible to cure, for the obvious reason that the focus of the immune response-self antigens cannot be eliminated. He concluded that hopefully understanding the genetics of autoimmune diseases will teach us about the causal derangements, and perhaps lead to new therapeutic strategies.

## Conclusion & Outcome of the Advanced Course in Basic & Clinical Immunology

In summary, participants improved their ability in understanding fundamental mechanisms and principles underlying protective immune responses, immunologic diseases, and biotherapeutics. Participants also acquired and improved their clinical immunology knowledge by discussing the recent advances in immunology research and mechanisms associated with strategies for therapeutic modulation of the immune system. The course provided timely and critical information about the immunologic advances pertinent to the patients, cites the rationale for use of new immunodiagnostic and immunotherapeutic modalities in the patients, and served as thought leaders within the medical community.

This course work helped me to advance new strategies that use the exquisite specificity of the body's natural defenses to destroy tumors with minimal toxicity to healthy tissues. We are now extending our studies to investigate the humoral and cellular arms of the immune system for new treatment opportunities for cancer a global health problem. The course also led to a better understanding of immunology of how cancer cells manipulate the immune system for the development of new drugs that block those processes and thereby improve the effectiveness of cancer treatment vaccines. While the development of cancer vaccines has been challenging and more complex than anticipated, its future appears to be promising. At the conclusion of this course, I must say that I have improved my knowledge in understanding the fundamental mechanisms underlying protective immune responses, and also the recent advances and emerging themes in immunology research.

I would certainly like to place on record that all organizers and Professors who organized and taught this course were very helpful. I am sure in future many more will benefit from this course.