Immunonomics Reviews
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This peer-reviewed book series offers insight on immunology for 21st century. The technological revolution has borne advances in high-throughput instrumentation and information technology, initiating a renaissance for biomathematics, and biostatistics. Cross-fertilization between genomics and immunology has led to a new field called immunomics, transforming the way in which theoretical, clinical and applied immunology are practiced. Immunomics Reviews will cover integrative approaches and applications to the theory and practice of immunology and explore synergistic effects resulting from a combination of technological advances and the latest analytical tools with the traditional fields of basic and clinical immunology.
Contents

Integrative Systems Approaches to Study Innate Immunity ................................. 1
Timothy Ravasi

Immunomics: At the Forefront of Innate Immunity Research ........................... 15
Hongtao Guan, Steven K Dower, and Endre Kiss-Toth

Epitope-Based Immunome-Derived Vaccines: A Strategy for Improved
Design and Safety ........................................................................................................ 39
Anne S. De Groot, Leonard Moise, Julie A. McMurry, and William Martin

Immunodeficiencies and Immunome: Diseases and Information Services ........ 71
Mauno Vihinen

Immunomics of Immune Rejection ........................................................................... 87
Ena Wang, Marianna Sabatino, and Francesco M Marincola

Spectrum, Function, and Value of Targets Expressed in Neoplastic
Mast Cells ................................................................................................................... 107
Peter Valent

Structure, Allergenicity, and Cross-Reactivity of Plant Allergens ...................... 127
Christian Radauer and Heimo Breiteneder

The Live Basophil Allergen Array (LBAA): A Pilot Study ................................. 153
Franco H. Falcone, Jing Lin, Neil Renault, Helmut Haas, Gabi Schramm, Bernhard F. Gibbs, and Marcos J.C. Alcocer

Emerging Therapies for the Treatment of Autoimmune
Myasthenia Gravis ....................................................................................................... 171
Kalliopi Kostelidou, Anastasia Sideri, Konstantinos Lazaridis, Efrosini Fostieri, and Socrates J. Tzartos
New Diagnostic and Therapeutic Options for the Treatment of Multiple Sclerosis .............................................. 205
Paolo Riccio, Heinrich Haas, Grazia Maria Liuzzi, and Rocco Rossano

Glycoimmunomics of Human Cancer: Relevance to Monitoring Biomarkers of Early Detection and Therapeutic Response ................. 227
Mepur H. Ravindranath

Translational Immunomics of Cancer Immunoprevention .......... 253
Pier-Luigi Lollini

Index .......................................................... 269
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Introduction: Clinical Immunomics; A New Paradigm for Translational Research

V. Brusic and A. Falus

Rapid improvement in accessibility to molecular databases as well as availability of high-throughput genomic, proteomic, and other 'omics' methodologies are forcing a considerable shift in research and development strategies for biomedicine. The recent change in research paradigm focusing on biology as system science is still difficult to grasp. Systems biology, a systematic study of complex interactions in biological systems, is currently closely related to the development and application of bioinformatics and biostatistics tools to genomic and proteomic data. Clinical immunology translates achievements of immunological research to medically relevant applications, that is, diagnosis, prevention, and therapy. It covers a broad area including complex disorders of the immune system (immunodeficiencies, autoimmune diseases, allergy, and lymphoproliferative disorders), immune responses (to pathogens, cancers, transfusion, and transplantation), and immunotherapies (Béné et al. 2000).

The complexity of the human immune system has several sources: combinatorial variability, plasticity, degeneracy and adaptivity of the immune system; interactions of the immune system and other self cells, tissues, and organs; the variability of pathogens, self, and environmental antigens; and the presence of multiple regulatory pathways. This complexity ensures that huge amounts of data must be produced and analyzed for deciphering the workings of the immune system. To effectively use these huge databanks, we need increasingly sophisticated tools of biostatics, bioinformatics, and mathematical modeling. The integrative approaches combining multiple tools are particularly important in clinical research comprising large cohorts of usually non-homogenous groups where disease phenotype, clinical progression, molecular profiles, and patient characteristics show huge variation.

Clinical immunology is not clearly differentiated as a clinical specialty because it involves a number of medical disciplines. Nevertheless,

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immunological approaches are increasingly being used as means of medical intervention (Béné et al. 2000).

Clinical immunology has a long history. Early writings date back to ancient Greece as far as 2400 years ago when Thucydides described the concept of acquired immunity to an infectious disease: “… for the same man was never attacked twice – never at least fatally” and the use of animal models for medical research: “But of course the effects which I have mentioned could best be studied in a domestic animal like the dog” (Thucydides 1982). The first text recognized (by the WHO) as scientific treatise on infectious disease is a 1100 years old essay by Rhazes, a Persian physician, describing discoveries about smallpox and measles (The Islamic Medical Manuscript Collection 2003). The later stages of the European scientific revolution of late 17th through 19th century brought both the advanced technologies (such as microscope) and the transformation of scientific ideas in chemistry and biology to provide the foundation of modern western medicine. The 19th century saw the development of successful vaccines, while 20th century produced large quantities of knowledge of fine details describing the cellular, molecular, and genetic basis of immunity.

A major driver for the advancement of immunology is the expansion of knowledge of structural and functional elements of the immune system at the cellular, organ, organism, and population level. This knowledge is accumulated, thanks to scientific and technological progress, which continues unabated; the volume of scientific information is estimated to double every 15 years (Lukasiewicz 1994). The key enabling technologies of genomics (Falus 2005), proteomics (Purcell and Gorman 2004; Brusic et al. 2007), and bioinformatics (Schönbach et al. 2007), and systems biology (including such genomic pathway analysis) (Tegnér et al. 2006) provide large quantities of data describing molecular profiles of various physiological and pathological states. Advanced methods for quantification of immune responses provide means for detailed study of human immune pathology and complex host–pathogen interactions. Flow cytometry enables measurement and characterization of individual cells and molecules representing various experimental states, for example, measurement of antigen-specific immune responses (Li Pira et al. 2007). Improvement of assays for immune monitoring (e.g., multiparametric flow cytometry, nanotechnology for quantitation of cytokine production, ELISPOT, intra-cytoplasmic cytokine staining, and mRNA as well as micro-RNA based assays) continuously expands our ability to measure profiles of cytokines and other molecules that direct and modulate immune responses (Sachdeva and Asthana 2007). Latest developments in laser scanning cytometry allow the measurement and analysis of effector function of individual cells in situ thus representing molecular and cellular events in physiological and pathological states (Harnett 2007).

This volume brings together examples of various topics in clinical immunology, and various tools of immunomics. This collection of articles is not a complete collection of works in this field. Rather, it is a starting point where examples of various immunomics approaches are studied for advancement of knowledge and translation of these results into new products, methods, and
therapies. Translating basic immunology advances into medical applications increasingly requires multidisciplinary approach and teams comprising clinicians at the bedside, basic immunologists at the laboratory bench, engineers who develop advanced instrumentation, along with biostatisticians and bioinformaticians who perform data analyses and interpretations. Immunomics, therefore, is a powerful new technology that combines basic and clinical immunology with high-throughput instrumentation and bioinformatics for the analysis and interpretation of the data. Immunomics is similar to genomics and proteomics in that a major challenge is the understanding and manipulating genes and proteins involved in the functioning of the immune system. In addition, immunomics must address factors arising from the complex micro-environment affecting the immune function, as well as external challenges arising from pathogen diversity. Immunomics screening of markers of the immunologic status will in near future be used to determine who should be enrolled in a particular clinical trial and follow-up of these markers throughout the course of therapy (Tremoulet and Albani 2005). The likely major advances of immunomics will be seen first in the fields of vaccines and high-throughput diagnostics. In addition, immunomic approaches herald the development of the new generation of vaccines and immunotherapies to be tailored precisely to both the genetic make-up of the human population and of the disease profile, be it cancer, allergy, or infection (Brusic and August 2004).

This volume has 11 chapters covering a range of immunomic topics. In Chapter “Integrative Systems Approaches to study Innate Immunity”, Tim Ravasi describes systems approach to the study of cellular aspects of innate immunity, focusing on macrophages. He offers an insight into applications of systems biology, in which all main components and their interactions within a biological system are measured and then assembled into modules for further study. This approach makes no assumptions about underlying mechanisms – the measurement is direct; the disadvantage is that it the scale of information that can be obtained is enormous. Systems biology uncovers relations between entities in a biological system and their regulation. Macrophages are in our primary line of defense against pathogens, and they also mediate the pathology of infectious, inflammatory, and malignant disease, and therefore understanding the control of their function is expected to translate into rational development of therapies.

In Chapter “Immunomics: At the Forefront of Innate Immunity Research”, Guan and Kiss-Toth describe the immunomics of innate immunity as a novel viewpoint in immunology research, integrating the approaches of cellular immunology, bioinformatics, genomics, proteomics, immuno-informatics, and other related scientific fields, with the aim to derive integrated models of immune modulatory processes. This chapter focuses on the system-based approaches to characterizing in detail the molecular mechanisms of regulatory processes in innate immune responses. The authors have demonstrated the power of integrated approach to characterization of master cytokines, their receptors, signaling pathways, and identification of novel components of innate immunity.
In Chapter “Epitope-Based Immunome-Derived Vaccines: A Strategy for Improved Design and Safety”, De Groot et al. have explored the immunomics applications in vaccine science. They discuss the combination of bioinformatics prediction tools and an array of experimental models (biochemical assays and animal models). Two case studies, including tularemia and human papilloma virus are presented to demonstrate the utility of immunomics for epitope-based subunit vaccine development.

In Chapter “Immunodeficiencies and Immunome: Diseases and Information Services”, Mauno Vihinen introduces the concept of Essential Human Immunome, and informatics resources for storage and computational analysis of genes and proteins of the immunome. This chapter focuses on primary immunodeficiencies and the analysis of related immunome entries from some 5000 patients. These resources assist health professionals to select suitable genetic and clinical tests for immunodeficiencies.

In Chapter “Immunomics of Immune Rejection”, Wang et al. discuss the combination of high-throughput screening of samples representing autologous tumor rejection, clearance of pathogen, acute allograft rejection, and flares of autoimmunity. The use of systems biology helps identify common elements between these pathologies and precise identification of factors that balance host–target interactions. They investigate the interactions of innate and adaptive arms of human immune system and their effects to different disease scenarios.

In Chapter “Spectrum, Function, and Value of Targets Expressed in Neoplastic Mast Cells”, Valent explores a number of attempts made to identify novel targets and to develop targeted drugs for mast cell leukemia. In the current paper, emerging new molecular targets expressed in neoplastic mast cells are discussed in light of novel therapeutic concepts, availability of drugs, and forthcoming clinical trials.

In Chapter “Structure, Allergenicity and Cross-Reactivity of Plant Allergens”, Radauer and Breiteneder provided a detailed review of plant allergens, their structure, allergenicity, and allergic cross-reactivity. Grouping of allergens into structural families enables the identification of shared molecular properties of allergens and the basis for the prediction of allergenicity and analysis of cross-reactivity. The authors have made a case for allergy immunomics that combines allergology, structural biology, and bioinformatics.

In Chapter “The Live Basophil Allergen Array (LBAA): A Pilot Study”, Falcone et al. have described a study where protein microarrays were used to profile activation of basophil cells. The activation of basophils was measured by detecting basophil activation surface marker CD63, as an indirect measurement of basophil degranulation. Combining protein arrays with functional cell-based assays provides a novel method for detection of allergic sensitization. The authors also discussed the limitations and potential pitfalls of the usage of live basophil allergen array in basophil immunobiology studies.

In Chapter “Emerging Therapies for the Treatment of Autoimmune Myasthenia Gravis”, Kostelidou et al. have written about emerging therapies for the