

Commentary

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Changing paradigm through a genome-based approach to clinical and basic immunology

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Published: 17 January 2004

Received: 14 January 2004

Journal of Translational Medicine 2004, 2:2

Accepted: 17 January 2004

This article is available from: <http://www.translational-medicine.com/content/2/1/2>

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Genomics or, in other words, genome-based biology offers an entirely new prospective on strategies applicable to the study of distinct physio-pathological conditions through a "discovery-driven" approach that may complement traditional "hypothesis-driven" scientific thinking [1-3]. Indeed, analysis of genomic variation at the DNA level and functional genomics that addresses transcriptional variations of biological material have been extensively used by bio-scientists to study distinct pathological conditions and this trend has spread, more recently to applications in basic and clinical immunology [4-9]. This shift in paradigm in the study of biology and, for the purpose of this Commentary, in immunology may very well be suitable for the understanding of immune regulation in sickness and in health which represents a particularly complicated biological matter due to the extreme versatility of the immune system in adaptation to environmental changes. The study of immune regulation in response to pathogen invasion, presence of malignant or allogeneic tissue and, in some cases, toward normal autologous tissue may require global approaches that could study in parallel the behavior of whole-systems. In fact, the study of single immunological parameters has, so far, failed to unlock several questions related to the immune-system complexity. This may be particularly true for tumor immunology that is a compound field in which the dynamic heterogeneity of cancer cells [10] supplements the complexity of polymorphic variation and epigenetic adaptation characteristic of human immunology [11]. In fact, new tools have been developed that allow a global vision of genetic processes in parallel at various levels that encompass genetic variation (single nucleotide polymorphism analysis), epigenetic changes (i.e. methylation-

detection arrays or comparative genomic hybridization that can detect gene methylation or deletion / amplification respectively) and global transcription analysis (i.e. cDNA- or oligonucleotide-based microarrays like the lympho-chip or the peptide-MHC microarrays) that combined with bio-informatics tools provide a new approach to the description of complex immunological phenomena [3,9,11-14].

It is likely that, database mining will supplement classical experimentally-driven scientific thinking with a more interactive "*in-silicon*" processing of information integrated by software programs capable to link information accessible from the literature with extensive data bases from different laboratories for the simple purpose of increasing the data pool from which generate new hypotheses. Thus, we propose the new word: "immunogenomics" to describe the switch from the paradigm of solely hypothesis-driven immunological research to a more interactive and flexible relationship between classical research and a discovery-driven approach. It also appears to us that immunogenomics may particularly suit clinical immunology for the simple reason that genetic variation of patients and their diseases is not as controllable in humans as it is in inbred animal models [15]. Thus, since simplification is not an option when studying human biology, approaches that could collect information about such variation whether relevant or irrelevant to a physio-pathological condition may offer the opportunity to sort causative relationships from simple associations among molecular pathways. We want to emphasize, however, that immunogenomics is not in competition with traditional hypothesis-driven science but rather the

"fishing expedition" of large data set formation should complement traditional approaches by identifying new or validate known concepts that best fit the reality of human diseases.

At least four major aspects of immunogenomics could be identified. Immunogenomics covers:

1. The convergence of distinct elements of the immune system into a network of information regarding the localization, gene structure and expression profile of various players of the innate and/or acquired immune response;
2. Genetic regulation of physiological immune functions by inherited or epigenetic processes such as immunoglobulin or T cell receptor gene rearrangement, somatic hypermutation, immune selection in primary and peripheral immune tissues, antigen processing and presentation by major histocompatibility molecules, cytotoxic interactions, etc.
3. Genetic changes in immune function in pathological conditions such as onco-hematological diseases, allergy, immune deficiencies, infections, chronic inflammation, autoimmunity and cancer.
4. Suggest personalized approaches to immune therapy by predicting successful treatment or deleterious side effects and, therefore, helping in the selection of treatments appropriate for individual patients. This new era will start when such alterations could be easily collected during clinical trials through inexpensive high-throughput methods for detection of genomic variation or for expression profiling that could be applied to large patient populations [3,11,14]. With this strategy it will then be possible to immune phenotype individuals according to their genetic make-up and the epigenetic adaptations of their immune system. Hopefully, the kinetics of individual immune responses, the network in which they will operate and their vulnerability in sickness or in health may be predicted for each individual [16].

The global- immunogenomics approach stands on three foundations; (i) the revolutionary expansion of genome knowledge that is now available in giant computer databanks [17,18]; (ii) robust nanotechnology such as microarray chips and similar tools that allow real-time measurement of gene variants and gene expression and (iii) availability of improving software principles in immune bioinformatics that could generate data-mining tools for an efficient interpretation of otherwise unmanageable biological information.

This interdisciplinary thinking process asks for active cooperation among related scientific fields. The impor-

tance of scientific workshops and conferences inclusive of convergent topics and expertise may significantly increase the potential for a multi-directional transfer of knowledge. Good examples are the Workshop on Cancer Biometrics for Immunological Monitoring recently held at the National Institutes of Health, Bethesda, MD [19] and the First Conference on Basic and Clinical Immunogenomics soon to be held in Budapest this October <http://www.diamond-congress.hu/bci2004/>. In fact, although the potentials of high-throughput analyses applied to human biology are conceptually obvious, several obstacles remain not only of technological nature but also in the design of clinical trials and education of clinical scientists about the opportunities available for the selection, treatment and monitoring of patients entered in clinical trials. Comprehensive reviews on this subject, contrary to those detailing technical information, are scant and communication between bench and clinical scientists remain below a threshold likely to produce efficient therapy development and ultimately benefit patients. Although, tools are available nowadays to study biological processes in their globality [3], clinical samples of appropriate relevance and quality are not easily accessible. In spite of the fact that individual genetic predisposition to disease and response to treatment [14,11] could be studied in combination with that of epigenetic changes during life and disease progression [3] and that of real-time adaptation in the transcriptional profile of biological samples in relevant conditions [3] very little has been done to prospectively collect clinical material. Thus, availability of relevant samples to study remains the central problem. In particular, functional genomic studies rely on the fine measurement of messenger RNA levels highly susceptible to metabolism and degradation. Thus, the design of clinical studies should incorporate strategies that may lead to the understanding of the biology of tissues or pathogens targeted by immune effectors, their relationship with the host and their response/adaptation to therapy while testing at the same time the clinical efficacy of a given treatment [15]. In fact the understanding of disease is a requirement for the design of rational therapies. High-throughput technologies [3] will allow, when applied to relevant samples, the efficient screening in humans of theoretical models generated from animal experimentation, *in vitro* studies or speculation and, in turn, the discovery of new patterns through the direct observation of human pathology but this will only occur through the integrated efforts of multiple basic and clinical research disciplines.

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