AUTOIMMUNE AND INFLAMMATORY DISEASES BIOMARKERS

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Abstract
One of the major challenges facing the healthcare industry is how to personalize, or tailor healthcare products and services to individuals' unique genetic and biomarker make-ups. Biomarkers are characteristics that can be objectively measured and evaluated. They provide information about normal or patho-physiological processes to detect or define disease progression or to predict or quantify therapeutic responses. Once these footprints have been identified and measured, they can then be used to personalize or tailor treatment plans, products and services to each individual's unique makeup and background. Biomarkers enable early diagnosis, guide molecularly targeted therapy and monitor the activity and therapeutic responses across these diseases. Development of new, predictive safety and efficacy biomarkers is expected to reduce the time and cost of drug development. This review summarizes the integration and use of biomarkers in drug development, regulation and clinical practice with special emphasis on autoimmune and inflammatory diseases biomarkers.

Keywords: Autoimmune diseases, Biomarker, Drug development, Inflammatory diseases, Personalized medicine

1. Introduction
Autoimmune diseases are a family of more than 80 chronic and often disabling illnesses that develop when underlying defects in the immune system lead the body to attack its own organs, tissues and cells. Since cures are not yet available for most autoimmune diseases, patients face a lifetime of illness and treatment. They often endure debilitating symptoms, loss of organ function, reduced productivity at work, and high medical expenses. And because most of these diseases disproportionately afflict women, and are among the leading causes of death for young and middle-aged women, they impose a heavy burden on patients’ families and on society.

Autoimmune diseases are commonly considered complex immune disorders. While many autoimmune diseases are rare, collectively these diseases afflict millions of patients. 5–8% of the US population suffers from this group of chronic, debilitating diseases. Despite their clinical diversity, they have one similarity, namely the dysfunction of the immune system. It is suspected that genetic defects play a role in the etiology of these diseases. Modern high throughput technologies, like mRNA micro arrays have enabled researchers to investigate diseases at a genome-wide level. In contrast to classical inherited genetic diseases like sickle cell anemia, autoimmune diseases are not caused by the defect of a single gene but by the dysfunction of the complex interaction of a group of genes. Although no autoimmune disease has been completely analyzed, there has been tremendous success in recent years in identifying major players in the development of autoimmune diseases.

The factors that trigger an autoimmune disease are still unknown. Studies with monogenetic twins have revealed that genetic influences only account for 25–40% of the disease risk making gene environment interactions or environmental influences the predominant factors. The environmental influences are very diverse rendering research in this area extremely difficult. These influences may be toxic substances like mercury in one case and ultraviolet light or even certain nutrients in another. Moreover, several bacteria, viruses or hormones are among the suspected triggers of autoimmune disorders.

Main autoimmune and inflammatory diseases include asthma, allergic rhinitis, alopecia areata, atopic dermatitis, autoimmune hepatitis, autoimmune pancreatitis, autoimmune urticaria, autoimmune uveitis, celiac disease, chronic obstructive pulmonary disease/emphysema, Crohn’s disease, dermatomyositis, diabetes mellitus type 1, graft versus host disease,
Graves' disease, Hashimoto's thyroiditis, irritable bowel syndrome, juvenile idiopathic arthritis, lupus erythematosus, multiple sclerosis, myasthenia gravis, myositis, pemphigus vulgaris, polymyositis, primary biliary cirrhosis, psoriasis, psoriatic arthritis, rheumatoid arthritis, solid organ transplant rejection, Sjogren's syndrome, ulcerative colitis and vasculitis.

2. Biomarkers and personalized medicine

A biomarker, as defined by the Food and Drug Administration (FDA) of the United States, is any “characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”\(^{34}\). Biomarkers are characteristics that can be objectively measured and evaluated. They provide information about normal or pathophysiological processes to detect or define disease progression or to predict or quantify therapeutic responses. Traditional biomarkers have encompassed surrogate physiological measurements such as heart rate, blood pressure and performance status, imaging such as chest X-rays and mammograms, and individual protein molecules such as prostate-specific antigen (PSA) and carcinoembryonic antigen (CEA)\(^{12}\).

With the recent explosion of high-performance ‘omic’ technologies – genomics, proteomics and metabolomics, among others – the rate at which biomarker candidates are being discovered is now faster than ever. During the discovery phase, single or multiple platforms are used to identify potential candidate biomarkers in a given patient population, typically from a small geographical area. This quest involves selection of patients with clear clinical phenotypes, and standardized operating protocol-driven collection and processing of single or multiple time point samples for analysis\(^{36}\). In the case of multiplatform ‘omic’ biomarker discovery, data within each platform are analyzed using suitable, tiered statistical methods to identify differentially expressed genes, proteins or metabolites in normal subjects versus patients in cohorts, from baseline status throughout the course of illness, addressing patients with different stages of disease. Bioinformatical tools are also applied in parallel to other strategies to help deduce potential functional or pathway associations among candidate biomarkers. It is not always practical to pursue validation of all candidate biomarkers identified during the discovery stage. Thus, it is important from both time and cost point-of-views to establish parameters for scientifically rational, statistically sound, evidence-based selection or rejection of biomarker candidates\(^{37,38,39}\). Only the ‘best’ candidates should move forward into the validation stage. The decision to move a candidate biomarker forward is not only dependent on its statistical or bioinformatical significance, but also largely based on its potential to contribute cost-effectively to disease management or prevention\(^{40}\).

Biomarker validation is currently a lengthy and complex process. Not surprisingly with the availability of ‘omic’ platforms, candidate biomarker discovery now commonly outruns the rate at which the candidates are being validated. This situation has created a bottleneck in the biomarker development and translation process\(^{45,41}\). The FDA classifies (pharmacogenomic) biomarkers as exploratory or valid. Valid biomarkers are further classified as ‘probable’ or ‘known’, depending on the level of confidence they attain during the validation process. Biomarkers that are measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiological, toxicological, pharmacological or clinical significance of the results are known valid biomarkers and biomarkers that are measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiological, toxicological, pharmacological or clinical significance of the test results are probable valid biomarkers\(^{45}\).

The US FDA, recognizing the continued divergence of increasing resources going into drug development and the decrease in output (productivity), issued a white paper entitled “Innovation or Stagnation, Challenge and Opportunity on the Critical Path to New Medical Products” in March 2004\(^4\). The document details why the agency believes drug development is stagnating and proposes a series of opportunities to increase productivity. A key prospect described in detail in the Critical Path document, and illustrated with a series of concrete proposals in the list of opportunities\(^5,6\), is the use of biomarkers in drug development. Effective
integration of biomarkers into clinical development programs (to enrich a responder population or identify patients at risk for an adverse event) may facilitate new medical product development and promote personalized medicine. Personalized medicine allows pharmacists to practice true patient-centered care as they help patients learn what they really want to know about their treatment instead of just what pharmacists’ think is best. Having more complete data when pharmacists meet with patients allows them to make better treatment decisions. Personalized medicine is a process of lifelong, self-directed learning aimed at providing the best possible patient care using the clinically important available information about diagnosis, prognosis, therapy, and other clinical and health care issues. The important elements of personalized practice include: a) collection of evidence; b) categorize the level of evidence; c) critically appraise the evidence for its validity and applicability; d) applying results of appraisal in clinical practice; and e) clinical outcome. Single nucleotide polymorphisms (SNPs) are now recognized as the main cause of human genetic variability and are already a valuable resource for mapping complex genetic traits. Thousands of DNA variants have been identified that are associated with diseases and traits. By combining these genetic associations with phenotypes and drug response, personalized medicine will tailor treatments to the patients' specific genotype. Although whole genome sequences are not used in regular practice today, there are already many examples of personalized medicine in current practice. Chemotherapy medications such as trastuzumab and imatinib target specific cancers, a targeted pharmacogenetic dosing algorithm is used for warfarin (International Warfarin Pharmacogenetics Consortium) and the incidence of adverse events is reduced by checking for susceptible genotypes for drugs like abacavir, carbamazepine and clozapine. Biomarkers have been used in drug development and treatment monitoring for a long time. However, development of new, predictive safety and efficacy biomarkers is expected to reduce the time and cost of drug development. 3.1 Preclinical Development: In preclinical/animal toxicology studies, the goal of using novel qualified predictive safety biomarkers is to assist in selecting drug candidates that are more likely to be tolerated in humans thereby reducing cost and time required for preclinical safety evaluation. The qualification of novel biomarkers requires a concerted effort of a team of experts, with expertise in areas including pharmacology/toxicology, clinical pharmacology, clinical medicine, biostatistics and other relevant disciplines. Qualifying preclinical (and also clinical) safety biomarkers for regulatory purposes is likely to be more feasible in collaborative approach that includes representation from industry, academia and government. An example of such collaboration is the Predictive Safety Testing Consortium (PSTC), which includes 16 different pharmaceutical companies and is led by the C-Path Institute. The initial focus of PSTC is on preclinical biomarkers. 3.2 Clinical Development: Biomarkers can be used in early or late drug development for enrichment of patient populations to increase the odds of detecting a phenotypic or clinical efficacy signal. For example, data from early
clinical trials that enroll patients with poor metabolizer (PM) genotypes in early phases of clinical trials to evaluate dose–concentration–response relationships in patients with different genotypes can inform the study design of later-phase clinical studies. In later stages of development, stratification approaches might be employed for looking at response in subgroups of patients.

In most cases, proper validation of the clinical utility of a biomarker requires a prospectively designed randomized clinical trial (RCT). This applies to the biomarkers intended to identify a sensitive subpopulation in testing a new molecular-targeted therapy, as well as to the biomarkers that are designed to select between existing treatment options. The choice of the appropriate RCT design depends on the strength of the preliminary data for the biomarker. If there is compelling evidence that the potential benefit from a new therapy is limited to the biomarker-positive subgroup, then the most efficient way to evaluate the new therapy is with an enrichment design in which the biomarker is assessed in all patients, but randomization is restricted to the biomarker-positive patients. If several new therapies and their corresponding biomarkers are available for testing in a given disease setting, efficiency can be further increased by combing the evaluations in a single multi-arm RCT. This RCT would use the biomarkers to direct patients to the appropriate biomarker-defined component, in which they are randomized between the appropriate new and control treatments. Use of interim monitoring with this approach would allow for the independent stopping of each of the components for efficacy or inefficacy as soon as the corresponding question is answered. Often a biomarker to separate patients into putative biomarker-positive (sensitive) and biomarker-negative (non-sensitive) subgroups is available. However, there is no compelling evidence that the benefit of the new therapy is limited to the biomarker-positive subset. The most efficient approach is then the biomarker-stratified design in which all patients are randomized regardless of biomarker status, but the analysis plan is structured for testing treatment effect dependence on the biomarker.

It has proven very difficult to establish robust clinical trial endpoints based on biomarkers. A perfect trial-level surrogate endpoint would be one for which the surrogate (e.g. biomarker) could be substituted for a definitive trial endpoint in a new trial and that trial would reach the same conclusion regarding treatment effect. To make this assessment, usually a meta-analytic approach is needed where data are analyzed from a series of trials in which both the putative surrogate endpoint and the definitive trial endpoint were measured. The series of trials allows for proper inference about whether the surrogate endpoint could be used reliably in a new trial conducted in a similar patient group, with therapies having mechanisms of action similar to the therapies used in the previous trials.

Despite the difficulties in establishing that a biomarker is a reliable surrogate endpoint, biomarker measurements made during and after therapy may still be helpful in understanding how a therapy is interacting with its target or may give earlier indication of the likely effectiveness of a therapy than more traditional clinically based outcome measures, particularly in the setting of cytostatic agents. Even if the biomarker endpoints do not replace more conventional clinical endpoints in clinical trials, they might, for example, be useful as early indicators of treatment efficacy that could be used in the conduct of screening trials. The drug development community will also have to accept that phase II trials may need to be somewhat larger and more complex and more randomized phase II trials may be needed to fully evaluate the potential of biomarkers for their usefulness in the conduct of phase III trials and ultimately for clinical decision-making. For example, to get an early indication of whether a kinase inhibitor may be effective only in patients with a mutated target, one may want to perform a phase II study both in patients with the wild-type target and the mutated target to assess whether there is evidence for differential efficacy. With greater investment and more rational approaches to biomarker research in earlier stages of drug development, greater rewards await at the end.

3.3 Post marketing: The usefulness of a biomarker may also be discovered in studies carried out as Phase IV commitments (or long after the drug approval). Serious and rare adverse effects of drugs are often observed only after marketing of the drug, since premarketing clinical trials are limited in the number of patients being studied. For example, post-marketing study of monoclonal antibody (mAb) therapy for the treatment of autoimmune diseases, particularly those treated with...
natalizumab, efalizumab and rituximab suggested that bioenergetic parameters such as iATP may assist in risk stratification under mAb immunotherapy. Progressive multifocal leukoencephalopathy (PML) is an opportunistic central nervous system (CNS) infection that typically occurs in a subset of immunocompromised individuals. An increasing incidence of PML has recently been reported in patients receiving monoclonal antibody (mAb) therapy for the treatment of autoimmune diseases, particularly those treated with natalizumab, efalizumab and rituximab. Intracellular CD4+-ATP-concentration (iATP) functionally reflects cellular immunocompetence and inversely correlated with risk of infections during immunosuppressive therapy. Ideally, biomarkers that predict adverse events would be available to screen patients before prescribing the drug.

4. Biomarkers of autoimmune and inflammatory diseases

The identification, qualification, and application of diagnostic and prognostic biomarkers remain the holy grail of the current omics paradigm. Biomedical researchers keep a watchful eye for any gene, protein, or metabolite expressions that could serve as biomarkers indicative of early disease phenotypes and sub phenotypes, or predictive of disease progression and outcome. More highly desirable are biomarkers that can be tagged to drug targets and therapy. We have summarized some of the putative and validated biomarkers of autoimmune and inflammatory diseases in Table 1.

Table 1 Examples of putative and validated biomarkers of autoimmune and inflammatory diseases.

| Name                              | Other Names                                      | Involvement in disease                  |
|-----------------------------------|--------------------------------------------------|-----------------------------------------|
| Ribonuclease, RNase A family, 3   | Ribonuclease 3, Eosinophil cationic protein       | Asthma<sup>61</sup>, Allergic rhinitis<sup>82</sup> |
| Interleukin 5                     | T-cell replacing factor                          | Asthma<sup>43</sup>                     |
| Interleukin 13 receptor, alpha 2  | Interleukin-13-binding protein                   | Asthma<sup>44</sup>                     |
| ADAM metallopeptidase domain 33  | Disintegrin and metalloproteinase domain-containing protein 33 | Asthma<sup>25</sup>                     |
| interleukin 4                     | B-cell stimulatory factor 1                       | Asthma<sup>46</sup>                     |
| leukotriene C4 synthase           | Leukotriene-C(4) synthase                        | Asthma<sup>47</sup>                     |
| Adenosine A1 receptor             |                                                  | Asthma<sup>48</sup>                     |
| signal transducer and activator of transcription 6 | IL-4 Stat                           | Asthma<sup>49</sup>                     |
| Type IV phosphodiesterase        | cAMP-specific 3',5'-cyclic phosphodiesterase     | Asthma<sup>28</sup>                     |
| C-C chemokine receptor type 4     | K5-5                                            | Asthma<sup>1</sup>, Atopic dermatitis<sup>103</sup> |
| E-selectin                        | Endothelial leukocyte adhesion molecule 1        | Asthma<sup>22</sup>                     |
| High affinity interleukin-8 receptor B | CXCR-2                                        | Asthma, COPD<sup>77</sup>               |
| Interferon gamma                  | Immune interferon                               | Asthma<sup>44</sup>                     |
| Interleukin-17A                   | Cytotoxic T-lymphocyte-associated antigen 8      | Asthma<sup>5</sup>                      |
| Peroxisome proliferator-activated receptor gamma | Nuclear receptor subfamily 1 group C member 3 | Asthma and COPD<sup>35</sup>, Atopic dermatitis and Psoriasis<sup>102</sup> |
| Histamine H4 receptor             | G-protein coupled receptor                       | Asthma, Allergic rhinitis<sup>77</sup>  |
| L-selectin                        | Lymph node homing receptor                       | Asthma<sup>8</sup>                      |
| Prostaglandin E2 receptor, EP3 subtype | Prostanoid EP3 receptor                        | Asthma<sup>9</sup>                      |
| Glucocorticoid receptor           | Nuclear receptor subfamily 3 group C member 1    | Asthma<sup>40</sup>, COPD<sup>35</sup>  |
| Beta-1 adrenergic receptor        | Beta-1 adrenoreceptor                            | Asthma<sup>41</sup>                     |
| Beta-2 adrenergic receptor        | Beta-2 adrenoreceptor                            | Asthma<sup>42</sup>                     |
| Histamine H1 receptor             |                                                  | Asthma<sup>43</sup>                     |
| Prostaglandin D2 receptor         | Prostanoid DP receptor                           | Asthma, Allergic rhinitis<sup>34</sup>  |
| Tyrosine-protein kinase ITK/TSK   | T-cell-specific kinase, Tyrosine-protein kinase Lyk, Kinase EMT | Asthma<sup>25</sup>                     |
| Tyrosine-protein kinase           | Spleen tyrosine kinase                           | Asthma, Allergic rhinitis<sup>36</sup>  |
5. Future outlook and opportunities

Much of current biomarker development efforts are aimed at identifying noninvasive ways of monitoring progression and diagnosing clinical events in relation to current or new therapeutic agents. While interventions during later stages of disease development can still provide significant impact on patient management, the cost of medical care can be quite high and the pathological condition may have already become irreversible. Moreover, no solution is yet available that efficiently retrieves and processes biomarker information pertaining to autoimmune and inflammatory diseases. The bioinformatics community does many things, but we can roughly summarize most activities as either building algorithms or building databases. We are developing a freely accessible online database which will be the one of the first efforts to build an easily accessible and comprehensive literature-derived database covering known autoimmune and inflammatory disease biomarkers. Database will allow users to link autoimmune and inflammatory diseases to protein, gene or carbohydrate biomarkers through the use of search tools. It will support various types of data searches and application tools to analyze sequence and structure features of potential and validated biomarkers. It is believed that this approach will help alleviate stagnation and foster innovation in the development of new medical products, and, ultimately, lead to more personalized medicine in autoimmune and inflammatory diseases. The coming few years will see many breakthroughs in this regard.

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