BIOMARKERS AND BIOINFORMATICS (B&B)

ENABLING PLATFORM

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OBJECTIVE

For over seven years, AllerGen has united leading scientists across the country to discover and develop diagnostic, prognostic, therapeutic and mechanistic biomarkers for asthma and allergies. Studies include: profiling of urine metabolites predictive of asthma; identification of gene polymorphisms linked to allergic inflammation and disease; and discovery of stem, immune and inflammatory cell markers, cytokines and profiles/phenotypes diagnostic or predictive of susceptibility, severity or type of allergic responses. Parallel efforts have been made to identify environmental markers of allergic disease, which include stress, toxicants, pollutants and microbial agents.

Biomarkers and Bioinformatics brings together members of AllerGen's diagnostics and biomarkers research team, new partners with various 'omics' capabilities, biological sampling standard operating protocols (SOPs) and animal models into an integrated, world-leading systems-biology and bioinformatics approach to development and commercialization across AllerGen's Legacy Projects.

NEED FOR RESEARCH

Biological markers are characteristics that are measured and evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. Phenotypes result from the expression of genes as well as the influence of environmental factors. To fully comprehend complex phenotypes such as those related to allergy and asthma, there is an emerging need to understand the interdependency between genes and proteins that may influence the impact of a specific gene mutation.

Comprehensive validation of these interactions—the identification of biomarkers for allergic diseases—offers remarkable benefits, including susceptibility prediction, disease subtype differentiation, diagnostic potential, and possibly the identification of novel therapeutics.

Projects under this Enabling Platform are focused on accelerating discoveries in three strategic areas:

1. Near-term therapeutics targets, which are likely to be validated quickly and show promise for rapid partnerships with industry;
2. Diagnostic methodologies for patient identification, diagnosis and monitoring; and,
3. Bioinformatics platforms that facilitate biomarker identification and analyses *in silico*.

Biomarker discovery for disease diagnosis and management is being fuelled by the growth of personalized medicine (U.S. market $450 billion by 2015) and biomarker markets ($42 billion globally by 2015). Both markets represent opportunities for AllerGen.

The B&B platform holds great transformative promise, given the potential applications of its ambitious research goals and growing global interest in these areas.

Biomarkers & Bioinformatics Enabling Platform Projects

122B&B1: *Genome-wide Association Results*
(PI: Daley)

Asthma and related phenotypes are complex genetic diseases with multiple gene variants, where gender and environmental factors may produce specific clinical manifestations. This study cross-references high-throughput genetic polymorphisms (SNPs) susceptibility loci data with environmental data and linkage to allergic diseases, to identify novel gene-environment interactions in the development of asthma. This study capitalizes on an international consortium that developed a large patient data set to link DNA polymorphisms with susceptibility to asthma. The analysis of these results will inform the development of novel data analysis tools to facilitate detection of gene-environment factors that, in isolation, show minimal effects.

12B&B2: *A network biology approach to allergy: Annotated database of molecular interactions*
(PI: Brinkman)

Based on previous systems-based research of innate immunity, coupled with preliminary investigations of allergy and asthma, this research team hypothesizes that there is a rich collection of allergy and asthma data in the literature that can be integrated into a molecular interaction database, providing a networked framework that will allow AllerGen researchers to view allergic responses in a more holistic way. The team hypothesizes that this framework, overlaid with different types of allergy and asthma data, will allow new insights to be gained regarding key players in the allergy and asthma molecular response, leading to new ideas for approaches to controlling allergic diseases.

12B&B3: *Biomarkers of a Sympathetic Anti-inflammatory Pathway, Neuro-regulation of Sympathetic Anti-inflammatory Activity*
(PI: Befus)

To understand mind-body interactions, this research team studies how the nervous system regulates allergic inflammatory responses. Early outputs of this research include the discovery of an anti-inflammatory protein whose production is controlled by the nervous system in a model of allergic asthma. This research investigates the effects of this anti-inflammatory protein in several disease models, so as to develop experimental drugs and provide evidence of the pathway in humans. These studies will provide new knowledge on components of a neuroendocrine pathway that regulates inflammation, will determine whether it is abnormal in asthma, and will capitalize on new drug development arising from this knowledge.

12B&B4: *CD34 as a therapeutic target for allergic inflammation and asthma*
(PI: McNagny)

Although some allergic asthma can be controlled in part through the use of inhaled steroids, such therapies can have undesired side effects, and steroid resistant asthma is increasingly common. Thus, there is a large unmet need for therapeutics that can ameliorate this common disease. This research team has demonstrated that the cell surface protein CD34 is expressed by a number of inflammatory cell types (precursors for dendritic cells [DCs], eosinophils and mast cells) that play key roles in allergic inflammation. The ultimate goal is to provide scientific evidence that blocking the expression of this gene could potentially have therapeutic results, without unwanted side effects.

12B&B5*: Urine NMR-based Metabolomics for Asthma Diagnosis*
(PI: Adamko)

This research team has developed a novel method to measure inflammation produced by atopic asthma in pediatric and adult patients using a combination of urine samples and Nuclear Magnetic Resonance (NMR) measurements. A unique core metabolites signature for asthma is the basis of Respirlyte©, an AllerGen spin-off company. It is anticipated that identification and analysis of additional metabolites will enhance the sensitivity and specificity of the assay. Respirlyte© commercializes respiratory diagnostic assays through the use of metabolomics-based technologies that could be used in a doctor's office.

12B&B6: *Allergic Asthma Functional & Pharmaco-genomics for Early & Late Phase Response Biomarkers*
(PI: Tebbutt)

This research uses high-performance genomic profiling to investigate the changes in peripheral blood cell gene expression that underpin the physiological and cellular characteristics of allergic responses to allergen challenge. The project will identify gene expression "signatures" and evaluate their performance as biomarkers for late phase response. The project aims to discover, validate and employ predictive and diagnostic molecular biomarkers of early and late phase responses to allergen inhalation challenge to improve therapies.

12B&B7 - *Hemopoietic stem cell biomarkers in the diagnosis and prediction of allergic inflammation and disease: STEM (Stem cell Team for Emerging Markers)* (PI: Denburg)

This study builds upon AllerGen's investments in the discovery of novel diagnostic biomarkers in cord blood, bone marrow, peripheral blood and tissues to predict the development of and monitor ongoing allergic diseases and asthma. This project is refining a diagnostic test using infant cord blood and studying factors that could be used for that diagnostic array, or which could serve as novel targets for therapy. The project uses cord blood stem cells obtained primarily from infants enrolled in AllerGen's Canadian Healthy Infant Longitudinal Development (CHILD) Study birth cohort.