# How did computers help us to find biomarkers for corticosteroid resistance in asthma through systems biology approach?

Asthma is a chronic disease that affects the lower airways, hampering the air movement in the lungs and the gas exchange. Asthma is characterized by bronchial inflammation that, particularly during an asthma attack, results in difficulty of breathing, wheezing, coughing and chest tightness.

About 300 million people worldwide have this disease and around 300,000 die every year. Most symptoms are controlled by inhaled corticosteroids (ICS), which are the first line of treatment. Corticosteroids mimic the effects of hormones naturally produced in our body, more specifically in the adrenal glands, which are located on top of the kidneys. When administered in doses higher than your body's usual quantity, corticosteroids promote anti-inflammatory responses, but significant adverse reactions. However, approximately 10% of the patients with asthma require very high doses of ICS and show variable degrees of insensitivity to corticosteroid treatment. These patients have severe asthma and consume a significant proportion of health care resources. Regardless of costs, the quality of life is hugely impaired in severe asthma, which is a great clinical challenge for medical doctors.

Thus, the search for biomarkers in patients with severe asthma regarding corticosteroid sensitivity is a priority. Unfortunately, the clinical diagnosis of corticosteroid insensitivity is difficult and not well established. The patient has to demonstrate a failure of response after a 7 to 14-day course of daily systemic corticosteroid treatment.

In a molecular level, *the scenario is not encouraging.* Multiple anti-inflammatory processes that should be activated by corticosteroid treatment seem to be reduced in patients with resistance to corticosteroids. Moreover, severe asthma is influenced by many environmental factors, which promote heterogeneous immune responses throughout the lungs. In this sense, nowadays, research groups are managing to describe how molecular processes in this disease can be used as diagnostic and prognostic tests. In this mission, computers can help us to understand large-scale data (*global analysis* of *genes* encoding *proteins)* derived from high-throughput techniques into comprehensive models.

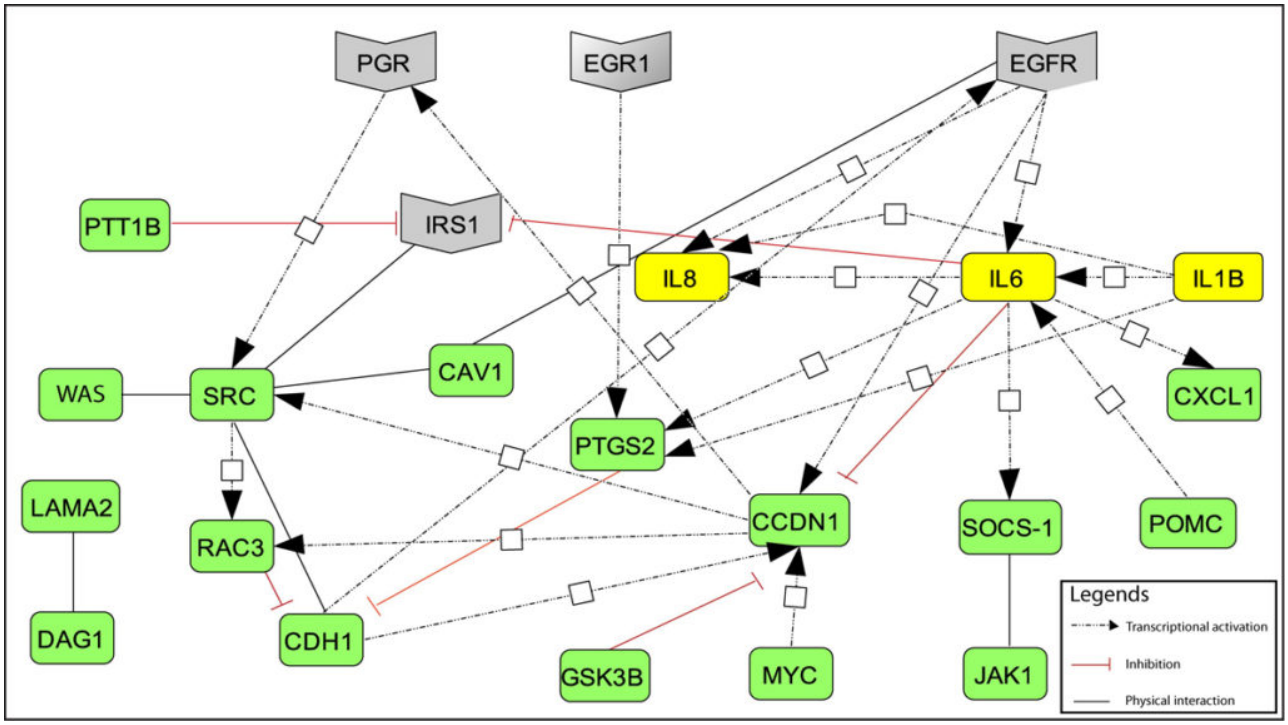


Fig. 1. Putative cell signalling pathways of severe asthma.

In the scientific world, we are living the post-genomic era, which is leading towards the insights into the complex biological system. This allowed the development of systems biology, a new scientific discipline that helps to explain a complex process in a single molecular perspective. Systems biology focuses on predictive models, quantifying all molecular entities (proteins or genes) of a biological system to evaluate their interactions into networks. The behavior of these networks may be considered a biomarker. Based on this principle, our group developed a strategy to find a biomarker network for severe asthma. Thus, we predicted a network using expression data of bronchoalveolar lavage of adults with corticosteroid-resistant asthma. This network consisted of genes with high connections and with a potential to regulate all dense regions (clusters) within the network itself. Thus, we identified 48 major and interacting genes. Some of these genes corresponded to receptors (EGFR, EGR1, ESR2, PGR), transcription factors (MYC, JAK), cytokines (IL8, IL6, IL1B), one chemokine (CXCL1), one kinase (SRC) and one cyclooxygenase (PTGS2), which were described to be associated with inflammatory environment and severe corticosteroid-resistant asthma (Fig. 1). These markers are candidates to clinical validation, after which would help for the early diagnosis of this very complex disease or for the development of new treatments.

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## Publication

Identifying a biomarker network for corticosteroid resistance in asthma from bronchoalveolar lavage samples.
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