Department of Systems Bioscience for Drug Discovery

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Research Projects:

With the advent of the post genomic era, the focus of life science has shifted from the functional analysis of individual genes to the elucidation of interactions of versatile biomolecules in a complex biological system. Concomitantly with this, the progress in Genomics has triggered the emergence of a new discipline, Systems Biology - as diverse as Functional Genomics, Systems Biology and Chemical Biology. On the other hand, current drug discovery still relies on molecular-targeted approaches, and much attention is being directed toward the identification and functional control of individual disease-causing proteins. Considering the fact that the emergence of side effects, which is a critical issue in drug development, can be largely attributed to unanticipated interactions between proteins and a drug, it is a challenging task to unravel the whole picture of pharmacological activities solely from the functional change of a single protein interacting with the drug. Therefore, drug discovery science is awaiting a breakthrough and innovation. With this in mind, our laboratory aims to apply the approach of Systems Bioscience to practical problems in drug development and to further develop new techniques dedicated to drug discovery science, thereby establishing a new paradigm termed “Systems Bioscience for Drug Discovery”.

1) Exploration of disease-causing and drug-target genes, and elucidation of the mechanisms by systematic simulation of the process of pathogenesis and pharmacological actions

By integrating chemical genomics information about interactions of vast amounts of chemical compounds and proteins, with gene expression and side effects information, we aim to construct a comprehensive drug-disease network that bridges between drugs, molecular-targeted proteins, disease-related proteins and diseases. We further develop a simulator for network-based drug discovery, and infer molecular networks specific to diseases and drugs from bioassay and gene expression data. These efforts will enable the exploration of disease-causing and drug-target proteins suitable for controlling the behavior of the biological system, and also lead to the systematic elucidation of the disease state and process, pharmacological actions as well as toxicological mechanisms.

2) Development of rational drug search methodology for improving pharmacological effects and safety, and establishment of drug design theory based on polypharmacology

With the use of machine learning techniques, we aim to extract rules on compound-protein interactions from chemical genomics information being accumulated on a large scale, thereby enabling rational compound search and generation of chemical structures that underlie the preference of interactions. We also construct a multi-dimensional structure-activity-correlation model to connect chemical structures and target proteins to activity information, and extract pharmacologically active structures. Importantly, we focus on the establishment of a new drug design theory based on polypharmacology (in particular, target selectivity). This study holds great promise for accelerating the development of more efficacious and safer drugs.

3) Analysis of brain-region specific genetic networks based on models of depression and antidepressant therapy, and systematic analysis of the involvement of inflammatory mediators

To date, little is known about the pathogenesis of depression and the underlying mechanism of antidepressant therapy. According to the “monoamine hypothesis”, depression does not only cause a decrease in the concentration of neurotransmitters (serotonin and adrenalin) in the synaptic cleft, but also causes neuronal plasticity. In order to explore how the brain changes at the cellular and molecular levels under depression, we create models of depression and antidepressant therapy using rats and mice, based on which biomolecular and histological analyses are performed. Specifically, gene expression changes are measured for slices from specific brain regions and subjected to global analysis. Gene expression networks are then constructed to capture cellular changes caused by the pathogenesis of depression or application of therapy. This will lead to the elucidation of functional changes that are common to depression.

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