A Systems Pharmacology Knowledgebase: On- and Off-Target Effects of Beta-Blockers
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Abstract
In silico analysis can provide valuable insights to how candidate drug compounds may modulate protein targets and can predict potential drug effects, both on- and off-target. Using MedScan, a proprietary, high-content linguistic tool, a database of protein networks associated with different diseases and small molecule effects has been compiled by extracting the information from scientific literature and further complimented with a curated collection of “canonical” signaling, metabolic and toxicity pathways.

The resulting database has been interrogated to find shared pathways modulated by 19 known beta-blockers (including Propranolol, Brevibloc, Carvedilol and Atenolol). Beta blockers, also known as beta-adrenergic blocking agents, are drugs that block norepinephrine and epinephrine from binding to beta receptors on nerves. Used to treat conditions such as cardiac arrhythmias, heart attack, and hypertension, they are also known to cause a wide variety of side-effects. Using this information, we predicted anti-inflammatory and prevention drug effects for beta-blockers in renal failure. Although many of these predictions have been confirmed by clinical studies of several beta-blockers, we predicted additional effects for diabetes and hyperplasia that were not previously reported. These effects include both harmful toxicities, as well as novel disease indications. This analysis provides a framework to generate and test hypotheses of mechanism of drug action that can be used to refine further experiments and interpret experimental design.

Workflow Overview

Workflow 1: 1. Start with the list of all known beta-blockers (19 drugs and compounds) 2. Identify all downstream protein targets for compounds inhibited by at least 2 beta-blockers (77) and activated by at least 2 beta-blockers (77) 3. Identify signaling and toxicity pathways enriched with beta-blocker targets.

Workflow 2: 1. Find disease-centric protein sub-networks whose beta-blocker compounds modulate proteins affected in a disease/toxicity. Identified by searching the Ariadne database of 3000+ disease/toxicity networks for the “signed” overlap with the list of beta-blocker protein targets.

MedScan® (Dictionaries & Rules)
MedScan extracts relationships from text in three major steps:
- Entities are recognized in a sentence using dictionaries
- Algorithms perform noun phrase normalization decomposing complicated sentences into primitive semantic blocks
- Pattern matching algorithms find semantic blocks describing biological interactions and record them in XML files classifying them according to pre-designed ontologies

Method
MedScan Technology works with abstracts, articles and other types of scientific text. It recognizes proteins, chemicals, cell processes, diseases, and other concepts using proprietary dictionaries to capture relationships between them such as binding, regulation, protein modification, and others. Curation of the extracted data ensures high quality of Pathway Studio databases. Ariadne databases have been created with MedScan from the entire PubMed and over 90 full text journals. As PubMed grows, regular updates keep the databases refreshed.

An integral part of Pathway Studio, MedScan can be used to update database daily. Additional public and proprietary sources can also be also imported to customize databases. Database customizations such as organism or topic-specific datasets can also be also ordered from Ariadne.

Conclusions
- MedScan compiles a comprehensive knowledgebase of protein/drug/disease networks
- Gene set/sub-network enrichment analysis assigns high scores to the biologically meaningful findings: known signaling pathways and disease indications affected by beta-blockers
- Analysis of two independent databases: (i) curated pathways and (ii) disease sub-networks, cross-validates the relevance of beta-blockers to effects on inflammation and kidney disease.
- Several beta-blockers may have side effect of diabetes and hyperglycemia, two conditions not found in the literature to be associated with these drugs.