Research outputs:

Nomenclature for alleles of the human carboxylesterase 1 gene

General information
State: Published
Organisations: Department of Bio and Health Informatics, Integrative Systems Biology, Department of Biotechnology and Biomedicine
Number of pages: 3
Pages: 78-80
Publication date: 2017
Peer-reviewed: Yes

Publication information
Journal: Pharmacogenetics and Genomics
Volume: 27
Issue number: 2
ISSN (Print): 1744-6872
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.5 SJR 0.933 SNIP 0.826
Web of Science (2017): Impact factor 2.25
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Peroxisome proliferator-activated receptor γ (PPARγ) is a well-known target for thiazolidinedione antidiabetic drugs. In this paper, we present the synthesis and biological evaluation of a series of dihydropyrano[2,3-c]pyrazole derivatives as a novel family of PPARγ partial agonists. Two analogues were found to display high affinity for PPARγ with potencies in the micro molar range. Both of these hits were selective against PPARγ, since no activity was measured when tested against PPARα, PPARδ and RXRα. In addition, a novel modelling approach based on multiple individual flexible alignments was developed for the identification of ligand binding interactions in PPARγ. In combination with cell-based transactivation experiments, the flexible alignment model provides an excellent analytical tool to evaluate and visualize the effect of ligand chemical structure with respect to receptor binding mode and biological activity.
ChemProt-3.0: a global chemical biology diseases mapping

ChemProt is a publicly available compilation of chemical-protein-disease annotation resources that enables the study of systems pharmacology for a small molecule across multiple layers of complexity from molecular to clinical levels. In this third version, ChemProt has been updated to more than 1.7 million compounds with 7.8 million bioactivity measurements for 19,504 proteins. Here, we report the implementation of global pharmacological heatmap, supporting a user-friendly navigation of chemogenomics space. This facilitates the visualization and selection of chemicals that share similar structural properties. In addition, the user has the possibility to search by compound, target, pathway, disease and clinical effect. Genetic variations associated to target proteins were integrated, making it possible to plan pharmacogenetic studies and to suggest human response variability to drug. Finally, Quantitative Structure-Activity Relationship models for 850 proteins having sufficient data were implemented, enabling secondary pharmacological profiling predictions from molecular structure.
Investigating the impact of missense mutations in hCES1 by in silico structure-based approaches

Genetic variations in drug-metabolizing enzymes have been reported to influence pharmacokinetics, drug dosage and other aspects that affect therapeutic outcomes. Most particularly, non-synonymous single-nucleotide polymorphisms (nsSNPs) resulting in amino acid changes disrupt potential functional sites responsible for protein activity, structure, or stability, which can account for individual susceptibility to disease and drug response. Investigating the impact of nsSNPs at a protein's structural level is a key step in understanding the relationship between genetic variants and the resulting phenotypic changes. For this purpose, in silico structure-based approaches have proven their relevance in providing an atomic-level description of the underlying mechanisms. The present review focuses on nsSNPs in human carboxylesterase 1 (hCES1), an enzyme involved in drug metabolism. We highlight how prioritization of functional nsSNPs through computational prediction techniques in combination with structure-based approaches, namely molecular docking and molecular dynamics simulations, is a powerful tool in providing insight into the underlying molecular mechanisms of nsSNPs phenotypic effects at microscopic level. Examples of in silico studies of carboxylesterases (CESs) are discussed, ranging from exploring the effect of mutations on enzyme activity to predicting the metabolism of new hCES1 substrates as well as to guiding rational design of CES-selective inhibitors.
Synthesis and biological evaluations of cytotoxic and antiangiogenic triterpenoids-jacaranone conjugates

Background: The development of antiangiogenic agents arises as a more effective and selective therapeutic approach for the treatment of cancer. In addition to reduced acute toxicity, the efficacy of chemotherapy could be improved when administered in combination specific antiangiogenic with cytotoxic agents. The conjugation or hybridization of bifunctional molecules is one of the alternative rational design strategies for co-administration of anticancer drugs. Objective and Methods: The goal of this work is to prepare the conjugates of an antiangiogenic triterpene, 3-oxo oleanolic acid, and structurally related triterpenoids with a cytotoxic semibenzoquinone, jacaranone. The cytotoxic, antiproliferative and antiangiogenic activities of segments and conjugates were determined. The possible targets of conjugates 6a-6h were predicted using Similarity Ensemble Approach (SEA). Results: The results showed that these conjugates are more potent in both cytotoxic and antiangiogenic assays than their corresponding parent molecules, and are also selectively more active against melanoma cells B16 and metastatic B16BL6 than the two other cancer cell lines (A549 and MCF-7) tested. The predicted antiangiogenesis related targets could involve glycogen phosphorylase, neuraminidase, interferon gamma, and tubulin beta chain. Conclusion: The bifunctional conjugates could be useful as dual acting antitumor/antangiogenic agents.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Chinese Academy of Medical Sciences, Hong Kong Baptist University, Nankai University
Number of pages: 11
Pages: 775-785
Publication date: 2016
Peer-reviewed: Yes

Publication information
Journal: Medicinal Chemistry
Volume: 12
Issue number: 8
ISSN (Print): 1573-4064
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Web of Science (2017): Indexed yes
Scopus rating (2017): CiteScore 1.44 SJR 0.372 SNIP 0.529
Web of Science (2017): Impact factor 2.631
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Evidence of interactions between aroma compounds and the CB1 receptor opens new routes for regulation of food intake

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Integrative Systems Biology, Universite de Bourgogne
Number of pages: 1
Pages: 280-280
Publication date: 2015
Peer-reviewed: Yes

Publication information
Journal: Chemical Senses
Volume: 40
Issue number: 3
ISSN (Print): 0379-864X
Ratings:
Evolution of substrate recognition sites (SRSs) in cytochromes P450 from Apiaceae exemplified by the CYP71AJ subfamily

Background: Large proliferations of cytochrome P450 encoding genes resulting from gene duplications can be termed as 'blooms', providing genetic material for the genesis and evolution of biosynthetic pathways. Furanocoumarins are allelochemicals produced by many of the species in Apiaceaeous plants belonging to the Apioideae subfamily of Apiaceae and have been described as being involved in the defence reaction against phytophagous insects. Results: A bloom in the cytochromes P450 CYP71AJ subfamily has been identified, showing at least 2 clades and 6 subclades within the CYP71AJ subfamily. Two of the subclades were functionally assigned to the biosynthesis of furanocoumarins. Six substrate recognition sites (SRS1-6) important for the enzymatic conversion were investigated in the described cytochromes P450 and display significant variability within the CYP71AJ subfamily. Homology models underline a significant modification of the accession to the iron atom, which might explain the difference of the substrate specificity between the cytochromes P450 restricted to furanocoumarins as substrates and the orphan CYP71AJ. Conclusion: Two subclades functionally assigned to the biosynthesis of furanocoumarins and four other subclades were identified and shown to be part of two distinct clades within the CYP71AJ subfamily. The subclades show significant variability within their substrate recognition sites between the clades, suggesting different biochemical functions and providing insights into the evolution of cytochrome P450 'blooms' in response to environmental pressures.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of Copenhagen, Université de Lorraine
Number of pages: 14
Publication date: 2015
Peer-reviewed: Yes

Publication information
Journal: B M C Evolutionary Biology
Volume: 15
Issue number: 122
ISSN (Print): 1471-2148
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.18 SJR 1.656 SNIP 1.16
Web of Science (2017): Impact factor 3.027
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.12 SJR 2.006 SNIP 1.32
Web of Science (2016): Impact factor 3.221
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3.37 SJR 2.133 SNIP 1.22
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.42 SJR 2.276 SNIP 1.31
Web of Science (2014): Impact factor 3.368
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 3.52 SJR 2.017 SNIP 1.234
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 3.43 SJR 2.027 SNIP 1.19
ISI indexed (2012): ISI indexed yes
Individualization of treatments with drugs metabolized by CES1: combining genetics and metabolomics

CES1 is involved in the hydrolysis of ester group-containing xenobiotic and endobiotic compounds including several essential and commonly used drugs. The individual variation in the efficacy and tolerability of many drugs metabolized by CES1 is considerable. Hence, there is a large interest in individualizing the treatment with these drugs. The present review addresses the issue of individualized treatment with drugs metabolized by CES1. It describes the composition of the gene encoding CES1, reports variants of this gene with focus upon those with a potential effect on drug metabolism and provides an overview of the protein structure of this enzyme bringing notice to mechanisms involved in the regulation of enzyme activity. Subsequently, the review highlights drugs metabolized by CES1 and argues that individual differences in the pharmacokinetics of these drugs play an important role in determining drug response and tolerability suggesting prospects for individualized drug therapies. Our review also discusses endogenous substrates of CES1 and assesses the potential of using metabolomic profiling of blood to identify proxies for the hepatic activity of CES1 that predict the rate of drug metabolism. Finally, the combination of genetics and metabolomics to obtain an accurate prediction of the individual response to CES1-dependent drugs is discussed.
Identification of Odorant-Receptor Interactions by Global Mapping of the Human Odorome

The human olfactory system recognizes a broad spectrum of odorants using approximately 400 different olfactory receptors (hORs). Although significant improvements of heterologous expression systems used to study interactions between ORs and odorant molecules have been made, screening the olfactory repertoire of hORs remains a tremendous challenge. We therefore developed a chemical systems level approach based on protein-protein association network to investigate novel hOR-odorant relationships. Using this new approach, we proposed and validated new bioactivities for odorant molecules and OR2W1, OR51E1 and OR5P3. As it remains largely unknown how human perception of odorants influence or prevent diseases, we also developed an odorant-protein matrix to explore global relationships between chemicals, biological targets and disease susceptibilities. We successfully experimentally demonstrated interactions between odorants and the cannabinoid receptor 1 (CB1) and the peroxisome proliferator-activated receptor gamma (PPAR gamma). Overall, these results illustrate the potential of integrative systems chemical biology to explore the impact of odorant molecules on human health, i.e. human odorome.

General information

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Universite de Bourgogne, University of Copenhagen
Number of pages: 12
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: PLOS ONE
Volume: 9
Issue number: 4
Article number: e93037
ISSN (Print): 1932-6203
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.01 SJR 1.164 SNIP 1.111
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.236 SNIP 1.101
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3.32 SJR 1.427 SNIP 1.136
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.54 SJR 1.559 SNIP 1.148
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 3.94 SJR 1.772 SNIP 1.153
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 4.15 SJR 1.982 SNIP 1.156
Web of Science (2012): Impact factor 3.73
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
Pharmacology profiling of chemicals and proteins

The central tenet in drug-development of one drug selectively interacts with one target is increasingly challenged by the vast amount of data released to the public domain in the past 10-15 years, documenting multiple targets for most of the FDA approved pharmaceuticals [1]. Unintended interactions between pharmaceuticals and proteins in vivo potential leads to unwanted adverse effects, toxicity and reduced half-life, but can also lead to novel therapeutic effects of already approved pharmaceuticals. Hence identification of in vivo targets is of importance in discovery, development and repurposing of pharmaceuticals, a process referred to as pharmacology profiling.

Pharmacology profiling of chemical and protein based pharmaceuticals has been proven valuable in a number studies [2], however missing values in the drug-protein interaction matrix limits the profile for novel or less studied compounds. This limitation complicates adverse effect assessment in the early drug-development phase, thus contributing to drug attrition. Prediction models offer the possibility to close these gaps and provide more complete pharmacology profiles, however improvements in performances are required for these tools to serve as an alternative to experimentally obtained measurements.

Here I present several different tools that aid pharmacology profiling of the two main classes of pharmaceuticals; chemicals (small molecules) and proteins (biopharmaceuticals). Biopharmaceuticals have the inherent risks of eliciting an immune response due to its nonself origin, which potentially alters the pharmacology profile of the substance. The neutralization of biopharmaceuticals by antidrug antibodies (ADAs) is an important element in the immune response cascade, however studies of ADA binding site on biopharmaceuticals, referred to as B-cell epitopes, are complicated by expensive experimental procedures thus making prediction models an appealing alternative. In general, B-cell epitope prediction tools have moderate performances, which to some extent originates from an incomplete understanding of what constitute a B-cell epitope and incomplete datasets used for model building and benchmarking. In the first paper included in this thesis we analyze the B-cell epitopes obtained from co-crystalized antibody-antigen complexes from the PDB database. We were able to describe the epitope area as a flat oblong area residing on the protein surface consisting of a hydrophobic core surrounded by hydrophilic/charged residues. This finding prompted us to update the B-cell epitope prediction method DiscoTope [3] by introducing a novel scoring function for describing the spatial neighborhood surrounding each residue as described in paper II of this thesis. Using the developed method we assessed the impact on performance using a more realistic benchmark definition compared to privies studies, by including multiple epitopes for each antigen and the biological unit used for raising the antibody
response, when available. On average, the Area Under the roc-Curve (AUC) performance was improved from 0.791 to 0.824 for the 13 proteins were additional information could be obtained, thereby indicating that the performance of B-cell epitope prediction tools in general are under-estimated.

Novel techniques such as Next Generation Sequencing (NGS) and peptide microarray facilitate novel strategies for experimental identification of B-cell epitopes. In chapter 4, a novel method for epitope identification is described, combining NGS with phage-display. Epitopes in peanut allergen ara h1 were successfully detected using sera from peanut allergic patients and confirmed using peptide micro-array technology, demonstrating the applicability of both methods. Adverse effect of small molecule based pharmaceutical is rarely mediated through an immune response but is predominantly the consequence of interactions with unintended proteins in vivo. To assists researchers in determine the binding profile of chemicals, thus their pharmacology profile, a database of chemical-protein interactions were developed and presented in chapter 5. The database integrates chemical-protein interaction information from 10 different databases as well as disease, functional and pathway mapping of proteins, SNP data through the Ensembl database and prediction tools for filling out gaps in the chemical-protein interaction matrix. Graphical representation of the pharmacology space is accomplished by the use of zoomable heatmaps, which enable traversing from an overview of the entire space to specific pharmacology profiles of a single chemical by zooming on specific areas of the heatmap. The compiled dataset together with the implemented visualization and prediction tools, facilitate pharmacology profiling of chemicals in all development stages, hence potentially enable identification of adverse effects in early drug development or identification of novel treatment paradigms for approved pharmaceuticals.

Finally, the visualization of the pharmacology space is addressed by developing a 2 dimensional zoomable heatmap inspired by country and city maps. Chemicals sharing similar scaffold or features are placed together on the map, thus enable a more detailed visualization of the pharmacology landscape surrounding one or more chemicals of interest. The tool, presented in chapter 6, enables researchers to couple scaffold and feature hopping with bioactivity data for the use in drug-discovery and development, thus avoiding unwanted adverse effects.

In summary, here I present several different tools that can assists researchers in determine essential properties in the pharmacology profile of both protein and small molecule pharmaceuticals and potentially detect adverse effects in drug development.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Contributors: Kringelum, J. V., Taboureau, O., Lund, O.
Number of pages: 159
Publication date: 2014

Publication information
Place of publication: Kgs. Lyngby
Publisher: Technical University of Denmark (DTU)
Original language: English
Research output: Research › Ph.D. thesis – Annual report year: 2015

Solid-Phase Synthesis and Biological Evaluation of N-Dipeptido L-Homoserine Lactones as Quorum Sensing Activators
Bacteria use small signaling molecules to communicate in a process termed “quorum sensing” (QS), which enables the coordination of survival strategies, such as production of virulence factors and biofilm formation. In Gram-negative bacteria, these signaling molecules are a series of N-acylated L-homoserine lactones. With the goal of identifying non-native compounds capable of modulating bacterial QS, a virtual library of N-dipeptido L-homoserine lactones was screened in silico with two different crystal structures of LasR. The 30 most promising hits were synthesized on HMB-functionalized PEGA resin and released through an efficient acid-mediated cyclative release mechanism. Subsequent screening for modulation of QS in Pseudomonas aeruginosa and E. coli identified six moderately strong activators. A follow-up library designed from the preliminary derived structure–activity relationships was synthesized and evaluated for their ability to activate the QS system in this bacterium. This resulted in the identification of another six QS activators (two with low micromolar activity) thus illuminating structural features required for QS modulation.

General information
State: Published
Organisations: Department of Chemistry, Organic Chemistry, Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark, University of Copenhagen
Pages: 460-465
Publication date: 2014
Peer-reviewed: Yes

Publication information
Journal: ChemBioChem
Volume: 15
Issue number: 3
ISSN (Print): 1439-4227
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.64 SJR 1.407 SNIP 0.721
Web of Science (2017): Impact factor 2.774
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.64 SJR 1.283 SNIP 0.735
Web of Science (2016): Impact factor 2.847
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 2.77 SJR 1.268 SNIP 0.749
Web of Science (2015): Impact factor 2.85
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.88 SJR 1.392 SNIP 0.85
Web of Science (2014): Impact factor 3.088
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 3.15 SJR 1.634 SNIP 0.847
Web of Science (2013): Impact factor 3.06
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 3.49 SJR 1.874 SNIP 0.901
Web of Science (2012): Impact factor 3.74
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 3.59 SJR 1.921 SNIP 0.952
Web of Science (2011): Impact factor 3.944
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Scopus rating (2010): SJR 1.981 SNIP 0.929
Web of Science (2010): Impact factor 3.945
BFI (2009): BFI-level 2
Scopus rating (2009): SJR 1.928 SNIP 0.927
BFI (2008): BFI-level 2
Scopus rating (2008): SJR 1.989 SNIP 0.867
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 2.048 SNIP 0.986
Scopus rating (2006): SJR 1.938 SNIP 0.956
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 1.877 SNIP 0.953
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.734 SNIP 1.026
Scopus rating (2003): SJR 1.662 SNIP 1.076
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 7.15 SNIP 1.347
ChemProt-2.0: visual navigation in a disease chemical biology database

ChemProt-2.0 (http://www.cbs.dtu.dk/services/ChemProt-2.0) is a public available compilation of multiple chemical-protein annotation resources integrated with diseases and clinical outcomes information. The database has been updated to > 1.15 million compounds with 5.32 millions bioactivity measurements for 15 290 proteins. Each protein is linked to quality-scored human protein-protein interactions data based on more than half a million interactions, for studying diseases and biological outcomes (diseases, pathways and GO terms) through protein complexes. In ChemProt-2.0, therapeutic effects as well as adverse drug reactions have been integrated allowing for suggesting proteins associated to clinical outcomes. New chemical structure fingerprints were computed based on the similarity ensemble approach. Protein sequence similarity search was also integrated to evaluate the promiscuity of proteins, which can help in the prediction of off-target effects. Finally, the database was integrated into a visual interface that enables navigation of the pharmacological space for small molecules. Filtering options were included in order to facilitate and to guide dynamic search of specific queries.
ChemProt: A disease chemical biology database

The integration of chemistry, biology, and informatics to study drug actions across multiple biological targets, pathways, and biological systems is an emerging paradigm in drug discovery. Rather than reducing a complex system to simplistic models, fields such as chemogenomics and translational informatics are seeking to build a holistic model for a better understanding of the drug pharmacology and clinical effects. Here we will present a webserver called ChemProt that can assist, in silico, the drug actions in the context of cellular and disease networks and contribute in the field of disease chemical biology, drug repurposing, and off-target effects prediction.
Discovery of a novel selective PPAR\(\gamma\) ligand with partial agonist binding properties by integrated in silico / in vitro workflow

Full agonists to the peroxisome proliferator-activated receptor (PPAR\(\gamma\)), such as Rosiglitazone, have been associated with a series of undesired side effects, such as weight gain, fluid retention, cardiac hypertrophy, and hepatotoxicity. Nevertheless, PPAR\(\gamma\) is involved in the expression of genes that control glucose and lipid metabolism and is an important target for drugs against type 2 diabetes, dyslipidemia, atherosclerosis, and cardiovascular disease. In an effort to identify novel PPAR\(\gamma\) ligands with an improved pharmacological profile, emphasis has shifted to selective ligands with partial agonist binding properties. Toward this end we applied an integrated in silico/in vitro workflow, based on pharmacophore- and structure-based virtual screening of the ZINC library, coupled with competitive binding and transactivation assays, and adipocyte differentiation and gene expression studies. Hit compound 9 was identified as the most potent ligand (IC50 = 0.3 \(\mu\)M) and a relatively poor inducer of adipocyte differentiation. The binding mode of compound 9 was confirmed by molecular dynamics simulation, and the calculated free energy of binding was -8.4 kcal/mol. A novel functional group, the carbonitrile group, was identified to be a key substituent in the ligand-protein interactions. Further studies on the transcriptional regulation properties of compound 9 revealed a gene regulatory profile that was to a large extent unique, however functionally closer to that of a partial agonist. © 2013 American Chemical Society.
Scopus rating (2015): CiteScore 4.27 SJR 1.575 SNIP 1.281
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 3.88 SJR 1.433 SNIP 1.244
Web of Science (2014): Impact factor 3.738
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 4.4 SJR 1.654 SNIP 1.334
Web of Science (2013): Impact factor 4.068
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 4.22 SJR 1.518 SNIP 1.342
Web of Science (2012): Impact factor 4.304
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 4.3 SJR 1.326 SNIP 1.31
Web of Science (2011): Impact factor 4.675
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.424 SNIP 1.265
Web of Science (2010): Impact factor 3.822
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.039 SNIP 1.227
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.14 SNIP 1.099
Scopus rating (2007): SJR 0.984 SNIP 1.298
Scopus rating (2006): SJR 1.006 SNIP 1.337
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 0.846 SNIP 1.144
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 1.115 SNIP 1.403
Scopus rating (2003): SJR 0.973 SNIP 1.424
Scopus rating (2002): SJR 0.806 SNIP 1.466
Scopus rating (2001): SJR 0.683 SNIP 1.668
Scopus rating (2000): SJR 0.952 SNIP 1.254
Scopus rating (1999): SJR 0.931 SNIP 1.223
Original language: English
Keywords: Binding energy, Cytology, Digital libraries, Diseases, Drug interactions, Functional groups, Gene expression, Molecular dynamics, Molecular weight, Ligands
DOIs: 10.1021/ci3006148
Source: dtu
Source-ID: n::oai:DTIC-ART:swets/385670935::28177
Research output: Research - peer-review › Journal article – Annual report year: 2013

HExpoChem: a systems biology resource to explore human exposure to chemicals
Summary: Humans are exposed to diverse hazardous chemicals daily. Although an exposure to these chemicals is suspected to have adverse effects on human health, mechanistic insights into how they interact with the human body are still limited. Therefore, acquisition of curated data and development of computational biology approaches are needed to assess the health risks of chemical exposure. Here we present HExpoChem, a tool based on environmental chemicals and their bioactivities on human proteins with the objective of aiding the qualitative exploration of human exposure to chemicals. The chemical–protein interactions have been enriched with a quality-scored human protein–protein interaction network, a protein–protein association network and a chemical–chemical interaction network, thus allowing the study of environmental chemicals through formation of protein complexes and phenotypic outcomes enrichment. Availability:
HExpoChem is available at http://www.cbs.dtu.dk/services/HExpoChem-1.0/. Contact: karine@cbs.dtu.dk Supplementary information: Supplementary data are available at Bioinformatics online.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Pages: 1231-1232
Publication date: 2013
Peer-reviewed: Yes

**Publication information**

Journal: Bioinformatics
Volume: 29
Issue number: 9
ISSN (Print): 1367-4803

Ratings:
BFI (2019): BFI-level 2
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 7.84
Web of Science (2017): Impact factor 5.481
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 6.42
Web of Science (2016): Impact factor 7.307
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 6.06
Web of Science (2015): Impact factor 5.766
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 5.5
Web of Science (2014): Impact factor 4.981
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 5.78
Web of Science (2013): Impact factor 4.621
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 6.73
Web of Science (2012): Impact factor 5.323
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 5.61
Web of Science (2011): Impact factor 5.468
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 2
Web of Science (2010): Impact factor 4.877
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 2
Identification of LasR Ligands through a Virtual Screening Approach

With the widespread occurrence of bacterial resistance to antibiotics, the development of new strategies beyond conventional treatments is a pursuit taken by public health institutions worldwide. LasR, a transcription factor that controls quorum sensing in Pseudomonas aeruginosa, has emerged as an attractive therapeutic target for the next generation of antimicrobial agents. In the present study, a virtual screening workflow combining pharmacophore- and structure-based approaches was used to identify new LasR ligands. Five novel inducers and three inhibitors of LasR activity were validated experimentally by use of a cell-based assay. Interestingly, these compounds are molecularly distinct from the native signal molecule, N-3-oxododecanoyl-L-homoserine lactone (OHN), and may serve as lead structures for the design of new drugs. The binding modes of these compounds to the OHN binding site in LasR were predicted and used to identify the key interactions that contribute to the induction and inhibition of LasR activity.

General information

State: Published
Organisations: Organic Chemistry, Department of Chemistry, Center for Biological Sequence Analysis, Department of Systems Biology, University of Copenhagen, Technical University of Denmark
Pages: 157-163
Publication date: 2013
Peer-reviewed: Yes

Publication information

Journal: ChemMedChem
Volume: 8
Issue number: 1
ISSN (Print): 1860-7179
Ratings:
  BFI (2019): BFI-level 1
  Web of Science (2019): Indexed yes
  BFI (2018): BFI-level 1
  Web of Science (2018): Indexed yes
  BFI (2017): BFI-level 1
  Scopus rating (2017): CiteScore 2.91 SJR 1.137 SNIP 0.805
  Web of Science (2017): Impact factor 3.009
  Web of Science (2017): Indexed yes
  BFI (2016): BFI-level 1
  Scopus rating (2016): CiteScore 3.11 SJR 1.156 SNIP 0.904
  Web of Science (2016): Impact factor 3.225
  Web of Science (2016): Indexed yes
  BFI (2015): BFI-level 1
  Scopus rating (2015): CiteScore 3 SJR 1.151 SNIP 0.902
Pharmacological profiling of drugs by linking chemoinformatics and bioinformatics data

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Contributors: Taboureau, O.
Publication date: 2013
Peer-reviewed: Yes

Publication information
Journal: Abstracts of Papers of the American Chemical Society
Volume: 245
Article number: 71-CINF
Scientific competency questions as the basis for semantically enriched open pharmacological space development

Molecular information systems play an important part in modern data-driven drug discovery. They do not only support decision making but also enable new discoveries via association and inference. In this review, we outline the scientific requirements identified by the Innovative Medicines Initiative (IMI) Open PHACTS consortium for the design of an open pharmacological space (OPS) information system. The focus of this work is the integration of compound–target–pathway–disease/phenotype data for public and industrial drug discovery research. Typical scientific competency questions provided by the consortium members will be analyzed based on the underlying data concepts and associations needed to answer the questions. Publicly available data sources used to target these questions as well as the need for and potential of semantic web-based technology will be presented.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novartis, Janssen Research and Development, LLC, GlaxoSmithKline, University of Seville, University of Vienna, Royal Society of Chemistry, Pompeu Fabra University, University of Hamburg, Swiss Institute of Bioinformatics, University of Manchester, Connected Discovery Ltd, Spanish National Cancer Research Centre, AstraZeneca Sweden
Pages: 843-852
Publication date: 2013
Peer-reviewed: Yes
Temporal variability in urinary phthalate metabolite excretion based on spot, morning, and 24-h urine samples: Considerations for epidemiological studies

Urinary phthalate excretion is used as marker of phthalate exposure in epidemiological studies. Here we examine the reliability of urinary phthalate levels in exposure classification by comparing the inter- and intrasubject variation of urinary phthalate metabolite levels. Thirty-three young healthy men each collected two spot, three first-morning, and three 24-h urine samples during a 3-month period. Samples were analyzed for the content of 12 urinary metabolites of 7 different phthalates. Variability was assessed as intraclass correlation coefficients (ICC). For the metabolites of diethyl-, dibutyl-, and butylbenzyl-phthalates moderate ICCs were observed in all three sample types, albeit highest in 24-h urine (0.51-0.59). For the metabolites of di(2-ethylhexyl) phthalate and di-iso-nonyl phthalates lower ICCs (0.06-0.29) were found. These low ICCs indicate a high risk of misclassification of exposures for these two phthalates in population studies and hence an attenuation of the power to detect possible exposure-outcome associations. The only slightly higher ICCs for 24-h pools compared to first-morning and spot urine samples does not seem to justify the extra effort needed to collect 24-h pools. © 2012 American Chemical Society.
The effect of network biology on drug toxicology.

Introduction: The high failure rate of drug candidates due to toxicity, during clinical trials, is a critical issue in drug discovery. Network biology has become a promising approach, in this regard, using the increasingly large amount of biological and chemical data available and combining it with bioinformatics. With this approach, the assessment of chemical safety can be done across multiple scales of complexity from molecular to cellular and system levels in human health. Network biology can be used at several levels of complexity. Areas covered: This review describes the strengths and limitations of network biology. The authors specifically assess this approach across different biological scales when it is applied to toxicity. Expert opinion: There has been much progress made with the amount of data that is generated by...
various omics technologies. With this large amount of useful data, network biology has the opportunity to contribute to a better understanding of a drug’s safety profile. The authors believe that considering a drug action and protein’s function in a global physiological environment may benefit our understanding of the impact some chemicals have on human health and toxicity. The next step for network biology will be to better integrate differential and quantitative data.

Association between chemical pattern in breast milk and congenital cryptorchidism: modelling of complex human exposures

During the past four decades, there has been an increase in the incidence rate of male reproductive disorders in some, but not all, Western countries. The observed increase in the prevalence of male reproductive disorders is suspected to be ascribable to environmental factors as the increase has been too rapid to be explained by genetics alone. To study the association between complex chemical exposures of humans and congenital cryptorchidism, the most common...
malformation of the male genitalia, we measured 121 environmental chemicals with suspected or known endocrine disrupting properties in 130 breast milk samples from Danish and Finnish mothers. Half the newborns were healthy controls, whereas the other half was boys with congenital cryptorchidism. The measured chemicals included polychlorinated biphenyls (PCBs), polybrominated diphenyl-ethers, dioxins (OCDD/PCDFs), phthalates, polybrominated biphenyls and organochlorine pesticides. Computational analysis of the data was performed using logistic regression and three multivariate machine learning classifiers. Furthermore, we performed systems biology analysis to explore the chemical influence on a molecular level. After correction for multiple testing, exposure to nine chemicals was significantly different between the cases and controls in the Danish cohort, but not in the Finnish cohort. The multivariate analysis indicated that Danish samples exhibited a stronger correlation between chemical exposure patterns in breast milk and cryptorchidism than Finnish samples. Moreover, PCBs were indicated as having a protective effect within the Danish cohort, which was supported by molecular data recovered through systems biology. Our results lend further support to the hypothesis that the mixture of environmental chemicals may contribute to observed adverse trends in male reproductive health.

**General information**

State: Published

Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, University of Turku, Helmholtz Zentrum München, National Institute for Health and Welfare, Copenhagen University Hospital


Pages: 294-302

Publication date: 2012

Peer-reviewed: Yes

**Publication information**

Journal: International Journal of Andrology

Volume: 35

Issue number: 3

ISSN (Print): 0105-6263

Ratings:

BFI (2019): BFI-level 1

BFI (2018): BFI-level 1

BFI (2017): BFI-level 1

BFI (2016): BFI-level 1

Web of Science (2016): Indexed yes

BFI (2015): BFI-level 1

Scopus rating (2015): SJR 1.215 SNIP 1.661

BFI (2014): BFI-level 1

Scopus rating (2014): SJR 1.211 SNIP 1.598

Web of Science (2014): Impact factor 3.695

BFI (2013): BFI-level 1

Scopus rating (2013): SJR 1.09 SNIP 1.665

Web of Science (2013): Impact factor 3.206

ISI indexed (2013): ISI indexed yes

BFI (2012): BFI-level 1

Scopus rating (2012): SJR 1.02 SNIP 1.284

Web of Science (2012): Impact factor 3.565

ISI indexed (2012): ISI indexed yes

Web of Science (2012): Indexed yes

BFI (2011): BFI-level 1

Scopus rating (2011): SJR 1.009 SNIP 1.35

Web of Science (2011): Impact factor 3.591

ISI indexed (2011): ISI indexed yes

Web of Science (2011): Indexed yes

BFI (2010): BFI-level 1

Scopus rating (2010): SJR 0.95 SNIP 1.044


Web of Science (2010): Indexed yes
A Steered Molecular Dynamics Study of Binding and Translocation Processes in the GABA Transporter

The entire substrate translocation pathway in the human GABA transporter (GAT-1) was explored for the endogenous substrate GABA and the anti-convulsive drug tiagabine. Following a steered molecular dynamics (SMD) approach, in which a harmonic restraining potential is applied to the ligand, dissociation and re-association of ligands were simulated revealing events leading to substrate (GABA) translocation and inhibitor (tiagabine) mechanism of action. We succeeded in turning the transporter from the outward facing occluded to the open-to-out conformation, and also to reorient the transporter to the open-to-in conformation. The simulations are validated by literature data and provide a substrate pathway fingerprint in terms of which, how, and in which sequence specific residues are interacted with. They reveal the essential functional roles of specific residues, e.g. the role of charged residues in the extracellular vestibule including two lysines (K76 (TM1) and K448 (TM10)) and a TM6-triad (D281, E283, and D287) in attracting and relocating substrates towards the secondary/interim substrate-binding site (S2). Likewise, E101 is highlighted as essential for the relocation of the substrate from the primary substrate-binding site (S1) towards the cytoplasm.
Enantioselective determination of methylphenidate and ritalinic acid in whole blood from forensic cases using automated solid-phase extraction and liquid chromatography-tandem mass spectrometry.

A chiral liquid chromatography tandem mass spectrometry (LC–MS-MS) method was developed and validated for quantifying methylphenidate and its major metabolite ritalinic acid in blood from forensic cases. Blood samples were prepared in a fully automated system by protein precipitation followed by solid-phase extraction. The LC–MS-MS method was linear in the range of 0.5 to 500 ng/g for the enantiomers of both analytes. For concentrations above the limit of quantification, coefficients of variation were 15% or less, and the accuracy was 89 to 94%. For 12 postmortem samples in which methylphenidate was not determined to be related to the cause of death, the femoral blood concentration of d-methylphenidate ranged from 5 to 58 ng/g, and from undetected to 48 ng/g for l-methylphenidate (median d/l-ratio 5.9). Ritalinic acid was present at concentrations 10–20 times higher with roughly equal amounts of the d- and l-forms. In blood from 10 living subjects that were not suspected of being intoxicated by methylphenidate, the concentration ranges and patterns were similar to those of the
postmortem cases. Thus, methylphenidate does not appear to undergo significant postmortem redistribution.

**General information**

State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, The INDICES Consortium, Copenhagen University Hospital, University of Copenhagen
Contributors: Thomsen, R., B. Rasmussen, H., Linnet, K., Brunak, S., Taboureau, O.
Pages: 560-568
Publication date: 2012
Peer-reviewed: Yes

**Publication information**

Journal: Journal of Analytical Toxicology
Volume: 36
ISSN (Print): 0146-4760
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.38 SJR 1.065 SNIP 0.982
Web of Science (2017): Impact factor 2.599
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 2.52 SJR 1.231 SNIP 1.094
Web of Science (2016): Impact factor 2.409
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 2.18 SJR 1.024 SNIP 1.001
Web of Science (2015): Impact factor 2.322
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.66 SJR 1.298 SNIP 1.051
Web of Science (2014): Impact factor 2.858
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 2.48 SJR 1.17 SNIP 1.105
Web of Science (2013): Impact factor 2.627
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 1.9 SJR 0.881 SNIP 1.034
Web of Science (2012): Impact factor 2.107
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 2.13 SJR 1.066 SNIP 1.191
Web of Science (2011): Impact factor 2.022
ISI indexed (2011): ISI indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.761 SNIP 0.863
Web of Science (2010): Impact factor 1.545
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.07 SNIP 1.052
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.802 SNIP 0.804
Scopus rating (2007): SJR 1.252 SNIP 0.922
Scopus rating (2006): SJR 0.828 SNIP 1.07
Established and Emerging Trends in Computational Drug Discovery in the Structural Genomics Era

Bioinformatics and chemoinformatics approaches contribute to hit discovery, hit-to-lead optimization, safety profiling, and target identification and enhance our overall understanding of the health and disease states. A vast repertoire of computational methods has been reported and increasingly combined in order to address more and more challenging targets or complex molecular mechanisms in the context of large-scale integration of structure and bioactivity data produced by private and public drug research. This review explores some key computational methods directly linked to drug discovery and chemical biology with a special emphasis on compound collection preparation, virtual screening, protein docking, and systems pharmacology. A list of generally freely available software packages and online resources is provided, and examples of successful applications are briefly commented upon.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of Melbourne, Barcelona Supercomputing Center-Centro Nacional de Supercomputación, University Paris Diderot - Paris 7
Contributors: Taboureau, O., Baell, J. B., Fernández-Recio, J., Villoutreix, B. O.
Pages: 29-41
Publication date: 2012
Peer-reviewed: Yes

Publication information
Journal: Chemistry & Biology
Volume: 19
Issue number: 1
ISSN (Print): 1074-5521
Ratings:
BFI (2019): BFI-level 2
BFI (2018): BFI-level 2
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 5.16 SJR 3.174 SNIP 1.345
Web of Science (2017): Impact factor 5.915
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 5.43 SJR 3.258 SNIP 1.304
Web of Science (2016): Impact factor 6.743
Scopus rating (2015): SJR 3.222 SNIP 1.404
Web of Science (2015): Impact factor 5.774
Scopus rating (2014): SJR 3.01 SNIP 1.385
Web of Science (2014): Impact factor 6.645
Web of Science (2014): Indexed yes
Scopus rating (2013): SJR 3.015 SNIP 1.355
Web of Science (2013): Impact factor 6.586
ISI indexed (2013): ISI indexed yes
Of possible cheminformatics futures

For over a decade, cheminformatics has contributed to a wide array of scientific tasks from analytical chemistry and biochemistry to pharmacology and drug discovery; and although its contributions to decision making are recognized, the challenge is how it would contribute to faster development of novel, better products. Here we address the future of cheminformatics with primary focus on innovation. Cheminformatics developers often need to choose between “mainstream” (i.e., accepted, expected) and novel, leading-edge tools, with an increasing trend for open science. Possible futures for cheminformatics include the worst case scenario (lack of funding, no creative usage), as well as the best case scenario (complete integration, from systems biology to virtual physiology). As “-omics” technologies advance, and computer hardware improves, compounds will no longer be profiled at the molecular level, but also in terms of genetic and clinical effects. Among potentially novel tools, we anticipate machine learning models based on free text processing, an increased performance in environmental cheminformatics, significant decision-making support, as well as the emergence of robot scientists conducting automated drug discovery research. Furthermore, cheminformatics is anticipated to expand the frontiers of knowledge and evolve in an open-ended, extensible manner, allowing us to explore multiple research scenarios in order to avoid epistemological “local information minimum trap”.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of New Mexico
Contributors: Oprea, T. I., Taboureau, O., Bologa, C. G.
Pages: 107-112
Publication date: 2012
Peer-reviewed: Yes

Publication information

Journal: Journal of Computer - Aided Molecular Design
Volume: 26
Issue number: 1
ISSN (Print): 0920-654X
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.7 SJR 0.941 SNIP 0.827
Web of Science (2017): Impact factor 2.356
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.23 SJR 1.163 SNIP 1.204
Web of Science (2016): Impact factor 3.028
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3.02 SJR 0.98 SNIP 1.124
Web of Science (2015): Impact factor 3.199
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.84 SJR 1.025 SNIP 0.967
Web of Science (2014): Impact factor 2.99
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 2.82 SJR 0.913 SNIP 0.934
Web of Science (2013): Impact factor 2.782
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 3.13 SJR 1.033 SNIP 0.928
Web of Science (2012): Impact factor 3.172
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 3.17 SJR 0.957 SNIP 0.936
Web of Science (2011): Impact factor 3.386
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 1.174 SNIP 1.154
Web of Science (2010): Impact factor 3.374
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.085 SNIP 0.994
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.989 SNIP 0.976
Scopus rating (2007): SJR 0.779 SNIP 0.852
Scopus rating (2006): SJR 0.683 SNIP 0.866
Scopus rating (2005): SJR 0.904 SNIP 0.837
Scopus rating (2004): SJR 1.063 SNIP 0.927
Scopus rating (2003): SJR 0.73 SNIP 1.254
Scopus rating (2002): SJR 0.457 SNIP 1.027
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 0.508 SNIP 0.685
Scopus rating (2000): SJR 0.786 SNIP 0.677
Scopus rating (1999): SJR 0.664 SNIP 0.641

Original language: English
Keywords: Drug discovery, Data mining, Forecast support, Decision-making tools, Semantic web technologies, Machine learning
DOIs:
10.1007/s10822-011-9535-9
Source: orbit
System chemical biology studies of endocrine disruptors

Endocrine disrupting chemicals (EDCs) alter hormonal balance and other physiological systems through inappropriate developmental or adult exposure, perturbing the reproductive function of further generations. While disruption of key receptors (e.g., estrogen, androgen, and thyroid) at the ligand binding domain (LBD) has been associated with EDCs, a significant number of EDCs do not appear to influence the LBDs of these receptors. Therefore, we evaluated the potential biological effects of EDCs in humans with the aim to rationalize the etiology of certain disorders associated with the reproductive function. We compiled 675 (known or suspected) EDCs and examined chemical-protein associations via ChemProt [http://www.cbs.dtu.dk/services/ChemProt/]. Over 1000 proteins susceptible to perturbation by one or more EDCs were subject to a protein-protein interaction network evaluation. Synergetic EDC effects resulting in the perturbation of different proteins associated to particular diseases (e.g., cryptorchidism) were evaluated.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of New Mexico
Contributors: Taboureau, O., Oprea, T. I.
Publication date: 2012
Peer-reviewed: Yes
Event: Abstract from 242nd National Meeting of the American-Chemical-Society (ACS), Denver, CO, United States.
Source: orbit
Source-ID: 318718
Research output: Research - peer-review › Conference abstract for conference – Annual report year: 2012

The impact of network biology in pharmacology and toxicology

With the need to investigate alternative approaches and emerging technologies in order to increase drug efficacy and reduce adverse drug effects, network biology offers a novel way of approaching drug discovery by considering the effect of a molecule and protein's function in a global physiological environment. By studying drug action across multiple scales of complexity, from molecular to cellular and tissue level, network-based computational methods have the potential to improve our understanding of the impact of chemicals in human health. In this review we present the available large-scale databases and tools that allow integration and analysis of such information for understanding the properties of small molecules in the context of cellular networks. With the recent advances in the omics area, global integrative approaches are necessary to cope with the massive amounts of data, and biomedical researchers are urged to implement new types of analyses that can lead to new therapeutic interventions with increased safety and efficacy compared with existing medications.

General information
State: Published
Organisations: Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Department of Systems Biology, Center for Biological Sequence Analysis
Contributors: Panagiotou, G., Taboureau, O.
Pages: 221-235
Publication date: 2012
Peer-reviewed: Yes

Publication information
Journal: S A R and Q S A R in Environmental Research
Volume: 23
Issue number: 3-4, Sp. Iss. SI
ISSN (Print): 1062-936X
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 1.96 SJR 0.49 SNIP 0.634
Web of Science (2017): Impact factor 2.227
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 1.57 SJR 0.412 SNIP 0.581
Web of Science (2016): Impact factor 1.642
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 1.62 SJR 0.469 SNIP 0.737
Web of Science (2015): Impact factor 1.897
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 1.37 SJR 0.415 SNIP 0.57
Web of Science (2014): Impact factor 1.596
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 1.94 SJR 0.471 SNIP 0.729
Web of Science (2013): Impact factor 1.924
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 1.72 SJR 0.444 SNIP 0.883
Web of Science (2012): Impact factor 1.667
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 1.97 SJR 0.533 SNIP 0.807
Web of Science (2011): Impact factor 2.086
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.435 SNIP 0.87
Web of Science (2010): Impact factor 1.56
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 0.523 SNIP 0.705
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 0.628 SNIP 0.827
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 0.513 SNIP 0.792
Web of Science (2007): Indexed yes
Scopus rating (2006): SJR 0.411 SNIP 0.5
Scopus rating (2005): SJR 0.518 SNIP 0.812
Scopus rating (2004): SJR 0.537 SNIP 0.636
Scopus rating (2003): SJR 0.523
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 0.462
Scopus rating (2001): SJR 0.376
Scopus rating (2000): SJR 0.29 SNIP 0
Scopus rating (1999): SJR 0.315 SNIP 0
Original language: English
Keywords: biomedical researcher, disease progress, drug discovery, existing medication efficacy comparison, existing medication safety comparison, large-scale database, molecule property, network biology impact, omics area, small molecules, 00530, General biology - Information, documentation, retrieval and computer applications, 12512, Pathology - Therapy, 22002, Pharmacology - General, 22501, Toxicology - General and methods, Computational Biology, bioinformatics analysis mathematical and computer techniques, computer software package computer software, global integrative approach mathematical and computer techniques, risk assessment clinical techniques, diagnostic techniques, Computer Applications, Information Studies, Pharmacology, Toxicology
DOIs: 10.1080/1062936X.2012.657237
Source: dtu
Source-ID: n:oai:DTIC-ART:pubmed/364072989::16027
**Toxicogenomics Investigation Under the eTOX Project**

Attrition of drug candidates during pre-clinical development due to toxicity, especially hepatotoxicity and nephrotoxicity, is an important and continuing problem in the pharmaceutical industry. The reasons for this trend may be multifactorial and there is a need to improve toxicity testing paradigms within the industry. Microarray technologies have the ability to generate massive amounts of gene expression information as an initial step to decipher the molecular mechanisms of toxicologic changes, i.e. toxicogenomics. In the context of the eTOX consortium, one of public private partnership within the framework of the European Innovative Medicines Initiative (IMI), we will discuss here how the integration and analysis of toxicogenomics data can help to understanding the mechanism of toxicity of a compound and so reduce the risk of late-stage failure in pharmaceutical development.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Novo Nordisk Foundation Center for Biosustainability, CFB - Metagenomic Systems Biology, Genome Research Limited
Number of pages: 5
Publication date: 2012
Peer-reviewed: Yes

**Publication information**

Journal: Journal of Pharmacogenomics & Pharmacoproteomics
ISSN (Print): 2153-0645
Ratings:
ISI indexed (2013): ISI indexed no
ISI indexed (2012): ISI indexed no
ISI indexed (2011): ISI indexed no
Original language: English
Keywords: Toxicogenomics, Gene expression;, Drugs, Rats
Electronic versions:
prod21341002918555.2153_0645_S7_001_1_.pdf
DOIs:
10.4172/2153-0645.S7-001
Source: dtu
Source-ID: u::4290

**Associating Drugs, Targets and Clinical Outcomes into an Integrated Network Affords a New Platform for Computer-Aided Drug Repurposing**

Finding new uses for old drugs is a strategy embraced by the pharmaceutical industry, with increasing participation from the academic sector. Drug repurposing efforts focus on identifying novel modes of action, but not in a systematic manner. With intensive data mining and curation, we aim to apply bio- and cheminformatics tools using the DRUGS database, containing 3837 unique small molecules annotated on 1750 proteins. These are likely to serve as drug targets and antitargets (i.e., associated with side effects, SE). The academic community, the pharmaceutical sector and clinicians alike could benefit from an integrated, semantic-web compliant computer-aided drug repurposing (CADR) effort, one that would enable deep data mining of associations between approved drugs (D), targets (T), clinical outcomes (CO) and SE. We report preliminary results from text mining and multivariate statistics, based on 7684 approved drug labels, ADL (Dailymed) via text mining. From the ADL corresponding to 988 unique drugs, the "adverse reactions" section was mapped onto 174 SE, then clustered via principal component analysis into a 5 x 5 self-organizing map that was integrated into a Cytoscape network of SE-D-T-CO. This type of data can be used to streamline drug repurposing and may result in novel insights that can lead to the identification of novel drug actions.

**General information**

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, University of New Mexico
Pages: 100-111
Publication date: 2011
Peer-reviewed: Yes

**Publication information**
ChemProt: a disease chemical biology database

Systems pharmacology is an emergent area that studies drug action across multiple scales of complexity, from molecular and cellular to tissue and organism levels. There is a critical need to develop network-based approaches to integrate the growing body of chemical biology knowledge with network biology. Here, we report ChemProt, a disease chemical biology database, which is based on a compilation of multiple chemical-protein annotation resources, as well as disease-associated protein-protein interactions (PPIs). We assembled more than 700,000 unique chemicals with biological annotation for 30,578 proteins. We gathered over 2 million chemical-protein interactions, which were integrated in a quality scored human PPI network of 428,429 interactions. The PPI network layer allows for studying disease and tissue specificity through each protein complex. ChemProt can assist in the in silico evaluation of environmental chemicals, natural products and approved drugs, as well as the selection of new compounds based on their activity profile against most known biological targets, including those related to adverse drug events. Results from the disease chemical biology database associate citalopram, an antidepressant, with osteogenesis imperfect and leukemia and bisphenol A, an endocrine disruptor, with certain types of cancer, respectively. The server can be accessed at http://www.cbs.dtu.dk/services/ChemProt/.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Romanian Academy
Pages: D367-372
Publication date: 2011
Peer-reviewed: Yes

Publication information
Journal: Nucleic Acids Research
Volume: 39
Issue number: Issue Suppl. 1
ISSN (Print): 0305-1048
Ratings:
BFI (2019): BFI-level 2
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 10.84 SJR 9.025 SNIP 3.028
Web of Science (2017): Impact factor 11.561
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 9.28 SJR 7.883 SNIP 2.744
Web of Science (2016): Impact factor 10.162
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 9.48 SJR 7.358 SNIP 2.631
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 8.74 SJR 6.64 SNIP 2.552
Web of Science (2014): Impact factor 9.112
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 8.46 SJR 6.801 SNIP 2.284
Web of Science (2013): Impact factor 8.808
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
In Silico Predictions of hERG Channel Blockers in Drug Discovery: From Ligand-Based and Target-Based Approaches to Systems Chemical Biology

The risk for cardiotoxic side effects represents a major problem in clinical studies of drug candidates and regulatory agencies have explicitly recommended that all new drug candidates should be tested for blockage of the human Ether-a-go-go Related-Gene (hERG) potassium channel. Indeed, several drugs with different therapeutic indications and recognized as hERG blockers were recently withdrawn due to the risk of QT prolongation, arrhythmia and Torsade de Pointes. In silico techniques can provide a priori knowledge of hERG blockers, thus reducing the costs associated with screening assays. Significant progress has been made in structure-based and ligand-based drug design and a number of models have been developed to predict hERG blockage. Although approaches such as homology modeling in combination
with docking and molecular dynamics bring us closer to understand the drug-channel interactions whereas QSAR and classification models provide a faster assessment and detection of hERG-related drug toxicity, limitation on the applicability domain of the current models and integration of data from diverse in vitro approaches are still issues to challenge. Therefore, this review will emphasize on current methods to predict hERG blockers and the need of consistent data to improve the quality and performance of the in silico models. Finally, integration of network-based analysis on drugs inducing potentially long-QT syndrome and arrhythmia will be discussed as a new perspective for a better understanding of the drug responses in systems chemical biology.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Technical Information Center of Denmark
Contributors: Taboureau, O., Sørensen, F. S.
Pages: 375-387
Publication date: 2011
Peer-reviewed: Yes

Publication information
Journal: Combinatorial Chemistry & High Throughput Screening
Volume: 14
Issue number: 5
ISSN (Print): 1386-2073
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 0.94 SJR 0.346 SNIP 0.436
Web of Science (2017): Impact factor 1.205
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 0.91 SJR 0.301 SNIP 0.361
Web of Science (2016): Impact factor 0.952
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 1.11 SJR 0.348 SNIP 0.408
Web of Science (2015): Impact factor 1.041
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 1.53 SJR 0.475 SNIP 0.559
Web of Science (2014): Impact factor 1.222
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 1.68 SJR 0.542 SNIP 0.636
Web of Science (2013): Impact factor 1.925
ISI indexed (2013): ISI indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 1.9 SJR 0.607 SNIP 0.685
Web of Science (2012): Impact factor 2
ISI indexed (2012): ISI indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 1.87 SJR 0.645 SNIP 0.573
Web of Science (2011): Impact factor 1.785
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 0.822 SNIP 0.729
Web of Science (2010): Impact factor 2.573
Web of Science (2010): Indexed yes
BFI (2009): BFI-level 1
Country-specific chemical signatures of persistent environmental compounds in breast milk

Recent reports have confirmed a worldwide increasing trend of testicular cancer incidence, and a conspicuously high prevalence of this disease and other male reproductive disorders, including cryptorchidism and hypospadias, in Denmark. In contrast, Finland, a similarly industrialized Nordic country, exhibits much lower incidences of these disorders. The reasons behind the observed trends are unexplained, but environmental endocrine disrupting chemicals (EDCs) that affect foetal testis development are probably involved. Levels of persistent chemicals in breast milk can be considered a proxy for exposure of the foetus to such agents. Therefore, we undertook a comprehensive ecological study of 121 EDCs, including the persistent compounds dioxins, polychlorinated biphenyls (PCBs), pesticides and flame retardants, and non-persistent phthalates, in 68 breast milk samples from Denmark and Finland to compare exposure of mothers to this environmental mixture of EDCs. Using sophisticated, bioinformatic tools in our analysis, we reveal, for the first time, distinct country-specific chemical signatures of EDCs with Danes having generally higher exposure than Finns to persistent bioaccumulative chemicals, whereas there was no country-specific pattern with regard to the non-persistent phthalates. Importantly, EDC levels, including some dioxins, PCBs and some pesticides (hexachlorobenzene and dieldrin) were significantly higher in Denmark than in Finland. As these classes of EDCs have been implicated in testicular cancer or in adversely affecting development of the foetal testis in humans and animals, our findings reinforce the view that environmental exposure to EDCs may explain some of the temporal and between-country differences in incidence of male reproductive disorders.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis
Pages: 270-278
Publication date: 2010
Peer-reviewed: Yes

Publication information
Journal: International Journal of Andrology
Volume: 33
Issue number: 2
ISSN (Print): 0105-6263
Ratings:
BFI (2019): BFI-level 1
BFI (2018): BFI-level 1
BFI (2017): BFI-level 1
BFI (2016): BFI-level 1
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): SJR 1.215 SNIP 1.661
BFI (2014): BFI-level 1
Scopus rating (2014): SJR 1.211 SNIP 1.598
Deciphering Diseases and Biological Targets for Environmental Chemicals using Toxicogenomics Networks

Exposure to environmental chemicals and drugs may have a negative effect on human health. A better understanding of the molecular mechanism of such compounds is needed to determine the risk. We present a high confidence human protein-protein association network built upon the integration of chemical toxicology and systems biology. This computational systems chemical biology model reveals uncharacterized connections between compounds and diseases, thus predicting which compounds may be risk factors for human health. Additionally, the network can be used to identify unexpected potential associations between chemicals and proteins. Examples are shown for chemicals associated with breast cancer, lung cancer and necrosis, and potential protein targets for di-ethylhexyl-phthalate, 2,3,7,8-tetrachlorodibenzo-p-dioxin, pirinixic acid and permethrine. The chemical-protein associations are supported through recent published studies, which illustrate the power of our approach that integrates toxicogenomics data with other data types.

General information
State: Published
Homology Modelling of the GABA Transporter and Analysis of Tiagabine Binding

A homology model of the human GABA transporter (GAT-1) based on the recently reported crystal structures of the bacterial leucine transporter from Aquifex aeolicus (LeuT) was developed. The stability of the resulting model embedded in a membrane environment was analyzed by extensive molecular dynamics (MD) simulations. Based on docking studies and subsequent MD simulations of three compounds, the endogenous ligand GABA and two potent inhibitors, (R)-nipecotic acid and the anti-epilepsy drug tiagabine, various binding modes were identified and are discussed. Whereas GABA and (R)-nipecotic acid, which are both substrates, are stabilised with residues located deep inside the occluded state binding pocket (including residues Tyr 60 and Ser 396), tiagabine, which contains a large aliphatic side chain, is stabilised in a binding mode that extends from the substrate binding pocket (i.e., stabilised by Phe 294) to the extracellular vestibule, where the side chain is stabilised by aliphatic residues. The tiagabine binding mode, reaching from the substrate binding site to the extracellular vestibule, forces the side chain of Phe 294 to adopt a distinct conformation from that found in the occluded conformation of the transporter. Hence, in presence of tiagabine, GAT-1 is constrained in an open-to-out conformation. Our results may be of particular interest for the design of new GAT-1 inhibitors.

General information

State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Contributors: Skovstrup, S., Taboureau, O., Bräuner-Osborne, H., Jørgensen, F.
Pages: 986-1000
Publication date: 2010
Peer-reviewed: Yes

Publication information

Journal: ChemMedChem
Volume: 5
Issue number: 7
ISSN (Print): 1860-7179
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 2.91 SJR 1.137 SNIP 0.805
Web of Science (2017): Impact factor 3.009
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 3.11 SJR 1.156 SNIP 0.904
Web of Science (2016): Impact factor 3.225
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 3 SJR 1.151 SNIP 0.902
Web of Science (2015): Impact factor 2.98
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 2.83 SJR 1.11 SNIP 0.902
Web of Science (2014): Impact factor 2.968
Web of Science (2014): Indexed yes
Mutational Mapping and Modeling of the Binding Site for (S)-Citalopram in the Human Serotonin Transporter

The serotonin transporter (SERT) regulates extracellular levels of the neurotransmitter serotonin (5-hydroxytryptamine) in the brain by facilitating uptake of released 5-hydroxytryptamine into neuronal cells. SERT is the target for widely used antidepressant drugs, including imipramine, fluoxetine, and (S)-citalopram, which are competitive inhibitors of the transport function. Knowledge of the molecular details of the antidepressant binding sites in SERT has been limited due to lack of structural data on SERT. Here, we present a characterization of the (S)-citalopram binding pocket in human SERT (hSERT) using mutational and computational approaches. Comparative modeling and ligand docking reveal that (S)-citalopram fits into the hSERT substrate binding pocket, where (S)-citalopram can adopt a number of different binding orientations. We find, however, that only one of these binding modes is functionally relevant from studying the effects of 64 point mutations around the putative substrate binding site. The mutational mapping also identify novel hSERT residues that are crucial for (S)-citalopram binding. The model defines the molecular determinants for (S)-citalopram binding to hSERT and demonstrates that the antidepressant binding site overlaps with the substrate binding site.
Web of Science (2007): Indexed yes
Web of Science (2006): Indexed yes
Scopus rating (2005): SJR 4.178 SNIP 1.352
Web of Science (2005): Indexed yes
Scopus rating (2004): SJR 4.376 SNIP 1.427
Web of Science (2004): Indexed yes
Scopus rating (2003): SJR 4.512 SNIP 1.42
Web of Science (2003): Indexed yes
Scopus rating (2002): SJR 4.815 SNIP 1.424
Web of Science (2002): Indexed yes
Scopus rating (2001): SJR 4.869 SNIP 1.518
Web of Science (2001): Indexed yes
Scopus rating (2000): SJR 6.065 SNIP 1.559
Web of Science (2000): Indexed yes
Original language: English
DOIs:
10.1074/jbc.M109.072587
Source: orbit
Source-ID: 258875
Research output: Research - peer-review; Journal article – Annual report year: 2010

Classification of Cytochrome P450 1A2 Inhibitors and Non-Inhibitors by Machine Learning Techniques
The cytochrome P450 (CYP) superfamily plays an important role in the metabolism of drug compounds, and it is therefore highly desirable to have models that can predict whether a compound interacts with a specific isoform of the CYPs. In this work, we provide in silico models for classification of CYP1A2 inhibitors and non-inhibitors. Training and test sets consisted of about 400 and 7000 compounds, respectively. Various machine learning techniques, like binary QSAR, support vector machine (SVM), random forest, kappa nearest neighbors (kNN), and decision tree methods were used to develop in silico models, based on Volsurf and MOE descriptors. The best models were obtained using the SVM, random forest, and kNN methods in combination with the BestFirst variable selection method, resulting in models with 73 - 76 % of accuracy on the test set prediction (Matthews Correlation Coefficient of 0.51 and 0.52). Finally, a decision tree model based on Lipinski's Rule-of-five descriptors was also developed. This model predicts 67 % of the compounds correctly and gives a simple and interesting insight into the issue of classification. All the developed models in this work are fast and precise enough to be applicable for virtual screening of CYP1A2 inhibitors or non-inhibitors, or can be used as simple filters in the drug discovery process.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology, Vrije Universiteit Amsterdam, University of Copenhagen
Pages: 658-664
Publication date: 2009
Peer-reviewed: Yes

Publication information
Journal: Drug Metabolism and Disposition
Volume: 37
Issue number: 3
ISSN (Print): 0090-9556
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 3.53 SJR 1.433 SNIP 1.204
The serotonin transporter (SERT) regulates extracellular levels of serotonin (5-hydroxytryptamine, 5HT) in the brain by transporting 5HT into neurons and glial cells. The human SERT (hSERT) is the primary target for drugs used in the treatment of emotional disorders, including depression. hSERT belongs to the solute carrier 6 family that includes a bacterial leucine transporter (LeuT), for which a high resolution crystal structure has become available. LeuT has proved to be an excellent model for human transporters and has advanced the understanding of solute carrier 6 transporter.
structure-function relationships. However, the precise structural mechanism by which antidepressants inhibit hSERT and the location of their binding pockets are still elusive. We have identified a residue (Ser-438) located within the 5HT-binding pocket in hSERT to be a critical determinant for the potency of several antidepressants, including the selective serotonin reuptake inhibitor citalopram and the tricyclic antidepressants imipramine, clomipramine, and amitriptyline. A conservative mutation of Ser-438 to threonine (S438T) selectively increased the Kᵢ values for these antidepressants up to 175-fold. The effects of introducing a protein methyl group into the 5HT-binding pocket by S438T were absent or reduced for analogs of these antidepressants lacking a single methyl group. This suggests that these antidepressants interact directly with Ser-438 during binding to hSERT, implying an overlapping localization of substrate- and inhibitor-binding sites in hSERT suggesting that antidepressants function by a mechanism that involves direct occlusion of the 5HT-binding site.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Contributors: Andersen, J., Taboureau, O., Hansen, K. B., Olsen, L., Egebjerg, J., Stromgaard, K., Kristensen, A. S.
Pages: 10276-10284
Publication date: 2009
Peer-reviewed: Yes

Publication information
Journal: Journal of Biological Chemistry
Volume: 284
Issue number: 15
ISSN (Print): 0021-9258
Ratings:
BFI (2019): BFI-level 1
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 1
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 2
Scopus rating (2017): CiteScore 4.04 SJR 2.672 SNIP 1.085
Web of Science (2017): Impact factor 4.01
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 2
Scopus rating (2016): CiteScore 4.17 SJR 2.825 SNIP 1.123
Web of Science (2016): Impact factor 4.125
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 2
Scopus rating (2015): CiteScore 4.4 SJR 3.126 SNIP 1.182
Web of Science (2015): Impact factor 4.258
Web of Science (2015): Indexed yes
BFI (2014): BFI-level 2
Scopus rating (2014): CiteScore 4.5 SJR 3.258 SNIP 1.216
Web of Science (2014): Impact factor 4.573
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 2
Scopus rating (2013): CiteScore 4.87 SJR 3.402 SNIP 1.227
Web of Science (2013): Impact factor 4.6
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 2
Scopus rating (2012): CiteScore 4.97 SJR 3.396 SNIP 1.243
Web of Science (2012): Impact factor 4.651
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 2
Scopus rating (2011): CiteScore 4.97 SJR 3.544 SNIP 1.258
Web of Science (2011): Impact factor 4.773
ISI indexed (2011): ISI indexed yes
Virtual Screening and Prediction of Site of Metabolism for Cytochrome P450 1A2 Ligands

With the availability of an increasing number of high resolution 3D structures of human cytochrome P450 enzymes, structure-based modeling tools are more readily used. In this study we explore the possibilities of using docking and scoring experiments on cytochrome P450 1A2. Three different questions have been addressed: 1. Binding orientations and conformations were successfully predicted for various substrates. 2. A virtual screen was performed with satisfying enrichment rates. 3. A classification of individual compounds into active and inactive was performed. It was found that while docking can be used successfully to address the first two questions, it seems to be more difficult to perform the classification. Different scoring functions were included, and the well-characterized water molecule in the active site was included in various ways. Results are compared to experimental data and earlier classification data using machine learning methods. The possibilities and limitations of using structure-based drug design tools for cytochrome P450 1A2 come to light and are discussed.

General information
State: Published
Organisations: Center for Biological Sequence Analysis, Department of Systems Biology
Pages: 43-52
Publication date: 2009
Peer-reviewed: Yes
hERG classification model based on a combination of support vector machine method and GRIND descriptors

The human Ether-a-go-go Related Gene (hERG) potassium channel is one of the major critical factors associated with QT interval prolongation and development of arrhythmia called Torsades de Pointes (TdP). It has become a growing concern of both regulatory agencies and pharmaceutical industries who invest substantial effort in the assessment of cardiac toxicity of drugs. The development of in silico tools to filter out potential hERG channel inhibitors in early stages of the drug discovery process is of considerable interest. Here, we describe binary classification models based on a large and diverse library of 495 compounds. The models combine pharmacophore-based GRIND descriptors with a support vector machine (SVM) classifier in order to discriminate between hERG blockers and nonblockers. Our models were applied at different thresholds from 1 to 40 μm and achieved an overall accuracy up to 94% with a Matthews coefficient correlation (MCC) of 0.86 (F-measure of 0.90 for blockers and 0.95 for nonblockers). The model at a 40 μm threshold showed the best performance and was validated internally (MCC of 0.40 and F-measure of 0.57 for blockers and 0.81 for nonblockers, using a leave-one-out cross-validation). On an external set of 66 compounds, 72% of the set was correctly predicted (F-measure of 0.86 and 0.34 for blockers and nonblockers, respectively). Finally, the model was also tested on a large set of hERG bioassay data recently made publicly available on PubChem (http://pubchem.ncbi.nlm.nih.gov/assay/assay.cgi?aid=376) to achieve about 73% accuracy (F-measure of 0.30 and 0.83 for blockers and nonblockers, respectively). Even if there is still some limitation in the assessment of hERG blockers, the performance of our model shows an improvement between 10% and 20% in the prediction of blockers compared to other methods, which can be useful in the filtering of potential hERG channel inhibitors.

General information
State: Published
Organisations: Department of Systems Biology, Center for Biological Sequence Analysis, University of New Mexico, University of Copenhagen
Contributors: Li, Q., Jorgensen, F. S., Oprea, T., Brunak, S., Taboureau, O.
Pages: 117-127
Publication date: 2008
Peer-reviewed: Yes

Publication information
Journal: Molecular Pharmaceutics
Volume: 5
Issue number: 1
ISSN (Print): 1543-8384
Ratings:
BFI (2019): BFI-level 2
Web of Science (2019): Indexed yes
BFI (2018): BFI-level 2
Web of Science (2018): Indexed yes
BFI (2017): BFI-level 1
Scopus rating (2017): CiteScore 4.86 SJR 1.572 SNIP 1.24
Web of Science (2017): Impact factor 4.556
Web of Science (2017): Indexed yes
BFI (2016): BFI-level 1
Scopus rating (2016): CiteScore 4.84 SJR 1.538 SNIP 1.213
Web of Science (2016): Impact factor 4.44
Web of Science (2016): Indexed yes
BFI (2015): BFI-level 1
Scopus rating (2015): CiteScore 4.88 SJR 1.605 SNIP 1.221
Web of Science (2015): Impact factor 4.342
BFI (2014): BFI-level 1
Scopus rating (2014): CiteScore 4.92 SJR 1.641 SNIP 1.291
Web of Science (2014): Impact factor 4.384
Web of Science (2014): Indexed yes
BFI (2013): BFI-level 1
Scopus rating (2013): CiteScore 5.26 SJR 1.903 SNIP 1.324
Web of Science (2013): Impact factor 4.787
ISI indexed (2013): ISI indexed yes
Web of Science (2013): Indexed yes
BFI (2012): BFI-level 1
Scopus rating (2012): CiteScore 5.41 SJR 2.152 SNIP 1.474
Web of Science (2012): Impact factor 4.57
ISI indexed (2012): ISI indexed yes
Web of Science (2012): Indexed yes
BFI (2011): BFI-level 1
Scopus rating (2011): CiteScore 5.62 SJR 2.351 SNIP 1.532
Web of Science (2011): Impact factor 4.782
ISI indexed (2011): ISI indexed yes
Web of Science (2011): Indexed yes
BFI (2010): BFI-level 1
Scopus rating (2010): SJR 2.252 SNIP 1.554
Web of Science (2010): Impact factor 5.4
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 1.841 SNIP 1.402
Web of Science (2009): Indexed yes
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.556 SNIP 1.184
Web of Science (2008): Indexed yes
Scopus rating (2007): SJR 1.277 SNIP 1.084
Scopus rating (2006): SJR 1.074 SNIP 1.021
Scopus rating (2005): SJR 0.542
Original language: English
Keywords: support vector machine, classification model, human Ether-a-go-go Related Gene, GRIND descriptors
DOIs: 10.1021/mp700124e
Source: orbit
Source-ID: 221408
Research output: Research - peer-review › Journal article – Annual report year: 2008

Projects:

**Mapping of Secondary Metabolism in Biotechnologically Important aspergillus Species**

Rank, C., PhD Student, Department of Systems Biology
Larsen, T. O., Main Supervisor, Department of Biotechnology and Biomedicine
Frisvad, J. C., Supervisor, Department of Biotechnology and Biomedicine
Gotfredsen, C. H., Supervisor, Department of Chemistry
Taboureau, O., Examiner, Department of Biotechnology and Biomedicine
Geisen, R., Examiner
Gloer, J. B., Examiner
Forskningsrådskontant
15/03/2006 → 04/06/2010
Award relations: Mapping of Secondary Metabolism in Biotechnologically Important aspergillus Species
Project: PhD

**Kemisk Biologi af Mikrobielle Anticancer Naturstoffer**

Bladt, T. T., PhD Student, Department of Systems Biology
Larsen, T. O., Main Supervisor, Department of Biotechnology and Biomedicine
Gotfredsen, C. H., Supervisor, Department of Chemistry
Prediction of protein structural features by use of artificial neural networks
Petersen, B., PhD Student, Department of Biotechnology and Biomedicine
Lundegaard, C., Main Supervisor, Center for Biological sequence analysis
Taboureau, O., Supervisor, Department of Biotechnology and Biomedicine
Peters, B., Examiner
Tolstrup, N., Examiner, Department of Chemistry
Institut stipendie (DTU)
01/02/2008 → 28/09/2011
Award relations: Prediction of protein structural features by use of artificial neural networks
Project: PhD

Deciphering the clinical effect of drugs trough large-scale data integration
Kjærulff, S. K., PhD Student, Department of Systems Biology
Kouskoumvekaki, E., Main Supervisor, Department of Systems Biology
Brunak, S., Supervisor, Department of Biotechnology and Biomedicine
Taboureau, O., Supervisor, Department of Biotechnology and Biomedicine
Workman, C., Examiner, Department of Biotechnology and Biomedicine
Askjaer, S., Examiner
Institut stipendie (DTU) Samf.
01/09/2009 → 29/05/2013
Award relations: Deciphering the clinical effect of drugs trough large-scale data integration
Project: PhD

Pharmacogenomics and personalized medicine in the treatment of ADHD
Nzabonimpa, G. S., PhD Student, Department of Bio and Health Informatics
Taboureau, O., Main Supervisor, Department of Bio and Health Informatics
Brunak, S., Supervisor, Department of Health Technology
De Masi, F., Examiner, Department of Health Technology
Jørgensen, F. S., Examiner
Xhaard, H., Examiner
Institut stipendie (DTU) Samf.
15/01/2013 → 06/06/2017
Award relations: Pharmacogenomics and personalized medicine in the treatment of ADHD
Project: PhD