Open PHACTS

Deliverable 8.3.3

Run OPS Workshop 3
"Introducing Open PHACTS"

Prepared by UNIVIE, RSC
Approved by UNIVIE, RSC, GSK, BIT, VUA, Pfizer, CD, DTU, AZ

September 2012
Version 1.0

Project title: An open, integrated and sustainable chemistry, biology and pharmacology knowledge resource for drug discovery
Instrument: IMI JU
Contract no: 115191

Start date: 01 March 2011
Duration: 3 years

Nature of the Deliverable	
Report	**x**
Prototype	
Other	
Dissemination level	
Public dissemination level	**x**
For internal use only	

1 Definitions

- Partners of the Open PHACTS Consortium are referred to herein according to the following codes:

  Pfizer – Pfizer limited – **Coordinator**
  UNIVIE – Universität Wien – **Managing entity of IMI JU funding**
  DTU – Technical University of Denmark – DTU
  UHAM – University of Hamburg, Center for Bioinformatics
  BIT – BioSolveIT GmbH
  PSMAR – Consorci Mar Parc de Salut de Barcelona
  LUMC – Leiden University Medical Centre
  RSC – Royal Society of Chemistry
  VUA – Vrije Universiteit Amsterdam
  CNIO – Spanish National Cancer Research Centre
  UNIMAN – University of Manchester
  UM – University of Maastricht
  ACK – ACKnowledge
  USC – University of Santiago de Compostela
  UBO – Rheinische Friedrich-Wilhelms-Universität Bonn
  AZ – AstraZeneca
  GSK – GlaxoSmithKline
  Esteve – Laboratorios del Dr. Esteve, S.A.
  Novartis – Novartis
  ME – Merck Serono
  HLU – H. Lundbeck A/S
  E.Lilly – Eli Lilly
  NBIC – Stichting Netherlands Bioinformatics Centre
  SIB – Swiss Institute of Bioinformatics
  ConnDisc – Connected Discovery
  EBI – European Bioinformatics Institute
  Janssen – Janssen Pharmaceutica
  OGL – OpenLink Software

- **Grant Agreement**: The agreement signed between the beneficiaries and the IMI JU for the undertaking of the Open PHACTS project.
- **Project**: The sum of all activities carried out in the framework of the Grant Agreement.
- **Work plan**: Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried, out as specified in the Grant Agreement.
- **Consortium**: The Open PHACTS Consortium composed of the above-mentioned legal entities.
- **Project Agreement**: Agreement concluded amongst Open PHACTS participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

2 Introduction

The Open PHACTS consortium is building a freely available web platform to integrate pharmacological data from a variety of information resources, along with tools and services to question this integrated data. It will give researchers in industry and academia the ability to look up answers to complex research questions over a wide range of data sources, and provide a unique open framework to mix public and proprietary data. The project development is being directed by example questions sourced from expert researchers, and the open framework encourages innovative free and commercial applications to be built on the underlying platform. Open PHACTS will offer a production-grade API that commercial software providers can license and use to augment their own product. There are also opportunities for Associated Partners who want to do some more specific development work together with us, leading to a Development Partnership with the Open PHACTs project.

On August 30, 2012 the 3rd Open PHACTS Community Workshop "Introducing Open PHACTS" was held in Vienna, co-located with the 19th EuroQSAR conference, where the Open PHACTS consortium publicly presented the upcoming public Beta releases from the Open PHACTS project. The workshop introduced the technical and scientific approaches driving the project and demonstrated the web-based Explorer interface to the underlying Open PHACTS platform, built to answer specific research questions prioritised by the consortium. Additionally, four Open PHACTS exemplar applications that represent specialized interfaces were introduced. The example applications are being developed by consortium members, sit on top of the Open PHACTS platform and aim to address specific needs in the field of drug discovery.

The workshop was attended by 65 scientists, comprising representatives of software vendors (Inte:Ligand, OpenEye, ChemAxon, Tripos, Accelrys), participants of the EuroQSAR, as well as members of the Open PHACTS consortium. The Open PHACTS Explorer as well as 2 of the example applications were presented in a live demo. For in depth discussions, Open PHACTS was also present with an exhibition booth throughout the EuroQSAR conference.

Program:

- Introducing Open PHACTS (Bryn Williams-Jones)
- The Open PHACTS Infrastructure (Lee Harland)
- The Open PHACTS Explorer (Lee Harland/Paul Groth)
- Open PHACTS Example Applications
    - PharmaTrek (Jordi Mestres)
    - GARField (Louis Wich)
    - Target Dossier (Victor de la Torre)
    - ChemBio Navigator (Christian Lemmen)
- Discussion & Feedback

Picture 1: Participants of 3rd Open PHACTS Community Workshop

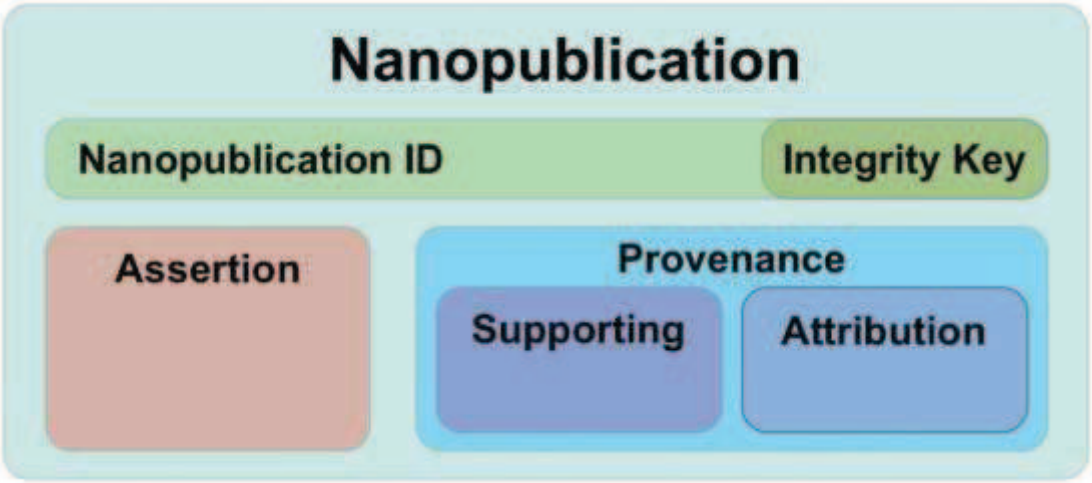
3 Introducing Open PHACTS

Open PHACTS acts like a search engine, allowing querying of data via a single platform while retaining provenance and traffic back to the original data source. Provenance is critical – users need to know where every data point comes from, and will visit the source. By promoting best practices for data publication and sharing, we want to simplify and clarify many of the problems around use and reuse of data from different sources.

Open PHACTS will be adopting a licensing framework which will be applicable to other, similar, data integration projects. This will provide clarity for the data sources and for the end user. The consortium wants to work with data providers to expose and enhance their data, and will build quality feedback mechanisms to help all its partners.

The power of nanopublication to capture core scientific assertions and promote data citeability will be demonstrated, and the project has already published nanopublication RDF guidelines. The first release of the Open PHACTS platform will include public sources of data and ontologies, but the licensing framework will allow the inclusion of different licenses, including the ability to include proprietary or commercial data. The project is building a window through which to query many data sources while retaining provenance.

Nanopublication Specifications



Picture 2: Nanopublication Specifications

Nanopublications provide support for provenance of data; credit to data providers and also allow user-annotations to be incorporated into the live system

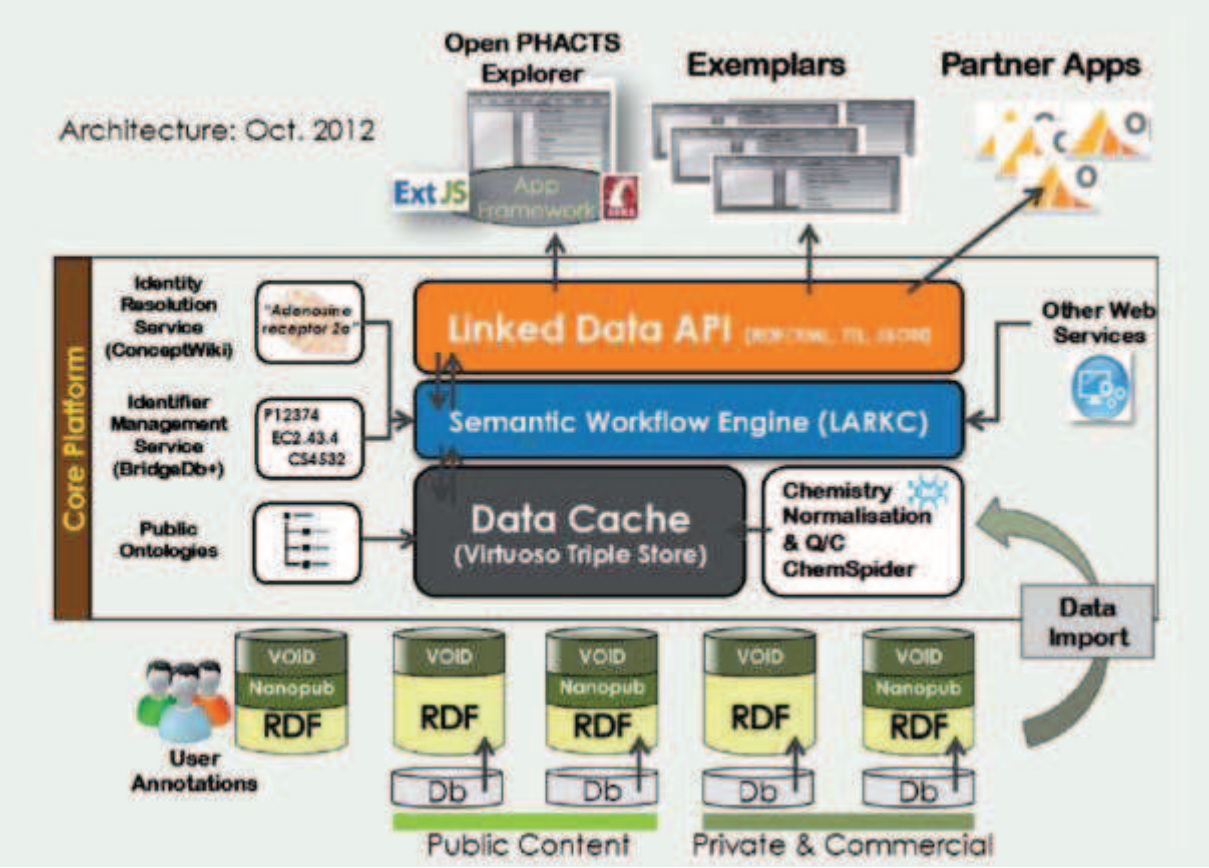
Timeline

November 2012	Planned public release of Beta version 1.0 of Explorer
April 2013	Alpha availability of the Open PHACTS API
4Q 2013	Beta version 2.0 of Explorer availability
1Q 2014	Final project release of Explorer

4 The Open PHACTS infrastructure

The Open PHACTS platform uses semantic technologies to provide a robust, adaptable framework for integration of multiple data sources into one coherent API. While the project has a pharmacological focus, it will create a set of modular, reusable software components that can be used to address other scientific challenges. Open PHACTS is promoting and augmenting existing open standards and ontologies, and are demonstrating their use in a large scale, real world application. The Open PHACTS platform will be production software: data sources will be maintained and regularly updated, and the system is hosted by Open Link, a professional semantic data company.

Implementation architecture



Picture 3: Implementation architecture

Open PHACTS is markedly increasing the quality and flexibility of mapping between different identifiers in life science data – though developments on an Identity Mapping Service, the use of the ConceptWiki, and the publication of open data mappings.

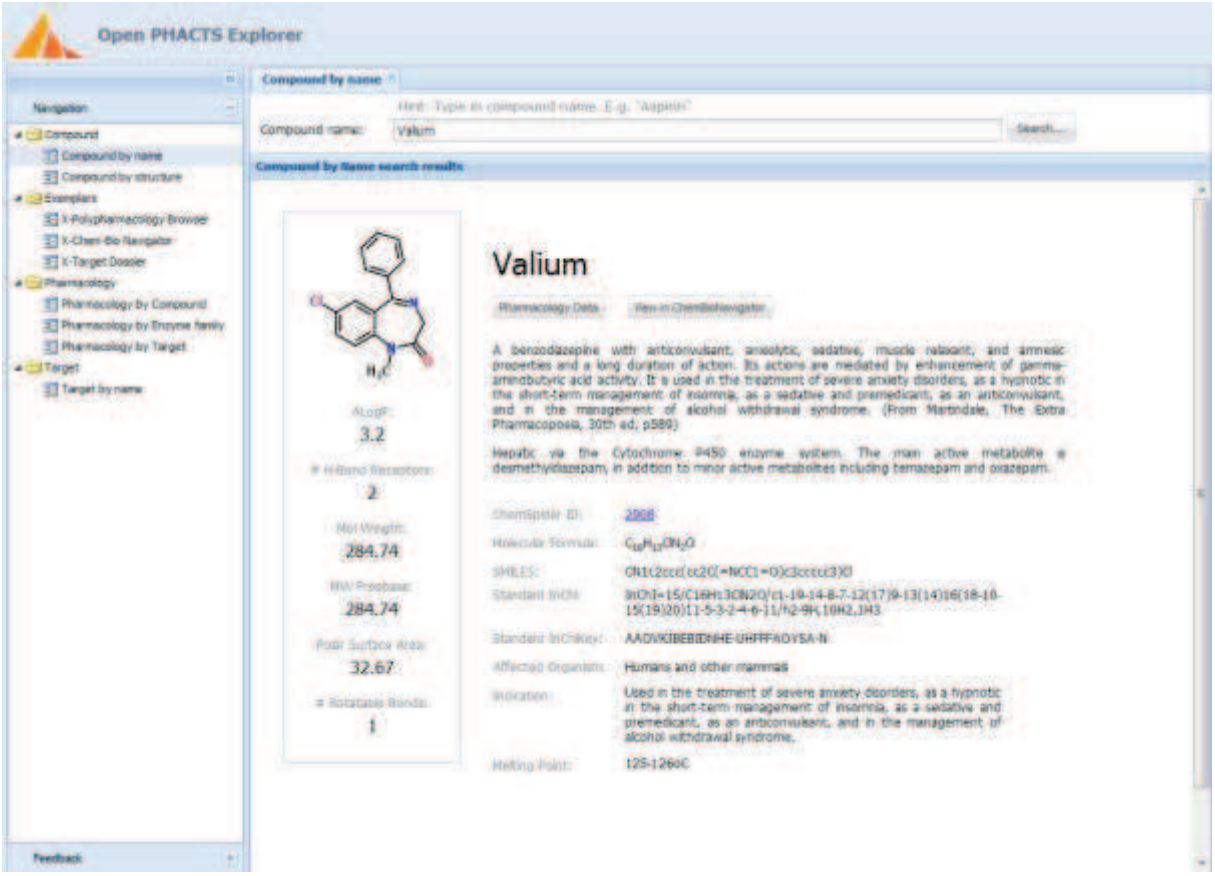
5 The Open PHACTS Explorer

The Open PHACTS Explorer provides a user interface to the Open PHACTS platform and is being built to answer the critical pharmacology questions defined by eight major pharmaceutical companies.

The first version of the platform includes data from ChEMBL, ChEBI, Uniprot, Gene Ontology, ChemSpider, WikiPathways, DrugBank, ENZYME, BridgeDB, predicted physical property data from ACD/Labs, and more.

The Explorer provides a way to query these up-to-date data sources; the integration process includes chemistry validation, and particularly deals with multiple identifiers for the same concept. The platform allows for rapid addition of new data sources, and the development of the platform and the Explorer has been use-case driven and tested by users in industry and academia.

It is being built, by experts, to offer a structured view of integrated pharmacological data. Open PHACTS gives you the ability to look up answers to complex research questions over a wide range of data sources. Unlike other tools it is built on an open vendor-neutral framework and allows license-compliant mixing of public and proprietary data with retained provenance.



Picture 4: Open PHACTS Explorer

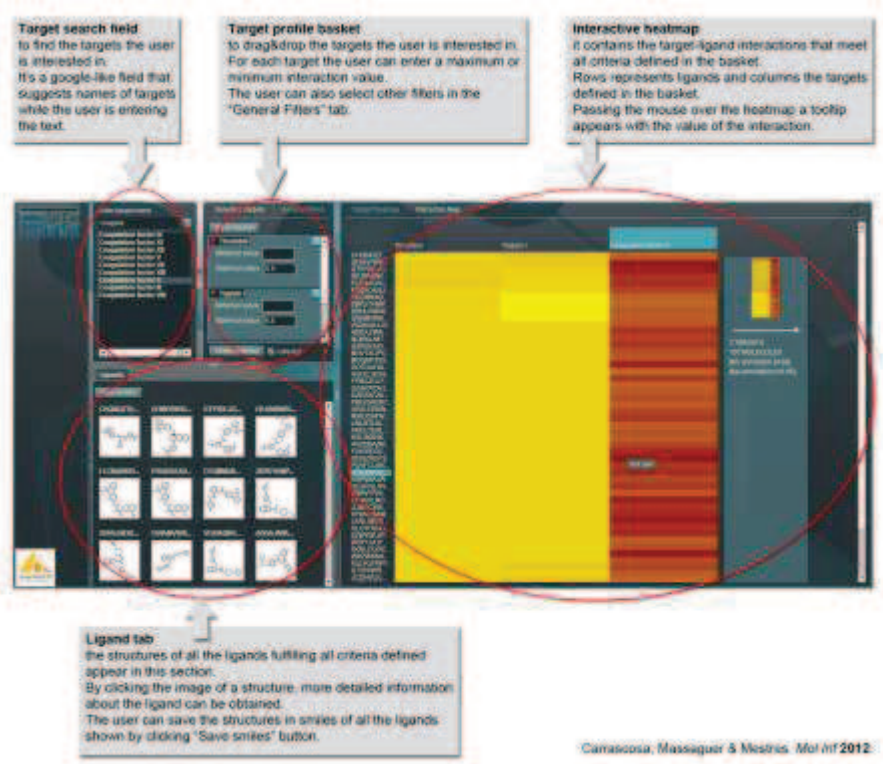
6 Open PHACTS Example Applications

Open PHACTS will offer a production-grade API that commercial software providers can license and use to augment their own product, generating revenue and long term sustainability. The API functions include general protein & compound information; pharmacology by target or compound; pharmacology by taxonomy, including ChEBI, GO, ENZYME and more.

Four example applications are being developed in the project to show how the data within the platform can be used to generate new insights:

6.1 PharmaTrek

PharmaTrek, developed by Consorci Mar Parc de Salut de Barcelona (PSMAR), proposes new mechanisms to navigate the Pharmacological space in a more interactive and flexible way. PharmaTrek is an integrative and interactive web application that will allow scientists to extract new knowledge from the Open Pharmacological Space created by OpenPHACTS. The main goal is to provide visual tools that allow the user to define custom questions, that is, that the users can create their own questions that will be answered in real time. The questions are related with the biological activity between drugs and targets.

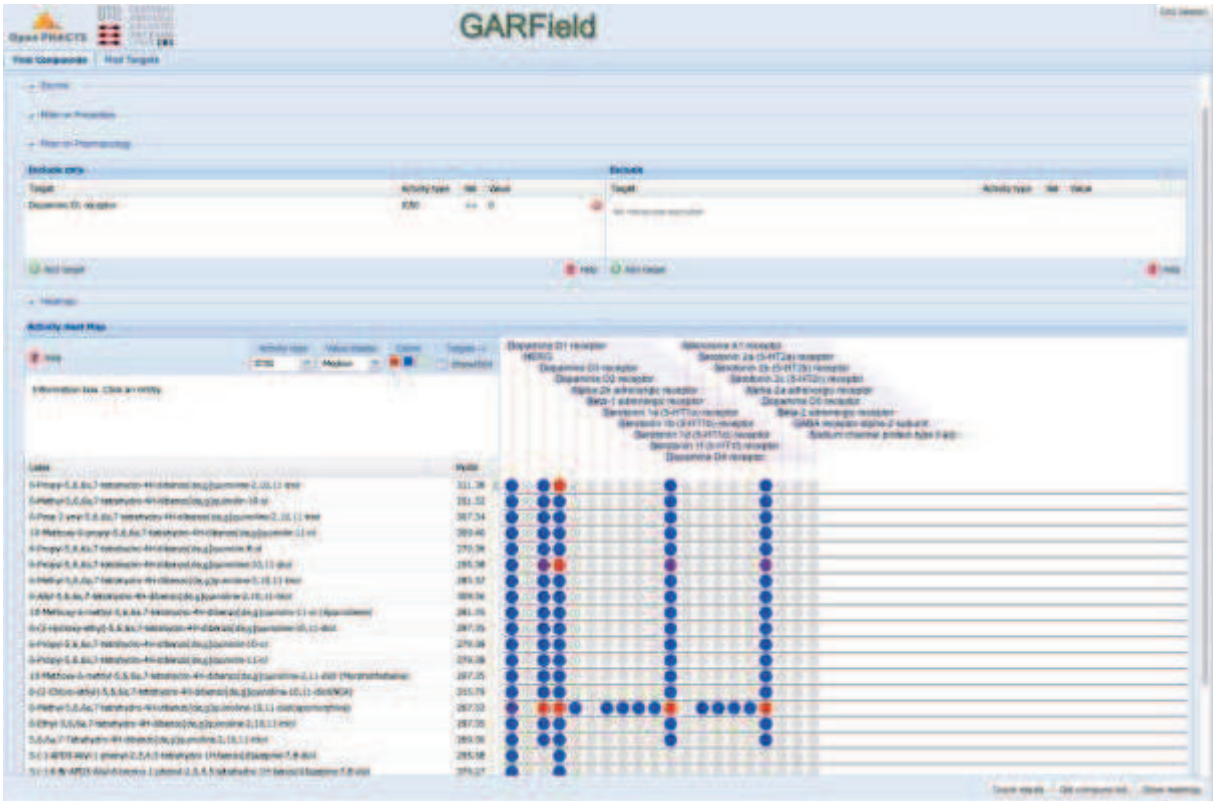


Picture 5: PharmaTrek

Picture 6: Jordi Mestres demonstrating PharmaTrek

6.2 Polypharmacology browser: GARField

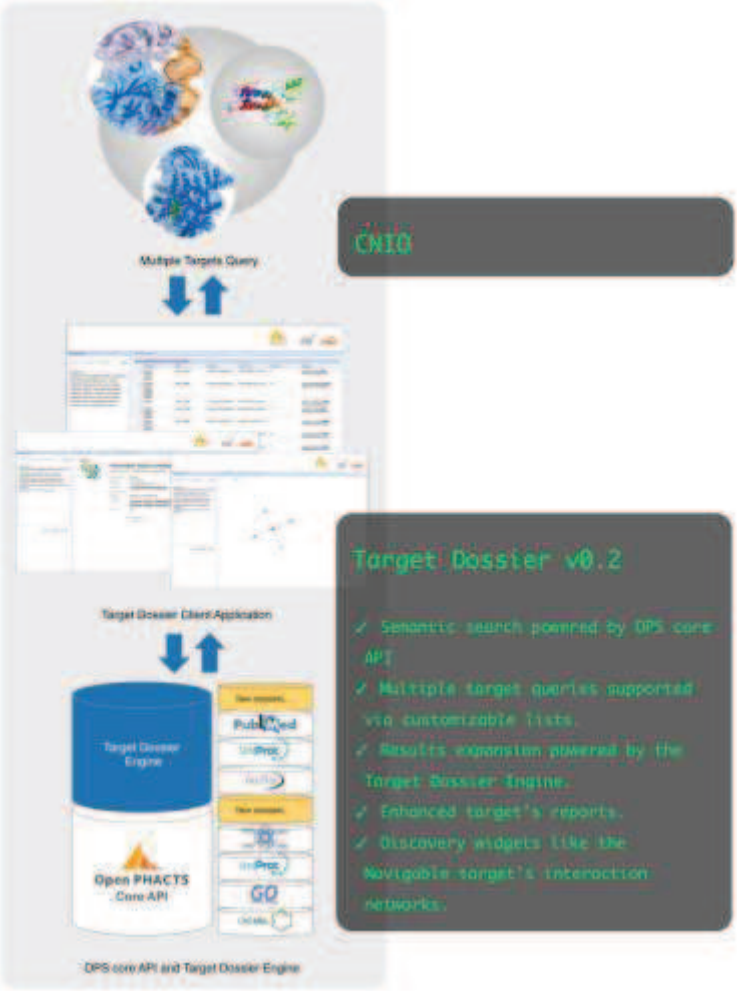
GARField, developed by the Technical University of Denmark, is a tool that facilitates the pharmacological profiling of small molecules and biological targets through the Open PHACTS services. It supports advanced searches for compounds that pass given criteria, e.g. fulfillment of certain chemical properties, and also filtering of the compounds by interaction with certain targets (for certain activity types). Likewise, the researcher can search for targets in similar queries, i.e. filtering by bioactivity to compounds. Results are presented visually in an interaction matrix. Besides the browsing capabilities, GARField will be an online platform for several bioactivity prediction algorithms, and so far implements the Similarity Ensemble Approach (Keiser et al. Nat. Biotechnol. 2007).



Picture 7: GARField

6.3 Target dossier

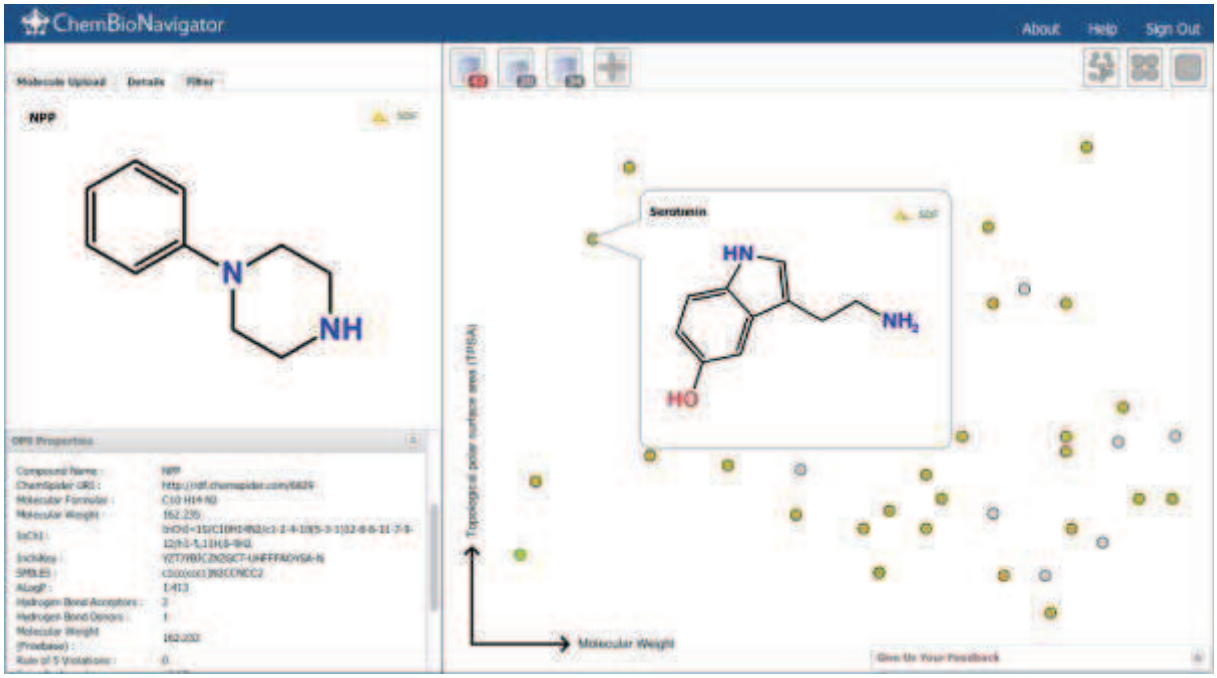
The Target Dossier, developed by the Spanish National Cancer Research Centre, uses the Open PHACTS platform for building comprehensive views of pharmacologically relevant targets to answer questions regarding druggability, tissue expression profiles and implications in pathways, disease states and physiological mechanisms. The Target Dossier will provide a decision support platform for target selection and progression.



Picture 8: Target Dossier

6.4 ChemBio Navigator

The ChemBioNavigator (CBN), developed by BioSolveIT, allows navigating at the interface of chemical and biological data. It is tailored for applications in pharmaceutical research. CBN lets you easily browse through sets of compounds. Different sorting and plotting options offer a quick and intuitive overview of the physio-chemical characteristics of the compounds. At the same time an in-depth analysis of individual molecules is supported using the versatile data available from the OPS platform. Hyperlinks into the original data sources as well as into the OPS Explorer allow for further investigation.



Picture 9: ChemBio Navigator

7 Discussion & Feedback

There was a discussion why the example applications look different from each other. This prompted an action item in the subsequent Steering Committee Meeting: Branding of Applications: How do we communicate clearly that Applications are developed by different organizations (under the umbrella of the project) and that they have their own identity/character (e.g. they don't use the same GUI design philosophy)?

8 How to get involved

Software vendors as well as other parties active in the area may join the Open PHACTS community by becoming an Associated Partner. Associated Partners will be the first to hear about the latest developments in the Open PHACTS project, and will also have the opportunity to present ideas and use cases to the core Open PHACTS team.

There are opportunities for Associated Partners who want to do some more specific development work together with the project team (e.g. develop APIs, new data, algorithms etc), leading to a Development Partnership with the Open PHACTS project.

For more information visit www.openphacts.org.

9 Presentations

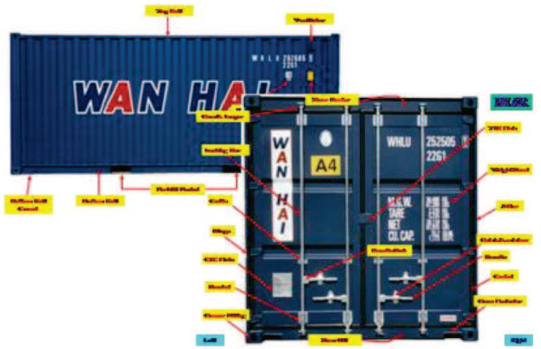
Open PHACTS

Open Pharmacological Space

(IMI KM call-topic 8, 2010)

www.openphacts.org

- The Challenge - Open standards for drug discovery data
  - Drug discovery research is increasingly data and information driven but we are **challenged to integrate content across domains (Chemistry, Biology, Clinical)**
    - Key content spread over many sources
    - Lack of agreed standards and formatting drives unsustainable efforts in content integration
    - Increasing volumes and privacy constraints (e.g. Biobanks) drives paradigm shift: We need to move analysis to data rather than retrieve data for analysis
- Open PHACTS Project **(28 partners: 9 pharma – 19 academic / SME)**
  - **Develop robust standards** for solid integration between data sources via semantic technologies
  - **Implement the standards** in a semantic integration hub ("Open Pharmacological Space")
  - **Deliver services** to support on-going drug discovery programs in pharma and public domain
- Benefit:
  - **Reduced costs and improved access** to inter-operable drug discovery information
    - Work on-going with RSC/Chemspider on data-models for handling drug formulations, combinations and public sources; Source most public data directly from RSC/Chemspider in correct format
  - **Development of critical skills** and organisational learning
    - **Access to leading European labs** in semantic data, workflow analysis and information mining (U Manchester, VU Amsterdam, NBIC, Frauenhofer)
    - **Structured plan to align AZ scientists** within work-packages to directly exploit developments in on-going internal initiatives



Open PHACTS
Open Pharmacological Space

Open PHACTS Project Partners

www.openphacts.org

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Universität Wien – Managing entity
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Consorci Mar Parc de Salut de Barcelona
Leiden University Medical Centre
Royal Society of Chemistry
Vrije Universiteit Amsterdam

Spanish National Cancer Research Centre
University of Manchester
Maastricht University
Aqnowledge
University of Santiago de Compostela
Rheinische Friedrich-Wilhelms-Universität Bonn
AstraZeneca
GlaxoSmithKline
Esteve

Novartis
Merck Serono
H. Lundbeck A/S
Eli Lilly
Netherlands Bioinformatics Centre
Swiss Institute of Bioinformatics
ConnectedDiscovery
EMBL-European Bioinformatics Institute
Janssen
OpenLink

Swiss Institute of Bioinformatics

Open Drug Discovery Intelligence Services

Open PHACTS and SciBite

Lee Harland

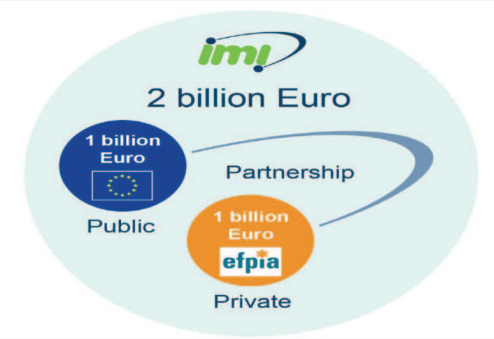
EuroQSAR 2012


Big Data
Patent Cliff
NP Drug Discov.
CROs
PPPs


Open PHACTS
Open Pharmacological Space

The Innovative Medicines Initiative

- EC funded public-private partnership for pharmaceutical research
- Focus on key problems
  - Efficacy, Safety, Education & Training, **Knowledge Management**



The Open PHACTS Project

- Create a *semantic integration hub ("Open Pharmacological Space")…*
- Delivering services to support on-going drug discovery programs in pharma and public domain
- *Not just another project*; Leading academics in semantics, pharmacology and informatics, driven by solid industry business requirements
- 23 academic partners, 8 pharmaceutical companies, 3 software SMEs
- Work split into clusters:
  - Technical Build
  - Scientific Drive
  - Community & Sustainability

Open PHACTS

Open Pharmacological Space

Open PHACTS Project Partners

www.openphacts.org

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Leiden University Medical Centre
Royal Society of Chemistry
Vrije Universiteit Amsterdam

Spanish National Cancer Research Centre
University of Manchester
Maastricht University
Aqnowledge
University of Santiago de Compostela
Rheinische Friedrich-Wilhelms-Universität Bonn
AstraZeneca
GlaxoSmithKline
Esteve

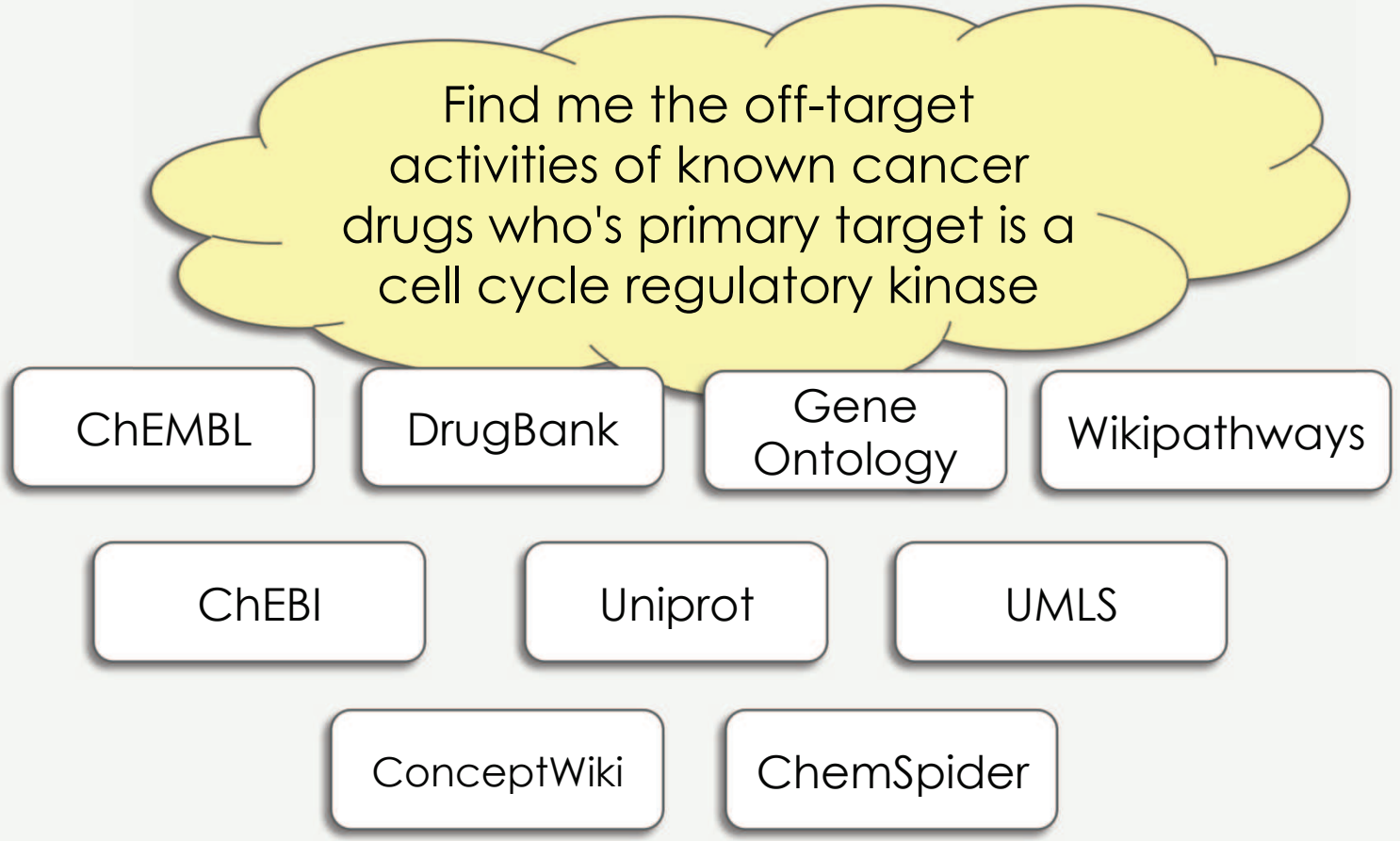
Novartis
Merck Serono
H. Lundbeck A/S
Eli Lilly
Netherlands Bioinformatics Centre
Swiss Institute of Bioinformatics
ConnectedDiscovery
EMBL-European Bioinformatics Institute
Janssen
OpenLink

Optimised To Business Questions

Example Research questions

- Give all compounds with IC50 < xxx for target Y in species W and Z plus assay data
- What substructures are associated with readout X (target, pathway, disease, …)
- Give all experimental and clinical data for compound X
- Give all targets for compound X or a compound with a similarity > y%

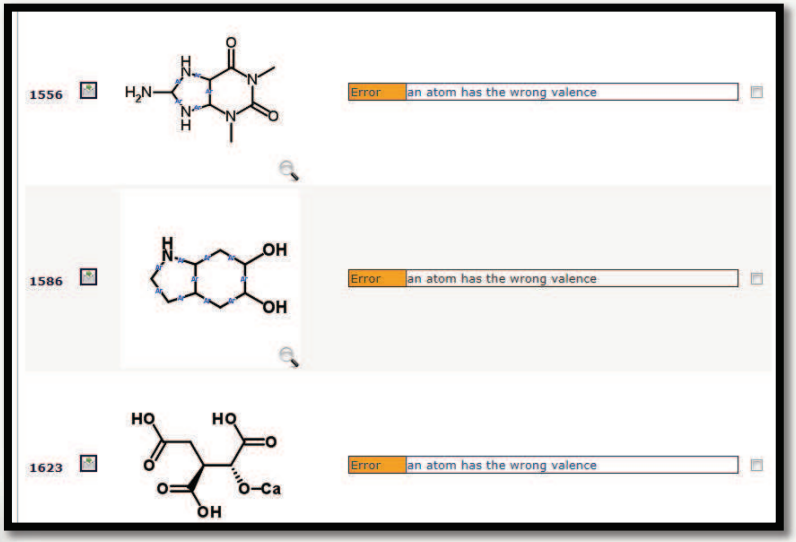
What Do You Need?



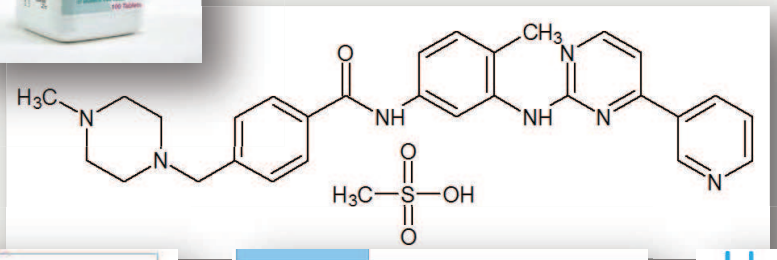
Connected Using Semantic Technology

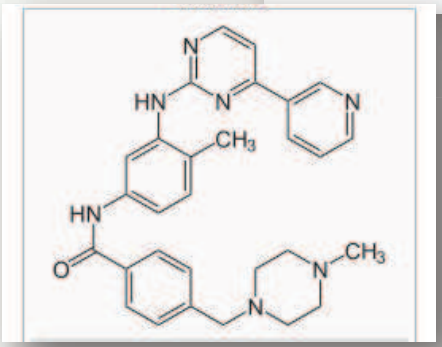
Chemistry Normalisation

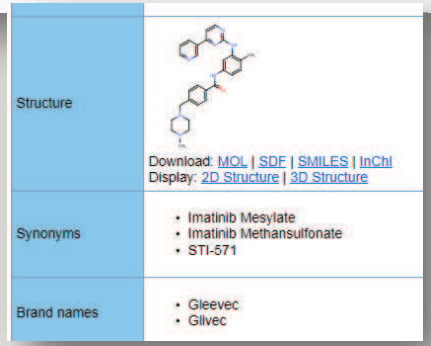
Tony Williams (ChemSpider/RSC)

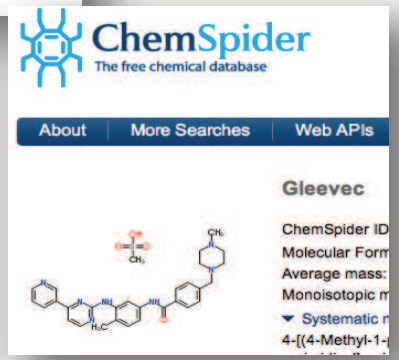


CVSP: http://bit.ly/NZF5VB









Wikipedia **Drugbank** **ChemSpider**

Dynamic Mapping

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ACD/Labs becomes an associate partner of Open PHACTS project

Media Room
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- Images
- Articles, Posters, Presentations, Reviews
- Company Info

The Open PHACTS consortium is pleased to announce an Associate Partner relationship with Advanced Chemistry Development, Inc., (ACD/Labs) who will be supplying a number of predicted physicochemical properties for inclusion within the project data. ACD/Labs is one of the primary suppliers of prediction algorithms to the life sciences industry and their contribution of data provides enhanced querying options for the users. Daria Thorp, President of ACD/Labs, comments "The Open PHACTS project represents a promising approach that leverages existing pharmacological knowledge to make new discoveries. ACD/Labs, with our 18 years of *in silico* physicochemical and ADME-Tox modeling experience, is excited to provide our industry leading molecular property predictions—notably log*D* at physiologically relevant pH, 'rule of 5', and log*P* values—to this project." The ACD/Labs data will be offered via RSC ChemSpider which provides the chemical compound data in a format consumable by the Open PHACTS platform.

The Open PHACTS consortium is building a semantic data integration platform for pharmacological data, to reduce the barriers to drug discovery, creating an Open Pharmacological Space. Open PHACTS will deliver a single view across available data resources, and will be freely available to users.

Scientific text, difficult to analyse by computer, will have factual assertions extracted as semantic triples, allowing for the first time the prospect of querying textual and database data together to give answers needed to identify new drug targets and pharmacological interactions. While the semantic approach has been delivered in small-scale and targeted approaches so far, its promise for multiscale data integration has remained largely unfulfilled —Open PHACTS is a major project including many of the top semantic web experts, committed to deliver on this promise.

About Advanced Chemistry Development (ACD/Labs)
Advanced Chemistry Development, Inc., (ACD/Labs) is a chemistry software company that develops and commercializes enterprise and desktop solutions to support R&D efforts, and preserve and re-use legacy knowledge. ACD/Labs' areas of expertise include a unique knowledge management solution; spectroscopic data processing and interpretation for NMR, MS, LC/MS, IR, UV, other optical, and hyphenated instrumental techniques; chemical structure confirmation, verification, and elucidation; impurity, metabolism, and degradation research; ADME-Tox and physicochemical property prediction, and property-based lead optimization; chromatographic method development and optimization; and chemical nomenclature. We provide integration with existing informatics systems and undertake custom projects including enterprise-level automation. A private company founded in 1994, ACD/Labs has worldwide sales and support presence, with offices in N. America, Europe, and Asia. (www.acdlabs.com)

About Open PHACTS
Open PHACTS is a 2-year knowledge management project of the Innovative Medicines Initiative, running from

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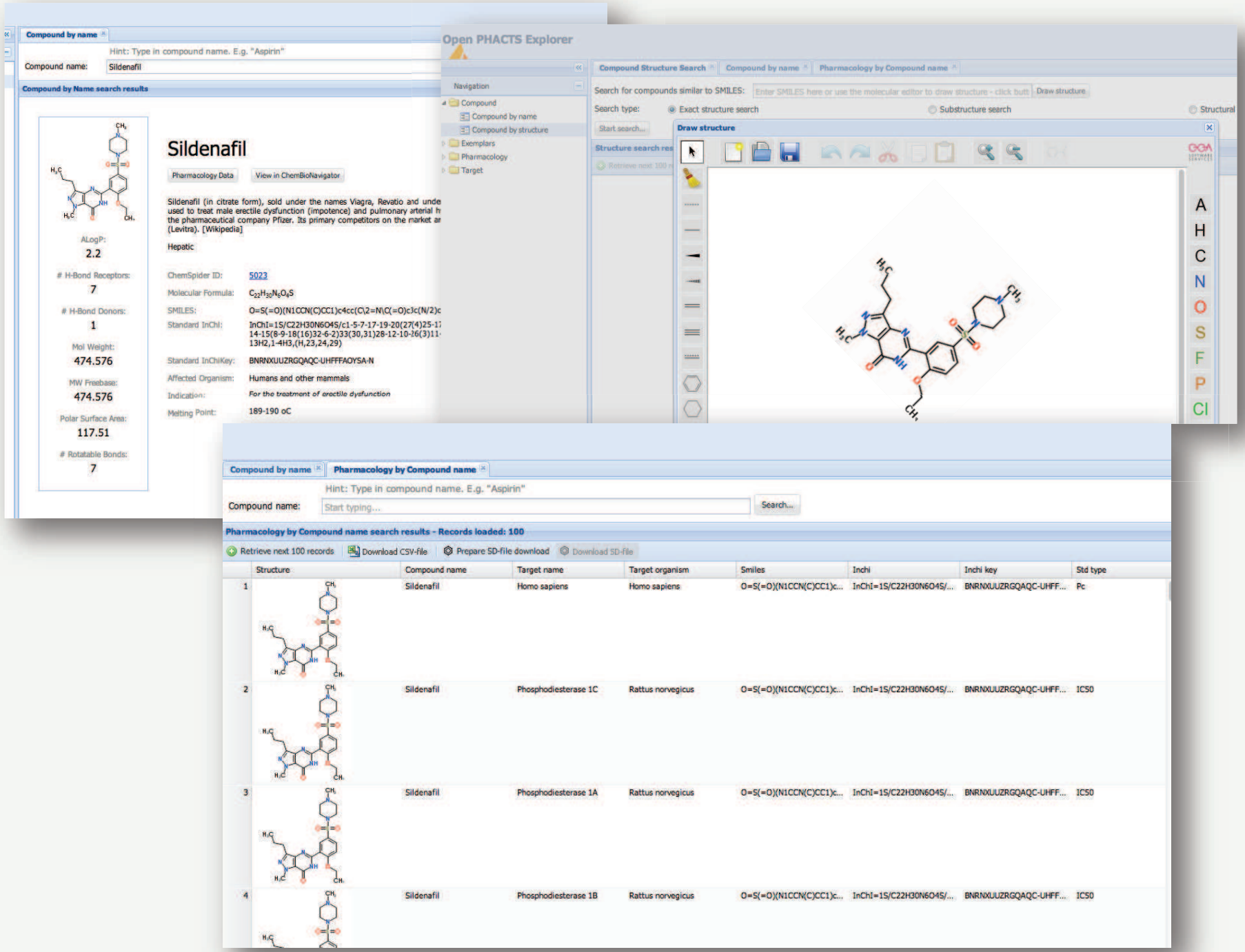
Latest News

June 2012
ACD/Labs' Version 2012 Chromatography Software Continues to Address the Challenge of Method Development

http://www.acdlabs.com/company/media/pr/120522_phacts.php


Compound by name
Hint: Type in compound name. E.g. "Aspirin"
Compound name: Sildenafil
Compound by Name search results
Sildenafil
Pharmacology Data
View in ChemBioNavigator
ALogP: 2.2
H-Bond Receptors: 7
H-Bond Donors: 1
Mol Weight: 474.576
MW Freebase: 474.576
Polar Surface Area: 117.51
Rotatable Bonds: 7
ChemSpider ID: 5023
Molecular Formula: C22H30N6O4S
SMILES:
Standard InChI:
Standard InChIKey: BNRNXUUZRGQAQC-UHFFFAOYSA-N
Affected Organism: Humans and other mammals
Indication: For the treatment of erectile dysfunction
Melting Point: 189-190 oC
Hepatic
Open PHACTS Explorer
Navigation
Compound
Compound by name
Compound by structure
Exemplars
Pharmacology
Target
Compound Structure Search
Compound by name
Pharmacology by Compound name
Search for compounds similar to SMILES:
Search type: Exact structure search
Substructure search
Draw structure
A H C N O S F P Cl
Compound by name
Pharmacology by Compound name
Hint: Type in compound name. E.g. "Aspirin"
Compound name:
Start typing...
Search...
Pharmacology by Compound name search results - Records loaded: 100
Retrieve next 100 records
Download CSV-file
Prepare SD-file download
Download SD-file
Structure
Compound name
Target name
Target organism
Smiles
Inchi
Inchi key
Std type
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Sustainability & Exemplars

- A vendor neutral, open "API" to allow others to use the Open PHACTS system within their own workflows (e.g. KNIME) and for Bio/ Chemo-IT vendors to build upon
- **Chem-Bio Navigator:** querying and visualization of sets of pharmacologically annotated small molecules, on basis of chemical substructures, pharmacophores, biological activities
- **Target Dossier:** *in silico* dossiers about targets, incorporating related information on sequences, structures, pathways, diseases and small molecules
- **Polypharmacology Browser:** map coverage of the chemo-biological space, to facilitate the polypharmacological profiling of small molecules
- **Utopia Documents:** See presentation; chemistry-aware PDF documents
- ++ More

Conclusion

- Key public & pharma drug discovery resource
- Emphasis on data quality, connectivity, provenance
- Science drive – real world questions joining multiple domains
- Long term sustainability – "we do the integration so you don't have to…"
- A platform for future precompetitive initiatives

SciBite

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Examples: Asthma , Jantoven, Thrombospondin 1, Pfizer

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Todays Prominent Topics

- PHENERGAN VC W/ CODEINE
- ACTIFED W/ CODEINE
- Methylmorphine
- Ocriplasmin
- Langerhans-Cell Histiocytosis
- Ro-21-5998/001
- Toyama
- Idenix
- IDX 184
- GRM5, glutamate receptor, metabotropic 5
- L-Glutamate
- Leucovorin
- CYP2C9, cytochrome P450, family 2, subfamily C, polypeptide 9
- Thrombogenics
- Thymol
- Retinal Perforations
- Cancer vaccine
- Rickets
- Keratoconus
- Leiormone
- GLP1R, glucagon-like peptide 1 receptor
- Progressive Supranuclear Palsy
- Calcium Folinate
- Pemetrexed Disodium
- Ironwood Pharmaceuticals
- Galena Biopharma
- Neural Tube Defects
- Sunesis
- ADM, adrenomedullin

Trending With Our Users

- DYSPORT
- Pain
- Breast Neoplasms
- Vincamine
- HIV Infections
- Eli Lilly
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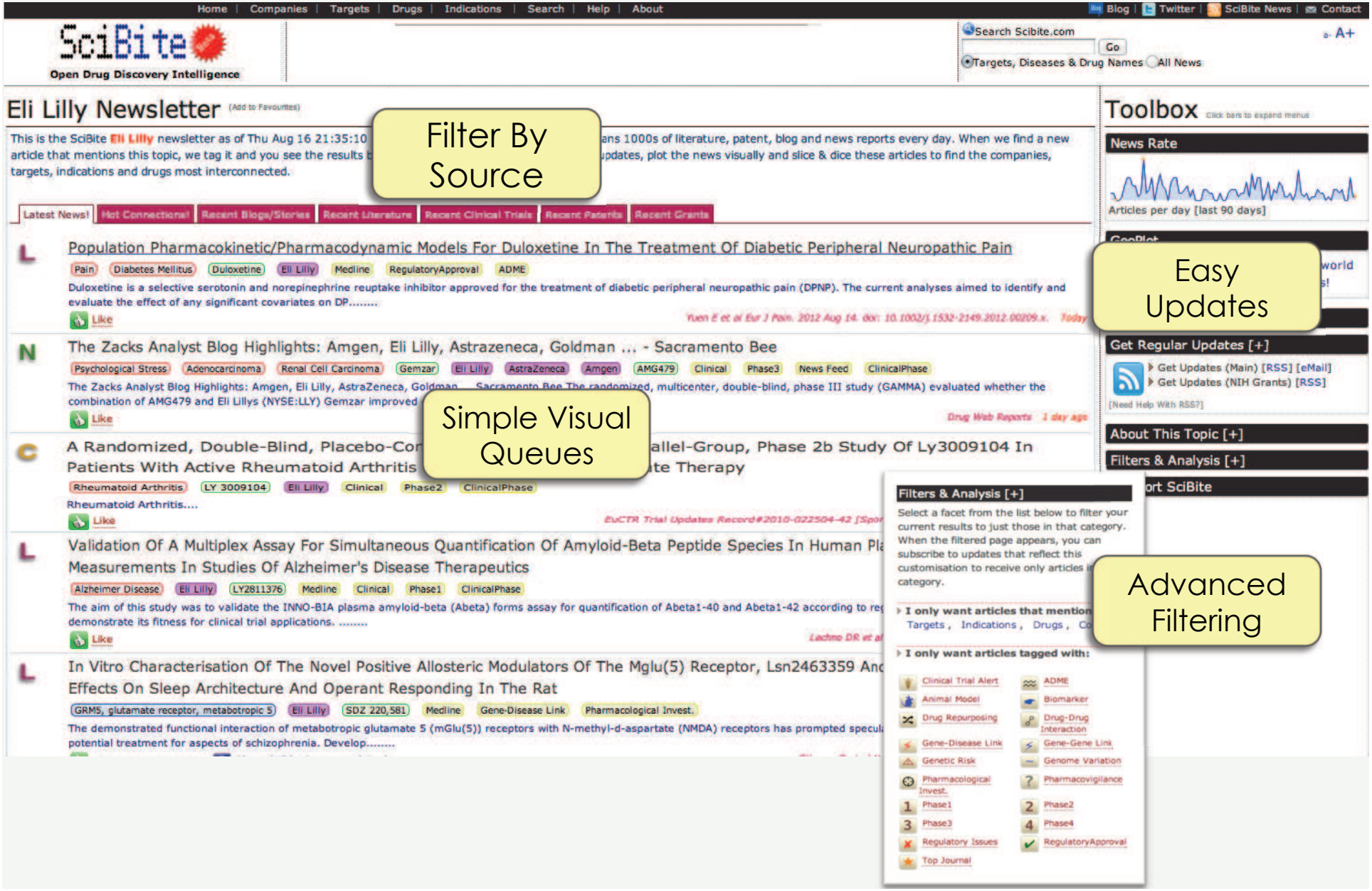
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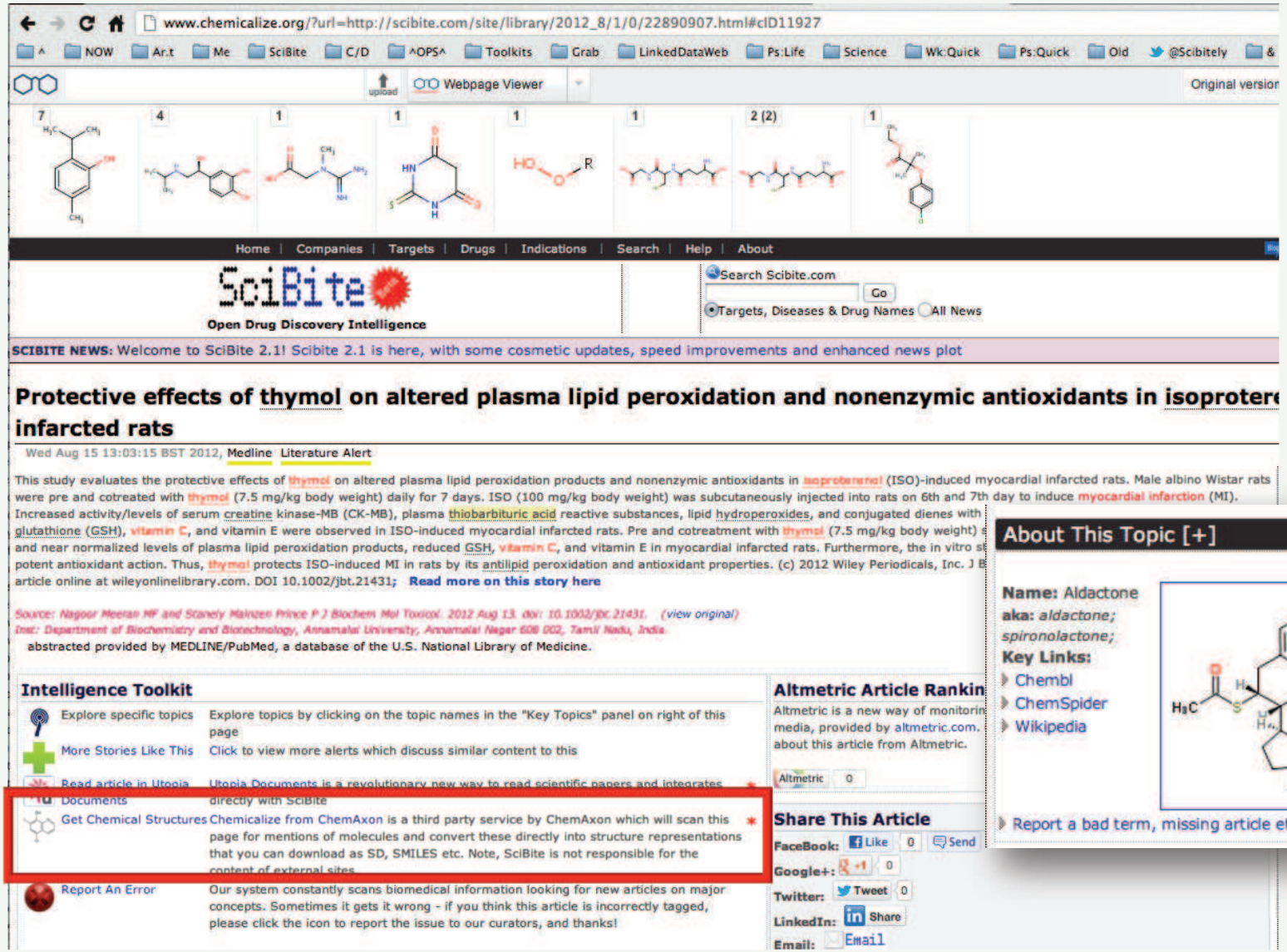
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Wed Aug 15 13:03:15 BST 2012, Medline Literature Alert
This study evaluates the protective effects of thymol on altered plasma lipid peroxidation products and nonenzymic antioxidants in isoproterenol (ISO)-induced myocardial infarcted rats. Male albino Wistar rats were pre and cotreated with thymol (7.5 mg/kg body weight) daily for 7 days. ISO (100 mg/kg body weight) was subcutaneously injected into rats on 6th and 7th day to induce myocardial infarction (MI). Increased activity/levels of serum creatine kinase-MB (CK-MB), plasma thiobarbituric acid reactive substances, lipid hydroperoxides, and conjugated dienes with glutathione (GSH), vitamin C, and vitamin E were observed in ISO-induced myocardial infarcted rats. Pre and cotreatment with thymol (7.5 mg/kg body weight)
and near normalized levels of plasma lipid peroxidation products, reduced GSH, vitamin C, and vitamin E in myocardial infarcted rats. Furthermore, the in vitro s
potent antioxidant action. Thus, thymol protects ISO-induced MI in rats by its antilipid peroxidation and antioxidant properties. (c) 2012 Wiley Periodicals, Inc. J
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Chronic Obstructive Pulmonary Disease Newsletter (Add to Favourites)

This is the SciBite **Chronic Obstructive Pulmonary Disease** newsletter as of Thu Aug 16 17:03:10 BST 2012. SciBite's information system scans 1000s of literature, patent, blog and news reports every day. When we find a new article that mentions this topic, we tag it and you see the results below. Use the toolbox on the right to get updates, plot the news visually and slice & dice these articles to find the companies, targets, indications and drugs most interconnected.

Latest News! | Hottest Connections! | Recent Blogs/Stories | Recent Literature | Recent Clinical Trials | Recent Patents | Recent Grants

SciBite's analytics scan 1000's of sources each day to build up a detailed picture of how this topic is related to others. We plot this information in the interactive "NewsPlot" below. Explore the chart to understand what other topics are connected to yours and identify hot new correlations. Currently these are limited to the 25 most recently connected topics for each type.

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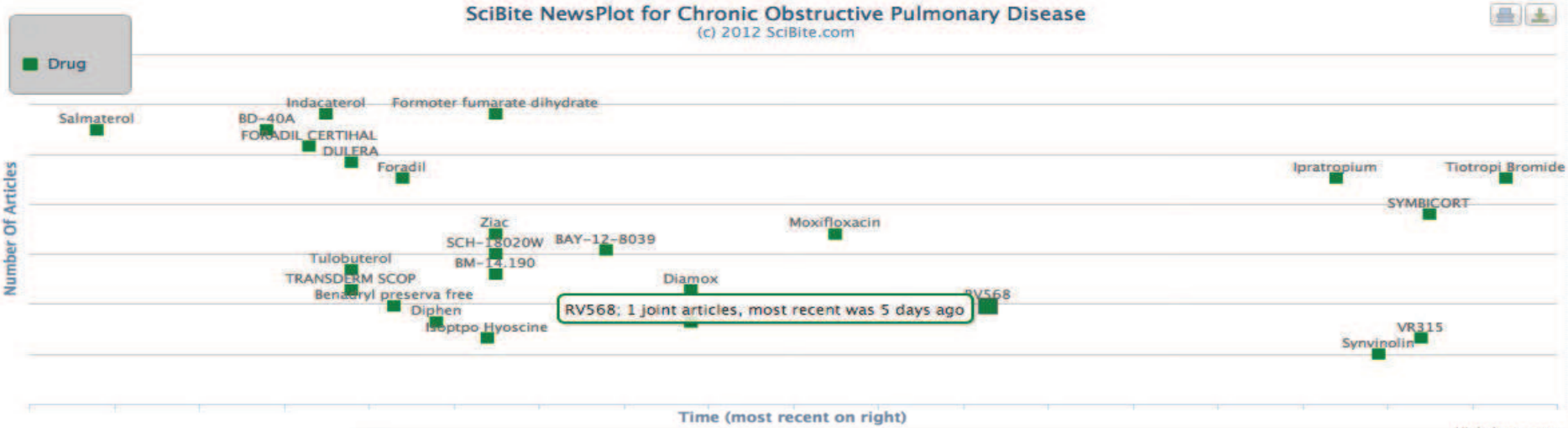
- Click and drag in the plot area to zoom in on a specific section.
- Click topics names on the chart legend to show/hide these.



Visualisation provided by HighCharts
Tabular data is available on request

SCIBITE NEWS: Welcome to SciBite 2.0! Read More about SciBite Pathways and SciBite GeoPlot by clicking here!

A Study to Investigate the Safety and Tolerability of a New Inhaled Formulation of RV568 in Healthy Volunteers

Fri Aug 10 17:01:08 BST 2012, Clinical Clinical Trial Alert New To SciBite

ClinicalTrial.gov Trial:NCT01661244
Conditions: COPD; Healthy Volunteers
Interventions: Drug: RV568 single dose; Drug: RV568 matching placebo single dose; Drug: RV568 repeat dose; Drug: RV568 matching placebo repeat dose
Sponsors: Respivert Ltd; Respivert Ltd
Not yet recruiting - verified August 2012; **Read more on this story here**
Keywords:

Source: ClinicalTrials.gov Trial Updates Record#NCT01661244 [Sponsor:Respivert Ltd; Respivert Ltd] (view original)
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SciBite GeoPlot

The GeoPlot shows the geographical location of the most recent articles for this topic (up to a maximum of 200 articles over 3 months). You can pan and zoom to identify regions of most interest and click the icons to get a small pop-up describing the article itself.

At present, this data covers Literature (from pubmed, shown in red), Grants (from the NIH, shown in pink) and Clinical Trials (from the International Clinical Trials Registry and ClinicalTrials.gov, shown in yellow). This is an early/experimental release of this visualisation so please treat the data with a bit of caution and feed back any issues to us. **Data was collected from July 1st 2012 onwards.**

SciBite Article GeoPlot

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SciBite Central is the home for important newsletters that span topics and areas of great interest within biomedical science and drug discovery. Here you will find feeds that allo
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Biomarkers

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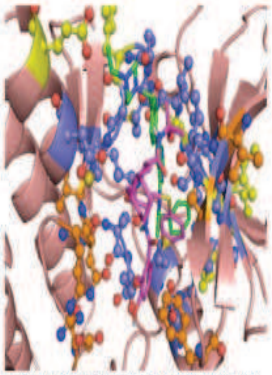
Kinase Central



EGFR with nelfinavir, Xie et al, PLOS Comp. Bio. 2011

Kinases represent critical targets in drug discovery. If you are interested in a specific kinase, use our text search to se
list below. Additionally, SciBite has also developed a more general newsletter that covers ALL human kinases.

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- Kinase-Disease Links, [feed]
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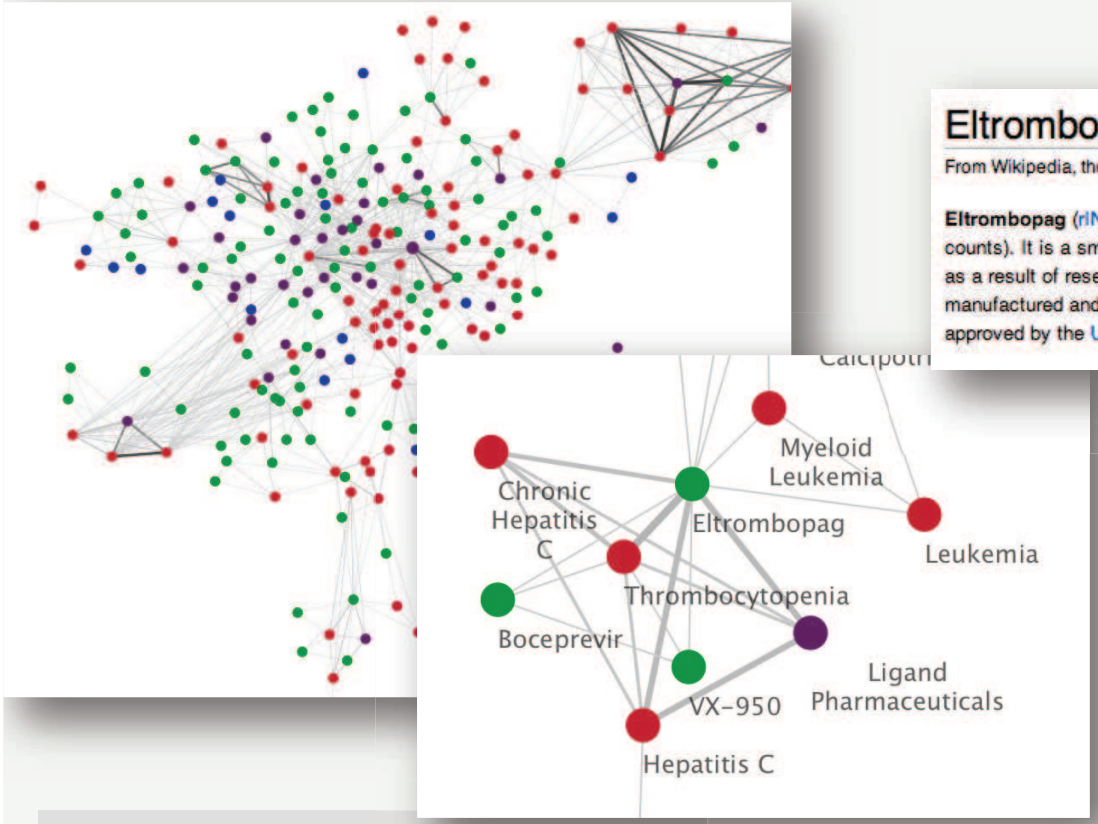

Eltrombopag

From Wikipedia, the free encyclopedia

Eltrombopag (rINN, codenamed SB-497115-GR) is a medication that has been developed for c
counts). It is a small molecule agonist of the c-mpl (TpoR) receptor, which is the physiological t
as a result of research collaboration between GlaxoSmithKline and Ligand Pharmaceuticals. De
manufactured and marketed by GlaxoSmithKline under the trade name **Promacta** in the USA ar
approved by the U.S. Food and Drug Administration on November 20, 2008. [1]

GSK/Ligand collaboration for Thrombocytopenia

But why is Eltrombopag connected to Leukemia?
Answer: New study from the US shows inhibits leukemia cell proliferation.
Repurposing Opportunity?

Display Settings: Abstract Send to:

Blood. 2012 Jul 12;120(2):386-94. Epub 2012 May 24.

Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation.

Roth M, Will B, Simkin G, Narayanagari S, Barreyro L, Bartholdy B, Tamari R, Mitsiades CS, Verma A, Steidl U.

Division of Pediatric Hematology/Oncology, Children's Hospital at Montefiore, Bronx, NY;

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PLoS one

Genetic Signatures of Exceptional Longevity in Humans

Paola Sebastiani[1]*, Nadia Solovieff[1], Andrew T. DeWan[2], Kyle M. Walsh[2], Annibale Puca[3], Stephen W. Hartley[1], Efthymia Melista[4], Stacy Andersen[5], Daniel A. Dworkis[6], Jemma B. Wilk[7], Richard H. Myers[7], Martin H. Steinberg[6], Monty Montano[6], Clinton T. Baldwin[6,8], Josephine Hoh[2], Thomas T. Perls[5]

1 Department of Biostatistics, Boston University School of Public Health, Boston, Massachusetts, United States of America, **2** Division of Chronic Disease Epidemiology, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut, United States of America, **3** IRCCS Multimedica, Milano, Italy; Istituto di Tecnologie Biomediche – Consiglio Nazionale delle Ricerche, Segrate, Italy, **4** Center for Human Genetics, Boston University School of Medicine, Boston, Massachusetts, United States of America, **5** Section of Geriatrics, Department of Medicine, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts, United States of America, **6** Department of Medicine, Boston University School of Medicine, Boston, Massachusetts, United States of America, **7** Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, United States of America, **8** Departments of Medicine and Pediatrics, Boston University School of Medicine and Boston Medical Center, Boston, Massachusetts, United States of America

Abstract

Like most complex phenotypes, exceptional longevity is thought to reflect a combined influence of environmental (e.g., lifestyle choices, where we live) and genetic factors. To explore the genetic contribution, we undertook a genome-wide association study of exceptional longevity in 801 centenarians (median age at death 104 years) and 914 genetically matched healthy controls. Using these data, we built a genetic model that includes 281 single nucleotide polymorphisms (SNPs) and discriminated between cases and controls of the discovery set with 89% sensitivity and specificity, and with 58% specificity and 60% sensitivity in an independent cohort of 341 controls and 253 genetically matched nonagenarians and centenarians (median age 100 years). Consistent with the hypothesis that the genetic contribution is largest with the oldest ages, the sensitivity of the model increased in the independent cohort with older and older ages (71% to classify subjects with an age at death>102 and 85% to classify subjects with an age at death>105). For further validation, we applied the model to an additional, unmatched 60 centenarians (median age 107 years) resulting in 78% sensitivity, and 2863 unmatched controls with 61% specificity. The 281 SNPs include the SNP rs2075650 in *TOMM40/APOE* that reached irrefutable genome wide significance (posterior probability of association = 1) and replicated in the independent cohort. Removal of this SNP from the model reduced the accuracy by only 1%. Further in-silico analysis suggests that 90% of centenarians can be grouped into clusters characterized by different "genetic signatures" of varying predictive values for exceptional longevity. The correlation between 3 signatures and 3 different life spans was replicated in the combined replication sets. The different signatures may help dissect this complex phenotype into sub-phenotypes of exceptional longevity.

Citation: Sebastiani P, Solovieff N, DeWan AT, Walsh KM, Puca A, et al. (2012) Genetic Signatures of Exceptional Longevity in Humans. PLoS ONE 7(1): e29848. doi:10.1371/journal.pone.0029848

Editor: Greg Gibson, Georgia Institute of Technology, United States of America

Received November 21, 2011; **Accepted** December 5, 2011; **Published** January 18, 2012

Funding: This work was supported by National Institutes of Health grants: R01 HL087681 (to MS), K24 AG025727 (to TP), R01 AR055315 (to MW), RO1 AG027216 (to CB), R01 NS36711-09 (to RM). In the study we included 254 subjects enrolled at ELIXIR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: In the study the authors included 254 subjects enrolled at ELIXIR. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

* E-mail: sebas@bu.edu

Introduction

The average human lifespan in developed countries now ranges from about 80 to 85 years. Environmental factors such as lifestyle choices and where we choose to live as well as genetic factors all contribute to healthy aging. Supporting the importance of environmental factors in survival to old age is the 88 year average life expectancy of Seventh-Day Adventists [1], who by virtue of their religion have health related behaviors conducive to healthy aging.

Human twin studies suggest that only 20–30% of the variation in survival to about 85 years is determined by genetic variation [2]. However, the existence of rare families demonstrating remarkable clustering for extreme ages [3,4], the increased relative risks of survival amongst siblings of nonagenarians [5] and of centenarians [6,7,8,9,10,11,12,13], the fact that children of centenarians experience a marked delay in age-related diseases [14], and the similarity of centenarians' lifestyles to the general population [15], all argue that genetic factors play a much stronger role in living 25–35 years beyond the mid-eighties [10,16,17]. Impressively, siblings of centenarians born in 1900 have a relative risk of living nearly 100 years that is 8 (females) to 17 times (males) greater than that for the average of their birth cohort [10]. The rarity of the trait – only 1 centenarian amongst approximately 5,000 people in the US and only 1 supercentenarian (age 110+ years) amongst seven million people [18] – places exceptional longevity in a very different category from both average life expectancy and common complex traits associated with aging.

Based upon the hypothesis that exceptionally old individuals are carriers of multiple genetic variants that influence human lifespan, we conducted a genome-wide association study (GWAS) of centenarians. We began with a traditional one SNP at a time analysis to identify SNPs that are individually associated with exceptional longevity. We then used a novel approach to build a

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High expression of the longevity gene product SIRT1, and apoptosis induction by sirtinol in adult T-cell leukemia cells Kozako T et al Int J Cancer. 2012 Feb 9. doi: 10.1002/ijc.27481. [sirtuin 1] [Aging] [Adult T-Cell Leukemia-Lymphoma]

Micronutrient (Zn, Cu, Fe)-gene interactions in ageing and inflammatory age-related diseases: implications for treatments Mocchegiani E et al Ageing Res Rev. 2012 Jan 31. [Aging] [Inflammation]

Hot topics in epigenetic mechanisms of aging: 2011 Berdasco M and Esteller M Aging Cell. 2012 Feb 9. doi: 10.1111/j.1474-9726.2012.00806.x. [Aging]

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Final Thought

- Data/Information challenge is only getting bigger
- New tools are now appearing, based on shared standards that make public and private data sharing easier
- Open efforts need support and can provide a springboard for future projects
- Thanks for listening, please visit us at:

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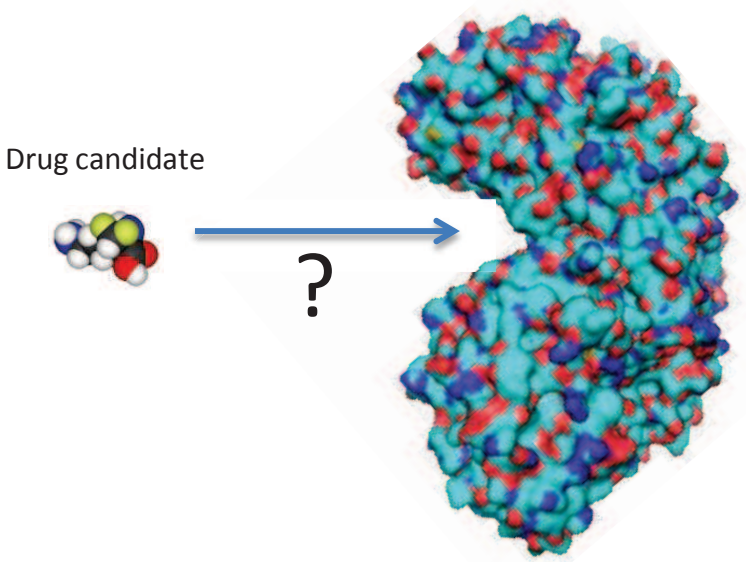
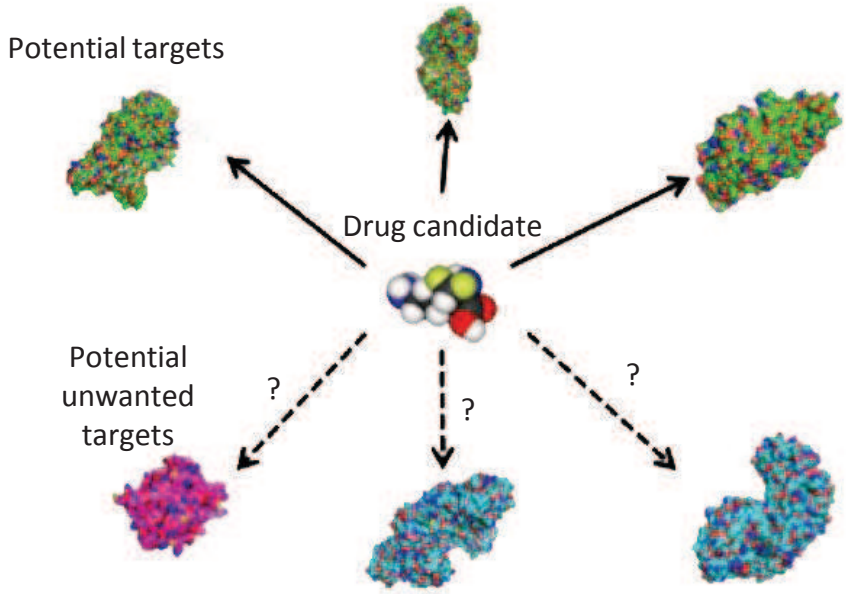
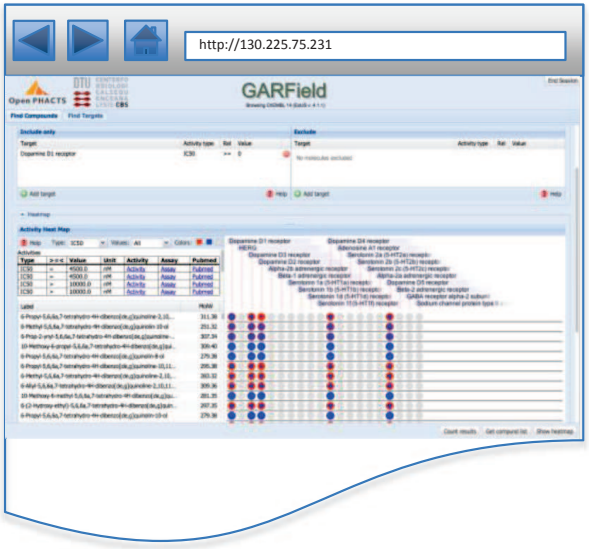
- Prediction of polypharmacology profile
- Integrate several other sources of related information



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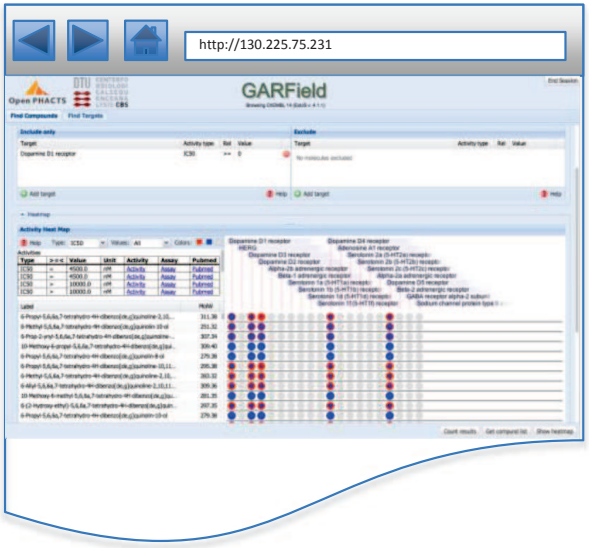
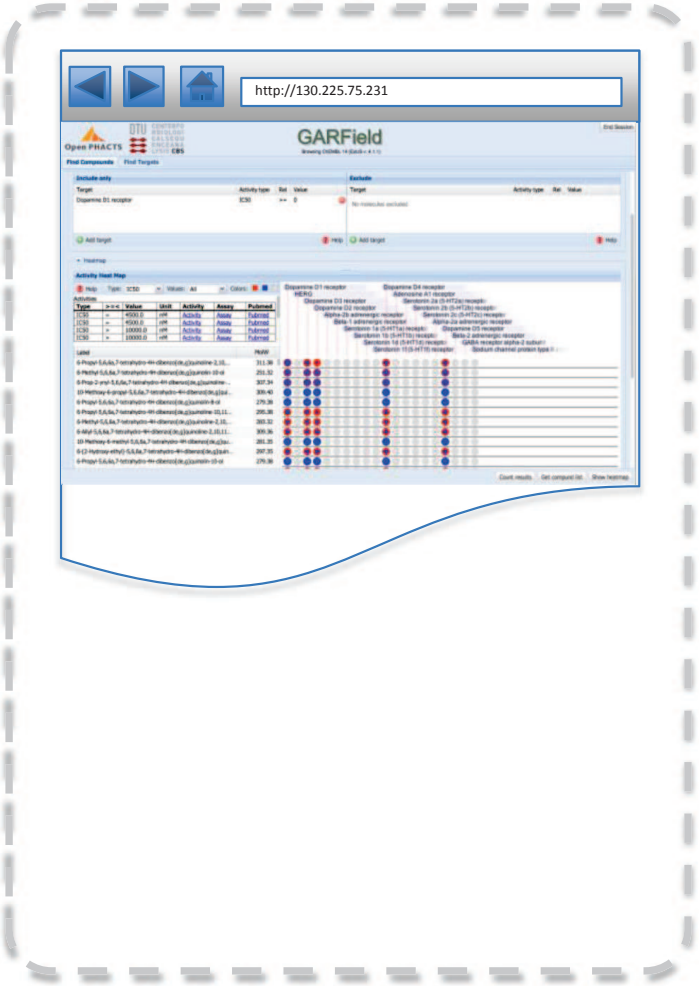
GARField

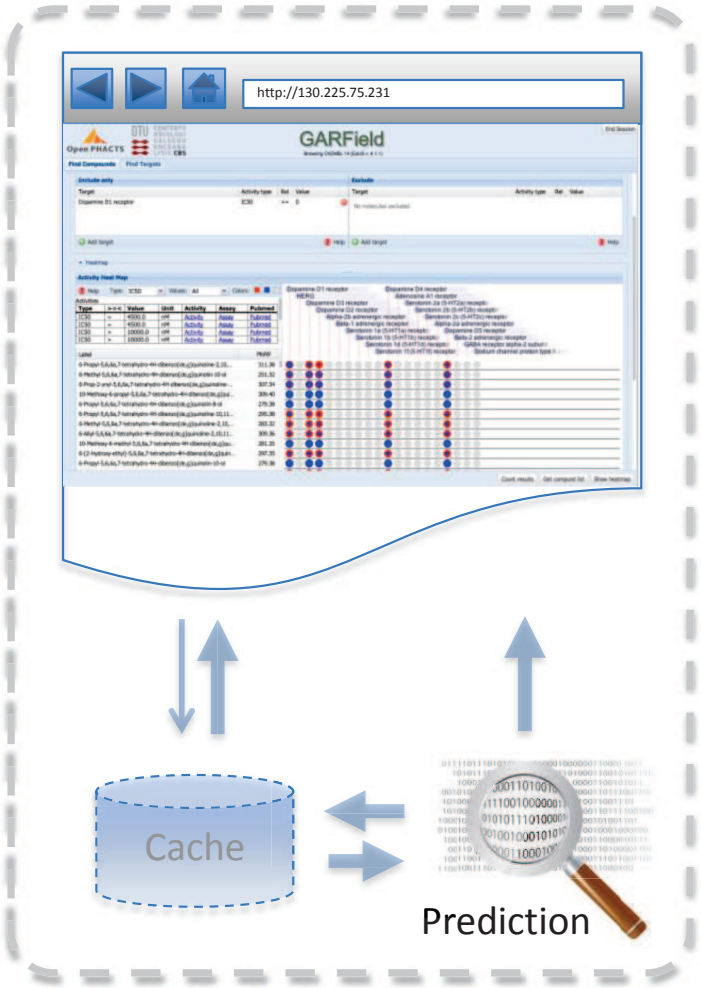


GARField version 0.2

- Web page application
  - HTML5
  - JavaScript
  - ExtJS 4
  - PHP

- Browse Open PHACTS data
- List compounds/targets from search criteria
  - Properties
  - Polypharmacology
- List manipulation (target/compound)
- Prediction of protein interaction
  - Similarity Ensemble Approach (SEA)


http://130.225.75.231
GARField
Open PHACTS API
ChEMBL
....
PDSP
....
OPS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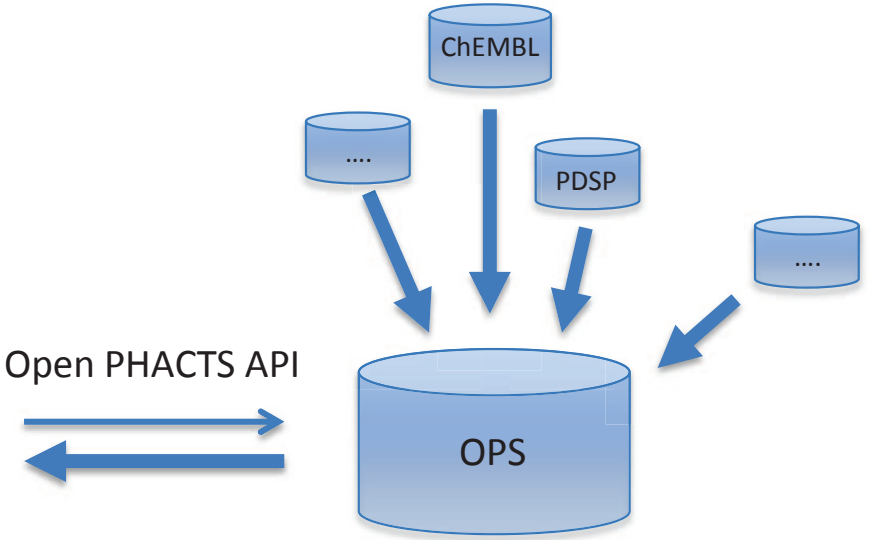
GARField
Cache
Prediction


ChEMBL
....
PDSP
....
Open PHACTS API
OPS

CBN

ChemBioNavigator

Universität Hamburg

Bio Solve IT

Open PHACTS

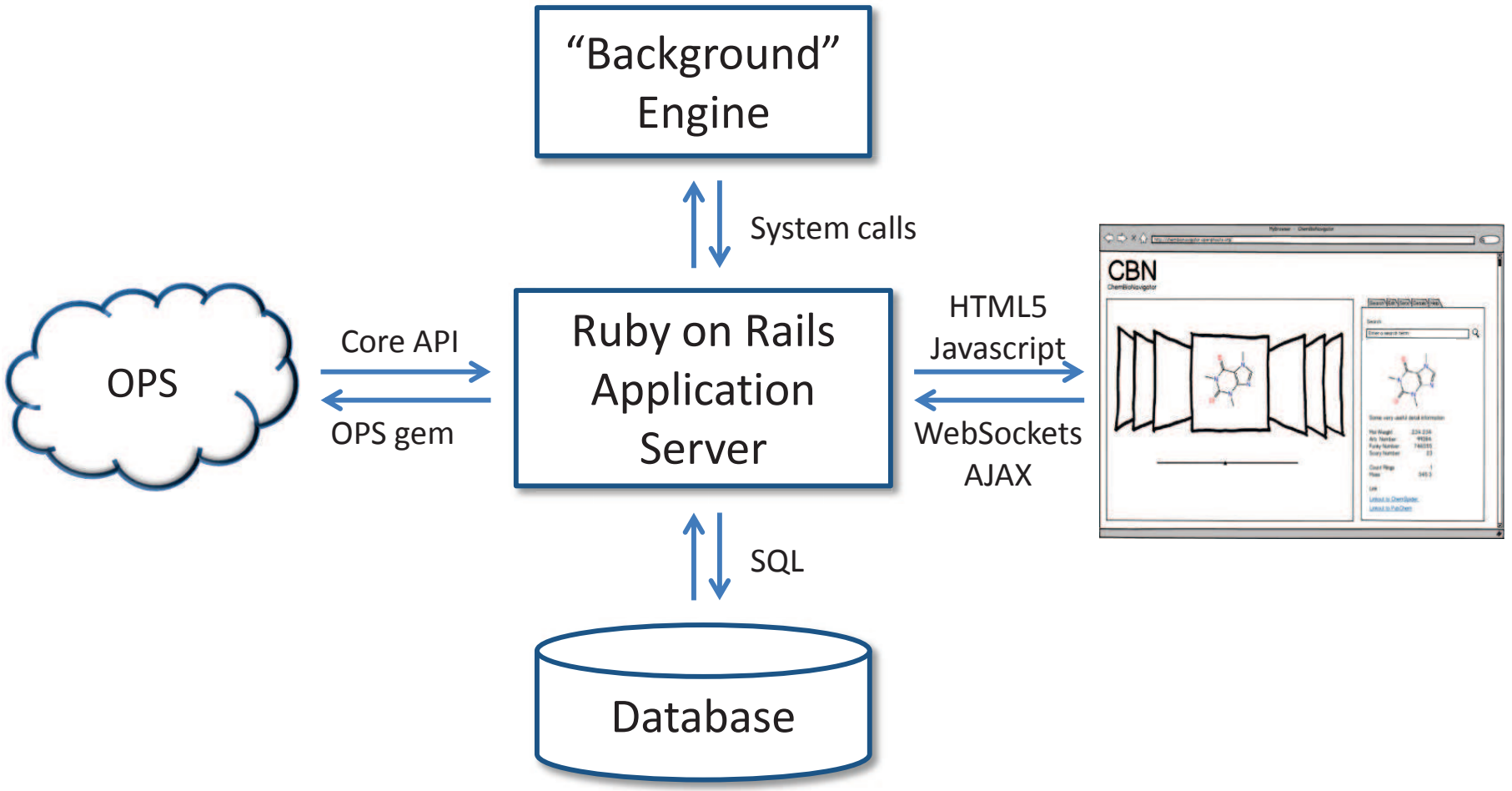
Open Pharmacological Space

CBN Design Goals

… a compound-centric data browser that is

- easy to … set up & run the application
  - standard (HTML5) web application
  - minimal intrusion on the client side
  - agile development: Ruby on Rails, CSS, JavaScript, AJAX
- easy to … use for non-technical scientists
  - intuitive/responsive GUI with optimum user-guidance
  - allow “jumping” between Exemplars
  - extensive “linking” into related data sources

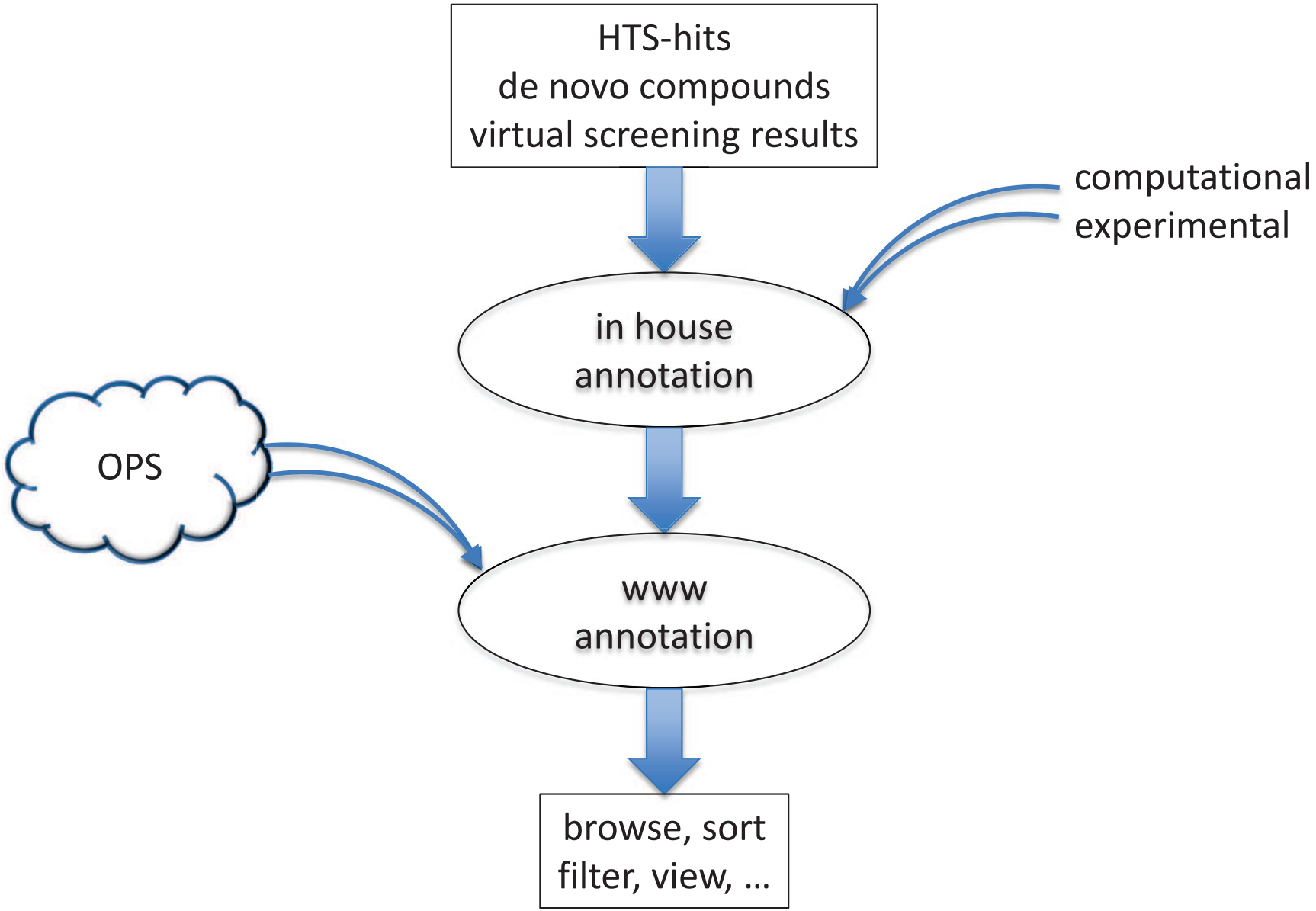
Architecture



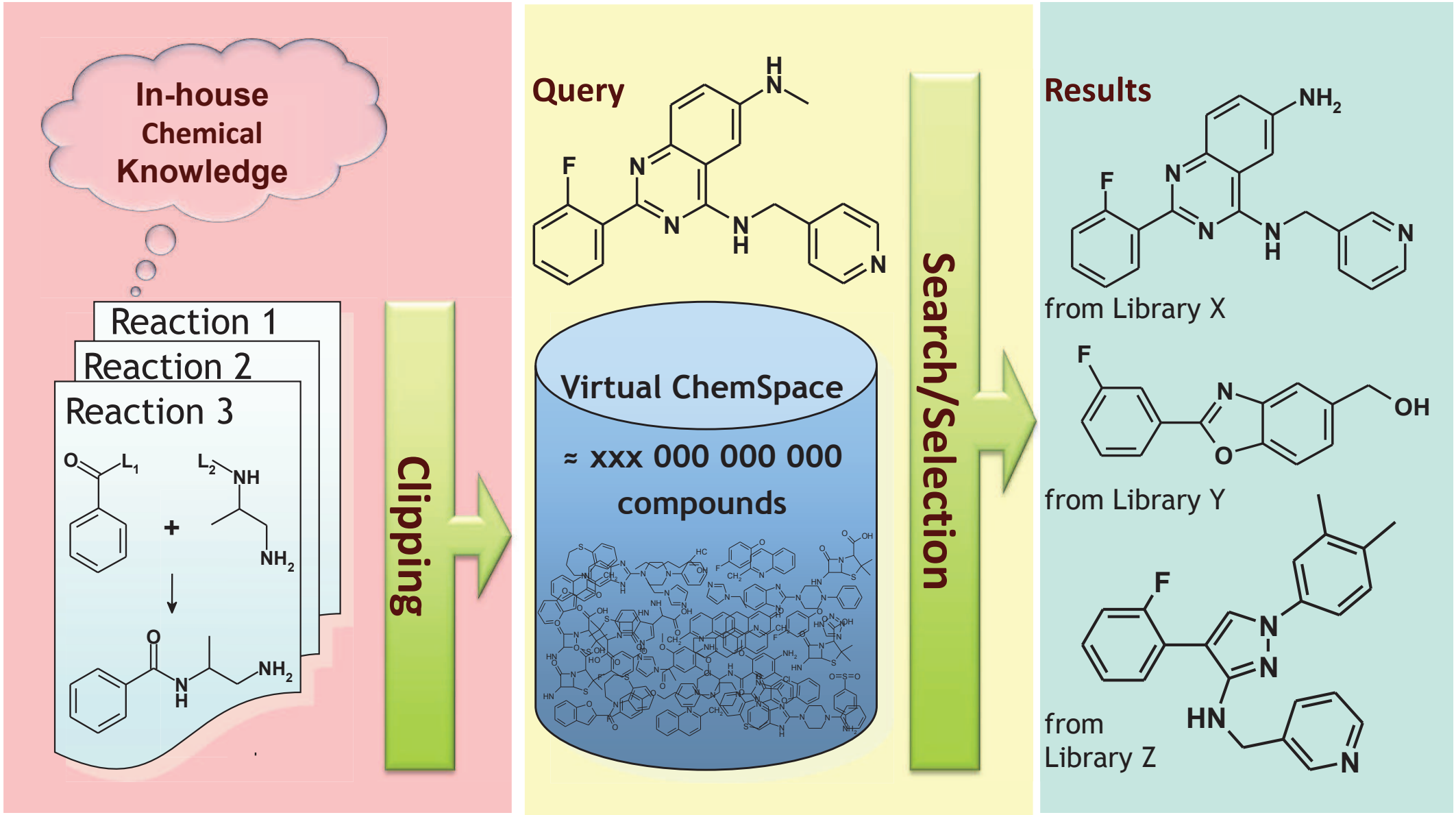
User Centric Design

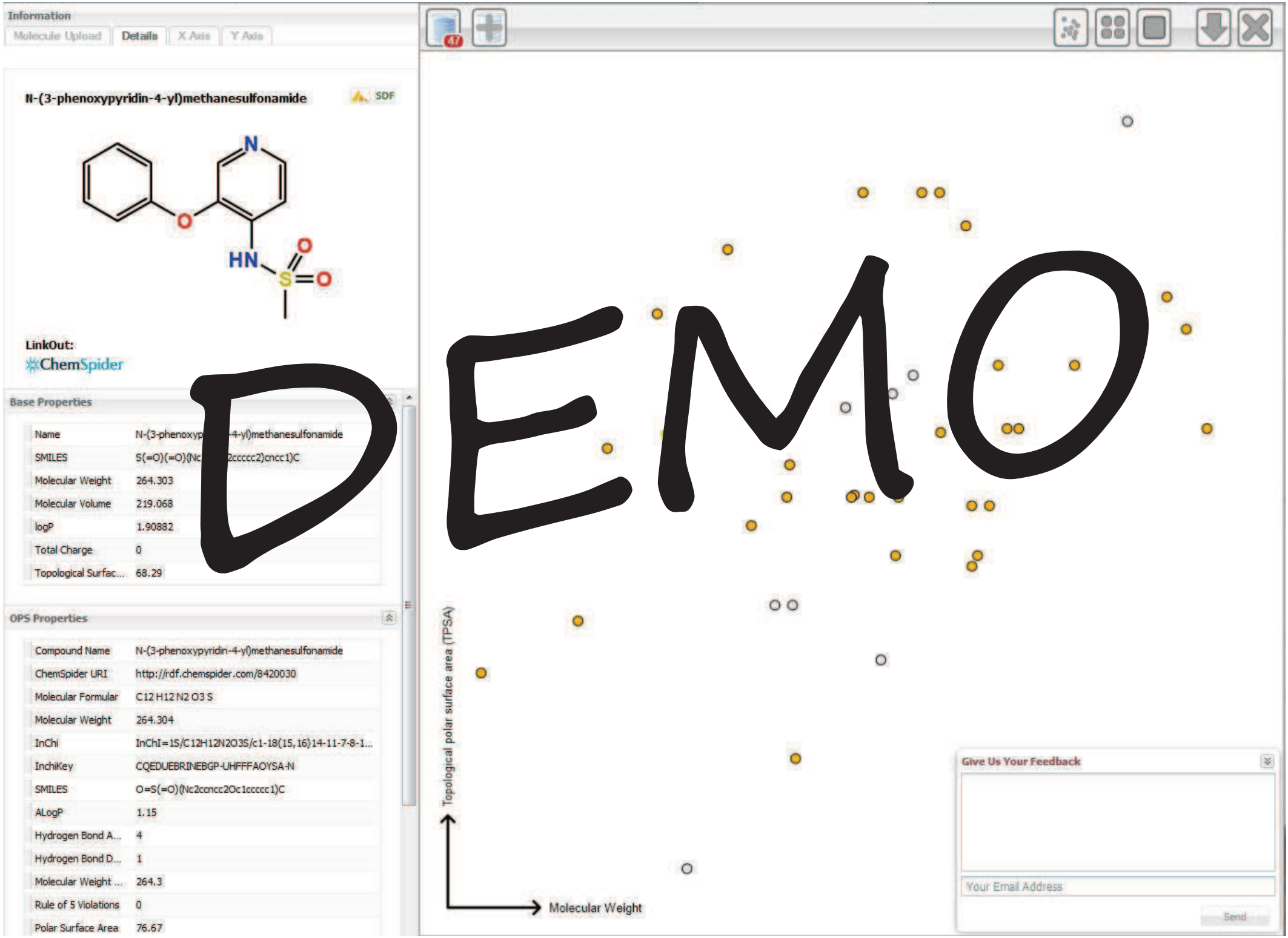
- Release 1: Goals & Use Cases
  - upload and browse molecules
  - connect to OPS-framework
  - merge external and internal data
  - display molecules / browse data
  - getting an overview of what is currently loaded
  - export combined data

Primary Workflow



Virtual Screening




Information
Molecule Upload
Details
X Axis
Y Axis
N-(3-phenoxypyridin-4-yl)methanesulfonamide
SDF
LinkOut:
ChemSpider
Base Properties
Name
SMILES
Molecular Weight
264.303
Molecular Volume
219.068
logP
1.90882
Total Charge
0
Topological Surfac...
68.29
OPS Properties
Compound Name
N-(3-phenoxypyridin-4-yl)methanesulfonamide
ChemSpider URI
http://rdf.chemspider.com/8420030
Molecular Formular
C12 H12 N2 O3 S
Molecular Weight
264.304
InChi
InChI=1S/C12H12N2O3S/c1-18(15,16)14-11-7-8-1...
InchiKey
CQEDUEBRINEBGP-UHFFFAOYSA-N
SMILES
O=S(=O)(Nc2ccncc2Oc1ccccc1)C
ALogP
1.15
Hydrogen Bond A...
4
Hydrogen Bond D...
1
Molecular Weight ...
264.3
Rule of 5 Violations
0
Polar Surface Area
76.67
DEMO
Topological polar surface area (TPSA)
Molecular Weight
Give Us Your Feedback
Your Email Address
Send

Status

- Prototype ready for testing
- Official release towards the end of the year

Limitations

- Max 500 molecules per session
- Anonymous users -> no storage

Outlook

- Similarity searches to expand sets
- Inclusion of target information
- Suport of tablet PCs

Availibility

Early testers are welcome

email: cbn@zbh.uni-hamburg.de

Please provides us with lots of feedback!