

Open PHACTS

Deliverable 5.3.4

**First release of Polypharmacology browser,
Pharmatrek, to community**

The Open PHACTS Poly-pharmacology Browsers

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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

OGI – 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.

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1 Introduction

With the increasing amount of pharmacological data provided by the scientific community, several initiatives aiming at collecting, organising and storing these data together with chemical structures were developed or underway. However, pharmacological information is vast and spread in numerous databases that are not easy to access and to interrogate and with not the entire information required.

To deal with such huge amount of information, Open PHACTS has recently created and released the first open access pharmacological space, applying semantic web technologies, with the aim to facilitate open innovation in drug discovery research. In addition, to the development of the OPS platform, that provides a mapping between ontologies (chemical, biological...), databases and scientific textual representations, allowing to users to address complex research questions, Open PHACTS has the objective to provide interactive applications, “eApps”, that helps users to explore, to analyze and to visualize such pharmacological information.

One of the eApps that has been introduced to the community in the same time as the OPS platform is PharmaTrek, an interactive semantic web explorer that allows to navigate in the pharmacological space defined by small molecules. Further details about PharmaTrek features are described below.

2 Release of PharmaTrek to the community

PharmaTrek is an **integrative** and **interactive** web-based tool to navigate in the pharmacological space defined by small molecules contained in the **Open PHACTS** platform. In particular, it currently allows for navigating on the contents of ChEMBL (v.13), one of the largest public repositories of chemical structures annotated with pharmacological data. **PharmaTrek** has been purposely designed to enable multidisciplinary teams of drug discovery scientists to visually process information on chemical structures and biological activities in an **efficient**, **organized** and **integrative** manner as a means to **extract knowledge** from the target profile of compounds as well as from the ligand profile of protein targets.

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2.1 Technical details

PharmaTrek is implemented using **Flex 4**. Flex is a free, **open source framework** for building and maintaining highly interactive, expressive applications (**Rich Internet Application**, RIA) that deploy consistently on all major browsers. Flex uses two languages to write applications: MXML and ActionScript. MXML is an XML markup language used mainly to lay out user interface components, but also to implement the visual aspects of an application. ActionScript is an object-oriented programming language. ActionScript 3.0 is designed to facilitate the creation of highly complex applications with large data sets and object-oriented reusable code bases. **FlashDevelop** was used as Integrated Development Environment (IDE) to build the application. FlashDevelop is a free and **open source** (MIT license) source code editor. Finally, PharmaTrek was developed following the Model-View-Controller design pattern to facilitate the reusability and maintainability of the application. Accordingly, the application is partitioned into three categories of components: model components that encapsulate data and behaviors related to the data processed by the application, view components that define the application's user interface, and the user's view of the data, and controller components that handle data interconnectivity in the application. Access to the Open PHACTS data is currently managed by an application webserver developed using **SCALA** that retrieves data through an application programming interface (API) provided by the OPS system. (See **Figure 1**).

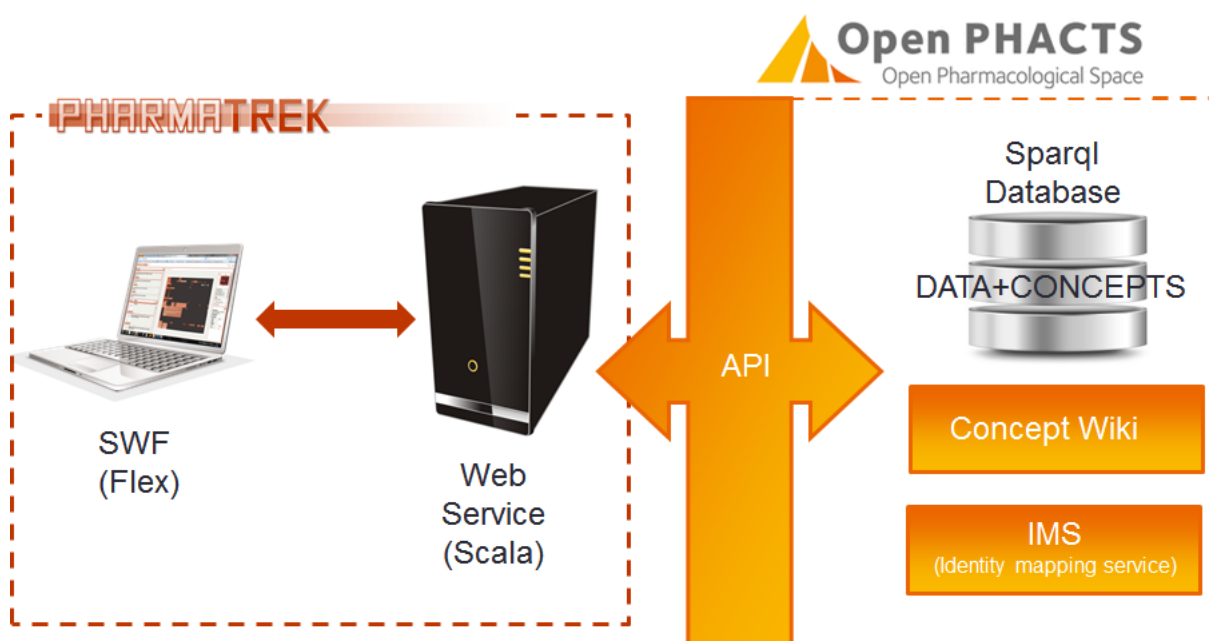


Figure 1. Application architecture

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2.2 Use case scenario

The application is located at <http://www.pharmatrek.org> and it is open to the public domain. **Figure 2** shows a snapshot of its main page. The user will see a prompt where he can select “Target” or “Ligand” to start the search. As an application example, we will show how to address the question of “extracting all potent Factor Xa inhibitors with selectivity of at least two orders of magnitude relative to thrombin and trypsin, two philogenetically related serine proteases”.

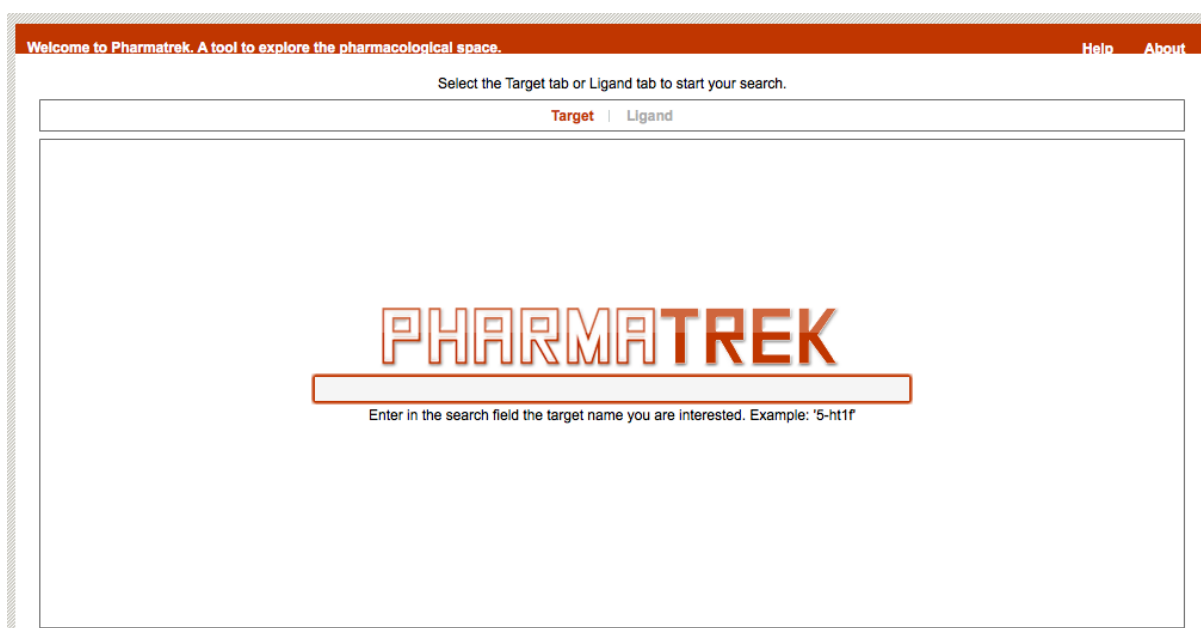


Figure 2. Pharmatrek main page

2.2.1 Defining the target profile

To start with, the user has to enter the target names into the field located in the middle of the page. It’s a Google-like search field that suggests names of targets while you are entering your search. The idea is that this field helps you to find the target that you are interested in. You are then automatically redirected to 2 tabs:

- The search tab that includes the search area and the basket area
- The browser tab with all the targets that are in the heatmap.

For example, if the user enters “coagulation Factor X (*Mus musculus*)”, it will match with the enzyme EC 3.4.21.6. The user will have the possibility to get more details about the enzyme by clicking on the icon “Show details” and “View this target in Explorer” or “Add to the basket”. For the last option, the user will then be able to create a heatmap in order to

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visualize all the compounds that show some bioactivities (such as K_i , K_d , IC_{50} or EC_{50}) for this enzyme.

2.2.2 The basket section

An interesting feature with the basket selection is the possibility to integrate several targets in the query and to filter the activity of interest for each target. For example, the user can address a complex query such as retrieve all the ligands having a $-\log(\text{Activity})$ value larger than or equal to 7.5 for the coagulation factor Xa and being at least two orders of magnitude selective against trypsin and thrombin (two phylogenetically related serine proteases). With the “Connect checkbox”, the heatmap is restricted to only the ligands that have some activity against all the targets in the basket whereas the “Expand checkbox” will expand the heatmap by adding targets that have some activity against the heatmap ligands.

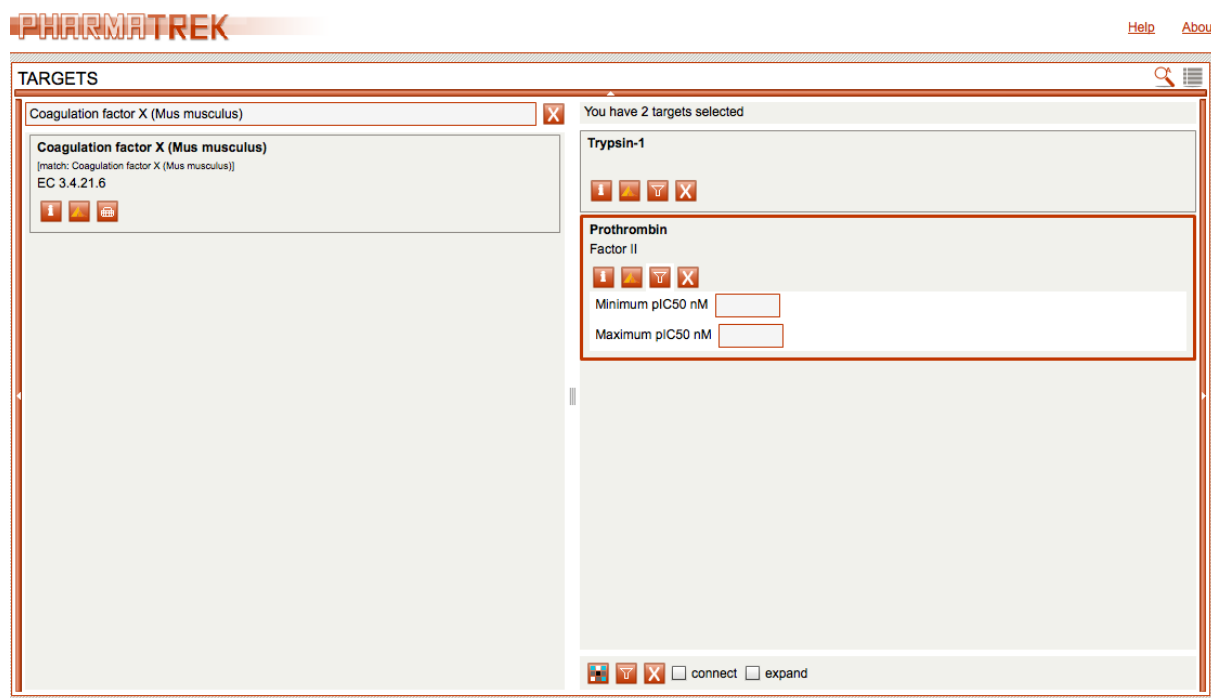


Figure 3. Target search layout

2.2.3 The interactive heatmap

Once you have entered the target or target profile and all the filters that you want to apply, you can click the “Show heatmap” button to obtain an interactive map containing all protein-

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ligand interactions that meet all criteria defined in the basket. As can be observed in the picture added below, an interactive heatmap appears in the Heatmap Panel.

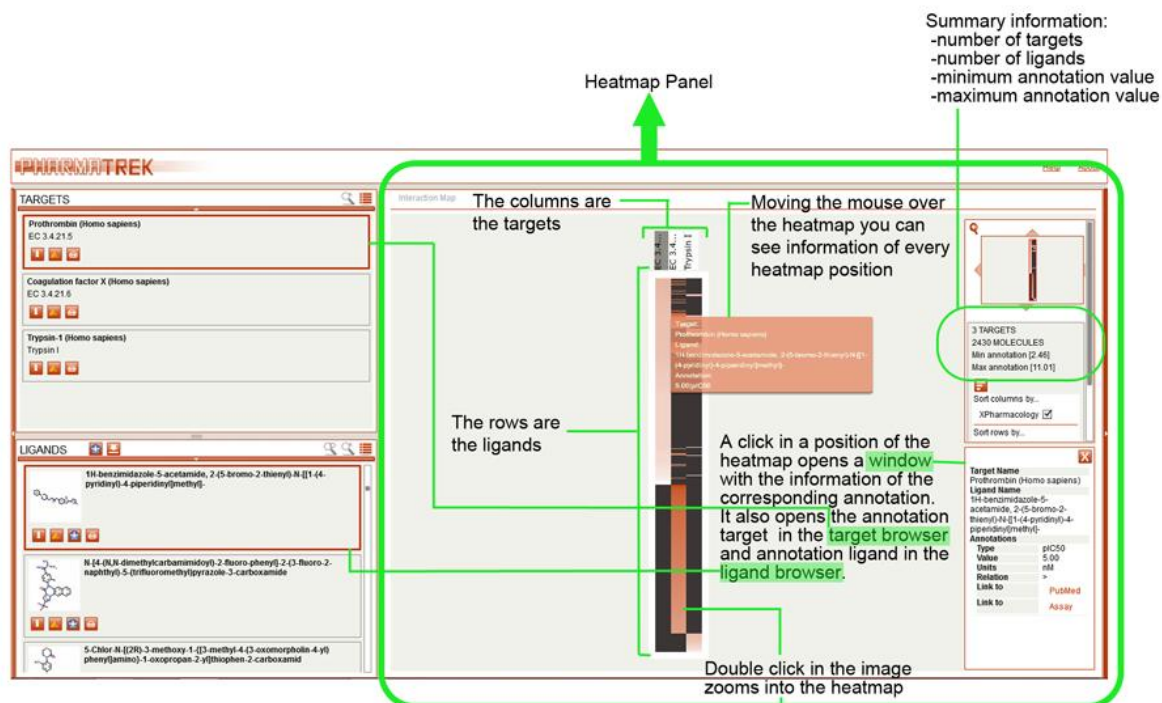


Figure 4. Heatmap layout.

In the interaction map, rows represent ligands and columns the targets defined in the basket. To keep only those ligands that have interaction with all of the targets of your search, you can click on the “connect” check box located at the bottom of the basket field. If you pass the mouse over the heatmap, a tooltip appears with the value of the interaction (in $-\log$ -arithmic scale) of the corresponding ligand/row-target/column.

At the right-hand side of the heatmap, you can see a summary with the number of targets and molecules displayed in the heatmap and also the maximum and minimum affinity values. There is also an image that represents the heatmap and a slider that allow you to make zoom in, zoom out and move into the heatmap. The default color is from white for a weak activity (Minimum annotation value) to red for a strong activity annotated to the protein (maximum annotation value). It is black when no annotation has been found. For the sake of convenience, one can also customise the colors of the heatmap with the color selectors that are located at the bottom-right corner of the heatmap.

Last but not least, one can also ask PharmaTrek to check whether the compounds fulfilling the criteria for the target profile defined in the basket have additional interactions on other

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targets in the source(s) being explored. To do that, you can click in the “Expand target space” check box. Upon activation of this check box, the application makes a request to expand the target space with additional targets not included originally in the target profile defined in the basket. A useful feature is that any new target appearing after this expansion can be added to the basket. Simply put the mouse on top of the target name appearing in the labels of the columns (zoom in if necessary) and drag & drop the name into the basket. You can then apply new filters and perform a new ligand extraction request.

2.2.4 The ligand tab

At any point during the PharmaTrek session, the structures of all ligands fulfilling all criteria defined appear in the “Ligands” section located below the basket. By clicking the image of a structure, more detailed information about the ligand can be obtained, such as name, molecular formula, molecular weight, InChI and InChI-keysm smiles, and any additional properties and descriptors that might be available in the source being explored. One can always save the structures in SMILES of all the ligands shown by clicking in the “Save smiles” button. An interesting feature is the connection to the ChemBioNavigator eApp. So, any ligand reported in the PharmaTrek session can then be transferred into ChemBioNavigator for further analysis of the ligand.

2.2.5 Defining the ligand profile

Finally, all the applications and features described previously for the “target profile” is also possible for the “ligand profile”, meaning that PharmaTrek will provide all the bioactivities annotated for a specific compound of interest. For example, a search for “sildenafil” will retrieve activities for 43 targets (see figure below).

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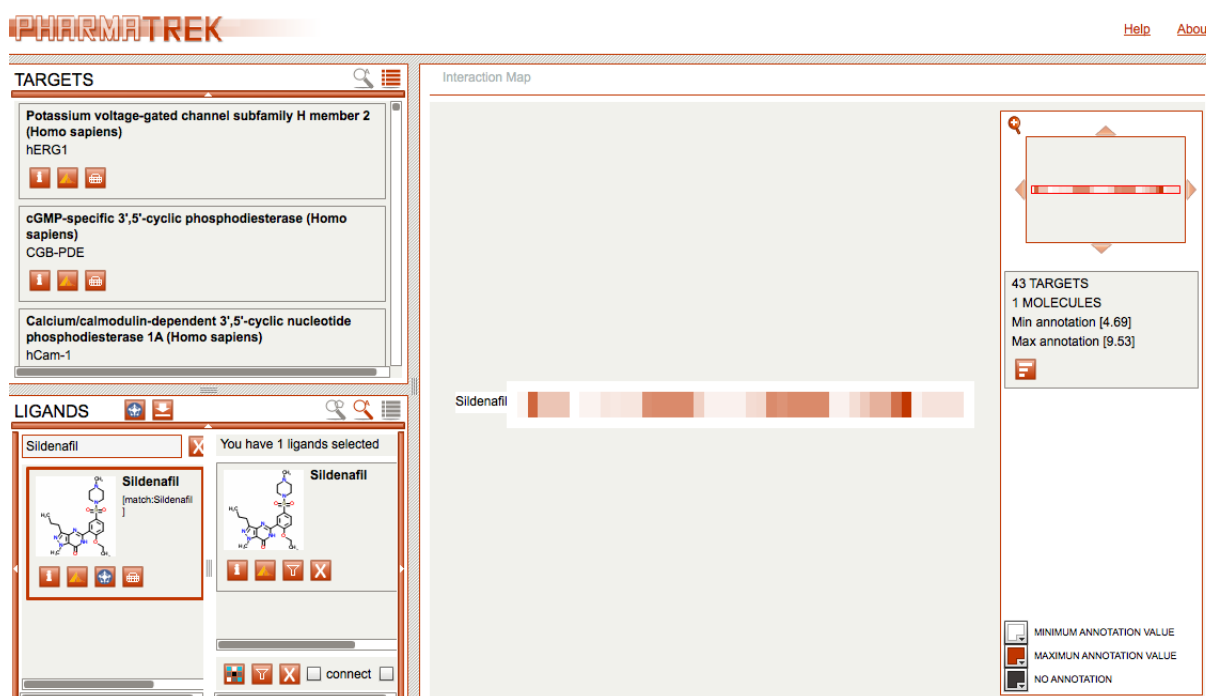


Figure 5. Heatmap layout for sildenafil

A short introduction and walk-through the PharmaTrek web browser is accessible under the “Help” menu of PharmaTrek and reported in the manuscript (Carrascosa MC, Massaguer OL, Mestres J. Pharmatrek: a semantic web explorer for open innovation in multitarget drug discovery. *Mol. Inform.* 2012; 31, 537-541).

3 Feedback

We encourage feedback for all aspects of our development of the exemplar. For instance, suggestion about missing features, alternative workflows, errors, etc