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D8.3 Interface for drug testing

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Executive summary

Deliverable “D8.3 Interface for drug testing” is the third deliverable of “WP8 - Report to FDA or EMA” and corresponds to the work, outcomes and results of the “Task 8.3 Interface drug database” that started on M24 and end on M40. The interface of the drug database is a key component of the SILICOFCM cloud platform to enhance the execution of *in silico* clinical trials for drug testing. In the specific deliverable the deployment of Drug search tool through the combination of well-established databases to the SILICOFCM platform is presented, after a thorough investigation in the literature of the publicly available databases that meet specific needs. The Drug search tool is a combination of DGIdb and UniProt databases, providing all the essential information and the pathway from drug to gene and finally, to protein and possible interactions among them. Information has been grouped in specific cards for drug, gene and protein, describing in detail all the functionalities of specific workflows that have been designed by the participating partners. The drug search tool provides to an expert and endpoint connected to multiple knowledge sources to retrieve information regarding the drug, drug protein interaction, drug-gene interaction. The later facilitates the experts to set the parameters for the PAK-FEM drug related simulation workflows. The architecture, back-end and front-end technologies and the dedicated UIs are extensively presented in the current deliverable. D8.3 also presents the Drug Interaction Tool, based on MINERVA framework, with a detailed description and analysis of the HCM disease pathway based on molecular interactions visualized on MINERVA detailed map. Moreover, a description of the integration of the externally established MINERVA framework to the SILICOFCM platform is presented. The deliverable includes 7 sections and the ANNEX. Thus, the structure of the D8.3 is as follows:

The objective of the Task 8.3 aims to design and develop a web interface onto the SILICOFCM platform in order to retrieve information for drugs with the use of open-source external established drug databases.

Section 1 presents the purpose, scope, structure of this deliverable and the relation to the work performed in relation to the Description of Action (DoA).

Section 2 presents the current state of the art in developing *in silico* cloud platforms and databases with huge amounts of data, capable of providing computational resources and tools for data analysis.

Section 3 describes the SILICOFCM Drug Interaction Tool, based on MINERVA framework, its integration to the SILICOFCM platform and also the molecular interaction networks that are usually used to map the organization of cellular function of HCM disease.

Section 4 demonstrates the SILICOFCM Drug Search Tool, the publicly available databases in order to design, develop and deploy the drug search tool, the description of its functionalities and its integration into the SILICOFCM platform.

Section 5 presents the code links of the Drug Search Tool to repositories.

Sections 6, 7 include the deviation from the work plan and the conclusions. Afterwards, the references and the Annex section is presented, with the latter to include the manual of drug search tool and the Drug Search Tool developed APIs.

Table of Contents

1	<i>Introduction.....</i>	9
1.1	Purpose and scope of the deliverable	9
1.2	Deliverable structure	9
1.3	Relation with the SILICOFCM DoA.....	10
2	<i>State of the art in Drug databases.....</i>	11
3	<i>SILICOFCM Drug Interaction Tool.....</i>	18
3.1	Description of MINERVA framework.....	19
3.2	Integration of MINERVA framework to the SILICOFCM platform	20
3.3	Analysis of the HCM disease pathway	22
3.4	The HCM pathway on the SILICOFCM platform	23
4	<i>SILICOFCM Drug Search Tool</i>	28
4.1	Identified open available databases for the Drug Search Tool	28
4.2	Description of functionalities.....	29
4.3	Integration of Drug Search tool into the SFCM platform.....	30
4.3.1	Architecture.....	31
4.3.2	Technologies.....	31
4.3.2.1	Front-End Technologies	31
4.3.2.2	Back-End Technologies	33
4.3.3	SILICOFCM Drug search tool UI and user access endpoint	33
4.3.4	Description of the workflow	36
5	<i>Code links to repositories.....</i>	42
6	<i>Deviation from the work plan.....</i>	43
7	<i>Conclusions</i>	44

List of Figures

Figure 1: Demonstration of SuperDrug interface: a) Navigation frame, b) Text query options, c) Query results with search options, d) Results of the 3D superposition of the most similar conformations and e) structure of the classification.....	11
Figure 2: Schematic representation of AMDD database.....	12
Figure 3: Compound report card for ChEMBL, with links to download metadata.	13
Figure 4: DGE-NET schematic representation to associate drugs with diseases.	13
Figure 5: Overview workflow of HEDD.	14
Figure 6: Rationale of the DGIdb components.....	14
Figure 7: The number of published works for drug databases for drug repurposing.	15
Figure 8: A representation of the databases classified based on data content.....	15
Figure 9: Minerva tool access from SILICOFCM cloud platform.....	18
Figure 10: End-user Minerva tool interface and options.	18
Figure 11: Placement of the MINERVA (HCM MAP) server in the SILICOFCM platform.....	21
Figure 12: Access point of the Minerva framework/ Drug interaction tool.....	23
Figure 13: Landing page of the drug interaction tool.....	24
Figure 14: Semantic zoom functionality.....	24
Figure 15: Drug interaction tool, adding comment on the map.	25
Figure 16 Select mode on the drug interaction tool of the HCM pathway map.....	26
Figure 17: Generic search on the HCM pathway map.	27
Figure 18: Protein search on the HCM pathway map.	27
Figure 19: Drug Search Tool Sequence Diagram.	30
Figure 20: Access point of the SILICOFCM tool on the main dashboard.....	34
Figure 21: Drug Search Tool Interface.....	36
Figure 22: Workflow for the Drug Search Tool.....	36
Figure 23: Set the name of the drug for searching.	37
Figure 24: Results of the drug search.....	37
Figure 25: Drug summary and its gene interactions.	38
Figure 26: Protein summary.....	38
Figure 27: 3D visualization of the protein structure.	39
Figure 28: Protein names.	39
Figure 29: DB References.	39
Figure 30: Keywords that are correlated with the protein and scientific references.	40
Figure 31: Set the name of the gene for searching.....	40

D8.3 Interface for drug testing

Figure 32: Results of the gene search.	40
Figure 33: Gene summary and its drug interactions.	41
Figure 34: Drug search tool selection from the home screen dashboard of the SILICOFCM cloud platform.	47
Figure 35: Drug search tool input drug name and table with search results.	47
Figure 36: Summary of the drug and proteins interactions and the more details button.	48
Figure 37: The summary information (more options button) regarding the interactions of the searched drug, that provides the user more data of the.	49
Figure 38: View protein extra information interface.	49
Figure 39: 3D visualization and further information regarding the selected protein.	50
Figure 40: Pop up detailed options after the selection of the user for more information of the 3D protein model.	50
Figure 41: 3D protein model with integrated the selected density model.	51
Figure 42: Additional information for the visualized protein.	53
Figure 43: Gene search from DGIdb based on entrzid parameter.	54
Figure 44: Drug information from ChEMBL with chembid parameter.	54
Figure 45: General API to obtain information from DGIdb for drug/genes, based on the resource parameter.	55
Figure 46: General information from DGIdb.	55
Figure 47: Information from UniProt database based on the accessionid parameter.	56

List of Tables

Table 1. Summary of well-known online drug databases that provide a variety of information regarding drugs, their structure, their impact and their chemical formula.	16
Table 2. Links to code repositories.....	42

List of Abbreviations

Abbreviation	Explanation
AMDD	Antimicrobial Drug Database
API	Application Programming Interface
DOA	Description of Action
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EPP	Essential evidence plus
FDA	Food and Drug Administration
HEDD	Human Epigenetic Drug Database
HCM	Hypertrophic Cardiomyopathy
MHRA	Medicines and Healthcare Products Regulatory Agency
MINERVA	Molecular Interaction NEtwork VisuAlization
NLM	National Library of Medicine
PPV	Positive predictive value
PPV	Positive Predictive Value

1 Introduction

1.1 Purpose and scope of the deliverable

This document corresponds to “D8.3 Interface for drug testing”, the third deliverable of “WP8 - Report to FDA or EMA”. This deliverable describes the work that has been performed in order to design and develop a web interface of the SILICOFCM platform to retrieve information for drugs/genes interaction, utilizing information derived from open source established databases. The main scope of the deliverable is to present the deployment of Drug search tool through the combination of well-established databases and the integration of MINERVA tool into the SILICOFCM platform. The Drug search tool interconnects drug and gene data from two commercially available databases DGIdb and UniProt, providing a detailed path from drug to gene and finally to protein, positively enhancing the workflow speed of a researcher in identifying the aforementioned paths. All information is grouped in cards specific for drug, gene and protein. The dedicated workflow that has been designed by the participating partners is presented in the current deliverable, displaying all the necessary information in steps and with brief/detailed mechanisms, allowing the researcher to focus only on the information he/she requires.

Also, the technical partners in collaboration with the experts have developed intuitive UIs for the specific tool along with the backend services (APIs, Database design, etc.). In addition, the MINERVA framework that includes a detailed map of signaling pathways in the Hypertrophic Cardiomyopathy model of cardiomyocytes is in detail, along with the analysis of the HCM disease pathway and its integration into the SILICOFCM platform.

1.2 Deliverable structure

The current deliverable is related to the presentation of a web interface for drug testing onto the SILICOFCM platform. Specifically it aims to present the necessary steps for the design and development of the web interface onto the platform during the lifecycle of the WP8, and also and the integration and further description of MINERVA tool to the SILICOFCM platform. The deliverable includes 8 sections and the ANNEX. Thus, the structure of the D8.3 is as follows:

Section 1 presents the purpose, the scope, the structure of this deliverable and the relation to the work performed in relation to the Description of Action (DoA).

Section 2 presents the current state of the art in developing *in silico* cloud platforms and databases with huge amounts of data, capable of providing computational resources and tools to analyze the data.

Section 3 describes the SILICOFCM Drug Interaction Tool, based on MINERVA framework, its integration to the SILICOFCM platform and also the molecular interaction networks that are usually used to map the organization of cellular function of HCM disease.

Section 4 demonstrates the SILICOFCM Drug Search tool, the publicly available databases in order to design, develop and deploy the drug search tool, the description of its functionalities and its integration into the SILICOFCM platform.

Section 5 presents the code links of the Drug Search Tool to repositories.

D8.3 Interface for drug testing

Section 6, 7 include the deviation from the work plan and the conclusions, while **sections 8, 9** present the references and the Annex section, with the latter to include the manual of Drug Search Tool and the Drug Search Tool developed APIs.

1.3 Relation with the SILICOFCM DoA

DoA Task Description	Addressed by D8.3
<i>T8.3: In order to choose from drug database, the user will use client application in a standard web browser, with or without WebGL functionality. WebGL functionality will be required for the WebGL viewer application, but not for upload/download functions. Non-interactive upload/download applications may also be provided. All connections to the cloud server computational framework will be secured and encrypted.</i>	This deliverable describes the design and development of a web interface onto the SILICOFCM platform to retrieve information for drugs using open-source external established drug databases. The Drug Search Tool, utilizes WebGL, through the UniProt Nightingale components, responsible for rendering a 3D View Model of the protein structure. Moreover, the drug search tool supports a non-interactive communication through an established Web API with the identified public available DGIdb and UniProt databases. The latter is performed in a seamless way without user's interface. The development has been implemented as a fully integrated component of the SILICOFCM platform. All security mechanisms provided by the SILICOFCM platform, as described in D7.3, are enabled and enforced for all the tool's access and communication requirements with the cloud and the user. In addition, communication with external databases is performed through the HTTPS protocol were permitted and consist of read-only fetch data commands. In detail, it presents the deployment of Drug search tool through the combination of well-established databases (section 4), its integration to the SILICOFCM platform (section 4.3) in a secure and encrypted way through the code development in private repositories (section 5) and also the description and integration of MINERVA tool by the consortium partners into the SILICOFCM platform (section 3).

2 State of the art in Drug databases

Recently the clinical domain and its community have been continuously integrating progressively and effectively more technological and computational solutions. Computational simulations have assisted the investigation of various diseases faster, with less cost, achieving a better connectivity among the clinical experts and the explainability of the diseases. The latest research trends, develop *in silico* cloud platforms and databases with huge amounts of data, capable to provide computational resources and tools to use, to analyze the data. These tools and databases are used mostly to perform *in-silico* clinical trials for drug development and testing.

In 2005 Goede *et al.* [1], published a study where they developed a new novel conformational drug database (SuperDrug, Figure 1). SuperDrug contains 2500 3D structures of low molecular weight, publicly accessible and available. Their study was one of the first published studies referring to drug databases.

The screenshot displays the Super Drug Database interface in a Microsoft Internet Explorer browser window. The address bar shows the URL: <http://bioinf.charite.de/superdrug/>. The interface is divided into several sections:

- (a) Navigation frame:** A vertical list of links including Home, Compound Search, 2D Similarity, 3D Superposition, FAQ, Contact, National Drug List, Links, ATC-Classification, and Registration.
- (b) Compound Search:** A section titled "Type of Search" with input fields for ATC - Code, CAS-Registry-Number, Name of Substance (containing "Fluanisone"), Chemical Name, Molecular Formula, and Mixture Name. A "Search" button is located below these fields.
- (c) Query results:** A table with columns: CAS, NAME, STRUCTURE, SIMILARITY, 3D SIMILAR, and 2D SIMILAR. It lists results for Fluanisone (CAS: 001480199) and Urapidil (CAS: 034661751). For each entry, it shows the similarity score and a table of similarity percentages for Molecule 1 and Molecule 2.
- (d) Results of the 3D superposition:** A section showing the superposition of two molecular structures. It includes statistics: Number Of Atoms Structure 1: 26, Number Of Atoms Structure 2: 28, Number Of Superimposed Atoms: 25, and Root Mean Square Distance: 0.065. Below the statistics are three chemical structures labeled STRUCTURE 1, SUPERIMPOSED, and STRUCTURE 2.
- (e) Structure of the classification:** A hierarchical tree view showing the classification of drugs. The tree is rooted at "L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS" and branches down through various systems (M, N, P, R) and specific drug classes (e.g., N01 ANESTHETICS, N02 ANALGESICS, N03 ANTIEPILEPTICS, N04 ANTI-PARKINSON DRUGS, N04A ANTICHOLINERGIC AGENTS, N04B DOPAMINERGIC AGENTS, N05 PSYCHOLEPTICS, N06 PSYCHONALEPTICS, N07 OTHER NERVOUS SYSTEM, P ANTIPARASITIC PRODUCTS, INI, R RESPIRATORY SYSTEM).

Figure 1: Demonstration of SuperDrug interface: a) Navigation frame, b) Text query options, c) Query results with search options, d) Results of the 3D superposition of the most similar conformations and e) structure of the classification.

D8.3 Interface for drug testing

Later, in 2012 *Danishuddin et al.* [2], developed an antimicrobial drug database (AMDD, Figure 2) of well-known synthetic antibacterial and antifungal compounds that were obtained from commercial available chemical databases. All this useful information and the availability that the platform's database provides, facilitates the virtual screening process for further development. Moreover, in 2012 *Gaulton et al.* [3], presented the ChEMBL database (Figure 3). ChEMBL is an open-source database, containing binding, functional and absorption, distribution, metabolism, excretion and toxicity (ADMET) information regarding bioactive drug compounds. ChEMBL database can be an efficient tool for drug discovery. In 2015 *Pinero et al.* [4], published a remarkable study, where a novel platform (DisGeNET) was presented. The DisGeNET platform contains over 380000 associations between 16000 genes and 13000 diseases and it is considered to be one of the largest repositories commercially available. DisGeNET platform doesn't include drugs, although it can contribute and facilitate in the development of novel disease models to enhance the investigation process of complex diseases.

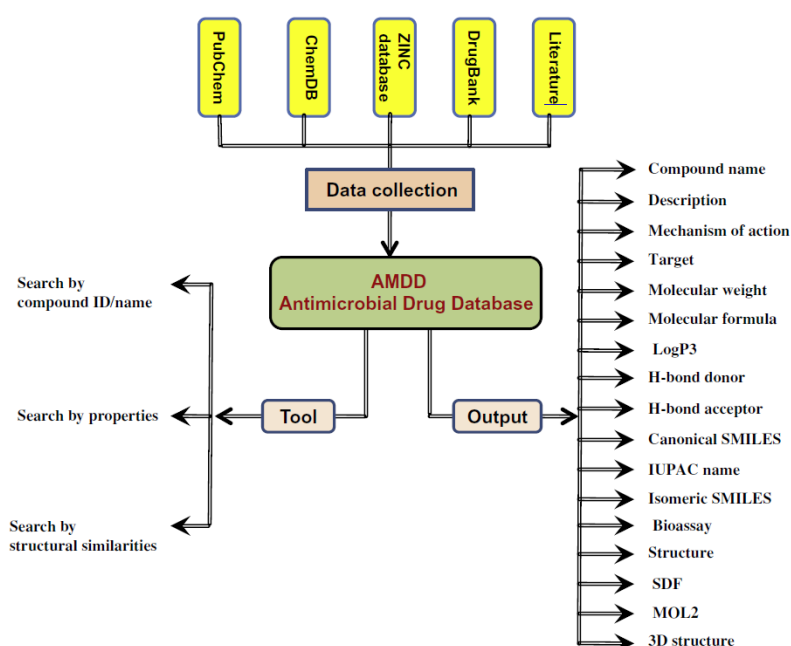


Figure 2: Schematic representation of AMDD database.

Furthermore, *Issa et al.* [5], in 2015 developed a novel computational platform (DrugGenEx-Net, Figure 4) capable to provide pharmacological systems and gene expressions. The main functionality of the platform focuses to predict targeted drug interactions. The generated interactions are integrated into a multi-tiered network and a prediction is performed using system-based gene expression analysis. The DGE-NET's predictions are validated through published literature values from annotated databases. In 2016 *Qi et al.* [6], presented an epigenetic drug database which contains experimental data from gene expressions. Epigenetic drugs are chemical compounds that have been developed to target disordered post translational modifications of histone proteins and DNA through enzymes. These data can be used in mining techniques for drug investigations and drug repurposing. In 2017 a study [7] presented the Essential evidence plus (EPP) tool, which aims to assist the clinicians at the clinical practice. The developers of that tool were based on the aspect to facilitate the clinical decision making. The tool contains information over 9,000 common diagnoses and provides access to 13000 resources. EEP can be very helpful to medical doctors, nurses and other healthcare providers, by supplying them all that gathered information.

D8.3 Interface for drug testing

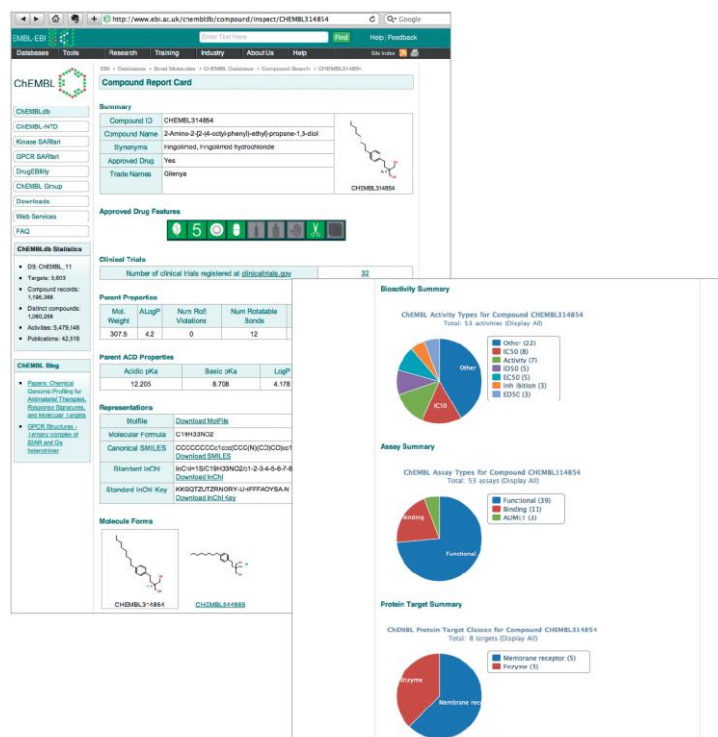


Figure 3: Compound report card for ChEMBL, with links to download metadata.

In 2018 *Wishart et al.* [8] published an updated version of a previously developed drug database known as DrugBank. DrugBank was developed as a database able to provide comprehensive molecular information and functionalities, mechanisms and interactions for well-known drugs. The published study presents that the updated DrugBank version is a significant upgrade, as the total number of the included drugs has been grown by 300%. Also, the database contains 300% more of drug-drug interactions and their functionalities. In addition, a remarkable study was published by *Marcath et al.*, [9]. The study's scope was to evaluate and compare the ability of some screening tools to detect clinically interactions with oral oncolytics. Some subscription-based tools (Lexicomp, Micromedex) and some free based tools (Drugs.com, Epocrates free, Medscape) were selected to be compared for their capabilities of detecting relevant interactions among 145 drug pairs. The results evaluated the Lexicomp and the Drugs.com are well performing tools, based on the positive predictive value (PPV) metric.

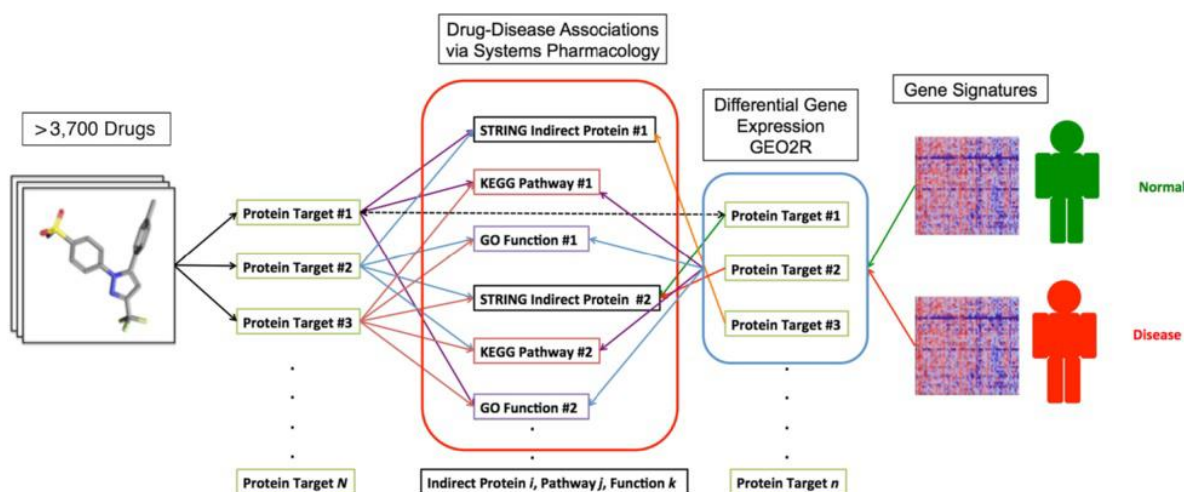


Figure 4: DGE-NET schematic representation to associate drugs with diseases.

D8.3 Interface for drug testing

The Human Epigenetic Drug Database (HEDD, Figure 5) can be used to provide segmental information of epigenetic drugs. In 2020 *Freshour et al.* [10], presented in their study the fourth version (v4.0) of a drug-gene interaction database. The drug-gene interaction database (DGIdb, Figure 6) is a web resource database that provides information and visualizations for drugs and genes. The database's information is provided to the users by a straightforward interface where the user searches for the targeted drug. All the included drugs, genes and interactions among them, have been classified into conceptual groups.

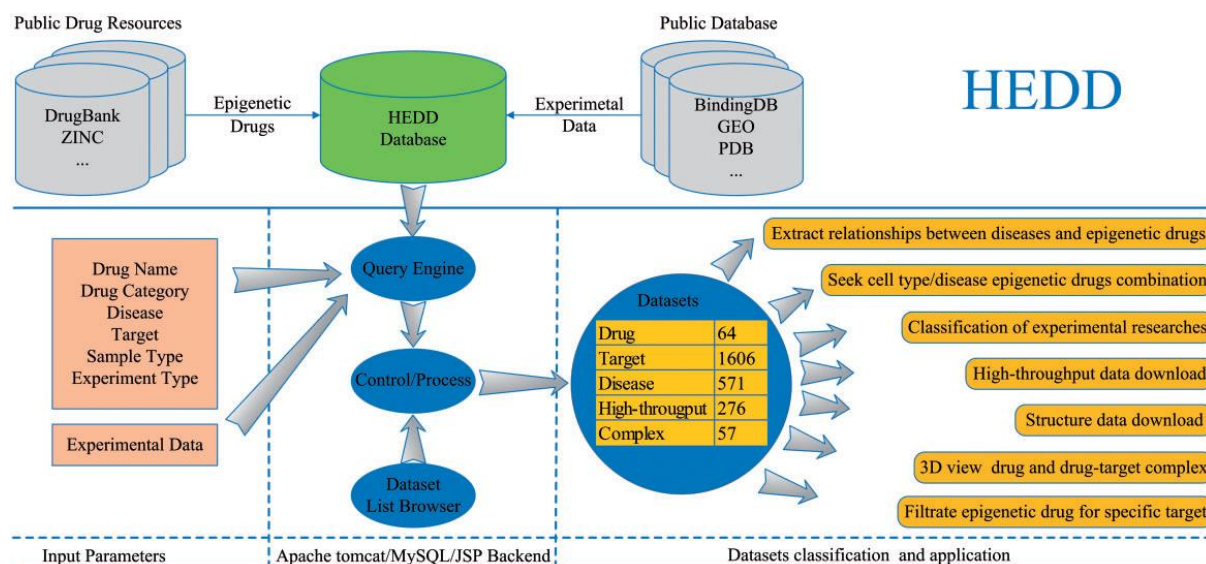


Figure 5: Overview workflow of HEDD.

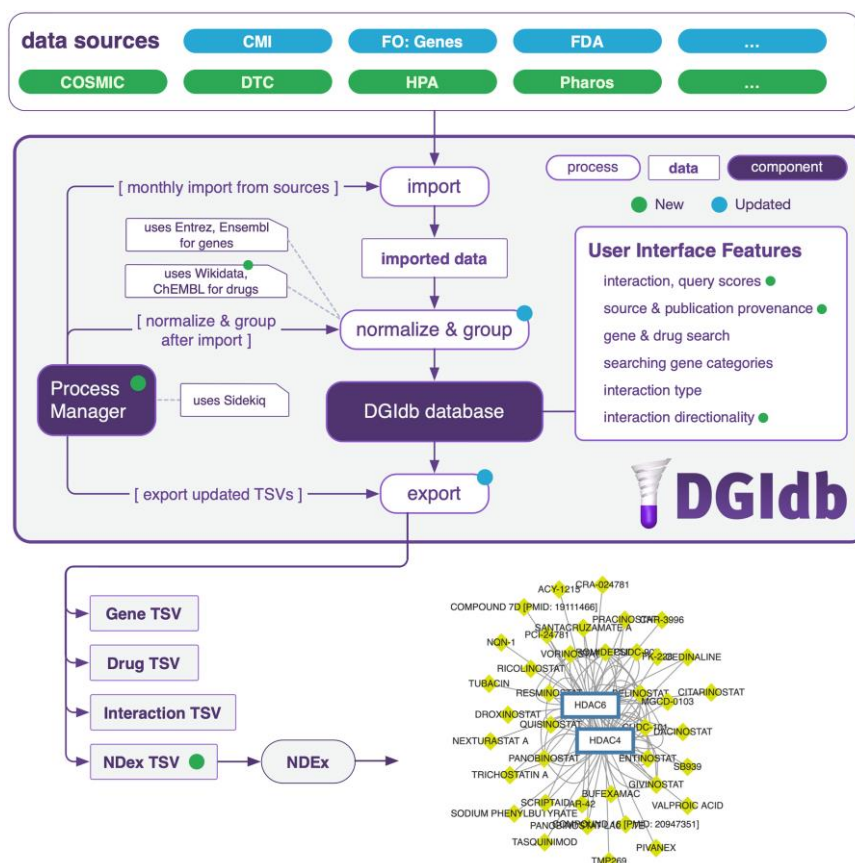


Figure 6: Rationale of the DGIldb components.

D8.3 Interface for drug testing

In 2020 *Sobhanzadeh et al.* [11], presented a complete review where they presented and proposed effective suggestions, regarding drug databases for drug repurposing. This work tried to classify several databases based on the data content and available applications in drug repurposing. The concluded classification categories were: i) raw data, ii) target-based, iii) specific, iv) drug design and v) tool-based databases. Also, descriptions of some limitations that can be tackled to improve the performance were presented. The limitations refer to the following aspects: i) availability, ii) update, iii) tool, iv) advanced search, v) query, vi) export, vii) application programming interface (API), viii) responsive, ix) full download, x) classified structure, xi) freely available. The implementation of the proposed modifications for the drug databases, can enhance the drug repurposing but also provide more advanced and completed information to the end-users. Figure 7 presents an analytical graph demonstrating the exponential growth for the published studies for the drug databases from 2000-2018. Also, in Figure 8 is depicted a representation of all the gathered databases classified based on their content and purpose.

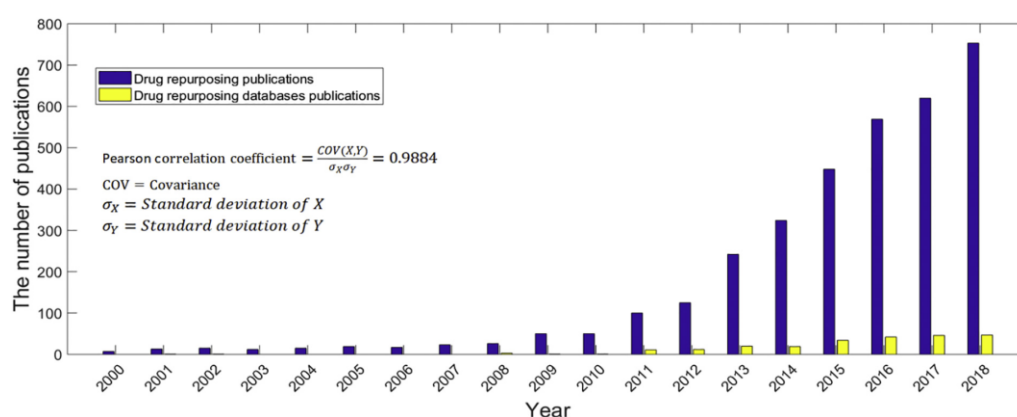


Figure 7: The number of published works for drug databases for drug repurposing.

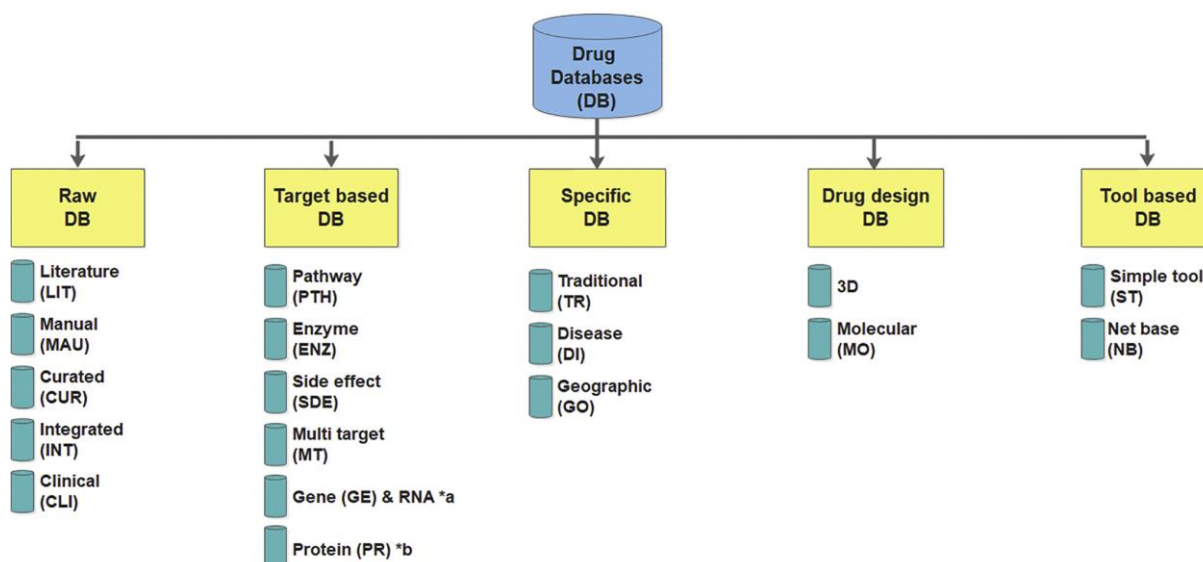


Figure 8: A representation of the databases classified based on data content.

In 2021 *Hu et al.* [12], published a work where they described a recently developed database (KinaseMD) which includes kinase mutations and drug responses. KinaseMD combines somatic mutations, network-rewiring events and drug response records. In general, the KinaseMD delivers information on mutations and unique annotations of drug responses. In 2021 *Troule et al.* [13],

D8.3 Interface for drug testing

developed a tool named DREIMT, a drug repositioning database and prioritization tool for immunomodulation. More specifically, DREIMT provides immunomodulatory drugs which target up to 70 immune cell subtypes from a curated database with 4960 drug profiles. The outcomes provided to the user include drug-signature association scores with downloadable content of large variety.

Table 1 provides some links for drug databases that are publicly available. The table provides the name of the platform-website and its corresponding link and a short description of their content/use.

Table 1. Summary of well-known online drug databases that provide a variety of information regarding drugs, their structure, their impact and their chemical formula.

ID	Database name	URL
1	Uniprot	https://www.uniprot.org/ UniProt is able to provide information at the scientific community with thorough high-quality and freely resources for drugs, protein sequences and functionalities.
2	Drugbank	https://go.drugbank.com/ DrugBank is a complete freely accessible online database which contains information for drugs.
3	Drugs	https://www.drugs.com/drug_information.html Drugs is one of the largest and most visited website for medicine's information. Its scope is to be the Internet's most trusted resource for drug and related health information.
4	Drugsinfo	https://druginfo.nlm.nih.gov/drugportal/ The Drugsinfo Portal gives users a gateway to selected drug information. The variety of the portal covers drugs from the time they are entered into clinical trials (Clinicaltrials.gov) through their entry in the U.S. marketplace (Drugs@FDA). The PubMed link provides medical literature describing research, and TOXLINE provides toxicology literature.
5	Drugcentral	https://drugcentral.org/ DrugCentral is an online resource created by Division of Translational Informatics at University of New Mexico. It provides information for chemical ingredients, pharmaceutical products, indications and functionalities. It is consistently updated based on FDA, EMA and PMDA monitoring for new drug approval.
6	DGIdb	https://www.dgidb.org/ DGIdb offers information about drug-gene interactions that is gathered from various sources like DrugBank, TTD and PharmGKB and provides third party services using APIs to query for drug-gene interactions.
7	KinaseMD	https://bioinfo.uth.edu/kmd/

D8.3 Interface for drug testing

ID	Database name	URL
		KinaseMD provides a hybrid approach including information for somatic mutations, network-rewiring events and drug responses. Overall, it provides mutations and unique drug responses.
8	CentralWatch	https://www.centerwatch.com/directories/1067 CentralWatch is a database which contains drugs that have been approved from FDA. Typical information includes names, approval status, indications of use and results from clinical trials.
9	National Library of Medicine	https://dailymed.nlm.nih.gov/dailymed/ National Library of Medicine (NLM) is a commercial database able to provide updated labeling submitted to the FDA. Its variety is extended to drugs for humans and animal use and for additional products such as cosmetics, dietary supplements etc.
10	Electronic medicines compendium	https://www.medicines.org.uk/emc The electronic medicines compendium (EMC) contains information about medicines licensed in the UK.
11	Epocrates	https://online.epocrates.com/ , (https://play.google.com/store/apps/details?id=com.epocrates), (https://apps.apple.com/us/app/epocrates/id281935788) Epocrates is a free online website (also application for android and iOS smartphones) which is capable to provide a variety of useful information for drugs and diseases.
12	Drugs Medscape	https://reference.medscape.com/ Medscape is a free website where clinical information regarding drugs, diseases, procedures and medical calculators are provided.
13	Merk Manual	https://www.merckmanuals.com/professional/resources/brand-names-of-some-commonly-used-drugs Merk Manual provide shorted alphabetically all the commercially available drugs. For each drug, specific topics including information are provided freely to the users.
14	PDR	https://www.pdr.net/ Trusted by generations of healthcare providers, PDR delivers innovative health knowledge products and services that support prescribing decisions and patient adherence to improve health.

D8.3 Interface for drug testing

3 SILICOFCM Drug Interaction Tool

The SILICOFCM Drug Interaction Tool is intended to be used in order to obtain initial detailed information on possible drug interactions with proteins within cardiomyocytes. For this purpose, a Minerva detailed map of signaling pathways in the Hypertrophic Cardiomyopathy model (HCM) of cardiomyocytes was created, based on the literature data of 102 scientific papers.

(ref <https://hcmmmap.bioirc.ac.rs/minerva/>, Figure 9, 10).

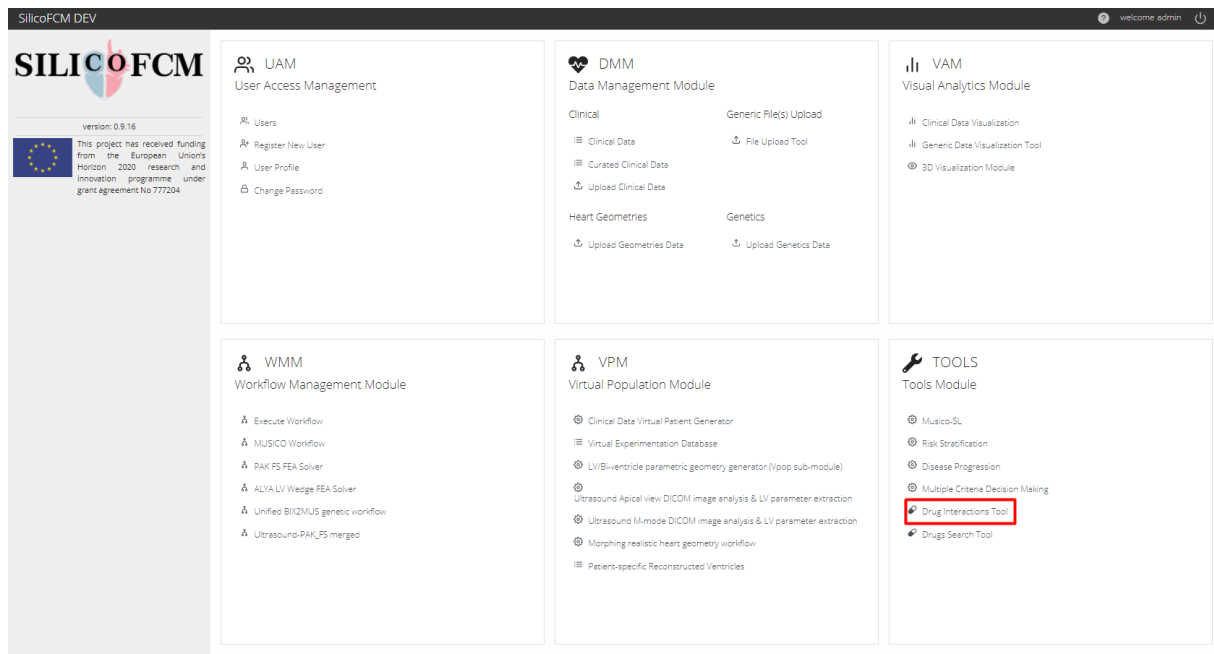


Figure 9: Minerva tool access from SILICOFCM cloud platform.

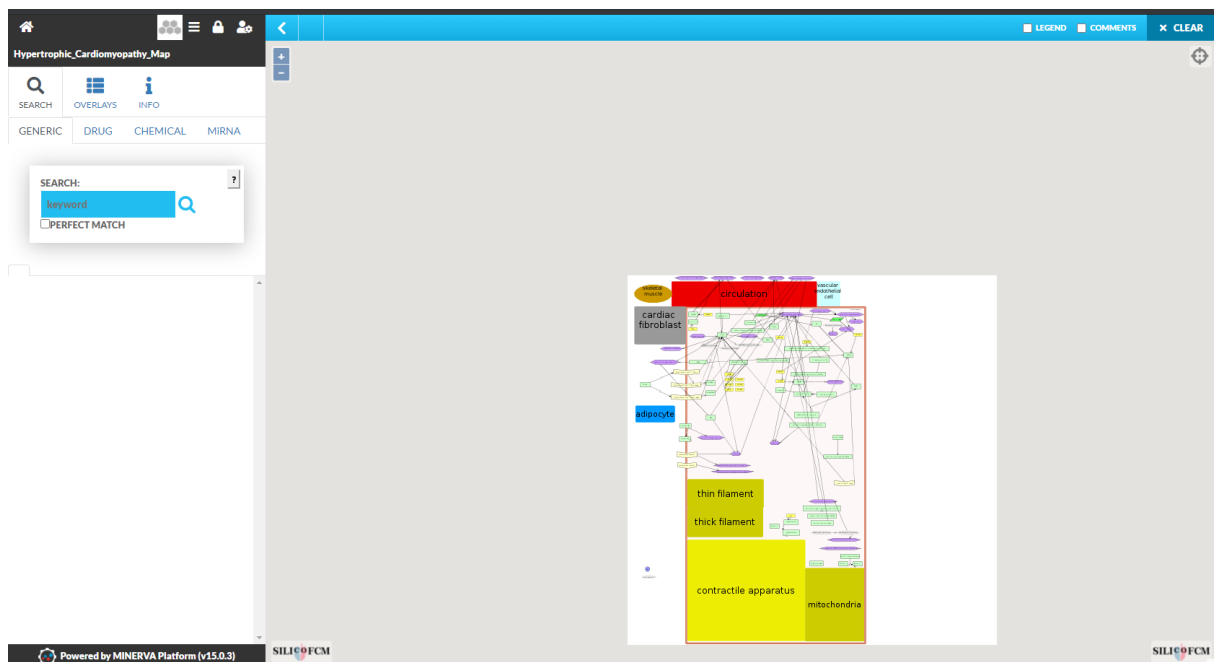


Figure 10: End-user Minerva tool interface and options.

D8.3 Interface for drug testing

The action of drugs used in the treatment of HCM is based on molecular interactions that are directly governed by the interaction of the used drug with proteins in cardiomyocytes. Proteins that first react with the drug, specifically change their conformation and participate in further cascading reactions within the cell. Such cascading interactions cause specific changes at the microcellular level, such as e.g. instantaneously controlled release of calcium from the endoplasmic reticulum that binds to troponin C and causes remodeling of the cytoskeleton, which further causes cardiomyocyte contraction. These small changes in cellular and subcellular changes cumulatively cause macro changes such as contraction of part of the heart tissue or the whole heart. However, as any physical action of the heart or any organ is actually a synergy of a huge number of cumulative and often simultaneous controlled interactions, the precision of the HCM Minerva created map allows the prediction of possible outcomes. Drug interaction with target proteins is possible in two ways: activation and inhibition of proteins, which leads to various biochemical changes.

On the other hand, the genome defines the ability to express different forms of proteins. If, as in HCM, a mutation occurs in certain genes, translational mechanisms synthesize mutant forms of the protein with often different and/or opposite functions from the native forms. In that sense, if the Map is enriched with information about possible biochemical interactions of drugs and other proteins with mutant forms of key proteins, it is possible to predict the molecular and physiological outcome in pathological conditions. Depending on whether the mutation is homozygous or heterozygous, we come to the conclusions that the cell e.g., produces both a native and a mutant form of the same protein. If the tested drug interacts with both forms of protein, it provides two possible outcomes, further information that can be given to the Map providing us the probabilities of these interactions and the prediction of the outcome. The use of the molecular docking simulation method, which provides us the binding energy of the drug and any protein with the quantification of possible interaction, can be extremely helpful. In addition to molecular docking analysis, the various web-available tools can also be helpful if they are either integrated with the Minerva map or an interaction calculation is entered into the Map.

3.1 Description of MINERVA framework

Minerva¹ HCM Map is structurally composed of 3 organizational levels. The level of molecular interactions, which is a network of structural proteins of the cytoskeleton, regulatory proteins and enzymes; then the organization at the level of the organelle; and the final presentation of the whole cardiomyocyte and its interconnection with ¹the circulatory system, adipocytes and skeletal muscles in the most basic details. Most of the details are directed towards the molecular mechanisms that underlie the cellular system, so that it is possible to monitor/predict the interaction of the drug first with the biochemical system of the cell, and then the cell's response to the applied therapy. Cardiomyocyte is presented as a simplified system consisting of contractile apparatus, sarcoplasmic reticulum, mitochondria, cytosol, thin and thick filament systems. Each of these simplified subsystems are clearly connected to the others on a functional level. This means that one biochemical reaction on the cell membrane causes at least one biochemical reaction in the cytosol, which in turn induces

¹ <https://minerva.pages.uni.lu/doc/>

D8.3 Interface for drug testing

further and further biochemical reactions within the organelles which ultimately result in a specific cellular response to a given input.

If we take into account that the average human cell expresses about 10,000 different proteins and their posttranslational forms at the same time, we understand how complex a cell is and that any cell today is impossible to fully represent mathematically or graphically. In that sense, it is necessary to simplify the system as much as possible to understand at least its most basic functions. As mentioned above that reactions of individual proteins are possible in the direction of mutual activation or inhibition, the labels are set in the form of arrows, → for cascade activation, and ⊣ for cascade inhibition or inactivation.

This intuitive display is important to researchers because it gives them possible interactions within a cell at a given input of a drug, on which they can further focus and examine the details. This saves time and potentially spent funds on preliminary screening of gene and protein expression in treatment with a particular drug, as it is done in practice. The map still does not give details about the intensity, i.e., quantification of these interactions, but some progress has been made in this direction using molecular docking analysis (see WP8 Deliverable D8.1 Workflow for drug testing, p. 4.1.2). When the Minerva HCM map is upgraded with this data, the researcher will be able to choose from the two or more molecular mechanisms offered the most likely one, regardless of whether it is molecular activation or molecular inhibition. For example, if we know that a certain drug affects one of the protein factors, which is presented in the map, and if we know that a given drug activates a given factor, then marking a given factor opens a cascade of further interactions with other factors with information about possible cascade activation or inhibition. Currently, the user can examine the probabilities of certain interactions using less precise but easily accessible and simple tools for such calculations, so Minerva is extremely helpful. A researcher examining the effect of a particular drug has several methodological approaches in optics before the start of experiments, which are usually extensive and expensive. First, the so-called rapid screening of basic parameters such as cell viability, apoptosis process, redox cell status. Then, the physiological response is monitored in terms of testing e.g. cell migration, contractility, macro-change. The molecular mechanisms that lead to these, and other above-described macro-changes are investigated. Using the HCM Map, it is also possible for a less experienced researcher to predict the possible response of cardiomyocytes to a particular therapy and to focus the research on a given direction.

As Minerva is linked to the ChEMBL drug database, many drugs that exist in the ChEMBL database can be tested. The significance of Minerva is not less if it works only in relation to already given drugs, and not to any chemical structure, because most drugs in ChEMBL have not been tested in many molecular directions, but only in precisely specific ones. For example, our detailed analysis of the drug Entresto® (combination sacubitril/valsartan) which is a commercially available drug, also presented in ChEMBL showed that there is very little information on the effect of this drug on many molecular mechanisms not only specifically in cardiomyocytes but generally *in vivo* results and results of macro changes in humans.

3.2 Integration of MINERVA framework to the SILICOFCM platform

The MINERVA (*Molecular Interaction NEtwork VisuAlization*) Platform is a standalone webserver for visual exploration, analysis and management of molecular networks encoded in systems biology formats. It was developed on the Java platform, using industry standard technologies for deploying

D8.3 Interface for drug testing

web applications such as Tomcat application server and PostgreSQL database. Its web portal provides sufficient guidelines to deploy MINERVA on Debian/Ubuntu, Red Hat/CentOS, using Docker images and manual installation instructions. It also provides a Debian-based virtual machine image that contains all necessary packages and is configured properly.

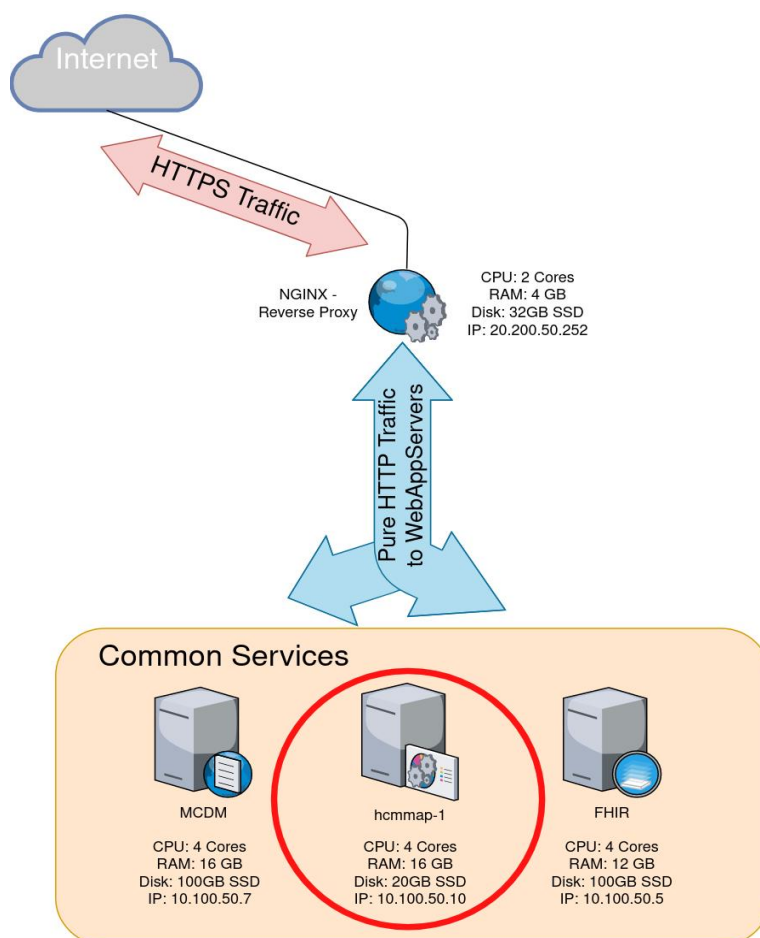


Figure 11: Placement of the MINERVA (HCMMAP) server in the SILICOFCM platform

In the SILICOFCM platform, we opted for the latter method, using a VM image. The image is in OVA format, native to Oracle VM VirtualBox. Our virtualization platform of choice, Proxmox VE provides a KVM tool capable to import various VM image formats. It was straightforward to employ it to convert OVA to KVM format, native to Proxmox VE. The deployment team also provided more resources such as system memory and disk space, to avoid bottlenecks in production. Providing more RAM (16GB) is trivial. However, providing more disk space was a bit more involved since it required file system growth, besides VM management. The MINERVA image uses a standard EXT4 file system, which is easy to grow and shrink.

As can be seen in Figure 11, further integration of MINERVA goes the same way (reverse proxy, etc.) as it was one of the tools developed and provided by the SILICOFCM platform. Since the user is capable of modifying maps, adding annotations, etc., the weekly backup job is established for the entire virtual instance. All the visualization of the uploaded networks (disease pathways) are produced on the web framework and are easily reached via a web browser to all viewers. It can display the molecular interaction diagrams, their annotations and links to open accessible and well-known databases.

D8.3 Interface for drug testing

It exploits the Google Maps API to render the content that is provided to the end user. It can provide functionalities such as pan-and-zoom functionalities. The user can interactively access it and examine the elements of it by simply clicking the elements of the designed content. The framework allows to have colored elements in order the exploration of the map to be comprehensive and easy to guide.

3.3 Analysis of the HCM disease pathway

The SILICOFCM platform is designed, among others, to predict the impact of a particular therapy on the behavior of the sarcomere and the patient's heart before its treatment. Based on several previously measured patient parameters, as described earlier, a patient-specific heart model is created. Another input is added to the mathematical model, i.e., drug of interest. Technically, *in silico* research is expected to indicate whether a particular therapy is potentially good for the patient or not optimal. PAK, MUSICO and other platforms of the SILICOFCM project rely to a significant extent on the Minerva HCM Map. The Map first analyzes the intracellular changes under the influence of the drug. It is assumed that the drug may affect some of the parameters that define the other above-mentioned *in silico* platforms. In fact, the *in silico* analysis of the effect of the drug on the heart requires a lot of steps and we, from the Minerva Map, through other platforms to the heart model itself, try to automate each step in the analysis as much as possible.

For easier understanding, it is best to explain the process through a concrete example. Literature data have indicated several drugs used in the treatment of cardiomyopathy, as well as heart failure. One of the newer and very effective drugs is Entresto® (Novartis, Switzerland). Two drugs (sacubitril, and valsartan) in Entresto® synergistically reduce left ventricular remodeling and reduce cardiomyocyte death. However, to better understand the effects of these two drugs, it is best to first examine the effects at the molecular level. An intensive search of the literature did not help us much in answering the questions and hypotheses. Namely, this drug is relatively new in use, and in addition to certain macro changes that have been documented in available clinical studies, there are not too many details about the mechanism of the drug's effect on molecular level. Some mechanisms have been tested on model animal systems. Using the MINERVA Map, it is possible to predict certain mechanisms, as described above. Further, by carefully selecting the biological model systems and parameters we want to examine in proving our thesis, we shorten our position (and the resources). In this way, we created a map of experiments for pathohistological, genetic and protein analyses that we conducted *in vivo* and came to certain conclusions about the importance of examining molecular mechanisms for better understanding and explanation of macro changes (data under journal revision, September 2021). Sacubitril, with its dilating effect on blood vessels, observing macro changes, has the effect of reducing blood pressure. In this process, sodium levels are reduced, and calcium is extensively expelled from the sarcoplasmic reticulum, all of which can be predicted by careful use of the MINERVA platform. Upon administration, sacubitril is metabolized by esterases to its active metabolite, sacubitrilat, which inhibits neprilysin, a neutral endopeptidase that cleaves natriuretic peptides such as atrial natriuretic peptide, brain natriuretic peptide, and c-type natriuretic peptide, as well as certain vasoconstricting peptides including as angiotensin I and II, and endothelin-1. On the other hand, valsartan exerts its similar macro effect through other molecular mechanisms, i.e. via angiotensin II receptor blockade. Overall, valsartan's physiological effects lead to reduced blood pressure, lower aldosterone levels, reduced cardiac activity, and increased excretion of sodium.

Molecular pathway-based analysis is an effective technique that overcomes the limitations of the single-locus methods. This procedure provides a comprehensive understanding of the molecular

D8.3 Interface for drug testing

mechanisms that cause complex diseases. Principally, a pathway-based MINERVA Map approach is similar to the Gene Ontology analysis and similar *in silico* based methods.

Such molecular interaction map networks are usually used to map the organization of cellular function. Similar approaches are firstly used in cancer research. Boundaries of such analyses are defined by interactions between genes, proteins, or even metabolites. However, as we described earlier the living cells are very complex and molecular interactions are multidiverse. Based on the efforts made so far, the context of changes and simplified prediction is possible, but a deeper and more accurate analysis requires work on this model over a very long period of time, in order to avoid misinterpretations, errors and increased relevance.

Our MINERVA approach for representing the explanation of human cardiomyocyte processes using pathways as the nodes in a network represents spatial sets of perspective-dependent interactions, making a high-level network for better understanding the molecular interaction data.

Analysis of the pathway network discovered linked processes indicating functional relationships between used drugs and their interaction in cell signaling, calcium and sodium release, cytoskeletal rearrangements and cell, sarcomere, and tissue contractions. The cardiomyopathy was mapped to target malformations and use these networks to find that the pathways associated with diseases tend to be functionally connected, emphasizing the disturbed functions that result in disease phenotypes.

It is showed that the disease pathways cluster in the network and analyzed the distribution of HCM pathways showing that HCM pathways tend to locate within the drug-protein, protein-protein and protein-gene interaction. Our interpretation delivers an intuitive functional understanding of cellular organization.

3.4 The HCM pathway on the SILICOFM platform

The HCM pathway is integrated into the SILICOFM platform exploiting the capabilities of the MINERVA platform. The user can access the tool from the dashboard of the platform (Figure 12).

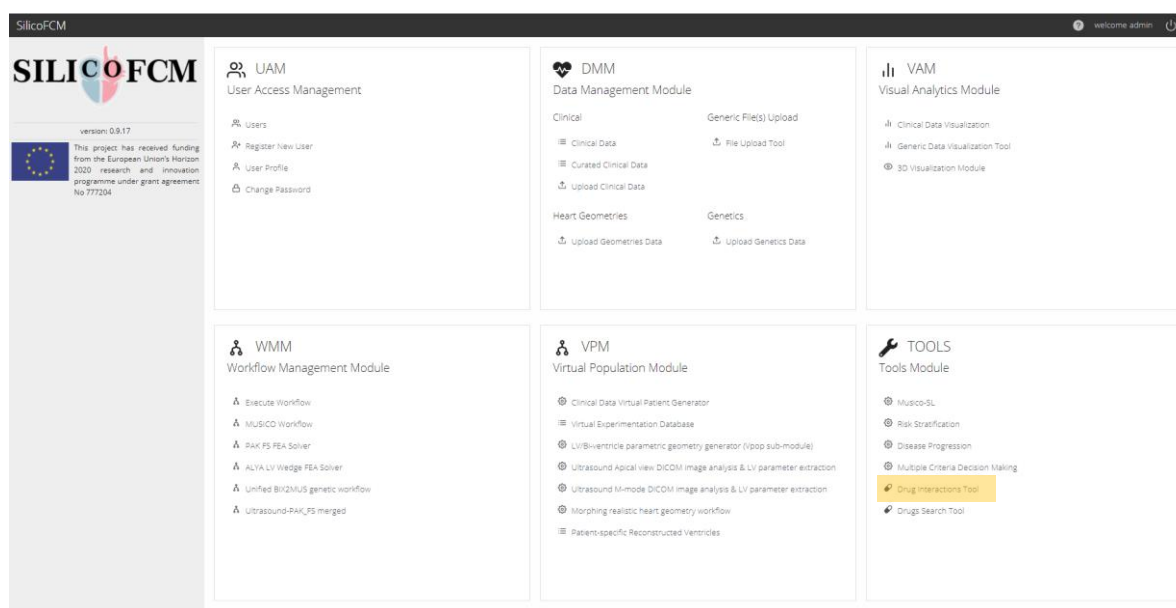


Figure 12: Access point of the Minerva framework/ Drug interaction tool.

D8.3 Interface for drug testing

The landing page of the tool can be seen in the Figure 13. In the main window, the HCM pathway can be seen where colored components are included. In the left, a panel exists with necessary and useful tools for the user to interact with it.

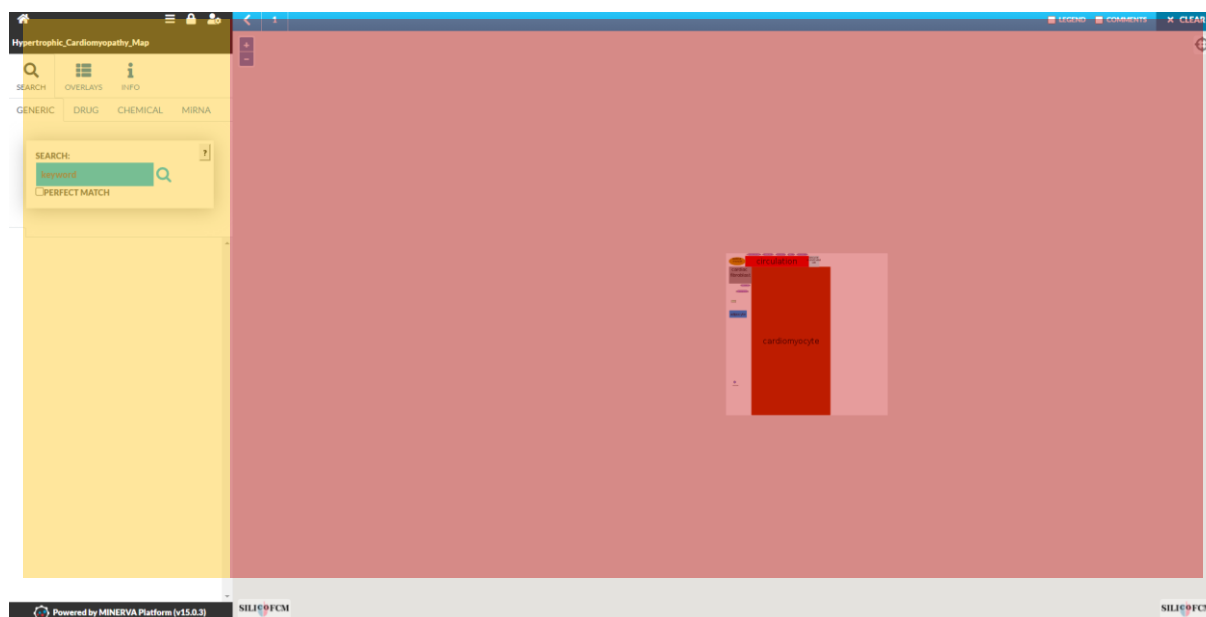


Figure 13: Landing page of the drug interaction tool.

The left panel is the functional area of the framework, and the central view is the display area. Thus, the main components are the:

- Display area
- Functional area (left pane)
- Information bar

One of the main functionalities of the provided framework is the so-called *semantic zoom*. The latter is the main view on the map which represents the HCM disease pathway provided and designed by the experts. The view is continuously rendered during the interaction with the end user and it can calculate which areas of all the incorporated components cover each other and assign the appropriate zoom level (Figure 14).

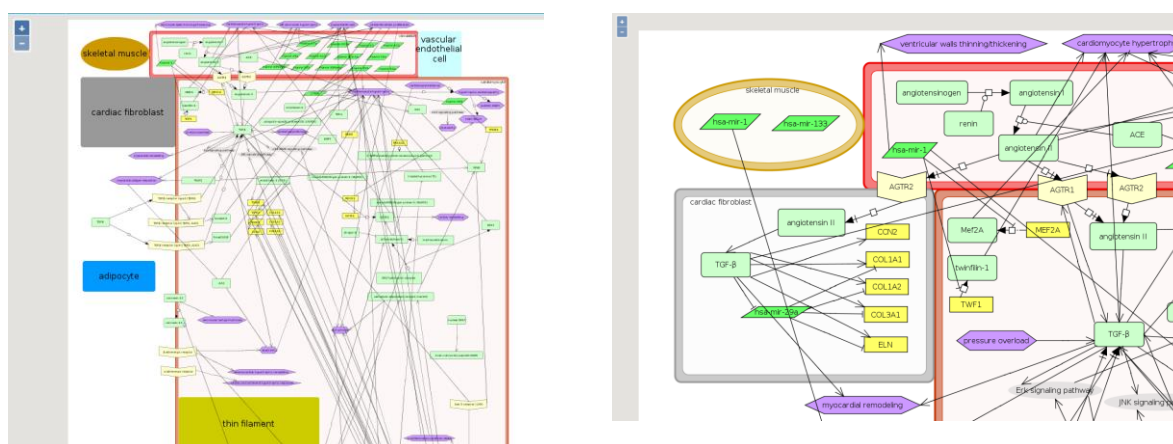


Figure 14: Semantic zoom functionality.

D8.3 Interface for drug testing

The semantic zoom functionality improves the render view clarity of the interaction map. The information necessary for the functionality to work is provided on an SBGN compliant file (produced either by *CellDesigner*² or SBGN editors like *SBGN-ED*³) which is produced by the experts, in order to generate the pathways and compartments view and uploaded to the tool by an administrator. The user can interact with the map/disease pathway to gain and retrieve information and cannot change it. Moreover, the semantic view functionality apart from the zoom levels, it provides also zoom transparency levels.

The system provides to the users exploration tools on the map by right clicking on it and invoking a new menu including:

- Protein structure visualization
- Adding comments
- Map downloading ability (part or whole)

In addition, the user can introduce comments on the map as depicted in the Figure 15.

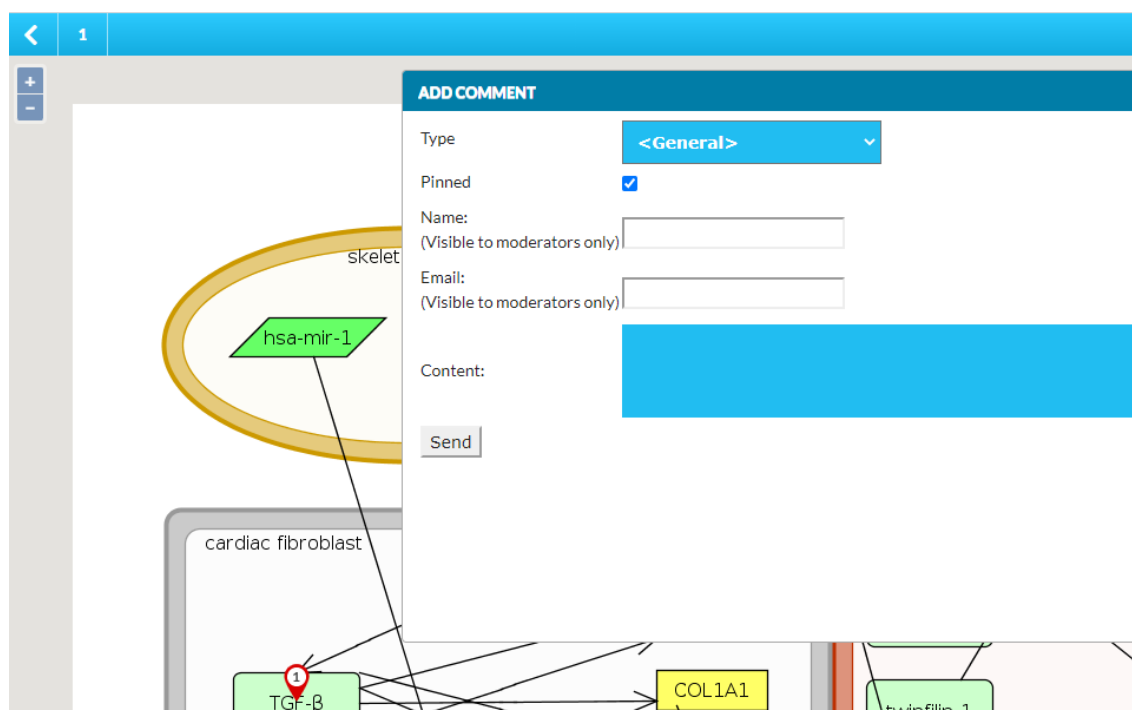


Figure 15: Drug interaction tool, adding comment on the map.

The functionality allows the user to send comments to the moderator of the map (experts of SILICOFCM). The comments' form that is invoked, includes a drop-down menu listing the elements that are near the click area thus he/she can easily select the component to be commented.

Once more, by right clicking on the map the user can invoke the select mode which enables them to arbitrary draw a shape on the map as shown in the Figure 16.

² <http://www.celldesigner.org/>

³ <https://immersive-analytics.infotech.monash.edu/vanted/addons/sbgn-ed>

D8.3 Interface for drug testing

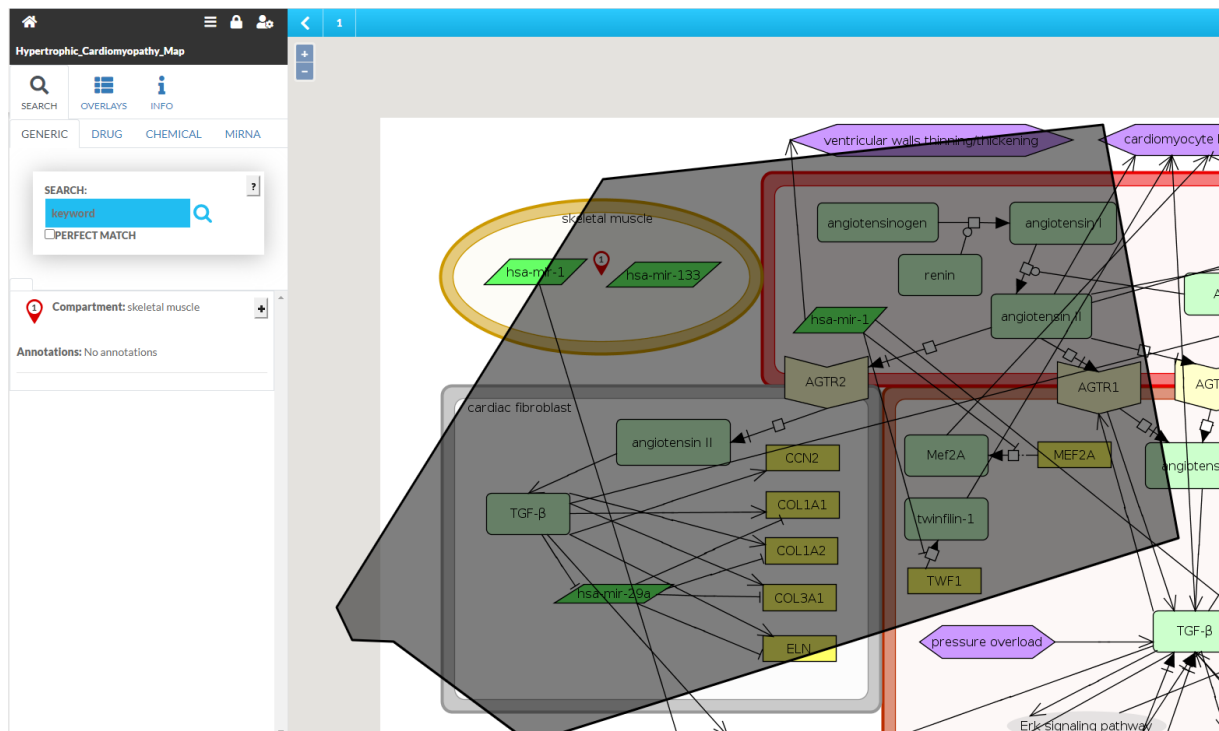


Figure 16 Select mode on the drug interaction tool of the HCM pathway map

The system provides the capability to the end user to export as an image the selected area. Specifically, it exports a rectangular image that contains the selection.

The drug interaction tool based on the MINERVA web framework also incorporates the left panel which is the functional area. One of the main functionalities is the search component which allows the user to search specific components on the pathway map. The search tab includes the following subtabs:

- GENERIC for regular search
- DRUG for drug target search
- CHEMICAL
- miRNA

In Figure 17 a search has been performed and the tool pinpoints on the map the component that match the search criteria. Specifically, it is a search in the generic tab.

D8.3 Interface for drug testing

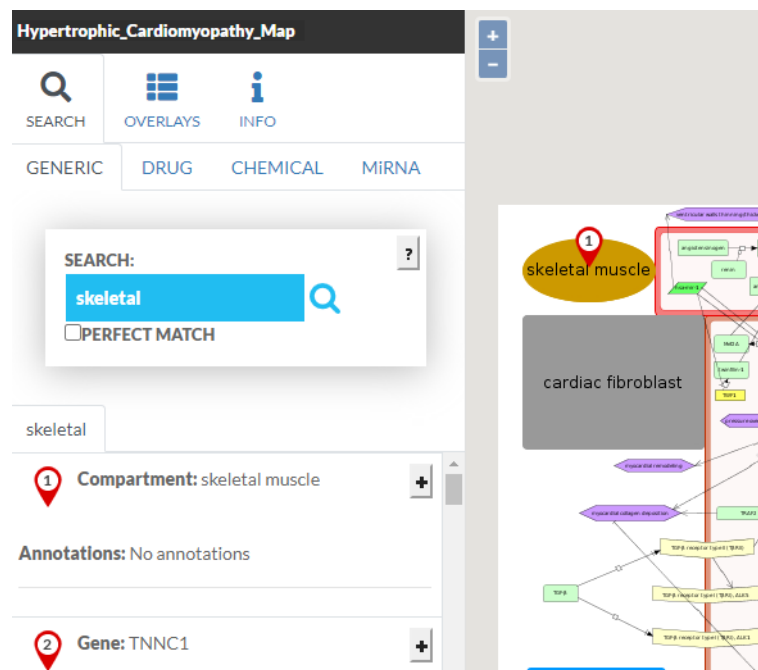


Figure 17: Generic search on the HCM pathway map.

And Figure 18 depicts a search for a protein that exists in the HCM pathway map.

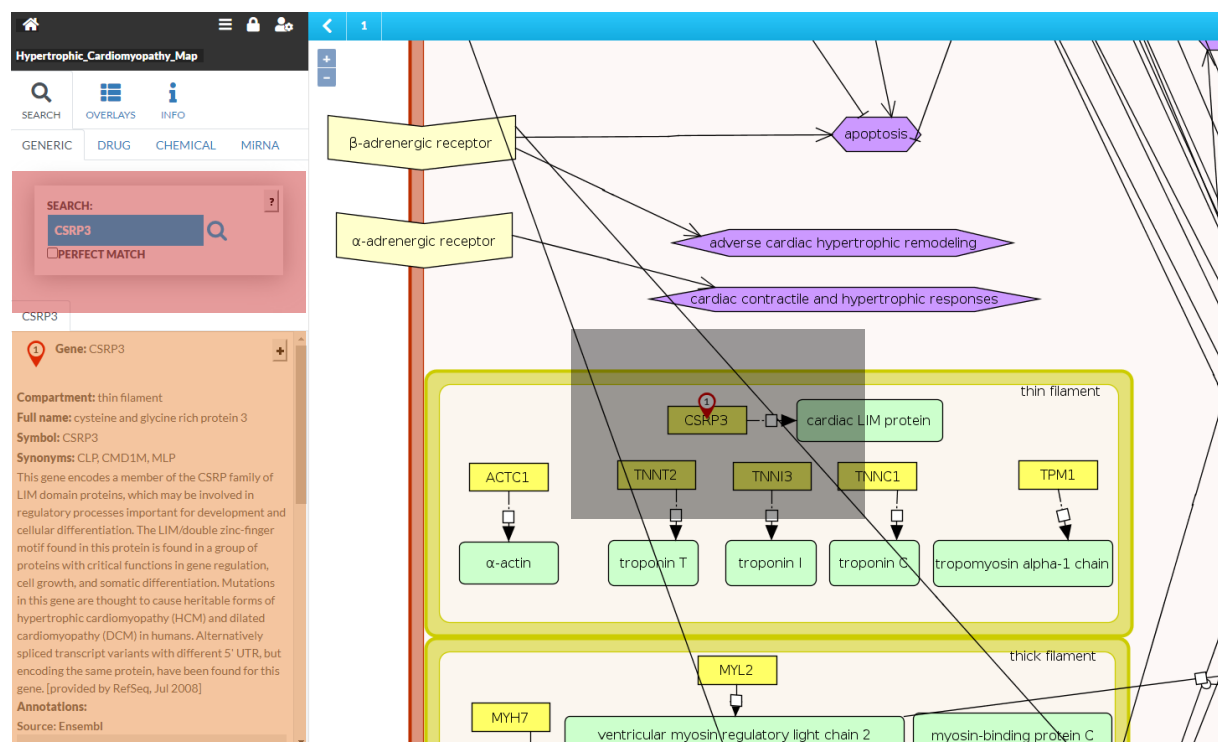


Figure 18: Protein search on the HCM pathway map.

The latter search functionality brings information about the protein in search from well-known sources in the web such as Ensembl⁴, EntrezGene⁵, ProteinDataBank, etc.

⁴ <https://www.ensembl.org/index.html>

⁵ <https://www.ncbi.nlm.nih.gov/gene>

4 SILICOFCM Drug Search Tool

The use of the above-mentioned functionalities greatly facilitates the creation of experiments and understanding of a particular scientific topic related to the examination of the effects of a particular drug. Namely, the use of available so-called atlases can be quite complicated for the average experimental biologist who does not have much knowledge about the use of more complex search mechanisms.





The SILICOFCM - Drugs Search Tool provides a user-friendly connection to external drug, drug-gene interaction database and examines the effects of specific drugs. A quick search for available information on the interaction of certain drugs with target genes is very important. The researcher can easily obtain information on the most likely drug interactions and quickly define the interests to focus on, especially for drugs that provide a very wide range of possible gene interactions. Also, for a more experienced researcher, the obtained panel of results is sufficient to notice whether there are specific antagonisms in the effect of the drug, i.e., whether it reacts controversially to two opposing biochemical mechanisms.

The Drug Search Tool, fully integrated into the SILICOFCM platform, enables the user to retrieve and access drug and/or gene information including the interactions between them as well as an easy pathway to the corresponding protein information. Another feature of the tool is the connection with external reference databases (PubMed⁶).

The literature search itself involves two important risks: whether the researcher searches the literature of adequate quality and the time required to analyze the vast amount of available information. Using the SILICOFCM - Drugs Search Tool, information is obtained from sources selected databases summarized in an adequate way so that any further analysis is easier.



However, as drugs generally do not act directly on genes, but indirectly through proteins, and as gene expression is only part of the required information, it is necessary to obtain data on the effect of a given drug on target proteins and consequently on their target genes. The drug most often interacts first with proteins, which further interact with genes by cascading biochemical reactions, increasing or decreasing their activity.

4.1 Identified open available databases for the Drug Search Tool

The partners in order to design, develop and deploy the SILICOFCM drug search tool have searched the state-of-the-art public available relevant drug, drug-gene, drug protein interaction databases. After thorough search in the literature, 5 possible drug databases were identified in order to retrieve information. DrugBank , offers a variety of information about drugs and drug targets including 2634 small molecule drugs and 1377 approved biologics. Moreover, ChEMBL  drug database gives information about bioactive molecules with drug-like properties encompassing chemical, bioactivity and genomic data. Furthermore, TTD  drug database provides information about target diseases, pathway information and the corresponding drugs while the results can be retrieved by searching by biomarkers, target sequence or drug similarity. Another drug database PharmGKB  involves clinical information about 708 Annotated Drugs, 150 Pathways and

⁶ <https://pubmed.ncbi.nlm.nih.gov/>

D8.3 Interface for drug testing

772 Drug Label Annotations. The last one, DGldb  offers information about drug-gene interactions that is gathered from various sources like DrugBank, TTD and PharmGKB and provides third party services using APIs to query for drug-gene interactions. Also, another worth mentioned database is the UniProt . A comprehensive, high-quality and freely accessible resource of protein sequence and annotation data. Access to key biological data, features, variation, proteomics and antigen information. In all the above-mentioned drug databases it is important to mention that the end-user can download the data in a raw format or using APIs in order to query for drug information.

Based on the extended and detailed research that was performed, the SILICOFCM partners concluded to utilize DGldb and UniProt in the SILICOFCM cloud platform, to act as the information source which the Drug Search Tool retrieves, combines and presents their information.

4.2 Description of functionalities

The Drug Search Tool has been developed in order to provide access to the end-user to a database with a huge variety of drugs. The user has access to a large bundle which can provide information for major drugs and their sub-components.

The functionalities of the Drug Search Tool are:

- Search for a drug or gene based on its name
- Display drug/gene search results
- Display summary and interactions information for every drug/gene that has been found on the previous functionality
- Display PMID links to transfer to the corresponding page of the online literature of the found drug/gene
- Display Uniprot link on a gene to initiate the retrieval of protein information
- Display protein information retrieved from Uniprot
- Visualize proteins in a 3D viewer
- Display keywords that are correlated with a selected protein along with scientific references

Communication between the front end and the back end is achieved through REST API calls, comprised of the following HTTP API GET commands:

- `/api/drugs/dgldb/genes/{entrezid}`: responsible for returning DGldb gene information using entrez id as identifier.
- `/api/drugs/dgldb/drugs/{chemblid}`: responsible for returning DGldb drug information using chembl id as identifier.
- `/api/drugs/dgldb/{resource}`: responsible for returning DGldb information based on resource passed as identifier. Can be used for both drug and gene search.
- `/api/drugs/uniprot/proteins/{accessionId}`: responsible for returning UniProt information for a specified protein by its accession identifier.
- `https://alphafold.ebi.ac.uk/api/prediction/{accessionId}`: utilized directly from the front end to retrieve protein model information required by the 3D Protein Model Viewer.

D8.3 Interface for drug testing

Furthermore, the complete integration of Drug Search Tool into the SILICOFM platform, enables the tool to utilize all the security services including authentication and authorization, as defined in the main SILICOFM platform documentation (D7.3). Figure 19 depicts the completed sequence diagram of the developed drug search tool.

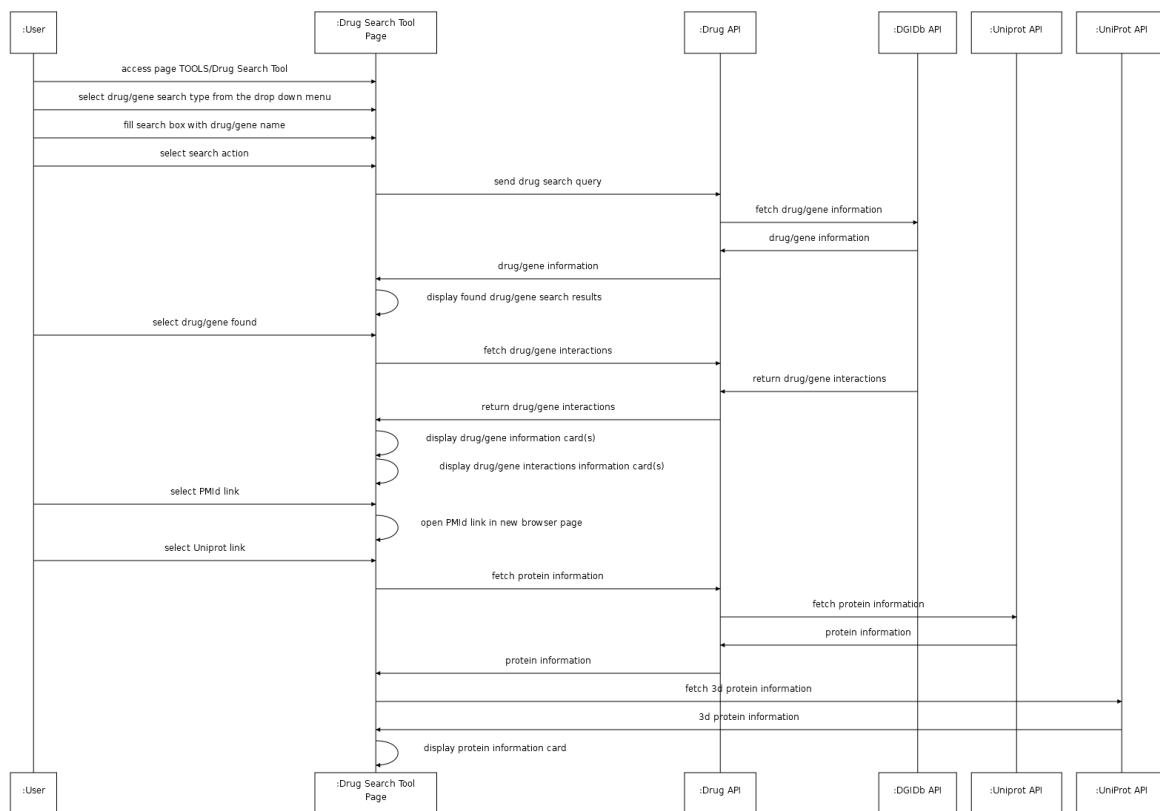


Figure 19: Drug Search Tool Sequence Diagram.

4.3 Integration of Drug Search tool into the SFCM platform

The SILICOFM Drug Interaction Tool, based on the MINERVA framework, is useful for examining of potential drug protein targets at the subcellular, cellular and tissue levels. The drug search tool provides to an expert and endpoint connected to multiple knowledge sources to retrieve information regarding the drug, drug protein interaction, drug-gene interaction. The later facilitates the experts to set the parameters for the PAK-FEM drug related simulation workflows. Namely, when PAK-FEM workflows are used, the first step is to select the appropriate drug by targeted examination or based on a doctor's recommendation (from a database table on the dedicated workflows). After drug selection and *in silico* testing which cell parameters are affected (calcium, sodium, related gene / protein expression, ...), information about the given drug and its specific boundary conditions are used as input for PAK-FEM workflows. In this way, complete information on the action of the drug at the cellular level and at the level of the heart model is obtained which induces macroscopic parameters change. In other words, the SILICOFM drug Interaction Tool and drug search tool is useful in two ways: i) as a source of information on the effect of a particular drug on cellular processes, which is in basic research of outmost importance; ii) as an initial source of information on the target drug and the parameters it changes, which are further used within their boundary conditions to obtain information on the effect on the whole heart.

D8.3 Interface for drug testing

4.3.1 Architecture

The Drug Search Tool architecture is comprised from the front-end and back-end sections. The front-end section is the visual interactive part of the Drug Search Tool, where the user can perform search on drugs and genes as display and use the information provided. It is further componentized to the search area and the information area. The search area handles the search type (drug or gene), the search term input area and finally the search action button.

Upon a search completion, the information area displays in the form of cards, the information for the drug or gene and its interactions. Visual indications in the form of descriptive icons, further enhance the visual indication of the information displayed for either a drug or gene. Due to the wealth of the information provided, particularly, was paid attention to display a brief information on the interaction panel with interactive buttons to display the detailed information of an interaction. Also, links to external reference databases is provided with interactive link buttons connected to these external resources.

On the gene information panel, a button to further retrieve the protein information exists. Upon retrieval, another panel, specific for the protein, displays all the collected information in a card form using visual identification icon of a protein.

The overall design of the Drug Search Tool was based on the following factors:

- User friendly information search and connection between drug, gene and protein
- Concise information on drugs, genes and proteins
- Precise and uncomplicated, where possible, flow paths on using the interface

4.3.2 Technologies

As mentioned earlier, the Drug Search Tool being fully integrated with the SILICOFCM platform, allowed the sharing of the established technologies used by the rest of the platform. The technologies are categorized as follows:

- Front-End technologies
- Back-End technologies

4.3.2.1 Front-End Technologies

The Front-End section, responsible for the interaction between the user and the Drug Search Tool functionalities, was designed and developed using the following major technologies:

- TypeScript⁷ language, a modern typed programming language
- HTML⁸ 5 for page layout
- Bootstrap⁹ CSS for theming and presentation of components

⁷ <https://www.typescriptlang.org/>

⁸ <https://html.spec.whatwg.org/>

⁹ <https://getbootstrap.com/>

D8.3 Interface for drug testing

- NodeJS¹⁰ development ecosystem
- ReactJS¹¹ Framework for front-end logic and component development
- Recoil¹² library for front-end state management
- Axios¹³ library for communication with the back-end REST API
- YUP¹⁴ library for form error handling
- AJV¹⁵ library for communication error handling, between front-end and REST api
- React Hook Form ¹⁶for logic handling of forms
- ThreeJS¹⁷ library for the development of the 3D Model visualization component
- JWT¹⁸ decoding libraries for handling authentication and authorization on the front-end
- Styled Components¹⁹ library for parameterized theming customization
- Storybook²⁰ for component development
- Webpack²¹ toolchain for application packaging
- ESLint²² library for finding and fixing code issues during development configured with the widely accepted Airbnb rules dataset
- Prettier²³ library for enforcing and adhering to standardized code formats during development
- GIT²⁴ for source management
- Nightingale²⁵ UniProt web component library for presenting in 3D, protein structures

¹⁰ <https://nodejs.org/>

¹¹ <https://reactjs.org/>

¹² <https://recoiljs.org/>

¹³ <https://axios-http.com/>

¹⁴ <https://github.com/jquense/yup>

¹⁵ <https://ajv.js.org/>

¹⁶ <https://react-hook-form.com/>

¹⁷ <https://threejs.org/>

¹⁸ <https://github.com/auth0/node-jsonwebtoken>

¹⁹ <https://styled-components.com/>

²⁰ <https://storybook.js.org/>

²¹ <https://webpack.js.org/>

²² <https://eslint.org/>

²³ <https://prettier.io/>

²⁴ <https://git-scm.com/>

²⁵ <https://github.com/ebi-webcomponents/nightingale>

D8.3 Interface for drug testing

4.3.2.2 Back-End Technologies

The Back-End REST section, responsible for mediating communication between the front-end and the Drug Search Tool API services, was designed and developed with the following major technologies:

- TypeScript⁷ language, a modern typed programming language
- NodeJS¹⁰ development ecosystem
- TS.ED²⁶ web server development framework using ExpressJS²⁷ as base server engine
- Swagger²⁸ for REST API documentation generation
- Axios¹³ library for communication with the back-end tools and services such as the Function Engine Server and the Virtual Population services
- AJV¹⁵ library for communication error handling of the REST api endpoints
- JWT¹⁸ encoding & decoding libraries for handling authentication and authorization on the back-end
- Passport²⁹ library for developing authentication and authorization strategies for the REST API server
- Crypto¹⁰ library responsible for strong encryption and decryption facilities
- ESLint²² library for finding and fixing code issues during development configured with the widely accepted Airbnb rules dataset
- Prettier²³ library for enforcing and adhering to standardized code formats during development
- Webpack²¹ toolchain for application packaging
- GIT²⁴ for source management

4.3.3 SILICOFCM Drug search tool UI and user access endpoint

The proposed developed tool is seamlessly integrated into the *in silico* cloud platform of SILICOFCM. The tool is accessed by the main dashboard as depicted in Figure 20.

²⁶ <https://tsed.io/>

²⁷ <https://expressjs.com/>

²⁸ <https://swagger.io/>

²⁹ <http://www.passportjs.org/>

D8.3 Interface for drug testing

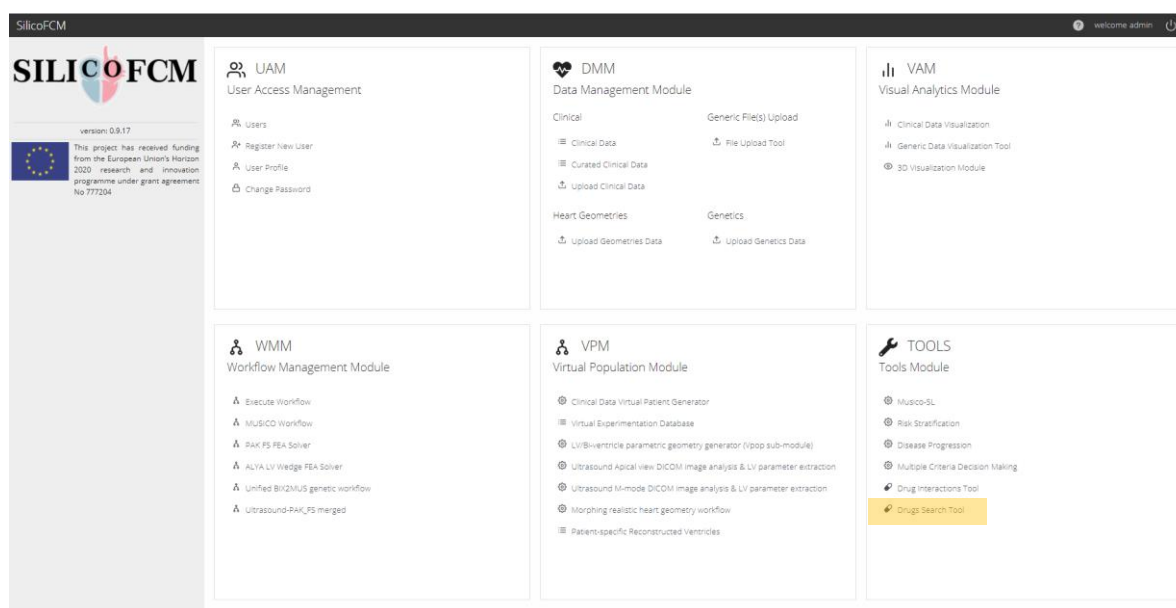
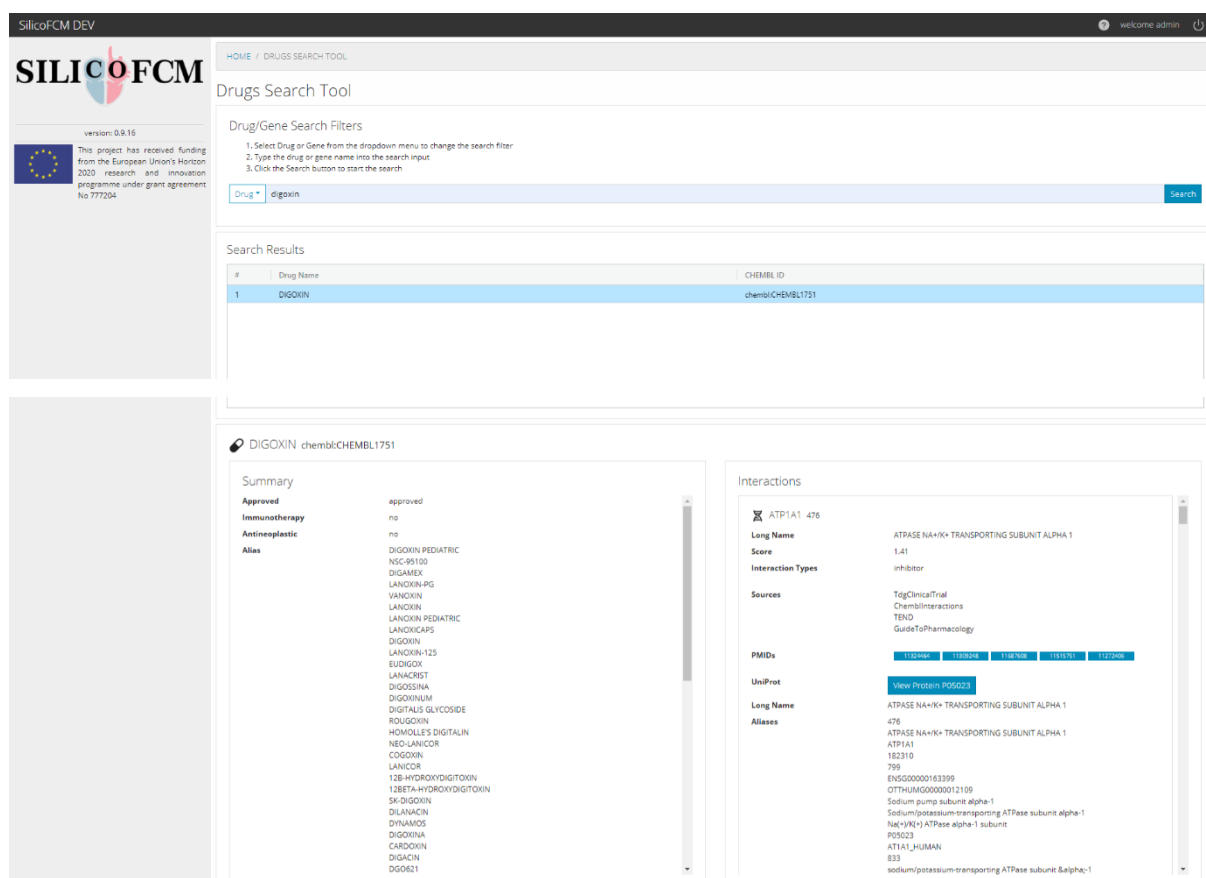
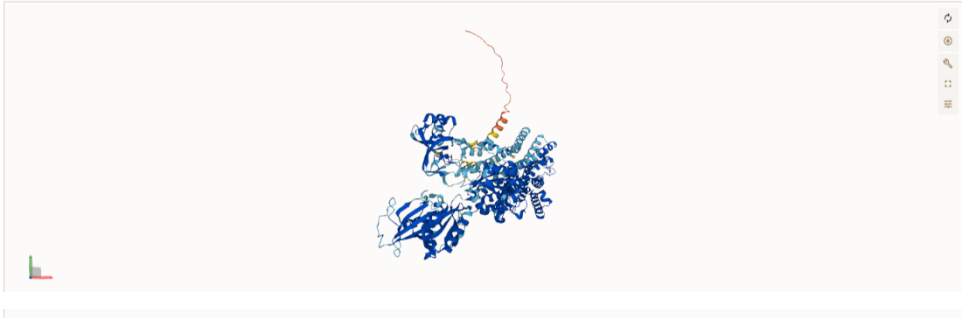


Figure 20: Access point of the SILICoFCM tool on the main dashboard.

Figure 21 depicts at a glance all the information that the tool could provide to the user expert in an interactive and progressive way. The uniqueness of the tool is that connects two well-known databases the DGIdb and the UniProt.



D8.3 Interface for drug testing

<div> <div></div> <div>P05023 AT1A1_HUMAN</div> </div>	
Summary	
Protein Existence	Evidence at protein level
Type	Swiss-Prot
Created	1987-08-13
Modified	2021-06-02
Version	243
Secondary Accession	B2PBR6 B7Z2T5 B7Z3U6 P5H3A1 Q16689 Q6LDM4 Q9UCN1 Q9UJ20 Q9UJ21
Protein Model	
Organism	
Taxonomy	9606
Names	Homo sapiens scientific Human common
Lineage	Eukaryota Metazoa Chordata Craniata Vertebrata Eumetazoa Mammalia Eutheria Euarchontoglires Primates Haplorhini Catarrhini Hominoidea Homo
Protein	
Recommended Name	Sodium/potassium-transporting ATPase subunit alpha-1
Alternative Names	Sodium pump subunit alpha-1
Gene	
Name	ATP1A1
Synonyms	

D8.3 Interface for drug testing

The screenshot displays the Drug Search Tool Interface, which is organized into several sections:

- Features:** A table with columns Type, Category, Description, and Molecule Evidences. It lists various biological features like PROPER, CHAIN, TOPO_DOM, TRANSMEM, etc., categorized under MOLECULE_PROCESSING, TOPOLOGY, and others.
- DB References:** A table with columns Type, Id, Molecule Type, and Protein Sequence Id. It lists database entries from EMBL, such as D00099, X04297, U16798, etc., categorized as mRNA or Genomic_DNA.
- Keywords:** A list of keywords including Acetylation, Alternative splicing, ATP-binding, Cell membrane, Cell projection, Charcot-Marie-Tooth disease, Direct protein sequencing, Epilepsy, Ion transport, Magnesium, Membrane, Mental retardation, Metal-binding, Neurodegeneration, Neuropathy, Nucleoside-binding, Phosphoprotein, Potassium, Potassium transport, Primary hypomyelination, Reference proteome, Sodium, Sodium transport, Sodium/potassium transport, Translocase, Transmembrane, Transmembrane helix, and Transport.
- References:** A section showing two references. The first reference is titled "Primary structure of the alpha-subunit of human Na,K-ATPase deduced from cDNA sequence" by Kawakami K, Ohta T, Nojima H, Nagano K, published in 1986 in J. Biochem. The second reference is titled "Characterization and quantification of full-length and truncated Na,K-ATPase alpha 1 and beta 1 RNA transcripts expressed in human retinal pigment epithelium" by Ruiz A, Bhat S, Bok D, published in 1995 in Gene. Both references list the NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 1) and (ISOFORM 2).
- Sequence:** A section showing the sequence of the protein, including the version (1), length (1023), mass (112896), and modified (1987-08-13). The sequence itself is a long string of amino acid codes.

Figure 21: Drug Search Tool Interface.

4.3.4 Description of the workflow

The workflow of the Drug Search Tool is shown in Figure 22.

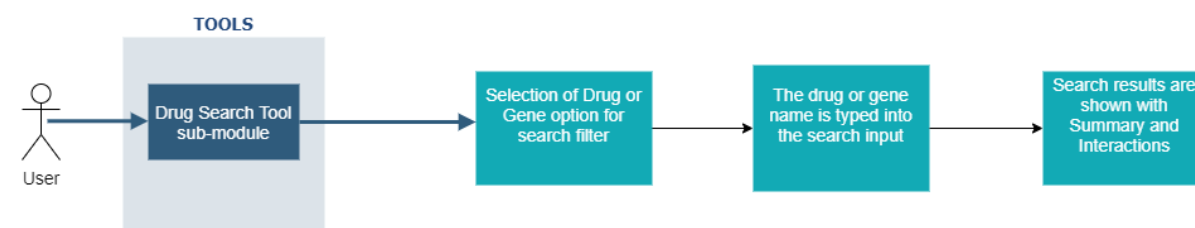


Figure 22: Workflow for the Drug Search Tool.

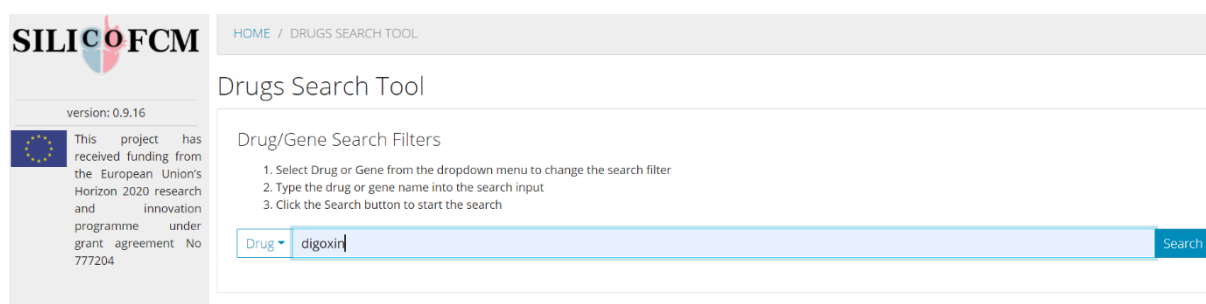
D8.3 Interface for drug testing

The workflow of the Drug Search Tool starts with the user accessing the Drug Search Tool Page. The user then selects the type of search to perform and enters the name of the drug or gene to search. The search button action initiates the search. The Drug API of the SILICOFM platform validates the search and communicates with the DGIdb Database to retrieve the searched information and its interaction data. The results are shown at the summary panel which depicts general information for the drug, and the interactions panel which provides details regarding the proteins that interact with the drug.

From the displayed drug/gene information the user selects the PMID links to traverse to the corresponding page of the online literature or select the UniProt link on a gene to initiate the retrieval of protein information. The Drug API communicates with the UniProt Database to retrieve the protein information. The information of the protein is displayed on the user interface. Also, some proteins can be visualized on a 3D viewer.

Drug Search

We are presenting two workflows of the Drug Search Tool, one workflow regarding a drug and one regarding a gene. We are starting by selecting the “Drug” option from the dropdown menu to investigate a specific drug with the name: **digoxin** (Figure 23).



version: 0.9.16

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

HOME / DRUGS SEARCH TOOL

Drugs Search Tool

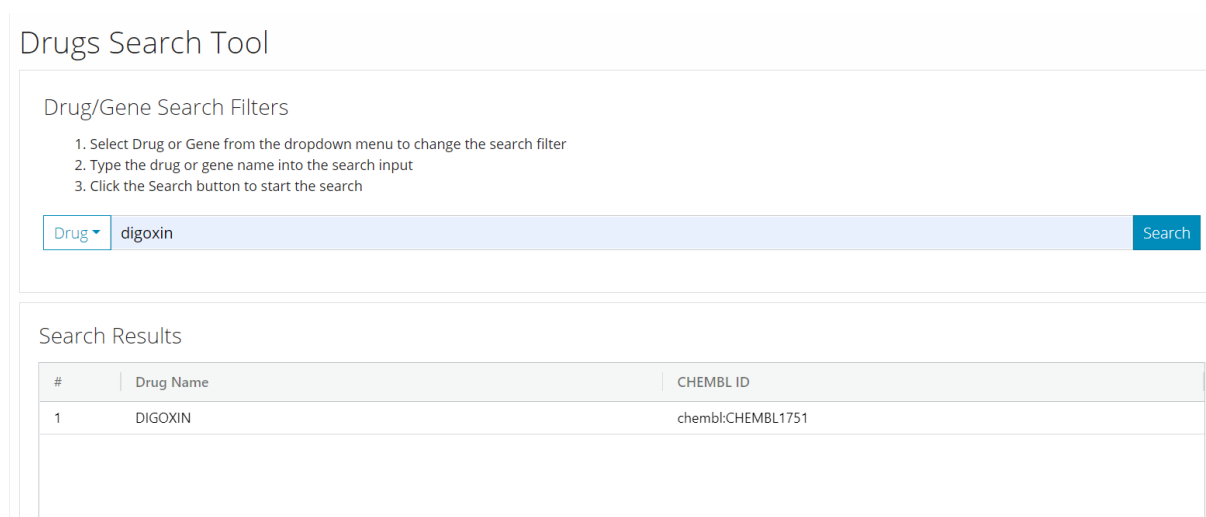
Drug/Gene Search Filters

1. Select Drug or Gene from the dropdown menu to change the search filter
2. Type the drug or gene name into the search input
3. Click the Search button to start the search

Drug Search

Figure 23: Set the name of the drug for searching.

The results are presented in Figure 24.



Drugs Search Tool

Drug/Gene Search Filters

1. Select Drug or Gene from the dropdown menu to change the search filter
2. Type the drug or gene name into the search input
3. Click the Search button to start the search

Drug Search

Search Results


#	Drug Name	CHEMBL ID
1	DIGOXIN	chembl:CHEMBL1751

Figure 24: Results of the drug search.

The first informational panel refers to general information illustrating a summary and the interactions of the drug. On the right side, the interactions panel provides details regarding the genes that interact with the specific drug and the corresponding proteins of each gene.

D8.3 Interface for drug testing

For every information that is shown, the user can refer to scientific publications for further research, by clicking the links on the “PMIDs” rows in order to move to the corresponding page of the online literature. Also, for every gene, the user can retrieve information about the protein that the UniProt platform sent to the SilicoFCM platform. For example, for the gene: ATP1A1, the Search Tool informs the user about the protein: P05023. The user can click on the corresponding button, as shown in Figure 25.

 DIGOXIN chembl:CHEMBL1751

Summary

Approved	approved
Immunotherapy	no
Antineoplastic	no
Alias	DIGOXIN PEDIATRIC NSC-95100 DIGAMEX LANOXIN-PG VANOXIN LANOXIN LANOXIN PEDIATRIC LANOXICAPS DIGOXIN LANOXIN-125 EUDIGOX LANACRIST DIGOSSINA DIGOXINUM DIGITALIS GLYCOSIDE ROUGOXIN HOMOLLE'S DIGITALIN NEO-LANICOR COGOXIN LANICOR

Interactions

ATP1A1 476

Long Name	ATPASE NA+/K+ TRANSPORTING SUBUNIT ALPHA 1
Score	1.41
Interaction Types	inhibitor
Sources	TdgClinicalTrial ChEMBLinteractions TEND GuideToPharmacology
PMIDs	11324464 11309248 11687608 11515751 11272406
UniProt	View Protein P05023
Long Name	ATPASE NA+/K+ TRANSPORTING SUBUNIT ALPHA 1
Aliases	476 ATPASE NA+/K+ TRANSPORTING

Figure 25: Drug summary and its gene interactions.

 P05023 AT1A1_HUMAN

Summary

Protein Existence	Evidence at protein level
Type	Swiss-Prot
Created	1987-08-13
Modified	2021-06-02
Version	243
Secondary Accession	B2RBR6 B7Z2T5 B7Z3U6 F5H3A1 Q16689 Q6LDM4 Q9UCN1 Q9UJ20 Q9UJ21

Figure 26: Protein summary.

The user has access to information regarding the selected protein. Also, for several proteins, the user has access to a panel that depicts a 3D visualization of the protein structure (Figure 27).

D8.3 Interface for drug testing

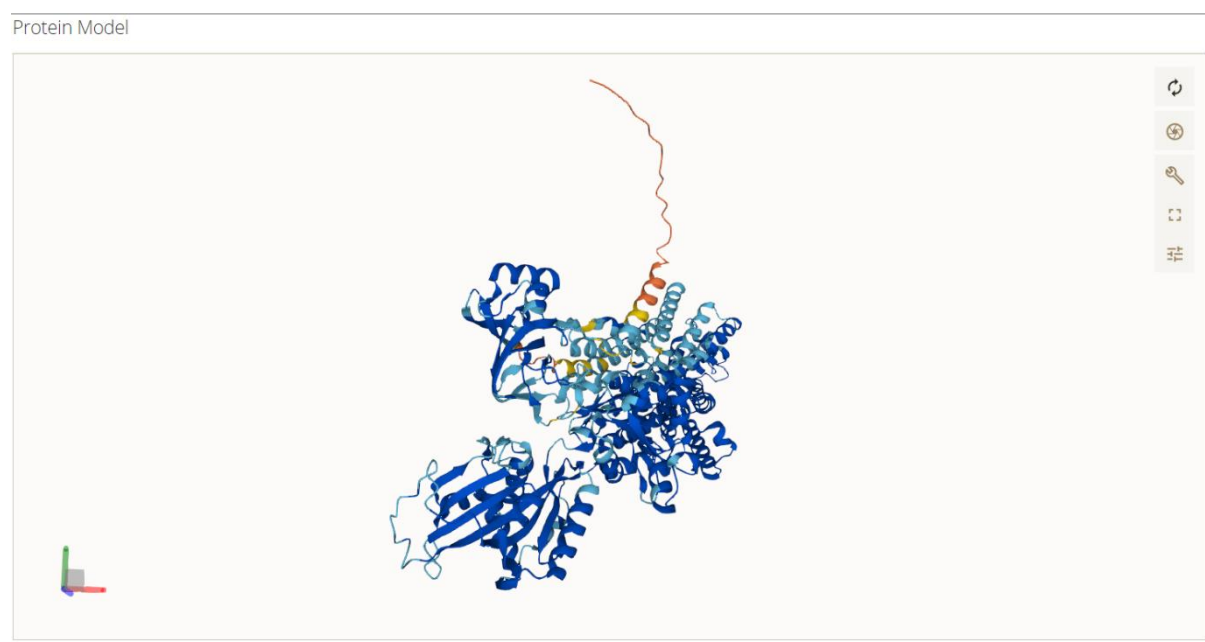


Figure 27: 3D visualization of the protein structure.

Moreover, some additional information is provided along with the visualization such as the standard scientific names of the protein as more alternatives (Figure 28).

Protein	
Recommended Name	Sodium/potassium-transporting ATPase subunit alpha-1
Alternative Names	Sodium pump subunit alpha-1

Figure 28: Protein names.

Some more specific features are given and some references regarding the database information (Figure 29).

DB References			
Type	Id	Molecule Type	Protein Sequence Id
EMBL	D00099	mRNA	BAA00061.1
EMBL	X04297	mRNA	CAA27840.1
EMBL	U16798	mRNA	AAC50131.1
EMBL	AK295095	mRNA	BAH11971.1
EMBL	AK296362	mRNA	BAH12332.1
EMBL	AK314777	mRNA	BAG37313.1
EMBL	AL136376	Genomic_DNA	
EMBL	CH471122	Genomic_DNA	EAW56644.1
EMBL	BC003077	mRNA	AAH03077.1
EMBL	BC004330	mRNA	AAH04330.1

Figure 29: DB References.

At the end, some keywords that are correlated with the protein and some scientific references are provided to the end-user (Figure 30).

D8.3 Interface for drug testing

Keywords	
Values	Acetylation Alternative splicing ATP-binding Cell membrane Cell projection Charcot-Marie-Tooth disease Direct protein sequencing Epilepsy
References	
Title	Primary structure of the alpha-subunit of human Na,K-ATPase deduced from cDNA sequence.
Authors	Kawakami K., Ohta T., Nojima H., Nagano K.
Publication Date	1986
Publication	J. Biochem.
Scope	NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 1)
Title	Characterization and quantification of full-length and truncated Na,K-ATPase alpha 1 and beta 1 RNA transcripts expressed in human retinal pigment epithelium.
Authors	Ruiz A., Bhat S.P., Bok D.
Publication Date	1995
Publication	Gene
Scope	NUCLEOTIDE SEQUENCE [MRNA] (ISOFORM 2)

Figure 30: Keywords that are correlated with the protein and scientific references.

Gene Search

The second workflow that is described regards the search for a specific gene. We are starting by selecting the “Gene” option from the dropdown menu in order to investigate a specific gene with the name: ATP1A1 (Figure 31).

HOME / DRUGS SEARCH TOOL

Drugs Search Tool

Drug/Gene Search Filters

1. Select Drug or Gene from the dropdown menu to change the search filter
2. Type the drug or gene name into the search input
3. Click the Search button to start the search

Gene

 ATP1A1

Search

Figure 31: Set the name of the gene for searching.

The results are shown in Figure 32.

Drugs Search Tool

Drug/Gene Search Filters

1. Select Drug or Gene from the dropdown menu to change the search filter
2. Type the drug or gene name into the search input
3. Click the Search button to start the search

Gene

 ATP1A1

Search

Search Results

#	Gene Name	Gene Long Name
1	ATP1A1	ATPASE NA+/K+ TRANSPORTING SUBUNIT ALPHA 1

Figure 32: Results of the gene search.

D8.3 Interface for drug testing

By clicking on the gene name, the user can read general information illustrating a summary and the interactions of the gene. On the right side, the interactions panel provides details regarding the drugs that interact with the specific gene (Figure 33).

⌕ ATP1A1 476

Summary

UniProt [View Protein P05023](#)

Long Name ATPASE NA+/K+ TRANSPORTING SUBUNIT ALPHA 1

Aliases 476
ATPASE NA+/K+ TRANSPORTING SUBUNIT ALPHA 1
ATP1A1
182310
799
ENSG00000163399
OTTHUMG00000012109
Sodium pump subunit alpha-1
Sodium/potassium-transporting ATPase subunit alpha-1
Na(+)/K(+) ATPase alpha-1 subunit P05023
AT1A1_HUMAN
833
sodium/potassium-transporting ATPase subunit α-1
SODIUM/POTASSIUM-TRANSPORTING ATPASE ALPHA-1 CHAIN PRECURSOR (EC 3.6.3.9) (SODIUM PUMP 1) (NA+/K+ ATPASE 1).

Interactions

ISTAROXIME chembl:CHEMBL2093999

Score 5.32

Interaction Types

Sources TdgClinicalTrial

PMIDs [17239702](#)

Approved no

Immunotherapy no

Antineoplastic no

Alias ISTAROXIME
PST-2744
(E,Z)-ISTAROXIME

PMIDs [17239702](#)

FDA Approval not approved [TdgClinicalTrial](#)

Drug Class Small molecule [TdgClinicalTrial](#)

Drug for treatment of heart

Figure 33: Gene summary and its drug interactions.

Finally, the user by clicking on the button with the name of the protein: P05023 has access to all the information that is described on the previous workflow. This information is a summary for the protein, a panel that depicts a 3D visualization of the protein structure, standard scientific names of the protein, references regarding the database information, keywords that are correlated with the protein and several scientific references regarding the protein.

5 Code links to repositories

In this section, Table 2 with the link of the code development for the drug search tool is provided. We must clarify that these are private repositories and in order for the reviewers and the PO to reach them, they have to provide an account to have access due to IPR issues.

Table 2. Links to code repositories

#	Module, tool	Link to the repository
1	SILICOFCM Drug Search tool	https://github.com/gkois/silicofcm-webapp.git

6 Deviation from the work plan

There are no deviations from the workplan for the current deliverable.

7 Conclusions

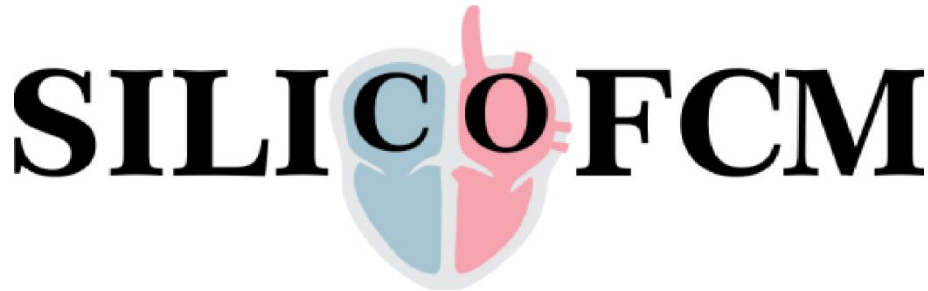
The current deliverable reports the work performed by the participating partners during the lifecycle of Task 8.3. Overall, it describes the design and development of a web interface within the SILICOFCM platform in order to retrieve information for drugs using open-source external established drug databases and also provides detailed maps of signaling pathways in the Hypertrophic Cardiomyopathy (HCM) through the drug interaction tool, which is based on the MINERVA framework. During internal user interface testing with expert researchers, the current implementation of the drug search tool drastically reduced their time, from several minutes needed to identify all information in several databases to a couple of minutes. Specifically, this service integrates external available public drug/gene/protein databases where the user can search all the information related to FCM directly from the platform. The use of such a tool greatly facilitates the creation of experiments and understanding of a particular scientific topic related to the examination of the effects of a particular drug. The SFCM - Drugs Search Tool provides a user-friendly connection to external publicly available databases and examines the effects of specific drugs. A quick search for available information on the interaction of certain drugs with target genes is very important. The researcher can easily obtain information on the most likely drug interactions and quickly define the interests to focus on, especially for drugs that provide a very wide range of possible gene interactions. Also, for a more experienced researcher, the obtained panel of results is sufficient to notice whether there are specific antagonisms in the effect of the drug, i.e., whether it reacts controversially to two opposing biochemical mechanisms. Using the SFCM - Drugs Search Tool, information is obtained from selected sources summarized in an adequate way so that any further analysis is easier.

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Annex

Manual of Drug Search tool



Project Title: *In Silico* trials for drug tracing the effects of sarcomeric protein mutations leading to familial cardiomyopathy

Project acronym: SILICOFCM

Grant Agreement number: 777204

The Drug Search Tool Instructions of Use



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 777204

D8.3 Interface for drug testing

A specific tool has been designed and introduced in the SILICOFM platform. The so-called drug search tool provides search capabilities to the end users for drugs linking external commercial databases.

This workflow was developed to provide access to the end-user to a database with a huge variety of drugs. The user has access to a large bundle which can provide information for major drugs and their sub-components.

The user after a successful login to the platform, can select the **Drug Search Tool** to execute the process.

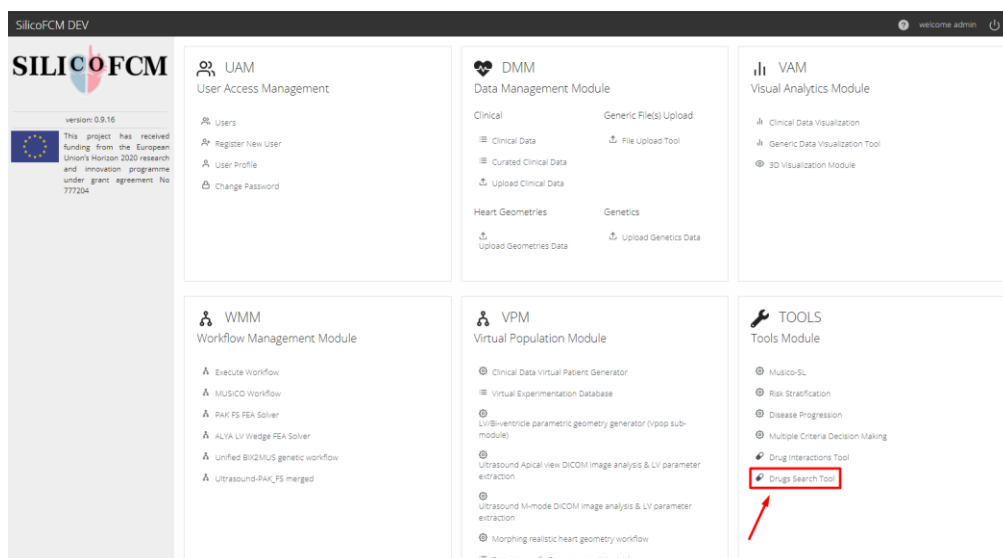


Figure 34: Drug search tool selection from the home screen dashboard of the SILICOFM cloud platform.

Afterwards, the user must select a Drug or Gene from the dropdown menu to investigate a specific drug.

1. Type the drug or gene name into the search input.
2. Click the Search button to start the search.

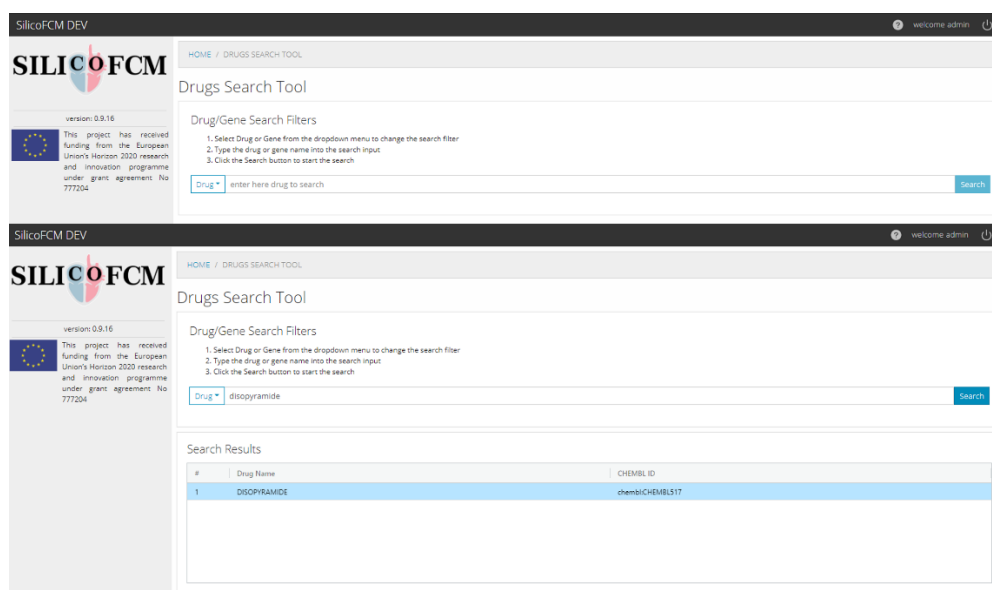


Figure 35: Drug search tool input drug name and table with search results.

D8.3 Interface for drug testing

The flow of the Drug Search Tool starts with the user accessing the Drug Search Tool Page. In Figure 36 the user selects the type of search to perform and enters the name of the drug or gene to search. The search button action initiates the search. The Drug API validates the search and communicates with the DGIdb Database to retrieve the searched information and its interaction data. The Drug API communicates with the UniProt Database to retrieve the protein information. The information of the protein is displayed on the user interface. The first informational panel refers to general information illustrating a summary and the interactions of the drug. The summary panel depicts general information for the drug, as the interaction panel provides details regarding the proteins that interact with the drug.

The screenshot displays the Drug Search Tool interface for DISOPYRAMIDE (chembl:CHEMBL517). The interface is divided into two main sections: Summary and Interactions.

Summary Section:

- Approved:** approved
- Immunotherapy:** no
- Antineoplastic:** no
- Alias:** DISOPYRAMIDE, SC-7031, H-3292, NORPACE, GAMMA-DISOPROPYLAMINO-ALPHA-PHENYL-ALPHA-(2-PYRIDYL)BUTYRAMIDE, DISOPYRAMIDA, SC-13957, RYTHMODAN-8, DISOPYRAMIDUM, ALPHA-(2-DISOPROPYLAMINO)ETHYL-ALPHA-PHENYL-2-PYRIDINEACETAMIDE, NORPACE-8, ncu_3541, pubchem.compound.3114, chemidplus.3737-09-5, chembl:CHEMBL517, drugbank:00280
- PMIDs:** 16842817, 11272006, 10028093, 11202552, 15897781, 1196253
- FDA Approval:** 1977, [TdgClinicalTrial](#)
- Drug Class:** small molecule, [TdgClinicalTrial](#)
- Drug Indications:** Anti-Arrhythmia Agents, [TdgClinicalTrial](#)
- Drug Class:** anti-arrhythmia agents, [TEND](#)
- Year of Approval:** 1977, [TEND](#)

Interactions Section:

- KCNH2 3757:**
 - Long Name:** POTASSIUM VOLTAGE-GATED CHANNEL SUBFAMILY H MEMBER 2
 - Score:** 0.31
 - Interaction Types:** blocker, inhibitor
 - Sources:** DTC, GuideToPharmacology, PharmGKB
 - PMIDs:** 16842817, 11272006
 - More Details:** [More Details](#)
- SCN5A 6331:**
 - Long Name:** SODIUM VOLTAGE-GATED CHANNEL ALPHA SUBUNIT 5
 - Score:** 1.91
 - Interaction Types:** inhibitor
 - Sources:** TdgClinicalTrial, TEND, PharmGKB, TTD

Figure 36: Summary of the drug and proteins interactions and the more details button.

The window that refers to the interactions with a variety of proteins. These interactions of the drug that the user searched for, are provided with extra information by pressing the “more details” button. Then the searched protein is presented with further details. Within all the aspects of the drug search tool, there are everywhere links with respectful scientific publications for further research and understanding. From the displayed drug/gene information the user selects the PMID links to move to the corresponding page of the online literature or select the Uniprot link on a gene to initiate the retrieval of protein information.

D8.3 Interface for drug testing

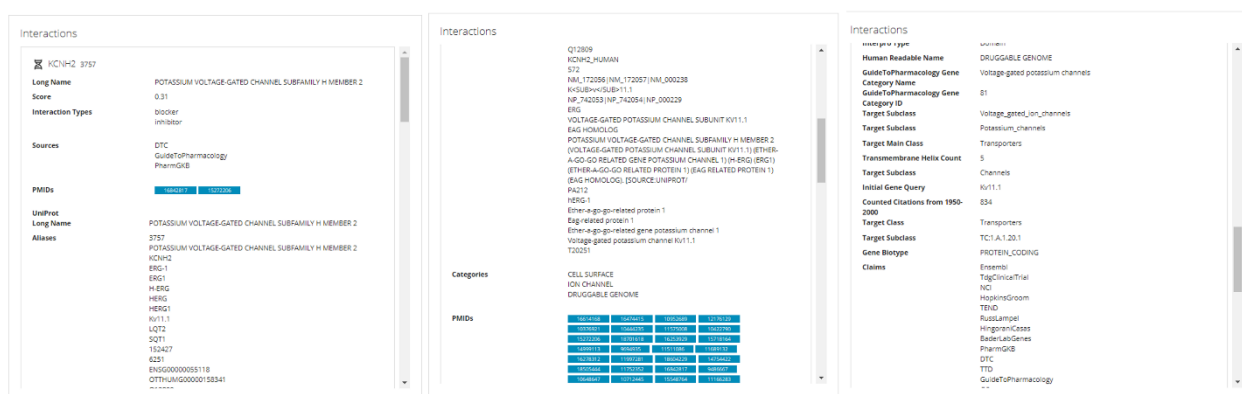


Figure 37: The summary information (more options button) regarding the interactions of the searched drug, that provides the user more data of the.

Also, some proteins have a more advanced option to be visualized (View Protein) in a 3D viewer, to enhance the end-user interface. A first summary of the selected protein, is presented in Figure 38 where the option to visualize the protein is presented.

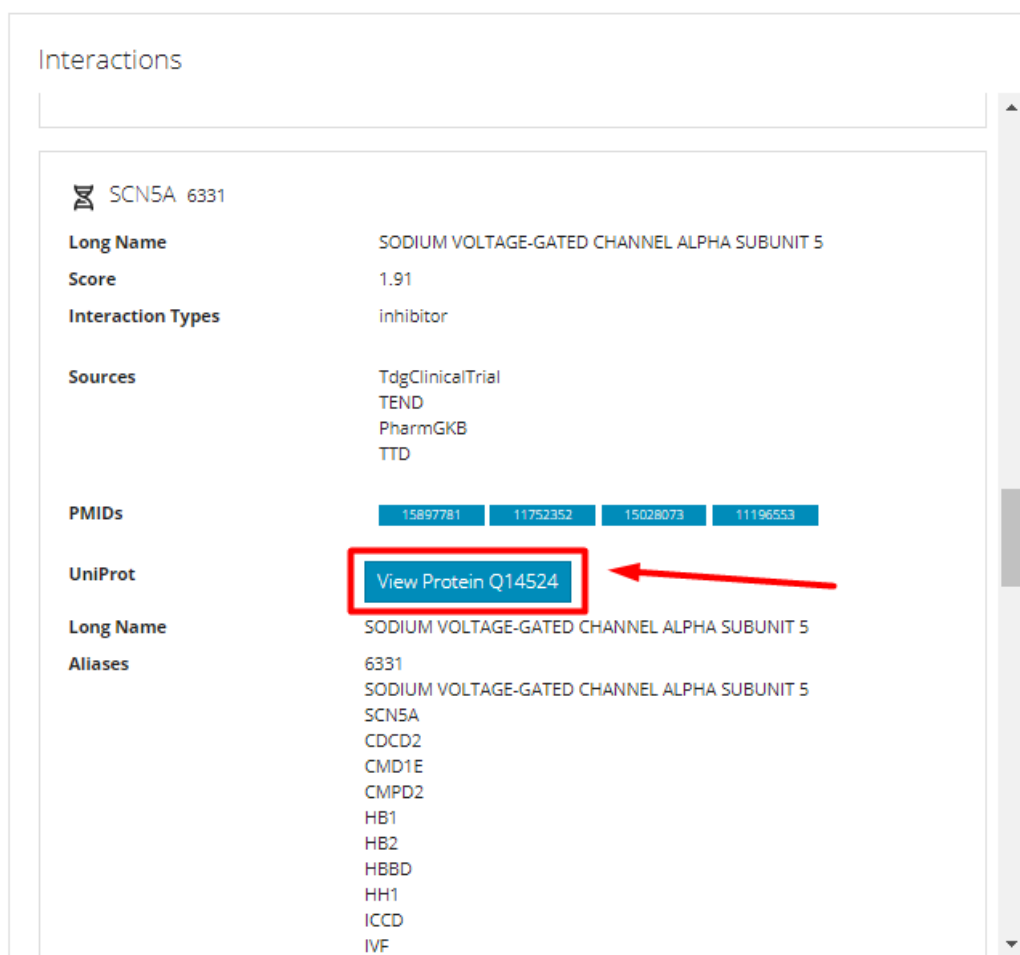


Figure 38: View protein extra information interface.

After the user selection to view (visualize) the protein, the first panel depicts a 3D visualization of the protein structure. Moreover, some additional information is provided along with the visualization such as the standard scientific names of the protein as more alternatives. Some more specific features are

D8.3 Interface for drug testing

given (Figure 38) and some references regarding the database information. At the end, some keywords that are correlated with the protein and some scientific references are provided to the end-user.

Figure 39 depicts a raw 3D visualization of the sequence, the molecules, and the bindings of the user selected protein. This first panel provides the end-user some options to investigate further information for the protein model. In Figure 39 these options are depicted in the red box, where the first button provides a camera reset view, the second enables the option to the user to capture a print screen. Moreover the 3rd button pops up more detailed options, as the last two buttons provide an expanded viewport option and some basic controls options such as few camera settings, the background color, the lighting and the clipping scale.

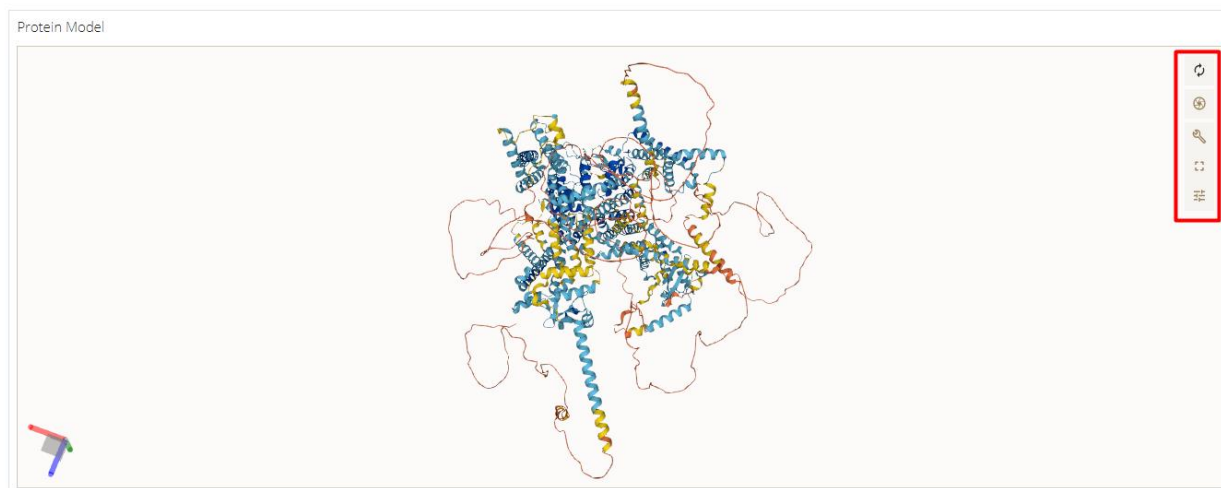


Figure 39: 3D visualization and further information regarding the selected protein.

The 3rd button option from the raw visualization, generates a new window panel which provides the end user with detailed information and settings. The end user selects this button and popup options are revealed in the right side of the panel, the whole chain sequence of the protein model is depicted at the top of the panel and 4 more buttons in the left side which provide advanced options. If the user deselects the 3rd button from the right side the window returns to the raw 3D visualization with the previous basic options.

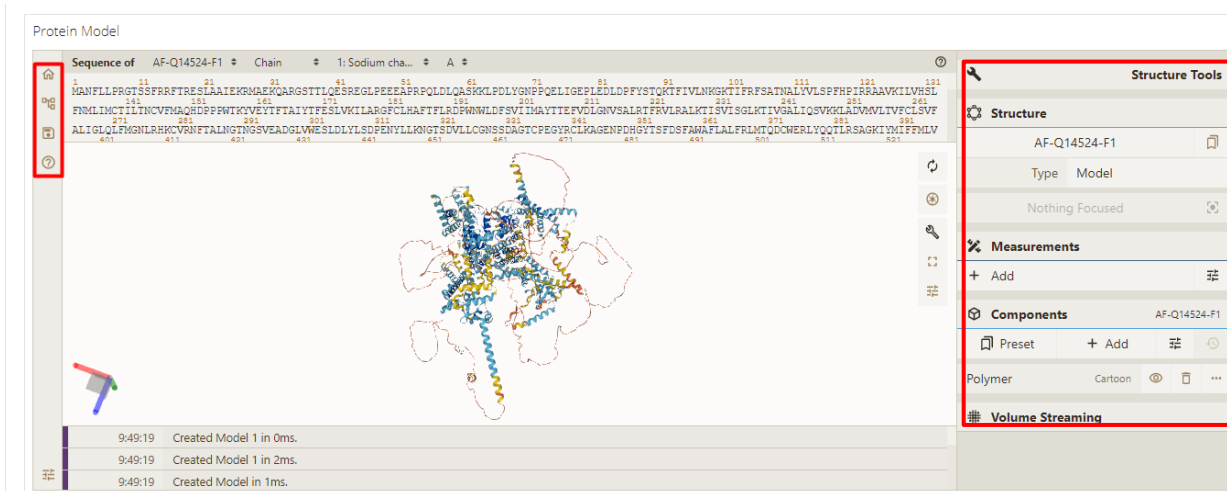


Figure 40: Pop up detailed options after the selection of the user for more information of the 3D protein model.

D8.3 Interface for drug testing

The revealed options in the right side of the panel provide the end users information regarding the protein structure, some measurements that he/she can perform, information regarding the selected protein components and volume streaming options for the visualization. The left side of the panel provides some more advanced options to the end user. The first button “home” enables some advanced aspects to the end user. These options include the download structure where the end user can download further structures to be incorporated into the main protein model. The “add trajectory” option, where the end user can select to visualize further trajectory models. Also, the “download density” option loads a density from the provided data source and create its default visual (Figure 41) from other into the main 3D protein model. Moreover, the “download file” option enables the option to load one or more files from a URL and incorporate it to the protein model. The next option “open files” provides the end user the capability to load one or more file and optionally he/she can create default visuals. At the end, the last option “download” enables the possibility to download strings or binary data from specified URLs.



Figure 41: 3D protein model with integrated the selected density model.

From the panel with the advanced options and the 3D visualization of the protein model, further information is provided. These data reports provide useful information regarding the organism, the taxonomy and the lineage of the selected protein. Also, recommended and alternative names of the protein and the specified genes names are presented. Furthermore, a lot of features such as the type, the category and the description of the protein’s chemical formula are presented. Next to the features panel, some published scientific references and few database references regarding the molecule type, the protein sequence ID is given. At the end, keywords are provided for specific research and the amino acid sequence of the protein.

D8.3 Interface for drug testing

Organism	
Taxonomy	9606
Names	Homo sapiens <small>scientific</small> Human <small>common</small>
Lineage	Eukaryota Metazoa Chordata Craniata Vertebrata Euteleostomi Mammalia Eutheria Euarchontoglires Primates Haplorhini Catarrhini Hominoidea Homo

Protein	
Recommended Name	Sodium channel protein type 5 subunit alpha
Alternative Names	Sodium channel protein cardiac muscle subunit alpha Sodium channel protein type V subunit alpha Voltage-gated sodium channel subunit alpha Nav1.5 HH1

Gene	
Name	SCN5A
Synonyms	

Type	Category	Description	Molecule Evidences
CHAN	MOLECULE_PROCESSING	Sodium channel protein type 5 subunit alpha	
TOPO_DOM	TOPOLOGY	Cytoplasmic	
TRANSMEM	TOPOLOGY	Helix# Name=S1 of repeat 1	
TOPO_DOM	TOPOLOGY	Extracellular	
TRANSMEM	TOPOLOGY	Helix# Name=S2 of repeat 1	
TOPO_DOM	TOPOLOGY	Cytoplasmic	
TRANSMEM	TOPOLOGY	Helix# Name=S3 of repeat 1	
TOPO_DOM	TOPOLOGY	Extracellular	
TRANSMEM	TOPOLOGY	Helix# Name=S4 of repeat 1	

Type	Id	Molecule Type	Protein Sequence Id
EMBL	M77235	mRNA	AA058644.1
EMBL	AY038064	mRNA	AA074265.1
EMBL	AY148488	mRNA	AA081120.1
EMBL	AF482983	mRNA	AA091669.1
EMBL	AB158469	mRNA	BA012084.1
EMBL	AB158470	mRNA	BA012085.1
EMBL	EP029346	mRNA	ABR12703.1
EMBL	CF619347	mRNA	ABR15764.1
EMBL	DQ784809	Genomic_DNA	ABQ01244.1
EMBL	U75199.2	Protein_Protein	AA058644.1

Keywords	
Values	3D-structure Alternative splicing Atrial fibrillation Brugada syndrome Calmodulin-binding Cardiomuscular

D8.3 Interface for drug testing

References	
Title	Primary structure and functional expression of the human cardiac tetrodotoxin-insensitive voltage-dependent sodium channel.
Authors	Gellens M.E., George A.L. Jr., Chen L.Q., Chahine M., Horn R., Barchi R.L., Kallen R.G.
Publication Date	1992
Publication	Proc. Natl. Acad. Sci. U.S.A.
Scope	NUCLEOTIDE SEQUENCE (MRNA) (ISOFORM 1)FUNCTIONSUBCELLULAR LOCATIONVARIANTS ARG-552 AND GLN-1027
Title	SCN5A is expressed in human jejunal circular smooth muscle cells.
Authors	Ou Y., Gibbons S.J., Miller S.M., Strege P.R., Rich A., Distad M.A., Ackerman M.J., Rae J.L., Scurszewski J.H., Farnugie G.
Publication Date	2002
Publication	Neurogastroenterol. Motil.
Scope	NUCLEOTIDE SEQUENCE (MRNA) (ISOFORM 2)TISSUE SPECIFICITYVARIANT ARG-552
Sequence	
Version	2
Length	2016
Mass	226940
Modified	2008-11-25
Sequence	MANFLPRGTSSFRRTRESLAAEKRMADKQARGSTTLQESREGLPEEEAPRPQLDQASKKLPDLYGNPPQELUGLEPLEDLPFYSTQKTRVNLNKGKTIFFRSATNALYVLSPF HPIRRAAYKLVHSLNMLIMCTILN.CYFMAQHDPPPWTKYVEYTFATVTFRESLWKLARGCLHAFTLRDPWNWLDPSVIMAYTTPVDLGNVSALRTFRVLRAKTKTSVSGL KTIYVGLICSVKRLADVMVNLTVFCLSVFALIGLQLFMGNLRHKCVRNFTALNGTNGSYEADGLWVESLDYLSDPENYLLKNGTSDVLCGNSSDAGTCPEGVCLKAGENPDH GYTSPDSFVWAPLALPRLMTQDCWERLYQTLRSAGKYMRFFMLVRLGSPYLVNLLAVVAMAYEEQNQATIAETEEKRFQEAEMLEKHEALTIRGVOTVSRSSLEMSPL APVNSHERRSKRRKMSGGTEEGEDRLKSDSESGPRAMNHLSTRLGSLRTSMKPRSSRGSGFTFRRDLGGEADPADDENSTAGESESHHTSLVFWPLRTSAQGGQSPG TSAPGHALHGKKNSTVDCNGVSVLLGAGDPEATSGSHLLRPVMLEHPDOTTTPSEEPGGPQMLTSQAPCDVGFEERSARQNALSAVSILTSLEEBESRHKCPQCNRLA QRYLIWECCPLWMSKQGVKLVMDPPTQLTITMACVNLTFMALEHYNMTSEFEMLQVGNLVFTGIFTAEMTKIALDIIFRILCGEWIETWDCMEVSGQSLCLLVFLVMV RFRLLRVFKLAKSWPTLNTLKIIGNSVGALGNLTIVAINRFVAVGMQLFGKNVSELROSDSGLLPRWHMMDFHAFUIFRILCGEWIETWDCMEVSGQSLCLLVFLVMV IGNLVNLFLALLSSFSADNLTPADEDEMNNLQALARIQIRGLRFVKRTTWDFCCGLLRQRPQKPAALAAQGLPSCIATPSPPPPTEKVPPTKETFEDEGEQPGQTP GDPEPCVPIAAVESDQDQDEEENSLGTEEESSKQESQVSGGPEAPDSRTWSQVSATASSEAEASASQADWQWKAEPQAPGCGETPEDSCSEGSTADMTNTEL LEQIPDLGQDWKDPEDCTEGCVRRCPCAVDTTQAPGKWWWRRLRKTCTYHIVEHSWFETTRIFMILLSGALAFEDYLEERTIKVILEYADKMFTYVPVLEMLKWWAYGPKKYF TNAWCWLDFLVNDSVLSVLANLTGFAEMGPKSLRLRALRPLRLSRFEGMRVYNALYGAIPSIMNVLVLCUFWLFSIMGNLFAKIGRCINQTEGDLPLNTYMNKYSQ CESLNLTGELYWTKVKNVNDVAGYVALLQVATKGMWMDIMYAVDSRGVEEQPQWEYNLYMYIYPIIFGSGFTLNLHGVINDNPNQKKLGGQDIHMTTEQKKYNA MKLGSKKPQKPIRPLNKYQGHFDTKQAPDTIMFLCLNMYMTMVEVDDQSPKINLAKINLLFVNFTGECVLAALRHYYFTNSWNIFQPVVILNSGTVLSQIKKYFF SPTLFRVRLARIGRLRLRGAKGRTLLFALMMSLPALFNIGLLFLVMRYISFGMANFAYVWKEAGIDDMFNFTFANSMLCLFQITTSAGWDGLLSPINTGPPYCDPTLPNS NGSRGDCGSPAVAGLFTTYYIIISPLVNMVIAILENFSVATEESTEPLESDOPDMFYELWEKDPPEATQRIEYVLSDFADALSEPLRAKPNQISLNMQLPMSVSGDRHICMDILFA PTKRVLGESGEMDALQKQEEKFMAANPSSISYEPITTTLRKHFEVSAMVQRAFRHLLQRLSKHASELFRQQAQSGSLSEEDAPEREGLIAYWMESENPSRLGGPSSSSISSTSF DPSYDVTYRATSDNLQVRGSDVSHSEDLADFPSPDRDRESIV

Figure 42: Additional information for the visualized protein

D8.3 Interface for drug testing

Drug search tool API

Figures 43-47 demonstrate the developed APIs for the drug search tool, that has been integrated to the SILICOFCM cloud platform. Further information and the source code, regarding the development of the SILICOFCM cloud platform APIs, can be found on the respectful link (<https://silicofcm-dev.bioirc.ac.rs/api/swagger/#/>) where all development and version control is presented.

The image shows the Swagger UI for the endpoint `GET /api/drugs/dgidb/genes/{entrezId}`. The description is "get specific resources from DgiDB database". The parameters section shows a required path parameter `entrezId` of type `string`. The responses section shows a 401 Unauthorized status with a media type of `application/json` and an example JSON response: `{ "name": "string", "message": "string", "status": 0 }`.

Name	Description
entrezId * required string (path)	entrezId

Code	Description	Links
401	Unauthorized	No links

Media type: `application/json`

Example Value | Schema

```
{
  "name": "string",
  "message": "string",
  "status": 0
}
```

Figure 43: Gene search from DGIdb based on entrzid parameter.

The image shows the Swagger UI for the endpoint `GET /api/drugs/dgidb/drugs/{chemblId}`. The description is "get specific resources from DgiDB database". The parameters section shows a required path parameter `chemblId` of type `string`. The responses section shows a 401 Unauthorized status with a media type of `application/json` and an example JSON response: `{ "name": "string", "message": "string", "status": 0 }`.

Name	Description
chemblId * required string (path)	chemblId

Code	Description	Links
401	Unauthorized	No links

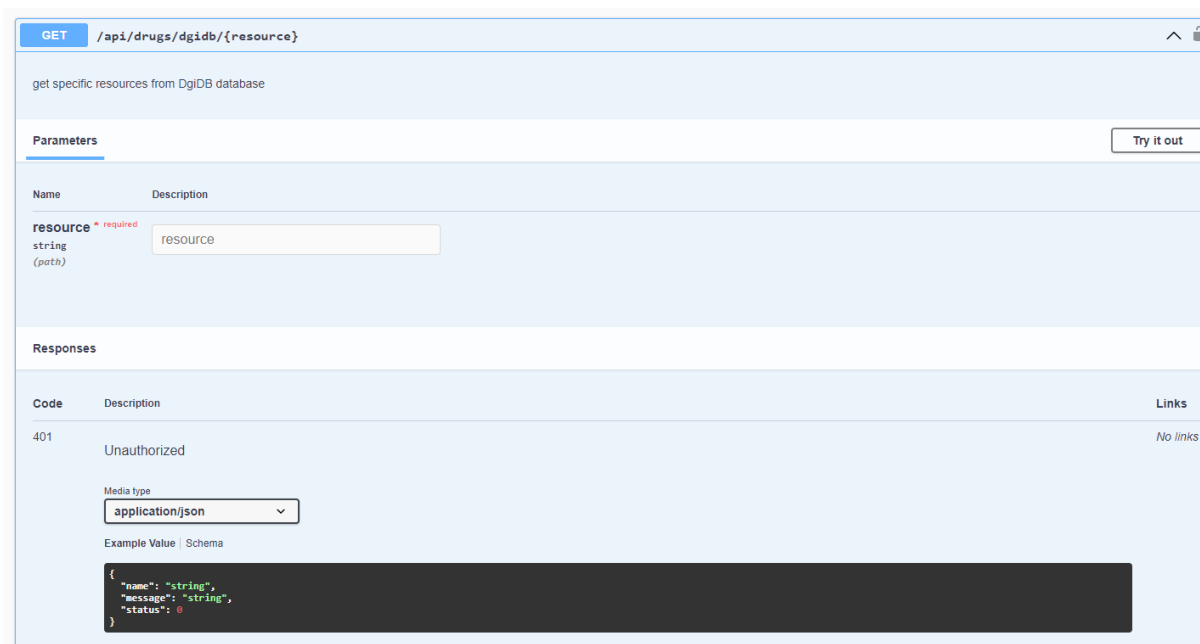
Media type: `application/json`

Example Value | Schema

```
{
  "name": "string",
  "message": "string",
  "status": 0
}
```

Figure 44: Drug information from ChEMBL with chembid parameter.

D8.3 Interface for drug testing



Swagger UI for the endpoint `GET /api/drugs/dgldb/{resource}`. The description is "get specific resources from DgIDB database".

Parameters

Name	Description
resource * required string (path)	<input type="text" value="resource"/>

Responses

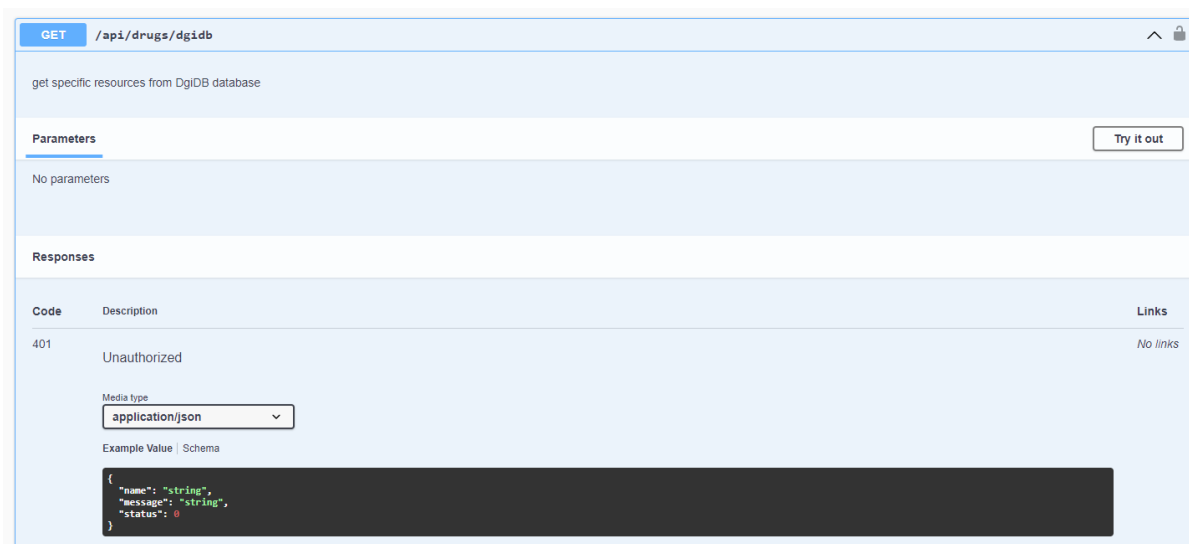
Code	Description	Links
401	Unauthorized	No links

Media type:

Example Value | Schema

```
{
  "name": "string",
  "message": "string",
  "status": 0
}
```

Figure 45: General API to obtain information from DGldb for drug/genes, based on the resource parameter.



Swagger UI for the endpoint `GET /api/drugs/dgldb`. The description is "get specific resources from DgIDB database".

Parameters

No parameters

Responses

Code	Description	Links
401	Unauthorized	No links

Media type:

Example Value | Schema

```
{
  "name": "string",
  "message": "string",
  "status": 0
}
```

Figure 46: General information from DGldb.

D8.3 Interface for drug testing

GET /api/drugs/uniprot/proteins/{accessionId}

get specific resources from UniProt database

Parameters [Try it out](#)

Name	Description
accessionId * required string (path)	<input type="text" value="accessionId"/>

Responses

Code	Description	Links
401	Unauthorized	No links

Media type:

Example Value | Schema

```
{
  "name": "string",
  "message": "string",
  "status": 0
}
```

Figure 47: Information from UniProt database based on the accessionid parameter.