Open PHACTS

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Report on analysis of IMI projects with respect to potential for joint scientific use cases

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Definitions

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

1 - GSK – GlaxoSmithKline – **Coordinator**
2 - UNIVIE – Universität Wien – **Managing Entity of IMI JU funding**
3 - DTU – Technical University of Denmark
4 - UHAM – University of Hamburg, Center for Bioinformatics
5 - BIT – BioSolveIT GmbH
6 - PSMAR – Consorci Mar Parc de Salut de Barcelona
601 - FIMIM – Fundacio Institut Mar d'Investigacions Mediques
602 - UPF – Universitat Pompeu Fabra
7 - LUMC – Leiden University Medical Centre
8 - RSC – Royal Society of Chemistry
801 - RSCWW – RSC World Wide Ltd
9 - VUA – Stichting VU-VUMC
10 - CNIO – Centro Nacional de Investigaciones Oncológicas
11 - UNIMAN – University of Manchester
12 - UM – Universiteit Maastricht
13 - ACK – ACKnowledge
14 - USC – Universidade de Santiago de Compostela
15 - UBO – Rheinische Friedrich-Wilhelms-Universität Bonn
16 - AZ – AstraZeneca AB
17 - Pfizer – Pfizer Limited
18 - Esteve – Laboratorios del Dr. Esteve, S.A.
19 - Novartis – Novartis Pharma AG
20 - ME – Merck
21 - HLU – H. Lundbeck A/S
22 - Lilly – Eli Lilly and Company Limited
23 - NBIC – Stichting Netherlands Bioinformatics Centre
24 - SIB – Swiss Institute of Bioinformatics
25 - CD – ConnectedDiscovery
26 - EMBL-EBI – European Molecular Biology Laboratory
27 - Janssen – Janssen Pharmaceutica NV
28 - OGL – OpenLink Group Ltd
29 - OPF – The Open PHACTS Foundation
30 - ALM – Laboratorios Almirall S.A.
31 - SciBite – SciBite Limited

1 Introduction

Open PHACTS has gained attention from other IMI projects dealing with data, such as eTOX, ELF, or K4DD, and has been mentioned in several recent IMI proposals (e.g. Webae). This offers the possibility to jointly develop new scientific use cases across IMI projects. This will feed back to the Open PHACTS project and stimulate the development of new API calls and functionalities, help to identify new data sources necessary for solving complex research questions, and further demonstrate the usability of the Open PHACTS Discovery Platform across different user communities. With this deliverable we analyse existing and upcoming IMI projects for the potential of conducting joint use cases. Basis for the analysis of the IMI projects were their description on the IMI website http://imi.europa.eu. The projects are ordered according to calls. If applicable, a potential use case is briefly outlined.

2 Potential IMI Projects for collaboration with Open PHACTS

eTOX (call 1)

eTOX aims at developing innovative strategies and novel software tools to better predict the safety and the side-effects of new candidate medicines for patients. For this, the complex relationships between the structure of a substance, its metabolism and disposition, and its toxic effects in the body are analysed. The combination of this knowledge will enable to create more reliable computer models to better predict potential side-effects that would otherwise only be discovered in a later stage of the drug development or when the drug is already on the market.

To overcome the lack of publicly available toxicological data of 'drugable' chemicals which hampered progress so far, the partners share and jointly exploit the archived results of more than 10.000 toxicological studies of the industry partners. This data, which was previously only accessible to the owning pharmaceutical companies, will be integrated with publicly available and new data, resulting in a unique database – VITIC, which will be analysed using innovative approaches in data analysis.

Potential joint use case with Open PHACTS: as one of the tasks in eTOX is the development of models for transporter associated liver toxicity, a joint use case could be to develop a predictive model for hyperbilirubinaemia, based on data derived from Open PHACTS and VITIC (the eTOX data warehouse).

MIP-DILI (call 3)

Drug-induced liver injury (DILI) ranks as the leading cause of liver failure and transplantation in western countries. However, predicting which drugs will prove toxic to the liver is extremely difficult, and often problems are not detected until a drug is already on the market. The IMI project MIP-DILI aims at developing new tests that will help researchers detect potential liver toxicity issues much earlier in development.

A major focus of MIP-DILI will be on a systematic and evidence-based evaluation of both

currently available and new laboratory test systems, including cultures of liver cells in one-dimensional and three dimensional configurations. The project will also develop models that take into account the natural differences between patients. Another strand of the project will develop computer models to unravel the complex, often inter-related mechanisms behind DILI.

Potential joint use case with Open PHACTS: once molecular mechanisms behind DILI have been identified, Open PHACTS could compile a list of compounds linked to the respective targets and pathways. Subsequent similarity and scaffold analysis might aid in the identification of new DILI alerts.

K4DD (call 4)

Currently, researchers spend a lot of time studying how strongly a potential drug binds with its target. However, less attention is given to the question of how long the drug remains bound to the target. Nevertheless, there is mounting evidence to suggest that the kinetics of the interaction between a drug and its target have a strong influence on the clinical success of a drug. For example, studies have shown that many recently marketed drugs have improved kinetic profiles. As drugs only work when they are bound to the target, the lifetime of the drug-target complex is key to the success of a drug.

By bringing together these diverse groups, K4DD is set to give a major boost to this important area of drug development. The first goal of the K4DD team is to enhance our understanding of binding kinetics. Ultimately, the project aims to develop a range of robust techniques, methods and models that could be easily incorporated into the drug development pathway and enable scientists and drug designers worldwide to reliably predict a molecule's kinetic properties (its 'kinotype').

Potential joint use case with Open PHACTS: for the targets selected by the K4DD consortium, an exhaustive analysis of the ligands linked to these targets available in the public domain, and later on also in the patent space, could be performed

eTRIKS (call 4)

Currently, every precompetitive translational study requires bespoke data management and analysis investments. This has resulted in significant and unnecessary individual project overheads and complex IP issues. As a consequence there have been delays in the sharing of translational data and know-how. Most importantly, there is now a substantial risk to the legacy of the transformational datasets being generated within IMI projects. Such a gap means wasteful, redundant translational research investments, and hinders the formation of a cohesive IMI informatics/KM community. The end result is a less than full realization of the potential of IMI projects to diminish bottlenecks in drug and diagnostic development and ultimately reduced pharmaceutical industry productivity.

The main objective of 'Delivering eTRIKS' is to address this gap by building a sustainable IMI translational research informatics/KM platform – eTRIKS, and to provide sustainable IMI KM services. The intent is to build a combined KM/analytics platform that can serve as a base for

continued development. A benchmark of success will be the establishment of a sustainable platform and service layer as well as a robust user and developer community.

Potential joint use case with Open PHACTS: given that there is a lot of shared interest in data standards, ontologies and vocabularies for drug, targets, biological entities, and disease, etc., joint work around the alignment of standards and ontologies should be undertaken to ensure that use cases and work flows are compatible, non-duplicative and interoperable. Exploring natural links through EFPIA partners engaged in both projects will be key, and also some alignment and complementarity of sustain approaches should be investigated.

ELF (call 5)

The European Lead Factory is a pan-European platform for drug discovery that is set to give a major boost to drug discovery in Europe. Comprising a collection of half a million compounds (derived from new public and existing private company collections) and a screening centre, the European Lead Factory will offer researchers in academia, small and medium-sized enterprises (SMEs) and patient organisations an unprecedented opportunity to advance medical research and develop new medicines.

The pharmaceutical companies in the consortium will contribute a total of over 300 000 compounds to the project to create a joint compound collection. To this will be added an estimated additional 200 000 novel compounds generated by public partner contributions during the project Proposals for novel compounds from the public partners will be submitted to a transparent selection and validation process addressing several criteria such as novelty, diversity potential, innovative design and synthetic tractability. Once approved, the SMEs together with the academic institutions will seamlessly translate the most compelling ideas into high quality compound libraries to be shipped to the consortium's HTS facilities.

Potential joint use case with Open PHACTS: despite the already established routine use of the Open PHACTS Discovery Platform for assessment of the proposals for chemical libraries, a potential joint use case could focus around the in depth analysis of a set of selected hits (or their main scaffolds) with respect to their potential target and pathway interaction profile. Open PHACTS could also assist in identifying/analysing frequent hitter and run similarity searches for ELF compounds across the public domain. Finally, Open PHACTS could assist in transferring some of the data generated by the ELF into the public domain.

Winning consortium of WEBAE (call 9)

WEBAE aims at mining social media for Adverse Drug Reactions (ADRs). This will add a new dimension to the current sources of information on the benefits and risks of medicines, which may have a considerable impact on human and computer resources of national competent agencies, pharmaceutical companies and EMA.

Potential joint use case with Open PHACTS: WEBAE is expected to provide information on ADRs which might be linked to drug-drug interactions. The Open PHACTS Discovery Platform could be used to unravel hitherto unknown drug-drug interactions on the molecular

basis by analyzing the target and pathway interaction profiles of the drugs. Special emphasis could be put on interactions at influx- and efflux transporter, such as ABC-transporter and OATPs, which are increasingly recognised as cause for severe DDIs.

3 Next Steps

In a next step, a workstream task will be generated within the Open PHACTS governance structure, and the respective IMI projects will be contacted in order to discuss the potential joint use cases. In case of agreement and availability of resources on both sides, the studies will be conducted. In case of success, joint publications are planned.