Deliverable D6.3

Project Title:	Developing an efficient e-infrastructure, standards and data-flow for metabolomics and its interface to biomedical and life science e-infrastructures in Europe and world-wide.	
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WP No.	6	
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WP leader:	Prof. Claudio Luchinat	CIRMMP
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Content

1. Executive summary 3
2. Project objectives 3
3. Detailed report on the deliverable 3
3.1 Background 3
3.2 Description of Work 4
3.3 Next steps 5
4 Publications 5
5 Delivery and schedule 6
6 Adjustments made 6
7 Efforts for this deliverable 6
Appendices 6
Background information 12
References 15

1. Executive summary

This deliverable aims at describing the grounds of interest of ESFRI infrastructures in the Biomedical Sciences for metabolomics that is shared with the BioMedBridges project. The involvement of BioMedBridges is relevant because it is a cluster initiative within which all ESFRI infrastructures in the Biomedical Sciences get together to identify common problems and bottlenecks, as well as to pursue common solutions to aspects of their activities that are mainly related to data management and sharing.

This frame provides an opportunity to enhance the usefulness of the COSMOS project for the current large-scale ESFRI infrastructures in the Biomedical Sciences as well as to improve the visibility and participation of COSMOS in the concertation activities and meetings related with the broader e-Infrastructures area.

A Joint consensus document between COSMOS and BioMedBridges has been produced and it is reported in the Appendix.

2. Project objectives

With this deliverable, the project has reached or the deliverable has contributed to the following objectives:

No.	Objective	Yes	No
1	Coordinate with the activities of BiomedBridges regarding the standardization of metabolomic data	x	
2	Gather requirements regarding the use of metabolomics data as a molecular phenotyping technique	x	
3	Integration between e-infrastructures	x	

3. Detailed report on the deliverable

3.1 Background

The aim of WP6 is to foster the interaction between COSMOS and the biomedical infrastructures with a particular interest in metabolomics (BBMRI, Elixir, EU-

Openscreen, EuroBioimaging, INSTRUCT, EATRIS, ECRIN, INFRAFRONTIER, MIRRI, EMBRC) that are also participating in the BioMedBridges project. The idea is to obtain indications useful to focus and prioritize the various activities in COSMOS in order to effectively respond to the needs of the current large scale EU biomedical infrastructures.

3.2 Description of Work

The interactions with BioMedBridges partners, especially on the occasion of the last Annual General Meeting of BioMedBridges (Florence, March 2014), highlighted the wide range of opportunities to exploit metabolomics data in the context of biomedicine. The Joint Consensus document reported in the Appendix provides an overview of how metabolomics can be relevant for ESFRI infrastructures in Biomedical Sciences (BMS RIs hereafter) that are involved in BioMedBridges. That document has been developed in cooperation with the BioMedBridges initiative and the representatives of the RIs has been involved in the drafting phase. It constitute a strong expression of interest and it has released in agreement with the BioMedBridges Steering Committee.

The document is based on D6.1, where metabolomics was described as crucially relevant to the following BMS RIs:

- BBMRI
- ELIXIR
- Euro-BioImaging
- Eu-OpenScreen
- INSTRUCT

In addition, potential applications involving EATRIS, ECRIN, INFRAFRONTIER, MIRRI, EMBRC and ISBE are also reported.

The interaction with BBMRI has been also extensively addressed within Deliverable 6.2. In fact, the usefulness of metabolomics for biobanking is well documented in the scientific literature[1]–[9] An initiative is ongoing to formally establish an expert center of metabolomics within BBMRI-ERIC.

A crucial point identified to foster the full exploitation of metabolomics techniques by BMS RIs was the lack of a tool that could handle the different data produced at these infrastructures, as well as metabolomics data, and analyze them to produce statistically relevant conclusions. One such tool has now been developed, with partial support also by the COSMOS project, called KODAMA [10]. KODAMA implements an innovative method to extract new knowledge from noisy and high-dimensional data. A crucial feature is that it has an integrated procedure of validation of the results through maximization of cross-validated accuracy. In many cases, this method performs better than existing feature extraction methods and offers a general framework for analyzing any kind of complex data in a broad range of sciences (from genomics and metabolomics to astronomy and linguistics). KODAMA thus relieves an important bottleneck for a wider usage of metabolomics, compound screening and imaging techniques, in an integrated fashion. The availability of this new tool enables closer scientific collaboration and will permit innovative applications in fields such as screening for multimodal / polypharmacology leads and chemical genetic studies. The development of KODAMA is perfectly integrated in the activities of COSMOS and this tools can be used, e.g. to analyze in an innovative way the metabolomics datasets deposited in Metabolights database.

3.3 Next steps

We are seeking to crystallize the extensive portfolio of opportunities for scientific collaboration into well-defined initiative(s), especially in the context of the first calls for proposals in the Horizon2020 program.

An update to the Joint Consensus document will be released by the end of the third project year.

4 Publications

N/A

5 Delivery and schedule

The delivery is delayed: ☐ Yes ☑ No

6 Adjustments made

This deliverable has been changed and resubmitted in order to include the Joint Consensus document.

7 Efforts for this deliverable

Institute	Person-months (PM)		Period
	actual	estimated	
CIRMMP	5	5	
EMBL-EBI	1	1	
Total	6		

Appendices

Joint consensus document between COSMOS and BioMedBridges

COSMOS (COordination of Standards in MetabOlomicS, http://www.cosmos-fp7.eu/) is a consortium of leading European groups in metabolomics which aims at developing and improving common standards to describe, exchange and query

both NMR metabolomics data and experimental metadata (e.g. source of study materials, technology and measurement types, sample-to-data relationships). This will guarantee that the NMR-metabolomics data will be stored, distributed, and managed according to well-established standards at the European level.

Specifically, COSMOS aims at ensuring that metabolomics data will be:

i) encoded in open standards to allow barrier-free and wide-spread analysis

ii) tagged with a community-agreed, complete set of metadata (minimum information standard)

iii) supported by a communally developed set of open source data management and capturing tools

iv) disseminated in open-access databases adhering to the above standards

v) supported by vendors and publishers, who require deposition upon publication

vi) properly interfaced with data in other biomedical and life-science e-infrastructures.

BioMedBridges (http://www.biomedbridges.eu/) is a joint effort of twelve biomedical sciences research infrastructures on the ESFRI roadmap. Together, the project partners will develop the shared e-infrastructure to allow interoperability between data and services in the biological, medical, translational and clinical domains and thus strengthen biomedical resources in Europe. The main aim of BioMedBridges is to build “bridges” between different sources and types of data.

Metabolomics is one of the latest -omics sciences and there is a growing interest for its application in prognosis, diagnosis, patient stratification and personalized medicine. For this reason, biomedical research infrastructures are strongly interested in the development of this technology. Because metabolomics is multidisciplinary in nature, it could rapidly become an “experimental bridge” between the different communities served by the research infrastructures. To

achieve this, a strong requirement is that any methodology deployed can be applied in the various biomedical contexts with little or no modification. In this sense, the COSMOS project represents an extremely successful ongoing effort, and BioMedBridges is instrumental in providing knowledge on how to harmonize data and metadata produced by users of the biomedical research infrastructures.

Regarding the individual infrastructures involved in BioMedBridges, metabolomics can be considered extremely relevant to, in particular, BBMRI-ERIC, ELIXIR, Euro-BioImaging, EU-OPENSCREEN, INSTRUCT, EATRIS, ECRIN and EMBRC.

The robustness of a metabolomic study relies on the availability of large sets of high quality samples. This creates an obvious link between metabolomics and biobanks: biobanks are sources of samples and associated data; metabolomics may provide a sensitive tool to assess degradation phenomena as intactness of the metabolome is a good indicator of the quality of stored materials. In terms of analytical platforms, NMR-based metabolomics may be preferred to mass spectrometry for this type of evaluation studies because it requires only minimal if no sample handling and is highly reproducible and fast, although able to detect only the most concentrated metabolites, i.e. only a few tens of molecules. The use of NMR profiles as further data to be associated to stored biological samples to assess their quality and to evaluate the impact of pre-analytical treatments can be an important added value for biobanks. Metabolomics may also provide a direct approach to monitoring the performance of different storage conditions on the molecular profiles of different types of samples. Nevertheless, systematic studies on large sets of samples are still lacking and, in particular, no precise data exist on the “shelf-life time” of samples stored in biobanks. Metabolomics may become an efficient means to fill this gap. Emphasis should be given to the fact that successful molecular analysis not only depends on the quality of the clinical data but also on the availability of the information on sample history: collection and handling times and temperatures should be carefully annotated and become part of the associated dataset. Inclusion of metabolomic profiles in the biobank databases would be a useful addition to assess sample quality and history. To take up advantage of the above opportunities for the development of

metabolomics as a crucial technique to flank the development of standard operating procedures and quality control in biobanks, an Expert Center for Metabolomics (EXCEMET) has been formally established (http://www.excemet.org/). EXCEMET proposes itself as a reference infrastructure for biobanks and has been described as a model of a BBMRI-ERIC Expert Center1. EXCEMET has been established as a not-for-profit public-private-partnership based on a consortium agreement between participants from academia and industry. The involvement of the Medical University of Graz, with a research unit lead by Prof. Kurt Zatloukal, who coordinated the preparatory phase of the European biobanking and biomolecular research infrastructure (BBMRI) during the 7th EU framework programme, testifies the close links that have been established between the metabolomics and the biobanking community. Prof. Zatloukal is also member of the Advisory Board of COSMOS.

BioMedBridges is providing a framework for the harmonization of metadata. This will involve ELIXIR (the European Life-sciences Infrastructure for biological Information) as the main submission hub for public release of data generated at the research infrastructures. ELIXIR is an infrastructure that will allow life science laboratories across Europe to share and store their research data as part of an organised network. Its goal is to bring together Europe's laboratories and data centres to help coordinate the collection, quality control and storage of large amounts of biological data produced by life science experiments. ELIXIR aims to ensure that biological data is integrated into a coordinated system in which all parts of the scientific community can access existing research easily. MetaboLights2, the only public repository for metabolomics data in Europe, is located at the European Bioinformatics Institute (EMBL-EBI) which is linked to ELIXIR as one of its Nodes.

Beside biological fluids, metabolomic profiles can be acquired on tumor biopsies. Metabolomics on biopsies, in general, allows for a more detailed fingerprinting of the tumor metabolism, while the systemic biofluids allow for the

[1] Gert-Jan B van Ommen et al. (2014) BBMRI-ERIC as a resource for pharmaceutical and life science industries: the development of biobank-based Expert Centres. European Journal of Human Genetics doi:10.1038/ejhg.2014.235
[2] http://www.ebi.ac.uk/metabolights/

study of the tumor–host interactions. An integration of this information with in vivo imaging data, especially NMR-based metabolomics with NMR-based imaging, could improve the translation of basic science to the clinical practice. These two worlds are going to communicate even more in the future, so there is a need for adopting common standards and ontologies in order to make the analysis of metabolomics data acquired with either technique faster and simpler and to enhance the interoperability of both platforms. Euro-BioImaging is a pan-European infrastructure whose mission is to build a distributed imaging infrastructure across Europe that will provide open access to innovative biological and medical imaging technologies for European researchers and it could play a crucial role in the interoperability of imaging and metabolomics.

Toxicology is another expanding field of research for metabolomics. Profiles of urine and serum of patients that have been treated with drugs in clinical trials may contribute to the prediction of efficacy and/or toxicity of the treatment, and provide hints about the underlying biochemical mechanisms. EU-OPENSCREEN would thus highly benefit from the development of consistent procedures to collect, store, interpret and report metabolomic data. Because of its conceptual and technical overlap with many aspects of pharmaceutical research, metabolomics is finding applications that span almost the full length of the drug discovery and development pipeline. Metabolomics can be used to facilitate lead compound discovery, to improve biomarker identification (for monitoring disease status and drug efficacy), to monitor drug metabolism and toxicity, to facilitate clinical trial testing and to improve post-approval drug monitoring. At the two extreme points of the development pipeline, metabolomics could complement both preclinical studies, monitoring the systemic effects of the drug candidates on treated mouse models, and phase 4 postmarketing surveillance, helping to clarify the molecular mechanisms of adverse effects onset. Metabolomics potentially offers drug researchers and drug regulators an effective, inexpensive route to addressing many of the riskier or more expensive issues associated with the discovery, development and monitoring of drugs.

Metabolomics on intact cells or on cell extracts can help structural biologists to understand how structural changes in the three-dimensional organization of a

protein at the atomic level dynamically affect its function, and how this function is reflected on variations in the metabolism of the cell. In this respect, INSTRUCT will benefit from new methods to characterize the cellular metabolome in a time-dependent manner and as a function of external stimuli. Parallel studies of protein structures in cells and cell metabolism may open new exciting perspectives for the mechanistic systems biology approach: the atomic view can be complemented by metabolomics as a tool to characterize and quantify small molecules in a biological sample, and the two views will help to connect molecular events at the cellular level to those occurring at the systemic level.

Personalized medicine is a topic of interest to various infrastructures, especially for EATRIS and ECRIN, in particular regarding the effects of dietary intake on the individual metabolome. There are sound indications that the metabolomic assessment of controlled dietary interventions may result in better evaluation of a research subject's diet than traditional observational data. These aspects can be readily extended to the analysis of patients' response to pharmaceutical and/or surgical treatments. This warrants the deployment of metabolomics as a tool to flank clinical trials and translational medicine efforts to obtain deeper insight as well as better predictive power for the outcome of treatments. Notably, this is a different area of application of metabolomics with respect to its relatively common involvement in the discovery/validation of biomarkers.

Closely related to the above concepts is the application of metabolomics within the context of translational studies on mouse models of diseases, again ranging from the identification and validation of biomarkers to the analysis of the response to diet and pharmacological treatment. Within this frame, some related applications may become interesting also for INFRAFRONTIER and MIRRI.

The genetic, taxonomic and ecosystem diversities in the marine environment far outweigh those of the terrestrial environment and as access to marine biological resources improves, marine biodiversity is increasingly becoming a focus for diverse fields of fundamental and applied research. The EMBRC infrastructure promotes the use of state-of-the-art metabolomic techniques in the study of emerging-model and non-model marine organisms in order to develop a

more comprehensive understanding of the novel biology of these organisms and impacts of environmental change on this diversity. Marine metabolomics is also of significant interest for applications in marine bioprospecting and marine biotechnology. In this context, EMBRC fully supports the COSMOS initiative for development of common standards to collect, manage, and interpret metabolomic data.

Systems biology, defined as the computational and mathematical modeling of complex biological systems requires significantly more multidisciplinary facilities than are typically present in any single institute. For this reason ISBE (Infrastructure for Systems Biology – Europe), was created as a large-scale European research infrastructure designed to tackle the grand challenge of developing a systematic understanding of complex biological processes in living organisms. ISBE recognizes that metabolomics is a key technology for systems biology: metabolites are system variables that can be used to model the dynamics of biological systems. The generation of metabolomic data for modeling and data integration purposes should be well harmonized with ISBE standard development and can contribute to the application of metabolomics to e.g. personalized medicine, in conjunction with EATRIS and ECRIN.

In light of what is stated in the present document, and in order to make more effective use of metabolomics in biomedical research, BioMedBridges, on behalf of the research infrastructures involved in the project, expresses strong interest in metabolomics and will help ease its adoption in the biomedical community. COSMOS and BioMedBridges agree on the emerging role of this technology in biomedical research and stress the need for further efforts in developing common standards and procedures to harmonize both experimental procedures and the data and metadata produced in metabolomics.

Background information

This deliverable relates to WP6; background information on this WP as originally indicated in the description of work (DoW) is included below.

WP6 Title: Coordination with BioMedBridges and biomedical ESFRI infrastructures

Lead: Claudio Luchinat
Participants: EBI-EMBL, LU-NMLC, CIRMMP, UOXF

This work package aims at maximizing communications with BioMedBridges and with its partner BMS infrastructures with an interest in metabolomics (Elixir, EU-Openscreen, BBMRI and Instruct), and helping steer the work of the other work packages to maximize the usefulness of the COSMOS activity for the current large scale EU biomedical infrastructures. The COSMOS consortium will actively participate in the concertation activities and meetings related with the e-Infrastructures area. We will help to optimise synergies between projects by providing input and receiving feedback from working groups addressing activities of common interest (e.g. from clusters and projects). If requested we will offer advice and guidance and be receptive for any information relating to 7th Framework programme implementation, standardisation, policy and regulatory, EU Member States initiatives or relevant international initiative.
Description of work and role

Work package number	WP6	**Start date or starting event:**	month 1
Work package title	Coordination with BioMedBridges and biomedical ESFRI infrastructures		
Activity Type	COORD		

Participant number	1: EMBL/EBI	2: LU/NMC	10:CIRMMP	14: UOXF				
Person-months per participant	6	2	12	2				

Objectives

1. maximizing communications with BMS infrastructures with an interest in metabolomics
2. helping steer the work of the other work packages to maximize the usefulness of the COSMOS activity for the current large scale EU biomedical infrastructures.

Description of work and role of participants

Task 1: Gather metabolomics requirements for BioMedBridges, BBMRI, ELIXIR and EU-OPENSCREEN CIRMMP will coordinate the gathering of requirements regarding the use of metabolomics data as a molecular phenotyping technique with the above-mentioned e-infrastructures. The University of Florence as a third party of CIRMMP will contribute to this task. EBI as coordinator of ELIXIR, BioMedBridges and responsible for database and standards development in EU – OPENSCREEN will contribute use cases from its on-going integration efforts.

UOX is leading the development of the ISA infrastructure, which assists in the annotation, and local management of experimental metadata from high-throughput studies employing one or a combination of omics and other technologies, and will work toward integrating the findings from Task 1 in the ISA development.

Task 2: Coordinate with the activities of BioMedBridges regarding the standardization of metabolomics data WP 7 of the BioMedBridges grant will work in particular on NMR metabolomics data and towards a standardized description of sample donors, sample collection; pre-processing, analysis and evaluation will be established as a prerequisite for the inter-species comparison of metabolomics results. In this task all contributors to this task will ensure the appropriate coordination of the developments in WP2 of COSMOS and WP7 of BioMedBridges.

Task 3: Coordinate the activities of COSMOS versus the needs of Biobanks with respect to the association of NMR profiles to stored samples. The primary objective of biobanks is not merely archiving, but also distributing conserved and documented biological samples for research, and so they represent an irreplaceable support for all those studies in which the impact of the results is linked to the large number of the collected samples. The quality of stored biological samples is crucial for the outcome of subsequent studies. The molecules constituting the metabolic fingerprint are generally very sensitive to handling procedures and storage conditions, so metabolomics is a useful tool for checking and assessing the quality of stored samples. The NMR profile of a sample allows its evaluation in entrance (to decide its acceptance) and in exit (to decide if it is still good to be distributed), so it is important to associate each stored sample to the respective NMR metabolic profile. The aim of this task is to coordinate the activities of COSMOS, taking into account the requirements of Biobanks with respect to the association of NMR metabolic profiles to stored samples. BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) was one of the first European Research Infrastructure projects funded by the European Commission (EC). The EC-funded preparatory phase of BBMRI came to its end in January 2011. During the past 3 years BBMRI has grown into a 53-member consortium with over 280 associated organisations (largely biobanks) from over 30 countries, making it the largest research infrastructure project in Europe (http://www.bbmri.eu/). In this task we will interface with BBMRI and develop a strategy for the use of Metabolomics for Biobank sample monitoring and deposition of the sample status data in COSMOS partner databases.

Deliverables

No.	Name	Due month
D6.1	Document describing requirements for relevant biomedical infrastructures with regard to Metabolomics	6
D6.2	Establishment of an NMR metabolomics working group between COSMOS and BioMedBridges	12
D6.3	Joint consensus document between COSMOS and BioMedBridges	18

D6.4	Joint consensus document between COSMOS and BioMedBridges (Updated)	36
D6.5	Report on the recommendations of the use of Metabolomics of Biobank sample monitoring	24

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