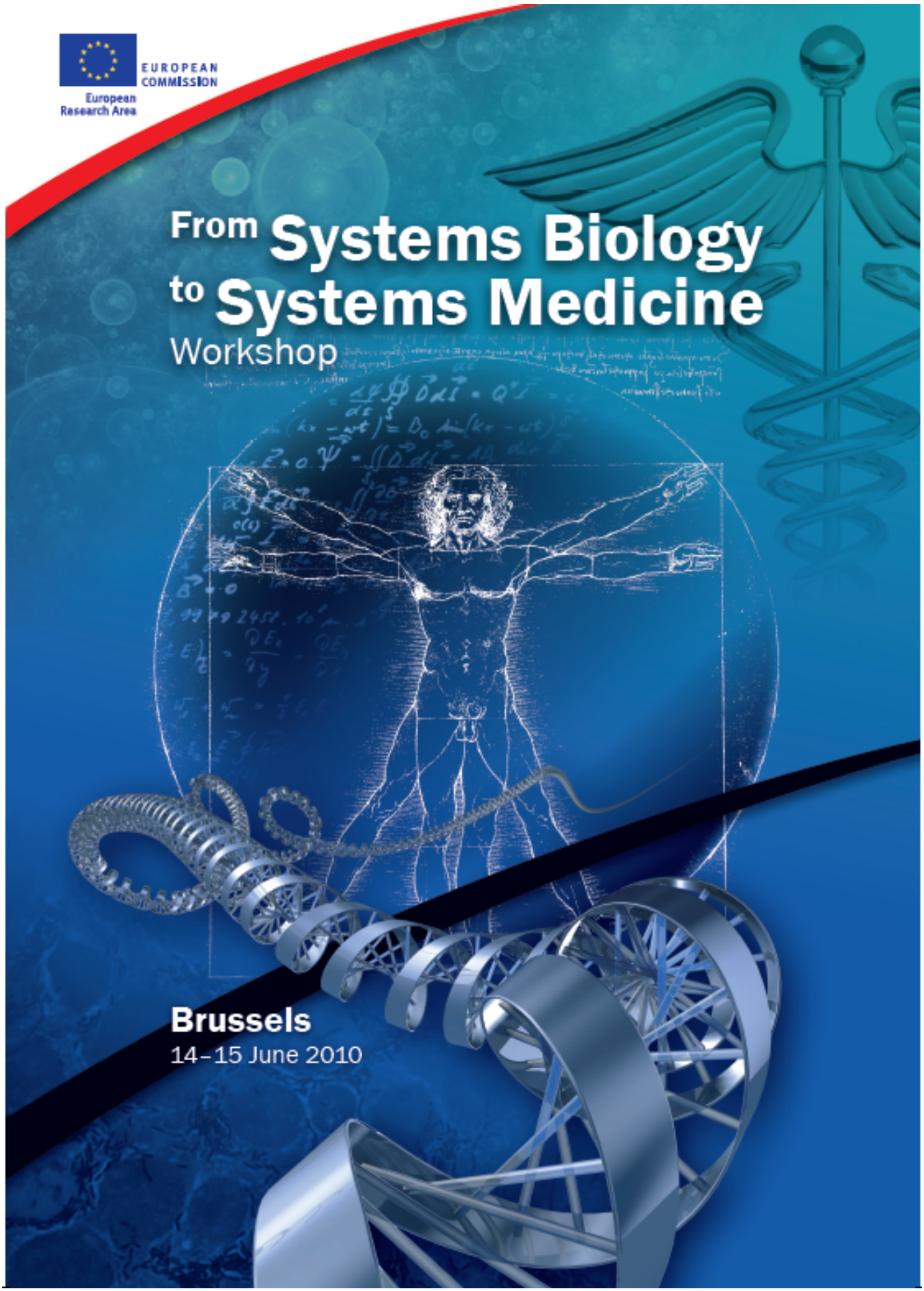
EUROPEAN COMMISSION

European Research Area

From Systems Biology to Systems Medicine

Workshop



Brussels

14–15 June 2010

REPORT ON

EUROPEAN COMMISSION, DG RESEARCH, DIRECTORATE OF HEALTH

WORKSHOP:

"FROM SYSTEMS BIOLOGY TO SYSTEMS MEDICINE"

Brussels, 14-15 June 2010

Workshop participants (in alphabetical order)

Charles Auffray, Rudi Balling, Mikael Benson, Michela Bertero, Helen Byrne, Marta Cascante, Morten Colding-Jörgensen, Edwin De Pauw, Leonardo M. Fabbri , Tom Foulkes, Igor Goryanin, David Harrison*, Adriano Henney*, Arnd Hoeveler, Francois Iris, Christina Kyriakopoulou**, Ursula Klingmüller ,Walter Kolch*, Riitta Lahesmaa, Thomas Lemberger, Francis Lévi, Hella Lichtenberg, Vincent Lotteau, Bernd Mayer, Antoine Mialhe**, Bernard Mulligan**, Damjana Rozman, Gerard Siest, Jonathan Swinton, Marius Ueffing, Leonard Van den Berg, Peter Wellstead, Olaf Wolkenhauer***

* Session chairs
** European Commission staff

Reports editors:
Christina Kyriakopoulou
Bernard Mulligan

Full information on the workshop can be found at:
http://ec.europa.eu/research/health/past-events_en.html

Workshop executive summary

The workshop "From Systems Biology to Systems Medicine" was organized by the European Commission, Directorate of Health and its aims were: (i) to analyze the state-of-the-art of systems biology for medical applications (ii) to identify key opportunities and bottlenecks for the translation of systems biology to medicine and the clinic and (iii) to identify key research and policy areas for European collaborative research in order to make systems medicine a reality.

"Systems medicine" is the application of systems biology approaches to medical research and medical practice. Its objective is to integrate a variety of biological/medical data at all *relevant l*evels of cellular *organization* using the power of computational and mathematical modelling, to enable understanding of the pathophysiological mechanisms, prognosis, diagnosis and treatment of disease.

The clinical needs should be the driver for the applications of systems biology approaches in medicine and for the development of the necessary new technologies. The following list summarises some potential actions:

- Clinical trials - systems biology approaches could guide clinical trial design, shortening times and costs
- Re-definition of clinical phenotypes based on molecular and dynamic parameters
- Discovery of effective biomarkers of multiple nature for disease progression (clinically useful for risk, prognosis, diagnosis)
- Combinatorial therapy (this approach would be useful to find out a combination and lower doses of effective drugs, in particular in the case of co-morbidity, where more than one disease is affecting the patient)
- Improvement of drug development (optimized drug efficacy, safety and delivery, timing and dosage of therapy)
- The healthy individual to be addressed in the long term

Strategic scientific areas for European collaboration in Systems Medicine could include:

- Understanding the pathophysiology of chronic diseases, multifactorial diseases (cancer, diabetes, obesity, metabolic disorders, aging …), through network analysis of disease processes, and the identification of biomarkers for early diagnosis and prognosis and personalized treatment
- Combinatorial therapies and combinatorial drug screening
- Integration of personalized genomics with personalized metabolomics, endocrinomics, proteomics and clinical phenotyping

The major challenge is for systems biology to contribute to a change in the medical paradigm in order to build the foundation for a prospective medicine that will be predictive, personalized, preventive and participatory.

In order for systems medicine to become a reality, the community must build a coordinated vision of all relevant stakeholders and a road-map at the same level of ambition as the Human Genome project. In addition, the creation of a strong networking effort among funded systems biology projects is essential, in order to share information/resources on successful methodological approaches and tools with the broader systems biology and clinical community.

Annex I- Workshop complete report

Concept of the workshop

Recent years have seen the rapid emergence of systems biology as a new discipline. In the biomedical sciences this trend is very apparent as research moves from a reductionist approach to a "*systems understanding*" paradigm that attempts to understand biology and pathophysiology in an integrative manner, making use of the rapidly increasing amounts of novel (-omics) data and other relevant quantitative biological/medical data that are becoming available.

However, despite the spectacular advances in the post-genomic era, there exists a chasm between experimental data and medical knowledge, and even a greater gap exists when we evaluate "new knowledge" in terms of clinical utility and benefit to patients. As a result, despite major technological advances, there are still obstacles that separate systems biology from medical applications. Systems medicine, a newly emerging area, has as its aim the bridging of this gap.

The workshop "From Systems Biology to Systems Medicine" was organized by the European Commission, Directorate of Health, Directorate General for Research, in Brussels on 14-15 June 2010. Experts in a wide range of relevant disciplines from clinical, diagnostics and pharmaceutical areas, to high throughput
–omics technologies, and computational and systems biology, including representatives from academia, industry, and funding agencies got together to explore opportunities and challenges for the development of systems medicine.

The aims of the workshop were: (i) to analyze the state-of-the-art of systems biology for medical applications (ii) to identify key opportunities and bottlenecks for the translation of systems biology to medicine and the clinic and (iii) to identify key research and policy areas for European collaborative research in the short, medium and long term in order to make systems medicine a reality.
The workshop was organized in different sessions. Before the workshop, by means of a short free text questionnaire (see appendix I), the participants were asked to identify key areas for action.
The main points of the discussions are described in the following paragraphs.

State-of-the-art of Systems Biology applications in Medicine

The following Definition of Systems Medicine was discussed:

"Systems medicine" is the application of systems biology approaches to medical research and medical practice. Its objective is to integrate a variety of biological/medical data at all *relevant l*evels of cellular *organization* using the power of computational and mathematical modelling, to enable understanding of the pathophysiological mechanisms, prognosis, diagnosis and treatment of disease.

Three short talks were presented illustrating case studies of systems biology approaches of benefit to medicine on:

- Identification of preliminary circadian biomarkers for more efficient and personalised drug treatments in cancer patients

- mechanistic insights into CJD and identification of new therapies for more effective treatment of psychiatric disorders
- Understanding of energy metabolism in Parkinson's disease and modelling of risk factors and better understanding the pathology

It was emphasized that the major challenge is how systems biology can contribute to changing the medical paradigm in order to build the foundation for a prospective medicine that will be predictive, personalized, preventive and participatory.

This workshop considered the state of the art in systems biology approaches to tackle health and disease relevant research questions. There was a general consensus that currently there exists substantial detailed information (data) on single biological entities associated with or linked to complex diseases. We can understand single components and, possibly for several of them, their function, but these are only parts of a complex system. Systems biology approaches have so far been successful in plants, animal, cellular models.

Studies are accumulating on interacting network analysis of basic biological mechanisms, as well as on analysis of cell-cell interactions to understand behaviour of cell populations. The applications of systems biology approaches are already delivering computational and mathematical models of basic biological pathways related to diseases in-vivo in animal models. The technology and tools, in particularly high-throughput methods for genome-wide analysis are now available to apply systems biology in humans/patients. Major and chronic diseases are multifactorial in nature and reductionist biology will not provide solutions. Human disease can be perceived as perturbations of complex, integrated genetic, molecular and cellular networks. Such complexity necessitates the power of mathematical modelling in predicting a systems response in health and disease. In the future, the applications of systems biology approaches would permit a comprehensive evaluation of underlying predisposition to disease, disease diagnosis and progression.

The discussion continued on some of the challenges ahead if systems biology would be applied to medicine. Success stories for medical applications are starting to appear in the literature. The first examples are at the edge of moving into clinical applications; some examples include: EGF-receptor system stratification in breast cancer; heart modelling – approval by FDA of the use of a model to test new cardiac drugs; Entelos has created "virtual asthma patients"; a model of CJD explaining the pathogenesis and disease progression, suggesting novel and more effective treatments *for psychiatric disorders*; chronobiological modelling of drug effects that could improve the efficacy of cancer chemotherapy. It was concluded that high quality and conclusive systems biology studies of human clinical samples are still rare and that a concrete impact of systems biology applications for patients is still to be proven.

Several areas, e.g. drug discovery, were discussed where systems biology approaches would bring an important contribution as a paradigm for understanding complexity. Despite the extraordinary advances in biomedical research over the past decade, the positive effect of these efforts on drug discovery and the identification of novel, more effective therapies have been limited, possibly because of the inability to visualize the complexity of biological systems. There is little or no information on cellular/ system interactions and there is a necessity to understand target response within physiological networks and not in isolation. A vast amount of data is being generated from clinical trials and from individual patients and it is becoming increasingly difficult to piece together this data and to maximise its content. **Systems medicine should provide a framework within which such disparate data can be integrated, so that medicine will move from a "*guess & pray*" mentality to "*predict & test*" strategies.** Big Pharma has also gradually started to incorporate systems biology approaches to create molecular models of disease and drug action.

However, it is necessary that systems biology efforts in Europe and world-wide deliver solid experimental evidence with clear added value and societal benefit. An important ingredient for developing Systems Medicine is *coordination* – a coordinated approach, across disciplines, and across academia and industry and all the relevant stakeholders. Furthermore, the systems biology community should make best efforts to communicate correctly its goals to the general public and to policy makers, remaining ambitious, but pragmatic and tangible and not overpromising what might be achieved, while considering all potential ethical aspects.

During the common discussion, participants agreed that challenges in systems biology and its future applications in medicine will require:

- **The coordination** of efforts of all relevant actors to take the first steps towards systems medicine and make a paradigm shift in classical medicine. The endeavour should have a scale of ambition and vision similar to that of the Human Genome project.
- The creation of a strong networking effort among the funded systems biology projects, in order to share information/resources on successful methodological approaches and tools with the broader systems biology and clinical community; there is a need to build on already existing systems biology initiatives without re-inventing.
- The establishment of proof-of-concept for medical applications in order to attract industry into the area.
- **Most importantly, the relevant clinical needs should be the driving force to pave the way for systems medicine**

Analysis of Systems Biology/Systems Medicine landscape (identifying the opportunities, bottlenecks and technology development needs)

The importance of formulating the right questions in systems biology was stressed. Systems biology is neither data gathering, nor solely predictive modelling but about a 'systems' understanding of biological systems in health and disease. The challenge is integration of complex data, across time, space and different organizational levels, without forgetting interactions with the external environment. Also fundamental is comparison across different experimental systems.

A short overview considered the novel technologies that have enabled systems biology: from -omics that detail our genome, transcriptome, metabolome and proteome to advanced imaging techniques in biology and medicine. The challenge lies now in transforming the data produced by the new technologies into novel knowledge in biological and medical sciences. This can be achieved by common questions that need to be formulated together by researchers and medical doctors. Short and long term goals need to be addressed.

During the common discussion, the participants were asked to identify opportunities for the future and the barriers/bottlenecks for systems medicine to become a reality in Europe.

Opportunities in Systems Medicine

- Elucidation of the pathophysiological mechanisms of multifactorial/chronic diseases
- Drug discovery; opening new avenues in combinatorial therapies; targeted therapies; predictive toxicology and safety

- Alternative approaches to test effective treatment (via improved computational and mathematical model-based treatment and better designed/ and optimized clinical studies)
- Better diagnostics
- Improvement of patient profiling (evaluation of human individual variation via computational and mathematical models, to enable refined patient stratification and personalized medicine;, and particularly patient stratification after treatment to understand failed trials)

The participants emphasized that systems medicine is expected to have a strong impact on healthcare costs and future economic benefits to pharma/industry due to rapid drug development. Europe is already a world force in systems biology research, which could facilitate its future leading role in the area of systems medicine.

The participants recognized that **training of the next generation of researchers** and education would be a key component in any successful systems biology/systems medicine programme. Europe should not miss the opportunity to implement multidisciplinary training for the next generation of scientists and medical doctors. Training needs to include multiple disciplines, from biology and medicine to mathematics, physics, and engineering. Summer schools and "exploratory" fellowships could represent simple tools towards this goal. In the UK, MRC is already supporting "discipline hopping" through fellowship schemes that enable scientists and clinicians to do research in fields different from their own.

Bottlenecks for the development of Systems Medicine

- A lot of scientific hypotheses are generated via computational and mathematical methods but there is need for testing and validation
- Modelling should to be associated strongly with the direct experimentation and clinical reality
- Need for development of multilevel modelling, across space and different organizational levels of cell/tissue/organ architecture
- Technology and methodological tools need further development to collect necessary data for model validation in a clinical context
- The access to clinical samples linked to detailed clinical and medical data
- Lack of multidisciplinary infrastructure (under one roof-one common vision).
- Need to have major funding effort at the same time in many areas in order to make Systems medicine a reality and to have a paradigm shift in medicine
- Lack of large-scale truly integrated research programmes in biomedical research

In terms of technologies, experts identified specific areas which should be further developed, which are summarized in the following paragraph.

Needs for key tools/technologies/ methodologies

- Combinations of state-of-the-art high-throughput –omics technologies, medium throughput technologies (proteomics, metabolomics), high-throughput quantitative single-cell analysis
- Biosensors and portable monitoring devices for multiple biological functions and miniaturized automated and fast molecular profiling devices
- Non-invasive imaging whole-body dynamic measurements technologies and in-vivo dynamic & quantitative clinical-relevant measurements at the cellular/tissue/organ level

- Development of validated computational and mathematical models for the clinical setting; for linking population level data from clinical trials with more detailed information from individual patients; computational and mathematical tools/methods for integration of different data types, for dynamic relationships, for cellular and tissue architecture, including multilevel modelling

Infrastructures & Technologies

Participants supported the need for specific infrastructures to enable systems medicine and the following ideas were recommended:

- Platforms for long term data storage are required as well as platforms for integration/analysis of multi-parameter data from patients.
- Secure data storage facilities, allowing controlled sharing of clinical data, medical records and molecular profiling data
- Standardisation of methodologies
- Technology platforms for –omics at reasonable cost
- Basic and clinical facilities effectively sharing material, space and human resources- the translational structure, a "European Virtual Institute for Systems Medicine"

The way forward

Funding agencies strategies

The workshop included a “Funders’ session,” where the current activities and plans in systems biology/medicine were presented by three funding agencies: EC, BMBF and MRC.

The EU is a world force in the area of systems biology and its applications and has committed over € 420M for research, training and infrastructure in the field from 2004 – 2010 in the context of the multinational, collaborative health research activities under the 6th and 7th Framework Programmes (FP6 & FP7).
The results in the systems biology area of the last EU Health call in were presented. The selected projects have an applied aspect to health and disease. Different funding instruments were illustrated, from the large high impact research initiatives, to infrastructures, public-private partnerships, and the more focused ERANETs.

The German (BMBF) Virtual Liver programme was presented; this is one of the largest initiatives in medically related systems biology involving 70 groups and funding of 43 million Euros.

The UK MRC is applying an “all inclusive model” to funding systems biology, funding larger and smaller projects. One observation is that “boutique” (focused) approaches seem to work more efficiently. Main success stories are driven by interesting questions. One barrier remains - communication between mathematicians and clinicians and biologists. One challenge is how to move to larger, higher impact initiatives.

During the common discussion, the participants were asked to identify the main strategic research and policy areas, such as research needs for the benefit of industry and SMEs, and for international

cooperation, that would need to be addressed through a European collaborative approach, for systems medicine to become a reality in Europe.

Strategic scientific areas in Systems Medicine for European collaboration in short, medium, long term

- Understanding the pathophysiology of chronic diseases, multifactorial diseases (cancer, diabetes, obesity, metabolic disorders, aging …), via the implementation of disease network analysis, and the identification of biomarkers for early diagnosis and prognosis and personalized medication in any complex disease
- Combinatorial therapies and combinatorial drug screening
- Integration of personalized genomics with personalized metabolomics, endocrinomics, proteomics and clinical phenotyping
- European collaborative projects should be based on clinical samples, involve clinicians and present realistic plans to identify markers whose clinical utility can be demonstrated at the end of the project.

Other policy actions to be taken to develop the field of Systems Medicine

- Establishment of a road map for research for systems medicine in Europe, with consultation across Europe, accompanied by short articles in a range of journals that will target all potential stakeholders
- Organization of focused workshops identified by discipline and/or application area
- Need for actions to overcome disparate national legal and ethical regulations concerning patients' data
- Actions that sponsor the creation of systems medicine research programmes in reference hospitals
- Media campaigns to engage the general public and dissemination
- Need for actions to expand systems biology from the borders of the basic biology and the mathematical communities into the medical/clinical world

Areas for international collaboration

- Establish standards for collecting, curating and pooling data
- Establish databases of validated computational and mathematical models

Research opportunities for SMEs in Systems Medicine

- Development of computational and mathematical modelling tools
- New technologies and instrumentation development: miniaturization and automation
- Identification of novel biomarkers and drug screening
- Drug development and drug screening
- Methods for quick validation of target genes
- European projects with clear deliverables for the clinic/patient ought to be attractive to SMEs

Research opportunities for Industries/Pharma in Systems Medicine

- Computational and mathematical tools to predict drugs effects and side-effects (especially toxicity)
- Predictable computational and mathematical models that guide the rational development of novel therapeutic strategies
- Personalized medications and understanding individual variations in drug responses
- Biomarkers and drug screening
- Success stories of examples where systems biology has led to the improvement of drug development process in terms of reducing times and cost
- An EU programme that focuses on collaboration between academia, industry and health authorities will be attractive to industry

Building a Vision and a Road-Map for Systems Medicine in Europe

The participants agreed that in order Systems Medicine to become a reality, the community has to build a coordinated vision and a road-map at the same level of ambition as the Human Genome project.

There was a consensus during the workshop discussions that the complexity of questions addressed in systems medicine makes it necessary:

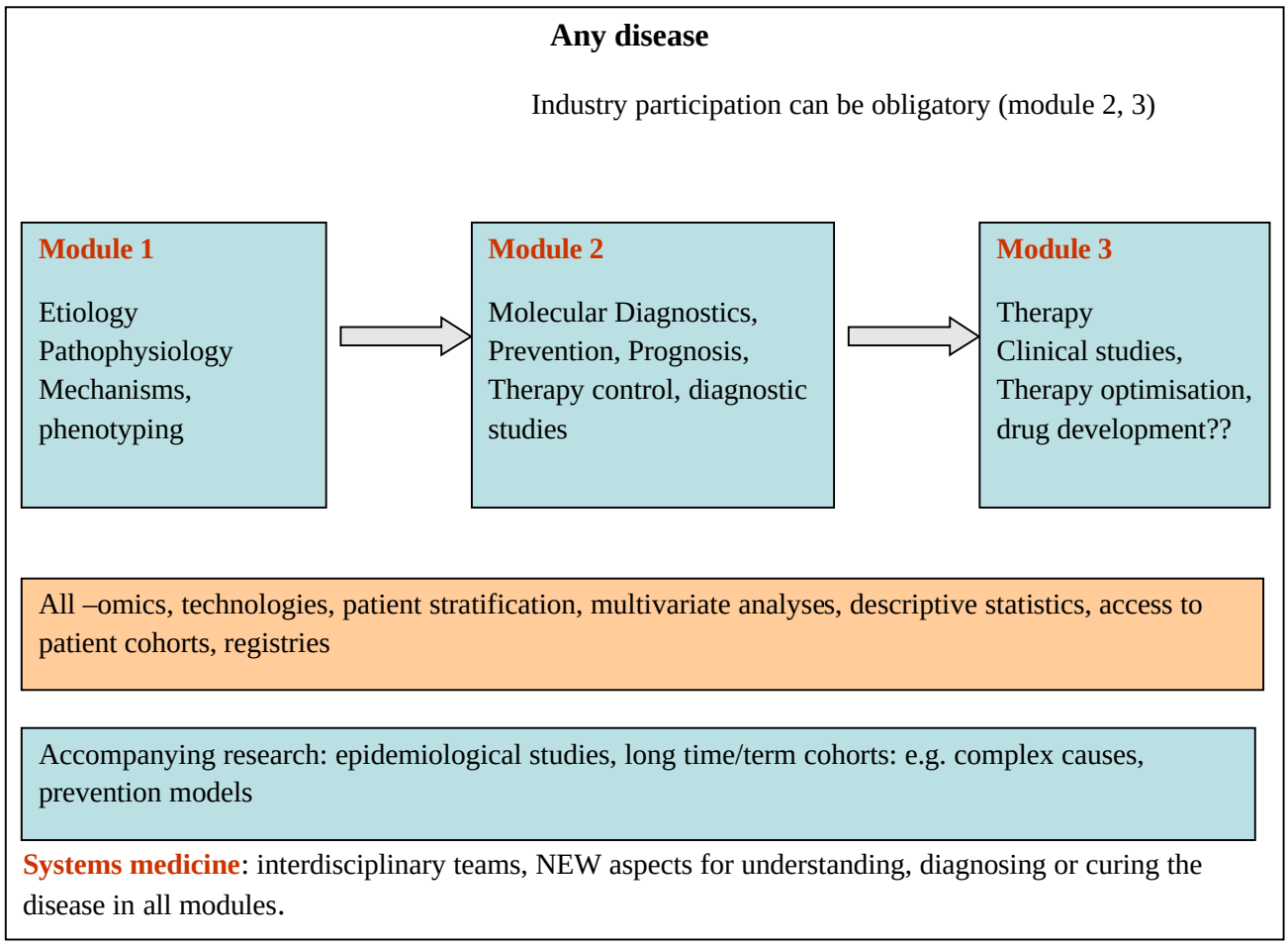
- To combine and compare experimental systems (e.g. patient samples, established cell lines, patient derived cell lines, genetic/mouse models, in vitro and in vivo models).
- To combine technologies, to integrate data from multiple sources (e.g. omics technologies, single-cell technologies, in vitro and in vivo quantitative and dynamic data)
- To combine and compare methodologies to analyse data, to formulate and test hypotheses. This includes a more comprehensive view of multiple levels of functional organization in cellular systems (gene regulation, signal transduction, metabolism) to the physiology of tissues/organs; different statistical, computational and mathematical approaches are required depending on the context and the questions raised.

No single approach is comprehensive by itself, the integration and comparison brings the added value. The reason why this has not been possible so far is the limited size of project funding and the fact that many approaches have been developed by separate communities. In order to bring these groups, approaches, technologies and methodologies together, a coordinated large scale effort is required.

A “tree model” was suggested as the way to think about systems medicine and its future development and coordination in Europe. The tree model represents a comprehensive approach where the trunk is built upon consensus in the community and the branches would represent focused deliverables. The trunk will represent the toolbox for systems medicine that will be developed driven by the needs of the community. This toolbox will comprise technologies, databases, modelling algorithms, modelling software, and other shared services that will arise in the future. The appropriate components of this "toolbox" then can feed the branches, i.e. targeted projects applied to specific diseases or areas of medicine as required. This design will make the development of the resources needed to grow the trunk more cost effective and faster, but above all also more accessible to the community as they will be developed with a specific remit and towards specific purposes defined by the community. This will permit the design of a joined up strategy where

different technologies and modelling approaches will be made connectable and compatible with each other, as well us with the different needs of the community.

Funding should be addressed to the stem and afterwards allocated on competitive basis to the branches. The model would be portable across diseases and it would define common procedures and thinking across clinical relevant questions, where systems medicine could have an important impact. For initiating the discussion to make systems medicine a reality, the participants proposed to have the primary focus on the patient and the clinical needs across any disease, as shown in the following diagram.



During the common discussion, participants agreed that challenges in systems biology and its future applications in medicine will require the main focus to be on clinical needs, of which examples are presented in the following paragraph.

Clinical Questions-needs to be addressed in the future

If clinical questions need to pave the way for systems medicine, the following list gives potential areas of interest:

- Clinical trials (short term)- systems biology approaches could guide clinical trial design, shortening times and costs
- Re-definition of clinical phenotypes based on molecular and dynamic parameters
- Discovery of effective biomarkers of multiple nature for disease progression (clinically useful: risk, prognosis, diagnosis); several biomarkers are often needed to make appropriate medical decisions.
- Combinatorial therapy for reducing toxicity (mid-term?); this approach would be useful to find out a combination and lower doses of effective drugs; in particular in the case of co-morbidity, in the frequent cases where more than one disease is affecting the patient
- Improvement of drug development, optimized drug efficacy and delivery, drug safety (via the of study drug-metabolizing enzymes pathways), timing and dosage of therapy
- It is important also to address the healthy individual (long term?)

Recommendations for follow-up actions

- It was agreed that a series of focused workshops would be needed to better define the specific needs for further coordination and building of a European strategy for systems medicine. The first workshop could be organized towards the end of 2010. Preliminary questionnaires addressed to different stakeholders would help in the preparation of such workshops.
- It is fundamental to analyse ongoing initiatives (at European and national level) in order to avoid duplication of efforts.
- A networking event-symposium among EU funded projects on systems biology, to exchange good practices and highlight available resources, and to identify successes would be welcomed
- All relevant stakeholders (including regulators) need to be involved at the early stages of discussions on potential future systems medicine actions
- There is a common need to bridge the gap between modellers, basic biologists and clinicians and patient groups need to be involved
- Dialogue with clinicians could be initiated with a 3-page article with crispy concepts on systems medicine addressed to a medical journal