

Plan for tailored interdisciplinary exchange programmes

CASyM report - training document

November 2014

IMPRINT

Publisher

CASyM administrative office
Project Management Jülich, Forschungszentrum Jülich GmbH
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Date

November 2014

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Comment

This document is linked to the CPD plan for clinical and pre-clinical MDs.

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PLAN FOR TAILORED INTERDISCIPLINARY EXCHANGE PROGRAMMES

Introduction

Human diseases can be viewed as dynamic perturbations of complex, integrated genetic, molecular and cellular networks sensing and responding to changes in the environment and lifestyle of individuals. Such a perspective emerges from recent developments in Systems Biology (SB) and fuels a paradigm shift in classical medicine which re-defines clinical phenotypes, thus enabling personalized medicine. CASyM aims at bridging the current gap between SB and medicine by implementing a multidisciplinary, inter-institutional doctoral training scheme in Systems Medicine across Europe. We will develop educational procedures and research projects that highlight the added value of SB approaches for pending clinical issues and unmet medical needs. Initial examples of application include malignant, autoimmune and metabolic chronic disorders. The pioneering actions acknowledge the rapidly increasing number of -omics, and other quantitative and temporal biomedical, environmental and lifestyle data that are relevant for the onset and development of any complex disease. We will supplement existing doctoral programmes at individual training sites with the new educational concepts proposed by stakeholders including Systems Medicine Centres, major Clinical Centres in Europe and Life Sciences industries. Training should address primarily clinicians and their clinical needs with a translational focus on personalized (P4) medicine, discovery of effective diagnostics and biomarkers and rational design of combinatorial and chronotherapies encompassing biological clocks. Complementary trainings should be available also to other life science and theoretical scientists. The systems approaches facilitate early intervention, anticipation and/or prevention of disease risk and/or onset, and aid in development of safer and more efficient personalized treatments. The CASyM concerted training effort represents a template for sustainable interdisciplinary Systems Medicine education programmes, and is a showcase of European training implementation actions. It will broaden the pool of biomedical researchers that combine quantitative techniques and systems approaches in translational and clinical medicine settings and integrate them with health applications of Information and Communication Technologies. By such systems training of the next generation biomedical researchers, CASyM will contribute towards reduction of chronic disease-related healthcare costs.

Objectives

Biomedical research can benefit from the rapid emergence of systems biology, an inter-disciplinary field bridging medicine, biological sciences and applied mathematics, computational and engineering sciences. A reductionist approach can now be upgraded with systems understanding of physiology and pathophysiology, leveraging increasing amounts of -omics and other biological/medical as well as environmental/lifestyle data. Despite the spectacular advances in the post-genome era there remains a gap between greatly expanded availability of experimental data and the implementation of improved medical knowledge. The tremendous expansion in experimental data has yet to be translated into improved medical knowledge.

This concept is based on the three systems medicine pillars (experimental, *in silico*, clinical practice) and is implemented through the following actions:

1. Provision of complementary courses in CASyM partner laboratories and groups (e.g. wet-lab, dry-lab and clinical work), on clinical examples of malignant, autoimmune and metabolic chronic disorders).
 Karolinska: Bioinformatics courses (R, biostatistics, and integrative bioinformatics analysis of data) targeting biology and medical PhD students.
 University College Dublin: modules on Bioinformatics and Systems Biology PhD Programme.
 Oxford: various courses (<http://www.dtc.ox.ac.uk>)
 University of Ljubljana: Systems medicine module for doctoral students of Biomedicine and other biomedical sciences, accredited by 10 ECTS
[\(http://www.uni-lj.si/study/study_programmes/postgraduate_studies_3rd_cycle/\)](http://www.uni-lj.si/study/study_programmes/postgraduate_studies_3rd_cycle/)
2. Launch of an internal call for the pilot systems medicine projects and secondment projects engaging CASyM partner and associate partner group members. The draft call will be prepared by the WP2 working group in December 2014.
3. To implement pilot research projects (2015-2016) and secondments (mentoring CASyM partner and associated partner PhD students and postdoctoral-fellows) in complementary systems medicine disciplines (clinical, genomic, experimental, mathematical, etc.) within another research group.

CASyM will pilot specialized training for future professionals to implement interdisciplinary approaches in medical research and clinical practice (Fig. 1). The goal is to embed into students' thinking and research the obligatory interactions between mathematical modelling and experimentation to address the defined clinical needs.

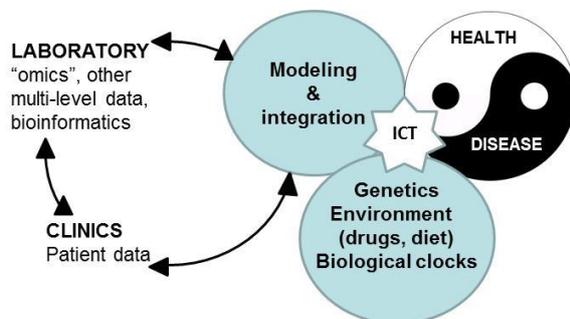


Figure 1. Outline of the interdisciplinary research training. Systems medicine requires strong interactions and iterative cycles between modeling and experimentation in the laboratory and the clinic. Outputs will be integrated into clinical practice through Information and Communications Technologies (ICT) systems.

The research and training will not focus on a single disease but rather on innovative systems approaches with obligatory (wet lab - dry lab - clinical) iterative cycles that are implemented across systems medicine and can be applied for any multifactorial disorder. Experiments, modelling and clinical work may, in each case, address a different question that has not been solved using classical, single-approach research.

Thus, our **core objective** is to implement systems medicine by the joint training in clinically oriented research projects from **three major multifactorial chronic disease groups** where CASyM partners and associates hold expertise:

1. **Cancer and tumor immunology** (eg. colorectal, liver, pancreas, melanoma, glioblastoma, neuroblastoma, colorectal cancer, breast cancer) (F. Levi, S. Parodi, J. Tegnér, C. Auffray, W. Kolch, H Byrne and associate partners: T. de Lumley - Cosmo, Lyon).
2. **Metabolic disorders** (eg. liver disease, diabetes) (D. Rozman, D. Harrison, F. Levi, C. Auffray and associate partners: F. Lammert, M. Laville - CENS, Lyon) .
3. **Chronic autoimmune, inflammatory and degenerative disorders** (eg. seasonal allergic rhinitis, chronic obstructive pulmonary disease, multiple sclerosis, psoriasis, Parkinsons, Alzheimer). (M. Benson; J. Tegnér, C. Auffray and associate partners: P. Sterk - AMC, Amsterdam; L. Fleming, I. Adcock and K.F. Chung - Imperial College, London; A. Agusti and J. Roca - Hospital Clinic, Barcelona; Irina Lehmann - Helmholtz Centre, Leipzig; Antoine Magnan - DHU2020, Nantes; P. Montuschi - Catholic University, Rome; C. Pison and J.L. Pépin - Pôle Thorax, Grenoble; J.P. Boissel - Novadiscovery, Lyon, G. Federoff, Georgetown University, Washington DC).

In cancer, systems medicine projects will focus on rational design of therapies by chronobiological administration, on population dynamics of different cell types that can explain the drug effect versus resistance, predicting combinatorial therapy, tumor immunology, on network analyses across and within different tumor types to consider possible linkages with preclinical / clinical treatments and last but not least, on cancer systems pathology, particularly on extended dynamical pathway of EGF signalling.

In liver disease we will address network perturbations and their relation to nutrition and lifestyle interventions to identify key players (from metabolism, immune/inflammatory response and the circadian rhythm) that result in fatal disease progression with no treatments currently available.

In chronic autoimmune, inflammatory and degenerative disorders with altered function of CD4+, CD8+ T cells, B-cells, and Monocytes, systems approaches will focus on action of known and novel drugs and the role(s) of these cells and their sub-types in driving or sensing disease. Multiscale modelling will be applied to address responses to environmental stimuli and exercise on Chronic Obstructive Pulmonary Disease, familial forms of Multiple Sclerosis, Alzheimer and Parkinson's diseases and to determine predictive factors for non-responders to therapeutic interventions.

In all cases, genomic, genetic, transcriptomic, proteomic and metabolomics data will be collected and analysed through integrative bioinformatics and computational modelling to identify new genes and pathological mechanisms, followed by clinical validation of the initial findings. Across all clinical questions addressed, we will aim for integrative management of multi-scale data, informing and refining efforts to adopt "data standard operating procedures".

Interdisciplinary systems medicine approaches offer significant added value in understanding, predicting and treatment strategies of complex disorders. To maximise use of the data, modern medicine requires highly interdisciplinary educated scientists with interdisciplinary knowledge bridging biology and medicine with mathematical, computational and engineering sciences. Such personnel are at present still very few. It is here that the CASyM research training network finds its place and will demonstrate that this approach will have a potential long lasting impact for the development of novel systems based training strategies in medicine.

Research Methodology and Approach (key elements)

The CASyM consortium, together with its associated partners, possess an internationally acknowledged multidisciplinary scientific expertise and a keen awareness of the need for Systems Medicine for medical progress and patient wellbeing to occur over the next 10 years. The expertise of the CASyM consortium expertise covers wet laboratory, dry laboratory and clinical work. At least two of these three pillars of Systems Medicine are present at each of the CASyM partner sites, which will give early stage researchers (ESR: i.e. doctoral students or post-docs in the first 5 years after the Ph.D.) and established researchers (ER: senior post-docs, medical doctors, other staff) unique opportunities for basic interdisciplinary training. This basic training will be broadened to include additional complementary skills during secondments.

Complementarity concept

The wet laboratory work at different CASyM partners will include: Basic training in genomic techniques: microarrays, qPCR, next generation sequencing, basic biochemistry and molecular biology techniques for protein, RNA, and DNA-protein interactions, primary and immortal cell cultures, enzyme kinetics, circadian studies (D. Rozman, J. Tegnér, W. Kolch); Laboratory animal experimentation basic chronobiology, cell cycle, anticancer drug pharmacology and molecular imaging and chronotherapy (F. Levi), reverse phase protein arrays, quantitative immunofluorescence and image analysis applied to human tissue, etc.

The dry laboratory work will include: Basic and advanced bioinformatics training (D. Higgins - UCD), techniques for functional validation studies, for example siRNA mediated knockdowns and animal models (D. Rozman, M. Benson, J. Tegnér); (network modelling in Matlab; Data management (handling of multi-level and multi-domain data (clinical data and bioinformatics data, simulation data); Database design, storage approaches, data warehouses; Data analysis; Semantic web technologies, RDF, bio2rdf, OWL, stochastic modelling-estimation from experimental data (clinical data and simulation data); Parameter estimation techniques); computational and mathematical modelling, and statistical technique (B. Kholodenko - UCD), multidimensional data analyses, mathematical modelling of chronotherapeutic data, integrating medical strategy; visualisation of signalling pathways using games technology and virtual reality training in clinical informatics and techniques enabling integration of molecular and health information in a research and hospital setting. Database techniques, security protocols, de-identification, and web-interface design (O. Wolkenauer, J. Tegner, H Byrne, C Auffray).

The clinical work will include training in clinical research methods, in which students can work in projects that integrate clinical, genomic, bioinformatics and functional studies, molecular oncology and molecular biology notions with medical oncology, chronopharmacology, clinical chronotherapy, physiology monitoring, e-medicine, and molecular pathology and acquisition of human tissue. (M. Benson, F. Levi and associate partners: F. Lammert - CENS, Lyon).

In addition, we strive to actively involve industrial partners and collect their systems medicine training needs. While at present, only a few companies apply the core concept of Systems medicine properly by informing their research through the iterative cycle between experimentation and modelling. But industrial R&D departments have the potential to focus on complex scientific problems and mobilize a combination of skills, knowledge and expertise that embraces multiple disciplines of Systems Medicine. An innovative private sector (SME and industry) is regarded as a very important component of the CASyM training network.

Establishing an innovative training concept for a new generation of medical doctors and scientists

By the proposed inter-institutional and international training scheme (see above) we will initiate an evolution in pedagogy to produce a new generation of PhD level medical doctors and scientists through interdisciplinary and systems-oriented curriculum.

The applicative value and originality of CASyM approach is that it is not single-disease oriented but applies innovative combination of research methodologies that are general and can thus be used to tackle complex

questions related to any disease. The CASyM consortium identified expertise in three multifactorial diseases groups that are among major threats for human health in developed societies: cancer, metabolic, and chronic (auto)immune, inflammatory and degenerative diseases. Particular aspects from the above disease groups will be addressed as study examples within the CASyM ESR and ER research projects.

By applying different experimental and *in silico* techniques, all research projects will address one of the clinically relevant questions, such as:

- ▶ The identification of biomarkers to stratify patients for personalized medication.
- ▶ Prediction of disease outcome.
- ▶ Optimized drug efficacy/delivery/safety in single or combinatorial therapies with reduced toxicity in cases of co-morbidity: the chronotherapy approach.
- ▶ Re-definition of clinical phenotypes based on molecular and dynamic parameters.
- ▶ Time and cost efficient clinical trials guided by systems approaches.

TRAINING

Quality and Structure of the Training Programme, Importance and Timeliness

This training programme addresses the current need for an overarching curriculum to educate and train future researchers and health care professionals including medical doctors and scientists from biological, clinical, mathematical, computational and engineering fields. Such profound and versatile training is a pre-requisite for systems understanding of biological/physiological processes and will generate novel generation of bio-medical scientists and clinicians.

In general, specific doctoral curricula in the highly supra-disciplinary fields of systems medicine are still rare, both in Europe and worldwide. Obstacles lie in the fact that biological fundamentals are sometimes difficult to explain to mathematicians, and *vice versa* – and that complex equations behind the living systems are difficult to comprehend for classically trained biologists. This can be true if teaching is performed *ex cathedra* and not in a combined environment of wet (experimental), dry (informatics, modelling) laboratories and in a clinical setting.

The CASyM training network will cover all important teaching aspects – from learning theoretical backgrounds in University courses (obligatory at some of the involved training sites), to workshops and tutorials, hands-on experience in wet and dry laboratories, that are spread among academic, research, clinical and private institutions.

Crucial for systems medicine training are interdisciplinary courses that ESR students will attend, acquire the credits, and become eligible to defend their PhD theses.

Here, the CASyM consortium will, with support of the broader CASyM consortium and its Scientific Advisory Board, implement some pioneering Systems Medicine Europe-wide training efforts:

1. Systems Medicine training at the doctoral (ESR) level. This will be achieved by combining the local Universities rules topped by CASyM tailored interdisciplinary accredited courses that will take place at different partner sites, also as e-courses, and at workshops (Explained already in D.2.5.)
2. Systems Medicine specialization at the postdoctoral level (ER). The ER students will carry out shorter (3 – 12 months), but more independent projects. ER trainees will, in addition to research, obligatory participate as local organizers (management skills) and also participants (knowledge gaps) in CASyM organized tutorials, workshops and schools.

Training at scientific workshops, tutorials and other Meetings

The main network-wide training events, conferences, tutorials, etc., and contribution of beneficiaries are listed in Table 1. CASyM workshops and Summer Schools will be opened for outside-network research and general communities and will contribute also to Dissemination and Outreach.

Table 1. Main Network-Wide Training Events 2014, Conferences and Contribution of Beneficiaries

Main Training Events & Conferences	Lead CASyM partner or associate	Date and place
CasyM tutorial: Modeling Tools for Pharmacokinetics and Systems Medicine (6 EACCME credits) https://www.casym.eu/events?cmd=showDetail&id=195	D. Rozman organizer, CASyM partners and associates as speakers and tutors.	18 May 2014, Stuttgart, Germany
Systems Biology and Systems Medicine: precision Biotechnology and Therapies Advanced School with training sessions, Como, Italy http://www.complexcomolake.it/sybsymcomoschool/call.html	Several CASyM partners as speakers and tutors	21-27 September 2014, lake COMO, Italy
CASyM tutorial: Systems approach to biological clocks and diseases (6 EACCME credits) http://www.srbr.org/Documents/FlyerSFC_SRBR-EBRS.pdf	F. Levi organizer	29 October 2014, Paris, France
CASyM/FEBS: Advanced summer school – Research approaches in systems medicine	J. Tegner organizer, CASyM partners and associates as speakers and tutors.	22 - 26 June 2015 Stockholm, DJURÖNÄSET, Sweden
ERS Research Seminar: Human Translational Medicine: A key bridge for development of new drugs for severe asthma, COPD and ILD, Dublin	I. Adcock, co-organizer; C. Auffray, M. Benson, F. Chung as speakers.	Dublin, Ireland, November 13-14, 2014

Research indicators of progress

CASyM will provide the following indicators of progress in its periodic, mid-term review and final reports.

Research Activities

- ▶ General progress with interdisciplinary (wet lab, dry lab, clinics) and inter-institutional research activities programmed at individual, participant team and network level.
- ▶ Timely identification and reporting of potential problems, justification for potential necessary adjustments to the original research work plan and/or timetable.

Highlights of scientific achievements and recognitions

- ▶ Progress on interactions among disciplines and between academic, clinical and industrial partners and relevant users groups.
- ▶ Specialist exchange among teams and visit of Senior Researchers from inside and/or outside the network.
- ▶ Individual and joint publications, directly related to the work undertaken within the project, including citation indices.

Interdisciplinary Training Activities

- ▶ General progress with training programme at individual, participant team and network level (Career personal development plan, supervision, coaching/mentoring at host institution). Time and duration of each individual appointment.
- ▶ Progress with training in interdisciplinary areas (experiments, clinics, *in silico*).
- ▶ The nature and justification for any deviation from the original plan or adjustments, if any, to the original research work plan and/or timetable.
- ▶ The number and place of the short visits/secondments undertaken or organised by each ESR and ER within the network.
- ▶ Participation in training events and network meetings and to international conferences. Achievements regarding the acquisition of complementary skills.
- ▶ Level of satisfaction of the trainees.
- ▶ Highlights on more particularly innovative and on wider societal and/or ethical components of the project, such as public outreach activities.

Management and impact

- ▶ Effectiveness of networking, communication and decision-making between partners (at all levels: coordinator, team leaders, supervisors, ESRs and ERs), between the network and the Commission, and with the Industrial and/or other relevant stakeholders.
- ▶ Effectiveness of the recruitment strategy in terms of equal opportunities (including gender balance) and open competition at international level.

- ▶ Effectiveness of the "training events and conferences", open to external participants and integration in the training programme.
- ▶ Effective contribution of Visiting Scientists to the research training programme.
- ▶ Development of any specific planning and management tools and databases; management of intellectual property and commercialisation of network research output.
- ▶ Nature and justification for adjustments, if any, to the original training plan and/or timetable (e.g. opportunities for new collaborations regarding training activities).

ACKNOWLEDGEMENTS

This deliverable (D2.2) is part of CASyM work package 2 – “Multidisciplinary training in systems approaches for the next generation of scientists and medical doctors”.

CASyM is funded by the European Union, Seventh Framework Programme under the Health Cooperation Theme and Grant Agreement # 305033.

STEERING COMMITTEE

The following officials, as part of the Scientific Steering Committee, are involved in the scientific coordination of CASyM:

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- Rob Diemel** - The Netherlands Organization for Health Research and Development, The Netherlands
- David Harrison (Chair)** - University of St. Andrews, United Kingdom
- Walter Kolch** - University College Dublin, Ireland
- Frank Laplace** - Federal Ministry of Education and Research, Germany
- Francis Lévi** - Institut National de la Sante et de la Recherche Medicale, France
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