

white paper
version 9-11-08

Systems Biology to combat Metabolic Syndrome

SBMS: a pan-European initiative

contact person

prof. Dr Roel van Driel
Netherlands Inst. for Systems Biology (NISB)
and
University of Amsterdam
Kruislaan 318
1098SM Amsterdam
tel +3120 525 5150
fax +31 20 525 7935
mail r.vandriel@uva.nl



Table of contents

1. Ambition and characteristics of the SBMS initiative
2. How the SBMS initiative started
3. Aim of the SBMS initiative
4. Systems biology as an integrator and driver of MetS research
5. Metabolic syndrome and systems biology: a powerful merger
6. Aim of this SBMS White Paper
7. Focus and hurdles
8. SBMS Road Map
9. SBMS governance
10. Aims of the first SBMS Workshop (Berlin, September 25-26, 2008)
11. Conclusions and follow up of Berlin Workshop

Updates of the SBMS White Paper

version 01-09-08: sections 1 through 10

version 05-10-08: section 11 added

version 09-11-08: section 11.2.2 updated

1. AMBITION AND CHARACTERISTICS OF THE SBMS INITIATIVE

Metabolic syndrome (MetS) constitutes a major threat to economy and human well-being in the Western world and in many upcoming countries. It is expected that in the 27 countries of the EU by 2030 close to 200 Million persons (33% of the total population) will be obese¹. Many of them will have one or more of the following comorbidities: diabetes, hypertension and heart disease. The direct costs (medical treatment) plus indirect costs (inability to work) in 2030 will amount to more than 100 Billion (10¹¹) Euro per year!

A large number of research groups in Europe is investigating different aspects of MetS. In the past 10 years many thousands of papers have been published in the scientific literature about topics related to MetS. There has been huge progress in developing technologies, collecting data and generating information. However, our understanding of this disorder is still remarkably limited. This has three major reasons:

- The underlying biological systems are extremely complex.
- We are lacking effective ways to extract key information from data sets.
- Research is highly fragmented.

The SBMS initiative takes an integrated approach.

- It coordinates and integrates efforts by effective governance.
- It standardizes and focuses experimental approaches.
- It approaches MetS as a multilevel network of components (molecules, cells, tissues, organisms) that interact in time and space.
- It employs systems biology (SB) to integrate and interpret data sets with quantitative and predictive mathematical models.
- It uses these predictive models to identify the most effective experiments.
- The models allow in-depth analysis of the behaviour and logic of the system.

Characteristics of the SBMS approach

- **integrative**
experimental data sets from different projects and different research groups are integrated in a single quantitative and predictive mathematical model
- **goal-oriented and cost-effective**
the predictive model is used to identify the best experiments to reach specific goals
- **understanding complex systems**
the iterative cycle of model-driven experiments and experimental data-driven modelling allows systematic analysis of the underlying principles and logic of complex biomedical systems

The SBMS initiative is timely for the following reasons:

- The MetS field has developed instruments for the acquisition of large and high quality quantitative data sets addressing many aspects of healthy and diseased humans and model organisms.
- The SB field is rapidly developing approaches to integrate data sets in predictive mathematical models that allow in depth analysis of the behaviour and architecture of complex multi-scale biological systems.

Combining the expertise of the MetS and SB fields has the potential to induce a paradigm shift in biomedical research, resulting in a new way of thinking and working in biomedical research, resulting in research efforts that are more:

- goal-oriented
- cost-effective
- productive

The SBMS program will be developed along the lines of a Road Map (Section 8) that defines a stepwise expansion of the effort, allowing go-no-go decisions as the program develops.

2. HOW THE SBMS INITIATIVE STARTED

The SBMS initiative started as a proposal by a number of European research institutions to the EuroBioFund organization, an action of the ESF and the EC. The SBMS vision has been presented and discussed at the EuroBioForum meeting in December 2007 in Lisbon, which was attended by scientists, policy makers, and funding agencies. The SBMS initiative was well received in Lisbon. More information can be found on www.esf.org/activities/eurobiofund.htm, including the SBMS presentation in Lisbon. The initiators were mainly institutes in the field of systems biology (SB²). In recent months, the SBMS coverage has widened to several

¹ based on a SBMS-dedicated report of Arthur D. Little management consultancy.

major European laboratories in the broad field of metabolic syndrome (MetS). This has resulted in formation of an international SBMS Steering Committee listed in Box 1.

3. AIM OF THE SBMS INITIATIVE

The SBMS initiative aims to achieve in depth understanding of biological processes that play a major role in metabolic syndrome (MetS). It has the ambition to acquire the scientific knowledge that is required for the rational (i.e. knowledge-based) development of

- effective prevention measures,
- drugs and therapies,
- healthy food that reduce MetS risks.

The SBMS initiative will accomplish this by running a highly focused and goal-oriented international research program that is of sufficiently large scale to cope with the extreme complexity of biological systems. The SBMS initiative intends to achieve its goal within 10 years and will set the scene also for other areas in the field of multifactorial diseases, including cancer and infection diseases.

SBMS will make a major contribution to the improvement of human well-being in and outside Europe. European biomedical/pharmaceutical companies and food industry (healthy food), will benefit from these efforts, although it must be stressed that it will take at least 5 years before sufficient basic knowledge is acquired that can be translated in commercial products.

4. SYSTEMS BIOLOGY AS AN INTEGRATOR AND DRIVER OF METS RESEARCH

The SBMS initiative uses SB as an integrator and driver of research, creating knowledge in a systematic, goal-oriented and cost-effective manner. This is achieved by integrating different experimental data sets in multi-scale quantitative and predictive mathematical models that describe the behaviour of the biological systems that is being studied. Such predictive models are subsequently used to identify the most informative experiments, making research more efficient and thereby cost-effective.

5. METABOLIC SYNDROME AND SYSTEMS BIOLOGY: A POWERFUL MERGER

5.1 What is metabolic syndrome?

The metabolic syndrome is characterized by a cluster of related biochemical and antropometric features including central obesity, glucose intolerance, dyslipidemia and hypertension. The diagnosis or even the

Box 1

SBMS Steering Committee

J. Auwerx; University Strasbourg, France
 U. Beisiegel; University Hamburg, Germany
 P. DeMeyts; NovoNordisk, Copenhagen, Denmark
 A.K. Groen; AMC, Amsterdam, Netherlands
 S. Hohmann; University Gothenburg, Sweden
 S. O'Rahilly; Cambridge University, UK
 M. Reuss; University Stuttgart, Germany
 R. van Driel, Netherlands Inst. for Systems Biology, Amsterdam, Netherlands

Table 1 Diagnostic criteria for the metabolic syndrome

Criteria	NCEP ATPIII	WHO	IDF
Central obesity (waist circumference or hip:waist ratio)	>102 cm (men) >88 cm (women)	waist: hip ratio: >0.9 (men) >0.85 (women) and/or BMI >30 kg/m ²	≥94 cm (male) ≥80 cm (female)
Fasting plasma glucose concentration (mmol/l)	>5.6 (>110 mg/dl)	≥6.1 mmol/l (≥120 mg/dl) or ≥7.8 mmol/l (2 hour plasma glucose or previously diagnosed type 2 diabetes)	≥5.6 or previously diagnosed type 2 diabetes
Blood pressure (mm Hg)	>130/85	≥140/90	≥130/85
Fasting triglyceride concentration (mmol/l)	≥1.7 (150 mg/dl)	≥1.7	≥1.7
HDL cholesterol concentration (mmol/l)	<1.0 (men) (<45 mg/dl) <1.3 (women) (<50 mg/dl)	≤ 0.9 (men) (35 mg/dl) ≤ 1.0 (women) (39 mg/dl)	<1.03 (male) <1.29 (female)

NCEP ATPIII, National Cholesterol Education Program, Third Adult Treatment Panel (2004); WHO, World Health Organization (1999); IDF, International Diabetes Federation (2005).

existence of metabolic syndrome as a separate entity has been the subject of major controversy. Several different expert groups have attempted to define what constitutes the metabolic syndrome. Table 1 depicts the most used classifications proposed by the international Diabetes Foundation (IDF), World Health Organization (WHO) and the National Adult Treatment Panel III (NCEP ATPIII). There are some important differences between the three recommendations, the WHO criteria focus on Type2 diabetes or insulin resistance, whereas the IDF requires central obesity to be present. NCEP ATPIII is most flexible by defining metabolic syndrome by presence of three of the five criteria listed in Table I. Many more features of the metabolic syndrome have been described in the literature which is not surprising considering that this is a typical “systems” disease.

5.2 What is systems biology?

Systems biology is the logical step following the information explosion mostly through genomics type of analyses of biological systems. Systems biology exploits the iterative cycle of at the one hand experimentation that is driven by quantitative and predictive models and on the other hand data integration and system analysis based on data-driven modelling (Fig. 1). In the context of the SBMS initiative SB approaches complex biological systems as networks of components (molecules, cells, tissues, organisms) that interact in time and space, spanning large temporal- and spatial scales.

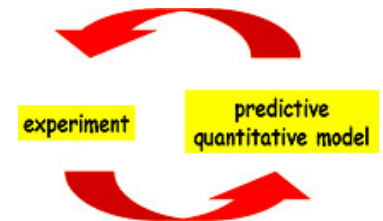


Figure 1 The systems biology iterative cycle

The information explosion in biology has not resulted in a true understanding of biological systems in the sense that useful predictions can be made. This is seen among others in the paucity in the rational development of new drugs and therapies for multifactorial diseases, including MetS and related disorders. A major hurdle is the extreme complexity of biological systems. Systems biology addresses this issue by integrating diverse types of biological information in computer-based models that integrate information, can be interrogated about system behaviour and allow the uncovering of underlying system principles. Biologists and biomedical investigators are generally not well-equipped to cope with the complexity hurdle. Therefore, they team up in the systems biology field with *physicists* and *engineers*, which are used to translating experimental data into computer models and are able to work with complex systems. At the same time *mathematicians* play a crucial role in developing the necessary methodologies for the identification and analysis of mathematical models.

6. AIM OF THIS SBMS WHITE PAPER

This SBMS White Paper will be continuously updated as our ideas and insights develop. It addresses scientists, granting agencies and science policy makers in all European countries:

- It describes the objectives, means and road map of the SBMS endeavour.
- It deals with the focus of the SBMS program and the up-scaling of biological and biomedical research, which is essential to cope with the immense complexity of biological systems.
- It outlines the consequences that this approach has on research and on funding. Among others it sets the scene for decision making on issues related to achieving coherent and goal-oriented research programs, standardization of experimentation, integration of data sets by predictive mathematical modelling, the format of calls for proposals, and how to manage such large-scale focused programs.
- The White Paper prepares for the first SBMS workshop to be held in Berlin on September 25 and 26, under auspices of the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung (BMBF)). In this workshop consensus should be reached about the contours of a first SBMS research program.

SBMS enters unknown territory. A focused large-scale research effort like this has never been done in biology or biomedical research before, except maybe the human genome project. Therefore, many questions that are addressed in this White Paper and in the September workshop will not have firm answers. We strongly believe in learning by doing, accepting that that we will have to change thing on the way. The road map presented below (Section 8) allows for this, incorporating go-no-go decisions on the way.

7. FOCUS AND HURDLES

7.1 Focus

The SBMS initiative focuses on the molecular, cellular, tissue and organismal levels of MetS with a time horizon of 10 years. The SBMS program will involve highly systematic studies on healthy and diseased human systems and one or more carefully selected model systems. Decisions will be made in the forthcoming 6 months on what

MetS topics will be addressed in the early stages of the program, beginning with Phase #2 of the Road Map (Section 8). This process will start at the First SBMS Workshop September 25 and 26 in Berlin.

7.2 Who will do the work?

The SBMS program is a highly focused and coordinated research effort on specific key issues in the MetS field. To a large extent this will be achieved by coordinating, focusing and synergizing ongoing research efforts by excellent European institutes in the fields of MetS and of SB. In addition it will be necessary to start new lines of research to fill specific gaps in our knowledge not covered by ongoing research efforts. For all parts of the SBMS programs calls will be published allowing selection of the very best consortia that are able to combine systems biology and biomedical research.

7.3 Hurdles that must be overcome

The SBMS endeavor has to overcome a number of hurdles.

- *The hurdle of integration of disciplines:* integrate efforts in the SB and MetS fields to drive experimental research by systematically implement data-driven mathematical modelling and model-driven experimentation.
- *The research fragmentation hurdle:* scaling up research efforts to a level that can cope with the extreme complexity of biological systems.
- *The data integration hurdle:* achieve standardization in experimentation and modelling, so that data sets from different research groups can be integrated into predictive mathematical models.
- *The funding hurdle:* combine different national and international funding opportunities to synergistic large programs and develop adequate formats for calls for proposals for this.

Below these four issues are briefly discussed, creating a basis for the decision making process to come.

7.3.1 *The integration of disciplines hurdle*

SB integrates heterogeneous, multi-scale experimental data sets in quantitative and predictive mathematical models. Such models act as quantitative working hypotheses and can be used to select in a rational way the most informative and cost-effective experiments. At the same time these models can be interrogated to learn more about the architecture, behaviour and logic of a complex system. Such knowledge is essential for progress in understanding MetS and eventually for developing in a fully rational way new effective drugs and therapies. In short, systems biology that builds on model-driven experiments and experimental data-driven modelling can act as a potent integrator and driver of MetS research.

Obviously, merging the MetS field and the SB field is a major enterprise by itself. Experience shows that scientific culture and language differ considerably between the biology/biomedical field and the SB field, the latter involving physicists, mathematicians and engineers. It will take a lot of effort, patience and perseverance of investigators to accomplish such merger. Therefore, the SBMS endeavour will initially move in small steps: learning by doing.

7.3.2 *The research fragmentation hurdle*

Biological systems will be approached as networks of molecules, cells, tissues, organs and organisms that interact in time and space. Such networks span time scales between seconds and decades and length scales from nanometers to meters. Moreover, in such systems the quantities and properties of the components continuously change. To map these networks, analyze their behaviour and unravel their underlying logic is a gigantic effort that is too big for a single laboratory and even a single country. Nevertheless, without resolving these networks we will not be able to understand, let alone cure, the MetS disorder.

Whatever the precise SBMS strategy will be, very large amounts of systematic measurements will be required. Importantly, these data sets must allow 'adding up' in quantitative and predictive mathematical models. This requires research programs that are much more coherent and generally much larger than present ones. Today's biomedical and biological research, as well as its funding, is highly

Box 2

Individual factors vs. a network approach

A case in point for a complex disease where the search on the etiology still focuses on single factors is diabetes type2, a direct consequence of the metabolic syndrome. Only in 2007, 18 genes have been identified that according to the authors of papers in high impact journals play a primary role in the disease. In most cases a knock-out of the gene in question causes insulin resistance in mouse models whereas overexpression renders the mice resistant to diet induced insulin resistance. Interestingly, the key role of these genes is localized to a variety of organs, such as liver, bone, pancreas, brain and the haematopoietic compartment. The function in insulin signaling is often not obvious. Considering that the complete list of genes deemed to be responsible for T2D is much longer, claims about dominant roles of all these genes in the etiology of T2D are clearly overstretched. The identification of so many causal factors merely underpins the complexity of a disease such as T2D. Only the elucidation of the networks that link all the genes and different organs will allow understanding of the interaction and mechanisms really responsible for the pathogenesis of T2D.

fragmented in various ways.

- A myriad of different aspects of MetS are being studied with little or no reference to the larger context of the network, often focusing on single factors.
- Many different model systems are used, obscuring a comprehensive view on the system
- Even within a specific model system many different experimental conditions are used, making it difficult to 'add up' data from different groups.
- Funding systems are almost without exception small-scale compared to efforts required to unravel the extreme complexity of biological/biomedical systems.

Obviously, the fragmented type of research has been and still is very successful and probably will be productive for at least another decade in that it generates important knowledge and can be published in leading journals. However, it is unlikely that this classic approach will lead to understanding of complex systems. Therefore, a new type of comprehensive, large-scale research programs should be initiated. A real life example in Box 2 illustrates this point. The size of a research program depends of its specific aim. Decisions in this respect require, much more than is the case now, a precise definition of the aims of a research program. Obviously, this is far from easy, because almost by definition the outcome of research efforts is difficult to predict. Therefore, the SBMS approach calls for new and intelligent project management strategies. These will be considered during the Berlin workshop.

7.3.3 *The data integration hurdle*

If one accepts that MetS research should scale up, this has several consequences. One is that data sets and modelling efforts of different research groups must allow integration in (eventually) a single comprehensive mathematical model. This requires standardization of model systems, experimentation and sample preparation, and modelling. From an early point on in developing the SBMS program SOPs (standard operation protocols) will have to be developed and subsequently adopted by all participants. A challenge will be to achieve standardization without hampering research efforts and make standardization procedures sufficiently flexible to allow adaptation if new insight requires this. There is some experience with this issue. One example is the German Hepatosys project (www.systembiologie.de/en/), which has internally agreed on working on one specific cell type and source of cells and has developed SOPs that are used successfully in different laboratories. Careful choices have to be made in the SBMS context in selecting one or more common experimental systems and developing SOPs. At the same time, it calls for adequate research program management, allowing adaptation of standards and SOPs if necessary. In developing the SBMS program, these aspects deserve special attention.

Standardization can be supported by setting up facilities for standard measurements and data analysis, as well as databases that can be used not only by program members, but also by investigators outside the SBMS program, provided that they commit themselves to the SBMS SOPs.

A key issue in the SBMS program will be data exchange and storage, data curation and data warehousing in general. This will require special efforts and investments. However, for the relatively small pilot program in Phase #2 of the Road Map we most likely can do with classical approaches and technologies in this in combination with the above-mentioned SOPs.

7.3.4 *The funding hurdle*

Funding of the SBMS program should come from coordinated action of different funding agencies, including the EC, national research councils and charities. These organizations already invest millions of Euros per year in the MetS and SB fields. In the context of an SBMS-like concerted effort, the cost-effectivity of these investments can increase considerably. Obviously, food and pharma industry also will have an interest in this. However, it is stressed that commercial benefits will become in reach only after a solid scientific foundation has been created by at least partially unravelling the highly complex networks that underlie the MetS disorder. A major challenge will be to convince major funding agencies that it is highly beneficial, if not absolutely necessary, to join forces and co-finance large scale research efforts, such as the SBMS program.

For very good reasons, research programs should start with competitive calls for proposals. To achieve a comprehensive research approach the format of SBMS calls will be somewhat different from classic calls. The format of an SBMS call must ensure that the program covers the specified field/problem in a truly comprehensive way. This requires precisely defining the aims of the program and splitting it up in a number of tightly interacting projects, each representing a specific task. Research groups/consortia of MetS and SB specialists may apply by presenting a proposal that describes in some detail the way they intend to carry out the tasks of one of the project in the context of the research program as a whole. This proposal is judged on the basis of scientific excellence and its fitting in and contribution to the aim of the program. We will have to develop

experience with this type of calls in the early stages of the SBMS endeavour.

8. SBMS ROAD MAP

The SBMS Road Map is shown in Fig. 2. Presently, Phase #1 is carried out. Preparations for Phase #2, the first SBMS research program, are on its way. This White Paper and the first SBMS workshop in Berlin (25-26 September 2008) are setting the scene for it.

	proposed main objectives	duration	approximate investment (M€)
Phase 1	<ul style="list-style-type: none"> ▪ develop governance structure ▪ agree on roadmap and major milestones 	12 months	0.2
Phase 2	<ul style="list-style-type: none"> ▪ start pilot research program 	18 months	6
Phase 3	<ul style="list-style-type: none"> ▪ expand research activities 	30 months	60
Phase 4	<ul style="list-style-type: none"> ▪ full-blast program execution 	60 months	200

Figure 2 The SBMS Road Map

8.1 Phase #1 is running

Phase #1 aims at developing the SBMS concept by discussing with fellow scientists, policy makers and funding agencies. Phase #1 activities have been financially and logistically supported by the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung (BMBF)). Phase #1 resulted in

- an international SBMS Steering Committee (Box 1),
- consultation of many key players
- organizing the first SBMS workshop September 25 and 26 (2008) in Berlin,
- this White Paper
- Both are starting points for defining the real start of the SBMS program in Phase #2.

8.2 Planning Phase #2

8.2.1 Aim of phase #2

In addition to addressing scientifically exciting issues, Phase #2 should help us to define best practices to overcome the hurdles defined in section 7.3.

- Integrate the MetS and SB disciplines.
- Integrate different projects that are carried out by different groups/consortia in different countries in a single synergistic research program.
- Develop procedures to define and implement standardization protocols.
- Acquiring experience with SBMS-type of calls for proposals.

8.2.2 Defining a research focus

Phase #2 of the SBMS Road map should start late 2009. Step one is to select a topic that suits the aims of Phase #2 as are listed below.

- It is scientifically exciting and challenging for both the MetS field and the SB field
- It allows the acquisition of experience with overcoming the hurdles addressed in section 7
- A research program that allows formulation of a precisely defined research aim that can be split up in a small number of tightly interrelated and synergistic projects, in order to formulate a goal-oriented call for proposals.
- A topic that is fit for standardization as alluded to in section 4.3.3.

How to select a topic for Phase #2? Ideas can be found for instance in the following fields: (i) functioning of the beta cell and (ii) insulin resistance. In these fields SBMS-like concepts have already developed here in the past few years. However, other ideas are welcome! It is proposed to start by drawing the contours of a small number

of potentials programs and subsequently select one among others based on the criteria defined above. The non-picked ideas should be used to develop Phase #3 of the SBMS Road Map (Fig. 2).

8.2.3 *Funding Phase #2*

Phase #2 requires between 5 and 10 M€ in order to initiate a useful pilot program, in which several aspects of the SBMS approach can be tried out and developed. Two main options will be pursued for financing Phase #2.

- Transnational funding in the order of 6 M€ by a small number of countries (2 to 3 years).
- Writing a FP7 application. The Health section will contain a call that in principle fits the SBMS aims (12 M€ 5 years).

Both options may be pursued in parallel, proposing closely related (adjacent) programs. Other funding opportunities are not excluded.

8.3 **Two examples of a Phase #2 research focus.**

Below two possible choices of a research focus for Phase #2 are briefly outlined. They are presented as examples, not excluding other choices. Decision making will start at the first SBMS Workshop in September.

8.3.1 *Contours of a Beta Cell program*

It is becoming increasingly clear that beta cell vulnerability is at the core not only of type 1 but also of type 2 diabetes. Glucose homeostasis is well maintained both in humans and in animal models as long as the ability of the beta cell to overproduce insulin in the face of insulin resistance is preserved. In fact, insulin sensitivity and beta cell response are not independent but are linked by a well known, albeit poorly understood, hyperbolic relationship, suggesting that the beta cell and peripheral tissues sensitive to insulin exchange a message of a still unknown nature. Interestingly, most of the 18 or so genes that have been detected in the genome wide-scans for type 2 diabetes are primarily genes that affect beta cell function; there is so far little evidence for major contributions of genes coding for proteins plausibly involved in insulin resistance. It has also become increasingly evident that the beta cell is not only a source of insulin, but also a major target of insulin signalling, and therefore may also be affected by insulin resistance. Thus, understanding the complex interrelationship between insulin secretion by the beta cell and insulin sensitivity in peripheral tissue is clearly key to modelling the pathogenesis of type 2 diabetes and metabolic syndromes.

Fortunately, there has been major progress in recent years in unravelling the complex developmental and physiological mechanisms that govern beta cell function, in part due to the drive to produce beta cells for transplantation of people with diabetes. We know the transcriptomics of beta cell development from stem cells and ductal cells, and maintenance of differentiated function, in great detail. The complex machinery involved in insulin secretion is also known in minute details, with some of the components being well-known druggable targets. The three-dimensional cellular architecture of the beta cell has been recently reconstructed in amazing detail by computerized electron tomography. The complex pathways of insulin signalling as well as apoptosis induced by immune processes, cytokines as well as glucose and lipid toxicity have also been unravelled. What is sorely lacking, and would be a major project of this proposal, is a multi-scale, multi-level model of a functional beta cell, in other words a “virtual beta cell”, that would integrate all the above mentioned levels of information into a workable dynamic model of the beta cell (not unlike the Hepatosys project), that would allow understanding its vulnerabilities and robustness. Information coming from the genome-wide scans should be integrated into the model.

8.3.2 *Contours of a Insulin Resistance program*

One of the hallmarks of the metabolic syndrome is insulin resistance. The term insulin resistance is in general not well defined. Here we consider insulin resistance to be defined by the effect of insulin on the rate of glucose utilization. The definition can be refined by specifying the organ which is considered i.e brain, muscle, adipose tissue, or liver. The effect of insulin on glucose utilization depends on a great number of signal transduction as well as metabolic pathways. Most of these pathways have been elucidated in detail. The dynamics and mechanisms of pathway regulation in a network environment are mostly not known. To investigate this crucial aspect, known pathways which are under coordinated control by for instance transcription factors will be lumped together to form modules. The metabolites and proteins that connect the modules in the network will be measured using metabolomics and proteomics. The activity of the modules will be modulated in the chosen models (human, mouse) and the effect on intermediary metabolites/proteins and glucose metabolism is determined. The resulting data-sets will form the basis for iterative model validation. Note that the networks will be different for the various organs under study but characteristics of regulation maybe similar.

9. **SBMS GOVERNANCE**

Running a highly goal-oriented research program requires special and in part novel management tools. At the one hand, participating groups should obviously have sufficient freedom to carry out excellent research, at the other hand the research effort should, throughout the program, remain highly focused and synergistic, leaving no space for 'take-the-money-and-run' attitude. Also, issues such as standardization and data integration across projects should be pursued and implemented in a convincing manner. This requires first of all a good overview what is going on, a strong vision where the program is heading and the ability to reformulate aims and standards whenever necessary, in good agreement with the participants. How to organize an efficient research management for SBMS program is still an open question that should be answered while developing the program and defining in more detail its aims and means. It is likely to have the following components.

- a strong scientific director
- an external high level advisory board
- an internal advisory board
- an small office for the paperwork and logistic activities, such as meetings, etc.

Any funding scheme should set money aside for this purpose.

10. **AIMS OF THE FIRST SBMS WORKSHOP (BERLIN, SEPTEMBER 25-26, 2008)**

The specific aims of the workshop include the following.

- discuss main aspects of the SBMS endeavour, in particular:
 - how to achieve integrative, goal-oriented and cost-effective MetS research by implementing SB as a driver and integrator
 - how to achieve standardization by SOPs (standard operating procedures) in experimentation, data collection, data analysis and integration and modelling
 - how to implement multi-scale approaches and analyses of biological systems, integrating the molecular, cellular, tissue and organismal levels
 - how to integrate disciplines, including biology, medicine, physics, mathematics and engineering
- make concrete recommendations for Phase 2 of the SBMS Road Map (which should prepare for expansion to Phase 3 and Phase 4 by a process of learning-by-doing), in particular about the following issues:
 - concrete research aim that fits the SBMS concept and that is realistic given an investment of in total 6 million Euro over a period of three years
 - contours of a multi-scale research program that achieves this aim
 - choice of model system(s)
 - standardization in experimentation, data collection, data analysis, data integration and modelling
 - effective program management and governance
 - approaches to achieve fruitful integration of MetS and SB disciplines
 - data management and data exchange
 - format of the call for proposals for a transnational Phase 2 program

The workshop will mostly consist of structured discussions, in part in break-out sessions, focusing on the above topics. There will be only a limited number of presentation. In the weeks before the workshop participants will interviewed to gather opinions and ideas, making the workshop as efficient as possible.

11. **CONCLUSIONS AND FOLLOW UP OF BERLIN WORKSHOP**

Based on the discussions in the breakout sessions and plenary meetings the following conclusions and follow up activities will be initiated.

11.1 **Long-term goal: the SBMS model and personal medicine**

The long-term (ten-years) goal of the SBMS program is to construct a predictive mathematical model (the SBMS model) that quantitatively describes the key aspects of the metabolic syndrome(s) in humans at the level of molecules, cells, tissues, organs and the whole body. This general SBMS model permits the projection of data from specific individuals (genetic and metabolic make up, food intake, etc.), allowing one to make an optimal personalized diagnosis, treatment and prognosis. The general model will play an essential role in developing effective prevention strategies and novel health food.

11.2 Developing SBMS Road Map Phase 2

Phase 2 of the SBMS Road Map will be pursued as follows. Two closely related grant applications will be submitted in December 2008. Both will be explicitly presented as part of the bigger integrated SBMS program and contribute directly to its aims and fitting its philosophy of cooperation and data integration as described elsewhere in this SBMS White Paper. One application will concentrate on the *molecular/cellular mechanism of insulin resistance*, the other on a *whole body model of interacting tissues*.

11.2.1 FP7 Health call September 3 2008

The relevant call is formulated as follows.

HEALTH-2009-2.1.2-1: Systems biology approaches for basic biological processes relevant to health and disease. FP7-HEALTH-2009-two-stage. The projects should focus on modelling important biological processes at any appropriate levels of system complexity by generating and integrating quantitative data sets (e.g. transcriptomics, proteomics, metabolomics, structural biology, RNAi screening, physiology and/or patho-physiology). These large multidisciplinary efforts should integrate the critical mass of excellence in Europe that is necessary for generating and validating the models using systems biology approaches. **Funding scheme:** Collaborative Project (Large-scale integrating project). **One or more proposals** are expected to be funded.
Topic for two-stage submission and evaluation; deadline 1st stage: 3 December 2008

Aim is to apply for a 5 years research program with a volume of 12 M€ The program will concentrate on the molecular/cellular mechanism of insulin resistance. Specific research groups in the SB and the MetS field will be invited to team up in this FP7 program. The deadline for the first stage proposal is December 3rd, 2008.

11.2.2 EraSysBio-Plus program

In this transnational program EU 10 countries cooperate to boost and coordinate the application systems biology in the life sciences. The call has been published October 15, 2008. See:

<http://www.erasysbio.net/AnnouncementCall>

EraSyBio+ call

The call focuses on “stimulating the widespread adoption of systems approaches in biomedicine, biotechnology and agri-food”, and it is open to joint transnational research proposals, with a maximum of 7 participants from a minimum of 2 ERASysBio partner countries (AT, DE, ES, FI, FR, IL, LU, NL, SI, UK). Regardless of its size, each collaborative consortium should have the optimal critical mass to achieve ambitious scientific goals and should clearly show the specific contribution of each research group and the added value from working together. Proposals may be submitted by research groups working in universities (or other higher education institutions), non-university public research institutes, hospitals and private companies. Small and medium-size enterprises (SMEs) are encouraged to participate. Applicants are advised to check for eligibility with their own funding organisation before applying. The submission and assessment of proposals will be performed in two steps and their evaluation carried out by an international peer review panel of experts.

In the context of this call we will submit a pre-application. This research program will concentrate on developing a whole-organisms model of the interactions between relevant tissues/organs, treating them essentially as black boxes. Specific research groups in the SB and the MetS field will be invited to team up in this FP7 program. The EraSysBio-Plus program has a two-stage application scheme. The deadline for the first stage proposal is January 3, 2009.

11.3 Initiating SBMS Road Map Phase 3

During the Berlin workshop it was concluded that we should make the first steps towards Phase 3 as soon as possible. Aim of Phase 3 is a transnational SBMS program of 60 M€ for 5 years. In this context we have started to draw the contours of such large-scale, highly coordinated program. We will shape Phase 3 in close contact with investigators in the fields of MetS and SB and with industry and funding agencies.

11.4 SBMS management

For each of the two proposals mentioned in 11.2 a formal coordinator will be selected from the participating scientists. Together with the Roel van Driel, Bert Groen and Johan van den Berg these two persons will

constitute the SBMS executive committee at least till the end of this year. This small group will ask for advise to the SBMS Steering Committee, which will be extended with several MetS and SB scientists that were active in and around the Berlin workshop.