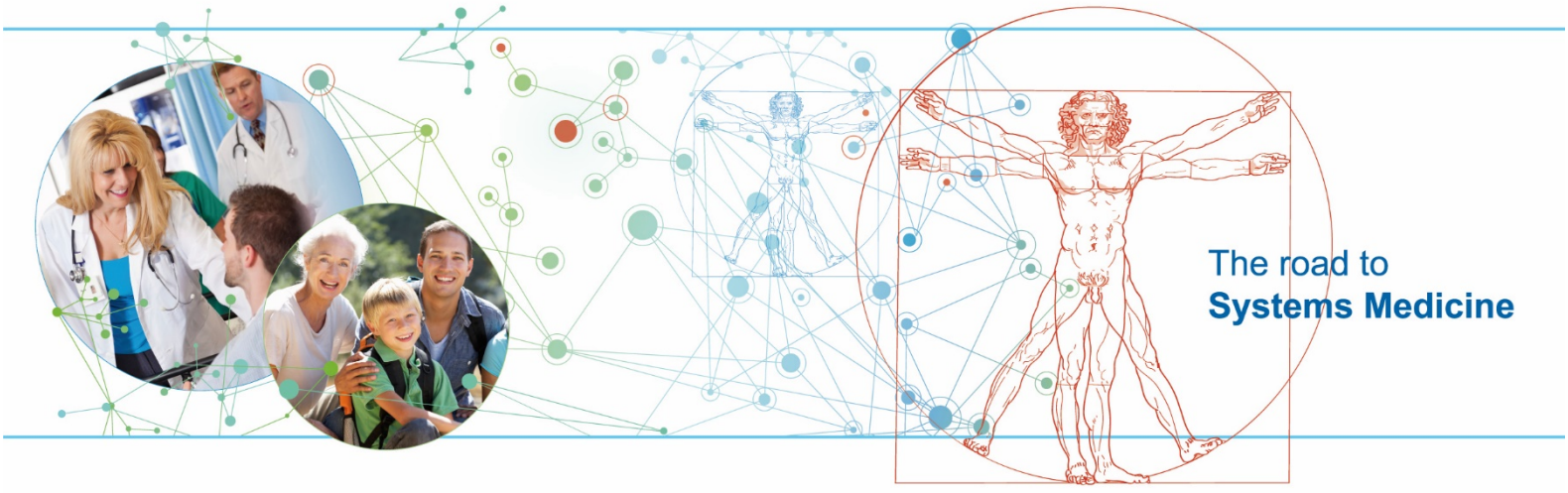
CASYM EUROPE

Coordinating Action Systems Medicine
Implementation of Systems Medicine across Europe

SEVENTH FRAMEWORK PROGRAMME



Europe-wide inventory of industry involved in Systems Medicine

REPORT

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IMPRINT

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INTRODUCTION AND AIM

Why an industry inventory for Systems Medicine?

Many consider modern medicine to bring huge potential to the healthcare market. The integration of clinical and omics data in computer models will lead to rationally based cost-effective drug and technology development. CASyM aims to speed up innovation in translational activities. As part of its objective to create an implementation strategy for *Systems Medicine* across Europe, CASyM inventoried the potentials and barriers of *industry* towards the medical and healthcare application of Systems Medicine (Systems Medicine). This inventory is part of CASyM Work Package 4 – Strengthening innovation activities, technology transfer and exploitation. In this report, CASyM outlines best practices with the aim of inspiring scientists, company management and investors to create new business based on a Systems Medicine approach.

METHODOLOGY

A three step methodology

This report is based on questionnaires and interviews with representatives from industry working in small and medium enterprises (SMEs) and large companies. As a general rule, a three-step methodology was used:

1) Online questionnaire
2) Telephone interview
3) Combined summary of questionnaire and interview

Interview candidates were initially contacted by e-mail. Candidates included full and associated CASyM partners, personal contacts of CASyM members and attendees at stakeholder events. There were no criteria for candidate selection and anyone interested in the subject could take part in an interview. Many of the interviewees were (co)founder of their company or CEO. Most of them came from European companies.
Several weeks before an interview, the candidate was sent an online questionnaire (see default questionnaire, section 7.1). Questionnaires were completed before interviews took place. During the interviews, the questions and answers from the questionnaire were discussed. When answers were unclear to the interviewer, additional questions were asked to clarify their meaning. The duration of each telephone interview was typically 45-60 minutes. All interviews began with the interviewer stating the *CASyM definition of Systems Medicine*: 'The implementation of systems biology approaches in medical concepts, research and practice, through iterative and reciprocal feedback between data-driven computational and mathematical models as well as *model-driven* translational and *clinical investigations and practice*'. In short, Systems Medicine is the *application of systems biology methods in medical practice*. Usually, within two weeks after the interview, the interviewer prepared a summary of the information provided in the questionnaire and the interview. This summary was sent to the interviewee for correction and approval. All approved summaries are included in the appendix (section 6). For privacy reasons, the answers to question 9 in the default questionnaire ('person or organization recommended for further contact') has been omitted from the interview summaries.

RESULTS

Numbers

This report is based on 31 interviews, mainly with representatives from industry (84 companies were contacted; response rate: 37%). In this report, the participating organizations are classified as large pharma (10), large technology (2), SME pharma (7), SME *in silico* (5) and other (3).

Systems Medicine – known and appreciated

Systems Medicine is highly appreciated by the companies interviewed. It is considered one of the key technological and scientific developments and challenges in the coming10-20 years. Industry considers the search for blockbuster medicine no longer sustainable because it involves huge costs and the outcomes of clinical trials are hard to predict and often disappointing. In the past, blockbuster drugs worked mostly for single-cause diseases and for 'the average person'. However, it is now clear that many diseases are multifactorial and cannot be treated with a single medicine. Moreover, recent technologies have shown us that the human being is complex and that humans can differ a lot from each other. Therefore, the companies interviewed identified alternative approaches and have started to implement them in their core business. Systems Medicine is one such approach. Industry uses Systems Medicine to model and simulate patients groups (generic, child, gender, genotype), drug action and drug distribution. This is followed by laboratory experiments and comparison with real patient data. In relation to the companies interviewed, Systems Medicine can be applied well in oncology, cardiovascular diseases, neurodegenerative diseases, ageing, immunology, inflammation and chronic disorders.

There are slight differences in the way that SMEs and large companies use Systems Medicine:

- Large pharma companies use Systems Medicine approaches in a translational way to get the best results out of their clinical trials, to understand diseases at a mechanistic and molecular level and to understand the action of drugs in human physiology using modelling and simulation. The pharmaceutical industry recognizes that it is generating more and more data, but that it often falls short in fully leveraging data for decision making. Applying Systems Medicine will improve the interpretation of available data. It should result in a holistic, integrated view of disease and treatment options. In this way, better and quantitative decisions are expected to be made for patients and the economy.
- Technology-driven industry aims to use Systems Medicine to predict the causes of disease and treatment results for use in medical imaging, personal diagnostics and personal therapy (*non-drug*, e.g. ultrasound, chemo, radio). It uses ICT-based tools to model and simulate human physiology and apply computer models for personalized and predictive healthcare.
- *SMEs* vary a lot in the way they use Systems Medicine approaches. Most SMEs are positioned on niche markets. Some companies specialize in silico approaches and make *models* in order to understand diseases. The models are based on the literature and are fed with patient data, either virtual data or data from real samples and biopsies, and are further developed for subsets of patients. Other SMEs are positioned in diagnostics and use Systems Medicine approaches to stratify patients in order to select those who will best respond to a treatment. Finally, some SMEs test approved drugs combination in order to find new treatments.

Successful application of Systems Medicine

Industry believes that Systems Medicine approaches will lead to better drugs or technology, further geared towards personalized treatments. There are various demonstrator and close-to-market projects that underpin the success of the approach, both in an industrial and academic setting, and show that in certain disease areas, Systems Medicine results in more accurate disease knowledge and treatment options than classical approaches. This has convinced some companies to proceed and expand the Systems Medicine approach in their area of business. Many others argue that a much larger portfolio of proof of concept studies is needed to convince the entire field of clinicians, academic and industrial collaborators and investors.

In pharmaceutical companies, many of the drug compounds tested using Systems Medicine are in the pre-clinical or clinical trial phase. As a defined concept, Systems Medicine has not been around long enough to have led to drugs that are already on the market. Companies need some ten years to translate new concepts into products. As a consequence, it is too early to prove that the application of Systems Medicine reduces a product's time to market.

A promising application of Systems Medicine that is already being used by several SMEs to develop new treatments involves *in silico* models of human disease pathways. They are based on literature research and non-confidential information on *existing* drugs and experimental results and are used to predict drug effects that may not be known and are not claimed by the manufacturer of the registered drug. Often a combination of two such registered drugs leads to the development of an innovative and more accurate therapy with fewer side effects.

Many companies consider *public-private partnership (PPP)* [1] a successful concept for an evolving field like Systems Medicine. In a PPP, industry (both large companies and SMEs) joins forces with academic groups of scientific excellence. Usually, a PPP is established in a field where fundamental knowledge is lacking and further exploration is needed. As such, a PPP is interesting for both types of partners. Industry rarely invests in a PPP in an area that it considers to be its own core business (e.g. development, clinical trials and marketing of specific drugs).

Gaps and needs in the application of Systems Medicine

Before Systems Medicine can become part of the daily routine in industry, several hurdles must be overcome:

- There is a need for a wide range of demonstrator and proof of concept (POC) studies, especially for *in silico* modelling:
  - In some *companies*, higher management wants additional proof to fully convince themselves of the suitability of *in silico* modelling approaches compared to traditional drug discovery methods (from lead to phase III trials).
  - In a *clinical* setting, systems and modelling approaches are considered too abstract. Its value is therefore not appreciated. Thus, confidence in this approach would benefit routine clinical practice.
  - *Regulators* must be convinced of the validity of *in silico* modelling approaches.
- There is a need for training and human resources. There are only a few trained systems biologists that understand clinical needs, and vice versa there are only a few medical doctors who are trained in data-driven and quantitative approaches. As a consequence, there are too few ambassadors for Systems Medicine in their respective daily practices.

[1] A public-private partnership is defined as collaboration between research institutions and industry, defined as a long-term arrangement whereby one or more research institutions collaborate(s) on a project with one or more private partners, each party retaining its own identity and responsibility, and working on the basis of a clear and appropriate allocation of tasks and risks.

- Sustainable funding is required to develop strong new business in this discipline. Such funding should come from industry as well as governments. SMEs are dependent on collaboration with academic and clinical partners, especially in the start-up phase, and they often find it difficult to obtain funding for projects that must lead to POCs.
- Many human diseases prove to be much more complex than anticipated. Understanding disease mechanisms costs a lot of time and effort.
- The quality and availability of clinical phenotypic data is presently insufficient. Patient samples need to be standardized. Access to data needs to be facilitated. Biobanks should have sufficient sample material to enable re-analysis of samples. These are prerequisites for the integration and interpretation of data.
- There are many European initiatives in systems approaches. These initiatives should work together and become a single voice for the community.
- Governmental rules and guidelines should be unified. There are too many country-specific laws and reimbursement mechanisms.
- Public-private partnerships in national or European consortia require early integration into emerging projects, easy-to-follow processes for project partnership and access to contact points and partnership forums.
- Potential buyers at large pharmaceutical companies have not yet developed the expertise to discriminate between providers of in silico approaches.

SMEs using in silico approaches mentioned gaps specific to their business:

- In the field of medical technology and informatics, SMEs face strong competition from academia and large companies
- IT know-how is difficult to protect
- SMEs have limited internal resources for joining projects outside the core business of the company
- There is a strong need for proof of concept to convince potential clients
- There is a need to communicate the different technologies developed, their complementarities and how they should be used

Business models for the application of Systems Medicine

Business models for Systems Medicine depend largely on the area of the research and type of industry.

For large pharma, the current business model for developing blockbuster drugs is no longer sustainable. Companies are therefore searching for different models in order to:

- Develop more patient-specific products in a shorter period of time. A holistic, integrated view of disease and treatment options is needed first. Once such fundamental knowledge has been obtained, drugs for specific subpopulations can be developed. Applying Systems Medicine will facilitate better and quantitative decisions for both patients and the economy.
- Gain access to knowledge through cooperation. A PPP with academia and SMEs is considered effective for rapidly obtaining scientific knowledge. The required scale of investment is so large that it will not be provided outside of a partnership model. In general, academic partners are best in up-front science. Moreover, university clinics have access to patients. On the other hand, industry is usually best in understanding diseases and turning a discovery into a marketable

product. In a PPP, research can be considered a “phase 0” trial (prospective, monitor efficacy, no treatment) using small patient groups. Risks and rewards should be shared between academia and industry.

For SMEs, several models are considered advantageous:

- Knowledge generation by modelling, where the intellectual property (the model) is kept within the company and the output of the model is sold.
- Discovery and development of drug candidates and generation of pieces of intellectual property (IP), until an inflection point is reached to trigger interest from large pharma. Then, either a licensing deal is agreed or a portfolio of IP is sold to a virtual standalone company (single asset company) financed by a venture capitalist and/or pharma company.
- Business services and intellectual property on new lead and drug targets facilitating industry collaborations.
- Combination of existing drugs (or drugs close to the market) and the beneficial effect of that combination predicted in silico. Regulative demands are expected to be easier met when existing drugs are used.
- Fee-for-service is valued by some, but is rendered unprofitable by others.
- Use of pension funds to attract a more stable and long-lasting investment. This approach consists of applying the financial engineering technique of securitization to drug candidate assets.
- Cooperation with healthcare insurance providers and healthcare providers. As an example, in the USA, health care providers cooperate with physicians in the clinic in order to minimize costs and optimize therapy.
- Awareness of the perspective and procedures of regulatory authorities and making that an integrated component throughout all steps of research and drug development.

Industrial needs from policy makers

Industry representatives mentioned several needs that must be met by national governments, funding agencies and the EU:

Proof of concept portfolio: industry would appreciate CASyM compiling and hosting a POC portfolio on its website. The interviewed persons believe that company management would be more open towards Systems Medicine if its success stories were validated and readily available. Moreover, POC may facilitate access to the market for the procedures of regulatory authorities.

Open access to data: the information and data generated in publicly funded research projects should be openly available for everyone. Open access to data, knowledge and expertise is crucial to ensure that not only funded projects but the field as a whole benefit from the massive amount of funding invested in this area.

Funding programmes specifically for disruptive industrial innovation: national governments and the EU should facilitate disruptive innovation by means of specific funding schemes allowing for cooperation between scientists from academia, industry and clinics.

International trade federation of SMEs: one SME explicitly recommends the creation of a trade federation of SMEs in order to help non-experts discriminate between the various approaches (bioinformatics, mathematical modelling, heuristic modelling, etc.). The main objective is to reduce the market's opacity and thus facilitate adoption.

CONCLUSIONS

Improve the interpretation of disease data

Industry is very interested in Systems Medicine, and many companies in the field of modelling, technology development and drug development are already applying it. Systems Medicine is considered a requirement for a better understanding of disease mechanisms, portfolio optimization and for identifying new technology, drug targets and patient subsets. Systems Medicine will accelerate the development of personalized medicine.

Collaborate

Public-private partnerships are highly appreciated and considered crucial because they combine different areas and traditions in science and healthcare. PPPs should always start and end with the needs of the patient. Open discussion should facilitate a clear focus on the gaps and technological challenges of the future (not of those of today).

Proof of concept

Presently, there are only a few cases showing proof of concept and this collection needs to be enlarged. However, there is a lack of robust and widespread proof of concept that restrains industry in making large-scale investments in the Systems Medicine approach. Industry would benefit from an online POC portfolio and a ‘global standard’ of quality guidelines for in silico approaches.

Provide access to data

Improved mechanisms for accessing and using patient data are required for research purposes while the privacy of the patient is ensured. Computational models can only be created and used accurately when a sufficient amount of high-quality data is available and a data management infrastructure has been implemented. The focus should be on specific disease subsets represented by homogenous and well-characterized patient subpopulations.

FOLLOW-UP INTERVIEWS

Systems Medicine development

At the end of CASyM, follow-up interviews were held with the four industrial CASyM partners (MicroDiscovery, AstraZeneca, Bayer Technology Service, Sanofi-Aventis) to evaluate progress in Systems Medicine over the years (2013-2017). In general, the CASyM industrial partners concluded that the Systems Medicine approach is adopted more broadly compared to the early phase of CASyM in 2013.

- Companies, including management and clinical collaborators, have now adopted the Systems Medicine and *in silico* approaches.
- There has been a paradigm shift from compound to patient centered data bases.
- Clinicians are getting involved earlier in the Systems Medicine approach, i.e. at the preclinical testing phase.
- Data access is being facilitated, however, the use of patient's data brings about regulatory hurdles that are reducing the speed of progress.
- Modelling has gotten a significant role in early-phase clinical trials.

In conclusion, in the past few years, several industrial hurdles and bottlenecks in the application of Systems Medicine have been overcome. Clearly, awareness of the approach has been increased. Now, with the new knowledge gained, questions and gaps can be identified more precisely and more focussed. So, we have come a long way, but we are not at the final destination yet.

ANNEXES

Interview summaries

Default questionnaire

Coordinating Action Systems Medicine
Implementation of Systems Medicine across Europe

WP4 - Strengthening innovation activities, technology transfer and exploitation

Systems Medicine is the **application of systems biology methods to medicine**, in CASyM defined as "The implementation of Systems Biology approaches into medical concepts, research and practice, through iterative and reciprocal feedbacks between data-driven computational and mathematical models as well as **model-driven** translational and clinical investigations and practice´´

Public-Private Partnership (PPP) is a collaboration between research institutions and industry, defined as a long-term arrangement whereby one or more research institutions collaborate(s) on a project with one or more private partners, each party retaining its own identity and responsibility, and working on the basis of a clear and appropriate allocation of tasks and risks.

Your organisation:

Name person:

Function person:

Address:

E-mail:

Website:

Organisation type:

Involved in CASyM:

Date interview

1.	**Are you familiar with the term Systems Medicine as defined above?**	*No / Yes, since…*	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**		
3.	**Does your organisation apply Systems Medicine according to the definition above?**	*Yes / No* *If yes, please elaborate here and below:*	
		Number of projects:	
		General topic of projects:	
		Type of projects: (e.g. PPP, purely industrial)	
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	*Please provide examples (innovations, case studies, proofs of principle and success stories):* - *Which one?* - *Who was involved? Contact names / details?*	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	*Please, provide examples*	
6.	**In which way can Systems Medicine be important for industry in the future?**	*Please, elaborate*	
7.	**What would be a good business model to apply for Systems Medicine?**	*Please, elaborate*	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	*If yes, please elaborate. E.g. type of projects, number of projects, which department, collaboration with other organisations*	
		Number of projects:	
		General topic of projects:	
		Type of projects: (e.g. PPP, purely industrial)	
		Approximate total budget of projects:	
9.	**Which person / organisation do you recommend we should contact as well?**	*Please provide us with the contact information (name, organisation, department, function , email and phone number.)*	
10.	**Any recommendation or comment on the subject of Systems Medicine ?**		

Interview Johannes Schuchhardt

Your organisation:	**MicroDiscovery**
Name person:	Johannes Schuchhardt
Function person:	Chief Scientific Officer
Address:	Marienburgerstrasse 1, 10405 Berlin, Germany
E-mail:	johannes.schuchhardt@microdiscovery.de
Website:	www.microdiscovery.de
Organisation type:	SME
Involved in CASyM:	Full partner
Date interview	7 February and 5 April 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes. MicroDiscovery is a full partner in CASyM. The reason to join is a fundamental scientific interest in systems medicine as well as the chance that systems medicine gets commercially important.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes. MicroDiscovery is a bioinformatics company providing software solutions and data analysis in the areas of innovative diagnostics, personalized medicine and biomolecular research. MicroDiscovery focuses on the areas of custom software development for biomedical applications, analysis of next generation sequencing data, statistical data analysis by targeted algorithms and houses a profile database containing various –omics data generated in cross-omics high throughput studies. It is an SME of approximately 20 people. MicroDiscovery's clients include biotechnology and pharmacy companies and academic institutions.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Partially according to the definition. MicroDiscovery is involved in data analysis and data management projects, including data-driven computational and mathematical (mainly statistical) models, developing concepts. The work does not yet include model-driven translational and clinical investigations and practice. In two projects (see below) data management is performed in the context of medical questions. Through a profile database high throughput data are made accessible for biologists and clinicians in terms of visualization, statistical analysis, correlation (e.g. gene-protein level) and integration. Beyond data analysis, previous research projects include the construction and simulation of mathematical models for metabolic diseases with a focus on type II diabetes. In addition projects in systems biology have been performed in cooperation with the Max Planck Institute for Infection Biology addressing dynamics of NFkappaB signalling. The project is model-driven, not aiming to understand a disease. So MicroDiscovery does have experience with mathematical modelling (models where formulated in terms of stochastic and non-stochastic differential equations) but sees its expertise and role primarily on the data driven side of systems medicine.	
		Number of projects:	A supportive role in several projects.

		General topic of projects:	Two projects are funded by the EU and by the Ministry of Education and Research (BMBF). - Colon cancer project, in cooperation with Charité University Berlin - Glioma / brain tumor project, in cooperation with the National Institute of Biology and the Blood bank of Slovenia
		Type of projects:	PPP
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	The opportunity to cooperate in PPP with outstanding academic groups is highly valued. The reason to work on governmental funded projects is that they give MicroDiscovery the opportunity to keep up with the scientific developments, come into contact with organizations, and gives the general option to develop novel methods.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	The impression is there is still a conceptual gap between the data driven approaches relying on simplified (usually linear) statistical models and the model driven approach usually coming along with the formulation of very specific questions. In any case, achieving full validation of a (molecular) model is usually very cost intensive, because many parameters need to be tuned or checked. Costumers usually have little interest in software improvements or new software from other companies. Next to this, excellent academic groups often produce open source products instead of trying to commercialize it in cooperation with a company. Finally, there is a fierce competition in getting a software product to the market.	
6.	**In which way can Systems Medicine be important for industry in the future?**	Commercially, Systems Medicine data management can be important for industry. The fields of image analysis in particular brain imaging may bring a number of interesting applications. For a bioinformatics oriented company commercialisation can be challenging, because the market is still very much guided by a hardware oriented paradigm, this is observed at least in biotechnology. Scientifically, it is difficult to judge if and which Systems Medicine tools and models can be important for industry.	
7.	**What would be a good business model to apply for Systems Medicine?**	- Model based consulting - Decision support processes, using mathematical models. These may be difficult to sell or to attract potential clients, though - Correlating imaging data (e.g. MRI) with statistical or mathematical models or data interpretation tools. In terms of systems medicine this should extend towards disease prognosis and diagnosis - Extending software products for data management towards clinical analysis - Supporting mobile access to patient information for the clinician - Supporting mobile testing of diseases	
8.	**Does your organisation**	Three projects are on the topic of translational research.	

	apply related methodologies (e.g. systems biology, translational medicine) ?	**Number of projects:**	3
		General topic of projects:	One of the projects is in cooperation with the Leiden University Medical Centre and focuses on Cancer biomarkers and the development of tools for decision support for clinicians. Other projects are addressing evaluation of clinical data in the context of neuro-degenerative diseases and typically employ classification systems (machine learning),and multiple markers for diagnostic or prognostic tasks.
		Type of projects:	PPP
		Approximate total budget of projects:	

Interview Claus Bendtsen

Your organisation:	**AstraZeneca**
Name person:	Claus Bendtsen
Function person:	Head Computational Biology
Address:	UK
E-mail:	claus.bendtsen@astrazeneca.com
Website:	www.astrazeneca.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date interview	12 March 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	In part. We recognize that we are increasingly generating data, but often fall short in our abilities to fully leverage data in our decision making.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, in order to form an integrated understanding of our data in support of investment decisions. AstraZeneca started 3 years ago in Systems Medicine.	
		Number of projects:	Over 10
		General topic of projects:	Many disease areas except for neuroscience. The aim of the projects is to increase quantitative understanding as well as hypothesis generation. In this way a more informed decision making in clinic and better understanding of disease will be generated. Models should be more than just descriptive and must show efficacy and safety. The models should be more than statistical and should help in design of pre-clinical assays, identify (plasma) biomarkers and aid in understanding the design and the results of clinical trials.
		Type of projects:	Mostly purely industrial but examples of PPP, CROs and consultancies.
		Approximate total budget of Systems Medicine projects:	(not disclosed)
4.	**What are best practices in Systems Medicine projects in terms of innovation and**	NIH white paper on Systems Pharmacology There are some proofs of concept in cardiovascular area and oncology.	

	exploitation?	In oncology, experimental data are generated, cells screens performed, xenografts and animal models used and clinical trials performed. In cardiovascular area, ion channels are modelled, electrophysiology performed, data are available and clinical trials performed.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	The limiting factor is not so much the limited number of successful models, but the complexity of human disease and the data availability Areas that are not yet well understood: - Inflammation (respiratory), infection (therapy resistance mechanisms) and immunology, since models are complex and difficult to make - Neuroscience, since in clinical trials brain measurements cannot be performed and good brain models are not available	
6.	**What would be a good business model to apply for Systems Medicine?**	The current business model in pharmaceutical industry is not sustainable. Therefore, AstraZeneca is searching for different models. One of them is Systems Medicine, in order to get a holistic, integrated view of disease and treatment options and make more sense out of available data. In this way, better and quantitative decisions are expected to be made for patient and economy.	
7.	**In which way can Systems Medicine be important for industry in the future?**	More informed decisions for drug development and better outcomes for patients.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, increasingly during the last 10 years	
		Number of projects:	Hundreds
		General topic of projects:	There are a few systems biology projects, in order to get a basic understanding of cell function. These projects are different from the abovementioned Systems Medicine projects
		Type of projects:	An increasing number of PPP are performed. These projects are beneficial for basic understanding of health and science.
		Approximate total budget of projects:	(not disclosed)

Interview Andreas Schuppert

Your organisation:	**Bayer Technology Services**
Name person:	Andreas Schuppert
Function person:	Key Expert
Address:	Germany
E-mail:	andreas.schuppert@bayer.com
Website:	www.bayertechnology.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date interview	13 March 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, we expect significant contributions to improved efficiency of the pharma R&D workflows. By using systems approaches, Bayer aims to obtain *information*. Bayer claims state of the art in Systems Medicine worldwide.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, since we do Systems Pharmacology since more than 10 years for customers in Pharmaceutical and Biotech Industry worldwide. Moreover, we invest significantly in own research and academic collaborations. We simulate patients by modelling the patient (generic, child, gender, genotype) and model drug action and distribution. Bayer employs well trained modellers and systems biologist, decreasing wet lab research in favour of in silico research.	
		Number of projects:	Appr. 10 running at present. In all, 50 projects have been initiated.
		General topic of projects:	Systems Pharmacology, modeling of drug action in man, optimization of clinical trials. Focus on cardiology, hematology, oncology, diabetes.
		Type of projects:	All kinds. Mostly industrial projects (clinical trials). PPP with academia through the Virtual Liver Network and in BMBF funded grants. The strategy for PPP is to extend existing, fundamental knowledge.
		Approximate total budget of Systems Medicine projects:	Appr. 3 million euro's annually
4.	**What are best practices in Systems Medicine projects in terms of innovation and exploitation?**	Real success stories are limited, due to the lack of PoC. It will take 10 years to get a drug, developed by using systems medicine approaches, into the clinic.	

5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	-Data driven approaches are sufficiently available, but mechanistic modelling is limited yet. -Human resources (trained systems biologists) are limited at the moment -Budget in clinic and health care sector is scarce -Medical doctors are not trained in data driven and quantitative approaches, thus need to get convinced that Systems Medicine is of help in their daily practice	
6.	**What would be a good business model to apply for Systems Medicine?**	- Cooperation with health care insurances and health care providers. In the USA health care providers cooperate with physicians in the clinic in order to minimize costs and optimize therapy - By providing Systems Medicine services to other companies. Overall, the business model depends on the scientific progress in a certain area	
7.	**In which way can Systems Medicine be important for industry in the future?**	Improvement of the drug R&D efficiency	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes. Systems Biology, however, has not proven to aid in curing disease or prediction in the clinic	
		Number of projects:	Appr. 10
		General topic of projects:	Biomarkers, Biological Networks, Multi-omics approaches, molecular approaches.
		Type of projects:	
		Approximate total budget of projects:	Appr. 3 million euro's annually
9.	**Any recommendation**	Through open discussion, get a clear focus on the gaps and technological challenges of the future, not of those of today. Focus on the need of the patient. International collaboration (including PPP) is crucial, since it combines different areas and traditions in science and health care.	

Interview François-Henri Boissel

Your organisation:	**Novadiscovery**
Name person:	François-Henri Boissel
Function person:	Chief Executive Officer
Address:	60 avenue Rockefeller 69008 Lyon, France
E-mail:	francois.boissel@novadiscovery.com
Website:	www.novadiscovery.com
Organisation type:	SME
Involved in CASyM:	Associated Partner
Date interview	13 and 27 March 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2000. The company Novadiscovery started in 2010, basing its science on this emerging field.
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Undoubtedly yes. The seamless integration of biomedical knowledge and real-world patient data will dramatically improve our understanding of disease processes, open up avenues for new treatments, rationalize R&D spending by reducing in-vivo/in-vitro trial-and-error, enable personalized treatment decision-making and optimize healthcare delivery.
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Systems medicine is at the core of Novadiscovery's expertise. We develop mathematical models of diseases in a variety of areas (cancer, cardiovascular, infectious diseases, etc.) in order to identify and develop innovative treatments as well as deliver personalized medicine capabilities. Novadiscovery applies Systems Medicine by working with a team of “biomodelers”, typically trained as engineers and/or mathematicians (MSc) supplemented by a strong background in biology/biomedical sciences (PhD). The biomodelers read scientific literature on specific diseases, extract information on all mechanisms involved in a particular disease (from genes to populations) and assign a strength of quality of the information extracted (or “quality score”) to the way the studies are set up. In most cases, studies and knowledge extracted are discussed with scientific experts (typically clinicians expert in the disease). The biomodelers then build a multi-scale (dynamic) mechanistic graphical model, using biological, clinical and real world patient data as well as data from drug candidates. This first deliverable is called the “Knowledge Model”. It is a multi-layered map of all the mechanisms involved in the disease of interest (see Appendix 1). This Knowledge Model is then converted into mathematical equations and ultimately computer code. It becomes a “Formal Model”. In parallel, a “Virtual Population” of patients is developed, taking into account real-world patient data drawn from epidemiological studies or biological datasets. By combining the Formal Model and the Virtual Population, a large number of assumptions can be tested in a predictive framework (see Appendix 2), thanks to the discovery of the Effect Model Law (see Appendix 3). In this framework, the

<table>
<tr><td></td><td></td><td colspan="2">benefit of a potential drug is reflected by the difference between the incidence of an event caused by illness in treated patients in relation to untreated patients, using the same virtual target population. By varying the characteristics of the target population, effects of drug candidates can be tested on specific patient populations, thereby leading towards personalized medicine.</td></tr>
<tr><td></td><td></td><td>Number of projects:</td><td>Currently 4 R&D programs, 1 fundamental research and 1 technology development project.</td></tr>
<tr><td></td><td></td><td>General topic of projects:</td><td>R&D: lung transplantation, acute stroke, sepsis, lung cancer.

Fundamental research: biomedical knowledge and uncertainty management.

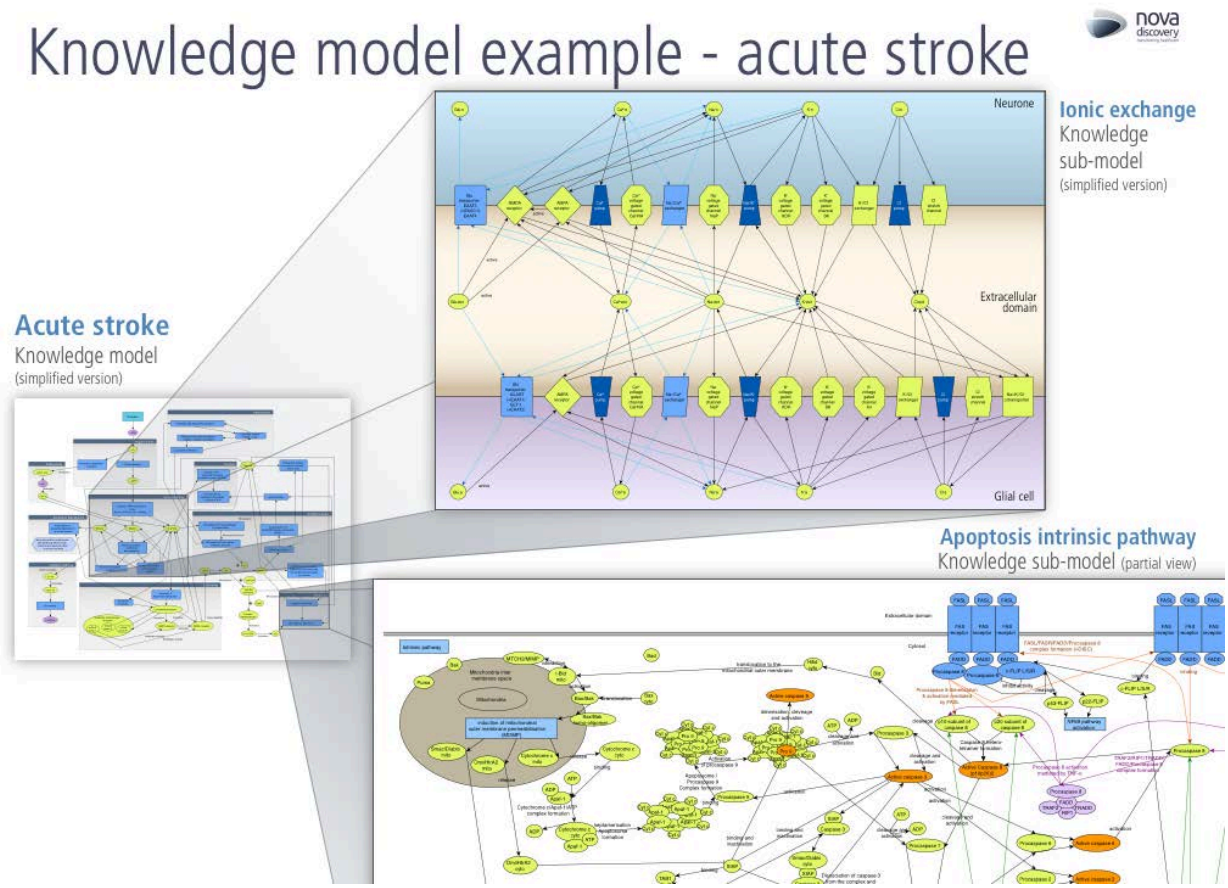
Technology development: knowledge and data management, modeling and simulation platform (see Appendix 4).</td></tr>
<tr><td></td><td></td><td>Type of projects:</td><td>A mix of (i) internal, (ii) collaborations partially funded through research grants and (iii) industrial partnerships.</td></tr>
<tr><td></td><td></td><td>Approximate total budget ofSystems Medicine projects:</td><td>Currently circa1 million euro’s, expected to grow 10x within the next 24 months.</td></tr>
<tr><td>4.</td><td>What are best practices in Systems Medicine projects in terms ofinnovation and exploitation?</td><td colspan="2">In terms of best practices, we are developing internally our own SOPs with regards to knowledge and uncertainty management, quality control, therapy responder profiling, etc. Another fundamental element Novadiscovery is engaged in is the development of a formal evaluation framework to help regulators and pharma companies understand how to assess Systems Medicine simulation results.
Novadiscovery has produced or assembled (based on previous work from Nova’s researchers before the company’s incorporation) a number of PoCs ranging from dose-effect prediction to new indication identification. Please refer to the PoC posters attached in a separate document.</td></tr>
<tr><td>5.</td><td>What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?</td><td colspan="2">Widespread adoption of Systems Medicine is currently hindered by a lack of convincing success stories and PoC. What is needed is a large-scale proof of concept applied to a drug R&D program where the value of in silico technology can be established.

Gaps towards widespread in silico modelling approaches and Systems Medicine:
- Regulators need to get convinced of its validity
- Higher management of large pharma companies need to be convinced of its suitability, compared to traditional drug discovery methods (from lead to phase III trials)
- Modelling is not yet understood by many people and is therefore not appreciated
The Systems Medicine field would benefit from a ‘global</td></tr>
</table>

		standard' of quality guidelines for in silico approaches. This standard should be made by scientific and clinical experts. Agencies (regulators & payers) should be involved in the process as they will be instrumental in the widespread adoption of systems-based approaches throughout the industry.
6.	**What would be a good business model to apply for Systems Medicine?**	There are broadly speaking two segments where Systems Medicine can be applied: new drug R&D and medical practice. With regards to the former, given the technology's lack of maturity and poor traction with large pharma, both modelling software licensing and fee-for-service models are currently thought not to be viable. Another approach would be to focus on a proprietary R&D model. This is highly capital intensive and should preferably not be executed along a traditional biotech model. The recommended approach is to structure a virtual pharma ecosystem where the original IP is generated using Systems Medicine (new target(s), repurposing, combinations) before it is transferred to a standalone single or portfolio Asset Company which in turns receives funding from venture capitalist firms. The assets are then licensed out to a large pharma once a first inflection point is reached. This approach consists in applying the financial engineering technique of securitization to drug candidate assets. The product/market fit for personalized medicine applications in daily medical practice is certainly easier to establish. However, start-ups will face issues with regards to distribution channels, direct involvement in regulatory matters (possibly so far as to conduct trials) and limited exit opportunities. More generally, Novadiscovery expects providers of Systems Medicine solutions to gradually evolve from a cost-plus pricing tactic to a value-based one once the ecosystem accumulates sufficient evidence.
7.	**In which way can Systems Medicine be important for industry in the future?**	Systems Medicine is the only way forward to put breakthrough innovation back at the heart of the drug discovery process. There is a significant amount of knowledge available about disease mechanisms that can only be structured and made actionable through Systems Medicine approaches.
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	The core is Systems Medicine. All of our aforementioned R&D projects draw on the full scope of systems-based methodologies, from cellular level up to population level.
		Number of projects: |
		General topic of projects: |
		Type of projects: |
		Approximate total budget of projects: |
9.	**Any recommendation**	We fully support the CASyM and similar initiatives as we are convinced that "coopetition" among the players is the most suitable strategy at this stage of the market's development. Unfortunately, a number of SMEs are stuck in a "competition" mode which effectively curtails the widespread adoption of these game-changing approaches. We strongly recommend the creation of an international trade federation of SME providers in order to help non-experts discriminate between the various approaches (bioinformatics,

		mathematical modelling, heuristic modelling, etc.). The main objective is to reduce the market's opacity and thus facilitate adoption. Novadiscovery has indicated it would gladly take the lead in setting up this federation. One of the single most important levers to accelerate adoption is, in our mind, the agencies (regulators & payers). Significant emphasis should be laid on helping these stakeholders understand the benefits of Systems Medicine. Once this primary objective is achieved, we can assume large pharma will naturally invest in it.

The knowledge model



The Knowledge Model consists in a series of entities involved in the disease mechanisms. These entities are grouped into submodels to facilitate exploration and documentation. In the particular case of sepsis, those submodels are:

- The inflammatory response;
- The molecular model of both the coagulation and the fibrinolytic pathways;
- The molecular model of cell energy metabolism cascade;
- A phenomenological model linking the fall in ATP production to the failure of a representative organ;
- The model of immune system response.

The modelling process

The modelling process at Novadiscovery consists in a series of sequential steps before the delivery of a validated disease model.

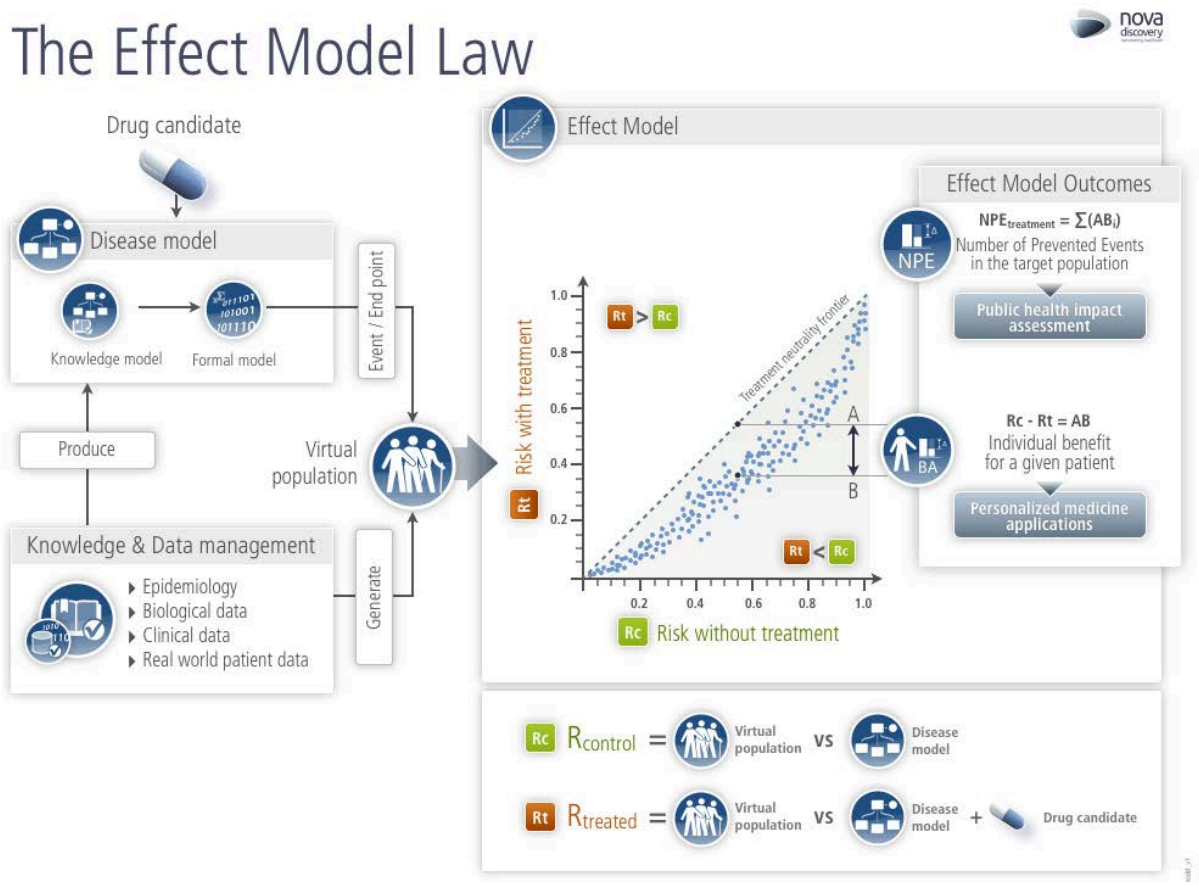
First, a Knowledge Model is developed in partnership with disease experts. It consists in a graphical representation of all the entities that have been identified as playing a role in the disease mechanism.

Once validated, the Knowledge Model is converted into a Formal Model, i.e. a series of mathematical equations. These are in turn converted into computer code to enable simulations.

The Virtual Population is developed in parallel to the disease model.

The calibration is performed with available data. Model validation consists in a two-step process: first, the model is operated to reproduce experimental data that was not used during the calibration process. Then, the model is operated to tryand reproduce knowledge that was not formerly incorporated into the Knowledge Model design phase.

The effect model law



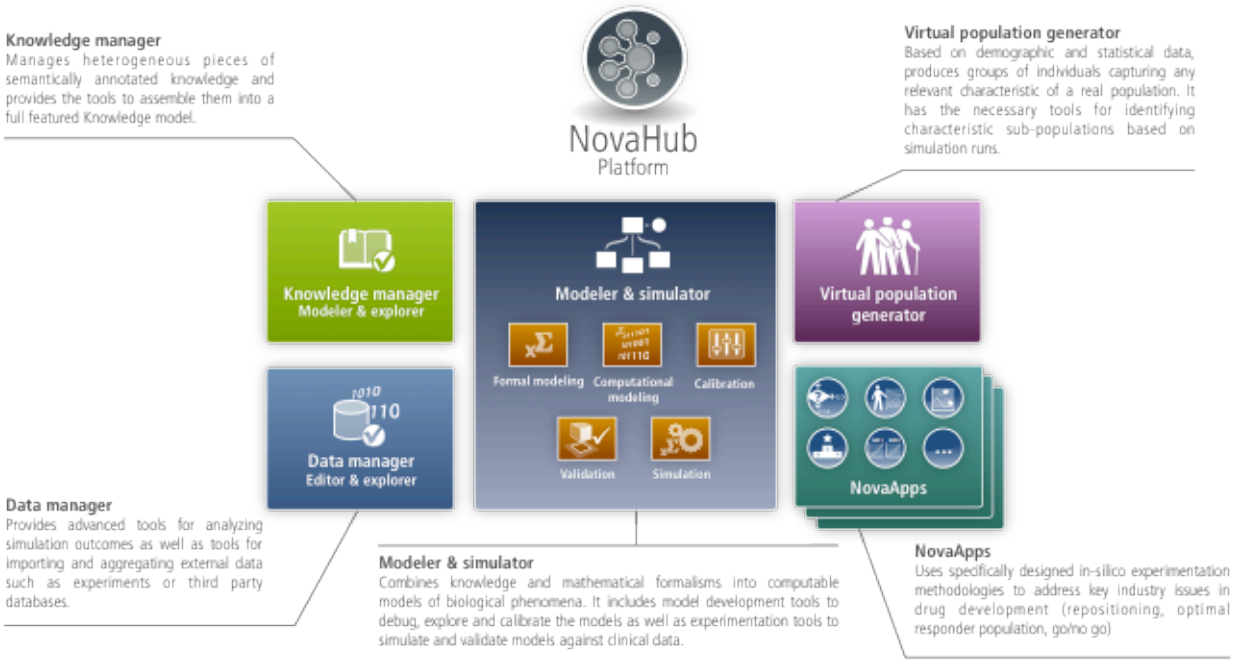
The Effect Model Law states that a natural relationship exists for each individual between the frequency (observation) or the probability (prediction) of a morbid event without any treatment and the frequency or probability of the same event with a treatment. This relationship is called the Effect Model. It applies to a single individual, individuals within a population, or groups. The relationship is specific to a therapy, a disease or an event, and a period of observation.

In a personalized medicine context, the effect model enables the prediction of the (absolute) benefit of a treatment for a given patient.

By summing up absolute benefits over the entire population of patients, it enables the early prediction of the treatment's public health impact with the estimation of the Number of Prevented Events.

Evidence of the existence of the Effect Model Law is supported by empirical observations, simulations as well as a theoretical demonstration.

Modelling simulation platforms



Novadiscovery is developing a modelling and simulation platform to support its research efforts. It is a collaborative environment which enables the seamless integration of partners to a given project.

Interview Phillipe Sanseau

Your organisation:	**GlaxoSmithKline**
Name person:	Philippe Sanseau
Function person:	Global head Computational Biology
Address:	Gunnels Wood Road, Stevenage, SG1 2NY, United Kingdom
E-mail:	philippe.x.sanseau@gsk.com
Website:	www.gsk.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	Associated partner; GSK was involved in preparative initiatives leading to CASyM
Date interview	14 March 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2011	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, Systems Medicine is an important scientific component within the next 10-20 years. This is driven by the nature of the data available and the computational tools being developed. For example, it is likely to impact our mechanistic understanding of drugs, their targets and the diseases context (potential impact is on all major phases of the drug development pipeline). It could reduce attrition and costs in drug development. Some of challenges are around, demonstrating clearly value in a medicine development context. We should not underestimate the cultural challenge, either since it is likely to lead to a different way of working with data, different interactions etc.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, mainly categorized as Systems Pharmacology. Biological modelling at GSK is relatively small and has limited resources, but would like to invest in this area. There is some mechanistic modelling going on, but at present it is mainly qualitative data analysis.	
		Number of projects:	Appr. 7
		General topic of projects:	Systems pharmacology Biological networks (e.g. genes, diseases, etc), Synthetic biology, Pathways analysis. Respiratory and immuno-inflammation. Near future: microbiome.
		Type of projects:	Industrial and in collaboration with academic researchers in a PPP. GSK chooses to work with academia as much as possible and has opened data from clinical trials to society. By sharing data GSK aims to attract new collaborators.
		Approximate total budget of Systems Medicine projects:	(not disclosed)

4.	**What are best practices in Systems Medicine projects in terms of innovation and exploitation?**	- Application to specific scientific questions where systems medicine approaches are the best way (scientifically and financially) to solve the problems. - In our case we work on specific case studies rather than large projects. We do it early in drug development, and integrate Systems Medicine with classical PK/PD modelling from phase I to phase II.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	Truth vs. buzz. We need realism in what can be delivered by Systems Medicine. Presently, biological in silico modelling is not yet really trusted as being beneficial in drug development outside PK/PD modelling	
6.	**What would be a good business model to apply for Systems Medicine?**	-Pre-competitive activities in common biological pathways, disease models, tools (especially if no compounds are included) -Shared risks and rewards between academia and industry (can include projects with compounds) -Work with external experts	
7.	**In which way can Systems Medicine be important for industry in the future?**	- Reducing attrition and costs (e.g. faster development, less patients, no animal studies, better biomarkers) - Improved mechanistic understanding of target/drug relationships - Greater understanding of diseases underlying physiology, pathways -Feasibility studies, providing value and competitive advantage -Potential to cure diseases / more personalised approaches -Making decision making faster: go on with drug candidate or stop the project	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes	
		Number of projects:	Appr. 20-25
		General topic of projects:	Examples: Translational biomarkers, Rapid translation into experimental studies, Pathways analyses, Diseases networks, Cell function
		Type of projects:	PPP, purely industrial and in collaboration
		Approximate total budget of projects:	

Interview Manfred Hendlich & Thomas Klabunde

Your organisation:	**Sanofi-Aventis**
Name person:	Manfred Hendlich (MH) Thomas Klabunde (TK)
Function person:	Translational Bioinformatics Coordinator (MH) R&D Head Computational Biology & Bioinformatics (TK)
Address:	Industriepark Höchst, Building H831, 65926 Frankfurt, Germany (MH)
E-mail:	Manfred.Hendlich@sanofi.com Thomas.Klabunde@sanofi.com
Website:	www.sanofi.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date interview	19 March 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since approximately 2010	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, - Improved translation of preclinical findings - Improved understanding of complex diseases - Patient stratification Furthermore, Systems Medicine can be used to find the correct dosing in the clinical situation and be used in telemetric medicine	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, in a systems pharmacology way in e.g. diabetes research, but not applied to the patient yet	
		Number of projects:	Appr. 10 (Sanofi employs 25 experts in this field)
		General topic of projects:	- Different aspects of Systems Medicine are applied in a variety of projects, e.g. target credentialing, biomarker discovery, PK/PD modelling. - Oncology and diabetes - Drivers of disease and drug candidates, including mechanistic modelling and data analysis
		Type of projects:	- PPP and purely industrial - In the IMI initiative (PPP) disease progression is researched and results flow toward clinical environment
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices in Systems Medicine projects in terms of innovation and exploitation?**	Not aware of any	

5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	Missing knowledge of context specific biological networks topology and dynamics. Access to patient data / not enough longitudinal epidemiologic studies. Improved mechanisms for using patient data for research purposes are required while ensuring data privacy aspects. Data management infrastructure is not optimal. In USA data from trials and patients are more easily shared than in Europe. The EU needs to focus more on data sharing and be less strict in data privacy. Otherwise, medical breakthroughs will not occur in EU.	
6.	**What would be a good business model to apply for Systems Medicine?**	- Cooperation of large pharma with SME and academia, in order to rapidly obtain scientific excellent knowledge. This can be considered as a “phase 0” trial (prospective, monitor efficacy, no treatment) using small patient groups (Charite university Berlin and Heidelberg university) - Systematic mapping of diseases - Model based drug discovery	
7.	**In which way can Systems Medicine be important for industry in the future?**	Improved translation of preclinical findings, Target credentialing, drug combinations, patient stratification	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, systems biology, translational medicine and model-based drug discovery	
		Number of projects:	Appr. 10
		General topic of projects:	-Improve translation of preclinical findings. IMIDIA to understand the role of the pancreatic beta cell in the generation of diabetes; modelling of glucose-insulin homeostasis and drug action to translate animal in vivo and human in vitro data into computational prediction of drug effect in humans -Pathway and network understanding -Omics
		Type of projects:	PPP and purely industrial
		Approximate total budget of projects:	

Interview Adriano Henney

Your organisation:	**Obsidian Biomedical Consulting (OBC) & Virtual Liver Network (VLN)**
Name person:	Adriano Henney
Function person:	Owner (OBC) Programme Director (VLN)
Address:	University of Heidelberg, Im Neuenheimer Feld 267, 69120, Heidelberg, Germany
E-mail:	adriano.henney@obsidian-biomed.com adriano.henney@virtual-liver.de
Website:	www.virtual-liver.de
Organisation type:	1-man consulting company (OBC) National flagship research programme (VLN): 250 participants, 69 Principal Investigators, 44 Projects and 40 Institutions in Germany, including SMEs and Pharma
Involved in CASyM:	Associated partner
Date interview	25 March 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since it was first proposed	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, the Virtual Liver programme is focused on delivering to the clinic in a way that reflects the Systems Medicine agenda	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, in my opinion Systems Biology represents a toolbox that can be used in various disciplines, like in medicine. In the VLN, liver physiology in health and disease is studied, e.g. fatty liver, inflammation, regeneration following injury. In the VLN board, several clinicians are present.	
		Number of projects:	44
		General topic of projects:	Multi-scale modelling of liver function and physiology
		Type of projects:	Academic and industrial, working as an integrated network. It's largely academic. The industrial partners are Bayer and one *in silico* SME. The companies have a more applied / translational view and projects are at the interface of clinical pharmacology. Two clinics (Stuttgart and Kiel) have patient studies. As a flagship programme, VLN does not have deliverables, but aims for scientific blueprints.
		Approximate total budget of Systems Medicine projects:	The VLN budget is 44 M€ over 5 years

4.	**What are best practices in Systems Medicine projects in terms of innovation and exploitation?**	'Systems Medicine' hasn't been going long enough as a defined concept to have success stories in my view, but SysBio applied to medicine as a forerunner has had some success stories: the use of the ion channel heart model to support registration by the FDA of Ranolazine is an example. Some other examples of utility were shown in cancer studies to understand mode of action also.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Many cultural aspects related to reluctance to accept the approaches; - Failure to understand what Systems Medicine and SysBio are; - Lack of clarity what precisely are the clinical imperatives to address and how best to deliver what a patient and clinician need to implement approaches; - Building confidence in the clinic that Systems Medicine is of added value - Time constraints of practicing clinicians - Fragmentation in EU, thereby lacking a single voice of the systems approach. CASyM should aim for leadership, with one person as the "ambassador". - Too few interactions with regulatory authorities We have to deliver: - Example models across scales - Evidence that Systems Medicine is of utility in the clinic	
6.	**What would be a good business model to apply for Systems Medicine?**	Difficult to pinpoint to one business model, since Systems Medicine by definition represents a variable toolbox. Joint ventures seem to be the most promising, presently. In general, business could profit from: -Improved understanding of the dynamics of disease, leading to more efficacious, tailored therapies. -Impacts on the patient, the discovery and development of new medicines and the design of more efficient clinical trials	
7.	**In which way can Systems Medicine be important for industry in the future?**	I would suggest that the model devised by the BMBF to fund the Virtual Liver Network could be a useful blueprint/ starting point to consider	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, see all the answers above	
		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	
9.	**Any recommendation**	CASyM should make a proposal for Horizon2020, in which physiology, medicine and patients are addressed.	

Interview Alain Huriez

Your organisation:	**EPEMED**
Name person:	Huriez
Function person:	Chairman
Address:	Luxembourg
E-mail:	ahuriez@epemed.org
Website:	www.epemed.org
Organisation type:	non for profit
Involved in CASyM:	No, but present at the second CASyM stakeholder meeting, round table 'What business models for industries involved in Systems Medicine?', Lyon, 25 March 2013.
Date interview	17 May 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2011. EPEMED is not involved in CASyM, but is in general aware of Systems Medicine, biomedicine and integration of data. On an international level, we are in contact with industry in France and with the Luxembourg Centre of Systems Biomedicine.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, as a method for discovery of new targets, portfolio and research optimization, data integration and validation of current marketed drugs. Systems Medicine may fundamentally alter biotechnology into generation of more precise drug targets. Analysis and knowledge about interaction and integration of genes and proteins will lead to optimized use of the data and will show the relevance of the data. Systems medicine or systems biology will bring another approach in optimization of current drug targets and the generation of new, better targets. EPEMED can be considered a think tank or lobby among stakeholders, developing a concept for realizing personalized medicine in Europe. Through the production of knowledge like by webinars, white papers, position papers and conferences and market assess studies we try to create awareness and guiding decision makers to stimulate research in personalized medicine. The goals of EPEMED are broader than just Systems Medicine. Partners in EPEMED include large and small pharma companies, IT and diagnostic companies, clinicians, etc. EPEMED members pay a member fee. In our view the difference between Systems Medicine and Personalized medicine is small, since both concepts focus on market access. In the future, our studies other project and might be systems medicine.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	No, EPEMED is a non for profit association dealing with Personalised medicine.	
		Number of projects:	N/A
		General topic of projects:	

		Type of projects:	
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	Not fully aware	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	My guess is that examples should be provided and sustainable funding would be required to develop strong new business in such discipline. Commercial proof of concept of new drug targets is needed. The discipline is fully recognized to qualify for funding. A full translational research towards business is needed. Investors should pay for it.	
6.	**In which way can Systems Medicine be important for industry in the future?**	For portfolio optimization and finding new drug targets. Areas include neurodegenerative disease like Parkinson, ageing, immunology, inflammation, chronic disorders and more. Systems biomedicine would very well apply in these areas.	
7.	**What would be a good business model to apply for Systems Medicine?**	Services business and intellectual property on new lead and drug targets, allowing industry collaborations. Service companies would be good, when the Intellectual Property is kept within the company. Fee-for-service companies will not be viable in this area.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, personalized medicine	
		Number of projects:	We finance one project, funded by our members.
		General topic of projects:	We organize a conference
		Type of projects:	Market access hurdles and challenges in Europe for drug diagnostics, The focus is on molecules that are already approved together with a biomarker that is approved by the EMA. In the future we will fund more projects, always with a maximum duration of one year.
		Approximate total budget of projects:	150 k€

Interview Manuel Gea

Your organisation:	**BIO-MODELING SYSTEMS**
Name person:	Manuel Gea
Function person:	Co-founder; CEO
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E-mail:	manuel.gea@bmsystems.net
Website:	www.bmsystems.net
Organisation type:	SME
Involved in CASyM:	No, but present at the second CASyM stakeholder meeting, round table 'What business models for industries involved in Systems Medicine?', Lyon, 25 March 2013.
Date interview	18 July 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2010. We pioneered this area and were invited by the EC for the workshop 'from systems biology to systems medicine' in 2010 where we presented best practices in late phase Creutzfeldt-Jakob disease.
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, BMSystems applies the systems medicine approach since 2004.
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, except we only develop non-mathematical models for discovery. In our view, life mechanisms cannot be described by Cartesian tools. Instead, we use heuristic models (problem solving approach evaluating each step in a process, from different points of view, using all available qualitative data, searching for satisfactory rather than optimal solutions). BMSystems develops *in silico* models of human disease pathways, based upon literature research, and non-confidential information of existing drugs and experimental results. By combining two of such registered drugs, we develop innovative therapy without side effects, since our models predict drug effects not known and claimed by the producer. Subsequently, collaborating companies validate our models in the lab and in small patient cohorts for their proof of concept. This approach is quite successful and since 2006 we make profit. We are already delivering results that led to patents and spin-off companies (Pherecydes Pharma) and out licenses (New Co). A new model for a novel therapy for Parkinson disease was developed and the validation phase will soon start. In the future, the spin-off companies may discover new drugs or perform clinical trials. BMSystems employs both biologists and informaticians. We developed Computer-Assisted Deductive Integration (CADI™) proprietary methodologies and tools for Disease understanding / (re)definition, Target discovery / validation, New therapeutic strategies, and New association / combination of existing drugs. CADI combines organic non-linear integration (brain intelligence) and *in silico* data processing power (collecting,

		structuring and manipulating data) to build validated biological interaction maps that describe biological reality. It can describe the dynamics of a pathological process and/or a pathological status vs. control and allows to switch from "symptomatic" to "causal" medicine, predicting and identifying pertinent biomarkers and proposing new therapeutic strategies. The CADI models belong to the non-mathematical holistic and heuristic class of models. It does not make exact maps of the complex reality, but makes pertinent representations that gather the minimum knowledge and intelligence necessary to describe a living process in a defined context and allows researchers to take the best possible decisions for the best possible results.	
		Number of projects:	5 programs under development: Decius(chronic anxiety) Idunn (neurodegenerative diseases therapy)Psy Lico (schizophrenia and bipolar diseases), New Co (done, spin-off company of CEA life Sciences one of our key our research partner launched; psychotropic medication) Pherecydes Pharma (done, spin-off company launched; developing bacteriophages (phages) to rapidly detect and/or kill a large range of bio threats). Synthons (industrial biotech) is now finished as a program.
		General topic of projects:	Discovery of new mechanisms and proposition of new therapies. Go / no go decisions for next phase programs.
		Type of projects:	These programs are collaborative programs with partners that have experimental capabilities and clinical expertise. These programs are self funded; because we do not want to disclose our methodology / models since that they are the basis of our company.
		Approximate total budget of Systems Medicine projects:	Self funded confidential programs of approximately 1M€ each.
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	Not aware of real success except our own programs, because of the complexity of systems medicine that requires multi-scale inter systems cross talks modelling.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	Scientists and experts should stop searching under the street light. We need disruptive thinkers that aim for things we can do instead of what we should do. We need to learn about human physiology, talk to patients and get a holistic view. We need generalists instead of specialists. Medical doctors need to understand modelling, and vice versa. Our company is looking for veterinarians, paediatricians or coroners with a strong broad biology physiology and genetic	

		background, because they are used to treat patients that cannot speak, so they are trained to use heuristic problem solving approach . And we search for informaticians/biologists from the former Eastern Europe, since due lack of availability of computers they are used to use their brain and imagination.	
6.	**In which way can Systems Medicine be important for industry in the future?**	The systems medicine could be of some help for diseases where animal models do not simulate the disease (CNS).	
7.	**What would be a good business model to apply for Systems Medicine?**	PPP with industrial partner, clinicians and SME. The business model of BMSystems is to develop heuristic models/platforms that are kept as own property of the company and are not sold. Costumers pay fee for service: pathways, results and visual representation for their specific aim and area. We prefer long-term relationships. Customers include major pharmaceutical and, cosmetics companies and for industrial biotech chemical, environment and energy companies. In an area that BMSystems has no experience in, we prefer to co-develop with a partner (academia or industry). In an area in which we are experienced, we are more in the lead and choose established partners to collaborate with. BMSystems as a company stays with its core business of heuristic modelling. When IP is generated, the patents are placed in spin-off companies, aimed at developing therapies.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, for areas where human tissue samples cannot be used (e.g. brain), we use animal models	
		Number of projects:	6
		General topic of projects:	Systems biology and Translational medicine
		Type of projects:	
		Approximate total budget of projects:	
9.	**Any recommendation**	How to support real disruptive innovations? The European Commission should better support and give real chances to people and companies that think differently. The European Commission should not structure its selection process on the consensus of experts only, since that eliminates disruptive innovation. The non-consensus of experts about a program should be a good starting point to orientate the program to a specific evaluation process BMSystems is working on.	

Interview Anthony Rowe

Your organisation:	**Janssen R&D (Johnson&Johnson)**
Name person:	Antony Rowe
Function person:	Informatics
Address:	High Wycombe, Buckinghamshire, UK
E-mail:	arowe4@its.jnj.com
Website:	www.jnj.com
Organisation type:	Healthcare/Pharmaceutical
Involved in CASyM:	No, but present at the CASyM stakeholder meetings in Lyon, 25 March 2013, and St.Andrews, 13 May 2013.
Date interview	19 July 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since I got involved in IMI projects in 2010. The Innovative Medicines Initiative (IMI) is an public-private partnership between the European Union and the European Federation of Pharmaceutical Industries and Associates (EFPIA) aiming to speed up the development of better and safer medicines for patients.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Systems Medicine is seen as a key areas of strategic importance to the informatics teams. To design better therapies, systems approaches are crucial in obtaining an overall, integrated view. Persons with a background in systems approaches, machine learning and simulation of disease pathways are working in each of the five therapeutic areas that J&J covers: Neuroscience, Immunology, Cardiovascular, Infectious Disease and Oncology.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, I am involved in eight IMI projects that have Systems Medicine approaches for collecting patient samples, do biological profiling, using systems biology in areas like severe asthma and colon cancer.	
		Number of projects:	Personally 5-10 J&J wide appr. 20-50
		General topic of projects:	In each of our five therapeutic areas there are elements of Systems Medicine research
		Type of projects:	PPP like IMI, internal, collaborations with university and sometimes collaboration with SME when they have specific expertise like IT
		Approximate total budget of Systems Medicine projects:	Not known, but might amount up to 80 M€
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	Some IMI projects that started 3 years ago are now starting to provide case studies, but they have not yet delivered a best practice. As an academic case study, the chronobiology project presented by Francis Levi in the CASyM stakeholder meeting in Lyon was a good example. It included patient recruitment, sample and data analysis, modelling and SOPs. Public-private partnerships are important in areas where	

		there is little knowledge, or when it gives access to additional patients for inclusion in trials. PPP provides a mechanism to share costs to enable studies at a scale that is cost prohibitive for any single organisation. Our best experience with PPP is when a new and specified area is investigated and a new dataset is built, since this often leads to a real shared vision and goal of the team. Especially the younger generation is very open to cooperate in such a team.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	Over-promising and under-delivering. At present, routine discovery and validation of biomarkers using a Systems Medicine approach still seems unrealistic. It needs more time and effort to become a routine. There are no short cuts. In this respect, the reductionist approach is of additional value, since it gives information on details and specified areas. Systems Medicine has to demonstrate its own effectiveness before it will be widely accepted as a methodology by our traditional drug discover teams.	
6.	**In which way can Systems Medicine be important for industry in the future?**	By developing reusable platforms for research that industry can contract/collaborate with to explore research into specific patient populations	
7.	**What would be a good business model to apply for Systems Medicine?**	Currently, it is only the PPP model that works for system medicine, since the technology is unproven and the costs are high. The required scale of investment is so large (20-40 M€ for a single study) that it will not be provided outside of a partnership model.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, systems biology approaches are becoming more common to help disease understanding and in the area of poly pharmacology. Informatics tools that help to translate between human and pre-clinical data are being evaluated and will see more use in the upcoming years.	
		Number of projects:	20
		General topic of projects:	Biomarker discovery and validation
		Type of projects:	PPP, internal, collaborations
		Approximate total budget of projects:	

Interview Birgit Schoeberl

Your organisation:	**Merrimack Pharmaceuticals**
Name person:	Birgit Schoeberl
Function person:	VP of Research
Address:	One Kendall Square, Suite B7201, Cambridge, MA 02139, USA
E-mail:	bschoeberl@merrimackpharma.com
Website:	www.merrimackpharma.com
Organisation type:	Biotech
Involved in CASyM:	Associate partner
Date interview	18 August 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes. I obtained my PhD in Systems Biology 13 years ago. The natural extension of Systems Biology is Systems Medicine i.e. implementation of Systems Biology approaches in medical concepts, research and practice. Personally, I expanded my work to Systems Medicine by joining Merrimack Pharmaceuticals about 10 years ago. Merrimack was founded on Systems Biology. We are using Systems Biology to understand the mechanisms underlying disease and use this understanding to design novel oncology drugs.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, Systems Medicine is part of our 'DNA' and we use it throughout the drug development process. Merrimack as a company emerged from Systems Biology efforts at MIT and Harvard. We plan to use our continuous learning to advance the field of Systems Biology and Medicine. The implementation of Systems Biology is a major challenge. At Merrimack, we believe that interdisciplinary teams are key to success. Currently, Merrimack has 260 employees; 90 percent of our researchers are experimentalists and 10 percent are modellers.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes. We aim to mechanistically understand the driving forces of tumor growth and to use those insights to develop novel medicines. Based upon literature, proprietary experimental preclinical and clinical data, we develop computational models with the goal to identify patients most likely to respond to our therapies and to define the clinical development strategy. Presently, we have six oncology therapeutics in clinical development.	
		Number of projects:	Six clinical, two pre-clinical and a number in discovery phase
		General topic of projects:	Oncology
		Type of projects:	Mostly private-academic partnerships. In PPP, we collaborate with scientific groups of academic excellence with common interests.

		Approximate total budget of Systems Medicine projects:	N/D
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	Merrimack internal projects: MM-121: signal inhibitor for multiple cancers (breast, ovarian, lung), currently being tested in a broad clinical development program in collaboration with Sanofi Oncology. MM-111: bispecific signalling inhibitor currently in Phase2 clinical testing for gastric cancer Academic work by Peter Sorger, Doug Lauffenburger and Mike Yaffe (Koch center at MIT) or LungSys project of the DKFZ in Germany.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Insufficient quantitative data of high quality available to allow the building and use of computational models - Broad, interdisciplinary education is needed - Pitfalls: inability to collaborate and communicate	
6.	**In which way can Systems Medicine be important for industry in the future?**	Systems Medicine helps Merrimack, and the industry as a whole, to understand complex biological systems, identify new targets, and to design better drugs. Systems Medicine ultimately helps scientists, doctors and researchers put personalized medicine to practice. A Systems Medicine approach can shorten development times and costs.	
7.	**What would be a good business model to apply for Systems Medicine?**	From a business perspective, Systems Medicine can best be implemented in an integrated pharmaceutical company or used by healthcare providers (hospitals, insurances) to help optimize care.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Systems Medicine, also known as Systems Biology at Merrimack, is part of our DNA. We also strive to do outreach as a platform for our research, as we have partnerships with patient advocacy organizations, like the Pancreatic Cancer Action Network (www.pancan.org) to educate patients and physicians about Systems Medicine.	
		Number of projects:	>6
		General topic of projects:	oncology
		Type of projects:	PPP
		Approximate total budget of projects:	N/D

Interview Bernd Eisele

Your organisation:	**VPM – Vakzine Projekt Management**
Name person:	Bernd Eisele
Function person:	CEO and Chief Medical Officer
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E-mail:	eisele@vakzine-manager.de
Website:	www.vakzine-manager.de
Organisation type:	Service provider
Involved in CASyM:	No
Date interview	27 August 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2011 when I visited LCSB in Luxemburg. They are performing Systems Medicine on Parkinson's disease.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes. Also, for VPM Systems Medicine will become of importance.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	No, not yet, but we plan to apply it in the future. VPM started 10 years ago. At that time a better vaccine for lung tuberculosis was needed, both in terms of immune efficacy as safety. The ministry funded the project; our collaborators were in the Paul-Ehrlich-Institute, involved in medicinal product legislation. We started with our philosophy of backward planning, from clinical testing backwards toward the lab. In that way, no important steps in a drug registration document will be missed. Now we are doing a similar approach on the subject of bladder cancer, driven by a clinical need.	
		Number of projects:	Currently we have 5 drug targets, of which 1 is in clinical phase and 3 are in pre-clinical phase. We would like to license in or license out and do the co-development.
		General topic of projects:	Vaccine candidates, e.g. for the prevention of human cytomegalovirus, (HCMV) infections, or interferon for treating multiple sclerosis and hepatitis C.
		Type of projects:	Our research is a collaboration of researchers, clinicians and regulatory bodies.
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms**	Not aware.	

	of innovation and exploitation?		
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	There are a lot of strict rules getting a drug candidate from the lab to phase III trials and ultimately the patient in a clinic. Not only rules on safety, but also on distribution and marketing and the starting material has to be clearly defined. We have to follow these, to get a product in a registration document. When there is only one red flag in all of the steps, nobody will licence it.	
6.	**In which way can Systems Medicine be important for industry in the future?**	- Identifying potential new products - Insight in the mechanistic level of disease - Address clinical needs	
7.	**What would be a good business model to apply for Systems Medicine?**	VPM would not change much in its current business model of 1) backward planning and 2) in collaboration with regulators. VPM uses a Project Management group, working in a structured way, keeping the regulators independent since VPM is in charge of preparing the advice. Systems Medicine might add to this business model.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Translational medicine and product development	
		Number of projects:	15
		General topic of projects:	Lung disease, cancer, vaccines, ALS. There are many common pathways in diseases.
		Type of projects:	collaboration with Academia, VC, biotech and big pharma
		Approximate total budget of projects:	
9.	**Any recommendation?**	Do not neglect challenges in the regulatory path, even when the idea is brilliant!	

Interview Hans Hofstraat

Your organisation:	**Philips Research**
Name person:	Hans Hofstraat
Function person:	Vice President
Address:	High Tech Campus 34, 5656 AE Eindhoven, the Netherlands
E-mail:	Hans.hofstraat@philips.com
Website:	www.research.philips.com
Organisation type:	Industrial Research Organization
Involved in CASyM:	No
Date interview:	28 August 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since we are working on many concepts derived from a systems medicine way of thinking in our healthcare research program. Philips is an active participant in the FP7 program Virtual Physiological Human that aims for i) patient-specific computer models for personalised and predictive healthcare and ii) ICT-based tools for modelling and simulation of hman physiology and disease-related processes.
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, since in the future healthcare will become quantitative, measurable, tailored to the person and to some extent pre-emptive, and hence cost effective. Systems Medicine is one of the approaches that supports reaching this objective. Philips is working at the interface of medical technology and biology. Our research often involves a solution based on a combination of Measurement (imaging, physiology, in vitro diagnostics) and Modelling (statistical and algorithmic). The model is a combination of biology and technology. Our research is data driven. It involves data generation and processing, and data-based modelling and prognosis. We aim to identify the cause of disease and predict the treatment result.
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, with noting that we do not develop medicines, but are involved in healthcare solutions based on medical technologies, such as medical imaging, personal diagnostics and therapy (e.g. digital pathology, image-guided interventions, electrophysiology, vital signs monitoring). Some areas and examples from Philips Research: - Radiation therapy and radiation oncology treatment planning: location of tumor and metastases, of vulnerable organs, tumor modelling, dosed radiation, modelling of damage to surrounding tissue. - Biological pathways underlying tumor growth: pathway diagnosis, study of tissue pathology and design of an optimal treatment plan.. - Cardiovascular modelling and interventions: minimally invasive image-guided treatment of atherosclerosis, ultrasound-aided local treatment of arrhythmia. - Neurology/neurodegenerative diseases: get a better, objective view on Alzheimer's disease. - Respiratory models of the lung, e.g. COPD: image and measure the respiratory performance of patients

		- Support in Intensive Care Units: patient monitoring (pO2, ECG, heart rate). Monitoring vital signs of patients at a distance in ICU's. Reduce false alarms and identify earlier life-threatening situations through intelligent interpretation of the data.	
		Number of projects:	Dozens
		General topic of projects:	Solutions based on medical technologies and data intelligence.
		Type of projects:	PPP and industrial. In our research always multidisciplinary teams are involved consisting of bioinformaticians, physicists, clinicians, biologists and engineers, most often involving clinical partners and users, including patients. We adopt a 'co-creation' approach to the research projects we are involved in.
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	Many of the VPH projects. A good example is the euHeart project (www.euheart.eu), which was a European research initiative targeting the personalized diagnosis and treatment of cardiovascular disease. It was a close collaboration between clinicians, researchers, SME and academia.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Systems biologists often work far from daily clinical practice. - Animal models and *in vitro* models are difficult to translate into the clinic	
6.	**In which way can Systems Medicine be important for industry in the future?**	By delivering healthcare solutions that improve people's lives: the patient and the healthcare system have to benefit from it. Some examples: - Prevent that people must seek complex treatment through the provision of earlier diagnosis or pre-emptive action. - Provide the most effective treatment, tailored to the person. - Provide more efficacious and higher quality solutions. - Provide effective treatment outside the hospital, e.g. manage patients at home.	
7.	**What would be a good business model to apply for Systems Medicine?**	Provision of meaningful solutions with proven outcomes by - Addressing a clinical unmet need. - Applying cost-effective care - Applying high-quality, 'first-time-right' care Systems medicine can provide the means to provide healthcare to patients in an objective (instead of subjective) manner, providing proven outcomes.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	User need inspired research and development. Every solution we develop is geared towards the patient in a translational approach.	
		Number of projects:	Dozens
		General topic of projects:	Solutions based on medical technologies and data intelligence.
		Type of projects:	PPP's, industrial (with partners), multidisciplinary research ('co-creation').

Interview Dimiter Dimitrov

Your organisation:	**Diavita Ltd**

Name person:	Dr Dimiter Dimitrov
Function person:	CEO
Address:	
E-mail:	dimiter.v.dimitrov@gmail.com
Website:	www.diavita.org
Organisation type:	SME
Involved in CASyM:	Associate partner
Date interview	25 September 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2011	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, it is the most promising challenge in medicine, concerning strategic aspects, role on portfolio and research plans. Systems Medicine should be focussed to improve health care, to address the needs of the patient. The term Systems Medicine should be popularized so that many stakeholders and the general public get familiar with it and get to appreciate it.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, Diavita is an SME investigating the nutritional systems biology of the gut microbiome and analyzes and implements large amount of data from the “gutome” funnel. The focus is on computational / medical bioinformatics. Disease areas include diabetes and obesity. The company started in 2011 and consist of a physician (Dimitrov) and two IT specialists. Currently, Diavita is interested in collaboration through FP7 and Horizon2020.	
		Number of projects:	2
		General topic of projects:	Modelling gut host-microbiome interactions. In the projects clinical samples are collected and hardware and software are installed.
		Type of projects:	Collaboration with local university and clinic
		Approximate total budget of Systems Medicine projects:	To be determined. The projects are temporarily on hold awaiting funding from local or European sources
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	eTricks and Transmart Initiatives. These projects are in their starting period, are based upon good ideas and contain PPP.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- For an SME, it is very hard to start up in an emerging field like Systems Medicine. We depend on local and European funding in order to establish collaboration and obtain proofs of concept. - Currently, the main challenge is to teach physicians and	

		medical researchers in systems approaches. - Similarly, it takes time to train IT specialist in biological and mathematical modelling. - Statistics and integration of data is a challenge	
6.	**In which way can Systems Medicine be important for industry in the future?**	Translatability. Systems Medicine seems very relevant for pharmaceutical companies when their projects are in late stage of clinical trials.	
7.	**What would be a good business model to apply for Systems Medicine?**	- Interaction between different parties (academic and industry) - Communicate and connect basic and clinical scientists, since they speak different languages	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, we try to, but their practical implementation depends on obtaining funding resources.	
		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	
9.	**Any recommendation?**	It is highly appreciated that there is a platform like CASyM that harbours a community for Systems Medicine stakeholders. In order to strengthen the community, I would suggest to increase the frequency of distribution of a CASyM newsletter.	

Interview Ad van Gorp

Your organisation:	**Lead Pharma**
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Function person:	CEO
Address:	Kapittelweg 29, Nijmegen, the Netherlands
E-mail:	Ad.vanGorp@leadpharma.com
Website:	www.leadpharma.com
Organisation type:	SME
Involved in CASyM:	Associate partner
Date interview:	4 October 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Not aware of this term, but we are very much involved in systems biology and drug development.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes and we are already applying it. Lead Pharma is an SME with 30 persons. We have a large bioinformatics group. The focus of our research is on small molecules using structure based drug design (crystallography and organic chemistry). By a systems biology approach we model proteins and pathways, validate targets and test substances in cell and animal systems.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	We work on a common mechanism in age related diseases in the areas of chronic heart failure, origin of tumor, auto immune diseases and nuclear receptors.	
		Number of projects:	3
		General topic of projects:	See above
		Type of projects:	Drug development is purely industrial. In other areas we cooperate a lot with universities.
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	We know that former company Organon used systems medicine in all their research, including data mining, RNA research and translational research.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Difficulties in re-producing data from literature / academic studies - Lack of means (budget and equipment) - Governmental funding of innovative and high risk research is mainly aimed at academia and not enough on industry - In a PPP, the academic and industrial partners can have different objectives, e.g. publication vs. product development	
6.	**In which way can Systems Medicine be important for industry in the future?**	Systems Medicine represents a mind shift in thinking about drug development. It should be used in a very focussed way in your company processes, otherwise you'll lose yourself in data and details.	
7.	**What would be a good business model to apply for**	Presently, we form partnerships with large pharmaceutical companies. This allows us to invest in our research.	

	Systems Medicine?	Ultimately, we aim to fully develop and produce a drug by ourselves.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	All of our projects are based upon data mining, -omics and profiling on protein and pathway level	
		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	
9.	**Any recommendation?**	Aim to get industry enthusiastic about and involved in CASyM.	

Interview Elena Sebokova

Your organisation:	**Elena Sebokova is reflecting her personal opinion, based upon experiences working at Hoffmannn La Roche**
Name person:	Elena Sebokova
Function person:	Vice Director Cardiovascular metabolism
Address:	Bachlettenstrasse 29, Basel, Switzerland
E-mail:	elena.sebokova@gmail.com
Website:	www.roche.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	No, but present at stakeholder meetings
Date interview	4 October 2013

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2006. In my department we are working on combining –omics data with clinical phenotypes, cohorts of healthy and diseased persons, and bioinformatics, statistics, modelling and prediction. The areas include diabetes, metabolism and cardiovascular diseases.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, I consider it very important, since blockbuster drugs are not likely anymore. Instead, we need more efficacious medicines, select subgroups of patients and treat them. In fact, many pharmaceutical companies are already applying systems medicine as research strategy.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Hoffmann La Roche is working in the areas of oncology, infectious diseases, cardiovascular and metabolism, and neuroscience. There is no department of systems medicine, but we have project task forces that use Systems Medicine approaches.	
		Number of projects:	>10
		General topic of projects:	Many in oncology and CNS, due to availability of biomarkers and imaging data. Somewhat less in polygenic disease like e.g. cardiovascular.
		Type of projects:	Depending on the questions and the knowledge we have and the availability of clinical samples, we may do the projects ourselves or join with academic partners in a PPP.
		Approximate total budget of Systems Medicine projects:	
4.	**What are best practices you are aware of in Systems Medicine projects in terms of innovation and exploitation?**	The best practices are in the area of single gene cancers, e.g. FDA approved medicines for breast cancer (her2 positive), lung cancer and skin cancer. In the area of osteoporosis we have developed tests, based upon proteomics data and biomarkers. The efficiency in treatment is now under investigation.	

<table>
<tr><td>5.</td><td>What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?</td><td colspan="2">This depends on the way Systems Medicine research is done.
- Quality and availability of clinical phenotypic data. Samples need to be standardized. Biobanks are needed, having sufficient sample material that makes re-analysis of samples possible.
- Standardization of methodology, preferably worldwide.
- Within the EU there are differences in governmental support in Systems Medicine.</td></tr>
<tr><td>6.</td><td>In which way can Systems Medicine be important for industry in the future?</td><td colspan="2">Coming from a pharmaceutical background, I’m certain that industry in personalized healthcare and pharma can gain from Systems Medicine application</td></tr>
<tr><td>7.</td><td>What would be a good business model to apply for Systems Medicine?</td><td colspan="2">The R&D combination of pharma and diagnostic industry can lead to development of better prototypes.</td></tr>
<tr><td rowspan="5">8.</td><td rowspan="5">Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?</td><td colspan="2">Yes, both pre-clinical and clinical research is necessary. It is basic research using imaging, in vitro and in vivo techniques, with a focus on application in a disease area.</td></tr>
<tr><td>Number of projects:</td><td></td></tr>
<tr><td>General topic of projects:</td><td></td></tr>
<tr><td>Type of projects:</td><td></td></tr>
<tr><td>Approximate total budget of projects:</td><td></td></tr>
<tr><td>9.</td><td>Any recommendation or comment on the subject of Systems Medicine ?</td><td colspan="2">- Existing funding programmes need consolidation
- The EC needs to be and stay involved
- The information and data that are gathered in publicly funded research projects should be openly available for everyone. Open access to data, knowledge and expertise is crucial, otherwise the field as a whole will not benefit from the massive amount of funding put into this area.</td></tr>
</table>

Interview Sylvie van Molle

Your organisation:	**Biomnis**
Name person:	Sylvie van Molle
Function person:	Vice Director Cardiovascular metabolism
Address:	17- 19 Avenue Tony Garnier, 69007 Lyon
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Website:	www.biomnis.com
Organisation type:	SME
Involved in CASyM:	No
Date interview	6 March 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, despite minimum involvement.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Indeed, this has to be part of the long term strategy of a Specialized Laboratory such as Biomnis. To be part of this next move, we are working on data exchange standards; we are looking about large data storage management, bioinformatics and other competences. Furthermore, we constantly develop new biomarkers and are working in close relationship with some pharmaceutical companies that are developing personalized “treatment” in order to offer them the right biomarkers analysis. We are convinced that targeted therapies are the future. Also, using prognostic tools will be a way to produce better diagnostic and by such better treatment at lower costs.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes but in a limited way. For example, we implement biomarkers analysis that will play a key role in personalised medicine. Furthermore, we participate in clinical studies for CROs, biotech and pharmaceutical companies around personalized medicine.	
		Number of projects:	7
		General topic of projects:	- Biomarkers only or biomarkers associated with a calculation of risk factor evaluation - Genotyping for the administration of appropriate therapy
		Type of projects:	Purely industrial
		Approximate total budget of SysMed projects:	The last 12 months it was k€ 250 with pharmaceutical companies. As a referral laboratory, we are a niche player meaning realising the very esoteric testing part of the project. However, outside these projects we have significant revenue from biomarkers analysis produced every day and delivered to prescribers that use of course those to adapt treatment.
4.	**What are best practices you are aware of in SysMed**	Being under confidential agreement, we are not able to deliver information regarding programs we conduct for	

	projects in terms of innovation and exploitation?	pharmaceutical companies that involve directly testing of precise markers in order to deliver targeted treatment. As a referral laboratory, we can produce and export results under specific format (CDISC), but at this date cannot perform statistic analysis. Yet, further development in bioinformatics may help us in the exploitation of the data.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**		
6.	**In which way can Systems Medicine be important for industry in the future?**	We are convinced of the benefits of the systems medicine, since it will lead in personalised medicine and better targeted treatment decreasing the costs of the healthcare systems. Also, not being expert in that field, we strongly believe that the industry will benefit from the data model and prognostic tools in the drug development approach, as well we expect a huge benefit for the patient that will receive treatment that may immediately be appropriate for him and so more successful.	
7.	**What would be a good business model to apply for Systems Medicine?**		
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Being a referral laboratory our main role is to provide the data/results and results interpretation on tests.	
		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	

Interview Thierry De Lumley

Your organisation:	**The CoSMo Company**
Name person:	Thierry De Lumley
Function person:	Development Director
Address:	5 passage du Vercors, 69007 Lyon, France
E-mail:	tdelumley@thecosmocompany.com
Website:	www.thecosmocompany.com
Organisation type:	SME
Involved in CASyM:	Associate partner
Date interview	27 March 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2011	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, we develop models and simulator of disease on-set and progress with a systemic view. It is at the core of our activity	
		Number of projects:	2
		General topic of projects:	Systemic modeling and simulation
		Type of projects:	1 PPP, 1 purely industrial
		Approximate total budget of SysMed projects:	Roughly 100k€/year
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	Best practices : - Data acquisition and processing standardisation - Acquiring multiple spatial and time scale data to monitor disease evolution at all systems level. Examples of projects are AirProm and U-biopred	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Lack of dynamics data - Lack of consistency and quality of data - Need for better understanding of mechanisms at different scales - Scale coupling	
6.	**In which way can Systems Medicine be important for industry in the future?**	- Go beyond the reductionist approach - Understand and predict emergent properties (good or bad) - Increase drug development success. - Earlier detection of failure and cost reduction of drug development	
7.	**What would be a good business model to apply for Systems Medicine?**		
8.	**Does your organisation apply related methodologies**	Yes	
		Number of projects:	4

	(e.g. systems biology, translational medicine) ?	**General topic of projects:**	- Systems biology model building cycle - Systems biology for epidemiology - Systems biology for biological mechanism understanding
		Type of projects:	2 PPP and 2 purely industrial
		Approximate total budget of projects:	Roughly 400 k€/year

Interview Greame Martin

Your organisation:	**Takeda Ventures**
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Website:	www.takedaventures.com
Organisation type:	Corporate venture of pharmaceutical company
Involved in CASyM:	No
Date interview	27 March 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, but it remains a specialized field of therapeutic discovery, development and application as far as I am aware.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	In some therapeutic areas, systems approaches are likely to be necessary to achieve truly holistic approaches to healthcare management. Currently Takeda views this as something that should be driven by each therapeutic area strategy, rather than as a company-wide initiative.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Not directly	
		Number of projects:	2
		General topic of projects:	1. CNS circuit and cell-specific drug target identification 2. Modelling of biochemical pathways involved in metabolism in healthy and diseased states
		Type of projects:	Internal; collaborative
		Approximate total budget of SysMed projects:	
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	- Structural Genome Consortium - Sage Bionetworks - Entelos TVI has no direct connection with any of these institutions, but regards them all as best examples of systems biology approaches to therapeutic R&D.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	Incomplete understanding of genome and how classes of gene products may yet have critical regulatory functions that we have dismissed to date.	
6.	**In which way can Systems Medicine be important for industry in the future?**	Goal has to be to bring individual patients much closer to their physician so that each patient can receive a truly individualized treatment plan rather than a generic treatment plan.	
7.	**What would be a good business model to apply for Systems Medicine?**	- Treatment of Type II diabetics - Treatment of cancers	
8.	**Does your organisation apply related methodologies**	Yes, at both preclinical and clinical stages of drug development	

	(e.g. systems biology, translational medicine) ?	**Number of projects:**	
		General topic of projects:	Patient stratification for tailored treatment
		Type of projects:	Internal; collaborative
		Approximate total budget of projects:	

Interview Dieter Maier

Your organisation:	**Biomax Informatics AG**
Name person:	Dieter Maier
Function person:	Head of Scientific and Applied Knowledge Management and Data Mining
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E-mail:	dieter.maier@biomax.com
Website:	www.biomax.de
Organisation type:	SME
Involved in CASyM:	Associate partner
Date interview	7 April 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since several years. Biomax was established in1997. The company focuses on knowledge management and integration, data management and data mining in all fields of biomedical research, from biochemistry to systems medicine. Biomax has some 50 employees with various backgrounds in biology, bioinformatics, medicine, physics, IT and mathematics. Biomax software for knowledge management is licensed to costumers. Either Biomax fills and analyses the data or the costumers do it themselves.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Absolutely, it will change how research will be done and it will change clinical practice.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, we participate in SysMed research, but we don't do mathematical and mechanistic modelling. We structure knowledge to enable others to do the modelling. Biomax services are custom made. In some cases we analyse literature and data bases for project partners. In general, computer programmes are not able to analyse literature automatically, since much information (e.g. isoforms, homologues) is hidden in the literature. Moreover, gene names are not unique. Furthermore, sometimes there is not an organism connected to a gene. With our knowledge management system we can connect the gene name or protein to an organism. We can structure data into a computer readable way in such a way that modelling groups can associate genes with diseases. Presently, many funding organizations stimulate data management for the projects they fund. There is, however, a difference between data management and knowledge management. In certain fields of life sciences sequences can be available, but there is not a way of storing and analysis.	
		Number of projects:	Currently, 7 innovative research projects funded publicly (FP7 and BMBF). Some are developing towards application and are being validated for clinical practice. Furthermore, 10

			more traditional projects funded by clinics or industry.
		General topic of projects:	Chronic disease, acute disease, cancer, mental disease and respiratory disease (e.g. asthma, COPD).
		Type of projects:	Both PPP and industrial. Projects with academia are more research related and projects with industry are related to drug research.
		Approximate total budget of SysMed projects:	About 50 percent of our total budget (i.e. half million euro annually).
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	SysMed is relatively new, so there are only few examples of solving a clinical problem. One successful project in which we have collaborated is on a heart model for understanding drug side effects and to guide drug development up to application in the clinic. Still, SysMed has made some good progress, explaining mechanisms involved in a disease, defining the method and developing a pipeline that is able to take research results into a clinical support system and clinical practice, thereby helping a physician in front of a patient to take a decision.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	The maturity of a model and model validation are our main bottle necks. Validation of a model takes some 3 years. It will take another 10 years to take it to the personalised level. One huge gap is the mindshift needed in the clinic to cope with the major change in the way medicine is going to be applied. Many partners will need to cooperate in SysMed. Besides researchers, it will be clinical management, medical doctors, regulators, payers (insurance company or other organisation rewarding drugs, indirectly through clinics) and patients. The patients need to make their priorities heard. In our projects, we always have clinical doctors as partner. But such physicians are the pioneers! Within their clinical situation they need to make themselves understood. On the technical side, a gap is knowledge structuring, from text literature towards applicability for computation. Furthermore, we need more multiscale models of complex systems.	
6.	**In which way can Systems Medicine be important for industry in the future?**	In the pharmaceutical sector it will completely change the way research is being done. There will be more engineering style research instead of the current trial and error. In the clinic and health care industry, research will shift from the population based way towards individual healthcare. Flexibility and treatment options will have to increase. For software and biotech companies, there will be many new options for software development.	
7.	**What would be a good business model to apply for Systems Medicine?**	Getting software fit for use in the SysMed approach, showing proof of concept, and gaining visibility for a knowledge management. There will be room for quite a number of business models: - Service providing companies - Companies covering specific aspects in IT, computational	

		models and technology - Companies applying SysMed to create intellectual property - Companies that show the efficiency of the SysMed approach for the health care system	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, mainly in systems biology, outside of the area of medicine, but applying the same principles. We integrate all the modern data production methods (-omics) with knowledge about specific organisms. For instance, metabolic models of certain organisms.	
		Number of projects:	Appr. 10
		General topic of projects:	Fine chemicals, agro and nutrition, synthetic biology
		Type of projects:	Mostly commercial / industrial projects. In systems biology we only have a few PPPs since the field is more mature than SysMed in terms of applications.
		Approximate total budget of projects:	The other 50 percent.
9.	**Any recommendation or comment on the subject of Systems Medicine ?**	Now is a good time to start contacting the stakeholders that will be important to apply SysMed in everyday clinical practice. These stakeholders include payers, insurance companies, regulators, EMA, clinical management. Start the discussion now and listen to how these stakeholders see things and what their needs are.	

Interview Anonymous

Your organisation:	**Multinational in electrical engineering and electronics**
Name person:	Anonymous
Function person:	Senior Research Scientist
Address:	
E-mail:	
Website:	
Organisation type:	Multinational in electrical engineering and electronics
Involved in CASyM:	No
Date interview	27 June 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 2009	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, as one of the key developments. It is important for healthcare (diagnostics and more), especially in the future. The first research projects with collaborators have started.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, we have just started with SysMed approaches in our research environment. There are no products based upon SysMed methodology today, but we aim at delivering products and solutions in our research and healthcare in a period of 10 years ahead. We have to make a focus on the disease area. It will include complex diseases, where our imaging information and prototypes will be integrated with information from biomarkers and molecular diagnostics and with decision support systems and mathematical modelling. We are interested in joining collaborative projects with clinics, academics and industry, e.g within Horizon2020.	
		Number of projects:	Multiple, in different size
		General topic of projects:	medical/clinical usability with patient related information and data
		Type of projects:	PPP and bilateral collaborations, grants
		Approximate total budget of SysMed projects:	not to be disclosed
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	Many started on small scale (limited scope). Some modelling efforts are underway. Application in the clinic is still limited or not existing. By integrating knowledge from clinical trials (also with virtual patients) we could avoid unnecessary treatment.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- There is still a lack of proven medical usability - There are limited Decision Support Systems in place - Lack of standardization and harmonization of data (ISO) - Analysis and interpretation of data - Capturing of data - Property of data: who owns it?	

6.	**In which way can Systems Medicine be important for industry in the future?**	- Society should move towards prevention and prediction of disease, rather than the current situation where people meet their doctor for the first time when they are already diseased. Nowadays, prevention is mostly paid by a concerned individual rather than by an insurance company. The focus on prevention and prediction is a disruptive concept that requires a change in European society (politicians, insurance companies, clinics, academia, patient organisations). The benefits are high, it will save lives and money. In the USA, this concept is being acknowledged. Reimbursement payments are no longer per test, but per patient who does not require further care. - Considering more data, diverse data and knowledge being incorporated into treatment and diagnosis. Modelling and SysMed is mandatory for this.	
7.	**What would be a good business model to apply for Systems Medicine?**	This is not clear yet. In any case, it requires a combination of statistics, mathematics, chemistry and data analysis. Public-private consortia to be established through the Horizon2020 programme may drive the field towards a good business model.	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	- Systems biology is very limited and if in the context of humans. - We apply various aspects of translational medicine, e.g. in diagnostics.	
		Number of projects:	not to be disclosed
		General topic of projects:	not public
		Type of projects:	PPP, Grants, bilateral collaborations
		Approximate total budget of projects:	not to be disclosed
9.	**Any recommendation or comment on the subject of Systems Medicine ?**	For Systems Medicine to become a success, many disciplines and stakeholders must work together.	

Interview Matthias Gottwald

Your organisation:	**Bayer Pharma**
Name person:	Matthias Gottwald
Function person:	Policy and Networking
Address:	Muellerstrasse 178, 13353 Berlin, Germany
E-mail:	matthias.gottwald@bayer.com
Website:	www.bayer.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date interview	18 August 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, we have been using it in our company for several years. Since 2012 also through Europe's largest public-private initiative: Innovative Medicines Initiative (IMI, www.imi.europa.eu). IMI is a joint undertaking between the European Union and the European pharmaceutical industry association EFPIA, aiming at the development of better and safer medicines for patients. This includes getting better understanding of genetic causes of disease (whole genome sequencing), modelling of disease and getting clinically validated safety markers. In general, each project has 3 to 10 pharma companies and several academic partners and lasts for 5 years. About half of the budget comes from the pharmaceutical industry and the other half from the EU. There are currently more than 50 projects running in IMI. Bayer is involved in 24 of them, both in scientific projects as well as training and educational projects (e.g. EMTRAIN, setting up master or PhD courses for specific subjects in biomedicine; Lifetrain, framework for continuous professional development; EUPATI, European Patients' Academy on Therapeutic Innovation, patient education material about methodologies and clinical trial setup, not being linked to products nor indications). For an overview of all ongoing IMI projects, see www.imi.europa.eu/content/ongoing-projects. Bayer joined IMI since it realizes that many current research projects have a subcritical mass and require the cooperation of many stakeholders. An important feature of IMI is having regulators and patient organizations on board of the projects. This is a major benefit for the development of standards in the R&D process to bring novel medicines faster to the patient. The first round in IMI was from 2008 to 2013. The second round started in 2014. In IMI-2 there is focus on 4 major areas: - Better understanding of diseases on a molecular level, leading to novel target and biomarkers - Improved clinical trial paradigms, e.g. using smaller, more specific patient cohorts, and novel approaches for benefit-risk evaluation. - Patient adherence and compliance (monitor disease and

		treatment after trial) - Innovative medicines development in areas where there is a high societal need, but no sufficient incentives for companies to do it on their own.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	It is an integral element of our translational medicine strategy, e.g. visible through the establishment of a Modelling and Simulation function in Early Clinical Development and through engagement in projects like IMI OncoTrack.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, e.g. in IMI OncoTrack a consortium of academia, SME's and Bayer sequenced the whole genome of 200 colon cancer patients, made models and simulations, patient stratification profile and predictions. We thereby develop methods for systematic next generation oncology biomarker development.	
		Number of projects:	Dozens. It is becoming an integral element of all future development projects.
		General topic of projects:	Use of molecular understanding of disease mechanisms for patient stratification. Mainly on oncology and cardiovascular diseases.
		Type of projects:	All types. When knowledge is scarce, we tend to cooperate with academia. And if we already have a good idea what we want, we cooperate with other companies.
		Approximate total budget of SysMed projects:	confidential
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	Interdisciplinary approach, from systems biology to SysMed. Use of modelling paradigms for clinical application, e.g. clinical trial design, dosage, stratification	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Missing the bridge from the theoretical findings to practical application - IT limitations for big data management - We should improve linking different disciplines together. We need an holistic view, beyond conventional education and boundaries of specific disciplines. There is already an improvement in becoming able to speak each other's scientific languages, but we are still in a steep learning curve here. An example is linking biomedicine to IT and bioinformatics and to the patient's needs. - Access to patient data and samples in an anonymised way. In Europe there are too many cultural and national differences in handling data privacy.	
6.	**In which way can Systems Medicine be important for industry in the future?**	Understanding of the molecular basis of diseases. This insight could be that there is synergy between diseases that are currently thought to have different causes and development. As a result, clinical trial can become better targeted to individual patients.	
7.	**What would be a good business model to apply for Systems Medicine?**	- Linking IT to pharma. A continuously growing and broad platform with standardized data management approaches and defined ontologies. - Performing proof of concept studies (e.g. out of the box projects from IMI) and use their results and insights to further improve clinical trials.	

8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, to make tools, as a basis for SysMed	
		Number of projects:	Dozens
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	
9.	**Any recommendation or comment on the subject of Systems Medicine ?**	CASyM is a timely and relevant initiative. Be sure to cooperate with other initiatives, e.g. IMI.	

Interview Olivier Brass

Your organisation:	**Sanofi Pasteur**
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Website:	www.sanofipasteur.com
Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date interview	9 December 2014

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, since 5 years (and in vaccines since 3 years)	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, Sanofi Pasteur clearly focuses on Systems Medicine. It is a scientific and clinical strategy to improve vaccine impact knowledge and validation of biomarkers and as a de-risking strategy.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes, it is a combination of clinical samples, lab work and modeling. In vaccine design we are improving the modeling to the level as used in drug design. An example is e.g. epitomic microarray optimization.	
		Number of projects:	More than 5 clinical trials and a preclinical study
		General topic of projects:	Vaccine efficiency (protection) and safety
		Type of projects:	PPP
		Approximate total budget of SysMed projects:	1 million euro per project
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	In general, Systems Medicine is a field in movement. New technologies are being implemented. In the field of vaccine development, routine work is being combined with exploratory research. This is combined with information from phase III trials. We now have the basic ideas in areas of validation, IP and marketing.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- The link between systems approaches and vaccine design is not easily made - Management of the complexity of data and the vast data expansion. This needs to be handled in a collaboration between academia (public data) and company data specialists (private data). Modeling is an issue here. - Cohort size for validation of biomarkers and pathways. There are few samples and biomarkers. For validation we need at least 2 or 3 clinical studies.	
6.	**In which way can Systems Medicine be important for industry in the future?**	- Modeling, validation and link with vaccine design - Data availability and standardization, facilitated by CASyM	
7.	**What would be a good**	- Start with gaining knowledge on a pre-competitive basis.	

	business model to apply for Systems Medicine?	- Create a team with multi-competences and translational thinking	
8.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, e.g. in a Sanofi vaccine project group in USA	
		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	
9.	**Any recommendation or comment on the subject of Systems Medicine ?**	Think about how to link dream (coming from therapeutic System Medicine studies) and reality in the prophylactic field. We are still at the beginning in Systems Medicine and need to combine the puzzle pieces from various technologies and data.	

Interview Françoise Le Vacon

Your organisation:	**Biofortis Mérieux NutriSciences**
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Function person:	Chief Scientific Officer
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E-mail:	francoise.le.vacon@mxns.com
Website:	www.merieuxnutrisciences.com
Organisation type:	Company ensuring the security of food and pharmaceutical products, cosmetics, agrochemicals and consumer goods
Involved in CASyM:	Associate partner
Date interview	12 October 2015

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes, but we are more familiar with the terms personalized medicine and P4 medicine. Patient participation is necessary for the future for P4 medicine.	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Yes, we are well engaged in Systems Medicine projects and in progress to get to the personalized level.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	We take part in large collaborative projects in the area of P4 Medicine. These projects focus on biological and clinical data, including –omics data from a cluster of patients who have a specific disease or get a specific treatment. We measure lipids, cytokines, biomarkers, genes and microbiology and do bioinformatic and statistic analyses. For computational modeling we collaborate with specialists in external companies. We do not use P4 in the clinic yet. Our company is a clinical research organization performing over 50 clinical trials. It is part of a larger family of Merieux companies. We aim to manage health in global diseases that arise in developed and emerging western countries. For biomarker discovery we collaborate with other companies. For modeling in biology systems we collaborate with academia.	
		Number of projects:	3 to 4 collaborative projects
		General topic of projects:	Our main focus is on cancer research and nutrition. We participate in a national 42 M€ project focusing on biomarkers for 8 cancer types. We use patient tumor to make graft mice models for drug testing for and treatment. Eventually the aim of this project is going to the personalized level. Other collaborative project are on food allergies, biobanking with healthy individuals and biomarker

			discovery.
		Type of projects:	Both collaborations with private and public partners
		Approximate total budget of SysMed projects:	400 k€
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	No specific areas.	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- A major hurdle is alternatives for designing clinical trial (e.g. adaptive or in silico trials). - Collection of patient samples can be seen as a hurdle, e.g. standardisation of the sampling. - Transport of the biomarkers - The small size of a cohort in Europe compared to the USA where there are more patients included and long term follow up. - Europe is not competitive with the budget of NIH in the USA. They fund competitive collaborations and the one generating the best results is taken for follow-up. - Ideally we should share public and private data in a single data centre that is available for everybody.	
6.	**Are there any hurdles to overcome in your organization to perform systems medicine projects?**	We need more bioinformatic and mathematical expertise. A clinical trial in a company is a fixed methodology with little or no budget for exploratory research or use of novel biomarkers. We have to justify to authorities why we need many patient samples.	
7.	**Does systems medicine within your organisation foster translational and personalized approaches?**	Yes, but we still are in progress to get to robust systems medicine.	
8.	**What would be a good business model for Systems Medicine industrial application or entrepreneurship?**	Biotech start-ups focussing on data integration. There are not so many companies who specialize in modelling and data integration. There are only few companies in biomarker discovery.	
9.	**Any recommendation or comment on the subject of Systems Medicine ?**	The topic is not so easy. The differences in terms and wording are not so easy to understand (systems, personalised, 4P medicine). Gap is to go to the patient. And the needs of the clinician the gap is also difficult.	

Interview Saverio Alberti

Your organisation:	**Oncoxx Biotech**
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Website:	www.oncoxx.it/oncoxx/en/
Organisation type:	Biotech Company as partnership between Chieti University Research Center and private entrepreneurs
Involved in CASyM:	Associate partner
Date interview	12 October 2015

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes	
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	The university that was the basis of our company is classical teaching in research institution, not specified at SysMed. Oncoxx is applying the SysMed concept and obtains knowledge and equipment from outside sources if it does not concern our own niche or expertise.	
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Yes. Oncoxx is a startup company comprising 10 people. It is a spin-off from the Chieti university with support from the regional government and private investors. We focus on the translation of basic research into cancer diagnostics and novel anti-cancer therapies, in particular on the humanization of monoclonal antibodies usable in the treatment of common cancer types. The company is involved in a pilot project sequencing the DNA of 25.000 people in Italy, performed in collaboration with the Moli-Sani group, the NEUROMED center and sequencing centers in Australia. During a 10 year follow-up information is gathered (e.g. proteome, lifestyle, diet, exercise, clinical data). From this multilayered information models will be made. The information will be compared through probabilistic matching to known DNA sequences.	
		Number of projects:	Many
		General topic of projects:	1) Anti-cancer therapies. Production of Anti-Trop-2 antibodies for therapy of 'big killers': - Lung tumors and metastases - Liver metastases of colon cancer - Ovarian cancer 2) Human safety 3) Tumor burden / cancer biomarkers
		Type of projects:	Public-private partnerships only

		Approximate total budget of SysMed projects:	It will follow a classical clinical phases trajectory. The testing phase will amount to appr. 9M€. The phased I & II may become 12M€. A full phase III will involve a big pharmaceutical company investing appr. 100 M€.
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	Not aware	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Every project should think about data storing, standardization and sharing. We really need all researchers to foster data standards. If you don't have reliable data to start a study nothing useful will come out of your study. Standards must be there for storage and retrieval of sensitive data. - Lack of long lasting follow-up of cohorts. - In case of working with patient data, regulations can be a hurdle. - The systems medicine approach can not be implied somewhere in the middle of a project. The mindset should be there from the beginning to the end of the project.	
6.	**Are there any hurdles to overcome in your organization to perform systems medicine projects?**	There is no single decisive hurdle. SysMed requires that many people with different expertises cooperate. If you don't have a certain knowledge or device, you rely on collaboration. In our case collaboration is needed in the areas of modeling, computer sciences and biostatistics. In general, funding can be a limiting source.	
7.	**Does systems medicine within your organisation foster translational and personalized approaches?**	Not yet, this is an ongoing process. We want to move from a cell to an animal model and ultimately to the human.	
8.	**What would be a good business model for Systems Medicine industrial application or entrepreneurship?**	- Acquire funding for each of the steps to get a product to the market - Guarantee data availability on the largest possible scale. - Stimulate full interchangeability of patient data between the EU and USA (human lifestyle, diet, genetics)	

Interview Yuval Tabach

Your organisation:	**Rethink Pharmaceuticals**
Name person:	Yuval Tabach
Function person:	Co-Founder and Chief Scientist
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E-mail:	tabachy@gmail.com
Website:	www.rethinkpharmaceuticals.com
Organisation type:	SME
Involved in CASyM:	No
Date interview	28 September 2016

1.	**Are you familiar with the term Systems Medicine as defined above?**	RethinkPharmaceuticals is a systems biology and bioinformatics company that develops drugs and does drug repurposing by using data. Yuval Tabach also works at the Hebrew University Hadassah Medical School as principal investigator. It is affiliated with the hospital being a source for data in the clinical part of our projects. We work a lot with data and one of the thing we try to do is similar to the CASyM definition, which is basically combining data from patients with demographic and clinical data and subsequently going to the resolution of genetic data for breast cancer disease and other heredity cancers. In essence, we are combining genetic, environmental and clinical factors and predict the risk factors of breast cancer on a personalised level. We use systems medicine is in order to develop better personalized medicine tools. We need to know the parameters of a whole population in order to be able to decide for a single person. Many data have been collected at the Hadassah Medical School, where they are being used by clinicians.
2.	**Does your organization render Systems Medicine as one of the key technological and scientific developments / challenges within the next 10-20 years?**	Researchers working at the Hebrew university and Hadassah medical school are very well aware of the importance of systems medicine. There is huge need for manpower in the fields of bioinformatics, systems biology and systems medicine. Bioinformatics and systems medicine should be more incorporated in educational programs for undergraduates. I am is in charge of developing a new educational program for genomics and genetics in the Hebrew university and they are trying to build courses that lay out the importance,
3.	**Does your organisation apply Systems Medicine according to the definition above?**	Researchers apply it, not so much the institutions. The company is using genomic data for drug development. It is mainly a systems biology and bioinformatics company. The end goal is to use clinical data, but presently we are mainly using genomics data.

		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of SysMed projects:	
4.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	New innovations include data sets and DNA sequencing	
5.	**What are gaps and pitfalls towards the medical and healthcare application of Systems Medicine?**	- Questions about privacy of patient data are a big issue. - Systems Medicine is an interdisciplinary field, so you need people from different fields. There is a huge gap in terms of language between a MD and a PhD from computer science. They don't understand each other. - Heads of the hospital need a better understanding of the needs for systems thinking and need to start invest in tools for Systems Medicine. - There is a need new for a generation of scientist trained in a multidisciplinary way - The complexity of the research field is a big challenge.	
6.	**In which way can Systems Medicine be important for industry in the future?**	Systems medicine by using big data is intrinsically able tell you anything. It will revolutionize medicine i.e. prediction to provide drugs in a personalized way.	
7.	**Does your organisation apply related methodologies (e.g. systems biology, translational medicine) ?**	Yes, there are several institutes that work on that.	
		Number of projects:	
		General topic of projects:	
		Type of projects:	
		Approximate total budget of projects:	
8.	**What would be a good business model for Systems Medicine industrial application or entrepreneurship?**	Taking the data that are freely available, that will be collected at the hospital, and that will be generated through technological apps (e.g. on a watch). These data allow to predict multiple things.	
9.	**Any recommendation or comment on the subject of Systems Medicine ?**	We need more opportunities for applying for grants in this field. It is potentially a gold mine for companies and hospitals, but their decision makers are not aware yet.	

Interview Efthymios Manolis

Your organisation:	**European Medicines Agency (EMA)**
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Organisation type:	Regulatory
Involved in CASyM:	No
Date interview	5 October 2016

1.	**Are you familiar with the term Systems Medicine as defined above?**	Yes. Regulators see the value of modelling and simulation in optimizing drug development and facilitating decision making both for the sponsor and the regulator. The regulatory value of modelling and simulation can be summarized below: Before marketing authorization application (MAA): - Enable early informed discussion with sponsors regarding study designs, endpoints, dose regimens, data needed to support benefit risk decisions At MAA: - Support benefit risk decisions by investigating uncertainties & untested scenarios, and their clinical consequences - Translate benefit risk from the population to individual - Inform about Summary of the Product Characteristics (SmPC), especially for special populations - Support Subgroup analysis Post Marketing: - Inform the contents of the RMP - Lifecycle management of products EMA has established the Modelling and Simulation Working Group (MSWG) in 2013 to discuss the modelling and simulation approaches in submissions and advance the science.
2.	**Does your organisation have experience with Systems Medicine according to the definition above?**	We only have one example of a project by a small company with the conceptual framework of Systems Medicine, that was discussed as part of a qualification procedure. Apart from that we have not seen another application based on Systems Medicine and thus are inexperienced with this type of approaches. Nevertheless regulators are familiar with physiologically based pharmacokinetic (PBPK) modelling, a bottom up modelling approach. Learnings from the PBPK can be applied more widely to systems pharmacology.
3.	**What are best practices you are aware of in SysMed projects in terms of innovation and exploitation?**	We are not familiar with Systems Modelling. Instead, we have drafted guidelines in population PK and PBPK modelling which can be found in our website. A best practice would be for EMA to get engaged early in the

		model development, because we like to add our perspective into the modelling exercise and objectives and also to get more familiar with systems modelling.
4.	**Are there any hurdles to overcome in your organization to perform systems medicine projects?**	To be more visible to academia and SME and stimulate them to engage with EMA.
5.	**Does systems medicine within your organisation foster translational and personalized approaches?**	I can see a lot of potential, but we haven't seen many examples yet. Even if companies are using this kind of approaches in drug discovery, this is not visible to us. In EMA we have been discussing the translation of pre-clinical biomarkers to clinical safety biomarkers. With systems pharmacology approaches modeling can support translation. Also personalised medicine is clearly supported and we have seen some innovative approaches in cancer therapy.
6.	**What would be a good business model for Systems Medicine industrial application or entrepreneurship?**	N/A
7.	**Any recommendation or comment on the subject of Systems Medicine ?**	Good communication is essential. I am advocating for qualification procedures, which is a very good way to get everybody on board and discuss systems medicines. The EMA has expertise in quality, preclinical and clinical development and post approval surveillance of medicinal products. Systems modelling is a new discipline with limited visibility as far as regulators are concerned. Discussing systems medicines in the context of a qualification procedure will raise awareness, and also help mobilize additional resources from the EMA European experts network to support regulatory work. What regulators can offer is to initiate discussions on how these models can be adapted to address practical questions in drug development and evaluation, and also on the qualification requirements for a specific context of use.

Default questionnaire follow-up interviews

Your organisation:

Name person:

Function person:

Address:

E-mail:

Website:

Organisation type:

Involved in CASyM:

Date follow-up interview

1. Are there any gaps and hurdles that were identified back then that are still relevant or have been overcome? With the implementation of Systems Medicine have new gaps and hurdles appeared?

2. Do you see an increase of best practices of Systems Medicine approaches in your company or externally?

3. What is a good business model for the application of Systems Medicine?

4. CASyM ends in April 2016 and its successor is the European Association of Systems Medicine (EASyM). What role do you see for EASyM and what should be their focus?

5. Any additional remarks?

Follow-up interview Claus Bendtsen

Your organisation:	**AstraZeneca**
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Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date follow-up interview	12 October 2016

1. Are there any gaps and hurdles that were identified back then that are still relevant or have been overcome? With the implementation of Systems Medicine have new gaps and hurdles appeared?

Since the previous interview in 2013, systems medicine approaches are currently being used much more routinely throughout the business. We have come a long way in addressing some of the gaps with respect to lack of available data. It's not yet fully overcome, it's still a challenge to collect enough information to capture the complexity of disease. And we will not be able to overcome this challenge anytime soon. We've made progress on the journey, but the gaps are still relevant.

We have clearly invested in the areas around inflammation and immunology and are making progress there. We're now much better in understanding for example exposure in our respiratory therapy area which is helping some of the understanding. In the neuroscience area we still have activities but this no longer is our core focus. Our focus is now more on oncology, cardiovascular diseases, and respiratory diseases. These areas are getting strong support from systems medicine initiatives. Also, steps that we have taken with our genomics strategy will help in understanding the complexity of the disease.

What I may not have recorded back then is the adoption of the approaches. This is something that has been overcome, people understand now why systems medicine is useful.

In terms of using models in clinical trials there are multiple things to it. On the clinical trial side, there is a very clear role of modeling in the early trials. The role here is to firm up the hypothesis, and prepare for testing that in clinical phase-III trials. In our late stage trials, the focus is on statistical modeling rather than improving our understanding. Systems medicine in late stage trials is therefore absent. For safety we use models to understand the risks towards patients.

2. Do you see an increase of best practices of Systems Medicine approaches in your company or externally?

Very clearly, you can see it at conferences and in the scientific literature, in journals and what we've known from competitors. A broader adoption of the approach is clearly visible.

3. What is a good business model for the application of Systems Medicine?

At the time of the previous interview we didn't have full adoption and were probably more in the experimental phase about the role of Systems Medicine and quantitative understanding of novel medicines in disease in general. It is very clear now that it's critical to have a quantitative understanding to be successful. New opportunities for unmet medical needs is increasingly of interest, also for other companies. In short, back then, the focus was more on execution of the projects that we had in our portfolio and how to use Systems Medicine to ensure that we use the right approach and right patient segment. This is still relevant, but now the scope is broadening into an area where we increasingly see a role for Systems Medicine in helping identify how you can address and treat a disease. This includes identifying new targets, or a combination of targets that we should pursue.

4. CASyM ends in April 2016 and its successor is the European Association of Systems Medicine (EASyM). What role do you see for EASyM and what should be their focus?

EASyM is the extension of CASyM. I think continuing with a focus on education should be a key role. And to emphasize that we should not look at disease as something that you can treat based on symptoms, but treat them based on the understanding of how to manage the overall system. Continue to spread the gospel of Systems Medicine in continuation of CASyM.

5. Any additional remarks?

I think it's important to look at the interface between academia and industry and how we continue to strengthen that interface. A big question that may be relevant to tackle is how to manage personalized healthcare and precision medicine. To drive Systems Medicine forward, there is a need to reach a compromise among all stakeholders how to use information from patients. There is a need for a compromise how to advance science and respect the personal information of individuals. It will be helpful to continue and widen our activities to address this issue.

Follow-up interview Andreas Schuppert

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Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date follow-up interview	20 October 2016

1. Are there any gaps and hurdles that were identified back then that are still relevant or have been overcome? With the implementation of Systems Medicine have new important ones appeared?

Many of the gaps and hurdles identified three years ago are still relevant today. Progress is in its infancy:

- Compared to the situation in systems biology research, in Systems Medicine there are many less well annotated heterogeneous data. Data Management in Systems Medicine is less established than in systems biology and I see no significant progress in this area.
- Algorithms and methods used in systems biology are not adapted to Systems Medicine. Those used in systems biology are on more homogenous and less complex datasets than the ones used in Systems Medicine. For Systems Medicine, deep mathematical knowledge relevant for both biology and medicine is needed. Many scientist are not aware that this gap exists. Currently, data are gathered and subsequently put in the hay stack, but no one knows where the needle is and how it looks like.
- Still more efforts are needed in extracting value for applications.
- There is progress in deep learning, but it is unknown whether that really works in Systems Medicine.
- There is progress in contacts based learning (e.g. IBM Watson), but the results are not yet reliable.
- Pharmacodynamics has proven very complex. There are algorithmic gaps in this area.
- Access to data for researchers can be very restricted depending on regulatory requirements per country.

Despite the gaps and hurdles mentioned above, we now see them more clearly and characterize it more precisely compared to the situation of our interview three years ago. That is an important step forward.

2. Do you see an increase of best practices of Systems Medicine approaches in your company or externally?

- Internally, indeed, progress has been made. There is a continuous method development of applications and tools. There is some progress in application of physiology based pharmacokinetics on a subpopulation level and on dosing strategy supported by computation models.
- Acceptance and awareness of data and IT solutions has increased significantly. This is a quantum leap progress. There is increased funding available to cooperate with pharmaceutical companies. This might be a game changer for the future, but Systems Medicine needs to deliver, show proof of concept. We will probably not change the world, but we can have a valuable solution that is accepted in certain applications and diseases.
- We can better integrate data from various sources.
- We are making progress from the science towards the policy makers and economics.

3. What is a good business model for the application of Systems Medicine?

Health care wellness products may become a business model. All other areas are still in proof of concept phase. In general, depending on the country and reimbursement, for big and small industry, it can be conceived that many different business models will exist in parallel.

4. CASyM ends in April 2016 and its successor is the European Association of Systems Medicine (EASyM). What role do you see for EASyM and what should be their focus?

EASyM and CASyM must be pro-active. The outside world will not ask for their opinion. EASyM could handle standardization of data and models and could communicate about test cases that give reliable answers. The academic community is diverse, while a company is just interested in itself, so there needs to be an organization that shows doctors and patients how Systems Medicine can contribute to them, what its reliability is, how it will affect the health of a patient. EASyM could set up a community that can give a clear opinion about the true value of Systems Medicine and in this way support decision makers. EASyM should diverge between hype and reliability.

5. Any additional remarks?

Awareness of modelling has not changed due to CASyM per se, but mainly since we have all come to realise that data need to be analysed to make sense out of them. This will get new industry to enter the field.

Follow-up interview Thomas Klabunde

Your organisation:	**Sanofi-Aventis**
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Organisation type:	Large pharmaceutical company
Involved in CASyM:	Full partner
Date follow-up interview	24 October 2016

1. Are there any gaps and hurdles that were identified back then that are still relevant or have been overcome? With the implementation of Systems Medicine have new gaps and hurdles appeared?

In the company we have two main directions in Systems Medicine:

- Quantitative Systems Pharmacology (QSP): gaining understanding of human physiology, performing in silico clinical trials prior to clinical testing in humans, supplementing results from animal testing.
- Big data, mainly originating from-omics data sets, aiming for personalised medicine. This is currently most advanced in the area of oncology.

With respect to the question on gaps and hurdle I will comment on the QSP part. One important aspect is the access to clinical patient data. E.g. in order to build dynamic systems pharmacology models for diabetes and to capture the subtle differences among diabetes patients access to the large set of clinical data (placebo cohort) from former clinical trials of diabetes drug candidates is needed. Pharma companies like Sanofi have been traditionally good at building large compound-centric data bases in order to capture results from e.g. high throughput screening or in-vitro profiling. At Sanofi, only more recently the shift from compound centric data bases to patient-centric databases covering the clinical data has been made. Obviously, this is a challenge for data management. In addition, in order to model the disease progression for diabetes there is a need for longitudinal data sets including biomarkers like HbA1c over a period of 5 years or longer. Clinical trials for new diabetes medications usually run for up to 6 months. Here, access to public health records is needed, which has been offered recently by companies like e.g. Quintiles. With access to this data the modeling of disease progression in diabetes appears to be possible. Also, the more recently established joint venture between Google Life Science and Sanofi – Onduo – is a big step in the right direction of Systems Medicine in diabetes. Besides the objective to provide a platform for patients to capture their glucose data, the long term objective of this joint venture is also the generation of an artificial pancreas.

Despite progress, we are not at in a fully mature stage of Systems Medicine yet. Within 10 years I expect a more personalised approach in the diabetes treatment.

2. Do you see an increase of best practices of Systems Medicine approaches in your company or externally?

For Quantitative Systems Pharmacology (QSP), yes, both internal and external. External this is evident from our feedback of our CROs in the area of QSP stating that all Big Pharma are now using QSP to improve their decision making and to improve their attrition rate especially for the phase II clinical trials. Internal: we want to understand human physiology to choose the right dose and target population in clinical trials. Thus, QSP modeling is now an integrated part of a new R&D platform at Sanofi, the “Translational medicine and early development platform (TMED)”. TMED consists of teams of clinicians, PK/PD modelers, biomarker specialists, and QSP modelers. This new structure reflects that the importance of a close interaction of these expertise and of a Systems Medicine approach in general has been understood and is now encouraged by the Sanofi management. The new structure is expected to bring the right people closer together and in the end choose the right targets, make the right compounds and get the right drug candidates into the clinic.

An internal best practice of a Systems Medicine approach is the application of a computational QSP model (type-1 diabetes simulator) to explore different titration rules and dosing regimens for an inhaled prandial insulin - Afrezza. Until recently Sanof co-marketed Afrezza together with Mannkind. Mannkind had performed phase III clinical trials using dosing regimens and titration rules that had been used for traditional subcutaneously injected insulins, likely to be not optimal for an inhaled insulin like Afrezza with a much faster on-set of action. The QSP model suggested that a significant improvement in HbA1c lowering could be achieved by an adapted dosing regimen (post-meal dosing) and titration rule leading to the design of a new clinical trial. Unfortunately, Sanofi stepped out of the partnership before the trial was started to proof the in-silico findings.

3. What is a good business model for the application of Systems Medicine?

The model we prefer is to have a good network between academic partners, CRO’s that provide technical skills, modellers and clinicians that serve as adviser when building the model. Close partnership is required when data are integrated into the model, to have a joined understanding and acceptance of the simulations results. This ensures that the results will be used to guide the clinical study design.

4. CASyM ends in April 2016 and its successor is the European Association of Systems Medicine (EASyM). What role do you see for EASyM and what should be their focus?

The CASyM stakeholders are diverse, since Systems Medicine has many flavours, from personalised medicine to big data and systems pharmacology. Each CASyM partner has a different background, a different focus and interest.

EASyM should have more structured modules, each focusing on a subfield (e.g. big data analysis, personalised medicine, pharmacology).

Follow-up interview Johannes Schuchhardt

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Organisation type:	SME
Involved in CASyM:	Full partner
Date follow-up interview	

1. Are there any gaps and hurdles that were identified back then that are still relevant or have been overcome? With the implementation of Systems Medicine have new gaps and hurdles appeared?

In terms of hurdles for the approach of Systems Medicine one of the persistent hurdles lies in defining what is a good business model in the field of bioinformatics. Several business models are being used, but there is not yet a model that is sufficient in making bioinformatics profitable. There are several reasons for this and they relate to the field of Systems Medicine. For bioinformatics the complexity lies in the fact that it consists of a theoretical component and a software or data analysis component. This is similar to Systems Medicine. Several challenges apply:

- The development of software is a very competitive field. In general, the life sciences are reluctant to invest in software. This might be different for systems biology research.
- On the side of data analysis and data integration (including modeling), it's difficult to generalize because a mathematical model is often used for solving a particular problem. It is a challenge to develop general and easy to use tools.
- Data availability and data handling still pose a lot of challenges, in particular technological challenges, in terms of making data accessible. However, the community is aware of challenges in data accessibility and this is a field of active research. Challenges arise mainly in the context of patient data.
- In Germany legislation and administrative hurdles in terms of the process of the accessibility of data is limiting progress. In other countries like UK or the Netherlands there might be more advances. There are examples of companies wanting to work on a project that involved monitoring patients, but specifically decided not to start it in Germany because it's too complicated. The administrative overload is blocking progress on such projects.
- Regulatory hurdles can block Systems Medicine in the early phase of development. It's a recognized problem, but there is not a short term solution yet.

Linear modeling versus nonlinear modeling:

- Recognition of the need of statistical methods in the medical field has increased, but the concept of modeling is perhaps less recognized. Therefore, the modeling part is a bit

detached from the statistical approach. For any model that you want to establish in practice, you need to do a statistical investigation, in this there is no distinction in linear or non-linear modeling. However, non-linear modeling may be tricky on the mathematical side and standard approaches are not generally available. There is still a bridge between the community of statisticians and modeling experts that needs to be overcome.

- To overcome this hurdle, we need experts educated in both fields. Along that line, training efforts in CASyM should be maintained in building and advancing communities. This is still in the non-commercial phase.

2. Do you see an increase of best practices of Systems Medicine approaches in your company or externally?

Yes, we have now one project in the company which is dealing with Systems Medicine where we are responsible for data integration and to a certain degree the data analysis. A lot of work goes into the data quality control and reliability. This is not a new message, but we see now much clearer how to perform data integration. Since most of work is done by hand, it doesn't directly lead to general tools. However, it's an evolving field.

In terms of standardization or protocols it remains a challenge. At the moment it's not even clear which observables (e.g. genes, proteins, phenotype parameters) are relevant for modeling and therefore it's difficult to define standard protocols or guidelines for data collection. Possibly for specific (high throughput or other) technologies SOP's may be defined. But it's unclear to what extend this kind of approach is really useful for the very diverse situations to be addressed in clinical studies or clinical practice. For different reasons high throughput data may be useful for initially defining the scope of a model, but the actual implementation focuses on a few relevant and validated parameters

It's an evolving field and there has certainly been progress which is also observed in the testing of new markers. This may lead to a change in clinical practice and may also lead to the formulation of more advanced ways of how to combine several parameters for diagnostics or predictive studies. It's an important part of the development and this is now becoming clearer. More complicated mathematical models will be needed and will be at the core of future diagnostics and clinical practice. This is still a difficult challenge and it's in the stage of being tried out and tested. There is quite some progress in the company and in the field in general.

3. What is a good business model for the application of Systems Medicine?

The points made around business models are still valid. What has evolved in the meantime is the application of high throughput techniques (i.e. gene profiling, protein profiling) for data generation. All these technologies have evolved:

There is more and more experience in applying high throughput technologies to patients. This is a step forward and it also implies certain business models in terms of data generation and data evaluation. This may also provide potential for a reasonable business model combining data generation and data analysis services.

To me the question to be addressed is, is there really a sustainable Systems Medicine business model based on the application of mathematical models and computational tools in the healthcare sector. Currently daily practice is still very much tilted towards the side of data generation. This is also related to the question how Systems Medicine should be positioned in 4P medicine and personalized medicine (PM). Since PM is more focused on measuring parameters, and SysMed is about making sense of parameters (analysis). The analysis and making sense of' (modeling) is not profitable as a business model unless you can give it a physical basis (w.r.t the modeling part) and you find a way to

protect it. Still, with establishing the viability of the SysMed approach, there will be ways to turn it into business.

4. CASyM ends in April 2016 and its successor is the European Association of Systems Medicine (EASyM). What role do you see for EASyM and what should be their focus?

- One aspect of CASyM should be maintained which is propagating teaching and training for young professionals. This is an important topic that helps to meet some of the challenges described above.

- For the application of SysMed, I think the goal must be to define good use cases ("success stories"). I can imagine that the techniques or the methods associated with SysMed may rather be useful for certain types of problems, typically where nonlinearity of the system is very important or where tricky probabilistic considerations come into play. Such situations really merit the development of dedicated mathematical models. In this sense one of the important goals is to define use cases and areas of application where SysMed is really of practical help.

- It's important to keep in touch with the SysMed community and also to find a position with respect to the other communities (e.g. personalized medicine projects). We need to define what we want to offer, and what we expect to get back,. We need to define the differences of what we do, and what others do. EASYM should be a forum for international networking to promote systems medicine.

- In terms of networking and communication, EASYM might try to address companies that have an interest in the SysMed approach. One way it can act there, is informing those interested in new developments and progress made in the field, and the other thing is to bring people together and enabling new projects for establishing the methodology. Or maybe bring together companies that have modeling tools with other companies making contact with the community or the patient. And also academic developing new tools for investigation of certain aspects of SysMed. A suggestion would be to have some kind of market place for interactions. Also for companies, because on the implementation side companies can be very efficient.

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