

SYSBIOMED Workshop on Diabetes and Systems Biology
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Roel van Driel presented "Systems Biology to combat Metabolic Syndrome (SBMS)", a EuroBioFund initiative. The EuroBioFund Programme was set up in 2006 by the European Science Foundation and the European Commission to identify future grand challenges in the life sciences which require a coordinated European approach for their financing and implementation. SBMS was selected a hot topic for several reasons, most important is the

insight that traditional approaches are obviously failing to achieve breakthroughs. Conceived for a ten years duration SBMS aims to achieve a "true understanding of MetS which allows rational and effective therapies and drugs." The programme builds on two pillars: 1. *Excellent ongoing MetS-related research* (strong research groups in Europe, large high quality data sets, national and international (EC) programs) and 2. *Rapid developments in systems biology* (data integration and system analysis; experimental design; integrate biology, physics, engineering, mathematics; national and international (EC) research programmes). Complexity of living systems, fragmented research activities, and data integration are considered essential hurdles. Driven by the huge socio-economic pressure from MetS/ diabetes funding is expected to come from many parties: EC, ESF, charities, research councils, governments, investors, banks, and industry (food, pharma, health insurances, others). SBMS is in its first phase, the outline for the whole duration is as follows:

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

SBMS Cost-Benefit Analysis by Arthur D. Little

SYBBIOMED is invited to join forces with SBMS, some of the scientists involved are already members of both initiatives.

Pierre De Meyts gave an in-depth introduction into the current understanding of type 2 diabetes (T2D). He discussed the different topics of diabetes research:

- Insulin resistance vs. beta cell defect in T2D, the two fundamental reductionist hypotheses on the pathogenesis of T2D, besides an "inflammation-centric" and a "brain-centric" view, which suggest that T2D is either mainly a signal transduction defect or a gene transcription defect, or both.
- The need to develop a Systems approach to investigate insulin signal transduction defects and the beta cell defect in T2D that incorporates insights from genome-wide scans for association, epigenetic studies, tissue interactions, metabolomics and the microbiome. He also briefly looked at diabetes type 1 (T1D) as a dynamical instability of intercellular communication.

Recent research has come across amazing puzzles, e.g. the conflicting results when comparing obesity and T2D incidences or the unexpected role of insulin as a signal molecule for beta-cells giving rise to the positive feedback of insulin secretion on beta cell function. Reversing the traditional dogma of translational medicine by quoting Sidney Brenner's motto "From bedside to bench!" Pierre DeMeyts presented the results of recent genome-wide scans: At least 10 genes/ loci have been validated as relevant for T2D. Among them were surprise candidates like SLC30A8 which codes for the zinc transporter ZnT8 or PPAR γ , a nuclear receptor for thiazolidinediones. Knockout studies with *C. elegans* revealed that as many as 112 genes increase fat storage when inactivated.

Flemming Pociot is investigating T1D which is an immune-mediated, multi-factorial disorder. Cytokines are specifically toxic to beta cells and may be key players in the pathogenetic processes. It is a multifactorial disease with polygenic predisposition and no disease-specific mutations exist so far. According to recent research, gene-gene interaction is important but, unfortunately, individual effects and sub-phenotypes are hard to identify. Novel analytical approaches, expression profiling and computational methods for positional candidate prioritizing are promising. A multidisciplinary approach is regarded very well suited for identification of genes and proteins involved in the disease.

Jørn Nerup reported on the epigenetic manipulation of gene expression in fetal rat islets of Langerhans. Some results from genetic research in this field are rather Lamarckian: Unfavorable intrauterine conditions (e.g. caloric or protein restriction, reduced placental blood supply) often produce a diabetes-like phenotype characterised by reduced body weight, reduced beta cell mass, reduced insulin secretion and glucose tolerance, enhanced sensitivity to cytokine toxicity and beta cell toxins. This phenotype persists for life and is transferable to subsequent generations.

Proteomic 2D-gel studies of islets from rat fetuses given a low protein (8 percent) and isocaloric diet showed statistically significant changes ($p < .01$) of expression levels of 70 proteins (total on gel 2810). They are involved in pathways which when perturbed most likely cause the enhanced sensitivity to cytokines and beta cell toxins. However, addition of taurine to the drinking water (2.5 %) of the pregnant rats throughout the gestational period normalises the diabetes-like phenotype.

One would presume that the phenotype associated with low protein diet and changed islet protein expression would result from changes in expression of genes controlling beta-cell

development/differentiation or genes responsible for islet hormone production/secretion, and the taurine transporter gene. Surprisingly, genes known to be involved in beta-cell development and differentiation (Pdx1, Hnf6, Hnf1, Ngn3, Nkx6, Pax4 and 6) were not affected. Both insulin genes, the glucagon, somatostatin, glucose transporter genes, and the taurine transporter gene (slc6a6) all did not show any change, too. Instead, changes occurred in genes involved in cell proliferation and cell cycle (CC), cellular defense mechanisms, and respiration (mitochondria).

Integrative approaches

The participants agreed to the conclusion that for decades reductionist approaches have failed to provide an understanding of the pathogenesis of T2D, methods to prevent or cure it, and drugs to treat it optimally. There are numerous puzzles left, e.g. the unclear correlation of diabetes and obesity. Thus, there is a high need for integrative approaches in order to understand the multi-layered complexity of diabetes mellitus. Pierre De Meyts expects that genome-wide scans for association will sooner than later establish a complete nomenclature of the common alleles that in unfavorable combination predispose to disturbed metabolism, and that these will reveal new critical nodes/pathways in metabolic regulation. Connecting these dots is regarded as the premier contribution of systems biology generating useful models.

Discussing which systems to study from a beta cell defect standpoint, beta cells appeared as a priority. Focussing on beta cells, however, carries the risk of missing important interactions, i.a. between cells of other tissues. Moreover, the quality of currently available primary beta cells is considered low. When studying the second hypothesis, insulin resistance, there is a number of cell types worth looking at: muscle cells, adipocytes, liver cells, and other tissue cells. Lines of muscle cells and adipocytes are available already. Hepatocyte cell lines have recently become accessible in course of HEPATOSYS, a German systems biology research programme dedicated to the hepatocyte system. A similar approach to study the beta cell may be worthwhile. The participants welcome the emphasis on diabetes/obesity in the current 'translating research for human health' call of FP7.

Data situation: Generating data from all levels - genes, proteins, metabolites – is considered possible, the latter type of data, however, not that well accessible. Genetic population studies are considered important, but difficult to perform. Protocols to produce standardised time

rows are required when studying the pathogenesis of diabetes. Standardisation is key issue and regarded as a matter of 'mind set' of the consortia's partners.

Current **technology trends** are pushing the limits of experimental design: Parallel high throughput (HT) sequencing of DNA at low cost has become a reality like the parallel monitoring of gene activities which has been available for some time. Metabolomics technologies are already delivering reliable results, while extracting such data from single cells remains on the wish list as does the option to measure intracellular metabolite gradients. Generating proteome data still bears difficulties with respect to quantification while recent progress in the development of 'capillary western blot' systems allows to identify phospho-isoforms of phosphoproteins in HT assays. Systems to perform HT microscopy/imaging experiments are not available yet, but in development. They promise to make a difference in protein analysis, especially for monitoring the intracellular spatial dynamics of proteomes. HT data on protein-protein interactions are highly desirable, the required technological advancements are currently being made. Data from combined RNAi experiments are considered highly important and the participants expect them to be a 'commodity' in the near future. There is a strong case for concentrating such technology facilities in HT centres as this would allow for efficient standardisation and access.

Education is a key issue of interdisciplinary research. Projects in medical systems biology, in particular, would require the cooperation of trained clinicians. Since systems biology is close to the clinicians way of thinking it should not be difficult to attract physicians to this research field. However, experience shows that the heavy non-research workload on clinicians and the far time horizon of publications from integrative projects are serious obstacles when trying to attract young scientists from medical disciplines. The participants proposed to organise summer schools devoted to relevant topics from medical systems biology. Endowed with travel grant money the courses should help to ease this problem.