

**EUGENE2 Scientific Advisory Board report:
Fourth year activities and 2008 General Assembly; Final report.**
Reporting members of the Scientific Advisory Board (SAB):

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Members of the Advisory Board were present throughout the October 2008 General Assembly and attended an executive session with Prof. Ulf Smith on the second day.

Fourth year activities and General Assembly

Overview:

The Scientific Advisory Board (SAB) continues to be most impressed by the EUGENE2 Network of Excellence and this will also be discussed under “Perspectives for the future” and “Implications for the European Commission”.

There has been remarkable scientific progress during the 4th year with all major milestones reached and a full list of deliverables. Once again, this has been driven by high-level science, innovative technology and an unusual degree of integration as well as by Prof. Smith’s leadership of this program. The SAB’s recommendations from the previous year have been implemented. There has been continuing training activity and the SAB continues to be particularly impressed by the full involvement of the more junior scientists (ESRs: Early Stage Researchers).

Progress, milestones and deliverables:

The following findings and recommendations are based on presentations at the General Assembly, written reports and discussions with Professor Smith.

Overall objectives:

The EUGENE2 program continues to be successful across the board. Joint publications have increased throughout the 4-year period including the landmark description of the EUGENE patient cohort, and the identification of a new diabetes/obesity susceptibility gene in rodents (Al-Hasani). There were again many short-term exchanges in the 4th year, bringing the total number to over 100. The General Assembly was as always an impressive showcase for EUGENE2 science and achievements, with lively discussion at all levels. As in previous years, the SAB noted that interactions were very clearly not limited to this meeting but maintained throughout the year: ***EUGENE2 is a truly integration-based network of excellence.***

Specific Workpackage reports:

WP1: *Communication and information:* there was no specific presentation but it is evident that these components continue to function perfectly with a well maintained website exploited to good effect by all members of EUGENE2. The SAB noted that all workshops and symposia throughout the 4-year period have been remarkably well organized and attended. Outside communication has also been excellent, providing a public face to EUGENE2 and reflecting well on the European Commission.

WP2: *Clinical and Molecular Genetic Study:* This Workpackage continues to be a major component of EUGENE2 with most impressive progress during the 4th year. Dr. Laakso stressed that the milestones and deliverables were in reality the result of 8 years of continuous activity and that the work was far from complete. There was

progress in all major areas (baseline study, novel DNA polymorphisms related to Type 2 diabetes), follow-up study and generation of mouse models). Five clinical centres have participated to generate the single largest collection of (well characterised normal glucose-tolerant) offspring of Type 2 diabetic patients (initially 874 individuals with a final number of 1155). There were 4 publications in this report period focusing on candidate genes possibly implicated in insulin secretion. The major thrust is now on the genome-wide association study (Illumina chip; 1000 individuals) with a primary variable of 1st phase insulin secretion. A close correlation was found between this variable and 30min AUC insulin/AUC glucose in an oral glucose tolerance test (a new and potentially useful variable for replication studies). Primary statistical analysis was completed in August 2008 and replication studies are ongoing (with €0.5 million additional funding from Kuopio University to accelerate the analysis). It has become evident that the statistical analysis is even more challenging than expected by this expert group of researchers. Thus, known genes were picked up but their rank order at medium stringency was surprisingly low (i.e. TCF7L2, $p=0.0076$; ranked 11087th). This work will obviously extend far beyond the lifetime of EUGENE2. The follow-up study focusing on progression to diabetes, central obesity or hypertension requires at least 3 years from the initial baseline observations. There are currently just 100 cases meeting the criteria from 722 patients re-examined. There has been equally remarkable progress using a mouse model of E1506K Sur1. This model reproduces hyperinsulinaemia of infancy with loss of 1st phase secretion and acquired insulin resistance driving diabetes in the adult mice. The team will now look for differential islet gene expression to explain this and hope to identify new islet "diabetes" genes.

WP3: Proteomics: Further to the SAB's recommendation, the budget for this Workpackage was decreased in Year 4. This notwithstanding, Dr. Samson has been very active in the 4th year. Samples of culture medium from insulin-resistant skeletal muscle were analysed but the amounts of protein were insufficient even for the highly sensitive apparatus used by the group in Nice. As mentioned last year, the new instrument can be used for metabolomics and lipidomics to evaluate changes in metabolite and lipid patterns associated with diabetes in both humans and animals. This has now been exploited by analysis of urine samples (sent by Dr. Häring's group) from control vs. non-diabetic offspring of diabetic patients. A major differential metabolite peak was detected and is currently being identified using 3 software packages. The goal will be to identify early biomarkers for type 2 diabetes. While the SAB were pleased to see this Workpackage starting to deliver useful preliminary data, it continues to believe that this is not one of the strongest components of the network. While this is admittedly due in part to under-exploitation by the network, there are also technical and analytical limitations that must be resolved in order to allow such a resource to be competitive in this rapidly evolving environment.

WP4 and 6: Common resources and integrated cell biology. These two packages were merged in Year 2 on the recommendation of the SAB. There has been remarkable activity in the 4th year. WP4 has developed a detailed MTA, the website is updated every 3 months (including new lab. tools) and most specifically has made available over the 4 year programme 10 antibodies (3 contributed by EUGENE2 members; 7 developed in-house) and 14 vectors (8 contributed; 6 developed in-house). There have been approximately 50 requests for reagents. A commercial agreement was signed in October 2008 with Abyntex Biopharma SL for marketing reagents under the EUGENE2 brand. Any money generated by this agreement will be used for continuing activities beyond the normal lifetime of EUGENE2. This is a significant achievement. The focus of WP6 has been on the in vitro model of insulin-resistant skeletal muscle; sex differences in gene expression in skeletal muscle; siRNA to understand insulin sensitivity (i.e. PDK4, IKKB). There are ongoing collaborations with 6 EUGENE2 groups with a heavy focus on DGK δ . Together, these

two Workpackages represent a major core component of EUGENE2 that drives much of the science in the focused projects and assures close integration and networking. It also contributes in a very important way to the training programme of the network.

WP5: *Engineering animal models.* All the milestones of this Workpackage have been met and the list of deliverables continues to grow in an impressive fashion. To date, the team has generated 22 transgenic models (in Barcelona) and 5 knock/in mice (Strasbourg). It was evident to the SAB that Dr. Bosch and her team in Barcelona are undertaking most of the work and that progress is due to her outstanding leadership and full involvement in the network's activities. Nine EUGENE2 groups are using these mouse models and there have already been several joint publications with more on the way. While several new adenoviral vectors were produced, there has been a major focus on developing new technology for gene delivery using AAV. Specifically, combining the appropriate serotype with specific methods for administration in small animals, it is now possible to target most major organs of interest to the Network including muscle, liver, islets and brain. The Barcelona group has also developed new generation vectors with higher titre/purity. The move to testing large animals was considered particularly impressive, with Dr. Bosch demonstrating a striking improvement in diabetic dogs injected with AAV expressing glucokinase and insulin directly into the hind-limb skeletal muscle. It was apparent that this Workpackage was fully integrated into EUGENE2 with most groups relying on its expertise and technology. There was useful synergy with other European networks including EUMODIC and CLINIGENE. In addition, the Al-Hasani group has successfully completed the positional cloning of a new mutant allele that protects against diet-induced insulin resistance and weight gain in mice. The work is currently in press in *Nature Genetics*, and represents a major scientific achievement that would not have been possible without EUGENE support.

WP7: *Training platform.* Training and workshops for younger investigators continue to play a central role in EUGENE2 and this is considered by the SAB to be an essential component of the network. There have been an impressive number of both short and long-term exchanges. These exchanges as well as the training courses have led to the development of an outstanding network of younger EUGENE2 investigators. There have been several joint grant applications from these investigators as well as individual Fellowship awards including Marie-Curie Fellowships. The Young Investigator Awards, suggested by the SAB, are a particularly successful element that binds groups together on a "bottom-up" basis. The 2008 training course in Anacapri was outstanding. Taken together, this Workpackage has met all its major goals, with a sustained impact on the future careers of the young investigators by fostering their transition to independence while attracting new talent to diabetes research.

WP8: *Management.* The SAB continues to be impressed by the EUGENE2 management and Dr. Smith's outstanding leadership role. Dr. Smith has been remarkably responsive to the SAB throughout the 4-year period and all recommendations were implemented rapidly. There has been a true dialogue between the SAB and management that is unusual and much appreciated.

Perspectives for the future

It will be apparent from the four progress reports from the SAB that EUGENE2 has been extraordinarily successful from every point of view. This success is based largely on integration of the scientific effort at every level. Far from being contrived for the sole purposes of obtaining this major European grant, EUGENE2 is one of the very few major networks in the world that truly functions in a coordinated and integrated fashion, with dynamic interaction and remarkable synergy: the whole is indeed much larger than the sum of the individual parts. The result is a great tribute to the European Commission's vision for European science and the specific way it can contribute towards developing the European Research Area (ERA: see also below). Strikingly, the science has driven the integration. Indeed, the scientific productivity has been outstanding to date but much more work is still in progress. The major deliverables have involved 4 and in some instance 8 years of investment in time and scientific endeavour. Many more years will be needed to realize the full potential of this investment and to allow EUGENE2 to have its intended sustained impact. When asked whether EUGENE2 should continue its activity beyond the intended 4-year funding period all the investigators agreed that this would be essential to allow this Network of Excellence to fulfil all its goals and contribute to the fullest extent possible to the European research effort.

The SAB considers EUGENE2 unique. The integrated scientific approach presents as a closed loop, linking the patient, genes, molecules, cells, organs, integrated physiology and experimental animal models. The network has invested massively in the development of new technology and analytical tools as well as patient recruitment and characterization. This started to provide a return on investment only in the 4th and last year. The SAB suggested last year that EUGENE2 could now be used a platform for creation of a "Virtual Centre for European Diabetes Research and the productivity in the 4th only serves to strengthen this recommendation.

The SAB strongly recommends continued activity.

Implications for the European Commission

The SAB is perfectly aware that European funding must always be competitive and that the Commission is bound by strict regulations put in place to respect subsidiarity and its unique role in the European research funding landscape alongside national research programmes. That being said, it is most unfortunate that there is no mechanism in place to ensure continued support for the most successful initiatives such as EUGENE2. Indeed, at present it is almost counter-productive for such large-scale and costly research networks to be successful and meet all their goals since there is no business plan that would allow for continued activity and return on investment. This would be unacceptable in industry and is shortsighted for a public funding agency. The National Institutes of Health have two mechanisms allowing for sustained support and development: 1. "Merit Awards": providing extended funding beyond the normal term only for the most successful projects considered of national importance; 2. Competitive renewal of major centres: diabetes networks similar in mission and scope to EUGENE2 (so-called DERs and DTRCs funded by the NIDDK) have been (competitively) refunded over many successive 5-year cycles. The SAB considers it imperative to have comparable measures in Europe. The European Commission has an ambitious programme for the development of research across the European Union and the promotion of excellence: ERA. To be credible and effective, ERA will have to foster success.

In discussions with Dr. Smith, the SAB urged EUGENE2 to find bridging funds from other funding agencies to allow activities to continue while discussions are under way to provide renewed funding from the Commission but this will never be sufficient in the longer-term.

The SAB encourages the Directorate General for Research to explore every opportunity to allow this integrated network of outstanding investigators to continue working together for the greater good of European research and individuals with diabetes.

October 14, 2008