LSHM-CT-2004-512013

EUGENE2

European Network on Functional Genomics of Type 2 Diabetes

Network of Excellence (NOE)

Life sciences, genomics and biotechnology for health

PUBLISHABLE FINAL ACTIVITY REPORT

Period covered: 1/11/2004 to 30/4/2009 Date of preparation: 12/6/2009

Start date of project: 1/11/2004 Duration: 54 months

Project coordinator name: Ulf Smith
Project coordinator organisation name: University of Gothenburg (UGOT)

1. PROJECT EXECUTION

EUGENE2 is a Network of Excellence focused on functional genomics, genomics, proteomics and bioinformatics to unravel the complex pathogenesis of Type 2 diabetes and the specific role of the key target organs for insulin. This involves the dedication and the development of common research infrastructures in human and mouse genomics and bioinformatics combined with cohesive research efforts in transcriptional regulation, insulin signalling and action in the target-tissues. A concerted effort in applying functional genomic approaches in target cells, animal models and humans will generate information necessary to make advances in health care, pharmaceutical development and public health policies. (Fig. 1)

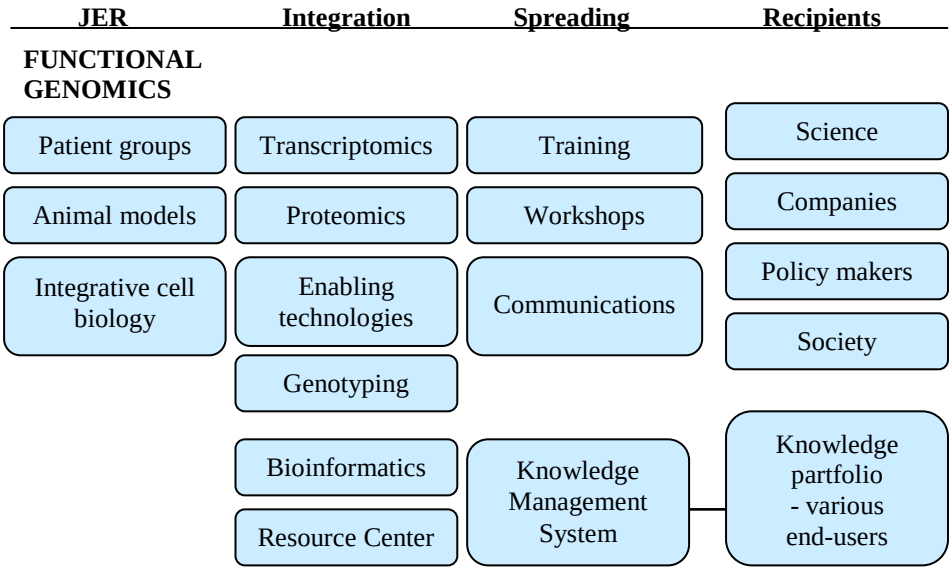

Fig. 1. The joint Programme of Activities of EUGENE2

BACKGROUND

Type 2 diabetes is a complex polygenic disease where genetic susceptibility interacts with environmental factors. An early event in the development of Type 2 diabetes is insulin resistance, i.e., an impaired effect of insulin in the target tissues (muscle, adipose tissue and liver).

To comprehensively study the pathogenesis of as complex a disease as Type 2 diabetes requires a broad array of experimental technologies, access to different experimental models (cells and animals), expertise in integrated physiology and cell- and molecular biology as well as well-characterized human populations with the disease and genetically predisposed individuals who have not yet developed Type 2 diabetes. Consequently, no single research group in Europe has the capacity to comprehensively

study such a complicated disease. The existing fragmentation of diabetes research in Europe is an important obstacle to success.

EUGENE2 integrates top scientists in diabetes research in Europe, thereby bringing together specific expertise in the required areas of cell- and molecular biology, animal models, biology of target organs for insulin action as well as combined access to unique patient populations allowing functional genomic and genetic studies. The establishment of common research protocols, technical platforms and databases promote durable and sustainable integration. The increased critical mass and the joint efforts of scientists with complementary expertise have allowed EUGENE2 to advance the current state of the art and provide new insights into the pathogenesis of Type 2 diabetes and to improve existing therapy.

AIM – Promote integration to reduce fragmentation in European diabetes research

EUGENE2 has taken many steps to strengthen European diabetes research and to reduce fragmentation. These include both ***direct*** integrating activities:

- *coordinated programming of research in order to strengthen the complementarity of the participants*
- *sharing of common research tools and platforms*
- *joint use of infrastructures*
- *using the jointly developed unique FDR database for studies relating phenotype to genotype; including genome-wide associations*
- *exchange of staff and training programmes*
- *integrated management of knowledge and intellectual property and implementation of a Joint Strategy for Immaterial Property rights*
- *reinforcement of electronic information and communication networks*
- *implementation of Young Investigators Award program to promote new collaborations and interactions between young scientists from different laboratories in EUGENE2*
- *promoting translational research with European biotech/pharmaceutical industry and commercialization of unique reagents developed by the consortium*

as well as ***indirect*** integrating activities based on jointly executed research (JER).

The jointly executed research is focused on generating new knowledge to fill existing gaps as well as to develop platforms for common use.

A JER programme is, by definition, an instrument for integration. Although intensive research has been focused on the genetics of type 2 diabetes during many years, only a few major genes contributing to this disease are known. The large database of carefully phenotyped FDR subjects allows genotype-phenotype information. This has been extensively used but must be further developed also after the termination of the project.

SUMMARY AFTER 54 MONTHS

The major milestones and deliverables focused on integration and shown in the Technical Annex have been achieved on or even before the dates indicated.

A major task during the last period was to perform Genome-Wide Associations (GWA) studies. To perform GWA studies is a major undertaking requiring many specific steps and extensive validation studies in other populations. A unanimous decision was taken at the last General Assembly to request an extension of the project by six months. This request was approved by the EC and the Scientific Officer. Thus, the EUGENE2 project was implemented during the period 1/11 2004-30/4 2009, i.e., 54 months.

Specifically, the following major results have been accomplished:

1. All management activities have been implemented, the required bodies established and the necessary decisions and goals agreed upon. A joint IPR strategy was developed and promoted.
2. Integrating activities related to common research platforms have been successfully established. These include the platforms for Communication, Proteomics, Common Resources and Cell-lines and Animal models. All these joint research platforms were extensively used by all partners. Research protocols for the use of jointly developed novel reagents were placed on the EUGENE2 intranet and accessible to participating scientists. Many new antibodies and cell- and molecular biology reagents were made available to the partners. These new reagents were sufficiently unique to attract European biotech companies as a source of sale. A contract was signed with Abyntek Biopharma, a Spanish company, which will sell EUGENE2® reagents under that very name as a registered trademark. This contract was signed by the UGOT Holding Company on behalf of the consortium.
3. Many new and unique genetically engineered animal models have been developed and are being studied.
4. A joint center for genotyping first-degree relatives (FDR) has been established. Twelve identified riskgenes have been genotyped and related to phenotype. Genome-wide associations have been performed for the unique FDR database (n=1155) established in EUGENE2. The GWA studies will be continued long after the termination of the EUGENE2 project. Newly identified genetic markers of risk for Type 2 diabetes have to be validated in other populations.
5. JER research has been carried out in order to fill the gaps in our knowledge about the causes and consequences of type 2 diabetes. Novel genes have been identified and their functions characterized. Important new genes involved in key pathogenetic steps of Type 2 diabetes have been identified and published in the best international Journals. These publications have evoked tremendous global interest and were also featured in media. For instance, one publication was followed by ~100 newspaper articles, four radio- and two TV interviews!
6. Five IPRs have been submitted; one as a joint IPR. Current negotiations are ongoing with biotech/pharmaceutical companies for further development of the IPR projects. One major joint development contract has already been signed, and initiated, as a spin-off of the EUGENE2 project.

7. Commercialization of own developed ®EUGENE2 reagents was started in 2008 with the Spanish biotech company Abyntek.
8. Spreading of excellence has been successfully done both in terms of public information and the generation of new knowledge published in scientific journals or presented at symposia. Both TV and other media reports about the project have appeared. In all, we know that at least 200 media publications about EUGENE2 have appeared. Fortythree joint publications have been produced. During the first year of EUGENE2, one joint publication! In total, around 187 scientific papers, with acknowledgement to the project, were published during 2004-2009. During the last period ~30 % of all publications were jointly produced!
9. Throughout the life span of EUGENE2, scientific exchange and training programs were implemented. In total, 115 short-term scientific exchanges were achieved. Four training courses with ~200 young European scientists were held (Fig. 2).
10. The activities of EUGENE2 were continuously evaluated by the prominent scientific advisory committee (SAC) as well as by the external reviewers for the EC. The overall conclusions, as expressed by the SAC *in October 2008* were:

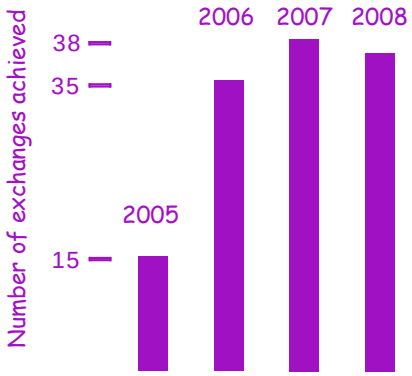

Fig. 2.

"The SAC 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 SAC suggested last year that EUGENE2 could now be used as a platform for creation of a "Virtual Centre for European Diabetes Research" and the productivity in the 4th year only serves to strengthen this recommendation.

The SAC strongly recommends continued activity".

In 2007 the EC Expert Reviewer states:

"It can be stated that EUGENE2 represents a project of outstanding quality which has even exceeded expectations. Objectives, workplan and milestones for the third period have been met and the joint research platforms have conducted successful work. Twenty joint publications in 2007 in high-ranking Journals emphasize that this NoE is conducting research of the highest calibre. Generation of the world's largest database of carefully phenotyped individuals at high risk of type 2 diabetes is extremely important for future research. The consortium is also very successful regarding commercialization of results and has performed tremendous efforts on training and integration of young researchers. Overall, EUGENE2 is of key importance and a major driving force of diabetes research in Europe."

Web-site: www.eugene2.com

Key words: diabetes, insulin resistance, cardiovascular disease, adipose tissue, liver, skeletal muscles

CONTRACTORS INVOLVED:

Particip. Role*	Partic. Number	Participant name	Participant short name	Country	Date enter project	Date exit project
CO	1	Ulf Smith	UGOT	Sweden	month 1	month 54
CR	2	Markku Laakso	UKUO	Finland	month 1	month 54
CR	3	Hans-Ulrich Häring	UTUB	Germany	month 1	month 54
CR	4	Giorgio Sesti	UNICZ	Italy	month 1	month 54
CR	5	Stephen O'Rahilly	UCAM-DCBIO	United Kingdom	month 1	month 54
CR	6	Oluf Borbye Pedersen	SDC	Denmark	month 1	month 54
CR	7	Juleen R. Zierath	KI	Sweden	month 1	month 54
CR	8	Hans-Georg Joost	DIfE	Germany	month 1	month 54
CR	9	Francesco Beguinot	UNAP	Italy	month 1	month 54
CR	10	Emmanuel Van Obberghen	INSERM	France	month 1	month 54
CR	11	Johan Auwerx	CERBM	France	month 1	month 54
CR	12	Fatima Bosch	UAB	Spain	month 1	month 54
CR	13	Peter Lind	BVT	Sweden	month 1	month 54

*CO = Coordinator
CR = Contractor

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Project public website: http://www.eugene2.com

Project internal website: https://intra.eugene2.com (password required)

Project logo:

2. DISSEMINATION AND USE

To general public and science audience

Planned/ actual dates	Type	Type of audience	Countries addressed	Size of audience	Partner responsible/ involved
Jan 2005	*Project external web-site*	*General public*	*All*		*1*
Feb 2005	*Project internal web-site*	*Partners*			*1*
Nov 2004	*TV*	*General public*	*Sweden*		*1*
Nov 2004	*Press x 2*	*General public*	*Sweden*		*1*
2005	*Press x 5*	*General public*	*Germany*		*8*
2005	*Press x 16 + TV*	*General public*	*Italy*		*9*
Oct 2005	*Conference*	*Research*	*SE, FI, DK, DE, IT, FR, ES, UK*		*9*
2005	*Publications*	*Research*	*All*		*All*
Feb 2006	*EU-conference, Vienna*	*EU/EASD members*	*EU-countries*		*1*
2006	*Website*	*Public website*	*Italy*		*9*
June 2006	*ADA Conference*	*Research*	*SE, IT*		*1, 4*
June 2006	*Press x 2*	*General public*	*Sweden/Spain*		*1, 12*
July 2006	*Press*	*General public*	*Sweden*		*7*
Sep 2006	*EASD satellite symposium, Denmark*	*Research*	*All, co-sponsored by EUGENE2*		*6*
Sep 2006	*EASD, Denmark*	*Research*	*All*		*1, 4, 6, 10, 12*
Oct 2006	*Press x 2*	*General public*	*Sweden/Spain*		*1, 12*
2006	*Publications*	*Research*	*All*		*All*
2007	*Book article*	*Research*	*All*		*12*
2007	*TV*	*General public*	*Germany*		*3*
June 2007	*ADA Conference*	*Research*	*Sweden/ Finland/Spain*		*1, 2, 12*
2007	*Press x 2*	*General public*	*UK*		*5*
2007	*Press x 7*	*General public*	*Germany, France*		*8, 10*
Sep 2007	*EASD, Ins. Rec. meeting*	*Research*	*All*		*1-4, 6-10, 12*
Sep 2007	*Claude Bernard presentation at the EASD Conf.*	*Research*	*All*		*10*
Sep 2007	*Biovitrum*	*Research/All*	*All*		*13*

	website – press release				
2007	*Publications*	*Research*	*All*		*All*
Feb 2008	*Invited lecturer*	*Research*	*SE, FR*	*30*	*1, 11*
Feb 2008	*DIfE-symposium*	*Research*	*SE, DE*	*150*	*1, 8,*
Feb 2008	*Press-release*	*General public*	*Sweden*		*7*
2008	*Interview (in Russian)*	*General public*	*Sweden*		*7*
May 2008	*DIAMAP(EU Support Action)*	*Research*	*Sweden (UGOT+KI)*		*1,2, 7,10*
June 2008	*ADA, San Francisco*	*Research*	*All*	*20000*	*1,2,3,7,10*
Sep 2008	*EASD, Rome*	*Research*	*All*	*18300*	*1,2,3,4,6,7,9, 10,12*
Nov 2008	*COST-meeting, BM0602*	*Research*	*SE, GE, FR*	*150*	*1, 8, 10*
2008	*Press x 8*	*General public*	*Germany*		*8*
2008	*TV x 2*	*General public*	*Germany*		*8*
2008	*Radio x 4*	*General public*	*Germany*		*8*
2008	*Press releases x 100*	*Research/General public*	*Germany*		*8, 7*
2008-2009	*Web*	*General public*	*Italy*		*9*
2008	*Publication, EU-profile PSCA EU16:352*	*General public*	*All*		*1*
2008-2009	*Publications*	*Research*	*All*		*All*

IPR and commercializations

Exploitable knowledge	**Exploitable product**	**Sectors of application**	**Timetable for commercial use**	**Patents**	**Owner & Partners**
EUGENE2® reagents	Molecular reagents	Research Medical	2008	---	EUGENE2 UGOT
PED function	Inhibitors	Medical	Unclear	IPR filed	SigmaTau UNAP
Nob1	Activators	Medical	Unclear	IPR	Tecnogen ongoing discussions
WISP2	Inhibitors	Medical	Unclear	IPR	Ongoing discussions
Sirt1	Activators	Medical	Unclear	IPR	Ongoing discussions
DGKδ	Inhibitors	Medical	Unclear	IPR	Ongoing discussions