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Luxembourg: Office for Official Publications of the European Communities, 2004

ISBN 92-894-8245-1

Printed in Belgium

PRINTED ON WHITE CHLORINE-FREE PAPER

Community-Funded Projects in the Field of Diabetes Research

Fifth Framework Programme 1998-2002

Quality of Life and Management of Living Resources Programme

Elmar Nimmesgern and Nathalie Vercruysse

Published on the occasion of the international conference
'Diabetes: Europe Rising to the Research Challenge',
Brussels, 12 November 2004

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Foreword

EU support for diabetes research in the Fifth Framework Programme (FP5)

Diabetes is a debilitating disease that affects an estimated 19 million people in the 25 Member States of the European Union (over 4% of the population) and is a major cause of death. Recent projections, based on the assumption of a stable obesity rate, foresee that at least about 26 million citizens in the EU (about 6% of the population) will be affected by 2030. This rate could go even higher as more as more people have a sedentary lifestyle/unbalanced diet and become overweight, thereby risking developing type 2 diabetes. Finally, it should be noted that an estimated one-third of diabetes incidence in Europeans is still undiagnosed.

Diabetes lowers average life expectancy by up to 15 years, increases cardiovascular disease risk two- to four-fold, and is the leading cause of kidney failure, lower limb amputations, and adult-onset blindness. In addition to these human costs, the estimated financial costs of diabetes are staggering. Effective therapy and life-style intervention can delay the onset of disease complications.

Research financed by the European Community aims to contribute to the fight against diabetes, as well as against related diseases, mainly obesity and syndrome X (a combination of obesity and insulin resistance).

Because of the importance of diabetes, research into its causes, diagnosis, prevention and treatment has received considerable support through EU research programmes. Research funding in the Union is made available through the Framework Programmes for Research. In FP5, life science research was funded within the 'Quality of Life and Management of Living Resources' programme (QoL programme). This specific programme was divided into six key actions (KA), research activities of a generic nature (Generic Activities), and support for research infrastructures. Projects related to diabetes research have been funded in four of the six key actions: KA 1, Food Nutrition and Health; KA 2, Control of Infectious Diseases; KA 3, The "Cell Factory"; and KA 6, The Ageing Population and Disabilities. Diabetes research was specifically mentioned in the section 7 Generic Activities: 'Chronic and Degenerative Diseases, Cancer, Diabetes, Cardiovascular Diseases and Rare Diseases'. The highest number of projects have been supported in this area of Generic Activities with eight studies receiving funding. Six projects were funded in KA 1. Three projects were funded in section 8 'Research into genomes and diseases of genetic origin' of the Generic Activities. Key Actions 2, 3, and 6, Generic Activities area 10 'Public health and health services research' and the section Research Infrastructures each supported one project in FP5. A total of 22 projects have been funded in FP5 with an EU contribution of €42.3 million out of a total cost for the projects of more than €56 million.

This publication gives an overview of the projects financed under the Fifth Framework Programme. Books of abstracts have previously been published for each of the individual parts of the QoL programme. This publication brings together diabetes research projects from all the different parts of the programme, as explained above.

Another feature of this catalogue is that it not only presents abstracts but also progress reports for each of the projects. It is clear that the projects funded at different times are at different stages: for some projects, the status after one year is reported, whereas other projects have already been concluded and some are at an intermediate stage.

Projects in this catalogue are sorted first by area of the programme from which they have been funded, and then in order of contract number. This listing starts with those funded in KA 1, then KA2, KA3, KA6, Generic Activities area 7, area 8, area 10, and concludes with the project funded in the Research Infrastructures part of the programme.

The fact that projects related to diabetes research have been funded in a number of different sections of the programme illustrates how this disease touches on many different aspects. The research addressed by the projects ranges from the nutritional aspects of obesity and the development of diabetes supported in KA 1, Food, Nutrition and Health, to the genomics of type 2 diabetes supported in Generic Activities. Some projects address both diabetes and cardiovascular disease research, reflecting the fact that diabetes is a major risk factor for CVD.

In FP5, the project types for the implementation of the programme were Research and Technical Development (RTD), Demonstration (DEMO), Combined RTD and DEMO, Concerted Actions (CA) and Thematic Networks (TN). The goal of the first three project types was to support innovative research, be it further from (RTD) or closer to (DEMO) the market. CAs and TNs aimed at networking scientists working either in a similar field (CA) or around a common technological or scientific platform (TN).

In addition to funding these projects, the programme also provided support for so-called Accompanying Measures (AM). AMs are aimed at supporting smaller activities, such as studies, workshops and conferences, and are not listed here.

The work programme for those parts of the QoL programme from which projects are listed is included at the end of this brochure.

In preparing this catalogue, the help of the project coordinators listed for each project and of colleagues from Directorates E and F of the Research Directorate-General, who follow the listed projects as scientific officers at the European Commission, was indispensable. We are grateful to Bill Baig, Jean-Marc Chourot, Philippe Cupers, Mary Fitzgerald, Liliana Galetescu, Gesa Hansen, Alkmini Katsada, Jürgen Lucas, Kevin McCarthy, Jacques Remacle and to the Heads of Units of the relevant sections of the QoL programme.

Stable isotope applications to monitor starch digestion and fermentation for the development of functional foods (EUROSTARCH)

Contract number:	*QLK1-CT-2001-00431*
QoL action line:	*Key Action 1, Area 3*
Type of project:	*Shared cost research and development*
Starting date:	*01.01.2002*
Duration:	*48 months*
Total project cost:	*€1 782 368*
EU contribution:	*€1 664 248*

Summary of achievements to date (31.12.2003):

Objectives:
The EUROSTARCH project aims to study small intestinal digestion and colonic fermentation of starch using stable isotope technology. One aspect of the metabolic quality of starch is the glycaemic response following starch consumption. Slowly digestible carbohydrates (low Glycaemic Index (G.I.) foods) induce a low glycaemic and insulinaemic response after the ingestion of these foods, which is considered to be metabolically advantageous.

Methodology:
This will be evaluated by measuring satiety, lipid and glucose metabolism and parameters of cognitive function. The factors influencing the glycaemic response – gastric emptying, intestinal transit and digestion rate – as well as the metabolic consequences, will be investigated. Retardation of the small intestinal influx of glucose will increase the distal absorption and colonic fermentation of starch. The metabolic consequences of these effects will also be studied.

Results to date:
13C-wheat and 13C-barley starch have been prepared by cultivation of plants under $13CO_2$ atmosphere and are being incorporated into model foods. Biscuits (low G.I.) and extruded cereals (high G.I.) containing 13C-wheat starch are being produced and will be evaluated in obese people by measuring parameters of glucose and lipid metabolism. Protocols for measuring gastric emptying, small intestinal transit time and small intestinal digestion have been developed and applied in pilot studies. Studies about the relationship between postprandial glycaemia and parameters of cognitive function are ongoing. To study the metabolic effects of (resistant) starch fermentation, techniques for bacterial characterisation (FISH, DGGE) are being developed and techniques for monitoring bacterial activity (*in vitro* fermentation, proteomics analyses of enzyme activity, and *in vivo* 13C- short chain fatty acid production) are in the process of development.

Results of the EUROSTARCH project will be published on the website: www.eurostarch.org. Subscription to an e-mailing list can be obtained through this website. The information concerning the metabolic effects of small intestinal digestion rates and large intestinal fermentation of 13C-starch will be used as rationale for optimising starch processing in the food industry and for developing starch-based functional foods. The first target will be breakfast products.

Newly developed gastrointestinal function tests applied in this project can be used in the clinical practice for the diagnosis of gastrointestinal dysfunctions.

Increased knowledge about digestion and fermentation of starch might lead to better advice to the general public concerning health aspects of starchy foods.

In the third year, the various protocols concerning gastric emptying, intestinal transit, intestinal digestion, colonic fermentation and cognitive function will be further applied in studies examining the effect of starchy model food products.

Web site:
www.eurostarch.org

Key words:
Starch, stable isotopes, digestion, fermentation, glycemia

Major publications (max. 3):
Not available

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Participant countries:
BE, 3 FR, NL, SE, 2 UK

Early malnutrition and programming of adult degenerative diseases: experimental, epidemiological and preventive studies (NUTRIX)

Contract number:	*QLK1-CT-2000-00083*
QoL action line:	*Key Action 1, Area 3*
Type of project:	*Shared cost research and development*
Starting date:	*01.03.2001*
Duration:	*48 months*
Total project cost:	*€2 603 557*
EU contribution:	*€1 952 035*

Summary of achievements to date (28.02.03):

Objectives:
The aim of NUTRIX is to provide the scientific basis for the concept of foetal origin of degenerative diseases, such as glucose intolerance, diabetes, obesity, hypertension and cardiovascular diseases, at the physiological, cellular and molecular level, and to identify key nutrients required for normal foetal development. This project will combine human and animal studies and focus on the insulin-producing cells (beta-cells), fat cells, liver cells and smooth muscle cells. Ultimately, we aim to formulate nutritional recommendations to pregnant and nursing mothers to improve long-term quality of life and to propose preventive and therapeutic nutritional supplements. The objectives are:

1. To better understand how a pregnant and lactating mother's nutrition affects early development, by using three animal models of decreasing nutritional deficiency (global food restriction, protein restriction and folate restriction);
2. To evaluate the relative importance of nutritional factors versus genetic factors in foetal programming by comparing genetic growth restriction models with the nutritional models;
3. To establish a link between experimental and human studies;
4. To identify key nutrients which serve as sensors of dietary deficiency and which, ultimately, may serve for preventive and therapeutic purposes.

Results and milestones:
By comparing the animal models of nutritional deficiency, we now have an indication that although maternal General Food Restriction and Protein Restriction lead to a reduced beta cell mass in the offspring at birth, the mechanisms involved are different. Maternal GFR (WP1) alters the islet neogenesis and directs the precursor cells toward the

exocrine phenotype rather than exocrine phenotype, via over-exposure to glucocorticoids. This will be investigated further next year. Maternal PR (WP2) affects the beta cell mass by decreasing the cell proliferation and islet vascularisation and by enhancing the level of apoptotic cell death which renders the beta cell more susceptible to aggression by immune cytokines at birth and later in life. Maternal Folate Restriction (WP3) has a long-term effect on growth of the offspring. FR leads to a reduction in insulin level without affecting the glucose tolerance. FR also reduces the cholesterol and triglycerides levels but does not affect blood pressure. These late consequences are similar to those observed in PR offspring. Poor maternal diet induces a common phenotype in the offspring, but the mechanisms involved are different.

Transgenic mice, in which the IGF-2 gene is made permanently deficient, have a smaller body weight at weaning that is maintained later, while placental IGF-2 knock-out mice undergo catch-up growth after birth (WP5). It was observed that a genetic growth restricted offspring has normal blood pressure and no difference in fasting plasma glucose level. Therefore, the lower catch-up growth observed in the placental IGF-2 knockout mice is not associated with poor glucose tolerance and hypertension. The animals will now be analysed at an older age. In comparison, 'recuperated' animals from a protein-restricted diet, displaying catch-up growth, have higher systolic blood pressures than controls at 17 months as well as significantly higher fasting plasma glucose at 13 months. This is consistent with findings in humans that suggest that early post-natal catch-up growth is associated with an increased risk of diabetes and hypertension in adulthood.

Cultures of two target tissues for insulin has demonstrated that the proliferation and differentiation of hepatocytes and adipocytes in pups are not affected by the maternal PR diet. This was confirmed by the absence of effect of the maternal diet on the DNA methylation of the cell in the offspring.

Two workpackages (WP6 and WP7) favour extrapolation of the results obtained in animal models to humans. The retrospective study done on the pancreas of an intrauterine growth retardation foetus failed to demonstrate the reduction of the beta cell mass as observed in rat. The retrospective study which was foreseen would have comfort or not this observation, but as autopsy material was not appropriate this WP6 milestone has not been achieved. It will be replaced by the analysis of a glucocorticoid receptor during human pancreas development in relation to WP1. This will give information about whether or not this altered pathway discovered in rat growth retarded *in utero* is also operating in humans. In the large epidemiological study in WP7, more than 105 000 women have now been recruited. The extraction of the data from the base commenced in order to analyse the relationship between maternal dietary intake and foetal growth.

The last Workpackage (WP8) comprises finding new perspectives for prevention. Sulphur amino acids appear to have particular properties. Last year, we found that the simple administration of taurine in the PR diet of the dams during gestation and lactation normalised the development of the endocrine pancreas in the foetus. This year, we demonstrated that the beneficial effect of taurine also appears at the level of islet vascularisation. Such early intervention reduced the increased vulnerability to cytokines at birth but, more importantly, the beneficial effect is maintained throughout life. However, this effect could not be attributed to a modification in the level of glutathione. The research will continue by trying to find what the action mechanism of this amino acid could be.

Benefits and beneficiaries:
Higher life expectancy and changing lifestyles have led to an increasing incidence of chronic illnesses such as obesity, diabetes, and cardiovascular diseases. The key to reducing the burden of these degenerative diseases on society and improving the individual's quality of life may be in improving the nutrition of the unborn child. Indeed, foetal growth is a complex, dynamic process depending on a continuous supply of nutrients from the mother. Epidemiological and experimental data reveal that deficient foetal nutrition, even over a brief period of time, may lead to irreversible changes in the offspring and to degenerative diseases in adulthood. This programming not only results from malnutrition due to poverty and social deprivation, but also from nutritional imbalances in affluent populations.

Future actions:
The results of this research will be disseminated in scientific publications in peer-reviewed journals and at presentations during local, national and international meetings. We will strive, by the end of the project, to produce a booklet featuring a summary of our results. Based on this, we will also propose guidelines for improving and/or supplementing diets. This booklet will be delivered to health care providers (physicians, obstetricians, paediatricians), people taking care of pregnant mothers and their offspring (midwives, social workers) and to public health authorities such as national associations and institutions, as well as to representatives of the European Commission.

Web site:
http://www.biol.ucl.ac.be/nutrix/

Key words:
Malnutrition, gestation, syndrome X, epidemiology, prevention

Major publications (max. 3):
Boujendar S., Reusens B., Merezak S., Ahn M.T., Arany E., Hill D. and Remacle C. (2002), "Taurine supplementation to a low protein diet during fœtal and early postnatal life restores a normal proliferation and apoptosis of rat pancreatic islets", *Diabetologia* 45:856-866.
Ozanne S.E. and Hales C.N., (2002) "Early programming of glucose-insulin metabolism", *Trends Endocr. Metab.*, 13:368-373.

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Participant countries:
BE, FR, 2 DK, ES, 3 UK

Dietary and genetic influences on susceptibility or resistance to weight gain on a high fat diet (DIET and OBESITY)

Contract number:	*QLK1-CT-2000-00515*
QoL action line:	*Key Action 1, Area 3*
Type of project:	*Shared cost research and development*
Starting date:	*01.02.2001*
Duration:	*41 months*
Total project cost:	*€3 416 060*
EU contribution:	*€2 462 930*

Summary of achievements to date (31.01.04):

Objectives:
The project will describe phenotypes associated with dietary preference and relative susceptibility or resistance to weight gain and obesity on a high-fat diet, and will investigate the genetic basis of this preference and susceptibility in human volunteers and patients. The mechanisms underlying susceptibility to diet-induced obesity, weight change following dietary manipulation, and the interaction of exercise with these phenomena will be investigated in a laboratory rodent model.

The project will investigate the effect of early-life nutrition on: (i) dietary preferences in juvenile or adult life; (ii) susceptibility to developing obesity; (iii) the programming of hypothalamic neuroendocrine systems involved in energy homeostasis; and (iv) the functioning of the small intestine, using both human volunteers and laboratory rodents.

A website will be established, targeted specifically at a lay rather than an academic audience. It will illustrate the basic relationships between diet, energy expenditure and genetic predisposition in the development of obesity.

Methodology:
The project employs a wide range of complementary approaches ranging from assessments and data collection in the clinical setting, to the study of free-living and laboratory-based human volunteers, and mechanistic laboratory rodent programmes.

The research into diet-induced obesity in humans involves analysis of existing databases, investigation of human phenotypes by questionnaires, and non-invasive behavioural, metabolic and physiological methodologies in both controlled laboratory environments (including metabolic nutrition laboratory) and in everyday life. Diets are imposed or chosen from a selection provided. Appropriate hardware and software are used to track accurately food intake and motivation to eat. Blood samples are taken for hormone and metabolite assay, and DNA isolation, the latter prior to polymorphism or mutation screening of candidate genes.

The research into diet-induced obesity in laboratory animals involves assessment of the activity and regulation of the animal's behaviour, energetics, body phenotype and peripheral and brain signalling systems following dietary, energetic or hormonal challenge. The range of techniques employed includes brain cannulation, calorimetry, body composition, enzyme activity, and molecular techniques such as in situ hybridisation. The animal model aspects of the project were amplified in 2003 by the addition of a new participant laboratory under the NAS funding scheme.

Results to date:
The ability to diagnose individuals who are susceptible to obesity on a Western diet and to dissect the mechanisms underlying this susceptibility or resistance would be likely to stimulate the development of novel or better-targeted interventions. The frequency of individuals within the population who could be classed as resistant or susceptible to obesity on a high-fat diet depends upon the criteria used to define 'high fat'. Through analysis of existing dietary/body phenotype datasets which we have assembled, we have estimated that lean, high-fat consumers probably represent around 2-5% of the population. We have recruited volunteers for intensive and extensive phenotyping studies on two sites and, in so doing, have established a DNA sample bank. Detailed analysis of individuals who have already completed the phenotyping studies is under way. We have competed the blood sampling of obese children and adolescents with a known percent of total energy intake as fat, and employed the DNA samples thus collected in candidate gene analysis. Candidate genes were selected on the basis of likely involvement in diet-induced obesity, and association tests for percent fat intake and susceptibility to diet-induced obesity are ongoing.

The Sprague-Dawley rat has been investigated in detail as a rodent model of diet-induced obesity. We have demonstrated that the body weight response to a high-energy diet similar in composition to that consumed in the Western world is normally distributed within a population, verifying that the rat model is an experimental equivalent of polygenic dietary obesity in the human population. Data on the effect of this diet on juvenile animals have highlighted the potential of this

as a model of childhood obesity. Hypothalamic signalling in this situation was consistent with an attempt to oppose further development of an obese body phenotype. We have investigated the early hormonal and neuroendocrine responses to dietary manipulations, as well as diet preferences, and interactions between diet and voluntary exercise activity in body weight development.

Provision of targeted nutritional advice during pregnancy may reduce the susceptibility of individuals to obesity and associated diseases in later life. We have completed and are in the process of analysing the database for the Stockholm Weight Development Study, examining the characteristics of children born to participants in an earlier pregnancy study. As a parallel, we have examined the effects of macro-nutrient imbalance during gestation and lactation in a rat model. Particular focus was on the effects of fat and carbohydrate imbalance during these critical phases. The programming effect of dietary manipulation on body weight at different points in development, feeding behaviour and dietary preference, and metabolic, endocrine and neuroendocrine parameters was examined.

The possibility of expanding the skills base of the project through inclusion of an additional participant under the NAS scheme enabled value to be added to many animal studies. Intestinal functioning was assessed in both early-life nutrition studies and in response to dietary manipulations carried out by other participants and by the NAS laboratory itself.

We have established an obesity website providing accessible information about energy balance and body-weight issues that will be beneficial to children and adolescents and their families, teachers and health care providers. The site was designed to generate a supportive environment that should reduce the social stigma attached to this debilitating condition.

Web site:
www.eurobesity.org; www.adipositas-online.com

Key words:
Obesity, high fat diet, susceptibility, phenotype, genotype

Major publications (max. 3):
Mercer J.G., (2001) "Dietary and genetic influences on susceptibility or resistance to weight gain on a high fat diet", *Nutrition, Metabolism and Cardiovascular Disease 11* (Suppl), 114-117.

Archer Z.A., Rayner D.V., Rozman J., Klingenspor M. & Mercer J.G., (2003) "Normal distribution of body weight gain in male Sprague-Dawley rats fed a high energy (HE) diet", *Obesity Research* 11: 1376-1383.

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Nutrient-gene interactions in human obesity: implications for dietary guidelines (NUGENOB)

Contract number:	*QLK1-CT-2000-00618*
QoL action line:	*Key Action 1, Area 3*
Type of project:	*Shared cost research and development*
Starting date:	*01.03.2001*
Duration:	*36 months*
Total project cost:	*€4 011 639*
EU contribution:	*€3 208 840*

Summary of achievements to date (17.03.2003):

Objectives:
The aim of the NUGENOB project has been to improve the understanding of the interaction between nutrition – i.e. fat intake – and genetic variations and functions in obesity. Obese and lean subjects (771 and 119, respectively) from eight European cities have been examined by scrutinising dietary habits and lifestyles, a one-day clinical investigation programme including a high-fat test meal, followed by a ten-week hypocaloric dietary intervention with either high- or low-fat content.

Metabolic and hormonal responses to the test meal, changes in body weight and composition, and in adipose tissue gene expression have been assessed and related to genotypes of selected known and novel candidate genes.

More specifically, the objective of the project has been to improve understanding of the role of the interaction between nutrition, especially fat intake, and genetic variations in obesity, which may be the basis for a revision of dietary guidelines.
The aims were:
1. To identify and characterise novel nutrient-sensitive candidate genes for obesity;
2. To assess differential gene expression in adipose tissue in relation to the acute intake of a high-fat meal as well as the long-term intake of a hypocaloric diet with either a high- or a low-fat content;
3. To assess effects of functional variants of the candidate genes on physiological responses in obese subjects to a high-fat test meal: appetite, energy expenditure, partitioning, and circulating obesity-related hormones and metabolites;
4. To identify, on this basis, predictors of changes in body weight and composition during dietary intervention, including changes in fat intake.

Methodology:
In eight European cities, source populations were defined from which the study population of a total of 771 obese

and 119 normal weight reference subjects were selected. Information on dietary habits and other lifestyle aspects of relevance to obesity was obtained from all subjects. All subjects completed a one-day clinical investigation with a test meal challenge with 95% of the energy intake from fat. Finally, the obese subjects were all randomised to a ten-week intervention programme consisting of a hypocaloric diet (~ 600 Kcal energy deficit per day), either with a low fat content (20-25% fat) or with a moderate fat content (40-45% fat).

During the one-day investigation, the physiological responses to the test meal in appetite, energy expenditure and nutrient partitioning, and circulating obesity-related substrates, hormones, and metabolites were assessed. Before the test meal, weight, height, waist-hip ratio, body composition measurements, and biopsies from the subcutaneous adipose tissue were obtained. All of these measurements were repeated in obese subjects following the ten-week intervention programme.

Changes in expression of relevant candidate genes in adipose tissue were quantified by mRNA measurements. From all the obese subjects fasting subcutaneous abdominal adipose tissue was obtained at baseline. From the obese subjects who completed the dietary intervention another biopsy was obtained after the completion of the intervention. mRNA has been purified from all the adipose tissue biopsies. Gene expression was examined in sub-groups of the study populations. Quantitative gene expression has addressed the change in the expression of 40 selected candidate genes from before to after the dietary intervention, addressing the overall effect of calorie restriction and the differential response to the two diets. Gene-expression profiling has been conducted in two sub-groups from the study population, using different set-ups for the gene profiling.

The project has included a thorough search for candidate obesity and nutrient-sensitive genes and gene variants. The genes have been identified by linkage analyses, genome wide scan, association studies, by studying changes in gene expression in adipose tissue in response to energy restriction and varying fat content of the diet, and finally by a bioinformatics search. Several candidate genes and gene variants have been identified. In addition, novel relevant, putatively nutrition-sensitive candidate genes has been identified from the gene expression experiments.

Using blood sample DNA from the entire study population, the genotypic distribution of functional variants of putative candidate genes has been determined and related to the responses to the test meal and the intervention programme.

All data on the study population are stored in one common databank, and statistical analyses have been carried out as a basis for the reporting and conclusions of the study.

The results are being disseminated both in the scientific community and in the public arena, internationally and nationally.

Results to date:
The possible differences in the response to the two diets, with respect to weight loss, weight loss composition (i.e. loss of fat mass or lean body mass), and changes in waist circumference are addressed, as is the effect of the two diets on insulin resistance, and blood lipids.

A large panel of putative predictors are being tested for their association with weight loss, changes in body composition and waist circumference, as well as drop out from the treatment regime. All predictors are tested for possible interaction with diet, i.e. whether specific baseline parameters are associated with a better outcome from either the moderate fat or the low fat diet. The panel of putative predictors includes parameters of energy and substrate metabolism and blood parameters in fasting, following the high fat test meal. Additional factors include habitual diet and lifestyle, history of obesity and previous dieting, familial predisposition to obesity, and health-related quality of life (SF36). The success of the search for predictors of weight loss is strongly guided by the result of the thorough analyses of determinants of postprandial substrate metabolism after the high fat meal.

The integration of the genotypic and phenotypic data is expected to lead to the identification of specific gene variants affecting the overall weight loss success or showing an interaction with diet. It is likely that, in future, it will be possible to sub-classify obesity according to genetic variation which has been shown to play a role in the development of obesity and in the response to controlled weight loss intervention. Genotyping obese subjects will then serve as a diagnostic tool, and genotype profiling will be an instrument for optimising the treatment.

The results of NUGENOB will aid clinicians and dieticians treating obese subjects, improving the platform for setting realistic weight loss expectations at the individual level, and for tailoring and optimising the diet in accordance with a subject's genotypic, phenotypic and lifestyle characteristics. In addition, the results will be implemented in future research, and is expected to be of interest to the pharmaceutical industry and the food industry.

Web site:
www.nugenob.com

Key words:
Obesity, weight reduction, diet, intervention, nutrient-sensitive gene, candidate genes, gene expression, dianoetic, tailored treatment regimens

Major publications (max. 3):
At the time of preparing the input to this catalogue, none of the core findings from the project has been published in scientific papers. However, preliminary results were presented at the 12th European Congress on Obesity 2003. The abstract was published in the International Journal of Obesity (S25, Volume 27, Supplement 1, May 2003).
In addition, four abstracts from the project were proposed for presentation at 13th European Congress on Obesity (Prague, 26-29 May 2003).

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Nutritional primary prevention of type 1 diabetes (DIABETES PREVENTION)

Contract number:	*QLK1-CT-2002-00372*
QoL action line:	*Key Action 1, Area 3*
Type of project:	*Shared cost research and development*
Starting date:	*01.05.2002*
Duration:	*48 months*
Total project cost:	*€2 668 443*
EU contribution:	*€1 585 037*

Summary of achievements to date (30.04.2003):

Objectives:
The specific aims of the Diabetes Prevention study are:
1. To determine whether weaning to a casein-hydrolysate-based infant formula reduces the frequency of diabetes-predictive autoantibodies in subjects with risk-associated HLA genotypes and a first degree relative (FDR) with type 1 diabetes; and
2. To determine whether weaning to a casein hydrolysate reduces the frequency of clinical diabetes in subjects with risk-associated HLA-genotypes and an affected FDR.

Results to date:
Randomisation in the study started in the first countries, according to the study protocol, in early May 2002. Recruitment in the various European countries, USA and Canada during the report year progressed well with more than 900 participants recruited.

During the second report year, we obtained 1 242 registrations and 1 136 randomised subjects, 529 of whom were eligible to continue in the intervention after the HLA-screening. All of these figures are clearly higher than during the first year of the project. In particular, the compliance situation has improved during the second report year due to various measures taken to help the centres to perform the study and document the events.

The trial will provide evidence-based data as to whether weaning to a highly hydrolysed formula in infancy subsequently decreases the frequency of diabetes-associated autoantibodies and clinical type 1 diabetes.

On completion of the project, the beneficiaries will be families with newborn infants of increased genetic risk. If the study hypothesis is correct, after exclusive breast feeding such infants may gain protection against type 1 diabetes by being given casein-hydrolysed formula instead of ordinary cow's-milk-based formula.

We envisage the recruitment and data collection will continue and expand with sufficient speed to complete the recruitment targets within a period of four years.

Web site:
www.trigr.org

Key words:
Type 1 diabetes, prevention, cow's milk formula

Major publications (max. 3):
Åkerblom H.K., Becker D., Dosch H.-M., Dupre J., Ilonen J., Knip M., Krischer J.P., Palmer J.P., Savilahti E., Vaarala O., Virtanen S., "Nutritional trial for primary prevention of Type 1 diabetes in children (TRIGR)", Abstract, *Diabetes Metab* 2003:29:4S46.

Nallamshetty L., Eschrich S.A., Cuthbertson D., Malloy J., Goldgof D.B., Alexander A.M., Trucco M., Ilonen J., Akerblom H.K., Krischer J.P., TRIGR Study Group: An Expert System for Evaluating Risk of Type-1 Diabetes. In Proceedings of the 2003 IEEE International Conference on Systems, Man and Cybernetics 1660-1665, 2003.

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Childhood obesity: early programming by infant nutrition?

Contract number:	*QLK1-CT-2002-00389*
QoL action line:	*Key Action 1, Area 3*
Type of project:	*Shared cost research and development*
Starting date:	*01.03.2002*
Duration:	*42 months*
Total project cost:	*€2 832 821*
EU contribution:	*€2 422 807*

Summary of achievements to date (28.02.2003):

Objectives:
Obesity is now considered to be a global epidemic. The increase is most marked in affluent parts of the world including Europe where obesity has become the predominant nutritional disorder in childhood and a major public health issue. The CHOPIN project addresses this issue. The key objective is to test the influence on growth (i.e. increase in length and weight) of the protein content of infant formula fed during the first two years of life.

A secondary objective is to compare the effects of different habitual protein intakes with traditional complementary feeding regimes in infants across five European countries (Germany, Belgium, Italy, Poland and Spain). The influence of these infant feeding regimes on body composition, energy expenditure, protein metabolism, renal function and size, leptin, its binding protein and insulin-like growth factor-I will be examined. Consumer attitudes and infant feeding practices will be explored in relation to parental obesity status. The possible correlation between diet and later growth via biochemical parameters, which might become detectable by the plasma concentrations of the corresponding compounds at the age of six months, will be investigated. Information on infant behaviour (crying, sleeping and feeding) will be obtained to quantify their effects on development of obesity. The evolution of weight and length of two formula fed study groups will be compared to a cohort of breastfed infants. Effects of different dietary regimes on total energy expenditure will be analysed and the relationships between total energy expenditure, body composition and obesity risk within a sub-group of children will be obtained.

Results to date:
Blédina has developed and produced two infant formulae and follow-on formulae with an equal energy density. These are being used in the intervention trial for Groups A (low protein content: 7% of energy in infant formula and 9% in follow-on formulae, respectively) and B (high protein content: 12% of energy in infant formula and 18% in follow-on formulae respectively). The difference in protein content is compensated for by adaptation of fat content. Overall protein quality and fatty acid profiles are similar in the two experimental formulae. The composition of all study formulae complies with recommendations of the 1991 EU Directive on Infant Follow-on Formulae.

Development and agreement on the biochemical assays to be performed had been completed by September 2002. Validated and robust procedures for assessing protein metabolism and renal function in infants from zero to two years of age were chosen together with procedures for assessing availability of leptin and analysing both concentrations of human growth hormone and insulin-like growth factor-I.

An electronic case report form, including standardised forms on screening procedure, socio-economics, pregnancy and delivery, medical history of mother and child, and laboratory parameters, has been developed. A methodology for the collection and recording of data covering post-partum depression, infantile diet and behaviour and mother's eating behaviour, including consumer attitudes, has been set up in five trial centres using age-specific parent questionnaires. These questionnaires and food records have been printed in the appropriate language and distributed within the five partner countries (Germany, Belgium, Italy, Poland, Spain) participating in the intervention trial.

A selection of the most appropriate anthropometric measurements has been made in order to evaluate the relationship between infant feeding and anthropometric markers of future obesity. This selection was based on current scientific literature and World Health Organisation recommendations. Appropriate age-specific case report forms have been designed. Validated and robust operating procedures for assessing total energy expenditure in infants at six months of age have been established by scientists at the Medical Research Council, Cambridge. These form guidelines for fieldworkers in charge of specialised urine sampling and measurements.

We are performing urine sampling on 30 children from group A, 30 children from group B and, in order to obtain total energy expenditure references for breastfed children, on 30 breastfed children. Urine sampling began in April 2003.

The intervention trial started on 1 October 2002. By the end of February 2003, 497 children (289 formula-fed and 208 breastfed) had been recruited. By November

2003, 1 520 children (931 formula-fed and 589 breast-fed infants) had been recruited. Due to the high breastfeeding rate in participating countries, recruitment of formula-fed babies was slower than anticipated. However, given the current rate of recruitment, the project team expected to have the necessary 1 250 formula-fed children by March 2004. Up to now, Spain has made the greatest contribution to the recruitment of formula-fed children. The most serious difficulties have occurred at the University Children's Hospital in Brussels. To help alleviate this problem, we have begun to draw on an additional centre in Liège.

Standard monitoring protocols for visits and inspections were delivered to each centre by September 2002 and standardised procedures for blinding and randomisation (randomisation via the internet) have been established. A database has been set up that includes parameters involved in hypotheses testing. The information technology architecture for the central database and 12 remote data entry stations, as well as mechanisms for quality assurance, have also been established. Regular status reports and data deliveries are planned for use in the monitoring process and uniform electronic case report forms have been provided. Data input and transfer to the central database are being supervised by the participating contract research organisation. As a result, each centre will be visited only once for a period of two to four days. Emphasis will then be placed on regular 'remote' database inspections to ensure quality control.

Each partner was asked to appoint a contact person and deputy in order to foster collaboration between the partners and facilitate coordination. Two Technical Committee Meetings (April 2002 in Bernried, Germany and October 2002 in Paris, France) and two Steering Committee Meetings (April 2002 in Bernried, Germany and October 2002 in Paris, France) were organised. Two Technical Workshops were also held (the first, a teaching session on anthropometry and food recording in September 2002 in Irsee, Germany and the second a teaching session on remote data entry in January 2003 in Munich, Germany).

Benefits and beneficiaries:

Peer-review publications, popular articles and other published material:

Toschke A., Vignerova J., Lhotska L., Osancova K., Koletzko B, von Kries R., "Overweight and obesity in 6- to 14-year-old Czech children in 1991: protective effect of breastfeeding", *J Pediatr* 2002; 141(6):749-57.
Koletzko B., Toschke A.M., Vignerova J., Osancova K., von Kries R., "Does Breastfeeding Protect Against Later Overweight and Obesity?", *Cesko-Slovenská Pediatrie* (Prag) 2003, 58:3-9.
Toschke A.M., Grote V., Koletzko B., von Kries R., "Is weight gain during the first two years suitable to identify children at high risk for overweight at school entry?", *Arch Pediatr Adolesc Med* 2004, in press.

Future Actions

To enhance recruitment in all study centres and compensate for drop-out rates currently running at 16.9 % for the formula-fed group and 27.7 % for the breastfed group. We will:

1. Extend the upper boundary of the time frame for inclusion from 28 days to 56 days of age;
2. Continue recruitment until we have 1 250 formula-fed children participating in the project.

To resolve the serious recruitment problem in Belgium, a second centre located in a suburb of Liège has been established. As a consequence of the marked delay in recruitment of formula-fed children in Belgium, the task of specialised urine analysis will be consolidated with the Spanish team.

Web site:

http//:www.childhood-obesity.org

Key words:

Infant nutrition, metabolic programming, metabolic imprinting, obesity

Major publications (max. 3):

Toschke A., Vignerova J., Lhotska L., Osancova K., Koletzko B, von Kries R., "Overweight and obesity in 6- to 14-year-old Czech children in 1991: protective effect of breastfeeding", *J Pediatr* 2002; 141(6):749-57.
Koletzko B., Toschke A.M., Vignerova J., Osancova K., von Kries R., "Does Breastfeeding Protect Against Later Overweight and Obesity?", *Cesko-Slovenská Pediatrie* (Prag) 2003, 58:3-9.
Toschke A.M., Grote V., Koletzko B., von Kries R., "Is weight gain during the first two years suitable to identify children at high risk for overweight at school entry?", *Arch Pediatr Adolesc Med* 2004, in press.

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Enterovirus infections as a risk factor for type 1 diabetes (VIRUSES IN DIABETES - VIRDIAB)

Contract number:	*QLK2-CT-2001-01910*
QoL Action Line:	*Key Action 2*
Type of project:	*Shared cost research and development*
Starting date:	*01.12.2001*
Duration:	*36 months*
Total project cost:	*€1 300 000*
EU contribution:	*€1 300 000*

Summary of achievements to date (30.04.2004):

Objectives:
Type 1 diabetes is a common chronic disease occurring mainly in children and young people. In Europe, its incidence is high and steadily increasing. The disease is caused by the destruction of insulin-producing cells in the pancreas. Many studies have suggested that enterovirus infections can induce this process. Recently, substantial new evidence has been obtained which supports their role further.

This study aims to confirm the link between enterovirus infections and type 1 diabetes in five EU countries and characterise the molecular determinants, which make these viruses diabetogenic. The final goal is to find out if type 1 diabetes can be prevented by an enterovirus vaccine and to provide the information needed for the development of such vaccines.

Methodology:
1. Collecting optimal samples for virus analyses from type 1 diabetic patients and prospectively followed pre-diabetic children, as well as matched control subjects in five EU countries with varying incidence of both type 1 diabetes and enterovirus infections. The samples include whole EDTA – blood, Ficoll-gradient purified mononuclear cells, serum and stools.
2. Analysing the samples in the three standardised virus laboratories to find the presence of enterovirus RNA and determine if the frequency of enterovirus infections is increased in newly diagnosed type 1 diabetic patients as well as in children who are initially non diabetic but subsequently develop clinical diabetes during a prospective observation. The time relationship between the enterovirus infections and appearance of autoantibodies in the birth-cohort series is also analysed. The frequency of enterovirus infections is compared between case and control subjects (case control and prospective birth – cohort series). Adenovirus infections are analysed as a control infection.
3. Analysing samples to find out if type 1 diabetic subjects and pre-diabetic individuals show signs of increased production of interferon (IFN)-alpha as a marker of recent or persistent virus infection. The responses are compared between cases and control subjects, and their relation to the signs of enterovirus and other viral infections is analysed.
4. Analysing samples to identify the serotypes of diabetogenic enteroviruses. The serotype is defined by measuring serotype specific antibodies from serum. The identification of the serotype is important for the possible development of preventative vaccines because vaccine-induced protection is serotype specific.
5. Analysing the samples to identify the genetic cluster serotype and the particular gene sequences which are characteristic of diabetogenic enterovirus strains.

Results to date:
A detailed study protocol has been developed and a collection of study series has progressed well. In addition, laboratory analyses and quality control tests have been conducted as planned. During the first 23 months, a total of 292 diabetic and 185 control subjects were recruited to the study and the recruitment is progressing well. The samples are being analysed, and the progress achieved is in line with the activities and schedule planned.

Web site:
http://www.uta.fi/laitokset/laaket/VIRDIAB/

Key words:
Type 1 diabetes, enterovirus, vaccine

Major publications (max. 3):
A poster describing the VIRDIAB project which was presented at 7th International Congress of the Immunology of Diabetes Society (IDS), Cambridge, UK, March 28-31 2004.

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Generation of bioengineered pancreatic islet micro-organs for insulin replacement therapy in diabetes mellitus (PSEUDOISLET)

Contract number:	*QLK3-CT-2002-01777*
QoL action line:	*Key Action 3, Area 1.3*
Type of project:	*Shared cost research and development*
Starting date:	*01.11.2002*
Duration:	*36 months*
Total project cost:	*€2 936 950*
EU contribution:	*€2 014 720*

Summary of achievements to date (31.10.2003):

Diabetes is a major health problem in Europe. Limited availability of donor tissue restricts conventional transplant treatments. Therefore, we propose to bioengineer pancreatic islet micro-organs (called pseudoislets) using glucose-responsive insulin-producing cells of differentiated stem cell origin. These micro-organs should be suitable substitutes to restore the function of the destroyed pancreatic islets in a diabetic individual. The combination of the bioengineering of insulin-secreting surrogate cells with techniques for the generation of a pancreatic islet micro-organ represents a highly innovative experimental approach. This 'cell factory' concept for an innovative insulin replacement therapy, applied to cells of human origin, can offer a cure to many diabetic patients, due to the unlimited supply.

Objectives:
Diabetes is one of the European Union's major health problems affecting more than 10 million inhabitants. This collaborative research project, involving key European groups in diabetes research and a SME biotechnology company, intends to provide a cure for insulin-dependent diabetes mellitus.

The aim of this project is to engineer pancreatic islet micro-organs (so-called pseudoislets) suitable for insulin replacement therapy in diabetes. To achieve this goal, gene therapy technologies will be applied to bioengineer glucose-responsive insulin-secreting surrogate cells of stem cell origin. These cells will be aggregated in an organised arrangement as micro-organs similar to normal pancreatic islets. The bioengineered pseudoislets will replace the destroyed pancreatic islets in the diabetic patient.

Methodology:
Insulin-secreting cells show their optimal functional capacity when organised in the form of pancreatic islets of Langerhans. They operate a machinery of regulated biosynthesis and secretion of insulin in response to physiological glucose stimulation.

It is now possible to aggregate insulin-secreting cells in tissue culture in the form of pseudoislet micro-organs, thereby mimicking the optimal natural anatomical structure. Recent progress in molecular biology and genetic engineering has made possible bioengineering of glucose-responsive insulin-secreting surrogate cells in sufficient quantities to generate bioartificial pancreatic islet micro-organs. For the first time, this advance opens up a realistic strategy to generate a substitute to restore the function of destroyed pancreatic islets in the diabetic patient.

A stepwise approach to generating such pancreatic islet micro-organs is envisaged:

1. Using insulin-producing differentiated stem cells, pseudoislet micro-organs composed of different cellular components, including insulin as well as glucagon- and somatostatin-producing cells, will be engineered.
2. The performance of these pseudoislets, both *in vitro* and *in vivo*, will be analysed after implantation into animal models of diabetes. The optimal micro-architecture and intercellular communication for a regulated insulin secretion will be determined and selected for normalisation of the diabetic metabolic state.
3. The study of pseudoislets will provide an explanation why insulin-secreting cells function much more effectively when organised in a micro-organ. This will enable an understanding of the underlying molecular and cellular basis for the unique form of micro-architecture of the endocrine pancreas.
4. In the final step, the knowledge acquired using tissue of mouse stem cell origin will be applied to a human stem cell-based model for the generation of pseudoislets. It will be the aim of this proposed project to acquire all the information necessary to define the ideal characteristics of pancreatic islet micro-organs for insulin replacement therapy for human diabetes.

Results to date:
The expected result of this project will be the successful construction of bioartificial pancreatic islet micro-organs from glucose-responsive insulin-secreting cells of stem cell origin. The proposal will represent a realisation of this entirely novel cellular engineering technology.

Embodying the key principles of the 'cell factory' initiative in this application offers the majority of diabetic patients a realistic perspective for a curative cell therapy based on human surrogate stem cells for insulin-dependent diabetes mellitus through an innovative micro-organ construction.

Web site:
http://www.mh-hannover.de/institute/clinbiochemistry/

Key words:
Insulin-dependent diabetes mellitus (T1DM), cell therapy, pancreatic islet micro-organs, embryonic stem cells, *in vitro*-grown organs

Major publications (max. 3):
Not available

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Obesity and disease in ageing (OB-AGE)

Contract number:	*QLK6-CT-2002-02288*
QoL action line:	*Key Action 6*
Type of project:	*Shared cost research and development*
Starting date:	*01.01.2003*
Duration:	*36 months*
Total project cost:	*€1 153 357*
EU contribution:	*€848 907*

Summary of achievements to date (31.12.03):

Objectives:
The average length of human life is increasing, but the quality of these extra years is questionable due to an age-related decline in physiological and endocrine functions. This decline effects body composition, with loss of muscle and an increase in fat mass. Obesity predisposes individuals to type 2 diabetes and cardiovascular disease, major causes of morbidity and mortality and key components of metabolic syndrome. Therefore, this project aims to:

1. Elucidate the mechanisms underlying age-related obesity and disease, in particular leptin insensitivity and the deposition of ectopic fat which are thought to be key components linking obesity and disease;
2. Evaluate prognostic/diagnostic biomarkers for the identification of those most at risk relatively early in life;
3. Evaluate novel natural therapeutic agents as preventive measures.

Methodology:
Human studies: young and middle-aged lean and obese men will receive either CLA plus n-3 PUFA supplements or a placebo. Percentage and location of body fat, cardiovascular fitness and ß cell function/insulin sensitivity will be tested. The levels of hormones secreted by white adipose tissue will be measured. Human white adipose tissue and cell lines will also be used to study the control of hormone secretion.

Animal models: the effects of varying levels of adiposity and CLA plus n-3 PUFA supplementation on ß cell function/insulin sensitivity, cardiac call function and the growth hormone axis will be measured in both dietary-induced obese and low body fat rodents. The production and secretion of hormones by white adipose tissue from different locations on obese and low body fat rodents will be studied.

Cell studies: cells transfected with leptin receptors will be used to study the desensitisation of the receptor response to leptin.

Results to date:
The diet-induced obese rodent models have been developed and the first symptoms of type 2 diabetes identified, i.e. insulin insensitivity. Insensitivity to leptin has also been identified in pancreatic ß cells from these animals along with ectopic lipid accumulation. CLA plus n-3 PUFA supplements given to rodents was found to specifically reduce the size of the white adipose tissue in two of the depots measured.

Web site:
http://www.rowett.ac.uk/obage

Key words:
Obesity, ectopic lipid, leptin insensitivity

Major publications (max. 3):
Buttriss J. (2003), "Metabolic syndrome: new research under way", *Nutrition bulletin* 28, 381-385.
Nugent A.P. (2004), "The metabolic syndrome: a review", *Nutrition Bulletin* 29, 36-43.

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Phenotypes and genes linked to insulin resistance and risk for type 2 diabetes (CAUSES OF TYPE 2 DIABETES)

Contract number:	*QLG1-CT-1999-00674*
QoL Action Line:	*Generic Activities 7*
Type of project:	*Shared cost research and development*
Starting date:	*01.02.2000*
Duration:	*48 months*
Total project cost:	*€4 613 971*
EU contribution:	*€3 095 947*

Summary of achievements to date (31.01.2003):

Objectives:
The overall objective of the project is to identify genetic causes of type 2 diabetes. Both specific diabetes genes as well as diabetes-related genes will be identified. To achieve this, the operational objectives are:

1. To perform extensive phenotyping of healthy relatives to type 2 diabetic subjects, focusing on insulin resistance and secretion;
2. To perform gene expression profiles in target tissues and identify differentially expressed genes;
3. To establish transgenic animal models of potential candidate genes;
4. To sequence potential candidate genes, identify genotypes in relation to specific and phenotypes.

Methodology:
The methodology involves extensive clinical phenotyping using state-of-the-art technology such as euglycemic and hyperglycemic clamps, ultrasound measurements of vessel wall intima/media thickness, PET-scans and NMR technology to measure intramyocellular and liver lipids. The extensive phenotyping is necessary to understand if different genes are involved in a complex condition such as type 2 diabetes. Gene expression analysis is performed in fat and muscle biopsies in these individuals using DNA arrays and real-time PCR. Novel genes are then identified and their functions characterised in cells and in genetically engineered animal models (knock-ins/knock-outs). Chromosomal location is analysed and DNA sequenced to identify genomic abnormalities. The project has extensive collaboration with the European pharmaceutical industries.

Results to date:
Novel genes related to risk for type 2 diabetes have been identified and animal models engineered and studied. The extensive phenotyping is combined with specific genotyping and, as an extension, we plan prospectively to follow this unique group of individuals with a genetic predisposition for type 2 diabetes. This will allow final proof of the importance of identified candidate genes and specific genotypes.

During the first three years, around 400 subjects have been studied, creating the largest collection of extensively phenotyped healthy relatives to type 2 diabetic subjects. The role of several different genes and proteins on insulin signalling and action as well as on insulin secretion has been examined. Gene analyses are ongoing and novel candidate genes are under intense study. Animal models are currently undergoing characterisation.

Web site:
www.eudg.org

Key words:
Diabetes, insulin resistance, insulin secretion, insulin signalling, diabetes genes

Major publications (max. 3):
Huopio H., Otonkoski T., Vauhkonen I., Reimann F., Aschcroft F.M., and Laakso M. (2003), "A new subtype of autosomal dominant diabetes attributable to a mutation in the gene for sulfonylurea receptor 1", *Lancet* 361: 301-307.
Kuotnikova H., Cock T.A., Watanabe M., Houten S.M., Champy M.F., Dierich A., and Auwerx J. (2003), "Compensation by the muscle limits the metabolic consequences of lipodystrophy in PPARgamma hypomorphic mice", *Proc. Natl. Acad. Sci. USA* 100: 14457-14462.

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The blood monocyte as a tool for the prediction of type 1 diabetes (MONODIAB)

Contract number:	*QLG1-CT-1999-00276*
QoL action line:	*Generic Activities 7.1.*
Type of project:	*Shared cost research and development*
Starting date:	*01.01.2000*
Duration:	*36 months*
Total project cost:	*€1 275 554*
EU contribution:	*€867 421*

Summary of achievements to date (31.12.2003):

Objectives:
Six European research groups and one research-based biotechnology firm, with expertise in the field of the cell biology of monocyte-derived cells, in chemokine action and cell trafficking, in islet morphogenesis and fuction, in gene technology, and in diabetology and immunology at large, are working together to design a novel approach to developing new clinically applicable tools to predict IDDM development. These tools are based on the new insight that monocyte-derived cells play key roles in the aetiology and pathogenesis of IDDM.

Our research is directed towards three main objectives:
1. To identify – using DNA micro-array technology – abnormally expressed 'autoimmune-related' molecules in blood monocytes of prediabetic and diabetic individuals;
2. To identify the cell biological consequences of such abnormal expression for IDDM pathogenesis;
3. To use some of the abnormally expressed monocytic 'autoimmune-related' molecules as tools to develop screening assays to identify individuals at risk of developing diabetes.

Methodology:
The following methodologies are being used:
1. Cell cultures to generate large numbers of dendritic cells (DC) and Macrophages (Mf) from human blood monocytes and cell cultures to test their T cell stimulatory/T cell deletion capability;
2. Assays to measure chemokine- and chemokine receptor-expression of monocytes and monocyte derived DC and Mf;
3. Migration assays for human and mouse monocytes, DC and Mf using novel chemokines;
4 Coculture assays of DC and Mf with normal mouse islets and fetal mouse islets;

5. Immunohistochemical methods using mouse and human thymuses and pancreases;
6. Cultures of mouse thymus cells;
7. DNA micro-assay technology based on bioinformatics.

Results to date:
The project has been completed, and important findings made:
We have identified – using DNA micro-array technology – abnormally expressed 'autoimmune-related' molecules in blood monocytes and monocyte-derived dendritic cells of pre-diabetic and diabetic individuals.
We know most of the cell biological consequences of the above-described abnormal gene expression in IDDM monocytes in relation to IDDM pathogenesis.

We are presently using some of the abnormally expressed 'autoimmune-related' molecules in monocytes as tools to develop clinically applicable screening assays (FACS analysis, Elisa's) to identify individuals at risk of developing diabetes.

Apart from the monocyte abnormalities, our research elucidated some aspects of the role of non-classical macrophages/dendritic cells, of macrophages/dendritic cells in pancreas morhogenesis, and of thymus macrophages/dendritic cells in tolerance induction.

With regard to pre-diabetes, a study on a limited number of ICA negative first degree relatives (FDR) of type 1 diabetics shows various aberrancies in the monocytes and monocyte-derived DC of the FDR, which are mirror images of those found in overt type 1 diabetics.

We favour the view that such aberrancies represent an anti-inflammatory and tolerogenic set point of the immune system instrumental in counteracting already existing harmful deviations in the immune system that heighten the risk of islet autoimmunity in FDR.

Web site:
Not available

Key words:
Diabetes, monocytes, dendritic cells, genomics

Major publications (max. 3):
Rosmalen J.G., Martin T., Dobbs C, Voerman J.S., Drexhage H.A., Haskins K., Leenen P.J. (2000), "Subsets of macrophages and dendritic cells in nonobese diabetic mouse pancreatic inflammatory infiltrates: correlation with the development of diabetes", *Lab. Invest.* 80: 23-30.

Homo-Delarche F., Drexhage H.A., "Immune cells, pancreas development/regeneration and type 1 diabetes", *Trends in Immunol.* (in press, May 2004).

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Therapeutic utilisation of a novel enzyme with unique adhesion properties (TUNEUP)

Contract number:	*QLG1-CT-1999-00295*
QoL action line:	*Generic Activities, Area 7.1*
Type of project:	*Shared cost research and development*
Starting date:	*01.02.2000*
Duration:	*48 months*
Total project cost:	*€2 075 264*
EU contribution:	*€1 553 980*

Summary of achievements to date (31.01.2004):

Objectives:
The overall goal of this project was to gain enough knowledge of vascular adhesion protein-1 (VAP) and its amine oxidase activity (semicarbazide sensitive amine oxidase, SSAO) to assess its usefulness as a target for drug development. The major achievements we have obtained at the end of the project are:

1. The involvement of VAP/SSAO enzyme activity in leukocyte adhesion has been resolved;
2. The intracellular signalling pathways activated via VAP/SSAO have been identified;
3. VAP/SSAO transgenic mice over-expressing VAP/SSAO have been produced and knock-out mice deficient in VAP/SSAO have been generated and further used for the disease evaluation;
4. The diseases in which VAP/SSAO targeted therapeutics or diagnostic tools are feasible have been identified.

Methodology:
The project utilised modern enzymological, cell biology and molecular biology methods to address basic biological questions. In addition, it employed elegant imaging methods, such as intravital microscopy and flow chamber assays, to observe mechanisms in leukocyte trafficking. The research also had a strong clinical emphasis as the patient material was of utmost importance in elucidating the role of VAP/SSAO in disease processes.

Results to date:
The project demonstrated that VAP/SSAO regulates leukocyte trafficking to sites of inflammation in in vitro and many animal models. In addition, promising phase I/IIa clinical trials have been performed. Therefore, it is highly likely that VAP/SSAO could be used as a target to cure and prevent harmful

inflammation. Moreover, in soluble form it increases in certain liver diseases and it seems most likely that measurements of soluble VAP/ SSAO can be used for diagnostic purposes. In addition, we have shown that VAP/SSAO participates in glucose metabolism and therefore seems to play an essential role in diseases such as diabetes.

Web site:
Not available

Key words:
Enzyme, adhesion, cell trafficking, glucose metabolism

Major publications (max. 3):
Abella A., Marti L., Camps M., Claret M., Fernandez-Alvarez J., Gomis R., Gumà A., Viguerie N., Carpéné C., Palacin M., Testar X., Zorzano A., "SSAO/VAP-1 activity exerts an anti-diabetic action in Goto-Kakizaki rats", *Diabetes* 52: 1004-1013, 2003. (partners 3 and 4)

Koskinen K., Vainio P.J., Smith D.J., Pihlavisto M., Ylä-Herttuala S., Jalkanen S., Salmi M., "Granulocyte transmigration through endothelium is regulated by the oxidase activity of vascular adhesion protein-1 (VAP-1)", *Blood*, Epub Jan 15, 2004. (partners 1 and 5)

Stolen C.M., Madanat R., Marti L., Kari S., Yegutkin G.G., Sariola H., Zorzano A., Jalkanen S., "Semicarbazide-sensitive amine oxidase overexpression has dual consequences: insulin mimicry and diabetes-like complications", *FASEB* J, Epub Feb 20, 2004. (partners 1 and 4)

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Participant countries:
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Relationship between insulin sensitivity and cardiovascular disease risk (RISC)

Contract number:	*QLG1-CT-2001-01252*
QoL action line:	*Generic Activities 7*
Type of project:	*Shared cost research and development*
Starting date:	*01.02.2002*
Duration:	*57 months*
Total project cost:	*€2 416 068*
EU contribution:	*€2 176 291*

Summary of achievements to date (28.02.2003):

Objectives:
The project aims to:
1. Establish whether insulin resistance predicts future development of cardiovascular risk markers and cardiovascular disease (CVD);
2. Determine the genetic and environmental contributions to insulin resistance;
3. Develop a method to identify insulin-resistant subjects in clinical practice.

Methodology:
This is a prospective, observational, multi-centre cohort study measuring insulin resistance and secretion by the euglycaemic hyperinsulinaemic clamp (the gold standard) in 1 500 non-diabetic normotensive subjects, in 20 European study centres. The carotid artery intima-media thickness (cIMT) is measured at baseline and after three years in healthy subjects (male and female) aged 30 to 60 years, and typical of the local population.

Examinations (undergone during two hospital visits)
1. Oral glucose tolerance test
2. Routine local laboratory assessment (including triglyceride and cholesterol for exclusion)
3. Anthropometry (body mass index, waist:hip ratio), body composition by bioimpedance
4. Resting sitting blood pressure, 12-lead ECG, ankle-brachial pressure ratio
5. Movement sensor for seven-day physical activity monitoring
6. Current medication questionnaire, which also ascertains treatment for diabetes, hypertension and dyslipidaemia for exclusion criteria
7. Lifestyle questionnaire and a modified Rose Questionnaire for CVD
8. Euglycaemic hyperinsulinaemic clamp (with central analyses of insulin, C-peptide, lipids as well as stable glucose isotope infusion in a subset of subjects)
9. Carotid artery ultrasound recording for measurement of the cIMT
10. Samples for central analysis of DNA, urine albumin: creatinine and future assays
11. (e.g. apolipoprotein B, proinsulin, pro-insulin split products)

Annual follow-up
Participants are telephoned annually to check contact details and to ascertain medical events. Hospital records with a diagnosis of CVD are reviewed and information extracted. Death certificates are abstracted for underlying causes of death.

Follow-up at three years
Baseline examination, fasting blood samples, cIMT (clamp not repeated) will be repeated after three years. It is hoped to extend the study for a total of ten years when the determinations of insulin sensitivity would be repeated.

Results to date:
Recruitment and annual follow-up has begun in 19 centres with a total of 1 150 subjects (approximately 76% of the total at mid-March 2004). Of these, 945 have undergone the euglycaemic hyperinsulinaemic clamp and 882 have undergone a carotid artery ultrasound scan. Several centres have commenced telephone follow-up interviews.

Personnel have been trained, certified in project procedures, and have access to information to carry out tasks and record and transfer data to the project office.
1. A website (www.egir.org) has been created for the dissemination of information to recruiting centres;
2. Clear instructions have been given in the RISC Operations Manual and in project newsletters, which highlight important information;
3. Teaching seminars have been made available on the website to ensure personnel are kept informed of key aspects of quality control;
4. A video has been produced describing the euglycaemic clamp, as carried out in RISC.

Data transfer and data management:
1. A flexible data transfer system (based on remote data entry into Epi Info 2002) has been developed, which allows data to be transferred by project website or as an e-mail attachment;
2. A method has been established whereby data are checked on arrival in the project office, clamp data

are graphed for immediate quality control, and data queries are sent to the recruiting centre.

Objectives 2 and 3 are being addressed by the following:

1. Genotyping to investigate the genetic background of the CVD/insulin sensitivity complex is being performed by polymerase chain reaction (PCR) amplification and variant detection. In total, around 945 samples have been collected. Samples from 14 recruiting centres have been sent to the central laboratory in Newcastle where two randomly selected samples from each centre have produced good quality and quantities of DNA. Full-scale extraction is now under way.

2. Physical activity is being measured quantitatively by an MTI actigraph (a small single-channel recording accelerometer capable of continuous data collection) is worn for five days (mean 5.6 days, maximum 8 and minimum 1 day). The data files are sent to the data management centre in Villejuif where data is processed to evaluate energy expenditure over the recording period. Qualitative data from the IPAQ (International Physical Activity) questionnaire (translated into each language of the study) is providing recalled information on physical activity.

3. Body composition is being characterised by the Tanita bioimpedance balance, which gives measures of total body weight, body water, fat free mass, bioimpedance, percent body fat, fat mass, body mass index, and basal metabolic rate. Measures are taken of waist, hip and thigh circumferences according to a standardised protocol. In two centres, DEXA scans are also being done.

4. Socio-economic and lifestyle indicators are being evaluated from the questionnaire on employment, years of education, personal medical history, body shape of family, age and causes of death in first-degree relatives, current medication (including contraceptive pill, hormone replacement therapy and non-prescribed), self-reported birth weight, smoking and alcohol habits; a modified Rose Questionnaire for CVD, and intermittent claudication.

The primary objective can only be addressed by a longitudinal study; thus, a three-year follow-up period is necessary, when progression to CVD is measured by change in intima-media thickness, together with other measures of existing atherosclerotic CVD and other cardiovascular risk factors including obesity.

Web site:
www.egir.org

Key words:
Insulin resistance, type 2 diabetes, cardiovascular disease, obesity, euglycaemic clamp

Major publications (max. 3):
Hills S.A., Balkau B., Coppack S.W., Dekker J.M., Mari A., Natali A., Walker M., Ferrannini E., on behalf of the EGIR-RISC Study group (2004): "The EGIR-RISC Study (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk): I. Methodology and Objectives", *Diabetologia* 47:566-570.

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The cellular fuel gauge AMP-activated protein kinase: a key player in type 2 diabetes, cardiovascular disease and the metabolic syndrome? (AMPDIAMET)

Contract number:	*QLG1-CT-2001-01488*
QoL Action Line:	*Generic Activities 7*
Type of project:	*Shared cost research and development*
Starting date:	*01.09.2001*
Duration:	*36 months*
Total project cost:	*€3 437 414*
EU contribution:	*€1 810 474*

Summary of achievements to date (31.08.2003):

Objectives:
The AMP-activated protein kinase (AMPK) complex can be regarded as a 'fuel gauge' that monitors the energy status of living cells by measuring the levels of two key chemicals, AMP and ATP, the latter being the 'fuel' that drives almost all energy-requiring processes in a cell.

A recent combination of results, in which the partners have played a leading part, has suggested that the AMPK system is a key player in the development and treatment of type 2 diabetes and the related metabolic syndrome. With this EC funding we have established a multidisciplinary consortium that is pursuing these opportunities in an integrated and coordinated manner. The overall objectives are to:

1. Increase the knowledge base about the AMPK system;
2. Extend and improve the range of reagents and protocols available for its study, which will allow studies in humans as well as animal models;
3. Identify new physiological processes and pathways regulated by the system;
4. Test the hypothesis that activation of the system, either via exercise or by pharmaceutical intervention, could reverse many of the metabolic abnormalities associated with type 2 diabetes and the metabolic syndrome;
5. Test the hypothesis that a low level of expression/activation of the system might be involved in development of type 2 diabetes and the metabolic syndrome;
6. Initiate work on the development of novel pharmaceutical agents targeted at the system.

Methodology and anticipated results:
The specific technical objectives (each corresponding to an individual workpackage) are to:

1. Develop a panel of isoform-specific antibodies that can be used to study the AMPK system, and its key cellular targets, in animals and in humans;
2. Develop improved methods to express recombinant AMPK complexes, and study their structure and regulation, as well as the associated upstream kinases;
3. Produce (via high-throughput screens) novel pharmaceutical agents that activate or inhibit the AMPK system and have potential as therapeutic agents;
4. Identify new targets for AMPK by studying their phosphorylation in cell-free systems;
5. Develop novel methods for manipulation of the AMPK system, and identify novel physiological processes, proteins and genes regulated by it, in intact cells;
6. Further develop AMPK knock-out mice and immortalised cell lines derived from these mice;
7. Use the genetic tractability of yeast to improve understanding of how glucose is sensed by the AMPK system in vivo;
8. Study the expression and regulation of AMPK in animal models for obesity and diabetes;
9. Test the applicability of results obtained in animal models to humans, by studying effects of exercise and training on the expression and regulation of AMPK in healthy volunteers, and in patients with type 2 diabetes.

Results to date:
Highlights from the research findings so far include:

1. Production of AMPK complex by genetic engineering of bacteria, greatly facilitating future studies on its structure and function;
2. Conclusive identification of the AMP binding regions of the complex, these being the most likely targets for future drug development;
3. Identification of several new physiological roles for the system, including its involvement in the mechanism of action of hormones involved in control of whole body energy balance (leptin and adiponectin) and of existing anti-diabetic drugs (metformin and rosiglitazone);
4. Demonstration that mice lacking one sub-unit of the complex exhibit features of type 2 diabetes and the metabolic syndrome, suggesting a role in those conditions in humans;
5. Validation of the use of yeast as a model for the manner in which mammalian cells sense glucose availability, allowing powerful genetic approaches to be used;

6. Establishment of 'proof-of-concept' that activation of AMPK by drugs can relieve insulin resistance and diabetes, using animal models;
7. Novel findings in humans and in animal models suggesting that AMPK may monitor cellular energy status by sensing the level of stored carbohydrate (glycogen) as well as ATP and AMP;
8. Development of an assay suitable for high-throughput screen.

Web site:
http://www.dundee.ac.uk/lifesciences/ampdiamet//

Key words:
AMP-activated protein kinase, obesity, diabetes, cardiovascular disease, pharmaceuticals

Major publications (max. 3):
Hawley S.A., Gadalla A.E., Olsen G.S., Hardie D.G. (2002),"The antidiabetic drug metformin activates the AMP-activated protein kinase cascade via an adenine nucleotide-independent mechanism", *Diabetes* 51: 2420-2425.
Olsen G.S., Hansen B.F. (2002),"AMP kinase activation ameliorates insulin resistance induced by free fatty acids in rat skeletal muscle", *Am. J. Physiol.* 283: E965-E970.

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Participant countries:
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Prevalence characterisation and prevention of latent autoimmune diabetes in adults (LADA) in Europe (Action LADA)

Contract number:	*QLG1-CT-2002-01886*
QoL action line:	*Generic activities 7*
Type of project:	*Shared cost research and development*
Starting date:	*01.12.2002*
Duration:	*36 months*
Total project cost:	*€2 428 254*
EU contribution:	*€1 698 163*

Summary of achievements to date (01.04.04):

Objectives:

1. To define the prevalence of LADA in European counties;
2. To characterise genetic, immunological and metabolic features of LADA;
3. To prevent or delay the progression to insulin requirements by limiting progression towards the destruction of beta-cells in LADA patients by running a double-blind trial with Diapep277 vaccine, a peptide analogue of heat shock protein.

Methodology:

We are screening 10 000 newly-diagnosed non-insulin-requiring diabetes cases for glutamic acid decarboxylase (GAD) antibodies. Patients with these autoantibodies are defined as having LADA. To estimate the prevalence and epidemiology of LADA in Europe, a sample size of around 1 200 people per centre (nine centres are involved in screening) will enable the prevalence to be estimated with 95% certainty, as being between 8% and 12% (based on the UK study (*Lancet* 1997: 350; 1288-93), by identifying 1 000 LADA cases (about 120 per centre).

Characterisation of LADA patients will include genetic, immunological and metabolic features. HLA genes are known to be relevant in LADA. Genetic analysis will include HLA, CTLA-4 and insulin genotype. IL-2 scintigraphy will be performed on selected LADA patients. Of the 1 000 LADA cases, 350 will be investigated for their T-cell responses to islet cell antigens. Cellular immune markers will be investigated using T-cell proliferation assays, ELISpot analysis and cytokine levels. In addition to characterising GAD antibodies, we will assay other potentially relevant organ-specific autoantibodies to determine the extent of the autoimmune process in LADA. Insulin secretory responses will be tested to define the natural history of loss of insulin secretory capacity.

A prevention trial using Diapep277 therapy will include: non-insulin-requiring diabetes subjects who are aged between 35-70 years; disease duration of less than five years; with GAD antibodies, and baseline C-peptide greater than 1.2 ng/ml. Pending results of a Phase II study of patients – about 175 in the treatment arm and about 175 in the placebo arm – will be followed to determine the natural history of the disease and the impact of Diapep277 therapy based on progression to insulin therapy and loss of C-peptide secretion.

Anticipated results:

1. We will define the prevalence of LADA in European countries;
2. We will characterise genetic, immunological and metabolic features of LADA, includingHLA genes, cellular and humoral immune features, and the natural history of residual insulin secretory loss;
3. We will define the value of Diapep277 vaccine in altering the natural history of LADA by preventing or delaying progression of loss of insulin secretory capacity.

Results to date:

The total number of serum samples received in London at the coordinating centre by April 2004 is 1 330; the number of samples tested for GAD autoantibodies to date is 1 138; number of samples positive for GAD autoantibodies is 127 (11%). These serum samples are held in storage by Partner 1 in London for subsequent analysis for other immunological and metabolic parameters. Samples held in each centre and not yet transferred to Partner 1 in London are to be transferred early in 2004 for the characterisation of GAD autoantibodies.

Web site:

http://www.actionlada.org/

Key words:

Latent autoimmune diabetes of adults (LADA), glutamic acid decarboxylase (GAD), Diapep277, diabetes, genetics, immunology

Major publications (max. 3):

Not available

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Generation and functional characterisation of neuro-endocrine cells for cellular replacement therapy (GrowBeta)

Contract number:	*QLG1-CT-2001-02233*
QoL action line:	*Generic Activities 7*
Type of project:	*Shared cost research and development*
Starting date:	*01.12.2001*
Duration:	*36 months*
Total project cost:	*€2 026 413*
EU contribution:	*€1 406 509*

Summary of achievements to date (30.11.2003):

Objectives:
Our collaboration aims at providing a bridge between developmental biology, physiology and neuronal control of pancreatic islet cells. We propose to exploit the emerging knowledge on developmental control processes for the establishment of cells and tissues with islet-like properties for cellular replacement therapy and, in addition, to guide regeneration. We want to characterise the function of such cellular assemblies and to study their interaction among themselves and with the nervous system in order to assure not only competence of insulin secretion, but also precise regulation of secretion by the metabolic state.

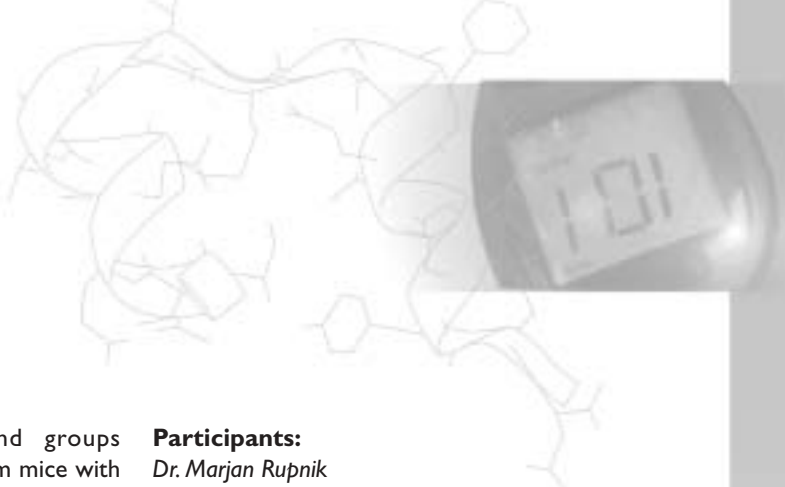
Methodology:
For the discovery of new genes and tissue differentiation factors we are using techniques of transgenic animal breeding, cell culture, molecular biology, and biochemistry. For manipulation of cells in tissue and organ culture, we use transfection methods and viral infection, as well as incubation of cell cultures with the discovered differentiation factors. To study such manipulated cells, we will have to adapt existing histochemical, biophysical and electrophysiological methods to be applied to tissue slice preparations, explants, and embryoid bodies.

Finally, we have to characterise secretory function, intercellular signalling and intracellular signalling cascades with these methods. This work programme would not be possible without a close interaction among researchers from the most diverse disciplines, such as developmental biology, genetics, cellular biology, neurobiology, and biophysics.

The work can be subdivided into two major areas:
1. An effort to discover further genes participating in the development of pancreatic islet cells, and to manipulate them in order to establish cell lines and tissues at various stages of differentiation, as well as transgenic animals;
2. Adaptation and application of methods for characterisation of the functional properties of such cells assemblies, including their neuronal control mechanisms.

Results to date:
The DeveloGen group constructed the cDNA library from mouse embryonic pancreatic buds. The screening of 55 000 clones yielded 100 secreted proteins including 40 high-priority candidates which are checked *in situ* and in functional assays. In parallel, the same group established optimal differentiation in ES-cell overexpressing certain transcription factors. ES cells transfected with Pax4 were found to release insulin in response to glucose, and transplantation of these cells into streptozotocin-treated diabetic mice resulted in the normalisation of blood glucose levels. The Milan group pursued a line of research connected with secretion deficiency in various neuroendocrine preparations, concerning the identification of a new type of exocytotic organelle, a little vesicle, present in many types of cells, both secretory or non secretory, which they have named enlargosomes. Existence of this type of organelle was expected based on previous electrophysiological results showing large membrane capacitance increases in cells, such as fibroblasts, when stimulated by photolysis of caged calcium. For the first time, the data have identified the organelle involved, which is distinct from all other known organelles of the cytoplasm. Enlargosomes appear to be involved in processes that require enlargement of the cell surface, such as differentiation and wound healing.

The Geneva project involved the effect of Pax4 and Pdx1 on ß-cell function. The transcription factor Pax4 is important in ß-cell development and mutations have been associated with type 2 diabetes in Japanese families. The islets transduced with Pax4 adenovirus express low levels of Pax4 mRNA before transduction, compared to the INS-1E cells which contain higher amounts. Pax4 enhanced the expression of the oncogene c-myc and the anti-apoptotic Bcl-xL gene. In a parallel study, Pdx1 target genes in rat ß-cells were identified by DNA microarray. The regulation of essential mitochondrial transcripts may explain impaired insulin-secretion in states of suppressed Pdx1 function.



The Goettingen, Oxford and Lund groups characterised the function of ß-cells from mice with ablated genes in Pax4 and Pax6. We failed to isolate the endocrine cells from Pax4 and Pax6 knock-out mice since they do not form islets that could be isolated by standard isolation procedures. Instead, a pancreatic slice preparation has been established. The major advantage of pancreatic tissue slices method is that it is rapid and an in situ preparation which enables us to address developmental issues and to understand regeneration processes better. Slices have intact paracrinicity and local neural networks so local feedback loops are mostly preserved enabling us to address questions such as the sex-related pathophysiology of diabetes. Establishment of the organotypic culture significantly reduces the number of used animals and, in the case of transgenic animals with perinatal lethality, extends the lifespan of the pancreatic endocrine tissue to developmental stages not possible *in vivo*.

And finally, the Ljubljana group developed the expertise in biosensor- (GLUT4 up-regulation in adipocytes) based insulin secretion assay.

Web site:
http://www.mpibpc.mpg.de/abteilungen/ENI/growbeta/

Key words:
Diabetes, chronic diseases, development

Major publications (max. 3):
Speier S., Rupnik M. (2003), "A novel approach to in situ characterization of pancreatic B-cells", Pflugers Arch – *Eur J Physiol*. 446: 553-558.
Borgonovo B., Cocucci E., Racchetti G., Podini P., Bachi A., Meldolesi J. (2002), "Regulated exocytosis: a novel, widely expressed system", *Nature Cell Biology* 4(12):955-962.

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Participant countries:
3 DE, IT, CH, UK, SE, SI

Heat shock protein 60 as a novel therapeutic target for diabetes and rheumatoid arthritis (HSPforTherapy)

Contract number:	*QLG1-CT-2002-01287*
QoL action line:	*Generic Activities 7*
Type of project:	*Shared cost research and development*
Starting date:	*01.09.2002*
Duration:	*34 months*
Total project cost:	*€1 409 275*
EU contribution:	*€1 299 892*

Summary of achievements to date (30.04.2004):

Objectives:
The HSP60 molecule and some of its peptides can be used as vaccines to abort the autoimmune destruction of beta cells leading to type 1 diabetes. Indeed, a peptide of HSP60 is currently in phase 2 clinical trials as a therapeutic vaccine. However, previously it was not understood how HSP60 administration actually aborts destructive inflammation. The major objective of these studies has been to learn the molecular mechanisms involved in HSP60 treatment. This information is critical to the rational planning of HSP60-based therapies.

Methodology:
The methods have involved detecting the binding of HSP60 to cells, the activation of signal transduction pathways, the activation of critical genes, and the detection of effects on target cells: cell adhesion, cell homing, chemokine receptors and responses to chemokines, and cytokine production. The cell types used have been rodent and human T cells, B cells and macrophages.

Results to date:
Macrophages: initial findings suggested that HSP60 might activate macrophages to secrete IL-12 and other pro-inflammatory mediators, but now it is not clear how much of this effect might be attributed to LPS and other contaminants. In any case, such an effect would not explain the beneficial effects of HSP60 in arresting inflammation.

B cells: this work has not yet been submitted for publication, but the results show that soluble HSP60 (independent of LPS) can indeed activate B cells to secrete IL-10, a major down-regulator of inflammation. The HSP60 molecule also induces up-regulation of MHC II expression, IgG3 isotype switching, and other factors compatible with an anti-inflammatory Th2 deviation. This, in fact, is noted in HSP60 treatment of diabetes; thus, HSP60 might have a beneficial effect via B cells – this was not previously suspected.

T cells: this work has been submitted for publication and can be summarised as follows: soluble HSP60 (or its active peptide) can up-regulate SOCS3 expression via TLR-2 and JAK/STAT signal transduction to down-regulate T-cell chemotaxis and migration into inflammatory sites. This effect would definitely contribute to the arrest of autoimmune destruction of beta cells and diabetes.

Website:
Not available

Key words:
Heat shock proteins, HSP60, arthritis, diabetes, immunotherapy, tolerance, innate immunity, T cells

Major publications (max. 3):
Cohen I.R., Quintana F., Nussbaum G., Cohen M., Zanin-Zhorov A., Lider O., "HSP60 and the regulation of inflammation: Physiological and pathological". In *Heat Shock Proteins and Inflammation,* ed. W. van Eden, Birhhauser Verlag, Basel, 2003, pp 1-13.

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Molecular mechanisms controlling pancreas organogenesis and differentiation of pancreatic cell types (Pancreas Development)

Contract number:	*QLG2-CT-1999-00149*
QoL action line:	*Generic Activities 8*
Type of project:	*Shared cost research and development*
Starting date:	*01.02.2000*
Duration:	*48 months*
Total project cost:	*€2 157 139*
EU contribution:	*€2 157 139*

Summary of achievements to date (31.01.2003):

Objectives:
The aim of this project is to elucidate the molecular mechanisms controlling proliferation and differentiation of the pancreatic cells. We will identify both intracellular regulatory factors
(e.g. transcription factors or receptors) and extracellular signalling molecules (e.g. cytokines and growth factors) controlling pancreatic cell fate. The cloning, analysis of the expression profile, and the function of these regulatory factors will be performed through a multidisciplinary approach, using three complementary biological models: i) the zebrafish, ii) murine pancreatic cell lines, and iii) the mouse. The ultimate goal of this project is to elaborate a model describing the cascade of regulatory events leading to pancreas organogenesis and beta cell differentiation. This knowledge will have a major impact on the design of novel therapies for diabetes.

Methodology:
The present research project comprises four stages. The first stage concerns the identification and the cloning of regulatory genes expressed in pancreatic cells. This part will be accomplished by a multidisciplinary approach: i) through a genetic screening for mutations affecting pancreas organogenesis in zebrafish (by chemical and gene-trap mutagenesis); ii) by the identification of signalling pathways involved in pancreas development, and then by the isolation of gene family members known to be part of these signalling pathways (PCR of pancreatic cDNA using degenerated oligonucleotide primers); and iii) by a systematic screening of genes expressed in a cell type-specific fashion notably in the endocrine beta cell (through RDA technology). The second stage of the project will be the detailed analysis of the expression pattern for each identified genes in developing zebrafish and mouse. These experiments will guide us towards those genes most likely to be of

biological relevance, and therefore worthy of attention in the context of functional studies. In the third part of the project, we will determine the actual functions of the identified genes. The zebrafish will permit a rapid functional evaluation of each factor through microinjection of appropriate mRNA molecules, of anti-sens Morpholino oligonucleotides, and through the use of a stable GAL4/UAS expression system. Genes showing significant effects on pancreas development will be further tested in mouse, both in pancreas explants, and using gene disruption technology to determine unequivocally the importance of gene function in pancreatic organogenesis. Pancreatic and beta cell defects in the resulting mice will be examined and compared with human pathologies, particularly diabetes.

Results to date:

1. The first steps of pancreas development in zebrafish have been studied by analysing the expression of a series of early pancreatic genes (see publication by Biemar et al.);
2. A first genetic screening for zebrafish mutants presenting defects in pancreas development led to the isolation of 26 zebrafish lines. The phenotype of these mutants, obtained by chemical mutagenesis, has been analysed and genomic mapping of eight mutated genes is in progress;
3. Transgenic zebrafish lines have been established expressing GFP in differentiating pancreatic cells using the insulin, glucagons, Pax6.2, NeuroD, HlxB9 and NK2.2 promoters. Some of these promoters are also used in a GAL4/UAS system in order to target expression of studied genes in pancreatic cells;
4. The FGF and Delta-Notch signalling pathways have been shown to be implicated in pancreas development by trangenesis in mice and zebrafish, respectively.

Several regulatory genes have been identified in pancreatic cells (as SOX4, meis and GRP). Their expression has been studied during ontogenesis and their functions are presently under investigation.

Web site:
Not available

Key words:
Pancreas, development, diabetes

Major publications (max. 3):

Biemar F., Argenton F., Schmidtke R., Epperlein S., Peers B., and Driever W. (2001), "Pancreas development in zebrafish: early dispersed appearance of endocrine hormone expressing cells and their convergence to the midline", *Developmental Biology*, 230:189-203.

Li H, Edlund H. (2001), "Persistent expression of Hlxb9 in the pancreatic epithelium impairs pancreatic development", *Developmental Biology*, 240(1): 247-53.

Zecchin E., Mavropoulos A., Devos N., Filippi A., Tiso N., Meyer D., Peers B.,
Bortolussi M., Argenton F. (2004), "Evolutionary conserved role of ptf1a in the specification of exocrine pancreatic fates", *Developmental Biology* 15;268(1): 174-84.

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Genomic integrated force for type 2 diabetes (GIFT)

Contract number:	*QLG2-CT-1999-00546*
QoL action line:	*Generic Activities 8*
Type of project:	*Shared cost research and development*
Starting date:	*01.02.2000*
Duration:	*42 months = 36 months + 6 months for the extension*
Total project cost:	*€5 022 092*
EU contribution:	*€3 248 190*

Summary of achievements to date (28.02.2003):

Objectives:
Identification of the regions in the genome of major importance for the development of type 2 diabetes in both human and rat. Identification of the T2D susceptibility genes within the regions of interest and characterisation of aetiologic gene variants. The elucidation of animal and human models of diabetes, which can be used for the development of drug targets for diabetes.

Methodology:
GIFT is composed of several complementary workpackages depending on resources, technical and analytic aspects that reflect the interdisciplinary nature of the research to understand a complex trait like T2D. Progress towards the goals of identifying T2D genes was supported by the establishment of new protocols for the study of T2D, then applying these developments in statistical methodology, genomics technology and genomics resources to GIFT clinical samples. This large degree of synergy between GIFT partners and expertise ensured the success of the project.

Results to date:
On the whole, GIFT was a great success. As a kind of generic activity, GIFT has generated important progress in resources and tools for the genetic dissection of T2D. Furthermore, GIFT partners have played a major role in the worldwide progress in identifying the molecular determinants of T2D: in mid 2003, more than 80% of the cases with monofactorial forms of T2D have been elucidated. In addition, about 40% of the genetic risk for the common forms of T2D is understood, and these achievement will certainly have implications for the management and treatment of diabetes in the coming years.

Web site:
www.gift.med.ic.ac.uk

Key words:
Diabetes, genomics, cloning

Major publications (max. 3):
Vasseur F., Helbecque N., Dina C., Lobbens S., Delannoy V., Gaget S., Boutin P., Vaxillaire M., Lepretre F., Dupont S., Hara K., Clement K., Bihain B., Kadowaki T., Froguel P., "Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians", *Hum Mol Genet* 2002, 11:2607-2614.
Demenais F., Kanninen T., Lindgren C.M., Wiltshire S., Gaget S., Dandrieux C., Almgren P., Sjögren M., Hattersley A., Dina C., Tuomi T., McCarthy M., Froguel P., Groop L.C., "A meta-analysis of four European genome screens (GIFT Consortium) shows evidence for a novel region on chromosome 17p11.2-q22 linked to type 2 diabetes", *Human Molecular Genetics*, 2003, 12(15):1865-73.

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European rational approach for the genetics of diabetic complications (EURAGEDIC)

Contract number:	*QLG2-CT-2001-01669*
QoL action line:	*Generic Activities 8*
Type of project:	*Shared cost research and development*
Starting date:	*01.09.2001*
Duration:	*42 months*
Total project cost:	*€2 851 626*
EU contribution:	*€1 840 603*

Summary of achievements to date (31.08.02):

Objectives:
The major objective of this interdisciplinary research collaboration between eight institutions is to identify the genes and pathways involved in the pathogenesis of diabetic complications in humans and in rodents. To achieve this goal, several complementary components have been identified. The first is to bring together a unique set of diabetic patients from three European countries that have been carefully assessed for relevant phenotypes for vascular complications. The second is to generate an inventory of validated candidate pathways for human nephropathy through combined physiological and genetic analyses in rat and mouse models for spontaneous type 2 diabetes. The third is to perform large-scale association studies of several hundreds of candidate genes including those identified in rodent models to identify these genes and genetic variants. And finally, to determine the mechanisms by which the susceptibility genes are involved in the pathogenesis of the disease.

Methodology:
1. The clinical institutions enter into this collaboration with a large number of DNAs (>8 000) from patients with type 1 or type 2 diabetes assessed for vascular complications, parents (trios) and non-diabetic controls;
2. Rodent studies: rat and mouse models will be characterized for diabetic nephropathy; genes that are differentially expressed between normal and diseased kidneys will be identified and characterised.
3. Genetic studies: the candidate genes selected are screened for polymorphisms (SNPs) by direct sequencing. Association studies for confirmed SNPs are performed in a case/control cohort of type 1 diabetic patients with or without nephropathy (3 000 samples) and in a family-based cohort for type 1 diabetes (1 500 samples) using high-

throughput genotyping methods including the taqman technology. New statistical methods are being developed to analyse several genes simultaneously.
4. Validation of associated gene variants will include in vitro and in vivo (in rodents) functional studies and clinical relevance for the disease through follow-up studies.

Results to date:
1. The largest case/control and family-based association studies for diabetic nephropathy have been assembled (4 500 samples in total).
2. Rat and mice with diabetic nephropathy have been selected and homologous human region identified in rat; about 500 genes have been identified in rat as potential candidate genes for diabetic nephropathy.
3. More than 1 000 polymorphisms have been identified in 63 candidate genes of which 60% are newly identified SNPs. About 200 polymorphisms which tag most frequent haplotypes have been selected for genotyping. Genotyping of the selected polymorphisms has been completed and analyses have been performed.

Web site:
http://www.ecgene.net/eurasite/

Key words:
Diabetic nephropathy, haplotypes, candidate genes, expression profiling, rodent models

Major publications (max. 3):
Ongoing

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Participant countries:
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Optimal organisation of health care in diabetic foot disease (EURODIALE)

Contract number:	*QLG4-CT-2002-01524*
QoL action line:	*Generic Activities 10*
Type of project:	*Concerted action*
Starting date:	*01.10.2002*
Duration:	*48 months*
Total project cost:	*€553 199*
EU contribution:	*€553 199*

Summary of Achievements to date: 01/09/2003

Objectives

The present project aims to determine the optimal health care organisation for diabetic foot patients, taking potential differences in patient characteristics and management strategies into account. Outcome variables will be used: 1) clinical end points; 2) quality of life; and 3) economic costs. Data will be collected in 14 diabetic foot centres from different regions of Europe.

The main objectives for the first reporting period consisted of the development of measurement techniques to provide instruments for the start of the data collection.

The development of measurement techniques comprised the following:

- Kick-off meeting
- Consensus meeting of diagnostic and outcome criteria
- Protocol on diagnostic and outcome criteria
- Case Record Form for baseline visit
- Case Record Form for follow-up visit
- Pilot study evaluating feasibility of the CRFs and data collection

Methodology:

The prospective data collection is the core of the EURODIALE project. In collaboration with the centre where central data handling and storage is carried out (MEMIC), a clinical case record form (CRF), both for baseline visits and follow-up visits, has been developed. Various aspects of diabetic foot disease, which the study group judged to be the most important factors for our projects, were included in the CRF. Based on the literature, these factors were: 1) individual and disease specific factors; 2) management strategies; and 3) health care organisation.

Based on the data from the data collection, interviews will be held in each centre with all health care professionals involved in the management of the patients.

Results to date:

• *CRF (Case Record Form)*

During two meetings (kick-off meeting in Waterloo 2003 and in Noordwijkerhout 2003) models for the CRF for baseline visits and for follow-up visits were discussed with all the members of the participating centres. The forms were adapted after these discussions and mailed several times to all participating centres to evaluate them and to comment on the forms. A pilot study has been performed to evaluate the feasibility of the forms. Using these discussions, comments and the conclusions of the pilot study, the final version of the CRF for baseline visits and for follow-up visits has been developed. With the help of the MEMIC-institute, a form that we are able to scan automatically has also been developed. The forms were printed and sent to all participating centres in July 2003. These data-collection procedures have been evaluated specifically on simplicity and reliability.

• *Questionnaire to obtain general data on local and national organisation of health care*

During the kick-off meeting in Waterloo 2003, we had discussions with all members about the network functioning in their foot clinics. Lists of all health care workers involved in daily foot care were produced. With the help of the department of 'Management, economics and organisation of health care' at the University of Maastricht, a questionnaire was developed to obtain general data on local and national organisation of health care. It was tested in the foot clinic at the University Hospital of Maastricht and was adapted following the conclusions of this test. During on-site visits by the technical project manager, all principal investigators and co-workers filled out the questionnaires. Data coming out of this questionnaire will be analysed in the next period, as planned.

An electronic version of the questionnaire can be found on:
http://www.beoz.unimaas.nl/Enquete/Diabetic/Default.htm

- Model for structured interview to obtain specific data on local and national organisation of health care

During the project, the relationship between health care organisation and the outcome of diabetic foot disease will be studied with the use of the concept of 'disease management'. Characteristics of disease management concepts are:

1. They integrate both the operational levels of treatment and monitoring with the system perspective;

2. The level at which care is given is taken into account making it possible to pay attention to substitution as many disease management programmes aim to provide care at the lowest level possible;
3. A distinction is made between process elements and the primary process.

The primary process is at the core of the model, and consists of the following stages: prevention, diagnostics, treatment, care, aftercare, and reintegration. In this study, the main elements to be studied are diagnostics, treatment and care.

Health care organisation will be analysed by a quantitative network analysis, using the concepts of the disease management model. Each participating diabetic foot centre (n=14) will be viewed as a network of inter-relating health care workers ('actors'). Some actors will play a more central role in the management of patients, while others will have a more peripheral role. By prospectively following the management of at least 75 patients per centre, the major characteristics of these 14 networks will be described in quantitative terms (the number and type of relations between the different actors). Furthermore, additional information will be obtained by in-depth interviews with the major actors at each participating centre.

Web site:
In process

Key words:
Diabetic foot disease, health care organisation, quality of life, health economics

Major publications (max. 3):
Not available

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Participating countries:
BE, CZ, 2 DE, 1 DK, ES, 2 IT, 5 NL, SE, 1 SO, 2 UK

Glucocorticoid hormone programming in early life and its impact on adult health (EUPEAH)

Contract number:	*QLRI-CT-2002-02758*
QoL action line:	*Infrastructures 14.4., pre-clinical research facilities*
Type of project:	*Shared cost research and development*
Starting date:	*01.11.2002*
Duration:	*48 months*
Total project cost:	*€3 988 050*
EU contribution:	*€3 165 602*

Summary of achievements to date (31.03.2004):

Objectives:
Lifestyle and genetic predisposition are considered to be the main determinants of non-communicable diseases in humans. Today, however, there is increasing evidence from studies in several distinct human populations in Europe and elsewhere that many disorders occurring in adult life date back to influences of the intra-uterine environment during the prenatal period. Examples of illnesses for which there is evidence of foetal origin are hypertension, coronary heart disease, diabetes and neurological disorders. In addition, behavioural disorders in childhood and adolescent life may also be programmed in the prenatal period. Since it is generally accepted that a multitude of pre- and postnatal influences are involved in pathophysiological processes that predispose individuals to such diseases, it is plausible to propose that there are factors triggering foetal development, thus amplifying or minimising certain long-term processes. One identified trigger is hormonal disturbance such as high glucocorticoid exposure during pregnancy. However, most of the respective studies in humans have been restricted to either epidemiological or some physiological measurements that, in sum, cannot explain the cause and basic mechanisms underlying the pathophysiological processes. Whilst many have argued on the basis of conventional rodent and ruminant animal models to explain the links between prenatal events and the commonest human disorders, none has shown strict relevance to human biology.

Understanding how such prenatal programming works, and knowledge of underlying patho-physiological changes provide one of the most exciting challenges in contemporary biomedical research. Since ethical constraints determine that mechanistic

observations can only remain indirect in humans, more profound studies need to be conducted in a non-human primate, a species closely related to humans. Therefore, using the marmoset monkey, a non-human primate species, the EUPEAH programme is investigating the evidence underpinning premature over-exposure to glucocorticoids as a key trigger of adult disease programming.

Methodology:
The EUPEAH consortium provides the infrastructure to breed and house marmoset monkeys and to perform multidisciplinary and strongly interconnected studies in a longitudinal approach by sharing biological material, technology, knowledge and data between the partners. The establishment of a European non-human primate bank (EPTB) for tissues and body fluids harmonise resource collection and distribution between diverse research facilities, preventing duplicate collections across Europe, reducing the number of experimental animals and thus contributing to animal welfare.

Besides state-of-the-art animal facilities, the consortium has methods for ultrasound examination of pregnancies, for measuring the endocrine and metabolic status in plasma and urine samples, for behavioural analysis, for telemetry to measure blood pressure, non-invasive brain imaging (MRI), and computer-assisted tomography (CT) to measure bone development as well as body fat deposits. Furthermore, the following techniques and respective equipment are also set up in the laboratories of the EUPEAH partners: immunohistochemistry and a wide spectrum of cell and molecular biological methods including proteomics (quantitative PCR, 2D-SDS-PAGE, MALDI-TOF, LC-MS/MS) to quantify the impact of prenatal dexamethasone treatment on various body systems. To unravel gene expression profiles of different organs and allow the delineation of complex biological pathways, a marmoset-specific cDNA microarray (EUMAMA) will be generated. In this way, the optimum exploitation of technical expertise and scientific knowledge of the various groups is guaranteed, thereby increasing the efficiency and performance of the individual partner institutions.

The need for non-human primates in biomedical research was defined by a statement of the Scientific Steering Committee and adopted at its meeting of 4-5 April 2002. Whether or not non-human primates are used for research will need to be decided on a case-by-case basis, and following a careful assessment which takes into account the justification, the possible existence of alternatives, ethical considerations and the problems that could result from not using the non-human primates. However, the Scientific Steering Committee considers that for certain experiments there are actually no alternatives to the use of non-human primates.

Results to date:
The effectiveness of oral dexamethasone treatment of pregnant marmoset monkeys was verified, and foetal and placental growth were monitored. Specimens from blood, urine and/or body tissues from parents and offspring under basal as well as during experimental conditions for further mechanistic analysis were collected and delivered to the participants of the EUPEAH consortium. For most participants, the official working programme will not start until the second year. However, during the first year a number of key techniques for the project have been established.

One major objective of the EUPEAH project is to generate marmoset-specific microarrays (EUMAMA) for high-throughput analysis. These arrays will be used within the EUPEAH consortium and, furthermore, will be accessible to the European scientific community. As a first step, a directionally cloned normalised cDNA library from marmoset hippocampus has been generated. Preliminary sequence analysis revealed that the quality of the library is very good in terms of average insert length and complexity. Recently, sequencing of 5 000 cDNA inserts from this library has commenced. To allow for the use of reduced amounts of input RNA, enabling expression profiling in complex heterogeneous tissues, such as the hippocampus, downscaling of expression profiling technology is mandatory. In this context, working protocols have been established for linear amplification of RNA isolated from laser microdissected hippocampal subfields.

Web site:
www.eupeah.org

Key words:
Early programming, glucocorticoids, hormonal programming

Major publications (max. 3):
Not available

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Work Programme

KEY ACTION 1: FOOD, NUTRITION AND HEALTH

OBJECTIVES AND DELIVERABLES

The contribution of improved nutrition to the prevention of diet-mediated illnesses will lead to significant social and health care benefits, both at the level of the individual citizen and that of defined population sub-groups.

However, a lack of scientific consensus and of understanding in how to communicate dietary messages effectively, alongside a changing regulatory environment are hindering the innovation of products that can contribute to consumer health, well-being and enhanced industrial competitiveness. In addition, potential undesirable components arising in the food chain pose a continuously evolving challenge to the safety of the food chain.

SMEs in the food sector play an important role in producing the great diversity of foods available in Europe, and the retail sector contributes increasingly to strengthening the links between production, processing, and the consumer.

This key action aims to provide a better understanding of consumer requirements, to provide a healthy, safe and high-quality food supply leading to reinforced consumer confidence in the safety and wholesomeness of the food supply. A multidisciplinary research effort bringing together a wide range of expertise will be essential to address the following objectives: (…)

- Understanding the role of nutrition in health and well-being: the objective is to improve understanding and awareness of the role of nutrition, diet and lifestyle in promoting and sustaining health and preventing disease, to support consumer choices for healthy and wholesome foods, and to facilitate the development and understanding of health-promoting products and diets.

Anticipated deliverables: new methodologies to determine the relation between nutrition and health, including pan-European databases of food composition and consumption; biomarkers of exposure and effect; a better understanding of the mechanisms underlying the relationship between food components, food habits and optimal health; foods with improved nutritional value; and new genetically engineered foods that have real health benefits for the consumer.

The creation of innovative pan-European networks, including regional and national networks, involving all appropriate actors will be required to achieve these deliverables and will contribute to the emerging European Research Area. The use of the implementation modalities available – Concerted Actions, Thematic Networks, Accompanying Measures (foresight, mapping, dissemination of results), Training – should be fully exploited as a way of facilitating such networks.

KEY ACTION 2: CONTROL OF INFECTIOUS DISEASES

OBJECTIVES AND DELIVERABLES

About one-third of all deaths occurring globally are due to infectious diseases. Whereas mortality is highest in developing countries, morbidity is considerable in the industrialised world, where direct and indirect costs from disease are very high. Population migration, massive travelling and climatic changes are all favouring the rapid spread of pathogens. Given the growing burden of infection in a global environment for trade and travel, Europe and its citizens remain vulnerable. Furthermore, drug resistance is an ever-growing health threat. As regards animal infectious diseases, in addition to the increasing risk to human health represented by zoonoses, outbreaks of infectious diseases in animals for livestock production and the aquaculture industry impose heavy costs on the economy.

The main objectives of this key action are: (i) to improve the prevention and treatment of those infectious diseases of major public health importance through the development of new and improved preventive and/or therapeutic vaccines and vaccination strategies; (ii) to identify and exploit new targets for anti-infective interventions; (iii) to develop new diagnostic tests; (iv) to develop tools for epidemiological monitoring and forecasting; and (v) to develop the research base for rational public health practices related to infectious diseases.
(…)

- Public health

Anticipated deliverables: identification of risk factors; development of risk-assessment methods; assessment of new risks for transmission of infection; the research base for an epidemiological surveillance and control network; improved surveillance systems for specific diseases; methods for assessing medicinal product safety and adverse reactions; and improved evidence-based public health practices.

In order to achieve a better integration at European level of efforts aiming at the control of infectious diseases, coordination projects (Thematic Networks and Concerted Actions) linking together Community and national activities are encouraged.

Research should take due account of relevant gender specificities.

PRIORITIES FOR THE CALLS IN 2001 (…)

2.3. Aspects of public health and care delivery systems

Support will be given to the development of improved systems for risk assessment, transmission and surveillance of infectious diseases in (and between) humans and animals, as well as for studying the development of new methods for medicinal product safety regarding infectious agents. Support will also be given to research on organisational and economic aspects of public health related to infectious diseases, including best practice studies.

2.3.1. Risk assessment, transmission and surveillance

Epidemiological research for the identification of factors (e.g. environmental, genetic) associated to increased risk of infectious disease transmission. Assessment of the infectious risk associated with xeno-transplantation. Research on transmission mechanisms. Epidemiological research on the evolution from infection to disease to determine optimal intervention strategies. Aetiological and epidemiological research on the role of infections in chronic diseases and in cancer. Methodologies to set up and evaluate local, national and Community-wide surveillance systems and early detection of communicable diseases in humans and animals, for example novel pathogens, microbial resistance, nosocomial infections and vaccination coverage.
(…)

KEY ACTION 3: THE "CELL FACTORY"

OBJECTIVES AND DELIVERABLES

The integration of innovative research and technologies with their exploitation by industry and/or other socio-economic entities in the fields of health, environment, agro-industry, agri-food and high-value-added chemicals is the aim of this key action. Particular attention will be given to the problem-solving approach of strengthening European industrial competitiveness by improving the potential for creation of small research-based biotechnology firms and entrepreneurial initiatives. These new knowledge-based industries are a reservoir for industrial competitiveness, scientific and technological innovation, opportunities for investors, and job creation, which is still under-exploited in Europe.

An environment in which scientific results could be rapidly exploited and transformed into products and processes of interest to society will be provided by integrating the whole process of innovation, from advanced research, through technological development up to demonstration. Such an integrated innovation approach is an absolute prerequisite in this key action, but the exploitation phase may also be a non-industrial one, depending on the particular socio-economic environment associated with a given scientific and technological area, e.g. biosafety research to be used by public-interest organisations, *in vitro* alternative testing to replace animal experimentation, and research results to be used by clinicians and in hospitals.

This key action will therefore mobilise the necessary operators (e.g. scientists, industrialists, venture capitalists, 'biovalleys' and 'bioincubators' for nurturing start-ups, consumer and patients' associations, public-interest groups) to address the following objectives in a coordinated and convergent way, linking the ability to discover with the ability to exploit:

– Innovative technologies mobilising mission-oriented research. New knowledge will be generated on the functioning of cells, including GMOs, as biological factories, by advanced research such as functional and structural genomics, proteomics, patterns of metabolites, combinatorial biochemistry, high-throughput screening, nanobiotechnology, structural biology, molecular evolution, bioinformatics, and genetic and biochemical engineering. These multidisciplinary technologies, which are applicable to many fields of the cell factories, will provide new processes and molecules for implementing the priorities given in the work programme. In the context of the "Genome research for human health" activities, the key action will link these innovative technologies, in particular functional and structural genomics, with exploitation strategies focusing on new diagnostics (3.1.1), therapeutic strategies (3.1.3), and functional biomolecules and biocatalysts (3.3.3).

– Exploitation of RTD results. Scientific and technological excellence is necessary but not sufficient. It must be closely linked to a firm commitment to knowledge transfer and to convincing exploitation by industry and/or public interest organisations. Efficient risk capital markets, creation and development of high-tech SMEs, and promoting the dialogue of technology producers with technology users are crucial for linking research to socio-economic needs, leading to future wealth and job creation. The challenge, therefore, is to set up a nurturing environment both for the development of established bio-industries and for a new generation of European entrepreneurs to start up and flourish.

Towards the anticipated deliverables: improving the competitiveness of established bio-industries and triggering the creation and sustaining the growth rate of new biotech research-based industries, European players should be mobilised to seize opportunities in the following three priority areas:

– Improving the diagnostic and therapeutic arsenal for health care.

Anticipated deliverables: new and improved health-related processes and products from living cells and biomolecules, in particular towards diagnostics tests, innovative technologies for biological production, novel targets for drug discovery, novel and improved therapeutics for health care (such as new antibiotics, anticancer therapies...), and development of in vitro tests as alternatives to animal experimentation. (…)

KEY ACTION 6: THE AGEING POPULATION AND DISABILITIES

OBJECTIVES AND DELIVERABLES

The ageing of Europe's population will be a crucial challenge for the 21st century. Society will have to face three major issues: first, increasing numbers of active older people demanding new social structures and opportunities; second, increasing numbers of disabled older people requiring new interventions and improved health and social care with the resulting economic consequences; and third, complex economic, technological, organisational and social challenges involved in the ageing of society. For society to cope with and, indeed, benefit from these changes, innovative social, organisational and technological responses are needed.

A global objective of this key action is to raise the issue of "The Ageing Population" as a priority subject for Community-wide cross-sectoral multidisciplinary research, combining and integrating efforts in the biological, biomedical, psychological, economic and social fields. More specific objectives and deliverables are:

- To promote healthy ageing

Anticipated deliverables: identification of major factors governing the ageing process as a means of promoting healthy ageing, delaying the onset of disability and preventing frailty.

- To improve the management of age-related illnesses and to cope better with disability

Anticipated deliverables: improved methods to prevent, delay the onset, diagnose and treat major illnesses and disabling conditions of older people; more competitive and adapted technological products and services for coping with disability and for promoting the quality of life, autonomy and social integration of older people.

- To improve the basis for the policy and planning of social welfare systems

Anticipated deliverables: improved tools for analysing the implications of population ageing on the sustainability of social welfare systems; improved and economically sustainable modes of delivering health and social care to older people.

To date, health systems have been largely oriented towards extending life. This key action will focus more on reducing morbidity and coping with disability, targeting the development of treatments, technologies and systems to prevent incapacitating diseases, to extend the quality of life and to enhance the functional independence of older people.

The imminent completion of the human genome sequence is opening up exciting prospects to deepen our understanding of why the human body declines in physiological vigour and becomes generally more vulnerable to disease and disorders as it ages. The key action will therefore support research into the basic molecular and cellular processes of ageing.

This key action adopts a problem-solving approach in which it aims "to put research to work" to meet the challenges posed by both the ageing of individuals and the ageing of society. It will achieve this by taking a well-balanced holistic approach towards the challenges of an ageing population, sponsoring research across all five action lines described below.

PRIORITIES FOR THE CALLS IN 2002

6.1. Age-related illnesses and health problems

This action line focuses on creating European added value in research of clinical significance for the early detection of, prevention or delay in onset of, treatment of and rehabilitation from age-related diseases and disorders of high morbidity among older people. In particular, it will sponsor the coordination of research projects already funded at the national and international levels and the networking of research teams with stakeholders in research. Priorities are:

- nervous system: stroke, Alzheimer's disease and other forms of cognitive impairment, depression, Parkinson's disease and peripheral neuropathies;
- musculo-skeletal system: muscular atrophy, osteoporosis and degenerative joint diseases;
- urogenital system: incontinence and prostate disorders;
- other gender-specific health problems;
- sensory systems: visual and auditory impairments;
- pain.

This action line will support Concerted Actions, Thematic Networks, Co-operative Research, Individual Fellowships and Accompanying Measures in all of these priority topics. In addition, for the year 2002, RTD projects and demonstration projects will be supported on depression, diseases and disorders of the musculo-skeletal system, pain, and gender-specific health problems.

Successful proposals must contain a strong representation from clinical research. Thematic Networks that bring together the research sector with the health and social care sectors and with representatives of older people are to be encouraged. (…)

RESEARCH AND TECHNOLOGICAL DEVELOPMENT ACTIVITIES OF A GENERIC NATURE

These activities aim to reinforce the knowledge base in chosen areas of strategic but generic importance for the life sciences related to humans, animals (both terrestrial and aquatic) and plants. This is in contrast to the mission-oriented problem solving approach in the key actions which place the emphasis on the linkage between discovery and exploitation.
Projects will be encouraged that promote interaction between basic and applied research and involve both the research and health sectors in order to ensure maximum transfer of knowledge between research and its users, including industry, as well as making a contribution towards the development of policy, for example, public health. Project networking will also be promoted in order to create a critical mass for optimum exploitation of results.

7. Chronic and degenerative diseases, cancer, diabetes, cardiovascular diseases and rare diseases

OBJECTIVES

The main objective of this activity is to reduce the impact of human multifactorial diseases (excluding neurological and mental disorders which will be covered within area 9), both on individuals and populations, by fostering the integration of basic and clinical research aimed at: a) elucidating the contribution of the cellular, molecular, genetic, environmental and lifestyle factors which determine disease; and b) integrating different disciplines and advanced technologies to develop effective approaches to prevention, diagnosis and treatment. Many of these diseases share a common multifactorial aetiology through the combination of multiple risk factors and similar basic mechanisms of initiation, progression and maintenance so that scientific progress in one disease will enhance understanding of others. In that context, priority will be given to multidisciplinary research into shared mechanisms underlying multifactorial diseases. Priorities are:
7.1. Elucidation of the common underlying pathogenic mechanisms involved in disease initiation, progression and maintenance.

Multidisciplinary research on the contribution of molecular, genetic, environmental and life-style factors and their influence on the above, concentrating on three main approaches: (i) mechanisms of inter- and intracellular signalling involved in disease processes, their role and interactions; (ii) cell differentiation, regulation and dysregulation, migration, injury, repair, apoptosis and death and their implications in disease development, as well as the role of immunity, inflammatory processes, angiogenic mechanisms and metabolic factors and defects (early markers of cell dysfunction), modelling of disease processes through cellular, tissue and animal models; and (iii) understanding of how risk factors, both genetic and environmental (including the evaluation of the role that those play in different European populations) for specific diseases bring about pathophysiological effects.

7.2. Evaluation of conventional and non-conventional therapies and diagnostic methods through multinational, large-scale studies/trials, taking into account advances in modern technology, with a focus on four topics: (i) development and evaluation of invasive and preferably non-invasive methods of imaging, both anatomical and functional (particularly for early diagnosis, clinical evaluation and monitoring of pathological processes) and of existing and new non-invasive monitoring devices; (ii) research into molecular and clinical markers of chronic, degenerative and rare disorders for diagnosis, prognosis and progression and for use in early diagnostic tests and screening methods for the identification of high-risk populations; (iii) clinical trials: treatment and prevention, assessment of the safety and efficacy of new and existing drugs or other therapies (comparison of different therapies and interventions), and establishment of harmonised guidelines and protocols for the best use of interventions; (iv) retrospective and prospective studies and trials to assess the impact of specific therapies and prevention on risk in the general population and groups at risk.

7.3. Optimised use of databases, registries, reagents and sample banks: Concerted Actions, Thematic Networks and RTD projects to improve the use of relevant registries, databases and sample banks, for data on risk factors, outcome and impact of specific treatments and interventions (see also Area 14, Support for Research Infrastructures).

8. Research into genomes and diseases of genetic origin

Research will aim to strengthen the strategic position already established internationally by the Community in the field of genome research, with an emphasis on functional genomics in plant, animal and microbial model genomes and in the human genome. Model genomes are hereby defined as those generally accepted for generic research by the wider community, and where the knowledge gained provides insight into other genomes of interest. Priorities are:

8.1. Interpretation of the meaning of genome information. Research should be aimed at: (i) improvement of the knowledge and understanding of the genetic basis of diseases (including chronic and degenerative diseases) leading to the identification of new genes and pathways as targets for therapeutics and diagnostics; (ii) access to most if not all genes, including the regulatory elements and the interactions between all genetic elements in relation to a specific metabolic disorder, as well as new avenues for prediction and control; (iii) identification/isolation of genes and families of genes responsible for genetic diseases, for the clarification of discrepancies between genotypes and phenotype and the development of new diagnostics and treatment modalities.

8.2. Acquisition of, access to and interpretation of genomic and functional data. The focus is on four topics: (i) contribution to the determination and interpretation of the sequence of the human genome and key genomes relevant to health, industry and agriculture, excluding farm animals with a direct and active participation of end-users; (ii) new experimental approaches to global searches on the function of genes, including prediction of protein structure and characterisation of functional networks; (iii) comparative analysis of genomes and proteomes, the aim being to understand molecular evolution patterns and their influence on the biological structure and function of living organisms; (iv) use of informatics tools for the exploitation of genome data, development of novel and user-friendly programs and computational approaches to enable acquisition, access to and interpretation of genomic and functional data for a better understanding of genetic expression.
(…)

10. Public health and health services research

10.1. Health services research and health and safety at work
Research will aim to improve the health of European citizens by supporting the Community's health strategy and its activities in the fields of public health, health services research, and health and safety at work. Priorities are: (i) to analyse the effectiveness, including cost-effectiveness of health interventions, health promotion and prevention; (ii) to analyse the variations in health care models and inequalities in health status among European countries; (iii) to analyse socio-economic and organisational aspects of health care systems, services, and health policy initiatives; (iv) to evaluate the effectiveness of non-conventional therapies; (v) to develop more sophisticated methods in epidemiology; (vi) to develop and test methodologies for identification of best practice for health interventions, and to acquire evidence for best practice in disease management for health policy decision-making; (vii) to develop and test methodologies for appraising the health impact of policy actions and/or large-scale projects, (viii) to identify aetiology of occupational accidents, in particular for specific high-risk situations for individuals, enterprise and society; and (ix) to determine exposure to and influence of physical and mental stress at work. (…)

14. SUPPORT FOR RESEARCH INFRASTRUCTURES

Within the Quality of Life and Management of Living Resources Programme, the term "research infrastructures" refers to facilities and resources that provide essential services to the research community in the life sciences. The objectives of the Programme in supporting research infrastructures (in this action line as well as elsewhere in the Programme where research infrastructures are supported) are: (i) to encourage the optimum use of Europe's research infrastructures, notably by fostering transnational co-operation in their rational and cost-effective use and development and, in conjunction with the Quality of Life and Management of Living Resources system of Marie Curie Fellowships, by broadening access to these infrastructures, particularly for young researchers; (ii) to improve the European-wide consistency and complementarity of these infrastructures and their competitiveness at world level; and (iii) to help improve the quality and user-orientation of services offered to the European research community. The role of the Programme's activities in supporting research infrastructures is to add value at the European level in the context that the construction and operation of research infrastructures is the responsibility of national authorities. This particular action of the Quality of Life and Management of Living Resources Programme will provide support for research infrastructures in the following fields:
(…)

14.4. Pre-clinical research facilities, notably: facilities for development of in vitro systems or cell cultures and, where no other means exist, breeding of animals, including non-human primates, to provide models of human diseases and facilitate development of vaccines, new drugs and medical devices.

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European Commission

Community-Funded Projects in the Field of Diabetes Research

Luxembourg: Office for Official Publications of the European Communities

2004 — 58 pp. — 21.0 x 29.7 cm

ISBN 92-894-8245-1

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ISBN 92-894-8245-1