European Foundation for the Study of Diabetes

The Research Foundation of the European Association for the Study of Diabetes

Request for Applications (RFA)

European Foundation for the Study of Diabetes (EFSD)

and

Eli Lilly and Company

ANNOUNCING UP TO EURO 900,000 IN ADDITIONAL FUNDS FOR DIABETES RESEARCH IN EUROPE

In the frame of the EFSD / Lilly European Diabetes Research Fund.

Plan and Research Focus

EFSD and Eli Lilly and Company have established the **EFSD / Lilly European Diabetes Research Fund** to promote increased European diabetes research and to increase public awareness and political understanding of the magnitude and burden of the disease.

To achieve its goals and objectives the fund is issuing a request for applications (RFA) for research grants. The EFSD / Lilly Fund will accept applications within any area of basic or clinical diabetes research.

Funding

Up to € 900,000 will be made available, over three years, for Focused Research Grants. Research will be performed in Europe and its associated countries. The grants will be distributed as follows:

2003 – Three grants, each of € 100,000
2004 – **Three grants, each of € 100,000**
2005 – Three grants, each of € 100,000

Mechanisms of Support and Review

Research will be supported through the award of fixed sum grants, each of € 100,000. The duration of each award may be one year or longer, depending upon the needs of the project and as justified in the application, so long as the total budget does not exceed the fixed sum of € 100,000, payable in the first year and in one installment.

Three awards will be granted annually for the period of three years. Applications for an EFSD / Lilly Research Programme Fund are invited from single non-profit institutions or groups of affiliated institutions from Europe and associated countries. Applications will be subject to scientific review by a specialised and independent ad hoc committee. Funding will require approval by a joint EFSD and Lilly Board convened for this purpose. Anticipated dates for application review and funding approval are given in the schedule at the end of this document.

Research Grant Applications

Applications for research grants may be subjected to pre-review (or triage) procedures. In this event, any application rejected at pre-review will not be subject to a complete scientific review.

The deadlines for receipt of research grant applications are given in the schedule at the end of this document.

For the purpose of this programme, the budget of the research grants is limited to € 100,000 per annum. All budgets are to be prepared in Euro. For countries in which the Euro is not yet the common currency, the exchange rate (between the Euro and the local curren-

cy in the country where the work is to be performed) used for calculating the Euro budget must be mentioned under "Budget Justification". EFSD and Lilly reserve the right to increase or decrease approved funding in Euro amounts to compensate for any significant change in the exchange rate.

Application forms are available at:
foundation@easd.org

All applications must be prepared on the official forms and completed in strict accordance with the detailed instructions to be found on these forms. In particular, applicants are reminded that any pages in addition to the maximum of 10 allowed for the scientific section of the application will be deleted prior to review. Similarly, no applications using a font or line-spacing smaller than defined in the instructions will be considered for review. Additional material (in the form of an appendix, attachment, reprints, etc.) is not acceptable and will not be sent to reviewers.

Applications should be submitted by 15 September 2004 (date of receipt) to:

Viktor Jörgens, M.D., Executive Director
European Foundation for the Study of Diabetes
Rheindorfer Weg 3
D-40591 Düsseldorf, Germany

Review Considerations

Completed applications will be evaluated in accordance with the criteria stated below for scientific / technical merit by an appropriate scientific committee convened by EFSD.

Review criteria are as follows:

- *Significance:* Does the study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of the proposed studies on the concepts or methods that drive this field?
- *Approach:* Are the conceptual framework, design, methods and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?
- *Innovation:* Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?
- *Investigator:* Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?
- *Environment:* Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?
- *Relevance:* A brief statement of the impact of the proposed study on diabetes mellitus.

Reporting Requirements

All Investigators funded by this programme are required to submit a scientific report at the end of the funding period. Investigators must provide EFSD with early notice of papers accepted for publication and must acknowledge the support of the Programme in such papers by use of the phrase: "This work was made possible by a grant from the EFSD / Lilly Research Fund".

Competitive Renewal

Applications for renewal of an EFSD / Lilly Research Fund Award will be accepted on a competitive basis, with the same review process as described in this announcement. Such applications will thus be considered in the same fashion as all other new applications received for review and without any special priority.

Schedule

Announcement:	May 2004 issue of *Diabetologia*
Application Deadline:	15 September 2004
Anticipated Award:	1 December 2004

Report on an EFSD/MSD Travel Fellowship for Young Scientists 2003

Anke Aßmann
German Institute of Human Nutrition, Department of Clinical Nutrition Bergholz-Rehbrücke, Germany

The following is a report about my scientific activities during my stay at the Joslin Diabetes Center of Harvard Medical School in Boston at the Department of Cellular and Molecular Physiology of Dr. Rohit N. Kulkarni in association with Dr. C. Ronald Kahn, which was supported by an EFSD/MSD fellowship.

The development of genetically engineered animal models is a useful tool to dissect the pathophysiology and genetics of diabetes mellitus. Since the laboratories I visited had extensive expertise in the creation and characterization of genetically engineered mouse models, my main focus was on gaining practical insight into these techniques. During my stay, I was able to participate in several projects involving ß-cell specific disruption of target genes (also termed knockout) mice.

Mice have been created using the technique of Cre-loxP mediated recombination to delete the insulin and/or IGF-1 receptors in pancreatic ß-cells. To achieve ß-cell specific inactivation a Rip2-Cre transgene (also called Ins-Cre) was used which is expressed at a high level in islet ß-cells from embryonic day 9 onwards. Besides gaining experience in PCR-based genotyping by standard techniques, I was involved in testing mutant animals for glucose tolerance (2 g/kg body weight glucose by intra-peritoneal (I.P) injection) and insulin sensitivity (0.75 U/kg body weight of Human regular insulin I.P.) in the fasted and random-fed states respectively. Furthermore, to evaluate the impact of altered nutrition on ß-cell function, both mutants and controls were maintained on a high fat diet with periodic physiological testing every 4 weeks.

The evaluation of alterations in islet function is usually determined by assessment of changes in morphology of the islet cells and/or gene expression profiles of the islets. This requires surgical techniques to prepare samples. I gained experience in surgical removal of the pancreas and islet isolation by the intraductal collagenase digestion method.

Briefly, after the mice have been anesthetized, the abdomen is exposed and the pancreas is outlined. The bile duct is clamped at its duodenal insertion with a bulldog clamp. A suitable needle is inserted into the proximal end of the bile duct and 2 ml of collagenase solution is rapidly injected to inflate the pancreas. The pancreas is removed carefully and placed in a 37° C water bath. All remaining steps of isolation are performed on ice. After the breaking up of the tissue and a series of washing steps to remove the collagenase, the tissue is filtered through a mesh to remove remaining undigested tissue. Then a gradient is made using Histopaque to separate the islet from contaminating acinar and fat tissue. After purification the islets can be used for transplantation, cell culture studies, or for DNA and RNA extraction depending on studies to gain specific information regarding transcription factors, glucose-sensing proteins, islet hormones, etc.

Insulin secretion is involved in the complex regulation of glucose homeostasis. In earlier experiments the Kulkarni Lab has demonstrated the significance of the insulin and IGF-1 receptors in pancreatic ß-cells using tissue-specific knockouts (Kulkarni et al 1999; 2002).

More recently, the insulin promoter has also been suggested to be expressed in some regions of the hypothalamus. To determine the potential implications of expression of the rat insulin promoter in the hypothalamus, I have been involved in studies to examine the expression of neuropeptides that are important for appetite control and lipid metabolism.

The hypothalamic agouti-related protein (AgRP) regulates body weight via central melanocortin receptors. Since Shuttler et al (1997) observed AgRP expression to be elevated 10-fold in the mouse models of obesity ob/ob and db/db, they suggest that AgRP is a participant in the control of feeding.

Neuropeptide Y (NPY) is a neuromodulator implicated in the control of energy balance and is overexpressed in the hypothalamus of ob/ob mice. Ericson et al (1996) generated ob/ob mice deficient in NPY. In the absence of NPY, ob/ob mice were less obese and less affected by diabetes.

Briefly, mice were anaesthetized and decapitated. The skull was reflected from the brain and the hypothalamus was isolated and snap frozen with liquid nitrogen and samples were stored at –80°C. For RNA

extraction tissue was homogenized and lysed with cold trizol reagent. Chloroform was added to the lysate and following centrifugation the aqueous layer was reserved for isopropyl alcohol precipitation. The resulting pellet of total cellular RNA was washed twice with 75% ethanol and re-suspended in 50 ul DEPC-treated water and quantified by spectrophotometry. A total of 25 ng RNA was used in multiplex one-step reverse transcription (48°C, 30 min) followed by 40 cycles of PCR amplification (95°C, 15 sec., 60°C 1 min.) in a 50 ul reaction mix (TaqMan One Step RT-PCR Mix) containing mouse specific neuropeptide forward and reverse primer and mouse specific neuropeptide fluorescent FAM labelled probe and GAPDH specific primers and VIC labelled probe. To exclude genomic DNA amplification all PCR-reactions were performed in the presence and absence of reverse transcriptase and samples were run in duplicate. To control for RNA input and integrity and for efficiency of the amplification reaction a housekeeping gene, gluceraldehyde-6-phosphate dehydrogenase (GAPDH), was simultaneously amplified in the same reaction tube. The expression of neuropeptides including Pro-opiomelanocortin (POMC), melanin concentrating hormone (MCH), neuropeptide tyrosine (NPY), and agouti-related peptide (AGRP) was not different between ßIRKO and ßIGFR knockouts and age- and sex-matched controls. Ob/ob mice which were used as positive controls showed appropriate changes reported in the literature.

Besides the practical work, I was instructed in data analysis and interpretation techniques using common programs including Sigma Plot and Statview.

I was also involved in plasmid construction and cell/tissue culture experiments for insulin stimulation and cell cycle analysis using thymidine and hydroxyurea.

In addition to scientific work, I participated in weekly seminars that also involved the laboratory of Dr. C. Ronald Kahn. In the data group new results, techniques and points of interest of different laboratories within the Joslin research laboratories were presented and discussed.

Also on behalf of Dr. M. Ristow, at the German Institute of Human Nutrition, I would like to thank sincerely the EFSD for the support. This Travel Fellowship provided me with the unique opportunity to extend my scientific training.

EASD
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EASD
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Report of the ADA/EASD/IDF Working Group of the HbA_1c Assay

London, UK, 20 January 2004

Present: Jean-Claude Mbanya (IDF, Chair)
Robert Rizza (ADA)
Edward Horton (ADA)
Jorn Nerup (EASD)
Robert Heine (EASD)
Thomas Pieber (EASD)
Tony O'Sullivan (IDF)
Sally Marshall (IDF)
Ryuzo Kawamori (IDF)
A Ramachandran (IDF)

Staff: Richard Kahn,
(American Diabetes Association)

Guests: Kor Miedema (IFCC)
David Sacks (NGSP)

Meeting objective

The charge to the Workgroup was to review the opportunities arising from the development of a new IFCC reference method for the measurement of HbA_1c, and to make recommendations on its implementation.

Meeting synopsis

The meeting began with a presentation on the current technology regarding the measurement of HbA_1c and in particular, the history of the new IFCC reference method. This was followed by a presentation demonstrating the convergent effect of standardisation within the global network of NGSP. Also, the status of NGSP certification was reviewed.

After some discussion the Workgroup agreed that the IFCC reference method should become the global reference standard ("anchor"), and that all manufacturers should now calibrate their instruments to the new method.

The workgroup acknowledged that such a change tentatively implies that the reported HbA_1c numbers would be 1-2% less than those currently reported. Thus, the cut-off points for what is normal, or good/poor control would shift downward.

The Workgroup then discussed how the HbA_1c results should be reported: should they be reported using the IFCC numbers, which would mean an abrupt lowering of individual test results? Or should the linear relationship with the DCCT method be used to convert the new numbers back to the current range of values, which would mean little or no perceptible change in reported numbers? Some of the pros and cons discussed were:

Method	**Report new IFCC range**	**Maintain current values**
Advantages	– the reported values reflect the actual values – opportunity to re-educate professionals and people with diabetes about meaning and value of the HbA_1c test – opportunity to redefine HbA_1c (see below)	– familiar to patients and clinicians – relates HbA_1c values to existing evidence base e.g. UKPDS, DCCT
Dis-advantages	– high cost, and prolonged timeline for education necessary to prevent confusion – partial or piecemeal implementation will worsen existing differences between laboratories – risk of deterioration in glucose control as experienced in a Swedish study[1] – lower numbers make it even more difficult to convince patients that small changes in percent A1C have a big impact on health	– not the 'pure' result – frequently confused with glucose levels in countries where mmol/l used – missed opportunity to reinforce the importance of the test.

The above points were discussed at great length and each Workgroup member articulated his or her concerns and recommendations. Discussion then centered on how we might use the opportunity / challenges pre-

sented by the introduction of the new IFCC method to re-define the HbA_1c and its importance in diabetes care. Of paramount importance was the agreement that the entire world should be using / reporting the same reference values.

All Workgroup members agreed that the very name of the test "A1C" or "hemoglobin A1C" was confusing, especially to patients who do not understand its connection to glucose / diabetes (since the name suggests a blood disorder). Also, everyone agreed that the small numbers (e.g. 7%, 9%) do not readily convey to patients that even a 0.5-1% change has a major effect on health. Consumers believe that since it takes a 10-40 unit change in most measurements for there to be a meaningful difference (e.g. outdoor temperature), so when their diabetologist reports a 1% change their response is "that's trivial".

The Workgroup decided that with the above concerns, we now have the opportunity to redefine the entire assay. A suggestion was made by both the European and American representatives, enthusiastically supported by all other members, that the name of the assay be changed to something that reflects the "MBG" (mean blood glucose) and that we should avail ourselves of the close relationship between HbA_1c and mean blood glucose. This relationship, which is one of direct proportionality, was observed on a retrospective examination of 7-point glucose assays during the DCCT study. The relationship is:

MBG (mmol/l) = 1.84 x IFCC HbA_1c

(Of course a different factor will arrive at MBG if expressed in mg/dl.) If this relationship can be confirmed in a prospective study, then we will have the opportunity to report the new IFCC figures as to mean blood glucose. Hence the HbA_1c test will have a new name (e.g. MBG), a new range (in familiar glucose units), and a more direct and recognizable link to glucose levels for people with diabetes and their health care professionals.

Advantages of this approach are: a clear revision of the test along with a new range, with no real opportunity for confusion (although substantial preparation and re-education will still be needed); a simplification of the range allowing every person with diabetes to understand their own target level, particularly if already using home glucose-monitoring; and more likely potential for future use as a diagnostic tool.

Disadvantages include the possibility that the simple proportionality, or even a straight linear relationship, may not apply to all populations or to extremes of MBG/HbA_1c, in which case we might be forced to adopt more complex conversions or reconsider the idea altogether. Also, to obtain the full benefit of a link with home tests, the MBG will be reported in two different units (mmol/l vs mg/dl) with the usual minor but frustrating conversion problems. Overall, the group favoured proceeding with this innovative approach to implementation of the new standard.

The Workgroup then voted unanimously to endorse this plan, and outlined the following steps:

Action	Timing	Lead Responsibility
1. Adoption of IFCC reference method as the new global standard for calibration	Immediate	IFCC/NGSP
2. Use the new IFCC methodology to anchor an "international certification process" within the existing international laboratory networks.	Immediate	NGSP/IFCC
3. The IFCC and NGSP will direct manufacturers NOT to change the HbA_1c report out values until further work, outlined below, has been completed i.e. DCCT/UKPDS range and numbers will continue to be used	Immediate	IFCC/NGSP
4. Determine if there are other retrospective data (in addition to references 2-4 below) that can be used to link HbA_1c to MBG. In particular, data for non-white Type 2 patients would be valuable	4–6 months	IFCC
5. Design and conduct prospective studies on various populations world-wide to confirm/establish the HbA_1c-MBG relationship	2004–2007	ADA/ EASD/IDF
6. Plan public and professional information programme about the new reporting system	2005–2007	Current Workgroup

The Workgroup now submits this final report to its respective sponsors for review and approval. If satisfactory, the above plan will be announced at the upcoming ADA and EASD meetings and a research consortium should be established as soon as possible to address item 5 above.

References

1. Hanas R. Psychological impact of changing the scale of reported HbA_1c results affects metabolic control. Diabetes Care, 25 (11) 11 Nov 2002, pp 2110–11
2. Manley SE, Cull CA, Holman RR. Relationship of A1C to fasting plasma glucose in patients with type 2 diabetes in the UKPDS randomized to and treated with diet or oral agents. Diabetes 2000; 49 Suppl 1:A180, 742
3. Rohlfing CL, Wiedmeyer HM, Little RR, England JD, Tennill A, Goldstein DE. Defining the relationship between plasma glucose and HbA_1c: analysis of glucose profiles and HbA_1c in the Diabetes Control and Complications Trial. Diabetes Care, 2002, 25:275–8
4. Mosca A, John GW. IFCC reference system for glycohaemoglobin/HbA_1c standardization. In: John GW (ed), Monitoring glycemic control in the diabetic patient, Excerpta Medica Publications, London, 2001, 123–40

Announcements

1. Annual DESG Awards for Research on Therapeutic Patient Education

In order to encourage relevant research in the field of Therapeutic Education of people with diabetes, the Diabetes Education Study Group of the EASD offers three awards of Euros 600.00 each to the presenting authors of the best abstracts on Therapeutic Patient Education, two to be chosen from those selected by EASD and one by FEND for presentation at their respective annual meetings.

Regulations for the award assignment:

The choice will be made by a 5-member DESG commission composed of four DESG officers: the President, the Director of Educational Strategies, the Honorary Secretary and a non-physician member of the Executive Committee, plus the current FEND president.

Once approved for presentation at the EASD Annual Meeting and at the FEND meeting, either as a poster or as an oral presentation, the abstracts will be evaluated by the award commission. The awards shall be delivered during the respective meeting, by the chairperson of the respective session.

2. DESG Sponsorship of Attendance to Grimentz Workshops

The Division of Therapeutic Education for Chronic Diseases of Geneva University Medical School, founded by Prof. Jean-Philippe Assal, and now directed by Prof. Alain Golay, annually organises two 5-day workshops, since 1987 in the Swiss village of Grimentz (Valais). The topic of the workshops – always different – regards a particular aspect of therapeutic education and the follow-up of people with chronic diseases.

Overall, more than 3000 HCPs have benefited from these workshops for their formative value in one or other human science linked to patient education, always associated with the highest concern for medical pertinence. They have, for many, been the starting point of a new professional approach, as well as a continuous source of inspiration and motivation.

In order to favour the participation in Grimentz workshops by interested Health Professionals, the Diabetes Education Study Group of EASD will grant a total of four 1-week fellowships covering registration fees and accommodation for the two Grimentz Workshops of 2004.

This year only one workshop will be run. The workshop title and date are as follows:

"MOTIVER NOS PATIENTS-
augmenter nos compétences pour faciliter le changement chez nos patients"

19–24 Juin 2004

Candidates are required to present a one page curriculum, together with a declaration of why they are interested in attending the Grimentz Workshops and an explanation of how this experience may be implemented upon their return to their place of work.

The DESG commission will be composed of the DESG president, vice-president and the Director of Educational Strategies. Preference shall be given to HCPs involved in diabetes Therapeutic Patient Education who have difficulty in raising the necessary funds.

Fluent knowledge of the French language is mandatory.

Applications should be sent by E-mail to
a.maldonato@iol.it, or by fax to +39 06 44703133.
The application deadline is 15 May 2004.

Symposium of the EASD Islet Study Group

Lake Chiemsee, Bavaria (80 km south of Munich), 9–12 September 2004

Organizer: Prof. Sigurd Lenzen, Hannover. This will be immediately after the end of the EASD Annual Meeting in Munich. Details including registration information can be found on the following web page: http://www.mh-hannover.de/institute/clinbiochemistry/Post_EASD2004/index.htm

4th Joint DSFG / Neurodiab Scientific Meeting

Regensburg, Germany, 2–5 September 2004

Official Announcement / Abstract Submission / Online Registration:
www.dfsg.org

22nd International Symposium on Diabetes and Nutrition Study Group of EASD

Såstaholm (Stockholm), Sweden, 1–3 July 2004

For further information:
www.akademikonferens.uu.se/diabetes

First Joint Meeting of the European Federation of Autonomic Societies & American Autonomic Society

Amsterdam, The Netherlands, 20–23 October 2004

For further information please contact:
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Deadline for abstract submission is 1 June 2004.

9th International Symposium on Insulin Receptors and Insulin Action

Nice, France, 14–17 October 2004

Please consult the website for further information:
http://ir04.lso-intl.com

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