EASD

EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

ASSOCIATION EUROPEENE POUR L'ETUDE DU DIABETE · EUROPÄISCHE GESELLSCHAFT FÜR DIABETOLOGIE
Rheindorfer Weg 3 · D-40591 Düsseldorf · Germany · Tel: +49-211-7 58 46 90 · Fax: +49-211-75 84 69 29

E-mail: easd@uni-duesseldorf.de · Homepage: http://www.easd.org

EASD

News Section 11/2002

Report of the 15th Annual General Meeting of the EASD European Diabetic Nephropathy Study Group (EDNSG)

held in Barcelona, Spain 3–4 May 2002

The 15th AGM of the EDNSG took place in Barcelona this year and was hosted by Dr Joan Mauri. Around 100 delegates attended an excellent meeting which kept to the now standard format of 3 guest lectures and oral presentations spread out over 2 days. In keeping with previous programmes there was ample time for discussion which was encouraged and facilitated by the Chairman of the various sessions.

After a brief opening ceremony the programme commenced with a lecture from guest speaker Francois Alhenc-Gelas from France, who updated us on genetic variations in vasoactive peptide systems and how they related cardiovascular and renal diseases, specifically, of course, concentrating on diabetes. He reviewed the published work on polymorphisms in genes affecting the renin angiotensin and kinin systems and this provided an excellent overview of the field. Specifically he underlined the importance of local tissue expression of components of the renin angiotensin system pointing out that ACE expression was particularly strong in the vasculature of the rat kidney, but was mainly seen in the proximal convoluted tubule in man. Some interesting new data on polymorphisms in the bradykinin system were presented; it must, of course, be remembered that ACE inhibitors also block bradykinin breakdown.

The following session was entitled experimental physiology and we learnt more about connective tissue growth factor and its role in experimental diabetic nephropathy in rats. This was followed by the description of an interesting model of diabetic nephropathy in transgenic rats which seems to produce classical nodular glomerulosclerosis. These animals develop fulminant hypertension due to over expression of renin. PKC beta inhibition attenuated the progression in this model.

After a coffee break there was a session on morphology. The first paper suggested that the baseline glomerular structure in normoalbuminuric Type 1 diabetic patients did not seem to predict outcome in terms of nephropathy progression. For some time it has been known that normoalbuminuric patients have a range of glomerular lesion from virtually none to severe, but it does not look as though this predicts long term outcome. This raises the serious question of the importance of the lesions in terms of disease progression. The rationale for a long term study looking at RAS blockade on the development of early lesions of glomerulopathy was then outlined and this important research is due to be reported in 4 or 5 years time. Other papers in this session looked at the prevalence of different types of glomerular pathology in patients with Type 2 diabetes, again underlining greater heterogeneity compared to Type 1 patients.

The third session looked at clinical trials exploring the role of sub-clinical inflammation and incipient nephropathy in Type 2 diabetes. This interesting hypothesis is going to form the basis of an intervention trial. There was then an interesting presentation looking at a small group of salt sensitive Type 2 diabetic patients who demonstrated abnormal nitric oxide biosynthesis. This raises an interesting issue as to whether this type of patient may be more prone to develop nephropathy. Finally, there was some discussion around the third paper looking at the optimum dose of Candesartan in terms of lowering proteinuria.

After lunch the second lecture of the meeting was given by the invited speaker, Leopoldo Raij, who reviewed endothelial dysfunction as a mechanism for the development of nephropathy largely based on experimental diabetes in rats and other rodents. At the core of the presentation was a discussion of the role of nitric oxide and how this could be modified by the renin angiotensin system and other agents such as endothelins and vascular smooth muscle cells. Again the interesting message was one of equating salt sensitivity to glomerular vulnerability.

The next session looked at clinical observations of levels of carboxymethylysine, soluble E-selectin and alterations in skin microhaemodynamics in patients with differing stages of nephropathy. This was followed by a second session on clinical observations showing that even in long duration Type 1 diabetic patients an elevated urinary albumin excretion was associated with increased mortality. There was then a somewhat depressing presentation explaining how patients starting on dialysis in Spain did so far too late and with much poorer risk factor profile for cardiovascular disease. The role of plasma triglycerides as one of these potential risk factors was underlined by the final presentation of the day.

After a wonderful social evening and dinner in the conference venue, proceedings opened the following morning with genetics; the first presentation failed to find an association between polymorphisms in the promoter region of the VEGF gene and diabetic nephropathy in Northern Ireland. A presentation on renal cell replication in different strains of rats with experimental diabetes showed that there are differences in cell proliferation in pre-hypertensive diabetic SHR's and cyclin-dependent kinases appear to mediate these changes. Other presentations looked at polymorphisms in platelet glycoproteins, the ACE gene and the advanced glycation end product receptor. This latter study demonstrated that albumin excretion in Type 1 diabetic patients with poor metabolic control was associated with a polymorphism in the RAGE gene implying a gene-environment interaction. The session was concluded by a presentation looking at sodium lithium countertransport and its links to an isoform of the sodium hydrogen antiporter.

An interesting development in the field of nephropathy research has been the dramatic increase in studies looking at kidney structure and function. In the early days of the EDNSG possibly 2 or 3 presentations may have been in this field, but this year there was a whole session dedicated to the podocyte alone. Two presentations demonstrated that podocyte number and structure changed as nephropathy developed in Type 2 patients. However, it is unclear whether these changes precede or go in parallel with the clinical condition. There were then 2 papers looking at nephrin expression in the podocyte in man and experimental animals. Interestingly expression was reduced in both studies suggesting a role for abnormalities of this protein in nephropathy progression.

The morning was completed by a lecture from a guest speaker, Professor Egido, talking about the role of inflammation in vascular and renal injury in diabetes.

The meeting closed with a session on cell biology exploring mechanisms including nitric oxide production, reactive oxygen species and the role of TGF beta and other mechanisms in extra-cellular matrix production from renal fibroblasts.

All in all this was a meeting which maintained the high quality of the Study Group events.

The group is always looking for new members. In order to join, applicants need to be fully paid up members of the EASD and have an abstract accepted for presentation. If members miss more than 3 consecutive meetings, they have to re-apply. The Group contains a broad range of researchers from pathologists to clinical nephrologists as well as diabetologists.

It is planned to hold the next meeting in Copenhagen from 2–3 May 2003. For more details on how to apply or submit an abstract please contact the Secretary, Dr Ole Torffvit at his e-mail address: Ole.Torffvit@med.lu.se.

We look forward to seeing you next year.

Rudy Bilous, Vice President of EDNSG
Ole Torffvit, Secretary of EDNSG

Diabetes and Nutrition Study Group of the EASD (DNSG)

Minutes of the General Assembly held at Samos on 29 June 2002

41 participated in the General Assembly.

1. **Minutes from the 19th International Symposium on Diabetes and Nutrition in Düsseldorf 2001** were accepted.
2. **Activities during the last year:**
   - We have provided responses to IDACE (Ass. of the food industries for particular uses of the EU) on their "report on dietary recommendations for persons suffering from carbohydrate –metabolism disorders (Diabetes)" as comments and criticism in e-mails.
   - DNSG has submitted an official response to the Consumers Protection Directorate Generals amendment to directives (SANCO/2002/888-EN and 889-EN) on "foods for particular nutritional uses". Regarding the desirability of special provisions on foods for persons with diabetes, DNSG has supported the legislative option B (Combination of position 1 and 3) stressing that there is no scientific justification for the introduction of "dietetic foods" for diabetic subjects.
   - A sub-committee has started a discussion on the present nutritional recommendations of DNSG for individuals with diabetes mellitus in the light of evidence-based nutrition (J. Mann, M. Toeller, B. Vessby, B. Karamanos, N. Katsilambros, M. Uusitupa, G. Slama, S. Rizkalla, G. Riccardi, A. Rivellese, K. Hermansen) and a pre-meeting was held at the 20th International Symposium on Diabetes and Nutrition. Nutritionists will also be included in the group (U. Schwab and B. Karlstroem).

- Members of the DNSG have commented on the American recommendations for nutrition for diabetic persons (Mann J, Hermansen K, Vessby B, Toeller M: Evidence-based nutritional recommendations for the treatment and prevention of diabetes and related complications: A European perspective. Diabetes Care 2002; 25:1256–1258).

3. WEB site

The DNSG web site www.DNSG.org is established. Annette Jarvi will be responsible for the updating of the web site (e.g. registration and abstract forms and the program for the next DNSG Meeting, other relevant meetings, links etc). Anette Jarvi can ask for technical assistance.

4. Treasurer's report

There is a positive balance of 111,055.75 D.Kr (equal to about 15,000 Euro).

5. Committee on International Affairs within DNSG (CIA).

K. Hermansen has proposed that a sub-committee within DNSG with direct reference to the DNSG committee be established.

The aim of the sub-committee should be:

a) To respond to inquiries from governments, international organizations
and
b) To up-date the nutritional recommendations for diabetic subjects on behalf of the DNSG

Previous chairmen should constitute the CIA together with the present chairman and present vice-chairman. One nutritionist should be included. Further members may be included in order to ensure a broad representation with regard to geography and special scientific insight.

CIA determines the term of office for the members and elects its chairman within the group. The chairman of CIA will report at the yearly business meeting and at the General assembly. The CIA refers directly to the committee of DNSG.

This proposal was unanimously accepted. The General Assembly elected nutritionist Ursula Schwab.

The previous chairmen i.e. Jim Mann, Monika Toeller, Gerard Slama, Basil Karamanos, Bengt Vessby will be asked if they will accept the invitation to participate in this work. The present chairman, Kjeld Hermansen, and Vice-chairman, Salwa Rizkalla, both agreed.

6. Changes in the composition of the DNSG committee:

The chairman thanked Ellen Aslander van Vliet, who wanted to leave the committee, for her contribution. Subsequently, Angela Rivellese, Italy was elected for the period 2002 – 2005.

7. New members of the Study group 2002 (confirmed by the General Assembly):

Andrijana Brankovic
Anne-Marie Aas
Bryndis-Eva Birgisdottir

8. The Novo Nordisk Pharmaca Scandinavia Young Investigator awards 2002:

From 12 candidates P. B. Jeppesen, U. Schwab and A. Thanopoulou were conferred with the Novo Nordisk Pharmaca Scandinavia Young Investigator Awards 2002.

9. Samos meeting 2002

The chairman expressed gratitude to Prof. Katsilambros and Prof. Karamanos for their great work with the arrangement of the 20th International Symposium that was very well organized and had a high scientific standard as well as an excellent social program:

3 Plenary lectures
32 oral presentations
11 posters

The list of participants contains 160 names.

10. Upcoming meetings

- **Brugge, Belgium, 19-22 June 2003**
  Suggested topics for abstracts:

  Alcoholic and non-alcoholic beverages and diabetes mellitus
  Obesity and diabetes
  Postprandial metabolism
  Lifestyle changes and implementation

  Additional proposals were:
  homocysteine; appetite and nutrition
- **Paris** – meeting is going to take place in connection with the IDF meeting in early September 2003; topics should differ from those of the Brugge meeting (e. g. cardiovascular risk factors)
- **Meeting 2004**: proposal Sweden (B. Vessby and B. Karlstroem have agreed)
- **Meeting 2005**: proposal Italy (must still be decided upon)

11. Eventually

- Monika Toeller suggested that the treasurer should be included as officer in the rules of DNSG.
- Attempts to obtain sponsorship from the food industry for travel awards, for a sub-committee meeting on evidence-based nutrition and diabetes (see above), and for grants will be made by the DNSG committee.

U. Julius
K. Hermansen

July 2002

7th EASD/JDRF OXFORD WORKSHOP

'New Frontiers in the Treatment and Prevention of Type 1 Diabetes and its Complications'

Keble College, Oxford, 3–5 August 2002

MEETING FORMAT AND PURPOSE

The annual EASD-JDRF Oxford Workshop is convened jointly by the European Association for the Study of Diabetes (EASD) and the Juvenile Diabetes Research Foundation International (JDRF). This workshop aims to bring together a small group of researchers focused on a specific area of relevance to research focused on Type 1 diabetes and its complications. Attendees are charged to identify emerging opportunities and key areas of need in the research areas addressed, so that EASD, JDRF and others can use feedback from the workshop to focus better their research funding programs and activities. These meetings are highly informal and there is a strong emphasis on audience discussion of topics presented. They are special in that research Fellows accompany more senior investigators and participate actively. Special attention is paid to inviting leading specialists from outside the immediate field of diabetes research.

The 7th EASD/JDRF Oxford Workshop, 'New Frontiers in the Treatment and Prevention of Type 1 Diabetes and its Complications', addressed two broad areas that are of importance to current diabetes research: stem cell technologies and gene therapy approaches. This was a stimulating meeting that was comprised of just a few "keynote lectures" and short presentations by senior scientists paired with junior fellows from their research laboratories, followed by substantial audience-wide discussions together with illuminating, entertaining and sometimes controversial questions from some of the distinguished participants present.

The Recommendations Overview attempts to capture the flavour of the meeting and the key concluding points and areas of need that emerged from the meeting. Following this is a brief summary of speaker presentations and the discussions that followed.

WORKSHOP RECOMMENDATIONS: OVERVIEW

Both stem cell therapy and gene therapy are at a critical juncture; their application as therapeutic approaches for the treatment of Type 1 diabetes and its complications is still in its infancy. Though both areas show remarkable promise, it is clear that they are likely to take some time to bear fruit and lead to useful therapeutic applications for Type 1 diabetes and its complications. This was the fundamental take-home message from the 7th EASD/JDRF Oxford Workshop.

As a result, a key recommendation of the workshop was that funding agencies should take into account the potentially long road to success for these therapeutic approaches, and make *long-term* commitments to supporting these areas. This should include not only financial commitments, but also:

– developing a 'resource sink' for techniques/materials to facilitate sharing as well as increasing uniformity of approaches used across the field
– fostering of collaborations and partnerships between investigators, via financial support (e.g. consortia)
– holding additional interdisciplinary meetings as forums for information sharing.

In the future, clinical trial infrastructure is most likely to emerge as the key area of need that could benefit from funding agency support. Gene therapy and stem cell therapy might encounter at least some similar problems in this area. As gene therapy clinical trials are already ongoing, they may provide a template for the stem cell field. Clinical trial infrastructure should ideally be modeled on pharmaceutical company trials; however, this could be expensive. Considering the potential lack of institutional commitment for such trials, this was identified as another area to which funding agencies should consider committing support.

The role of the funding agency in facilitating a clinical trial could include:

– Liaison for interaction with the Food and Drug Administration (FDA) or equivalent in other countries/areas - in particular, filing an application for an Investigational New Drug (IND) was pinpointed as an area where some guidance from a 'third party' – the funding agency – would be helpful.
– Supporting a successful trial into Phase I/II and providing additional guidance to investigators as to the necessities of clinical trial design.

Considering the risk to individual investigators – should funding agencies play a role? For example, the

funding agencies could facilitate investigator training for clinical trial design and execution. Giving a specific example of this, EASD or JDRF might consider initiating a type structure analogous to the existing 'TrialNet' to include relevant clinical trials in other areas such as diabetes complications.

Finally, diabetic complications represents a unique area – there are multi-factorial problems to address that need different approaches and funding agencies could play a role as mediators between academics, industry and small biotechnology companies.

STEM CELLS AND CLONING: SPECIFIC RECOMMENDATIONS

'Recreating the pancreas' – ß-cells or islets?

The fundamental goal of seeking to make an insulin-secreting cell, and the significance of developing ß-cells from stem cells in the context of missing islet components, was addressed. Some key questions were raised:

- Is there functional heterogeneity among insulin producing cells – i.e. are all ß-cells equal?
- Even if we can successfully induce a stem cell to become a ß-cell, can we generate enough cells to restore islet function?
- In transplanted insulin-secreting cells, is there an absence or breakdown of 'intermediate metabolism'?

In seeking to restore islet function in the individual with Type 1 diabetes, it may be essential to identify islet precursors able to reconstitute all cell types. Investigators are encouraged by the concept of looking for an 'islet precursor' rather than a 'ß-cell precursor'. Indeed there was some discussion as to whether the former might actually be easier to generate than the latter.

What information is still needed?

Here, the importance of developmental biology is the key. Fundamental to these questions is a need to understand more about different islet cell types and their individual gene expression patterns. The embryonic stem cell field is largely guided by what we know about pancreatic development. Currently we have quite a limited knowledge of islet cell biology. Recommended approaches to improve this information base include:

- design genetic screens for different pathways and couple this to therapeutic cloning research
- develop a better understanding of the temporal sequence of gene expression in the developing ß-cell and islet.

These studies should address the question: 'what environmental cues can be utilized to direct embryonic stem cells to develop into functional ß-cells?' In addition these studies will provide endpoints and markers of ß-cells. These issues need to be defined and utilized; *we cannot rely on insulin expression alone as a marker that we have a ß-cell*.

What about tolerance and rejection of stem cell derived ß-cells?

A fundamental concern is that stem cell derived islets will ultimately be destroyed by the host immune system. This is thought to be a valid concern for differentiated cells derived from human embryonic stem cells. However, the consensus of the workshop was: immune rejection concerns should not slow the embryonic stem cell field at this time. In essence, we cannot worry now about rejection of cells that have not yet been generated. To a large extent, we must rely on advances in the tolerance research field in the interim. Going forward, it might be useful to develop new tests to assess the immunogenic potential of stem cell derived tissues/cells – for example, the creation of oligoclonal cells in culture might be a useful approach.

General Issues: characterizing derivates of stem cells

There is a need to understand better 'modified' or 'engineered' cells in general.

In terms of islet/ ß-cell derivation the following needs exist:

- Better quality control guidance for human embryonic stem cell islet derivation.
- Define the expansion parameters 'from embryonic stem cell to pancreas'.
- Better define the potential of pancreatic ductal stem cells (there is only one case to support this concept). However it could be the case that adult stem cell needs are quite different from ES cells and indeed in the pancreatic duct it would seem that the duct cell precursor has great potential.
- Define the role and potential of embryonic stem cells when in an adult context.
- Good Manufacturing Procedure (GMP) issues: central to this is the elimination of mouse feeder layers – and the question of whether feeder layers should be used at all. We need cell lines without mouse feeder layers. It is now possible to grow human ES cells without feeder layers but with mouse conditioned medium (human feeder layers also reported in Nature Biotechnology September 2002).
- Better define the potential of 'surrogate ß-cells' (e.g. genetically altered liver cells)

Core technologies that would be helpful if coordinated by a funding agency

There is a need for coordination, facilitating accessibility and quality control for these newly emerging technologies, most notably; ß-cell chips (including human ß-cell chips, human antibody chips, genome chips, diagnostic chips and chips for all developmental stages). It was acknowledged that the 'chip need' might well be addressed by industry in the near future but this is not a certainty.

Finally, sharing of NIH resources was discussed. The NIH β-cell consortium is generating a ß-cell chip on which both mouse and human genes are represented. This should shortly become available to the research community.

Further recommendations for the funding agencies to consider:

- Arranging with companies manufacturing chips to 'bulk-buy' chips for dissemination – i.e. provide a 'core service'
- Serve as a liaison with NIH or other national agencies to ensure investigator access
- Development of a 'resource sink' for core technologies for application in human ES lines (e.g. cDNA promoters, antibodies and other materials). This would help to facilitate access to these reagents (especially those privately held) and increase uniformity of approaches used across the field

GENE THERAPY: SPECIFIC RECOMMENDATIONS

Though further progressed than the stem cell field, the gene therapy field is still in early stages in terms of moving towards therapeutic application. Researchers may be closer to having broadly applicable vectors but fundamental issues remain. Overall, the current state of the field can still be described as underdeveloped.

What issues need to be addressed for development and improvement of new vectors?

In the next 5 years many of these problems will be addressed – most likely in other disease scenarios - before being understood in diabetes. Fundamental problems with promoters need to be broadly addressed, as these tend to vary in function in different settings. There is a particular need for studies in human tissue since current studies rely on poor animal models of diabetic complications. The needs include:

- vectors that can express many genes
- address targeting issues, efficiency of delivery, long term gene expression
- address immune rejection, viral immunogenicity
- invest in new serotypes (for different animals)
- define vector action and expression efficacy/consistency in different tissue settings in humans – this is poorly understood - as is the potential toxicity of vectors in different tissues
- the potential utility of AAV or HSV needs further exploration
- single gene targeting is of increasing importance to achieve successful expression

Development of inducible systems (e.g. use the natural regulatory system of cell) issues:

'Piggybacking' on natural gene regulatory controls was seen as being of potential importance. The use of natural regulatory systems will allow for control of how much of the newly introduced gene is translated. This is important as it is undesirable to have cells turning out lots of protein in an unregulated fashion.

Core technologies that would be helpful if coordinated by the funding agency:

We should address the need for vector sharing. There is a need for a master source for comparison of vectors for diabetes research that exist in individual labs – to identify the best for individual needs requires sharing between investigators. There is a need for vector standardization and comparison in individual labs. In this regard, an NIH consortium for vector sharing intends to produce and make available gene vectors. This consortium is assembling large libraries of expressed genes and promoter-trap viruses to understand more about etiology of gene expression. However there could be an additional role for the funding agencies for specifically diabetes-related vector approaches.

Specific issues relating to gene therapy of diabetic complications:

It was considered imperative to develop (large) animal models of diabetic complications for pre-clinical trials of gene therapy. One approach would be to use current vector technology to induce complications by introduction of specific "disease" genes thereby short-circuiting the usual long period required for development of complications.

Meeting Report

Meeting Participants:

Keynote Lecturers:
Terence A. Partridge (MRC, Hammersmith Hospital, London UK), Richard Mulligan (Harvard Medical School, Boston USA), Ron Crystal (Weill Cornell Medical College, New York USA), Alan Colman (ES Cell International, Singapore). Invited Speaker: Lewis Wolpert (University College, London).

Senior Scientists and Fellows:
Roger Pedersen and Ludovic Vallier (Cambridge University, UK), Gerald Schatten and Christopher Payne (Magee-Womens Research Institute, Pittsburgh, USA), Jon Odorico and Brenda Kahan (University of Wisconsin, Madison, USA), Palle Serup and Ulrik Frandsen (Novo Nordisk, Denmark) Markus Stoffel and Vivian Lee (Rockefeller University, New York, USA), Henrik Semb and Anna Tonning (Gothenburg University, Sweden), Daryl Granner and Maureen Gannon (Vanderbilt University, Nashville, USA), Paul Robbins (University of Pittsburgh, USA), Joe Glorioso and Ed Burton (University of Pittsburgh, USA), Matthew Weitzman and Toni Cathomen (Salk Institute, La Jolla, USA), David Margolis (University of Pennsylvania, Philadelphia, USA), Aristidis Veves and Lalita Khaodhiar (Beth Israel Deaconess Medical Center, Boston USA), Michael Tolentino and Alberto Auricchio (University of Pennsylvania USA).

Overview:

Various therapeutic strategies for ß-cell replacement therapy are being considered. These include improved islet transplantation, cell-based therapies, gene therapy, and drug therapy to promote ß-cell proliferation and neogenesis. It is anticipated that these strategies will, in future, provide an effective line of attack to treat Type I diabetes. Gene therapy is also envisaged for treatment of diabetic complications and significant advances have been made in the area of wound healing, revascularization, neuropathy and retinopathy. The invited speakers addressed two key approaches that are currently being pursued towards these goals; stem cell biology and gene therapy. The session on stem cells and cloning discussed this emerging field from the perspective of (i) general features of embryonic and adult stem cells including the plasticity of adult stem cells and the derivation of embryonic stem cells via cloning techniques and (ii) the specific generation of islet ß-cells from stem cells. In the session on gene therapy, the speakers discussed (i) some general aspects of gene therapy, such as vector construction and delivery, and (ii) specific uses of gene therapy in the treatment of Type I diabetes and its complications. Lewis Wolpert gave a talk on the ethical issues involved in stem cell research and cloning and is cited below.

I Stem Cells and Cloning

(i) General Features of Stem Cells & Cloning

The presentations provided an introduction to some of the general features of stem cells including the plasticity of adult stem cells and introduced the subject of ‘cloning’ from the perspective of generating ES cells. Two keynote speakers, Terence Partridge and Richard Mulligan, talked on the properties of stem cells with respect to tissue regeneration and outlined some of the essential features of adult stem cells.

The prevailing view of the ‘stem cell concept’ can be described by the following hierarchy: Totipotent blastomere ⇒ Pluripotent stem cell ⇒ Multipotent stem cell ⇒ Uni-potent stem cell ⇒ differentiated tissue. However, evidence for individual stage transition is unclear and is somewhat conflicting; it is still unclear whether this ‘hierarchy’ is *reversible* or not.

The myofibers of skeletal muscle are analogous to ß-cells in that both cell types undergo slow-turnover. Twenty years of research is only now beginning to expose the role of endogenous stem cells in muscle. Skeletal muscle tissue is post-mitotic and its repair and regeneration is thought to occur via a population of stem cell like ‘satellite cells’. Recent findings have questioned the degree to which these satellite cells are a single homogeneous population and whether they are the only source of myogenic cells in mature muscle. It is becoming increasingly clear that these satellite cells have stem cell-like properties. Now, recent evidence is beginning to question the prevailing view that a *single* population of myogenic cells is present in skeletal muscle. The key question in this regard is whether skeletal muscle repair can be accomplished by adult hematopoietic stem cells (HSCs).

Recent work, using the *mdx* mouse model of Duchenne muscular dystrophy, has begun to answer some of these questions. A dual mechanism exists for the repair and maintenance of skeletal muscle. Regenerating muscle is derived largely from local sources. Typically, most satellite cells are a transitory population engaged in routine maintenance of muscle. These cells appear to be maintained by a rare population of ‘reserve cells’ that have many of the characteristics of uni-potent stem cells. In addition, circulating stem cells can also enter into muscle and HSC transplantation by intravenous injection has recently been shown to restore dystrophic myofibers *in vivo* [1]. Whether these transplanted HSCs can play a significant role in maintenance or repair is still unclear. Future directions include developing methods to augment the function of these cells to enhance their ability to regenerate muscle fibers.

"It is not birth, marriage, or death, but gastrulation, which is truly the most important time in your life" – Lewis Wolpert.

Roger Pedersen and Ludovic Vallier's talk entitled 'Embryonic steps to stem cell medicine' discussed stem cells in the context of embryonic development. Embryos have many features that enable us to understand pluripotent stem cells. The speakers addressed two important questions: what can embryos teach us about embryonic stem cell differentiation? and, can embryos be used to overcome the immune system responses to transplantation?

Recent work on embryonic development has begun to show how early polarity predicts axial organization, which is conferred on the embryo by localized signaling interactions. Gastrulation involves the differentiation of pluripotent cells which are induced by extra-embryonic tissue lineages. Similarly, the derivation of embryonic stem (ES) cells yields pluripotent cells capable of extended proliferation. ES cells are also responsive to signaling pathways that are active in the early embryo. Therefore a principle aim of current research in this area is to derive ES cells with 'normal' functions and properties compared with differentiated cell types.

Somatic cell nuclear transfer (SCNT) has recently been used in mice to generate ES cells. Murine ES cells derived after nuclear transfer are pluripotent and have undergone 'reprogramming', thus establishing proof-of-principle as models for cell-based transplantation therapies[2]. However, some problems arise when using this technique. Genomic replacement is often performed using failed fertilized oocytes: the developing embryos frequently arrest during early cleavage and therefore only a minority is usable. In addition most of the donor nuclei are poor, possessing chromosomal abnormalities. Therefore, while achievable in principle, SCNT has several practical limitations.

The immunogenicity of ES cell-derived cells is unknown – ES cells can express high levels of MHC-I proteins and thus may be rejected on transplantation [3]. The unique properties of ES cells also present an opportunity to explore novel mechanisms to *prevent* immune-mediated rejection. One potential approach to overcome rejection is the use of hematopoietic "mixed" chimerism as a means to successfully transplant cells and tissues derived from human ES cells [4]. "Mixed" chimerism refers to a state in which allogeneic hematopoietic cells coexist with recipient cells. The underlying premise is that the induction of tolerance may be achieved using mixed chimerism based on hematopoietic stem cells derived from human ES cells. The mixed chimerism method has already been shown using various animal models to be a very efficient method for inducing tolerance [5,6]. Production of hematopoietic stem cells from ES cells has also been recently demonstrated in mice [7,8]. Remaining challenges exist in the need for better quality control (GMP) and the validation of these techniques *in vivo*. If successful, ß-cell transplantation in the context of hematopoietic stem cell induced tolerance would be a logical next step.

Gerald P. Schatten and Christopher Payne gave a talk titled 'Accelerating juvenile diabetes research with non-invasive imaging of transgenic, cloned and stem cell-derived primates'. They gave an overview of current research with transgenic and stem-cell derived 'cloning' technologies that are being used to derive non-human primates for research purposes. One of the most compelling scientific rationales for the use of cloning is the study of disease models in which the genetics are invariable [9]. Using these techniques, it may be possible to develop and propagate new animal models of complex genetic diseases such as Type I diabetes via cloning. The advantages and disadvantages of several cloning methods that are now in use were discussed. These included intracellular sperm injection (ICSI), intra cytoplasmic nuclear injection (ICNI) or somatic cell nuclear transfer (SCNT) and 'embryo splitting' [10].

Primate embryo sources are generally high quality and current IVF techniques produce good embryos/blastocysts, however many of these do not implant – a single embryo usually has only a 30% success rate in normal IVF. This may be due to problems with the spindle apparatus which lead to chromosomal misalignment at metaphase. In human and non-human primates, the spindle apparatus is paternally derived – two centrioles from each sperm are critically important for formation of first meiotic spindle. Recent work has shown that during establishment of bipolar spindles at Metaphase II spindle the nuclear mitotic apparatus (NuMA) protein is required. NuMA associates with the pole of each spindle in primates and is necessary for establishing bipolarity. Other proteins involved in the process of establishing bipolarity include microtubule associated motor proteins such as members of the kinesin and dynein families of proteins.

Alan Colman discussed 'The Legacy of Dolly: Cloning and xenotransplantation'. This talk gave an introduction to some of the practical limitations of 'reproductive' and 'therapeutic' cloning techniques and possible future clinical/therapeutic applications. Previous work on amphibian embryos has been applied to mammalian embryos with limited success. However, techniques were eventually developed utilizing electroporation of cultured cells in contact with enucleated oocytes, thus achieving nuclear transfer. Cloning from adult cells can now be more easily achieved by SCNT and has been successfully carried out on mice, cats, rabbits and livestock. To date however, there have been several notable failures (e.g. in rats, dogs, monkeys and horses). This research leads to a key ques-

tion; *can highly differentiated cell nuclei undergo global 'reprogramming'?* Recently, cloning from mature T and B lymphocytes has been demonstrated [11]. The generation of 'monoclonal' B and T cell mice, then, demonstrates that the most specialized of cells may be completely 'reprogrammable'. However, several significant problems still remain. With current cloning techniques, the efficiency of transfer and thus the percentage of reconstructed embryos is low. In addition, cloning also leads to pre and post-natal abnormalities and losses. For example, cloned sheep are often undersized and have been shown to suffer adrenal defects, hypoxia, pulmonary problems, nephropathy, myopathy and neuropathy. Furthermore, in two recent reports, abnormal patterns of X-chromosome inactivation and abnormal gene expression have been reported in cloned cows and in cloned mice [12,13]. Although SCNT has worked with 8 mammalian species so far, it is inefficient and can introduce potentially deleterious mutations. Prospective uses of cloning technology include; the generation of cloned animals for xenotransplantation [14] and may lead to a unique supply of biocompatible donor organs including pancreatic islets. In summary, human ES cell-based transplantation therapy has great potential to treat successfully a number of diseases although many barriers remain: the eventual generation of islet cells is a primary goal in this area.

(ii) Generation of ß-cells from ES cells

'If I were to ask you "Are you a beta cell?" – how would you answer?' – Lewis Wolpert

Talks were given on the subject of generating ß-cells from adult and embryonic stem cells by the following speakers; John Odorico and Brenda Kahan, Palle Serup and Ulrik Frandsen, Henrik Semb and Anna Toning, Markus Stoffel and Vivian Lee, Daryl Granner and Maureen Gannon. What follows is a brief summary of these talks:

Since they have the dual ability to proliferate indefinitely and differentiate into multiple tissue types, human ES cells could potentially provide an unlimited supply of tissue for human transplantation. The generation of functional tissue-specific cell types from embryonic or adult sources of stem cells is dependent on the basic mechanisms of developmental biology. ES cell descendents coordinately express specific lineage restricted genes in proper temporal fashion. Multipotent precursors can be isolated and can complete diverse differentiation pathways *in vitro*. ES cell derivatives possess the ability to integrate into a host and function normally.

ES cells undergo many-fold expansion with routine culture conditions, are straightforward to manipulate genetically, can be isolated at various stages and manipulated in a controlled fashion, and can generate a variety of different cell types after exposure to individual growth factors [15]. However, there are some limitations to using *in vitro* techniques to generate specific cell types. Cultured ES cells give rise to heterogeneous populations of cells and the administration of individual growth factors has not been shown to direct differentiation exclusively to one particular cell type [15]. To achieve such lineage-restricted differentiation of human ES cells using soluble growth factors, a better understanding of the epigenetic events that control lineage commitment and differentiation is needed.

Whether ES cells can re-enter pancreatic islet-cell differentiation pathways is unclear; however, current research appears to indicate that this may indeed be possible. Several recent studies have begun to elucidate the genes controlling pancreatic differentiation. Studies of the roles of these islet specific transcription factors will be essential for the directed differentiation of ES cells to functional islet ß-cells. The transcription factor Pdx-1 plays an important role in pancreatic development as demonstrated by targeted disruption of the Pdx-1 gene in mice, which results in pancreatic agenesis [16]. During development, Pdx-1 is expressed in all pluripotential gut-derived epithelial cells destined to differentiate into the exocrine and endocrine pancreas at embryonic day (E)10.5. By E15, Pdx-1 expression is downregulated in exocrine cells, but remains high in endocrine cells. Other transcription factors that play a role in pancreatic development include PTF1-p48, PAX4, neuroD/BETA2 and neurogenin 3. The goal of current research in this field is to identify, characterize, and eventually isolate pancreatic islet-like endocrine cells and their precursors with proliferative capacity from ES cells. Work presented by Jon Odorico and Brenda Kahan suggested that ES cells are capable of producing endocrine cell types characterized by the extensive co-expression of each of the major pancreatic hormones, insulin, glucagon, somatostatin, and pancreatic polypeptide with the early endocrine cell markers, peptide YY and islet amyloid polypeptide (IAPP). The derivation of Pdx-1 positive pancreatic progenitors was also demonstrated, a finding corroborated by other studies presented at this meeting. Previous immunohistochemical studies of human pancreatic development, which showed that insulin was co-localized mainly with IAPP and glucagon while PYY occurred together with glucagon and pancreatic polypeptide, indicate that these are markers that could potentially be used to aid in the isolation of these early endocrine cell types from ES cells [17].

Palle Serup and Ulrik Frandsen presented a framework developmental fate map of ß-cells. During development, regional gene expression precedes morphological patterning, with transcription factors being expressed in different 'domains' of the embryo. In the chick embryo, the ventral pancreas is marked by the

expression of certain transcription factors, including Pdx-1at (Hamburger and Hamilton) stage 11, the earliest stage examined. Ectopic expression of these transcription factors leads to the repression of CdxA (a caudal-type gene previously shown to be expressed in the endoderm-derived gut epithelium during early embryogenesis) and Pdx-1 additionally induces pancreatic bud structures to form. Later in development the Notch signaling pathway plays a role in the control of cell fate or differentiation of endocrine precursors into mature endocrine cells. Three models are proposed for the role of notch signaling in fate control. In model 1, lateral specification of cell fate occurs via initiation of ngn3 expression, specifying endocrine progenitor fate. In model 2, lateral inhibition controls the differentiation of already committed endocrine progenitor cells. Whereas in model 3, Notch signaling controls multiple steps in pancreatic development.

The plasticity of hematopoietic stem cells is still a controversial area. Transdifferentiation of HSC was recently reported to show reconstitution of functional hepatic lobules using FAH-/- mice (an animal model of tyrosinemia type I) [17]. In order to investigate the potential for generating ß-cells from bone marrow, Vivian Lee (Stoffel lab) reported results of experiments conducted using transgenic mice generated with GFP under direction of the Pdx-1 promoter. In these animals, periductal cells, ß-cells and δ-cells express GFP and embryonic GFP correlates with normal Pdx-1expression. Bone marrow cells from these mice were transplanted into streptozotocin induced diabetic RAG-1-deficient mice (lacking functional lymphocytes). Some mice analyzed after 4 months showed the presence of GFP-positive cells in islets of Langerhans of recipient animals (these positive data were not reported at the meeting since the study had not been completed). Immunohistochemistry revealed overlapping staining of insulin with GFP expression. The data suggest that bone marrow cells may have the ability to contribute to insulin producing cells in pancreatic islets.

Switching to ES cells which are capable of self renewal and display unlimited undifferentiated proliferation *in vitro*, Markus Stoffel's lab has begun to study pancreatic islet differentiation *in vitro* using ES cells deficient in Pdx-1. Using haplo-insufficient (+/-) and Pdx-1 null (-/-) mice with lacZ as a marker, three independent ES cell lines were generated for both conditions. A modified Lumelsky method [19] was then used to expand ES cells through four stages resulting in terminal differentiation. These conditions generate cells expressing insulin and other pancreatic endocrine hormones. The cells self-assemble to form three-dimensional clusters similar in topology to normal pancreatic islets. Glucose and other secretagogues trigger insulin release from these cell clusters but the secretory capacity as well as total insulin content is extremely low. Using the marker system, clusters of lacZ positive cells were already observed in +/- and -/- cultures at early stages, however, -/- ES cells only generated clusters consisting of few hormone positive cells. The majority of hormone positive Pdx-1+/- cells lose co-expression at later stages of differentiation. Pdx-1-/- cells had lost their ability to secrete insulin in response to insulin secretagogues. In addition, they had a significantly lower insulin content compared to Pdx-1+/- and +/+ cells. Comparison of gene expression profiles of FAC-sorted LacZ positive +/- and -/- cells revealed reduced expression of insulin, glut-2, glucokinase , Pax4 and Nkx6.1 in cells lacking Pdx-1. Therefore, the phenotype of differentiated Pdx-1-/- ES cells shows striking similarities with the *in vivo* Pdx-1 mutant mouse model. ES cells may therefore constitute a model system to study gene function in pancreatic development and insulin secretion

Daryl Granner and Maureen Gannon discussed the issue of transcription factor function in relation to glucose metabolism and ß-cell differentiation. The speakers addressed current knowledge in this area beginning with an overview of glucose homeostasis. Metabolic control of insulin production is mediated through a medley of transcription factors. Members of the HNF family of transcription factors are known to play a critical role in the regulation of ß-cell gene expression and insulin secretion. Recent studies of maturity onset diabetes of the young (MODY), have implicated a number of these transcription factors in disease pathogenesis. One of the key pancreatic transcription factors that is also involved in glucose homeostasis is HNF6. This factor is important for the specification and differentiation of the islet endocrine lineage. Proper regulation of HNF6 is important for normal endocrine differentiation and mature function. HNF6 is directly upstream of the endocrine progenitor gene neurogenin 3 and it directly or indirectly regulates many genes shown to be involved in MODY.

Henrik Semb and Anna Tonning reviewed the potential for differentiation of human ES cells into insulin-producing cells. Human ES cells are derived from fresh or frozen pre-implantation embryos. After prolonged undifferentiated proliferation, marker analysis, karyotyping and telomerase activity can give an initial impression of whether the cells are indeed ES cells. However, the critical test for pluripotency of human ES cells can only be performed by transplantation of the cells to mice and proper analysis of the formed teratoma. It is hoped that human ES cells can be expanded indefinitely in culture, maintaining a normal karyotype and retaining the capability to produce any cell type in the body. However, many problems still remain to be solved in terms of establishing, characterizing, and culturing human ES cells without the frequent occurrence of spontaneous differentiation. Today, the latter is a particular problem in laboratories growing human ES cells. The speakers also discussed the need for applying the basic developmental biologi-

cal mechanisms that guide normal development of ß-cells in order to succeed with obtaining functional ß-cells from ES cells. One further issue that needs to be addressed is the cellular heterogeneity of islets: insulin producing cells alone may not be adequate to reproduce a fully functional islet. Finally, in order to be able to evaluate the insulin-producing cells derived from ES cells it is important to further characterize the ß-cell, in terms of its ontogeny, gene expression pattern, and physiology.

II Gene Therapy in Type I Diabetes

(i) Vector Construction and Delivery

Matthew Weitzman and Toni Cathomen discussed adeno-associated viral (AAV) vectors for gene therapy and gene targeting. These vectors exploit the wild-type AAV capsid as a vehicle, but are non-pathogenic in humans. Recombinant AAVs have many attractive features that facilitate their use *in vivo*; they have a wide range of hosts, exhibit long term expression, can transduce non-dividing cells, are non-immunogenic, and can be easily manipulated, deleted of all viral genes and produced to high titer. In addition rAAVs have been successfully targeted to many different tissues including; heart and skeletal muscle, brain, eye, lung and liver. Wild type AAV has a biphasic life cycle and needs external stimuli to reproduce. These stimuli include helper viruses such as adenovirus, and inducers of stress such as UV irradiation. Recombinant AAV vectors are replication incompetent and are produced in the *absence* of external stimuli by co-transfection of the required helper activities. Targeting of these vectors can achieve modest gene delivery to specific cell types. Several different serotypes of AAV exist and the most commonly used is AAV2. It is now possible to create hybrid vectors where exchanging capsids changes the transduction capability of vector. An alternative approach currently being used is to modify capsid coat proteins to target specific cell types. Some of the data presented showed that libraries containing modified targeting peptides can be produced and selection can be achieved for peptide binding clones that bind cell-specific binding motifs.

(ii) Gene therapy for Type I Diabetes and its Complications

Ron Crystal gave an overview of the uses of gene therapy in transplantation and discussed the use of gene therapy in the context of islet cell transplantation and wound healing. Islets may be subjected to ex-vivo gene transfer as a means to increase the survival of ß-cells in an autoimmune environment. To do this, anti-apoptotic strategies for specific therapeutic targets are now being utilized. The overall approach is to treat human pancreatic islets prior to transplantation with adenoviral vectors containing therapeutic genes. One drawback is that physical barriers may exclude adenovirus from the center of the islet, contributing to poor gene transfer to the islet interior. This situation may arise due to the differential expression of the coxsackievirus and adenovirus receptor (CAR). Higher levels of CAR are found on the periphery of islets than within the interior. To address this may well necessitate alternative experimental strategies such as vector modification or partial dissociation of islets to achieve adenoviral penetrance.

Angiogenesis and wound healing are also being advanced using gene therapy. VEGF gene therapy has been used as an adjunct treatment in coronary bypass surgery. Administration of VEGF by gene therapy is currently being investigated for its potential in wound healing using a rat hindlimb ischemia model monitored by angiography and has shown improvement. While there are some limitations to the use of VEGF, since there are multiple splice variants and the size of cDNA transcript that can be inserted into the adenoviral capsid is limited, mini-genes capable of producing all VEGF isoforms are now being engineered to increase efficiency.

Paul Robbins described gene transfer and protein transduction based approaches for facilitating islet transplantation. Gene therapy offers the possibility of providing specific antigen-targeted therapies, thus eliminating the toxicity associated with immunosuppression. Gene-based therapies include the manipulation of tolerance by antigen presenting cell engineering, pro-inflammatory cytokine blockade using soluble antagonists expressed from viral vectors and modulation of immune regulatory networks. Local immunosuppression can be delivered through gene therapy in the liver. The vectors used for gene transfer to islets include Adenovirus (Ad), Lentiviruses (LtV:HIV, EIAV) Adeno-Associated Virus (AAV) and Herpes Simplex Virus (HSV). Adenovirus Infected 50–70% of ß-cells in intact human and murine islets. Infection had no significant effect on ß-cell function. They have demonstrated greater than 3 months of gene expression in human and murine islets in SCID and immunocompetent murine recipients respectively.

Joe Glorioso and Ed Burton reported on HSV mediated gene transfer in the nervous system. HSV mediated gene delivery has a number of properties that are advantageous for the delivery of genes to the nervous system. These include a natural tropism for neurons, a large viral genome permitting the introduction of multiple exogenous genes, and the ability to establish asymptomatic life-long latent infections. Despite these advantages, the development of HSV vectors successfully exploiting all these properties has been difficult. This has largely been due to either vector toxicity or the failure to maintain long term transgene

expression. Recent progress has overcome these problems and several applications of the technology are being evaluated. One trial aims to drive enkaphalin expression to treat chronic pain using pre-proenkaphalins in the dorsal horn of the spinal cord. Gene therapy may be used to treat neuropathy caused by diabetes. Using pyridoxine induced peripheral neuropathy as a model, Ed Burton explained how transgene expression may be used to preserve structure and alter function in the PNS during neuropathies. Phase I clinical trials with gene therapy are now underway to treat glioblastoma, intractable cancer pain and taxol induced neuropathy. Clinical trials are scheduled to commence in 2003 which will target dorsal root sensory ganglia using HSV vectors containing nerve growth factor (NGF) to treat diabetic peripheral neuropathy.

David Margolis spoke on the rationale and lessons learned from the use of gene therapy for diabetic neuropathic foot ulcers. Diabetic neuropathic foot ulcers (DNFU) result in around 50,000 lower extremity nontraumatic amputations per year in the US. Lower extremity ulcerations develop primarily as a consequence of neuropathy and the goal in addressing any wound is to rapidly re-establish tissue integrity. The healing of wounds is a complex procedure involving multiple growth factors, some of which have multiple effects on different cell types. An important agent in the wound healing process is platelet derived growth factor (PDGF), which is active in all stages of healing. Several approved therapies for neuropathy include growth factors, such as recombinant PDGF (Regranex), however, little is known about the risk factors associated with success in neuropathic patients and few successful clinical trials have been carried out to date. To gain a realistic representation of current wound care practice a wound care database (curative health services database) was founded to monitor more than 120,000 patients with wounds in more than 150 centers. More than 70,000 of these patients have diabetes. Validation of the database was carried out by correlation with actual cases. Evaluation of treatment approaches of different centers showed few overall differences. The usefulness of such epidemiological studies is that they can determine who is at highest risk, who is least likely to benefit from standard care (e.g. who to refer) and additionally, they can estimate the burden on society, risks, benefits and costs of treatment.

The effects of recombinant PDGF are being evaluated in a gene therapy clinical trial.This Phase I trial aimed to use an adenoviral vector to insert recombinant PDGF into somatic cells (fibroblasts) of a chronic wound. Preclinical animal data previously demonstrated the efficacy of this vector on multiple animal models including diabetic mice, clearly showing that wound healing occurs more rapidly. The initial aims of the study were to evaluate the safety and feasibility of adenoviral delivered PDGF administered via a single subcutaneous injection in patients with DNFU (i.e., phase I dose escalation trial) and to initially evaluate the safety and efficacy of adenoviral-PDGF patients with DNFU (phase I/II trial). However, the FDA has put a hold on all new gene therapy clinical trials due to the death of a patient during a clinical trial at the University of Pennsylvania. Currently this trial is under re-review and will go forward subject to satisfying many new safety criteria. Another major take-home message from this talk related to the potential future use of stem cells in clinical trials. The speakers cautioned those present of the challenging regulatory problems faced in designing and executing a successful clinical trial and advised the group of the specific difficulties that may be met when new therapies are taken to the clinic.

Lalita Khaodhiar and Aristidis Veves discussed diabetes related changes in the skin microcirculation and their implications for wound healing. Impaired vasodilation in patients with diabetes and neuropathy in the lower extremities leads to functional ischemia [20]. Early changes related to endothelial dysfunction have been observed in healthy relatives of patients with Type 2 diabetes [21]. Recent animal studies have indicated that hyperglycemia stimulates the production of nitric oxide, which reacts with superoxide anion to form peroxynitrite, which is in turn damaging to the endothelium. These changes in endothelial function reflect significant correlations between poly-ADP ribose polymerase (PARP) levels and positive endothelial markers such as fasting blood glucose and resting blood flow. Inhibitors of PARP and peroxynitrite have been developed and will be further tested in models of impaired wound healing and in the clinic.

Michael Tolentino and Alberto Auricchio reviewed the use of gene therapy for the complications of diabetic retinopathy. Retinopathy is a decompensation of the retinal vasculature that results in microvascular abnormalities that can lead to increased vascular permeability, ischemia, retinal neovascularization and fibrosis. Current treatments for diabetic retinopathy include focal laser treatment for vascular permeability and pan-retinal laser treatment for neovascularization. These treatments are only 50% effective however, and new blood vessel formation often leads to scar development and eventual retinal detachment which can only be treated with surgery. The ideal treatment would be direct inhibition of the underlying defects. Such inhibition would need to be sustained and inducible, locally delivered, non-toxic and non-inflammatory. Therefore, gene therapy could represent an ideal treatment for diabetic retinopathy, since this method can be used to deliver inducible, potentially inhibitory genes locally to the retina over a long period of time.

Gene therapy can deliver specific factors for inhibiting vascular permeability. Potential strategies in-

clude the use of VEGF inhibitors using anti-sense and ribozyme based inhibitors, polypeptide inhibitors, soluble receptors to sequester VEGF and VEGF receptor inhibitors (dominant negative, peptide receptor agonists). Other strategies to inhibit vascular permeability pathways include the use of protein kinase C (PKC) inhibitor. Inhibition of retinal ischemia may also be targeted using direct inhibitors of VEGF and the basic helix-loop-helix transcription factor, hypoxia inducible factor 1 alpha (HIF-1α), and intracellular adhesion molecule 1(ICAM-1).

The eye presents certain advantages for gene delivery since it is a small self-contained organ system. Vector delivery can be accomplished using intra-vitreal injection and currently, AAV presents the most suitable viral vector to treat murine models of retinal disorders. Using hyperoxia as a mouse model of premature retinopathy, it is possible to study the use of gene therapy since after hyperoxic exposure, these animals undergo VEGF induction and subsequent neovascularization. Currently, several anti-angiogenic factors deliverable by gene therapy are under investigation and these include factors to block basement membrane breakdown such as tissue inhibitors of metalloproteinases (TIMP-3), anti-migration factors such as endostatin which binds tropomyosin in endothelial cells, anti-proliferative factors such as pigment epithelial derived factor (PEDF) and anti-VEGF /Anti-HIF/Endostatin – to block VEGF receptors and anti-maturation factors such as Angiopoietin-1 and Angiopoietin –2. In conclusion, AAV vectors are a powerful tool for gene delivery and offer a highly feasible means of delivering factors to inhibit proliferative diabetic retinopathy.

Acknowledgements: The Oxford Workshops are hosted and organized jointly by EASD and JDRF. The scientific Chairs for this 7th Workshop were Drs. Joe Glorioso and Philippe Halban (who also serves as the Workshop series scientific coordinator). EASD and JDRF thank Ms. Mary Hata (EASD), Drs. Kim Hunter-Schaedle and Antony Horton and Ms. Amanda Deflos (JDRF) and Ms. Caroline Wood (local organizer) for their help in organizing this meeting and the Aventis Company for their most generous and sustained support of this and previous Oxford Workshop meetings.

References

1. Gussoni E, Soneoka Y, Strickland CD, Buzney EA, Khan MK, Flint AF, Kunkel LM, Mulligan RC (1999), Dystrophin expression in the mdx mouse restored by stem cell transplantation. Nature 401(6751): 390–394
2. Piotrowska K, Wianny F, Pedersen RA, Zernicka-Goetz M (2001) Blastomeres arising from the first cleavage division have distinguishable fates in normal mouse development. Development; 128 (19): 3739–3748
3. Kawase E, Yamazaki Y, Yagi T, Yanagimachi R, Pedersen RA (2000) Mouse embryonic stem (ES) cell lines established from neuronal cell-derived cloned blastocysts. Genesis; 28: 156
4. Drukker M, Katz G, Urbach A, Schuldiner M, Markel G, Itskovitz-Eldor J, Reubinoff B, Mandelboim O, Benvenisty N (2002) Characterization of the expression of MHC proteins in human embryonic stem cells. Proc Natl Acad Sci USA; 99(15): 9864–9869
5. Kaufman DS, Thomson JA (2002) Human ES cells-haematopoiesis and transplantation strategies. J. Anat; 200 (3): 243–248
6. Spitzer TR, Delmonico F, Tolkoff-Rubin N, McAfee S, Sackstein R, Saidman S, Colby C, Sykes M, Sachs DH, Cosimi AB (1999) Combined histocompatibility leukocyte antigen-matched donor bone marrow and renal transplantation for multiple myeloma with end stage renal disease: the induction of allograft tolerance through mixed lymphohematopoietic chimerism. Transplantation; 68: 480–484
7. Sykes M, (2001) Mixed Chimerism and Transplant Tolerance, Immunity 4: 417–424
8. Kaufman DS, Hanson ET, Lewis RL, Auerbach R, Thomson JA (2001) Hematopoietic colony-forming cells derived from human embryonic stem cells. Proc Natl Acad Sci USA, 98 (19): 10716–10721
9. Kyba M, Perlingeiro RC, Daley GQ (2002) HoxB4 confers definitive lymphoid-myeloid engraftment potential on embryonic stem cell and yolk sac hematopoietic progenitors. Cell; 109: 29–37
10. Chan AW, Dominko T, Luetjens CM, Neuber E, Martinovich C, Hewitson L, Simerly CR, Schatten GP (2000) Clonal propagation of primate offspring by embryo splitting. Science; 287 (5451): 317–319
11. Hochedlinger K and Jaenisch R (2002) Monoclonal mice generated by nuclear transfer from mature B and T donor cells. Nature; 415 (6875): 1035–1038
12. Xue F, Tian XC, Du F, Kubota C, Taneja M, Dinnyes A, Dai Y, Levine H, Pereira LV, Yang X (2002) Aberrant patterns of X chromosome inactivation in bovine clones. Nature Genetics, 31: 216–220
13. Humpherys D, Eggan K, Akutsu H, Friedman A, Hochedlinger K, Yanagimachi R, Lander ES, Golub TR, Jaenisch R (2002)Abnormal gene expression in cloned mice derived from embryonic stem cell and cumulus cell nuclei. Proc Natl Acad Sci USA (Epub doi; pnas. 192433399)
14. Lai L, Kolber-Simonds D, Park KW, Cheong HT, Greenstein JL, Im GS, Samuel M, Bonk A, Rieke A, Day BN, Murphy CN, Carter DB, Hawley RJ, Prather RS (2002) Production of α-1,3-Galactosyltransferase Knockout Pigs by Nuclear Transfer Cloning Science, 295 (5557), 1089–1092,
15. Schuldiner M, Yanuka O, Itskovitz-Eldor J, Melton DA, Benvenisty N (2000) Effects of eight growth factors on the differentiation of cells derived from human embryonic stem cells. Proc. Natl. Acad. Sci. USA, 97(21): 11307–11312
16. Jonsson J, Carlsson L, Edlund T, Edlund H (1994) Insulin-promoter-factor 1 is required for pancreas development in mice. Nature 271: 606–609
17. Portela-Gomes GM, Johansson H, Olding L, Grimelius L (1999) Co-localization of neuroendocrine hormones in the human fetal pancreas. Eur J Endocrinol 141(5): 526–533
18. Lagasse E, Connors H, Al-Dhalimy M, Reitsma M, Dohse M, Osborne L, Wang X, Finegold M, Weissman IL, Grompe M (1999) Purified hematopoietic stem cells can differentiate into hepatocytes in vivo. Nature Medicine, 6(11): 1229–1234
19. Lumelsky N, Blondel O, Laeng P, Velasco I, Ravin R, McKay R (2001) Differentiation of embryonic stem cells to

insulin-secreting structures similar to pancreatic islets. Science 292(5520): 1389–94
20. Pecoraro RE, Ahroni JH, Boyko EJ, Stensel VL (1991) Chronology and determinants of tissue repair in diabetic lower-extremity ulcers. Diabetes 40: 1305–1313
21. Caballero AE, Arora S, Saouaf R, Lim SC, Smakowski P, Park JY, King GL, LoGerfo FW, Horton ES, Veves A(1999) Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. Diabetes 48(9): 1856–1862

Report prepared by Dr. Antony Horton (JDRF) on behalf of the organizers.

Second International Symposium on PPARs: From Basic Science to Clinical Applications

Florence, Italy, 19–22 March 2003

Co-chairpersons:
J.-C. Fruchart (France), A.M. Gotto, Jr. (USA),
R. Paoletti (Italy), W. Wahli (Switzerland)

Scientific Secretaries:
A.L. Catapano (Italy),
M. Crestani (Italy), B. Staels (France)

Session Topics (Oral and Posters):
PPAR Interacting Proteins and Cofactors
PPARs and Crosstalk with other Nuclear Receptors and Transcription factors
PPARs and Lipid and Lipoprotein Metabolism
Role of other Nuclear Receptors in Lipid Metabolsim
PPARs in Atherosclerosis
PPARs and the Cardiovascular System
PPARs in Diabetes: Preclinical Models
PPARs in Obesity - PPARs in Muscle
PPARs Agonists and the Metabolic Syndrome
PPARs, Inflammation and Immune Response
Macrophages
PPARs in Dermatology
PPARs in CNS
PPARs in Gastrointestinal Diseases
Cell Cycle, Differentiation and Cancer
Evolution and Comparative Biology of PPARs
PPARs and Genetics
Preclinical Models to Assess PPAR Agonists
New Drugs affecting PPARs
Pharmacological Implications of Targeting Nuclear Receptors
Clinical Applications of PPAR Ligands in Diabetes
Clinical Trials with PPAR Ligands and Combined Treatments
Combined Treatments with PPAR Ligands and other Drugs
Toxicology / Side Effects and Clinical Toxicity

Contributed Papers – Call for Abstracts (Oral or Poster Presentations):
The abstract must be sent to the Scientific-Organizing Secretariat by **15 December 2002**

Scientific-Organizing Secretariat:
PPARs 2003
Fondazione Giovanni Lorenzini
Via Appiani, 7
I-2001 Milan (Italy)
Tel: + 39 (02) 29006267
Fax: + 39 (02) 29007018
E-mail: ppars@lorenzinifoundation.org

The II Genoa Meeting on Hypertension, Diabetes and Renal Disease

Genoa, Italy, 28 February–1 March 2003

The Meeting is organised by Giacomo Deffari and aims at bringing together experts and practicing physicians to discuss current information related to high blood pressure, diabetes and renal damage. The deadline for abstrac submission is **15 December 2002**.

For furher information please contact:

Roberto Pontremoli, M.D.
Department of Internal Medicine
Section of Nephrology
University of Genoa
Italy
Fax: +39-010-3538959
e-mail: rpontrem@medicina.unige.it
www.aristea.com/diredi03

Meeting of European Diabetic Nephropathy Study Group (EDNSG)

Helsingor, north of Copenhagen, Denmark, 2-3 May 2003

All abstracts on any topic relating to diabetic nephropathy research are welcome and should be submitted **by 10 January 2003** to:

Dr Ole Torffvit, Secretary of EDNSG
Dept. of Medicine
University Hospital
S-221 85 Lund
Sweden
Fax: +46-46-2110908
E-mail: Ole.Torffvit@med.lu.se

Please submit the abstract as an e-mail with the abstract as an attachment in a Rich Text Format (RTF) or as a Word file. If you decide to admit the abstracts by fax please remember to submit also five hard copies by post. Abstracts should be written with a breakdown in the following headings: Objective, Design, Setting, Patients, Main Outcome Measurements, Results and Conclusions. Please make sure that the length of the abstract does not exceed one side of an A4 paper, that you leave margins of 2.5 cm, and that you use a font size no smaller than Times 12.

Islet Development and Stem Cells in Diabetes

Helsinki, Finland, 3–5 April 2003

This international symposium is organized by Dr. Timo Otonkoski (timo.otonkoski@helsinki.fi) as a satellite of the 38th annual Scandinavian Society for the Study of Diabetes meeting. The program will cover transcription factors and growth factors regulating islet development, and the differentiation of beta cells from embryonic and adult stem cells.

For further information, please contact the symposium secretary:

Milla Mikkola
Biomedicum Helsinki, Room C504b
PO Box 63, Haartmaninkatu 8
FIN-00014 University of Helsinki
Finland
Fax: +358-9-19125664
E-mail: milla.mikkola@helsinki.fi

Fourth Molecular and Cellular Biology Meeting: APOPTOSIS 2003 – From signaling pathways to therapeutic tools

European Conference Center (Luxembourg), 29 January–1 February 2003

In 2003, the meeting will be organized again at the European Parliament Conference Center (Luxembourg) and we will focus on the most recent developments in the area of signal transduction and gene expression related to diseases and their therapy. For this meeting, we expect more than 750 molecular and cellular biologists.

– Speakers are invited to contribute to a regular number issue of Biochem Pharmacol (referenced by Medline, ISI-Current Contents);
– Speakers and authors of posters are invited to submit papers for a future volume of the Annals of the New York Acad Sci (Medline, ISI-Current Contents); abstracts and full text will also be published in the Annals Online (available 2002 through HighWire Press);

For further information please contact:

Marc DIEDERICH
RSL / Centre Universitaire de Luxembourg
162A avenue de la Faiencerie
L-1511 Luxembourg (Luxembourg)
Phone : + 352 46 66 44 434
Fax : + 352 46 66 44 438
E-mail: meeting@cu.lu
http://www.transduction-meeting.lu

Eighth WHO/IDF Cambridge Seminar on the Epidemiology and Public Health Aspects of Diabetes Mellitus

Clare College, Cambridge, UK, 6–13 April 2003

For further information please contact:

Dr. Nick Wareham
Institute of Public Health
University of Cambridge
Robinson Way
Cambridge CB2 2SR
United Kingdom
Fax: +44-223-330 330
E-mail: njw1004@medschl.cam.ac.uk
http://www.iph.cam.ac.uk/diabetes/

European Foundation for the Study of Diabetes (EFSD)

and

Servier

European Research Programme on Vascular Complications of Type 2 Diabetes

Request for Applications

The European Foundation for the Study of Diabetes and SERVIER announce up to Euro 1 Million in Additional Funds for Research in Europe into the Vascular Complications of Type 2 Diabetes

Background

The European Association for the Study of Diabetes (EASD) was founded in Montecatini, Italy, in 1965. In 1999, the Association created the *European Foundation for the Study of Diabetes (EFSD)***. The aims of EFSD are to encourage and support research in the field of diabetes, to rapidly diffuse acquired knowledge and to facilitate its application.**

SERVIER is a research-based pharmaceutical company with an established reputation in diabetes research, therapeutics and education. Present in 135 countries worldwide, the company is proud to maintain a number of tight long-term collaborations with key diabetes organisations.

Plan

The **EFSD and SERVIER** have established a new **European Research Programme on vascular complications of Type 2 Diabetes** to encourage quality new projects aimed at advancing current knowledge in this domain. The programme invites applications from not-for-profit organisations. Applications are particularly welcome for projects that aim to clarify the molecular mechanisms of such complications.

To achieve the goals and objectives of this Programme, EFSD and SERVIER invite applications by issuing this "Request for Applications" (RFA), which indicates joint funding as well as areas of research emphasis.

The EFSD/SERVIER Research Programme Grants are intended to stimulate and accelerate European research into the vascular complications of Type 2 diabetes.

In particular, the Programme seeks to support original, quality investigation into the molecular mechanisms of such complications.

Funding

Up to Euro 1 million will be made available over 3 years for research performed in Europe and its associated countries within the framework of the Programme. The grants will be distributed as follows:

2002 – Four grants, each of Euro 100,000
2003 – Three grants, each of Euro 100,000
2004 – Three grants, each of Euro 100,000

Mechanism of Support and Review

Research will be supported through the award of fixed sum grants, each of Euro 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 Euro 100,000 payable over one year in two instalments (May and November).

Four awards will be granted in the first year, and three in each of the second and third years. Applications for an EFSD / SERVIER Research Programme Grant are invited from single not-for-profit institutions or groups of affiliated institutions from Europe and associated countries. Applications will be subject to scientific review by a specialised ad hoc committee. Funding will require approval by a joint EFSD and SERVIER 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.

The budget of Research Grants for the purposes of this Programme is limited to **Euro 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 currency in the country where the work is to be performed) used for calculating the Euro budget must be mentioned under "Budget Justification". EFSD and SERVIER 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:

www.EuropeanDiabetesFoundation.org and
www.servier.com

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 receivable and will not be sent to reviewers.

Applications should be submitted by 1 February 2003 (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.

The 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 the vascular complications of Type 2 diabetes. Preference will be given to applications focusing on molecular mechanisms of such complications.

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 the 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 an EFSD / SERVIER Research Grant".

Competitive Renewal

Applications for renewal of a Research Programme 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

Announcements:	November	2001, **2002,** 2003
Application Deadlines:	1 February	2002, **2003,** 2004
Peer Review:	April	2002, **2003,** 2004
Anticipated Awards:	May	2002, **2003,** 2004

Inquiries concerning the Programme are encouraged and should be directed to:

Viktor Jörgens, M.D., Executive Director
European Foundation for the Study of Diabetes
Rheindorfer Weg 3
D-40591 Düsseldorf, Germany
Tel: +49-211-758469-0
Fax: +49-211-75846929
e-mail: Diabetes.Foundation@t-online.de

European Foundation for the Study of Diabetes (EFSD)

and

Johnson & Johnson

European Research Programme in Type 2 Diabetes

Request for Applications

ANNOUNCING Euro 700,000 IN ADDITIONAL FUNDS FOR RESEARCH IN EUROPE INTO TYPE 2 DIABETES

Background

The European Association for the Study of Diabetes (EASD) was founded in Montecatini, Italy, in 1965. In 1999, the Association created the ***European Foundation for the Study of Diabetes (EFSD)***. The aims of EFSD are to encourage and support research in the field of diabetes, to rapidly diffuse acquired knowledge and to facilitate its application.

Founded in 1886 in New Brunswick, New Jersey, ***Johnson & Johnson*** is the world's most comprehensive and broadly based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical and medical devices and diagnostics markets. Johnson & Johnson is committed to developing important new therapies that will address the needs of patients with diabetes.

Plan

In 2002 the **EFSD** and **Johnson & Johnson** established a new **European Research Programme in Type 2 Diabetes** to encourage quality new projects aimed at advancing current knowledge in this domain. The programme invites applications from not-for-profit organisations.

To achieve the goals and objectives of this Programme, EFSD and Johnson & Johnson invite applications by issuing this "Request for Applications" (RFA), which indicates joint funding as well as areas of research emphasis.

The EFSD / JOHNSON & JOHNSON Research Programme Awards are intended to stimulate and accelerate European research into Type 2 diabetes.

Funding

Up to Euro 700,000 were made available over 2 years for research in the framework of the Programme and performed in Europe and its associated countries. The awards were / will be distributed as follows:

2002 – Four grants, each of Euro 100,000
2003 – Three grants, each of Euro 100,000

Mechanism of Support and Review

Research will be supported through the award of fixed sum grants, each of Euro 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 Euro 100,000.

Four awards were granted in 2002, three will be granted in 2003. Applications for an EFSD/JOHNSON & JOHNSON Research Programme Award are invited from single not-for-profit institutions or groups of affiliated institutions from Europe and associated countries. Applications will be subject to scientific review by a specialised ad hoc committee. Funding will require approval by a joint EFSD and Johnson & Johnson Board convened for this purpose. It is anticipated that applications for the grant year 2003 will be received, reviewed and approved for funding by May 2003.

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 deadline for receipt of Research grant applications for funding in 2003 is **1 February 2003**.

The budget of Research grants for the purposes of this Programme is limited to **Euro 100,000**. 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 currency in the country where the work is to be performed) used for calculating the Euro budget must be mentioned under "Budget Justification". EFSD and Johnson & Johnson 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:

www.EuropeanDiabetesFoundation.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 receivable and will not be sent to reviewers.

*Applications should be submitted by **1 February 2003** (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 Type 2 diabetes.

Reporting Requirements

All Investigators funded by this Programme are required to submit a scientific report at the end of the funding period.

Competitive Renewal

Applications for renewal of a Research Programme Award funded in 2002 will be accepted only 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:	November 2002
Application Deadline:	February 1, 2003
Peer Review:	April 2003
Anticipated Award:	May 2003

Inquiries concerning the Programme are encouraged and should be directed to:

Viktor Jörgens, M.D., Executive Director
European Foundation for the Study of Diabetes
Rheindorfer Weg 3
D-40591 Düsseldorf, Germany
Tel: + 49-211-75 84 69-0
Fax: + 49-211-75 84 69 29
e-mail: Diabetes.Foundation@t-online.de

European Foundation for the Study of Diabetes

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

"Members' Award"

Dear Member,

If you attended our 38th Annual Meeting in Budapest you will have heard that our Foundation, ***EFSD***, has been very active in the two years since its creation, with **over 16 million Euro** committed to European diabetes research (for information, please see: http://www.EuropeanDiabetesFoundation.org/banner.html). This has been possible thanks to the most generous support of our partners from industry.

I am writing to you today to ask for your help. If our foundation is to continue to grow and flourish, in turn allowing us to support yet more high quality diabetes research in Europe, EASD members must become more involved. To this end, I should like to ask you to consider EFSD with a donation.

It is the intention of EFSD to use money raised from EASD members to **create a "Members' Award"** in support of a research grant or a fellowship in 2003. In addition to raising much needed money, this will send a strong signal to prospective corporate or major private donors that the membership supports actively their own Foundation.

Any contribution from you as an individual member, however small, will be welcome. You will find attached a form for you to FAX back to the Düsseldorf office, allowing you to pay your contribution by credit card. Information for bank transfer is also given. As a rough guide, EFSD is hoping to receive contributions in the 10-50 Euro range from junior/fellow members and of more than 50 Euro from senior/full members. Major donors (200 Euros and above) will be listed by name in the News pages of Diabetologia (unless they request not to be so named) along with the total sum raised from members.

This is your Foundation! Now is the time for you to help us grow and serve you better. My aim is to have **ALL members contribute**. Please do your best. This is a really important campaign for all of us.

Thank you in advance for your support.

Yours sincerely,

Philippe Halban
President

R 90

European Foundation for the Study of Diabetes

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

Please return to:

European Foundation for the Study of Diabetes (EFSD)
Rheindorfer Weg 3
D-40591 Düsseldorf
Germany

Fax: +49-211-75846929

Donation Form

First Name: _____

Surname: _____

Address: _____

Street: _____

City: _____

Country: _____

Tel: _____ Fax: _____

E-mail: _____

Amount in Euro: _____

By Credit Card: ☐ Mastercard / Eurocard / Access ☐ Visa

Card Number: _____ Expiry Date: _____

Date, Signature: _____

By bank transfer to the following account:

Account holder:	**EFSD**
Account Number:	**6 002 146 00**
Bank Code (BLZ):	**300 800 00**
Bank:	Dresdner Bank AG PF 10 11 07 D-40002 Düsseldorf Germany
Reference:	**“Members’ Award”**

Major donors of Euro 200 and above will be listed in the News Section of Diabetologia along with the total sum raised.

☐ I do **not** want my name to be listed in the News Section of *Diabetologia.*