EASD
EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES
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EASD

News Section
11/2005

EASD Young Scientists Training Course 2006

Supported by Eli Lilly

EASD will hold its Thirteenth Young Scientists Training Course in Perugia, Italy from 1 to 6 October 2006. By organising the Scientists Training Course, EASD hopes to attract new talent to diabetic research, in addition to fostering diabetes research in new centres throughout the world. The Selection Committee (Chair: D. Geremia Bolli; co-Chair: Dr. Claes Hellerström) will be looking for candidates under the age of 40 with some experience in research and who work in an academic environment. A letter of support from the head of the academic department will be considered an essential part of the application. The Course will be held in English and it is understood that all applicants will be able to communicate in this language. All participants will be required to attend the entire Course.

Venue and organisers

The thirteenth Course will be hosted by the University of Perugia, Italy (www.unipg.it) and organised by Professor Geremia B. Bolli and colleagues.

Format

A hands-on practical course will be provided for a maximum of 16 participants, who will rotate in groups through the laboratories. Each day will begin with an overview of the day's schedule followed by thematic blocks, which will consist of brief introductory lectures and practical training sessions. A discussion on the day's topics will conclude each day.

Focus

This course is designed to provide hands-on training in some of the basic aspects of clinical research in metabolism such insulin action, insulin secretion, glucose metabolism and turnover in vivo, glucose clamp, lipid metabolism and turnover, protein metabolism and turnover. Each topic will be introduced by a broad lecture, followed by practical experients in small groups. The modular concept of sessions will provide for intensive interaction with trainers and trainees. Overall the principal goal of this course is to provide detailed knowledge and skills in various methods, so that the participants should be able to set up those techniques at their home institutions.

Techniques

Methods for assessing insulin secretion and action in vivo
Euglycaemic, hyperglycaemic and hypoglycaemic glucose clamp in normals subjects and patients with diabetes mellitus
Feed-back insulin infusion in patients with diabetes mellitus
Indirect calorimetry
Glucose turnover in vivo
Lipid metabolism turnover
Protein metabolism turnover

Criteria and eligibility for acceptance to the Course

Any member of EASD who is still under the age of 40 on 1 October 2006 is eligible. The number of participants is strictly limited and the most suitable candidates will be selected by the sub-committee on the basis of the information provided in the application form.

Cost of the Course

Applicants will be asked to pay Euro 300 registration fee, as well as their transportation to and from Perugia, Italy. All other expenses, including board and lodging, will be covered by EASD funds, supported by Eli Lilly. Each applicant will be evaluated for eligibility and following individual requests, the registration fee may

be waived. In exceptional circumstances and following a formal application, EASD may, if necessary, also provide a travel grant.

Application procedures

Interested candidates should submit their application as a Word file attachment to secretariat@easd.org or by post (4 copies) to:
EASD Secretariat
Rheindorfer Weg 3
D-40591 Düsseldorf
Germany

The application must include the following:

1. A curriculum vitae giving date and place of birth, current professional address (with telephone and fax numbers and email address) and full details of education and academic and/or clinical career to date. There should be a complete list of publications and mention of any meetings or workshops attended.
2. A one-page letter of support from the Head of the applicant's current Department. Aside from attesting to the qualities of the candidate, this letter should clearly state how the department proposes to provide the necessary facilities and support to allow the candidate to continue in diabetes research.
3. A one-page description of the applicant's current research interests, including a brief explanation of how the applicant feels the Course will help in a future career in diabetes research.
4. EASD membership number

Applications not including these pages will not be considered.

Applications must be received at the EASD Secretariat in Düsseldorf before **15 April 2006** (regardless of postmark).

EASD Robert Turner Clinical Research Course

Oxford, UK, 20-24 March 2006

Supported by an educational grant from Johnson & Johnson Pharmaceutical Research and Development LLC.

Aims of the Course

The European Association for the Study of Diabetes is pleased to announce the 3rd Robert Turner Course on clinical research in diabetes for young physicians. The Course is intended to allow participants to become familiar with major theoretical and practical aspects of clinical research and will consist of lectures as well as interactive sessions. By organising this course, EASD hopes to attract young clinicians to clinical diabetes research, in addition to fostering diabetes research in new centres.

Venue

The 3rd EASD Robert Turner Course will be hosted by the Oxford Centre for Diabetes, Endocrinology and Metabolism.

Organiser

The Course is organised by Prof. David R. Matthews.

Format

The Course will be provided for a maximum of 20 participants. There will be an international faculty and the Course will cover many aspects of clinical research, including:

- Design of experiments
- Ethical review
- Grant applications
- Physiological studies
- Trials and trial theory
- Statistics and statistical review
- Good Clinical Practice
- Handling samples
- Handling data
- Science writing methodology

- Publication
- Pitfalls of research.

The Course will be held in English. It is understood that all applicants must be able to communicate in this language. All participants will be required to attend the entire Course. There will be no exception to this rule.

Criteria and eligibility for acceptance to the Course

The Course is open to all medical doctors who are EASD members under the age of 40 years. It is designed as an introduction to enter clinical diabetes research or for more experienced researchers from other fields who wish to obtain some basic training in this area.

Cost of the Course

Participants will be asked to pay **Euro 240** registration fee as well as their transportation to and from Oxford. All other expenses including board and lodging will be covered by EASD funds, supported by Johnson & Johnson. It is not intended that the registration fee prevent any individual from attending and those with limited funds at their disposal may request EASD to waive this fee on the understanding that this will be accorded only to those considered truly in need and without financial support from their home institution. In exceptional circumstances and following a formal application, EASD may, if necessary, also provide a travel grant.

Application procedures

Interested candidates should submit two (2) copies of their application to:

EASD Secretariat
Rheindorfer Weg 3
D-40591 Düsseldorf
Germany

The application must include the following:

I. A curriculum vitae giving age, place of birth, current professional address (with fax number and email address) and full details of education and academic and/or clinical career to date. There should be a complete list of publications and mention of any meetings or workshops attended.
II. A **one-page** letter of support from the Head of the applicant's current Department attesting to the qualities of the candidate. This letter should also describe the department's activities in clinical research.
III. A **one-page** description of the applicant's current research interests, including a brief explanation of how the applicant feels the Course will help in a future career in diabetes research.
IV. EASD membership number

Applications not including these pages will not be viewed favourably.

Applications must be received at the EASD Secretariat in Düsseldorf before **15 January 2006** (regardless of postmark).

EASD has nominated a sub-committee to review applications for the EASD Robert Turner Course. When selecting participants, the members of the Robert Turner Course Sub-committee will be looking for candidates with some experience in clinical research and who work in an academic environment favourable to clinical diabetes research. A letter of support from the head of the academic department will be considered as an essential part of the application.

The Rising Star Symposium – Request for Applications

The "Rising Star Symposium" aims to identify promising and innovative young researchers who are developing their research activities in Europe. Selected candidates will have the opportunity to present an overview of their past and ongoing research activities during a multidisciplinary research symposium at the EASD Annual Meeting. Four candidates will be selected every year, two in basic research and two in clinical research. Selected candidates will be invited by EASD to present a 30 min (25 min lecture + 5 min question time) lecture, and will receive a commemorative diploma. EASD will cover travel expenses, hotel and registration costs for the selected scientists.

The Candidate:

Candidates for the Rising Star Symposium must be paid-up members of EASD and have a PhD, MD or equivalent degree. The candidate must be under the age of 35 (for basic research) or 37 years (for clinical research) on 1 January 2006. Preference will be given to individuals who normally reside in Europe and who have consistently pursued a well-defined, logical and innovative research line, leading to several publications in high impact peer-reviewed journals.

The application to deliver a lecture at the "The Rising Star Symposium" should include:

a. A two-page description of the applicant's research line, including supporting references to his/her publications, where appropriate.
b. Full name, address, date of birth and brief curriculum vitae of the applicant (two pages maximum), plus complete list of publications.
c. Proof of current EASD Membership.
d. Date and nature of the present appointment held by applicant.
e. Letter of recommendation by the Head of the Department.
f. Clear statement on whether the candidate wishes to apply in **basic** or **clinical** research (the basic and clinical tracks are evaluated separately)

Applications should be sent as an attached Word document to:

secretariat@easd.org
to arrive not later than **20 February 2006**. Selection of the 4 speakers will be made by the EASD Scientific Programme Committee. Applicants will be informed on the outcome of their application in May 2006.

10th EASD/JDRF Oxford Workshop What is a beta-cell and can we improve it?

Keble College, 5-8 August 2005

Frans Schuit, Philippe Halban and Christopher Rhodes

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 (JDRF). The aim of these workshops is to gather together a select group of researchers for a focused discussion and exchange of ideas on a particular area of research relevant to type 1 diabetes and its complications. These meetings are informal with an emphasis on audience participation in the discussion of topics presented. The aim is to chart the future course of research in the chosen area with suggestions as to how to overcome potential roadblocks. These meetings are special in that postdoctoral research fellows accompany their more senior investigators to the meeting, present their work along with their mentors and participate in the discussions. Leading scientists from outside of the field of diabetes research, yet who are specialists in some of the topics of the meeting, are also invited, so as to give an interesting outside perspective to the workshop.

The 10th EASD/JDRF Oxford Workshop, '*What is a Beta-Cell and can we improve it?*' visited contemporary thinking on the beta cell and its central relevance to diabetes research. The current knowledge about beta-cell function and its primary task to produce, store and secrete insulin was examined, with a view to highlighting important gaps in this knowledge to better guide future research. Emerging new technologies were considered to see how these might be applied to help fill these gaps. As a theme, the beta-cell was considered an insulin producing factory[1] where its genetically predisposed business plan, molecular assembly lines and unique ability to respond rapidly to the metabolic load were scrutinized. Stresses and demands on the beta-cell factory were considered at the molecular level, which, if left unattended, lead to its ultimate destruction. In this light an assessment of whether the beta-cell factory can be repaired or protected was made. Questions as to whether the endogenous beta-cell population can be regenerated or resurrected *in vivo* to alleviate diabetes were discussed. It was also considered if renewable sources of surrogate beta-cells could be obtained *in vitro* for an effective beta-cell replacement therapy to treat type 1 diabetes, and, if so, via what means. Finally, if insulin-producing cells can eventually be produced from alternative sources the possible guidelines and practicalities as how these might be evaluated as really being *bone fide* beta-cells, prior to any transplantation therapy, were deliberated.

This report attempts to capture the flavour of the meeting, accenting its concluding, forward-looking approach to these issues, and areas of research that emerged from the discussions to which more attention should be paid. Consensus opinion and recommendations of the workshop are also emphasized in bullet points.

WHAT IS A BETA-CELL?

The workshop agreed that, despite the spectacular progress over the past decades, more research is required to fully understand how beta-cells function during normal life, as well as how far they can be pushed before they are stressed in the pre-diabetic state. In an introductory lecture, Dr. Franz Matschinsky set the overall inquisitive tone of the meeting by pointing out that the beta-cell appears to be constantly 'living on the edge', continually sensing the metabolic milieu and secreting (or not) insulin correspondingly in a rapid and efficient manner. He reiterated that the beta-cell has a unique inventory of metabolic enzymes compared to other cell-types (including expression of a beta-cell specific isoform of glucokinase, unusually high expression of pyruvate carboxylase and negligible lactate dehydrogenase activity as others have shown), that is geared for generating secondary signals to regulate insulin secretion as well as energy production. It was suggested that the beta-cell's uncommon metabolic makeup might well contribute to its apparent susceptibility to metabolic stresses. Beta-cell metabolism also generates distinct secondary signals to control other parameters, such as proinsulin synthesis at the translational level, but unlike nutrient-regulated insulin secretion these metabolic stimulus-response coupling mechanisms are relatively undefined. Dr. Matschinsky had an important message for the group and larger beta-cell research community: "don't just look at things; measure them!". Speaking from his perspective as an analytical biochemist, he thus stressed the absolute need for quantification in order to understand biological

[1]This concept was first introduced by Lelio Orci over twenty years ago - 'Orci L (1985) The insulin factory: a tour of the plant surroundings and a visit to the assembly line. Diabetologia 28:528-546.

processes. He also lamented the general tendency for contemporary scientists (he included himself in this category with his lifetime interest in glucokinase) to "dance on a pinhead", limiting their studies to a minute area of expertise rather than adopting a more integrative approach better suited to the understanding of complex biological circuits. This point was well taken and discussion throughout the meeting often focused on trying to escape from pinheads. Dr. Matschinsky closed his talk by reminding participants that the beta-cell, although certainly special in many regards, shared common properties with other glucose-sensing cells, presenting a "Ptolemaic cellularscope" of the glucose-sensing cellular universe.

SESSION-1 *Visiting the assembly lines: a tour of the production process*: Michael German, Francis Lynn, Christopher Rhodes, Barton Wicksteed, Michele Solimena, Mirko Trajkovski, Guy Rutter, Laura Parton, David Ron, Seeichi Oyadomari: This session looked into mechanisms of insulin production, transit of newly synthesized (pro)insulin through the beta-cell secretory pathway to its eventual storage in secretory granules or secretion via secretory granule exocytosis. Current concepts on the regulation of human insulin gene expression were presented with some intriguing insight. Although many of the key transcription factors that associate with regulatory cis-elements in the insulin gene promoter have been identified, there was still much to learn particularly in the upstream regions of the insulin promoter. It was noted that the so-called 'Z-element' of the human insulin promoter (a region at -292 to -243 of the human insulin promoter) has surprisingly received little attention, especially since it has a major influence over control of insulin gene transcription. After 15 years, it remains unknown what transcription factors specifically associate to this Z-element. Further investigation of this region and others further upstream in the human insulin promoter could yield some novel important transcription factors that contribute to controlling not only insulin gene transcription but also beta-cell differentiation. The specific nature of glucose-induced translational regulation of proinsulin synthesis in beta-cells was also looked into and the importance of discrete elements in the untranslated regions of preproinsulin mRNA that encode this regulation emphasized. It was pointed out that this specific translational control of proinsulin synthesis was only found in primary islet beta-cells, not in the transformed beta-cell lines, and thus is a useful functional marker of a fully differentiated beta-cell. A longer-term mechanism for regulating proinsulin synthesis is via stabilization of the preproinsulin mRNA, which might occur (at least in part) via the polypyrimidine tract binding protein (PTB). Furthermore, Ca2+-dependent proteolysis of the secretory granule membrane protein ICA-512 at the plasma membrane may be implicated in this process, indicating a possible regulatory mechanism whereby secretory granules lost during the process of exocytosis can be replenished via a coordinated upregulation of secretory granule biogenesis. The 'kiss and run' mechanics of insulin exocytosis was looked at in a little more detail and it was emphasized that transient formation of a fusion pore between secretory granules and the plasma membrane is the predominant way in which insulin is released from the beta-cell. Exposure of beta-cells to high glucose for prolonged periods of time may influence these transient events and it will be interesting to understand better the difference in the mechanics of exocytosis of newly formed or older, stored granules. Exocytosis is perturbed in animal models of diabetes and over-expression of SREBP1c (for example in the ZDF fa/fa rat) may underlie this in part, with discrete changes in the levels of expression of key genes. The question was also posed as to what happens when too much demand is placed on the beta-cell to produce insulin. In particular, the folding of newly synthesized (pre)proinsulin in the endoplasmic reticulum (ER) and the cellular stress that is caused by accumulation of unfolded molecules was scrutinized. Like any cell type, the beta-cell has to find a continuous equilibrium between maintenance of a sufficient protein synthetic rate as this renews secreted or degraded molecules and a sufficient chaperone reserve for proper folding. Failure to find and maintain this equilibrium may cause an unfolded protein response (UPR) and, when this is uncompensated, pathological ER-stress. The signalling mechanisms that induce the physiological UPR and trigger ER-stress were examined. In particular, how these might lead to beta-cell apoptosis was discussed in the context of the pathogenesis of diabetes. It was pointed out that transgenic knockout mice deficient in certain elements of ER-stress response (e.g. PERK, p58 PERK-kinase, and eIF2alpha phosphorylation) gain diabetes because of preferential beta-cell loss or dysfunction. The molecular circuitry underlying ER-stress regulation of protein synthesis is currently under intense scrutiny. There seems to be a physiological balance between protein synthesis and ER-chaperone reserve in healthy cells that can be perturbed in disease states including obesity. Again, this raised the unanswered question as to why beta-cells have a greater vulnerability to metabolic related stresses than other cell types. Despite the recent focus on ER-stress in the beta-cell as a possibly important pro-apoptotic force, surprisingly there is no evidence for this pathway being relevant to decreased beta-cell mass in human diabetes. Furthermore, if this is indeed an important mechanism, as was generally agreed, what tilts the balance in favour of ER-stress and beta-cell death as

an individual moves from hyperinsulinemia and high BMI to clinically manifest diabetes and hyperglycemia? To what extent can compensatory beta-cell growth limit ER-stress by preventing increased insulin demand on individual cells?

In the overall discussion, the question of whether all beta-cells are equal was raised. Are some beta-cells more susceptible to stress than others because they are in a different metabolic state? It was generally felt that beta-cell heterogeneity within an islet should always be considered based on data from older studies on isolated rat islet cells. However, it was noted that such heterogeneity has yet to be further studied in human islets let alone in their natural *in vivo* setting. It was pointed out that there was also secretory granule heterogeneity within a beta-cell. There may be preferential selection of newly formed secretory granules to undergo exocytosis but the mechanism behind this remains unknown, and it has yet to be documented unequivocally in beta-cells using modern granule tracking technology. Indeed, the only experiments suggesting preferential insulin exocytosis of new granules are based on pulse-chase experiments performed decades ago. Also, relatively few secretory granules undergo exocytosis so that their eventual intracellular degradation is an underappreciated mechanism that keeps beta-cell stores of insulin at optimal levels. The means by which senior secretory granules are retired at the molecular level is not understood, and there was felt to be the need to understand the entire lifecycle of individual granules in much greater detail.

SESSION-2 *The packaging and dispatch department – control of insulin secretion*: Marc Prentki, Erik Joly, Daniel Drucker, Laurie Baggio, Nicolai Doliba, Frances Ashcroft, Helen Freeman, Tom Martin, Declan James: Here the stimulus-coupling mechanism for regulation of insulin secretion by nutrients and incretins was considered. It was pointed out that fatty acids or some related lipid-moiety are essential for normal glucose-regulated insulin secretion, and in this regard the importance of intracellular lipases in the beta-cell was emphasized. The concept of glucose metabolism via anaplerosis and lipid moieties working in consort to normally control insulin secretion was highlighted. But then, it was also indicated that one can get too much of a good thing. Chronically elevated glucose and lipid levels can lead to beta-cell death – a concept referred to as 'glucolipotoxicity'. The mechanism by which this occurs at the molecular level requires more research, but could involve oxidative-, ER-, and other metabolic stress responses. And, once again, the issue of the unusual susceptibility of the beta-cell to such stress was underlined. The acute potentiating effect of the incretins (GLP-1 and GIP) on glucose-induced insulin secretion via a mechanism involving the cAMP signalling pathway, was also addressed. In the long-term, GLP-1 also promotes beta-cell growth and survival. It was noted that long-acting GLP-1 analogues and inhibitors of dipeptidyl peptidase IV (the enzyme that rapidly degrades GLP-1 and GIP *in vivo*; DPP-IV) are now being used in clinical trials to treat type 2 diabetes, and although they alleviate some symptoms they do not cure diabetes and whether or not there is any sustained impact of long-term treatment remains to be documented. Model organisms such as mice lacking expression of GLP-1 receptors, GIP-receptors or both receptors (DIRKO mice) were shown to be very useful in this context. It will be interesting to follow the clinical trials using DDP-IV inhibitors given the resulting different dynamics and levels of active GLP-1 compared with long-acting GLP-1 analogues. These inhibitors will impact GIP levels as well as GLP-1, possibly with additional effects that are expected to be for the most part beneficial even if there is the risk that GIP, but not GLP-1, may increase insulin resistance and adiposity with altered fat distribution. Also, the effects of long-acting GLP-1 analogues are not all directed at the beta-cell. GLP-1 has effects on the CNS inducing satiety, slows down gastric emptying and acts directly on the so called 'portal glucose sensor' in the liver. The CNS and portal effects may well have secondary influence on beta-cell function, and thus neuronal connections to the endocrine pancreas that control insulin secretion should be studied in more detail. In this regard, the important role that acetylcholine plays to potentiate glucose-induced insulin secretion, even in the absence of a key component in the metabolic stimulus secretion-coupling pathway, the K_{ATP}-channel, was underlined during the meeting. There was a focus on the K_{ATP}-channel as the major controller of beta-cell plasma membrane potential and thus the key component of the metabolic-Ca^{2+} signalling pathway controlling insulin secretion. It was stressed that absolute concentrations of ATP (to shut the channel) and of ADP (to open it) were more important than their ratio, even if the ADP-opening mechanism was not well understood. It was emphasized that so-called K_{ATP}-channel independent pathways that control insulin secretion are somewhat artificial in that cytosolic $[Ca^{2+}]_i$ must be elevated (and thus bypassing the need for the K_{ATP}-channel) for them to become apparent. Nonetheless, K_{ATP}-channel independent pathways may have physiological relevance in amplifying the K_{ATP}-channel dependent induced insulin secretion, particularly in the second phase of the biphasic insulin secretory response to nutrients. Studies on SUR1-/- beta-cells are informative in this regard but it was emphasized that more attention should be paid to regulation of alpha-cell secretion and the cross-talk between beta- and alpha-cells. In addition, several human

polymorphisms in the K_{ATP}-channel subunits, SUR1 and Kir6.2, were examined that have various degrees of severity of impact on regulated insulin secretion. This further emphasized the important role that the KATP-channel plays in control of insulin secretion with the caution from its champions that they were guilty of dancing on a small, albeit critical, pinhead!

The basic 'nuts and bolts' of the large dense-core exocytotic machinery that is likely to be required for regulated insulin exocytosis in beta-cells was examined. This included the so-called SNARE proteins (including syntaxins, synaptobrevins and SNAP-25), synaptotagmins (probably V, VII and IX isoforms as found in other neuroendocrine cell types), phosphatidylinositol 4,5-bisphosphate (PIP2), CAPS-1 (Ca^{2+}-dependent activator protein for secretion), Ca^{2+} and ATP. Remarkably, these components alone are all that is needed to replicate a regulated membrane fusion event in an *in vitro* assay. However, *in vivo*, auxiliary exocytotic proteins are likely required to fine-tune the final steps in the mechanism of regulated insulin exocytosis. It was felt that more data was needed on the compartmentalization of all components of the exocytotic machinery, to include a better molecular definition of so-called "active zones" of exocytosis that appear to reside in non-conventional lipid rafts. Finally, with all this focus on the intimate molecular details of exocytosis it was discouraging to note that we do not yet understand what "basal" insulin secretion actually means. Is this the reflection of random exocytotic events in an unstimulated cell or a truly regulated event important for fine-tuning fasting insulinemia? Is basal secretion, whatever the mechanism, actually increased in Type 2 diabetes or is this the result of an altered set-point for glucose regulation of insulin secretion?

SESSION-3 *Obtaining the blueprint of the plant*: Frans Schuit, Katleen Lemaire, Lloyd Fricker, Christopher Newgard, Mette Jensen, Markus Stoffel, Pinar Akpinar, Mark Montminy, Robert Screaton: The insulin producing beta-cell factory was looked at from two different angles in this session. First, the application of current screening technologies was examined with a view to exploring the feasibility of conveniently gaining the beta-cell's genomic, proteomic and/or metabolomic profile under varying conditions. Second, certain transcription factor/signalling networks that might influence the beta-cell genomic profile were presented. The specialized function of the beta-cell is clearly influenced by the regulated expression of a set of specialized genes. As the products of such genes make a beta-cell what it is, it is informative to identify them in a systematic integrated approach. New technologies like mRNA expression profiling allow investigators to get off their pinheads in a manner that was unthinkable a few years ago, but it creates at the same time a problem of interpretation of huge data sets. Microarray experiments are beginning to offer a first glimpse into the nature and scope of the control of islet beta-cell gene expression under varying conditions and in animal models of diabetes. For instance, overnight fasting in mice affects the expression level of hundreds of transcripts, many of which are preferentially or specifically expressed in islets. On the contrary, repression of a physiologically "forbidden" gene set in the fed state is relaxed to some extent in the fasted state. The signalling mechanisms underlying this phenomenon of fasting-induced islet cell dedifferentiation are still largely unknown and require further insight. Here, the application of bioinformatics and additional biological models that explore the networks of regulators, detectors and transducers to coordinate such adaptation in gene expression are valuable. For example, mice lacking both incretin receptors (DIRKO mice) are used to assess the contribution of GLP-1 and GIP receptors in the transcriptional adaptation following food intake. In addition, simplified model organisms such as yeast are useful to examine certain details of the molecular mechanism for nutrient sensing in beta-cells, where the power of yeast genetics is combined with data mining from a complex biological system.

The power of using proteomics, and the more recent field of "peptidomics" with its focus on smaller peptides of particular interest in neuroendocrine cells, was also presented using a liquid chromatography tandem mass spectrometry (LC/MS/MS) approach, which can also yield a wealth of information. Various protocols were examined to quantitatively analyze neuropeptides, where ~ 100 peptides can be examined in a single sample. Not only can this approach quantify changes in peptide levels between samples, but it has also allowed for discovery of novel neuropeptides. Moreover, a proteomics approach can also pick up unrealized and novel post-translational modifications to peptides that may have biological significance. There are >50 individual peptides found in an insulin secretory granule and application of this approach to beta-cells has the intriguing possibility of finding novel peptides that are co-secreted with insulin. There is the real hope that stable isotope methods will allow for detailed analysis of the rate of peptide synthesis and turnover.

The rapidly developing technology of metabolomics was also presented using the example of nuclear magnetic resonance (NMR) and MS analysis that has the current capability of measuring in the order of 50 metabolites in a relatively small sample size, an important consideration for islet studies. This can be applied to beta-cells to examine links between metabolic signalling and certain beta-cell functional parameters,

including regulation of insulin secretion. It was shown that manipulation of the expression of certain key metabolic enzymes in beta-cells can have consequences for glucose-induced insulin secretion and that changes in key metabolic intermediate levels, such as pyruvate and the NAD(P)H:NAD(P)$^+$ ratio, are important for this control. This illustrated how metabolomic and genomic technologies might synergize to gain a more detailed insight into nutrient control of insulin secretion. Other techniques (i.e. LS/MS) will allow for "unbiased" analysis of a far greater number of metabolites per sample (at least 103) but without internal standards these approaches will be more useful for comparison of two samples followed by identification of any product present at different levels in the two. NMR-based analysis will also allow for metabolic flux measurements and just as for proteomics techniques mentioned above the dynamics of biological pathways are ultimately more informative and relevant than static "snapshots".

In the discussion of these technologies and their application to beta-cells, some current strengths and weaknesses of a research strategy involving mRNA expression arrays were discussed. It was suggested by some that one often got little return from enormous investment. When trying to interpret the data, involving several investigators with non-overlapping expertise could increase this return. Use of cell lines as well as inbred mouse strains was discussed with the general sentiment that compromises need to be made to match biological complexity to the power of experimental design and interpretation. Because of the wealth of experimental data generated with these novel technologies the current challenge is at the level of deciding what molecules/pathways to explore in-depth first. Despite such drawbacks, it was acknowledged that the "age of -omics" has already transformed modern biology even if it has not yet had an equivalently great impact in the beta-cell field. Interestingly, for proteomic/peptidomic approaches large changes in peptide levels are difficult to quantify, and some peptides do not 'fly' appropriately for a reasonable MS analysis and can be missed. The metabolomic approach can be hindered by the 'old fashioned' chemical extraction of the cells/tissue that is required to isolate the metabolites prior to NMR or MS analysis. However, all these disadvantages were considered surmountable as the technologies develop. Certainly, the consensus was that the pros far outweighed the cons of these techniques. Of course these approaches can produce massive amounts of data that require bioinformatics analyses to be applied but this was not considered a disadvantage; as one attendee put it "this should be viewed as being very interesting and not at all scary". At the least, Dr. Matschinsky's earlier recommendation not to just look but to measure is respected to the letter by these new technologies, even if one must then be careful not to take this to the extreme of measuring without looking at all! There was general agreement that these techniques were not useful as "stand alone" technology but would benefit from close integration with complementary approaches in addition to informatics including robotics, multiplex hormone assays and measurement of physiological variables such as body composition, indirect calorimetry, glucose tolerance, islet morphology and function of isolated beta-cells.

The importance of transcription factor signalling networks that likely influence the genomic, proteomic and/or metabolic profile of the beta-cells was examined. It has become apparent from recent exciting studies that close examination of islet gene expression in transgenic mice lacking key transcription factors may lead to identification of downstream genes critical for beta-cell function or survival and possibly even to surrogate markers of beta-cell functional mass. As an example, new insight was presented into the regulation by the cAMP response element binding protein (CREB) transcription factor of the expression of certain beta-cell genes which in turn promote beta-cell survival. Phosphorylation of CREB by PKA (perhaps activated by GLP-1) increases CREB transcriptional activity. But CREB has to be translocated to the nucleus to drive gene transcription, which is mediated by Ca^{2+}-dependent dephosphorylation of TORC (transducers of regulated CREB) by calcineurin. This indicates how cAMP and Ca^{2+} signalling mechanisms may synergize to specifically drive expression of a group of beta-cell genes.

Other emerging mechanisms that specifically control protein expression in beta-cells were considered, including that by microRNAs. This led to a more general discussion on the validity of transformed cell lines as a model of primary cell function. There are certain situations where transformed cells may be quite misleading such as the enormous differences in microRNA levels in primary hepatocytes vs. HepG2 cells. When it comes to the beta-cell, the gold standard is obviously a pure population of sorted primary cells, with "next best" being isolated islets with their mixed population of cells (but possibly representing a more physiological environment for beta-cell function than sorted cells) and certain well-differentiated cell lines. The discussion was extended to mouse models. Clearly, such small animal studies offer fantastic opportunities for studying select genes or as models of human disease states. The danger is that only the "best" model is selected for study: in other words the one that works as we should wish. This may bias such studies in ways as yet not understood and too often overlooked.

SESSION-4 *Delivery and export: maintaining a balanced functional beta-cell mass*: Charles Burant, Joseph Dosch, Jake Kushner, Marc Donath, Jan Ehses, Steven Kahn, Rebecca Hull: Pancreatic beta-cell mass is maintained as a balance between beta-cell growth and death. Beta-cell neogenesis, the apparent emergence of new beta-cells from the ductal epithelium, is a contributing mechanism to overall beta-cell growth. Although beta-cell neogenesis likely contributes significantly to net beta-cell growth in humans, this has not been demonstrated directly and it has been controversial in mice where beta-cell replication might predominate. However, evidence was presented at the workshop that beta-cell neogenesis does indeed take place in mice and is probably mediated via activation of Smad signalling pathways in ductal precursor cells. If this can be reproduced in human ductal epithelial cells *in vitro* then a renewable source of beta-cells with potential for cell replacement therapy could be envisaged. It is considered that beta-cell replication plays a very important role neonatally and during the following early stages of mammalian life to provide sufficient beta-cell mass, but in adult life beta-cell turnover may be much lower. Indeed, it was suggested that beta-cell turnover in the adult might be even lower than previously appreciated, aside perhaps from special situations such as pregnancy. The experimental basis for this postulate was however the subject of intense discussion since it depended on long-term administration to mice of BrdU that following uptake into dividing cells may block cell replication and/or induce apoptosis. Notwithstanding, if the rate of beta-cell apoptosis outweighs that of beta-cell growth, then beta-cell mass is reduced and eventually reaches a point where it can no longer compensate for the metabolic load and diabetes ensues. Although aspects of the beta-cell killing mechanisms might be distinct, this general concept applies to both type 1 and type 2 diabetes. Cytokine-mediated killing of beta-cells is well described in the pathogenesis of type 1 diabetes, but there is a growing consensus discussed at this meeting that cytokine-induced beta-cell apoptosis is also a significant factor in the pathogenesis of type 2 diabetes. Chronic hyperglycemia can induce local synthesis of certain cytokines (e.g. interleukins-1ß, -6 and –8) within pancreatic islets, perhaps both from beta-cells themselves and increased presence of macrophages. In addition, chronic exposure to fatty acids also increased beta-cell production of interleukins-6 and –8, which could contribute to fatty acid induced beta-cell apoptosis. As such, inflammatory stress can be added to oxidative-stress, metabolic-stress and ER-stress, among others (see below), as contributory stress-mechanisms which promote beta-cell apoptosis in the pathogenesis of type 2 diabetes.

Insulin secretory dysfunction also contributes to the pathogenesis of human type 2 diabetes, as well as loss of beta-cell mass, especially in the loss of 'first phase' glucose-induced insulin secretion. This is an important clinical consideration. The relationship between the acute insulin secretory response and insulin sensitivity (i.e. the degree of insulin resistance) is important and consequently, when considering beta-cell replacement therapy, one must always consider insulin output vs. demand and the need for beta-cells to adapt to changes in demand with changing lifestyle or aging.

CAN WE IMPROVE THE BETA-CELL?

In the latter part of the workshop the focus on whether we need to improve the beta-cell, perhaps by protecting it in making it less susceptible to various stresses and subsequent apoptosis. Also, current progress in obtaining plentiful numbers suitable for cell replacement therapy was explored, including generating beta-cells from alternative sources as well as expanding beta-cells *in vitro*.

SESSION-5 *Can we improve the business plan and product?*: Matthias Hebrok, Patrick Heiser, Shimon Efrat, Limor Yaholom, Bruce Verchere, Lucy Marzban: Many different strategies for generating large numbers of surrogate beta-cells in vitro for cell replacement therapy of diabetes are currently envisaged. There was healthy debate as to whether defining and then reproducing the normal steps in the developing endocrine pancreas was the only way to achieve this or whether alternative routes including trans-differentiation of adult tissue would be equally successful. Clearly, the endpoint must be well defined and this is ultimately more important than the means, bringing the group back to the central question: "What is a beta-cell and can we improve it?".

Many of the steps leading down the developmental pathway to beta-cells have been characterized and the key transcription factors identified. The current challenge is to determine the precise spatial, temporal and quantitative features of these often complex cascades of interacting factors. The ß-catenin – hedgehog – Wnt closed-loop cascade is a good example. Transgenic mice with selective knock-out of key genes in any given pathway or of "master-switch" genes will be critical for these studies. However, it was stressed that the penetrance of the same trans-gene in different mouse lines can be a confounding factor. For example, of the two Pdx1-Cre mice commonly used for crossing with mice carrying a Floxed gene of interest, one leads to knockout of the target gene in all cells having expressed Pdx1 whereas the other only seems to target ~30% of them.

Regardless of the roadmap followed for creating surrogate beta-cells, a major obstacle will be the inverse relationship between proliferative capacity and differ-

entiated status. Thus, the challenge is to allow cells to proliferate in a largely undifferentiated state and to then induce differentiation. Recent work using adult human liver is promising in this regard with insulin-producing cells obtained by differentiation of a more primitive cell type after many rounds of replication. This primitive cell type will have to be identified (by lineage tracing) before its identity is known. Only then will it be possible to determine whether hepatocytes have truly been transdifferentiated into beta-cells or if the liver contains a reserve of progenitor/stem cells that one can marshal in vitro after extensive replication to produce a beta-cell. Again, the end-product is more interesting than the pedigree and general discussion focused on the characterization of insulin-producing cells intended for implantation in man: what are the minimum requirements that must be met for such cells to obtain ratification as a true "beta-cell surrogate" (see below under "Recommendations")? Clearly, this "gold-standard" will be the starting point when devising means to improve the beta-cell. Improving this cell type with regard to its function is not considered an option. Indeed, the challenge will be to reproduce all critical aspects of normal regulation of insulin secretion in a surrogate beta-cell. However, it may be possible to improve survival by creating a more robust surrogate with increased resistance towards metabolic stress or inflammation. Although not relevant in rodents due to differences in primary sequence structure, in humans the disposition of islet amyloid caused by fibril formation from polymeric units of islet-associated amyloid polypeptide (IAPP) may augment beta-cell apoptosis, further exasperating loss of beta-cell mass in type 2 diabetes. The mechanism of amyloid formation in type 2 diabetes is unclear, but if prevented, might delay the onset of the disease. Recent studies suggest that it may be possible to use pharmacological and/or molecular tools to limit amyloid deposition by human beta-cells or to prevent the toxicity of already formed islet fibrils. This would be an additional way to increase survival of the surrogate cell.

EMERGING CONSENSUS/RECOMMENDATIONS FROM THE WORKSHOP

In keeping with the spirit of the EASD/JDRF Oxford Workshops, the final session was devoted to wide-ranging general discussion and formulation of specific recommendations for the advancement of the field. Which areas are ripe for immediate research? Where are the gaps in our understanding of key pathways? Are our research methods and models adequate? Are we capitalizing on advanced contemporary technology? Is there a need for core facilities? How should we test beta-cell function and should this be centralized? The major recommendations were:

Technology and experimental tools:

1. *Optimising (the use of) mRNA, proteome and metabolite profiles*: Microarrays, proteome and metabolome readouts can generate enormous amounts of data, the interpretation of which is an unprecedented challenge in biological research. At the dawn of the "age of omics" the need is felt increasingly to develop systems and tools that will help the interpretation of increasingly larger data sets. However, such data sets will be of value to the whole diabetes research community. Ideally, it would be of great value to establish a centralized and public database that integrates all data sets that are relevant for beta-cell research. Comparison of beta-cell gene changes between data sets could be an excellent filter to identify consistent and relevant gene changes.
2. *Mouse models and mice as models*:

    i. The genetic background of transgenic mouse models is important. In terms of extrapolation to the human situation it is better to be dirty (i.e. a mixed background) than clean (i.e. inbred strains), for a phenotype to stand out
    ii. Mice are not men and are not a good model in particular for studies on insulin action in vivo since they have a major insulin-independent component of glucose clearance.

Research focus areas and approaches; unanswered questions:

What more do we need to know about the beta-cell, what methods will be most useful, how can we make new and possibly better beta-cells?

1. The upstream region of the human insulin promoter is 'untapped', and may yield some novel important transcription factors key to insulin gene transcription and beta-cell development/differentiation.
2. Currently, there is no clear leading approach to generate/expand beta-cells from alternate sources for an ultimate cell replacement therapy (embryonic or adult stem cells, transdifferentiation, beta-cell replication etc.). All need to be attempted at this moment in time, with appropriate quality control, until one can be shown clearly superior for focused effort and investment.

3. The current roadblock along the developmental pathway to generating new beta-cells is the transition from embryonic stem cell to definitive endoderm. Once you "hit the pancreas" the roadmap is quite well defined and should be possible to follow.
4. It is clear that there are similarities in the pathogenesis of type 1 and type 2 diabetes, in that they are both diseases of insulin/beta-cell deficiencies possibly with inflammation as a common underlying trigger or cause. Protecting the beta-cell mass, by whatever means, could serve to delay or even prevent the onset of either disease.
5. There should be more focus on residual beta-cells in type 1 diabetes. What is their growth potential? Are they normally differentiated? If not, can their function be restored?
6. Can an impaired 'type 2 diabetes beta-cell' be repaired? Should "restoration" of beta-cell function be the target rather than "improvement"? There is an urgent need for better access to islets from cadaver organ donors with type 2 diabetes patients.
7. Lessons from non-diabetic obesity may help unravel mechanisms of beta-cell growth.
8. For beta-cell replacement therapy, it may be critical to transiently protect the beta-cell during the trauma of transplantation. Some gene therapy approaches could be used.
9. What should we be aiming to implant? A pure population of beta-cells however perfect may not be adequate. It might be better to re-create and implant whole islets. More attention should be paid to the islet as a micro-organ and also to alpha-cell function and survival.
10. Research in the field should be allowed to proceed in stages. Each stage is important even if it does not create the desired final product. Making an insulin-producing cell from, say, a liver cell is thus an important stage although the surrogate cell is not yet in a terminal differentiated state.

Quality control of surrogate beta-cells:

How perfect does a surrogate beta-cell have to be? How can we best determine its differentiated status?

1. *Differentiated status*: There is a real need for clear markers of beta-cell differentiation. Compilation of a master list of such markers would help us define better beta-cell differentiation. Quantification of expression of select genes at both the mRNA and protein level, the activity of specified enzymes/pathways and perhaps the concentration of metabolites will then be critical to obtain a true beta-cell "signature". Morphology and specifically electron microscopy may provide additional important documentation of differentiated status.
2. *Functional characterization by centralized facilities*: Parameters and standardized protocols need to be established. Analysis of the dynamics of insulin secretion will be essential. It will be just as important to evaluate the turning off of insulin secretion as its switching on. Centralized 'beta-cell analysis facilities' should be established to evaluate 'insulin positive cells' as bone fide fully-differentiated functional beta-cells using such standardized protocols.

As might be expected of such a forward-looking meeting, more questions were asked than answered. Scientists are not soothsayers and neither should they be. Clearly we need to know more about the beta-cell before we can hope to create new, possibly more robust ones for cell replacement therapy. Where to start? Two quotes from participants sum this up quite well: "The major problem of our times (sic) is deciding what to work on"; "It is easy to mess up the beta-cell but very hard to make it better"!

The community must work together to provide guidelines: what standards must be met to ensure safe and efficacious treatment of diabetes and possibly a cure? This in turn provides a unique opportunity and challenge to organizations such as EFSD and JDRF. They will be looked to not only to provide funds for specific individual projects and central facilities, but also to serve as coordinators of this major worldwide effort to cure diabetes. This meeting was a perfect way to start.

The two co-chairs of the 10th EASD/JDRF Workshop, Christopher Rhodes and Frans Schuit, and the workshop series' scientific coordinator, Philippe Halban, thank all the participants for their outstanding presentations and strong input to the discussions. They also thank in particular Ms. Mary Hata for her outstanding organization of the meeting and Ms. Caroline Wood as local organizer. The organizers are greatly indebted to Sanofi-Aventis for their continuing generous support of the EASD/JDRF Oxford Workshops.

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Figure 1. *The attendees of the 10th EASD-JDRF Oxford Diabetes Workshop 'What is a beta-cell and can we improve it?'*

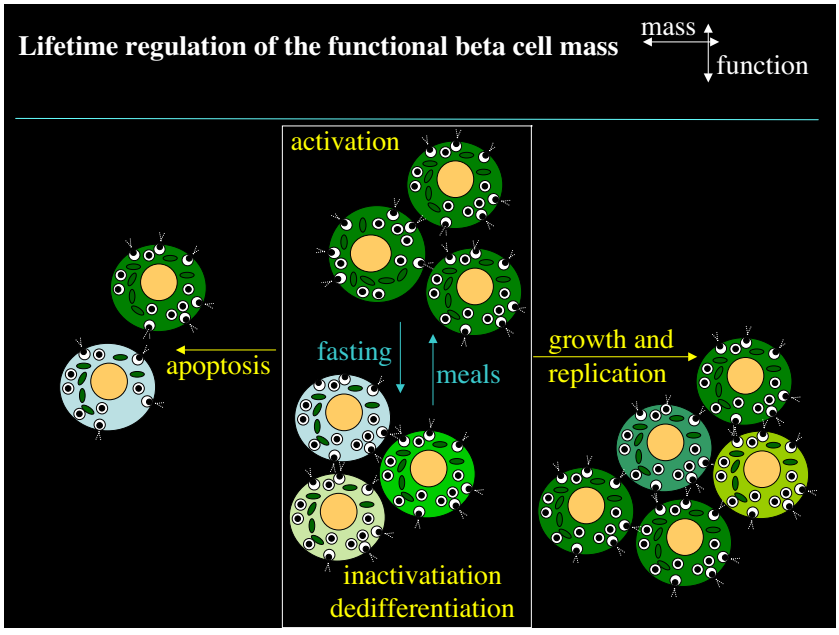

Figure 2. *'Functional beta-cell mass' and its lifetime regulation by genetic and environmental factors* - is a central theme in current beta-cell oriented diabetes research. Functional beta-cell mass implies the combination of the number of primary beta-cells and their individual function, and the status of both is strictly controlled any moment in life. During a meal, nutrients and incretins are known to stimulate acutely the expression of the insulin gene, the synthesis of new insulin molecules and the release of insulin to regulate blood glucose. Short term absence of meals (typically a day of fasting) can already induce significant loss of the functional beta cell mass which is mostly based upon altered gene expression in existing beta-cells. Long-term changes in the insulin requirements of an individual can drive (still unknown) signalling pathways that can alter the balance between decreasing beta-cell mass by apoptosis and enhancing beta-cell mass by growth, replication and differentiation.

EASD Robert Turner Clinical Research Course

The second EASD Robert Turner Research Course was held at The Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) 25-29 April 2005. The course, established under the auspices of the EASD, is intended to give young and aspiring research workers a chance to engage both theoretically and practically in the process and methodology of clinical research.

The Course was organised by Prof. David R. Matthews, and the faculty included Prof Robert Heine (Netherlands), Dr Fredrik Karpe, Prof Keith Frayn, Prof Rury Holman, Dr. Jonathan Levy, Dr Anne Clark, Prof Geoff Gibbons, and Dr Brian Shine. The topics covered included

- Design of experiments
- Ethical review. Video of ethics and research dilemmas.
- Grant applications
- Physiological studies
- Trials and trial theory
- Statistics and statistical review
- Good Clinical Practice
- Handling samples
- Handling data
- Science writing methodology
- Publication

Interactive sessions and problem solving.

The attendees came from diverse backgrounds, and included participants from:
Austria, Czech Republic, Georgia, Germany, Greece, India, Italy, Nigeria, Pakistan, Peru, Poland, Rumania, Russia, Slovakia and Sweden

The course covered theoretical and practical aspects of clinical research design and implementation, including group work related to statistical problems, protocol construction and GCP. The teaching material ranged from apples and oranges to video presentations of ethical aspects of research. The course was designed for small numbers and so was highly interactive. Part of the course involved designing and undertaking an experimental protocol.

The attendees in the foyer of OCDEM.

A cannulation is in place for an experimental protocol designed by the course members.

Keeping records from the experimental practical day.

Sample handling and centrifugation.

From our feedback forms we identified that some of the participants wanted more complex statistics and others felt that we covered the mathematics too fast. Some participants wanted greater depth of design, and others more practical aspects. The faculty feedback was that it was a challenge to cater for the diversity of wishes and needs, but overall we hoped that the balance had been good. On a score of 1-4 (insufficient to good), most of the sessions had modal scores of 3 or 4.

We thank Mrs Carol Hill from OCDEM, who undertook much of the infrastructure support, Dr Paul Chester from Novo Nordisk who taught the GCP aspects, all our faculty and Johnson and Johnson for an education support grant.

Prof David R. Matthews
Oxford Centre for Diabetes,
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Churchill Hospital, Oxford. OX3 7LJ, UK.

The Rising Star Symposium

Four candidates, two from basic research and two from clinical research, were selected by the final Programme Committee to present an overview of their past and ongoing research activities during a multidisciplinary research symposium, 'The Rising Star Symposium', at the EASD Annual Meeting. Following is a short report from each of the 4 awardees.

Per-Ola Carlsson.
Departments of Medical Cell Biology and Medical Sciences, Uppsala University, Uppsala, Sweden

Blood Vessels in Transplanted Pancreatic Islets

Pancreatic islet transplantation is a tempting strategy to treat patients with type 1 diabetes, since if successful it could provide a cure for the disease. At present, there is, however, a poor long-term outcome of such transplantations when compared to the results for whole pancreas transplantation. Lack of proper vascular engraftment with concomitant cell death, loss of function and reduced cell proliferation may provide one explanation to poor islet transplant outcome. When isolated by collagenase digestion prior to transplantation, the pancreatic islets become disconnected from their vascular supply. Moreover, during culture that often precedes transplantation the remnant endothelium degenerates. A rapid and adequate revascularization post-transplantation is necessary for optimal oxygen and nutrient transport to the islet cells, glucose sensing and efficient transport of secreted hormones to target organs to maintain glucose homeostasis. In our studies, we have observed that the acquired capillary network is much less dense than the original. Moreover, the blood flow regulation in the newly formed blood vessels differs from that of blood vessels in native islets e.g. due to upregulation of the local renin-angiotensin system in islets following transplantation. Both the low vascular density and hypoperfusion of individual blood vessels seem to contribute to a chronically decreased oxygen tension within transplanted islets. Our further studies have shown that transplanted islets have increased lactate/pyruvate ratios and decreased pH within the tissue suggesting oxygen-dependent restrictions in their glucose metabolism. Different strategies have been attempted by us and others to improve islet revascularization and function. One tempting strategy may be to block angiostatic factors normally present within the islets that restrict endothelial cell migration and proliferation.

Anna L Gloyn
Diabetes Research Laboratories, Oxford Centre for Diabetes, Endocrinology & Metabolism,
University of Oxford, UK

Insights into beta cell function from naturally occurring mutations

Naturally occurring mutations which result in monogenic forms of beta-cell dysfunction can help to elucidate critical points in stimulus-secretion coupling pathways for insulin secretion and provide insight into the structure and function of key components. In 2004 we identified a novel genetic aetiology for permanent neonatal diabetes (PNDM) resulting from heterozygous activating mutations in the gene (*KCNJ11*) which encodes for the inwardly rectifying potassium channel Kir6.2, a key component of the beta-cell ATP sensitive potassium (K_{ATP}) channel[1]. Functional characterisation has shown that the mutational mechanism is a decrease in sensitivity to ATP, such that glucose metabolism fails to result in channel closure and the subsequent membrane depolarisation and insulin release[1,2]. In addition to causing PNDM characterised only by diabetes some different *KCNJ11* mutations result in a novel syndrome of developmental delay, epilepsy and neonatal diabetes (DEND) which can be explained by the expression profile of Kir6.2 in brain and muscle in

addition to the pancreas[1,2]. Earlier this year we reported that activating mutations in KCNJ11 could also result in TNDM[3]. The clinical spectrum of diabetes in all these cases can be explained by the functional severity of the mutation[3]. The determination of the genetic aetiology in these patients and the elucidation of the mutational mechanism have resulted in the successful treatment of some patients with this type of diabetes by oral sulphonylurea tablets rather than subcutaneous insulin injections.

The key role of glucokinase in insulin secretion has been known for sometime. However, insights into the regulation and activation of glucokinase are still being gained from naturally occurring mutations resulting in both hyper and hypoglycaemia. Our identification of novel glucokinase (*GCK*) mutations in patients with hyperinsulinism which were localised to a specific region of the protein suggested the presence of an allosteric activator site, which is now a target for therapeutic agents[4]. A novel GCK mutation (V62M) which results in Maturity-onset diabetes of the young (MODY) has provided me with an interesting avenue of research since this mutation was paradoxically kinetically activating rather than inactivating[5]. We have performed the most thorough structural and functional characterisation of a *GCK* mutation to date which has illustrated the complexity of the regulation of this enzyme and provided the first evidence in humans to support the existence of an endogenous activator of glucokinase. The identification of this activator will provide an additional target for therapeutic agents.

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From bedside to bench: the role of fat in beta-cell loss in type 2 diabetes

There is a progressive increase in the prevalence of type 2 diabetes (T2D) worldwide, due to the dramatic augmentation of obesity. In our *clinical* research, we have studied the relative contributions of insulin resistance and pancreatic beta-cell dysfunction in the pathogenesis of T2D. We have examined the metabolic effects of obesity, and the relationship between body fat distribution and adipokines, and obtained novel evidence to suggest that the intra-abdominal fat compartment is the main fat depot determining plasma adiponectin levels and insulin sensitivity. On the other hand, leptin levels are determined by the subcutaneous fat mass, which is not related to insulin sensitivity. Adiponectin also appears to be a crucial link between visceral obesity and an atherogenic lipoprotein profile. The insulin resistance, associated with intra-abdominal fat accumulation and low adiponectin levels, contributes to glucose intolerance, but it is the worsening of pancreatic beta-cell function that essentially determines the development of impaired glucose tolerance. Indeed, beta-cell dysfunction was the principal determinant of the progressive deterioration of glucose tolerance in individuals at high risk for T2D in a cross-sectional and longitudinal study. This decline in beta-cell function over time was correlated with increasing abdominal obesity, suggesting that abdominal adipocytes may exert deleterious effects on the beta-cell.

To investigate the mechanisms leading to pancreatic beta-cell dysfunction in T2D and to clarify whether

adipocyte-derived products, such as free fatty acids (FFA) and adipokines, exert direct detrimental effects on beta-cells, we have used an *in vitro* research approach. FFA can cause beta-cell apoptosis and necrosis (lipotoxicity), in particular when their storage as triglycerides is inefficient. We observed that FFA lead to apoptosis via the induction of an endoplasmic reticulum stress response. It is of interest that endoplasmic reticulum stress has recently been proposed as the cellular/molecular mechanism linking obesity with insulin resistance. FFA might thus be responsible for the endoplasmic reticulum stress response observed in hepatocytes and adipocytes, while hampering in parallel pancreatic beta-cell function/viability, as suggested by our own observations. We have also shown that beta-cells express receptors for LDL and VLDL that are internalized by receptor-mediated endocytosis. Uptake of LDL and subsequent oxidative reactions also cause beta-cell death. Further evidence for the crosstalk between adipocytes and pancreatic beta-cells comes from our demonstration that beta-cells abundantly express adiponectin receptors. It remains to be investigated whether the decrease in adiponectinemia in visceral obesity contributes to beta-cell dysfunction. Our future research will attempt to elucidate the molecular mechanisms by which FFA and adipokines cause pancreatic beta-cell dysfunction and apoptosis. Hopefully, these experiments will provide novel alternatives for the prevention of progressive beta-cell loss in T2D.

Nikolaus Marx, Prof. Dr. med.
University of Ulm, Department of Internal Medicine II

Anti-atherogenic effects of PPARgamma activators – from bench to bedside

Peroxisome proliferator-activated receptor-gamma (PPAR) is a nuclear transcription factor, controlling gene expression in response to their ligands. PPAR can be activated by antidiabetic thiazolidinediones (TZDs, glitazones), thus regulating genes involved in glucose homeostasis and adipogenesis. In addition to these metabolic effects, we were interested to examine the effect of PPAR activators on mechanims involved in atherogenesis. First, the expression of PPARgamma in the vessel wall in arteriosclerotic lesions has been demonstrated and it has been shown that anti-diabetic PPARgamma-activating TZDs exhibit anti-inflammatory and anti-atherogenic properties in vascular cells. As such, we found inhibitory effects on endothelial cell and T-cell activation, modulatory function on the release of matrix-degrading enzymes from human monocytes / macrophages, as well as a reduction of smooth muscle cell migration by PPARgamma activation. Given the critical role of these processes in lesion development, these in-vitro data suggested that anti-diabetic PPARgamma activators may modulate the inflammatory response in the vessel wall and as such provide a potential novel therapeutical option to influence vascular disease in the high risk population of type 2 diabetic patients. Subsequently, clinical studies from our group showed that treatment of patients with diabetes mellitus type 2 and coronary artery disease with PPARgamma-activating TZDs reduces serum levels of novel inflammatory biomarkers of arteriosclerosis, improves endothelial function, and reduces restenosis after coronary stenting in non-diabteic subjects, suggesting that this concept of anti-inflammatory effects of TZDs holds true in treated patients.

European Foundation for the Study of Diabetes (EFSD)
and
SERVIER

European Research Programme on
Vascular Complications of Type 2 Diabetes

Request for Applications

EFSD and Servier
announce
up to 4 Grants of Euro 100,000 this year

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

EFSD and **SERVIER** established the **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 non-profit organisations.

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. Grant distribution is as follows:

2005 – Two grants, each of Euro 100,000
2006 – Three to four grants, each of Euro 100,000
2007 – Three to four grants, each of Euro 100,000

Over the three years one extra grant of Euro 100,000 will be made available.

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. The Programme Board, at the suggestion of the Review Committee, may at its discretion recommend an award in a lesser amount considered more appropriate for the proposed studies.

An average number of three awards will be granted each year. Applications for an EFSD/SERVIER Research Programme Grant are invited from single non-profit institutions or groups of such institutions from Europe

and associated countries. The principal investigator and any co-investigators must be normally employed at a non-profit institution and the study must be performed at such a place of work.

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 may be requested from:

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 receivable and will not be sent to reviewers.

Applications should be submitted by **1 February 2006** (date of receipt) to:

Dr Viktor Jörgens, 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 Type 2 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 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".

Winning an award implies participating in the next three symposia organized every year by EFSD and Servier to present their work.

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

Announcement:	December 2005
Application Deadline:	1 February 2006
Anticipated Award:	May 2006

Enquiries should be directed to:

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2nd National Conference on Obesity and Health

Manchester Conference Centre, UK, 20 – 21 March 2006

For further information, please visit the following site:
www.obesityandhealth.co.uk

Contact e-mail address:
ncoh@indexcommunications.com

10th Pan Arab Conference on Diabetes PACD10

Concorde Al-Salam Heliopolis Hotel, Cairo, 28 – 31 March 2006

For further information, please visit the following site:
http://www.arab-diabetes.com

International Conference on Recent Advances in Diabetes Mellitus and ist Complications

Hotel Hilton, Al Ain, UAE, 6-9 March 2006

For further information, please visit the following site:
www.dcrg-uae.com

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