IDS IMMUNOLOGY OF DIABETES SOCIETY

News Letter

2009 - VOLUME 1, ISSUE 2 (April To June)

Dear IDS Members,
The next issue of the of the IDS Newsletter is here. Three months have gone since we came with the first issue. The excitement of the 10th IDS meeting is visible in the IDS community, based on the increase in new membership as well as the questions I receive directly from the IDS website.

The recently made, new IDS website(www.immunologyofdiabetessociety.com) has received several hits in the last few months. They range from information about the IDS, IDS membership as the traffic to the 10th IDS webpage. I sincerely than Mrs. Mamata Tripathy in coordinating the functioning of the website with input from me and others in IDS and the website developers.

In this issue, I am carrying a letter from our President and the latest program of the 10th IDS from Prof.Åke Lernmark and Dr.Corrado Cilio. They have done a massive job in putting the whole meeting together.

We have a new Councillor, Prof. Mathias von Herrath elected unopposed to serve in the council for 3 years. We welcome Mathias, who is not new to IDS. He had served as our treasurer before.

The Annals of New York Academy of Sciences volume entitled 'Immunology of Diabetes 5: From Bench to Bedside' came out in December 2008. There will be no proceedings of the 10th IDS from the Annals. This is because, the there is a big backlog of volumes to be published by the Annals of the New York Academy and they are not accepting to produce new volumes. This is rather unfortunate. I hope for the next IDS, we can come out with a proceedings.

We warmly welcome you to Malmö and hope to see you in this beautiful city for the 10th IDS.

Hope you enjoy reading this Newsletter.

Yours Sincerely

C.B.Sanjeevi

Letter from the President

Dear Colleagues,

On behalf of the IDS membership, I would like to thank Carani Sanjeevi and Sedimbi Saikiran for publishing this IDS-2 Newsletter. They continue to generously provide their time and effort towards making this Newsletter newsworthy, informative, and a joy to read.

I would also like to thank all IDS Councilors and administrative staff who have provided me with their excellent guidance and contributions as well as their very pleasurable and constructive interactions during the last 16 months of this IDS Administration. We are very grateful to Matthias Von Herrath for his outstanding and lengthy service on IDS Council as our past-Treasurer and IDS rep to FOCIS. We sincerely hope that Matthias remains very active in IDS affairs. Recently, Corrado Cilio was elected as Treasurer and Bart Roep as IDS rep to FOCIS. Our IDS membership continues to grow while still retaining a size that fosters ease of interaction and collaboration amongst its members.

The purpose of IDS is "to foster research related to the genetics and pathogenesis, prevention and cure of type 1 diabetes and to act as an international forum for scientific discussion of all aspects of the immunology of insulin-dependent diabetes, including studies of the genetics, immunology, prediction and prevention of the disease and of pancreatic transplantation, in animal models and humans". With this mission in mind, we eagerly await the IDS-10 meeting to be held in Malmo, Sweden, from May 17-20, 2009. The IDS-10 co-organizers, Ake Lernmark and Corrado Cilio, together with the JDRF, Workshop Chairpersons and local co-organizers are to be highly commended for assembling an outstanding IDS-10 program. Thanks also to our IDS-10 administrator, Thomas Gard, for his administrative and budgetary support. We also express our sincere thanks to JDRF, National Institutes of Health (grant R13DK08379901), Lund University Medical Faculty, Malmö City Council, RSR Ltd., Diamyd Medical AB, and Becton Dickinson for their generous financial support of IDS-10.

IDS-10 promises to be a very exciting and informative meeting that will present the most recent accomplishments in the areas of immunodiagnosis, immunogenetics/genomics, immunoregulation, autoreactive T cell repertoire, immunotherapy, beta cell regeneration and stem cells, innate and adaptive immunity, biomarkers, and allergy and autoimmunity in Type 1 diabetes.

I very much look forward to some hot discussions and debates and to seeing you all at IDS-10!

Best regards,

Terry L. Delovitch, PhD

IDS President

WELCOME TO MALMÖ AND THE 10TH INTERNATIONAL CONGRESS OF THE IMMUNOLOGY OF DIABETES SOCIETY (IDS-10).

Dear participant,

It is a pleasure to welcome you to IDS-10 in Malmö. The IDS has come a long way since it's inception. The mission of IDS to promote and foster research in the immunology of diabetes has grown and we have witnessed tremendous progress in the understanding of type 1 diabetes. As the disease is close to the heart of immunology it exciting to observe the way immunologist pay attention to improving the understanding of type 1 diabetes as the progress is made in to uncover the many secrets of our immune system. Most importantly, it is critical that IDS will dwell in the very forefront of immunology research and discovery to advance our ability to predict, prevent and cure type 1 diabetes. IDS-10 is no exception and we trust that you will enjoy the program, which shows great promise to a great extent due to your own abstract.

We're excited about the fact that more than 160 abstracts were submitted. As the abstracts are the backbone of the meeting we wanted to ensure that they all get proper attention whether they are presented in an oral presentation session or as a poster. In order to enhance the posters there will be poster viewing with wine and cheese and a guided poster walk at each of the poster sessions.

The IDS-10 Scientific Program Committee (Bob Harris, Kristina Leijon, Dan Holmberg, Ingrid Kockum, Johnny Ludvigsson, Susanna Cardell, Petter Höglund, Olle Korsgren, Olle Kämpe and Carani Sanjeevi) was instrumental in putting the program together including scoring all the abstracts. We also got valuable advice and input from the IDS Council.

Backbone activities to IDS, the Diabetes Autoantibody Standardization Program (DASP) and the T -Cell Workshop Committee figure prominently in IDS-10. You will also have the opportunity to enjoy several Hot topics, Symposia and Debates. Novel to IDS-10 is the *Industry presentations & Buffet* followed by T Cell Karaoke event on Tuesday night. We trust that you will find the program both interesting and rewarding.

Despite the worldwide economic downturn IDS has friends who are staying with us. We thank the Juvenile Diabetes Research Foundation, the Society of Experimental Diabetes Research, RSR Ltd, Diamyd Medical AB, Coulter Beckman, Electra-box, LRI Instrument AB, and Becton Dickinson for their support and interest.

Finally, we also thank Malmö City for their support and for hosting the Welcome reception. Malmö is the most continental and international city in Sweden. There are more than 100 languages spoken by people living in Malmö. While the Turning Torso is the landmark, the bridge to Denmark is the gateway to Europe and the World.

We hope that you will enjoy your participation in IDS-10 and your visit to Malmö!

Åke Lernmark & Corrado Cilio

Malmö, May 05, 2009.

IDS-10 Scientific Program

SUNDAY, MAY 17

08.30 -11.00 *Antibody workshop*

Clinical Research Center (CRC), University Hospital MAS, Malmö

11.00 Light buffet

11.30 Bus to conference venue

12.15 *Welcoming Remarks*

Åke Lernmark and Corrado M. Cilio, IDS-10 Co-Chairs

Terry Delovitch, IDS President

12.30 *Keynote introductions:*

Chairperson: Jerry Palmer, USA

Matthias von Herrath, USA; *Viral Infections and Immunotherapy or How to Best Cure 'Mouse' Diabetes*

Allison Green, UK; *TNF-αand TGF-β; a Clash of Titans in Type 1 Diabetes*

13.30 BREAK (Coffee, fruit and refreshments)

14.00 *Oral Presentations I*

Chairpersons: Dan Holmberg, SE and Elisabeth P. Blankenhorn, USA

8. N. Mpofu, et al. USA: *Beta Cell Specific Regulatory T Cells Create Long-Lasting Tissue Specific Tolerance in Type 1 Diabetes.*

115. S. Oak, et al. USA: *The Lack of GAD65 Autoantibody-Specific Anti-Idiotypic Antibodies Identifies Islet Autoimmunity in Type 2 Diabetes Patients.*

17. A. Tada, et al. JPN: *Fulminant Type 1 Diabetes Like Phenotype Can Be Induced in Animal Model with Autoimmune Background.*

95. B. vanZyl, et al. UK*: Maternal Microchimerism in T1D Pancreases*.

137. H. Brauner et al. SE: *Distinct Phenotype and Function of Natural Killer Cells in the Pancreas of Non Obese Diabetic Mice.*

56. C. Gysemans, et al. BE *Histone Deacetylase Inhibitors (HDI) Inhibit Type 1 Diabetes in the Non Obese Diabetic Mouse, in Part by Enhancing T Regulatory Cells*.

15.30 *Hot topics – 1: Immunoregulation*
Cristoph Benoist, USA (Moderator)

Akira Shimada, JP, *Central Role of CXCL10-CXCR3 in the Disease Process of Type I Diabetes*

Christiane Hampe, USA, *Anti-idiotypic antibodies as regulatory elements in autoimmune disease.*

Cecile King, AUSA, *A loss of Parity Between the Linked alleles, Interleukin-2 and Interleukin-21, in Autoimmune Diabetes*

17.00 *Poster viewing and guided poster walk*

20.00 Get-together reception, Congress Venue

22.00 Late bar with music and scientific topics

MONDAY, MAY 18

08.30 *Oral Presentations II*

Chairpersons: Susanna Cardell, SE and Henry Erlich, USA

106. E. P. Blankenhorn, et al. USA*: Autoimmune Diabetes in the Lew.1wr1 Rat Requires Iddm14 and a New Genetic Locus Proximal to the Major Histocompatibility Complex.*

57. F. Moore, et al. BE: *PTPN2, A Candidate Gene for Type 1 Diabetes, Modulates Interferon-□-Induced Pancreatic Beta Cell Apoptosis*.

100. D. Zipris, et al. USA*: Altered Toll-Like Receptor Signaling in Human Type 1 Diabetes*

34. H. Beyan, et al. UK: *Monocyte Gene-Expression Profiles in Type 1 Diabetes; a Study of Identical Twins.*

09.30 *Hot topics – 2: T1D genes: humans– mice –rats*

George Eisenbarth USA (Moderator)

Jayne Danska, CA, *Immunogenetic Analysis of T1D: Analysis of Candidate Genes and Gene-Environment Interactions*

Flemming Pociot, DK, *T1DGC Report*

10.30 BREAK (Coffee, fruit and refreshments)

11.00 *Debate 1: Type 1 Diabetes Genes – Needed or Not?*

Moderator: Edwin Gale, UK

Gerald T. Nepom, USA vs Stephen Rich, USA

12.00 LUNCH

13.00 *Diamyd Medical hot topics-3: Combination therapy*

Moderator Jeffrey Krisher USA

Carla Greenbaum, USA, *Combination Therapy Requiring Interaction: IL2 + Rapamycin*

David Harland, USA, *NIDDK Efforts to Preserve or Promote Pancreatic β-cell Function in T1D- the Next Step*

14.00 *Oral Presentations III*

Chairpersons: Bart Roep NL and Johnny Ludvigsson, SE,

92. R. Casas et al. SE: *Specific Immunomodulatory Effect of GAD65 in Type 1 Diabetics*

26. R. Planas, et al. ES: *Gene Expression Profiles of Purified Human Islets and Pancreases in Type 1 Diabetes: New Findings at Clinical Onset and Longstanding Diabetes.*

128. B. Brooks-Worrell, et al. USA: *Rosiglitazone Suppresses T Cell Autoimmunity and Slows the Decline in Beta Cell Function in Phenotypic Type 2 Diabetes Patients*.

15. S.A. Brod, et al. USA*: Effect of Ingested Interferon Alpha on Beta Cell Function in Children With New Onset Type 1 Diabetes MellitUSA in a Phase II Randomized Clinical Trial (Rct).*

15.00 *Antibody workshop (DASP) Report*

15.30 BREAK (Coffee, fruits and refreshments)

16.00 *JDRF Symposium: Antigen-specific therapies*

Richard Insel, USA (Moderator)

Stephen D. Miller, USA, *An Antigen-Specific Tolerance Approach to the Therapy of T1D and Islet Transplantation*

Mark Peakman, UK, *Using Natural Beta Cell Epitopes for Peptide Immunotherapy*

Pere Santamaria, CA, *Reversal of Autoimmune Diabetes by Boosting Autoregulatory T Cell Memory*

Michael P. Czech, USA, *RNAi-Based Therapeutic Strategies for Type 1 Diabetes*

18.00 *Poster viewing and guided poster walk*

20.00 IDS gala dinner, Congress venue

TUESDAY, MAY 19

08.15 *T Cell Workshop (TCW)*

Corrado M. Cilio, SE, *Presentation of the TCW Working Group*

Tim Tree, UK, *PBMC freezing study*

Alessandro Sette, USA, *Epitope database in infectious diseases*

Ivana Durinovic-Belló, USA and Roberto Mallone, FR

Tetramer Directed Epitope Validation Initiative (TDEVI)

TCW selected abstracts

Chairpersons: Nanette Schloot, DE and Susan Wong UK

65. B.O. Roep et al. NL: *Detection of Islet-Specific Autoreactive T-Cells by a Novel Robust and High Through-Put Screening Strategy in Stored Blood Samples of Type 1 Diabetic Patients*

39. S.I. Mannering, et al. AU: *The □-Chain of Insulin is a Hot-Spot for CD4+ T-Cell Epitopes in Human Type 1 Diabetes.*

164. H.W. Davidson, et al. USA: *CD4 T Cell Autoreactivity to the Major Diabetes Autoantigen Znt8.*

10.30 BREAK (Coffee, fruit and refreshments)

11.00 *Oral Presentations IV*

Chairpersons: Bob Harris, SE and Roberto Mallone FR

140. I. Durinovic-Belló, et al. USA: *Combined Effect of HLA, Ins-VNTR and PTPN22 Genotypes on Function and Phenotype of Autoantigen Specific T Cell Responses.*

126. S.C. Kent, et al. USA: *Autoreactive B Cells in Pancreatic Draining Lymph Node from Type 1 Diabetes Subjects*.

159. M. Falcone, et al. IT*: Defective Gut Immune Regulation in Type 1 Diabetic Patients*.

30. S. Mayans, et al. SE: *3D Imaging and Quantification of B-Cell Mass and Lymphocyte Infiltration In Murine Type 1 Diabetes*.

12.00 LUNCH

13.00 *Hot topics – 5: Beta cell regeneration and stem cells*

Henrik Semb SE (Moderator)

Harry Heimberg, BE , *Elusive Beta Cell Progenitors in the Adult Pancreas*

Ole Madsen, DK, *Stem Cells in Future Diabetes Therapy*

14.00 *Symposium 2: Innate and adaptive immunity*

Moderator: Mark Aktinson, USA

Terry Delovitch, CA, *Development of Glycolipid Antigen Agonists for iNKT Cell-Mediated Protection from Type 1 Diabetes*

Giovanni de Libero, CH, *Lipid molecules stimulating human CD1-restricted T cells: new players*

B. Pulendran, USA, *Modulating Adaptive Immune Responses with Innate immunity*

15.30 BREAK (Coffee, fruit and refreshments)

16.00 *Debate 2: How Much Type 1 is Type 2 Diabetes?*

Moderator: Åke Lernmark, SE

Leif Groop SE vs Jerry Palmer, USA

17:00 *IDS Business Meeting*

18:00 *Poster viewing and guided poster walk*
Industry presentations & buffet

18.30 Elisabeth Lindner, Diamyd Medical

19.00 Mike Powell, RSR Ltd

21.00 *IDS travel awards reception* (sponsored by the Society of Experimental Diabetes Research)

21.45 *Late bar with T Cell Karaoke*

WEDNESDAY, MAY 20

08.30 *Symposium 3: New biomarkers in Type 1 Diabetes*

Terry Delovitch USA (Moderator)

Martin J. Hessner, USA, *Transcriptional signatures in type 1 diabetes*

Matej Oresic, FI, "Metabolome en route to type 1 diabetes"

Decio Eizirik, BE, *USAe of a genomics-based approach to identify novel beta-cell biomarkers*

10.00 BREAK (Coffee, fruit and refreshments)

10.30 *Oral presentation Late Breaking News*

Chairpersons: Abner Notkins, USA and Carani Sanjeevi, SE

153. T. Delong, et al. USA: *A New Antigen for Autoreactive T Cells in Type 1 Diabetes.*

158. A. Criscimanna, et al. IT: *Limbal Stem Cells As A Potential Source of Pancreatic Beta Cells*

143. M. Kalis, et al. SE, *Beta Cell Specific Disruption of Dicer-1 Leads to Defective Insulin Secretion and Diabetes Mellitus*

3. Y. Zhao, et al. USA*: Human Cord Blood Stem Cell-Modulated Regulatory T Lymphocytes Reverse the Autoimmune-CaUSAed Type 1 Diabetes in Non Obese Diabetic (NOD) Mice*.

139. H. Hyöty et al. FI: *Co-Occurrence of Allergic Sensitization and Type 1 Diabetes*

12.00 LUNCH

13.00 *Symposium: Allergy & Autoimmunity*

Corrado M. Cilio SE (Moderator)

Mark S. Anderson, USA, *Using extrathymic Aire-expressing cells to control diabetes*

Cezmi A.Akdis, CH, *Mechanisms of Allergic Inflammation*

14.00 *Concluding Remarks*

Olle Kämpe, SE

14.30 *IDS-11 invitation*

15.00 *End of meeting*

Farewell refreshments

IDS TCW QUARTERLY NEWLETTER – 1/2009

http://www.immunologyofdiabetessociety.com/committee_t-celll.htm

March 23 2009

Dear Colleagues,

We would like to update you about the progress of the T Cell Workshop initiatives.

As proposed in our previous newsletter, three projects have now been successfully launched:

1) T1D T Cell Epitope Database: starting from her recently published review article, Teresa DiLorenzo has updated and posted on our website a comprehensive database including both CD4+ and CD8+ epitopes, mouse and human. This database will be periodically updated, and you can notify omissions, errors or additions directly to the Author, as indicated on the website. Please note that data will be entered based exclusively on published reports, and scored according to different "degrees of evidence", depending on results included in the quoted report.

2) IDS TCW Freezing Study I: this protocol – coordinated by Tim Tree - has been launched on January 2009 and involves 10 different T-cell Laboratories worldwide, each enrolling 5 T1D patients and 5 healthy controls. The aim is to compare two mainstream freezing/thawing protocols, namely cold vs. warm freezing medium (DMSO-human serum). These protocols will be compared to local ones performed by each Laboratory, when available. The aim is to define starting "gold standard" freezing procedure(s) performing superiorly across different T cell assay formats (i.e., best cell recovery and viability, preservation of beta-cell-specific T cell responses as compared to fresh PBMC samples). The selected protocol(s) will subsequently be validated in larger multicentre studies during the second phase of this initiative, and compared to other promising protocols when available. Details about this study can be found on our website.

(**IDS-TCW Freezing Study I analysis : http://www.immunologyofdiabetessociety.com/IDS-TCW%20Freezing%20Study%20I%20analysis.pdf ; and IDS-TCWFreezingStudyISOP http://www.immunologyofdiabetessociety.com/Fresh%20v%20Frozen%20SOPs%20Final.pdf**)

3) Proto-TDEVI Study: this is the first phase of a larger TDEVI (Tetramer-Directed Epitope Validation Initiative) promoted by the Benaroya Research Institute in Seattle under the sponsorship of JDRF and coordinated by Ivana Durinovic-Bello. The aim of TDEVI is to promote a novel collaborative strategy of epitope validation, based on independent, blinded tetramer testing performed in multiple Laboratories on a limited number of blood samples. This first phase has been launched on March 2009. It includes a CD4+ and a CD8+ T cell arm and involves the 9 Labs of the TCW Committee. It is expected to provide proof of principle about the feasibility of the strategy along with independent validation of a first limited set of epitopes: HLA-DR4-restricted $GAD_{270-285}$, $GAD_{554-567}$, PPI_{76-90}; and HLA-A2-resticted $GAD_{114-122}$, $GAD_{536-545}$, PPI_{34-42} and $PPI_{101-109}$. To this end, each Lab will enroll 10 T1D patients. Although the aim of this study is one of epitope validation and not of assay validation, tetramer-based assays will be run in parallel to local CD4+ and CD8+ T cell assays, in order to identify promising formats which could later be tested in other multicentre initiatives. Details about this study will soon be posted on our website.

Finally, do not miss the TCW session at the IDS-10 in Malmö on Tuesday May 19th at 08.30. We have an outstanding program where we will discuss these TCW initiatives. The program also includes a lecture from Dr. Alessandro Sette and selected oral presentations.

In addition, we would like to remind you to join the "T Cell Karaoke" evening in Malmö on Tuesday May 19th at 21.00. This is thought as an informal event where to openly discuss T cell issues and enjoy good music and good company.

Hoping that these initiatives will catalyze the interest of additional investigators, we look forward to your feedback and to see you soon in Malmo!

Roberto Mallone,

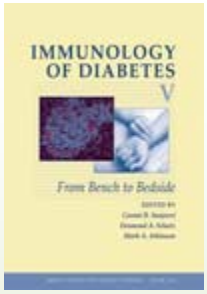
The IDS TCW Steering Committee

New councilor in IDS

Mathias von Herrath (MD, PhD), is a Professor and currently the director of the La Jolla Institute for Allergy and Immunology Type 1 Diabetes Center, CA, USA. He has received numerous awards which include outstanding scientist award from ADA in 2008, JDRF Grotzky Award in 2006 etc. The main theme of Dr. von Herrath's research program is to understand the regulation of autoimmune and anti-viral responses. Dr. Herrath has previously served as treasurer of the IDS. He will be a Councilor for the next term of three years.

BECOME A MEMBER OF IDS

Become a member now and take advantage of the low registration fee. To become a member, please visit http://www.immunologyofdiabetessociety.com/. Click on the link 'membership' and follow the instructions to pay online.



Immunology of Diabetes V

Edited by: Carani B. Sanjeevi (Center for Molecular Medicine, Karolinska Institute, Stockholm, Sweden); Desmond A. Schatz (University of Florida College of Medicine, Gainesville, Florida); Mark A. Atkinson (University of Florida College of Medicine, Gainesville, Florida)

This volume is an overview of current research in the field of immunology as it relates to diabetes. Topics covered include: autoantibody markers for type 1 diabetes; cellular immune markers for type 1 diabetes; animal models of type 1 diabetes; the pancreas in type 1 diabetes; genetics of type 1 diabetes; the role of toll-like receptors and innate immunity in type 1 diabetes; cell-based therapies for type 1 diabetes; environmental and mechanistic causes of type 1 diabetes; mechanisms of beta-cell death; role of the immune response in type 1 diabetes; and islet transplantation.

To read the full table of contents click on the link below:

http://www3.interscience.wiley.com/journal/121570814/issue

THE DIABETES NEWS-I

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GENETICS

1.Three microsatellites from the T1DGC MHC data set show highly significant association with type 1 diabetes, independent of the HLA-DRB1, -DQA1 and -DQB1 genes.

AIM: The aim of this study was to test the microsatellites in the Type 1 Diabetes Genetics Consortium major histocompatibility complex (MHC) data set for association with type 1 diabetes (T1D) independent of the HLA-DRB1, -DQA1 and -DQB1 genes.

METHODS: The data set was edited to contain only one affected child per family, and broad ethnic subgroups were defined. Genotypes for HLA-DRB1, -DQA1 and -DQB1 were replaced by a haplotype code spanning all three loci, with phase inferred based on common haplotypes. The final data set contained 8190 samples in 2301 families, 59 microsatellites and the DRB1-DQA1-DQB1 haplotype code. Statistical analyses consisted of conditional logistic regression and haplotype estimations and linkage disequilibrium calculations.

RESULTS: The data set was screened using a main effects test approach adjusted for DRB1-DQA1-DQB1, and significant results tested for validity. After these procedures, four markers remained significant at the Bonferroni-corrected threshold: D6S2773 ($p = 0.00014$), DG6S185 ($p = 0.00015$), DG6S398 ($p = 0.00043$) and D6S2998 ($p = 0.00015$). These results were supported by allelic tests conditioned on DRB1-DQA1-DQB1 haplotypes, except for DG6S185, which may contain artefacts.

CONCLUSIONS: We have identified three microsatellites that mark additional risk factors for T1D at highly significant levels in the MHC. Further analyses are needed to establish the relationship with other possible genetic determinants in this region.

Source: Diabetes Obes Metab. 2009 Feb;11 Suppl 1:17-24 (Eike MC, Humphreys K, Becker T, Olsson M, Lie BA; Diabetes Genetics Consortium.)

2.IL2RA genetic heterogeneity in multiple sclerosis and type 1 diabetes susceptibility and soluble interleukin-2 receptor production.

Multiple sclerosis (MS) and type 1 diabetes (T1D) are organ-specific autoimmune disorders with significant heritability, part of which is conferred by shared alleles. For decades, the Human Leukocyte Antigen (HLA) complex was the only known susceptibility locus for both T1D and MS, but loci outside the HLA complex harboring risk alleles have been discovered and fully replicated.

A genome-wide association scan for MS risk genes and candidate gene association studies have previously described the IL2RA gene region as a shared autoimmune locus. In order to investigate whether autoimmunity risk at IL2RA was due to distinct or shared alleles, we performed a genetic association study of three IL2RA variants in a DNA collection of up to 9,407 healthy controls, 2,420 MS, and 6,425 T1D subjects as well as 1,303 MS parent/child trios. Here, we report "allelic heterogeneity" at the IL2RA region between MS and T1D.

We observe an allele associated with susceptibility to one disease and risk to the other, an allele that confers susceptibility to both diseases, and an allele that may only confer susceptibility to T1D. In addition, we tested the levels of soluble interleukin-2 receptor (sIL-2RA) in the serum from up to 69 healthy control subjects, 285 MS, and 1,317 T1D subjects. We demonstrate that multiple variants independently correlate with sIL-2RA levels.

Source: PLoS Genet. 2009 Jan;5(1):e1000322. Epub 2009 Jan 2 (Maier LM, Lowe CE, Cooper J, Downes K, Anderson DE, Severson C, Clark PM, Healy B, Walker N, Aubin C, Oksenberg JR, Hauser SL, Compston A, Sawcer S; International Multiple Sclerosis Genetics Consortium, De Jager PL, Wicker LS, Todd JA, Hafler DA)

3.Cytotoxic T-lymphocyte antigen 4 gene polymorphisms are associated with latent autoimmune diabetes in adults.

BACKGROUND: Cytotoxic T lymphocyte antigen-4 (CTLA-4) molecule is an important regulator of T cell activation involved in the down-regulation of immune response. Polymorphisms within the CTLA-4 gene have been suggested to confer susceptibility to autoimmune endocrine disorders.

METHODS: In order to evaluate the impact of allelic variants of the CTLA-4 gene in latent autoimmune diabetes in adults (LADA), the CT60 A/G SNP and the CTBC217_1 C/T SNP were studied in a population of Estonian origin, including 61 LADA patients and 230 controls.

RESULTS: It was found that the CT60 GG genotype (p=0.004) and the CTBC217_1 TT genotype (p=0.007) were significant associated with LADA.

CONCLUSIONS: Our investigation revealed that not only type 1 diabetes but also LADA is associated with CTLA-4 gene polymorphisms. The role of CTLA-4 gene in the pathogenesis of LADA is open and needs further investigations.

Source: Clin Chim Acta. 2009 May;403(1-2):226-8. (Douroudis K, Prans E, Kisand K, Nemvalts V, Uibo R.)

IMMUNOLOGY

4.How can we improve the translational landscape for a faster cure of type 1 diabetes?

Translation of novel therapies for type 1 diabetes and other autoimmune diseases to the clinic has been slow despite significant new initiatives from funding agencies. One reason for this is that different incentives drive industry, academia, and funding bodies. These communities therefore lack common goals and often communicate poorly, resulting in unintended obstacles that hamper progress in efficiently translating basic scientific discoveries into medical practice. Here, based on our own personal experiences, we discuss some of the drivers within each community that cause these problems, existing mechanisms to facilitate the translation of science into medical practice, and remaining issues that need to be solved

Source: J Clin Invest. 2009 May;119(5):1061-5. (von Herrath M, Chan A.)

5.Regulatory T cells enter the pancreas during suppression of type 1 diabetes and inhibit effector T cells and macrophages in a TGF-beta-dependent man.

Treg can suppress autoimmune diseases such as type 1 diabetes, but their in vivo activity during suppression remains poorly characterized. In type 1 diabetes, Treg activity has been demonstrated in the pancreatic lymph node, but little has been studied in the pancreas, the site of autoimmune islet destruction. In this study we induced islet-specific Treg from the BDC-6.9 TCR transgenic mouse by activation of T cells in the

presence of TGF-beta. These Treg can suppress spontaneous diabetes as well as transfer of diabetes into NOD.scid mice by diabetic NOD spleen cells or activated BDC-2.5 TCR transgenic Th1 effector T cells. In the latter transfer model, we observed infiltration of the pancreas by both effector T cells and Treg, suggesting that Treg are active in the inflammatory site and are not just restricted to the draining lymph node. Within the pancreas, we demonstrate that Treg transfer causes a reduction in the number of effector Th1 T cells and macrophages, and also inhibits effector T-cell cytokine and chemokine production. Although we found no role for TGF-beta in vitro, transfection of effector T cells with a dominant-negative TGF-beta receptor demonstrated that in vivo suppression of diabetes by TGF-beta-induced Treg is TGF-beta-dependent.

Source: Eur J Immunol. 2009 May;39(5):1313-22 (Tonkin DR, Haskins K.)

6.Coxsackievirus Infection as an Environmental Factor in the Etiology of Type 1 Diabetes.

Susceptibility to type 1 diabetes (T1D) is dictated by a complex interplay between genetic determinants and environmental influences. Accumulating evidence strongly supports viral infection as an important factor in the etiology of T1D. To this effect, several viruses have been associated with the capacity to induce or exacerbate T1D in both humans and mice. The most convincing evidence linking viral infection and autoimmunity comes from studies on enteroviruses, particularly coxsackievirus. In this review we will discuss the evidence associating coxsackievirus infection to T1D and present the current state of knowledge on the potential mechanism of coxsackievirus-mediated T1D.

Source: Autoimmun Rev. 2009 Feb 10. [Epub ahead of print] (Richer MJ, Horwitz MS.)

7.Antiviral effect of nicotinamide on enterovirus-infected human islets in vitro: effect on virus replication and chemokine secretion.

Type 1 diabetes is a chronic disease characterized by the selective destruction of insulin-producing cells in the pancreas. Enterovirus (EV) is the prime candidate to initiate this destruction and several inflammatory chemokines are induced by EV infection. Nicotinamide has been shown to protect isolated human islets, and to modulate chemokine expression. The aim of this study was to evaluate the effect of nicotinamide on EV replication and EV-induced chemokine secretion and cytolysis of human islets. Two EV strains were used to infect human islets in vitro, one lytic (Adrian) isolated from a child at onset of type 1 diabetes, and one non-lytic (VD2921). Secretion of the chemokines IP-10 and MCP-1, viral replication, and virus-induced cytopathic effect (CPE), were measured at different time points post-infection. Addition of nicotinamide to the culture medium reduced viral replication and virus-induced islet destruction/CPE, significantly. Both EV strains increased secretion of IP-10 and MCP-1, when measured days 2-3, and days 5-7 post infection, compared to mock-infected control islets. IP-10 was not produced by uninfected isolated islets, whereas a basal secretion of MCP-1 was detected. Interestingly, addition of nicotinamide blocked completely (Adrian), or reduced significantly (VD2921), the virus-induced secretion of IP-10. Secretion of MCP-1 was also reduced in the presence of nicotinamide, from infected and uninfected islets. The reported antiviral effects of nicotinamide could have implications for the treatment/prevention of virus- and immune-mediated disease. Also, this study highlights a possible mechanism of virus-induced type 1 diabetes through the induction of MCP-1 and IP-10 in pancreatic islets.

Source: J Med Virol. 2009 Jun;81(6):1082-7. (Moëll A, Skog O, Ahlin E, Korsgren O, Frisk G.)

8.Specific association of type 1 diabetes mellitus with anti-cyclic citrullinated peptide-positive rheumatoid arthritis.

OBJECTIVE: The co-occurrence of autoimmune diseases such as rheumatoid arthritis (RA) and type 1 diabetes mellitus (DM) has been reported in individuals and families. In this study, the strength and nature of this association were investigated at the population level in a Swedish case-control cohort.

METHODS: For this case-control study, 1,419 patients with incident RA diagnosed between 1996 and 2003 were recruited from university, public, and private rheumatology units throughout Sweden; 1,674 matched control subjects were recruited from the Swedish national population registry. Sera from the subjects were tested for the presence of antibodies to cyclic citrullinated peptide (anti-CCP), rheumatoid factor (RF), and the 620W PTPN22 allele. Information on a history of diabetes was obtained by questionnaire, telephone interview, and/or medical record review. The prevalence of type 1 DM and type 2 DM was compared between patients with incident RA and control subjects and further stratified for the presence of anti-CCP, RF, and the PTPN22 risk allele.

RESULTS: Type 1 DM was associated with an increased risk of RA (odds ratio [OR] 4.9, 95% confidence interval [95% CI] 1.8-13.1), and this association was specific for anti-CCP-positive RA (OR 7.3, 95% CI 2.7-20.0), but not anti-CCP-negative RA. Further adjustment for the presence of PTPN22 attenuated the risk of anti-CCP-positive RA in patients with type 1 DM to an OR of 5.3 (95% CI 1.5-18.7). No association between RA and type 2 DM was observed.

CONCLUSION: The association between type 1 DM and RA is specific for a particular RA subset, anti-CCP-positive RA. The risk of developing RA later in life in patients with type 1 DM may be attributed, in part, to the presence of the 620W PTPN22 allele, suggesting that this risk factor may represent a common pathway for the pathogenesis of these 2 diseases.

Source: Arthritis Rheum. 2009 Mar;60(3):653-60 (Liao KP, Gunnarsson M, Källberg H, Ding B, Plenge RM, Padyukov L, Karlson EW, Klareskog L, Askling J, Alfredsson L).

9.Specific immunoassays confirm association of Mycobacterium avium Subsp. paratuberculosis with type-1 but not type-2 diabetes mellitus.

BACKGROUND: Mycobacterium avium subspecies paratuberculosis (MAP) is a versatile pathogen with a broad host range. Its association with type-1 diabetes mellitus (T1DM) has been recently proposed. Rapid identification of infectious agents such as MAP in diabetic patients at the level of clinics might be helpful in deciphering the role of chronic bacterial infection in the development of autoimmune diseases such as T1DM.

METHODOLOGY/PRINCIPAL FINDINGS: We describe use of an ELISA method to identify live circulating MAP through the detection of a cell envelope protein, MptD by a specific M13 phage--fMptD. We also used another ELISA format to detect immune response to MptD peptide. Both the methods were tested with blood plasma obtained from T1DM, type-2 diabetes (T2DM) patients and non-diabetic controls.

Our results demonstrate MptD and fMptD ELISA assays to be accurate and sensitive to detect MAP bacilli in a large fraction (47.3%) of T1DM patients as compared to non-diabetic controls (12.6%) and those with confirmed T2DM (7.7%). Comparative analysis of ELISA assays performed here with 3 other MAP antigen preparations, namely HbHA, Gsd and whole cell MAP lysates confirmed comparable sensitivity of the MptD peptide and the fMptD based ELISA assays. Moreover, we were successful in demonstrating positive bacterial culture in two of the clinical specimen derived from T1DM patients.

CONCLUSIONS AND SIGNIFICANCE: The MptD peptide/fMptD based ELISA or similar tests could be suggested as rapid and specific field level diagnostic tests for the identification of MAP in diabetic patients and for finding the explanations towards the occurrence of type-1 or type-2 diabetes in the light of an active infectious trigger.

Source: PLoS ONE. 2009;4(2):e4386. Epub 2009 Feb 10 (Rosu V, Ahmed N, Paccagnini D, Gerlach G, Fadda G, Hasnain SE, Zanetti S, Sechi LA.).

TREATMENT

10.GAD65 vaccination: 5 years of follow-up in a randomized dose-escalating study in adult-onset autoimmune diabetes

Aims/hypothesis The aim of this study was to ascertain whether treatment of GAD65 autoantibody (GADA)-positive diabetic patients with alum-formulated recombinant GAD65 (GAD-alum) is safe and does not compromise beta cell function.

Methods This Phase 2, placebo-controlled, dose-escalation clinical trial, which was randomized through a central office, was performed in 47 GADA-positive type 2 diabetic patients, who received subcutaneous injections ofGAD-alum (4 [n=9], 20 [n=8], 100 [n=9] or 500 [n=8] μg) or placebo (n=13) at weeks 1 and 4 of the trial. Participants and caregivers were blinded to group assignments. The primary outcome was safety as assessed by neurological tests, medications and beta cell function evaluated over 5 years, representing the end of the trial.

Results No severe study-related adverse events occurred during the 5 year follow-up. None of the dose groups was associated with an increased risk of starting insulin treatment compared with the placebo group. The use of oral hypoglycaemic agents did not differ between the dose groups. After 5 years, fasting C-peptide levels declined in the placebo group (−0.24; 95% CI −0.41 to −0.07 log10 nmol/l; p=0.01) and the 500 μg dose group (−0.37; 95% CI −0.57 to −0.17 log10 nmol/l; p=0.003), but not in the 4 μg (−0.10; 95% CI −0.28 to 0.07 log10 nmol/l; p=0.20), 20 μg (0.04; 95% CI −0.12 to 0.19 log10 nmol/l; p=0.58) and 100 μg (0.00; 95% CI −0.20 to −0.20 log10 nmol/l; p=0.98) dose groups.

Conclusions/interpretation The primary outcome of safety was achieved, since no severe study-related adverse events occurred.

Source: Diabetologia DOI 10.1007/s00125-009-1371-2 (E-pub) (C.-D. Agardh & K. F. Lynch & M. Palmér & K. Link & Å. Lernmark)

11.Schistosoma mansoni egg antigens induce Treg that participate in diabetes prevention in NOD mice.

Schistosoma mansoni soluble egg antigens (SEA) profoundly regulate the infected host's immune system. We previously showed that SEA prevents type 1 diabetes in NOD mice and that splenocytes from SEA-treated mice have reduced ability to transfer diabetes to NOD.scid recipients. To further characterize the mechanism of diabetes prevention we examined the cell types involved and showed that CD25(+) T-cell depletion of splenocytes from SEA-treated donors restored their ability to transfer diabetes. Furthermore, SEA treatment increased the number and proportional representation of Foxp3(+) T cells in the pancreas of NOD mice. We have used in vitro systems to analyze the effect of SEA on the development of NOD Foxp3(+) T cells. We find that SEA can induce Foxp3 expression in naïve T cells in a TGF-beta-dependent manner. Foxp3 induction requires the presence of DC, which we also show are modified by SEA to upregulate C-type lectins, IL-10 and IL-2. Our studies show that SEA can have a direct effect on CD4(+) T cells increasing expression of TGF-beta, integrin beta8 and galectins. These effects of SEA on DC and T cells may act in synergy to induce Foxp3(+) Treg in the NOD mouse.

Source: Eur J Immunol. 2009 Apr;39(4):1098-107 (Zaccone P, Burton O, Miller N, Jones FM, Dunne DW, Cooke A.)

12.CD103 is dispensable for anti-viral immunity and autoimmunity in a mouse model of virally-induced autoimmune diabetes.

Recent studies suggest a beneficial role for blocking CD103 signaling in preventing islet allograft rejection and thus Type 1 diabetes (T1D) in non-obese diabetic (NOD) mice. However, antibody blockade approaches generally raise anti-microbial safety issues, necessitating additional studies to address the possible adverse effects of antibody therapy.

Here we report that CD103 had no significant impact on the development of primary and memory CD8(+) or CD4(+) responses after acute lymphocytic choriomeningitis virus (LCMV) infection. In addition, CD103 was found to be dispensable for T1D progression in a rapid, CD8-mediated virally-induced T1D model (the rat insulin promoter [RIP]-LCMV), suggesting that its previous efficacy in the NOD mouse model may not be related to its effect on the generation, memory conversion and/or effector function of CD8(+) or CD4(+) T cells.

While the data does not preclude a role for CD103 in T1D in its entirety, the current study does provide much evidence to suggest that CD103 blockade may prove to be a safe intervention for autoimmunity and allo-transplantation. While in cases of rapid microbial (CD8)-driven T1D CD103 antibody blockade may not limit disease progression or severity, in mucosally-driven cases of T1D anti-CD103 antibody treatment may provide a new and safe therapeutic avenue.

Source: J Autoimmun. 2009 Feb;32(1):70-7. Epub 2009 Jan 21. (Fousteri G, Dave A, Juntti T, von Herrath M.).

TRANSPLANTATION

13.C-peptide levels and insulin independence following autologous nonmyeloablative hematopoietic stem cell transplantation in newly diagnosed type 1 diabetes mellitus.

CONTEXT: In 2007, the effects of the autologous nonmyeloablative hematopoietic stem cell transplantation (HSCT) in 15 patients with type 1 diabetes mellitus (DM) were reported. Most patients became insulin free with normal levels of glycated hemoglobin A(1c) (HbA(1c)) during a mean 18.8-month follow-up. To investigate if this effect was due to preservation of beta-cell mass, continued monitoring was performed of C-peptide levels after stem cell transplantation in the 15 original and 8 additional patients.

OBJECTIVE: To determine C-peptide levels after autologous nonmyeloablative HSCT in patients with newly diagnosed type 1 DM during a longer follow-up.

DESIGN, SETTING, AND PARTICIPANTS: A prospective phase 1/2 study of 23 patients with type 1 DM (aged 13-31 years) diagnosed in the previous 6 weeks by clinical findings with hyperglycemia and confirmed by measurement of serum levels of anti-glutamic acid decarboxylase antibodies. Enrollment was November 2003-April 2008, with follow-up until December 2008 at the Bone Marrow Transplantation Unit of the School of Medicine of Ribeirão Preto, Ribeirão Preto, Brazil. Hematopoietic stem cells were mobilized via the 2007 protocol.

MAIN OUTCOME MEASURES: C-peptide levels measured during the mixed-meal tolerance test, before, and at different times following HSCT. Secondary end points included morbidity and mortality from transplantation, temporal changes in exogenous insulin requirements, and serum levels of HbA(1c). RESULTS: During a 7- to 58-month follow-up (mean, 29.8 months; median, 30 months), 20 patients without previous ketoacidosis and not receiving corticosteroids during the preparative regimen became insulin free. Twelve patients maintained this status for a mean 31 months (range, 14-52 months) and 8 patients relapsed and resumed insulin use at low dose (0.1-0.3 IU/kg). In the continuous insulin-independent group, HbA(1c) levels were less than 7.0% and mean (SE) area under the curve (AUC) of C-peptide levels increased significantly from 225.0 (75.2) ng/mL per 2 hours pretransplantation to 785.4 (90.3) ng/mL per 2 hours at 24 months posttransplantation ($P < .001$) and to 728.1 (144.4) ng/mL per 2 hours at 36 months ($P = .001$). In the transient insulin-independent group, mean (SE) AUC of C-peptide levels also increased from 148.9 (75.2) ng/mL per 2 hours pretransplantation to 546.8 (96.9) ng/mL per 2 hours at 36 months ($P = .001$), which was sustained at 48 months. In this group, 2 patients regained insulin independence after treatment with sitagliptin, which was associated with increase in C-peptide levels. Two patients developed bilateral nosocomial pneumonia, 3 patients developed late endocrine dysfunction, and 9 patients developed oligospermia. There was no mortality.

CONCLUSION: After a mean follow-up of 29.8 months following autologous nonmyeloablative HSCT in patients with newly diagnosed type 1 DM, C-peptide levels increased significantly and the majority of patients achieved insulin independence with good glycemic control.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00315133.

Source: JAMA. 2009 Apr 15;301(15):1573-9. (Couri CE, Oliveira MC, Stracieri AB, Moraes DA, Pieroni F, Barros GM, Madeira MI, Malmegrim KC, Foss-Freitas MC, Simões BP, Martinez EZ, Foss MC, Burt RK, Voltarelli JC.)