IDS
IMMUNOLOGY OF DIABETES SOCIETY

News Letter

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

Dear IDS Members,

The venue for the 11th IDS had been selected. It is going to be Incheon,South Korea. The dates are between October 31 to November 3, 2010.Prof.Yangsoo Park will be the convenor for the 11th IDS meeting. More information on the 11th IDS is given in this newsletter. Please mark the dates in your calender.

The organizers of the 11th IDS will also host a website soon, to which we will provide a link from the IDS website.

In this issue, I am carrying a letter from the President of the IDS, a letter from the convenor of the 11th IDS and a report from the Antibody workshop. As usual, I have taken selected abstracts from the literature that are relevant for the IDS members, which I hope you will enjoy reading.

Yours Sincerely
C.B.Sanjeevi

Letter from the President

Dear Colleagues,

Thanks to Carani Sanjeevi and Sedimbi Saikaran for guiding the publication of this very timely and informative IDS-3 Newsletter.

Reflecting back on the second year of this IDS administration, IDS has enjoyed another very successful year. In particular, we recently held receive excellent generously provide their time and effort towards making this Newsletter newsworthy, informative, and a joy to read.a very successful IDS-10 meeting (May 17-20, 2009) in Malmo, Sweden co-organized by Drs. Ake Lernmark, Corrado Cilio and their colleagues. We were also thrilled to obtain a grant from JDRF to initiate the Tetramer Directed Epitope Validation Initiative (TDEVI) project currently being coordinated by Drs. Ivana Durinovic Bello and Roberto Mallone and their many colleagues on the T Cell Workshop (TCW) committee. Please consult the IDS website for a detailed description of this initiative. IDS is also pleased to announce the recent publication of an IDS position paper on "Current advances and travails of islet transplantation co-authored by David Harlan, Norma Kenyon, Olle Korsgren and Bart Roep, which appeared in Diabetes 58(10): 2175-2184 (2009).

Going forward, we are very grateful to Drs. Yongsoo Park, Myung-Shik Lee, George Eisenbarth and their team and committees for their time they dedicated to the planning of what promises to be a very informative and highly successful IDS-11 meeting in Seoul, Korea from Oct. 31 – Nov. 3, 2010. Again please consult this newsletter and the IDS website for more details. Similarly, we also extend our sincere thanks to Drs. Matthias von Herrath and Bart Roep for helping to organize an "au courant" and exciting IDS-JDRF Satellite Symposium to be held on June 24, 2010 at the FOCIS meeting from June 24-27, 2010 in Boston, MA. See the IDS website for further information.

Thus, it is evident that the IDS has thrived and flourished in 2009, and I anticipate that it will continue to do so in 2010. Our success in 2009 has been due in large part to all IDS Councilors and members who have given much of their time, effort and ideas to our goals and initiatives. My sincere thanks to you all for enhancing and facilitating my role in IDS.

I very much look forward to seeing you next year at IDS-11 and at our FOCIS Satellite meeting. Best wishes to you and yours for the upcoming Festive Season.

Best regards,

Terry L. Delovitch, PhD

IDS President

Welcome to the 11th IDS

Incheon, South Korea

October 31 to November 3, 2010

Dear Friends,

It is our great pleasure to invite you to the 11th Meeting of the Immunology of Diabetes Society scheduled from October 31 to November 3 in Incheon, Korea.

This meeting will be the arena for professionals and experts in the field of type 1 diabetes all over the world to discuss the recent research and deal with several topics to clarify the cause of type 1 diabetes and develop new forms of treatment.

While we would like to discover the cause of type 1 diabetes and contribute to the development of new treatment for our patients, the ultimate aim of this meeting is to protect our patients' lives and improve their quality of life through these sincere discussion and debates.

Even our current level of medicine and science have reached the top standard in the world, the quality of care is still far from completeness and life prognosis of type 1 diabetes patients is limited, especially in Asia. Based on this situation, having the IDS meeting in Korea will be very meaningful not only for us but also for the diabetes patients in Korea. We sincerely expect that IDS-11 will increase hope among patients with type 1 diabetes.

We hope that you will visit a memorable city Incheon, a business hub in Northeast Asia. Incheon has been reborn as an international, state-of-the-art city where world-class medical, educational and cultural services are provided with the world's best international airport as well as Incheon port, an important logistics center in Northeast Asia.

We would dare to promise that we would like to make our meeting most compelling not only in terms of its scientific value but also the benefits and welfare of the participants. To improve the quality our meeting, an astonishing agenda of the meeting is being prepared and to encourage participation from all over the world in this era of economic recession, we are planning to give travel grants to as many as 50 young scientists.

Expecting your deep interest in and full support for this gathering, the organizing committee of the 11th Meeting of the Immunology of Diabetes Society cordially requests you to participate in the IDS Incheon.

Sincerely yours,

Yangsoo Park

President of the local organizing committee, the 11th IDS, Kwang-won Kim, MD

Secretary-general of the local organizing committee, the 11th IDS, Yongsoo Park, MD

Report on the Diabetes Autoantibody Standardization Program (DASP)

The Diabetes Antibody Standardization Program (DASP) is a collaboration between the Immunology of Diabetes Society (IDS) and US Centers for Disease Control and Prevention (CDC), set up to evaluate and improve assays for diabetes-associated autoantibodies.

November 30, 2009

Dear Colleagues,

We would like to update you on activities of the DASP Committee.

First, we would like to thank Polly Bingley very much for her outstanding long-term commitment in DASP! Polly has left the committee after successfully chairing DASP from its start in year 2000 until the IDS-9 in 2007.

Also, many thanks to Carina Törn for previous service on the committee!

DASP 2009 Workshop

The major task in 2008/2009 was the planning, organization and running of the DASP 2009 Workshop, which we believe was very successful. Forty-five laboratories from 19 countries participated in this workshop and contributed a total of 232 assays. Besides the evaluation of assays measuring autoantibodies to GAD (GADA), IA-2 (IA-2A) and insulin (IAA), more recent markers such as ZnT8 autoantibodies (ZnT8A), IA-2β autoantibodies (IA-2βA), GAD anti-idiotype antibodies, gastric H^+/K^+ATPase antibodies and IAA affinity have been assessed in extra sub-studies or using data contributed by individual laboratories. Materials and protocols for these sub-studies were provided by our committee and partners. In this regard we wish to particularly thank Janet Wenzlau and John Hutton from Denver who made large efforts to support the ZnT8A sub-study.

Preliminary results were presented in our session at the IDS-10 meeting in Malmö (program details on the IDS website), and further data analysis is ongoing. We would like to announce that a *Certificate on DASP Workshop Performance* will soon be available on request for participating laboratories.

Overall, the DASP 2009 workshop showed that laboratories with highly sensitive and specific assays achieved a high degree of concordance for several antibodies, but performance in some assays can still be improved. In addition, DASP has continued to provide a platform for evaluation and validation of new antigens and new methods in order to facilitate translation of promising research developments into more common laboratory practice.

Autoantibodies to GAD, IA-2, and insulin. Laboratories contributed 53 GADA assays, 52 IA-2A assays, 31 IAA assays, and 4 combined and ICA assays. In addition, 14 assays using the new GADA and IA-2A standard method protocols were contributed, which clustered well with in-house Radio Binding Assays (RBAs) for GADA and IA-2A. As in DASP 2007, the sensitivity of GADA assays continued to cluster well with ELISA kits providing somewhat more sensitivity and better assay characteristics than the RBA kits. For IA-2A, RBA and ELISA kits gave more comparable performance than in previous DASP Workshops. Combined GADA and IA-2A ELISAs performed well. IAA assays remained highly variable and IAA RBA kits did not perform as well as most in-house IAA assays.

The Antibody Assay Harmonization Program. Efforts are ongoing to develop harmonized standard assays for islet autoantibodies that allow concordance in measurements between laboratories. IDS-10 provided another opportunity to evaluate the performance of the harmonized standard IA-2A and GADA assays in DASP. Seven laboratories ran the standard assays with the DASP sera, including five NIDDK consortia laboratories. Of the seven laboratories, six achieved a laboratory-reported sensitivity for IA-2A of at least 60% (median 63%, range 60 to 66%) at an adjusted specificity of 98.9%. These six laboratories also achieved a laboratory-reported sensitivity for GADA of at least 66% (median 69%, range 66 to 80%) at adjusted specificities greater than 92% (median 94.2%, range 92.6 to 98.9%). The five NIDDK consortia laboratories showed excellent concordance in ranking of samples for IA-2A, with 29 of 50 cases above 5 DK Units/ml and 16 below 5 DK Units/ml in all laboratories. Concordance in ranking of samples for GADA by the five consortia laboratories was not as good; 29 cases were found positive and 11 negative for GADA in all laboratories. We conclude that use of harmonized assays can allow good agreement between laboratories for islet autoantibody measurement, particularly for IA-2A. We aim to repeat this sub-study for IDS-11 and hope that more laboratories will evaluate the standard assays in 2010.

DASP 2009 ZnT8A sub-study. This sub-study was aimed at evaluating the sensitivity and specificity of ZnT8A assays and concordance of reported results among laboratories, as well as determining the target specificity and levels of antibodies against the two major allelic variants of ZnT8, aa325-Arg and aa325-Trp. In addition, sensitivity and specificity of ZnT8A assays measuring antibodies to the ZnT8 aa325-Arg and aa325-Trp allelic variants separately vs. assays measuring antibodies to both variants combined were also verified. There was high interest in participating in this sub-study. Twenty-six laboratories from 9 countries submitted results from a total of 67 assays. Most of the laboratories used the RBA format for ZnT8A measurement, with two laboratories also using the Luminescent Immunoprecipitation System (LIPS) and one an Indirect Immunofluorescence Assay (IFA) on transfected cells. Measurements included ZnT8A to the aa325-Arg and 325-Trp C-terminal domain variants, assessed separately or in combination, to the N-terminal domain of ZnT8, to a chimeric construct joining the N and C terminal domains, and in one case to full length ZnT8. A preliminary analysis of submitted assays suggests a good concordance of results between laboratories for assays measuring ZnT8A to the C-terminal domain and that the highest sensitivity is achieved by assays measuring simultaneously antibodies to both aa325-Arg and aa325-Trp variants.

DASP 2009 IAA competition sub-study. IAA affinity has been evaluated by 10 laboratories in the DASP 2007 Workshop and was shown to improve sensitivity, specificity and concordance of IAA measurements when combined with IAA titer. In order to facilitate the transfer of these improvements to routine IAA screening we aimed to evaluate a more feasible method that could provide a similar amount of information as the 2007 IAA affinity assay. The 2009 sub-study therefore assessed whether using one additional lower concentration of unlabelled insulin in the common competitive micro-IAA assay would help distinguishing between diabetes-associated (high affinity) and non-associated (low affinity) IAA responses and therefore improving the diagnostic performance of IAA assays. Nine laboratories participated in this sub-study. Data showed that discrimination between high and low affinity IAA is possible by using the proposed method, but determination in samples with low IAA titer requires high assay precision and results are more reliable in samples with IAA titer above a certain laboratory-defined threshold.

IA-2β autoantibodies. Three laboratories participated in DASP 2009 with IA-2βA assays. Two laboratories used LIPS and one laboratory used IFA for antibody measurement. All assays were based on C-terminal human

recombinant IA-2β generated in different expression systems. Both LIPS assays showed good and comparable assay performance, with remarkable concordance of reported results and significant correlation of IA-2βA titer. Only five serum samples, all with low titer IA-2βA, were discordantly designated positive or negative. The IFA demonstrated a high specificity but lower sensitivity. IA-2βA detected by LIPS were strongly correlated with IA-2A and to lesser extent with ZnT8A, but not with GADA.

Autoantibody patterns. The combined appearance of islet autoantibodies was analyzed in order to assess antibody patterns and their relationship with antibody titer in DASP samples. Reported results from 53 GADA assays, 52 IA-2A assays, 31 IAA assays and 19 ZnT8A assays were used to address these questions. As expected, the number of patients with multiple antibodies was markedly increased among laboratories with the most sensitive assays for GADA, IA-2A, IAA, and ZnT8A. Simultaneously, the number of single antibody-positive (n=5) and antibody-negative (n=4) patients was low among these laboratories. The majority of patients' samples contained all four autoantibodies, followed by the combination of GADA, IA-2A and ZnT8A. Among single antibody-positive samples, GADA were detected most frequently in both patients and controls.

DASP materials

As you know, all DASP activities depend on the availability of appropriate material, particularly serum samples from patients with new-onset T1D.

We would like to thank ALL who have contributed material to DASP. Your help is very much appreciated! A complete list of names from all colleagues who have provided samples will soon be posted on the IDS website.

In particular, we wish to thank colleagues from The Children's Mercy Hospital in Kansas City (Sue Ellen Weigel, Lois Hester, Robert Fletcher, Candy Schmoll, Michelle Farthing) who have contributed 42 patients' samples over the last 3 years!

Many thanks also to Aureli Esquerda, David Harlan, Howard Zissers, Pat Goubert, Ondrej Cinek, Markus Walter, and Michael Schlosser for recent sample contributions!

Since fresh samples are continuously needed in order to provide sufficient workshop material to the large number of participating laboratories, we would like to renew our *Call for Samples*, which will also be posted on the IDS website, and hope that many of you may be able to help!

DASP Publications

Results for GADA and IA-2A from three workshops (DASP 2002-2005) have been published in 2008 (Törn C et al., *Diabetologia* 51: 846-52).

A manuscript on IAA covering results from the same workshops is prior to submission.

Results of the pilot-workshop on IAA affinity (DASP 2005) have been published in 2007 (Achenbach P et al., *Clin Immunol* 122: 85-90).

Manuscripts on the results of the last two workshops (DASP 2007-2009) are currently being drafted. For the future, our aim is to realize publication of workshop results prior to the next following IDS meeting.

DASP 2010 Workshop

Finally, we would like to announce the DASP 2010 Workshop and hope that again many laboratories will evaluate their autoantibody assays in an international proficiency test. We will circulate a *Call for Registration* beginning of next year.

In DASP 2010, we will introduce slight changes to the traditional workshop format. This will concern the proportion of new-onset T1D patients and respectively controls within the sets of 150 coded workshop samples that are usually distributed among participating laboratories. Thus, the number of cases will become less predictable and, in addition, there will be space for including pre-selected samples that may serve for investigating specific questions outside the common assay proficiency test. As in the last workshops, we also aim to organize sub-studies in order to evaluate more recent markers/new assays in our field. Since we are currently still at an early stage in the planning of the next workshop, suggestions from the IDS community on particular sub-studies are welcome.

Your DASP Committee,

Pat Mueller, Atlanta, USA

Michael Schlosser, Greifswald, Germany

Alistair Williams, Bristol, UK

Vito Lampasona, Milan, Italy

Peter Achenbach, Munich, Germany

IDS TCW QUARTERLY NEWLETTER – 2/2009

www.immunologyofdiabetessociety.com/committee_t-celll.htm

Sept 4, 2009

Dear Colleagues,

During IDS-10, organized by Ake Lernmark and Corrado Cilio in Malmö on May 17-20 2009, the TCW group presented the rationale and outline of the current projects.

Tim Tree introduced the project on PBMC freezing and thawing (IDS-TCW Freezing Study I), Ivana Durinovic-Bello and Roberto Mallone reported on the initial phase of the Tetramer Directed Epitope Validation Initiative (proto-TDEVI Study) and Alessandro Sette presented data on epitope databases around infectious diseases.

In addition, selected abstracts on T cell studies were presented by Bart Roep (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), Stuart Mannering (The A-Chain of Insulin is a Hot-Spot for CD4+ T-Cell Epitopes in Human Type 1 Diabetes) and Howard Davidson (CD4 T Cell Autoreactivity to the Major Diabetes Autoantigen ZnT8).

Furthermore, we had our first "T Cell Karaoke" on one of the evenings in Malmö as an informal event where we openly discussed T cell issues and enjoyed good music and good company. For the next IDS, we thought of moving this nice event at an earlier evening hour, perhaps parallel to poster sessions.

Besides this meeting in Malmö, the group keeps interacting through monthly telephone conferences, initially by Skype, and now kindly supported by JDRF (Olivia Lou) with a telephone line conference of much better quality. During these meetings, we perform project planning and updating on a regular basis, and open issues are discussed among the group members. We are currently preparing a review manuscript to outline the background and rationale for current studies. Also, in press manuscripts regarding T cell projects are circulated amongst the group members. The chair of the telephone conference and the secretary (taking minutes) rotate every month. As announced previously, the TCW is focusing on three major projects:

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: the goal of this study is to compare two mainstream PBMC freezing/thawing protocols, namely cold vs. warm freezing medium (DMSO-human serum), along with other local protocols which may be considered as promising alternatives. The aim is to define starting "gold standard" freezing procedure(s) which perform superiorly across different T cell assay formats (i.e., best cell recovery and viability, preservation of beta-cell-specific T cell responses from frozen aliquots as compared to starting fresh PBMC preparations).

In an effort to blind the study, we elected to do so with antigens rather than with PBMC samples (see website for details). So far, antigens provided by each laboratory have been coded by Tim Tree and sent back to the requesting laboratories. Two out of 9 labs already tested freshly isolated and frozen PBMCs from 5 patients with type 1 diabetes and 5 control subjects and thereby finished the first part of this study. The remaining labs are expected to finish within the next few months. All raw data will be sent to Tim Tree lab for de-coding and will be analysed by a group of people. Antigen identity will thus be unblinded only after data has been locked.

3) Proto-TDEVI Study: this is the first phase of a larger TDEVI (Tetramer-Directed Epitope Validation Initiative) study 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 strategy of epitope validation, based on independent, blinded tetramer testing performed in multiple Laboratories on a limited number of blood samples.

This first phase is ongoing, and includes a CD4+ and a CD8+ T cell arm involving 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-DR0401-restricted GAD270-285, GAD554-567, PPI76-90; and HLA-A2-restricted GAD114-122, GAD536-545, PPI34-42 and PPI101-109. The required reagents and tetramers have been kindly provided by Dr. Jerry Nepom's laboratory and have been sent to participating laboratories. Detailed protocols have been distributed and lab personnel trained where necessary.

Three laboratories have started CD4+ Tetramer analyses and three more have commenced the CD8+ T cell arm. This phase of the study should be completed by spring 2010.

Please note that the IDS TCW activities are open to participation and anyone interested is welcome to join. Please contact any of us in case you want to be involved. Further details about these studies can be found on the IDS-TCW website.

Nanette Schloot and Roberto Mallone

on behalf of The IDS TCW Committee

THE DIABETES NEWS-I

CONTENTS

1. Rituximab, B-lymphocyte depletion, and preservation of beta-cell function

BACKGROUND: The immunopathogenesis of type 1 diabetes mellitus (T1D) is associated with T-lymphocyte autoimmunity. However, there is growing evidence that B lymphocytes play a role in many T-lymphocyte-mediated diseases. It is possible to achieve selective depletion of B lymphocytes with rituximab, an anti-CD20 monoclonal antibody. This phase 2 study evaluated the role of B-lymphocyte depletion in patients with T1D.

METHODS: We conducted a randomized, double-blind study in which 87 patients between 8 and 40 years of age who had newly diagnosed type 1 diabetes were assigned to receive infusions of rituximab or placebo on days 1, 8, 15, and 22 of the study. The primary outcome, assessed 1 year after the first infusion, was the geometric mean area under the curve (AUC) for the serum C-peptide level during the first 2 hours of a mixed-meal tolerance test. Secondary outcomes included safety and changes in the glycated hemoglobin level and insulin dose.

RESULTS: At 1 year, the mean AUC for the level of C peptide was significantly higher in the rituximab group than in the placebo group. The rituximab group also had significantly lower levels of glycated hemoglobin and required less insulin. Between 3 months and 12 months, the rate of decline in C-peptide levels in the rituximab group was significantly less than that in the placebo group. CD19+ B lymphocytes were depleted in patients in the rituximab group, but levels increased to 69% of baseline values at 12 months. More patients in the rituximab group than in the placebo group had adverse events, mostly grade 1 or grade 2, after the first infusion. The reactions appeared to be minimal with subsequent infusions. There was no increase in infections or neutropenia with rituximab.

CONCLUSIONS: A four-dose course of rituximab partially preserved beta-cell function over a period of 1 year in patients with type 1 diabetes. The finding that B lymphocytes contribute to the pathogenesis of type 1 diabetes may open a new pathway for exploration in the treatment of patients with this condition.

Source: NEJM, 2009: 361 (22): 2143 (Pescovitz MD et al)

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2. Autologous umbilical cord blood transfusion in very young children with type 1 diabetes.

OBJECTIVE: Interest continues to grow regarding the therapeutic potential for umbilical cord blood therapies to modulate autoimmune disease. We conducted an open-label phase I study using autologous umbilical cord blood infusion to ameliorate type 1 diabetes.

RESEARCH DESIGN AND METHODS: Fifteen patients diagnosed with type 1 diabetes and for whom autologous umbilical cord blood was stored underwent a single intravenous infusion of autologous cells and completed 1 year of postinfusion follow-up. Intensive insulin regimens were used to optimize glycemic control. Metabolic and immunologic assessments were performed before infusion and at established time periods thereafter.

RESULTS: Median (interquartile range [IQR]) age at infusion was 5.25 (3.1-7.3) years, with a median postdiagnosis time to infusion of 17.7 (10.9-26.5) weeks. No infusion-related adverse events were observed. Metabolic indexes 1 year postinfusion were peak C-peptide median 0.50 ng/ml (IQR 0.26-1.30), P = 0.002; A1C 7.0% (IQR 6.5-7.7), P = 0.97; and insulin dose 0.67 units * kg(-1) * day(-1) (IQR 0.55-0.77), P = 0.009. One year postinfusion, no changes were observed in autoantibody titers, regulatory T-cell numbers, CD4-to-CD8 ratio, or other T-cell phenotypes.

CONCLUSIONS: Autologous umbilical cord blood transfusion in children with type 1 diabetes is safe but has yet to demonstrate efficacy in preserving C-peptide. Larger randomized studies as well as 2-year postinfusion follow-up of this cohort are needed to determine whether autologous cord blood-based approaches can be used to slow the decline of endogenous insulin production in children with type 1 diabetes.

Score: Diabetes Care. 2009 Nov;32(11):2041-6. (Heller MJ et al)

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3. Autoantigen-specific regulatory T cells induced in patients with T1D mellitus by insulin B-chain immunotherapy.

There is a growing body of evidence to suggest that the autoimmunity observed in type 1 diabetes mellitus (T1DM) is the result of an imbalance between autoaggressive and regulatory cell subsets. Therapeutics that supplement or enhance the existing regulatory subset are therefore a much sought after goal in this indication. Here, we report the results of a double blind, placebo controlled, phase I clinical trial of a novel antigen-specific therapeutic in 12 subjects with recently diagnosed T1DM. Our primary objective was to test its safety. The study drug, human insulin B-chain in incomplete Freund's adjuvant (IFA) was administered as a single intramuscular injection, with subjects followed for 2 years. All subjects completed therapy and all follow-up visits. The therapy was generally safe and well- tolerated. Mixed meal stimulated C-peptide responses, measured every 6 months, showed no statistical differences between arms. All patients vaccinated with the autoantigen, but non e who received placebo, developed robust insulin-specific humoral and T cell responses. Up to two years following the single injection, in peripheral blood from subjects in the experimental arm, but not the control arm, insulin B-chain-specific CD4+ T cells could be isolated and cloned that showed phenotypic and functional characteristics of regulatory T cells. The induction of a lasting, robust immune response generating autoantigen-specific regulatory T cells provides strong justification for further testing of this therapy in type 1 diabetes.

Source: J Autoimmun. 2009 Nov 18. [Epub ahead of print]. Orban T, et al. Joslin Diabetes Center, Boston, MA 02215, USA.

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4. Clinical Applications of Diabetes Antibody Testing.

Context: Autoantibodies to glutamate decarboxylase, islet antigen-2, insulin, and zinc transporter-8 are characteristic of type 1 diabetes. They are detectable before clinical onset and define the subgroup of patients with latent autoimmune diabetes in adults. Autoantibody assays are increasingly available to clinicians. This article reviews the prognostic significance of autoantibodies and considers the utility of diabetes antibody

testing in routine clinical practice.

Evidence Acquisition: The medical literature to May 2009 was reviewed for key articles and consensus statements covering use of islet autoantibody testing for prediction and classification of diabetes and implications for therapy.

Evidence Synthesis: Sensitive and specific glutamate decarboxylase and islet antigen-2 antibody assays are widely available, although to insulin autoantibody assays remain variable. Islet autoantibodies appear early in life, and testing for multiple antibodies identifies unaffected individuals at very high risk of type 1 diabetes with high sensitivity. This is important for research, but currently no intervention prevents or delays diabetes, and evidence of benefit from awareness of risk is weak. In non-insulin-treated diabetes, patients with autoantibodies progress to insulin requirement more rapidly, but evidence that testing benefits the individual patient is limited. Antibody testing is useful in classifying diabetes of other types.

Conclusions: Islet autoantibody testing allows prediction of type 1 diabetes and definition of the latent autoimmune diabetes in adults subgroup of non-insulin-treated patients. Although useful for research, until therapies modulating the disease process become available, the benefit to individual patients is generally questionable. With a few exceptions, diabetes antibody testing does not yet have a role in routine clinical care.

Source: J Clin Endocrinol Metab. 2009 Oct 29. [Epub ahead of print] (Bingley P)

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5. Latent Autoimmune Diabetes in Adults.

Context: Autoantibodies that are reactive to islet antigens are present at the time of diagnosis in most patients with type 1 diabetes. Additionally, approximately 10% of phenotypic type 2 diabetic patients are positive for at least one of the islet autoantibodies, and this group is often referred to as "latent autoimmune diabetes in adults (LADA)." These patients share many genetic and immunological similarities with type 1 diabetes, suggesting that LADA, like type 1 diabetes, is an autoimmune disease. However, there are differences in autoantibody clustering, T cell reactivity, and genetic susceptibility and protection between type 1 diabetes and LADA, implying important differences in the underlying disease processes. Evidence Acquisition and Synthesis: In this clinical review, we will summarize the current understanding of LADA based on the MEDLINE search of all peer-reviewed publications (original articles and reviews) on this topic between 1974 and 2009. Conclusions: In LADA, diabetes occurs earlier in the beta-cell-destructive process because of the greater insulin resistance. Complexities arise also because of variable definitions of LADA and type 1 diabetes in adults. As immunomodulatory therapies that slow or halt the type 1 diabetes disease process are discovered, testing these therapies in LADA will be essential.

Source: J Clin Endocrinol Metab. 2009 Oct 16. [Epub ahead of print] (Naik RG et al)

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6. Therapy of experimental type 1 diabetes by isolated Sertoli cell xenografts alone.

Type I diabetes mellitus is caused by autoimmune destruction of pancreatic beta cells, and effective treatment of the disease might require rescuing beta cell function in a context of reinstalled immune tolerance.

Sertoli cells (SCs) are found in the testes, where their main task is to provide local immunological protection and nourishment to developing germ cells. SCs engraft, self-protect, and coprotect allogeneic and xenogeneic grafts from immune destruction in different experimental settings. SCs have also been successfully implanted into the central nervous system to create a regulatory environment to the surrounding tissue which is trophic and counter-inflammatory.

We report that isolated neonatal porcine SC, administered alone in highly biocompatible microcapsules, led to diabetes prevention and reversion in the respective 88 and 81% of overtly diabetic (nonobese diabetic [NOD]) mice, with no need for additional beta cell or insulin therapy. The effect was associated with restoration of systemic immune tolerance and detection of functional pancreatic islets that consisted of glucose-responsive and insulin-secreting cells. Curative effects by SC were strictly dependent on efficient tryptophan metabolism in the xenografts, leading to TGF-beta-dependent emergence of autoantigen-specific regulatory T cells and recovery of beta cell function in the diabetic recipients.

Source: J Exp Med. 2009; 206(11):2511-26. (Fallarino F et al)

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7. T cell islet accumulation in type 1 diabetes is a tightly regulated, cell-autonomous event

Type 1 diabetes is a T cell-mediated autoimmune disease, characterized by lymphocytic infiltration of the pancreatic islets. It is currently thought that islet antigen specificity is not a requirement for islet entry and that diabetogenic T cells can recruit a heterogeneous bystander T cell population.

We tested this assumption directly by generating T cell receptor (TCR) retrogenic mice expressing two different T cell populations. By combining diabetogenic and nondiabetogenic or nonautoantigen-specific T cells, we demonstrate that bystander T cells cannot accumulate in the pancreatic islets. Autoantigen-specific T cells that accumulate in islets, but do not cause diabetes, were also unaffected by the presence of diabetogenic T cells. Additionally, 67% of TCRs cloned from nonobese diabetic (NOD) islet-infiltrating CD4(+) T cells were able to mediate cell-autonomous islet infiltration and/or diabetes when expressed in retrogenic mice.

Therefore, islet entry and accumulation appears to be a cell-autonomous and tightly regulated event and is governed by islet antigen specificity.

Source: Immunity. 2009 Oct 16;31(4):643-53

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8. How punctual ablation of regulatory T cells unleashes an autoimmune lesion within the pancreatic islets

CD4(+)Foxp3(+) regulatory T cells (Treg cells) are known to control the progression of autoimmune diabetes, but when, where, and how they exert their influence in this context are questions still under vigorous debate.

Exploiting a transgene encoding the human diphtheria toxin receptor, we punctually and specifically ablated Foxp3(+) cells in the BCD2.5/NOD mouse model of autoimmune diabetes. Strikingly, overt disease developed within 3 days. The earliest detectable event was the activation of natural killer (NK) cells directly within the insulitic lesion, particularly the induction of Ifng gene expression within 7 hours of Treg cell ablation. Interferon-gamma had a strong impact on the gene-expression program of the local CD4(+) T effector cell population, unleashing it to aggressively attack the islets, which was required for the development of diabetes.

Thus, Treg cells regulate pancreatic autoimmunity in situ through control of a central innate immune system player, NK cells.

Source: Immunity. 2009 Oct 16;31(4):654-64. (Feurer M et al)

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9. Interactions between PD-1 and PD-L1 promote tolerance by blocking the TCR-induced stop signal

Programmed death 1 (PD-1) is an inhibitory molecule expressed on activated T cells; however, the biological context in which PD-1 controls T cell tolerance remains unclear. Using two-photon laser-scanning microscopy, we show here that unlike naive or activated islet antigen-specific T cells, tolerized islet antigen-specific T cells moved freely and did not swarm around antigen-bearing dendritic cells (DCs) in pancreatic lymph nodes.

Inhibition of T cell antigen receptor (TCR)-driven stop signals depended on continued interactions between PD-1 and its ligand, PD-L1, as antibody blockade of PD-1 or PD-L1 resulted in lower T cell motility, enhanced T cell-DC contacts and caused autoimmune diabetes. Blockade of the immunomodulatory receptor CTLA-4 did not alter T cell motility or abrogate tolerance.

Thus, PD-1-PD-L1 interactions maintain peripheral tolerance by mechanisms fundamentally distinct from those of CTLA-4.

Source: Nat Immunol. 2009 Nov;10(11):1185-92 (Fife BT et al)

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10. Genetic-induced Variations in the GAD65 T-cell Repertoire Governs Efficacy of Anti-CD3/GAD65 Combination Therapy in New-onset Type 1 Diabetes

To enhance efficacy of forthcoming type 1 diabetes (T1D) clinical trials, combination therapies (CTs) are envisaged.

In this study, we showed that efficacy of a CT, using anti-CD3 antibody and glutamic acid decarboxylase of 65 kd (GAD65)-expressing plasmid, to reverse new-onset T1D was dependent upon the genetic background.

Synergism between both treatments was only observed in the RIP-LCMV-GP but not in the nonobese diabetic (NOD) or RIP-LCMV-NOD models. Efficacy was associated with an expansion of bystander suppressor regulatory T cells (Tregs) recognizing the C-terminal region of GAD65 and secreting interleukin-10 (IL-10), transforming growth factor-beta (TGF-beta), and interferon-gamma (IFN-gamma). In addition, we found that frequency and epitope specificity of GAD65-reactive CD4(+) T cells during antigen priming at diabetes onset and Tregs detected after CT correlated. Consequently, NOD mice harbored significantly lower levels of GAD65-reactive CD4(+) T cells than RIP-LCMV-GP before and after treatment.

Our results demonstrate that antigen-specific T cells available at treatment may differ between various major histocompatibility complex (MHC) and genetic backgrounds. These cells play a major role in shaping T-cell responses following antigen-specific immune intervention and determine whether a beneficial Tregs response is generated. Our findings hold important implications to understand and predict the success of antigen-based clinical trials, where responsiveness to immunotherapy might vary from patient to patient

Source: Mol Ther. 2009 Aug 18. [Epub ahead of print] (Bresson D et al)

ANNOUNCEMENT

Dear Members of the IDS,

Medpedia's Diabetes Community (www.medpedia.com/communities/47-Diabetes) is a virtual space for medical professionals, patients, caregivers,researchers, and advocates to exchange and access information regarding diabetes. I wanted to offer the Immunology of Diabetes Society the opportunity to get involved at the ground level and use this space to advance your research among other experts and advocates.

Is this something you would be interested in learning more about?

Kind regards,

Jennifer

Jennifer HawkinsCommunity Manager, Medpedia703 Market St, Suite 470San Francisco, CA(415) 281-3931


11th IDS Incheon Korea
October 31(Sun) ~ November 3(Wed), 2010
Songdo Convensia, Incheon, Korea
The 11th International Congress of the Immunology of Diabetes Society
Date: October 31(Sun) ~ November 3(Wed), 2010
Venue: Songdo Conventia - Ballroom (meeting place)
Sheraton Incheon - Main accomodation
Best Western Premier Songdo Park Hotel (accomodation)
BENKIA Premier Songdo Metro Hotel (accomodation)
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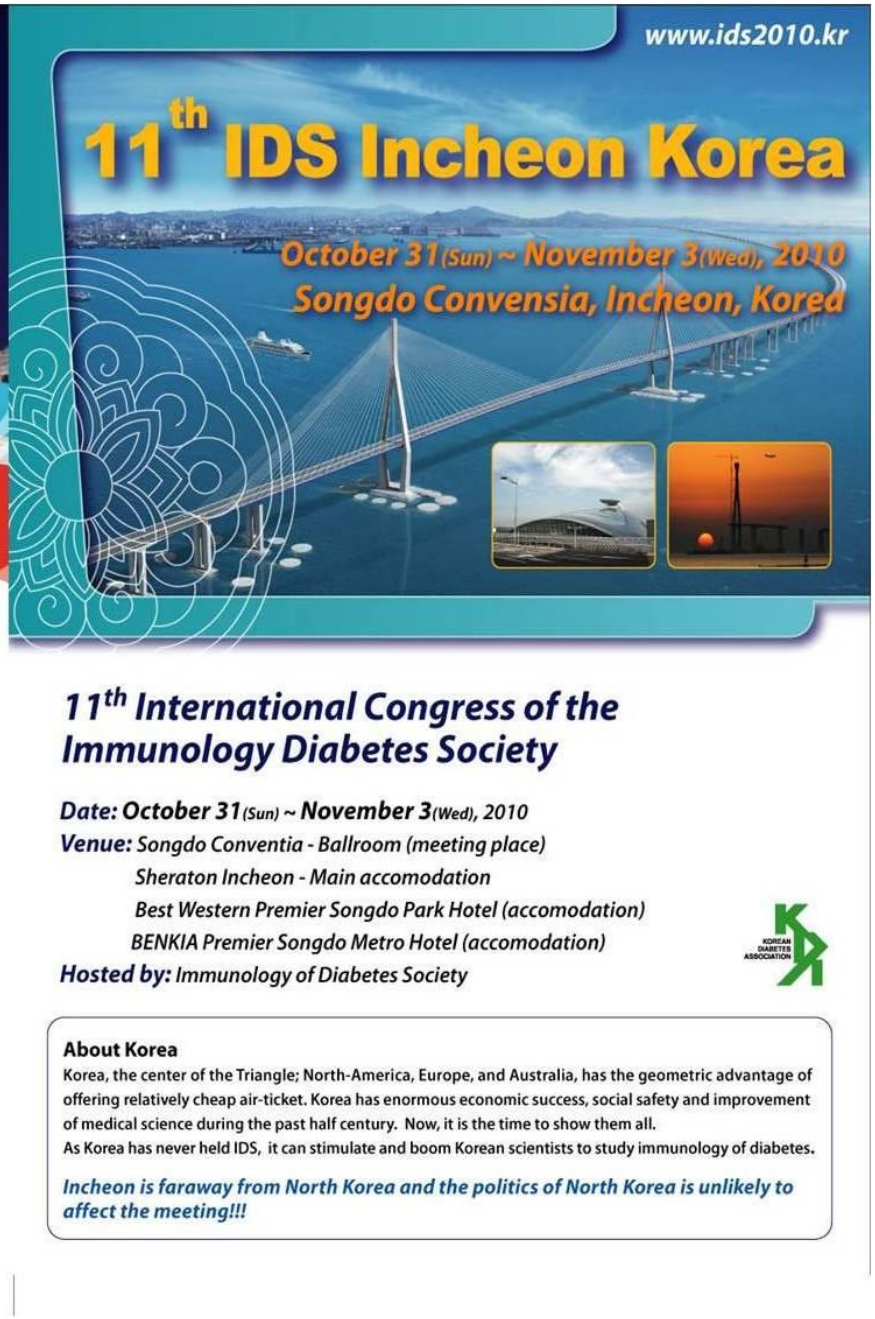
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About Korea
Korea, the center of the Triangle; North-America, Europe, and Australia, has the geometric advantage of offering relatively cheap air-ticket. Korea has enormous economic success, social safety and improvement of medical science during the past half century. Now, it is the time to show them all.
As Korea has never held IDS, it can stimulate and boom Korean scientists to study immunology of diabetes.
Incheon is faraway from North Korea and the politics of North Korea is unlikely to affect the meeting!!!