

Novartis Foundation Symposium 292

# DEFINING OPTIMAL IMMUNOTHERAPIES FOR TYPE 1 DIABETES

 **WILEY-BLACKWELL**

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# **DEFINING OPTIMAL IMMUNOTHERAPIES FOR TYPE 1 DIABETES**

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# Contents

*Novartis Foundation Symposium on Defining optimal immunotherapies for type 1 diabetes,  
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*This symposium is based on a proposal made by Matthias von Herrath and  
Jeffrey Bluestone*

**Matthias von Herrath** Chair's introduction 1

**Alan K. Foulis** Pancreatic pathology in type 1 diabetes in human 2  
*Discussion* 13

**Daniel Pipeleers, Peter In 't Veld, Miriam Pipeleers-Marichal and  
Frans Gorus** The  $\beta$  cell population in type 1 diabetes 19  
*Discussion* 24

**Peter Reifsnyder, William Schott, Darcy Pomerleau, Mark D. Lessard,  
Brian W. Soper and Edward H. Leiter** Bone marrow expressing a  
diabetes resistance MHC class II allele: diabetes deviation by chronic  
immune stimulation 32  
*Discussion* 46

**Damien Bresson and Matthias von Herrath** Resuscitating adaptive  
Tregs with combination therapies? 50  
*Discussion* 60

**Thomas W. H. Kay, Nadine L. Dudek, Kate Graham, Eugene Estella,  
Eveline Angstetra, Mark D. McKenzie, Jan Allison and  
Helen E. Thomas** Cytotoxic T cell mechanisms of  $\beta$  cell destruction in  
non-obese diabetic mice 68  
*Discussion* 78

**Li Zhang, Roberto Gianani, Maki Nakayama, Edwin Liu, Masakazu Kobayashi, Erin Baschal, Liping Yu, Sunanda Babu, Abby Dawson, Kelly Johnson, Mohamed Jahromi, Theresa Aly, Pamela Fain, Jennifer Barker, Marian Rewers and George S. Eisenbarth**

Type 1 diabetes: chronic progressive autoimmune disease 85

*Discussion* 94

**Teodora Staeva** Current and past prevention and intervention trials in type 1 diabetes 99

*Discussion* 109

**Mark Peakman** CD8 and cytotoxic T cells in type 1 diabetes 113

*Discussion* 119

**General discussion I** 122

**General discussion II** 126

**Pere Santamaria** Genetic and therapeutic control of diabetogenic CD8<sup>+</sup> T cells 130

*Discussion* 136

**General discussion III** 141

**Frank Waldron-Lynch, Matthias von Herrath and Kevan C.**

**Herold** Towards a curative therapy in type 1 diabetes: remission of autoimmunity, maintenance and augmentation of  $\beta$  cell mass 146

*Discussion* 155

**Bart O. Roep** Immune markers of disease and therapeutic intervention in type 1 diabetes 159

*Discussion* 171

**Silvia Gregori, Manuela Battaglia and Maria-Grazia Roncarolo**

Re-establishing immune tolerance in type 1 diabetes via regulatory T cells 174

*Discussion* 183



<b>Ezio Bonifacio, Anette Ziegler, Peter Achenbach, Jennifer Barker</b> and <b>George S. Eisenbarth</b> Translating mucosal antigen based prevention of autoimmune diabetes to human	187
<i>Discussion</i>	199
<b>Matthias von Herrath</b> Closing remarks	202
Index of contributors	204
Subject index	206

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# Chair's introduction

Matthias von Herrath

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Diabetes is a disease where we still have many gaps in our knowledge. It is a special disease because we can't access the organ very well, especially during the prediabetic phase in humans. Perhaps by linking animal studies with *in vitro* studies of human cells and then actual human studies we can close some of these gaps during this meeting. This pertains to both the basic pathogenesis of the disease as well as clinical translations.

There are many areas that are important to me in this field. I want to learn more about how the human disease actually comes together. I want to understand the kinetics. There are certain things that continue to puzzle me: I don't understand how an immune-mediated disease is sustained for such a long time (in some cases the prediabetic phase can last more than seven years). How can it be that cells are continuously regenerated to attack islets in this chronic fashion? That a comparatively low-grade inflammatory immunological process can continue like this for several years puzzles me.

Understanding these types of kinetics will not only translate into understanding the pathogenesis, but also devising an optimal therapy: for example, we do not know for how long we would have to stop aggressive cells for in order to circumvent recurrence of disease. Does immunosuppressive or immune modulatory therapy have to be administered continuously, even if bystander regulation and other immunological control mechanisms that can be self-sustained by auto-antigens are being invoked? Here we should discuss these issues, and others, for example with the question of the number of important autoantigens in type 1 diabetes: is there just one antigenic 'driver' pathway? I would also like to see parallels made with other diseases, where applicable, and we have therefore invited speakers whose main expertise is in multiple sclerosis and other autoimmune disorders.

Retrospectively, this conference turned out to be a treat in many respects even for those who would consider themselves to be seasoned investigators in the pathogenesis of type 1 diabetes. We uncovered crucial 'forgotten' human data sets that should be revisited and expanded, we learned much more about the human aspects of type 1 diabetes pathogenesis which will be important to properly adjust current animal models, and we better comprehended crucial therapeutic and kinetic issues of the disease.

# Pancreatic pathology in type 1 diabetes in human

Alan K. Foulis

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*Abstract.* In type 1 autoimmune diabetes there is a selective destruction of insulin-secreting  $\beta$  cells. Around the time of clinical presentation, insulinitis, a chronic inflammatory infiltrate of the islets affecting primarily insulin containing islets, is present in the majority of cases. The inflammatory infiltrate consists primarily of T lymphocytes; CD8 cells outnumber CD4 cells, there are fewer B lymphocytes and macrophages are relatively scarce.  $\beta$  cell death may involve the Fas apoptotic pathway since they have been shown to express Fas, infiltrating T lymphocytes express Fas-L and apoptotic  $\beta$  cells have been described. Hyperexpression of class I MHC by all the endocrine cells in many insulin-containing islets is a well recognized phenomenon, characteristic of the disease. It has been argued that this is an earlier event than insulinitis within a given islet and appears to be due to secretion of interferon  $\alpha$  by  $\beta$  cells within that islet. A recent study has found evidence of Coxsackie virus infection in  $\beta$  cells in three out of six pancreases of patients with recent-onset type 1 diabetes. Coxsackie viruses are known to induce interferon  $\alpha$  secretion by  $\beta$  cells and this could initiate the sequence of events that culminates in their autoimmune destruction.

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There are a number of different ways of obtaining pancreas specimens from patients with type 1 diabetes. Historically, the most common source was retrospective collections of autopsy pancreases from children who had died around the time of clinical diagnosis (Foulis et al 1986, Gepts 1965). The disadvantage of this approach was that there was usually a degree of autolysis in the tissues and the pancreas would almost certainly have been fixed in formalin and paraffin embedded. These factors and the lack of access to peripheral blood of the patient limited the range of possible studies on these pancreases.

A radical departure from this historical practice has been the approach of the group from Osaka. They performed laparoscopic pancreatic biopsies on patients who had been diagnosed with type 1 diabetes in the previous three months. A great range of tests has been done on this tissue and the results have been correlated with clinical findings. The disadvantage is that the biopsies were small

(20–30 mg) leading to a possible sampling problem. Thus the biopsies of three out of the first seven patients had no insulin-containing islets (Hanafusa et al 1990). While pancreatic biopsy has proven to be safe, no other research group has adopted this practice.

Finally, in the last 15 years a number of patients with recent-onset disease have died in intensive care units and permission has been given to remove organs for transplantation. The pancreas has thus been removed immediately after death, there has been no shortage of tissue and a full range of tests could be done (Dotta et al 2007).

### Insulitis

If the pancreas of a patient who has had type 1 diabetes for more than five years is studied, the great majority of islets will be seen to be insulin deficient. They consist of a normal number of the other hormone-secreting cells found in the islets of the pancreas (pancreatic polypeptide-secreting PP cells, glucagon-secreting A cells and somatostatin secreting D cells) (Foulis & Stewart 1984). There has thus been selective loss of the  $\beta$  cells. If the pancreas is studied at or within a year or two of clinical diagnosis, three types of islet are found (Gepts 1965, Foulis & Stewart 1984). Firstly, approximately 70% of the islets are insulin deficient (identical to those found in patients with prolonged disease). Secondly, there are islets containing  $\beta$  cells that are affected by insulitis (a chronic inflammatory infiltrate within the islet, Fig. 1) and, thirdly, there are insulin-containing islets which appear essentially normal. The finding that 18%

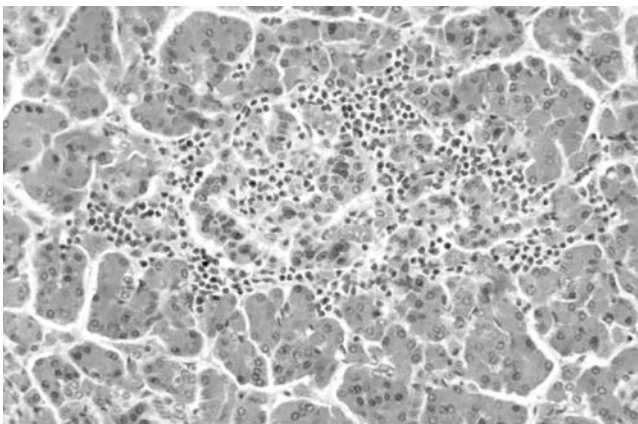


FIG. 1. Insulitis. There is a predominantly lymphocytic infiltrate in this islet.