7th Dresden Symposium on Autoantibodies

Dresden, 1.-4. September 2004

Ort der Veranstaltung:
Hörsaalzentrum der TU Dresden
Bergstraße 64, 01069 Dresden

Teilnehmer: 295 aus 31 Ländern

Das 7th Dresden Symposium on Autoantibodies stand unter dem Motto„ From Animal Models to Human Genetics: Research on the Induction and Pathogenicity of Autoantibodies“. Im gleichnamigen Buch (eds. K. Conrad, M.P. Bachmann, M.J. Fritzler, R.L. Humbel, U. Sack, Y. Shoenfeld; Pabst Science Publishers, Lengerich 2004) wurden die Ergebnisse hierzu ausführlich vorgestellt. Schwerpunkte waren Tiermodelle zur Erforschung der Pathogenese und therapeutischen Beeinflussbarkeit von Autoimmunerkrankungen, molekulare Mechanismen xenobiotisch induzierter Autoimmunität sowie genetische Faktoren der Autoimmunität.

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7TH DRESDEN SYMPOSIUM ON AUTOANTIBODIES

DRESDEN, SEPTEMBER 1–4, 2004

FINAL PROGRAMME

22th June 2004, a historical day for Dresden:
The reconstruction of the “Church of our Lady“ is finished by the setup of the church spire.
(Picture: Bernd Bierwolf)

WELCOME

Dear Colleagues,

On behalf of the organizers, the Medical Faculty of the Technical University Dresden and the "Gesellschaft zur Förderung der Immundiagnostik e.V." (Society for the Advancement of Immune Diagnostics), I am honoured and pleased to welcome you to the 7th Dresden Symposium on Autoantibodies.

The revolutionary techniques of modern molecular and cellular biology enhance almost daily our knowledge of immunity and autoimmunity in men and experimental animals. Our fragmentary puzzle of the immune system is going to form a fascinating picture of a master piece of evolution. Although many of these aspects were achieved by analysis of human body fluids and tissues, the etiopathogenesis of autoimmune diseases cannot readily be analyzed without appropriate animal models. Therefore it is not a surprise that the current Dresden meeting on autoantibodies entitled "From Animal Models to Human Genetics – Research on the Induction and Pathogenicity of Autoantibodies" will focus on experimental autoimmune models. In 12 sessions we will have the opportunity to hear and discuss about the pathogenesis and therapy of autoimmunity in experimental mouse models, natural and pathogenic autoantibodies, molecular mechanisms of xenobiotic-induced autoimmunity as well as the genetic background of autoimmune diseases. We will extend our current knowledge about novel autoantibodies and their pathogenic and/or clinical relevance, autoantibodies in systemic and neurological diseases, the occurrence and measurement of therapy-induced antibodies, and methodical aspects as well as novel diagnostic strategies including multiplex assays for autoantibody profiling.

Since the last symposium many exciting changes were happened in Dresden. The vast damages of the once-in-a-thousand-years flood of 2002 are completely eliminated also due to the nationwide and international help. But the most important change you will find in the skyline of Dresden: The famous "Church of our Lady", destructed in 1945, has been reconstructed. So the habitants and the visitors can enjoy again the view of the historical skyline of Dresden which already has inspired the famous italian painter Canaletto, therefore named "the Canaletto view".

I am very grateful to all participants for their active contribution. I express my gratitude towards all organisers and sponsors who made this symposium possible. We will do our best to make the 7th Dresden Symposium on Autoantibodies an unforgettable event.

Karsten Conrad

Wednesday September 1

08.30–10.15 **Registration**

10.15–10.30 **Welcome and Introductions**

10.30–11.15 **PLENARY LECTURE:**
Autoimmunity in systemic diseases: Past, present and future
M. Reichlin (Oklahoma City, USA)

11.15–11.45 COFFEE BREAK

11.45–13.15 **ANIMAL MODELS I**
Co-Chairs: W.H. Reeves (Gainesville, USA)
Y. Shoenfeld (Tel Hashomer, Israel)

Main Lectures

11.45–12.25 Novel autoimmune models: Lessons from recent transgenic and knock in animals
M.P. Bachmann (Dresden, Germany)

12.25–13.05 Role of long-lived autoreactive plasma cells in autoimmunity
F. Hiepe (Berlin, Germany)

13.05–13.15 ***Short Lecture***

P1 The role of proinflammatory stimuli in the pathogenesis of MPO-ANCA associated vasculitis in a mouse model using MPO-deficient mice
D. Huugen, H. Xiao, A. van Esch, C.J. Peutz-Kootstra, J.C. Jennette, J.W. Cohen Tervaert, P. Heeringa (Maastricht, The Netherlands)

13.15–14.15 LUNCH BREAK – POSTER AND EXHIBITION VIEWING

Poster Session ***(P2–6)*** 13.45–14.15
Chair: M.P. Bachmann (Dresden, Germany)

P2 Syngeneic cells in late apoptosis mature DC in vivo and induce antibodies to dsDNA and neo-epitopes of La/SS-B in immunized mice
P. Zi-jian, K. Davis, S. Maier, J. Workman, M.P. Bachmann, A.D. Farris (Oklahoma City, USA)

P3 Rheumatic Fever: an animal model for a human disease
F.F. Alcantara, E. Postol, E.R. Alencar, J. Kalil, L. Guilherme (Sao Paulo, Brazil)

P4 Binding properties of a sequence-specific pathogenic Lupus anti-ssDNA autoantibody
M. Bobeck, J. Cleary, G.D. Glick (Ann Arbor, USA)

P5 IgM anti-dsDNA antibodies as a treatment of murine systemic Lupus erythematosus (SLE)
S. Werwitzke, D. Trick, K. Kamino, T. Matthias, K. Kniesch, B. Schlegelberger, R.E. Schmidt, T. Witte (Hannover, Germany)

P6 Peptide mimetics of anti-dsDNA idiotypes as a tool for Lupus-specific IVIG preparation: Specificity and efficacy in the treatment of experimental SLE
M. Blank, I. Nur, R. Meidler, L. Bar, L. Slutzki, B. Gilburd, Y. Shoenfeld (Tel Hashomer, Israel)

ANIMAL MODELS II **14.15–16.15**
Co-Chairs: M.P. Bachmann (Dresden, Germany)
F. Hiepe (Berlin, Germany)

Main Lectures

Innate immunity and interferon production in the pathogenesis of autoantibodies in lupus 14.15–14.55
W.H. Reeves (Gainesville, USA)

Autoantibodies – predictive, pathogenic and protective 14.55–15.35
Y. Shoenfeld (Tel Hashomer, Israel)

Wednesday September 1

Short Lectures

15.35–15.45 **P7** Selective suppression of DNA-specific B cells in lupus mice by a chimeric antibody/peptide molecule
A. Tchorbanov, E. Voynova, N. Mihailova, T. Vassilev (Sofia, Bulgaria)

15.45–15.55 **P8** Demonstration of humoral autoimmunity in the tight skin-2 mouse: a model for systemic sclerosis
J. Gentiletti, S.A. Jimenez, P. Christner (Philadelphia, USA)

15.55–16.05 **P9** Pathogenicity of autoantibodies reactive with the endogenous retroviral envelope glycoprotein gp70
M. Miyazawa, E. Kajiwara, N. Tabata, T. Ogawa, T. Yuasa, H. Matsumura (Osaka, Japan)

16.05–16.15 **P10** Enhancement of autoantibody pathogenicity by viral infections in mouse models of anemia and thrombocytopenia
A. Musaji, M. Meite, L. Detalle, S. Franquin, F. Cormont, V. Préat, S. Izui, J.-P. Coutelier (Bruxelles, Belgium)

16.15–16.45 COFFEE BREAK – POSTER AND EXHIBITION VIEWING

16.45–18.40 **NATURAL AND PATHOGENIC AUTOANTIBODIES**
Co-Chairs: P.L. Meroni (Milano, Italy)
A. Kromminga (Hamburg, Germany)

Main Lectures

16.45–17.20 Beneficial aspects of natural autoantibodies
S.V. Kaveri (Paris, France)

17.20–17.55 Disease idiotype specific IVIG – Novel therapeutical approach
Y. Shoenfeld (Tel Hashomer, Israel)

17.55–18.30 Receptors of the innate immunity as targets for circulating autoantibodies: antiphospholipid syndrome as a paradigm
P.L. Meroni (Milano, Italy)

Short Lecture

P11 Catalytically active antibodies in patients with autoimmune diseases
G.A. Nevinsky (Novosibirsk, Russia)

18.30–18.40

Welcome Reception

19.00

THURSDAY SEPTEMBER 2

09.00–10.20

MOLECULAR MECHANISMS OF XENOBIOTIC-INDUCED AUTOIMMUNITY

Co-Chairs: P. Hultman (Linköping, Sweden)
H. Schellekens (Utrecht, The Netherlands)

Main Lectures

09.00–09.40 Immunology and genetics of xenobiotic-induced autoimmunity
K.M. Pollard (La Jolla, USA)

09.40–10.20 Xenobiotic-induced autoimmune responses and protein aggregation diseases share a common subnuclear pathology
A. von Mikecz (Düsseldorf, Germany)

10.20–11.00 COFFEE BREAK – POSTER AND EXHIBITION VIEWING

10.30–11.00 ***Poster Session*** ***(P12–16)***
Chair: K.M. Pollard (La Jolla, USA)

P12 Proteasomal-dependent antigen processing of topoisomerase I in scleroderma
M. Chen, A. Tanbajewa, A. Kuhn, T. Ruzicka, A. von Mikecz (Düsseldorf, Germany)

P13 The immunotoxin mercury chloride induces specific alterations in the cell nucleus
A. Scharf, M. Chen, A. von Mikecz (Düsseldorf, Germany)

P14 Exposure to the organic mercury compound thimerosal leads to immunosuppression followed by systemic autoimmunity
S. Havarinasab, B. Häggqvist, E. Björn, K.M. Pollard, P. Hultman (Linköping, Sweden)

P15 The importance of Fc-receptors in mercury-induced autoimmunity
K. Martinsson, P. Hultman (Linköping, Sweden)

P16 An autoimmune response to tyrosine-nitrated autologous IgG: immunogenicity of a self protein bearing the inflammation-associated marker
H. Ohmori, M. Oka, H. Shigemitsu, Y. Nishikawa, M. Takeuchi, M. Magari, N. Kanayama (Okayama, Japan)

GENETIC FACTORS AND AUTOIMMUNITY

11.00–12.45

Co-Chairs: Y. Shoenfeld (Tel Hashomer, Israel)
W.J. van Venrooij (Nijmegen, The Netherlands)

Main Lectures

Genetic predispositions of autoimmune diseases — 11.00–11.40
J.B. Harley (Oklahoma City, USA)

Identification of peptidyl arginine deiminase type 4 as a rheumatoid arthritis-associated gene — 12.20–12.30
R. Yamada (Yokohama City, Japan)

Short Lecture

P17 Gene identification of single chain format variable (scFv) anti-ß2-Glycoprotein-I (aß2GP-I) and anti-prothrombin (aPt) antibodies obtained from a primary anti-phospholipid syndrome (PAPS) patient by phage display — 12.30–12.45
J. Cabiedes, M. Languren, B. Becerril, L.E. Fernández-Altuna, V. Pascual, D. Alarcón-Segovia, A.R. Cabral (Mexico City, Mexico)

LUNCH BREAK – POSTER AND EXHIBITION VIEWING — 12.45–13.30

Poster Session — 13.00–13.30
Genetic Susceptibility and Pathogenesis
(P18–21)
Chair: M.P. Bachmann

P18 The contribution of FcgRIIIA and interleukin 10 (IL-10) gene promoter polymorphisms to genetic susceptibility of systemic lupus erythematosus (SLE) and lupus nephritis in Russian population
I. Guseva, A. Gelonkina, E. Luchihina, M. Ivanova, V. Myakotkin (Moscow, Russia)

P19 Anti-cyclic citrullinated peptide antibody production in rheumatoid arthritis is controlled by HLA-DRB1
I. Senkpiehl, M. Marget, M. Wedler, S. Jenisch, J. Georgi, D. Kabelitz, J. Steinmann (Kiel, Germany)

P20 Exploring the role of caspase-3 in human dermal endothelial cell apoptosis induced by scleroderma serum
S. Ahmed (Boston, USA)

P21 CD11c high expressing dendritic cells (DCs) are upregulated in SLE
V. Gerl, P. Großmann, D. Panne, M. Gerl, A. Waka, B. Hostmann, K. Reiter, J. Kaufmann, A. Jacobi, T. Alexander, A. Radbruch, F. Hiepe (Berlin, Germany)

13.30–15.20 **NOVEL AUTOANTIBODIES OF PATHOGENETIC AND/OR CLINICAL RELEVANCE I**
Co-Chairs: M. Fritzler (Calgary, Canada)
E. Matsuura (Okayama, Japan)

Main Lectures

13.30–14.10 Autoantibody target GW bodies – cytoplasmic foci of mRNA decay and regulatory functions
E.K.L. Chan (Gainesville, USA)

14.10–14.40 Some considerations about structure, function and pathogenicity of Ro ribonucleoproteins
G. Steiner (Vienna, Austria)

14.40–15.20 Autoantibodies to the LEDGF (DFS70) autoantigen: what are they telling us?
C. Casiano (Loma Linda, USA)

15.20–16.00 COFFEE BREAK – POSTER AND EXHIBITION VIEWING

15.40–16.00 ***Poster Session (P22–24)***
Chair: E.K.L. Chan (Gainesville, USA)

P22 False-positive perinuclear antineutrophil cytoplasmic antibody (P-ANCA) in hemodialysis patients and analysis of their target antigens
T. Uchimura, S. Yamada, K. Inoue, Y. Motomiya, T. Hashiguchi, I. Maruyama (Kagoshima City, Japan)

P23 Clinical correlations of anti-CENP-F antibodies in a cohort of patients from Southern Spain
I. Wichmann, R. Magariño, I. Magariño, A. Torres, N. Respaldiza, M. Encarnación, A. Fernández-Suarez, A. Nuñez-Roldán (Sevilla, Spain)

P24 Presence of antibodies against GSTT1 (glutathion S-transferase T1) in non-transplanted patients
I. Wichmann, I. Aguilera, J.M. Sousa, A. Bernardos, J.R. García-Lozano, A. Núñez-Roldán (Sevilla, Spain)

HUMORAL AUTOIMMUNITY IN NEUROLOGICAL DISEASES

16.00–18.00

Co-Chairs: R.L. Humbel (Luxembourg)
F. Blaes (Giessen, Germany)

Main Lectures

Role of humoral autoimmunty in demyelinating diseases of the CNS — 16.00–16.40
T. Ziemssen (Dresden, Germany)

Citrullination of CNS proteins during the development in multiple sclerosis and EAE — 16.40–17.20
R. Raijmakers (Nijmegen, The Netherlands)

Short Lectures

P25 Anti-glycolipid IgG functionality predicts clinical symptoms in a Guillain-Barré syndrome animal model — 17.20–17.30
N.M. van Sorge, L.H. van den Berg, M.D. Jansen, J.G.J. van de Winkel, N.Yuki, W-L. van der Pol (Utrecht, The Netherlands)

P26 Autoantibodies to hnRNP-A1 in neuropsychiatric Lupus and other neurological diseases — 17.30–17.40
G. Burguera, K. Adolph, A. Förster, G. Riemekasten, G.R. Burmester, K. Skriner (Berlin, Germany)

17.40–17.50

P27 Complex regional pain syndrome (M. Sudeck) is associated with autoantibodies against autonomic nervous system structures
F. Blaes, K. Schmitz, M. Tschernatsch, O. Matz, M. Kaps, M. Bräu (Giessen, Germany)

17.50–18.00

P28 Frequencies of anti-MOG IgG autoantibodies in serum and cerebrospinal fluid of patients with multiple sclerosis depend on the nature of the antigen and western blotting assay conditions
U. Wurster, R.B. Lindert, I. Torens, F. Heidenreich (Hannover, Germany)

Poster

P29 Association between circulating C1q- and C3d-immune complexes and the course of Alzheimer's disease
M. Cojocaru, I.M. Cojocaru, D. Iordanescu (Bucharest, Romania)

P30 IgG and IgM antibodies to neurofilaments in patients with multiple sclerosis
I.M. Malbohan, A. Bartos, L. Fialová, J. Soukupová, J. Kozeny (Prague, Czech Republic)

NOVEL AUTOANTIBODIES OF PATHOGENETIC AND/OR CLINICAL RELEVANCE II

09.00–10.30

Co-Chairs: E.K.L. Chan (Gainesville, USA)
C. Casiano (Loma Linda, USA)

Main Lectures

Autoantibodies to mitotic chromosomes and spindle apparatus — 09.00–09.30
R.L. Humbel (Luxembourg, Luxembourg)

Anti-laminin-1 autoantibodies in reproductive failure: human and animal studies — 09.30–10.00
E. Matsuura (Okayama, Japan)

Short Lectures

P31 Elevated anti-serum amyloid component P (SAP) antibodies in SLE patients correlate with disease activity — 10.00–10.10
G. Zandman-Goddard, M. Blank, P. Langevitz, M. Pras, Y. Levy, T. Witte, A. Doria, J. Rovensky, Y. Shoenfeld (Tel Hashomer, Israel)

P32 The translational suppressors TIA-1 and TIAR are targeted by autoantibodies and are overexpressed in inflamed skin of lupus patients — 10.10–10.20
E. Jimenez-Boj, N. Kedersha, M. Tohidast-Akrad, F. Karlhofer, G. Stummvoll, C. Zimmermann, E. Höfler, S. Hayer, G. Schett, P. Anderson, J. Smolen, G. Steiner (Vienna, Austria)

P33 The 40/38 kDa hnRNP-A3, a component of the mRNA transport particle, is a novel autoantigen in patients with systemic rheumatic diseases — 10.20–10.30
K. Adolph, A. Sternjak, A. Förster, G. Steiner, G.R. Burmester, K. Skriner (Berlin, Germany)

COFFEE BREAK – POSTER AND EXHIBITION VIEWING — 10.30–11.00

Friday September 3

11.00–13.00 **AUTOANTIBODIES IN SYSTEMIC AUTOIMMUNE DISEASES**

Co-Chairs: F. Hiepe (Berlin, Germany)
G. Steiner (Vienna, Austria)

Main Lectures

11.00–11.30 Anti-CCP, a specific marker for early rheumatoid arthritis
W.J. van Venrooij (Nijmegen, The Netherlands)

11.30–12.00 The diagnostic and prognostic significance of autoantibodies in patients with very early rheumatoid arthritis
V. Nell (Vienna, Austria)

12.00–12.30 Atherogenic role of protein-modified oxidized low-density lipoproteins and their autoantibodies
E. Matsuura (Okayama, Japan)

Short Lectures

12.30–12.40 **P34** Anti-La (SSB) autoantibodies are strongly associated with internal organ damage in patients with primary Sjögren's syndrome
R. Pelck, H. Locht, R. Manthorpe (Copenhagen, Denmark)

12.40–12.50 **P35** Identification and characterization of a SLE specific SmD3 mimotope peptide
M. Mahler, M.J. Fritzler, M. Blüthner (Neuss, Germany)

12.50–13.00 **P36** Autoimmune sera preferentially recognize the apoptotic 40 kDa fragment of the U1-70K antigen
G.J.M. Pruijn, D. Hof, K. Cheung, W.J. van Venrooij, J.M.H. Raats (Nijmegen, The Netherlands)

13.00–14.30 LUNCH BREAK – POSTER AND EXHIBITION VIEWING

13.30–14.30 ***Poster Session (P37–39, 44–46, 49, 52–54, 56, 57)***
Chair P37–49: W. J. van Venrooij (Nijmegen, The Netherlands)
Chair P52–57: P.L. Meroni (Milano, Italy)

P37 Immunomic analysis of synovial fluid exosomes reveals cirullinated proteins in patients with rheumatoid arthritis
K. Adolph, F. Schumann, P. Jungblut, G.R. Burmester, K. Skriner (Berlin, Germany)

P38 Anti-CCP antibodies may occur in patients with true psoriatic arthritis
I.E.A. Hoffman, B.V. Cruyssen, H. Zmierczak, M. Vandenberghe, E. Kruithof, L. De Rycke, D. Baeten, H. Mielants, E.M. Veys, F. De Keyser (Ghent, Belgium)

P39 Low prevalence of anti-citrullinated peptide antibodies in polyarticular juvenile idiopathic arthritis
I.E.A. Hoffman, P. Dewint, S. Rogge, R. Joos, J. Dehoorne, A. Union, E.M. Veys, F. De Keyser, D. Elewaut (Ghent, Belgium)

P40 Anti-CCP antibodies: Diagnostic sensitivity in Canterbury health laboratories
M.B. Spellerberg, K.K. Solanki, P.T. Chapman, P.W. Moller, J.L. O`Donnell (Christchurch, New Zealand)

P41 Antibodies to recombinant human 60 kDa heat shock protein in sera of patients with juvenile idiopathic arthritis
I. Hromadnikova, D. Zlacka, H. Nguyen, P. Vavrincova (Prague, Czech Republic)

P42 Cell responses to heat shock proteins 60, 65, 70 and synthetic hsp-derived peptides in patients with juvenile idiopathic arthritis
L. Sedlackova, P. Vavrincova, J. Velek, I. Hromadnikova (Prague, Czech Republic)

P43 ANCA and coagulation dysfunction in patients with rheumatoid arthritis
V.V. Bazarny, O.M. Lesnyak, O.V. Berdugina, E.A. Garbovnichaya, N.S. Aphonkina (Ekaterinburg, Russia)

P44 The diagnostic and prognostic role of anti-C1q antibodies in SLE
N. Bizzaro, D. Villalta, E. Tonutti, R. Tozzoli , S. Zampieri, A. Ghirardello, A. Doria (S. Donà di Piave, Italy)

P45 Anti-C1q antibodies in Lupus nephritis
N. Miehle, F. Petschner, B. Nettlenbusch, S. Bartschat-Dominke, U.A. Walker, K. Warnatz, M. Schlesier, H.H. Peter (Freiburg, Germany)

P46 TNF-alpha-induced surface expression of 52 kDa Ro/SS-A autoantigen is not sufficient for induction of ADCC in normal human keratinocytes.
P. Großmann, V. Gerl, C. Johnen, B. Hostmann, K. Bräutigam, N. Toman, F.-W. von Hesler, A. Radbruch, F. Hiepe (Berlin, Germany)

P47 Antinuclear and lymphocytotoxic autoantibodies in SLE: does ANA act as lymphocytotoxic antibodies?
D. Kozáková, V. Bosák, L. Cebecauer, J. Lukác, J. Rovensky (Piestany, Slovak Republic)

P48 Thyroid autoantibodies in patients with systemic lupus erythematosus and rheumatoid arthritis
I. Kostic, R. Petrovic, M. Bukilica, S. Zivancevic-Simonovic (Belgrade, Serbia)

P49 PM/Scl-75 is the main autoantigen in patients with the polymyositis/scleroderma overlap syndrome
R. Raijmakers, M. Renz, C. Wiemann, W.V. Egberts, H.P. Seelig, W.J. van Venrooij, G.J.M. Pruijn (Nijmegen, The Netherlands)

P50 Anti-topoisomerase I (anti-Scl-70) autoantibodies are specific to scleroderma and are not present in patients with SLE
T. Prestigiacomo, M. Watkins, S.R. Binder (Hercules, USA)

P51 Autoantibodies reacting with antigen(s) of the cleavage furrow and the midbody region – specific for patients of the systemic sclerosis spectrum ?
B. Roch, K. Conrad, U. Kießling, A.K. Menzel, M.P. Bachmann, H.E. Schröder (Dresden, Germany)

P52 Anti-a fodrin antibodies in patients with primary Sjögren's syndrome: poor analytical sensitivity or low nosographic prevalence?
N. Bizzaro, D. Villalta, E. Tonutti, R. Tozzoli (S. Donà di Piave, Italy)

P53 Antibodies against 25-mer synthetic peptide of M3 muscarinic acetylcholine receptor in patients with Sjögren's syndrome and SLE
P. Zigon, S. Cucnik, B. Bozic, B. Rozman, M. Plesivcnik - Novljan, M. Tomsic, T. Kveder (Ljubljana, Slovenia)

P54 Autoantibodies against M3 muscarinic acetylcholine receptors in patients with Sjögren's syndrome
T. Sumida, Y. Naito, E. Wakamatsu, D. Goto, S. Ito, A. Tsutsumi, I. Matsumoto (Tsukuba City, Japan)

P55 Patterns of anti-nuclear antibodies (ANA) among patients with primary Sjögren's syndrome with correlation to internal organ affection
H. Locht, R. Pelck, M. Høier-Madsen, A. Wiik, R. Manthorpe (Malmö, Sweden)

P56 Heterogeneous avidity of anti-β2-glycoprotein I antibodies
S. Cucnik, T. Kveder, B. Rozman, B. Bozic (Ljubljana, Slovenia)

P57 Identification of a peptide mimicing the binding pattern of anti-Cardiolipin antibodies
C. Buschmann, C. Fischer, A. Stachl, K.J. Lackner, P. von Landenberg (Mainz, Germany)

P58 The clinical significance of the determination of antiphospholipid antibodies – a retrospective study
Z. Vanková, K. Malícková, T. Fucíková, I. Janatková, H. Marecková (Prague, Czech Republic)

THERAPY-INDUCED ANTIBODIES

14.30–15.40

Chair: Srini V. Kaveri (Paris, France)

Main Lectures

Antibodies to therapeutic proteins: immunization or autoimmunity? 14.30–15.00
H. Schellekens (Utrecht, The Netherlands)

15.00–15.30 Heterogenity of antibody against endogenous and exogenous components
A. Kromminga (Hamburg, Germany)

Short Lecture

15.30–15.40 **P59** Anti-nuclear antibody profiles during infliximab and etanercept treatment in spondyloarthropathy: Is induction of humoral autoimmunity by TNF-alpha blockade a class effect?
L. De Rycke, E. Kruithof, F. Van den Bosch, I.E.A Hoffman, E.M. Veys, D. Baeten, F. De Keyser (Ghent, Belgium)

Poster

P60 Infliximab therapy in Crohn's disease induced autoantibodies restricted to antinuclear and anti-doublestranded DNA autoantibodies without autoimmune clinical manifestations
E. Blanvillain, B. Parmentier, D. Boucaud-Maitre, S. Nancey, B. Flourié, A. Moreira, J. Bienvenu, N. Fabien (Lyon, France)

15.40–16.30 COFFEE BREAK – POSTER AND EXHIBITION VIEWING

17.30 **Departure to Pillnitz Castle**

18.30 Guided walking tour

19.30 Social Dinner

METHODICAL ASPECTS AND DIAGNOSTIC STRATEGIES I

08.30–10.20

Co-Chairs: A. Wiik (Copenhagen, Denmark)
R.L. Humbel (Luxembourg, Luxembourg)

Main Lectures

Evaluation of addressable laser bead assays in the detection of autoantibodies — 08.30–09.10
M. Fritzler (Calgary, Canada)

Autoantibody profiling and B cell characterization using autoantigen and lysate arrays — 09.10–09.50
P.J. Utz (Stanford, USA)

Short Lectures

P61 Multiplexed analysis of thirteen autoantibodies using the BioPlex™ 2200 fully automated immunoassay analyzer — 09.50–10.00
T. Prestigiacomo, R.L. Humbel, B. Larida, S.R. Binder (Hercules, USA)

P62 Sensitivity and specificity of the FIDIS multiplex immunoassay system for the detection of dsDNA and nuclear specific antibodies in autoimmune rheumatic diseases — 10.00–10.10
R. Tozzoli, G. Kodermaz, N. Bizzaro, D. Villalta, E. Tonutti, A. Ghirardello, A. Doria (Latisana, Italy)

P63 Development of a sensitive and reliable biochip for detection of autoantibodies in rheumatic diseases — 10.10–10.20
W. Schoessler, C. Hentschel, J. Schulte-Pelkum, J. Kreutzberger, F. Hiepe (Berlin, Germany)

COFFEE BREAK – POSTER AND EXHIBITION VIEWING — 10.20–11.20

Poster Session ***(P68, 70, 71, 78, 83, 85)***
Chair: N. Bizzaro (S. Donà di Piave, Italy)

P64 Multicentre evaluation of the new multiplex assay FIDIS Connective. Comparison with convencional methods
I. Abreu, A. Bastos, C. Cardoso, H. Ribeiro, N. Couceiro, A. Bodas, A.M. Pereira, J. Candeias, J.A.M. Caetano (Lisboa, Portugal)

P65 Comparison of two multiplex assays for anti-ENA/ANA determination
I. Lochman, A. Kloudova, J. Lupac (Ostrava, Czech Republic)

P66 Comparison of different test systems for simultaneous autoantibody detection
T. Lüttich, M. Sticherling, D. Scholz, K. Hennig, P. Eißfeller, M. Motz, A. Kromminga (Martinsried, Germany)

P67 VIDAS-EDRA: the first automated testing for autoantibodies to citrullinated proteins
L. Nogueira, A. Foussadier, A. Constantin, C. Clavel, C. Vincent, A. Cantagrel, M. Jolivet, G. Serre (Toulouse, France)

P68 An image inspection system for the automatic classification of Hep-2 cell pattern
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METHODICAL ASPECTS AND DIAGNOSTIC STRATEGIES II

Co-Chairs: M. Fritzler (Calgary, Canada)
U. Sack (Leipzig, Germany)

11.20–12.30

Main Lectures

Cutting edge diagnostics' in rheumatology — 11.20–11.50
A. Wiik (Copenhagen, Denmark)

Isotype pattern of autoantibodies — 11.50–12.10
R.L. Humbel, N. Wernert (Luxembourg, Luxembourg)

Distinctive features of autoantibodies in normal individuals and in patients with autoimmune diseases — 12.10–12.30
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Informations

Venue

The modern Lecture Hall Centre of the Technical University of Dresden is located in the South of the city, about 15 minutes walk away from the Central Railway Station.

Hörsaalzentrum der Technischen Universität Dresden
Bergstrasse 64, D-01069 Dresden

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September 1: 07.30–18.30
September 2: 08.30–18.30
September 3: 08.30–18.30
September 4: 08.30–14.00

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Registration fee

Participants	EUR 350
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One day ticket	EUR 120

(includes unlimited access to all scientific sessions, welcome reception, industrial exhibition, 4th volume of the book series "Autoantigens, Autoantibodies, Autoimmunity", coffee and lunch breaks)

Social programme
Wednesday,
September 1, 2004
19.00

Welcome reception in the Lecture Hall Centre of the Technical University of Dresden

Friday,
September 3, 2004
18.30

Guided tour and Social Dinner at Pillnitz Palace
Pillnitz Palace, the former summer residence of the Saxon royal court is today the home of the Museum of Decorative Arts. The main palace wings were built 1720–1722 for August the Strong (1670–1733), elector of Saxony and king of Poland. The park deserves closer attention as it combines the strict forms of the baroque period with those of an English landscape garden. Before the Social Dinner in the historical Orangery of the Pillnitz Palace we offer a guided walking tour visiting Palace and park. Alongside many rare trees the over 200-year-old Japanese camellia is a particular magnet for visitors.
(17.30 Departure by bus)

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From animal models to human genetics: research on the induction and pathogenicity of autoantibodies☆

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Abstract

The revolutionary techniques of modern molecular and cellular biology enhance almost daily our knowledge of immunity and autoimmunity in men and experimental animals. Our fragmentary puzzle of the immune system is going to form a fascinating picture of a masterpiece of evolution. Although many of these aspects were achieved by analysis of human body fluids and tissues, the etiopathogenesis of autoimmune diseases cannot readily be analyzed without appropriate animal models. Therefore, the 7th Dresden Symposium on Autoantibodies has focused on experimental autoimmune models. The 295 attendants of the symposium listened to and discussed about the pathogenesis and therapy of autoimmunity in experimental mouse models, natural and pathogenic autoantibodies, molecular mechanisms of xenobiotic-induced autoimmunity, the genetic background of autoimmune diseases, novel autoantibodies and their pathogenic and/or clinical relevance, autoantibodies in systemic and neurological diseases, the occurrence and measurement of therapy-induced antibodies and methodical aspects as well as novel diagnostic strategies including multiplex assays for autoantibody profiling. Those who are interested to read the full length articles are referred to the book published in parallel to this meeting ([Conrad K, Bachmann MP, Chan EKL, Fritzler MJ, Humbel RL, Sack U, Shoenfeld Y, editors. From animal models to human genetics: research on the induction and pathogenicity of autoantibodies, Report on the 7th Dresden Symposium on Autoantibodies held in Dresden on September 1–4, 2004. Germany: Pabst Science Publishers; 2004.]; www.pabst-publishers.de).

☆ Summary on the 7th Dresden Symposium on Autoantibodies, September 1–4, 2004.

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Contents

The symposium started by an overview delivered by M. Reichlin (USA) summarizing the *history and the current knowledge on autoantibodies in systemic autoimmune diseases*. As a prototype of systemic autoimmune diseases, he focused on systemic lupus erythematosus (SLE) but also covered systemic sclerosis and the autoimmune inflammatory myopathies. He showed the development from the first autoantibody detection in SLE patients, the LE cell phenomenon, to the discovery of dsDNA antibodies, the identification of individual antigen–antibody reactions by the Ouchterlony test, the molecular analysis of autoantigens targeted by disease-specific autoantibodies as well as the investigations on the pathogenicity and diagnostic relevance of known and novel autoantibodies.

1. Animal models in the research on autoimmune pathology

M.P. Bachmann (Germany) focused on more recent, in part controversially discussed autoimmune mouse systemic lupus erythematosus (SLE) models, including the p21- and the Ro60 knock-out mouse and the mouse transgenic for a mutant form of the autoantigen La/SS-B. At a first glance, these three animal models seem to have little in common. However, Bachmann tried to provide some first inside for a potential common mechanism in these autoimmune models and their potential link to systemic autoimmunity in SLE patients: *A lupus like syndrome in mice transgenic for a mutant form of the La autoantigen: a link between p21, Ro60 and mutant La?* In mutant La-transgenic mice SLE typical autoantibodies, immune complex deposits in tissues and various cytopenias were found. p21 was clearly upregulated in all analyzed tissues including liver, kidney, spleen, heart and thymus. The data obtained by Bachmann et al. suggest a dysregulation of the mdm2, p53 and p21 regulatory loop by mutant La, and support the idea that inhibition of the cell cycle can lead to autoimmunity. One possible link between the mutant La form and the Ro60 knock-out could be at the level of internal initiation of translation. La protein and Ro60 may be required for this function.

As La requires the dimerization site also for an interaction with the Ro60 protein, this interaction could be impaired in both the mutant La mouse and the Ro60−/− mouse. This is one possible explanation for the common phenotype of the mutant La, Ro60−/− and p21+/+ mice. Bachmann summarized that mutations in genes encoding regulators of the cell cycle, which may either be inherited or acquired during life span of the individual, may not only increase the risk of tumorigenesis but also predispose to autoimmunity.

P. Zijian et al. (USA) investigated the *immunogenicity of late apoptotic cells expressing heterologous or syngeneic forms of the La/SS-B (La)*. Their studies support mechanistic roles for DC maturation and revelation of neo-epitopes in the development of ANA following exposure of the immune system to an excess of cells in late stages of apoptosis.

F. Hiepe et al. (Germany) analyzed the *role of long-lived plasma cells in autoimmune pathology* in a murine lupus model. Bromodeoxyuridine (BrdU), which is incorporated into the DNA of dividing cells, was added to the drinking water of 5-month-old NZB/W mice with anti-dsDNA autoantibodies for a period of 12 weeks. They then used a plasma cell marker (CD138) in order to cytometrically distinguish between proliferating (short-lived) and non-proliferating (long-lived) cells in plasma cell compartments of the spleen. About 60% of all CD138+ cells became BrdU-positive within 10 days of BrdU feeding. The other 40% remained unlabeled and BrdU-negative for the entire 12 weeks of BrdU feeding, indicating that these cells are *long-lived, non-dividing plasma cells*. The total number of BrdU-negative CD138+ plasma cells did not change during these 3 months. All long-lived BrdU-negative plasma cells expressed little MHC II. The discovery of an unusually prominent, long-lived splenic plasma cell population in NZB/W mice raises the question whether these cells are responsible for treatment-resistant (auto) antibody titers. In NZB/W mice treated experimentally with cyclophosphamide, a generation of short-lived plasma blasts is blocked efficiently, but long-lived plasma cells do survive. Since long-lived autoreactive plasma cells are responsible for the *continuous production of pathogenic autoantibodies*, methods of targeting them should provide potent therapeutic approaches. Autologous stem cell transplantation (ASCT), for example, can result in the complete disappearance of all autoantibodies in patients with refractory SLE. ASCT conditioning regimens, including immunoablation by antithymocyte globulin, may therefore be effective modalities for targeting the long-lived plasma cell compartment.

Matsuura's (Japan) and *Shoenfeld's* (Israel) group recently reported a significant association between *anti-laminin-1 antibodies and reproductive failure*, such as recurrent abortions and infertility-associated endometriosis in both human and mouse studies. *E. Matsuura* reported that they established an IgM monoclonal anti-laminin-1 antibody (AK8) by immunizing mice with mouse Engelbreth–Holm–Swarm sarcoma (EHS)-derived laminin-1. The AK8 monoclonal antibody reacted with particular peptide sequences from the globular G domain of mouse laminin-α chain by using ELISA and Western blot techniques. The peptide tertiary structure of the epitope recognized by AK8 monoclonal antibody was predicted using eight synthesized domain peptide sequences and three consensus sequences obtained by phage displayed random peptide library. Basement membranes of endometrium of pregnant mice and humans were immunostained with AK8 antibody. Thus, anti-laminin-1 antibody (AK8) recognized a common structure present in the G domain of the laminin-α-1 chain in both mice and humans. The passive immunization of mice with AK8 antibody may represent a suitable animal model for anti-laminin-1 antibody-mediated reproductive failure.

The *role of proinflammatory stimuli* in the pathogenesis of MPO-ANCA associated vasculitis was studied by *D. Huugen et al.* (The Netherlands) in MPO-deficient mice. They showed that systemic administration of LPS aggravates anti-MPO IgG-induced glomerulonephritis in mice in an at least partly TNF-α-dependent way. These results are consistent with the in vitro observations that proinflammatory stimuli enhance ANCA-mediated neutrophil activation.

The *enhancement of autoantibody pathogenicity by viral infections* was studied by *J.-P. Coutelier* (Belgium) using mice infected with lactate dehydrogenase-elevating virus (LDV) and treated with anti-erythrocyte or anti-platelet monoclonal autoantibodies at a dose insufficient to induce clinical disease by

themselves. The virus sharply enhanced the pathogenicity of autoantibodies, leading to severe anemia or thrombocytopenia. This effect was observed only with antibodies that induced disease through phagocytosis. In addition, the phagocytic activity of macrophages from infected mice was increased and the enhancing effect of infection on autoantibody-mediated pathogenicity was strongly suppressed by treatment of mice with clodronate-containing liposomes. The disease induced by LDV after administration of autoantibodies was largely suppressed in animals deficient for IFN-γ receptor. Together, these results suggest that viruses may trigger autoantibody-mediated anemia or thrombocytopenia by activating macrophages through IFN-γ production, a mechanism that may account for the pathogenic similarities of multiple infectious agents.

M. Bobeck et al. (USA) analyzed the *binding properties of a sequence-specific pathogenic lupus anti-ssDNA autoantibody*. Hybridoma technology was employed to generate a panel of anti-DNA mAbs from an autoimmune MRL-*lpr* mouse for injection into normal mice. The results showed that small changes in amino acid sequence can produce large changes in both specificity and pathogenicity. Moreover, they demonstrate that the interaction of mAb 11F8 with its high affinity consensus DNA sequence is a model system that is relevant to human lupus. By comparing the primary sequence of 11F8 with clonally related antibodies suggests that somatic mutations, which confer sequence-specificity may be a feature that distinguishes pathogenic anti-DNA from those that are benign.

1.1. Innate immunity and interferon production in the pathogenesis of autoantibodies in lupus

Y. Shoenfeld (Israel) discussed animal models for the investigation of the pathological relevance of autoantibodies. He demonstrated that inrathecal injection of *anti-P ribosomal (aPR) antibodies to mice induced depression-like behaviour*, passiveness and reduction in the locomotor exploratory activities expressed in different behavioral tests (swim maze, etc.). Thus, pointing to the association of aPR with psychosis and depression in SLE. Shoenfeld also reported on the protective role of: (1) anti-oxLDL in experimental induced autoimmune atherosclerosis, (2) the IgM anti-DNA in B/W mice and (3) vitiligo derived anti-tyrosinase antibodies in melanoma induced in mice.

The fashionable subject of type I interferons (IFN) in SLE was discussed by *W.H. Reeves* (USA). He found *increased expression of IFN-I inducible genes* in both SLE patients and in an experimental model of lupus in mice. In both cases, there was a *dysregulation of responses to TLR3 (Toll-like receptor) and TLR4 ligands*, consistent with abnormalities in either the function or distribution of monocytic dentritic cells (MDCs). Flow cytometry revealed a depletion of MDCs as well as plasmacytoid dentritic (PDCs) in the peripheral blood of SLE patients. The peritoneal cavity of pristane-treated mice, in contrast, contained large numbers of MCDs. Finally, there was a strong association between increased IFN-I production and the production of certain autoantibodies characteristic of SLE, including anti-nRNP/Sm, anti-Ro60, and anti-dsDNA. The researchers are investigating the possibility that the association of cellular TLR3 or TLR9 ligands with these self-antigens may promote the maturation of DCs presenting them by stimulating IFN-I production.

1.2. Retroviruses and SLE

M. Miyazawa et al. (Japan) have shown that monoclonal anti-gp70 autoantibodies established from MRL/lpr lupus mice are directly pathogenic when transferred into non-autoimmune mice. A high proportion of these anti-gp70 antibody-producing hybridoma clones induced proliferative or wire loop-like glomerular lesions with massive depositions of gp70, IgG and C3 in affected glomeruli when transplanted into syngeneic non-autoimmune or severe combined immunodeficiency mice. Furthermore, it was demonstrated that repeated intravenous injections of purified monoclonal anti-gp70 autoantibodies induce glomerular pathology associated with gp70 deposition. The development of the glomerular pathology after injection of purified anti-gp70 autoantibodies was dependent on the amounts of serum gp70 expressed in the injected mice, and the development of granulomatous arteritis was also observed after repeated injections of one of the pathogenic clones of anti-gp70 autoantibodies. These results directly prove the long-debated

pathogenicity of anti-retroviral autoantibodies in the mouse lupus models.

1.3. Streptococci and rheumatic fever—experimental model

F.F. Alcantara et al. (Brazil) have injected Lewis rats with streptococcus recombinant M1 protein 500 μg on day 0 followed by 500 μg boost on day 7 and sacrifice on day 21, in order to reproduce a recently described animal model of rheumatic fever (A. Quinn et al. Infect. Immun. 2001, 69:4072–4078). Rat hearts were subjected to histopathological analyses. Spleen and lymph node lymphocyte cells, as well as sera, were harvested and probed against ABC domains, AB domains (N-terminus) or C domain (C-terminus) of the M1 complete protein and myosin or control proteins. They have obtained specific lymphoproliferative responses against selected M protein fragments and specific cardiac proteins, as seen in their previous results with patient samples. They are currently using the rat-immunized cells for FACS analysis to study their phenotypic profile and cytokine production. The aim of their studies was to map the minimal M protein epitope(s) responsible for rheumatic fever after immunization with different recombinant M protein fragments.

1.4. Autoantibodies in a scleroderma animal model

P. Christner et al. (USA) showed that autoantibodies against topoisomerase I and centromeres are present in the plasma of the tight skin 2 mouse (Tsk2/+), an animal model with phenotypic features resembling those of systemic sclerosis (SSc). This indicates that Tsk2/+ mice display humoral immune alterations, which are similar to those found in patients with SSc.

1.5. Specific IVIG in experimental models of SLE

Y. Shoenfeld (Israel) addressed the specificity and efficacy of affinity purified IVIG, purified on peptide mimetics of anti-dsDNA idiotypes, in vitro and in vivo, as a novel treatment for experimental lupus. Specific natural polyclonal anti-dsDNA anti-idiotypic antibodies (IVIG-aID) were affinity purified from IVIG on anti-dsDNA-sepharose column constructed with anti-dsDNA idiotypes affinity purified from 55 patients with SLE. This compound improved the clinical manifestations of NZBXWXF1 mice in 200 time lower concentrations than IVIG (Int. Immunol. 2002, 14:1303). This lupus specific IVIG was introduced to a peptide phage display library (C-7mer-C). The identified synthetic peptides (idiotypes mimetics) were synthesized and used to replace the human anti-dsDNA idiotypes column. IVIG affinity purified on the synthetic peptides column were determined as psIVIG (peptide-specific IVIG). The psIVIG compound was tested for specificity by ELISA and competition assays. Each psIVIG inhibited the binding of anti-dsDNA antibodies from 12 lupus patients, to dsDNA, differentially by 15% up to 46% or as a mix up to 87–94%. A cocktail of peptide-specific-IVIG was introduced to mice with experimental SLE at an active stage of disease development. The following groups were studied: NZBxWxF1, mice actively immunized with 16/6 idiotype or with polyclonal anti-dsDNA affinity purified from 7 lupus patients. The efficacy of the treatment on mouse circulating anti-dsDNA antibodies, leucopenia, proteinuria and immunoglobulin deposits in the kidneys were discussed.

Shoenfeld et al. introduced herein an IVIG compound specific for anti-dsDNA treatment for lupus patients, and discussed its higher efficacy and beneficial effect in suppression of humoral and clinical signs of SLE versus regular IVIG.

1.6. Protective IgM anti-DNA in experimental models of SLE

S. Werwitzke et al. (Germany) showed that prophylactic and therapeutic treatment of NZB/NZW F1 mice with IgM anti-dsDNA antibodies reduced glomerular deposition of immune complexes (IC) resulting in less severe inflammatory response, reduced organ damage, delayed onset of proteinuria and significantly improved survival. Moreover, the intensive staining of IgG seen in liver sections of treated mice suggested an enhanced clearance of soluble ICs by the reticuloendothelial system of the liver. This might be due to altered characteristics of IgM-enriched ICs. These data are encouraging to further clarify the mechanism of therapeutic benefit of

IgM anti-dsDNA antibodies and may provide new specific therapeutic approaches of SLE.

1.7. Selective suppression of DNA-specific B cells in lupus mice

A. Tchorbanov et al. (Bulgaria) constructed a hybrid molecule by coupling the 2.4G2 rat monoclonal antibody (specific to mouse CD32) to the DNA-mimicking DWEYSVWLSN peptide (J. Immunol. 2000, 164:2542). Groups of the female MRL/lpr mice (7-week-olds with initial diseases and 16-week-old sick ones) were injected i.v. twice weekly for 6 weeks with 20 μg of the chimeric antibody-DNA peptide, with the same amount of the control chimera or with PBS alone. The administration of the chimeric antibody to 7-week-old animals prevented the appearance of the disease-associated IgG anti-DNA antibodies and of proteinuria during the next 6 weeks. The levels of the antibodies with this specificity in the groups treated with PBS or with the control chimera rise dramatically during the same period. At the age of 16 weeks, the animals had already a full-blown disease. Intravenous infusion with the chimeric antibody-DNA peptide resulted in maintaining a flat level of IgG anti-DNA antibody levels and in prevention of the aggravation of lupus glomerulonephritis. The PBS-injected control mice had a sharp rose in the anti-DNA IgG antibody levels and four out of five died before reaching the age of 24 weeks. These data show that it is possible to suppress selectively the activity of targeted autoreactive B lymphocytes and to change the natural course of an autoimmune disease by administrating a chimeric molecule that cross-links inhibitory with immunoglobulin B-cell receptors. This presentation won the Dresden Price on the Study of Autoantibodies.

2. Molecular mechanisms of xenobiotic-induced autoimmunity

The findings of *K.M. Pollard* (USA) revealed that genetic deficiencies can affect development of murine mercury-induced autoimmunity in various ways. Absence of a number of genes (e.g., IL4, TNFR, STAT-4, ICE) had no effect on disease, while deficiency in some genes (e.g., IFN-γ, IFN-γ receptor, CD28, CD40L) completely abrogated induction of all disease parameters. Deficiencies in other genes (e.g., ICAM-1, IL-12p35) affected different features of disease. Significantly these studies confirm the important role of a single cytokine, IFN-γ, in systemic autoimmunity. The pleiotropic nature of the biological responses that follow IFN-γ/IFN-γ receptor interaction suggests that multiple complex pathways may be responsible for the spectrum of disease features that characterize systemic autoimmunity, single gene deficiencies in B10.S mice and their effects on the development of murine mercury-induced autoimmunity. *A proteasomal-dependent antigen processing of DNA topoisomerase I* was shown by *M. Chen et al.* (Germany). *A. von Mikesz* (Germany) suggested that *xenobiotic-induced autoimmune responses* and protein aggregation diseases share a common subnuclear pathology. *P. Hultman et al.* (Sweden) studied the *effect of thimerosal*, which is rapidly metabolized to ethylmercury (EtHg), on the immune system primarily in mice genetically susceptible to induction of autoimmunity by heavy metals. They concluded that exposure to the organic compound ethylmercury first leads to immunosuppression, which does not inhibit subsequent induction of a T-cell-dependent immunostimulation and systemic autoimmunity. *The role of Fc-receptors in mercury-induced autoimmunity* (HgIA) was investigated by *K. Martinsson et al.* (Sweden) using female BALB/c mice, which respond to Hg with immune complex deposits and hypergammaglobulinemia. Two strains with targeted mutations were used, one deleted in the inhibitory receptor FcγRIIB and the other deleted in the activating receptors FcγRIII and FcγRI. Results showed that the activating receptors FcγRIII and FcγRI are involved in the induction and the development of immune complex deposits in HgIA in BALB/c mice but not in the development of ANA. The inhibitory receptor, FcγRIIB, does not function as a down-regulator of HgIA in BALB/c mice, since the loss of the receptor did not induce a more severe development of the disease.

3. Genetic factors and autoimmunity

J.B. Harley (USA) critically discussed *methodological aspects in the research for genetic factors of autoimmunity* and problems with complex genetic phenotypes like SLE (no model, epistasis, hetero-

geneity, small pedigrees, case definition). Relatively little is known about the susceptibility genes for such complex diseases, where the polymorphisms of multiple genes and epistatic interactions among them produce the disease phenotype. Many researchers suspect that the disease-causing genes in common complex diseases will prove to be common genetic polymorphisms present in 5% or more of the population rather than rare disease-causing mutations such as those involved in cystic fibrosis. At this time, there are at least 150 potential linkages with $p<0.01$, when all of the genome scans are considered together. Not surprisingly, there is both consistency and variation in these results. Indeed, even in each of the "convincing" linkages, the evidence for linkage is dominated by the data from only one of the studies done to date. In addition, differences in the methods of analysis lead to the identification of very different linkage effects, even when done using the same pedigree collection. One of the first linkage effects that have been originally identified by Harley's group was at 1q23. Because of the importance of this genomic region, which is also syntenic with a linkage in a murine model of lupus, he concentrated upon this region (see Ref. [1]). He showed that serological subdivision (anti-Ro positive SLE) increases genetic homogeneity and leads therefore to more significant linkages. Furthermore, he showed that there is a 15-fold increase of SLE in XXY males.

3.1. Peptidylarginine deiminase type 4 (PADI4) and citrullination

PADI4 is one of five known PADI genes that code enzymes to change the arginine in proteins into citrulline. Post-translational protein-modifications, including peptidyl citrullination, are related to autoimmunity, and peptidyl citrulline is known to be recognized by one of the most rheumatoid arthritis (RA)-specific autoantibodies, anti-citrullinated peptide antibodies. *R. Yamada* (Japan) reported that PADI4 gene had a RA-susceptible haplotype by linkage disequilibrium (LD) approach using single-nucleotide polymorphisms (SNPs). They reached the conclusion that citrullination by PADI, one of the post-translational modifications, seems to have a key role in breaking immune tolerance of RA. It is important to investigate the role of PADI in physiologic and pathologic conditions and the detailed mechanism of the break in tolerance to citrullinated self-peptides in conjunction with many molecules during various cellular events.

4. Autoantibodies in systemic autoimmune diseases

4.1. Autoantibodies in rheumatid arthritis (RA)

In the last years, the great importance of autoantibodies against citrullinated proteins has been shown. *W.J. van Venrooij* (The Netherlands) summarized the history and the diagnostic and prognostic relevance of anti-CCP antibodies. Recent data from many independent laboratories indicate that the anti-CCP antibody meets criteria of an ideal serological marker for RA. CCP-antibodies are not only highly specific for the disease but also able to distinguish RA from other arthritides that mimic RA. They are also present in the majority of patients, preferentially very early in the disease and have the ability to predict disease outcome. Because RA is most likely a multifactorial disease, future investigations will focus on combination models to identify individuals who have the highest probability of developing RA. *V. Nell* (Austria) discussed the diagnostic and prognostic significance of autoantibodies in patients with very early rheumatoid arthritis. *K. Skriner et al.* (Germany) have made immunomic analysis of synovial fluid exosomes. The analyses revealed that fibrin-α-fragment, fibrin-β, fibrinogen-β-chain-precursor, fibrinogen-D-fragment and the Sp-α CD5 antigen-like receptor are citrullinated. This observation suggests that the synovial exosomes contain specific autoantigens found in RA.

4.2. Autoantibodies in the overlap syndromes

R. Raijmakers et al. (The Netherlands) demonstrated that the long PM/Scl-75 isoform is the main autoantigen in patients with the polymyositis/scleroderma overlap syndrome. His data indicate that the use of the long PM/Scl-75 isoform in addition to PM/Scl-100 in ELISA significantly increases the number of patients in which anti-PM/Scl autoantibodies can be detected. *G.J.M. Pruijn et al.* (The Netherlands)

showed that autoimmune sera preferentially recognize the apoptotic 40-kDa fragment of the U1-70 K antigen. He concluded that the apoptotic 40-kDa fragment of the U1-70 K protein is a better antigen for the (early) detection of anti-RNP autoantibodies than the intact U1-70 K protein and that anti-40-kDa antibodies seem to be more specifically associated with MCTD than anti-U1-70 K antibodies.

4.3. Autoantibodies in systemic lupus erythematosus

M. Mahler et al. (Germany) identified and characterized a SLE-specific SmD3 mimotope peptide. Using immobilized peptides, they were able to confirm that the symmetrical dimethylation of arginine residues plays an essential role in the formation of SmD3 major autoepitopes. They demonstated that the SmD3 mimotope peptide ELISA may offer new possibilities to diagnose and discriminate SLE from other autoimmune disorders. *N. Bizzaro et al.* (Italy) evaluated the diagnostic and prognostic role of anti-C1q antibodies in SLE. When present at high concentrations, their specificity for SLE was 99% and correlated with the kidney involvement.

4.4. Autoantibodies in Sjögren's syndrome

H. Locht et al. (Sweden) showed that anti-La (SSB) but not anti-Ro (SSA) autoantibodies are strongly associated with internal organ damage in patients with primary Sjögren's syndrome (pSS). As autoantibodies are present early in the disease course, anti-La may be a useful marker for future internal organ complications in pSS. Anti-α fodrin antibodies are a new serological marker recently proposed for the diagnosis of pSS. However, preliminary studies indicating a good sensitivity of the new test (T. Witte et al. J Rheumatol 2000, 27:2617–2620) have not been confirmed by subsequent experiences. *N. Bizzaro et al.* (Italy) have evaluated the sensitivity and specificity of two ELISA methods for anti-α fodrin antibodies. The obtained low analytical sensitivity was discussed as a result of the antigen formulations. Antibodies against the M3 muscarinic acetylcholine receptors (M3mAChR) are described as novel autoantibodies in Sjögren's syndrome by *P. Zigon et al.* (Slovenia) and T. Sumida et al. (Japan). They analysed the prevalence of anti-M3mAChR antibodies in patients with SS by using a 25-mer synthetic amino acid encoding the second extra-cellular domain of M3mAchR. Autoantibodies were more commonly detected in the serum of patients with primary (9%) ($p<0.05$) and secondary SS (13.7%) ($p<0.05$) than in those with other autoimmune diseases such as rheumatoid arthritis (1%) and systemic lupus erythematosus (0%), or healthy subjects (2.3%).

4.5. Atherogenic role of protein-modified oxidized low-density lipoproteins and their autoantibodies

Oxidative stress is thought to be etiologically related to atherosclerosis. Experimental evidence clearly demonstrates the presence of oxidized LDL (oxLDL) in the intima of arteries and that it contributes to the initiation and progression of atherosclerotic lesions. *E. Matsuura* (Japan) demonstrated that oxLDL interacts with an endogenous plasma protein, β2-glycoprotein I (β2GPI), to form complexes and that these complexes circulate in the blood stream of patients with systemic inflammatory diseases (e.g., SLE, APS, several kinds of infectious diseases). Their novel ELISA systems allowed the measurement of circulating β2GPI/oxLDL complexes and autoantibodies to these complexes to study their association with various thrombotic manifestations. Their recent results indicate that β2GPI/oxLDL complexes may be implicated as autoantigens relevant in atherogenesis. Their in vitro experiments showed that oxLDL quickly interacts with β2GPI via specific ligands generated by Cu^{2+}-oxidation in which the negative charge of oxLDL is neutralized by the complex formed. OxLDL uptake by macrophages is significantly increased by the interaction with β2GPI and IgG anti-β2GPI autoantibodies but not with IgM anti-oxLDL natural antibodies. Even though many questions still remain, β2GPI/oxLDL complex can be described as a common metabolic form in atherogenesis and a significant participant in autoimmune-mediated atherosclerosis. Receptors of the innate immunity as targets for circulating autoantibodies:

4.6. Role of β2GPI antibodies in the pathogenesis of the antiphospholipid syndrome

The binding of autoantibodies to endothelial β2GPI had been reported to be responsible for endothelial activation with the induction of a pro-

inflammatory and a pro-coagulant phenotype. It was postulated that such an event might be one of the pathogenic mechanisms leading to the thrombophilic diathesis characteristic of the antiphospholipid syndrome (APS). *P.L. Meroni et al.* (Italy) showed that both human monoclonal IgM as well as polyclonal anti-β2GPI IgG antibodies induced an endothelial signaling cascade comparable to that activated by LPS or IL-1 and involving TRAF6 and MyD88. It is known that IL-1 receptor-activated kinase (IRAK) autophosphorylation time kinetic depends on the agonist. Anti-β2GPI antibodies and LPS followed the same time kinetic, suggesting that the autoantibodies activated EC through the TLR-4 involved in LPS pathway. Interestingly, anti-β2GPI antibodies were shown to recognize β2GPI peptides displaying a molecular mimicry with common bacteria and viruses, both at the level of amino acid sequence and conformational structure. Such a homology was suggested to represent the rational for the possible infectious origin of the syndrome. Since common microbial structure do represent the natural ligands for TLRs, Meroni et al. speculate that β2GPI might interact with TLRs and that anti-β2GPI antibodies recognizing the molecule might cross-link it together with TLRs eventually triggering the inflammatory cascade. Such a possibility likely appears to have a major role particularly during the "thrombotic storm" in the so-called catastrophic variant of APS. Catastrophic APS is actually characterized by multiple microvascular thrombotic events, presenting over a short period of time and causing a multiorgan failure, a picture reminiscent of the septic shock in which a massive and acute inflammatory response (mainly mediated by the innate immune effectors) does occur.

5. Methodical aspects and diagnostic strategies

A. Wiik (Denmark) summarized the *cutting edge diagnostics' in rheumatology* and discussed the influence of assay technology, the importance of indirect immunofluorescence, guidelines and approaches to autoantibody testing as well as algorithms for autoantibody testing. Distinctive features of autoantibodies in normal individuals, and in patients with autoimmune diseases were shown by *L.E.C. Andrade* (Brazil). *Y. Shoenfeld* (Israel) discussed the three PPP *characteristics of autoantibodies—predictive, pathogenic and protective*. He detailed on new predictive antibodies on inflammatory bowel diseases. Patients with Crohn's disease had anti-*saccharomyces cerviciae* antibodies (ASCA) 4.2 years before clinical diagnosis, while pANCA preceded the diagnosis of ulcerative colitis by 4.9 years in average. These diseases with their respective autoantibodies join other 30 different autoimmune conditions, being predicted by the presence of autoantibodies long before overt clinical findings are noted. *M. Schlosser et al.* (Germany) presented the *stratification of type 1 diabetes (T1D) risk on the basis of islet autoantibody characteristics* in the general population and showed that combined screening for GAD/IA-2A or GAD/IAA autoantibodies in the general population identifies 98% of probands at risk for T1D, also bearing the genetic susceptibility for the disease.

5.1. New technologies in the detection of autoantibodies

Several different platforms have been developed for autoantibody profiling. *M. J. Fritzler* (Canada) summarized the recent experience in a clinical laboratory setting with addressable laser bead immunoassays (ALBIA). Such luminex-based multiplex assays (Bio-Plex™, FIDIS™) were also evaluated by *T. Prestigiacomo et al.* (USA), *I. Abreu et al.* (Portugal) and *R. Tozzoli et al.* (Italy). *P.J. Utz* (USA) focused on planar array-based platforms (protein microarrays) for profiling of autoantibodies and intracellular signaling molecules. W. Schoessler: cursive et al. (Germany) constructed membrane carrier chips for simultaneous detection of up to 30 diagnostically relevant autoantibodies associated with rheumatic diseases. Furthermore, improvements or modifications in the analysis of autoantibodies against goblet cells, SmD, ribosomal P proteins, PR3-ANCA, ASCA, actin and GAD were discussed [1]. Comparison of performance and costs of some of the newer assays to conventional assays suggest that they are reliable, highly sensitive and cost-effective. However, "clinical analyses suggest that gains in accuracy and repeatability obtained in these new technologies may be clouded by a need to re-evaluate current paradigms of the diagnostic and prognostic specificity of autoantibodies" (*M. Fritzler*). Besides improvements of diagnostics of autoimmune

diseases, protein arrays and other proteomics technologies in combination with novel animal models and studies of the genetic background and environmental factors have the potential to revolutionize the research on the autoimmune pathology as will be discussed in the next Dresden Symposia on Autoantibodies (www.advidx.org or www.gfid-meeting.com).

Reference

[1] Conrad K, Bachmann MP, Chan EKL, Fritzler MJ, Humbel RL, Sack U, Shoenfeld Y, editors. From animal models to human genetics: research on the induction and pathogenicity of autoantibodies, Report on the 7th Dresden Symposium on Autoantibodies held in Dresden on September 1-4, 2004. Germany: Pabst Science Publishers; 2004.

Defective lymphocyte caspase-3 expression in type 1 diabetes mellitus

Activation-induced cell death (AICD) is a major mechanism in the regulation of peripheral tolerance and its impairment can determine the development of autoimmunity. Vendrame et al. (Eur J Endocrinol 2005;152:119) report that caspase-3 mRNA expression was reduced in resting lymphocytes in 18 of 37 studied type 1 diabetes mellitus patients and in 1 of 36 normal controls. Patients studied for both Fas-mediated AICD and caspase-3 mRNA expression revealed that a reduced caspase-3 mRNA expression in resting lymphocytes occurred in all patients showing resistance to Fas-mediated apoptosis with the exception of 3 patients who exhibited normal caspase-3 expression levels. The authors concluded that defective expression and function of caspase-3 in peripheral lymphocytes of type 1 diabetes mellitus patients may contribute to the development of AICD resistance in type 1 diabetes.

European register of babies born to mothers with antiphospholipid syndrome

Neonatal SLE is a severe disease that might be life-threatening. Much less is known about babies born to mothers having the antiphospholipid syndrome (APS), and even if there is neonatel APS. Boffa et al. (Lupus 2004;13:713) described the initiation of a European register of babies born to APS mothers. This prospective multicentric register was initiated by the European Forum of Antiphospholipid Antibodies (APL) in 2003 after approval by local ethic committees. It collects mothers' clinical pattern of APS, course and outcome of pregnancy, treatment and immunological status. For the babies, clinical and immunological examinations are performed at birth; neurodevelopmental conditions followed up to five years. A re-evaluation of lupus anticoagulant, anticardiolipin or other antibodies will be done if they are positive at birth to follow their kinetics. A descriptive and a case control study of babies with versus without antiphospholipid antibodies at birth will be possible in the authors' view after the inclusion of 300 cases.

Heat-shock protein 47 autoantibodies in systemic sclerosis

Heat-shock protein 47 (HSP47) is expressed by collagen-secreting cells such as fibroblasts and serves as a collagen-specific molecular chaperone that plays a crucial role in collagen metabolism. Abnormal collagen accumulation and autoimmunity characterize systemic sclerosis. Fujimoto et al. (Clin Exp Immunol 2004;138:534) determined the presence and prevalence of autoantibodies to HSP47 in patients with systemic sclerosis and in tight-skin (TSK/+) mice, which provide an animal model for systemic sclerosis. Anti-HSP47 autoantibodies were present in 26% of systemic sclerosis patients group, while these antibodies were not detected in patients with systemic lupus erythematosus, dermatomyositis, keloid or in healthy subjects. The postive patients for anti-HSP47 had a significantly shorter duration of disease than those who were negative. Anti-HSP47 autoantibodies were also positive in 79% of TSK/+ mice. These novel autoantibodies might be associated with systemic sclerosis pathogenesis, as should be further studied.