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G.16 Oral suppression with IRBP in the acute and chronic relapsing mouse models of experimental autoimmune uveitis (EAU)

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Uveitis is an inflammatory autoimmune disorder in man, which affects ocular tissues (uvea and retina) and can cause blindness in severe therapy refractive cases. Mouse EAU serves as a model for human uveitis. EAU is a T cell-dependent autoimmune disease, which is experimentally induced by footpad immunization with the retinal antigen interphotoreceptor retinoid binding protein (IRBP) emulsified in complete Freund's adjuvant. In the following study we investigated the potential of antigen feeding to downregulate acute as well as chronic relapsing EAU in B10.A mice. In the first set of experiments mice were fed 4 times with IRBP or with Keyhole Limpet Hemocyanin (KLH) prior to the active immunization with 100 μg IRBP, which induces an acute uveitis. Three weeks later histology revealed significantly reduced damage of the retina in the IRBP fed mice. *In vitro* proliferative responses to IRBP were also reduced in treated mice. In the second set of experiments chronic relapsing EAU was induced with a low dose immunization scheme and feeding was started 8 weeks later after mice had recovered from their first attack of uveitis as determined by fundoscopy. For the following 5 weeks animals received IRBP or KLH. On fundoscopy control mice developed a relapse of uveitis 3 weeks after the first attack, while the relapse was inhibited in mice fed with IRBP. Again, histology showed significantly reduced retinal destruction in treated mice. Interestingly, specific antibody titers were not reduced, while cellular responses to IRBP did not always correlate with the clinical responses in the various groups.

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G.17 A clinically successful protocol to suppress autoantibody production in SLE patients is analyzed for its efficacy to inhibit natural xenophile antibodies (NXA)

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Plasmapheresis in conjunction with a defined, time-related course of CY injections has been shown to be very effective in treating patients who suffer from severe forms of systemic lupus erythematodes (SLE). It was the aim of our study to analyze the effect of this established clinical protocol on the kinetics of natural xenophile antibodies (NXA) against porcine pancreatic islet cells, which are known to be responsible for acute and hyperacute rejection of islet xenografts. For this purpose, sera from 5 SLE patients were additionally tested for NXA against porcine pancreatic cells by quantitative immunofluorescence (a) before, (n) immediately after, and (c) long-term after treatment. Results: (1) In contrast to healthy individuals, SLE patients are strongly positive for disease-related anti-nucleic antibodies (ANA), but negative for NXA. (2) Immediately after treatment, both ANA and NXA are negative. (3) Six to twelve months after treatment, only a marginal reoccurrence of ANA is observed. Reoccurrence of NXA reaches titers, considered normal. (4) ANA and NXA are of IgG rather than IgM isotype. Conclusions: (I) Plasmapheresis combined with a short-term course of the alkylating agent CY appears to be very effective in eliminating activated B cell clones but rather

ineffective in eliminating «resting» clones, such as NXA clones. (II) In the context of xenotransplantation, this clinical protocol could be particularly effective in eliminating those antibodies which may be produced by xenograft-activated B cells.

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G.18 Antigen-specific therapy of experimental autoimmune myasthenia gravis with acetylcholine receptor-gelonin conjugates *in vivo*

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The major pathophysiological deficiency in myasthenia gravis as well as in its animal model, experimental autoimmune myasthenia gravis (EAMG) is the T cell-dependent production of autoantibodies against acetylcholine receptors (AChR) in the muscle membrane by specific B cells. This leads to an accelerated degradation of functional AChR and associated ionic endplate channels giving rise to the clinical symptoms of impaired neuromuscular transmission (i.e., weakness and various degree of paralysis). In order to eliminate these specific B cell clones, rats with EAMG were injected with antigen toxin conjugates constructed by specific coupling of purified AChR with the plant toxin gelonin. This led to a marked improvement of clinical symptoms and an increase in the number of ionic endplate channel density compared to untreated animals with EAMG. The immune response to irrelevant control antigens was not altered by this treatment. Injections of equivalent amounts (molar basis) of gelonin or AChR alone had no therapeutic effect.

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G.19 Increased number of macrophages and monocyte precursor cells in organs of autoimmune male BXSB mice

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BXSB mice spontaneously develop progressive fatal autoimmune disease which resembles human systemic lupus erythematosus (SLE). During their lifetime male BXSB mice develop a high level of serum immunoglobulins, including anti-nuclear antibodies (ANA), a progressive diffuse proliferative glomerulonephritis and an increasing monocytosis in the peripheral blood which is unique among lupus mice. As we could show previously there is a strain-specific high number of myeloid precursor cells in the bone marrow especially monocyte precursor cells (M-CFC). The number of M-CFC is especially high in male BXSB mice and increases with progressing disease. Our latest data show that there is an extramedullary appearance of M-CFC in spleen and liver of male BXSB mice which increases with progressing disease. In addition to a morphologic alteration of the organs there is a change in the number and distribution of organ resident macrophages. The alteration of the macrophage population may be one reason for the rapid progression of the autoimmune disease in male BXSB mice.

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