

OR.55 Transcription Profiles of Rheumatoid Arthritis Patients Reveal Genes Characterizing Different Response to Anti-TNF Therapy

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The Autoimmune Biomarkers Collaborative Network (ABCoN) has enrolled a longitudinal cohort of RA patients beginning anti-TNF treatment in order to identify biomarkers influencing response to anti-TNF therapy. 116 patients beginning anti-TNF therapy (54 etanercept, 25 adalimumab, 37 infliximab) were followed for 14 weeks, with DAS28 measurements and RNA collection at three time points: pre-treatment, 6 weeks and 14 weeks post-treatment. Using the hgu133plus2 Affymetrix chips we have completed genome-wide transcript profiling for these 116 patients as well as 65 healthy controls. Defining response as a DDAS28 >40% and non-response as DDAS28 <20%, analysis of the gene expression differences between patients and controls indicates that the overall number of differentially expressed genes is different for responders and non-responders. Furthermore, the responders are characterized by a unique list of genes differentially expressed as compared to controls at 14 weeks post-treatment. This observation suggests that anti-TNF therapy recruits specific biological pathways in responders. In order to identify the biomarkers that predict the response to anti-TNF therapy we have analyzed the gene expression profiles of responders and non-responders using blood collected at the pre-treatment visit. Using the machine learning technique Random Forest we have identified a set of over 100 genes that are predictive of the anti-TNF response. Using a selected set of 25 candidate biomarkers we can distinguish the responders versus non-responders with 75% accuracy. We are validating the proposed biomarkers using an independent cohort of patients as well as low-density RT-PCR arrays.

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New Animal Models of Disease

Saturday, June 9
2:45 pm–4:45 pm

OR.56 Development of Latest-generation HU-PBMC-NOD/SCID Mice to Study Human Islet Allo-reactivity

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Small animal models have been used to study a number of human diseases, including autoimmune diseases such as type 1 diabetes (T1D). Unfortunately, translating therapies from animal models to human patients has been hindered by differences in rodent and human immune systems. "Humanized" mouse models hold great promise in the development of efficacious therapies to treat a wide array of human immune-mediated conditions, without putting human subjects at risk during protocol development. However, developing a system that faithfully recapitulates human immunity in a murine host has proven difficult. Recently, the generation of a new stock of immunodeficient hosts, the NOD.Cg-Prkdcscid Il2rgtm1Wjl/Sz (NOD-scid Il2rgnull) strain, has overcome many of the previous limitations of humanized mice. We have characterized the engraftment of human PBMC into NOD-scid Il2rgnull hosts and document that this stock supports higher human cell engraftment at lower cell input levels. Importantly, we further demonstrate that human PBMC-engrafted NOD-scid Il2rgnull mice allow for allogeneic rejection of transplanted HLA-mismatched human islets, even when the islets are allowed to heal-in prior to PBMC engraftment. Collectively, these data suggest that humanized NOD-scid Il2rgnull mice may be superior to previous immunodeficient recipients for generation of humanized mice for studies of *in vivo* human immune function.

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OR.57 TSLP-dependent Induction of Airway Inflammatory Disease is Antigen-driven in an Acute Model of Allergic Airway Inflammation

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The cytokine, Thymic Stromal Lymphopoietin (TSLP), has been shown to play an important role in the mediation of Th2-biased inflammatory diseases in particular the atopic diseases: asthma and atopic dermatitis. Mice expressing a TSLP transgene driven by the lung-specific Surfactant Protein C promoter (SPC-TSLP) develop a severe and chronic asthma-like disease characterized by airway hyperresponsiveness, leukocytic infiltration of the lung, eosinophilia, goblet cell hyperplasia, sub-epithelial fibrosis, and elevated serum IgE. Previous studies have indicated that TSLP alone is sufficient to induce all of the hallmark features of asthma in mice. Here we show that an acute airway inflammatory disease, similar both to that seen in asthmatics as well as SPC-TSLP mice, can be induced in BALB/c mice through direct intranasal administration of TSLP in conjunction with a foreign antigen, sans adjuvant. This has been observed with multiple antigens, including ovalbumin, chicken gamma globulin, and bovine serum albumin. In contrast, mice treated with either TSLP alone, the antigens alone, or TSLP in conjunction with the self-protein, mouse serum albumin, fail to develop disease. These data demonstrate for the first time that in an acute model of TSLP-mediated airway inflammation, both thymic stromal lymphopoietin and antigen are required in order to develop full disease symptoms.

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OR.58 Disrupting Mer Receptor Tyrosine Kinase Expression Prevents Autoimmune Chronic Graft-versus-host Disease

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The Mer receptor tyrosine kinase mediates apoptotic cell phagocytosis and modulates macrophage cytokine production. Mer knockout mice (Mer-KO) have defective clearance of apoptotic debris and develop SLE-like autoimmune disease. Because of their spontaneous autoimmune propensity, we wondered if Mer-KO mice (backcrossed 10 generations onto C57BL/6) might be particularly susceptible to the SLE-like autoimmunity induced by chronic GVH. Using the well-established cGVH model (bm12/B6 mice), we were surprised to observe that the Mer-KO mice were protected from the development of GVHD. Mer-KO recipients of bm12 spleen cells failed to develop detectable anti-dsDNA and anti-chromatin autoantibodies, while the B6 hosts produced significant amounts of these antibodies that peaked at week 2. Slightly increased levels of rheumatoid factor were found in Mer-KO mice, though much lower than B6 control hosts. Mer-KO mice did not develop splenomegaly. The lack of autoantibody formation was not due to absence of alloreactivity because spleen cells from bm12 mice proliferated equally in response to irradiated WT and Mer-KO irradiated spleen cells. These findings indicate a hitherto unrecognized requirement for Mer in the genesis of alloreactivity-induced autoimmunity. Future

experiments will determine whether this reflects the role of this kinase in recognition and phagocytosis of apoptotic cells, its function in regulating cytokine production, or perhaps a new function in the immune response.

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OR.59 In Vivo and In Silico Modeling the Dynamics of Autoimmune Diabetes

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Progression of autoimmune diabetes results as a consequence of an imbalance of Teff and suppressive regulatory T cells (Tregs). A novel mathematical model of type 1 diabetes (T1D) in the non-obese diabetes (NOD) mouse (T1D Physio-Lab® platform) was developed that encompasses the dynamics of key immune components in the pancreatic lymph nodes (PLNs) and islets, and beta cell physiology. Research using this platform predicted that autoimmunity was controlled in the PLN, as shown by an increase in Tregs over the course of disease. This unexpected behavior was confirmed experimentally by functional and histological data. Additionally, laboratory analysis of individual islets demonstrated an inverse relationship between Teff and Treg infiltration of the tissue. Specifically, as Teff infiltration increases, the Treg fraction decreases. However, differential proliferation of Teffs and Tregs *in vivo* was found to be insufficient to explain this relationship although evidence of reduced expression of CD25 on the resident pancreatic Tregs could alter Treg survival accounting for the observed effects. Based on these *in vivo* results, the relative turnover and recruitment of Tregs and Teffs were tested in the T1D platform. Results of these *in silico* investigations demonstrated that the ultimate determination of disease activity depends on dynamic changes in intra-islet Treg turnover and changes in the Teff/Treg balance. These combined experimental and mathematical modeling results emphasize the central importance of both PLN and intra-islet Treg function in regulating disease pathogenesis and the power of integrating *in vivo* and *in silico* modeling to dissect mechanisms leading to disease pathogenesis.

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