lymphocytes. We further confirm the abundance of such dendritic cells *in situ*, closely associated with microvascular BBB-endothelial cells within acute multiple sclerosis lesions, as well as a significant number of CD4⁺ IL-17⁺ T lymphocytes in the perivascular infiltrate. Our data support the notion that functional perivascular myeloid CNS dendritic cells arise as a consequence of migration of CD14⁺ monocytes across the human BBB, through the concerted actions of BBB-secreted TGF- β and GM-CSF.

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Genetic Variation & Disease Sunday, June 8 2:45 pm–4:45 pm

OR.100. Gene Candidates for the *Iddm1*-linked Diabetes Susceptibility Locus in Inbred and Recombinant Congenic Rats

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The MHC is the major genetic factor for autoimmune type 1 diabetes (T1D) susceptibility (and thus is known as *Iddm1*), but the identity of all culprit gene(s) within the MHC locus is unknown. MHC class II allotypes likely dictate susceptibility via the selective presentation of immunodominant T-cell epitopes, but it has been shown that HLA-linked genes provide additional strong influences on T1D susceptibility. In the DAISY study of high-risk children, the likelihood of a second child becoming diabetic in a family with one diabetic child rises to 55% if the siblings share by descent the HLA haplotype of the proband (Aly et al., 2006). We study T1D in a rat model in which susceptible and resistant animals share the permissive MHC class II haplotype RT-1B/Du. We discovered linkage to T1D in an F2 cross of inbred rats (LEW.1WR1 and WF) that maps within or near the RT-1 region. Classical class I and II genes are excluded as candidate genes for this new T1D QTL (which we designate *Iddm25*). Fine mapping of this MHC-linked locus and comparison of single nucleotide polymorphisms (SNP) of informative recombinant RT-1 congenic rats on the LEW background point to diubiquitin (UBD) as a culprit gene. Sequence comparisons between UBD alleles from T1D susceptible and resistant rat strains support this identification. Rat and human genomes are highly syntenic for gene content in this region. Of interest, the human UBD gene (Jahromi, 2007) is one of two found in the DAISY study that could be the T1D-promoting locus.

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OR.101. Time-dependent and Tissue-specific Changes in Gene Expression During Disease Induction and Progression in NOD Mice

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Studies to be presented identified tissue-specific and time-dependent (bi-phasic) changes in gene expression patterns that correlate with non-obese diabetic (NOD) mouse disease progression. Agilent 41K mouse whole genome oligo-microarrays were used to characterize gene expression patterns in multiple tissues (pancreatic lymph nodes, spleen, and peripheral blood cells) from individual female NOD mice over time compared to tissue matched pooled female NOD.B10 control samples. Changes in gene expression (either the result of expression of non-canonical splice variants or changes in transcript level) were seen among genes within previously demarcated diabetes susceptibility regions (Idd regions) leading to the concept that disease associated genes result from changes in expression, not polymorphism or mutation. Using hierarchical clustering, genes showing uniform patterns of changes in expression over time were seen in these tissues, but the patterns of distribution and kinetics of expression were unique to each tissue. These studies identified unique tissue and age-specific gene expression patterns that may play an important role in the induction or perpetuation of T1D in NOD mice. The data suggest that changes in gene expression resulting from inflammation and not from structural changes encoded in the genome may better define disease related "candidate genes" in autoimmune diseases.

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OR.102. The CD58 Pathway is Implicated in MS Susceptibility

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system associated with demyelination, axonal loss, and brain atrophy. Our recent admixture scan of African-American subjects with MS identified a susceptibility locus that contains a cluster of genes encoding T cell costimulation molecules on human chromosome 1p12. Since MS is associated with dysregulated immune responses characterized in part by defects in CD4⁺CD25^{high} regulatory T cell function, we pursued a gene discovery effort within this gene cluster. Here, we report the association of the "G" allele of rs2300747 with reduced susceptibility to MS (OR 0.80, P = 1.1 × 10⁻⁶). This Single Nucleotide Polymorphism (SNP) resides in a block of

linkage disequilibrium (LD) that contains a single gene, CD58 (LFA-3). In 89 unrelated lymphoblastic cell lines, the level of expression of CD58 RNA is increased in a dose-dependent manner in the presence of the rs2300747 "G" allele ($P=1.1 \times 10^{-10}$). Furthermore, we show that enhanced expression of CD58 is associated with a clinically quiescent state in MS and that stimulation of the CD58 receptor, CD2, induces the expression of FoxP3, a master regulator of CD4+CD25high regulatory T cells. Thus, individuals who harbor this putative protective CD58 allele may be less susceptible to MS because of increased CD58 expression resulting in increased FoxP3 expression and enhanced CD4+CD25high regulatory T cell function.

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OR.103. Combined Analysis of Three Genome-wide Scans Reveals Additional Loci Associated with Rheumatoid Arthritis

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Three large genome-wide association scans for rheumatoid arthritis (RA) have been completed recently in Swedish, British, and U.S. Caucasian samples, and initial results have been published. Because most risk altering variants confer only a modest increase in risk of disease, large sample sizes are needed to detect all but the most significant effects. Here we report the results of the first meta-analysis of these three studies, analyzing 1,742,343 SNPs that have been directly genotyped or imputed on the basis of haplotypes observed by the HapMap Project. RA has at least two clinically distinct forms, characterized by the presence (ACPA+) or absence (ACPA-) of autoantibodies to citrullinated peptides. We thus consider ACPA+ and ACPA- cases separately, and find that significant aspects of the genetic architecture underlying these two patient subtypes also differ. For ACPA+ disease (3,103 cases and 4,797 controls), in addition to highly significant signals of association at previously known loci - the MHC region, PTPN22, and TNFAIP3 - we find 761 SNPs with $P < 0.0001$ in meta-analysis, including SNPs in a number of genes that have been associated with other autoimmune conditions (e.g., CD40, PTPN2, IL2RA, and IRF5). For ACPA- disease (872 cases and 3,579 controls), we find 306 SNPs with $P < 0.0001$. Much of the difference reflects reduced statistical power in the smaller study of ACPA- cases, but we find few overlapping associations, even for SNPs with high odds ratios in ACPA+ RA. Attempted replication of these associations is underway in additional samples from each of the three original populations.

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OR.104. Association of Sjögren's Syndrome (SS) and Systemic Lupus Erythematosus (SLE) with BLK

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Objective: The shared clinical and laboratory features of Sjögren's syndrome and SLE suggest that these two, sometimes co-existing, autoimmune disorders have related genetic origins, which we sought to reveal. **Methods:** We performed a whole genome scan using a DNA pooling approach with four independent European-derived SS cohorts (381 cases and 354 controls) on the Affymetrix Gene Chip® Mapping 100K Set (Santa Clara, CA). The most promising 288 SNPs, selected on the basis of probability and candidate gene promise, were genotyped in 10,936 SLE cases and controls on the iSelect Infinium™ platform from Illumina (San Diego, CA) (6,276 European-derived, 1,822 Asian, and 1,858 African-American). **Results:** The expected powerful associations at HLA were observed in SS DNA pooling and in the SLE individual replication genotypes; however, the SS pooling data showed European-derived association at HLA-DPB1 (pCOMBINED=1.54E-05) that was not present in the SLE subjects. The other most convincing shared association was at BLK. Markers in BLK were associated on chromosome 8 from 11.38 to 11.45 Mb. In the SS samples all four SS cohorts had associated markers, with the strongest signal at rs1478890, 11393011 bp (pCOMBINED=2.45E-05), while the SLE samples had 6 to 11 associated markers in each individual ethnicity, with the strongest combined results surviving Bonferroni correction ($p=1.16734E-08$, pCORRECTED=0.000968). Multiple other genes and regions show promise of being robust genetic associations shared between SLE and SS. **Conclusions:** The HLA association of SLE and SS is not identical. BLK is probably associated with European-derived SS and SLE and with Asian and African-American SLE.

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