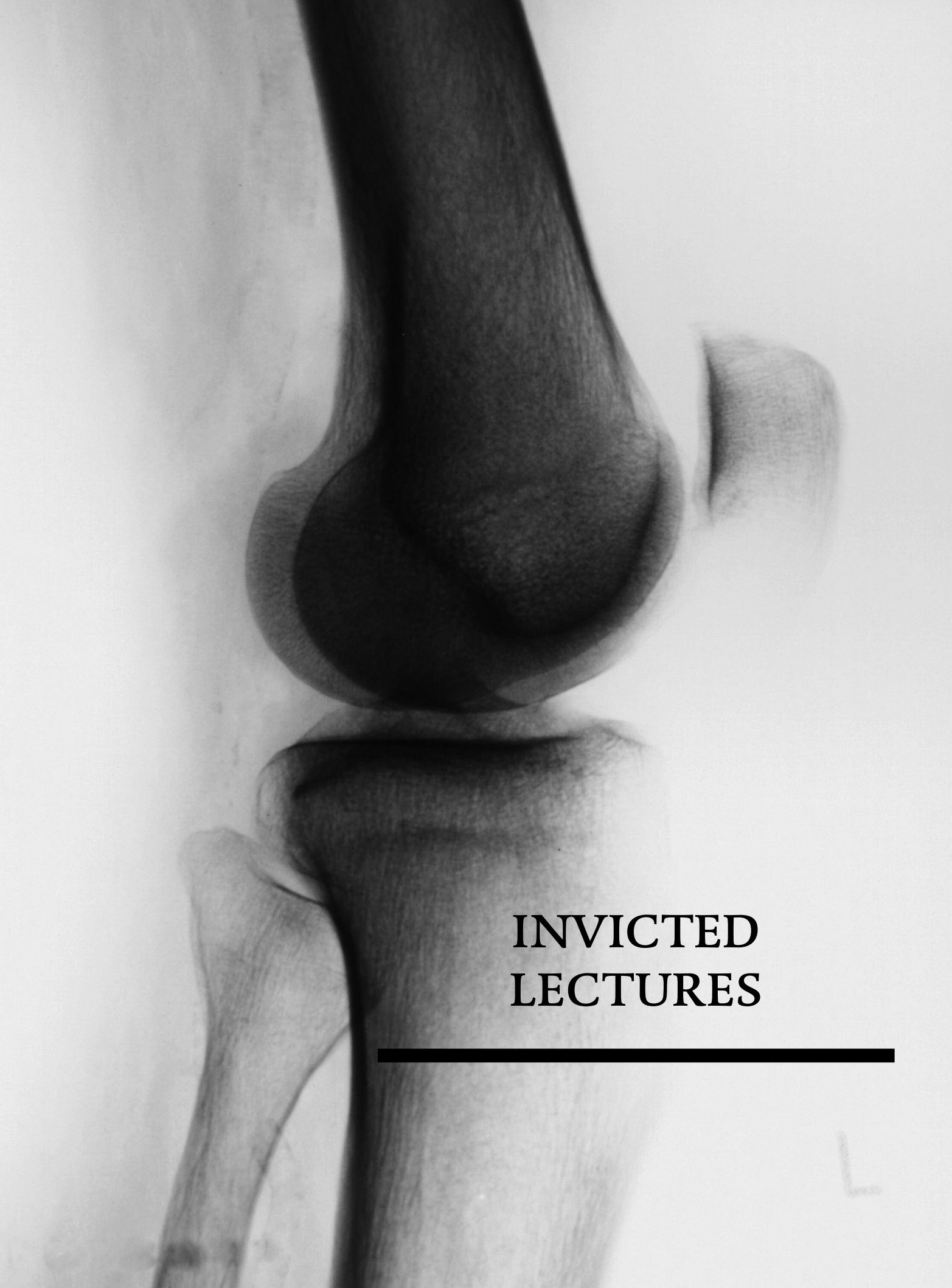

INVICTED LECTURES

Invited Lectures

ACTA REUMATOL PORT. 2014:39:7-16 (SUP)

I1

MECHANISMS THAT DRIVE CHRONICITY IN RA SYNOVITIS

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Rheumatoid arthritis (RA) is characterized by perpetuation of inflammatory cascades that in turn are mediated primarily by cells of the myeloid lineage within the synovial compartment.

Our group have for several years sought those pathways that lead to effector cytokine production and in turn that could thereby represent novel therapeutic targets or biomarkers for stratification of disease. Recently we have focused especially on the role of microRNA species contained in monocytes and macrophages, and in dendritic cell subsets that might participate in the evolution of the synovial lesions. We have identified a number of moieties that appear to regulate cytokine expression and other elements of cellular effector function.

These include miR155, miR34a and miR 125. The role played by these molecules in the activation of macrophages has been refined in vivo in models of disease and also in ex vivo cell culture systems. We are now in the process of defining a complex regulatory network that 'fine tunes' the effector cytokine response.

I2

CD28 EXPRESSION IS REQUIRED AFTER T CELL PRIMING FOR HELPER T CELL RESPONSES AND PROTECTIVE IMMUNITY TO INFECTION

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The costimulatory molecule CD28 is essential for activation of helper T cells. Despite this critical role, it is not known whether CD28 has functions in maintaining T cell responses following activation. To determine the role for CD28 after T cell priming we generated a strain of mice where CD28 is removed from CD4+ T cells after priming. We show that continued CD28 expression is important for effector CD4+ T cells following infection; maintained CD28 is required for the expansion of T helper type 1 cells, and for the differentiation and maintenance of T follicular helper cells during viral infection. Persistent CD28 is also required for clearance of the bacterium Citrobacter rodentium from the gastrointestinal tract. Together, this study demonstrates that CD28 persistence is required for helper T cell polarization in response to infection, describing a novel function for CD28 that is distinct from its role in T cell priming.

I3

HUMAN TFH SUBSETS IN HEALTH AND DISEASE

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T follicular helper (Tfh) cells represent the major CD4+ T cell subset providing help to B cells. Tfh cells are essential for the generation of high-affinity memory B cells through the germinal center (GC) formation. Tfh cells express the chemokine receptor CXCR5, which guides their migration into B cell follicles. Inducible co-stimulator (ICOS), expressed at high density by Tfh cells in human tonsils, plays a critical role for their de-

velopment and functions. Tfh cells support the differentiation and survival of GC B cells through the secretion of interleukin-21.

Tonsillar Tfh cells express the transcription repressor B cell lymphoma 6 (Bcl-6), which is essential for Tfh cell generation in vivo. In addition to GC response, CD4+ T cells also provide help to B cells at extrafollicular sites, and induce their differentiation into plasma cells that contribute to the early generation of specific antibodies after antigen challenge.

Extrafollicular helper cells share developmental mechanisms, phenotypes, and functional properties with Tfh cells.

Tfh response needs to be regulated, as both insufficient and increased Tfh responses cause health problems. Insufficient Tfh response causes failure in the development of antibody responses, for example in response to vaccination. Increased Tfh response causes autoimmunity by activating self-reactive B cells and promoting the generation of autoantibodies. Therefore, understanding the biology of human Tfh cells is essential to define the mechanisms responsible for altered antibody responses in humans. Recent studies including ours show that human Tfh cells are composed of functionally distinct subsets. In my talk, I will discuss how functionally distinct Tfh cell subsets regulate antibody responses and how they develop in humans.

I4

BETA CELL DEFECTS CONTRIBUTE TO DIABETES SUSCEPTIBILITY IN NON-OBESE DIABETIC MICE

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Introduction: Type 1 diabetes (T1D) results from the autoimmune destruction of pancreatic islets. The primary model of T1D is the non-obese diabetic (NOD) mouse, with immunological defects that parallel human T1D.
Materials and Methods: Here we find a new immune--independent component of diabetes susceptibility in the NOD mouse, revealed through transgene-induced unfolded protein stress.
Results: In the baseline state, NOD islets have a qualitatively different transcriptional profile to resistant B10 islets. These differences are propagated through the response to cellular stress, resulting in stressed survival on the B10 background and apoptosis and diabetes on the NOD background. Susceptibility to transgene-induced diabetes is controlled by three dominant loci in NOD mice, the effect of which can be replicated in B10 mice through brief exposure to an elevated fat diet or through increased autoimmune burden.
Discussion: Together, these results demonstrate that NOD diabetes susceptibility is broader than genetic defects in immune tolerance, and includes an islet-intrinsic survival defect. In the human context, these results also suggest a mechanism by which the "Western diets" may contribute to the steady growth in T1D incidence.

I5

T CELLS IN NEUROINFLAMMATION

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The CNS is confronted to a double challenge regarding its interactions with the immune system. On the one hand it should allow the immune system to fight invading pathogens and on the other it should prevent inflammatory damage given its vital functions and poorly regenerative capacity. A series of mechanisms,

collectively referred to as 'immune privilege', ensures that immune reactions are kept minimal and are rapidly controlled within the CNS.

However, accumulating evidence show that T cells readily penetrate the brain and spinal cord parenchyma in numerous inflammatory, infectious or degenera_tive neurological diseases. The consequence for CNS resident cells, and more specifically for neurons, of their encounter with activated T cells is a question that we have addressed recently using experimental rodent models. I will present our efforts to understand how cytotoxic CD8 T cells and helper CD4 T cells can target neuronal antigens and thereby contribute to CNS tissue damage. Intriguingly, some autoreactive T cells recognize several autoantigens but the functional significance of such 'cross-reactivity' is not fully understood. We have identified, in mice, autoreactive CD4 T cells recognizing both MOG and NF-M and have investigated their pathogenic contribution using animals deficient for one or the other self-antigens.

Shedding light on the mechanisms by which T cells promote CNS tissue damage may allow the design of more refined therapeutic strategies for immune--mediated neurological diseases, including multiple sclerosis.

I6

REGULATORY T CELL THERAPY IN ORGAN TRANSPLANTATION

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Immune regulation is fundamental to any immune response to ensure that it is appropriate for the perceived threat to the host. Strategies for the induction of specific unresponsiveness to donor alloantigens currently under investigation in the clinic take advantage of two of the major mechanisms for the induction of tolerance to self antigens – deletion and immunoregulation/suppression.

We have demonstrated that human regulatory T cells expanded ex vivo can protect human allografts (skin and vessels) from rejection. Together with other leukocyte populations, including regulatory T cells, B cells and macrophages as well as myeloid derived suppressor cells and dendritic cells, Treg contribute to the regulation of immune responses in vivo after cell or solid organ transplantation.

The identification and characterisation of Treg that can control immune responsiveness to alloantigens has opened up exciting opportunities for new therapies in transplantation. Phase1/2a clinical trials are in progress – www.onestudy.org.

I7

ANTHRACYCLINES INDUCE DNA DAMAGE RESPONSE-MEDIATED PROTECTION AGAINST SEVERE SEPSIS

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Severe sepsis remains a poorly understood systemic inflammatory condition with high mortality rates and limited therapeutic options in addition to organ support measures. We have recently shown that the clinically approved group of anthracyclines acts therapeutically at a low dose regimen to confer robust protection against severe sepsis in mice. This salutary effect is strictly dependent on the activation of DNA damage response and autophagy pathways in the lung, as demonstrated by deletion of the ataxia telangiectasia mutated (Atm) or the autophagy-related protein 7 (Atg7) specifically in this organ. The protective effect of anthracyclines occurs irrespectively of pathogen burden, conferring disease tolerance to severe sepsis. These findings demonstrate that DNA damage responses, including the ATM and Fancony Anemia pathways, are important modulators of immune responses and might be exploited to confer protection to inflammation--driven conditions, including severe sepsis.

I8

CONTROL OF CENTRAL NERVOUS SYSTEM AUTOIMMUNITY BY REGULATORY T CELLS DEPENDS ON TNF/TNFR2

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Anti-TNF drugs have significantly improved the treat-

ment of rheumatoid arthritis and several other auto--immune diseases. Unfortunately, these therapies cannot be proposed to patients with multiple sclerosis because of disease exacerbation, for unknown reasons. Interestingly, mice deficient for the TNF receptor type 2 (TNFR2) developed an exacerbated experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. These findings suggest that TNF has an immuno-regulatory facet, besides the well-established pro-inflammatory properties of the cytokine. Our recent findings may bring a mechanistic explanation of this observation. We found that TNF efficiently boosted expansion of Foxp3 expressing regulatory T cells (Tregs) during type 1 diabetes in mice[1]. Also, we observed high levels of Treg expansion in the infiltrated central nervous system (CNS) during EAE, which was critical for disease control and was dependent on TNFR2 expressed by Tregs. We showed that TNF blockade in wild type mice induced disease exacerbation and reduced Treg expansion in the CNS. Finally, mice that have a conditional knock-out of TNFR2 only in Tregs have a very severe disease compared to controls, showing that spontaneous disease remission was due to a direct effect of TNF on Tregs via TNFR2. From these observations, we propose that TNFR2 expressed by Tregs is critical for their expansion and/or function and progressive accumulation in the CNS during EAE, reducing disease severity.

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I9

SUPPRESSION AND RESISTANCE TO SUPPRESSION BY HUMAN TREGS IN HEALTH AND DISEASE

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Regulatory T cells (Tregs) play a fundamental role in maintaining tolerance in the healthy individual. Tregs have been suggested to exert their suppressive function via multiple mechanisms that include their surface expression of CTLA4, LAG3, CD39, and PD-1 ligands, as well through their secretion of IL-10 or production of Granzyme B. Over the years, Tregs have been isolated from patients with various autoimmune diseases and shown to exhibit decreased suppressive activity, as a potential reason for the unchecked immune response in these individuals. Many of these initial reports of deficient Treg function have now been complemented by findings that the patient's non-regulatory T cells actually resist Treg mediated suppression. It is currently unclear how cells mediate this Treg resistance.

The shear number of potential mechanisms by which Tregs exert their suppressive activity, makes it difficult to determine why patient-derived cells show decreased suppression. Also, it is important to note that Treg suppression in vitro and in vivo may not always be identical.

However, since the goal is to be able to modulate Treg suppression in human patients to alter disease activity, it is important to note that in vivo models of Treg function may not necessarily always translate to human in vivo Treg function, due to species differences in gene expression or protein function. For example, although it is widely accepted that the FoxP3 transcription factor is expressed by all Tregs, it is also weakly expressed by activated, non-regulatory human CD4 T cells – a situation that does not appear to be recapitulated in the mouse.

To make matters more complicated, all FoxP3 expressing, suppressive Tregs are not identical. Not only are there induced Tregs (iTreg) and natural Tregs (nTreg) that are derived from different cells, but there are also mature effector nTregs, and less mature, naïve nTregs. Much of the research to date has not examined the potential different roles that these individual Treg subsets may play in different diseases. Thus, it appears that it is not only quite possible that different types of Tregs might be altered in different diseases, but actually, quite likely.

Our group has been separately isolating and studying the functional differences between specific subsets of human FoxP3+ Tregs. In these studies we have found that iTregs and nTregs can strongly differ in their mechanism of suppression. Furthermore, we have found that while iTregs are not altered in patients with Multiple Sclerosis, it is the nTregs that show reduced suppressive capacity when isolated from these patients. In addition, further studies have demonstrated that this reduced suppression reflects Treg resistance by the patient-derived CD4 T cells. Treg resistance is a conceptually important finding as it indicates that merely increasing the number of Tregs in the patient may not reduce immune activation.

However, by studying how CD4 T cells resist sup-

pression, we have identified a molecule that is produced by activated CD4 T cells that inhibits nTreg function. As the therapeutic blockade of this molecule could potentially overcome Treg resistance, we are currently setting out to examine whether this same mechanism contributes to Treg resistance in different inflammatory diseases and states.

I10

PERSONALISED MEDICINE AND PERSISTENCE IN BIOLOGIC THERAPY: THE PERSPECTIVE FROM RHEUMATOLOGY

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Although great progress has been made in the past 20 years in the understanding of the pathogenesis of rheumatoid arthritis (RA) and biologic targeted therapies have revolutionized its treatment, moving therapeutic intervention from the "try and see" approach to a rational, individualised based algorithm remains an elusive goal.

There are two main reasons for this: first RA is a highly heterogeneous clinical and pathobiological condition, characterized by a diverse disease evolution and response to therapy[1,2]. Second, the high rate of therapy discontinuation related to toxicity and/or ineffectiveness.

Interestingly, although at group level the response to biologic therapies appear to be stereotypically similar, with a comparable ACR-20 (60%), ACR-50 (40%), ACR-70 (20%) response rates to all agents (TNF inhibitors, Rituximab, Tocicilizumab, Abatacept), individual patients who fail one mechanism of action by one drug are not necessarily the same as those failing a different mechanism of action by another.

Thus, the search for biomarkers capable of predicting response to biologic therapies and, consequently therapy persistence, has been an investigational focus for many years. However, no reliable makers have been so far identified in the peripheral blood where, for example, gene expression profiles, as pharmacological signatures, were significantly modulated post-TNF-blockade in all patients irrespectively of clinical response.

On the other hand, we have recently reviewed[3] published evidence reporting that specific histomorphological pattern associated with different cellular and molecular signatures within synovial tissues (pathotypes) are associated with diverse clinical evolution and therapeutic response/resistance.

In addition, we have reviewed the importance of ectopic lymphoid structures (ELS) in the development and persistence of autoimmunity[4].

The next challenge is to determine in randomized clinical trials (RCT) the relationship and predictive value of different synovial pathotypes (and associated molecular signatures) with regard to the known diverse disease evolution and therapeutic response/resistance.

This may lead to the development of synovial tissue analysis as a potential clinical tool for patient stratification and construct predictive algorithms incorporating pathobiology into existing clinical, laboratory and imaging modalities, if not for all, at least for the most difficult-to-treat patients.

The establishment of ultrasound-guided synovial biopsy as a rapid, safe and well-tolerated procedure in the hands of rheumatologists that enables synovial tissue collection from most joints in most patients[5], combined with the development of high-throughput miniaturized technologies, should facilitate testing the clinical utility of synovial pathobiology in appropriately powered RCT.

This lecture will review current literature on synovial biomarkers and discuss the rationale for considering integrating synovial pathobiology into clinical therapeutic algorithms to predict therapeutic response to biologic therapies to personalize treatment in RA.

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I11

MARCO-TARGETING CARBOXYLATED PLG NANOPARTICLES PROMOTE TOLERANCE INDUCTION AND SUPPRESSION OF INFLAMMATORY MONOCYTES

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Ag-specific tolerance is the desired therapy for immune-mediated diseases. Our recent phase I clinical trial showed that infusion of myelin peptide-coupled autologous apoptotic PBMCs induces dose-dependent regulation of myelin-specific T cell responses in MS patients. Experiments in EAE and T1D models showed that antigen-coupled apoptotic leukocytes accumulate in the splenic marginal zone (MZ) and are engulfed by F4/80+ MZ macrophages and CD8+ DCs inducing up-regulation of PD-L1 in an IL-10-dependent manner.

Tolerance results from the combined effects of PD--L1/PD-1-dependent T cell anergy and activation of Tregs recapitulating how tolerance is normally maintained in the hematopoietic compartment in response to uptake of senescing blood cells.

To further advance clinical translation of tolerogenic therapies, we have shown that long-lasting tolerance is inducible by i.v. administration of (auto)antigens covalently linked to 500nm carboxylated poly(lactide-co-glycolide) (PLG) nanoparticles (Ag-NP) abrogating development of Th1/Th17-mediated autoimmune diseases (EAE and T1D) and Th2-mediated allergic airway disease when used prophylactically and ameliorating progression of established disease when administered therapeutically. Ag-NP-induced tolerance is mediated by the combined effects of cell-intrinsic anergy and Treg activation and is dependent on route of administration, particle size and charge, uptake by MZ macrophages via the MARCO scavenger receptor, and can be induced either by NP covalently coupled with or encapsulating the (auto)antigen. Additionally, we have shown that i.v. infusion of 'naked' carboxylated PLG NP targets inflammatory monocytes/macrophages in a MARCO-dependent fashion leading to their sequestration in the spleen and eventual apoptosis and is a potent therapy for ameliorating acute inflammatory diseases, including myocardial infarction, peritonitis, acute spinal cord injury, and virus encephalitis. These findings demonstrate the utility of Ag-NP as a novel, safe and cost-effective means for inducing antigen-specific tolerance for therapy of MS and other (auto)immune-mediated diseases using an FDA-approved biomaterial easily manufactured under GMP conditions.

ACKNOWLEDGEMENT
Supported by grants from NIH, JDRF and the Myelin Repair Foundation.

I12

ORGAN-SPECIFIC CHRONIC INFLAMMATION: THE PARADIGM OF LIVER DISEASES

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The liver plays a pivotal role not only in the induction of the immune response against pathogens but also in the maintenance of tolerance against self-molecules, being one of the largest lymphoid organs. It is therefore not surprising that the liver may be targeted by a tissue--specific inflammatory process as observed in autoimmune diseases, such as autoimmune hepatitis (AIH) and primary biliary cirrhosis (PBC) and chronic inflammatory conditions such as primary sclerosing cholangitis (PSC). Primary immune diseases of the liver are characterized by peculiar histopathology and progressive courses while virtually all rheumatologic diseases can affect the liver.

AIH is a chronic hepatitis caused by the autoimmune injury of hepatocytes, rapidly progressing to liver cirrhosis and failure. PBC is a chronic cholestatic liver disease characterized by lymphocytic infiltrate of the small bile ducts, along with the frequent finding of non caseous granulomas. More pertinent to the present lecture, PSC is a chronic cholestatic liver disease characterized by the chronic inflammation of the intrahepatic and/or extrahepatic biliary ducts and fibrosis, leading to large duct stenosis and eventually liver cirrhosis from long-standing cholestasis. The etiopathogenesis of PSC is largely unknown, but genetic (HLA-B8 and HLA-DR3) and immune factors are involved in the disease onset, as supported by the significant association with inflammatory bowel disease (IBD), particularly ulcerative colitis. As many as 2.4-7.5% of patients with

IBD, primarily ulcerative colitis, have PSC. The presence of both conditions leads to a poor prognosis and higher risk to develop both colorectal and cholangiocellular carcinoma. Different from PBC, PSC is a male-predominant disease by a 3/1 ratio, and the peak age for PSC diagnosis is 20-30 years. A recent work on patients listed for liver transplantation demonstrates that different PSC phenotypes characterize ethnic and racial groups, similar to what observed for IBD, with African Americans developing an end-stage liver disease at an earlier age. Most patients with PSC have serum autoantibodies, but these are not specific, as in the case of anti neutrophil cytoplasm antibody (80%), ANA, and anti-smooth muscle antibody (20%-50%). Treatment options for PSC are largely unsatisfactory.

I13

FOLLICULAR HELPER T CELLS IN TYPE 1 DIABETES

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The strong association of MHC class II genes with Type 1 Diabetes (T1D) implicates CD4 T cells as key players in disease. The immune response in T1D has traditionally been considered to reflect a T-helper 1 (Th1) differentiation programme. However, not all the evidence from mouse models and patient samples supports this conclusion. More recently, patient-derived data has suggested T1D may be associated with Th17 differentiation.

To re-visit the question of CD4 T cell differentiation in T1D, we initially used a mouse model.

In the DO11 x rip-mOVA model, transgenic CD4 T cells recognise ovalbumin (OVA) expressed in pancreatic islet cells under the control of the rat insulin promoter. In these mice, the transgenic CD4 T cells respond to pancreas-expressed OVA in a manner that initiates autoimmune destruction of islet cells. The mice develop autoantibody responses and progress to frank diabetes with 100% penetrance.

To gain insight into the nature of CD4 T cell differentiation in these animals, we isolated antigen-specific T cells from pancreas-draining lymph nodes and performed microarray analysis. This revealed a characteristic gene expression pattern for follicular helper T cell differentiation. Follicular helper T cells are specialised to provide "help" to B cells for antibody production and there is considerable precedent for involvement of this subset in autoimmunity.

Since the CD4 T cell response to islet-derived antigen appeared to involve follicular helper T cell differentiation in mice, we initiated experiments to examine this differentiation pathway in humans with T1D. These experiments have identified of a follicular helper signature in the peripheral blood of T1D patients. This analysis provides new insight into the nature of T cell differentiation in the setting of T1D and offers the potential to identify new biomarkers and therapeutic targets.

Acknowledgement: This work was supported by JDRF and an MRC Senior Fellowship to LSKW.

I14

GENETICS OF MUCOSAL INFLAMMATORY DISEASES: FOCUS ON INFLAMMATORY BOWEL DISEASE

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Heritable components have been suggested long before confirming molecular discoveries were made by the observations of clustering of inflammatory bowel disease in large families and an increased concordance between monozygotic twins. Analysis of heritability suggested that IBD represents a "complex disease" and may involve a large number of interacting disease genes.

Crohn disease has since become a paradigm example for the successful molecular exploration of a polygenic etiology. In 2001 three coding variations in the NOD2 gene were identified that are highly associated with development of the disease. All variants affect a part of the gene that codes for the leucin rich part of the protein, that appears to be involved in bacteria induced activation of NFkB in macrophages and epithelial cells. A particular subphenotype with localization of the disease in the ileocecal region is highly associated with the variants in the NOD2 gene.

Variants in the NOD2 gene by far not explain the genetic risk for Crohn disease. With the advent of high-density, genome wide association studies enormous progress has been made to discover the remaining disease genes. More than 170 disease genes have been

identified until today, which however still do not fully explain the total genetic risk. In addition to innate immune barrier genes, cytokine response genes (e.g. IL--23R, IL12B, STAT3) and autophagy related genes (e.g. ATG16L1, IRGM) have been identified.

In ulcerative colitis GWAS studies are lagging behind the progress in Crohn disease. The first GWAS studies pointed among several cytokine and macrophage function related genes point to a locus in the 3' end of the IL10 gene. Now more than 50 disease genes are known through large meta-analyses similar to the ones conducted in Crohn disease.

The further genetic exploration of Crohn disease and ulcerative colitis will result in molecular risk maps that are presently completed with amazing speed. Most interestingly, parallel GWAS in psoriasis, atopic dermatitis and other inflammatory diseases shows an unexpected overlap in identified disease genes and regions between the different types of inflammatory barrier diseases. While these insights are challenging news for a novel understanding of disease there is no black-and--white differentiation between healthy and diseased individuals in polygenic diseases. Prediction by individual genetic variants is not possible and even individuals with disease vary only slightly from the normal population. This is different in early and extreme phenotypes where oligogenic or monogenic causations have been identified and where this has guided therapeutic interventions.

I15

IL-17 IN SPONDYLOARTHRITIS

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Cytokines play a central role in the initiation and perpetuation of tissue inflammation. The IL-23/IL-17 cytokine axis recently emerged as a novel master driver of chronic inflammation in experimental models. The role and relevance of this pathway, however, is highly dependent on the exact immunological and tissue context in which it is operating (Baeten, Nat Med 2013). Detailed cellular and molecular characterization of the IL-23/IL-17 axis in specific types of human tissue inflammation is thus required to define how and when this pathway should be therapeutically targeted.

Here, we will first review our current basic understanding of the IL-23/IL-17 axis. Second, we will review the early proof-of-concept studies with drugs targeting this axis in psoriasis, rheumatoid arthritis, and Crohn's disease. Next, we will discuss the evidence pointing towards a central role of this cytokine axis in spondyloarthritis, including genetic data, functional links with HLA-B27, experimental models, and human expression data. Finally, we will review the emerging phase II and III data with drugs targeting IL-23 and IL--17 in the two major subtypes of spondyloarthritis: ankylosing spondylitis and psoriatic arthritis.

Collectively, the emerging basic, translational and clinical data consistently points towards a central role of the IL-23/IL-17 axis in spondyloarthritis and indicate novel opportunities for powerful therapeutic interventions in this severe and debilitating condition.

I17

INDUCTION AND REGULATION OF IL-17+ T CELLS IN HUMAN INFLAMMATORY DISEASE

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IL-17A (henceforth called IL-17) is a pro-inflammatory and osteoclastogenic cytokine, which can be produced by various cell types, including T cells. Recent results from in vitro studies, experimental models and clinical trials indicate that IL-17 plays a role in the immunopathology of several inflammatory diseases, including psoriasis, psoriatic arthritis (PsA) and rheumatoid arthritis (RA).

RA is a debilitating disease caused by chronic inflammation of the joint tissue, leading to joint swelling, pain and damage to cartilage and bone. We and others have shown that IL-17 producing CD4+ T cells (Th17 cells) are present at increased levels in the blood, synovial tissue and synovial fluid of patients with RA, and that the presence of these cells in the joint correlates with clinical parameters of active disease. In addition, we found that both in vitro activated (LPS-stimulated) and in vivo activated CD14+ cells from the inflamed RA joint are potent drivers of IL-17 production in CD4+ T cells. Recent work from the lab has shown that TNF- blockade induces IL-10 expression in CD4+ T

cells, including IL-17 producing CD4+ T cells, which may contribute to the anti-inflammatory action of TNF inhibitors. Current work is aimed at defining the cellular and molecular mechanisms underlying anti-TNF induced IL-10 expression in CD4+ T helper cells and at determining the functional consequences of IL-10 induction.

PsA is an inflammatory arthritis that is genetically, radiologically, serologically and clinically distinct from RA. We recently showed that the inflamed joints of patients with PsA are enriched for IL-17 producing CD8+ T cells (Tc17) and that these cells correlate with clinical parameters of disease. These data suggest that Tc17 cells may constitute a hitherto unrecognized pathogenic immune cell population in PsA. Current work is aimed at the functional and molecular characterization of human Tc17 cells. We are also interested in periodontitis, which is a chronic inflammatory disease affecting the gum and in severe cases the underlying bone. Our current research is aimed at investigating the presence and induction of IL-17 producing T cells in periodontitis and whether this relates to severity of disease.

I18

THE SYSTEMIC AUTOINFLAMMATORY DISEASES

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The umbrella term 'autoinflammatory diseases' was coined to describe the clinical consequences of disordered innate immunity. The best exemplars are the monogenetic hereditary periodic fever syndromes including familial Mediterranean fever, tumour necrosis factor (TNF) receptor associated periodic syndrome (TRAPS), cryopyrin associated periodic syndromes (CAPS) and mevalonate kinase deficiency. Since the recognition of pyrin as the gene responsible for familial Mediterranean fever in 1997 there has been dramatic progress with now more than 20 separate genetic syndromes identified. The advent of new genetic sequencing techniques has greatly expanded our ability to seek novel genes even in sporadic cases and to explore the impact of somatic mutations. These diseases provide the best human evidence for the role of IL-1 in disease and the availability of specific anti IL-1 agents has transformed management of a number previously untreatable diseases and allowed insights into the regulation of IL-1 itself, most notably the discovery of the IL-1 inflammasone. Recent findings of inflammasone activity in T cells suggest mechanisms by which acquired and innate immunity may interact.