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The Yin and Yang of Inflammation

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Abstract

Inflammation is an essential protective part of the body's response to infection, yet many diseases are the product of inflammation. For example, inflammation can lead to autoimmune disease and tissue damage, and is a key element in chronic health conditions such as heart disease, diabetes, rheumatoid arthritis, and also drives changes associated with aging. Animal models of infectious and chronic disease are important tools with which to dissect the pathways whereby inflammatory responses are initiated and controlled. Animal models therefore provide a prism through which the role of inflammation in health and disease can be viewed, and are important means by which to dissect mechanisms and identify potential therapies to be tested in the clinic. A meeting, "The Yin and Yang of Inflammation" was organized by Trudeau Institute and was held April 4–6' 2014. The main goal was to bring together experts from biotechnology and academic organizations to examine and describe critical pathways in inflammation and place these pathways within the context of human disease. A group of ~80 scientists met for three days of intense formal and informal exchanges. A key focus was to stimulate interactions between basic research and industry.

Keywords

Animal models; Autoimmunity; Disease; Industry; Infection; Inflammatory pathways

Positive and Negative Consequences of Inflammation

Several of the presentations illustrated the critical importance of maintaining the delicate balance between the positive and negative aspects of inflammation. A cellular response which has evolved to protect against insult or infection causes inflammation which, if not properly controlled, may have severe pathological consequences. This brings into stark relief the importance of immune regulation, which was the subject of a number of the speakers.

Denise Monack, Stanford University, talked about the essential role of inflammation in the persistence of infections with various species of *Salmonella* bacteria. An inflammatory response is initiated as part of the immune response to *Salmonella* and, paradoxically, this inflammatory response is essential for the persistence of the bacteria. Inflammation helps the bacteria to establish its niche and compete with the intestinal microbiota. Intracellular salmonella are recognized by NOD-like receptors (NLR), specifically NAIP/NLRC4 and

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NLRP3, the recognition of which leads to the assembly of inflammasomes. The inflammasomes serve as an activation platform for caspase-1, which is essential for the release of inflammatory cytokines- key components of innate immunity. Salmonella replicates efficiently in macrophages producing anti-inflammatory cytokines, including IL-4 and IL-10, but cannot replicate in the absence of inflammasome assembly.

Joanne Turner, Ohio State University, discussed the impact of aging-associated lung inflammation on immune control of *Mycobacterium tuberculosis* (M. tb). Her data suggested that inflammation enhanced activation of macrophages in the lung, improving infection control. Thus, although inflammation associated with aging is normally considered deleterious, in this case it could have a beneficial effect.

Another example of the positive and negative aspects of inflammation was presented by **Wenjun Ouyang (Genentech)**, who discussed the control of reactive oxygen species (ROS). On the one hand, ROS are produced by macrophages and are essential for host defense (defective ROS production leads to chronic granulomatous disease). On the other hand, excessive ROS can lead to inflammation-induced tissue damage. ROS therefore needs to be tightly regulated. Dr. Ouyang described a protein, NRROS (negative regulator of ROS) which is essential for controlling excessive ROS-mediated inflammation. Mice deficient in NRROS have enhanced bactericidal activity but develop severe tissue damage which leads to the onset of experimental autoimmune encephalomyelitis. Thus inflammation is essential for protective immunity, but can lead to autoimmunity if left uncontrolled.

Vojo Deretic, University of New Mexico Health Sciences Center addressed the central role of autophagy in both inflammation and immunity to infection. Autophagy, or “self-eating” is a cytoplasmic pathway for removal of damaged or surplus organelles and an important mechanism for the elimination of intracellular microorganisms. Autophagy plays multiple roles in infection, inflammation and immunity and it has been implicated in cancer, neurodegeneration, development and aging. Autophagy, besides its ability to directly eliminate intracellular microbes, also controls inflammation. It has multiple effects on adaptive immunity and on the secretion of immune mediators. Inflammatory cytokines activate autophagy, which influences many aspects of innate and adaptive immunity. Thus, defective autophagy can lead to inflammation and autoimmunity.

The Importance of the Microbiome

The trillions of microorganisms that colonize the mammalian intestine, collectively referred to as the microbiota, have co-evolved over 560 million years with metazoan hosts in a symbiotic relationship. These microorganisms, the majority of which are bacteria, maintain a healthy internal balance by protecting the intestine against colonization by exogenous pathogens and overgrowth of commensal microorganisms. A major theme of the meeting was to discuss advances in our understanding of the interactions of the microbiota, bacterial pathogens, and the host. Studies addressed the twin goals of manipulating the microbiota to prevent or cure pathogenic infections and minimizing disruption of the protective commensal bacterial through misuse of antibiotics.

Eric Pamer (Memorial Sloan Kettering Cancer Center) described the effects of allogeneic hematopoietic stem cell transplantation (HSCT) on the diversity of the microbiome. Evidence was presented that the microbiome changes rapidly and dramatically following HSCT, sometimes being dominated by only one type of bacteria such as vancomycin-resistant enterococcus (VRE). VRE is usually non-pathogenic, however, if antibiotic-resistant bacteria proliferate to a high density in the intestine, as they do after HSCT, they can cause disease by disseminating into deeper tissues and into the bloodstream. Because of their antibiotic resistance, VRE strains are particularly difficult to treat. Indeed, HSCT patient survival was shown to correlate strongly with microbiota diversity. Re-introducing normal flora to mice via fecal-transplantation can reduce and even clear VRE colonization. Although the exact mechanism of how this occurs is not known, data were presented which indicate that colonization with *Barnesiella* spp. negatively correlates with colonization by VRE but is not sufficient to clear the infection alone, suggesting that other bacteria play a role. Additionally, it was shown that secondary bile salts are highly inhibitory for VRE growth. Antibiotic treatment experiments revealed that intestinal microbiota are required to convert primary bile salts into secondary bile salts, suggesting a possible mechanism of VRE growth inhibition by commensal bacteria.

Marsha Wills-Karp (Johns Hopkins University) discussed the link between the intestinal microbiota and asthma severity. The hygiene hypothesis predicts that a major contributing factor to the increased prevalence of asthma in developing countries over the past 50 years is the decreasing incidence of infections. As a corollary to this hypothesis, experiments utilizing antibiotic treatments and measuring microbiota diversity have shown that decreased diversity in the gut microflora in early life may be associated with the development of asthma. However, the specific microbes which are providing protection from asthma are not known. Using mice colonized with segmented filamentous bacteria (SFB) in the gut and mice without SFB, Wills-Karp demonstrated that mice colonized with SFB display significantly increased airway hyperresponsiveness (AHR) and neutrophilia in response to house dust mite challenge compared to SFB negative mice. Furthermore, the enhanced AHR of SFB positive mice was associated with elevated IL-17A expression, and IL-17A positive cells which persist even after SFB levels decline later in life. Going a step further, blocking IL-17A reduced both AHR and neutrophilia in SFB-colonized mice. Evidence was presented that SFB induce a shift in bone marrow-derived dendritic cell (BMDC) cytokine production from a tolerogenic phenotype towards a Th17-promoting pattern. Additionally, transferring BMDCs from SFB colonized mice to SFB negative mice was sufficient to transfer the disease phenotype. RNA-seq was used to begin to define the mechanism of SFB induced asthma exacerbation. The data revealed that SFB colonized mice express higher levels of serum amyloid A1 (SAA1) in the terminal ileum. SAA instillation was shown to drive IL-17A, neutrophilic inflammation, and IL-23 production in rheumatoid synoviocytes. SAA1 has also been shown to bind to several innate immune receptors including FPR11 which induces BMDCs to produce IL-23 and stimulate Th2 and Th17 cell differentiation leading to severe asthma.

Rounding out discussion of the microbiome, **Avery August (Cornell University)** spoke on the relationship between eosinophils and Th2 cells in the development of allergic asthma.

Using eosinophil-deficient *dblGATA* mice on a C57BL/6 background August was able to show that eosinophils are critical to the development of allergic asthma in a mouse model of OVA-induced asthma. Eosinophil-deficient mice had reduced airway hyperresponsiveness, lung inflammation, and mucous production compared to their wild-type counterparts. Furthermore, adoptive transfer of one million eosinophils is sufficient to induce allergic asthma in mice. August went on to show that eosinophils produce IL-13 in response to Th2 cytokines thereby recruiting additional Th2 cells to the lung, amplifying the Th2 response in a positive feedback mechanism and driving lung inflammation in allergic asthma. Interestingly, August found that the genetic background of the eosinophil-deficient mice was important as *dblGATA* mice on a BALB/c background, unlike those on a C57BL/6 background, were sensitive to OVA-induced allergic inflammation. Additionally, when the *dblGATA* mice on a C57BL/6 background were embryonically re-derived into a cleaner animal facility they were able to develop all the symptoms of allergic asthma. Upon transfer back to a dirtier room, they again became resistant to developing symptoms of allergic asthma after 2-3 generations. Analysis of the microbiome revealed significant differences in the lung microbiome but not the gut microbiome. These observations suggest a potential role for the microbiome, which in addition to genetics, may regulate eosinophil-dependent allergic asthma.

Fibrosis

Fibrosis is a type of tissue pathology common between many different diseases which is responsible for tremendous morbidity and mortality worldwide. Fibrosis occurs when a wound-healing response continues unchecked resulting in chronic inflammation, remodeling of the extracellular matrix, and formation of permanent scar tissue. Fibrosis can be triggered by a variety of events including infections, autoimmune reactions, and mechanical injury. Scientists are searching for a universal therapeutic approach to this problem, one which could be independent of the etiology of the fibrosis. Currently there are no approved treatments that directly target the mechanisms underlying fibrosis; however, some excellent research was presented which offered insights into novel treatment strategies for fibrotic disease.

Thomas A. Wynn (National Institute of Allergy and Infectious Diseases) spoke on the mechanisms regulating fibrosis following chronic infection with the helminth parasite *Schistosoma mansoni*. Wynn explained that Th1 responses cannot clear the worms, and Th2 responses are mounted in an attempt to repair the damaged tissue in their wake. Wynn identified IL-13 as a dominant inducer of the wound healing process and of fibrosis, which was TGF β independent. Additionally, he described the anti-fibrotic role of the IL-13 decoy receptor, IL-13R α 2. Using IL-4 and IL-13 deficient mice, Wynn found that while IL-13 drives fibrosis, beneficial tissue repair depends on the combined actions of both IL-13 and IL-4. Wynn also spoke on the importance of IL-17 in the induction of fibrosis and described the usefulness of an IL-10, IL-12/23(p40), and IL-13R α 2 triple knockout mouse system for evaluating the efficacy of acute fibrotic drugs.

Linda Burkly (Biogen Idec) discussed the role of the TWEAK/Fn14 pathway in chronic inflammatory disease and fibrosis. Tumor necrosis factor-like weak inducer of apoptosis

(TWEAK), a cytokine of the TNF ligand superfamily, acts through its only known signaling receptor, FGF-inducible molecule 14 (Fn14). Fn14 is induced by injury, can be expressed by epithelial and endothelial cells and other mesenchymal cell types, and mediates downstream activation of canonical and noncanonical NF- κ B and MAPK pathways. Burkly presented histological evidence that mice lacking Fn14 expression are protected against chronic 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis. Additionally, she found that the expression of thymic stromal lymphopoietin (TSLP) is significantly reduced in Fn14-deficient mice during acute and chronic colitis. Upon further investigation Burkly found that TWEAK (signaling through Fn14) potentiates the induction of TSLP by IL-13 in naïve colons. Like Fn14-deficient mice, Burkly showed that TSLP receptor-deficient mice also exhibit milder chronic colitis in the TNBS colitis model. Based on these data Burkly proposed a model in which TWEAK, acting in concert with IL-13, induces signaling through Fn14 which leads to a Th2 immune response and Th2-type colitis with fibrosis. In addition to chronic colitis, Burkly also discussed the role of the TWEAK/Fn14 pathway in a model of persistent renal injury with fibrosis. Burkly found that TWEAK or Fn14 deficiency ameliorates renal fibrosis in this model, reducing the appearance of myofibroblasts. She also presented evidence that TWEAK can directly promote the proliferation and migration of pericytes, a cell type shown by others to be a major progenitor pool for myofibroblasts in the kidney, and that their differentiation to myofibroblasts is driven by TWEAK signaling.

Inflamm-ageing

Enhanced inflammation that occurs with aging is thought to be a consequence of an imbalance between inflammatory and anti-inflammatory networks, the consequence of which is the low grade chronic pro-inflammatory status termed inflamm-ageing. This overall increase in the inflammatory status of elderly individuals leaves them susceptible to inflammation-associated pathologies including autoimmune disease, frailty, poor immune defense against infection, and reactivation of latent viral infections. A number of investigators at the meeting provided insight into the as-yet-unexplained connection between increased age and enhanced inflammation.

Cornelia Weyand (Stanford University) spoke on the association between aging, inflammation and DNA instability, focusing on patients with the autoimmune syndrome, rheumatoid arthritis. Rheumatoid arthritis is associated with telomere loss, damaged DNA and metabolic reprogramming, providing an ideal model system for these studies. Weyand's experiments identified molecular defects in T cells from RA patients which indicate that inefficient sensing and repair of DNA damage is an upstream event that changes T cell survival and energetics. The data indicate that nuclear instability in rheumatoid arthritis causes premature senescence and inflammation.

Jorg Goronzy (Stanford University) discussed the association between an increased inflammatory state characteristic of aging and its correlation with several autoimmune diseases, with a focus on the role of T cells. He proposed that two factors in the elderly contributed to the increased inflammatory state. The first factor is an accumulation of inflammatory T cells as a consequence of their reduced activation thresholds and enhanced expression of regulatory molecules. The second factor is a decline in adaptive immunity,

such that the aged immune system is no longer able to prevent the reactivation of latent viruses which leads to innate immune stimulation. However, these models for inflammation do not explain the increased propensity toward autoimmunity. Therefore, he proposed that with increasing age, there is also selection of the antigen-specific repertoire of T cells toward autoreactivity, which he tested with next generation sequencing. The data confirmed that the naïve T cell repertoire in the elderly continues to be very diverse but is biased toward self-reactivity. He hypothesized that enhanced autoreactivity and aging-associated autoimmune disease are consequences of uneven homeostatic proliferation driven by self-recognition and response to homeostatic cytokines throughout life. He concluded that this would result in a T cell repertoire with increased affinity to self.

Gregory Sempowski (Duke University Human Vaccine Institute) spoke of the role of inflammation in age-associated thymic involution, a key consequence of aging. Thymic involution is associated with loss of thymocytes and results in the loss of self-renewing potential for naïve peripheral T cells. IL-6-mediated inflammation that increases with aging contributes to atrophy of the thymus. Sempowski showed that thymic involution can be introduced artificially with endotoxin (i. e. LPS) that induces systemic and intra-thymic inflammation. He also showed that experimental intervention by treatment with anti-IL-6 receptor over a two-week period in animal models increased thymocyte development through four distinct stages of differentiation.

Laura Santambrogio (Albert Einstein College of Medicine) spoke about mechanisms underlying and targeting immune senescence. Immune senescence of primary lymphatic organs is characterized by a decrease in the self-renewing potential of precursor cells as well as the reduced generation of lineage-committed cells. The consequences of this immune decline are increased susceptibility to infections and cancer, as well as reduced responses to vaccinations. Thus far, successful therapeutic interventions for immune senescence remain elusive, despite the vast potential benefit of such therapies. Santambrogio mapped age-related changes in hematopoietic cells in order to determine which changes might be amenable to therapeutic intervention. She found that a hallmark of bone marrow cell precursors (CD34+), as well as lineage committed antigen presenting cells (B cells and conventional dendritic cells), from aged populations is the presence of an extensively glycosylated, carbonylated and lipoxidated proteome. Using a series of biochemical and biophysical approaches she quantitated how increases in carbonylation of the proteome, as well as endosomal accumulation of carbonylated protein aggregates, interfere with MHC class II restricted immune functions. Additionally, she demonstrated the role of autophagy in disposing of the damaged proteome and restoring cellular proteostasis. Finally, she also evaluated therapeutic interventions aimed at decreasing cellular proteotoxicity and restoring the efficiency of MHC II-mediated immune responses.

Cecilia Marta (Sanofi-Aventis) described the unmet medical need related to frailty, a common geriatric syndrome associated with poor clinical outcomes (disability, hospitalizations, mortality, etc). Sarcopenia (defined as loss of muscle mass) is a component of frailty. While the pathogenesis of frailty and sarcopenia is not fully elucidated, a role for inflammation is proposed. High levels of IL-6, C-reactive protein and TNF α are associated with the progression of frailty and sarcopenia in the elderly, accurately predicting permanent

disability and mortality. Studies showed that exercise programs can reduce inflammation and frailty. Therefore, there is a potential interest in therapies that modulate inflammation to ameliorate the progression of this condition.

Dissecting mechanisms for therapy development

Understanding mechanisms underlying inflammatory responses makes possible the development of rational therapeutic approaches. Several speakers addressed approaches to therapy or vaccine development based on newly gained mechanistic insights.

Dania Rabah (Biogen Idec) spoke of a possible therapy for Systemic lupus erythematosus (SLE), an autoimmune disease in which an inappropriate inflammatory response against “self” causes disease. SLE patients display an interferon (IFN) signature characterized by the increased expression of type 1 interferon-inducible transcripts in peripheral blood mononuclear cells (PBMCs). Type 1 interferons are secreted polypeptides that induce the expression of interferon-stimulated genes in responding cells. Plasmacytoid dendritic cells (pDCs) are known to be a major source of type 1 interferons, producing up to 1000-fold more interferon α (IFN α) than other cell types. Primate pDCs express blood dendritic cell antigen 2 (BDCA-2), a C-type lectin that is capable of initiating a B cell receptor-like signaling pathway. The potential clinical benefit of modulating the type 1 interferon signaling pathway may be mediated through the inhibition of BDCA-2 in human pDCs. She showed that administration of anti-BDCA2 monoclonal antibodies to whole blood cultures resulted in BDCA2 internalization, inhibition of TLR9 signaling, and inhibition of type 1 interferon production in human pDCs. Administration of these anti-BDCA2 monoclonal antibodies is being investigated as a potential therapy to block type 1 interferon production in SLE patients.

Tania Watts (University of Toronto) spoke of the critical role of the TNFR superfamily of receptors in the modulation of T cell responses to viral infections. 4-1BB and glucocorticoid-induced TNFR-related protein (GITR) are TRAF-binding members of the TNFR superfamily that are expressed or induced on CD8 T cells during viral infections, and play a pro-survival role in these cells. Watts showed that both 4-1BB and GITR are required to control viral loads in influenza infected mice. In addition, Watts discussed the role of GITR and potential therapeutic interventions in chronic viral infection.

Jean Gariépy (Sunnybrook Research Institute, Toronto) described the development of functional aptamers for modulation of immune responses. The aptamers used in his studies were composed of ssDNA, 75 nucleotides in length, folded into a 3-dimensional structure, and were selected for their ability to bind intended targets by the systematic evolution of ligands by exponential enrichment (SELEX) process. Gariépy and his colleagues identified a short ssDNA aptamer that specifically blocks the action of human TNF α as well as aptamers behaving as CD200R1 agonists. In both cases, these aptamers were potent inhibitors of inflammatory responses both in *in vitro* and *in vivo* settings. Overall, functional DNA aptamers, are easy to identify and to chemically synthesize, are non-immunogenic and have the potential to be used or to replace monoclonal antibodies as immunotherapeutic agents in the clinic.

Jay Kolls (Children's Hospital of Pittsburgh) has been investigating the role of cytokines in immune defense and vaccine design. He has shown that CD40L can serve as a vaccine adjuvant to induce protective B-cell responses in CD4 deficient mice against the opportunistic pathogen, *Pneumocystis murina*. Human genetic deficiencies in both CD40L and IL-21R also show susceptibility to *Pneumocystis* infection. A long-standing interest of the Kolls lab has been the function of IL-17 in host defense. IL-17A and IL-17F, the two IL-17 family members expressed in Th17 cells, co-evolved with Rag genes, suggesting an evolutionary advantage of TCR recombination and the Th17 lineage. Mucosal immunization of mice with *Klebsiella pneumoniae* elicited a unique population of Th17 cells that were able to provide antibody independent immunity against challenge infection. Importantly this protection was also serotype independent as the vaccine elicited Th17 cells recognized several clinical serotypes of *Klebsiella pneumoniae* suggesting that one evolutionary advantage of Th17 cells is their ability to confer serotype independent immunity to extracellular pathogens. Together, this work shows that modulation of cytokine responses has the potential to impact future therapies and vaccine design.

Stephen Jameson (University of Minnesota) presented data on an unusual type of CD8 T cell memory, termed virtual memory (VM), which develops early in life by homeostatic mechanisms in unimmunized mice. Both VM and antigen-primed "true memory" (TM) cells exhibit rapid trafficking into influenza-infected lungs, but the relative efficacy and inflammatory properties of VM compared with TM cells are not clear. VM cells were found to produce IL-10 (which modulates inflammation) in response to IL-27 and therefore do not cause immunopathology in response to influenza virus infection. TM cells, on the other hand, do not produce IL-10 in the same way, and hence cause more immunopathology during influenza infection. These data suggest VM cells exhibit properties that are intermediate between naïve and TM cells, and that VM cells may contribute to pathogen control without attendant immunopathology.

Academic/Industry Collaborations

One of the primary goals of this meeting was to encourage interactions between academia and industry. The keynote speaker, **David Lee (Novartis Institutes for Biomedical Research)**, discussed strategies for developing successful collaborations between academic and industrial scientists. David offered several key strategies to overcoming barriers and establishing mutually beneficial collaborations between academic and industrial partners. First and foremost, he stressed that the focus of any successful collaboration should be the science. Clearly defined common interests and goals should be established for both partners, with no commercial agenda in mind. He recommended to start first with a scientific question and then to identify the most appropriate partner, irrespective of academic or industry affiliation. Together, both collaborators can then determine the resources needed to meet the common goals. Since miscommunication and misplaced expectations are a common barrier to successful collaborations, an in-house program champion should be established that can facilitate effective communication between the collaborating parties. Finally, bureaucracy can be minimized by interacting with a well-established technology transfer office to provide an uncomplicated, efficient, legal framework for the collaboration. Any resulting agreement should be focused on enabling scientific activity, and capturing the synergies of

the collaboration. In summary, cultivating a relationship between academic and industrial scientists can be a win-win for both sides. Therefore, he advised to focus on the science, and just do it!

A facilitated panel discussion on academic/industry collaborations followed up on some of the key themes mentioned in David Lee's keynote address. The panelists included **Linda Burkly (Biogen Idec)**, **Cecilia Marta (Sanofi)**, **Wenjun Ouyang (Genentech)**, **Dominic Eisinger (Myriad RBM)** and **Ronald Goldfarb (Trudeau Institute)**, in addition to **Dr. Lee**. The panel discussion concluded that identifying an industrial partner for a particular project should be no different than looking for a similar academic partner for that project. Identifying the best industrial partner should be done with a comprehensive literature search to determine the experts in your field of interest. Therefore, corresponding authors listed in relevant publications are good place to start when looking for a contact person at a particular company.

The panel of industrial scientists was asked to discuss strategies for transitioning from an academic institution into industry, and what criteria are used when making hiring decisions. The main consensus among the panel members was that what makes a person desirable for a job in academia is much the same as what will get a person noticed by industry. The most important criteria considered by hiring committees were the number of publications authored by the applicant and what impact factor journals they were published in. Interestingly, panelists recommended that industry hiring committees, in particular, prefer to see evidence that an applicant has been able to deliver high quality publication-worthy science in at least two areas of research, indicating a wide breadth of knowledge as well as a flexible capability to master new areas of interest. Most often, scientists hired into industrial research positions have already completed two post-doctoral fellowships, and have a broad knowledge base on which to build.

Stephen Miller (Northwestern University) provided an excellent example of how basic research at an academic institution can lead to clinical trials and the development of a new company. Miller studied the basic mechanisms underlying tolerance of myelin-specific T cell responses in the experimental autoimmune encephalomyelitis (EAE) system, with the goal of developing antigen-specific tolerance as a therapy for immune-mediated disease. These studies led to a demonstration that infusion of myelin-coupled apoptotic peripheral blood mononuclear cells can induce suppression of myelin-specific T cell responses in patients afflicted with multiple sclerosis. Phase 1 clinical trials have been completed and the studies are the basis for ongoing Phase 2 clinical trials. To improve the clinical translation of this antigen-specific therapy, various auto-antigens were covalently linked to bio-degradable nanoparticles (Ag-NP), rather than apoptotic blood cells. Miller and his colleagues were able to show that Ag-NPs have the ability to induce antigen-specific tolerance and ameliorate disease in several mouse models of autoimmunity, including EAE, type-1 diabetes, and Th2-mediated allergic airway disease. He has now founded Cour Pharmaceutical Development Company, Inc. to further develop immune therapies based on this Immune Modifying nano-Particle (IMP) platform.

The “Yin and Yang of Inflammation” meeting was the seventh in a series of small, focused meetings/workshops hosted and organized by the Trudeau Institute. The interactions between attendees from academia and industry during the sessions and in the breaks were lively, engaging, and productive. Surveys of the meeting attendees overwhelmingly indicated that the meeting was a great success. The intimate atmosphere fostered stimulating discussions and the speakers generously shared unpublished data, new ideas, and probing questions with their co-attendees, triggering many new interactions and hopefully long-term collaborations.

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List of Abbreviations

NLR	NOD-like receptor
M. tb	Mycobacterium tuberculosis
ROS	Reactive oxygen species
NRROS	negative regulator of ROS
HSCT	hematopoietic stem cell transplantation
VRE	Vancomycin-resistant enterococcus
SFB	Segmented filamentous bacteria
AHR	Airway hyperresponsiveness
BMDC	Bone marrow-derived dendritic cell
SAA1	Serum amyloid A1
TWEAK	necrosis factor-like weak inducer of apoptosis
Fn14	FGF-inducible molecule 14
TNBS	2,4,6-trinitrobenzene sulfonic acid
TSLP	thymic stromal lymphopoietin
SLE	systemic lupus erythematosus
IFN	interferon
PBMC	peripheral blood mononuclear cell
pDC	plasmacytoid dendritic cell
BDCA-2	blood dendritic cell activity 2
GITR	glucocorticoid-induced TNFR-related protein

VM	virtual memory
EAE	experimental autoimmune encephalomyelitis
IMP	immune modifying nano-particle