EDITORIAL

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In this special conference issue of *JADR,* I would like to thank everyone who helped to organize Autoimmunity in 2017; Where Are We Now? which was held at Roulette Intermedium in Brooklyn, NY, USA, on April 28-29, 2017. In addition, I would like to thank all of our incredible faculty and poster presenters who made this conference the global, seismic educational and networking event it turned out to be.

Extra special thanks go to our inspired organizing secretary, Mr. Ahmed Ullah, our inexhaustible executive secretaries, Ms. Hoor Fatima and Ms. Madiha Rauf, our resourceful marketing director, Mr. Muaaz Ahmed, our brilliant techno-geek, Mr. Zeeshan Hanif, our New York based members of the scientific organizing committee, Drs. Gül Bahtiyar and Jocelyne Karam. Extraordinary thanks also go to super-organizer, Mr. Noman Pirzada and speaker-turned-organizer Professor David Naor of Hebrew University, without whose constant attention we would never have been able to attract the stellar faculty that we did, representing some of the world's most prestigious learning centers. I would also like to thank Ms. Kathleen Daniel outreach director from the office of the Brooklyn Borough President, Mr. Eric Adams, for opening our 2 day conference with such passion and eloquence and preparing such a beautiful citation for the conference. Heartfelt thanks also go to Ms. Stephanie Palmer and her wonderful staff at Roulette Intermedium, who seamlessly assisted with all arrangements, sound, lighting, projection, poster board delivery, and catering coordination and to our wonderful caterers, who met a number of special dietary needs deliciously and efficiently.

The meeting venue, Roulette Intermedium, is a wonderful, historic theater, filled with the nostalgia of an earlier era, yet equipped with state of the art electronics.

I gave the keynote lecture on day 1 of the meeting which focused on the observation that most people with autoimmune disorders have concomitant non-classic adrenal hyperplasia and that insulin resistance plays a crucial role in the expression of both families of disorders and provides a potential target for the prevention and treatment of both types of disorder. These observations, in turn, have complex, reciprocating interactions with our gut biome, vitamin D status, inflammatory cytokines, and adipokines, lymphocytes, and activities of the MAPK and JAK/STAT expression pathways.

The second keynote address was offered by Sir Marc Feldman from Oxford University, the patriarch of anti-TNF-α therapy in autoimmune connective tissue disorders. Sir Marc suggested that by combining methotrexate, a TNF-α inhibitor, and a carefully selected monoclonal antibody we can approach a cure for rheumatoid arthritis and many other chronic inflammatory diseases.

The first plenary session was presented by Prof. Jeffery Ravetch of New York's Rockefeller Univeristy, who enriched our understanding of the pleiotropic effects of antibodies through his discoveries of distinct interactions of the IgG Fc domain with specific receptors expressed by different immune cell types. This appealed to my endocrine mind set, because it made IgGs seem like hormones that trigger diverse expression cascades depending upon which receptor types they bind with.

The second plenary lecture was given by Prof. Gregg J. Silverman of New York University, who spoke on the microbiome and autoimmune disease. He provided us with emerging concepts and new data on the intricate, reciprocating dance of the gut microbiome with the passive and active immune system, a dance that shares many elements with the simultaneous

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dance occurring between the gut microbiome and our metabolism. In general, a gut biome with a smaller and less diverse bacterial population is associated with both a greater risk of developing autoimmune disorders and a greater risk of developing the metabolic syndrome.

Our third plenary was delivered by Dr. Bollyky from Stanford University, who discussed the tissue microenvironment in autoimmune insulitis and in a model for multiple sclerosis. He shared recent data showing that inhibition of the extracellular matrix polymer, hyaluronic acid, which is abundant in inflamed tissues and involved in the pathogenesis of autoimmunity, using 4-methylumbelliferone (4-MU) prevented progression of autoimmunity in models of multiple sclerosis and type 1 diabetes. 4-MU reduced hyaluronic acid synthesis and content, but not polymer size in these experimental disorders and changed lymphocyte expression toward Th2 and Treg and away from pathologic Th1 and TH17 phenotypes.

Our fourth plenary was provided by Dr. Ming Li of Memorial Sloan Kettering Cancer Center in New York, who spoke on T cell metabolism and autoimmunity. Dr. Li explained that aerobic glycolysis (the Warburg effect) is characteristic of activated T cells, as it is of cancer cells, and is implicated in augmenting the production of the pro-inflammatory cytokine IFN-γ via the 3' untranslated region (3'UTR). Lactate dehydrogenase A (LDHA) is induced in activated T cells to support the Warburg effect independently from 3'UTR by maintenance of high levels of acetyl-CoA, which increases histone acetylation and transcription of IFNγ. Knockout of LDHA in T cells protected mice from immunopathology caused by either IFNγ excess or deficiency of Tregs. These findings suggest that LDHA may be a future therapeutic target in autoimmune disorders.

Our fifth plenary lecture was given by Dr. Yaron Tomer of Albert Einstein College of Medicine in Bronx, New York, who discussed autoimmune thyroid diseases-translating immunogenetic mechanisms into novel drug targets. He reviewed the fact that most of the genes predisposing to autoimmune thyroid disease are part of the "immunologic synapse" and take part in antigen presentation and activation of T cells; foremost among these is HLA-DR and the variant containing an arginine residue at position 74 of the β chain (DRb1-Arg74 imparts the most risk for thyroid autoimmunity. This discovery hopefully will result in future antigen-specific targeted treatments.

The first session lecture was given by Dr. Ciriaco Piccirillo from McGill University in Montreal, who spoke of the requirement for FOXP3/TIP60 in autoimmune suppression by Treg cells. Some FOXP3 mutations result in a broad range of severity in IPEX (immunodysregulation polyendocrinopathy enteropathy X-linked syndrome) patients. One of these mutations, $FOXP3^{A384T}$ results in impaired FOXP3 interaction with the histone acetyltransferase, TIP60. This defect could be ameliorated with allosteric modifiers that enhance FOXP3/TIP60 interaction.

Dr. Vivek Vasdev of Army Hospital Research and Referral in New Delhi, did a session lecture on assessment of ideal serum dilution for screening of antinuclear antibodies by indirect immunofluorescence in the diagnosis of autoimmune disorders. Receiver operator curve analysis showed that the optimal combination of sensitivity and specificity was achieved by a combination of 1:80 and 1:160 dilutions, thus providing a very pragmatic guidepost for clinicians.

Dr. Wen-Ming Chu of the University of Hawaii Cancer Center, presented a session lecture on the IKK-NF-κB axis in dendritic cell homeostasis, maturation, and function. He showed that there is a link between IKKβ and dendritic cell homeostasis, maturation, and function, which includes cytokine production and T cell activation stimulated by Cpg-DNA and lipopolysaccharide and further determined whether there was activation of NFκB by fms-like tyrosine kinase 3 ligand and whether IKK was important for such activation.

Dr. Daniel Sanchez of the Czech Academy of Sciences in Prague, offered a session lecture on autoantibodies to calreticulin in selected autoimmune diseases, especially celiac disease, where calreticulin becomes an epitope after being translocated from the endoplasmic reticulum to the cell surface, where it becomes an important pro-phagocytosis signaling molecule and mediator of cell death.

In session lecture 5, Dr. Suniti Misra from the Medical University of South Carolina, spoke about the role of CD44, the hyaluronan receptor, in inflammation. She explained that CD44 and especially its variants have an important role in the migration of cancer cells and fibrogenic fibroblasts to injured tissues. Increased levels of the variant CD44v6 induced transcriptional co-activation, including p300 induction of histone acetyl transferase activity, resulting in loosening of condensed

chromatin structure. This promoted the availability of the transactivation machinery targeting BCL2, an anti-apoptotic gene, rendering lung myofibroblasts apoptosis-resistant. The same mechanism operates in colon cancer cells to render them drug-resistant.

In session lecture 6, Dr. David Leader from Tufts University School of Dental Medicine in Boston, presented a fascinating case report of an extremely rare finding in scleroderma patients- external resorption of a tooth root.

In session lecture 7, Dr. Mary Cowan of New York University, discussed changes in hyaluron content and size in relation to inflammation. She noted that increased hyaluron content, but with decreased mean molecular mass and a broader range of sizes present is found in fluids and tissues during tissue remodeling and inflammatory processes. Hyaluronidases and reactive nitrogen/oxygen species can cause fragmentation of hyaluronic acid. These smaller fragments of hyaluronic acid alter cell behavior by binding to receptors eg, CD44 and RHAMM. These ligand-receptor complexes then signal via toll-like receptors 2 and 4. Targeting receptor interactions with fragmented hyaluronic acid may offer new approaches to tissue regeneration, while analysis of hyaluronic acid fragmentation may be helpful in developing diagnostic/prognostic tests.

Dr. Ellen Pure from the University of Pennsylvania in Philadelphia shared her work on regulation of collagen-rich matrix remodeling in wound healing, inflammation, and cancer in session lecture 8. She and her colleague, Dr. Govindaraju, reported that deletion of the CD44 gene was associated with increased fibrillary collagen accumulation in healing wounds, inflammation, and the micromilieu of solid tumors. This same phenotype is recreated in isolated, fibroblast derived matrices created by CD44-deficient fibroblasts.

Dr. Olgun Guvench from the University of New England College of Pharmacy in Portland Maine, shed light on atomic-resolution understanding of N-glycosylation and protein conformational switching that modifies CD44-hyaluron binding. He shared studies showing that N-glycosylation of and conformational alterations in the hyaluronic acid binding domain of CD44 alter its binding affinity for its ligand. These studies were performed using all-atom explicit molecular dynamics simulations. As an endocrinologist, I wondered if such N-glycosylation might play a role in the pathogenesis of diabetic arthropathies.

Dr. Gang Li from Brigham and Women's Hospital in Boston, shared his insights on progress from genome wide association studies to functional single nucleotide polymorphisms and their contribution to the pathophysiology of autoimmunity in session lecture 10.

Dr. Mary Crow from Weill Cornell Medical College in New York, spoke on the topic Type I interferon; pathways inform therapeutic approach. She explained support for the theory that type I interferons (IFN-I) are key mediators of host anti-viral response and central actors in the pathogenesis of systemic lupus erythematosus (SLE). Considering the data available, she explained, provides a rationale for several unique approaches to therapeutically alter the IFN-1 pathway in SLE and other autoimmune disorders.

Dr. Monserrat Anguera of the University of Pennsylvania in Philadelphia, offered groundbreaking insights on the topic of maintaining X-chromosome inactivation in female lymphocytes; a new therapeutic target for female-biased sautoimmunity (the vast majority of autoimmunity). She explained that the X-chromosome is home to many immunity-related genes. Mammalian females use X-chromosome inactivation to produce a transcriptionally silent X-chromosome with heterochromatic modifications and XIST RNA, which equalizes gene expression across the sexes. During lymphocyte maturation XIST RNA disappears from the inactive X-chromosomes. Healthy female lymphocytes biallelically express the immunity genes CD40LG, TRL7, and CXCR3 and their inactive X-chromosomes appear euchromatic. Return of XIST RNA back to the inactive X in activated lymphocytes requires YY1, a transcription factor. YY1 deletion prevents return of XIST RNA to the inactive X and the development of heterochromatic characteristics. In patients with SLE mislocalized XIST RNA was encountered as well as biallelic transcription of immunity-related genes from both X-chromosomes, suggesting that targetable, epigenetic factors are involved in failure of maintenance of X inactivation and consequent female-biased autoimmunity.

Professor David Naor of Hebrew University in Jerusalem, our scientific program co-organizer, delivered section lecture 13 on anti-inflammatory regenerative activity of a CD44-derived peptide. He

shared data showing that a 5 amino acid residue peptide derived from the hyaluronic acid receptor, CD44 exerted a potent anti-inflammatory effect in a murine model of rheumatoid arthritis and was able to restore the normal anatomy and function of the damaged joint. This effect is not dependent upon neutralizing antibodies and is specific to autoimmune joint damage Serum amyloid A (SAA) may be the target for this peptide. An epitope of SAA, which is deeply involved with the pathogenesis of both rheumatoid arthritis and multiple sclerosis is recognized and neutralized by this peptide. This same epitope may be involved in the pathogenesis of non-alcoholic fatty liver disease and Type 2 diabetes.

Rina Aharoni from the Weizmann Institute of Science in Israel, discussed the potential for neuroprotection by immunomodulatory treatment in multiple sclerosis with the synthetic copolymer, glatiramer acetate, in session lecture 14. She explained that glatiramer acetate has an immunomodulatory action in experimental MS characterized by neuroprotection and repair, increase in neurotrophic factor expression, remyelination, and neurogenesis. As conference chair, I wondered if such actions could have applicability in the treatment of diabetic neuropathy as well. Studies thus far suggest that glatiramer acetate may also help to prevent transplant rejection, improve the success of stem cell grafting and ameliorate inflammatory bowel disease.

Prof. Charles Malemud of Case Western Reserve University in Cleveland, Ohio, delivered our final session lecture on articular cartilage as a target in autoimmune disorders. He noted that the pathophysiology of RA is associated with two seemingly contradictory observations: apoptosis resistance of inflamed synovial tissue leading to perpetual survival of activated immune cells together with an increased frequency of chondrocyte apoptosis, blocking cartilage repair efforts. Chondrocyte apoptosis is initiated by inflammatory cytokines including TNF-α, IL-1β, IL-6, and IL-17, which activate the MAPK and JAK/STAT pathways (interestingly, the same cytokines and signal transduction pathways are involved in insulin resistance/hyperinsulinemia –my observation).These cytokines stimulate matrix metalloproteinase (MMP) and the apoptosis of cartilage cells so characteristic of RA. MMP-9 synthesis is inhibited by the monoclonal antibody, cilizumab directed against the IL-6 receptor. The small molecule inhibitor of JAK3, tofacitinib, reduces MMP gene expression and reduces the frequency of cartilage cell apotosis in RA.

Our posters were no less thought-provoking than our oral sessions.

Dr. Emma Rodriguez of Instituto Nacional de Cardiologia in Mexico City, reported that healthy umbilical cord vein endothelial cells from mothers with inactive lupus have increased expression of toll-like receptors 1,7, and 9 associated with a pro-inflammatory state which is overstimulated by TNF-α.

Dr. Minan Al-Ezzi from the Institute of Dentistry in London, UK, presented data showing that primary Sjögen's syndrome has a negative impact on olfaction, taste, sexual function, and quality of life in female patients.

Dr. Arthur S. Walters of Vanderbilt University in Nashville, Tennessee, made a strong evidentiary argument for considering the restless leg syndrome to possibly be an autoimmune disorder and appealed to other researchers for further suggestions and collaboration.

Ms. Barbara Hertz of Greenwich, Connecticut, presented an inspiring multimedia exhibit on her late father, Dr. Saul Hertz, the father of nuclear medicine. He labored hard despite obstacles of anti-Semitism, institutional politics, and intellectual piracy to develop this modality, which is important in the diagnosis and treatment of autoimmune thyroid disease, as well as many disorders not currently considered to be autoimmune.

Dr. Ingo Hartig of University Medical Center, Schleswig-Holstein in Kiel, Germany, shared a case report of a patient who suffered from a previous insular lobe stroke, that apparently protected him from developing rheumatoid arthritis on the same body side as the stroke. Previous reports of hemiplegia being protective vs. RA development on the affected side have also appeared in the literature.

Dr. Sarah J. Blossom of the University of Arkansas for Medical Sciences College of Medicine in Little Rock, discussed her group's finding that female autoimmune-prone female mice were more likely than their male counterparts to show early signs of autoimmune hepatitis during development, when exposed to the

common environmental disrupter, trichloroethylene (TCE). This presentation won one of the 3 coveted conference poster awards.

Dr. Robert Greenstein of the James J. Peters Veterans Affairs Medical Center in Bronx, New York, presented interesting data and a provocative hypothesis that autoimmune disorders may be due to chronic, low grade infection with Mycobacterium avium, subspecies paratuberculosis and suggesting that specific treatment of such infections with methotrexate and 6 mercaptopurine may prevent autoimmune disease.

Dr. Haruhiko Suzuki of Nagoya University Graduate school of Medicine in Nagoya, Japan, shared evidence for his conclusion that T cells, but not NK cells are needed for FasL-dependent immune suppression.

Dr. Holger Kronsbein of Franziskus hospital in Bielefeld, Germany, presented the case of a man with autoimmune pancreatitis and membranous nephropathy who developed hepatic artery aneurysms, that were initially misdiagnosed as micrometastases and were associated histologically with eosinophilic infiltration and serologically with increased serum IgE, which were successfully treated with a combination of coil embolization and immunosuppression with azathioprine and prednisolone.

Dr. Nemanja Zdradovic of the University of Kragujevac in Serbia, showed that different cell populations are responsible for diabetes induction in 2 different rodent models. Multiple low dose streptozotocin (MLD-STZ) causes diabetes in C57/Bl6 mice via a cell mediated process directed against the beta cells. His group asked whether splenocytes and pLNC cells from these mice could induce diabetes in 6 week old mice of this type as well as what the role of different cell populations was in diabetes induction in the donors. They found that intraperitoneal introduction of donor splenocytes and pLNc cells induced diabetes in recipients characterized by histologic insulitis, increased serum TNF-α, IFN-γ, and decreased IL-17. They found that $CD3^{+}CD8^{+}$ cells play a major role in induction of diabetes in both donor and recipient mice, while M1 macrophages and Th1 cells play a major part in diabetes induction in recipients only, and NK, Th1, and TH17 in donors. Thus, splenocytes and pLNC celss of MLD-STZ diabetic male mice can transfer diabetes to young syngeneic mice, suggesting distinct roles for various cell population in autoimmune diabetes induction.

Dr. Shri Ram Sharma of the Eastern India Gandhi Regional Institute in Megjalaya, India, presented a fascinating case of a pediatric patient with Churg-Strauss syndrome who presented with recurrent hemorrhagic stroke and mitral valve prolapse with regurgitation.

Dr. Olga Jachimowicz-Duda of The medical University of Gdansk, Poland, discussed the relationship between IL-34 level and selected biochemical and clinical parameters in type 2 diabetes. She reported that IL-34 levels are significantly higher in type 2 diabetics than in pre-diabetics. Using multiple regression analysis she found that Hb A1C, LDL, waist/hip ratio, and C-reactive protein were all independently positively correlated with IL-34.

Dr. Isaac Sachmechi of the Icahn School of Medicine in New York, presented fascinating data on a significant association between the consumption of artificial sweeteners and Hashimoto's thyroiditis. There appeared to be a significant dose effect as well. In discussions during the poster session he said that a similar relationship is emerging with Graves' disease and some patients with Hashimoto's thyroiditis have remitted following discontinuation of artificial sweeteners.

Dr. Vithoulkas of the Alonissos International Academy of Homeopathy in Athens, Greece, discussed his study which showed that the ability to mount a high fever during acute illnesses was inversely correlated with the tendency to subsequently develop an autoimmune disorder.

Dr. Yong Zhao of Hackensack University Medical Center in New Jersey, shared his data on the use of platelet-derived mitochondria, which display embryonic stem cell markers which are immunomodulatory, such as autoimmune regulator (AIRE), which contribute to the efficacy of stem cell educator therapy in Type 1 diabetes.

Finally, Dr. Michel Tovey of the Ecole Normale Superieure de Cachan in Cachan, France, presented information on a novel system for improved quantification of antibody-dependent cell-mediated cytotoxicity.

The meeting ended with a free-flowing round table conversation mediated by Prof. David Naor.

The conference provided a free flow of ideas among clinicians, clinical researchers, translational researchers, basic researchers, and medical historians. New connections were established and old ones reinforced. Everyone returned to work inspired by what they had learned.

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