

Rheumatology

Research Spotlight: Dr. Tomas Mustelin

At present, leading hypotheses propose that neutrophils are pivotal in the initiation and propagation of both rheumatoid arthritis and lupus. The Mustelin lab is investigating how and why neutrophils are made to undertake an extensive citrullination of their own proteins, a post-translational modification that appears to lie at the heart of rheumatoid arthritis. Citrullinated proteins act as autoantigens and may serve to kick-start the immune response that, over several years, results in clinical disease. Antibodies against citrullinated proteins, termed ACPA or CCP, are also well known for their diagnostic value. That neutrophils are involved is also supported by their abundance in synovial fluid at the time of disease onset and by the finding that their elimination by apheresis alleviates the symptoms of RA. It therefore seems plausible that inhibition of citrullination may be therapeutic.



On a similar line of reasoning, the Mustelin lab is asking why lupus patients have an immune response that centers on proteins present in the RNA-processing organelle called the stress granule, as well as the nucleic acids themselves. In addition, most SLE patients have an elevated production of type I interferons, which are hallmarks of nucleic acid detection by cellular sensors, for example, during viral infections. The lab is particularly intrigued by the two proteins encoded by so called 'long interspersed nuclear elements' (LINE1), which bind RNA, associate with Ro, La, and other RNPs, and have reverse transcriptase activity, which may be driving interferon production. It turns out that SLE patients have lots of autoantibodies against LINE1, stimulating further research into the potential role of these 'rogue transposons'.

Dr. Mustelin, had a very successful academic career in San Diego from 1991 -2007. He then was appointed to leadership positions at Amgen, MedImmune and Gilead before taking a position of Professor of Medicine in the Division of Rheumatology in 2018.

DOM Grand Rounds: Dr. Erika Noss



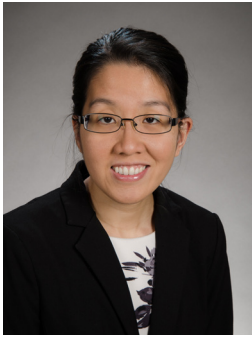
On February 21, 2019, Dr. Erika Noss presented at the Department of Medicine Grand Rounds, giving a talk entitled "Looking Inside the Arthritic Joint: Lessons from RA and OA Synovium". The lecture began by discussing the current treatment limitations in rheumatoid arthritis (RA). Dr. Noss reviewed recent data suggesting that RA therapies have reached a plateau in treatment response, with the majority of patients still not achieving disease remission. She proceeded to examine how RA research is moving toward phenotyping how the joint synovial tissue responds to autoimmune attack. New studies show distinct patterns of synovial responses between RA patients, pointing to novel treatment targets and new biomarkers to guide therapeutic decisions.

In the second part of the talk, Dr. Noss discussed another joint disease, osteoarthritis (OA). She reviewed the data suggesting that synovial inflammation plays a role in accelerating pain and joint damage in OA. Dr. Noss then presented data from her laboratory characterizing the synovial responses from knee OA patients undergoing joint replacement surgery. Clustering analysis of this characterization suggested that there may also be specific patterns of synovial responses in OA. The talk concluded by drawing parallels between RA and OA, suggesting that better understanding of how the synovial tissue functions in these diseases will shed new light on disease mechanisms and lead to development of better biomarkers to predict patient responses to therapy.

Dr. Noss joined the Division of Rheumatology in 2016 and is currently an Assistant Professor in the Division.

RESEARCH HIGHLIGHT: DR. JEAN LIEW

Jean Liew, MD is a current second-year rheumatology fellow at the University of Washington who is on the physician-scientist pathway. Dr. Liew completed her internal medicine training at Oregon Health & Science University in Portland, Oregon prior to coming to UW.



Dr. Liew's main area of interest is in cardiovascular diseases and ankylosing spondylitis (AS), an inflammatory condition that

affects the spine and sacroiliac joints. It is known that inflammatory rheumatic diseases such as lupus and rheumatoid arthritis are associated with increased risk for cardiovascular disease and outcomes like heart attack and stroke. We are starting to recognize that this is also the case in AS. Dr. Liew is particularly interested in how the main treatments for AS, like nonsteroidal anti-inflammatory drugs (NSAIDs) and biologics, can shift the balance of cardiovascular risk.

Dr. Liew is currently working with Dr. Lianne Gensler, who runs the Axial Spondyloarthritis clinic at the University of California – San Francisco (UCSF). Dr. Gensler is one of several investigators who runs a large cohort of over 1200 individuals with AS, some of whom have been followed for 15 years. A large amount of longitudinal information has been collected from these individuals, and Dr. Liew is utilizing this data to answer several research questions she has posed. Dr. Liew also has the support of the NIH-funded T32 training grant through the UW Division of Rheumatology. This has allowed Dr. Liew to work on these projects and complete graduate level coursework in epidemiology and biostatistics, so that she can lay the groundwork for a career in clinical research.

DIVISION ADMINISTRATOR



In March 2019, the Division welcomed our new Division Administrator, Lykheng Huot. Before joining Rheumatology, Lykheng served as the Senior Grants Manager for the Division of Nephrology, the Kidney Research Institute and the Center for Dialysis Innovation for over six years. We are excited to have her onboard and believe that her financial and administrative expertise will serve the Division well.

2019 LANE LECTURE SERIES & RECEPTION

On March 14th and 15th, the UW Division of Rheumatology held the Annual Lane Lecture & Reception. The Division was honored to host Antony Rosen, M.B.Ch.B., B.Sc. as this year's Visiting Speaker. Dr. Rosen is a Professor of Medicine, Professor of Cell Biology, and Professor of Pathology at Johns Hopkins University, as well as being the Vice Dean for Research and the Director of Rheumatology.



Dr. Rosen gave two full lectures at both the Department of Medicine and Division of Rheumatology Grand Rounds, titled "Autoantibodies in the rheumatic diseases" and "Scleroderma as a model of human cancer immunoediting," as well as an additional talk during the evening reception. Both lectures and the evening reception were well attended by Faculty, Staff and supporters of the Division. This annual event is honor of James J. Lane Jr, M.D., who was the first fellowship trainee of the UW Division of Rheumatology in 1958.

FACULTY AWARDS

Gregory C. Gardner, MD, FACP, received the Mastership Award from the American College of Physicians. Masters are those who have "integrity, positions of honor, eminence in practice or in medical research, or other attainments in science or in the art of medicine."

Jenna Thomason, MD, MPH, Acting Instructor in the Division of Rheumatology was a recipient of the UW Medicine PRAISE Award. The PRAISE Award is given biannually to physicians, PAs, and ARNPs for their measured patient satisfaction. Dr. Thomason was also named a 2019 Top Doctor by the Seattle Met.

MEDICAL STUDENT SUMMER PROGRAM

The Division of Rheumatology hosts a 10-week research program that is specifically designed for medical students who are interested in hands-on basic biomedical, translational, or clinical research and have completed their first year of medical school. Participants receive a stipend of \$4,000 for the complete 10-week period. For more information, visit our website at <https://rheumatology.uw.edu/education/medical-student-summer-program>.

OPPORTUNITIES FOR GIVING

You can support programs and initiatives in the Division of Rheumatology. We have established four Professorships and eight endowments through generous donations. In addition, several gift funds target specific programs such as the Rheumatology Fellowship Fund, the Rheumatology Discretionary Fund, and the Rheumatology Research Fund for Junior Faculty.

Send Checks to:

Division of Rheumatology, Campus Box 356428,
1959 NE Pacific St, Seattle, WA 98195

To learn more about these opportunities for giving, please visit: <http://depts.washington.edu/rheum>

DIVISION PUBLICATIONS

Neutrophil extracellular traps (NETs) are increased in the alveolar spaces of patients with ventilator-associated pneumonia. Mikacenic C, **Moore R**, Dmyterko V, West TE, Altemeier WA, Liles WC, **Lood C**. *Crit Care*. 2018 Dec 27;22(1):358. doi: 10.1186/s13054-018-2290-8. PubMed PMID: 30587204; PubMed Central PMCID: PMC6307268.

Perioperative Use of Methotrexate and Tumor Necrosis Factor α Inhibitors Combination Therapy Is Not Likely to Increase Post-Operative Infection Rate in the National Veterans Health Administration Administrative Databases. Hsin-Hsuan Juo, Anders Peck, Sarah E. Monsell, **Bernard Ng**. *Open Journal of Rheumatology and Autoimmune Diseases*; Vol.9 No.1, February 2019, pp. 1-13.

Calpain drives pyroptotic vimentin cleavage, intermediate filament loss, and cell rupture that mediates immunostimulation. Davis MA, Fairgrieve MR, Den Hartigh A, Yakovenko O, **Duvvuri B**, **Lood C**, Thomas WE, Fink SL, Gale M Jr. *Proc Natl Acad Sci U S A*. 2019 Mar 12;116(11):5061-5070. doi: 10.1073/pnas.1818598116. Epub 2019 Feb 22. PubMed PMID: 30796192; PubMed Central PMCID: PMC6421439.

Cell-Free DNA as a Biomarker in Autoimmune Rheumatic Diseases. **Duvvuri B**, **Lood C**. *Front Immunol*. 2019 Mar 19;10:502. doi: 10.3389/fimmu.2019.00502. eCollection 2019. Review. PubMed PMID: 30941136; PubMed Central PMCID: PMC6433826.

The Contribution of PTPN22 to Rheumatic Disease. **Mustelin T**, Bottini N, Stanford SM. *Arthritis Rheumatol*. 2019 Apr;71(4):486-495. doi: 10.1002/art.40790. Epub 2019 Mar 2. PubMed PMID: 30507064; PubMed Central PMCID: PMC6438733.

Determinants of Positive Temporal Artery Biopsies in the Veterans Health Administration National Database Cohort. **Chung SH**, **Morcos MB**, **Ng B**. *Arthritis Care Res (Hoboken)*. 2019 Apr 1. doi: 10.1002/acr.23897. [Epub ahead of print] PubMed PMID: 30932359.

DIVISION GRANTS

Jean Liew, MD, Senior Fellow in the Division of Rheumatology, was awarded €25,000 from the Assessment of SpondyloArthritis International Society (ASAS). Dr. Liew also received a \$5,000 fellowship grant from the SPARTAN Group. Both grants support a fellow performing research with a spondyloarthritis expert at another institution and begin in July 2019.

James Andrews, MD, Acting Assistant Professor in the Division of Rheumatology, received a \$257,000 grant from Grifols, Inc for his project "Gamunex in Anti-HMG-CoA Reductase Antibody Positive Myopathy," scheduled to begin in Summer 2019. Dr. Andrews also received an R03 award of \$200,000 over 2 years by the NIA/NIH for his project "Sarcopenia as a Predictor of Hospital Associated Disability in Older Adults with Dementia," which launched in April.

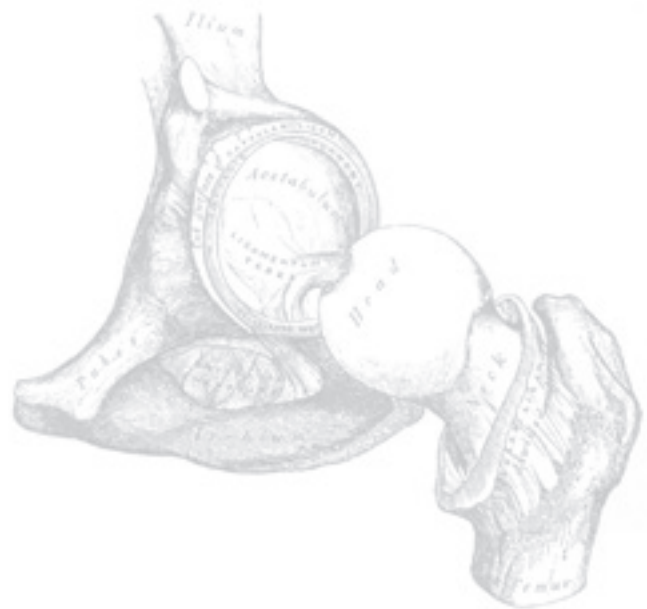
Christian Lood, PhD, Assistant Professor in the Division of Rheumatology, was recently awarded two grants. The first grant is for \$100,000 from the Arthritis National Research Foundation for his project "Mitochondrial-mediated inflammation and autoimmunity in rheumatoid arthritis". Additionally Dr. Lood was awarded a grant in the amount of \$57,151 from Horizon Pharma for his project "NET-mediated inflammation in gout". Both projects are scheduled to begin in June 2019 for one year terms.

Erika Noss, MD, PhD, Assistant Professor in the Division of Rheumatology, was awarded \$100,000 from the Arthritis National Research Foundation for her project titled "Targeting Platelet-Derived Growth Factor Receptor-Alpha (PDGFR α) in Rheumatoid Arthritis". The project is scheduled to begin in June for a one year term.

Tomas Mustelin, MD, D.Med. Sci, Professor in the Division of Rheumatology, received \$150,000 from the NIH for 2 year project titled, "The roots of SLE: Can we cure it with a reverse transcriptase inhibitor?" This project commenced in May 2019.

THE FINE PRINT

The Division of Rheumatology Newsletter is published 2 times a year. For information regarding any content in this issue please contact the Division Office at 206-543-3414 or email rheum@uw.edu. Editors: Keith Elkon, MD, Jenna Thomason, MD, MPH, Peter Simkin, MD, Lara Rich, and Kathryn McGhee.



RECENT DIVISION PUBLICATIONS (CONTINUED)

Not so crystal clear: observations from a case of crystalline arthritis with cytokine release syn-drome (CRS) after chimeric antigen receptor (CAR)-T cell therapy. Chung SH, Hughes G, Koffman B, Turtle CJ, Maloney DG, Acharya UH. *Bone Marrow Transplant.* 2019 Apr;54(4):632-634. doi: 10.1038/s41409-018-0357-4. Epub 2018 Oct 5. PubMed PMID: 30291306.

Low plasma concentrations of apolipoprotein M are associated with disease activity and endothelial dysfunction in systemic lupus erythematosus. Tydén H, **Lood C**, Jönsen A, Gullstrand B, Kahn R, Linge P, Kumaraswamy SB, Dahlbäck B, Bengtsson AA. *Arthritis Res Ther.* 2019 May 2;21(1):110. doi: 10.1186/s13075-019-1890-2. PubMed PMID: 31046824; PubMed Central PMCID: PMC6498515.

Demographic, Clinical, and Immunologic Correlates among a Cohort of 50 Cocaine Users Demonstrating Antineutrophil Cytoplasmic Antibodies. **Morcos MB, Lood C, Hughes GC.** *J Rheumatol.* 2019 May 15;. doi: 10.3899/jrheum.180771. [Epub ahead of print] PubMed PMID: 31092720.

Aspirin meets cGAS. **Elkon KB.** *Nat Rev Rheumatol.* 2019 May;15(5):254-255. doi: 10.1038/s41584-019-0205-y. PubMed PMID: 30914774.

Pharmacist-managed titration of urate-lowering therapy to streamline gout management. Huang IJ, **Liew JW, Morcos MB, Zuo S, Crawford C, Bays AM.** *Rheumatol Int.* 2019 May 30;. doi: 10.1007/s00296-019-04333-5. [Epub ahead of print] PubMed PMID: 31147732.

Interactions between cadherin-11 and platelet-derived growth factor receptor-alpha signaling link cell adhesion and proliferation. **Madarampalli B, Watts GFM, Panipinto PM, Nguyen HN, Brenner MB, Noss EH.** *Biochim Biophys Acta Mol Basis Dis.* 2019 Jun 1;1865(6):1516-1524. doi: 10.1016/j.bbadis.2019.03.001. Epub 2019 Mar 13. PubMed PMID: 30876808; PubMed Central PMCID: PMC6502653.

Cardiovascular morbidity and mortality in ankylosing spondylitis and psoriatic arthritis. **Liew JW, Ramiro S, and Gensler LS.** *Best Pract Res Clin Rheumatol.* 2019. Doi:10.1016/j.berh.2019.01.002.

The contribution of PTPN22 to rheumatological disease. *Arthritis & Rheumatism.* **Mustelin, T, Bottini, N. & Stanford, S.M.** (2019). 71, 486–495.

Corrigendum: Increased Binding of Specificity Protein 1 to the IL21R Promoter in B Cells Results in Enhanced B Cell Responses in Rheumatoid Arthritis. Dam EM, Maier AC, Hocking AM, Carlin J, **Ng B, Buckner JH.** *Front Immunol.* 2019;10:1122. doi: 10.3389/fimmu.2019.01122. eCollection 2019. PubMed PMID: 31156654; PubMed Central PMCID: PMC6532707.

Sources of Pathogenic Nucleic Acids in Systemic Lupus Erythematosus. **Mustelin T, Lood C, Giltiy NV.** *Front Immunol.* 2019;10:1028. doi: 10.3389/fimmu.2019.01028. eCollection 2019. Review. PubMed PMID: 31139185; PubMed Central PMCID: PMC6519310.