Cedars Sinai

Advancement

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December 21, 2020

Mr. Vlady Cornateanu
Fashion Industries Guild
291 S. La Cienega Blvd., Ste 405
Beverly Hills, CA 90211-3311

Dear Vlady,

Thank you for all that you've done for Cedars-Sinai. Over the past several months, the world and the ways in which we all conduct our everyday lives has drastically changed because of COVID-19 (coronavirus). In our response to this pandemic, Cedars-Sinai continues to partner with medical centers across the community to realize a larger, global solution to treatment and care for patients everywhere. Committed friends like you play a crucial role in these and other lifesaving discoveries. We are pleased to share reports on the following initiatives:

- *GUESS?/Fashion Industries Guild Chair in Community Child Health*
- *Fashion Industries Guild Congenital Heart Laboratory and Hal Kaltman Fashion Industries Guild;*
- *Diana and Steve Marienhoff Fashion Industries Guild Endowed Fellowship in Pediatric Neuromuscular Diseases*

Your support has strengthened our work in pediatric research. Over the last year, Moshe Arditi, MD, Tyler Pierson, MD, PhD, and Evan Zahn, MD, have made important progress that has shaped the landscape of medical science, and your gifts helped to advance these crucial efforts as detailed in the enclosed report. In addition to this report, if you would like to schedule a meeting with Drs. Arditi, Pierson or Zahn to discuss recent progress, please contact Jess Gerisch, senior donor relations officer, to make the arrangements. She can be reached at 310-423-2069 or jessica.gerisch@cshs.org.

It is because of your commitment, compassion and vision that we are able to provide exquisite healthcare and advance the most promising medical science. On behalf of Dr. Arditi, thank you again for all that you do for Cedars-Sinai and for the patients and families we serve.

Warmest regards,

Arthur J. Ochoa, JD
Senior Vice President, Advancement
Chief Advancement Officer

Enclosure

cc: Moshe Arditi, MD
Evan Zahn, MD
Paola V. Werstler
Tyler Pierson, MD, PhD
Gregg Simpson
Chelsea Irvin

PROGRESS REPORT FOR OUR DONORS

GUESS?/Fashion Industries Guild Chair in Community Child Health

Fashion Industries Guild Congenital Heart Laboratory and Hal Kaltman Fashion Industries Guild Congenital Heart Research Endowment

Diana and Steve Marienhoff Fashion Industries Guild Endowed Fellowship in Pediatric Neuromuscular Diseases

PREPARED FOR

Fashion Industries Guild

Cedars Sinai

INTRODUCTION

Moshe Arditi, MD
GUESS?/Fashion Industries Guild Chair in Community Child Health
Executive Vice Chair, Department of Pediatrics
Director, Division of Pediatric Infectious Diseases, Allergy and Immunology
Director, Immunologic Diseases Research Center

Since 2013, resources from the *GUESS?/Fashion Industries Guild Chair in Community Child Health* has helped to further the work of Moshe Arditi, MD. Because of your philanthropy, Dr. Arditi's clinical research continues to make critical inroads into our understanding of pediatric infectious diseases, immunology and allergies.

Dr. Arditi is an investigator/co-investigator on a number of grants and is a member of several prestigious professional organizations including the Association of American Physicians, Infectious Disease Society of America, Pediatric Infectious Disease Society, American Association for the Advancement of Science, Western Society for Pediatric Research, International Endotoxin Society and Society of Pediatric Research. Additionally, he has served on state, national and local committees and advisory panels of these and other organizations.

Support from the *GUESS?/Fashion Industries Guild Chair in Community Child Health* has played a vital role in Dr. Arditi's ongoing success. We are tremendously grateful for your investment, and we are pleased to present the following update on the exciting advances your partnership has made possible over the last year.

Dr. Arditi seeks to broaden all that we know about pediatric infectious diseases, immunology and allergies. He is an international leader in studies of host pathogen interactions and innate immunity and has authored and co-authored more than 159 articles in peer-reviewed publications and serves on the editorial board and as an ad hoc reviewer for numerous top tier journals. His research addresses issues of immunology and disease for children today and for generations to come.

The development of research programs that focus on lung infections and injury and asthma as well as Kawasaki disease-induced heart diseases among children are high priority for Dr. Arditi. He is currently participating in several basic infectious diseases and immunological studies, including the following:

BCG vaccination to prevent COVID-19 among healthcare workers at Cedars Sinai Medical Center. (PI: Moshe Arditi, MD)
https://www.cedars-sinai.org/discoveries/covid-19-vaccine-development.html
Scientists are now testing whether a decades-old vaccine for tuberculosis (BCG) could provide stopgap protection against the coronavirus known as COVID-19 until more precise vaccines are available. The BCG vaccine won't prevent people from getting infected with the SARS-CoV-2 virus but may strengthen the immune system to diminish the effect of infection, resulting in fewer COVID-19 hospitalizations and deaths.

The idea was born of researchers' observations that the rates of COVID-19 deaths and serious illness are lower in some developing countries where the BCG vaccine is widely used. Dr. Arditi is the primary investigator of the BCG vaccine trial, which aims to protect healthcare workers. Dr. Arditi is partnering with investigators at Texas A&M University, MD Anderson Cancer Center and Baylor College of Medicine, and recruitment of 1,800 volunteers at these four centers is already underway.

The BCG vaccination could make a huge difference in the next year or two until a specific and safe vaccine has been developed for COVID-19 and made widely available. Repurposing the tuberculosis vaccine, called TICE® BCG, represents a speedy way to address COVID-19 because the drug has already been proven safe and is approved by the Food and Drug Administration to prevent tuberculosis and has also been used to treat bladder cancer.

SARS-CoV-2 Research: Discovery of a superantigen-like structure in SARS-CoV-2 that may play a role in the pathogenesis of MIS-C and cytokine storm in adults with severe COVID-19 infection. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19, is a coronavirus closely related to SARS-CoV (SARS) and Middle East Respiratory Syndrome (MERS).

COVID-19 can manifest in adults as a severe interstitial pneumonia with hyper-inflammation, though severe respiratory manifestations are rare in children. Recently, however, multisystem inflammatory system in children (MIS-C) has been recognized in patients that either tested positive for COVID-19 (by PCR or serology or had epidemiological links to COVID-19. After initial reports in the United Kingdom, many cases have now been reported in Europe and New York. MIS-C manifests as persistent fever and hyperinflammation with multi-organ system involvement including cardiac shock, and very severe gastrointestinal, renal, hematologic, dermatologic and neurologic symptoms.

Although MIS-C was initially described as a “Kawasaki Disease-like”, it soon became clear that that these diseases are totally different, and the symptoms and laboratory findings of MIS-C are highly reminiscent of toxic shock syndrome (TSS), rather than Kawasaki disease (KD). Indeed, several recent studies have concluded that MIS-C is a distinct disease from KD and KD shock. The similarities to TSS and the association of MIS-C with COVID-19 indicate that SARS-CoV-2 may possess super-antigenic fragments that induce an inflammatory cascade, which may also contribute to the hyperinflammation and cytokine storm features observed in severe adult COVID- 19 cases. We therefore hypothesized that SARS-CoV-2 Spike (S) protein may possess super-antigenic fragments that could elicit such reactions upon binding proteins involved in the host cytotoxic adaptive immune response.

Using computational biology and bioinformatics, we and our colleagues at the University of Pittsburgh have discovered a novel superantigen-like structure in the S1 subunit of the SARS-CoV-2 spike protein, which has the structural characteristics to bind to both TCR and MHCII (https://www.biorxiv.org/content/10.1101/2020.05.21.109272v1). We also discovered that this SARS-CoV-2-specific superantigen-like structure has a remarkable similarity in both sequence and structure to the Staphylococcal Enterotoxin B Superantigen toxin (SEB). These discoveries may unlock the mechanisms that lead to MIS-C as well as to the cytokine storm seen in adults with severe COVID-19 infection. We are currently working on proving the biological relevance of this newly discovered viral structure.

Vascular Immunobiology: Atherosclerosis and Kawasaki Diseases Research with a focus on vascular inflammation-atherosclerosis- vasculitis mouse models, including Kawasaki disease vasculitis, coronary arteritis, abdominal aorta aneurysms and myocarditis.

Kawasaki disease (KD) among children is the leading cause of acquired heart disease among children and predisposes them for development of atherosclerosis in adolescence and adulthood. Our laboratory has discovered novel treatments to prevent the cardiac complications and the long-term heart damage that occurs in KD. We also made the seminal discovery that mitochondrial oxidative DNA binds and activates NLRP3 inflammasome for IL-1beta release, a key inflammatory cytokine in the pathogenesis of atherosclerosis and KD vasculitis. The role of apoptosis, autophagy and mitophagy in atherosclerosis, vasculitis and sepsis- induced myocardial dysfunction are actively pursued areas in the lab.

Atherosclerosis and Ischemic heart disease and myocardial injury
The Arditi lab has been investigating the role of innate immunity and various infections in high fat diet-induced atherosclerosis using various genetically defined hypercholesterolemic mouse models. The Arditi Lab was the first that first discovered the connection of Toll-Like receptors (TLRs) and pathogenesis of atherosclerosis. Our lab collaborates with the Smidt Heart Institute and specifically with Dr. Roberta Gottlieb—the Dorothy and E. Phillip Lyon Chair in Molecular Cardiology, MD and Dorothy and E. Phillip Lyon Chair in Molecular Cardiology— to investigate the role of mitochondria, oxidative DNA damage and inflammation in myocardium following ischemia and reperfusion models.

Systemic Lupus Erythematosus (SLE) and increased atherosclerosis
Dr. Arditi and his team started a new collaboration with Caroline Jefferies, PhD, in the division of Rheumatology, to investigate the role of mitochondrial oxidative DNA damage and increased IL-1 production as a mechanism to explain the significant increase of incidence of atherosclerotic heart in women with SLE. Using various SLE mouse models, we were published in a major journal, *Circulation Research* and Dr. Arditi obtained a new R21 award from the National Institutes of Health (NIH) based on these collaborative studies.

Lung injury/acute and chronic lung inflammation and asthma
LPS-induced, acute lung injury, mechanical ventilation-induced lung injury, allergic asthma and COPD mouse models and role of aging. Specific areas of expertise include molecular pathogenesis of chlamydia pneumonia (CP) lung infections and inflammation, innate immune responses against CP and CP-induced acute and chronic lung inflammation-allergic asthma and lung fibrosis and COPD. Particular focus is on childhood asthma studies in a basic immunology laboratory setting using various experimental allergic asthma models to discover novel therapies.

Funds provided by the *GUESS?/Fashion Industries Guild Chair in Community Child Health* continue to support one postdoctoral researcher and provide supplies for the basic immunology research conducted in the Arditi lab. The data generated has directly helped the team receive one new NIH grant and one new American Heart Association grant in the last year. This has helped advance Dr. Arditi's research program and has helped make the work more sustainable over time.

The Arditi team submitted over 22 papers in the last year, with 17 of them already published. Dr. Arditi has submitted four new NIH grants and has been awarded one new NIH grant (1 R01 and received one new AHA grant). He continues to bring solid NIH indirect funding to the Institution for the 22nd year in a row. As the Director of the Infectious and Immunological Research Center (IIDRC) of the Biomedical Science Department, he is proud to report that his research team still collectively holding 5 NIH RO1s and 3 R21 Awards and 2 AHA grants.

FACULTY HONORS:

Pioneer in Medicine Award – October 30, 2019

Invited Visiting Professor, University of Pittsburgh,
Department of Computational Biology – April 2019

CURRENT ACTIVE GRANTS

NIH/NIAID R01 AI157274
(PI: Arditi M.) (Co-PI) and Noval Riva 09/01/2020 -08/31/2025 ($348,720/yr) – reviewed on 07/29 - 7 percentile.
"Role of neutrophils and eosinophils in bacterial ligand-induced vasculitis". The goal of this project is to investigate is neutrophils and eosinophils promote murine Kawasaki Disease vasculitis through NETs and EETs release and the production of bioactive IL-1β.

NIH Administrative Supplm (PI: Arditi, M) 08/2020 – 08/2021 ($110,000/yr)
Emergency COVID -19 Supplemental Funding
"Biological role of SARS-CoV2 Superantigenic structure in Hyperinflammatory syndrome", "Role of IL-1 in Bacterial Ligand induced vasculitis and myocarditis, parent RO1".

NIH Administrative Supplm (PI: Arditi M) 08/2020 – 08/2021 ($198,592/yr)
Supplemental Funding for Rip2-IL-17 RO1
"Alzheimer's Disease (AD) funding. "Interaction with Rip2 and Th17 in Chronic Inflammation". "The role of Chlamydia pneumoniae infection in Alzheimer's Disease".

Texas A&M Health Science Center Supplm
(PI: Arditi M) 05/01/2020 – 04/30/2023 ($277,808/yr)
Supplemental Funding Bacillus Calmette- Guerin vaccination As Defense Against SARS-CoV-2. (BADAS study), "Role of IL-1 in Bacterial Ligand induced vasculitis and myocarditis".

5. IRP Supplm (PI: Arditi M) 05/01/2020 – 04/30/2021 ($100,000/yr)
Supplemental Funding Bacillus Calmette-Guerin vaccination As Defense Against SARS-CoV-2. (BADAS study), "Role of IL-1 in Bacterial Ligand induced vasculitis and myocarditis".

6. AHA Grant (PI: Arditi M) 7/01/2019 – 6/30/2022 ($100,000/yr)
"Role of Rip2 in T cells and Atherogenesis." This study investigates the effects Rip2-/-T-cells and Rip2 CARD domain in atherosclerotic progression.

7. R21 NIH/NIAID AI139865-01 (PI: Arditi MD) 2/01/2019 – 2/28/2021($275,000/year)
"Role of ER and Mitochondrial Stress in Coronary Arteritis and Vasculitis." The goal of this grant is to fully elucidate what role ER stress plays in NLRP3 inflammasome activation and IL-1β release, which drives the cardiovascular pathology in KD. (MP grant)

8. 2RO1 AI072726-06 (PI: Arditi M) 2/14/ 2016 – 2/13/2021 ($ 250,000/yr)
"Role of IL-1 in Bacterial Ligand induced vasculitis and myocarditis". The goals of this grant are to investigate the role of IL-1 in the immunopathology of the cardiovascular lesions in the Kawasaki Disease vasculitis mouse model.

9. RO1 AI117968-01A1 (PI: Arditi M) 2/1/2016 – 1/31/2021($250,000/yr)
"Interaction with Rip2 and Th17 in Chronic Inflammation". The goals of this new grant are to investigate the novel interactions of Rip2 with the Th17 skewing as it relates to chronic lung infection and COPD and Chlamydia pneumonia-infection induced chronic lung inflammatory diseases and lung fibrosis.

10. RO1 NIH/NHLBI-HL130353-01 (PI: Shimada K) 2/20/15 – 12/19/20($250,000/yr)
"Sequential release of IL-1alpha and IL-1beta leads to a two-hit model of acute lung injury." This study focuses on the role of early release of pro- IL-1α from necrotic alveolar MΦ and mechanical ventilation (MV) causes alveolar MΦ mitochondrial dysfunction activating the NLRP3 inflammasome for IL-1β secretion. The sequential release of these two cytokines works in synergy to drive ALI and hypoxemia in the "two-hit" model of LPS+MV. Role: Arditi M (Co- Investigator; 5%).

MENTORED GRANTS by PI

1. AHA Career Development Award 20CDA35260258 07/01/2020 – 06/30/2023
PI: Rebecca Porritt (Mentor: M. Arditi)
Title: "Mechanisms of sex disparity in Kawasaki Disease vasculitis"

PUBLICATIONS

Das MM, Godoy M, Chen S, Moser A, Avalos P, Roxas KM, Dang I, Yáñez A, Wenxuan Zhang W, Bresee C, **Arditi M**, Liu GY, Svendsen CN, Goodridge HS. "Young bone marrow transplantation preserves learning and memory in old mice".*Commun Biol.* 2019 Feb 20;2-73. PMID: 30820468 PMCID: PM6382867.

Matundan H, Sin J, Noval Rivas M, Fishbein, MC, Lehman TJ, Chen S, Roberta A. Gottlieb RA, Crother TR, Abe M, and **Arditi M**. "Myocardial Fibrosis after Adrenergic Stimulation as a Long- Term Sequela in a mouse model of Kawasaki Disease Vasculitis". *JCI Insight*. 2019 Feb 7;4(3). PMID: 30728329.

Onat U.I., Yildirim, A.D., Tufanli O., Cimen I., Kocaturk, B., Hamid, S.M., Chen, S., Sin, J. Shimada K, Shah, P.K., Gottlieb R.A., **Arditi M**., and Erbay E. "Intercepting the Lipid-Induced Integrated Stress Response Reduces Atherosclerosis". *J Am Coll Cardiol*. 2019 Mar 19; 73(10):1149-1169. PMID: 30871699.

Roberts SC, Jain S, Tremoulet AH, Kim KK, Burns JC; Anand V, Anderson M, Ang J, **Arditi M**, Ashouri N, Bartlett A,..."The Kawasaki Disease Comparative Effectiveness (KIDCARE) trial: A phase III randomized trial of second intravenous immunoglobulin versus infliximab for resistant Kawasaki disease." *Contemp Clin Trials*. 2019 Mar 3;79:98-103. PMID:30840903.

Crother TR, Porritt RA, Dagvadorj Jm Tumurkhuu G, Slepenkin AV, Peterson EM, Chen S, Shimada K, **Arditi M**. "Autophagy Limits Inflammasome During Chlamydia pneumoniae Infection". *Front Immunol*. 2019 Apr12;10:754. PMID 31031755, PMCID: PMC6473188.

Gorelik M, Lee Y, Abe M, Andrews T, Davis L, Patterson J, Chen S, Crother TR, Aune GJ, Noval Rivas M, **Arditi M**. "IL-1 Receptor Antagonist, Anakinra, Prevents Myocardial Dysfunction in a Mouse Model of Kawasaki Disease Vasculitis and Myocarditis" *Clin Exp Immunol*. 2019 May 17. PMID:31099056.

Noval Rivas M, Wakita D, Franklin MK, Carvalho TT, Abolhsen A, Chen S, Lehman TJ, Sato K, Shibuya A, Fasano A, Kiyono H, Abe M, Tatsumoto N, Yamashita M, Fishbein MC., Crother TR, Shimada K, and **Arditi M**. "Intestinal permeability and IgA provoke immune vasculitis linked to cardiovascular inflammation". *Immunity*. 2019 Sep 17;51(3):508-521.e6. PMID: 31471109

Porritt RA, Markman J L, Maruyama D., Kocaturk B., Fishbein M C, Chen S., Noval Rivas M., and **Arditi M**. "IL-1-mediated sex differences in Kawasaki Disease vasculitis development and response to treatment". *Arterioscler Thromb Vasc Biol*. 2020 Jan 30: ATVBAHA119313863. PMID: 31996019.

Abe M, Rastelli DD, Gomez AC, Cingolani E, Lee Y, Soni PR, Fishbein MC, Lehman TJA, Shimad K, Crother TR, Chen S, Noval Rivas M, **Arditi M**. "IL-1 dependent electrophysiological changes and cardiac neural remodeling in a mouse model of Kawasaki disease vasculitis." *Clin Exp Immunol*. 2019 Nov 23. PMID: 31758701.

Markman JL, Porritt RA, Wakita D, Lane ME, Martinon D, Noval Rivas M, Luu M, Posadas EM, Crother TR, **Arditi M**. Loss of testosterone impairs anti-tumor neutrophil function. *Nat Commun*.2020 Mar 31;11(1):1613. doi: 10.1038/s41467- 020-15397-4. PubMed PMID: 32235862; PubMed Central PMCID: PMC7109066.

Nosaka N, Martinon D, Moreira D, Crother TR, **Arditi M**, Shimada K. "Autophagy protects against developing increased lung permeability and hypoxemia by down regulating inflammasome activity and IL-1β in LPS plus mechanical ventilation- induced acute lung injury". *Front. Immunol*. 2020 Feb 14. PMID: 32117318.

Chen S, Markman JL, PhD, Shimada K, Crother TR, Lane M, Abolhesn A, Shah PK, **Arditi M**. "Sex-specific effects of the Nlrp3 inflammasome on atherogenesis in LDL receptor-deficient mice". *JACC Basic Transl Sci*. 2020;5(6):582-598. Published 2020 May 20. doi:10.1016/j.jacbts.2020.03.016.

Soni PR, Noval Rivas M, **Arditi M**. "A Comprehensive Update on Kawasaki Disease Vasculitis and Myocarditis". *Curr Rheumatol Rep*. 2020 Feb 5;22(2):6. doi: 10.1007/s11926-020-0882-1. Review.

Noval Rivas M, **Arditi M.** "Kawasaki disease: pathophysiology and insights from mouse models". *Nat Rev Rheumatol*. 2020 Jul;16(7):391-405. doi: 10.1038/s41584-020-0426-0. Epub 2020 May 26.

Rolfes V, Ribeiro LS, Hawwari I, Böttcher L, Rosero N, Maasewerd S, Santos MLS, Próchnicki T, Silva CMS, Wanderley CWS, Rothe M, Schmidt SV, Stunden HJ, Bertheloot D, Rivas MN, Fontes CJ, Carvalho LH, Cunha FQ, Latz E, **Arditi M**, Franklin BS. "Platelets Fuel the Inflammasome Activation of Innate Immune Cells". *Cell Reports*. 2020 May 12;31(6):107615.

Madelyn McCauley, Jacqueline Gire O'Rourke, Alberto Yanez, Janet Markman, Ritchie Ho, Xinchen Wang, Mengyao Jin, AK Muhammad, Shaughn Bell, Jesse Landeros, Viviana Valencia, Matthew Harms, **Moshe Arditi**, Caroline Jefferies, Shuang Chen, Deepti Lall. "C9orf72 in myeloid cells suppresses STING-induced inflammation". In Press, *Nature*, August 2020.

Tumurkhuu G, Chen S, Montano EN, Laguna DE, Santos G, Yu JM, Lane M, Michifumi Yamashita M, Janet L. Markman JL, Blanco LP, Kaplan MJ, Shimada K, Crother TR, Ishimori M, Wallace D, Jefferies C1*, **Arditi M.** "Oxidative DNA damage accelerates skin inflammation in pristane-induced lupus model". In Press, *Front Immunol*, August 2020

CONCLUSION

Your Philanthropy Matters

Since our very beginning, Cedars-Sinai has been committed to serving the public—from advancing promising research in our laboratories and providing the most effective therapies to children in our clinics, to training the next generation of scientists and developing initiatives that reduce health disparities and increase access to care.

Today, we remain dedicated to improving the lives of patients, and *GUESS?/Fashion Industries Guild Chair in Community Child Health* is playing a pivotal role in reshaping the landscape of medical science and patient-centered care. Your support of Dr. Moshe Arditi and his team of researchers helps move innovative science from the bench to meaningful and curative solutions for our most vulnerable patients and families who come to us for better health and hope Thank you for your continued partnership and dedication to this shared mission.

INTRODUCTION

Thank you for your support of the *Fashion Industries Guild Congenital Heart Laboratory* and the *Hal Kaltman Fashion Industries Guild Congenital Heart Research Endowment*. Your philanthropy helps make our work possible—and because of your support, Evan Zahn, MD, director of the Vera and Paul Guerin Family Congenital Heart Program and director of the Division of Pediatric Cardiology, improved the health and hearts of children born with congenital heart disease.

Last year, we were thrilled to report that the Abbott Piccolo device, the first device ever approved for minimally invasive treatment of the most common heart defect in premature babies received approval from the Food & Drug Administration (FDA) thanks to the continued support of the *Fashion Industries Guild Congenital Heart Laboratory* and the *Hal Kaltman Fashion Industries Guild Congenital Heart Research Endowment*. Since receiving FDA approval, we have seen worldwide rapid adaptation of this minimally invasive approach, saving hundreds of babies from open surgery. A landmark manuscript was recently published describing the results of the U.S. trial as well as numerous other important papers which will lead to further advancements in the care of our most vulnerable patients.

In another effort made possible by Fashion Industries Guild, Dr. Zahn has advanced the development, testing and implementation of a radically new minimally invasive approach to replace the pulmonary valve, which is the most commonly effected valve in children born with congenital heart disease. The *Alterra* pre-stent is a unique, self-expanding stent that reconfigures a previously unsuitable heart to be able to undergo minimally invasive valve replacement. Dr. Zahn and the team at Cedars-Sinai have led a high profile, national pivotal trial of this device involving 14 sites across the United States, and enrollment is now complete. The results look remarkably promising, and Dr. Zahn and his colleagues believe this device will be approved by the FDA within the year—providing children and young adults everywhere with an option to avoid open-heart surgery and instead, undergo a procedure that culminates with a bandage on the leg and a 23-hour hospital stay.

Dr. Zahn and his team are grateful for your philanthropic partnership. Your support of this novel clinical research has resulted in life-changing approaches to treatment for children here and across the country.

PUBLICATIONS

1. Sathanandam SK, Gutfinger D, O'Brien L, Forbes TJ, Gillespie MJ, Berman DP, Armstrong AK, Shahanavaz S, Jones TK, Morray BH, Rockefeller TA, Justino H, Nykanen DG, **Zahn EM.** Amplatzer Piccolo Occluder clinical trial for percutaneous closure of the patent ductus arteriosus in patients ≥700 grams. *Catheter Cardiovasc Interv*. 2020 May 20.

2. Nomura T, Miyasaka M, **Zahn EM**, Makkar RR. Transcatheter aortic valve replacement for bicuspid aortic valve regurgitation in a 17-year-old patient with congenitally corrected transposition of great arteries: a case report. *Eur Heart J Case Rep*. 2020 May 8;4(3):1-6. doi: 10.1093/ehjcr/ytaa102. PMID: 32617485; PMCID: PMC7319830.

3. Shumeli H, **Zahn EM**, Odudu G, Flint N, Siegel RJ, Tompkins R. Coronary Artery Fistula, An Unexpected Cause of Heart Failure in a 58-Year-Old Women. *Journal of American Cardiology College: Case Reports*. DOI: 10.1016/j.jaccas.2020.04.021 2020 Jul, 2 (8) 1192-1195

4. Shahanavaz S, Berger F, Jones TK, Kreutzer J, Vincent JA, Eicken A, Bergersen L, Rome JJ, **Zahn EM,** Søndergaard L, Cheatham JP, Weng S, Balzer D, McElhinney D. Outcomes After Transcatheter Reintervention for Dysfunction of a Previously Implanted Transcatheter Pulmonary Valve. *JACC Cardiovasc Interv*. 2020 Jul 13;13(13):1529-1540. doi: 10.1016/j.jcin.2020.03.035. PMID: 32646693

5. Garg R, **Zahn EM**. Utility of Three-Dimensional (3D) Modeling for Planning Structural Heart Interventions (with an Emphasis on Valvular Heart Disease). *Curr Cardiol Rep*. 2020 Aug 13;22(10):125. doi: 10.1007/s11886-020-01354-6. PMID: 32789652.

6. Almeida-Jones M, Tang NY, Reddy A, **Zahn E.** Overview of transcatheter patent ductus arteriosus closure in preterm infants. *Congenit Heart Dis*. 2019 Jan;14(1):60-64

7. Naidu SS, Coylewright M, Hawkins BM, Meraj P, Morray BH, Devireddy C, Ing F, Klein AJ, Seto AH, Grines CL, Henry TD, Rao SV, Duffy PL, Amin Z, Aronow HD, Box LC, Caputo RP, Cigarroa JE, Cox DA, Daniels MJ, Elmariah S, Fagan TE, Feldman DN, Forbes TJ, Hermiller JB, Herrmann HC, Hijazi ZM, Jeremias A, Kavinsky CJ, Latif F, Parikh SA, Reilly J, Rosenfield K, Swaminathan RV, Szerlip M, Yakubov SJ, **Zahn EM**, Mahmud E; SCAI 2020 Think Tank Consortium: David Baker, Bhavsar SS, Blumenthal T, Boutin E, Camp CA, Cromer AE, Dineen D, Dunham D, Emanuele S, Ferguson R, Govender D, Haaf J, Hite D,

   Hughes T, Laschinger J, Leigh SM, Lombardi L, McCoy P, McLean F, Meikle J, Nicolosi M, O'Brien J, Palmer RJ, Patarca R, Pierce V, Polk B, Prince B, Rangwala N, Roman D, Ryder K, Tolve MH, Vang E, Venditto J, Verderber P, Watson N, White S, Williams DM. Hot topics in interventional cardiology: Proceedings from the society for cardiovascular angiography and interventions 2020 think tank. *Catheter Cardiovasc Interv*. 2020 Aug 25.

8. Shahanavaz S, Balzer D, Babaliaros V, Kim D, Dimas V, Veeram Reddy SR, Leipsic J, Blanke P, Shirali G, Parthiban A, Gorelick J, **Zahn EM.** Alterra Adaptive Prestent and SAPIEN 3 THV for Congenital Pulmonic Valve Dysfunction: An Early Feasibility Study**.** *JACC Cardiovasc Interv.* 2020 Oct 11:S1936-8798(20)31396-0.

INTRODUCTION

Thanks to generous support from the *Diana and Steve Marienhoff Fashion Industries Guild Endowed Fellowship in Pediatric Neuromuscular Diseases*, Tyler Mark Pierson, MD, PhD, is helping to advance new possibilities in our approach to neurogenetic/neuromuscular disorders. His work in the Pediatric Neurogenetics Clinic (PNG)–as well as in the Cedars-Sinai Center for the Undiagnosed Patient (CUP) as its pediatric lead–offers key insights capable of transforming the treatment landscape.

This past year presented unique challenges, as Dr. Pierson's laboratory and clinics were closed for an extended period of time due to the COVID-19 (coronavirus) pandemic. Over the past many months, he and his team learned to redefine how they perform clinical medicine and laboratory research.

Despite the closures forced by the coronavirus, this year was among Dr. Pierson's most productive ever, resulting in the publication of several major studies, the completion of numerous long-term projects, the receipt of multiple independent research grants, and the initiation of new studies with promise for patients today and in the future.

This was also another banner year for Dr. Pierson vis-à-vis recognition by peer-reviewed journals: He had 10 manuscripts published or accepted for publication. These manuscripts focus on new or rare disorders linked to genes including:

- GATAD2B (Genetics in Medicine)
- NuRD complex (AJMG part C)
- CACNA1A (Epilepsia)
- DEAF1 (Genetics in Medicine)
- MAST1 (Neuron)
- UGDH (Nature Communications
- CHD8 (AJMG part C)
- CACNA1H (Molecular Brain)
- MCT8 (Thyroid)
- SATB2 (Pediatric Neurology)

Dr. Pierson was also a principal organizer of several high-impact studies:

- GATAD2B (Genetics in Medicine)
- HPDL (Brain, in submission)
- NuRD Complex (AJMG, part C)
- USP9X (Biological Psychiatry)

Each of these publications highlights vital contributions of the *Fashion Industries Guild and the Diana and Steve Marienhoff Fashion Industries Guild Endowed Fellowship in Pediatric Neuromuscular Diseases.*

In addition, Dr. Pierson has several other manuscripts currently in preparation that explore rare disorders:

- SATB2
- LMNA
- GATAD2B
- AFG3L2
- CLN6

The Pierson laboratory has also continued work on its collaborative international study involving a neurogenetic disorder associated with the gene HPDL. The study has now been completed and is in the revision stages of publication. This gene has not been previously associated with adisease, and Dr. Pierson and his colleagues are investigating its bimodal presentation in children (infantile onset is very severe, while adolescent onset only features spastic paraplegia).

Previous reports have detailed Dr. Pierson's research into disorders associated with the CLN6 and GATAD2B genes, which utilizes patient-derived induced pluripotent stem cells (IPSCs) to model these disorders in tissue culture. Dr. Pierson was recently awarded a prestigious grant from the National Institutes of Health (NIH) to continue this work.

This year, Dr. Pierson and his team are continuing their clinical and IPSC-based studies of GATAD2B-associated neurodevelopmental disorder (GAND). The results of their primary research study were just published this year in Genetics in Medicine.

Dr. Pierson also continued to present lectures on his work at local, national and international meetings. The exposure from these talks raise the profile of the Pediatric Neurogenetics Clinic and the Center for the Undiagnosed Patient, drawing patients from across the country (Pennsylvania, Idaho, Florida and Massachusetts) and the globe (Brazil, the United Kingdom and Dubai).

In his work as pediatric lead of the Center for the Undiagnosed Patient, Dr. Pierson has played a key role in several families' ability to get genetic diagnoses for their children and to use this information to become more involved with family research groups and research studies, as well as to aid in family planning.

PUBLICATIONS

Papers in preparation and submission:

1. Zarate YA, Bosanko KA, Cusmano-Ozog K, Thomas MA, Miller DT, Lacro RV, Martinez-Monseny A, Curry CJ, Graham Jr JM, Pierson TM…et al: Growth, development and phenotype outline of individuals with deletions of 2q involving the SATB2 gene. In submission.

2. M Wiessner, R Maroofian, M-Y Ni, L Bartesaghi, A Pedroni, JS Müller, R Stucka, C Beetz, S Efthymiou, FM Santorelli, AA Alfares, … H-J Lee, K Ampatzis, TM Pierson, Jan Senderek. Biallelic variants in intronless HPDL as a cause of mitochondria-associated pure and complicated hereditary spastic paraplegia. Under revision.

3. Y Kumar, J Kim, G Otero, PJ Kenny, TM Pierson. White matter abnormalities in Neuronal Ceroid Lipofuscinosis type 6: neuroimaging and modeling with IPSCs. In preparation.

4. MG Otero, D Ho, Y Kumar, J Kim, J Martinez, JM Graham Jr, J Mackay, JI Young, TM Pierson. Modeling GATAD2B-associated Neurodevelopmental Disorder with Induced Pluripotent Stem Cells: Abnormal neuronal differentiation and division. In preparation.

5. S Magri, D DiBella, C Toro, D Landis, P Lee, D Adams, S Jayadev, P Suwannarat, G Lesca, W Gahl, F Taroni, and TM Pierson. Phenotypic variation in dominant and recessive AFG3L2-associated disorders. In preparation

6. J Kim, Y Kumar, G Otero, PJ Kenny, TM Pierson. Human IPSC models of neuronal ceroid lipofuscinosis type 6 reveal defects in lysosomal/autophagic function. In preparation.

Papers:

1. Lewis H, Samanta D, Orsell J-L, Bosanko K, Rowell A…McNamara N, Smith D, Raggio V, Cruz M… **Pierson TM**…et al: Epilepsy and electroencephalographic abnormalities in SATB2-associated syndrome (SAS). *Pediatr Neurol*. (20)30122-3. doi: 10.1016/j.pediatrneurol.2020.04.006.

2. Nabais Sá MJ, Jensik PJ, McGee SR, Parker MJ, Lahiri N, McNeil EP, Kroes HY, Hagerman RJ, Harrison RE…**Pierson TM**…et al: *De novo* and biallelic *DEAF1* variants cause a phenotypic spectrum. *Genet Med*. 2019;21(9):2059-2069. doi: 10.1038/s41436-019-0473-6.

3. Sheih C, Jones N, Vanle B, Au MG, Huang A, Silva APG, Lee H, Douine E, Otero MG…**Pierson TM**, et al: *GATAD2B*-associated neurodevelopmental disorder (GAND): genetic and clinical insights. *Genet Medicine*. (Accepted)

PUBLICATIONS

4. Ostrowski P, Zachariou A, Loveday C, Beleza A, Bertoli M, Dean J, Ellis I, Foster A, Graham Jr J …**Pierson TM**…et al: The *CHD8* overgrowth syndrome: a detailed evaluation of an emerging overgrowth phenotype in 26 patients. *Am J Med Genet Part C*. doi: 10.1002/ajmg.c.31749.

5. Fu J, Korwutthikulrangsri M, Ramos-Platt L, **Pierson TM**, Refetoff S, Weiss RE, Dumitrescu AM: Sorting variants of unknown significance identified by whole exome sequencing: genetic and laboratory investigations of two novel *MCT8* variants. *Thyroid*. 2019. doi: 10.1089/thy.2018.0703.

6. **Pierson TM**, Otero MG, Grand K, Choi A, Mackay J, Young JI, Graham Jr JM, Mackay J: The NuRD complex and macrocephaly-associated neurodevelopmental disorders. *Am J Med Genet Part C*. 2019. doi: 10.1002/ajmg.c.31752.

7. Johnson B, Kumar R, Oishi S, Alexander S, Sanchez Vega M, Ivancevic A, Pérez-Jurado L, Gardner A, Domingo D…**Pierson TM**…et al: Missense variants in *USP9X* lead to a distinct male neurodevelopmental disorder characterised by a loss of TGFβ signalling. *Biol Psychiatry*. 2019;S0006-3223(19)31479-9. doi: 10.1016/j.biopsych.2019.05.028.

8. Souza IA, Gandini MA, Zhang F-X, Mitchell WG, Matsumoto J, Lerner J, **Pierson TM**, Zamponi GW: Pathogenic Cav3.2 channel mutation in a child with primary generalized epilepsy. *Mol Brain*. 2019;12:86. doi: 10.1186/s13041-019-0509-5.

9. Hengel H, Bosso-Lefèvre C, Grady G, Yu EP, Szenker-Ravi E, Yau M, Li H, Pierce S, Lebigot É… **Pierson TM**, et al: Loss-of-function mutations in UDP-glucose 6-dehydrogenase are a novel cause of recessive developmental epileptic encephalopathy. *Nat Commun*. (Accepted)

10. Jiang X, Raju PK, Nazzareno D'A, Lachance M, Pepin J, Dubeau F, Mitchell W, Bello-Espinosa L, **Pierson TM**, Minassian B…et al: Both gain-of-function and dominant-negative *de novo CACNA1A* mutations cause severe developmental epileptic encephalopathies including Lennox-Gastaut syndrome. *Epilepsia*. 2019;60:1881-1894. doi: 10.1111/epi.16316.