2020

ANNUAL REPORT

Arthritis, Rheumatology and Autoimmune Diseases

NEW HORIZONS IN **DIAGNOSTICS AND EARLY INTERVENTIONS**

ADVANCEMENTS IN **CELLULAR REJUVENATION**

GENETIC VARIANCES IN AUTOIMMUNITY

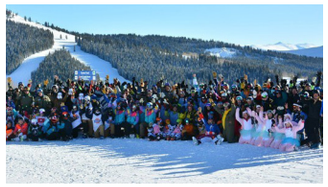
★★★★
CHARITY NAVIGATOR
Four Star Charity

A publication of the Arthritis National Research Foundation | CureArthritis.org

Throughout the year the #CureArthritis community hosts their own events to raise funds and awareness for research. We've highlighted a few below and encourage you to start your own project to help support this vital research!

Dancing for the Joints

JA Awareness Advocates



Blue Sky Cup | Skiing For A Cure

Facebook Fundraising Birthdays!

Racing for a Cure

A MESSAGE FROM THE CHAIR OF THE BOARD OF DIRECTORS

Dear supporter,

2020 has proven to be a difficult year for many organizations. ANRF, however, is pleased to report that we have weathered the storm as we have sufficient resources to continue to fund much needed research even in the absence of the level of funding we had expected for this year. We continue to focus on our singular mission: of funding innovative early stage research conducted by upcoming young researchers.

Our ability to continue to fulfill our mission during these challenging times is the result of a decades long commitment to fiscal responsibility and transparency. ANRF has always operated with the belief that our mission must come first and that our supporters should be able to see the tangible evidence of our dedication to that mission. We have always operated with austerity to ensure that donor funds would be allocated for their intended purpose: innovative research.

In this annual report, you will find a brief account of the research ANRF funded in 2020. The extraordinary work of 18 of the most promising scientists in their fields has leant new understanding to the origin of autoimmune diseases and has sewn the seeds of treatments that will better the lives of patients for years to come. Their work is, of course, a testament to their own dedication to hard work and innovative ideation. But it is also a testament to you, our community of supporters who choose to help us fund tomorrow's most extraordinary scientists as they nurture the beginnings of a life's work.

We know that supporting ANRF this year may not have been easy. Many have faced hard times this year. To those who have, we wish better times ahead. But those who could give a little, did. We know the significance behind your donations this year is greater, perhaps, than it has ever been. To those who have supported us in any way, we thank you. We promise, as always, to ensure that we uphold our mission, of supporting the most promising early research and in encouraging rising young researchers. When we find a cure, it will be likely the result of pursuing ideas that were not obvious nor conventional. In closing let me also affirm our commitment to always manage this organization with the highest level of integrity and transparency in respect of the trust you place in us to prudently invest your funds.

Sincerely,

Schalon Newton, DBA
Chairman, ANRF Board of Directors

Dr. Craig Walsh,
Chairman of the Scientific Advisory Board

The ANRF is delighted to announce that Dr. Craig Walsh has taken on the role of Chairman of the Scientific Advisory Board. Dr. Walsh boasts an impressive career in the field of autoimmunology. Currently a professor of Molecular Biology and Biochemistry at the University of California, Irvine, he is also Director of the Multiple Sclerosis Research Center.

Dr. Walsh is committed to ANRF's mission and vision and credits the organization with playing a major role in the foundation of his own career. His commitment is evident as he speaks about his involvement with ANRF:

> **"As a recipient of an ANRF award when I first started as an assistant professor, I know the major impact that this award can have on a scientific career. I am deeply committed to the goal of funding scientists and physicians at this important and challenging career stage. I am also passionate about understanding the causes of autoimmune diseases such as rheumatoid arthritis, lupus and others, areas targeted by the ANRF."**

Dr. Walsh's exemplary professional achievements, commitment to ANRF's mission and vision, and proven leadership traits will help ensure that the Scientific Advisory Board continues to stand as one of the foremost intellectual bodies in the field of rheumatology and immunology.

FINANCIAL REPORT
2018, 2019 & 2020

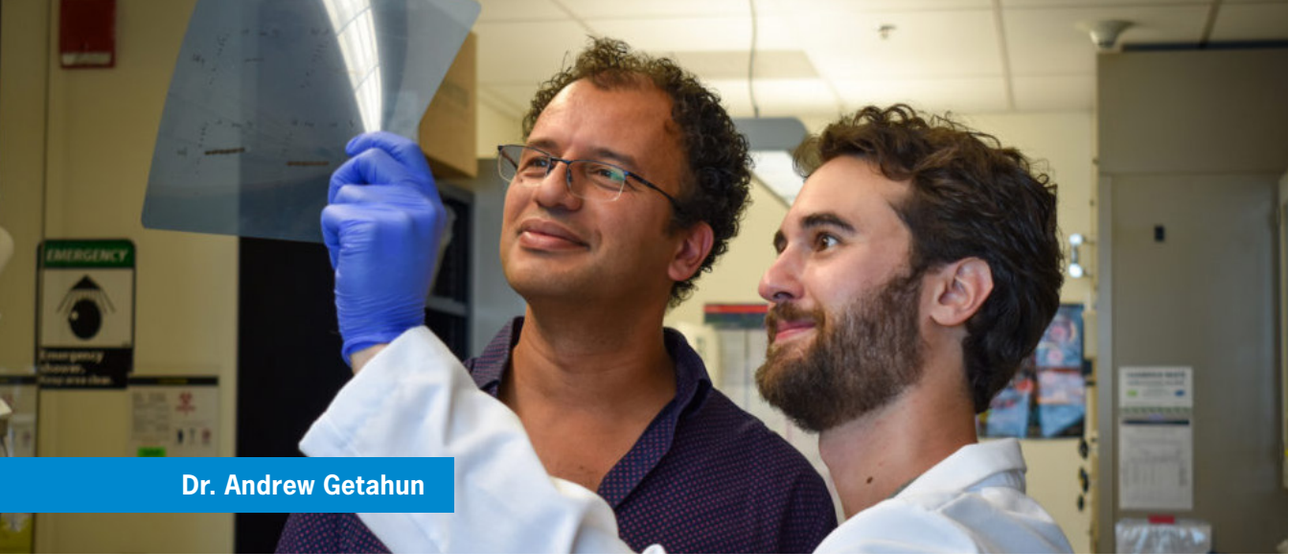
AUDITED STATEMENTS OF PUBLIC
FISCAL YEARS ENDING MARCH 31st

REVENUE AND EXPENSES			
PUBLIC SUPPORT AND REVENUE	2018	2019	2020
Contributions and Bequests	2,564,271[A]	1,391,531	1,799,375
Investment Income Net	378,310	224.639	741,837
Unrealized Gain (loss) on Investments	399,538	142.447	(1,268,816)
TOTAL SUPPORT AND REVENUE	**$3,342,119**	**$1,758,617**	**$1,272,396**
EXPENSES			
Program Services			
Research	1,537,187	1,828,753	1,802,401
Education	236,428	250,165	308,666
Total Program Services	$1,773,615	$2,078,918	$2,111,067
SUPPORTING SERVICES			
Management and General	115,912	144,304	194,436
Fund Development	120,016	111,029	92,897
Total Supporting Services	235,928	255,333	287,333
TOTAL EXPENSES	**$2,009,543**	**$2,334,251**	**$2,398,400**
Change in Net Assets	1,332,576	(575,634)	(1,126,004)
Net Assets at Beginning of Year	8,209,489	9,542,065	8,966,431
NET ASSETS AT END OF YEAR	**9,542,065**	**8,966,431**	**7,840,427**

BALANCE SHEET SUMMARY			
*Total Unrestricted Assets**		$8,530,041	$7,504,037
*Total Restricted Assets**		$436,390	$336,390
Total Assets	$9,586,356	$8,966,431	$7,840,427
Total Liabilities	$44,291	$37,323	$32,830
NET ASSETS AT END OF YEAR	**$9,542,065**	**$8,966,431**	**$7,840,427**

*Beginning in 2019, new accounting regulations require reporting restricted and unrestricted assets as seen above.

[A] Bequests (planned gifts) in 2018 totaled $1,239,201.73



Dr. Andrew Getahun

SIGNALS OF SILENCE

Dr. Andrew Getahun is a tenure-track assistant professor at the University Colorado Denver in the department of immunology and microbiology. Despite not having personal experience with autoimmune conditions, Dr. Getahun developed a deep fascination with immunology, along with a passion for getting answers through experimentation. This has led to a valuable researcher with an unyielding need to find solutions.

It is important that our immune system recognizes cells that are our own (self), and those that are foreign (non-self). It is therefore necessary for our body to eliminate immune cells (B and T cells) that are self-reactive. Central tolerance, also known as negative selection, is the process by which our B and T cells are sorted and any that are self-reactive are removed. This process is not perfect and some autoreactive cells escape central tolerance. Peripheral tolerance is a secondary process which attempts to ensure that self-reactive B cells do not lead to autoimmune conditions through mechanisms including making the cells unresponsiveness (anergy).

As an ANRF grant holder, Dr. Getahun sought to unravel the mechanisms by which autoreactive B cells are kept in a state of anergy. Mouse models, as well as peripheral blood studies determined that in a number of autoimmune conditions autoreactive B cells lose their anergic phenotype, become activated and participate in disease development and progression. Dr. Getahun has made progress towards defining inhibitory signaling pathways that are important in establishing a state of unresponsiveness in autoreactive B cells and understanding how they are established so that these cells can again be "switched off".

"Knowing the signaling pathways, it will be easier to predict which factors may synergize to increase the risk of developing autoimmune disease. This will be important, in a time of increased genetic screening, to identify individuals at risk and possibly start treatments before the damage is done."

A COMPLEMENT TO RA RESEARCH

Dr. Christian Lood is an Assistant Professor in the Division of Rheumatology, University of Washington. Spending his formative years on his family's farm laid the foundation for an interest in biology. The complement system is a part of the immune system that enhances (complements) the ability of antibodies and phagocytic cells to clear microbes and damaged cells from an organism, promote inflammation, and attack the pathogen's cell membrane. In his first year studying biomedicine, Dr. Lood became increasingly fascinated by this system, eventually leading him to engage in studies on lupus, a disease wherein the complement system is impaired. Since then, his work has expanded to encompass, more broadly, inflammatory rheumatic diseases including RA and dermatomyositis.

In his role as an ANRF scholar, he investigated the role of mitochondria in the development of Rheumatoid Arthritis. Mitochondria are the powerhouses for our cells, producing the energy that fuels our biological processes. Recently, Dr. Lood's team observed that mitochondria may be forced out of the cell upon cell death leading to a hypothesis that extruded mitochondria act to induce inflammation, as well as promoting autoimmunity. Dr. Lood hopes that markers associated with mitochondrial extrusion will act as early markers of disease and will aid in predicting disease outcomes. His research was done, and continues to be done, with the hope that identifying novel biomarkers will lead to improved monitoring of disease and identification of high risk patients requiring preventative treatment.

"Intriguingly, what I started working on more than 15 years ago is still central to my current research, that is, removal of cell debris (such as mitochondria) to avoid unwarranted inflammation and organ damage. The ANRF grant is very prestigious, and we were honored at recognition of the high quality of our work."

Dr. Christian Lood

Dr. Halima Moncrieffe

SINGLE PROTEIN REGULATION OF MULTIPLE JIA GENES

Halima Moncrieffe is an assistant professor at the Cincinnati Children's Hospital Medical Center. Despite medical advances, there are a number of diseases for which we still do not understand the cause. Diseases that lack a known cause are termed as idiopathic. Juvenile Idiopathic Arthritis (JIA) is one such disease. Dr. Moncrieffe aims to solve the unknown 'idiopathic' cause of JIA, providing new treatment hope for patients and their families. This has been the focus of her research as an ANRF scholar.

JIA is an extremely complex condition. Studies have identified multiple genes involved, each making small but significant contributions to the development of the condition. Dr. Moncrieffe hoped to identify how variation in genes and the interactions between these genes leads to the unwanted and unnecessary inflammation associated with JIA. Her research has advanced our knowledge in this area.

She believes that with technological advances we are in a position to start to understand our complex genetic architecture in a way that gives us the capacity to not only recognize what each cell is doing but how it is affecting the dynamic environment that is our bodies. Multiple layers of data regarding our genetics, epigenetics (external factors that impact how our genes are expressed), bacterial and viral exposure and the wider environment in which we exist can be combined to hopefully provide a holistic view of a condition leading to improved treatment options.

Our genes are initiated and regulated by proteins known as transcription factors. Dr. Moncrieffe had previously identified a transcription factor with a common regulatory target that binds to half of all known JIA genes. If a single protein regulates many JIA genes, there would be a foundation for a new type of treatment to turn off many JIA genes at once.

"New treatments continue to emerge and thankfully joint replacements are few and far between. I am inspired to accelerate the hard-earned progress in the field towards a cure. So many talented and brilliant minds are working hard to find the cure, and we always need more so I mentor students and trainees at all stages and let them know that they could be the one to find a cure and impact millions of lives!"

Dr. Jolien Suurmond

A JOURNEY OF SELF DISCOVERY

Jolien Suurmond is a postdoctoral researcher at The Feinstein Institute for Medical Research. Throughout her research career, she has been intrigued by the immune system and how it is able to distinguish between our own cells (self) and cells from a foreign origin (non-self). An antigen is a toxin or foreign substance which elicits an immune response, especially the production of antibodies. B cells are white blood cells that have two key roles in launching an immune response – presentation of antigens to other cell types and secretion of antibodies. In her time as an ANRF scholar, Dr. Suurmond sought to identify how the B cell response to self (autoreactive) differs from the response to foreign antigens.

Antinuclear antibodies (ANA) are a group of autoantibodies produced by a person's immune system when it fails to adequately distinguish between "self" and "non-self" and are a feature in a number of autoimmune conditions including lupus. There are different ANA+ B cells arising from different pathways and resulting in different characteristics. Categorizing Lupus patients based on these different B cells provides a unique opportunity to target disease-specific pathways using precision medicine, thereby decreasing the degree of immunosuppression in different patient groups. Dr. Suurmond is hopeful that defining these differences in B cells in lupus will offer up alternative therapeutic targets specific to distinct differentiation/activation pathways.

"Only one new therapeutic has been approved for the treatment of SLE in the past 60 years. As most current therapies for SLE and other autoimmune diseases are highly immunosuppressive and therefore increase susceptibility to infection, there is an urgent need for more specific therapies that affect only autoreactive cells or pathways. I am highly motivated to contribute to such discoveries."

As a second-year grant holder in 2021, Dr. Suurmond will be studying the gene expression in these B cells with a goal of discovering new molecules on these B cells that can be used to treat the two groups of SLE patients.

IF I COULD TURN BACK TIME

Dr. Charles Chan is an Assistant Professor at Stanford in the Department of Surgery, Division of Plastic and Reconstructive Surgery, with co- appointments in the Immunology Program and the Stem Cell Institute. Dr. Chan has always been fascinated by the process of aging both as a biological phenomenon as well as association with highly prevalent diseases such as cancer and cardiovascular disorders. After the celebrated cloning of Dolly the sheep, Dr. Chan realized that cloning could have therapeutic applications and could therefore mean molecular rejuvenation, essentially reversing aging, might be feasible.

Stem cells are cells that are capable of differentiating into numerous different types of cells, making them a great potential resource to address aging. This young researcher is studying skeletal aging from the perspective of its regenerative stem cells. Recently their data suggests that it is in fact possible to reverse cartilage degeneration by activating skeletal stem cells. Stimulating the cells surgically and providing essential factors the resting stem cells can be directed to differentiate into cartilage. Dr. Chan is now applying state of the art techniques to characterize the molecular changes that tissue-specific stem cells undergo with age in hopes of finding new ways to rejuvenate tissues by revitalizing and directing their stem cells. This could offer innumerable new ways to treat diseases such as osteoarthritis in which aging plays a significant role.

With the first year of support from the ANRF, Dr. Chan showed that the frequency of skeletal stem cells (SSC) in limb joints progressively decreases in both mice and humans, corresponding to diminishing chondrogenesis (the process by which cartilage is formed from condensed mesenchyme tissue) in mature adult tissue. However, their data also showed that a localized injury response triggered by microfracture (MF) surgery could induce a local expansion of SSC in the chondral surface of adult limb joints. Co-delivery of BMP2 and VEGF inhibitors in a chemical hydrogel to the MF sites can drive the differentiation of MF-activated SSC towards generation of chondrocytic hyaline cartilage. This regenerated cartilage is stable and the same combination of BMP2 and VEGF inhibitors can also induce cartilage formation in xenografted human limb tissue.

The additional funding provided as a second year ANRF scholar allows Dr. Chan and his team to test this approach in a larger animal model (rabbit model) to show that following MF, there is a therapeutic window to skew MF-activated SSC fate towards robust formation of new cartilage for resurfacing of osteoarthritic joints. They also aim to test different types of 3D printed scaffolds to deliver the factors. These findings could provide a new stem cell paradigm for regenerating hyaline cartilage that is validated in both mouse and human tissues.

Dr. Charles Chan

Dr. Mattias Svensson

RA LEADS TO LOSS OF OUR NATURAL PROTECTION

Dr. Svensson is a career scientist at the UC San Diego School of Medicine. A number of his family members and friends are affected by Rheumatoid Arthritis and he has seen the suffering that this inflammatory disease can bring. Many experience ongoing pain and physical limitations despite trying several therapies currently available.

Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body. These mechanisms include physical barriers such as skin, chemicals in the blood, and immune system cells that attack foreign cells in the body. Antigens are the structures on toxins or foreign substances that alert our immune cells to raise an attack. The major functions of the innate immune system are to recruit immune cells to the site of infection, present antigens to activate the adaptive immune system, remove foreign substances and induce inflammation as a protective response. Inflammation can either be acute or chronic. Acute inflammation is a normal initial response to harmful stimuli. Chronic inflammation on the other hand can occur even when there is no apparent injury or disease. Unchecked, the immune system prompts cells to attack nearby healthy tissues and organs, setting up a chronic inflammatory process that plays a central role in some of the most challenging diseases of our time, including RA.

Dr. Svensson's research focuses on the role of the innate immune system in RA. As an ANRF grant recipient, Dr. Svenson focused on a subset of innate immune cells known as invariant Natural Killer T cells (iNKT). These cells are able to rapidly respond to pro-inflammatory molecules or danger signals. Once activated, they activate other immune cells such as B and T cells and macrophages.

Previously, the laboratory identified a protective function for iNKT cells, particularly iNKT1, during development of arthritis. It was found that as the severity of the disease worsens, iNKT1 disappeared from the arthritic joints. The reason for the loss of this protective cell is not known. Therefore, Dr. Svensson, with the aid of his ANRF grant, looked to clarify the role of iNKT1 in RA and answer the question of what causes the loss of this cell as the disease progresses.

> **"I believe that if we can answer this question, it can lead to the identification of novel mechanisms of disease that in the future can be exploited for the development of new treatments for RA."**

Not only does this research offer exciting potential avenues for treatment of autoimmune conditions characterised by chronic inflammation, but it has also helped to establish Dr. Svensson as an independent investigator.

ANRF | GIVING GUIDE

Suggestions to Support our Foundation

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EVERYTHING GIFT

Every donation to the ANRF, regardless of size, supports advancing research through a combination of the programs listed below. If you wish to donate to a specific area, please note the suggested contribution amounts. We are grateful for the generosity of the community and thank you for your support.

100K

BIOMEDICAL RESEARCH GRANTS

Fund groundbreaking research in Arthritis, Rheumatology and Autoimmune Diseases conducted by talented MD and PhD professionals at prestigious institutions. This is critical for filling knowledge gaps, identifying new therapies and finding longlasting cures.

50K

SCIENTIFIC SYMPOSIUMS

Convene top minds in scientific research and clinical care to collaborate and cross-pollinate. Information sharing is a key component in accelerating the discovery process and improving the quality of research and clinical care.

25K

MEDICAL EDUCATION & AWARENESS

Disseminate the latest news in Arthritis, Rheumatology and Autoimmune Diseases through credible and FREE newsletters, webinars, fact sheets and other digital and print mediums. Access to accurate and concise information to stay up-to-date is needed in a constantly changing medical field.

10K

RESEARCH TRAVEL GRANTS

Facilitate the direct access of young trainees and scientists with limited resources to participate in professional meetings and publish their work. This is indispensable for sharing ideas, receiving feedback and sustaining the pipeline of new talent entering the field of Arthritis and Rheumatology.

5K

INFRASTRUCTURE & READINESS

Keep our grantmaking systems, research platforms and Medical Education channels up-to-date for optimal impact. This will enable us to perform our functions effectively and remain competitive as a leading Medical Foundation.

LEAVE A LEGACY

Make a planned gift or donation today to leave a lasting impact in the search to cure arthritis!

- Give Online at CureArthritis.org
- Leave a gift in your will
- Give through your workplace
- Donate through Amazon Smile, PayPal, or start a Facebook fundraiser
- Donate your car
- Make monthly or annual gifts
- Give through the Combined Federal Campaign (CFC)
- Give us a call at 800.588.2873 or email us at info@curearthritis.org

Use the enclosed envelope or go to CUREARTHRITIS.ORG/DONATION

CONNECTING THE DOTS OF SCLERODERMA RESEARCH

Dr. Skaug provides Rheumatology care and consultation at the UT Professional Building and Memorial Hermann Hospital in the Texas Medical Center and at Lyndon Baines Johnson Hospital within the Harris Health system. Being both an MD and PhD gives Dr. Skaug the ability to see the real-life applications of research, giving him unique insight into what this condition means to the patients that have it. Understanding what gaps in our knowledge mean for those with autoimmune conditions inspires this physician and researcher to keep pushing for answers that will lead to improved treatments and maybe even a cure.

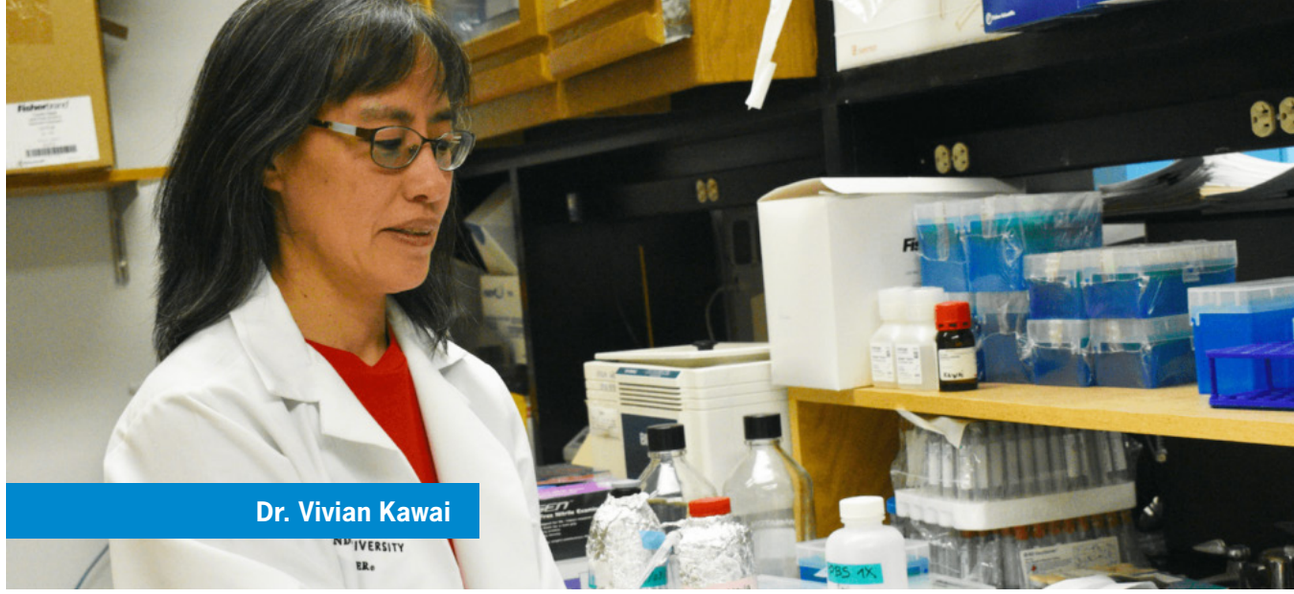
Dr. Skaug's research is focused on identifying mechanisms that drive dysfunction of the immune system in the autoimmune disease scleroderma. Scleroderma is a disease that affects connective tissues, resulting in thickening of the skin, scar tissue on organs such as the lungs and kidneys and thickening of blood vessels leading to high blood pressure and tissue damage.

Previous research in the division identified dysfunction of a gene, *DNASE1L3,* as a risk factor for developing scleroderma. Dysfunction of this gene appears to be a risk factor for multiple autoimmune diseases including systemic sclerosis, lupus, vasculitis, and rheumatoid arthritis, suggesting that *DNASE1L3* is important for maintaining proper function of the immune system.

Results from research conducted in his first year as an ANRF scholar supports the hypothesis that this scleroderma-associated genetic variant impairs the ability of *DNASE1L3* to clear the DNA from cells that have died during normal cell turnover. Given this progress, Dr. Skaug was awarded a second year of funding.

"The focus of my research for the second year is to determine how this excess DNA contributes to the imbalanced immune system commonly observed in scleroderma patients. This work will include searching for the cell types that interact with this excess DNA and determining the downstream effects of this DNA on immune cell function. Completion of this work could help us understand a mechanism underlying the excess immune cell activity observed in systemic sclerosis and other autoimmune diseases."

Dr. Brian Skaug



Dr. Vivian Kawai

PREDICTING LUPUS RISK

Dr. Kawai is a medical doctor undertaking clinical research as a faculty member at Vanderbilt University. Throughout her career she was always surprised to see how patients with the same diagnosis had vastly different disease progression and vastly different responses to the same therapeutic treatments. This directed her research to focus on the role of genetic variability in inflammatory disorders—including autoimmune diseases—and how this variability can be used to predict risk and drug response.

Our own cells have the same glycoproteins, in this case they are referred to as autoantigens, in a healthy individual the immune system recognizes autoantigens as self, not foreign, and as such does not launch a response against them. In order to ensure this self-tolerance occurs correctly lymphocytes that do recognize autoantigens undergo programmed cell death (apoptosis) or become non-functional. Sometimes, however, this process malfunctions and antibodies are produced against human antigens (autoantibodies), which may lead to autoimmune disease.

Antinuclear antibodies (ANAs, also known as antinuclear factors) are a type of autoantibody that bind to contents of the cell nucleus and are found in a number of disorders including autoimmune conditions. ANAs can therefore be helpful in the diagnosis of some of these disorders with the ANA test detecting the autoantibodies present in a sample of blood serum.

Dr. Kawai pursued defining the consequences of the presence of antinuclear antibodies in individuals that do not have an autoimmune condition. This data provides the initial steps towards forming the basis for an immunological test which looks at ANA as a way to predict the risk of developing lupus.

"I expect that defining the clinical outcomes and genetic determinants giving positive ANA result will inform future studies about the role of autoimmunity in disease risk."

ANRF funding allowed for important preliminary data to further understand the role of autoimmunity in disease risk, for diseases such as lupus. It will also be helpful in order to start to resolve the question of how much of this risk is driven by genetic variability.

A BONE TO PICK WITH OSTEOCLASTS

Dr. Christian Jacome-Galarza is a research fellow in the Department of Orthopedics at Brigham and Women's Hospital in Boston. As an avid sportsman, enjoying activities such as hiking, skiing and soccer, he understands the devastation that diseases that limit physical ability can have. Through his research, he hopes that the damage caused by diseases such as arthritis can be halted or completely prevented, giving patients the ability to embrace a more active lifestyle.

Osteoclasts (OC) along with osteoblasts form part of a partnership of cells responsible for balancing our bone remodeling. Osteoclasts breakdown bone whilst osteoblasts rebuild it. OCs develop in the bone marrow and are usually found in the pits in the bone surface. In patients with inflammatory arthritis, OCs appear in joints, an anatomical site in which they do not normally occur. Their presence contributes to damage in the joint. Currently, not all patients are treated with available therapeutics that prevent this damage. Dr. Jacome-Galarza planned on using his ANRF grant to fund research which looked at how OCs are formed, genetic factors that induce their activation and how they cause tissue destruction. The research specifically looked at OC precursor cells, known as macrophages and monocytes, that under certain conditions give rise to OCs and how they form OCs in the inflamed joints. The research began to address what makes OCs in arthritic joints different to normal OCs. The aim was to highlight mechanisms that offer novel treatment targets thus preventing joint erosion.

Dr. Jacome-Galarza discovered that osteoclasts originated from two distinct progenitor cells in inflammatory arthritis, suggesting alternative pathways of activation during osteoclast formation that regulate bone and cartilage destruction. In addition to these findings, Dr. Jacome-Galarza discovered that macrophages also derived from two different cellular origins, i.e. embryonic progenitors and bone marrow derived progenitors. He found that both populations of macrophages are present in the inflamed synovium in arthritis, and he is currently isolating these distinct macrophages populations to study the transcriptional regulatory mechanisms that determine their function.

Dr. Jacome-Galarza's first year of research showed great promise in achieving the above-mentioned objectives and as such we look forward to seeing even progress now that he has been awarded a second year of funding by the ANRF. During his second year, his research will focus on investigating the identity of the progenitors responsible for the activation of this alternative pathway and the precise mechanisms that control their differentiation into osteoclasts. He will also try to determine the functional heterogeneity of macrophages in inflammatory arthritis.

SPINE-TINGLING AS RESEARCH

Joerg Ermann is an associate physician in the division of Rheumatology, Immunology and Allergy at Brigham and Women's Hospital. He is a member of the Board of Directors and chair of the Education Committee of SPARTAN (Spondylarthritis Research and Treatment Network) and has over 25 years of experience in the field of medicine.

Ankylosing Spondylitis (AS) is an inflammatory disease of the spine and sacroiliac joints. Patients with AS experience back pain and stiffness. Moreover, spinal inflammation may result in abnormal bone formation leading over time to fusion of vertebrae, severe restriction of mobility and increased risk for spinal fractures. HLA-B27 is a cell surface protein found in white blood cells, a positive result for this protein is indicative of a higher risk for autoimmune conditions such as AS. HLA-B27 is a ligand for killer cell immunoglobulin-like receptors (KIR). Disease mechanisms, including the role of HLA-B27 and its receptor, in triggering AS are not fully understood.

As an ANRF scholar, Dr. Ermann looked at the role of HLA-B27 in AS, as well as its association with pro-inflammatory molecules such as IL-17A which are produced by immune cells. IL-17A is significantly elevated in HLA-B27 positive patients. IL-17A are produced by the immune cells – T helper cells. IL-17A once bound to its corresponding receptor results in the induction of chemoattractants, which are responsible for recruiting other immune cells such as monocytes and neutrophils to the site of inflammation.

Flow cytometry is a technique used to detect and measure physical and chemical characteristics of a population of cells. Dr Ermann's research used flow cytometry to analyze and compare immune cells from AS and healthy patient blood samples. Specifically measuring the expression of KIR receptors and the production of IL-17A and other mediators in relation to the HLA-B27 of the study participants.

Most previous studies of immune cells in AS have focused on individual cell types such as CD4+ T cells, here multiple cell types were analyzed at the same time. It is expected that full analysis will reveal that there are small clusters of immune cells in AS patients, but not in controls, that express both KIR receptors and IL-17A. These cells are likely important players in the AS disease process and may offer new therapeutic targets.

Dr. Christian Jacome-Galarza

Dr. Joerg Ermann

Dr. Theresa Wampler Muskardin

Dr. Matlock Jefferies

PROFILING RA FOR PERSONALIZED TREATMENT

Theresa Wampler Muskardin is a junior faculty member at New York University School of Medicine. Her goal as a researcher is to one day be able to provide therapy which is tailored to the individual patient's disease and personal immunology. Her goal as a researcher is to one day be able to provide therapy which is tailored to the individual patient's disease and personal immunology resulting in more effective treatment and eventually a cure.

Worldwide rheumatoid arthritis (RA) is the most common inflammatory joint disease, with serious manifestations of the disease also occurring beyond the joints. Effective treatment as soon as possible after diagnosis is critical to good outcomes. Remission within the first 3 months of therapy is now the goal, and is the best predictor of remission at one year. Huge strides have been made in how we treat this disease. Unfortunately for many, the approach to treatment is one of trial and error, with physicians unable to predict which medications may work for which patients. TNF inhibitors (TNFi) are the most common biologic treatment employed. Responses are variable, with approximately 30% not responding and another 30% achieving only partial response. It commonly takes between 3-6 months to trial medications for a patient before some level of success is achieved. Active disease persists in a substantial number of patients even after a trial of a couple of medicines, during which time the disease seems to become more difficult to treat and damage accrues.

To improve these statistics Dr. Wampler Muskardin planned on using ANRF funding to analyze blood and synovial tissue (the fluid that lubricates joints) from RA patients to define biological subgroups that will predict an individual patient's response to TNFi treatment. Dr. Wampler Muskardin and her team demonstrated that baseline levels of serum type-1 interferon) activity can predict which RA patients would not respond to TNFi. Building on these findings, as an ANRF scholar she worked to analyze blood from RA patients to define biological subgroups, categorized according to levels of serum type-1 interferon that will predict an individual patient's response to tumor necrosis factor inhibitor (TNFi) treatment.

In conjunction with the blood analysi,s Dr Muskardin examined synovial tissue (the fluid that lubricates joints). The synovial tissue from rheumatoid arthritis patients will be stained to help clarify the underlying biology of the type 1 interferon pathway and its ability to predict whether a patient will respond to TNFi. The results obtained will hopefully provide powerful validation of this finding which will be necessary to translate the findings into more effective patient treatment.

COULD A CURE FOR OA BE AS SIMPLE AS FLICKING A SWITCH?

Epigenetics is the study of biological mechanisms that turn our genes on and off. This controls when and how much protein a gene makes, which controls a multitude of biological processes. Epigenetics is everywhere: your diet, where you live, who you interact with, when you sleep, how you exercise, even aging – all of these can ultimately cause chemical modifications around the genes that will turn those genes on or off over time.

Dr. Matlock Jefferies is a physician and researcher that is delving into the world of epigenetics in order to find new osteoarthritis (OA) treatments. Both of Dr. Jefferies' parents have early, rapidly progressive knee OA. During his research training he realized just how common a disease OA is.

"I am hoping that we will be able to define the specific epigenetic changes that are associated with reversible risk factors (obesity) compared to those which are not reversible (due to aging or trauma). This will offer us considerable insight into potential future therapies, which could focus efforts on blocking or activating those genes and pathways which the patient will be unable to. Furthermore, by performing the first large-scale whole-genome epigenetic study, I hope that we will find additional drug targets which undergo epigenetic changes that have been missed by previous studies using microarrays that only cover parts of the genome."

Funds from the ANRF grant were employed to create a large-scale epigenetics study. Using a mouse model, Dr. Jefferies is hoping to tease out which of these epigenetic differences are related to the most common risk factors for OA. In order to do this the team introduced OA risk factors individually and then examined epigenetic changes within knee cartilage. For example, OA is induced in mice, the impact of factors such as age and diet induced obesity are then added and addressed. Cumulatively this data will be used to produce the first-of-its-kind detailed epigenetic map of mouse knee cartilage while defining the changes that occur as OA develops. Using whole-genome bisulfite sequencing a complete picture of the epigenetic changes occurring throughout the mouse genome will hopefully be revealed.

THE ROLE OF THE LESSER KNOWN T CELL AND AN ASSOCIATED PROTEIN - GRANZYME K

Dr. Anna Helena Jonsson is an Instructor in Medicine at Harvard Medical School and an associate physician at Brigham and Women's Hospital in Boston. The transition from post-doctoral work to faculty is critical in a researcher's career path. In the current research climate where funding is often a limiting factor, it is at this point that many researchers are forced to leave academia. Dr. Jonsson believes that the support she received by being awarded an ANRF grant early on in her research career meant that she was able to continue to contribute to this field of research in a very meaningful way. "Receiving the grant felt like a big vote of confidence from a team of established arthritis researchers, their support showed me that I am on the right track and will successfully navigate through this transition."

Much of the research surrounding rheumatoid arthritis (RA) focuses on CD4 T cells, a type of white blood cell that helps to coordinate the immune system's response to infections and other attacks. Far less investigation has been undertaken looking at the potential role of CD8 T cells in RA, even though they are found in large numbers in inflamed joints in RA and produce many of the same cytokines as CD4 T cells, indicating that they too may have an important role. Based on this, Dr. Jonsson began researching CD8 T cells and their possible link to RA.

It was found that blood from RA patients contained an expanded CD8 T cell population that expressed CCR2. CCR2 is a protein on the surface of certain cells in the immune system that directs the cells to travel to certain places in the body. CCR2 is a receptor for CCL2, which is a molecule produced at sites of inflammation, such as tissue injury, infection, or inflamed joints in RA. In other words, the CD8 T cells that Dr. Jonsson found may be on their way toward inflamed joints in these patients with RA.

Synovial fluid in healthy individuals acts to reduce friction between the articular cartilage in joints during movement. In RA and other types of autoimmune arthritis, the synovial fluid fills up with inflammatory cells and compounds. Dr. Jonsson found that there were several connections between the CCR2+ CD8 T cells discovered in the previously mentioned blood samples and the largest population of CD8 cells in inflamed joints in RA, determined by analysis of the synovial fluid and tissue samples. A key finding was that both populations express a protein that can activate other cells, such as fibroblasts, to make inflammatory molecules. This protein is called granzyme K, which up to this point has received very little attention in the field of arthritis and autoimmunity. The role of CD8 T cells and the associated protein, granzyme K, in autoimmune arthritis has thus far been underappreciated and under researched. Dr. Jonsson continues to hope that she will be able to uncover new mechanisms of inflammation relating to these cells that could be potential novel therapy targets.

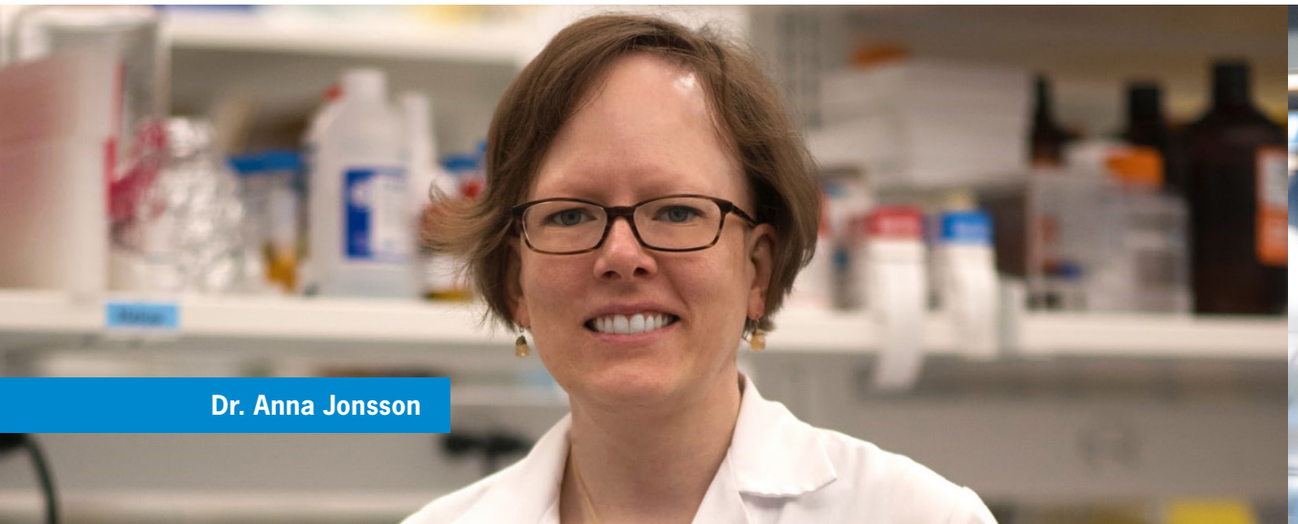
DEFICIENT SIGNALING AND THE DEVELOPMENT OF ARTHRITIS

Dr. Ashouri-Sinha has a personal connection to Rheumatoid Arthritis (RA) which has been the driving force behind her motivation to work in this research area. As a child she experienced the impact of RA in her own home, witnessing the struggles her mother had to endure as a sufferer of severe and debilitating RA, eventually leading to her death due to RA-related complications. Instead of allowing these experiences to hamper her efforts she used them as the foundation from which to begin her fight against this devastating disease.

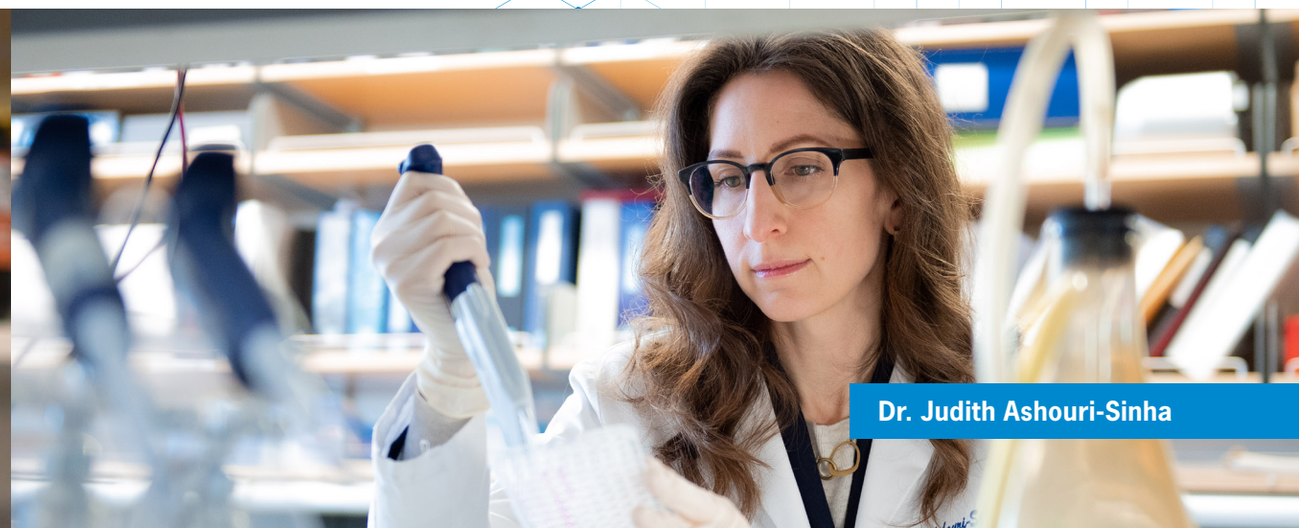
During her medical studies the significance of defining and understanding intricate cell-signalling pathways as a means of improving immune therapies became apparent. As such after completing her residency, she was motivated to enter a career in rheumatology and immunology. In her capacity as an assistant professor of Rheumatology in the department of medicine at the University of California San Francisco Dr. Ashouri-Sinha is using both mouse and human models to investigate CD4 T cells in the context of arthritis development. These cells help suppress or regulate immune responses and it is generally accepted that they contribute to the progression of RA.

T-cell receptor (TCR) is a complex of integral membrane proteins on the surface of T cells, which takes part in the activation of T-cells in response to an antigen. Dr. Ashouri-Sinha's research is concentrating on how T cells with relatively deficient T cell receptor (TCR) signalling are responsible for arthritis development. Key evidence revealed a sharp TCR signaling threshold for commitment to cell division using a novel reporter of TCR signaling. Furthermore, the use of this reporter to identify human Ag-specific T and B cell clones was validated, which has important implications for understanding early events in human disease. Determining the contribution of these activated cells to the development of RA could lead to the discovery of therapeutic targets offering alternative treatment targets.

Although she has achieved a great deal, Dr. Ashouri-Sinha has higher ambitions for herself and her research. In order to advance her skillset in translational immunology she is looking to undertake training in advanced human immune phenotyping. Thus, furthering her ultimate goal of identifying targets through which to mitigate early events in the development of RA. ANRF is delighted to have played a part in assisting to achieve this goal and wish Dr. Ashouri-Sinha well as she continues to wage war against RA.



Dr. Anna Jonsson



Dr. Judith Ashouri-Sinha

Dr. Pierre Cunin

A NEW ROLE FOR MEGAKARYOCYTES AS IMMUNE CELLS

Rheumatoid arthritis remains an inadequately understood disease, with many knowledge gaps regarding its pathophysiology (altered physiological processes associated with disease or injury). Part of the reason for this is the variety of cell lineages involved in the development of arthritis. Macrophages, B and T lymphocytes, mast cells, neutrophils, and most recently platelets and megakaryocytes have all been found to be contributors. Understanding the role of these cell types in joint injury and how the immune cells interact and communicate, aggravating the condition will undoubtedly offer opportunities to discover novel drug targets.

Dr. Cunin is an instructor in medicine at Harvard Medical School and has undertaken several training posts in research laboratories, including the Curie Institute and the University of Bath. Based on a great need to fill in these knowledge gaps, Dr. Cunin focused his research on unravelling the role some of the above-mentioned cell types have in the development and progression of inflammatory arthritis. Currently the particular research focus is on an intriguing biological phenomenon, termed emperipolesis, whereby neutrophils (white blood cells key in innate immunity) enter into, and then exit a megakaryocyte (a large bone marrow cell). Emperipolesis occurs in the bone marrow, where neutrophils mature. The research indicates that during emperipolesis, megakaryocytes transfer biological material to the neutrophils, which is transported with them upon exiting the megakaryocytes. This event enhanced inflammatory functions. Interestingly, he found that emperipolesis is increased in patients with arthritis. Therefore, pharmacological manipulation of emperipolesis may have significant implications for arthritis and other neutrophil-driven inflammatory disorder treatment strategies. This research has also been elemental in defining a new role for megakaryocytes as immune cells in their own right as well providing insights into the overlap of haematology and immunology, both areas of research critical to the study of arthritis.

As an ANRF fellow, Dr. Cunin has published two peer-reviewed journal articles and boasts a third under review. He is hopeful that the ANRF grant will contribute to a fundamental change in our understanding of megakaryocytes as participants in immunity, and potentially open new avenues for intervention in systemic inflammation. Additionally, the grant afforded the opportunity to hire a technical research assistant, dedicated to the support of this project. This demonstrates the way in which these grants create a community of researchers striving towards the same goal.

ANSWERS FROM WITHIN

Mohamed Khass, PhD, is a post-doctoral fellow in the Division of Clinical Immunology and Rheumatology at the University of Alabama. A strong research background in numerous areas including pharmacology, biochemistry, genetics, microbiology and immunology has not only created a researcher capable of unique insights from a multidisciplinary perspective but has set Dr. Khass apart as a researcher to watch. The ANRF grant received as a 2019-2020 ANRF scholar was certainly a contributing factor in this researcher's career trajectory, he firmly believes that the ANRF grant facilitated his promotion at the University of Alabama to assistant professor.

Increasingly interested in immunology, Dr. Khass had his eureka moment when he observed an interesting phenomenon – B cells (cells that play a significant role in our immune systems) that lacked a specific signaling molecule on their surface were linked to increased bone fragility. Bone biology and the interplay between early B cell and skeletal homeostasis became the focus of Dr. Khass' research. "The focus of my research is the mechanism of crosstalk between early B lineage cells and bone forming cells."

B cells have surface molecules that allow them to recognize foreign cells. These signaling molecules are known as B cell receptors (BCRs), which allow the B cells to bind to a specific antigen (a toxin or substance capable of producing an immune response, in other words the enemy!). As these B cells develop and mature the body decides whether they should survive and multiply or whether they should be destroyed. If the B cells lack the BCRs necessary to identify their targets or if the BCRs are defective the B cell will not survive.

During the early stages of B-cell development, one such receptor molecule is the pre-B-cell receptor (pre-BCR). If this signaling molecule is not functioning correctly our bones are simply not as strong. Dr. Khass determined that a portion of this pre-BCR called the surrogate light chain (SL), if absent or malfunctioning, could influence bone health and the development of arthritis as we age. So ironically, we need a light chain to make our bones heavy enough!

Dr. Khass' data has demonstrated that mice deficient in both immunoglobulin joining genes and preB cell product, lambda 5, have signs of accelerated arthritis. Dr. Khass and his team evaluated bone and joint integrity during development and upon aging, concluding that the absence of lambda 5 leads to premature bone loss affecting joints. The data also showed that this phenotype is more prominent in female than male mice, resembling the natural history of rheumatic disease in humans.

Currently the laboratory is in the process of dissecting the mechanistic details behind the pathophysiology of these rheumatic changes. "A second manuscript revealing our findings is in process of being published delineating the importance of our findings. This work is the fruit of the generous and continuous support of ANRF and all its team."

These findings could form the basis for the identification and introduction of new diagnostic and therapeutic targets for rheumatic diseases using immune system products.

Dr. Mohammed Khass

Dr. Erika Noss

Dr. Michael Waterfield

ROLLING THE DICE ON TREATING RHEUMATOID ARTHRITIS

Dr. Noss is an assistant professor, division of rheumatology, Roosevelt Clinic, University Washington Medical Center. Despite the improvements in RA treatment that have been made in the last two decades, there are still sizeable challenges facing rheumatologists today, particularly relating to selection of treatment options for patients. Striving to treat patients, these difficulties come to the fore for Dr. Noss. "The hardest part about being a rheumatologist is starting patients on the right drug. With rheumatoid arthritis (RA), all you can do is give it your best shot. You're simply rolling the dice."

Around 80% of patients do find some level of relief after trying a number of different treatments. Dr. Noss hopes to improve this percentage and offer relief to a greater number of patients. Funding as an ANRF fellow and grant recipient has allowed Dr. Noss to pursue this goal. Fibroblasts are biological cells key in the synthesis of the extracellular matrix and collagen, necessary in providing structural support in our cells as well as being a component in wound healing. In patients with RA these cells are produced at a vastly accelerated rate. Dr. Noss is attempting to find mechanisms that can block these rogue fibroblasts. Data has highlighted the role of a protein important for cellular adhesion, cadherin 11, as a marker and regulator of fibroblast function in our joints in inflammatory arthritis and is therefore a potential means of fibroblast regulation, preventing over production of these cells.

Dr. Noss's research has focused on the role of cadherins in fibroblasts. Cadherins are cell adhesion molecules that are important in the formation of adherens junctions and protein complexes, which allow cells to bind to one another. Cadherin 11 is a protein expressed in the cell lines responsible for bone formation (osteoblasts), it is upregulated during the differentiation of these cells, suggesting a specific function in bone development and maintenance. In studies published in the prestigious journals - Science and PNAS, Dr. Noss showed that deficiency or blockade of cadherin 11 resulted in protection in mouse models from arthritis and also demonstrated that ligation of this adhesion molecule leads to induction of pro-inflammatory cytokines. Cadherin 11 is a marker and regulator of synovial fibroblast function in inflammatory arthritis. Unpacking the mechanisms behind this relationship may lead to new therapeutic targets that prevent long-term joint destruction resulting from RA.

Noss and her team have made substantial progress in this area of research. Expanding on early data, Dr. Noss has proposed the platelet-derived growth factor-alpha (PDGFRA), a molecule highly present on the joint fibroblasts, as a potential treatment target. Data generated in her time as an ANRF scholar has shown, using a mouse model, that silencing PDGFRA reduced the severity of arthritis. The ANRF grant allowed an expanded understanding of PDGFRA biology in the joint more generally, which Dr. Noss believes led to recent NIH support to more extensively study the roles of PDGFRs and its ligand in arthritis biology.

"Maybe a cell that's not traditionally a drug target, like a fibroblast, will someday put people completely into remission."

PATHWAYS IN THE PROGRESSION OF JIA

Arthritis is not a disease of the elderly. Arthritis does not discriminate based on age and many do not know it is also a disease that affects children. Juvenile idiopathic arthritis (JIA) leads to children that experience swollen and painful joints, limiting their ability to simply be children enjoying their childhood. One researcher that has geared up to fight JIA is Dr. Michael Waterfield, a paediatric rheumatologist at UCSF Benioff Children's Hospital in San Francisco. Presently there are around 300 000 children in the US with JIA, and through his work Dr. Waterfield sees first-hand the devastating consequences of this disease.

"While we have many new drugs, we have not cured the disease and we do not understand why one child will respond to treatment and another will not," says Dr. Waterfield. The aggressive inflammation that frequently accompanies JIA can lead to impaired growth and on-going joint problems. In around 50% of cases, this will persist throughout a patient's life. Assisted by an ANRF grant, Dr. Waterfield is attempting to demystify pathways involved in the progression of JIA.

T-cells are the stormtroopers that our body unleashes in order to fight disease-causing molecules. One such T cell, T-helper 17 (Th17), is seen in large numbers in patients with autoimmune conditions. Inhibiting Th17 is increasing in use as a therapeutic tool against these conditions. In order to fully be able to utilize this approach it is necessary to understand how Th17 drives inflammation.

Using mice in which certain genes had been "turned off", it was determined that the activating transcription factor 7 interacting protein (ATF7ip), a regulator of genes, was essential for the development of properly functioning Th17 cells. Building on this the team were able to identify ATF7ip as an inhibitor of interleukin 2 (IL-2) production. IL-2 is a molecule that is crucial for T-cell proliferation and other activities central to properly regulated immune responses. Mice in which the ATF7ip gene was switched off had abnormal overproduction of IL-2 and in turn impaired Th17 differentiation. These results demonstrated a new epigenetic pathway by which IL-2 production is hampered, and this in turn may provide novel avenues for modulating its production and treating autoimmune conditions.

"Over the course of the ANRF grant, I have continued to study the role of ATF7ip in controlling the Th17 response secondary to the aberrant expression of IL-2. This data was published in a recent JEM article. The article showed that ATF7ip is a general regulator of IL-2 which not only has implications for the inhibition of Th17 responses, but also causes increased regulatory T cell differentiation."

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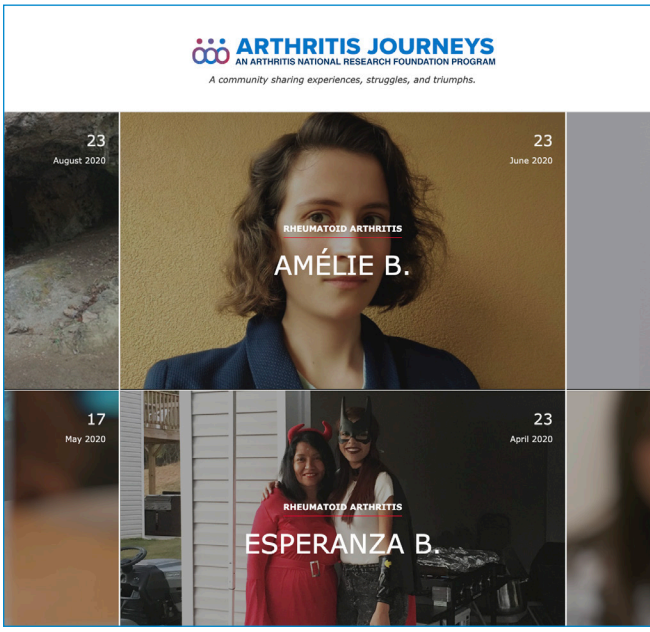

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