WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care *through* Groundbreaking Research

2017 ANNUAL REPORT

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MESSAGE FROM THE DIRECTOR

During our thirteen years as a multi-disciplinary clinic care and research enterprise, the Washington University Neurofibromatosis (NF) Center has many new developments to report. In 2018, we look forward to expanding our research initiatives aimed at developing personalized medical approaches for people affected with NF. We are grateful for the continued partnership with our families that make these high-risk, high-payoff ventures possible.

INTRODUCING NEW MEMBERS

In 2017, Dr. Corina Anastasaki was promoted to the rank of Senior Research Scientist. Dr. Anastasaki has been a leader in the establishment of NF1 patient induced pluripotent stem cell (iPSC) lines from skin and urine samples. These human stem cell lines have been critical resources to study brain cells important to the discovery of new treatments for learning and behavioral problems in NF1. The Washington University NF Center houses one of the largest NF1-patient iPSC repositories in the world, and we have shared the one-of-a-kind resources with many researchers.

The clinical program celebrated the addition of Erika Ramirez, our nurse coordinator, and Jennifer Traber, our Center coordinator, to improve the care we provide for our families. Under Jen's leadership, we improved our NF1 complementary care programs, including the bimonthly Club NF program for school-age children, the Beat NF jazz music motor therapy program for toddlers, and the Teen NF social skills therapy program for adolescents.

ADVANCING NF RESEARCH

There has been exciting progress in our understanding of neurofibromatosis, with numerous researchers in the Washington University NF Center publishing new discoveries. These include advancing our understanding of why girls with NF1 optic glioma are at greater risk for vision loss, establishing how progressive vision loss in mice with Nf1 optic glioma can be stopped, and how immune system molecules affect brain tumor growth. In addition, one of our Pediatric Neurology residents completed the largest study of brainstem tumors in children with NF1, while Dr. Anastasaki identified the first genetic mutation in dermal neurofibromas arising in people without NF1. We also continue to expand our unique collection of resources essential to making these advances, including the NF1 Genome Project used to discover subtle DNA changes that might one day serve to predict the risk of developing specific medical problems in people with NF1.

RAISING NF AWARENESS

In addition, Washington University NF Center neuroscientists participated in the SCIFEST: Brain Matters event, held at the St. Louis Science Center. Visitors to the NF Center booth had the opportunity to learn more about Neurofibromatosis Type 1 (NF1), and NF Center research, through a variety of interactive games and activities. DNA bracelet-making demonstrated how easy it is to isolate DNA, and showed that people can have different *NF1* gene mutations. A "spot-the-difference" iPad game had visitors becoming real scientists by spotting the differences between normal and abnormal brain cells.

Finally, we welcomed a delegation of freshman Missouri State House Representatives to meet our researchers, clinicians, and families. During this session, they learned more about NF, and how the Washington University NF Center is working to improve the lives of people affected with these conditions.

Warm regards,

David H. Gutmann, MD, PhD
Donald O. Schnuck Family Professor
Director, Washington University NF Center
Vice Chair for Research Affairs, Neurology

RESEARCH GRANTS

NATIONAL INSTITUTES OF HEALTH RESEARCH PROGRAM AWARD

>> to **DAVID H. GUTMANN, MD, PHD.** This prestigious eight-year grant allows Dr. Gutmann to devote half of his efforts to study why people with NF1 develop markedly different signs and symptoms. This funding permits him to attack the problem of precision medicine from many angles.

FRANCIS S. COLLINS SCHOLAR AWARD FOR NEUROFIBROMATOSIS CLINICAL AND TRANSLATIONAL RESEARCH

>> to **ANGELA C. HIRBE, MD, PHD.** As a result, she will be obtaining additional training in NF clinical practice at the National Cancer Institute and Johns Hopkins University, and will be expanding her role in the care of adults with NF1-associated plexiform neurofibromas and malignant peripheral nerve sheath tumors.

BERLIN INSTITUTE OF HEALTH EINSTEIN FELLOWSHIP AND ALEXANDER VON HUMBOLDT AWARD

>> to **DAVID H. GUTMANN, MD, PHD** to establish an international research team at the Max Delbrück Center for Molecular Medicine. In collaboration with Professor Helmut Kettenmann, a leading authority in brain support cells (astrocytes and microglia), Dr. Gutmann will be exploring the role of microglia in autism and brain cell function, as well as to generate human brain microglia from NF1 patient induced pluripotent stem cells.

THE ST. LOUIS MEN'S GROUP AGAINST CANCER

>> awarded a second grant to **ANGELA HIRBE, MD, PHD** to continue her research on a deadly cancer seen in young adults with NF1. Dr. Hirbe will be using these funds to develop cancer cell lines from people with NF1-associated malignant peripheral nerve sheath tumors (MPNSTs) as a first step toward identifying and evaluating more effective therapies for these malignancies.

PATIENT SPOTLIGHT: *ALEXANDRA SCHROEDER*

My introduction to the world of Neurofibromatosis began when I was only three years old. It started with a bug bite on my neck and fevers. This was in 1998, and at that time, not a lot was known about NF. On a visit to our local pediatrician, he could not explain the fevers that I was experiencing at night. Also, on further examination while looking at my back, they noticed that it appeared to be curving to one side. After a CAT scan, he decided to send me to the "big guns" St. Louis Children's Hospital. After a CAT scan and an MRI, the doctors discovered a tumor in my back. They then performed surgery to try to remove the tumor. At this point, I was diagnosed with Neuroblastoma—a childhood cancer with a survival rate of 50%. As a result of this diagnosis, I stayed on the oncology floor for five days. At this time in my early life, Batman was my hero, so I had a Batman doll at my side at all times, through the various tests and even surgeries.

After the fifth day, before I was to begin chemotherapy, a young doctor entered my hospital room with tears in her eyes, and told us that I did not have Neuroblastoma, but rather something called Neurofibromatosis Type 1 (NF1). Soon after this diagnosis and more tests, I was introduced to Dr. David Gutmann, who over the past eighteen years, has always been there for us whenever we had any questions or concerns regarding NF1.

I ended up developing severe scoliosis as a result of the neurofibroma in my back. It was necessary to have instrumentation, or rods, put into my spine, which was followed by six months of wearing a hot, plastic brace. The upside to that, was that my brace was decorated with kitties, which was very important to a three-year-old girl. That is what we did—making the most of each situation. Each new challenge always looked like a new adventure.

After all of that, I had one more challenge. More surgery faced me in the fall of my sixth grade year. The curvature of my spine had become more severe, so I went through six weeks of traction. I was in the good hands of a world-renowned orthopedic surgeon at St. Louis Children's Hospital. My mother and I had a seven week stay in the hospital and to say the least, we made the most of it. To begin with, I had a halo put into place for traction, and it was decorated with the most beautiful rhinestones. My stay was during the month of October, so my hospital room was decorated for Halloween, which allowed us to go on many "journeys" throughout the hospital. The last night before my six-hour surgery just happened to be Halloween, and in the spirit of St. Louis Children's Hospital, there was trick-or-treating and fun Halloween festivities to take our minds off where we were heading. Oh, and I dressed up as a leopard with great face paint. The next day began with a six-hour surgery, now the fun was over, but it was worth it, because the traction had made me straighter and a few inches taller.

Fast forward a few years. I have always had big dreams, so when I was in high school, I really wanted to attend the University of Illinois to study graphic design. Throughout high school, I was in love with biology, music, and the arts. Those were the classes that I exceled in, but I had always had problems with mathematics (I had found out later that could be caused by NF1), which sometimes did make high school a little difficult for me. I was always worried that I wasn't good enough to get into so a prestigious school, but through hard work and dedication, I made it, and entered The University of Illinois as a freshman in the fall of 2014.

The University of Illinois has provided me with some of the best times of my life. I am taking design classes to prepare me for my future career, and have joined various clubs and a sorority on campus. In addition, I cheer for my school in sporting events until my voice gives out. I can't begin to count the number of amazing people that I have met and I am continuing to meet.

Halfway through my college career, I became more curious about NF1 and

what it could have in store for me. I remember one night after I researched it for hours, I learned so many things about the condition I have had my entire life. Why or how I would do things and why I looked the way I did, and also why I had gone through so many of those tribulations as a kid.

NF1 has made me a very strong person, and continually makes me stronger every day. I will never let it stop me from doing the things that I love. During my junior year, I decided to combine my interest in graphic design with a deep passion for medicine. I'm not sure if that stemmed from being in and out of the hospital as a kid or from reading countless National Geographic magazines. After researching potential career options in medicine and graphic design, I stumbled upon The Association of Medical Illustrators website. These are the people who design all of those colorful pictures in your biology or anatomy book. This is exactly what I want to do with my life.

In the summer of 2017, I was awarded an internship as a graphic designer at the Washington University Neurofibromatosis Center, where I have been creating medical illustrations. I am so appreciative for this opportunity. A big thank you to Dr. Gutmann and his staff. This internship has provided me with an amazing opportunity to have a taste of what my dream job would look like.

Please check out Alexandra's wonderful illustrations as they are posted on the Gutmann Laboratory website this fall (gutmannlab.wustl.edu).

Written by Alexandra Schroeder

PROVIDING EXCEPTIONAL PATIENT CARE

PATIENT CARE PROGRAM
The care of children and adults with NF requires a dedicated team of medical professionals from nearly all clinical disciplines. We are fortunate to work with a large number of talented colleagues at St. Louis Children's Hospital and Barnes-Jewish Hospital. These physicians, nurses, and therapists work together to provide the most integrated and up-to-date care for our patients.

CLINICAL RESEARCH INTEGRATION
In addition to offering these cutting-edge medical treatments, Dr. Gutmann and his colleagues are members of the Department of Defense NF Clinical Trials Consortium. This consortium includes thirteen large NF Centers worldwide that work together to rapidly evaluate promising new therapies for children and adults with NF1 and NF2. Treatments that prove successful in these clinical trials will become the therapies of tomorrow.

Uniquely, the Washington University NF Center seamlessly integrates research into each clinic visit, so that we can discover new ways to manage the medical problems that arise in people with NF. During clinic, multiple assessment tools are employed to identify those children at greatest risk for brain tumors, learning problems, autism, and developmental delays.

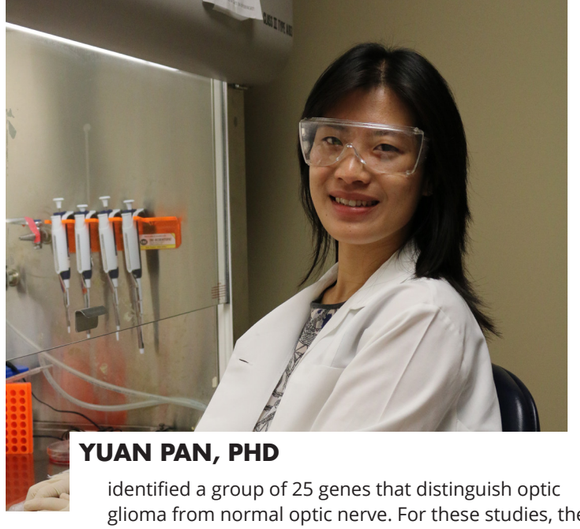
COMPLEMENTARY CARE & RESOURCES
Finally, we recognize the need to provide services that complement standard medical therapies. To meet this challenge, our team has established a series of free complementary care programs that include Beat NF, Club NF, and Teen NF. In addition, the recently-redesigned Washington University NF Center website houses other unique resources, such as App recommendations and a series of informative educational brochures.

Collectively, we strive to provide the best possible care for individuals with NF, both today and tomorrow.

NF Center Clinical Team at St. Louis Children's Hospital:
Top Row, left to right: Clinical Research Assistant: Courtney L. Monroe, and Physician: David H. Gutmann, MD, PhD.
Bottom Row, left to right: NF Center Coordinator: Jennifer N. Traber, CRC, Physician: Stephanie M. Morris, MD, Clinical Nurse Coordinator: Erika A. Ramirez, RN, BSN and Physical Therapist: Courtney M. Dunn, PT, DPT.

CORINA ANASTASAKI, PHD

recently found mutations in a gene responsible for the development of neurofibromas in some individuals without NF1. Using advanced sequencing methods, she discovered mutations in a gene, called *KIR2DL5,* previously implicated in immune system function, leading to loss of *KIR2DL5* expression. To demonstrate that *KIR2DL5* was the likely reason for the formation of sporadic neurofibromas, she expressed the mutated *KIR2DL5* gene in normal human Schwann cells. Dr. Anastasaki found that mutant *KIR2DL5* expression or *KIR2DL5* loss increased the growth of Schwann cells, and controlled Schwann cell growth in a manner similar to the *NF1* protein, suggesting that treatments that work for NF1-neurofibromas might also be effective for their sporadic counterparts.



YUAN PAN, PHD

identified a group of 25 genes that distinguish optic glioma from normal optic nerve. For these studies, they employed several different mouse models of *Nf1* optic glioma, and showed that this core set of genes was also found in human tumors. They were specifically looking for treatments that would result in reduced expression of these tumor-related genes, making the tumors more closely resemble the normal optic nerve. While all treatments caused the mouse optic gliomas to shrink, one therapy caused normalization of the 25-core signature. The treatment with the most robust effect used a drug that impairs the function of immune system-like cells in the brain, called microglia.

A YEAR OF GROUNDBREAKING RESEARCH

During 2017, researchers in the Washington University NF Center made many groundbreaking discoveries. Additionally , we continue to expand the resources required to make these advances, including the NF1 Genome Project (>520 patient DNA samples), NF1 Clinical Research Database (>730 patients enrolled), and the NF1 Brain Trust (>15 patient stem cell lines). These critical resources only exist because of the enthusiastic involvement of our families.

ANGELA HIRBE, MD, PHD

demonstrated that treating cancer patients with ifosfamide and epirubicin chemotherapy before surgery resulted in 60% of patients exhibiting a response to this combination therapy. These exciting data show that MPNSTs can shrink in response to chemotherapy. Dr. Hirbe and her team are planning prospective studies to determine whether this treatment approach should become the standard of care for people with MPNST.

ANNE SOLGA, PHD

and her colleagues report that optic gliomas develop from both neural stem cells and progenitor cells. Using novel genetically-engineered mouse strains, she found that loss of *Nf1* expression in neural stem cells leads to optic glioma formation by 3 months of age. In striking contrast, *Nf1* loss in progenitor cells, called pre-oligodendrocyte precursor cells (pre-OPCs), causes optic gliomas to form nearly 3 months later (at 6 months of age). These findings demonstrate that pre-OPCs do not arise from neural stem cells, indicating two separate paths to tumor formation exist.

JOSEPH DOUGHERTY, PHD

Dr. Susan E. Maloney, a scientist in the laboratory of Dr. Joseph D. Dougherty, examined the high-frequency sounds used by very young mouse pups to communicate with their mothers. Working with Drs. Corina Anastasaki and David Gutmann, she demonstrated that *Nf1* mutant mice had abnormalities in the frequency and pitch of their ultrasonic vocalizations. In addition, she found that the levels of a brain neurotransmitter, called serotonin, were increased in these mice.

JOSEPH TOONEN, PHD

FEMALE HORMONES INCREASE RISK OF VISION LOSS IN NF1

Girls with a rare genetic disorder caused by mutations in a gene known as *NF1* are much more likely to lose their vision than boys with mutations in the same gene. And now, researchers at Washington University School of Medicine in St. Louis believe they know why: Female sex hormones activate immune cells that damage the nerves necessary for vision.

The study was carried out in mice to mimic a common brain tumor arising in a genetic condition called neurofibromatosis type 1 (NF1). The findings, available online in The *Journal of Experimental Medicine,* suggest that blocking female sex hormones or suppressing the activation of specific immune cells in the brain could save the eyesight of children with NF1-associated brain tumors.

Nearly 20 percent of children with NF1 develop brain tumors that involve the optic pathway, affecting the nerves that carry vision-related signals from the eye to the brain. In some children, these tumors cause vision loss; however, it is not currently possible to predict who will experience vision decline and who will not.

Two years ago, Gutmann and colleagues were the first to report that girls with NF1 were five times more likely to lose their sight than boys, even though there were no clear differences in the size of the tumors between boys and girls.

To discover why girls are more likely to experience vision decline from their tumors, Gutmann, postdoctoral researcher Joseph A. Toonen, PhD, and colleagues studied mice with *Nf1* gene mutations specifically engineered to develop tumors on the optic pathway. Both male and female mice developed tumors that were identical in size and growth rates; however, only the female mice exhibited significant nerve damage and vision loss.

The researchers found that the tumors contain a type of immune cell called microglia. Strikingly, female mice had three times more microglia within these tumors than male mice. When activated, microglia release a range of toxic compounds that can cause collateral damage to nearby nerve cells. When they are activated, they release those compounds and sometimes cause collateral damage to nearby cells. They also found that the microglia within the optic tumors from female mice were activated, and the neurons near the tumors were damaged.

To test whether sex hormones could account for these differences, Dr. Toonen removed the ovaries from female mice and the testes from male mice. The number of damaged and dying cells in the retina – a light-sensitive layer of nervous tissue in the eye – did not change in the castrated males. But in the females without ovaries, fewer cells in the retina died and the number of activated microglia within the tumors was also decreased. These findings suggest that female sex hormones may cause microglial activation and subsequent neuronal damage.

When researchers used a drug to block the action of the female sex hormone in female mice carrying the *Nf1* mutation, they saw a drop in the number of activated microglia and a decrease in retinal damage and nerve cell death. Moreover, their team identified the specific nerve-damaging toxins produced by these activated microglia. Future therapies to attenuate vision loss in children with NF1-optic tumors might target these compounds.

Gutmann stressed that boys with NF1 also experience vision loss, just not as frequently as girls, and that male *Nf1* mice harbor some activated microglia within their tumors. He believes that the process of microglial activation and ensuing neuronal damage is the same in males and females, but that the presence of female sex hormones increases the microglial activation, leading to greater optic nerve damage and vision loss.

This article, written by Tamara Bhandari, originally appeared in the Washington University School of Medicine News Hub on December 13, 2016. Read more of about this article at https://medicine.wustl.edu/news/female-hormones-increase-risk-vision-loss-rare-genetic-disease/

JASIA MAHDI, MD

studied 133 children with NF1-associated brainstem gliomas and found that they tend to be older than those who have optic pathway gliomas, and most had no clinical symptoms as a result of their tumor. However, those who required treatment for their brainstem gliomas tended to have particular features on brain magnetic resonance imaging (MRI).

SUPPORT BEYOND THE CLINIC

Because children with NF1 can experience such a wide variety of physical, social and scholastic challenges, we have partnered with St. Louis Children's Hospital to establish programs that support general development while also empowering families to manage the types of medical, behavioral, and school problems common in this condition.

Targeting toddlers with NF1, Beat NF is a jazz music motor therapy program employs a small group approach to address the social, motor and behavioral delays specific to each child. Capitalizing on the collaborative, interactive, and improvisational spirit of jazz, each session is creatively designed to strengthen parent/child relationships and to foster positive peer interactions through interactive and cooperative motor play.

Club NF is our program for children with NF1 (K - 8) and their families. During these free therapy events, St. Louis Children's Hospital therapists work directly with each child to improve gross motor, fine motor, attention and social skills by engaging in fun activities like swimming, bowling and ice skating.

Teen NF is for teenagers with NF1 (ages 13 - 18) who struggle with fostering positive interpersonal relationships at home, at school and in the community. Focusing on common challenging situations that teens encounter, the goal of this program is to further social and conversational skills, encourage appropriate selection of friends, learn to read social cues and enter/exit conversations with peers.

In addition to these complementary care programs, we offer a robust website featuring a wealth of information about NF, including research updates, patient stories, and therapy blogs.

Thanks to generous support from the St. Louis Children's Hospital Foundation, Jazz St. Louis and the Saigh Foundation, these programs and resources are offered at no cost to our patients and their families.

CLUB NF: PLAY-BASED MOTOR THERAPY

>> Children participated in a painting and pottery event as part of the 2017 Club NF program.

BEAT NF: JAZZ MUSIC MOTOR THERAPY

> "WE NOTICED THAT KIDS WITH NF1 REQUIRE A MULTIDISCIPLINARY APPROACH, AND WE NEEDED TO BRING A NUMBER OF DIFFERENT IDEAS AND APPROACHES TO BEAR...THE BEAT ESTABLISHED IN JAZZ PROVIDES A FRAMEWORK FOR US TO BEGIN TO ADDRESS MOVEMENT, TIMING AND ATTENTION, THINGS THAT ARE REALLY PROBLEMATIC FOR THESE YOUNG KIDS."
>
> **- DR. DAVID H. GUTMANN**

>> Children participating at a Spring 2017 Beat NF event.

The sight of a group of children dancing happily to live music never gets old. And when those kids have been diagnosed with a genetic disorder called neurofibromatosis type 1 (NF1), and exposure to jazz has proven to have a positive factor in their therapy, the joy factor skyrockets. NF1, which can cause a litany of problems, affects one in 2,500 to 3,000 people of all ages—it's more common than muscular dystrophy. In young children, it can lead to numerous medical, motor and learning issues, as well as problems with socialization. Traditional therapies can help, but for many kids, they're not enough.

That's where Dr. David Gutmann comes in. A professor of neurology and director of the Washington University Neurofibromatosis (NF) Center in St. Louis, Mo., Dr. Gutmann and his team, in tandem with St. Louis Children's Hospital and Jazz St. Louis, two years ago created Beat NF, a therapy program that uses live jazz to treat toddlers with NF1, for which there is no known cure as yet.

"We noticed that kids that have NF1 require a multidisciplinary approach," he says, "and we needed to bring a number of different ideas and approaches to bear. The reason that we decided to use jazz is that the beat established in jazz provides a framework for us to begin to address movement and timing and attention, things that are really problematic for these young kids. The live interaction helps them make connections. It provides visual cues and a more interactive experience."

Why jazz? "Jazz and medicine share a bunch of common principles," Dr. Gutmann says. "One is improvisation and the other is collaboration. What we do all the time with our kids, particularly our young kids, is try to solve medical problems with information and tools that are immediately at hand, as you try to do when you're onstage improvising. We don't always have all the information. We don't always have the most advanced tools at any one time. We have what we have and we apply that to the situations that we're dealing with."

The toddlers, of course, do not know they are hearing jazz played by area pro musicians. For them it's just fun to respond to music, which is always performed live, never in recorded form. But for many of the children, it's their first exposure to live music of any kind, and thus the therapeutic process also becomes a teaching moment. They even get to join in. "They're mesmerized," says Dr. Gutmann.

"And the inclusion of [specialized educational] instruments, where you actually can't play a wrong note, allows them to become further engaged. It's the same sort of feedback that we get in a live jazz concert. You get to see how the music is made, how the fingering of the piano actually produces music, what's happening with the innards of the piano. The kids are fascinated by that."

Dr. Gutmann says that the program, which uses "kid-friendly jazz, nothing too extreme," has produced measurable results. "The more you activate parts of the brain, the more the kids become functional and new connections are made. It could be healing in that respect." Jazz, with its pronounced rhythms, seems to have a more noticeable effect than other genres of music. "We can vary the music in terms of speed and tailor it to just the right challenge for these kids," he says.

He hopes to expand the program within St. Louis at first, but eventually it could be used in other locations, and could possibly be applied to other conditions, including cerebral palsy and autism.

This article, written by Jeff Tamarkin, originally appeared in JazzTimes on March 24, 2016. View additional JazzTimes articles at jazztimes.com.

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As we celebrate our successes in 2017 and look forward to 2018, we want to thank everyone who has supported our mission. We are particularly indebted to our partners at the St. Louis Children's Hospital Foundation and Schnuck Markets Inc.
Washington University NF Center 2017 Annual Report created and designed by Jennifer N. Traber.