WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care through Groundbreaking Research

2018 ANNUAL REPORT

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Explore the array of NF Center complementary care programs that we offer for children with NF1, providing outstanding care beyond the clinic walls, and supporting patients from early childhood through adulthood.



Warm regards,

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

MESSAGE FROM THE DIRECTOR

In 2018, as we celebrate 25 years of Neurofibromatosis research and clinical care at Washington University, Neurofibromatosis (NF) Center research and clinical members have continued to expand investigative 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

We are delighted that Dr. Stephanie M. Morris joined the faculty as an Assistant Professor in the Division of Pediatric Neurology at the Washington University School of Medicine. Dr. Morris now serves as the co-Director of the NF Clinical Program at St. Louis Children's Hospital.

ADVANCING NF RESEARCH

It has been another year of progress in our understanding of neurofibromatosis, with numerous researchers in the Washington University NF Center publishing important new discoveries. These include advances in our understanding of the contribution of immune system cells to brain tumor growth, discovering a correlation between the location of the NF1 gene mutation and autism, identifying a new marker for malignant peripheral nerve sheath tumors, and studying autism behaviors in mice engineered with *Nf1* gene mutations. In addition, two of our Pediatric Neurology residents completed the largest study of MRI scans in children with NF1, demonstrating that brain tumors are more frequently detected than previously appreciated. Moreover, we have forged new collaborations with our colleagues in the Institute for Informatics and the Intellectual and **Developmental Disabilities Research**

Center at Washington University, as well as expanded our international efforts with Professor Helmut Kettenmann at the Max Delbrück Center in Berlin. We also continue to enlarge 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

September 5, 2018 marked the 4th biennial Washington University NF Center Symposium. Highlighted by two internationally-renown keynote speakers, Dr. Frank McCormick and Dr. Eric Legius, numerous NF Center investigators presented advances in NF research and clinical care.

In addition, Washington University NF Center neuroscientists participated in CAMP NEURO, a program designed to educate and expose high school students to medical research. Visitors to the NF Center learned how laboratory studies have advanced our understanding of the health problems affecting children and adults with NF1. Following the tour, one student from the group was inspired to become a neuroscientist and contacted us about working in one of our laboratories next summer.

THE ST. LOUIS MEN'S GROUP AGAINST CANCER

awarded DR. ANGELA HIRBE another one-year grant to continue her important work on malignant cancers in adults with NF1. Dr. Hirbe's laboratory is generating a collection of human malignant peripheral nerve sheath tumor (MPNST) cell lines suitable for preclinical drug testing.

THE NEUROFIBROMATOSIS THERAPEUTIC ACCELERATION PROGRAM (NTAP)

awarded DRS. CORINA ANASTASAKI and DAVID GUTMANN a three-year grant to study previously unexplored interactions between nerves and tumor cells relevant to skin neurofibroma growth. Based on exciting research findings made by Dr. Anastasaki, this grant aims to determine whether nerve cells increase neurofibroma tumor growth.

THE GILBERT VISION RESTORATION INITIATIVE (GVRI)

awarded DR. DAVID GUTMANN a one-year grant to identify new strategies to prevent vision loss from optic gliomas in children with NF1. This initiative involves multiple laboratories throughout the country, whose collective expertise is being collaboratively leveraged to discover new treatments to restore vision in children with NF1 optic gliomas.

CHILDREN'S TUMOR FOUNDATION YOUNG INVESTIGATOR AWARD

MICHELLE WEGSCHEID, a combined MD-PhD trainee in the laboratory of Dr. David H. Gutmann, was recently awarded a Children's Tumor Foundation Young Investigator Award to continue her exciting work on how mutations in the NF1 gene affect human brain development.

THE NATIONAL CANCER INSTITUTE

>> awarded **DR. CORINA ANASTASAKI** a five-year grant to continue her pioneering work on the use of human induced pluripotent stem cells to understand cancer development in children with NF1.

PATIENT SPOTLIGHT: LEXI'S JOURNEY WITH NF1



Forward Strides 4NF: Walking for awareness, Racing towards a cure! Forward Strides 4NF is a charity that I started in 2016 in honor of two very special people who both deal with Neurofibromatosis (NF) on a daily basis – my husband, Alex, and my daughter, Lexi.

Alex was diagnosed with Neurofibromatosis type 1 (NF1) when he was in the second grade. NF1 caused some learning difficulties that he was able to overcome with the help of some wonderful teachers at St. John's Lutheran School. After learning of his NF1, he had a team of incredible doctors in St. Louis who monitored his condition on an annual basis. Alex had some minor surgeries to remove some of the neurofibromas on his body. He feels very fortunate that he has been able to live a normal, happy life. He has a passion for the outdoors, and enjoys hunting and fishing.

Lexi was born with a plexiform tumor on the bottom of her left foot and a leg length discrepancy. As a result, Lexi currently wears leg braces and inserts in her shoes, as well as a lift on the bottom of her right shoe. Since the age of 5 months, she has had several MRI scans and routine eye exams. She has also had an ankle surgery, where they placed a plastic implant to help with the stability of her ankle, and two staples to slow down the growth of her ankle bone.

Lexi receives both physical and speech therapy each week to help with her low muscle tone and communication skills. She is a very strong, independent four-year-old who doesn't allow NF1 to limit her daily activities. She loves to swim, has participated in tumbling, and is currently taking dance lessons. Even with her braces and shoe lifts, she keeps up with the other children to the best of her ability.

NF1 is a worrisome genetic disorder because of the "unknown." No one individual is the same. You don't know what to expect. Alex has overcome minor hurdles with his NF1, but we still face hurdles with him. Education is key with any genetic disorder. Staying abreast of all the research and medical advancements going on in the NF world is very important. We are very thankful for the progress that Lexi has made overcoming some obstacles that she has faced with already. We could not have done this without Dr. Gutmann and his amazing team. Since Lexi was 10 months old, she has been seeing Dr. Gutmann annually for her exams. We have also been so fortunate to have one of the best physical therapists, Dr. Courtney Dunn, who is also a part of the NF Center team. Since she was 18 months old. Lexi has attended the Beat NF music motor therapy program offered through the Washington University NF Center.

Trying to reach out in the St. Louis city community to see who else is affected with NF1 is challenging. In 2015, I helped organize a Great Steps 4NF walk in conjunction with NF Midwest. After raising over \$16,000 for Great Steps, I decided that I wanted to help raise money that stayed here in the St. Louis community. In 2016, Forward Strides 4NF was formed. For the past 2 years, we have hosted a 2-mile family fun walk in Valley Park, MO. These events occur at the end of September each year, and 100% of our proceeds go to the Washington University NF Center.

Our walks have definitely been a huge success. We raised \$19,351.00 in 2016 and \$18,679.00 in 2017. We have had over 200 registered walkers both years, with over 30 volunteers. Entertainment at the event included an inflatable slide and bounce house, bubble bus, face painting, Minnie Mouse and a clown that handed out balloon animals. In addition, the participants were greeted by Fred Bird and Louie at the finish line. We also hold a raffle, which included over 120 amazing items; this proved to be a HUGE attraction that alone generated over \$4,300. Lastly, local restaurants donate beverages, snacks and food for all the participants after the walk is completed.

Trying to maintain a positive outlook given the diagnosis of NF1 is sometimes hard. There is a not a day that goes by when we don't think about the NF community. However, we don't let NF1 control our life, we try to run it ourselves. We keep up with our weekly therapy appointments, we are always learning more about NF1, and we stay up to date about new medical advancements. Importantly, we do our best to raise money to support the outstanding research at the Washington University NF Center. We are walking for awareness every day, and racing towards finding a cure in the future.

PROVIDING EXCEPTIONAL PATIENT CARE

NF CENTER WELCOMES NEW FACULTY MEMBER

We are delighted to announce that Dr. Stephanie M. Morris has joined the faculty as an Assistant Professor in the Division of Pediatric Neurology at the Washington University School of Medicine. Dr. Morris has been caring for children and young adults with NF for the past several years, and has recently been appointed to the position of co-Director of the NF Clinical Program at St. Louis Children's Hospital.

Dr. Morris received her pediatric neurology training at Washington University, where she served as the administrative chief resident. Following her residency, she was a clinical research fellow working with Dr. John Constantino (Chief, Child Psychiatry) and Dr. David H. Gutmann (Director, NF Center) to understand autism and developmental disabilities in children with NF1.



BRAIN TUMORS OCCUR OFTEN IN KIDS WITH COMMON GENETIC SYNDROME

The frequency of brain tumors has been underestimated in children with the common genetic syndrome Neurofibromatosis type 1 (NF1), according to a new study. This disorder is characterized by birthmarks on the skin and benign nerve tumors that develop in or on the skin. Brain tumors also are known to occur in children and adults with NF1.

Neurologists have estimated that only 15 to 20 percent of kids with NF1 develop brain tumors. Of these brain tumors, the vast majority are located within the optic nerve or the brainstem. However, a recent study of brain scans performed on children with NF1 at Washington University School of Medicine in St. Louis found that the frequency of brain tumors in this population was more than three times higher. These previously

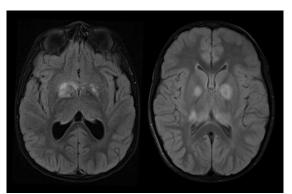
under-recognized brain tumors can cause neurologic problems that require treatment.

The findings, available online in the journal Neurology: Clinical Practice, suggest that brain tumors may be a more significant problem for children with NF1 than previously appreciated.

Brain MRI scans of children with NF1 characteristically show bright spots that are absent in the scans of unaffected children. Unlike tumors,

they are generally thought to disappear in teenage years. Since brain tumors can be confused with harmless bright spots, it has never been clear whether finding these abnormalities via MRI should be a cause for concern.

Robert C. McKinstry, MD, PhD, the William R. Orthwein Jr. and Laura Rand Orthwein Professor of Radiology and Pediatrics, and Manu Goyal, MD, an assistant professor of radiology, developed a set of criteria to distinguish tumors from other bright spots, using features such as the location and shape of the bright spot, the sharpness of its border and whether the brain tissue surrounding the bright spot appears displaced or compressed.



Brain MRI scans of children with NF1 often show bright spots, and it has been difficult for doctors to distinguish bright spots that indicate a tumor (left scan) from those that are probably harmless (right scan).

Using these criteria, co-first authors Jennifer Griffith, MD, PhD, and Stephanie Morris, MD, assistant professors of neurology and of pediatrics, and colleagues studied brain scans from children with NF1 performed at the School of Medicine from 2006 through 2016. They analyzed scans from 68 NF1 patients as well as 46 children without NF1 for comparison. Most of the children had undergone multiple scans, so the researchers examined a total of 190 brain scans from NF1 patients and 104 scans from children without NF1.

> All but four (94 percent) of the children with NF1 had bright spots, and none of the children without NF1 did. Further, in 57 percent of the children with bright spots, at least one of the spots was deemed likely to be a tumor.

It is difficult to prove that the researchers correctly distinguished tumors from less worrisome bright spots. Doing so would require extracting bits of the bright spots for

examination, which would not be practical. However, 10 of the children whose bright spots were classified as probable tumors underwent brain biopsies as part of their medical care, and all 10 were proven to be brain tumors. Furthermore, 28 percent of these probable tumors eventually required treatment, providing further evidence that they had been correctly classified. The remainder did not cause symptoms and did not require treatment.

Applying the new criteria to MRI scans will help physicians identify probable tumors, but that does not mean that all children with NF1 should be scanned regularly, the researchers cautioned.



CORINA ANASTASAKI, PHD

Corina Anastasaki, PhD, a senior Staff Scientist in the laboratory of David H. Gutmann, MD, PhD, was recently awarded one of the first Research Specialist (R50) grants from the National Cancer Institute (NCI).

The Research Specialist Award was specifically designed to encourage the development of stable research career opportunities for exceptional scientists who want to continue to pursue research within the context of an existing NCI-funded cancer research program.

Dr. Anastasaki first joined Dr. Gutmann's laboratory in 2012 to leverage human induced pluripotent stem cell (iPSC) technology as a platform to understand the role of Neurofibromatosis type 1 (NF1) gene mutations in NF1 brain disease pathogenesis. During her postdoctoral training, she was instrumental in establishing this invaluable resource at Washington University, which has resulted in a large number of novel insights. In addition, her pioneering efforts have culminated in numerous publications, as well as six federal and private foundation grants.

Human iPSCs are capable of forming nearly every cell type in the body. Dr. Anastasaki has used these cells to study how mutations in the *NF1* gene lead to differences in human NF1-associated clinical features, brain developmental defects, nerve cell dysfunction, and tumor development. Future studies aim to define how the *NF1* protein functions in human tissues, as well as to establish new human preclinical models of nerve sheath and brain tumors.

A YEAR OF GROUNDBREAKING RESEARCH

During 2018, 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 (~500 patient DNA samples), NF1 Clinical Research Database (~740 patients enrolled), and the NF1 Brain Trust (~20 patient stem cell lines). These critical resources only exist because of the enthusiastic involvement of our families.

ABBY HOLLANDER, MD

Children with Neurofibromatosis type 1 (NF1) are commonly shorter than typically developing children in the general population. While this short stature results from a change (mutation) in the NF1 gene, the reasons for this reduced height have not been identified.

In a new study, St. Louis Children's Hospital resident, Nick Zessis, MD, under the direction of Dr. Abby Hollander, Professor of Pediatrics and Clinical Director of the Division of Endocrinology and Diabetes, examined the growth rates in children with NF1 over time. Longitudinal height information was collected from 188 patients with NF1, revealing short stature in fewer than 10% of all children with NF1. Moreover, by tracking growth velocity, they showed that both boys and girls demonstrated subnormal height acquisition during puberty. This blunted pubertal growth could reflect abnormalities in growth hormones or the response of bones to circulating growth factors.

ANGELA HIRBE, MD, PHD

In a recent study, Dr. Angela Hirbe and her team analyzed β III-spectrin expression in a series samples from patients cared for in the Washington University NF Center and the Siteman Cancer Center Sarcoma Program. While strong β III-spectrin expression was detected in all high-grade MPNSTs, it was found in only half of the low-grade MPNSTs and in none of the benign tumors. These exciting results suggest that β III-spectrin may be a sensitive marker for MPNSTs, which may aid in the diagnosis of these tumors.

Ongoing work in the Hirbe laboratory is currently aimed at developing a clinic-grade monoclonal antibody, validating these findings using samples from other institutions, and correlating βIII-spectrin immunostaining with clinical outcome.



STEPHANIE MORRIS, MD

Although every person with Neurofibromatosis type 1 (NF1) is born with a mutation (change) in one of their two *NF1* genes, the problems arising in any one person can be quite different. In an attempt to better understand the relationship between the specific *NF1* gene mutation and autism, Dr. Stephanie Morris examined over 50 people with NF1.

Leveraging existing data generated in the Washington University NF Center, Dr. Morris, working with David H. Gutmann, MD, PhD, found that people with mutations within the first half of the *NF1* gene were less likely to have severe autism symptoms than people with mutations in the second half of the gene. This is the second study to demonstrate that the location of the mutation within the *NF1* gene may be an important predictor of specific medical problems.

While these findings are compelling, they are currently not specific enough to allow doctors to predict which child will (or will not) develop autism symptoms. Future studies are currently underway to identify additional factors that may improve our ability to identify those children at greatest risk for autism and other neurodevelopmental problems.

AMITA SEHGAL, PH.D.

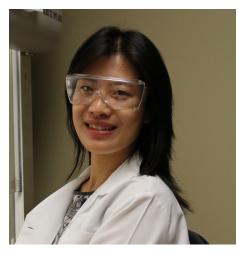
Investigators from the Perelman School of Medicine at the University of Pennsylvania, led by Dr. Amita Sehgal, have uncovered that the *NF1* gene controls the brain's perception of time of day signals.



Working in flies, her team previously found that the *Nf1* gene is important for establishing and maintaining time of day (circadian) rhythms. However, the circadian clock was normal in *Nf1* mutant flies, suggesting that the *Nf1* gene might be important for relaying the signals from the clock to other regions of the brain involved in sleep-wake cycling.

In their new study, they demonstrate that the *Nf1* gene in flies is critical for the function of multiple different cell types involved in rest/activity rhythms. Moreover, they worked with investigators in Dr. David H. Gutmann's laboratory to show that the *Nf1* gene also controls these daily rhythms in mouse brain cells.

These exciting findings suggest that the *Nf1* gene is a key regulator of daily rhythms in fly and mammalian cells relevant to the sleep disturbances common in children and adults with NF1.



YUAN PAN, PHD

Children with NF1 are prone to develop brain tumors, specifically gliomas affecting the optic nerve and brainstem. These tumors are typically slow growing, and usually cannot be surgically removed. For this reason, most treatments involve

the use of agents (chemotherapy) that slow the growth of the tumor cells. While these therapies have been effective in some children with NF1-associated gliomas, there remains a pressing need to develop alternative treatments. Previous studies from the laboratory of NF Center Director Dr. David H. Gutmann have shown that immune system cells, called microglia, are abundant in both human and mouse NF1-associated brain tumors, and that blocking their function in *Nf1* mouse models of optic glioma reduces tumor growth. However, it was not clear how these microglia become activated to support tumor formation and growth.

In a new study, led by postdoctoral fellows, Yuan Pan, PhD and Min Xiong, MD, PhD, they now show that microglia can be programmed to support tumor formation and growth by T cells. T cells are important immune system cells found in the blood, which recently have emerged as exciting new targets for cancer therapy.

Drs. Pan and Xiong discovered that T cells produce signals that act on microglia to allow them to secrete growth factors that facilitate tumor growth. The findings that T cells instruct microglia to support NF1 glioma growth suggests new therapies that block T cell function.

>> WASHINGTON UNIVERSITY EXPERTS PRESENT AT THE 2018 NF CENTER RESEARCH SYMPOSIUM

The Washington University NF Center hosted its fourth biennial NF Center Symposium on September 5, 2018 in the Eric P. Newman Education Center on the Medical School Campus. In addition to our two keynote speakers, Drs. Frank McCormick and Eric Legius, we were delighted to showcase research and clinical advances made by some of our faculty in the Washington University NF Center.

ERIC LEGIUS, MD, PHD is Professor of Human Genetics at the University of Leuven, Belgium. He and his colleagues have been leaders in characterizing NF1-like syndromes, and in identifying genotype-phenotype correlations important for precision medicine.

FRANK McCORMICK, PHD is Professor of the UCSF Helen Diller Family Comprehensive Cancer Center and holds the David A. Wood Chair of Tumor Biology and Cancer Research at UCSF. He and his team were one of the first to define the role of RAS in human disease, and to demonstrate that the *NF1* protein is a key regulator of RAS.

DAVID H. GUTMANN, MD, PHD is the Donald O. Schnuck Family Professor and Vice Chair for Research Affairs in the Department of Neurology at Washington University. He established and currently directs the Washington University NF Center. Dr. Gutmann is one of the world's leading experts on NF.

PHILIP PAYNE, PHD, FACMI is the founding director of the Institute for Informatics at Washington University, where he serves as the Robert J. Terry Professor. Dr. Payne is an internationally recognized leader in the field of clinical research informatics and translational bioinformatics.

JOHN CONSTANTINO, MD is

the Blanche F. Ittleson Professor of Psychiatry and Pediatrics and Director of the William Greenleaf Eliot Division of Child & Adolescent Psychiatry. In addition, he serves as the Director of the Intellectual and Developmental Disabilities Research Center at Washington University. Dr. Constantino is an international authority on autism.

ANGIE HIRBE, MD, PHD is an Assistant Professor in Medical Oncology at the Washington University School of Medicine. Dr. Hirbe directs a translational research laboratory focused on developing more effective therapies for malignant peripheral nerve sheath tumors (MPNSTs). As one of the recipients of the Francis S. Collins Neurofibromatosis Scholar Award, her clinical practice is focused on the care of adults with NF1-associated plexiform neurofibromas and MPNSTs.

ROBERT C. McKINSTRY, MD, PHD is the William R. Orthwein, Jr. and Laura Rand Orthwein Professor of Radiology and Chief of Pediatric Radiology at St. Louis Children's Hospital. Dr. McKinstry is an international expert on pediatric neuro-radiology and advanced applications of magnetic resonance imaging (MRI).

STEPHANIE M. MORRIS, MD is an Assistant Professor in Pediatric Neurology at the Washington University School of Medicine. She is the codirector of the Neurofibromatosis Clinical Program at St. Louis Children's Hospital. Dr. Morris is the leader of the International NF Autism Collaborative Team (INFACT) and an authority on NF1 developmental disabilities.

COURTNEY DUNN, PT/DPT graduated from the University of Missouri-Columbia with a Bachelor's degree in physical therapy and then completed her Doctorate of Physical Therapy with an emphasis in pediatrics. Dr. Dunn provides physical therapy services and resources for children with NF1, including outpatient therapy, schoolbased services and community-based services. Courtney has researched motor delays in children with NF1, and based on her findings, established Club NF, a play-based therapy program for children with NF1. In addition, with our partners at Jazz St. Louis, she has designed a jazz music motor therapy program for toddlers with NF1.

NICOLE WECKHERLIN, OT/OTRL

received her BS in Occupational Therapy from St. Louis University. She is a licensed and registered occupational therapist currently working in the Cerebral Palsy and Neurofibromatosis Clinical Programs at St. Louis Children's Hospital. Based on her success using iPAD Apps to address delays in children with NF1, Nicole has launched an Apps Therapy Program at St. Louis Children's Hospital.



Dr. Eric Legius receiving a Keynote Speaker award from Dr. David H. Gutmann



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

In keeping with its mission to lead the St. Louis community in advancing jazz as a uniquely American art form, Jazz St. Louis is extremely proud of its partnership with the Washington University NF Center. Together, they have developed a novel complementary care for children with Neurofibromatosis type 1 (NF1). Integrating elements of



motor therapy with a "Kinder Music" class approach, Beat NF provides a vehicle for toddlers with NF1 to learn and practice motor and socialization skills, while being exposed to musical instruments, jazz music, and famous jazz musicians.

The Beat NF curriculum combines a weekly motor skill program with ageappropriate teaching about a specific jazz musician and instrument. The children learn about the musician, the instrument they played, and a song that they made famous. The song is then played by the musicians, which the facilitator uses to reinforce the chosen motor skill. Each week, a new song and motor skill are added, while previous songs and skills are reviewed. This approach establishes a framework for the toddlers to advance their skills throughout the five-week program. The final session is a review of the previous weeks with a full, five-piece jazz band, composed of local musicians from those prior sessions.

The curriculum for Beat NF has undergone several transformations, as Jazz St. Louis education staff and NF Center therapists have endeavored to refine this special collaboration. Using a repertoire of simple original songs and classroom musical instruments, the Beat NF team has worked together to pair jazz compositions with the specific motor skills to be emphasized.

Finally, the Beat NF curriculum includes take-home materials to help parents reinforce motor skills with their children at home. These include special recordings of the songs used in the program, arranged by Jazz St. Louis staff and recorded at Jazz St. Louis.

This article written by Andy Ament, Education Manager at Jazz St. Louis.







nfcenter.wustl.edu

As we celebrate our successes in 2018 and look forward to 2019, 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 2018 Annual Report created and designed by Jennifer N. Traber.