

WASHINGTON UNIVERSITY NEUROFIBROMATOSIS (NF) CENTER

Exceptional Care *through* Groundbreaking Research

2019 ANNUAL REPORT

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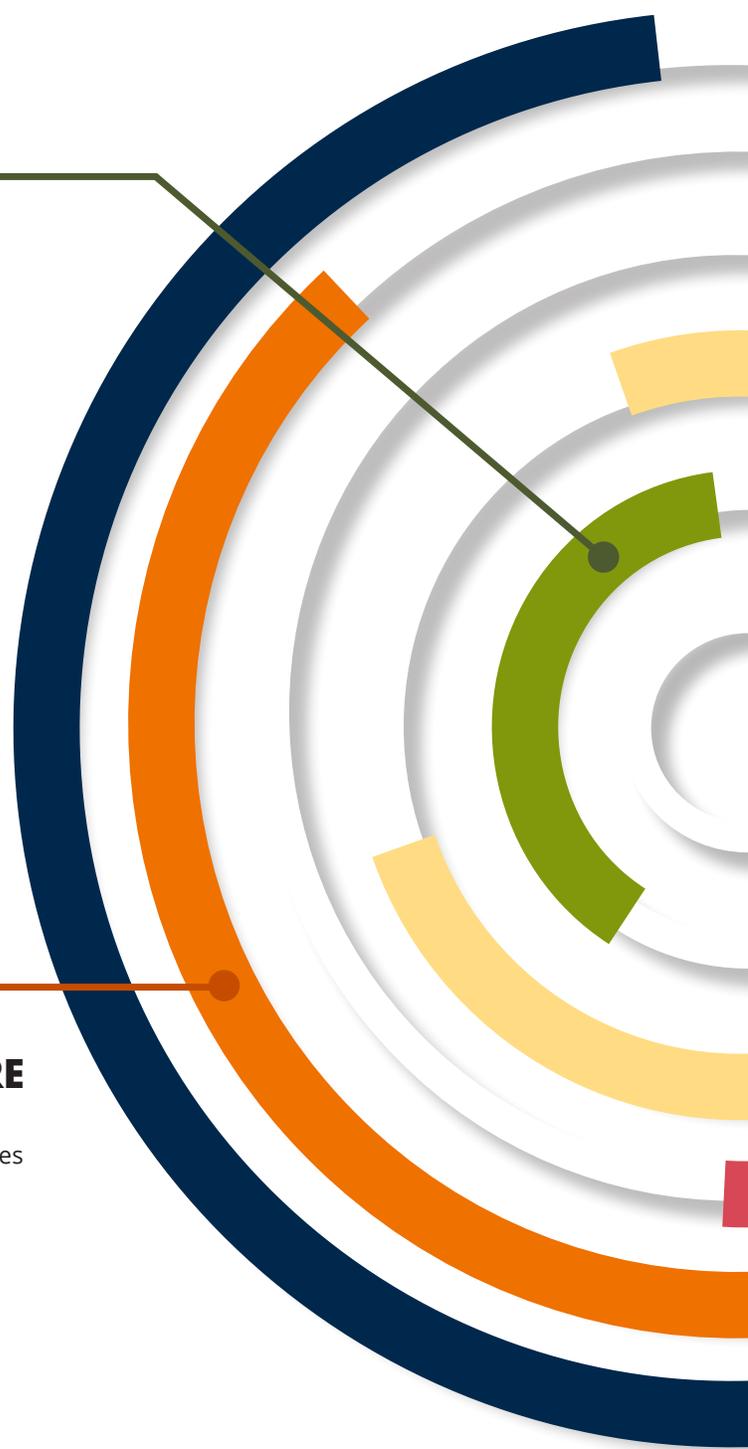
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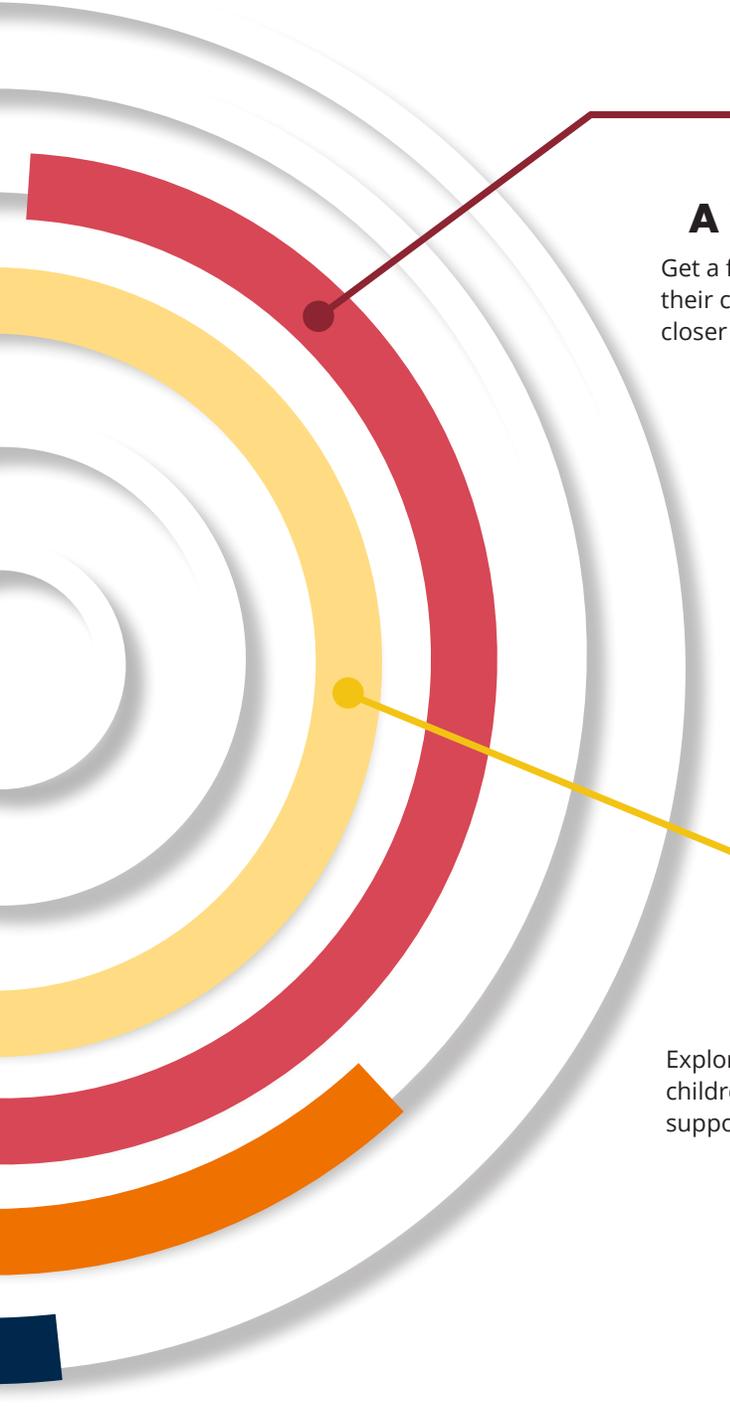
Groundbreaking research requires funding from numerous sources, including the federal government, private foundations, and individual donors. We appreciate the generous support we have received from each of these important sources over the past year.

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MESSAGE FROM THE DIRECTOR

It has been another exciting and productive year of advances in research and clinical care at the Washington University Neurofibromatosis (NF) Center. Our clinical and laboratory investigators continue to expand their research initiatives aimed at developing personalized medical approaches for people affected with NF. In addition, we are so grateful for the ongoing partnerships with our families that make these high-risk, high-payoff ventures possible.

INTRODUCING NEW MEMBERS

We are delighted to share the news that Mrs. Erika Ramirez was promoted to full-time Clinical Nurse Coordinator of the NF Clinical Program at St. Louis Children's Hospital. Erika previously worked with Drs. Stephanie Morris and David Gutmann as a part-time nurse for our families, but has recently expanded her role to facilitate specialty scheduling and coordinate patient care planning, thus serving as a critical liaison for our families.

In addition, Dr. Nicole M. Brossier was promoted to Instructor in the Division of Pediatric Hematology/Oncology. While she is currently completing her postdoctoral fellowship training in my laboratory, she will be taking a leadership role in the management of children with NF-related brain tumors.

Lastly, we have recently welcomed Dr. Amy E. Armstrong to our management team. Dr. Armstrong completed her training in Pediatric and Pediatric Hematology/Oncology at Lurie Children's Hospital (Northwestern University) with Dr. Robert Listernick and Riley Children's Hospital (Indiana University) with Dr. Wade Clapp. She brings her expertise in NF1 plexiform neurofibroma clinical trials to St. Louis Children's Hospital.

ADVANCING NF RESEARCH

It has been another year of progress in our understanding of neurofibromatosis, with scientists and clinicians in the Washington University NF Center publishing important new discoveries. These include studies defining how immune system cells control optic glioma growth in mice,

developing a mouse model for sleep disturbances in NF1, identifying new genetic markers for brain immune system cells, and characterizing optic gliomas in a pig model of NF1. In addition, one of our Pediatric Neurology residents (Dr. Cristina Gaudioso) completed a large multi-center study of NF2 in children younger than ten years of age. Moreover, we have expanded ongoing collaborations with our colleagues in the Institute for Informatics (Drs. Philip Payne, Randi Foraker, and Aditi Gupta) and the Intellectual Developmental Disabilities Research Center at Washington University (Drs. John Constantino, Susan Maloney, and Kristen Kroll), as well as fortified our international research studies with Professor Helmut Kettenmann at the Max Delbrück Center in Berlin. We also continue to recruit families to participate in clinical research (NF1 Genome Project, NF1 Stem Cell Repository, and Longitudinal NF1 Autism Study), which aim to improve our ability to predict the risk of developing specific medical problems in people with NF1 (precision medicine).

RAISING NF AWARENESS

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.



Sincerely,

A handwritten signature in black ink that reads "David H. Gutmann". The signature is written in a cursive style and is followed by a long horizontal line that extends to the right.

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

HYUNDAI HOPE ON WHEELS

- awarded **DR. NICOLE BROSSIER** a career development grant for her studies on the cells of origin for pediatric brain cancers. This award will allow Dr. Brossier to understand what risk factors underlie glioma development in children with NF1 and related conditions.

THE ST. LOUIS MEN'S GROUP AGAINST CANCER

- awarded **DR. ANGELA HIRBE** a third 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 tumors (MPNSTs) suitable for preclinical drug testing.

ALEX'S LEMONADE STAND FOUNDATION

- awarded **DR. NICOLE BROSSIER** a career development grant for her studies on the cells of origin for pediatric brain cancers. This award will allow Dr. Brossier to identify the risk factors that dictate brain tumor formation in children with NF1.

THE GIORGIO FOUNDATION

- awarded **DRS. CORINA ANASTASAKI** and **DAVID GUTMANN** a two-year collaborative grant with Dr. Lu Le at the University of Texas, Southwestern to develop and characterize new models of human NF1-associated skin (dermal) neurofibromas.

THE GILBERT FAMILY FOUNDATION

- awarded **DR. DAVID GUTMANN** a three-year grant, as part of the Vision Restoration Initiative, to accelerate the development of innovative therapies for vision loss from NF1 optic gliomas.

PATIENT SPOTLIGHT



I'm often asked what brought us to St. Louis, since neither my husband nor I have family in the area. A promising job offer in 2000 prompted us to move from North Dakota, but it wasn't until years later that I would come to realize our move was "meant to be" for an entirely different reason.

Our son, Phillip, was born in 2003. At his six month exam, our pediatrician noticed

several birth marks on his torso, which led to a referral to Dr. David H. Gutmann at St. Louis Children's Hospital. We would learn that these birthmarks were actually cafe'-au-lait spots and one indicator of Neurofibromatosis Type 1 (NF1). Phillip was five years-old when a second indicator, Lisch nodules on the iris of his eyes, was found, and the diagnosis of NF1 was confirmed. People with NF1 are at risk for developing tumors throughout their bodies. Naturally, we were scared and confused about what this meant for our child's future.

Dr. Gutmann was wonderful, and he patiently answered our questions, as well as assured us that Phillip was capable of leading a normal, productive life. He introduced us to his team of specialists at St. Louis Children's Hospital and the powerful network of support they provide: physical therapy, occupational therapy, speech pathology, pediatric neuropsychology, orthopedic surgery, and ophthalmology – a group of talented and caring professionals that we've utilized over the years.

Another support that has been beneficial to our family is Club NF, offered through the Washington University NF Center. Phillip was six years old when we first attended a Club NF activity, and he loved it immediately. As he's grown older, these free activities have allowed him to learn and practice social and motor skills by swimming, ice-skating, cooking, playing chess, dancing, painting, wall-climbing, animal encounters at the zoo, learning about dinosaur digs at the Science Center, and even yoga surfing! While the kids play and interact, parents have the opportunity to hear from various speakers and enjoy making friendships, as well. Questions from parents may vary from educational (IEP, 504, technology), emotional, social, and behavioral, and the Washington University NF Center staff does a fantastic job finding the right speakers to address these concerns.

Fast forward to 2019... Phillip is now 15 and a typical teenager with his driver's permit, cell phone, and love of gaming. A sophomore in high school, he's an honor student, enjoys golf and weight conditioning, plays piano, and works to perfect his German. NF1 does not limit him. He now participates in Teen NF, which provides a friendship group that understands and accepts him because they are going through the same journey. Knowing that there are other teens with NF1 has helped him be comfortable with his diagnosis. He now enjoys volunteering at Club NF and taking on a mentor role for the younger kids.

I do believe our move to St. Louis was "meant to be" and we were guided here to have access to St. Louis Children's Hospital and Dr. Gutmann and his team of specialists at the NF Clinic. We will be forever thankful for the dedication and compassion they show for their NF patients and continued research.

– Written by Suzy Effertz (Mom)

NF CENTER WELCOMES A NEW FACULTY MEMBER: AMY ARMSTRONG

The NF Clinical Care Program at St. Louis Children's Hospital welcomes Dr. Amy E. Armstrong to the Division of Pediatric Hematology and Oncology, where she will spearhead our NF1 clinical trials for plexiform neurofibromas. Dr. Armstrong received her medical degree from Virginia Commonwealth University. Following internship and residency in Pediatrics, she completed a fellowship in Pediatric Hematology and Oncology at the Ann & Robert H. Lurie Children's Hospital of Chicago. In 2018, she was recruited to Riley Children's Hospital as an Instructor in the Division of Pediatric Hematology/Oncology, where she began her work on NF1-related tumors. Dr. Armstrong brings expertise in developmental therapeutics and NF1 clinical trials.



PROVIDING EXCEPTIONAL PATIENT CARE

GUTMANN HONORED FOR 25 YEARS AT WASHINGTON UNIVERSITY

David H. Gutmann, MD, PhD, FAAN, Donald O. Schnuck Family Professor and Vice Chair for Research Affairs for Neurology, was recently honored for twenty five years of service as faculty at Washington University. Upon his arrival in St. Louis in late 1993, he established the Neurofibromatosis (NF) Clinical Program at St. Louis Children's Hospital to care for children and adults with neurofibromatosis, as well as a basic research laboratory focused on using NF as a genetic model system to better understand normal brain and brain tumor development relevant to improving treatments for people affected with NF. In 2004, Dr. Gutmann worked with Washington University to create the NF Center, a collaboration between clinicians and laboratory scientists focused on accelerating the pace of scientific discovery and its application to the care of individuals with NF.

Dr. Gutmann is internationally recognized for his clinical and research contributions, including the Children's Tumor Foundation Frederick von Recklinghausen Award and the Washington University School of Medicine Distinguished Faculty Research Award. In 2017, he was awarded an Alexander von Humboldt Professorship, Germany's highest academic award for researchers outside the country, as well as named an Einstein Visiting Fellow by the Berlin Institute of Health.



STEPHANIE MORRIS, MD

Most children with Neurofibromatosis type 1 (NF1) have difficulties with learning and/or behavior; however, these problems vary significantly between individuals. While deficits may affect all areas of learning and behavior, other impairments only affect one area.

Adaptive functioning measures an individual's ability to achieve age-appropriate maturity, judgment and reasoning, social sensibility, and personal independence. Adaptive functioning affects all areas of early childhood development and is closely linked to long-term outcomes in individuals with intellectual disability, autism spectrum disorder, and attention-deficit/hyperactivity disorder (ADHD).

In a new report published in *Developmental Medicine and Child Neurology*, Dr. Stephanie Morris, Assistant Professor of Neurology, and her colleagues showed that deficits in adaptive functioning are common in children with NF1. In her study, nearly half of

children with NF1 exhibited adaptive behaviors in the borderline or impaired range. Moreover, they discovered three distinct subgroups of children with NF1 – those with poor adaptive and cognitive functioning, those with normal adaptive and cognitive functioning, and those with a relative dissociation in adaptive and cognitive functioning (poor adaptive functioning, and normal cognitive ability). They further demonstrated that impairments in adaptive functioning were highly correlated with deficits in executive functioning, externalizing behaviors, and attention.

These findings strongly support the use of formal neuropsychological testing, including assessment of adaptive functioning, for any child with NF1 who displays difficulty at home, in school, or in personal relationships, despite relatively normal academic achievement.



CORINA ANASTASAKI, PHD

Researchers at Washington University School of Medicine in St. Louis, studied mice genetically modified to mimic the genetic disease Neurofibromatosis type 1 (NF1), which is associated with sleep problems. They found that the animals, like some people with NF1, slept in short, irregular spurts. Studying these mice could help identify the molecular and cellular mechanisms

that go awry and cause fragmented sleep patterns in people with and without the disease, the researchers said.

As many as half of people with NF1 – a condition that causes benign tumors in the brain and on nerves throughout the body – have difficulty falling or staying asleep. Learning disabilities and attention problems also are common in children with NF1, and both may be exacerbated by poor sleep. But doctors don't know why some children with NF1 develop sleep problems and others don't, nor can they do much to help them sleep better.

Co-first author Corina Anastasaki, PhD, an Instructor in neurology, bred mice with a mutation in their *Nf1* gene similar to what is seen in people with NF1. Then, co-first author Nicholas Rensing and Michael J. Wong, MD, PhD, the Allen P. and Josephine B. Green Professor of Pediatric Neurology, fitted onto the mice miniature versions of the caps people wear for sleep studies, enabling them to measure brain waves and identify sleep patterns.

Mice normally sleep during the day and, like people, cycle several times from deep, dreamless sleep to REM sleep – or dreaming – and back again. Mice with an *Nf1* mutation, however, tended to wake up soon after they entered deep sleep. The result was a fragmented, and probably not restful, day of sleep.

“Throughout the whole night and day, they fell asleep and woke up when they shouldn't have,” Anastasaki said. “They fell into deep sleep, but they didn't stay there.”

Although the mice were engineered to mimic human NF1, they could yield insights about the biological underpinnings of sleep in general, which could help people with sleep problems unrelated to NF1. About a third of American adults report some degree of insomnia, and 15 percent have chronic insomnia that lasts three months or more.

- Written by Tamara Bhandari - Washington University News Hub

A YEAR OF GROUNDBREAKING RESEARCH

During 2019, 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 (~550 patient DNA samples), NF1 Clinical Research Database (~800 patients enrolled), and the NF1 Brain Trust (~28 patient stem cell lines). These critical resources only exist because of the enthusiastic involvement of our families.



CRISTINA GAUDIOSO, MD

Young adults with Neurofibromatosis type 2 (NF2) typically come to medical attention when they develop hearing and balance problems, leading to the discovery of bilateral vestibular schwannomas (BVS). However, school-age children frequently do not present with BVS.

In order to identify the earliest signs of NF2 in these young

children, Cristina Gaudioso, MD, a pediatric neurology resident at Washington University, spearheaded a four institution study involving NF2 experts at Children's Hospital of Philadelphia, Stanford University, Lurie Children's Hospital, and St. Louis Children's Hospital.

INTERNATIONAL NF1 COLLABORATION

Monocytes/macrophages are immune system-like cells important for normal brain function. In the healthy brain, resident microglia are the major macrophage cell population; however, in brain tumors, peripheral monocytes/macrophages can infiltrate the brain and participate in brain tumor growth. Distinguishing these two populations is often challenging, owing to a paucity of universally accepted and reliable markers.

To identify discriminatory marker sets for microglia and peripheral monocytes/macrophages, Verena Haage, a graduate student in the laboratory of Dr. Helmut Kettenmann, employed a large meta-analytic approach. This project was performed in collaboration with Dr. David H. Gutmann, Director of the Washington University NF Center. Using this approach, they discovered a robust set of microglia and peripheral monocyte/macrophage expression markers to discriminate these monocyte populations in both health and disease.

XIAOFAN GUO, MD

Tumors arise when cells shake off their restraints and start to multiply out of control. But how fast a tumor grows does not depend solely on how quickly the cancer cells can divide, a new study has found.

By examining brain tumors in mice, researchers at Washington University School of Medicine in St. Louis discovered that immune cells that should be defending the body against disease sometimes can be enticed into providing aid and comfort to tumor cells instead. The more immune cells a tumor can recruit to its side, the faster the tumor grows, the researchers found.

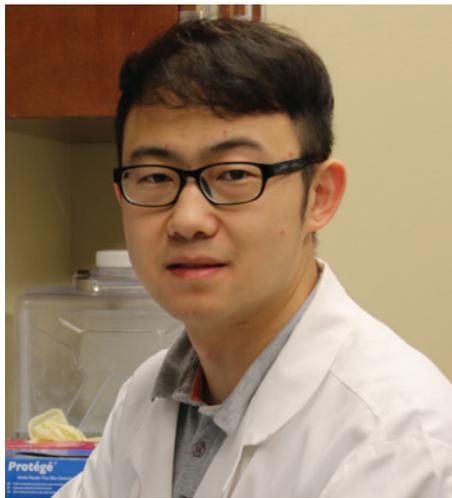
The findings, published May 29 in the journal *Neuro-Oncology*, suggest that targeting immune system cells could potentially slow brain tumor growth in people with the genetic condition Neurofibromatosis type 1 (NF1).

While people with NF1 usually come to medical attention for birthmarks on their skin, they are also at increased risk of developing tumors. One of the most common of these tumors in children is a low-grade brain tumor called an optic glioma, which affects the optic nerve that connects the brain and the eye. Some of these tumors can cause vision loss.

Unfortunately, NF1 is a notoriously variable disease. Doctors can't predict what kinds of tumors a person will develop, how fast these tumors will grow, or what types of medical problems the tumors will cause – all of which make it difficult for doctors to decide when a tumor needs to be treated with chemotherapy and when it is safe to simply watch and wait.

To better understand why some tumors grow faster than others, first author Xiaofan Guo, MD, a graduate student in Gutmann's research laboratory, created five mouse strains with different genetic changes in the *NF1* gene and elsewhere in the mouse's genome.

The five strains varied widely in tumor development and growth. Mice belonging to three of the strains grew tumors



starting at about 3 months of age, with the tumors in one strain of mice growing particularly fast. Members of the fourth strain didn't grow tumors until they were about 6 months old, and only a quarter of mice in the fifth strain developed brain tumors on the optic nerve at all.

When the researchers isolated tumor cells from the mice and grew them in a dish, they found little difference in tumor cell growth. The growth rates and other properties of the cancer cells were very similar, no matter which mutation the tumor cells carried.

What did correlate with overall tumor proliferation in mice was the presence of

two kinds of immune cells – microglia and T cells – within the tumors. Guo and former postdoctoral research fellow Yuan Pan, PhD, discovered that the tumor cells themselves were releasing proteins that attracted immune cells to the tumor.

The researchers now are trying to take advantage of this relationship between tumor cells and immune system cells to find new ways to treat brain tumors in people with NF1. One strategy is to slow tumor growth by preventing microglia or T cells from providing support to the cancer cells. However, a more ambitious strategy is to reprogram the T cells to no longer aid tumor cell growth.

"The idea is to use T cells as Trojan horses," Gutmann said. "These are experiments currently ongoing: We're trying to change the T cells so that when they enter the brain, instead of promoting the tumor, they shut it down."

- Written by Tamara Bhandari - Washington University News Hub

Dr. Guo's study was spotlighted with a commissioned editorial by Dr. Michelle Monje in the journal *Neuro-Oncology*, as well as featured in the *Drug Target Review*, the American Association for the Advancement of Science *EurekaAlert!*, and *Neurology Today*.



ADRIENNE WATSON, PHD

Children and adults with NF1 can develop a wide variety of clinical features, including brain and nerve tumors. While small animal models of NF1 have been successfully generated in flies and mice, none of these animals display the complete spectrum of clinical problems found in people with NF1.

Spearheaded by Dr. Adrienne Watson of Recombinetics, Inc. and Dr. David Largaespada at the University of Minnesota, a novel swine model of NF1 was recently developed. These minipigs exhibit many of the clinical hallmarks of NF1, including café-au-lait macules, neurofibromas, and optic pathway glioma. In contrast to previously reported *Nf1* mouse models, these animals spontaneously develop these features, similar to people with NF1.

In this regard, this minipig platform provides an unprecedented opportunity to study the complex biology and natural history of NF1. Moreover, deployment of these NF1 swine could prove indispensable for the development of advanced imaging methods and disease biomarkers, as well as the evaluation of future NF1 targeted therapies.

SUPPORT BEYOND THE CLINIC

PATIENT ENGAGEMENT

- Our patients and their families are critical to the NF Center mission of providing exceptional care through groundbreaking research. Because of their generosity, we are able to conduct cutting-edge investigations and provide outstanding complementary care resources.



Every May and June, Peggy Dohlke rallies her family and friends to participate in a fundraiser supported by her employer, The Louvre Salon, in Fairview Heights. Friends, family, and the Louvre staff and clients, all offer generous donations to support NF and the Washington University NF Center. Peggy and her team raise money through raffle baskets, employees paying to wear jeans on weekend work days, product donations, and gift certificates.

The Washington University NF Center would like to thank the The Dohlke Family for their generous support.

FuNFest is a family-friendly festival designed to promote awareness about NF and to raise funds for NF research. The event includes games, bounce houses, music, a live auction, silent auction bidding, and the now infamous Cow Patty Bingo.

FuNFest raised money to support laboratory research focused on developing personalized medicine approaches for people with NF1. The Washington University NF Center extends its heartfelt gratitude to Amanda and Brian Walk, who work tirelessly to plan and direct this event.



Forward Strides 4NF is a charity started in 2016 by Gina Wilburn to honor her daughter and husband, who both have Neurofibromatosis type 1 (NF1). Each year, the event has had over 200 registered walkers, with more than 30 volunteers. Entertainment at the event includes a bounce house, bubble bus, face painting, food and beverages donated from local restaurants, as well as sports mascots to cheer participants at the finish line. Additionally, a raffle, which included over 120 amazing items, has proven to be a huge attraction every year.

The Washington University NF Center extends its warm gratitude, and congratulations, to the Forward Strides 4NF committee, on their largest yearly fundraising total to date.

COMPLEMENTARY CARE PROGRAMS

At the Washington University NF Center, we believe that the care of our families extends beyond the walls of the clinic. To supplement our medical services at St. Louis Children's Hospital, we have partnered with the St. Louis Children's Hospital Foundation and Jazz St. Louis to create complementary care programs for all age groups that address the ongoing needs of children with NF1.



BEAT NF (Ages 2 – 5 years)

Together with Jazz St. Louis education staff, the Washington University NF Center has developed this one-of-a-kind therapy program that specifically focuses on frequently delayed skills in young children with NF1. During each session, professional jazz musicians play live music, while the children review social engagement rules as a group, learn about a “mystery instrument”, and engage in gross and fine motor therapy. Educators and musicians from Jazz St. Louis compose and play original music expressly written for these activities. In addition, Beat NF Team members carefully design each week's program to work on improving particular social and motor delays in toddlers with NF1.

During each session, toddler participants enjoy five weeks of a jazz music motor therapy curriculum utilizing jazz music and physical therapy to promote social, attention, and motor skills in toddlers with NF1, while also fostering healthy parent-child interactions, peer relationships, and jazz appreciation.



CLUB NF (Grades K – 8)

Through our partnership with St. Louis Children's Hospital, the Washington University NF Center proudly provides Club NF as a free, bimonthly, play-based therapy program for children with NF1. Each event is designed to address a specific set of skills often delayed in school age children with NF1. While the children are working on those skills with their therapists, parents have the opportunity to speak with NF specialists to learn more about NF1 and to implement the strategies used in Club NF activities.

Club NF aims to empower families and children with NF1 through the use of play-based therapy and education. By creating a safe, fun environment, families with NF1 learn more about this condition, as well as understand how to foster healthy communication and interactions with peers.

Past Club NF events include: Schnucks Cooking School, Glass Blowing, Penguin Encounters at the St. Louis Zoo, Dancing, and Ice Skating.

TEEN NF (Ages 13 – 18 years)

Our program, Teen NF, is open to all teenagers with NF1, with the objective of fostering positive interpersonal relationships at home, at school and in the community. Focusing on common challenging social 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. Additionally, the program has been expanded to include peer support, social gathering opportunities used to practice learned social skills, and leadership development through volunteer opportunities.



nfcenter.wustl.edu

As we celebrate our successes in 2019 and look forward to 2020, 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 2019 Annual Report created and designed by Jennifer N. Traber.