WASHINGTON UNIVERSITY
NEUROFIBROMATOSIS (NF) CENTER
Exceptional Care through Groundbreaking Research

2016 ANNUAL REPORT
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MESSAGE FROM THE DIRECTOR
Learn how the NF Center is providing exceptional care through groundbreaking research with 2016 highlights directly from NF Center director, David H. Gutmann, MD, PhD.

RESEARCH GRANTS
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.

PROVIDING EXCEPTIONAL PATIENT CARE
Discover the difference that the patient care team at the NF Center Clinical Program at St. Louis Children’s Hospital is making in the lives of our patients and their families.

A YEAR OF GROUNDBREAKING RESEARCH
Get a first-hand look at the discoveries made by NF Center researchers and collaborators, and learn more about early-phase findings that bring us closer to offering personalized medicine to individuals with NF1.

SUPPORT BEYOND THE CLINIC
Explore the array of NF Center complementary care programs for children with NF1, providing exceptional care beyond the clinic walls, and supporting patients from early childhood through adulthood.
MESSAGE FROM THE DIRECTOR

During our twelfth year as a multi-disciplinary clinic care and research enterprise, the Washington University Neurofibromatosis (NF) Center has many new developments to report. Looking forward to 2017, as we expand our research initiatives aimed at developing personalized medical approaches for people affected with NF, we are grateful for the continued partnership with our patients and their families who make these high-risk, high-payoff ventures possible.

INTRODUCING NEW FACULTY
In 2016, two of our research trainees, Dr. Stephanie Morris (Pediatric Neurology) and Dr. Angela Hirbe (Medical Oncology), have joined us as medical school faculty, while Dr. Kimberly Johnson (Brown School of Social Work) was promoted to the rank of Associate Professor.

ADVANCING NF RESEARCH
There has also been exciting progress in our understanding of neurofibromatosis, with numerous researchers in the Washington University NF Center publishing new discoveries. These include advances in our understanding of autism in NF1, the importance of the NF1 gene mutation in brain tumor formation, and how non-cancerous cells control optic glioma growth. In addition, we 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 an optic glioma in a child with NF1, and the NF1 Brain Trust, employed to find potential markers for learning and behavioral problems in NF1.

EXPANDING PATIENT CARE
The clinical care program celebrated the addition of Dr. Stephanie Morris and a new nurse coordinator, Erika Ramirez, dedicated to improving the care we provide for individuals with NF1. Over the past year, we have also fortified our 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.

RAISING NF AWARENESS
In addition, we welcomed a delegation of 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 neurofibromatosis.

Finally, we hosted the third Washington University NF Center Research Symposium on April 1, 2016, with Dr. Alcino Silva (University of California, Los Angeles) and Dr. David Largaespada (University of Minnesota) as keynote speakers.

ST. LOUIS MEN’S GROUP AGAINST CANCER GRANT
Dr. David H. Gutmann and his colleagues are developing new models of these common skin tumors in order to develop better therapies for people with NF1-associated neurofibromas.

NATIONAL CANCER INSTITUTE GRANT
Dr. David H. Gutmann and his colleagues will be investigating how patient sex and NF1 gene mutation dictate how will develop an optic glioma and how does tumor formation cause reduced vision. For these studies, they will use a series of novel NF1 mouse strains generated in their laboratory.

HEMATOLOGY T32 FELLOWSHIP
Dr. Matthew Stroh, PhD to better understand how the NF1 gene controls cell growth under different conditions. Dr. Stroh is specifically interested in how the NF1 gene works in varying contexts, with the hope of discovering how this important gene functions as a tumor suppressor in the brain.

SARCOMA ALLIANCE CAREER DEVELOPMENT GRANT
Dr. Angela Hirbe, MD, PhD to launch her independent career as a physician-scientist. Dr. Hirbe recently joined the faculty at Washington University where she will direct a research laboratory focused on developing new treatments for malignant peripheral nerve sheath tumors (MPNSTs) arising in people with NF1. In addition, she will be the primary oncologist for patients with NF1-associated malignant peripheral nerve sheath tumors (MPNSTs) as a first step toward identifying and evaluating more effective therapies for these malignancies.

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

THE GIORGIO FOUNDATION COLLABORATIVE GRANT
To study dermal neurofibromas. In collaboration with investigators at the University of Texas-Southwestern (Lu Le, MD, PhD) and the University of Alabama-Birmingham (Robert Kesterson, PhD), Dr. David H. Gutmann and his colleagues are developing new models of these common skin tumors in order to develop better therapies for people with NF1-associated neurofibromas.

MCDONNELL FOUNDATION FELLOWSHIP
To Yuan Pan, PhD to study the role of immune system cells in malignant brain tumor growth. Dr. Pan plans to define how signals typically made by cells of the immune system control the growth of brain tumors. These studies are aimed at developing new therapies for these deadly brain cancers.

ST. LOUIS MEN’S GROUP AGAINST CANCER 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.
Our son Garrett was diagnosed with Neurofibromatosis type 1 (NF1) when he was just 5 years old. We had never heard of this disorder before, and our family was devastated. As parents, we tend to have certain dreams and expectations for our children’s lives, no matter how realistic or unrealistic they may be. As I started to research this condition, I became even more scared and confused; it’s so complex and every person can be affected in different ways.

We connected with the Washington University NF Center Clinical Program at St. Louis Children’s Hospital within a couple of months of receiving the diagnosis. Dr. Gutmann and every member of the staff there have been so kind, helpful and supportive. Our perspective began to change immediately.

We began attending the Club NF play-based therapy events, and Garrett and I have both enjoyed them so much that we try to make it to all six events throughout the year. These events are just one example of how Dr. Gutmann and his team have been so inspirational in our journey, always focused on what truly matters for our life, health and the well-being for all members of our family.

Garrett has struggled with learning, balance, handwriting, speech and social skills, but he loves working on skills that are difficult for him and seeing the “NF family” at these events. He fits in there, and he has overcome many of the issues that have arisen as a result of his NF1. He struggled for years to learn how to ice skate for his love of hockey. I’m still not sure how he did it, but he plays ice hockey and loves it! He also has worked very hard in speech therapy and has discovered a love of the stage. He has performed in several small theatre productions at his school, even landing the lead role in last year’s performance of “Murder’s in the Heir”. He did a wonderful job! This year, as a freshman in high school, he is participating in the Speech and Acting club and is competing in meets all over the region. He has a terrific sense of humor, and the irony of participating in this club having been a kid who was in speech therapy most of his life has not gotten past him; go figure!

We can’t express how much gratitude we have for 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.

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.

Collectively, we strive to provide the best possible care for individuals with NF, both today and tomorrow.
ANNE SOLGA, PHD
identified a key growth factor made by immune system-like cells (microglia) in NF1 mouse brain tumors (optic gliomas). By blocking the activity of this growth factor, she revealed another potential treatment strategy for these common brain tumors in children with NF1.

LAURA SMITHSON, PhD
discovered a new protein important for NF1 growth control in the brain. While the Gutmann laboratory previously showed that the NF1 protein regulates cell growth in the brain by suppressing the function of a protein complex, called the mechanistic target of rapamycin (mTOR), exactly how this occurs remained unclear. In this new study, Dr. Smithson identified a novel mTOR complex in brain cells, and demonstrated how it is controlled by the NF1 protein.

ANGELA HIRBE, MD, PhD
developed an exciting new small-animal model of NF1-associated malignant peripheral nerve sheath tumor (MPNST). Using a combination of genetic approaches, she generated mice where the timing and location of additional genetic changes can be controlled, leading to mice that develop neurologic signs of a growing MPNST, similar to adults with NF1-MPNST.

STEPHANIE MORRIS, MD
completed the first large-scale international study of autism in NF1 including over 500 children. She found several features that distinguish autism in NF1 from autism arising in the general population.

Y-HSIEN CHEN, PHD
was the first to show that the NF1 protein controls brain stem cell function by suppressing RAS function in different ways. In these studies, he demonstrated that RAS controls stem cell growth using one set of RAS signaling molecules, whereas stem cell formation of nerve and other cell types involves a distinct RAS signaling pathway. These findings have important implications for treatments that aim to more precisely block particular abnormalities resulting from impaired NF1 protein function.

KIMBERLY JOHNSON, MPH, PHD
and her colleagues found new associations between brain tumors and other medical conditions. In one of these studies, she demonstrated that children with NF1 who had asthma were less likely to develop a brain tumor.

JOSEPH TOONEN, PhD
published the first description of mice engineered with different NF1-patient NF1 gene mutations. In this study, he demonstrated that the formation and continued growth of mouse NF1 optic gliomas is dictated by the particular NF1 gene mutation.

NEW CLUES IDENTIFIED IN CHILDHOOD CANCER SYNDROME

Children with the inherited cancer syndrome neurofibromatosis type 1 (NF1) are prone to developing brain and nerve tumors as well as myriad other medical problems, including autism, epilepsy and bone defects. While the disorder is caused by a mutation in a single gene, the range and severity of clinical abnormalities vary widely, making the impact of NF1 on children and adults difficult to predict and treat.

But new research at Washington University School of Medicine in St. Louis may help doctors determine which issues are likely to manifest in patients with NF1. The findings indicate that varying mutations in the NF1 gene may lead to different clinical outcomes. The research is published online in Human Molecular Genetics.

“This discovery could enable us to better predict how NF1 will affect specific individuals, showing us what problems are likely to develop and how best to address them,” said senior author David H. Gutmann, MD, PhD, the Donald O. Schnuck Family Professor of Neurology. “These early-phase findings bring us one step closer to being able to individually tailor how we monitor and treat people with NF1.”

A YEAR OF GROUNDBREAKING RESEARCH

During 2016, 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 (>650 patients enrolled), NF1 Brain Trust (>12 patient stem cell lines), and NF1 Patient Registry Initiative (>2300 patients participating). These critical resources only exist because of the enthusiastic involvement of our patients and their families.

While all individuals with the disorder are born with a mutation in the NF1 gene, there are thousands of different NF1 gene mutations. To determine whether specific mutations of the gene increase the risk of developing optic gliomas, one of the most common brain tumors affecting children with NF1, the researchers used mice genetically engineered with patient-specific NF1 gene mutations.

Surprisingly, Gutmann and his colleagues found that mice harboring one specific patient-derived NF1 gene mutation developed optic gliomas, while mice with another patient-derived NF1 gene mutation did not. The mice with optic gliomas also had greater eye dysfunction. Optic gliomas are known causes of vision loss in children with NF1.

To determine why the specific mutation had such a dramatic effect on optic glioma formation and vision, Joseph Toonen, PhD, a postdoctoral research fellow, built upon previous research in the Gutmann laboratory that demonstrated a critical role for microglia — immune cells in the central nervous system that defend against invaders — in mouse brain tumor growth.

Toonen discovered that the number and activity of microglia were affected differently by each mutation. There were more microglia in mice with one patient-derived mutation, leading to greater tumor growth and increased optic nerve injury. In striking contrast, these findings were not observed with the other patient-derived mutation.

The scientists now are researching how microglia promote optic glioma growth and vision loss. “Based on these exciting results, we can now envision using a mini-clinic of mice with different NF1 gene mutations,” said Gutmann, who also directs the Washington University NF Center. “This would offer us a valuable representation of the spectrum of clinical variability in this very heterogeneous disorder.

“Moreover, should specific gene mutations play a major role in determining brain tumor development, families could be better informed about the risk that their children may develop such tumors,” Gutmann said. For this reason, the researchers are incorporating the mice into preclinical drug discovery and evaluation efforts as a means of developing precision medicine strategies for children and adults with the disorder.

This article, written by Jessica A. Williams, originally appeared in the Washington University School of Medicine News Hub on March 30, 2016.
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.

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 skyniacets. 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.
As we celebrate our successes in 2016 and look forward to 2017, 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 2016 Annual Report created and designed by Courtney L. Monroe.