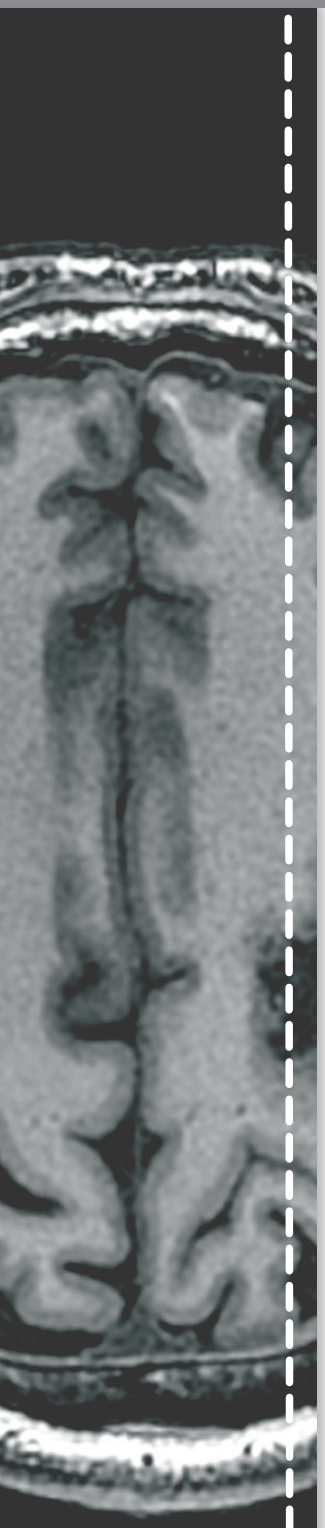
Le Bonheur Children's Hospital
Memphis, Tennessee

Brain Waves

Neuroscience Institute

Winter 2022



Code Break: *New alliance provides hope for genetic neurological diseases*

On Dec. 23, 2016, the U.S. Food and Drug Administration (FDA) approved the first successful genetic intervention for spinal muscular atrophy (SMA) — a genetic neurological condition that was then the No. 1 genetic killer of infants.

It was the first glimmer that scientists could "break the genetic code" and address underlying causes of disease, not just resign themselves to keeping babies comfortable in their short lives.

New discoveries seemed possible, but they would require a higher level of collaboration and partnership among physicians and scientists. Those at Le Bonheur, the University of Tennessee Health Science Center (UTHSC) and St. Jude Children's Research Hospital were ready to take advantage of the opportunity.

"We know there are new discoveries in basic sciences that are close to having a real impact for children with neurologic disorders," said Le Bonheur Neuroscience Institute Co-director James Wheless, MD. "The time is right for us to play a large role in translating these discoveries to treatments for patients as quickly as possible."

In a new collaborative effort, Le Bonheur's Neuroscience Institute and the St. Jude Pediatric Translational Neuroscience Initiative (PTNI) have partnered to provide basic research, clinical trials and multispecialty care that will rapidly deliver new therapies to children living with genetic neurologic diseases. For many of these children, it is their first, best chance at a better quality of life — or even at surviving into adulthood.

THE VISION

A neurologist by training, J. Paul Taylor, MD, PhD, director of the St. Jude Pediatric Translational Neuroscience Initiative, had experienced firsthand the pessimistic view that neurologic diseases were untreatable. But he saw this starting to change.

"I could see that a revolution was coming with many therapies in the works for previously untreatable diseases," he said. "So, we designed the Pediatric Translational Neuroscience Initiative to leverage and build upon the experience and infrastructure of St. Jude. Our aim was to address catastrophic pediatric neurological disorders and speed up the time from basic research to therapeutics."

Since the gene responsible for SMA was uncovered in 1995, years of basic science followed to uncover new genes related to neurological diseases, determine what mutations occurred, the mechanisms of the disease and how to deliver gene-targeted therapies. To bridge the gap between basic research and treatments, Taylor knew he already had a partner with clinical care expertise in Memphis — Le Bonheur's Neuroscience Institute and its renowned epilepsy program.

In the past few years, Le Bonheur's Chief Neurologist Wheless, Taylor and UTHSC Chair of Pediatrics Jon McCullers, MD, explored a new collaborative framework. By working together, they hope to leverage the strengths of each institution — translating basic research into treatments or even cures for children with devastating genetic neurologic diseases as quickly as possible.

"The St. Jude oncology model is unparalleled in its ability to conduct clinical trials for rare diseases that bring the latest treatments to children around the globe," said Wheless. "And we have the clinical care expertise and programs to support children with neurological disease and conduct clinical trial protocols specific to those diseases."

Le Bonheur Neuroscience Co-director James Wheless, MD, sees 3-year-old McCall Wright in neurology clinic. McCall is one of many children with Dravet syndrome who relies on clinical trials held at Le Bonheur and is waiting for a gene-targeted treatment for the syndrome to become widely available.

The collaborative effort will initially focus on two major categories of neurological disease — neuromuscular conditions, including SMA and Duchenne muscular dystrophy (DMD), and genetic epilepsies such as Dravet syndrome. The existing infrastructure for clinical trials through the Children's Foundation Research Institute at Le Bonheur allows a unique focus on rare diseases with smaller patient populations.

THE RESEARCH

The collaborative research effort will focus on moving discoveries across the continuum from basic science to clinical trial protocols conducted at both St. Jude and Le Bonheur.

Through PTNI, basic research will be led by Peter McKinnon, PhD, in the newly-formed St. Jude Center for Pediatric Neurological Disease Research. Clinical research will be led by Pediatric Neurologist Richard Finkel, MD, through the St. Jude Center for Experimental Neurotherapeutics. The goal: accelerate the translation of that research into therapies for kids.

Wheless has already initiated protocols for clinical trials at Le Bonheur for genetic epilepsies, through the hospital's well-established epilepsy program. One of the most imminent treatments that will be a focus of the collaboration is a gene-targeted treatment for Dravet syndrome.

Neuromuscular disease clinical trials will be conducted out of Le Bonheur's Muscular Dystrophy Association (MDA)/Neuromuscular Clinic. Led by Le Bonheur Neurologist Elena Caron, MD, the clinic will host clinical trials at Le Bonheur and provide expert clinical care in coordination with Finkel, who is recognized as a pioneer of many of the clinical trials leading to FDA approval of the first genetic therapy for SMA.

Continued on page 2

A Beacon of Hope: Le Bonheur participates in clinical trial for Dravet syndrome

Dravet syndrome, a rare genetic epilepsy previously only managed by treating symptoms, causes seizures and developmental delays. Thanks to a new clinical trial, Le Bonheur is investigating a novel potential therapy to address the genetic root of Dravet syndrome. This is the first disease-modifying therapy to ever be in clinical trials for Dravet syndrome.

A defective SCN1A gene, which controls production of a specific protein needed for movement of sodium within brain cells that is critical to proper brain function, causes Dravet syndrome. Where most people have two functioning copies of this gene, children with Dravet have only one. The new, genetically-based therapy works by modifying the functioning gene to produce up to twice as much protein in an effort to restore protein levels to a more functional degree.

The delivery system is called TANGO — targeted augmentation of nuclear gene output — and is delivered into the spinal fluid via lumbar puncture.

"Potential treatments like this are a paradigm shift — in the past we could only treat the symptoms," said Wheless. "Now we can target the underlying genetic cause."

Referrals: 866-870-5570
www.lebonheur.org/neuroscience

A pediatric partner with The University of Tennessee Health Science Center/College of Medicine and St. Jude Children's Research Hospital

BEST CHILDREN'S HOSPITALS U.S.News & WORLD REPORT NEUROLOGY & NEUROSURGERY 2021-22

Code Break: *New alliance provides hope for genetic neurological diseases* continued from page 1

"Our ultimate goal is to combine what works best to push the envelope on moving treatments forward," said Wheless. "Some protocols will take place at St. Jude, and some will integrate at Le Bonheur. But no matter what, we're all talking and collaborating to do what's best for this patient population."

THE CARE

Patients who come to Memphis to participate in clinical trials on either campus have a range of unique clinical care needs, and Le Bonheur already has well-established multispecialty clinics that can handle these needs, says Wheless.

For example, Finkel oversees St. Jude protocols at Le Bonheur's MDA/Neuromuscular Clinic for children who have clinical needs beyond the scope of the trial. Since this clinic is already set up with Le Bonheur providers from multiple specialties, patients can participate in a trial and have medical needs related to their condition coordinated in one visit. Patients will also be screened for eligibility in the Le Bonheur clinics for any of the protocols underway in the collaboration.

"We are also pleased to be able to share our high-level technology resources," said Wheless. "With transcranial magnetic stimulation (TMS), high-density EEG (hdEEG) and the latest generation of magnetoencephalography (MEG), we can provide cutting-edge brain imaging and analysis of brain connections for all children who are treated through this collaboration."

Pediatric Neurologist Richard S. Finkel, MD, (pictured above) director of St. Jude's Center for Experimental Neurotherapeutics, will conduct clinical trial protocols at Le Bonheur's MDA/Neuromuscular Clinic. Finkel is recognized as a pioneer of many of the clinical trials leading to FDA approval of the first genetic therapy for SMA.

THE FUTURE

Taylor and Wheless say they hope the collaboration ultimately moves the needle for pediatric neurology therapies in Memphis, the country and the world. The partnership will bring more complex patients to Le Bonheur's campus, elevating research and clinical discoveries to improve the lives of children with devastating neurological disorders.

Furthermore, this collaborative effort also has implications for patients down the road as they begin to outlive their current life expectancies.

"With many of these diseases, children die young or have significant development issues," said McCullers. "If we're able to significantly treat these diseases, we have an entirely new set of issues to address if they live to adulthood that we haven't seen before."

The hope is that these forthcoming therapies will change thinking in the medical community that neurological diseases are untreatable.

"The collaboration has the potential to enhance care and research protocols on both sides of the street," said Wheless. "We're fortunate to partner with an organization where we can raise standards of care together and challenge each other to discover, test and deliver the most innovative care for the patients who depend on us."

Neuroscience Institute launches Comprehensive Headache Center

While typically a minor inconvenience, headaches can turn into a chronic, debilitating condition for some children causing disruption in their lifestyle, school performance and relationships. Pediatric Neurologist Ankita Ghosh, MD, director of Le Bonheur's Comprehensive Headache Center, aims to help these kids not just address their pain but understand the headache disorder process, too.

"The patients who come to our center seek pain relief, but we also want to address the disease process. Our goal is not just to treat patients but also to educate them so that they feel confident in managing their condition," says Ghosh.

Which is why Ghosh, a trained pediatric headache specialist, makes it a priority to meet directly with each new patient in the Headache Center for as long as it takes to thoroughly understand their history, concerns and potential treatment options. Ghosh completed a fellowship in pediatric headache at Cincinnati Children's Hospital and specializes in primary headache disorders. In clinic, patients have access to Ghosh, Nurse Practitioner Olivia McComb, DNP, CPNP-PC, and Psychologist Gwen Beard, PsyD, in the same visit.

Ghosh addresses acute and preventive headache treatment, lifestyle management and cognitive behavioral therapy for migraines taking a holistic approach to managing headache disorders. Studies have shown that the combination of preventive therapy along with cognitive behavioral therapy for chronic migraine provides the best outcomes, says Ghosh. She ensures that every patient and family can meet with a psychologist to address relevant concerns such as comorbid disorders (anxiety, phobias, difficulty with pill swallowing, etc.) and learn coping skills.

"Our goal is that by the end of clinic our patients feel more self-confident about their management of care," said Ghosh. "It's rewarding to see when your patient's headaches improve."

As treatment for pediatric headache expands and changes, Ghosh plans to bring Le Bonheur to the forefront of these new treatment opportunities. Ongoing research in this field is poised to open new avenues of treatment including uncovering the genetic components of headaches – specifically migraine.

For example, Ghosh is participating in several current research efforts for pediatric headache including determining dosage amounts and protocols for dihydroergotamine (DHE) in the Emergency Department and the connection between joint hypermobility and pediatric migraines. But her interest in genetics of headache could also unlock cures and provide answers for the origin of pediatric headaches.

"We are more than just a clinic, we are a headache center," says Ghosh. "We want to give patients the opportunity to enroll in research trials that might benefit them."

Study: *Trigeminal autonomic cephalalgias can begin early in life and exhibit similar symptoms as adults*

All five headache disorders comprising trigeminal autonomic cephalalgias (TAC) can begin early in life and exhibit many of the same symptoms as TACs in adult populations, according to a study published in *Cephalalgia* by Director of Le Bonheur's Comprehensive Headache Center Ankita Ghosh, MD. Literature on TACs in pediatric populations has been very limited and little is known about these headaches in children.

TACs include cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) and hemicrania continua.

"In cluster headache, the most common TAC, there is typically a delay in diagnosis of several years because of atypical headache features and lack of awareness of cluster headache in younger patients," said Ghosh. "The objectives of our review and meta-analysis were to report on the full age ranges of pediatric TACs and determine if kids and adults with TACs display similar symptoms."

Director of the Neuroscience Institute's Comprehensive Headache Center Ankita Ghosh, MD, examines a patient in headache clinic. Ghosh spends time with each patient to fully understand their headache disorder and history.

In the meta-analysis, Ghosh and colleagues identified 86 studies for systematic review. Results showed that every type of TAC can begin early in life. The youngest age of diagnosis for each TAC in this review was 1 year old for cluster headache and SUNA, 2 years old for paroxysmal hemicrania and SUNCT and 6 years old for hemicrania continua.

In this review, cluster headache was the pediatric TAC with the most available data. Cluster headaches were shown to be present in every pediatric age (1-18 years) and met the full criteria for cluster headaches established for adults in the ICHD-3 (International Classification of Headache Disorders). The most common differences between adult and pediatric symptoms were the frequency and location of attacks. Cluster headache diagnosis was also delayed or misdiagnosed as migraine in pediatric patients because pediatric patients had less cranial autonomic features and restlessness but similar rates of migraine symptoms.

The other types of TACs reviewed in this meta-analysis met most but not all ICHD-3 criteria, and very few studies examined these headache disorders in children. Further study is needed to understand the differences between adult and pediatric onset for these headache disorders.

"Our review of current literature strongly suggests that all five TACs can start very early in life," said Ghosh. "These results have clinical implications for neurologists caring for pediatric patients with headache disorders to better diagnose and treat them appropriately."

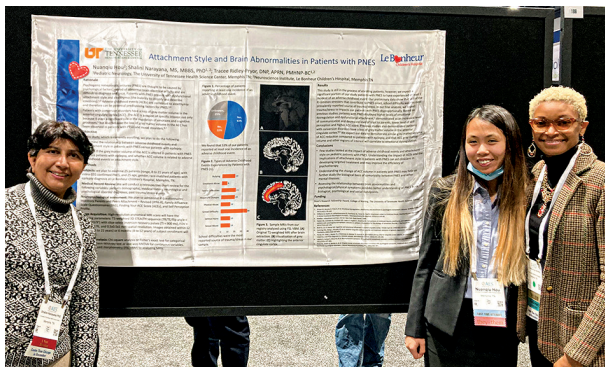
Clinical implications

1. **All five TACs can start early in life. Data is strongest for cluster headache.**
2. **Pediatric-onset and adult-onset cluster headache have similar features. Cluster headache may be confused with migraine in children because of lower rates of cranial autonomic features and a similar rate of prototypically migrainous features.**
3. **Pediatric cluster headache can be distinguished from migraine by attack duration less than two hours (more consistent with cluster headache) or more than three hours (more consistent with migraine). When the attack duration is two to three hours, pediatric cluster headache can be distinguished by number of attacks per day (more than one), presence of restlessness and strictly unilateral pain.**

Le Bonheur pediatric neurology experts present at American Epilepsy Society (AES)

Pediatric experts from the Neuroscience Institute at Le Bonheur Children's Hospital and the University of Tennessee Health Science Center (UTHSC) presented their research at the annual meeting of the American Epilepsy Society (AES) held Dec. 3-7, 2021.

AES is a community of professionals engaged in the understanding, diagnosis, study, prevention, treatment and cure of epilepsy with the goal of improving outcomes for persons with epilepsy. The annual meeting is held each year for the epilepsy community to learn best practices and review breakthrough research.



Pediatric experts from Le Bonheur's Neuroscience Institute recently presented at the annual meeting of the American Epilepsy Society (AES), including Director of Le Bonheur's TMS Laboratory Shalini Narayana, MS, MBBS, PhD, (left) and Nurse Practitioner and University of Tennessee Health Science Center (UTHSC) Pediatric Neurology Director of Research Strategies and Collaboration Tracee Ridley-Pryor, DNP, PMHNP-BC (far right).

Le Bonheur Children's and UTHSC presentations included:

Epilepsy and Behavior: What Physicians and Providers Need to Know

- Le Bonheur Neurodevelopmental Disabilities Specialist Tanjala Gipson, MD

Prevalence and Treatment of Dysphagia in Children with Infantile Spasms

- Director of Le Bonheur Children's Infantile Epilepsy Center Amy Patterson, MD
- Co-director of Le Bonheur Children's Neuroscience Institute James W. Wheless, MD
- Pediatric Neurology Nurse Practitioner Brittany Williams, DNP

Attachment Style and Brain Abnormalities in Patients with PNES

- Director of Le Bonheur Children's Transcranial Magnetic Stimulation (TMS) Laboratory Shalini Narayana, MS, MBBS, PhD
- Le Bonheur Nurse Practitioner and Director of Research Strategies and Collaboration for the University of Tennessee Health Science Center Pediatric Neurology Tracee Ridley-Pryor, DNP, APRN, PMHNP-BC

Presurgical Language Mapping Using Transcranial Magnetic Stimulation is Effective in Surgical Planning and Preserving Language Function in a Predominately Pediatric Cohort with Epilepsy or Brain Tumor

- Director of Le Bonheur Children's Transcranial Magnetic Stimulation (TMS) Laboratory Shalini Narayana, MS, MBBS, PhD

Standardizing TMS Language Mapping Protocols in Children with Epilepsy or Brain Tumor: A Multicenter Study

- Director of Le Bonheur Children's Transcranial Magnetic Stimulation (TMS) Laboratory Shalini Narayana, MS, MBBS, PhD

Initial Real-World Experience with Cenobamate (Xcopri®) in Adolescents and Adults: A Single Center Experience

- Le Bonheur Children's Nurse Practitioner and Director of Research Strategies and Collaboration for the University of Tennessee Health Science Center Pediatric Neurology Tracee Ridley-Pryor, DNP, APRN, PMHNP-BC
- Co-director, Le Bonheur Children's Neuroscience Institute James Wheless, MD

Speaking Up for Children with TSC, continued from page 4

combinations) and the canonical babbling ratio (canonical syllables/total syllables) and compared results between TD infants and infants with TSC.

Volubility for infants with TSC was less than half that of TD infants from laboratory recordings. TD infants had a mean of 9.82 syllables per minute compared to 3.99 for those with TSC. When compared with LENA recordings, the rate of vocalization was more than three times higher in TD infants compared to infants with TSC, with a mean of 14.65 syllables per minute. The canonical babbling ratio (CBR) of infants with TSC was a mean of .117 compared to .346 in the laboratory recordings and .173 in the LENA recordings.

"Our results showed delays across all study parameters — canonical babbling, volubility and CBR," said Gipson. "This data suggest that at 12 months many, perhaps most, infants with TSC show signs of delay in the vocal foundations for speech and language. The current results provide a benchmark suggesting that vocal development may be substantially delayed in TSC."

Gipson's long-term goal is to develop a body of knowledge in TSC about a variety of precursors to speech and language to help illuminate the development of language difficulties and other neurodevelopmental disorders in infants with TSC. Gipson and her team intend to conduct further research to standardize methodology, increase sample size and further assess the correlation between early vocalizations and language outcomes in infants with TSC. Their next step is assessing vocal precursors to language in all 130 infants in the TSC Autism Center of Excellence Research Network and relating them to the infant's language outcomes at 36 months.

IN BRIEF

Neuroscience Institute welcomes new providers

Ankita Ghosh, MD

Ankita Ghosh, MD, joins Le Bonheur as a pediatric neurologist and director of the Neuroscience Institute's Comprehensive Headache Center. She completed her residencies in pediatrics and child and adolescent neurology at McGovern Medical School, University of Texas Health Science Center. She recently completed a pediatric headache fellowship at Cincinnati Children's Hospital. Ghosh is a member of the Child Neurology Society, American Academy of Neurology, American Headache Society and International Headache Society.

Olivia McComb, DNP, CPNP-PC

Olivia McComb, DNP, CPNP-PC, joined Le Bonheur as a neurology nurse practitioner. She received her doctor of Nursing Practice from the University of Tennessee Health Science Center. McComb is a member of the National Association of Pediatric Nurse Practitioners.

Ashmitha Raja, MD

Ashmitha Raja, MD, joined Le Bonheur's Neuroscience Institute as a pediatric neurologist. She completed her residency in child neurology at Wake Forest Baptist Health. Raja is a member of the American Academy of Neurology and the Indian Medical Association.

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Le Bonheur Neuroscience Institute

15th Annual Pediatric Neurology Symposium

May 6-7, 2022

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Visit **https://www.lebonheur.org/conference/pediatric-neurology-symposium** to learn more and register.

Le Bonheur Children's Hospital

Brain Waves is a quarterly publication of the Neuroscience Institute at Le Bonheur Children's Hospital. The institute is a nationally recognized center for evaluation and treatment of nervous system disorders in children and adolescents, ranging from birth defects and learning and behavioral disorders to brain tumors, epilepsy and traumatic injuries.

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Speaking Up for Children with TSC

Research shows infants with tuberous sclerosis complex (TSC) have delayed precursors of speech development

In the first published research of its kind, Le Bonheur Pediatric Neurologist and Neurodevelopmental Disabilities Specialist Tanjala Gipson, MD, and her colleague, Psycholinguist Kimbrough Oller, PhD, with his team at the University of Memphis, have found that precursors of speech development are delayed in infants with tuberous sclerosis complex (TSC). These findings may signal poor language and developmental outcomes, according to a study published by Gipson, who is director of the TSC-Associated Neuropsychiatric Disorders (TAND) Clinic, and colleagues in *Pediatric Neurology*. Delays in early vocalizations were seen across all parameters in the study.

Children and infants with TSC can experience associated neurodevelopmental issues that are known as TSC-associated neuropsychiatric disorders (TAND), including significant problems with communication and language. Only 28% of people with TSC have typical lingual function and up to 50% of those with TSC have autism spectrum disorder, which also impacts communication and language.

"The earlier we can detect delays, the earlier we can provide intervention," said Gipson. "Currently children with TSC are diagnosed with autism at 7 years old on average. This research may allow us to detect autism as early as 6 to 9 months old."

The study analyzed 74 audio-video recordings from the TSC Autism Center of Excellence Research Network of 40 randomly-selected infants with TSC. Researchers reviewed samples and determined the number of canonical (well-formed syllable structure typified by consonant-vowel combinations) and non-canonical syllables produced by the infants. Results were compared with two groups of typically-developing (TD) infants – 41 infants recorded in a laboratory setting and 39 infants recorded all day in the home through Language Environment Analysis (LENA). All recordings analyzed were taken at 12 months old.

Researchers determined volubility (total number of protophone syllables per minute), canonical babbling (number of consonant-vowel

CONTINUED ON PAGE 3

Le Bonheur Pediatric Neurologist and Neurodevelopmental Disabilities Specialist Tanjala Gipson, MD, meets with a patient during tuberous sclerosis complex (TSC) clinic. Gipson's research into TSC found that precursors of speech development are delayed in infants with TSC and may signal poor language and development outcomes.