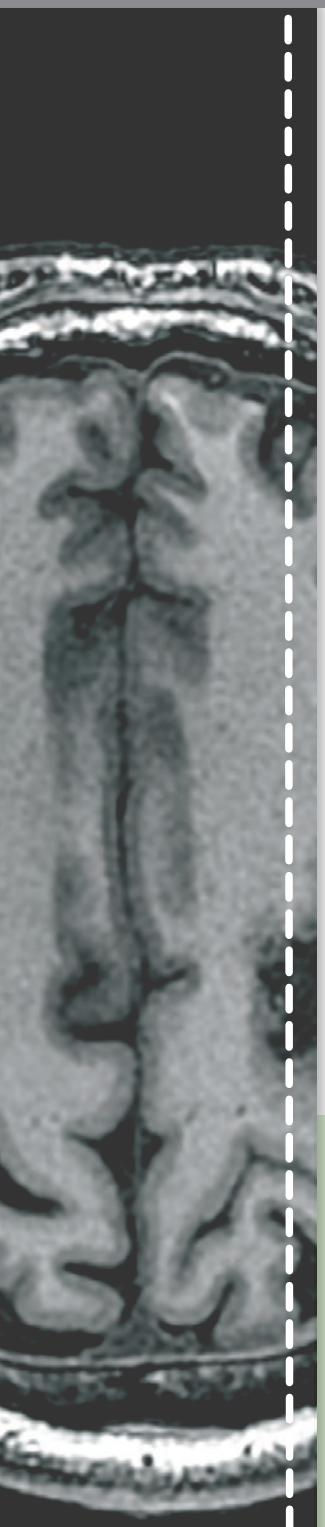
Le Bonheur Children's Hospital
Memphis, Tennessee

Brain Waves

Neuroscience Institute

Spring 2021



Molecular biology of brain tumors impacts prognosis, treatment of pediatric brain tumors

Understanding the molecular biology of brain tumors is key to prognosis and treatment, said Le Bonheur Neuroscience Institute Co-Director Frederick Boop, MD, in his presentation "How Molecular Biology Impacts Clinical Practice" at the International Society for Pediatric Neurosurgery (ISPN) 2020 Virtual Meeting.

"Historically we have depended on what we see under a microscope to differentiate tumor types and determine prognosis and therapy," said Boop. "We know now that what we see doesn't necessarily predict how these tumors are going to behave."

Physicians are able to send a piece of a child's tumor to FoundationOne, an FDA-approved tissue-based broad companion diagnostic (CDx) for solid tumors, which provides the genomic alterations of that particular tumor. This explanation of the genetic aberrations includes its significance, best available treatment with mechanism of action and studies open for enrollment.

Manipulation of tumors based on molecular

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Neuroscience Institute Co-Director Frederick Boop, MD, presented on the molecular biology of brain tumors at the International Society for Pediatric Neurosurgery 2020 Virtual Meeting.

Pediatric Stroke Program provides stroke treatment, prevention through collaboration, advanced technology

"While strokes can look similar in adults and kids, strokes in children can occur for many different reasons, which need different treatments and means of prevention," said Beth Anne Cavanaugh, MD, the new director of the Le Bonheur Neuroscience Institute's Pediatric Stroke Program.

The Pediatric Stroke Program provides comprehensive care for children recovering from acute stroke as well as essential stroke prevention for children at risk for stroke due to underlying conditions. Led by Cavanaugh, who is board-certified in vascular neurology, the Pediatric Stroke Program is a collaboration among various specialties and organizations to create a one-stop clinic for children. Neuro-interventionists are always on call for stroke emergencies. St. Jude Children's Research Hospital Director of Clinical Hematology Cliff Takemoto, MD, works within the Pediatric Stroke Program as a close partner with a special interest in preventing stroke in children with sickle cell disease.

"Children at risk for stroke or recovering from stroke need support from a variety of specialties," said Cavanaugh. "Le Bonheur has specialists who can care for each of these unique needs including cardiologists, orthopaedists and epileptologists who help address underlying conditions or care for post-stroke complications."

Director of Le Bonheur's Pediatric Stroke Program Beth Anne Cavanaugh, MD (left), evaluates a patient during a clinic visit at the Pediatric Stroke Program.

Le Bonheur's advanced technology enables physicians to quickly and accurately provide treatments and prognostication for this patient population. Le Bonheur has a dedicated interventional radiology suite available for the treatment of acute strokes as well as transcranial magnetic stimulation (TMS) and magnetoencephalography (MEG) to provide the most accurate brain imaging for assessment of brain function, research and aid in prognostication.

Treatment of pediatric stroke and its complications doesn't end after a clinic visit. Physicians collaborate with physical, occupational and speech therapy as well as early intervention and development to provide the best recovery possible for children after a stroke.

"Our collaborative approach allows children to have comprehensive care for any and all of the complications they are experiencing after stroke or the risk factors they have for stroke," said Cavanaugh.

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

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Molecular biology of brain tumors impacts prognosis, treatment of pediatric brain tumors, continued from page 1

genetics began more than 35 years ago with shrinking prolactinomas before turning to neurosurgery. Boop and his team now use a molecular biological approach with medulloblastomas, low-grade gliomas, congenital glioblastomas and many more types of brain tumors. Closer study of molecular genetics has revealed different variants within each type of tumor, each with a different treatment approach and prognosis based on the genetic variant. Further study is needed into treatment side effects and long-term consequences for some of these therapies.

"As neurosurgeons, it is important for us to get tissue to the lab in every instance for us to understand what's going on so that these children can have a chance," said Boop.

For tumors that can't be removed surgically but tissue is needed for diagnostics, biopsies provide better understanding and treatment of the tumor. Previously, neurosurgeons avoided these biopsies because it was believed that the cells required were closest to necrotic areas that could cause catastrophic complications. Better understanding of tumors means that the tumor can be biopsied in a safer area in order to obtain the molecular profile of the tumor.

"Molecular genetics has completely changed our field and will continue to do so," said Boop. "There may come a time when the role for surgeons is much less than it is today."

Comprehensive Epilepsy Program receives Level 4 NAEC reaccreditation

Le Bonheur's Comprehensive Epilepsy Program recently received a two-year reaccreditation from the National Association of Epilepsy Centers (NAEC) as a level 4 epilepsy center, the highest level available for pediatric centers. Level 4 epilepsy centers have the professional expertise and facilities to provide the highest level medical and surgical evaluation and treatment for patients with complex epilepsy.

Dravet Syndrome: *A Review of Current Management*

Early genetic diagnosis, new medications and novel acute care options for Dravet syndrome raise questions and challenges for clinicians, according to a review of current management for Dravet syndrome published by Le Bonheur Neuroscience Institute Co-Director James Wheless, MD, and Le Bonheur Epileptologists Stephen P. Fulton, MD, and Basanagoud D. Mudigoudar, MD, in *Pediatric Neurology*. The review provides an overview of the challenges and opportunities for pediatric epileptologists caring for children with Dravet syndrome in light of treatment and diagnosis advances.

Le Bonheur Neuroscience Institute Co-Director James Wheless, MD (above left), and Le Bonheur Epileptologists Stephen P. Fulton, MD, and Basanagoud D. Mudigoudar, MD, recently published a review highlighting the advances in treatment for Dravet syndrome as well as the challenges epileptologists face with this patient population.

Since 2018, three new drugs have been approved for the treatment of Dravet syndrome – stiripentol, cannabidiol and fenfluramine. Prior to that, no medications were approved in the United States specifically for treating Dravet syndrome. In 2019, no-charge genetic testing was made available for any child 0 to 60 months who had an unprovoked seizure and for siblings at risk of inheriting the disease. Finally, 2020 brought new options for acute seizure emergencies including intranasal diazepam and midazolam. Early diagnosis resulting in earlier treatment with these and other medications may improve prognosis of long-term outcomes.

Updated published clinical practice guidelines incorporating these advances do not yet exist, which means clinicians must consider a wide array of issues before changing a patient's medication regimen, including efficacy, drug-drug interactions, pediatric-friendly formulations and more.

"With this changing landscape in diagnostic and treatment options comes questions and controversies for the practicing clinician," said Wheless. "Critical decision points include when to start treatment, what pharmacotherapy combinations to try first, which rescue medication to recommend and how to advise parents on controversial topics."

Basanagoud D. Mudigoudar, MD, a Le Bonheur epileptologist, examines a patient in Neurology Clinic.

The increased availability of genetic testing, which identifies mutation of the SCN1A gene indicative of possible Dravet syndrome, can result in earlier testing and a shorter time between symptom onset and definitive diagnosis. However, some children with a confirmed mutation in the SCN1A gene may not meet clinical criteria for Dravet syndrome. Clinicians may choose to treat the child with a Dravet syndrome-approved medication immediately after a patient presents with a single, prolonged febrile seizure and a confirmed mutation in SCN1A before meeting clinical criteria for Dravet syndrome as early control of seizures tends to result in less severe developmental delays.

Historically, Dravet syndrome was treated with valproate or clobazam and the ketogenic diet. Vagus nerve stimulation was an option if seizures did not respond to pharmacotherapy and the ketogenic diet. Three medications have recently been approved for treating Dravet syndrome – stiripentol, cannabidiol and fenfluramine.

Clinicians must also consider medications that are also prescribed for treating comorbidities including behavioral symptoms. Until more data is available, monitoring and dose adjustments may be warranted, says Wheless. The new acute seizure medications are unlikely to cause significant drug-drug interactions with these new medications.

Early management of Dravet syndrome can impact comorbidities and outcomes. Managing status epilepticus and reducing seizure duration and frequency early in the disease will reduce the risk of sudden unexpected death in epilepsy (SUDEP) and improve neurocognitive prognosis. Severity, frequency and duration of seizures also tends to be closely correlated to the severity of nonseizure comorbidities such as ataxia, abnormal gait, developmental delay and behavioral impairment.

Le Bonheur Epileptologist Stephen P. Fulton, MD, checks the vagus nerve stimulation (VNS) device of a patient with Dravet syndrome.

"Dravet syndrome is a devastating childhood epilepsy syndrome that, for the first time in history, has FDA-approved agents that can significantly impact the seizure burden and help prevent or reduce the negative impact of Dravet syndrome on the quality of life for patients and their families," said Wheless. "New advances raise questions with no definitive answers, but the clinician must be knowledgeable of all emerging advances to improve the care of children with Dravet syndrome."

Le Bonheur Neuroscience Institute 2020: *By the Numbers*

Despite the challenges and interruptions that 2020 produced, our Neuroscience Institute was able to continue serving the children who needed us throughout the pandemic. Here are just some of our highlights from 2020:

10
consecutive years of ranking as a top program by *U.S. News & World Report*

120
magnetoencephalography (MEG) scans conducted on the latest generation of MEG technology – TRIUX™ neo MEG

153
brain tumor surgeries

446
admissions to the Epilepsy Monitoring Unit (EMU)

Current Clinical Trials at the Neuroscience Institute

Le Bonheur's Neuroscience Institute is committed to discovering the best ways to care for kids with neurologic conditions. Our goal in pediatric neurological research is to find the best methods for treating disorders of the brain and nervous system in children. Below are our current clinical trials. If you have a patient that might benefit from these novel interventions, please contact us at neuroscience@lebonheur.org or Le Bonheur Connect at 901-287-PEDS or 1-866-870-5570.

Le Bonheur Nurse Practitioner and Director of Research for the University of Tennessee Health Science Center Pediatric Neurology Tracee Ridley-Pryor, DNP, PMHNP-BC (above right), oversees the neuroscience clinical trials conducted at Le Bonheur. Here she examines patient Charlie Byrd, a child participating in drug trials for Dravet syndrome.

Intervention	Diagnosis	Age	Description	Study or Sponsor
Ganaxolone	Status epilepticus (SE)	12 years and older	Evaluate the safety and efficacy of intravenous ganaxolone to decrease or cease seizure activity in patients with SE	Raise/Marinus Pharmaceuticals
EpiWatch	Epilepsy	5 years and older	Evaluate the efficacy of seizure detection using a mobile application, EpiWatch, on the Apple Watch for patients admitted to the EMU	EpiWatch/Johns Hopkins University
Risk factor study	Stroke	28 days to 18 years	Study the relationship between infection and increased risk factors for children experiencing acute ischemic stroke	The Vascular Effects of Infection in Pediatric Stroke (VIPS II)/NIH: National Institute of Neurological Disorders and Stroke
Antisense Oligonucleotide (STK-001)	Dravet syndrome	2-18 years	Investigate the safety of single dose antisense oligonucleotide (STK-001) in children and adolescents with Dravet syndrome	Monarch/Stroke Therapeutics
Human Tissue Study	Epilepsy surgery and brain tumor surgery	7-11 years	Utilize extra tissue samples obtained during brain surgery to examine if human brain specimens have neuropathology that correlates with related cell culture and animal models of human disease	Investigator-initiated
Natural history study	Dravet syndrome	6-60 months	Natural history study designed to describe the seizure, neurodevelopmental, and behavioral characteristics of Dravet syndrome. Data collected from this study will serve as an external control to a clinical trial examining a gene therapy investigational drug that aims to improve the seizure burden and neurodevelopmental outcomes in patients with SCN1A-positive Dravet syndrome.	Envision/Encoded Therapeutics
Privigen	Pediatric Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	2-16 years	Investigate the safety and efficacy of IV privigen, immune globulin in the treatment of pediatric CIDP	IgPro10_4001/CSL Behring
EPX-100	Dravet syndrome	2-17 years	Evaluate the efficacy of EPX-100 (clemizole hydrochloride) and change in seizure frequency in patients with Dravet syndrome experiencing uncontrolled seizures	EPX-100/Epygenix Therapeutics

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.

Scan to learn more about our Neuroscience Institute.

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Join us for the 14th annual

Pediatric Neurology Symposium

June 4-5, 2021

Guest Speakers:

Gregory L. Holmes, MD
University of Vermont Medical Center

Jeffrey Waugh, MD, PhD
UT Southwestern Medical Center

This symposium has been designed to encompass state-of-the-art practices and trends in treating pediatric neurology patients. Through case-based learning and didactic lectures, faculty who are both clinically and academically oriented will address relevant issues and provide valuable information and insight into situations commonly presented to subspecialists in pediatric neurology.

Learn more and register at **methodistmd.org/cme**.