Pioneering New Therapies for Pediatric Patients

BY KIMBERLY MCGHEE

PHOTOGRAPHY BY BRENNAN WESLEY

Clinicians at MUSC Children's Hospital are not content with providing the best in current therapies for sick children but are pushing the frontiers of care through clinical trials. Profiled here are trials of some of the most innovative therapies—including a gene therapy for sickle cell disease and targeted therapies for pediatric brain tumors and cystic fibrosis—as well trials seeking to improve outcomes after pediatric heart surgery and to ensure healthier pregnancies through adequate vitamin D supplementation.

Gene Therapy Clinical Trial for Severe Sickle Cell Disease

A phase 1 clinical trial (NCT02140554) of a treatment for severe sickle cell disease (SCD) using gene therapy opened at MUSC in 2015 and is currently recruiting patients. The National Institutes of Health is also recruiting patients, and additional U.S. sites are planned to open later this year. According to **Julie Kanter, M.D.**, Director of Sickle Cell Research and principal investigator for the MUSC Children's Hospital site of the study, "This could be the first step toward a potentially curative treatment for patients with severe SCD."

In SCD, a mutation in the beta-globin gene causes the normally round and flexible red blood cells to take on a rigid sickle shape that makes it difficult for them to pass through small blood vessels. Blood vessels become blocked, depriving organs of oxygen and leading to painful vaso-occlusive crises and organ dysfunction. The sickled cells do not live as long as healthy red blood cells, cause blood vessel damage, and put affected patients at risk of stroke.

Currently, the only cure for a child with SCD is a hematopoietic stem cell bone marrow transplant (HSCT) from an HLA-matched donor, but less than 10% of affected patients have such a donor. Thus, although successful, HSCT remains only a rare option and poses the risk of graft-versus-host disease and graft failure.

The phase 1 gene therapy clinical trial to be conducted at MUSC, which is enrolling adult patients (18 years and older), adopts a different approach: the patient's own hematopoietic stem cells (HSCs) are harvested from the bone marrow, transduced with a lentivirus carrying a functional copy of the human beta-globin gene with anti-sickling properties (the LentiGlobin BB305 Drug Product; *bluebird bio, Inc.*), and then reinfused into the patient (after chemotherapy to clear existing marrow). These "genetically corrected" HSCs are designed to serve as a self-renewing source of healthy red blood cells, and so a single instance of gene therapy has the potential to cure the disease or drastically lessen its severity.

Dr. Julie Kanter

In a letter published in *Nature* (September 16, 2010), a group of French researchers conducting an early-phase clinical trial of a similar gene therapy in patients with ß-thalassemia major reported that a formerly transfusion-dependent patient remained transfusion-free two years after treatment. At the annual meeting of the American Society of Hematology in December 2014, clinical researchers reported that the first four patients with ß-thalassemia major enrolled in phase 1/2 studies using the same gene therapy are currently transfusion free. Although preliminary, these results point the way to a better future for patients with ß-thalassemia and severe SCD.

Novel Therapies for Cystic Fibrosis

The MUSC Health Cystic Fibrosis Center is among the top-enrolling sites for the Cystic Fibrosis Foundation's Therapeutics Development Network (TDN), the largest cystic fibrosis (CF) clinical trial network in the world. MUSC helped collect data that led to the approval in 2012 of ivacaftor (Kalydeco™; Vertex Pharmaceuticals), the first drug to target one of CF's underlying causes.

All CF patients have a problem with chloride channels, but, according to **Isabel Virella-Lowell, M.D.**, Director of Pediatric Clinical Trials at the center, the specific mutations that characterize a patient's CF subtype determine whether the chloride channel is missing, is made but does not reach the cell surface, or reaches the cell surface but does not open correctly. Ivacaftor was approved for the 4% to 5% of CF patients with a gating mutation after it was shown to dramatically increase lung function, decrease sweat chlorides by as much as 50 mmol/L, and reduce infections and exacerbations.

In patients with a gating mutation, the chloride channel reaches the surface but does not open correctly; ivacaftor binds to the chloride channel and holds it open.

Studies are under way to assess whether combination therapies with ivacaftor can be used to help the 85% of CF patients with the F508del mutation. In these patients, the chloride channel is improperly folded and cannot bind to the cell surface. A successful combination therapy would include an agent(s) to refold the chloride channel and ivacaftor to open the channel once it reached the cell surface. Through the TDN, the MUSC Health Cystic Fibrosis Center has conducted trials of such combination therapies in adults and has opened enrollment for one in children.

Dr. Isabel Virella-Lowell

Targeted Therapies for Pediatric Brain Tumors

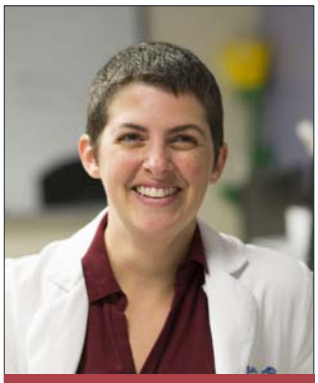
Amy-Lee Bredlau, M.D., MSCI, Director of the Pediatric Brain Tumor Program at MUSC Children's Hospital, is the principal MUSC site investigator for two trials, one led by St. Jude and one by Harvard, investigating whether targeting therapy based on the molecular subtype of brain tumors improves outcomes in pediatric patients. Both trials are currently recruiting patients.

The Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma Trial (NCT01878617)

Treatment for medulloblastoma is typically based on clinical risk, which is defined by the amount of tumor left after resection. However, recent studies suggest that prognosis varies widely among molecular subgroups of medulloblastoma (WNT, SHH, non-WNT non-SHH). More than 90% of patients with the WNT subtype and 75% of those with the SHH subtype survive on current therapy, whereas only 40% to 60% of those with non-WNT, non-SHH tumors do so. The St. Jude–led trial is assessing whether choosing the intensity of radiation therapy based upon a stratification of patient risk including molecular subtypes in addition to clinical risk prolongs progression-free survival compared with treatment stratification based upon clinical risk alone. An SHH inhibitor is used in patients with the SHH subtype.

Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas (NCT01182350)

Diffuse intrinsic pontine glioma (DIPG), an aggressive brain tumor located in the pons, typically occurs in children of elementary school age and is uniformly lethal. Radiation is the only treatment known to slow progression. Despite scores of clinical trials, no therapy has been found to improve on the progression-free survival (6.5 months) and overall survival (9 months) achieved with radiation. Biopsies have rarely been obtained for DIPG due to its position in the pons, hampering molecular profiling that could lead to the development of targeted therapies. Better imaging and surgical guidance technology have made biopsy of DIPG, once considered a dangerous surgery, much safer, opening the way for molecular analysis of these tumors.



Dr. Amy-Lee Bredlau

This Harvard-led trial tests whether basing treatment decisions on the molecular profile of a biopsied DIPG tumor leads to better overall survival than that seen in historical controls. Biopsy samples will be analyzed for overexpression of epidermal growth factor receptor (EGFR) and MGMT promoter methylation, both of which are thought to be prognostic in DIPGs. All patients will receive standard-of-care radiation and bevacizumab, which has been shown in preclinical studies of gliomas to enhance the effects of radiation. In addition, patients with $EGFR^+$ tumors will receive the tyrosine kinase inhibitor erlotinib, those with $MGMT^+$ tumors will receive temozolomide, and those with $EGFR^+$ $MGMT^+$ tumors will receive both agents.

"If these targeted therapies succeed in improving survival for children with medulloblastoma and DIPG, the results will likely be translated for treatment of other aggressive pediatric brain tumors, such as anaplastic astrocytomas and glioblastomas," says Bredlau.

For more information on these trials, contact study coordinator Kate McCormack at mccormk@musc.edu.

Corticosteroid Therapy in Neonates Undergoing Cardiopulmonary Bypass

In the United States, approximately 40,000 babies are born with a heart defect annually, and 10,000 of those undergo cardiac surgery requiring cardiopulmonary bypass (CPB). These complex surgeries would not be possible without CPB, which performs all of the functions of the heart and lungs, removing carbon dioxide and adding oxygen to the baby's blood and pumping it throughout his or her body.

However necessary, CPB is not without its drawbacks. Patients undergoing CPB develop a potent inflammatory response that may lead to poor heart, lung, and kidney function after the heart surgery. This in turn can lead to edema, longer times on the ventilator, the need for higher doses of heart medications, and a longer stay in the hospital. Children and especially neonates (<1 month old) are particularly vulnerable because of the immaturity of their organs and the disparity in size between them and the CPB machine.

Whether corticosteroids help mitigate the inflammatory response after CPB remains hotly debated. Most clinical trials to date have had limited patient enrollment and variations in clinical trial design (i.e., type, dose, and timing of corticosteroid) have undercut efforts to pool data in meta-analyses. Better efficacy data in neonates undergoing cardiac surgery are needed to determine whether the potential benefit of corticosteroids in controlling the inflammatory

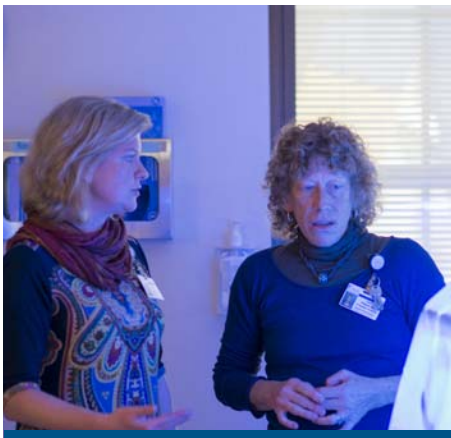
Vitamin D and Maternal and Fetal Health

Vitamin D deficiency has been linked to lower birth weights and higher rates of preterm delivery. Recent clinical trials at MUSC Children's Hospital have explored how much vitamin D is required by pregnant women to ensure their own and their baby's health and how much is needed by nursing mothers to render their breast milk replete.

In a clinical trial (NCT00292591) led by **Bruce W. Hollis, Ph.D.**, and neonatologist **Carol L. Wagner, M.D.**, 502 pregnant women were randomized to receive 400, 2000, or 4000 IU/d of vitamin D. At study initiation, the daily reference intake (DRI) recommended by the Institute of Medicine (IOM) was 400 IU/d. More than half of all women and more than 80% of black women receiving 400 IU/d did not achieve sufficiency (*Journal of Bone and Mineral Research* 2011;26(10):2341–2357). The study also showed that maternal levels of 25(OH)D (25-hydroxyvitamin, a metabolite of vitamin D) of 80 nmol/L were needed to achieve IOM-defined sufficiency (50 nmol/L) in the cord blood that supplies the fetus. In stark contrast to current IOM recommendations (600 IU/d, 1-69 years), the study authors concluded that a DRI of 4000 IU best meets the needs of mothers and neonates. Those results were confirmed by a community-based trial supported by the Thrasher Research Fund, which also showed a strong correlation between vitamin D deficiency and preterm birth, even after controlling for race (*Am J Obstet Gynecol* 2013;208:137.e1-13).

Evidence suggesting a link between vitamin D deficiency and pregnancy complications led the W.K. Kellogg Foundation to fund a trial by Wagner and colleagues randomizing pregnant women to 400 or 4400 IU/d to study how 25(OH)D levels affect immune function and alter placenta architecture.

In May 2013 at the annual meeting of the Pediatric Academic Societies, Hollis and Wagner reported results of a lactation trial conducted jointly by MUSC and the University of Rochester to test whether supplementing the nursing mother could ensure sufficient levels of vitamin D in the exclusively breast-fed infants born at term (NCT00412074). The trial randomized 476 mother/infant dyads into three vitamin D treatment groups: 400 IU (mother)/400 IU (infant), 2400 IU/placebo, or 6400 IU/placebo. Infants receiving 400 IU daily and those whose only source was via breast milk of mothers receiving 6400 IU daily attained adequate 25(OH)D levels, suggesting that maternal supplementation with 6400 IU of vitamin D is at least as effective as infant supplementation in preventing deficiency.



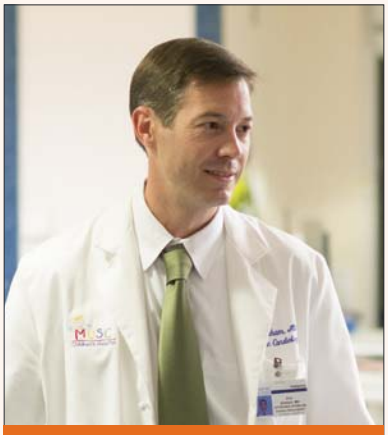
Dr. Sarah Taylor (left) and Dr. Carol Wagner (right)

Preterm babies cannot grow exclusively on breast milk and require nutritional supplementation. Neonatologist **Sarah N. Taylor, M.D.**, studied 89 preterm babies weighing less than 1500 grams to see whether they were deficient in vitamin D and whether supplementation would help them grow better. More than 90% of infants in this NIH-supported trial were deficient in vitamin D at birth, with black infants showing the most dramatic deficiencies (unpublished results). All achieved sufficiency by term age when supplemented with an average of 600 IU/d of vitamin D. Improved bone mineralization and density were significantly associated with higher 25(OH)D levels. More studies are needed to determine the level of vitamin D supplementation required to achieve optimal bone density.

response outweigh side effects such as delays in wound healing and an increased likelihood of infection.

Hoping to address that gap in the literature, **Eric M. Graham, M.D.**, Director of the Pediatric Cardiac Intensive Care Unit (PCICU) at MUSC Children's Hospital, is leading a multicenter clinical trial (NCT01579513) that is randomizing neonates to either a single dose of methylprednisolone or placebo to be administered in the operating room just before cardiac surgery requiring CPB. The primary endpoint will be a composite mortality-morbidity outcome, but data will also be collected on the time spent on a ventilator, in the hospital, and in the PCICU. In addition, babies will undergo testing at one year to see if surgery and recovery caused any neurodevelopmental delays. "This trial's results will clearly define the clinical utility of steroids in pediatric cardiac surgery, improving the care we provide to these children," says Graham.

To learn more about this trial, contact Tricia Infinger at infingep@musc.edu.



Dr. Eric Graham