Spotlight on Jacksonville Endocrinology Team Research

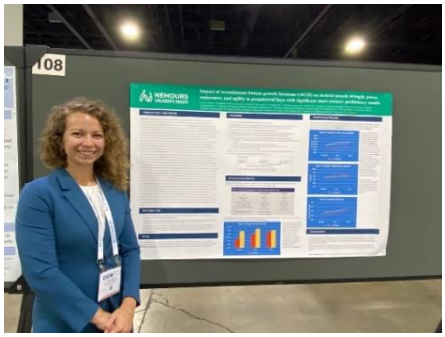
This has been a busy season for the highly productive Pediatric Endocrinology team in North Florida. A flurry of important presentations this spring and summer highlight the high-quality, translationally relevant clinical research being done at Nemours. See below for some highlights!

Insulin-only Bionic Pancreas Improves Diabetes Control in Children with Type 1 Diabetes

In a pivotal study, 326 patients with type 1 diabetes, 165 of them children 6 to less than 18 years old, were randomized to use either their standard diabetes care or the bionic pancreas (BP) closed-loop device. The latter algorithmizes insulin delivery based on continuous glucose monitoring (CGM) using solely the patient's body weight. Contrary to all other devices thus far, it does not require carbohydrate counting or any manual programming of insulin doses. The study was funded by the National Institutes of Health, and devices were supplied by Beta Bionics. **Dr. Nelly Mauras**, principal investigator, led the Nemours team in Jacksonville and was one of only 16 centers in the US participating; **Dr. Matthew Benson** was a co-investigator and **Keisha Bird, DNP, APRN,** and **Joe Permuy, APRN,** coordinated the study. Results of this study were presented at the Advanced Diabetes Technology Meeting in Barcelona (April 2022), and several papers are currently under review. After 3 months, participants using this device had a lower hemoglobin A1C level, the global metric of control, and greater time in normal range for the glucose compared with the standard of care. This device is likely to be an important contribution to simplify and automate type 1 diabetes care. This line of work is ongoing, and Dr. Mauras will soon start new studies using both insulin and glucagon in a completely closed-loop system. "There is a lot of hope for better treatments for our children with type 1 diabetes; it is exciting," Dr. Mauras said.

Original cohort of children in the Bionic Pancreas study – back row – Nelly Mauras, MD, Nemours JAX; Ed Damiano, PhD, Boston University (developer of device); Steven Russell, MD, Massachusetts General Hospital; Keisha Bird, DNP, APRN, senior coordinator, Nemours JAX; and Courtney Ballino, RN, coordinator, Massachusetts General Hospital

Impact of Human Growth Hormone (GH) on Skeletal Muscle Function, Agility, Power, and Endurance in Prepubertal Children Treated with GH



Dr. Lurah Welch, senior Pediatric Endocrinology Fellow at Nemours Jacksonville, working with **Dr. Nelly Mauras**, Principal Investigator, presented data at the Endocrine Society Meeting in Atlanta (June 2022) on the preliminary results of a study on muscle function in 45 prepubertal boys, 30 with profound short stature and 15 healthy normally statured controls. The investigators, who also included Dr. Ashish Malpani, former fellow, and **Drs. Matthew Benson** and **Mauri Carakushansky**, teamed up with Dr. Daniel Plummer, PT, at Wolfson Children's Hospital, as well as Dr. James Churrilla, chief of the Kinesiology Department at the University of North Florida in Jacksonville, and performed a series of protocolized exercises testing muscle strength, endurance, power, and agility before and

Isokinetic Dynamometry | *Mat Jump (Power)* | *Modified Push Ups (Endurance)* | *Timed Shuttle Run (Agility)*

after 6 months and 12 months of administration of human growth hormone (GH). The healthy normally statured children were studied similarly without GH. **Dr. Jobayer Hossain** is the study's biostatistician.

Investigators found there were significant differences, with lower fat-free mass and lower skeletal muscle strength and endurance in prepubertal boys with severe short stature compared with healthy age-matched controls. The fat-free mass accrual and isokinetic measures of muscle strength, endurance, agility, and power improved after 12 months of daily GH administration, changes approaching measures of those of healthy controls.

"I am very proud of this team and Drs. Malpani and Welch, our fellows, in particular, who shared in the conduct of these complex studies. This is precisely the type of translationally relevant work being done here in Jacksonville that impacts care but also allows us to train the next generation of pediatric endocrinologists," said Dr. Mauras, senior investigator and Director of Research in Jacksonville and Vice Chair of Pediatrics for Research.

This is an ongoing investigator-originated study funded competitively through the clinical research arm of Novo Nordisk (Mauras – PI).

Severe Hyperparathyroidism in a Newborn: Response to Cinacalcet

Dr. Lurah Welch, third-year endocrinology fellow in Jacksonville, also presented a unique case of a newborn baby born with multiple bone fractures, initially thought to be a form of osteogenesis imperfecta, at the Endocrine Society Meeting in Atlanta (June 2022). The endocrinology team diagnosed the baby with neonatal severe hyperparathyroidism (NSHPT), a rare potentially lethal disorder caused by inactivating mutations in the calcium sensing receptor (*CASR*) gene. Dr. Welch reported their experience using a novel calcium-sensing receptor mimetic, cinacalcet, which allowed for the normalization of calcium and parathyroid hormone (PTH) and remarkable improvement in all clinical aspects of the baby's status, including ability to eat, discontinuation of oxygen supplementation, and, eventually, healing of all fractures. Gene sequencing revealed a known heterozygous pathogenic variant in an exon 4 hotspot of the *CASR* gene, confirming the clinical impression. Now followed for an entire year, the baby is neurodevelopmentally intact and, so far, continuing to do well on medication. Activators of the *CASR* are a promising therapy for heterozygous *CASR* loss-of-function pathogenic variants and can lead to reversal of skeletal demineralization and markedly improved clinical status. "Dr. Welch's curiosity and willingness to put in writing the findings of a beautifully worked up, diagnosed, and treated patient exposed our fellow to the challenges and rewards of clinical research. This not only enriches her clinical acumen but strengthens our fellowship program," said **Dr. Nelly Mauras**, senior author of the presented work. Other Nemours Jacksonville coauthors include **Dr. Reham Hasan**, **Dr. Matthew Benson**, and **Dr. Leopoldo Maldonado**. The resulting paper is being submitted for publication.

Urinary Calcium Excretion in a Patient with Autosomal Dominant Hypocalcemia Type 1 due to a Novel Gain-of-function Mutation in the Calcium-sensing Receptor Gene

Dr. Matthew Benson was the lead and presenting author at the International Conference of Children's Bone Health in Dublin, Ireland (July 2022), for this unique study of a 10-year-old boy who presented with short stature and hypocalcemia. He had a gain-of-function mutation in the calcium-sensing receptor that causes hypoparathyroidism. Dr. Benson teamed up with his coauthors Dr. Michael Levine from Children's Hospital of Philadelphia and Dr. Caroline Gorvin from the University of Birmingham, UK, to better characterize this mutation including protein expression and G protein activation. The patient's positive response to amiloride and hydrochlorothiazide was also presented. "Dr. Benson is one of our most dedicated clinical researchers in endocrinology and has made a commitment to expand work in pediatric bone disease and diabetes in particular. We are excited to see his career grow at Nemours in Jacksonville," said **Dr. Mauras**, Vice Chair of Pediatrics for Research.

The Division of Endocrinology in Jacksonville currently has 13 active clinical research studies in diabetes technologies, novel drugs and immunotherapy, disorders of growth and puberty, and obesity. Funding includes NIH, private foundations, and industry. There is also ongoing collaborative work with psychology and other divisions including cross-campus collaboration. Sixteen papers are currently in press or being submitted by this group in 2022.