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Four-year old Michael Pirovolakis and his parents, Terry and Georgia, prepare for his unique clinical treatment for spastic paraplegia 50.

A PRECISION APPROACH TO 'UNTREATABLE' PAEDIATRIC CONDITIONS

At SickKids, scientists and clinicians work together to **TRANSLATE BASIC RESEARCH INTO VIABLE THERAPIES** for some of the most intractable childhood diseases.

As a young child diagnosed with Pitt-Hopkins syndrome, Ellie Tomljanovic exhibited extreme features of autism spectrum disorder (ASD), and her symptoms manifested in behaviour that was often harmful to herself and to others. "We have seen children die from their severe self-injurious behaviour," says George Ibrahim, a paediatric neurosurgeon and scientist at The Hospital for Sick Children (SickKids), in Toronto's city centre.

Non-verbal and frustrated, Ellie frequently hurt herself and her caregivers — including incidents that caused her physical harm and left her mother and nurses with bruises and bites. Fearing for their child's life, Ellie's parents reached out to Ronald Cohn, a physician and scientist, and the chief executive officer of SickKids. Cohn had been providing medical care for Ellie for most of her life, and had assembled a multidisciplinary team to treat her.

Ibrahim was the neurosurgeon on the team. In 2018 he pioneered Canada's first paediatric deep brain stimulation (DBS) surgery to treat childhood epilepsy, and since then had framed methods to adapt DBS for other paediatric neurological disorders.

DBS is approved by the US Food and Drug Administration (FDA) under a humanitarian device exemption to reduce the severity of obsessive-compulsive disorder (OCD) in adults. "Some elements of severe self-harm exhibited by autistic children overlap with OCD in adults," says Ibrahim. "We looked at the brain circuits in self-injurious behaviour and in OCD, and mapped them to a common pathway."

In 2019, Ibrahim and his colleagues established a clinical trial of DBS in self-injurious behaviour in children with autism (NCT03982888). In December 2020, Ellie was the first to be enrolled in the trial. During the surgical procedure, Ibrahim and his team placed electrodes in Ellie's brain in an area known as the nucleus accumbens, which forms part of the circuit involved in regulating self-harm behaviour. "DBS is an extremely personalized treatment; its effects are specific to the circuit that that you're trying to modulate," says Ibrahim. Post surgery, Ellie's self-harm behaviour reduced significantly, and she was able to attend school.

Ellie's story is only one example of the life-changing treatments that SickKids is pioneering. Using what the hospital calls Precision Child Health, a care model based on integrated data about each individual, SickKids is helping find novel treatments for patients with 'untreatable' conditions. The crucial elements in the hospital's success are its discovery research, which powers a deeper understanding of these conditions, and diverse and multi-disciplinary teams that bring a broad range of skills and experience to each challenge.

RESEARCH BASICS

"Two-thirds of research at SickKids is fundamental research, and much of the current medicine developed here is based on our own research," says geneticist, Stephen Scherer, who is chief of research at SickKids.

Scherer's own research seeks to identify genes and signalling pathways associated with autism development. Copy number variants (CNVs) are genetic alterations arising from deletions and duplications of segments of DNA. CNVs are often implicated in the development of complex behavioural conditions such as ASD. Scherer's group has identified more than 100 CNVs and autism-associated genes[1], which are used to enable early identification of ASD.

While Scherer applies genomic tools to uncover the molecular mechanisms of autism, Sheena Josselyn, a neuroscientist at SickKids, focuses on understanding memory formation and the consequences of disrupted information processing. "A group of neurons, termed an engram, is important for storing and recalling particular memories," explains Josselyn. "We think that a myriad of disorders, from autism to Alzheimer's disease, have a disruption of information processing at their heart. Understanding engram ensembles, how they are formed and used, is critical."

Josselyn's research combines molecular biology, advanced imaging and optogenetics to locate specific engrams in a mouse brain, then retrieve or erase the associated memories. By understanding how engram ensembles are formed, her group was able to implant an artificial memory in a mouse for an event that never actually occured[2].

▲ Neurosurgeon George Ibrahim is a pioneer of paediatric deep brain stimulation.

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Scherer's and Josselyn's areas of research demonstrate SickKids' commitment to the basic sciences, and its strong tradition of turning basic research into novel therapies. In the late 1980's, geneticist Lap-Chee Tsui propelled SickKids into the limelight with the discovery of the gene and protein involved in cystic fibrosis[3]. The discovery led to the development of novel drug treatment protocols used to treat the majority of the cystic fibrosis patients at SickKids. Today, structural biologist Julie Forman-Kay continues to build on Tsui's work by researching new mutation mechanisms in cystic fibrosis, as well as in cancer and neurodevelopmental conditions[4].

Other renowned scientists at SickKids include Janet Rossant, a developmental biologist whose contributions to the field of embryogenesis led to the discovery of trophoblast stem cells[5], and Peter Dirks, a neurosurgeon and brain researcher who discovered cancer stem cells in brain tumours[6]. SickKids is also home to rising stars like molecular biologist Jean-Philippe Julien, whose immunological research informs the development of novel treatments for infectious diseases[7].

INDIVIDUALIZED CLINICAL CARE

In 2019, SickKids diagnosed one-year old Michael Pirovolakis with a neurodegenerative disorder known as spastic paraplegia 50 (SPG50). SPG50 is an ultra-rare genetic disorder caused by mutations in a gene known as *AP4M1*. The condition presents with poor muscle tone and developmental delay, and progresses to include severe neurocognitive impairment and loss of the use of arms and legs. With approximately 80 patients worldwide, including just one (Michael) in Canada, and no known cure, Michael's treatment options were extremely limited.

In a race to find a viable treatment, Michael's parents set up a charitable organization known as CureSPG50. The organization brought together an international team of clinicians and scientists to develop a targeted gene therapy for Michael and others like him. Rigorous preclinical testing investigated the ability of the candidate gene therapy to target neuronal cells, compensate for faulty copies of *AP4M1* with functional genes, and halt disease progression[8].

After three years of testing and development, the gene therapy was ready. SickKids received Health Canada approval to use it for Michael. In March 2022, under the leadership of James Dowling, a clinician and scientist at SickKids, four-year-old Michael became the first patient ever to receive a treatment for SPG50 — a therapy that had been specifically designed for him. The trial was unique in another way, too: it was the first to

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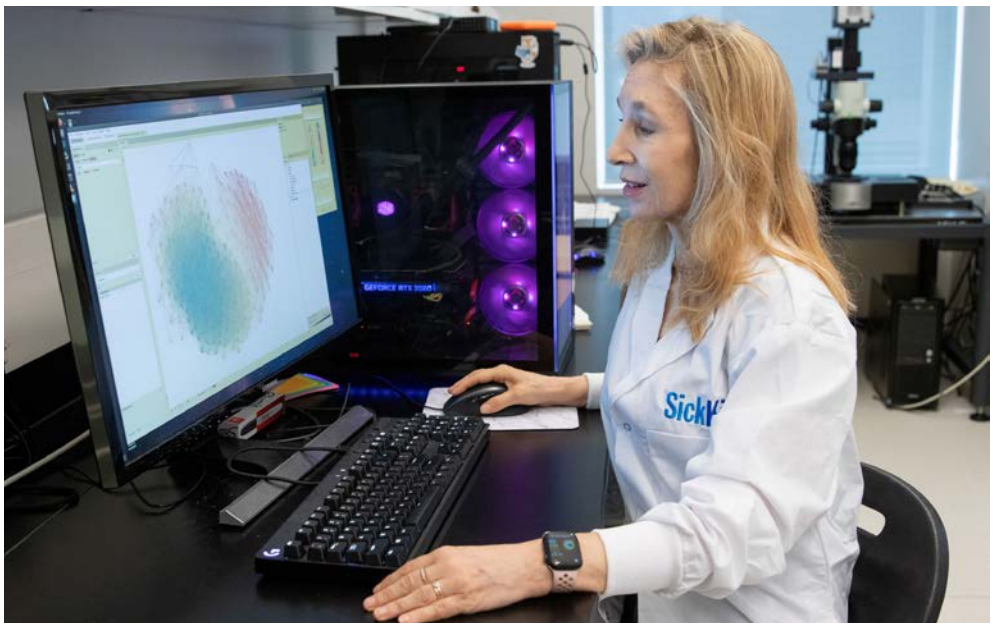
test a clinical intervention in a single patient with an ultra-rare disease.

Michael responded well to the treatment and the clinical team observed improvement in his health. Currently, the SPG50 gene therapy clinical trial is recruiting other paediatric patients with the condition (NCT05518188).



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▲ **Neuroscientist Sheena Josselyn explores the relationship between memory formation and conditions such as autism and Alzheimer's disease.**

HOLISTIC APPROACHES

SickKids' Precision Child Health approach relies on data, taken across the life span of a child. "Our holistic approach measures all data sets, from the genetic code to the postal code," says Cohn. The data need to be analysed and processed to be of clinical use, so SickKids is developing artificial intelligence capacity, through programmes such as AI in Medicine for Kids, to enable automation, prediction and early detection of diseases.

"Precision Child Health will encompass everything we do across all the conditions we treat, from cancer to mental health," adds Cohn. "This approach can ensure all children and families — including those with rare diseases, common illnesses and even healthy populations — are empowered to access care and benefit from research opportunities." Ongoing efforts include developing comprehensive and sustainable data architecture and infrastructure, with the computational power needed for big data management.

SickKids also has state-of-the-art core facilities housing microscopes, high-throughput robotics and the latest proteomics and genomic technologies. The Centre for Applied Genomics is a part of CGEn, a national platform that supports genome sequencing and informatics across Canada. The mouse models generated at The Centre for Phenogenomics are used by researchers across North America. And the world-class imaging facilities at the Nanoscale Biomedical Imaging Facility allow clinician-researchers to visualize fundamental biological processes and how they are impaired in diseases.

SickKids' high level of investment in research and innovation makes it eager to recruit the best talent from across the world. This talent includes international leaders like Tamorah Lewis, a clinician-scientist developing a pharmacogenomics strategy to support precision medicine at the hospital, and Zulfiqar Bhutta, award-winning co-director of the SickKids Centre for Global Child Health. Around 25% of SickKids' clinical and basic research trainees are from outside Canada. Set against the multiethnic backdrop of Toronto, SickKids embodies the pluralistic and welcoming philosophy of both the city and of Canada. "We are the Statue of Liberty for research," says Scherer.

To spark creative thinking and knowledge exchange, SickKids encourages symbiotic collaborations, across departments and disciplines, including with the University of Toronto. "Multidisciplinary approach is mission critical, which involves not just researchers and clinicians talking to each other, but all personnel: nurse practitioners, therapists, allied health providers and operational staff should be a part of the conversation," Cohn and Scherer both emphasize.

THE FUTURE OF MEDICAL CARE

The model developed at SickKids brings basic and translational research together with therapy development and medical care. The hospital's culture combines scientific advances and human intelligence to develop paediatric precision medicine. SickKids is poised to develop more novel therapies of the sort that saved Ellie's and Michael's lives.

"Our patients motivate us, and we are committed to helping them in the best way," says Josselyn. "And while cool discoveries are wonderful, it is our commitment to the families that keeps us coming back to work." ■

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