

Transfer to Transform

THE OFFICE OF TECHNOLOGY COMMERCIALIZATION
AT NATIONWIDE CHILDREN'S HOSPITAL

SUMMER 2018





| Our Mission |

The Research Institute at Nationwide Children's Hospital is dedicated to enhancing the health of children by engaging in high-quality, cutting-edge research according to the highest scientific and ethical standards.

The Office of Technology Commercialization at Nationwide Children's facilitates the transfer of new technologies, research, and innovations to outside partners to benefit pediatric care, our community and the general public.

| Affiliations |



Rev1 Ventures partners
with The Research
Institute at Nationwide

Children's Hospital to accelerate the formation and growth of life science companies in central Ohio. Through our partnership, we seek out high growth opportunities and advise entrepreneurs who are developing innovative therapies and technologies at Nationwide Children's. The goal is to improve children's health in central Ohio and throughout the world by catalyzing ideas developed by innovators and researchers who may provide solutions that improve patient outcomes.



As Ohio's bioscience
membership and development
organization, BioOhio is
focused on networking the

state's outstanding bioscience assets to accelerate growth of a globally competitive bioscience industry. High on this list of assets is pediatric research, in which Nationwide Children's exhibits leadership every day. The Research Institute at Nationwide Children's has been a Pillar Member of BioOhio for the past ten years.



VentureOhio
facilitates the

vibrancy and growth of the Ohio entrepreneurial ecosystem through advocacy, community organization, and evangelism.

| Centers and Institutes |

Battelle Center for Mathematical Medicine

Biobehavioral Health

Biopathology Center

Cardiovascular and Pulmonary Research

Childhood Cancer and Blood Diseases

Clinical and Translational Research

Gene Therapy

Injury Research and Policy

Innovation in Pediatric Practice

Institute for Genomic Medicine

Microbial Pathogenesis

Perinatal Research

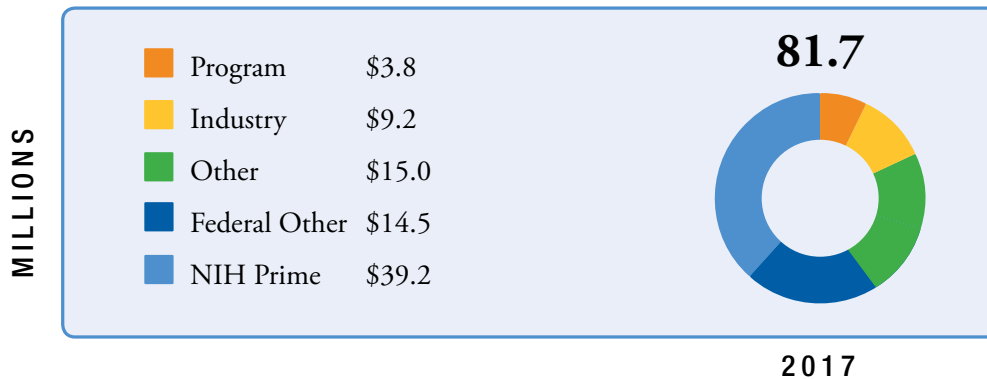
Regenerative Medicine

Vaccines and Immunity



| Funding |

2017 EXTERNAL AWARDS BY SOURCE



RESEARCH BY THE NUMBERS

	2015	2016	2017
Principal Investigators*	184	182	188
Research Fellows	66	75	70
Graduate Students	41	34	37
Employees	1121	1075	1310
Publications	823	1067	1171

**Includes faculty from The Research Institute and faculty from Nationwide Children's Hospital with \$50,000 or more in research funding support.*

| Nationwide Children's Hospital Startups |



Milo Biotechnology

The company was founded in 2012 to develop a therapy that would increase muscle strength and improve the quality of life of muscular dystrophy patients and is based on a discovery by scientists at Nationwide Children's Hospital. The therapy uses an adeno-associated virus (AAV) delivered follistatin protein, which inhibits the activity of myostatin, a protein that impedes muscle differentiation and growth. A clinical trial evaluating the safety and efficacy of Milo's follistatin therapy in patients with Becker muscular dystrophy, Duchenne muscular dystrophy, and Inclusion Body Myositis is underway at Nationwide Children's Hospital.



AveXis

AveXis, a clinical stage gene therapy company, is developing a new gene therapy treatment for patients with spinal muscular atrophy (SMA), a motor neuron disease that affects one in 6,000 live births in the U.S. and is the leading genetic killer of children under the age of 2. The technology, invented by researchers at Nationwide Children's Hospital allows for the delivery of a replacement gene to target motor neurons throughout the brain and spinal cord. The company recently received "Fast Track" designation from the Food and Drug Administration and completed enrollment of Phase I for SMA type I patients.



Abeona Therapeutics

Abeona Therapeutics, formed in early 2013 based on technology developed at Nationwide Children's Hospital, is focused on developing a cure for Sanfilippo Syndrome, MPS IIIA and MPS IIIB, rare genetic disorders caused by the body's inability to properly break down certain sugars. The disease leads to progressive muscular and cognitive decline in children after the age of 2. With no cure or approved treatments, children with Sanfilippo Syndrome usually die before the age of 20. The company is using technology invented by Nationwide Children's Hospital researchers to deliver a corrective gene to the central nervous system in children with the disorder. A Phase 1 clinical trial for MPS IIIA is underway at Nationwide Children's to evaluate the safety and efficacy of the treatment.



ENTvantage Dx

ENTvantage Dx provides primary care physicians and otolaryngologists with rapid, in-office diagnostic tests to determine the cause of ear, nose and throat illnesses. The technology was developed as a result of the research collaboration between The Ohio State University and Nationwide Children's Hospital, for rapid diagnosis of bacterial sinusitis. ENTvantage Dx is currently developing this technology to be used as point-of-care for patients with symptoms of sinusitis.



GenomeNext

GenomeNext, LLC, formed in 2014, is a leader in genomic data management and integrated analysis platform. The current strategies for analysis of this data rely upon parallelization approaches that have limited scalability, lack reproducibility and are complex to implement, requiring specialized IT solutions. In order to overcome these challenges, inventors at Nationwide Children's Hospital have developed a unique platform that fully automates the analytical process and provides genomic data and analysis ready for further clinical evaluation.



Myonex Therapeutics

Myonex Therapeutics, a new startup formed in 2017, is a clinical stage gene therapy company developing first ever treatments for Limb-girdle muscular dystrophy (LGMD) types 2D, 2B, 2E, 2L, and 2C based on research at Nationwide Children's Hospital, a leader in muscular dystrophy gene therapy discovery and translational research.



Scioto Biosciences

Scioto Biosciences was founded in 2017 to develop treatments for diseases associated with microbial dysbiosis. The technology platform, developed by researchers at Nationwide Children's Hospital, is a novel formulation that primes the colony-forming mechanisms of probiotic bacteria by combining beneficial bacteria with polysaccharide microspheres. These natural mechanisms induce 'biofilm' formation, enhance probiotic function, and allow for non-spore forming bacteria to survive passage through the gastrointestinal system. Among the first therapeutic indications being pursued is necrotizing enterocolitis, a high-morbidity disease that affects seven percent of premature births.

| Nationwide Children's Hospital Start-Ups |



Lyst Therapeutics

LYST Therapeutics, based in Columbus, OH, was founded in 2017 to develop a platform technology for treatment of fibrotic diseases. The technology, invented by researchers in the Center for Tissue Engineering at Nationwide Children's Hospital, is a novel immunomodulatory therapeutic antibody, and has potential applications in treating stenosis, myocardial infarction, and other conditions involving fibrosis. For their first therapeutic indication, LYST Therapeutics is applying their technology to the prevention of stenosis in tissue engineered vascular grafts.



LittleSeed

LittleSeed, Inc. was formed in 2018 in Powell, OH with the goal of delivering clinically driven, evidence-based fun to pediatric patients. The foundational technology, Voxel Bay, was developed by a team of clinicians and game designers at Nationwide Children's Hospital. Voxel Bay provides an interactive virtual reality platform designed to distract and calm children undergoing uncomfortable medical procedures. The Voxel Bay VR platform is being expanded to include other virtual environments and games tailored to specific needs within the pediatric environment.



Celenex

Celenex is a clinical stage gene therapy company targeting several variants of Batten Disease and other genetic diseases.



Deep Lens

Deep Lens is extending VIPER, one of the world's first digital pathology cloud platforms that for over ten years has allowed pathology groups to collaborate on groundbreaking cancer research across dozens of cancer types. Based on feedback from hundreds of expert global users, Deep Lens is enhancing the system to include AI-powered image detection and workflow support, telepathology, collaboration, cloud storage, and built in APIs for integration by hardware and software vendors and biopharma companies.



Thrive Neuromedical

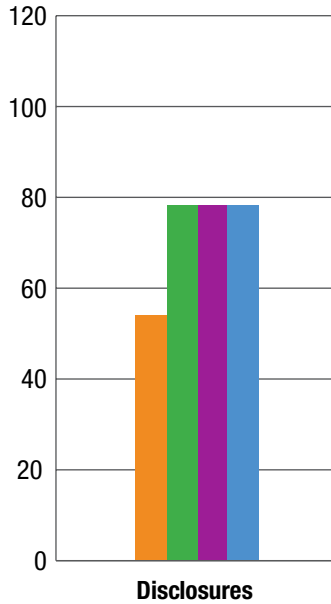
Thrive Neuromedical, an Ohio-based spinout of the Research Institute at Nationwide Children's Hospital, is developing the DinoEgg™ platform to enrich the neurological development of babies who don't have regular, consistent access to their parent's voice. The DinoEgg™ is a unibody Bluetooth-enabled speaker which transmits the parent's recorded voice with the appropriate sound characteristics to provide a clinical, therapeutic effect.



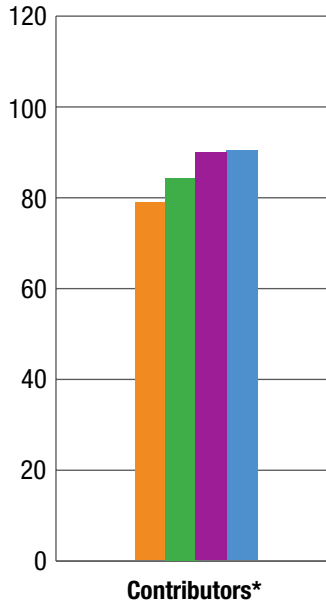
| Metrics |

2014 2015 2016 2017

DISCLOSURES

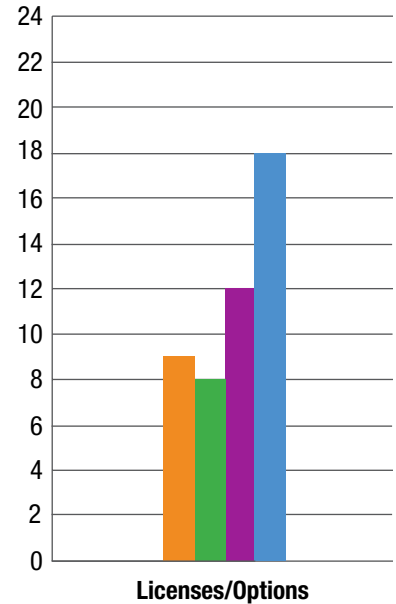


CONTRIBUTORS

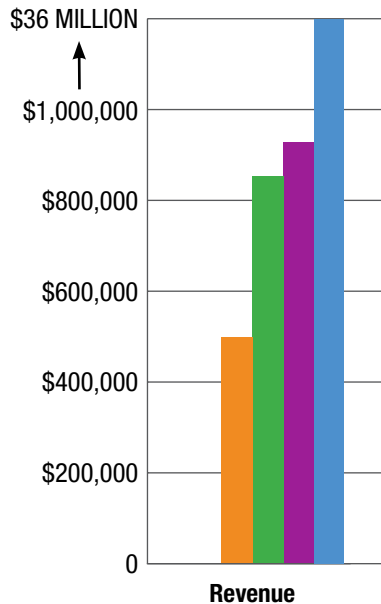


**Contributors are all NCH staff and each contributor is only listed once (even if had more than 1 disclosure).*

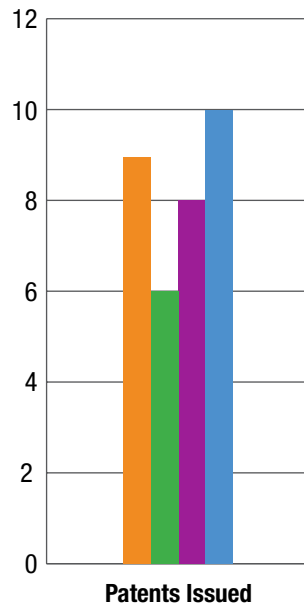
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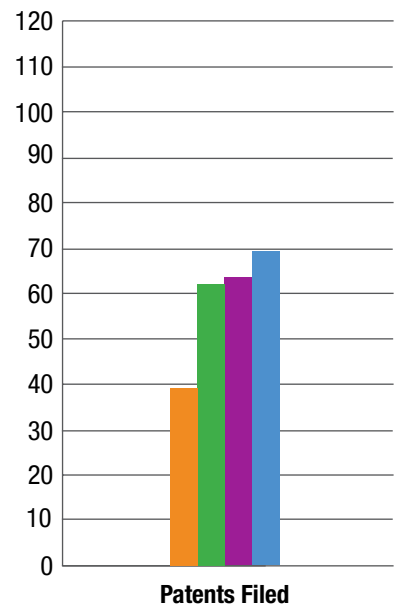
TOTAL REVENUE



U.S. PATENTS ISSUED

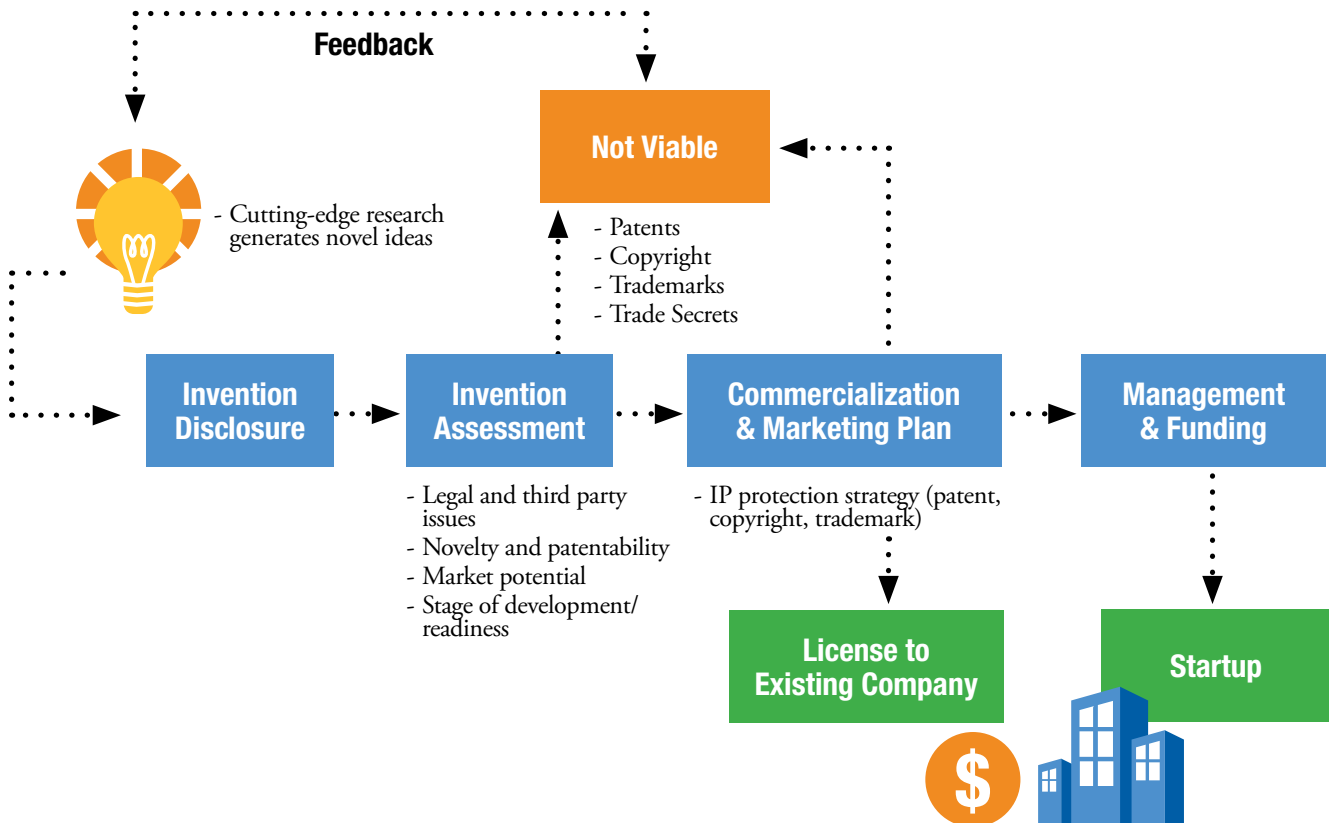


PATENTS FILED

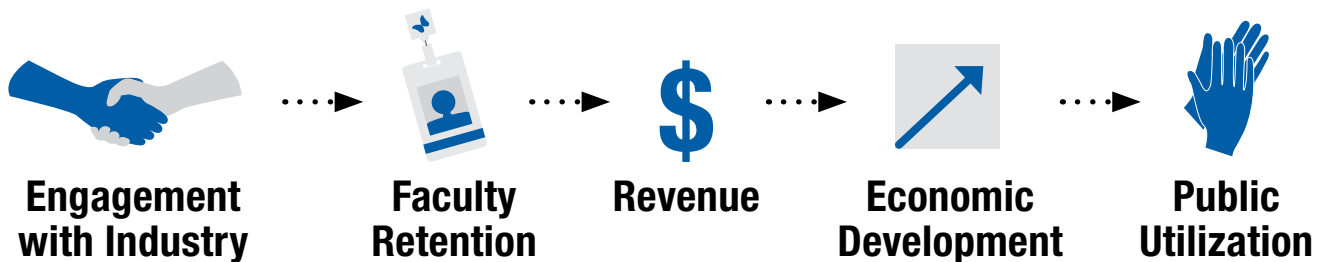


| Our Process |

When our doctors, nurses, researchers and other staff members have an idea, they head to our Office of Technology Commercialization. Together, we take these ideas and innovations and translate them into the commercial sector, bringing about new patents, start-up companies and innovations.



GOALS FOR TECHNOLOGY COMMERCIALIZATION



ENTvantage Enters Trial Phase

ENTvantage Dx, which has licensed rapid sinusitis diagnostic technology developed by researchers at Nationwide Children's and The Ohio State University, is nearing the start of a major milestone – a multicenter clinical trial in the United States and Australia. Results of the trial will be submitted to the U.S. Food and Drug Administration for clearance to begin marketing the sinusitis test kit, which primary care physicians and otolaryngologists may use in their offices or clinic.

“We hope to have all patients recruited by the end of the year. We’re hopeful we’ll have the clearance to market the product in the United States in the second half of 2019,” says Joe Skraba, president and CEO of ENTvantage.

The vast majority of sinusitis cases are caused by viruses, but because there is currently no accurate test outside of a lab to determine the underlying cause, doctors rely on symptoms and greatly overprescribe antibiotics, researchers say.

Despite efforts by the medical community to be good stewards of antimicrobials, concerns of overuse of antibiotics for sinusitis and other upper respiratory infections remain. “These doctor’s office tests can help fill that need,” Skraba says. “It’s still a large medical challenge.”

The diagnostic kit is designed to test for the three most common bacterium that cause sinusitis: non-typeable *Hemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pneumoniae*. A physician will take a sample swab from a patient’s nose, perform a rapid analysis and in five minutes know which, if any, bacteria is the cause of the infection.

If biomarkers – proteins – of a bacterium are present, knowing the cause behind the infection will help the doctor to choose the most effective antibiotic. If none are found, no antibiotic would be prescribed.

The labs of Subinoy Das, MD, former director of The Ohio State University Sinus and Allergy Center, and now an adjunct assistant professor at Ohio State; and Lauren Bakaletz, PhD, director of the Center for Microbial Pathogenesis in The Research Institute at Nationwide Children's, collaborated to develop the diagnostic technology. Both institutions have an equity position in ENTvantage.

The upcoming trial will take place at 10 locations in the United States and four in Australia, during the height of their respective sinusitis seasons. Each patient with symptoms will receive two swabs, one that will be tested at a lab and one used in the kit, to test how accurate the kit is.

The company raised \$4.5 million in financing in early 2018 to help support the effort, Skraba said. ENTvantage has also gotten some additional patent coverage in Europe, a possible future market. The company is also looking to offer the kits in Australia and Asia.

While the test is designed for sinusitis, the technology is more broadly applicable. The same viruses and bacteria responsible for sinusitis are responsible for acute bronchitis, acute otitis media and acute tonsillitis, the researchers behind the technology say. The medical community estimates that more than 70 million people annually suffer from the four types of infections, Skraba says. “All have the same overuse of antibiotics associated with them.”

Tapping Natural Killer Cells to Combat Cancer

Host and donor cells grown in the lab show promise against AML and neuroblastoma



During the past 40 years, the overall survival rate for childhood cancers has increased from 10 percent to nearly 90 percent. This improvement, however, appears to have plateaued. And, for children suffering rare cancers, survival remains a greater challenge.

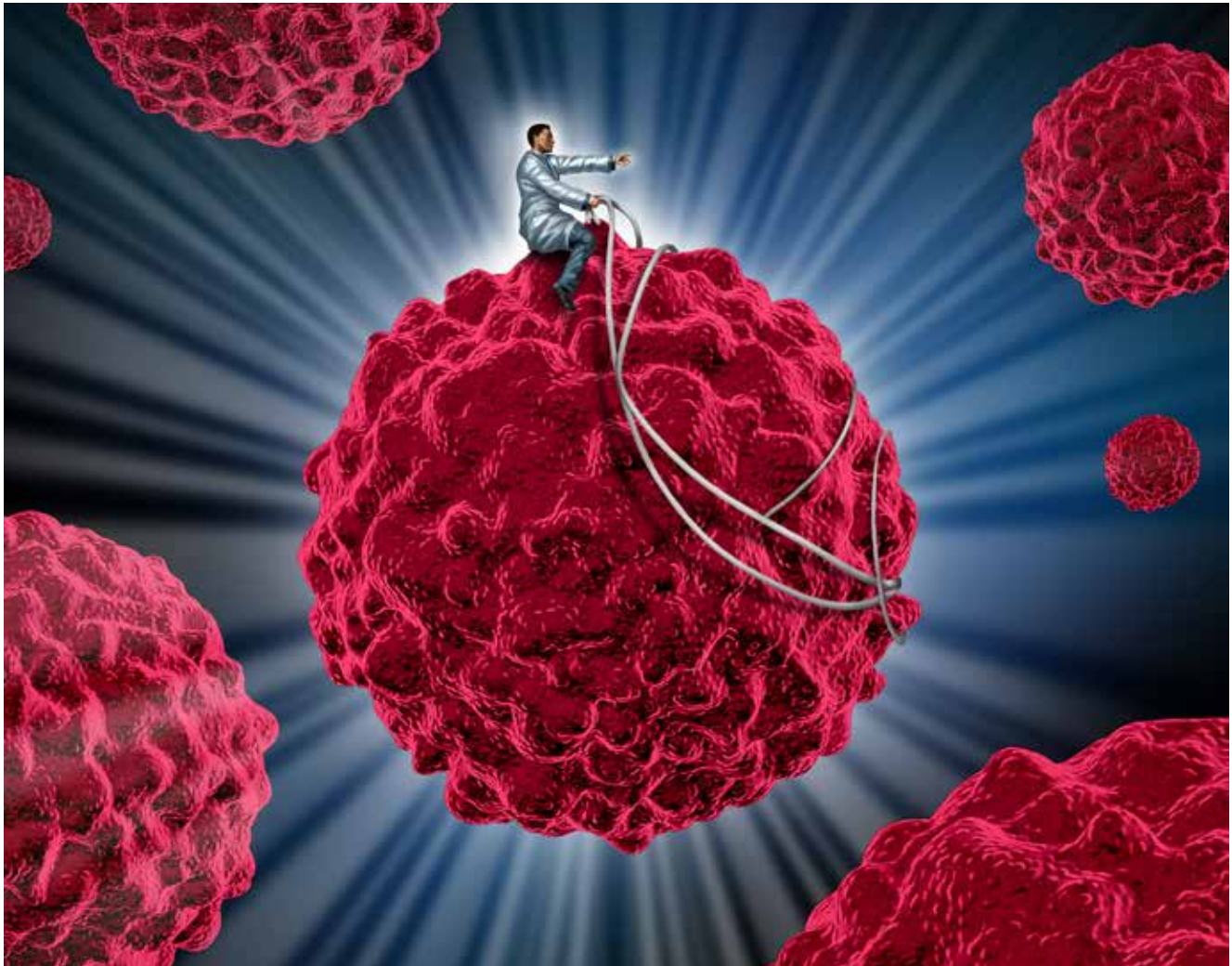
Progress has been largely due to decades of improvements in surgery, radiation therapy and chemotherapy, oncologists say. But from these traditional fields, “The likelihood that we’re going to come up with something that revolutionizes our care is less and less likely,” says Dean Lee, MD, PhD, director of the Cellular Therapy and Cancer Immunotherapy Program at Nationwide Children’s Hospital.

Radiation and chemotherapies have been successful because they’re tuned to kill fast-growing cells, a hallmark of cancer. But that feature can also cause serious side effects in children whose cells are, compared to adults, also fast-growing, Dr. Lee says. In addition, the marrow infiltration that occurs from the disease itself - as well as the treatment for leukemias - can suppress or wipe out fast-growing immune cells that might otherwise recognize and attack cancer cells.

Thus, a promising alternative to traditional treatments is to restore the body’s own immune system, which unlike traditional therapies can discriminate between normal and cancerous cells.

Most immunotherapy researchers have focused on T cells and CAR T cells, which are T cells engineered to recognize a target, such as a cancer, and initiate immune responses. Dr. Lee was studying them at the University of Texas MD Anderson Cancer Center in 2007 when he found natural killer (NK) cells growing in the cultures where he was trying to grow T cells. Like weeds, the cells kept coming back when he tried to get rid of them. A colleague suggested he intentionally grow the NK cells, which were also known to have a potential benefit against cancer. Other researchers had tried to grow the cells, concentrating on using cytokine IL15, with limited success. Dr. Lee and colleagues made a large number of feeder cells with different cytokines and found that IL21 worked much better.

By 2012, Dr. Lee and his collaborators reported they could draw blood from a patient or donor, isolate the cells and in three weeks grow more than 40,000 times the NK cells. In addition to the high numbers, the lab-made cells maintained high cytotoxicity.



“They can kill all kinds of cancer cell lines,” says Dr. Lee, who is also a professor of pediatrics at The Ohio State University College of Medicine. “They have the potential to kill any cell that looks dangerous to them.”

Both T cells and NK cells kill by releasing toxins into the cells they target. However, they differ in how they identify targets. “T cells are like assassins because they are trained to recognize specific features, homing in on one target protein among a population of cells,” Dr. Lee explains. “NK cells, in contrast, are on the lookout for cells that just look dangerous or don’t belong in a population.” Specifically, NK cells monitor a wide number of proteins on the surface of cells to determine whether a cell belongs in the body or is a threat.

NK cells appear to operate in a niche well suited for pediatrics, Dr. Lee says. Many of the newest methods of enabling T cells to recognize cancer, outside of CAR T

cells, depend on high mutation rates. Almost no pediatric cancers have high mutation rates so it is less likely T cells would see these mutations in cancer cells and attack them. But, pediatric cancers, especially those being treated by traditional therapies, have high rates of stress. Stressed cells produce signals that help NK cells identify them as dangerous and destroy them.

Dr. Lee is currently involved in several clinical trials testing NK cell therapy. He and his colleagues have found that in children, some individual cancers are resistant to NK cells and some are extremely responsive, but no particular cancer type is uniformly resistant. In addition, cancer cells that have developed resistance to chemotherapy are often very sensitive to NK cells.

There are, however, types of cancers that appear to be more sensitive than others. Preclinical tests were most successful treating acute myeloid leukemia, or AML, and

the solid tumor neuroblastoma. The researchers began clinical trials with these cancers.

For AML, there have been two trials: one that combines NK cells with ordinary chemotherapy and a second that gives NK cells to patients receiving a bone marrow transplant (both of which he began while in Texas).

“If ordinary chemotherapy wipes out the NK cells, we want to add them back right away,” Dr. Lee says. “In transplants, we know NK cells recover in a couple of weeks, but we’ve found they are actually immature and not very functional for almost six months afterward. We wanted to shorten up that time.”

The transplant group received NK cells from their respective marrow donors. The chemo group received NK cells from a family member. In both cases, the cells were isolated from blood and grown in the lab. Both groups observed encouraging results that suggest the NK cells can increase remission, and decrease relapse and infections.

However, the studies in Texas have only treated adults so far. Lee is working with collaborators at Nationwide Children’s and OSU to restart the chemotherapy study and treat both children and adult patients who are otherwise resistant to treatment. The studies will determine if adding NK cells to chemotherapy can get the patients into remission more often than chemotherapy alone.

The transplant study yielded strong results. “What’s really exciting is that among the 24 patients who have been treated with this approach so far, there have only been two who have relapsed. We would normally expect at least 40 percent of these patients with high-risk leukemia to relapse.” Phase II studies of this approach are also being developed at Nationwide Children’s and OSU, to prove whether the cells provide the extra benefit.

In another trial, eight children with brain tumors received infusions of their own NK cells into the brain via a catheter. After the infusions, the researchers noted an increase in NK and T cells and other improvements. “There’s evidence that the NK cells survive in this environment and are bringing in more immune cells,” Dr. Lee says. “Not only are the NK cells important in killing foreign cells, they appear to communicate with

other immune cell types and set up the initial immune response.”

In another trial that will start this fall, Lee’s team has added NK cell therapy to a treatment for neuroblastoma. “One thing that has improved outcomes for neuroblastoma in the last 20 years is a new antibody targeted to a protein called GD2,” Dr. Lee says. “But for the antibody to work, it needs NK cells.”

For both NK and T cells, Lee says, the keys to successfully fighting an invasion of cancer cells are to:

- Have enough of them
- Make sure they are trained to recognize the invaders
- Raise the body’s signals that put these cells on high alert
- Give them the ability to quickly locate invaders
- Make sure cancer cells don’t escape

Faculty at The Research Institute at Nationwide Children’s are investigating all of these criteria.

Dr. Lee is also working with the Office of Technology Commercialization (OTC) at Nationwide Children’s to patent and license his discoveries and approaches to developing, generating and using NK cells. With OTC, he’s filed five invention disclosures so far, including cell media that outperforms the current standard for NK cell growth and expansion, particles that improve bone marrow homing by NK cells, and on methods to produce NK cells that are resistant to TGF- β . Resistance enhances anticancer activity against TGF- β -secreting tumors.

He is currently collaborating with CytoSen Therapeutics and he, OTC and the company are in stages of licensing discussions for some of the technology. Other companies have also shown interest in aspects of the NK work.

“We’re seeing successes,” Dr. Lee says. Therapies, some of them the first for human trials, are currently made in the hospital’s Good Manufacturing Practice facility. Lee says that’s an important step but the treatments and training in how to use them need to be exported to other institutions and then, through licensing agreements with pharmaceutical companies, “delivered to the rest of the country and world.”



A Better Way to Administer Probiotics?

Researchers have designed a delivery system to treat premature infants with necrotizing enterocolitis that may have applications beyond the NICU. Scioto Biosciences is bringing it to market.

Most of the time, we think biofilms are bad news. And when pathogenic microbes form biofilms, they are. The biofilms created by pathogenic microbes create fortresses that make them resistant to attack by the immune system and to current antimicrobial treatments. These fortresses make eradicating infections difficult.

But what if you could use biofilms for good? That's just what Gail Besner, MD, Steve Goodman, PhD, Michael Bailey, PhD, Lauren Bakaletz, PhD, and their teams at Nationwide Children's Hospital are investigating. Their research findings have resulted in the preclinical stage company, Scioto Biosciences.

The teams have developed *Lactobacillus reuteri* biofilm formulations that protect against experimental necrotizing enterocolitis (NEC), first described in *The Journal of Pediatric Surgery* in 2016. A new iteration of the technology may help further reduce the incidence of NEC.

“NEC is a devastating problem for premature infants. Despite decades of research, 10 percent of infants born under 1500 g will develop NEC, and we haven’t made significant progress in the prevention or treatment over the years – mortality remains as high as 30 percent for these babies,” says Dr. Besner, chief of Pediatric Surgery at Nationwide Children’s.

Bacterial colonization of the infant’s gut is critical to healthy development. Although variability exists among individuals, premature infants tend to have reduced microbiome diversity and stability and increased numbers of pathogenic Gammaproteobacteria, according to the publication.

“Using probiotics to treat NEC is not a new idea, but administering free-living probiotics has had variable results in clinical trials,” explains Dr. Besner, also a professor of Surgery and Pediatrics at The Ohio State University. “Our idea was to develop a safe, effective delivery mechanism to support a one-dose treatment to prevent NEC. In our animal models of the disease, this is what we appear to have accomplished.”

To create the biofilm, cultures of *L. reuteri* are introduced to porous, biocompatible, biodegradable 50 µm diameter dextranomer microspheres. During a brief incubation, the bacteria adhere to the microspheres and form a biofilm. In the biofilm state, the probiotics have increased resistance to gastric acidity and increased adherence to the gastrointestinal mucosa compared to free-floating bacteria.

Now, the team has published the results of their latest iteration of the technology – testing the effects of enhancing the microspheres with sucrose or maltose as diffusible cargo. The study, published in *The American Journal of Physiology*, reports enhanced performance of the single dose *L. reuteri* biofilm in experimental NEC.

According to the authors, in addition to reducing the incidence of NEC in animals, the enhanced formulation improved animal survival, reduced intestinal mucosal barrier breakdown and limited intestinal inflammation. The *L. reuteri* microspheres loaded with maltose also augmented the persistence of numerous *Lactobacillus* species in the intestinal tract and shifted the gut microbiome to be more similar to that of breast-fed babies.

“Given the microbiome disruption observed in preterm infants who go on to develop NEC, a treatment that

preserves the microbiome holds great promise as an intervention to prevent NEC,” says Dr. Besner, who is senior author of the recent publication. “Furthermore, our novel probiotic delivery system limits the expansion of pathogenic bacteria such as *Enterobacter* species, providing further evidence that it attenuates detrimental NEC-induced dysbiosis.”

All of the components – the probiotic, the microsphere, the sucrose/maltose – used in the proposed intervention are “Generally Recognized as Safe” (GRAS) by the U.S. Food and Drug Administration (FDA). The scientists hope that this will be an advantage as they begin to work to develop clinical trials using the *L. reuteri* biofilm preparation.

“The use of these microspheres represents an exciting development in improved probiotic administration. As we continue to learn more about the human microbiome and its relationship to health and disease, probiotic administration may play an increasingly important role in disease prevention and management – not just for the application to NEC,” says Dr. Besner.

Previous clinical trials of probiotics to prevent NEC have had inconsistent results. Dr. Besner and her colleagues believe that the novel delivery system they have developed will offer significant advantages over *L. reuteri* delivered in its free-living form. To that end, they are in talks with the FDA to design a clinical trial to test the delivery system in humans.

Drs. Besner, Goodman, Bailey and Bakaletz are the scientific founders of Scioto Biosciences, a collaboration between The Research Institute at Nationwide Children’s and the Indiana business accelerator, Monon Bioventures (MBCV). The Scioto Biosciences Platform has the potential to enhance efficacy wherever probiotics are used such as diabetes, neurological disorders, gastrointestinal health, alternatives to in-feed antibiotics (livestock) and others.



A Vaccine to Prevent Respiratory Syncytial Virus Disease

RESEARCHERS ARE WORKING ON A LIVE, ATTENUATED VACCINE FOR THE COMMON INFECTION.

Efforts are underway in the Center for Vaccines and Immunity at The Research Institute at Nationwide Children's Hospital to develop a vaccine to prevent disease caused by respiratory syncytial virus, or RSV.

RSV is a common infection in infants and young children; in fact, almost everyone will be infected by age two, with two to three percent being hospitalized because of their infection. In the United States, that makes RSV a major cause of hospitalization for young children, and with medical care most survive. But in the developing world, RSV is an even bigger threat,

causing more deaths in the first year of life than any other cause, except malaria.

Initially, the symptoms of RSV resemble those of a bad cold but can progress, making it very difficult to breathe. There is no antiviral drug treatment, but some children require supplemental oxygen to assist with breathing, and IV fluids.

Mark Peeples, PhD, a principal investigator in the Center for Vaccines and Immunity, is one of a team of investigators researching how RSV evades the immune system and causes severe disease. Along with Asuncion Mejias, MD, PhD, and Octavio Ramilo, MD, also in

the Center, his goal is to develop a safe and effective vaccine for the virus.

To tackle this problem, the team has received a grant from the National Institutes of Health, in collaboration with researchers at The Ohio State University and the University of South Florida. Dr. Peeples and his colleagues are working to produce a live attenuated vaccine for RSV. Other groups have found that some attenuated vaccine candidates can still cause symptoms, while weaker ones that don't also don't stimulate an immune response.

Dr. Peeples and his collaborators are working on multiple fronts, using new approaches to attenuate the virus while also increasing its ability to arouse a protective immune response. In addition, the team aims to improve the production efficiency of the vaccine so that it will be affordable, and use new methods that they have developed for evaluating the immune response to the vaccine and its safety.

"We are trying to make a logical vaccine with a whole spectrum of attenuation levels to choose from," says Dr. Peeples, who is also professor of pediatrics at The Ohio State University College of Medicine. "Once we get to clinical trials, if we find that one candidate vaccine causes too much nasal congestion, we'll go down the list to one that's less virulent and test it right away."

One of the 11 RSV proteins suppresses a patient's own immune response. But the same protein is required for RSV to replicate, so it can't simply be removed from the virus. A live attenuated vaccine virus must be able to grow well in the lab to manufacture a vaccine. So, team member Dr. Michael Teng at the University of South Florida is mutating that protein to find a version that does not interfere with the immune response but can still perform its other functions for the virus.

Working with another team fifteen years ago, Dr. Peeples learned that the virus only infects the ciliated cells in our airways. Now, his lab isolates progenitor cells from donated human lungs and grows them into miniature airway cultures complete with ciliated cells and mucus-producing cells. As the cilia beat, they push the mucus around the well.

"The process to generate these specialized cells takes five weeks, but once we have them we can test each virus mutant in a situation that is more like real-life, in the

real cells that RSV targets in a person," says Dr. Peeples.

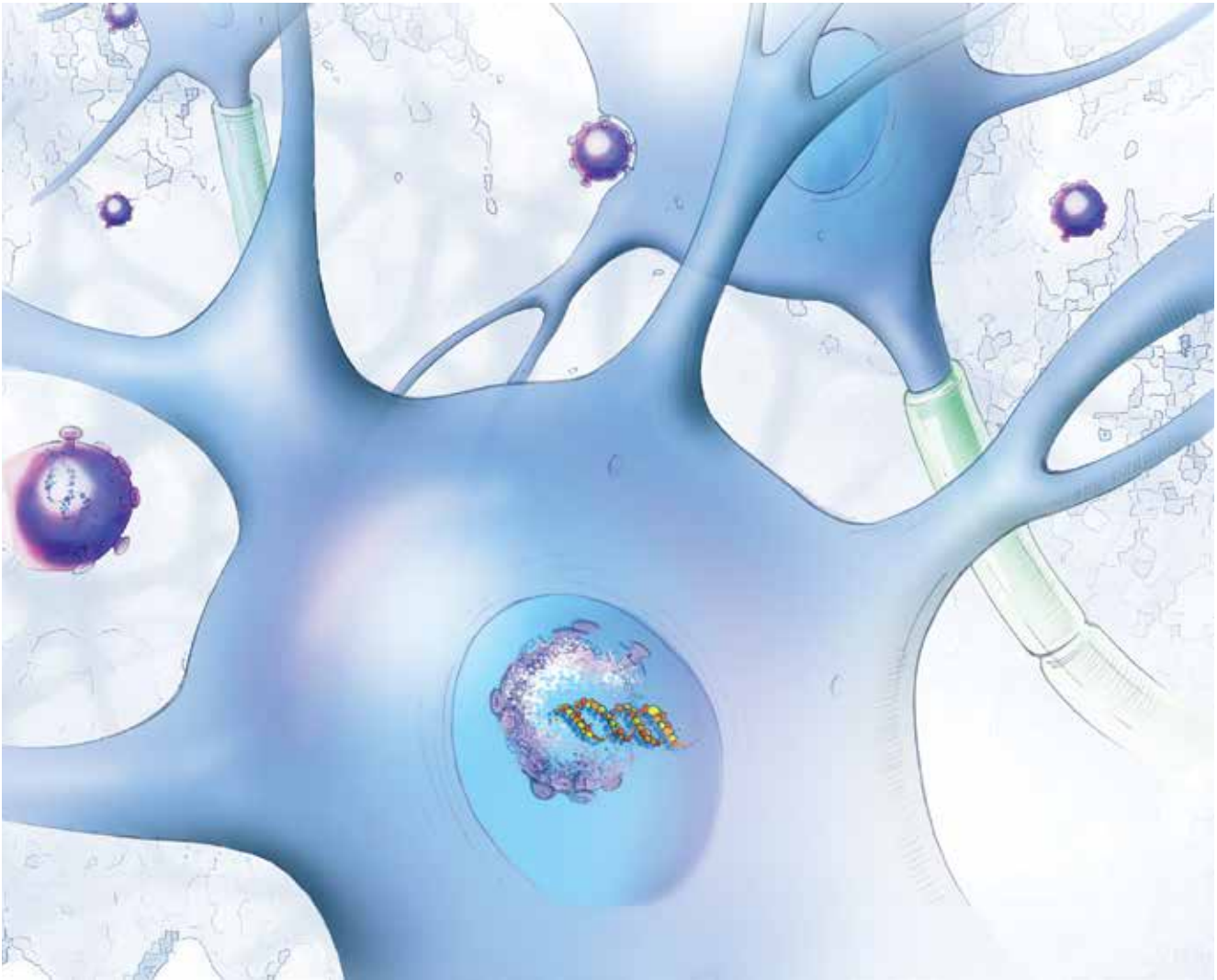
The other system they have is the cotton rat. Dr. Peeples says these rodents are much better than the standard mouse model for studying RSV. One of the team's members, Dr. Stefan Niewiesk, at the OSU College of Veterinary Medicine is an expert in using the cotton rat to study virus infections.

Dr. Niewiesk is testing the attenuated viruses in cotton rats to see if they induce a good immune response without causing sickness and if they protect the animal from developing disease when they are infected later with RSV.

Dr. Jianrong Li, also from the OSU College of Veterinary Medicine, is continuing to produce viruses with attenuating mutations to create a full spectrum of attenuated viruses. These mutants are being tested in the ciliated airway cultures and in cotton rats and those with the best characteristics combined.

"We want to develop a vaccine that induces a better immune response and is more protective than even the original RSV," says Dr. Peeples. The live, attenuated RSV vaccine would be given as nose drops to infants at six months to one year of age.

After the team chooses the best group of candidate attenuated vaccine viruses, the next step will be the FDA for approval of Phase I clinical human trials.



Gene Therapy for Fascioscapulohumeral Dystrophy

Work in animal models and human cells shows the approach can silence the target gene safely and effectively.

Fascioscapulohumeral dystrophy (FSHD) is a dominantly inherited muscular dystrophy. It was named for the muscle groups that are classically affected but there is wide variability in presentation. Additionally, the age of onset, rate of progression, and severity of muscle weakness can all vary between patients.

“It’s among the most complex genetic disorders that we know about,” says Scott Harper, PhD, principal investigator in the Center for Gene Therapy in The Research Institute at Nationwide Children’s Hospital.

The complexity is not just clinical; it was only within the last ten years that researchers discovered the molecular mechanisms behind FSHD. The condition

is caused by the de-repression of a gene called DUX4 (double homeobox 4). This gene helps the embryo divide very early on in development and then normally turns off. In FSHD, DUX4 turns back on, or is de-repressed, in muscle cells, eventually causing them to die.

Since FSHD is caused by the expression of the toxic DUX4 gene in muscle, Dr. Harper is developing a gene therapy approach that involves suppression of DUX4 with targeted microRNA delivered via viral vectors.

There was no way to silence a dominant disease gene until RNA interference emerged as a potential molecular therapy about 20 years ago. The technique takes advantage of the fact that the cells of all organisms, including humans, use noncoding sequences called microRNAs to regulate gene expression. These microRNAs bind to other RNA in the cell and cause them to be degraded. It is one method that organisms use to control which genes are turned on and off in different tissues.

Although RNA interference shows great promise for treating dominant genetic conditions, such treatments are still experimental with limited clinical safety and efficacy data.

Dr. Harper, who is also associate professor of Pediatrics at The Ohio State University College of Medicine, has been leading efforts at Nationwide Children's to develop an RNA interference gene therapy for FSHD. His group is modifying microRNA sequences to target DUX4 and then packaging them in an adeno-associated viral vector that can be injected into the muscle tissue. The microRNA is produced in cells, where, if it finds DUX4, it sends the gene to be silenced.

But before new therapies can be used in human patients, they must first be exhaustively tested in animal models to ensure that they work and are safe. Dr. Harper has developed two mouse models of FSHD to test the safety and efficacy of delivering interfering RNA to DUX4 in small animal preclinical studies.

"I started working with Scott in 2010," says Margaret Barkett, PhD, a senior licensing associate for the Office of Technology Commercialization. "It has been a bumpy ride because there were no good animal models to validate the therapeutic candidates until Scott and his group developed theirs fairly recently."

Dr. Harper and his team have also made three dozen candidate microRNA sequences capable of silencing DUX4. Toxicology testing narrowed the candidates down to a single sequence that seems most promising – it safely reduced DUX4 protein and mRNA and improved muscle damage in mice.

"This candidate sequence seems to be safe when we inject it in mice or deliver it to human cells at very high levels," says Dr. Harper.

The next step is more toxicology research on this particular RNA sequence, hopefully leading to a Phase I clinical trial.

Dr. Harper hopes to develop a treatment for FSHD that could be delivered systemically or intramuscularly to effectively reduce DUX4 expression. Dr. Barkett says that Nationwide Children's has the infrastructure to support these efforts.

"In addition to our clinical services capability, we have very good basic science as well as the capability to manufacture the gene therapy product here at Nationwide Children's," says Dr. Barkett.

And although Dr. Barkett says there is a lot of interest from companies to license this gene therapy, Dr. Harper is taking the necessary time to make sure they get it right.

"Even though this concept of RNA interference has been around for a couple decades, there have been only a limited number of clinical studies done," says Dr. Harper. "We are taking a conservative approach, making sure this is safe and effective before using it in humans."

Therapeutics



Inhibition of Notch Signaling Reduces the Incidence of Aortic Abdominal Aneurysm (Reference # 2011-010)

Abdominal aortic aneurysm (AAA), defined as a localized dilatation of the abdominal aorta, is a life-threatening disease, which has an estimated incidence of 2-4% in the adult population. AAA is characterized by activation of the inflammatory response causing extensive remodeling of the aortic wall. Researchers at Nationwide Children's Hospital have demonstrated that decreased levels of Notch1 protect against the formation of AAA by preventing macrophage recruitment and down regulating the inflammatory response in the aorta.

Improved Delivery of Antisense Oligonucleotides (Reference # 2012-025)

A major hurdle for designing effective therapeutics is delivery, especially throughout the neural tissue. Researchers at Nationwide Children's Hospital and The Ohio State University have discovered that when a morpholino is mixed with a particular omnipaque dye, iohexol(omnipaque1-N,3-N-bis(2,3-dihydroxypropyl)-5-[N-(2,3-dihydroxypropyl)-acetamido]-2,4,6-triiodobenzene-1,3-dicarboxamide) the morpholino is delivered efficiently to all regions of the brain. Unlike other methods that have been used to increase delivery, such as charged moieties or peptides, which can elicit toxicity or an immune response, this dye is used routinely in the clinic.

Long Term Pyruvate Supplementation in Drinking Water ad Libitum Ameliorates Neuropathy in the Animal Model for Charcot-Marie-Tooth (CMT) Neuropathy (Reference # 2014-038)

Charcot-Marie-Tooth neuropathies (CMT) affect approximately 1 in 2,500 people in the United States, but there is currently no treatment for CMT. Researchers at Nationwide Children's Hospital have found that oral delivery of sodium pyruvate as an energy source for peripheral neurons results in functional improvement in a mouse model of CMT. Sodium pyruvate has been used to safely treat a variety of conditions, suggesting that oral delivery will be a safe, effective treatment for CMT.

Therapeutics

Supplemental Triple Antioxidant Therapy as a Treatment for Anoctamin 5 Deficient Muscular Dystrophies (Reference # 2015-062)

Limb-girdle muscular dystrophy 2L (LGMD2L) is a progressive disease that results in muscle weakness, pain and exercise intolerance. There is currently no treatment for LGMD2L. Researchers at Nationwide Children's Hospital and the Ohio State University have found that impaired mitochondrial function results in disease pathogenesis. The current invention uses triple anti-oxidant therapy to reverse mitochondrial damage and correct exercise intolerance. Because LGMD2L is slowly progressive, this treatment can delay disease progression, either alone or in conjunction with gene therapy.

Novel VSV-Based Vaccine Platform for Zika Virus (Reference # 2017-028)

There is currently no vaccine available for protecting against Zika virus (ZIKV) infection and disease. Researchers at Nationwide Children's Hospital and The Ohio State University have developed novel candidate ZIKV vaccines that use vesicular stomatitis virus to express ZIKV proteins. The protection conferred by our vaccines does not rely on antibodies against the ZIKV envelope protein, eliminating the potential problem of antibody dependent enhancement of other species of flavivirus. Our candidate vaccines are highly attenuated while still inducing a protective immune response against ZIKV infection.

Maternal Administration of Ethyl Pyruvate (EP) to Extend Gestation and Optimize Newborn Outcomes (Reference # 2017-039)

Preterm birth is a significant public health problem worldwide, yet the underlying biological mechanisms remain unclear. There is currently no treatment to prolong pregnancy or provide fetal neuroprotection in the setting of inflammatory preterm labor. Researchers at Nationwide Children's Hospital have identified a role for ethyl pyruvate in preventing inflammation-induced preterm birth and providing fetal neuroprotection during acute intra-uterine inflammation. This novel pharmaceutical intervention has the potential to lower neonatal morbidity and mortality.

Vaccines for Prevention of Respiratory Syncytial Virus (RSV) Infections (Reference # 2017-079)

Respiratory syncytial virus (RSV) is the most frequent cause of lower respiratory disease and hospitalization in infants, but there is currently no vaccine available to prevent or treat RSV disease. Researchers at Nationwide Children's Hospital and The Ohio State University have developed a novel method for designing RSV vaccines using a Vesicular Stomatitis Virus (VSV) vector. VSV is attenuated in humans, so it can infect people and express inserted genes without causing disease. Additionally, VSV grows to high titers in culture, allowing for efficient vaccine production.

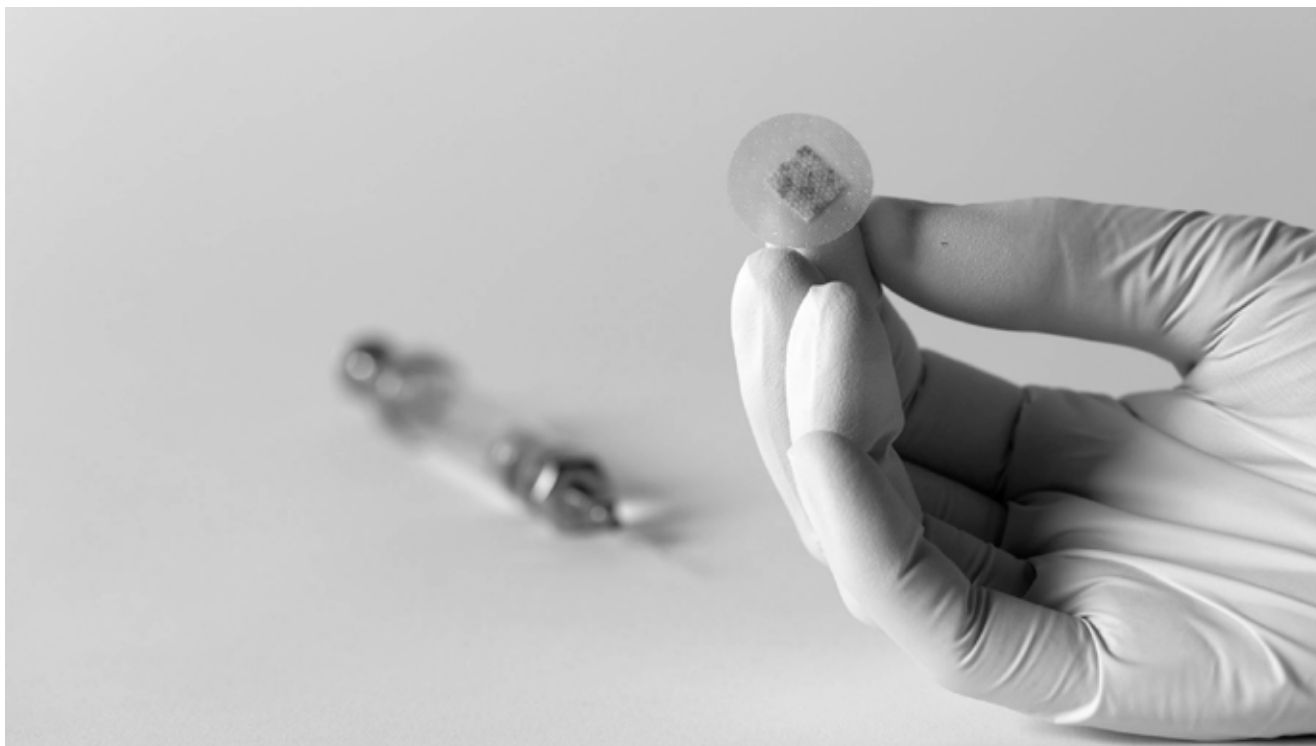
Methods of Treating and Preventing Intestinal Injury Related to Hemorrhagic Shock and Resuscitation (Reference # 2007-006)

Hemorrhagic shock and resuscitation (HS/R)-induced injuries often result from trauma or severe blood loss and can quickly progress to organ failure. Researchers at Nationwide Children's Hospital have developed a novel method for treating subjects at risk for HS/R by administering Heparin Binding-Epidermal Growth Factor (HB-EGF). Administration of HB-EGF protects intestinal epithelial and endothelial cells from HS/R-induced injury in a rat model. This novel method may have broad clinical availability for treating or preventing a range of intestinal injuries in pediatric and adult patients.

Immunotherapeutic Method for Preventing Uropathogenic *Escherichia coli* from Infecting Host Epithelial Cells (Reference # 2012-030)

Chronic and recurrent infections can result from bacterial persistence within human host cells. Intracellular bacteria are protected from the immune system and antimicrobial therapies and can cause lysis of cells allowing subsequent re-infection. Researchers at Nationwide Children's Hospital and the University of Southern California have identified a novel method for preventing uropathogenic *Escherichia coli* from invading host cells by using antisera directed against the *E. coli* family of DNABII proteins.

Therapeutics



Patch Delivery System for Vaccines against Ear Infections (Reference # 2013-041)

Non-invasive immunization tends to be more cost effective and has increased compliance compared to invasive vaccination methods, making it ideal for both the developed and developing world. Researchers at Nationwide Children's Hospital have designed a method of immunizing against bacterial diseases of the respiratory tract, including ear infections, by applying a vaccine formulation to a patch and placing it on the skin behind the ear. Placement in this unique location is a non-invasive way of promoting an immune response to prevent or resolve infections.

Anti-LYST Therapeutic Immunomodulation (Reference # 2014-002)

Approximately 1 in 100 infants are born with a congenital heart defect and 10% of these defects result in death. Tissue engineered vascular grafts (TEVG) are an ideal way of mending these defects. Stenosis is the most common graft-related complication for TEVGs, affecting approximately 30% of patients. Inventors at Nationwide Children's Hospital have discovered that LYST, or lysosomal trafficking regulator, modulates the immune system and thereby contributes to TEVG stenosis formation. The current work focuses on developing an anti-LYST therapy, as a novel method of inhibiting the formation of TEVG stenosis.

Method of Using Neural Stem-Cell Derived Exosomes to Protect Against Necrotizing Enterocolitis (Reference # 2014-003)

Stem cells protect the intestines from necrotizing enterocolitis through a combination of engraftment and release of secreted components such as growth factors. However, local stem cell delivery is linked to increased risks and side effects. Researchers at Nationwide Children's Hospital have developed a novel cell-free method for delivering secreted components and growth factors to the intestine through the use of exosomes derived from stem cells. This method provides a safer alternative to treat intestinal injury.

Therapeutics

Therapeutic Heat Shock Dulation of SMN Levels in Spinal Muscular Atrophy (SMA) (Reference # 2014-013)

Spinal Muscular Atrophy (SMA) is a neurodegenerative disease that occurs in 1 of every 6,000 births, and is caused by low levels of the SMN protein. SMA patients have inherited deletions or mutations of *SMN1*, one of two genes encoding SMN. *SMN2* contains a translationally silent single nucleotide switch that causes mis-splicing of its transcript, rendering the protein non-functional thus unable to compensate for the loss of *SMN1*. Current efforts to combat SMA revolve around increasing the stability or altering the splicing of *SMN2*. Researchers at Nationwide Children's Hospital have developed a novel method for modulating *SMN2* splicing in a therapeutic context by inducing the heat shock response. This novel splicing-corrective treatment is capable of increasing protein levels of SMN *in vitro* and is being further developed for use in murine models of SMA.

Utilizing Antisense Oligonucleotides to Modulate *MDM2* Alternative Splicing (Reference # 2014-014)

Murine Double Minute 2 (*MDM2*) is an E3 ubiquitin ligase and negative regulator of the tumor suppressor protein p53. Under normal conditions, *MDM2* is constitutively spliced to generate a full-length protein, and promotes the proteasome-mediated degradation of p53. However, under stress *MDM2* undergoes alternative splicing, generating splice variants that are unable to bind and regulate p53. Subsequently, p53 becomes upregulated and activates downstream targets involved in apoptosis and cell cycle arrest. Investigators at Nationwide Children's Hospital have developed a novel splicing-corrective treatment to modulate the splicing of p53-modifier *MDM2* in cancer.

Exosomes as a Novel Therapy for Fibrosis (Reference # 2014-024)

Fibrosis (chronic scarring) accounts for up to 45% of deaths in the developed world, but there are no FDA-approved anti-fibrotic therapies. Researchers at Nationwide Children's Hospital have found that exosomes from healthy cells contain molecular signals reflective of a healthy state and can be delivered to fibrotic cells that mitigate or reverse fibrosis. This novel therapy will have an impact on numerous diseases, including liver disease, cardiovascular disease, pulmonary fibrosis, kidney disease, and macular degeneration.

Novel Treatment for Otitis Media by Preventing NTHI Invasion of Host Epithelial Cells (Reference # 2014-029)

Otitis media (OM) is a leading cause of hearing loss in children in the U.S. Nontypeable *Haemophilus influenzae* (NTHI) is a major causative agent of OM and other diseases of the respiratory tract. NTHI-mediated OM often persists despite repeated antibiotic therapies, due in part to the ability of NTHI to invade host epithelial cells. Researchers at Nationwide Children's Hospital have developed a novel approach to treating or preventing OM by inhibiting Arp2/3-mediated invasion of host cells.

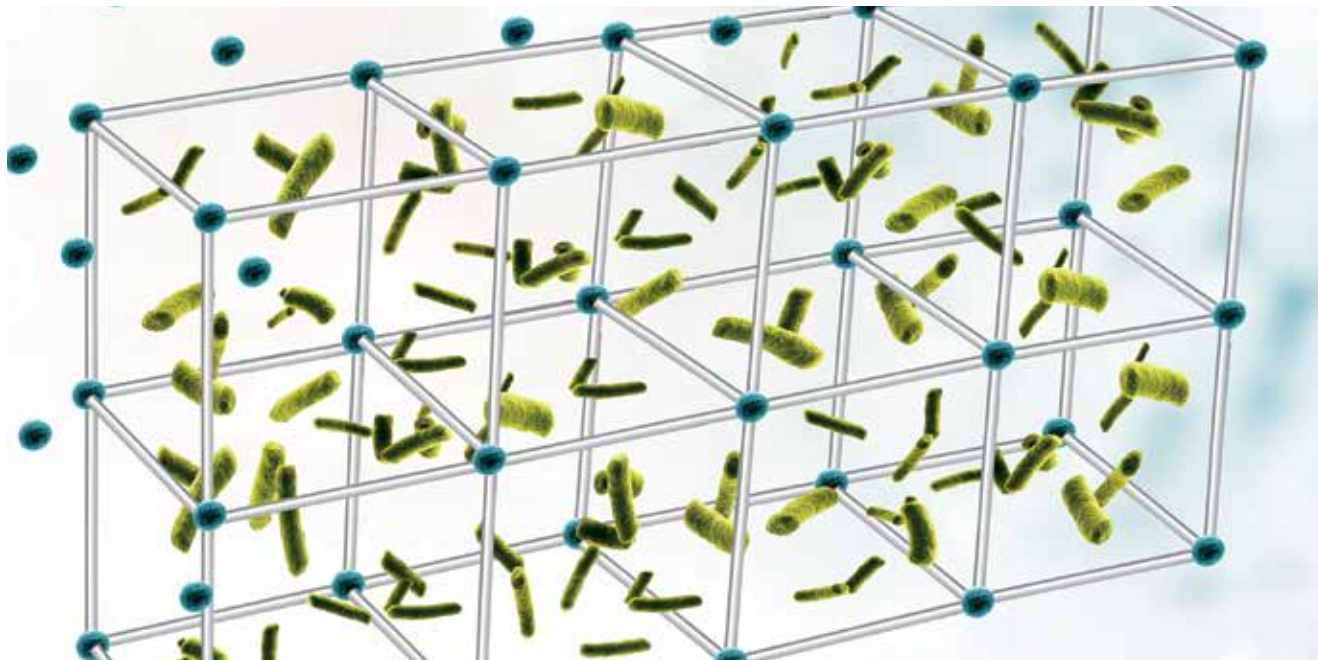
Novel Approach for Removal of Caries Causing Bacteria within the Oral Cavity (Reference # 2015-023)

Dental caries, or tooth decay, affects 84% of adults and is caused by the demineralization of the tooth surface by bacteria (*Streptococcus mutans* and other Streptococcal species) residing in the oral cavity. These bacteria possess surface-associated glucosyltransferases, which convert sucrose to glucan, thus facilitating their attachment to the tooth surface and further colonization. Current treatments for the prevention of tooth decay involve flooding the oral cavity with oral health care products which harm both healthy (commensal) and pathogenic (harmful) bacteria. Investigators at Nationwide Children's Hospital have developed a novel anti-cariogenic formulation that provides targeted elimination of cariogenic and harmful bacteria with minimal disturbance of commensals.

A Novel Therapeutic Agent for the Treatment of *Neisseria gonorrhoeae* (Reference # 2015-033)

Resistance of *Neisseria gonorrhoeae* to antibiotics has developed rapidly in recent years, leading to increased efforts to identify novel antimicrobials. Researchers at Nationwide Children's Hospital and The Ohio State University have found that AR-12, a drug used in oncology, has antimicrobial properties in the context of *N. gonorrhoeae* infection of normal human mucosa. Further, AR-12's antimicrobial activity targets the human pathways required for infection, not the pathogen itself, suggesting that it is unlikely to encourage the development of bacterial resistance mechanisms.

Therapeutics



Chimeric Peptide Vaccine for the Treatment of Biofilm-Associated Disease (Reference # 2016-054)

Sixty-five to 80% of infections involve biofilm-associated microorganisms. The major challenge with bacterial biofilms is the inability of the host immune system and/or antibiotics and other antimicrobials to gain access to the bacteria protected within the biofilm. Inventors at Nationwide Children's Hospital have developed a novel chimeric polypeptide vaccine candidate for the disruption of biofilms.

Methods for Increasing Autophagy and CFTR Expression in Patients with Cystic Fibrosis (Reference # 2016-037)

Cystic fibrosis (CF) is a systemic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR). Multi-drug resistant pathogens remain a major cause of chronic morbidity and mortality in CF patients, due in part to deficient autophagy in CF macrophages. Researchers at Nationwide Children's Hospital and The Ohio State University have identified a novel therapeutic agent that increases CFTR expression and restores autophagy function in CF affected cells.

Novel Approaches for the Disruption of Bacterial Biofilms (Reference # 2010-002; 2010-016; 2015-030; 2017-008; 2015-057)

The major challenge with bacterial biofilms is the inability of the host immune system and/or antibiotics and other antimicrobials to gain access to the bacteria protected within the biofilm. Inventors at Nationwide Children's Hospital have developed a portfolio of approaches to induce catastrophic collapse of the biofilm matrix to allow host or antibiotic-mediated clearance of the resident bacteria. These approaches include targeting the DNABII proteins in the extracellular matrix of biofilms formed by both respiratory and oral pathogens, as well as the generation of biofilm-targeted and epitope specific monoclonal antibodies for biofilm disruption. Additionally, the inventors have developed methods to disrupt bacterial biofilms without causing accompanying inflammation.

Use of Fab Antibody Fragments for the Removal of Biofilms (Reference # 2016-048)

Biofilms are surface-attached communities of microorganisms that play a critical role in the vast majority of chronic and recurrent infectious diseases. The CDC and the NIH recently estimated that 65% to 80% of infections involve biofilm-associated microorganisms. DNABII proteins and extracellular DNA (eDNA) are integral to the structural

Therapeutics

integrity of biofilms formed by all human bacterial pathogens tested to date. Inventors at Nationwide Children's Hospital have developed novel, biofilm-specific Fab antibody fragments to target the DNABII proteins either as a therapeutic or potential vaccine candidate to disrupt and/or prevent bacterial biofilm formation.

Method to Prevent Phagocytosis-Internalization of Pathogenic Bacteria into Host Cells (Reference # 2013-027)

Burkholderia cenocepacia is a gram negative opportunistic pathogen that is a major causative agent of infection in patients with cystic fibrosis (CF). *B. cenocepacia* exists extracellularly in a biofilm lifestyle, but recently has been shown to also proliferate in macrophages in the lungs of CF patients as an intracellular pathogen. Researchers at Nationwide Children's Hospital, University of Southern California and The Ohio State University have identified methods for diminishing and eradicating reservoirs of *B. cenocepacia* from the lungs of CF patients by targeting the DNABII family of DNA binding proteins.

Enhanced Immunogenicity of a modified RSV vaccine with mutations in one or both non-structural protein (Reference # 2011-001)

Respiratory syncytial virus (RSV) is the leading cause of upper and lower respiratory tract infections in infants and young children, and the most common cause of bronchiolitis and pneumonia in children younger than 1-year of age. A vaccine does not exist in part because RSV non-structural protein genes (NS1 and NS2) suppress the immune system rendering the host unable to elicit an appropriate adaptive immune response. Researchers at Nationwide Children's Hospital and University of South Florida have identified mutations in NS1 and NS2 that allow the virus to induce a measurable interferon response, thus a more robust adaptive immune response. Their findings have built a solid foundation that could be exploited to generate a more immunogenic RSV vaccine.

Respiratory Syncytial Virus (RSV) Expressing Two Added Genes, Green Fluorescent Protein (GFP) and Renilla Luciferase, but Not the RSV G (attachment) Glycoprotein (Reference # 2013-043)

Respiratory syncytial virus (RSV) is the leading cause of upper and lower respiratory tract infections in infants and young children. Preclinical therapeutic studies require simple readouts for viral replication (e.g. readouts for high throughput screening of compound libraries). Researchers at Nationwide Children's Hospital and the NIH have constructed a recombinant RSV that expresses both green fluorescent protein (GFP) and Renilla luciferase that in turn allow for rapid quantifiable real time readout of virus replication or titer. In addition, the RSV virus is constructed with a G glycoprotein mutation that could reduce false positive hits during compound library screens.

Novel Live Attenuated Vaccines for Human Pneumoviruses (Reference # 2014-004 & 2015-004)

Pneumoviruses include many important human and animal pathogens. Among these viruses, human respiratory syncytial virus (RSV) and metapneumovirus (MPV) is a leading cause of acute respiratory tract infection in infants and children. Despite major efforts, there is no vaccine to combat these diseases due to the difficulty of constructing a virus that is stable, attenuated and can still provoke an adaptive immune response. Infectious disease experts at Nationwide Children's Hospital and The Ohio State University have developed a panel of recombinant RSV (rhRSV) and MPV (rhMPV) that are defective in zinc binding activity. The inability of these viruses to bind zinc has rendered them genetically stable and highly attenuated in an animal model. Therefore, our rhRSVs and rhMPVs are excellent vaccine candidates for hMPV.

Increasing the Yield of Respiratory Syncytial Virus Live Attenuated Vaccines (Reference # 2014-045)

A widespread economic problem of RSV vaccine candidates is their inefficient production. RSV vaccine candidates are produced in Vero, a cell line isolated from African green monkey kidney. Infectious disease experts at Nationwide Children's Hospital have discovered RSV grown in Vero cells has a cleaved, non-functional attachment glycoprotein (G protein). Our experts identified mutations in the G protein that prevent its cleavage during production in the Vero cell line. Importantly, these mutations increase RSV vaccine production efficiency up to 10 times, making vaccine production now economically feasible.

Gene Therapies and AAV Production



Gene Therapy Approach for Charcot-Marie-Tooth Neuropathy (Reference # 2008-002)

Charcot-Marie-Tooth (CMT) neuropathies are one of the most common inherited neurological conditions affecting 1 in 2,500 people in the United States. Both children and adults are affected, causing sensory and motor dysfunction, pain, and a need for ambulatory aids. Researchers at Nationwide Children's Hospital have developed a gene therapy approach that delivers neurotrophic factor NT-3 by intramuscular injection to promote nerve regeneration in CMT disease as well as other nerve diseases with impaired nerve regeneration.

MicroRNA Delivery as a Novel Therapeutic Strategy for Liver Cancer (Reference # 2009-002)

Therapeutic strategies based on small RNA-guided gene regulatory pathways hold great promise for many diseases. Gene therapy experts at Nationwide Children's Hospital and John Hopkins University have identified a microRNA (miRNA) that when expressed can induce cell-cycle arrest in a hepatocellular carcinoma (HCC) cell line. Our experts further demonstrated systemic adeno-associated viral (AAV) delivery of this particular miRNA protected mice from liver cancer progression without toxicity. This invention identifies a miRNA with potent tumor suppressor activity that exhibits great promise as a liver cancer therapeutic agent and further demonstrates safety of delivering a miRNA-based therapy with AAV in an animal model.

RNAi Therapy for Dominant Limb Girdle Muscular Dystrophy Type 1A (Reference # 2011-002)

Researchers at Nationwide Children's Hospital have designed novel microRNAs that specifically knock down the expression of the protein Myotilin. Animal studies assessing decreased expression of Myotilin suggest that targeting the protein may be a viable therapeutic strategy for treatment of Limb Girdle Muscular Dystrophy Type 1A (LGMD 1A). This RNAi strategy can also be adapted to broadly impact a large class of dominant muscle disorders.

Gene Therapies and AAV Production

Use of U7snRNA Vector to Skip Duplications in DMD Exon 2 (Reference # 2013-012)

Duplicated exons in the DMD gene represent approximately 6% of the Duchenne muscular dystrophy (DMD) patient population, with the duplication of exon 2 being the most common. The laboratory of Dr. Kevin Flanigan at Nationwide Children's Hospital has found that expression of four U7 small nuclear RNA carrying two new antisense sequences results in efficient skipping of exon 2. This novel treatment will restore protein function and persist over years due to its expression from an AAV vector.

Rescue of Protein Function by Activating an Internal Ribosome Entry Site in the DMD Gene (Reference # 2014-021)

Mutations in exons 1-4 of the DMD gene are present in 6% of patients with Duchenne muscular dystrophy (DMD). Researchers at Nationwide Children's Hospital have identified a novel internal ribosome entry site (IRES) in exon 5 of DMD and have developed an AAV vector encoding antisense sequences to remove exon 2, resulting in a premature stop codon and activation of this IRES. Activation of this IRES results in production of a functional N-truncated protein, and this will correct the pathologic and physiologic features of muscle injury.

Use of Gene Product to Treat Nerve Injury and Sarcopenia (Reference # 2015-008)

High levels of survival motor neuron (SMN) protein is critical for repair of motor unit connectivity after muscle damage. Neuromuscular disease experts at Nationwide Children's Hospital and The Ohio State University predicted high levels of SMN protein will reduce degenerative susceptibility of the motor unit during both injury and aging (sarcopenia). Our experts have designed a method to reduce sarcopenia or nerve damage by administering a SMN protein-increasing substance to be used as a therapy to treat nerve damage from age-related or trauma-induced muscle damage.

DUX4 Exon Skipping Strategies for FSHD Therapy Using U7-snRNA (Reference # 2015-049)

Facioscapulohumeral muscular dystrophy (FSHD) is the third most common genetic disease of skeletal muscle. The *DUX4* gene is implicated in FSHD and the full-length protein encoded by this gene is toxic to muscles and other tissues. However, a shorter isoform, which lacks the C-terminal transactivation domain, is non-toxic. Researchers at Nationwide Children's Hospital have developed U7-based snRNAs that bias protein production toward the short nontoxic version of *DUX4* or to block incorporation of exon 3. This new strategy represents a novel therapy for FSHD.

CrispRCas9 Therapeutic Strategies for Titin-Based Cardiomyopathies (Reference # 2015-074)

Titin is a large protein that is important for muscle elasticity and mutations in *Titin* result in muscle impairment, including cardiomyopathies. Researchers in the Lab of Dr. Rodino-Klapac at Nationwide Children's Hospital have developed a method for correcting mutations in *Titin*. Using the CRISPR/Cas9 system of genome editing, they are able to modify the *Titin* gene and resulting protein. This method can be delivered directly via intracoronary delivery to correct *Titin* mutations and rescue protein function.

Recombinant Adeno-Associated Virus Vector Gene Therapy for MPS II (Reference #2016-001)

Hunter's syndrome, or mucopolysaccharidosis II (*MPS II*), is a lysosomal storage disease caused by a deficiency of enzyme iduronate-2-sulfatase (I2S). The greatest challenge in developing therapies for *MPS II* is to achieve efficient central nervous system (CNS) delivery across the blood-brain barrier (BBB). Researchers at Nationwide Children's Hospital are developing a gene therapy vector (systemic delivery) to cross the BBB for treatment of the CNS and also for somatic manifestation of MPS.

Gene Therapies and AAV Production



AAV Delivery of Mir29 to Suppress Fibrosis in Muscular Dystrophy (Reference #2016-007)

Duchenne muscular dystrophy (DMD) is caused by dystrophin deficiency resulting in muscle loss and progressive muscle weakness and fibrotic scarring. Fibrotic infiltration is profound in DMD and is a significant impediment to any potential therapy. Researchers at Nationwide Children's Hospital have addressed this problem using an adeno-associated virus (AAV) approach to deliver MicroRNA 29 (miR-29) to suppress fibrosis. Initial results using AAV-delivered miR-29 as an anti-fibrotic therapy suggest that there is significant beneficial effect with reduced collagen and elastin levels, which are key contributors in fibrosis. This work provides a rationale for overexpression of miR-29 to reduce fibrosis along with dystrophin replacement in translational, pre-clinical studies.

Induction of dystrophin DelCH2 isoform (Reference # 2016-069)

Absence of the dystrophin protein leads to the severe muscle disorder Duchenne muscular dystrophy (DMD). Nearly asymptomatic patients have been identified to produce a functional N-terminal truncated dystrophin protein. Gene therapy experts at Nationwide Children's Hospital are developing a U7-snRNA exon skipping strategy to facilitate expression of a truncated dystrophin protein for patients carrying mutations within exon 6 to 9 of the DMD gene, rendering their dystrophin nonfunctional. Our experts have effectively skipped exon 8 in patient-derived cell lines and, in turn, produced a functional truncated dystrophin protein product.

AAV-Mediated Gene Therapy for Wilson's Disease (Reference # 2017-053)

Wilson's disease is a rare inherited disorder that causes copper accumulation in the liver, brain and other vital organs. The primary genetic insult leading to the disease is mutations in *ATP7B*, a copper-transporting enzyme. Left untreated, Wilson's disease causes serious complications or death. Gene therapy experts at Nationwide Children's Hospital have designed a gene therapy to improve the molecular defects associated deficient copper metabolism in Wilson's disease patients. Specifically, adeno-associated virus (AAV) will be used to deliver the human *ATP7B* gene systemically.

Gene Therapy for LGMD Type 2A (Reference # 2017-060)

Limb girdle muscular dystrophy 2A (LGMD2A) is the most common form of adult onset muscular dystrophy and there is currently no cure or effective treatment for this condition. Gene replacement therapy has the potential to be a meaningful treatment that does not exist. Previously, gene therapy experts at Nationwide Children's Hospital found they could restore muscle regeneration by delivering the *CAPN3* gene via adeno-associated virus (AAV) gene therapy in a mouse model of LGMD2A. Now, our experts have redesigned this gene therapy so that *CAPN3* expression is under control of a promoter that will reduce potential off-target effects and thus has advantages over their previous approach.

Gene Therapies and AAV Production

Induction of Dystrophin isoforms lacking at least exon 44 (Reference # 2017-001)

Absence of a functional dystrophin protein leads to the severe muscle disorder Duchenne muscular dystrophy (DMD). Exon skipping strategies are being developed to treat diseases caused by the production of mutated non-functional proteins, like DMD. Gene therapy experts at Nationwide Children's Hospital are developing a U7-snRNA exon skipping strategy to induce expression of *dystrophin* (DMD) missing exon 44 as a therapy for patients carrying mutations including exonic deletion of exon 43 or 45, and exonic duplication of exon 44 of *dystrophin*. Our experts have constructed several lead antisense sequences in an adeno-associated virus (AAV) vector to cause skipping of exon 44 and have begun to test their effects in patient-derived cells as well as mouse models of the disease. Injection of antisense sequences has been largely investigated however not explored as an AAV gene therapy. Pre-IND submission is planned in the near future.

QC Assays for GMP Production (Reference # 2015-068, 2015-069, 2015-070, 2018-010, 2018-011, 2018-012, 2018-013, 2018-014, 2018-015)

GMP Quality Control experts at Nationwide Children's Hospital have been diligently working to develop optimal methodologies for testing adeno-associated virus (AAV) vectors for gene delivery. Their efforts have produced nine novel methods focused on the following: (1) determining replication competent AAV, (2) determining infectious unit titer for AAV, (3) quantifying DNase resistant particles (DRP), (4) quantifying AAV total protein, (5) assessing AAV purity by SDS-PAGE, (6) determining the ratio of full to empty AAV particles, (7) identifying AAV DNA by NextGen sequencing, (8) identifying AAV capsid by western blot, and lastly (9) measuring the pH of a drug product. Overall, these methods enable the successful production and testing of GMP quality AAV vectors.

Adeno-Associated Virus (AAV) GMP Production (Reference # 2013-033, 2013-044, 2016-017, 2016-047)

GMP production experts at Nationwide Children's Hospital continually optimize their adeno-associated virus (AAV) production methods. Their diligent work has led to novel methodologies that could be utilized by others in the gene therapy field, including (1) a scalable AAV production and purification scheme utilizing plasmid DNA transfection of human embryonic kidney (HEK) 293 cells, and (2) chromatography and ultracentrifugation purification schemes that reduce contamination and improve yield. Overall, these methods enable development of increased clinical grade vector production to support trials requiring high vector dosing regimens.

Adeno-Associated Virus (AAV) Vectors Coupled to CRISPR/Cas9 (Reference # 2016-012 & 2017-009)

CRISPR/Cas9 gene editing technology is a promising tool for treating disease but requires the delivery of the large Cas9 enzyme. Gene therapy experts at Nationwide Children's Hospital have taken two different approaches to couple the CRISPR gene editing machinery with AAV, including constructing Cas9 enzyme as a stable component of the AAV particle, as well as expressing Cas9 on the surface of the viral particle.

Adeno-Associated Virus (AAV) Vectors with Modified Capsid Proteins (Reference # 2000-004)

Gene therapy experts at Nationwide Children's Hospital have recognized there is a need for constructing AAV vectors that display immunogenic peptides/polypeptides or display targeting peptides that promote delivery of DNA to a specific target cell. Our inventors have elucidated regions of the AAV2 capsid protein that are amenable to insertion of peptides that cause altered characteristics in comparison to wildtype AAV, including, but not limited to, altered cellular tropism and/or antigenic properties. Our experts' technology could vastly increase the utility of AAV vectors for clinical gene transfer.

Gene Therapies and AAV Production

Site-Specific Integration of Recombinant Adeno-Associated Virus (AAV) Vector Genomes by Rep68 Protein Expressed on the Surface of AAV Particles (Reference # 2016-055)

Adeno-associated virus (AAV) vectors are replication defective viruses that are engineered to deliver therapeutic genetic cargo to cells. The structural and enzymatic AAV proteins are traditionally supplied “in trans” to generate engineered particles for gene delivery. One constraint of AAV vectors is the size limitation of the genetic insert. Gene therapy experts at Nationwide Children’s Hospital have engineered an AAV vector that expresses the Rep78 protein on the surface of the viral particle thus eliminating the need to package the rep coding region within the particle. This strategy allows for delivery of a functional Rep78 protein while increasing the overall therapeutic gene insert size.

Optimized GMP-Grade Adeno-Associated Viral Vector (AAV) Products (Reference # 2016-018, 2016-019, 2016-020, 2016-021, 2016-024, 2016-043, 2016-044, 2016-068, 2017-022, 2017-066, 2017-069)

Gene therapy experts at Nationwide Children’s Hospital have made significant advancements in designing optimal viral vectors for producing Good Manufacturing Practice (GMP)-grade viral vector products. Our experts have optimized properties of vectors for a wide variety of adeno-associated virus (AAV) serotypes, including AAV2, 2.5, 3, 5, 6, 8, 9 and rh74. In particular, our experts have optimized virus packaging efficiency, reduced potential to form replication competent AAV and replaced the beta-lactam resistant gene with kanamycin in order to be compliant with European Union (EU) regulations. Our experts have made additional optimized vectors for AAVrh74, and AAV9 that allow for more efficient purification and improved CNS transduction, respectively.

Gene Therapy for the Treatment of Galactosemia (Reference # 2017-016)

Galactosemia is a rare metabolic disorder that occurs due to a missing or nonfunctional galactose-1-phosphate uridylyltransferase (*GALT*) gene. Currently, there are no treatment options for Galactosemia other than dietary restriction of galactose-containing food. Even with strict adherence to a galactose-free diet, many patients suffer from long-term mental and physical deficits due to small amounts of galactose found in foods. Researchers at Nationwide Children’s Hospital and the University of Utah have developed a concept for a long-term treatment option for Galactosemia patients by efficiently delivering a codon-optimized version of the human *GALT* gene using adeno-associated virus. Our gene therapy approach is engineered for a sustained expression of functional *GALT* protein and alleviation of disease symptoms.

Increasing Tissue Specific Gene Delivery by Capsid Modification (Reference # 2018-002)

Researchers at Nationwide Children’s Hospital have identified modified capsid sequences of the adeno-associated virus rh74 (AAVrh74) native capsid that improve delivery of genes to specific target cells or overall global gene delivery. These include modifications that increase specific gene delivery to either the heart or muscle stem cells.

Stem Loop RNA Mediated Transport of Mitochondria Genome Editing Molecules (Endonucleases) into the Mitochondria (Reference # 2016-032)

Pathogenic mutations and deletions in the maternally inherited mitochondrial genome (mtDNA) affect as many as 1/500 births and have poor prognosis for treatment. While the CRISPR/Cas9 system for genomic editing has created a new platform for treatment of genetic diseases, researchers have yet to apply the system to mtDNA due to the challenges of transport into the mitochondria. Inventors at Nationwide Children’s Hospital have developed a novel system for importing the CRISPR/Cas9 system into the mitochondria for editing of mtDNA.

Biomarkers



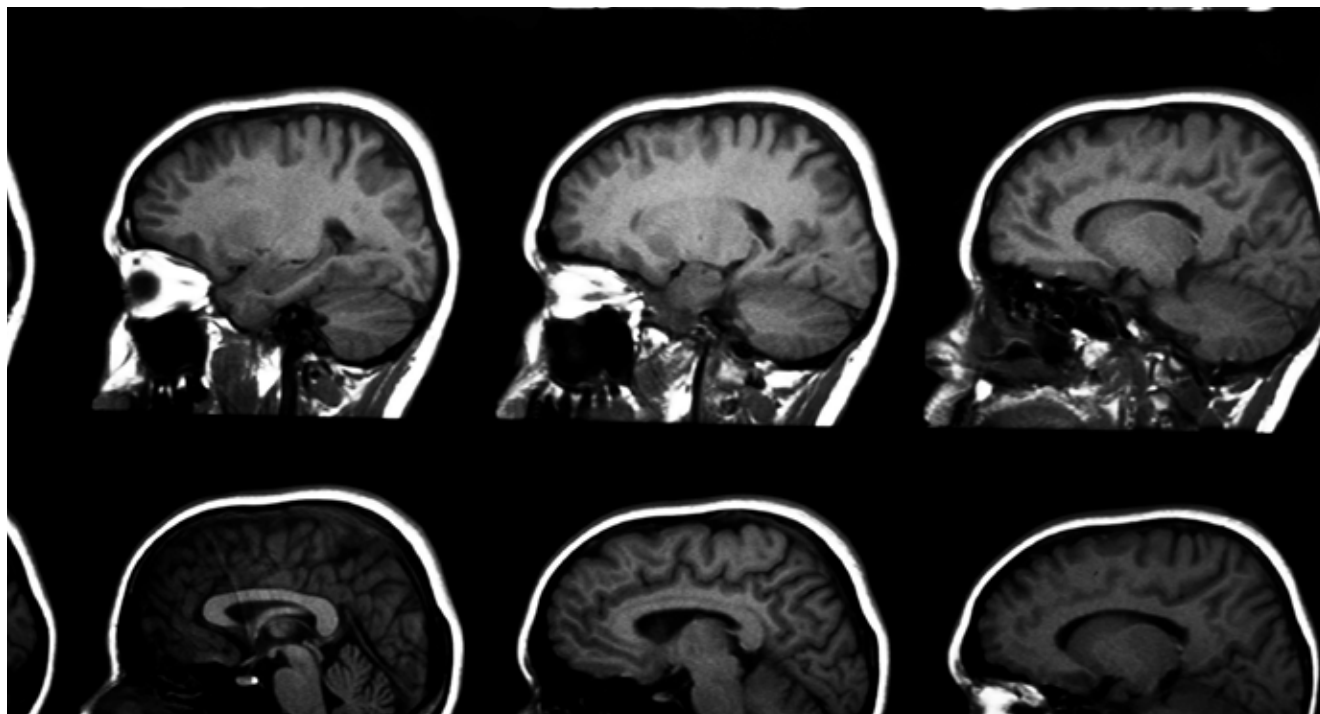
Assessment of Cirrhosis and Resolution of Liver Fibrosis Using the MicroRNA Content of Circulating Exosomes (Reference # 2015-047)

Determining the severity or progression of liver fibrosis in patients with Hepatitis B virus (HBV) allows for appropriate treatment management, but current methods to determine this are highly invasive (liver biopsy) or often inaccurate (serum indices or imaging). Inventors at Nationwide Children's Hospital have developed a minimally invasive method for assessing liver fibrosis by screening for microRNA biomarkers present in circulating exosomes. In addition to defining the current state of fibrosis, this method also predicts which patients will respond to therapy and the effectiveness of therapy.

Use of LPS Serotypes as Predictors of Disease Severity (Reference # 2013-022)

Determining the severity of urinary tract infections (UTIs) relies on patient reporting of symptoms, a difficult task when working with pediatric populations. Failure to identify severe cases of UTI can result in dangerous complications including renal scarring and urosepsis. Researchers at Nationwide Children's Hospital have found that lipopolysaccharide (LPS) serotype correlates with magnitude of pro-inflammatory responses and is predictive of clinical UTI severity. Screening for the predominant LPS serotype in a sample will determine which patients are likely to develop severe disease and require therapeutic interventions.

End User Innovation



Integrated Process and Apparatus to Prepare and Predict Pediatric Patients Who Will Successfully Undergo MRI Procedures without Sedation (Reference # 2017-047)

To ensure image quality and reduce repeat MRI exams, sedation is typically required for younger pediatric patients who will undergo MRI exams. Researchers at Nationwide Children's Hospital have developed a new process combining devices, immersive virtual reality simulation, and predictive analytics to better educate and prepare pediatric patients or research participants for routine MRI exams. Additionally, this technology will aid in predicting which patients are best suited to undergo an MRI without sedation and in predicting which research participants are likely to successfully complete a functional MRI study. This technology will improve pediatric MRI clinical throughput and reduce patient and family apprehension towards MRI exams.

PS Rocker: A Multi-Head Skin Allergy Testing Device (Reference # 2012-028)

There are 10 skin testing devices marketed in the United States for diagnosing allergies. These include single-tipped devices for testing allergens one at a time, as well as multi-head devices containing multiple testing tips on one device. One of the recently introduced multi-head devices is designed to decrease pain associated with skin testing. Current multi-head testing devices with fixed horizontal surfaces do not provide consistent intra-device contact with skin, while the single-prick devices can be impractical for children and time consuming. Clinicians at Nationwide Children's Hospital and The Ohio State University, in collaborations with other independent inventors, have developed a new allergy skin testing device, PS Rocker, which improves upon existing products by combining the precision of a single-prick test with the ease and speed of a multi-head device. Additionally, PS Rocker is less painful than traditional skin prick testing. The PS Rocker's crescent-shaped, ergonomic design enables more reproducible tip contact with the skin than conventional horizontal multi-head devices, efficiently leading to more reliable results.

End User Innovation

Medical Line Safety Enclosure (Reference # 2006-015)

In health care settings, accidental suffocation and strangulation can occur due to medical line entanglement. Nurses at Nationwide Children's Hospital have developed and clinically tested a novel medical line organizer that prevents accidental entanglement, suffocation, and strangulation of hospitalized individuals.

Child-Proof Spray Bottle (Reference # 2010-020)

A collaborative team of researchers and engineers from Nationwide Children's Hospital and The Ohio State University have designed a two-stage trigger system to prevent accidental operation of a spray bottle containing household or other chemical and dangerous solutions. The design restricts the ability of young children to trigger spray bottles in at least two ways. First, young children lack the development capability to perform the correct sequence of pressing down and keeping down the safety level first and then squeezing the trigger. Second, the size and strength of a child's hand are not sufficient to activate the mechanism.

Disposable Device to Protect Patients' Lips during Surgery (Reference # 2014-032)

Lip lacerations and burns can occur during surgical procedures in the mouth and throat. Surgeons at Nationwide Children's Hospital have developed a disposable device to cover a patient's upper and lower lips during surgery. This device adjusts to fit the patient's mouth and will act as a physical and thermal barrier to prevent injury.

Chest Tube Securing Device (Reference # 2015-037)

Chest tubes are used to remove air, liquid or pus from the intrathoracic space. Tape or sutures are currently used to prevent unintentional chest tube removal, but these cannot be used on neonatal infants due to the sensitivity of their skin. Inventors at Nationwide Children's Hospital have developed a first-of-its-kind device for securing chest tubes. This flexible device allows for the securing of chest tubes and other main lines while bending and flexing with the patient.

Novel Coin and Button/Coin Cell Battery Detection, Localization, and Discrimination Method for Objects in the Esophagus (Reference # 2015-045)

Ingestion of button cell batteries by children occurs more than 3,000 times per year in the United States and early identification of a battery in the esophagus is required to prevent severe injury or death. Inventors at Nationwide Children's Hospital and The Ohio State University have developed a handheld device to detect and localize foreign metallic bodies in a patient. Further, this device will be able to differentiate between a coin and a battery without the use of radiation (x-rays).

Portable Image Diagnostic Device (Reference # 2015-051)

There are many adapters to turn a mobile device, such as an iPod Touch, into an image-capturing, diagnostic device. However, these can yield inconsistent results because there is no standardization of lighting or distance. Researchers at Nationwide Children's Hospital have developed a platform to use with a mobile device that controls for light exposure and sample distance from the camera, thereby allowing for accurate and consistent sample analysis. Additionally, the corresponding software guides the user through the use of the device and encrypts and transfers the image to allow for file sharing.

End User Innovation



Virtual Reality Program for Pediatric Pain Management (Reference # 2016-067)

Pain and anxiety are common amongst pediatric patients who undergo medical procedures. However, few non-pharmaceutical interventions have been developed to successfully manage pain and distress associated with these procedures. Researchers at Nationwide Children's Hospital have developed a virtual-reality approach to pain management that provides attentional distraction in an immersive environment. The software consists of active or passive modes and runs on multiple computing platforms that are compatible with smartphones.

Virtual Reality-Based Pediatric Traumatic Brain Injury Assessment and Rehabilitation Platforms (Reference # 2016-011; 2017-033)

Traumatic brain injury (TBI) is a leading cause of acquired disability in U.S. children and adolescents. Impairment of executive functions post-TBI has broad and profound implications for everyday life of pediatric patients, and the development of effective rehabilitation strategies is of significant clinical importance. Researchers at Nationwide Children's Hospital have developed virtual reality (VR)-based programs for assessing cognitive function and providing subsequent rehabilitation. This pediatric TBI assessment software provides VR-based cognitive-assessment tasks and an additional training platform that pairs with the Oculus Rift virtual reality viewer. The training program is designed with a series of environmentally-enriched three-dimensional cognitive exercises that aid in rehabilitation of executive core functions among pediatric patients with TBI in a highly controlled, safe, and automated manner.

Methods and Apparatus to Improve Diagnostic Sensitivity and Scan Efficiency of Brain Diseases (Reference # 2015-013)

Neonatal and infant brain MRI is increasingly utilized to diagnose brain injury and abnormal brain developmental

End User Innovation

disorders. The T1-weighted sequence provides the most detailed information about injury, lesions and maturation. Perinatal research experts at Nationwide Children's Hospital and The Ohio State University have designed MPRAGE, an optimized T1-weighted MRI sequence for neonatal and infant brain imaging. Their optimized methodology has greatly reduced the scan time by two-thirds and improved image quality without the use of additional hardware or increased workload for the MRI technologists or radiologist. This new method will not only reduce cost of the MRI scan but also improve sensitivity for detecting a variety of pediatric diseases/disorders.

Transcranial Doppler Ultrasound Determination of Pathologic Mechanisms and Treatment Strategies for Cerebral Malaria (Reference # 2017-045)

Worldwide, malaria affects 2 million individuals annually. Cerebral malaria is the most severe neurological manifestation of malaria with case fatality rates ranging from 15-40%. Researchers at Nationwide Children's Hospital have developed a method for using Transcranial Doppler to detect distinct waveform morphologies and identify pathogenic mechanisms leading to neuronal injury in children with cerebral malaria.

Handheld Needle Recapping Guard (Reference # 2017-071)

The Center for Disease Control and Prevention estimates that 380,000 sharps-related injuries occur annually among health care workers in hospitals. Medical professionals at Nationwide Children's Hospital have developed a handheld needle recapping guard to help prevent needlestick injury. The plastic guard is easily held in the non-dominant hand and is designed to block accidental needle sticks when recapping a needle.

Redesigned Health Literacy Sensitive Baby Bottle (Reference # 2016-070)

Inventors at Nationwide Children's Hospital have designed a new baby bottle that provides directions and modifications to increase the accuracy of preparing a bottle of infant formula. This design is aimed at decreasing errors that can be dangerous to infants and better meets the needs of individuals who struggle with low health literacy.

A Simple Bedside Device to Open the Newborn Baby's Eyes Easily (Reference # 2017-049)

Pediatricians need to examine the eyes of all newborn infants to check for infections, structural defects, or cataracts. Opening a newborn infant's eyes wide enough for a thorough exam can be challenging because a newborn's eyes are often covered with slippery vernix and exhibiting some degree of edema following birth. Physicians at Nationwide Children's Hospital have developed a novel, simple bedside device to easily and quickly open a newborn infant's eyes for examination. Our technique uses a handheld device that opens the baby's eyes with rotating Q tips. This device saves time and frustration during the newborn physical examination.

Video-based upper extremity assessment - A.C.T.I.V.E. Suite (Reference # 2012-011 & 2014-001)

Many clinical trials are currently being conducted for Duchenne muscular dystrophy (DMD); however functional outcome measures are not equally accessible to all individuals with this disease (e.g. non-ambulatory individuals). Experts at Nationwide Children's Hospital have designed a low-cost motion-capture system to evaluate upper extremity function in individuals with neuromuscular diseases. Researchers and clinicians can use this device to track upper extremity function to monitor disease progression for clinical trials in neuromuscular diseases or other diseases affecting upper extremity functions. More recently, our experts have designed ACTIVE-mini, a user-friendly camera-based tool to detect the presence and absence of key indicators of normal infant development. Infant movements can be easily compared to age-matched controls in order to identify movement-based characteristics that could be indicative of motor disorders or delay. Our experts ACTIVE-mini technology evaluates movement based on a computer learning algorithm that can quantify fine-grained changes in movement not necessarily detected by the human eye. Importantly, their ACTIVE Suite technology helps remove evaluator or parent-reported bias and quantifies movement on a linear scale.

Research Tools



Cmah-Deficient mdx Mice: A Better Mouse Model for Duchenne Muscular Dystrophy (Reference # 2010-019)

Putative cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein is an enzyme that in humans is encoded by the *CMAH* gene. A new *CMAH*-Deficient mouse model for DMD-related research has been created at Nationwide Children's Hospital in association with research done at University of California, San Diego. A double knock-out mouse strain was generated that better mimics the human disease than the current standard model and thus provides a model for DMD where translational research will be more relevant to issues affecting humans with the disease.

Novel Screening Assay to Identify and Evaluate Drugs that Target Familial and Sporadic Amyotrophic Lateral Sclerosis (ALS) (Reference # 2011-016)

This is an in vitro, cell-based assay that enables investigating molecular disease mechanisms and evaluating potential therapies for sporadic amyotrophic lateral sclerosis (als) and was developed at Nationwide Children's Hospital. This assay utilizes human derived cells from individuals with the disease.

A Novel Mouse Model of Duchenne Muscular Dystrophy with a Duplication of DMD Exon (Reference # 2013-037)

A novel mouse model for testing exon skipping therapies for DMD disease has been generated at Nationwide Children's Hospital. This mouse model carries a duplicated exon (exon2) in the DMD gene as compared to a point mutation in the most common mdx mouse model. This unique dystrophic mouse can serve as a preclinical testing model to test various therapies that mediate exon skipping.

An Inducible Facioscapulohumeral Muscular Dystrophy (FSHD) Mouse Model Expressing *DUX4* (Reference # 2014-019)

FSHD is the third most common muscular dystrophy, affecting 1 in 20,000 individuals. There is no current treatment for FSHD. Researchers at Nationwide Children's Hospital have developed a mouse model that recapitulates FSHD phenotypes and develops myopathy. This is the first FSHD mouse model that stably expresses the *DUX4* gene from the mouse genome using the human *DUX4* promoter. This model also circumvents lethality, leakiness problems and transient expression inherent in the standard mouse model.

Research Tools

Anoctamin 5 Deficient Mouse Model for the Study of Limb-Girdle Muscular Dystrophy 2L (LGMD2L) (Reference # 2015-018)

Limb-girdle muscular dystrophy type 2L (LGMD2L) is caused by recessive mutations in Anoctamin 5 (*ANO5*). Researchers at Nationwide Children's Hospital have developed the only *ANO5* deficient animal model. The constitutive knockout of *ANO5* in C57BL/6 mice allows for the study of LGMD2L and exceeds current cell culture and *in vitro* models.

Coronary Flow Analysis Program (Reference # 2017-023)

Vessel mechanical properties such as stiffness or stress are indicators of specific heart failure or disease, but these parameters are difficult to measure and, at times, unreliable. The current gold standard for measuring arterial stiffness is by pulse wave velocity which is limited to large arteries. Investigators at Nationwide Children's Hospital have designed an automated MATLAB program that utilizes non-invasive Doppler echocardiography to assess coronary microvascular remodeling as well as different cardiovascular disease states.

Electronic Whack-A-Mole: An Interactive Device for Measuring Task Performance and Motion Parameters (Reference # 2017-056)

Researchers at Nationwide Children's Hospital have developed a system for measuring motion (speed or reach) or cognitive (focus or prioritization) variables using an interactive game as an interface. By evaluating these variables using performance on a game-based system, the electronic Whack-a-Mole reduces volitional variation in measured performance and provides a platform for testing the impact of motivational stimuli at the same time as tracking performance variables particularly valuable for benchmarking the severity of muscular dystrophy or other upper extremity mobility disorders.

NK Cells with Intrinsic Resistance to TGF- β Inhibition of Anti-Tumor Cytokine Secretion (Reference # 2017-078)

TGF- β is a potent immune-modulatory cytokine. Levels of TGF- β are increased in the tumor microenvironment, and TGF- β suppression of natural killer and T cell anti-tumor immunity is believed to be the primary reason for the failure of immune therapies to eradicate residual disease. Researchers at Nationwide Children's Hospital have developed a novel method of generating natural killer cells with intrinsic resistance to TGF- β that is accomplished without genetic modification of the cells. TGF- β resistant natural killer cells can be used as a new immune therapy for cancers and as a non-genetic method of decreasing TGF- β suppression of anti-tumor immunity.

Transfected Cell Line for Drug Discovery Aimed at Splicing Correction (Reference # 2009-014)

Researchers at Nationwide Children's Hospital have developed a stably transfected cell line that expresses wild type survival motor neuron gene-2 (*SMN2*) that can be used as a drug discovery tool aimed at gene splicing correction. *SMN2* is a potential therapeutic target for Proximal Spinal Muscular Atrophy (SMA), an autosomal recessive neuromuscular disease. SMA is caused by a homozygous loss of the *SMN1* gene. Humans have two nearly identical SMN genes, *SMN1* and *SMN2*. *SMN2* generates a truncated protein due to a nucleotide alteration in exon 7, which leads to inefficient RNA splicing of exon 7. Stable cell lines expressing *SMN2* minigene have been generated that allow for detection of correct splicing of the *SMN2* gene.

Vitrification Insert Device for Cryovials (Reference # 2014-005)

Vitrification provides many advantages over slow cooling cryopreservation methods, but requires the use of expensive, specialized tools. Investigators at Nationwide Children's Hospital have invented a vitrification insert device that can be manufactured with inexpensive, sterilization-durable material and fit securely into multiple cryovial models. Further, this cost-effective solution can include various end designs to suit many functions, such as preventing sample contact with cryovial walls.

Research Tools

A Novel Genetic Mouse Model of Aging (Reference # 2016-049)

Demographers predict that the number of people over age 65 will triple over the next 35 years in the U.S. alone. Understanding what contributes to healthy old age begins with understanding the basis of the biological aging process. Currently available rodent models of aging are based on changes in metabolism either by modification of glucose uptake or calorie restriction. Researchers at Nationwide Children's Hospital have developed a novel model of aging as a result of genetic modification in a murine model. This novel mouse model may be useful for studying the aging process at the most basic level in addition to age-related diseases.

Wound Assay Device (Reference # 2017-031)

The scratch test/wound assay is a commonly used method for testing wound healing rates in the laboratory and can be applied to numerous fields of study including morphogenesis, repair, tissue remodeling and cancer. Current methods for this assay use commercially available pipette tips for scratching the cell monolayer, introducing variability and issues with reproducibility between users. Researchers at Nationwide Children's Hospital have designed a wound assay device to ensure a reproducible scratch is applied to a monolayer of cells. Our device has been designed to lock into a trans-well plate which helps ensure that the scratch applied to the cell surface is straight and uniform in depth.

Clinical Cohort Discovery and Analysis Tool (Reference # 2015-016)

Health care datasets often have complex relationships that limit the possibility of self-service analysis. Defining a precise population in a complex data model is difficult for an end-user. Researchers at Nationwide Children's Hospital have developed an intuitive and fast tool for defining complex populations in health care data sets and analyzing the data related to the population. This application allows sophisticated exploration and comparisons within and between datasets, making them more accessible to researchers.

Myotubularin (MTM1) (R69C) Knock-In Mice (Reference # 2012-017)

X-linked myotubular myopathy (MTM) is a severe disease of infancy and is caused by myotubularin (*MTM1*) mutations. The traditional mouse model of disease, the *MTM1* knockout (KO) mouse, exhibits a severe phenotype and short lifespan, which makes testing preclinical therapeutics challenging. Researchers at Nationwide Children's Hospital have developed a myotubularin-deficient mouse model (*MTM1* p.R69C) by modeling the mutation associated with the phenotype seen in MTM-affected individuals. Importantly, the *MTM1* p.R69C mouse model exhibits a less severe phenotype than the traditional *MTM1* KO model which would be more beneficial for testing preclinical therapies.

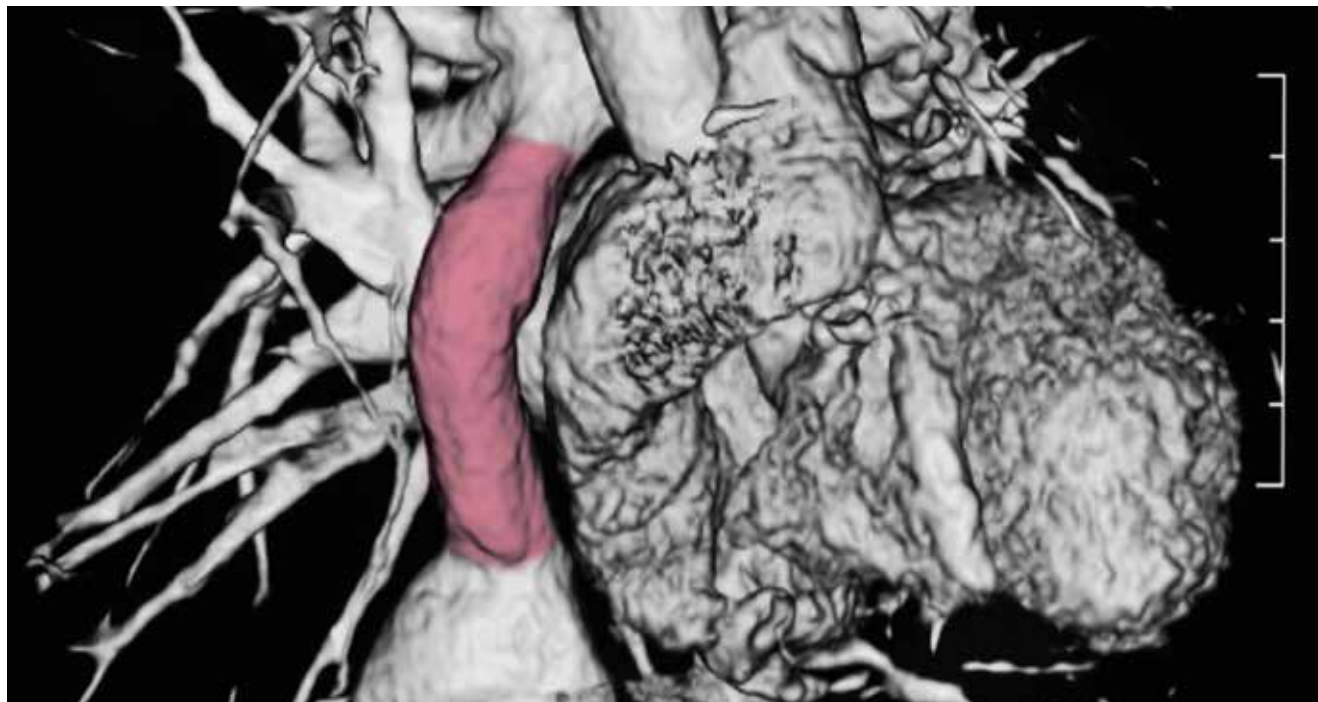
Titin (TTN) Based Cardiomyopathy Mouse Model TTN326 (Reference # 2018-022)

Titin (*TTN*) plays essential roles in both skeletal and cardiac muscle and when functioning improperly has devastating effects on muscle like dilated cardiomyopathy. Gene therapy experts at Nationwide Children's Hospital have utilized CRISPR/Cas9 technology to develop a new mouse model of dilated cardiomyopathy referred to as *TTN*-326. Utilizing the CRISPR/Cas9 technology to produce a mouse model instead of traditional methods has reduced the time required to modify the Titin gene as well as off-target insertions into the mouse genome. Our experts have demonstrated functional deficits in skeletal muscles of the *TTN*-326 mouse model and plan to test therapeutic strategies intramuscularly and systemically in this model to restore Titin protein function.

Titin (TTN) Based Cardiomyopathy Mouse Model TTN219 (Reference # 2018-023)

Experts at Nationwide Children's Hospital have developed a novel Titin-deficient mouse, *TTN* 219, in order to study limb girdle muscular dystrophy type 2J (LGMD2J) based on a documented patient mutation. The *TTN* 219 mouse model was developed using CRISPR/Cas9 technology therefore the time required to modify the Titin gene is reduced as well as off-target insertions into the mouse genome. Our experts have demonstrated functional deficits in skeletal muscles of the *TTN* 219 mouse model and plan to use this model to test therapeutic strategies intramuscularly and systemically to restore Titin protein function.

Tissue Engineering



Production of Tissue Engineered Intestine to Treat Short Bowel Syndrome (Reference # 2013-009)

Short bowel syndrome is a consequence of massive bowel resection performed in patients with various diseases. Transplantation of the small bowel may be beneficial, but results in risk of graft rejection and complications. Investigators at Nationwide Children's Hospital and Nanofiber Solutions have developed a method of generating tissue engineered intestine. This process uses multiple cell types of a patient's own cells and multi-layered nanofiber scaffolds to generate full thickness, functional intestine that can be used to treat and manage short bowel syndrome.

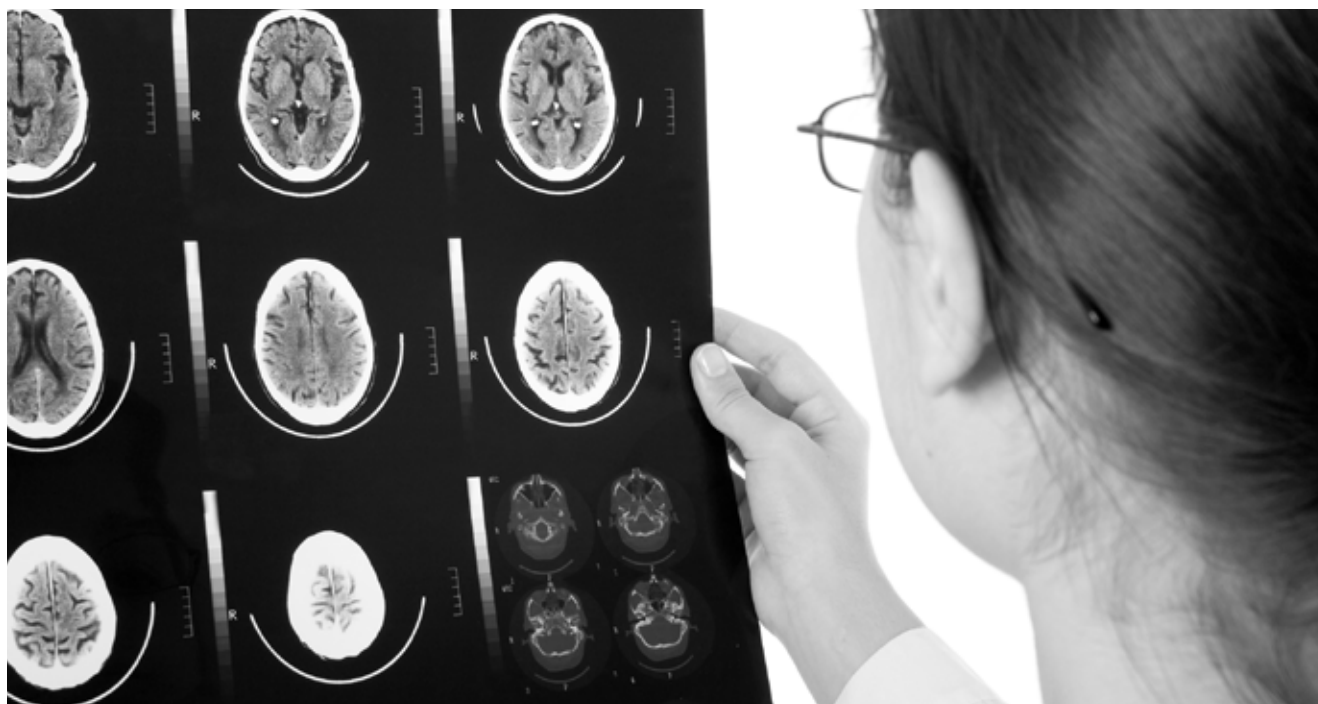
Closed Seeding System for the Tissue Engineered Vascular Graft (Reference # 2015-076; 2016-010)

Physicians at Nationwide Children's Hospital have developed a Tissue Engineered Vascular Graft (TEVG) by seeding patient cells onto a biodegradable tubular scaffold. The scaffold degrades by hydrolysis, ultimately leaving only the growing vessel in the patients. The Closed Seeding System enables efficient collection and seeding of patient cells onto the TEVG scaffold, which has been further optimized by using patient imaging data and 3D-printing capabilities to create patient-specific vascular grafts for implantation.

Cell-Free Tissue Engineered Vascular Grafts (Reference # 2015-034; 2015-035; 2015-036)

Researchers at Nationwide Children's Hospital have developed a novel method for increasing the patency of biodegradable, synthetic vascular grafts. Administration or controlled release of one or more cytokines or chemokines was found to promote outward tissue remodeling of the vascular grafts and vascular neotissue formation. As a result, this method does not require cell seeding of the vascular graft, eliminating many problems associated with cell seeding such as contamination, loss of clinical utility due to added time for cell expansion, and difficulty in obtaining healthy autologous cells from diseased donors.

Bioinformatics



Genome Archiving and Communication System (GACS) (Reference # 2016-056)

To handle the demands of genomic data archiving and access our researchers at Nationwide Children's Hospital have designed a scalable and secure genome archiving and communication system (GACS). GACS computer system software is scalable to archive and query large amounts of genomic data in a clinical setting with the ability to interact with lab systems and electronic medical records for real-time data access. Our researchers have chosen the Hadoop framework due to its horizontal scalabilities, high performance data ingestion, fault toleration and access auditing capacity. Importantly, they have also utilized a National Institute of Standards and Technology (NIST)-derived, enterprise-supported risk management framework for data security.

Dose Wizard: a Method of Calculating Anatomically Correct Radiation Exposure during CT Imaging (Reference # 2015-001)

Calculation of radiation exposure during computed tomography (CT) imaging helps physicians estimate a patient's risk of future radiation-related cancer. Physicians at Nationwide Children's Hospital have developed a program that uses anatomically correct models to determine radiation exposure. This program can be used to determine the total radiation dose a patient receives over a period of time and allows for a personalized assessment of the risk of negative effects.

| Our Team |



Matthew McFarland, RPh, PhD, Vice President, Commercialization and Industry Relations

Matthew joined Nationwide Children's Hospital as director of the Office of Technology Commercialization in the spring of 2012 and currently serves as Vice President of Commercialization and Industry Relations. In this role, he works closely with Nationwide Children's faculty and staff to identify intellectual property with commercial potential and to facilitate the transfer of new technologies to outside partners, ultimately for the benefit and enhancement of pediatric care. He has a diverse background in technology transfer, technology valuation and licensing, academic research and pharmacy practice.

Prior to joining Nationwide Children's, Matthew was the associate director of commercialization, innovation strategy manager and technology manager in the Office of Technology Commercialization at the Purdue Research Foundation. He received a Bachelor of Science degree in pharmacy from Ohio Northern University and his PhD in medicinal chemistry and molecular pharmacology from Purdue University. He also completed a postdoctoral research fellowship in translational genetics and pharmacogenomics of neuropsychiatric disorders at the Institute of Psychiatric Research, Indiana University Medical School.

Matthew has authored several articles for peer-reviewed journals including *Molecular Pharmacology*, *Journal of Biological Chemistry and Medical Innovation & Business*. He also received the Jenkins/Knevel Award for Excellence in Research and the Albert and Anna Kienley Award for Excellence in Teaching from the School of Pharmacy at Purdue University.

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Susan S. Allen, Intellectual Property Manager

Susan joined Nationwide Children's Hospital in the summer of 2013. She manages the intellectual property and patent portfolio, as well as agreements records for the Office of Technology Commercialization. She assists the team with invention evaluation and efforts aimed at marketing and licensing. Susan also manages compliance with regard to reporting requirements for federal and/or non-government research sponsors.

Susan has 23 years of experience including work for federal and state governments, academia, private industry and nonprofits. She has a strong background in intellectual property management and research administration; research education and communications; and budget management and accounting practices including patents, agreements, contracts, and grants management and compliance.

Susan has a Bachelor of Science degree in biology from The Catholic University of America in Washington DC. She is a member of the Association of Technology Managers. Past professional memberships include: National Council of University Research Administrators, American Medical Writers Association, and American Management Association.

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| Our Team |



Margaret Barkett, PhD, Associate Director

Margaret joined Nationwide Children's Hospital as a licensing associate in February 2012, and currently serves as Associate Director for the Office of Technology Commercialization. In her role with the office Margaret manages the assessment, protection, valuation and out-licensing of a portfolio of intellectual property assets owned by the Research Institute. She is also actively involved in managing many of the office's relationships with both internal and external stakeholders.

Margaret has a Bachelor of Arts degree in biology from Emory University and earned her PhD degree in molecular and cell biology from Boston University where she continued her training as a postdoctoral fellow. Her doctoral and postdoctoral research in cell death biology spanned different areas including cancer biology and development. Prior to joining The Research Institute, she completed a one-year technology licensing internship at Massachusetts Institute of Technology focusing on medical devices and biotechnology.

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David Bellamy-Bise, Administrative Support III

David joined Nationwide Children's Hospital in July 2017. His primary responsibilities include supporting both the Office for Technology Commercialization as well as the Drug & Device Development Services department. David is responsible for calendar management and meeting coordination as well as assisting each member of the Office of Technology Commercialization with various duties as needed. David also supports the team with department projects, event coordination, supply orders and provides assistance with record keeping.

David has over 10 years of experience working in an administrative support role for a health care system. He has a Bachelor of Arts degree from Kentucky Christian University.

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Andrew M. Corris, PharmD, JD, BS, Licensing Associate

Andrew joined Nationwide Children's Hospital in March 2015. In his role as a licensing associate, he promotes technology transfer through the evaluation, protection, and out-licensing of technologies developed at Nationwide Children's Hospital.

Andrew has a Bachelor of Science in chemical engineering and a minor in chemistry from the University of Pittsburgh, a Doctor of Pharmacy degree from The Ohio State University, and a Juris Doctor, cum laude, from Capital University, specializing in intellectual property law.

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| Our Team |



Isabella Gomez Rueda, LLB, LLM, *Agreements Coordinator*

Isabella joined Nationwide Children's Hospital in March 2018. As Agreements Coordinator she is responsible for the negotiation and administration of Material Transfer Agreements, Data Use Agreements and Confidential Disclosure Agreements. Isabella also manages the agreements docket and provides assistance to the office's licensing team.

Isabella has a Bachelor of Laws LLB from the Universidad Industrial de Santander and is a licensed attorney in Colombia. She also has a graduate degree in Trade Law from the Universidad Autonoma de Bucaramanga and a Master of Laws LLM in Intellectual Property and Technology

Law from The Ohio State University. She has experience in the areas of university transactions, contracts, commercial and intellectual property law.

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Kyle Murrah, PhD, *Licensing Associate*

Kyle joined Nationwide Children's Hospital as a licensing associate in the Office of Technology Commercialization in July 2014. In his role as a licensing associate, he promotes technology transfer through the evaluation, protection, and out-licensing of technologies developed at Nationwide Children's Hospital.

Kyle has a Bachelor of Science degree in biological sciences from North Carolina State University and a PhD in microbiology and immunology from Wake Forest University. His doctoral research focused on polymicrobial interactions in middle ear infections. While earning his doctorate, he completed a two year technology transfer internship at Wake Forest Innovations.

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Susannah Wolman, BA, *Business Compliance and Finance Coordinator*

Susannah joined Nationwide Children's Hospital in July 2016. She is primarily responsible for information and business systems. She tracks invoices, licenses terms and follows up to ensure licensee compliance, in addition to overseeing the annual budget, purchasing and the file management database. Susannah also assists technology transfer professionals with department initiatives, events management and operational issues.

Susannah has over 10 years of experience working in product liability and commercial litigation. She has a Bachelor of Arts degree in Criminology and Psychology from Marquette University.

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Amy Yoder, *Intellectual Property Coordinator*

Amy joined Nationwide Children's in June of 2018. She manages the intellectual property and patent portfolio for the Office of Technology Commercialization. She works with external law firms, inventors, and licensing staff to coordinate the execution of all legal documentation associated with the patent application process.

Amy has her bachelor's degree in Political Science from the University of Kentucky and her Paralegal Certificate from Columbus State. She has experience in the areas of intellectual property and corporate law.

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