

Spring/Summer 2019

Pediatrics

NATIONWIDE

Advancing the Conversation
on Child Health

A detailed microscopic illustration of the intestinal mucosa, showing the characteristic villi and crypts. The central lumen is a bright, circular area, while the surrounding tissue is rendered in various shades of red and orange, with fine details of the epithelial cells and their nuclei. The overall appearance is that of a cross-section of the gut wall.

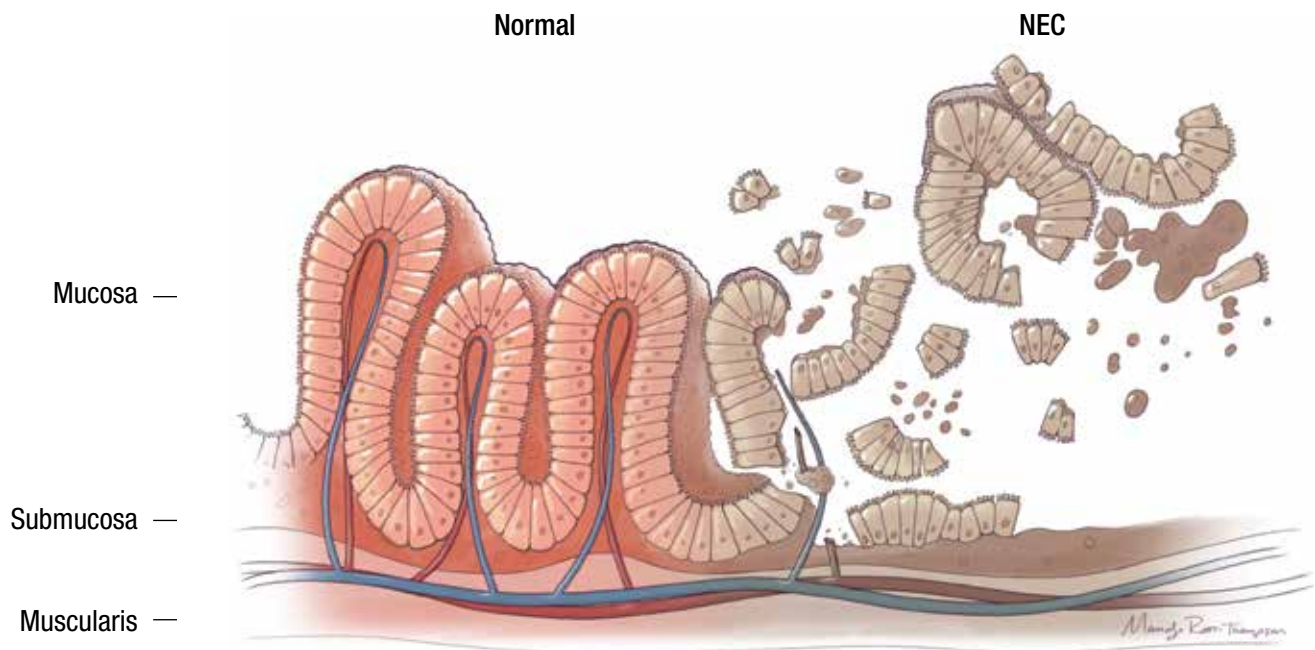
What's next for
NEC?

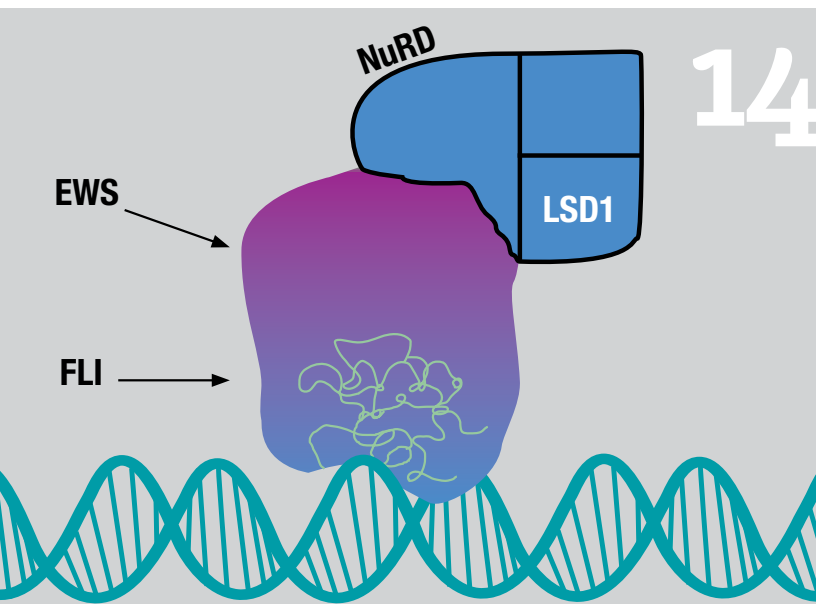
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WHAT'S NEXT FOR NEC?

Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in neonatal intensive care units. Primarily affecting premature (less than 32 weeks gestation) and low birth weight (less than 1500 g) infants, NEC involves the inflammation, infection and often necrosis of the premature intestine. The intestinal lining pictured below shows a healthy mucosal layer compared to that devastated by NEC. The microbiome of the intestine also contributes to the integrity of the mucosal layer. The health of the mucosal layer is vital to preventing and treating NEC.

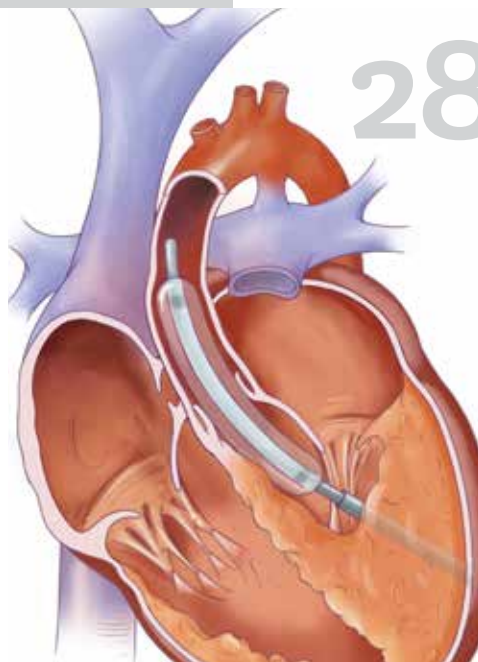
In the cover story, you will learn about researchers who are forging new paths to treat the many influences that lead to NEC. From developing new delivery systems for probiotics to preserve the harmony of the gut microbiome to developing drugs that inhibit inflammatory processes associated with NEC, researchers are poised to bring to the clinic new therapies that could alter the history of the disease.





FEATURES

- 10** Targeting Therapies for Children With Multiple Organ Dysfunction
- 12** Profile of a Cancer: Getting to Know Ewing Sarcoma
- 18** What's Next for NEC?
- 24** Worth It. Why Wrestling Through the Logistical Challenges of a Multidisciplinary Colorectal Center Matters



DEPARTMENTS

- 4** In Practice: News From the Field
- 28** In Sight: Fetal Balloon Aortic Valvuloplasty for Critical Aortic Stenosis
- 30** Second Opinions: How Research Reinforces the Collaborative Culture of a Children's Hospital
- 34** Connections: Advancing the Conversation on Child Health

“ This is a totally new concept in biochemistry. Instead of having hundreds of proteins with perfectly complementary surfaces ... these sticky microsatellites and EWS/FLI proteins seem toglom onto each other, likely causing the EWS portions to phase separate, similar to oil and water. ”

— Stephen Lessnick, MD, PhD, director of the Center for Childhood Cancer & Blood Diseases in The Research Institute at Nationwide Children's Hospital

“ In premature infants you have a perfect storm of factors that can lead to NEC. Mucosal injury and bacterial overgrowth compromise the immature intestinal epithelium, while abnormal flora takes advantage of the immature immune system. ”

— Maria Talavera, DO, neonatologist at Nationwide Children's Hospital

Pediatric Patients Receive Higher Radiation at Non-pediatric Trauma Centers

A novel software tool for calculating radiation burden has determined that pediatric trauma patients, evaluated using CT imaging primarily at adult trauma centers, demonstrate higher radiation exposure than those imaged primarily at a pediatric trauma center.

Computed tomography (CT) is a mainstay of the diagnosis and treatment of trauma, the leading cause of death in young adulthood. Through CT imaging, a physician utilizes ionizing radiation to visually differentiate between internal tissues of the body. This radiation, however, may confer risk toward developing a malignancy if given many times, in high doses, throughout childhood.

In a recent publication in the *Journal of Surgical Research*, Katherine Deans, MD, director of the Center for Surgical Outcomes Research at Nationwide Children's Hospital, and her team determined a difference in the radiation burden of CT scanning in patients initially evaluated at a pediatric trauma center (PTC) compared to those initially evaluated at a non-PTC.

"We showed that patients initially evaluated at non-PTCs received significantly more radiation from head CT scanning, C-spine CT scanning, chest CT scanning and abdomen/pelvis CT scanning," says Dr. Deans.

The results indicated that patients treated at non-PTCs received a higher dose of radiation, and that CT scans of all body regions except the abdomen/pelvis were more frequently prescribed at non-PTCs.

"Medical imaging is the largest source of ionizing radiation in the United States," says Dr. Deans. "Community and adult centers are doing a great job triaging pediatric trauma patients, but what this study shows is that there may be an opportunity to educate and improve imaging practices in this population. As one of the largest children's hospitals in the nation, we can share imaging protocols that use lower doses to image children. And locally, we can assist in more rapid transfer of pediatric patients, perhaps prior to imaging."

The team obtained these results by creating a novel software tool that can calculate radiation exposure data and merge it with data from the electronic health record. This enables the team to identify cohorts of children who may be receiving higher radiation burden from medical imaging. Only by identifying these groups can investigators then work to reduce CT prescribing and/or radiation dosing in selected patients.

"The software can be used to power clinical decisions support at the point of care," says Dr. Deans, whose team has already started a variety of other studies using the same technology. "We calculated that it would take seven years for a Master's level physicist to manually derive the results that we received in about an hour of using the technology. Our hope is that this type of technology is adopted at other centers, so that we can look at the actual radiation burden across a broader and more diverse population of children in the United States."

Lodwick DL, Cooper JN, Gonzalez DO, Lawrence AE, Lee C, Krishnamurthy R, Minneci PC, Deans KJ. Disparities in radiation burden from trauma evaluation at pediatric versus nonpediatric institutions. *Journal of Surgical Research*. 2018 Dec; 232:465-483.

— Bailey Dye





Can Brain Imaging Help Predict Bipolar Disorder in High Risk Children?

Patterns in connectivity in a portion of the frontal lobe called the inferior frontal gyrus appears to be an early biomarker in children of parents with bipolar disorder.

Researchers report a potential neural marker of individual risk in those with a family history of bipolar disorder. The study, published in the journal *Neuropsychopharmacology*, points to particular patterns of brain connectivity as future potential targets for early intervention.

Children of parents with bipolar disorder (BD) are at increased risk of developing the condition themselves. To distinguish children that are likely to develop BD from those who will not, Danella Hafeman, MD, PhD, assistant professor of Psychiatry at the University of Pittsburgh, helped devise a risk calculator. Using diagnostic and dimensional predictors from the literature, Dr. Hafeman and her colleagues can predict the risk of a particular child developing BD within the next five years with high accuracy.

In the new study, Dr. Hafeman and her colleagues examined how individual risk scores correlate with changes in neural circuitry. The researchers set out to replicate and extend the findings of a recent study that found reduced resting state functional connectivity between the inferior frontal gyrus (IFG) and three target regions in young adult children of parents with BD. These brain areas are involved in subjective reward value encoding, cognitive control and emotion regulation, behavioral processes that are abnormal in individuals with BD and their first-degree relatives.

“We looked at how these parts of the brain fluctuate together in terms of blood flow while people are at rest with their minds wandering,” says Dr. Hafeman. “It turns out that even when you’re doing nothing, your brain is very active.”

Contrary to their predictions, the researchers did not

find any group differences in resting state functional connectivity between children of individuals with BD and healthy controls. They speculate that it could be because their sample is smaller and younger (7-17 years old versus 16-30 years old) than that of the earlier study. However, the researchers did find correlations between resting state functional connectivity and risk score (in children of parents with BD) and mood lability (across the sample).

“We found that the higher the risk score, the lower the connectivity between the IFG and the left insula,” says Dr. Hafeman. “Mood lability is an important predictor of BD and that was also negatively correlated with connectivity between those two regions.”

This study supports the hypothesis that IFG resting state functional connectivity is an important risk marker for the development of BD, at least partially through effects on mood lability. If confirmed, this pattern could represent a marker of individual risk in those with a family history of BD and a potential neural target of treatments aiming to decrease emotion-related impulsivity and mood lability.

“This work is significant because it links brain activity with a clinical profile that is associated with a higher risk of developing bipolar disorder” says David Axelson, MD, section chief of Psychiatry and Behavioral Health at Nationwide Children’s Hospital and a collaborator on the new study. “If replicated, it could help us develop better ways to combine brain imaging with clinical assessment to improve our ability to predict whether a child may have bipolar disorder in the future.”

Hafeman DM, Chase HW, Monk K, Bonar L, Hickey MB, McCaffrey A, Graur S, Manelis A, Ladouceur CD, Merranko J, Axelson DA, Goldstein BI, Goldstein TR, Birmaher B, Phillips ML. Intrinsic functional connectivity correlates of person-level risk for bipolar disorder in offspring of affected parents. *Neuropsychopharmacology*. 2018;44:629-634.

— Mary Bates, PhD

Keeping Young Congenital Heart Disease Survivors in the System

Race, type of insurance and severity of disease affect likelihood of experiencing a lapse in care.



Lapse in care is prevalent among congenital heart disease survivors by age five, with nonwhites demonstrating elevated risk, according to a new study from Nationwide Children’s Hospital researchers. Medicaid patients and those with less severe diagnoses also had an increased risk for lapse in care.

Medical advancements over the past 20 years have allowed more people with congenital heart disease (CHD) to survive into adulthood. For these individuals, routine surveillance and follow-up care by a cardiologist are critically important. However, lapse in care among CHD survivors is common.

While most of the literature focuses on lapses in care during the transition from pediatric to adult care, the new study, published in *Congenital Heart Disease*, sought to determine the rate of lapses in care in CHD survivors through age five.

“Our population consisted of patients who had moderate or complex CHD, which often requires immediate intervention at birth or soon after birth,” says Jamie Jackson, PhD, a principal investigator in the Center for Biobehavioral Health at The Research Institute and The Heart Center at Nationwide Children’s Hospital and the study’s first author. “We wanted to see if these patients stay in the system.”

Analysis of the electronic medical records available through Nationwide Children’s revealed that overall, 75.7 percent of patients experienced a lapse in care, with only 41.6 percent of those returning by age 5. Nonwhites had a greater risk for lapse in care and tended to leave the system earlier. Additionally, Medicaid patients and those with CHD diagnoses of moderate severity had an increased risk for lapse in care.

“Disease severity ended up being one of the strongest predictors of lapse in care, with folks that have less severe disease at greater risk,” says Dr. Jackson, who is also an assistant professor of Pediatrics in The Ohio State University College of Medicine.

“This could be because it seems like they are doing well, and if that is the explanation, there might be a lack of understanding about the importance of regular care at the time of initial intervention,” she says.

Dr. Jackson and her colleagues don’t know the reasons behind the racial disparities. Their analysis showed that insurance type is part of the picture but does not account for the racial differences identified. Based on racial disparities found in other disease populations, they speculate that nonwhite patients may receive different messages about the importance of follow-up care than white patients, or they may be less satisfied with their care.

“The takeaway message to medical providers is that we know we lose patients for some reason in these early stages and for clinic staff to be mindful of that – and to be particularly mindful of the fact that we might especially lose individuals from nonwhite families and patients with less severe disease,” says Dr. Jackson.

“More prospective research is needed to figure out what might explain these initial lapses in care so we can identify appropriate interventions to keep patients in the system.”

Jackson JL, Morack J, Harris M, DeSalvo J, Daniels CJ, Chisolm DJ. Racial disparities in clinic follow-up early in life among survivors of congenital heart disease. *Congenital Heart Disease*. 18 Dec 2018; [Epub ahead of print]

— Mary Bates, PhD

Long-Term Follow Up of Patients Receiving Novel Gene Therapy for SMA Type I

Spinal muscular atrophy type 1 (SMA1) is a rare neuromuscular disease in which 75 percent of affected children die or require permanent ventilation by 13.6 months. Researchers recently published the long-term outcomes of patients who received the investigational drug AVXS-101 – an adeno-associated virus serotype 9 mediated gene replacement therapy.

Twelve children aged 1 to 8 months were treated and followed for 24 months. Longer-term follow up results are included as available for motor milestones.

Notably, for motor milestones, the patient who was the oldest at treatment achieved fewer milestones than those treated at younger ages.

PULMONARY SUPPORT

10/12 patients were free of pulmonary support at time of treatment

7/10 remained free of pulmonary support through follow-up



RESPIRATORY INFECTIONS

10 patients in the study had at least
1 hospitalization during the trial
0 exceeded 8 days length of stay

NUTRITION, SWALLOWING AND SPEECH

7/12 patients were feeding orally at time of treatment

6/7 continued to eat exclusively by mouth

11/12 achieved safe swallowing for at least partial oral feeds during follow-up



MOTOR MILESTONES AFTER LONG-TERM FOLLOW-UP

12/12 can bring hand to mouth

11/12 achieved head control

9/12 can roll over

11/12 can sit with assistance

11/12* can sit unassisted for up to 30 seconds

4/12* can stand with assistance

**Two patients reached this milestone after the 24-month visit*

“Treatment of SMA1 with gene therapy has the potential to transform the disease course, in addition to improving patient and caregiver quality of life. Reduced use of ventilation and nutritional support, as well as decreased hospitalization, could significantly decrease the overall health care utilization of these patients.”

— Richard Shell, MD, section chief of Pulmonary Medicine at Nationwide Children’s Hospital and senior author of the publication

Al-Zaidy S, Pickard AS, Kotha K, Alfano LN, Lowes L, Paul G, Church K, Lehman K, Sproule DM, Dabbours O, Maru B, Berry K, Arnold WD, Kissel JT, Mendell JR, Shell R. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatric Pulmonology*. 2019;54:179-185.

— Abbie Roth

Novel Metric Predicts Severity of Community-Acquired Pneumonia

Researchers utilize a biomarker to predict disease severity during early stages of pneumonia.

Community-acquired pneumonia (CAP) is a leading cause of hospitalization and mortality in children. Each year, 4 percent of children under 5 years of age will develop CAP in industrialized countries. Although pneumonia is common, diagnosing and treating it remains a challenge for clinicians – largely due to a number of unknowns associated with the early stages of CAP.

“When a child comes to the emergency room with CAP, we often don’t know what’s causing it. And we can’t predict if that patient is going to get worse and have to go to the intensive care unit or if we can send them home with antibiotics,” says Rebecca Wallihan, MD, an Infectious Diseases specialist at Nationwide Children’s Hospital and assistant professor at The Ohio State College of Medicine. “We know a lot about CAP, but the reality is that we still don’t know enough to be practical.”

To address these unknowns, clinicians need a way to quickly and accurately predict disease severity in children with CAP. Working with Octavio Ramilo, MD, division chief of Infectious Diseases and principal investigator in the Center for Vaccines and Immunity in The Research Institute at Nationwide Children’s, Dr. Wallihan initiated a clinical study to determine if they could use transcriptional profiling to identify better markers of disease severity in children hospitalized with CAP.

Specifically, the researchers used a novel metric called Molecular Distance to Health (MDTH). MDTH is a single numerical score that summarizes the overall change in expression of immune-related genes in a patient compared to a healthy, age-matched control. The researchers collected blood samples from 152 patients hospitalized with CAP and completed transcriptomic analysis to examine gene expression patterns and assign an MDTH score to each patient.

When the researchers compared MDTH to traditional markers of disease severity such as C-reactive protein, procalcitonin and white blood cell counts, they found that MDTH was more significantly associated with disease severity of CAP as measured by the length of



hospitalization and duration of fever. These findings were recently published in *Frontiers in Cellular and Infection Microbiology*.

“Our approach gives us a detailed sense of how the immune system is responding to each case of CAP, and this score directly correlates with the severity of disease,” says Dr. Ramilo. “Looking at the host in addition to the pathogen is a key aspect.”

The ultimate goal is identifying pneumonia-specific biosignatures that could be used to diagnose and manage CAP more effectively than current practices. With funding from the Ohio Children’s Hospitals Association, the researchers expanded the study to six children’s hospitals in Ohio. This provides a large database for the researchers to explore the utility of MDTH as a clinical biomarker for disease severity.

“We are trying to build a database of the knowns, and use that data to reveal the unknowns,” says Dr. Ramilo. “That’s the ongoing effort, and this study has been the first return on an investment that we hope will eventually lead to best outcomes for children with CAP not only in Columbus, but worldwide.”

Wallihan RG, Suarez NM, Cohen DM, Marcon M, Moore-Clingenpeel M, Mejias A, Ramilo O. Molecular distance to health transcriptional score and disease severity in children hospitalized with community-acquired pneumonia. *Frontiers in Cellular and Infection Microbiology*. 2018;8:382.

— Rachael Hardison, PhD



Toward a Cell-based Therapy for Cystic Fibrosis Lung Disease

Because cystic fibrosis (CF) is a genetic disease caused by mutations in the CFTR gene, the pulmonary disease could be reversed if CF airway epithelial cells were replaced with basal cells expressing CFTR without mutations. That is one of the ideas underpinning the Cystic Fibrosis Foundation's Epithelial Stem Cell Consortium, but there are a number of complicated questions that must be addressed before such a replacement is possible.

A recent study from physicians and researchers at Nationwide Children's Hospital, and funded by the CF Foundation, provides some important answers. It also helps show that such a cell-based therapy for cystic fibrosis lung disease is realistic.

"Ideally, we would like to use a patient's own cells for a therapy. For that to be an option, we also need to know how difficult it will be to harvest those cells and to generate the numbers we need for a therapeutic dose," says Susan Reynolds, PhD, a principal investigator in the Center for Perinatal Research in The Research Institute at Nationwide Children's Hospital and senior author of the study in *Stem Cells Translational Medicine*.

First, Dr. Reynolds and her colleagues wanted to know if basal cells from patients with CF would be as functional as cells from people without CF. They compared the proliferation of the cells from the bronchial tissue of the two groups. Regenerative basal cell frequency declined among both groups as cells were passaged, but generally, the frequencies were the same in CF and non-CF samples. So it seems a patient's own cells, once gene corrected, could be used in a therapy.

But how would those cells be recovered? In the lab, basal cells are usually isolated using explanted tissue,

meaning a patient already has end-stage disease. Bronchial brushing could recover basal cells earlier, but it would require surgery. Nasal brushing, though, would be relatively easy.

To test this idea, the authors collected basal cells in each of those ways, then amplified them to a therapeutic dose (estimated at 60 million cells in a previous publication from Dr. Reynolds). The authors found that while it does take longer to amplify nasal basal cells to the needed level (16 days for tissue-derived cells versus 24 days for brushed cells), it can be done.

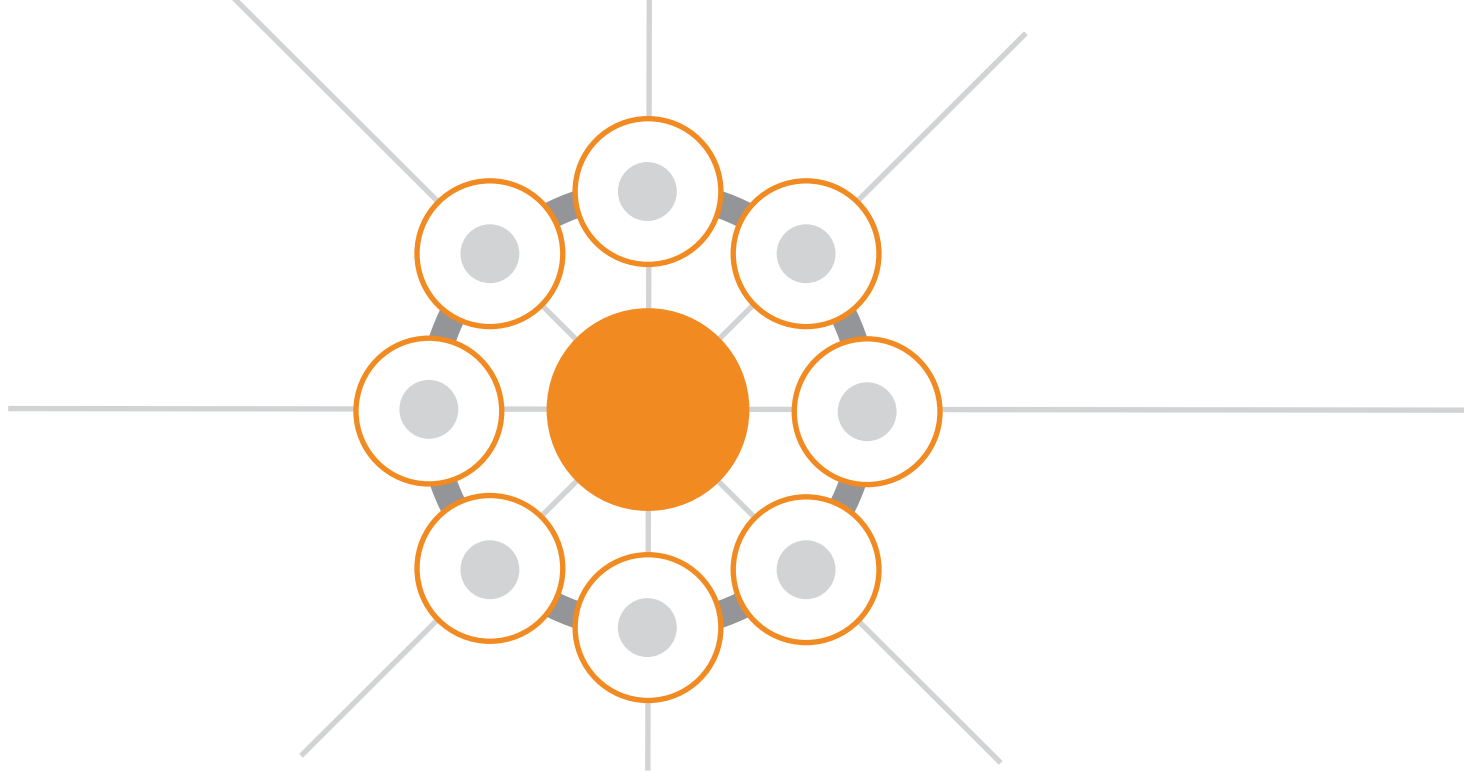
They also found that the frequency of the regenerative cells was approximately 20 percent after amplification to a therapeutic level, and their data indicate the frequency would be similar in cells that undergo gene correction. A small subset of those regenerative cells were particularly long-lived; one theory is that these basal cells could be tissue stem cells, the best candidates for transplantation.

The work at Nationwide Children's was because of a collaboration between Dr. Reynolds and Don Hayes, MD, medical director of the hospital's Lung Transplant Program. Dr. Reynolds says that other members of the Epithelial Stem Cell Consortium are working on their own amplification strategies and analyzing cell functionality. The work is promising, if slow.

"We are being careful, but we are making progress," says Dr. Reynolds.

Hayes DJ Jr, Kopp BT, Hill CL, Lallier SW, Schwartz CM, Tadesse M, Alsudayri A, Reynolds SD. Cell therapy for cystic fibrosis lung disease: Regenerative basal cell amplification. *Stem Cells Translational Medicine*. 2018 Dec 1. [Epub ahead of print]

—Jeb Phillips



TARGETING THERAPIES for Children With Multiple Organ Dysfunction

ANAKINRA, AN INTERLEUKIN-1 RECEPTOR ANTAGONIST, MAY BE EFFECTIVE FOR SELECT CHILDREN WITH MODS WHO MEET DIAGNOSTIC CRITERIA FOR HLH.

by *Kevin Mayhood*

Multiple organ dysfunction syndrome (MODS) involves altered function of two or more organ systems and is among the most severe forms of critical illness, with mortality rates up to 50 percent in children. MODS can result from a variety of acute conditions, including sepsis, trauma, cancer, or status-post cardiopulmonary bypass. Causes for MODS are not well understood, but are likely multifactorial; and current therapies for MODS are largely supportive, with few targeted therapeutic options.

A subset of children with MODS also meet diagnostic criteria for hemophagocytic lymphohistiocytosis (HLH). HLH is a life-threatening condition caused by natural killer cell dysfunction, which leads to unfettered systemic inflammation. Primary HLH is caused by mutations in genes responsible for NK cell function, is treated with highly immunosuppressive chemotherapy (such as etoposide), and often requires bone marrow transplant for cure. Some patients without gene

mutations can acquire an HLH-like illness in the setting of an acute inflammatory condition, such as infection. This is often referred to as secondary HLH or hyperferritinemic MODS. The optimum therapy for these children is unclear.

Previously published survival rates for critically ill children meeting HLH diagnostic criteria and treated with standard HLH therapy are about 50 percent.

In a recent small retrospective study, children suffering from MODS and meeting the criteria for HLH were treated differently: with the drug anakinra, which is often used to treat macrophage activation syndrome (MAS), a complication of rheumatic disease with similar pathophysiology. Their survival rate was 89 percent.

“Many of the children had viral and infectious triggers,” says Celia Ligatorski, DO, a resident at Nationwide Children’s Hospital and study co-leader. “Immunosuppressive medications would hinder their ability to fight

infection. Anakinra may be a more targeted therapy.”

Anakinra is a manmade version of the chemical recombinant interleukin-1 receptor antagonist the body produces. The drug blocks the IL1 receptor and thereby reduces the cytokine storm that leads to tissue damage and organ failure.

By the end of treatment, the majority of HLH criteria were resolved in the children, Dr. Ligorski says. She presented the study’s findings at the Society of Critical Care Medicine’s Annual Congress in February.

Despite indications, “we’re not sure these children have HLH,” says Jennifer Muszynski, a critical care physician and principal investigator in the Center for Clinical and Translational Research at Nationwide Children’s. She was also the study co-leader.

To study outcomes, Drs. Ligorski and Muszynski and their colleagues collected and analyzed the data of nine children who were treated with anakinra for hyperferritinemic MODS, from 2013 through 2017.

The average child’s age was 11. Eight children had acute bacterial or viral infection or both; all had two or more organ dysfunctions and all met five or more criteria for HLH. Bone marrow biopsies on seven children indicated six had hemophagocytosis.

The children received anakinra in larger doses than typically used by rheumatologists, Dr. Muszynski says.

The mean dose delivered in the first week was 9.4 mg/kg/day. All patients also received steroids, five underwent therapeutic plasma exchange, three required extracorporeal membrane oxygenation support and five required renal replacement therapy.

The average Pediatric Logistic Organ Dysfunction score for the group improved from a 7 on the day before beginning treatment to a 4 after three days on anakinra

to a 3 after a week of treatment. The scores suggest organ function improvements.

Eight out of nine children survived to hospital discharge. One child with no apparent underlying immune dysfunction had immunoparalysis, a severe form of critical illness-induced immune suppression, in parallel with the child’s pro-inflammatory response, Dr. Ligorski says.

Testing after treatment showed the immunoparalysis was completely corrected, she says. “The data suggests that treatment with anakinra may preserve systemic immune function and allow immunologic recovery and reset the inflammatory system.”

The study replicates findings from a retrospective study of eight children with presumed secondary HLH at DeVos Children’s Hospital, published in 2014. A post-hoc analysis of a 2016 multi-site study on adults with sepsis and features of MAS also concluded anakinra treatment may provide a survival benefit.

Drs. Muszynski and Ligorski say a larger, prospective multi-site study, including evaluation of immune function and anti-inflammatory response, is needed.

Rajasekaran s, Kruse K, Kovey K, Davis AT, Hassan NE, Ndika AN, Zuiderveen S, Birmingham J. Therapeutic role of anakinra, and interleukin-1 receptor antagonist, in the management of secondary hemophagocytic lymphohistocytosis/sepsis/multiple organ dysfunction/macrophage activating syndrome in critically ill children. *Pediatric Critical Care Medicine*. 2014 Jun;15(5):401-8.

Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, Cron RQ, Opal SM. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. *Critical Care Medicine*. 2016 Feb;44(2):275-81.

Carcillo J, Berg R, Wessel D, Pollack M, Meert K, Hall M, Newth C, Lin J, Doctor A, Shanley T, Cornell T, Harrison R, Zuppa A, Reeder R, Banks R, Kellum J, Holubkov R, Notterman D, Dean JM, Tamburro R. Three pediatric sepsis-induced multiple organ failure inflammation phenotypes: a multicenter study. *Critical Care Medicine*. 2019 Jan;47(1):42.

“The data suggests that treatment with anakinra may preserve systemic immune function and allow immunologic recovery and reset the inflammatory system.”

– Celia Ligorski, DO, resident at Nationwide Children’s Hospital

PROFILE OF A CANCER:

Getting to Know Ewing Sarcoma

Understanding how to fight a deadly enemy requires knowledge of its back story, its habits, where it hangs out and how it behaves under pressure. Ewing sarcoma has been called in for questioning.

by Katie Brind'Amour, PhD

Ewing sarcoma – a tumor type affecting the bone or soft tissue that primarily affects children and adolescents – has a 5-year survival rate of 70 percent among those with localized disease at diagnosis. Among children whose disease is metastatic, only 30 percent survive 5 years or longer. As a comparison, of all children diagnosed with cancer in the United States, 80 percent survive at least 5 years and many are cured.

What makes Ewing sarcoma so different from other types of common and highly treatable pediatric cancers, such as leukemia, is its primary driver: a chromosomal translocation, called EWS/FLI, that is at the root of about 85 percent of Ewing cases. Although a translocation is not unique to Ewing, it is coupled with a series of other molecular circumstances that together create a challenge in terms of understanding what is going on and how best to treat this cancer type.

Some of the traits that make this sarcoma a current medical challenge also give scientists hope that the disease will, in time, give them great potential to treat not just patients with Ewing, but also those with other cancers.

WHAT IS EWING SARCOMA?

The father of the field of oncology, James Ewing, MD – the man behind the American Cancer Society and the *Journal for Cancer Research* – first described his eponymous cancer cells in a published case series in 1921.

The modern characterization of Ewing sarcoma still agrees with Dr. Ewing's initial description: It affects both flat and long bones, most commonly appearing in the legs and arms, pelvis, trunk, or head and neck. It primarily affects adolescents and requires radiation therapy. Current treatment modalities add in aggressive surgery, chemotherapy and combination therapies, especially in the case of metastatic or recurrent disease.

Ewing sarcoma affects about 10 out of every 1 million people aged 10-19 years. When combined with similar cancer subtypes, Ewing and related sarcomas become the fourth most common cancer among children and young adults.

Unfortunately, Ewing sarcoma is notoriously difficult to treat. Prognosis depends on age at diagnosis, the location of the tumor, metastasis, sex, certain genetic differences in Ewing sarcoma subtypes, and the patient's cancer-

related history, among other traits. Despite many advances in therapy and survival in the past several decades, researchers and clinicians alike have become frustrated with the uphill battle facing Ewing patients.

“We can palliate or comfort patients with metastatic Ewing sarcoma, and hold off the inevitable for a few years, but that’s not enough. Our goal is a cure,” says Timothy Cripe, MD, PhD, chief of the Division of Hematology/Oncology/Blood and Marrow Transplant at Nationwide Children’s Hospital and a clinician-scientist studying Ewing and other pediatric cancers. “It’s incredibly frustrating as a doctor to see patients week after week and know that they’re in trouble.”

WHO IS WORKING THE CASE?

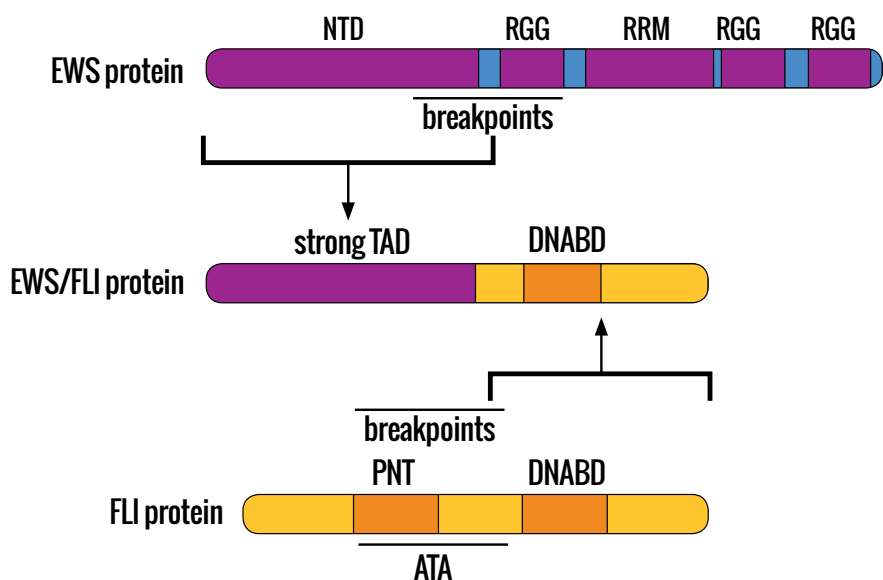
Dr. Cripe and his research team have been studying ideal combination therapies for Ewing tumors. Recent publications reveal a promising synergy between two FDA-approved therapies: an oncolytic herpes virotherapy and trabectedin, a chemotherapy drug with a less toxic side effect profile than many currently in use. When given together to a mouse model of Ewing sarcoma, trabectedin appeared to clear out about half of the tumor’s macrophages, which fight infection and spur wound healing. Once macrophage levels dropped, the virotherapy effectively raised inflammation in the tumor, helping the immune system better fight the tumor.

Manipulation of the tumor microenvironment to attack cancer cells is also under study by other investigators. Elizabeth Lawlor, MD, PhD, associate director of

education and training at the Rogel Cancer Center and an associate professor in the departments of Pediatrics and Pathology at the University of Michigan, is one of the researchers behind recent studies indicating that the origin of Ewing sarcoma appears to be hijacked stem cells that were originally destined to become bones and supporting soft tissues. Her lab is also analyzing the factors in the tumor’s surrounding cells that trigger the switch from progressive growth as a solitary tumor to migration and metastasis.

“My lab is trying to figure out how cells switch back and forth between different states, and which pathways drive these switches, since we are finding that the ability of Ewing cells to change states is essential for tumor progression,” says Dr. Lawlor. “We want to know how cells come to play different roles at different times. Then if we can find a way to interfere with those transitions, that could be a good way to inhibit tumor survival and prevent metastasis.”

The concept of interference is paramount in numerous research and therapeutic approaches for Ewing sarcoma, and not just in the microenvironment. Other researchers focus on targeting the cancer’s key oncogene and associated subcellular processes: epigenetics, protein binding, coregulatory complexes and DNA transcription. For these approaches, the idea is to hit the cancer as close as possible to the origination of the cancer’s developmental activity as possible, to stop the disease in its tracks, kill existing cancer cells and prevent the creation of new ones.



HOW THE CLASSIC EWING SARCOMA TRANSLOCATION OCCURS

The classic oncogenic fusion protein, associated with the vast majority of Ewing sarcomas, arises from a balanced, reciprocal translocation at the molecular genetic level. A portion of the EWS protein fuses to a portion of the FLI protein at the t(11;22)(q24;q12) breakpoint.

In order to do so, however, scientists must first figure out what is going on inside Ewing sarcoma cells.

For decades, researchers have known the cancer is driven by the mutant EWS/FLI fusion protein. Recent research suggests that the EWS and FLI portions of the fusion protein each have their own characteristics and functions. The FLI portion binds to DNA microsatellites (strings of repetitive DNA previously believed to be “junk” DNA), and the EWS portion binds to groups of proteins and enzymes (called coregulatory complexes) that help the fusion protein regulate transcription.

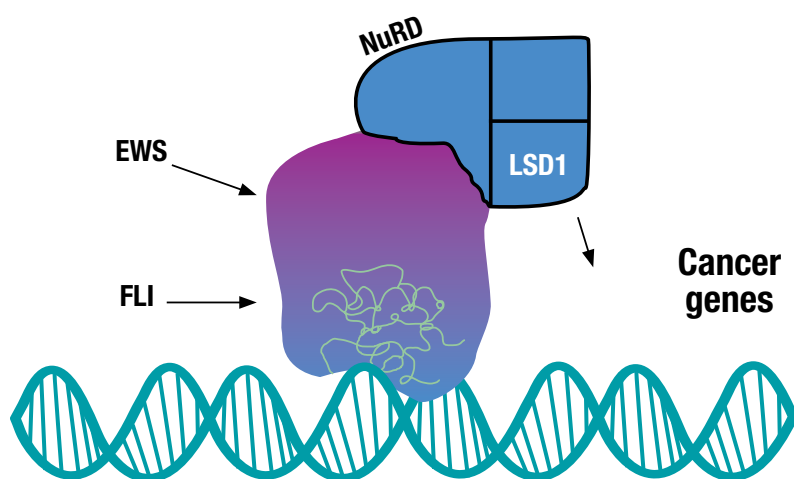
The microsatellites and EWS/FLI literally seem to be sticky – they start grabbing onto other EWS/FLI oncogenes and microsatellites, pulling portions of DNA together in the cell’s nucleus.

“This is a totally new concept in biochemistry,” says Stephen Lessnick, MD, PhD, director of the Center for Childhood Cancer and Blood Diseases in The Research Institute at Nationwide Children’s. Dr. Lessnick’s lab uncovered the presence and role of microsatellites in Ewing sarcoma and recently received a Cancer Moonshot U54 grant from the National Cancer Institute to continue studying the mechanics of these processes. “Instead of having hundreds of proteins with perfectly complementary surfaces – the exclusive way we have long believed proteins to operate and interact with one another – these sticky microsatellites and EWS/FLI proteins seem toglom onto each other, likely causing the EWS portions to phase separate, similar to oil and water.”

This process likely allows other proteins to interact with EWS/FLI and the microsatellite DNA, which may be important in gene expression. Paired with coregulatory complexes, the EWS/FLI fusion protein and its sticky buddies appear to kick off transcription (by “opening” DNA or making it more accessible) or silence transcription (via the physical squashing of DNA into inaccessible structures) of entire groups of genes at a time, even if they are usually distant from each other.

In his studies on the function of EWS/FLI within the cell and its connections to microsatellites, Dr. Lessnick has also uncovered the critical role of a coregulatory complex called NuRD in enabling EWS/FLI to do its dirty work. When paired with an enzyme called LSD1, NuRD appears to enable EWS/FLI to regulate gene transcription.

“When researchers hear the word ‘enzyme,’ our ears perk up – enzymes have pockets you can drug,” says Dr. Lessnick. When Dr. Lessnick made the discovery of LSD1’s role in Ewing during his time at the University of Utah, he serendipitously had a colleague there – Sunil Sharma, MD, FACP, MBA, deputy director of Huntsman Cancer Institute and the director of the Center for Investigational Therapeutics – who had been studying the use of LSD1 inhibitors in models of breast cancer. Of 100 different types of cell lines Dr. Sharma had tested for sensitivity to the inhibitor drug, Ewing was the most sensitive. Fast-forward a few years, and a clinical trial targeting LSD1 in Ewing with Dr. Sharma’s inhibitor is in progress at multiple children’s hospitals across the country.



HOW THE FUSION PROTEIN PROMOTES CANCER

The FLI portion of the EWS/FLI fusion protein binds to DNA. When paired with key enzymes (the NuRD and LSD1 complex), the protein appears to physically scrunch up DNA, allowing the protein to activate or turn off large batches of genes at a time. The new transcribed and suppressed genes are believed to result in the development of Ewing sarcoma cancer cells.

Dr. Lessnick hopes that better understanding intracellular mechanics will reveal what type of interference will be deadliest to the activity of the cancer. The physical manipulation of DNA within the nucleus also represents an epigenetic change, which makes Dr. Lessnick eager to explore the possibility of new and existing epigenetic therapies that may help fight the machinery-based cancer processes at work in Ewing sarcoma.

WHERE ARE EWING SARCOMA'S VULNERABILITIES?

To speed along the identification of druggable targets, some teams are focusing on screening Ewing sarcoma for its genomic vulnerabilities. Patrick Grohar, MD, PhD, associate professor and program leader of Skeletal Disease and Cancer Therapeutics in the Van Andel Research Institute's Center for Cancer and Cell Biology – a chemist by training, prior to his foray into medicine and oncology – cast a wide net in his initial search for potential drug options.

Dr. Grohar set about doing a genome-wide small molecule screen for 50,000 compounds, looking at what kills or turns off the fusion protein, and has

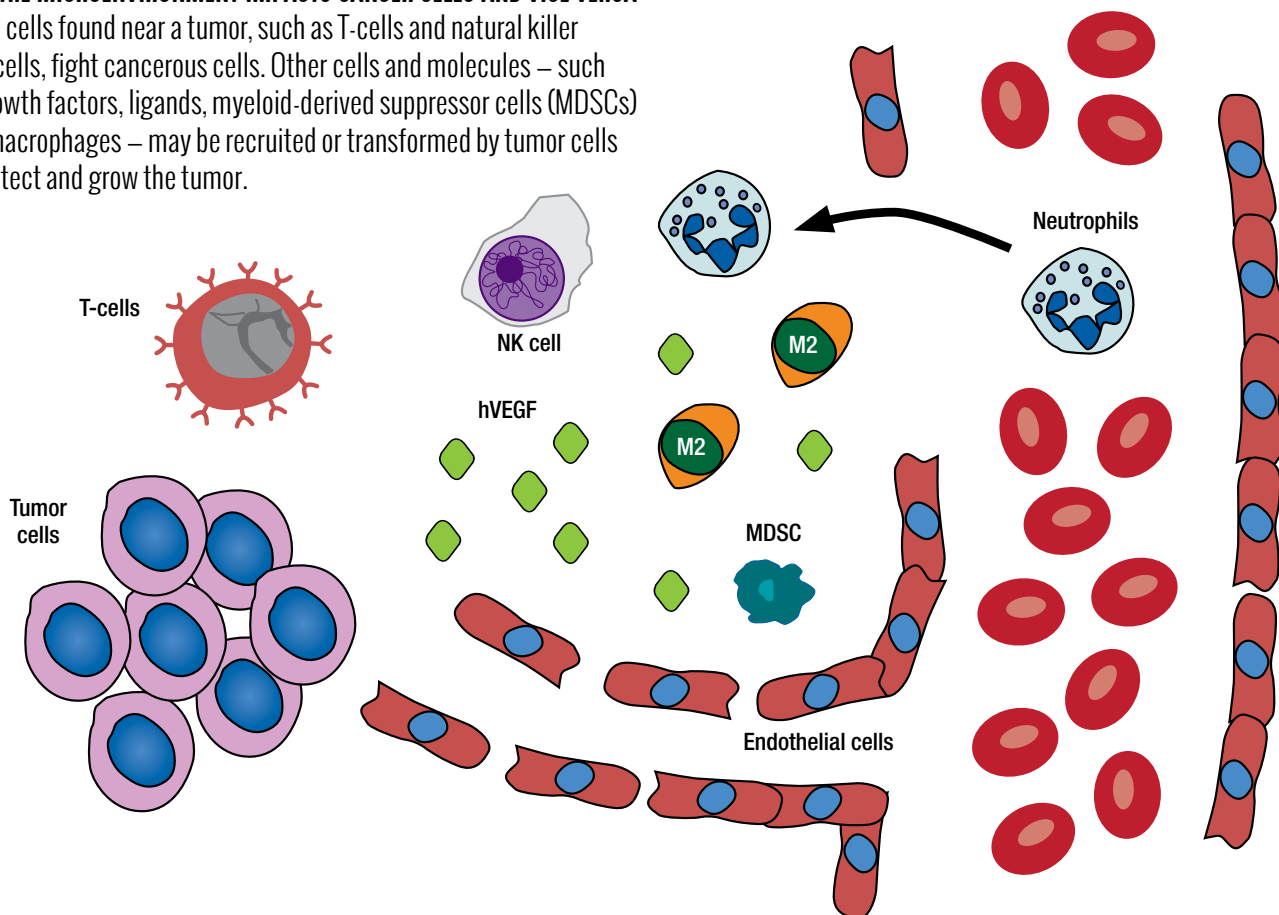
screened with other large libraries of compounds as well. His work first revealed that mithramycin inhibits the fusion protein. The screens also demonstrated the EWS-FLI-inhibition abilities of trabectedin – the chemotherapy drug now used by Dr. Cripe in his preclinical studies.

“Ewing sarcoma is driven by a transcription factor. The mantra when I was in med school was that it’s a non-druggable target,” says Dr. Grohar, who is also an oncologist in the Division of Pediatric Hematology/Oncology at Spectrum Health Helen DeVos Children’s Hospital and an associate professor in the Department of Pediatrics at Michigan State University. “But as a chemist I believe everything is druggable. You just have to figure out how to do it.”

After identifying compounds with anti-Ewing potency, Dr. Grohar does in-depth molecular and preclinical testing to determine which may be good drug candidates. Mithramycin is currently in clinical trials, and Dr. Grohar hopes that continued research will reveal more effective second- and third-generation iterations of

HOW THE MICROENVIRONMENT IMPACTS CANCER CELLS AND VICE VERSA

Some cells found near a tumor, such as T-cells and natural killer (NK) cells, fight cancerous cells. Other cells and molecules – such as growth factors, ligands, myeloid-derived suppressor cells (MDSCs) and macrophages – may be recruited or transformed by tumor cells to protect and grow the tumor.



screen-identified compounds that he can also quickly transition to the clinic.

Taking a similar approach, Kimberly Stegmaier, MD, vice chair of pediatric oncology research and co-director of the Pediatric Hematologic Malignancy Program at the Dana-Farber Cancer Institute, used genome-scale CRISPR-Cas9 screening (a gene editing tool) to find druggable target pathways in TP53 wild-type Ewing sarcoma – a form that differs from many cell line models of the disease but that represents the cancer more accurately as it occurs in most human patients.

Her search revealed multiple possible targets (MDM2, MDM4, USP7 and PPM1D) critically involved in cancer survival, some of which already had compounds available to test for *in vitro* impact on human Ewing cell lines and mouse models. After successful and synergistic lab-based studies, this p53 pathway activation approach has entered clinical trials in children with Ewing sarcoma and other childhood cancers with a normal TP53 gene. Dr. Stegmaier also has NCI Cancer Moonshot U54 funding to find new therapies for Ewing sarcoma.

To make an even broader view of Ewing sarcoma’s genomic make-up possible, Dr. Lessnick collaborates with teams led by Richard Wilson, PhD, and Elaine Mardis, PhD, co-executive directors of the Institute for Genomic Medicine at Nationwide Children’s, to do a long-read genomic sequence of Ewing sarcoma. One cell line is complete, and Dr. Lessnick has several others in progress or planned.

Ideally, long-read sequencing will reveal the true locations of certain genes and hint at the purpose and weaknesses of various chunks of the cancer’s DNA.

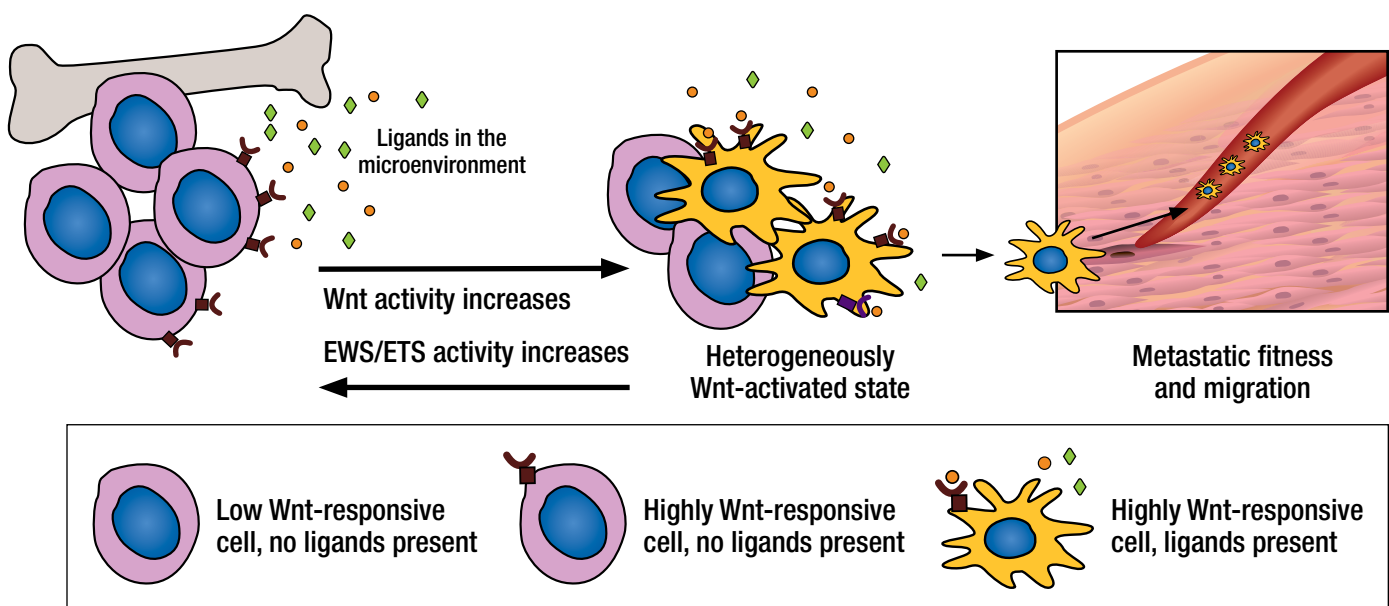
WHY PUT SO MANY RESOURCES INTO EWING SARCOMA?

“Ewing sarcoma serves as a paradigm for a whole series of tumors seen in children, adolescents and young adults,” says Dr. Lessnick. “Better understanding Ewing sarcoma could have direct impact on our ability to treat rhabdomyosarcoma, clear cell sarcoma, desmoplastic small round cell cancers, and a variety of tumors with translocations that generate transcription factors.”

Dr. Stegmaier agrees that discoveries in Ewing sarcoma could mean big advances in other diseases.

HOW TUMOR CELLS BECOME METASTATIC

Tumor cells may be influenced toward or against metastasis by their microenvironment. When the Wnt/beta-catenin pathway is highly active, for example, receptive tumor cells bind to ligands in the microenvironment that help the cells spur the growth of extracellular matrix, structural collagen, and proteins associated with metastasis. It is believed that the proteins secreted by these activated cells then enhance the cells’ ability to travel throughout the body.



“Ewing sarcoma serves as a paradigm for a whole series of tumors seen in children, adolescents and young adults. Better understanding Ewing sarcoma could have direct impact on our ability to treat a variety of tumors with translocations that generate transcription factors.”

- Stephen Lessnick, MD, PhD, director of the Center for Childhood Cancer and Blood Diseases in The Research Institute at Nationwide Children's

“The approaches and technologies that are used to study EWS/FLI could be applied to studying the host of other fusion proteins present in pediatric and adult cancers, such as the Tmprss2/ERG fusion in the majority of adult prostate cancer tumors,” says Dr. Stegmaier, who is also an attending oncologist at Boston Children's Hospital.

Recent dramatic successes in chemically targeting kinase fusions, which relate to but are more readily druggable than transcription factors, provide incentive for persevering toward targeting fusions such as EWS/FLI. Moreover, new advances in chemistry offer hope for success in targeting EWS/FLI directly – hence Dr. Stegmaier's U54 proposal to collaborate heavily with academic chemists in her upcoming research. Once these molecular components are targetable, cancers with similar structural proteins, fusions and transcription factors may also benefit.

The disease also offers researchers a uniquely distraction-free “background” for studying cancer.

“Because Ewing sarcoma in particular, and pediatric cancer in general, are genetically very quiet tumors, not full of thousands of mutations, we can do cleaner genetic and biology studies. These studies are much more challenging with cancers that have scrambled genomes, like you find in most adult carcinomas,” says Dr. Lawlor. This fact also gives Dr. Lawlor hope that Ewing may, when the right biology is understood, become highly treatable.

“The concept is that pediatric cancers can be considered developmental disorders, created when plastic stem cells are hijacked to become a sort of cancer stem cell,” says Dr. Lawlor. “You don't need 50 mutations to create a cancer stem cell, you just need a couple to give a normal stem cell malignant properties. It didn't take as much to create them, and so hopefully it will not take as much to dismantle them.”

WHEN WILL NEW THERAPIES REACH PATIENTS?

Drs. Lessnick, Stegmaier, and Grohar have Ewing-related clinical studies underway, and Dr. Cripe's and

Dr. Lawlor's research is expected to hit the clinic in the next few years.

Experts in Ewing sarcoma research agree that treatment advances will, at least in the near future, involve sophisticated regimens of therapy administration and carefully timed and dosed combinations of epigenetic and chemotherapy drugs. They are also working to combat the toxicity of current therapies, as many surviving Ewing patients suffer from long-term treatment-related side effects.

“We have a great field in Ewing sarcoma because we all are willing to talk to each other – we share our unpublished data and what we're thinking,” says Dr. Lessnick. “Our collaborative, open approach will make a big difference in how quickly we make a difference for patients.”

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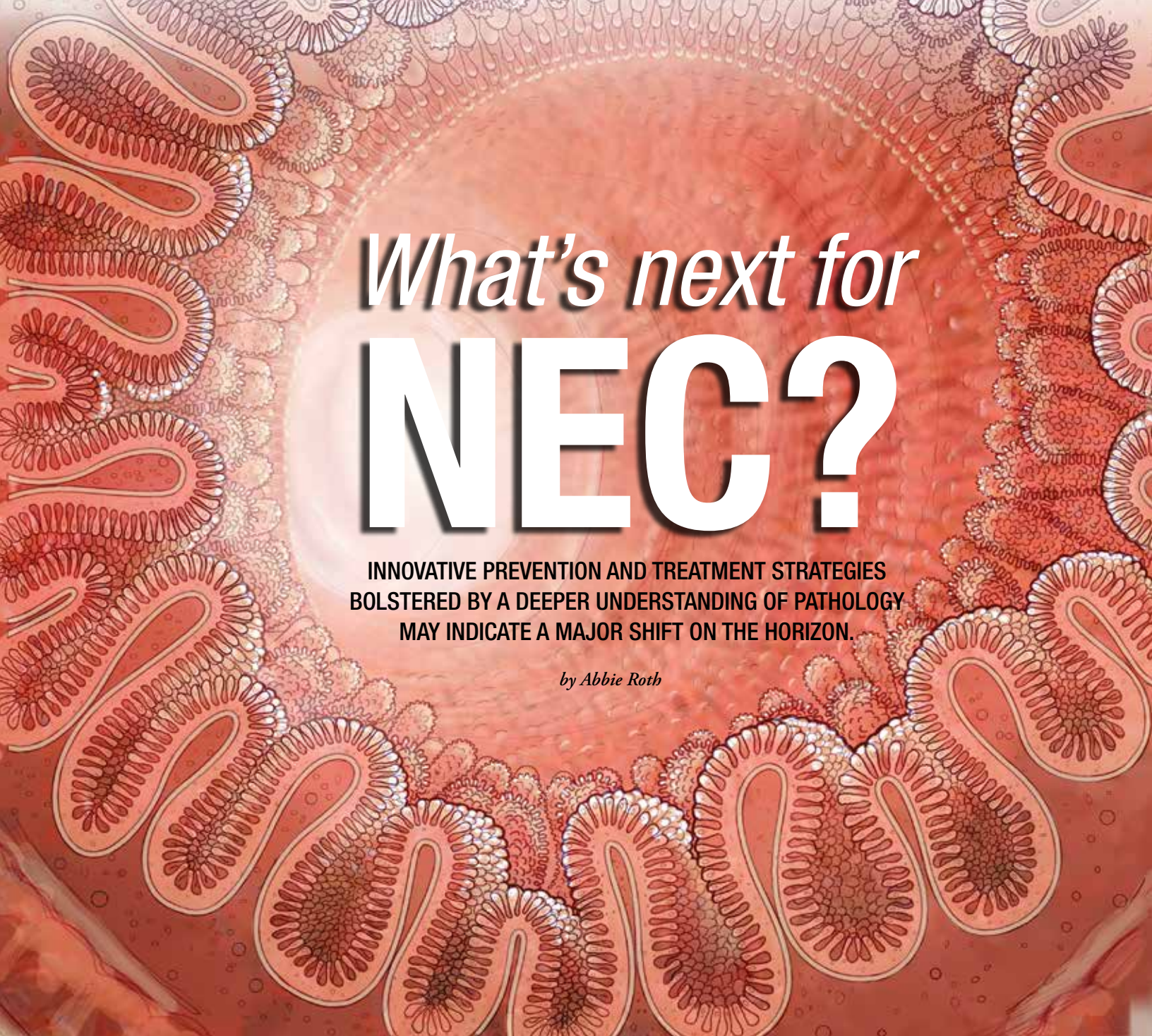
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What's next for **NEC?**

**INNOVATIVE PREVENTION AND TREATMENT STRATEGIES
BOLSTERED BY A DEEPER UNDERSTANDING OF PATHOLOGY
MAY INDICATE A MAJOR SHIFT ON THE HORIZON.**

by Abbie Roth

Red. White. Black.

These are the colors of necrotizing enterocolitis, or NEC. When surgeons open the distended abdomens of the tiny infants affected by NEC, they see a mottled mixture of red (inflamed), white (ischemic) and black (dead) tissue. Their first task is to assess whether or not there is enough viable tissue to save. Then, they get to work.

Many things had to happen to get to that moment and those colors. What was the cause? And how can it be prevented?

A DISEASE OF PREMATUREITY

The term necrotizing enterocolitis was first used to describe the death of intestinal tissue in premature infants in 1965. In the early 1970s, surgeons developed the surgical protocol to treat the disease.

In 1978, Bell's criteria, an algorithm developed by Martin Bell, MD, at the Washington University School of Medicine and St. Louis Children's Hospital, became the uniform clinical staging for infants with NEC. At stage I, NEC is suspected and symptoms are treated medically. At stage II, NEC is proven and medical care continues.

In stage III, NEC is advanced: the infant is critically ill with a perforated intestine, and surgery is necessary.

In the past decade or so, advances have focused on preventing the occurrence of NEC, and on developing a deeper understanding of the pathology.

“Despite decades of research, little has changed in terms of prognosis for infants who develop NEC,” says Gail Besner, MD, chief of Pediatric Surgery at Nationwide Children’s Hospital and principal investigator in the Center for Perinatal Research in The Research Institute at Nationwide Children’s. “But the preclinical work that is being reported in the last few years tells us that all of that is about to change. We’re really on the cusp of something big here.”

NEC occurs in 1 to 3 per 1,000 live births, making it a rare disease as classified by the National Institutes of Health. But for clinical professionals in advanced neonatal intensive care units (NICUs) like the one at Nationwide Children’s Hospital – where doctors and nurses care for the smallest and sickest infants – NEC is far too common. More than 90 percent of cases of NEC occur in very low birth weight (<1500 g) infants born at less than 32 weeks gestation.

“It’s on our mind daily,” says Maria Talavera, DO, neonatologist at Nationwide Children’s. “We all struggle with NEC. You’ll see a baby with a little abdominal distention or trouble with a feed, and by the end of your 12-hour shift, the baby could die. Sometimes, it’s that fast. Other times, it lingers, starts, seems to get better, then worsens without notice. For the lucky ones, NEC responds to medical treatment and we never have to operate on them.”

That sudden downward spiral after a fragile infant has survived the first weeks to month of life in the NICU is something that clinicians and scientists want to predict and prevent. But in order to do so, they need to understand what causes NEC.

NEC is characterized by acute and chronic intestinal inflammation. The convergence of many factors, including intestinal immaturity, the microbiome, the immune response and pathogen exposure, can ultimately lead to systemic sepsis and multi-system organ failure in patients with NEC.

Risk factors for the development of NEC in premature infants include hypoxia, formula feeding, abnormal bacterial colonization of the bowel, increased release of inflammatory mediators, intestinal ischemia-reperfusion injury, use of acid-reducing medications and transfusion-associated gut injury (TRAGI).

“In premature infants, you have sort of a perfect storm of factors that can lead to NEC,” says Dr. Talavera. “Mucosal injury and bacterial overgrowth compromise the immature intestinal epithelium, while the abnormal flora takes advantage of the immature immune system.”

According to Dr. Besner, finding the answer to NEC has been challenging.

“One challenge regarding NEC is the inability to identify exactly which babies are most likely to get the disease. If we could predict this with certainty, then we would know exactly which babies to treat with potential novel therapeutics for the disease,” she explains. “As our understanding of NEC pathology increases and as biomarkers predictive of NEC are identified, novel strategies to treat the disease can be employed.”

COMMON SIGNS AND SYMPTOMS OF NEC

SYMPTOM	INCIDENCE (%)
Abdominal Distention	89
Lethargy	84
Temperature Instability	81
Occult/Frank Blood	80/43
Gastric Residuals	73
Fecal Reducing Substance	71
Apnea	66



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HARNESSING THE POWER OF BREAST MILK

Most premature babies are initially placed on total parenteral nutrition (TPN) intravenously until their immature intestines are capable of tolerating feeds.

Giving breast milk orally is the first step in preventing NEC, according to Dr. Talavera.

“Just a drop of breast milk – preferably mom’s but possibly from a donor – can start the process of coating the digestive tract with all the good things that will help the baby thrive,” she says. “We can even just paint the mouth with a little breast milk from day zero. Getting more oral feeds as early as possible is an important goal for preventing NEC.”

So what is it about breast milk that is so protective? This is an area of research currently being explored by clinician-scientists around the world. It is likely that many components of breast milk play a role in modulating the microbiome, immune system and gut development to prevent NEC.

One such component includes exosomes, nano-sized vesicles that are secreted by all cell types including stem cells.

“We have shown that several different types of stem cells can protect the intestines from NEC in animals,” says Dr. Besner. “Furthermore, exosomes secreted by these stem cells provide the same benefit as the stem cells themselves without the potential risks associated with stem cells, such as tumor growth. And, exosomes are present in human breast milk.”

In preclinical studies, Dr. Besner’s team has purified breast milk-derived exosomes and fortified breast milk feeds with them. The exosome-fortified breast milk reduced the incidence of NEC in animal models.

“Exosomes from donor milk are easily purified and could be used to fortify the feeds for premature infants at risk for NEC,” she says.

“Breastfeeding prevents NEC, but even with best nursing practices, NEC persists,” Dr. Besner adds. “You can do

everything right, and NEC can still develop. We need advanced strategies for prevention and treatment if we are to eliminate NEC from the NICU.”

PROBIOTICS – GOOD FOR THE GUT

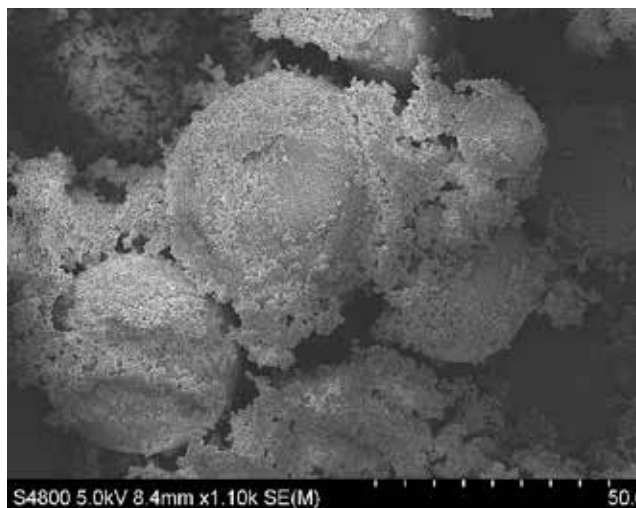
Researchers have long been investigating the possibility that probiotic therapy could prevent NEC. And some probiotic protocols are in place in some NICUs across the country. However, none of them have produced the compelling results that researchers hope for.

One of the problems with traditional approaches to probiotic therapy is the delivery system. For probiotics to work, they must survive the acidity of the stomach and the host immune system, and then take root in the gut, where they are expected to compete with pathogenic bacteria and flourish. All probiotic clinical studies to date have used free-living (planktonic) probiotic formulations, which do not optimally display these required characteristics.

“The practice of giving high doses of probiotics daily or even with every feed has its risks,” says Dr. Besner. “One of those risks is bacteremia, or bloodstream infection, from the probiotic administered. It is desirable to increase the efficacy of the probiotic in order to decrease the amount needed while still maintaining protective effects.”

Dr. Besner and her colleagues, including Steve Goodman, PhD, Michael Bailey, PhD, and Lauren Bakaletz, PhD, recently licensed a technology that solves this problem – administering the probiotic in a biofilm state provides near elimination of NEC with one dose in preclinical studies.

Their probiotic of choice, *Lactobacillus reuteri*, is incubated with maltose-filled dextranomer microspheres



(Lr-DM-Malt). In one study published in the *Journal of the American College of Surgeons* in 2017, the administration of a single dose of Lr-DM-Malt reduced the incidence of NEC from 70 percent to 21 percent in the animal model. Administration of Lr without the microspheres, that is, without being in biofilm state, did not protect against the development of NEC. In a follow-up study published in *American Journal of Physiology Gastrointestinal and Liver Physiology*, the investigators filled the microspheres with sugars that promoted increased biofilm formation, making the probiotic formulation even more effective.

“We know that bacteria are stronger and more resistant in the biofilm state,” says Dr. Goodman. “They are in their optimal physiologic state in a biofilm, and this gives them a better chance to affect the digestive tract.”

Dr. Goodman uses the following analogy to explain. Imagine that you have two runners who are getting ready for a race. One has just rolled out of bed and might not have had breakfast. This one is like the planktonic probiotics. The other has been fed, warmed up, and is in peak physiologic state. This is probiotics in the biofilm state. Which do you think will be the most effective?

Another aspect of the Lr-DM-malt microsphere technology that excites the researchers is the GRAS designation of each of the components. GRAS is a Food and Drug Administration category that stands for “Generally Recognized as Safe.”

“We’re hopeful that the GRAS designation of each of the components will be helpful in getting the technology into the clinic,” says Dr. Besner. “These are all well-known components combined in a new way to produce what we believe will be an extraordinary outcome.”

Lactobacillus reuteri forms a biofilm on maltose-filled dextranomer microspheres. When administered as a single dose to an animal model, Lr-DM-Malt reduced the incidence of NEC dramatically.

“The good news is that TLR4 is ultimately targetable. We know that some things help to regulate TLR4. Specifically, amniotic fluid and breast milk.”

– David Hackam, MD, PhD, surgeon-in-chief and principal investigator at Johns Hopkins Children’s Center

THERAPEUTICS BASED ON TLR SIGNALING

David Hackam, MD, PhD, surgeon-in-chief and principal investigator at Johns Hopkins Children’s Center, and his team are adding their own approaches to the arsenal against NEC. In the past several years, they have published a series of papers that demonstrate the role of toll-like receptors in the pathology of NEC, specifically, the role of TLR-4.

TLRs are part of the innate immune system and play a key role in identifying pathogens. But that’s after birth. In utero, TLRs – specifically TLR4, which has been associated with NEC – play a different role.

“TLR4 expression in the fetal gut helps the gut develop properly,” explains Dr. Hackam. “Typically, that high level of expression is turned off before birth.”

Dr. Hackam and his team have shown experimentally that high levels of TLR4 expression in animal models lead to NEC. They’ve supported the bench work with evidence from the NICU. Levels of TLR4 in the intestines of infants with NEC are also high. Conversely, babies without NEC have low levels of TLR4.

NEC occurs after bacteria enter the gut. Recall the onset is typically a week to months after premature delivery. In the presence of bacteria, the TLR4 takes on an inflammatory role, prompting a cytokine storm that ultimately causes inflammation and restricted blood flow to the gut – in other words, NEC.

“The good news is that TLR4 is ultimately targetable,” says Dr. Hackam. “We know that some things help to regulate TLR4. Specifically, amniotic fluid and breast milk.”

These substances serve as inspiration for his team as they are working to develop several drugs that prevent TLR4 activation.

Another avenue they are exploring is the TLR9 pathway. “In NEC, you have too much expression of TLR4 and

not enough TLR9,” says Dr. Hackam. “By increasing TLR9, we could balance the ratio of TLR4 to TLR9 in an effort to prevent NEC.”

BEYOND SURVIVAL

NEC carries a 30 to 50 percent mortality rate. And for those patients that survive, the downstream effects can be lifelong. Depending on how much of the intestine is surgically removed, the infant may require G-tube feeding for the short or long term. Short gut syndrome, also called intestinal failure, requires long-term follow up with gastroenterologists. For some survivors of NEC, getting proper nutrition will be a lifelong challenge.

Nearly 50 percent of survivors of NEC develop significant developmental and cognitive disability.

“The neurodevelopmental injury that results from NEC is both more severe and more difficult to treat than that caused by prematurity in general,” says Dr. Hackam. “Our program is also investigating the pathways that cause the neurodevelopmental problem.”

The best way to prevent NEC-associated neurodevelopmental problems is to prevent NEC. But in the cases where NEC is present, a therapeutic approach to minimize or eliminate the damage to the brain would be life altering.

In an article published last year in *Science Translational Medicine*, Dr. Hackam and his team show that TLR4 expression could be a culprit in the brain injury in addition to the intestinal injury. Using their animal model of NEC, they showed that TLR4 activation induced microglial activation in the brain. The study also tested an intervention – a dendrimer-based nanotherapeutic approach – that targeted the activated microglia to prevent NEC-associated neurologic dysfunction in the model.

In an effort to help mitigate the effects of short bowel syndrome, Drs. Hackam and Besner each have research



At Nationwide Children's NICU, a quality improvement project reduced the incidence of NEC to only 3.1 percent among very-low birth weight babies.

“In Ohio, we're fortunate to have a milk bank resource,” says Dr. Talavera. “Mothers of NICU infants need additional support to pump and maintain a supply. The importance of breastfeeding and providing breast milk is engrained in the NICU, but still, it may not be an option for every mother. That's why donor milk is so important.”

programs dedicated to developing tissue engineered intestinal grafts. As with other tissue-engineered organs, the idea involves using a biodegradable scaffold seeded with stem cells that will ultimately develop into a living, growing, functional intestine.

“Tissue engineering is a quickly growing field. We're excited about the prospect of being able to help children who have lost a significant portion of their intestine,” says Dr. Besner. “We are still in early preclinical work and look forward to further developing this program.”

A BRIGHT FUTURE

“NEC is scary for parents, it's scary for physicians,” says Dr. Talavera. “But we've shown that little changes can improve outcomes.”

For example, a three-step quality improvement protocol implemented in the Nationwide Children's NICUs reduced the incidence of NEC from 8 percent to only 3.1 percent among very low birthweight babies.

“The three strategies we employ from a QI perspective include early human milk feedings, no feedings during blood product transfusions and restricting the use of acid suppressive medication, such as ranitidine,” says Dr. Talavera, who was the lead author on the publication in *Pediatrics* that reported the findings of the protocol.

Access to human donor milk is an important part of the equation.

Through QI, therapeutic development and a deepening understanding of how NEC forms, the future is looking bright for infants who are at risk for NEC.

“For many years, the treatment of babies with NEC has been plagued with many unknowns that add to the pain and suffering caused by this disease,” says Dr. Hasham. “Now, we're finally able to offer hope. All of the advances in the last several years were inconceivable before.”

Dr. Besner agrees, “With the advances that are in the pipeline, I think we can expect big changes in outcomes. It is our hope that in another few years, NEC could be a relic of the past. That's what we work toward.”

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WORTH IT

Why Wrestling Through the Logistical Challenges of a Multidisciplinary Colorectal Center Matters

by Jeb Phillips

Consider the complex case of a girl born with rectal, vaginal and urinary tracts fused into a common channel – a cloacal malformation.

The child needs reconstructive procedures across three different organ systems and three different surgical specialties. It could take months or years to manage the surgeries needed for the colorectal portion, then the gynecological portion, then the urological portion. Multiple anesthetic inductions, intubations, inpatient stints and recovery periods.

The definitive surgical repair could also take just eight hours in a single day, if those different specialties operated in the same room together. But in most institutions, they almost never do because it's a logistical nightmare to plan, schedule, bill and share resources between divisions.

Or consider the case of a boy with severe functional constipation, referred for surgery after failure of medical management. A gastroenterologist, working closely with a colorectal surgeon, could conduct motility testing to help guide treatment. The motility testing may actually suggest that surgery isn't the best option, that a Botox injection, or even behavioral health interventions, make more sense.

But most often, a GI doctor does one thing, a colorectal surgeon does another. Maybe they talk and maybe they don't.

"Intuitively, it's better for the child if the surgeon and I plan and carry out the best course of action together," says Carlo Di Lorenzo, MD, chief of Gastroenterology at Nationwide Children's Hospital. "It's better for the patient if a colorectal surgeon, a gynecologist and a

urologist collaborate on a complex case. But I always thought, if this were a model that worked, other institutions would already use it."

That's how Dr. Di Lorenzo described his attitude about an integrated center approach several years ago. This is Dr. Di Lorenzo describing it this year: "Now it would be really hard to do it any other way."

In the spring of 2014, Marc Levitt, MD, a colorectal surgeon, created the Center for Colorectal and Pelvic Reconstruction at Nationwide Children's. Dr. Levitt and his collaborators across the hospital have spent the last five years showing how the model can, in fact, succeed.

The collaboration has not always been easy. For those who have participated, though, and those who are adopting some of the same methods outside of Nationwide Children's, it's worth it.

A "LEAP OF FAITH"

In the first full year of existence, the Center for Colorectal and Pelvic Reconstruction performed 132 combined procedures on 82 patients. A total of 87 procedures were urological, gynecological and colorectal, and the rest were either urological and colorectal or gynecological and colorectal.

Had the procedures been done independently instead of in combination, there would have been a total of 346 anesthetic inductions. There were actually 132. There would have been 101 endotracheal intubations. There were actually 50. Hospital length of stay was shorter and there were fewer post-operative clinic visits. Patients went home sooner. Families had to travel to the hospital less frequently.

The Center for Colorectal and Pelvic Reconstruction (CCPR)

Geri Hewitt, MD,
chief of Gynecology

Marc Levitt, MD,
chief of CCPR

V. Rama Jayanthi, MD,
chief of Urology

Carlo Di Lorenzo, MD,
chief of Gastroenterology



“ We understood why it would work. How it would work was the hard part. ”

– Geri Hewitt, MD, chief of Gynecology at Nationwide Children’s

Those were the benefits seen across 82 patients in 2015. In 2018, the center handled 1,000 cases.

When Dr. Levitt first proposed the center to Dr. Di Lorenzo and what would become the center’s other primary service line chiefs – Geri Hewitt, MD, of Gynecology, and V. Rama Jayanthi, MD, of Urology – he had none of these statistics. He just had an idea of what could happen if everyone came together.

“Dr. Di Lorenzo, Dr. Jayanthi and Dr. Hewitt did not know this would work,” says Dr. Levitt, who is himself chief of the Center for Colorectal and Pelvic Reconstruction at Nationwide Children’s. “They knew the concept could help patients. It was a leap of faith in the beginning.”

Or, as Dr. Hewitt put it: “We understood why it would work. How it would work was the hard part.”

The primary solution Dr. Levitt proposed was making the center its own service line with its own faculty and staff members. The center would not be stealing resources from other divisions, or asking those divisions to contribute out of the goodness of their hearts; those divisions would themselves be receiving value from the cases the center brought in.

As a practical matter, 14 surgeons and gastroenterology physicians now divide their work between their home divisions and the center (two surgeons, including Dr. Levitt, are essentially full-time center faculty). For example, several urologists spend 25 percent of their time on collaborative cases, and the remainder of their time on pure urology cases. That has allowed Nationwide Children’s to hire additional urologists in the division.

“There are some inefficiencies – a urologist may have to block off an entire day for a single, complex center case, when the urological portion of that case may last only two hours,” says Dr. Jayanthi, the Urology chief. “We accept that, because we know it’s better for the patient.

We also know that some patients are coming to this hospital who wouldn’t have before, because they can get this comprehensive care. This is bigger than Urology alone. We recognize it, and the hospital recognizes it.”

Dr. Hewitt had to reorganize her entire practice routine, and request that her gynecological partners reorganize theirs, to make it work. Dr. Di Lorenzo says that in a weekly center meeting, there can be four surgeons, a handful of GI motilitists, plus behavioral health and social work talking about a single child for more than an hour.

The center published a study in 2018 explaining in detail how all of this works, from intake meetings for a very young child through the transition to adult care. Dr. Levitt believes other institutions can use this model to help their patients, or to use information from the center to create other multidisciplinary programs.

Some institutions are doing just that.

A DIFFERENT WAY

At Seattle Children’s Hospital, the system has grown gradually over time, as it became clear that a multidisciplinary approach could work there, says Jeffrey R. Avansino, MD, a general pediatric surgeon and founding member of Seattle Children’s Reconstructive Pelvic Medicine Program.

“I looked at it the same way I look at writing a grant,” says Dr. Avansino. “You have to do the experiments before you apply for a grant to provide proof the future experiments will be successful.”

The Reconstructive Pelvic Medicine Program did not have the same initial institutional investment of the center at Nationwide Children’s, but the program has ultimately been able to make a similar business argument, after the clinic was established.

“Of course it’s better for the patient, but it’s also true that some patients come for the program who never would have made it to Seattle otherwise.” says Dr. Avansino.

Patients with complex anorectal malformations often have other conditions that must be addressed, and those patients can be referred to an institution’s neurosurgeons or heart specialists. It becomes clear that while a gynecologist is perhaps not doing as many individual gynecological procedures, the entire hospital actually benefits from the multidisciplinary program, say both Dr. Levitt and Dr. Avansino.

“ We want other centers to understand this is worth doing. This is how we can give the best possible care to these patients across the country. ”

– Marc Levitt, MD, chief of the Center for Colorectal and Pelvic Reconstruction at Nationwide Children’s

“Most importantly, multidisciplinary care benefits the patients,” says Dr. Avansino. “You realize that if you need to examine the child under anesthesia, and a urologist also needs to scope the same child, it would be better if everyone worked together. If you do a complex repair together, perhaps you can share tissue, which ultimately creates the best outcome for the patient.”

But Seattle and Nationwide Children’s have significant resources and large potential patient volumes. What about other pediatric institutions that don’t?

Dr. Avansino credits Dr. Levitt and others with building an international network of like-minded providers who are engaged with that very issue. Some large pediatric colorectal programs have joined to create the Pediatric Colorectal and Pelvic Learning Consortium (PCPLC.org), both to advance research and create common definitions for terms like “failure of medical management” in constipation. (The Center for Colorectal and Pelvic Reconstruction at Nationwide Children’s runs a “Bowel Management Boot Camp,” which often finds that an intensive initial medical regimen allows children with severe constipation to avoid surgery.)

Those large centers can help develop knowledge and take care of the most complex cases. What they learn can be transmitted to smaller institutions, so they can better take care of less complex cases, or help with ongoing management after centers like Nationwide Children’s and Seattle Children’s have completed surgical repairs.

“We want other centers to understand this is worth doing,” says Dr. Levitt. “This is how we can give the best possible care to these patients across the country.”

THE FRUITS OF COLLABORATION

Consider, again, the complex case of a girl born with a cloaca. For decades, the length of the common rectal, vaginal and urinary channel was the main guide for

surgical strategy. The Center for Colorectal and Pelvic Reconstruction has been referred a number of patients who have already undergone reconstruction elsewhere using the traditional strategy, and who have post-operative urinary complications.

The center’s urologists, colorectal surgeons and gynecologists together analyzed what they were seeing, and realized surgeons also needed to use urethral length to guide reconstruction. A short urethral length, or an especially long common channel length, suggests a technique that is not routine. They published a new algorithm for cloacal management in 2018, in the *Journal of Pediatric Surgery*, considering both common channel and urethral length. According to Dr. Levitt, this is the first change in cloacal surgery technique in more than two decades. So far, the outcomes have been excellent.

“The importance of collaboration with urology on the management of cloacal malformations cannot be over-emphasized, and this urethral issue is a great example,” wrote the authors, including Dr. Levitt, Dr. Hewitt, Dr. Jayanthi and many of their center partners.

This new algorithm is exactly the reason the Center for Colorectal and Pelvic Reconstruction exists. Maybe it was a leap of faith in the beginning. Maybe the logistics are difficult. But in the end, the patient gets better care.

“This works,” says Dr. Levitt.

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Fetal Balloon Aortic Valvuloplasty for Critical Aortic Stenosis

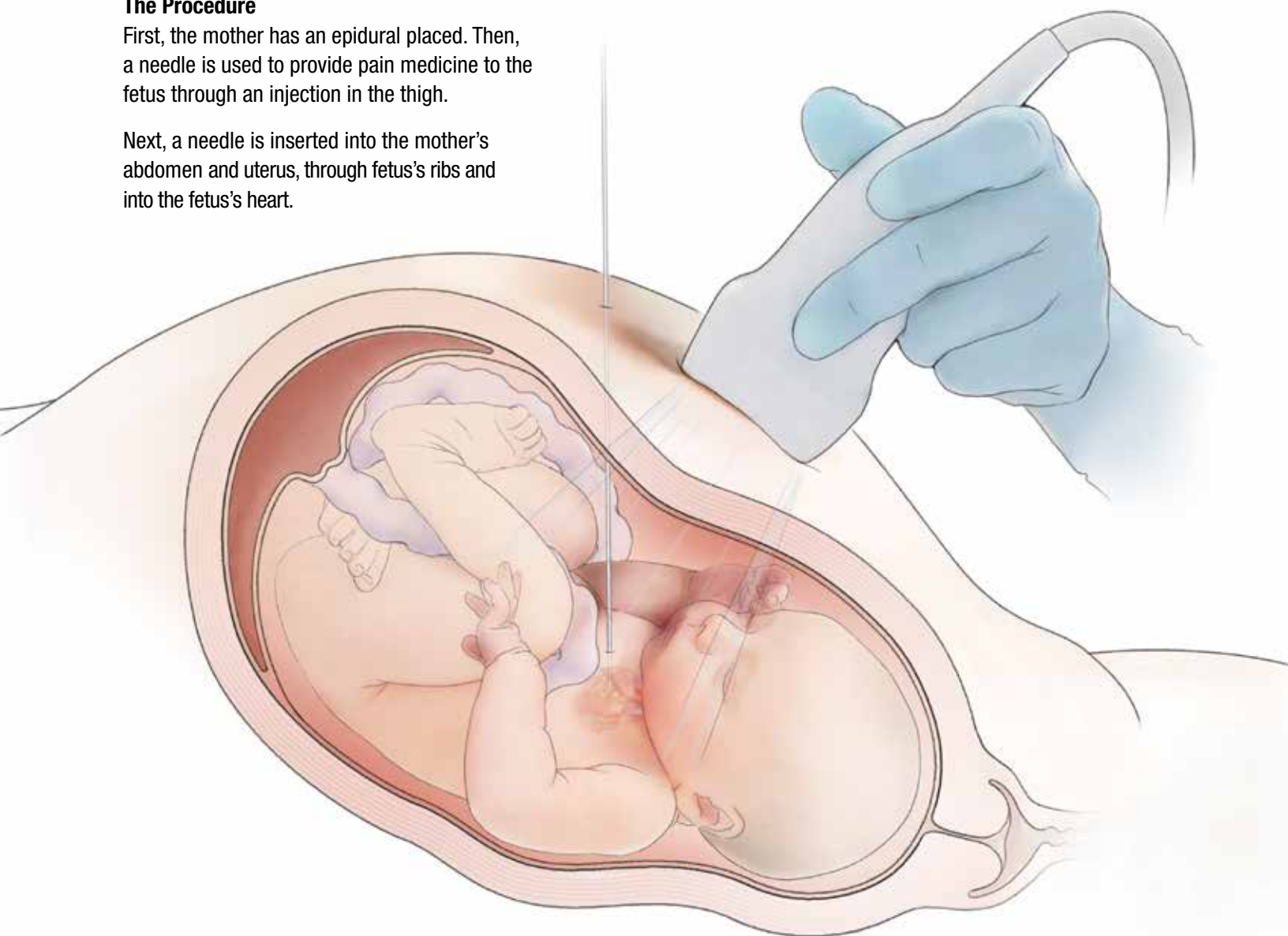
Some heart defects, such as aortic stenosis can be detected on fetal ultrasound. For some fetuses, an intervention can be beneficial before birth. Aimee Armstrong, MD, director of Cardiac Catheterization and Interventional Therapies at Nationwide Children's Hospital, performs fetal balloon aortic valvuloplasty among other fetal heart catheterization procedures as part of the Congenital Heart Collaborative, a partnership between University Hospital's Rainbow Babies and Children's and Nationwide Children's.

When critical aortic stenosis is present in a second trimester fetus, the left ventricle becomes enlarged and weak. As a result, there is less blood flow through the left side of the heart. This can cause the left ventricle to stop growing, leading to hypoplastic left heart syndrome (HLHS). Through fetal treatment of the critical aortic stenosis, doctors hope to prevent the formation of HLHS.

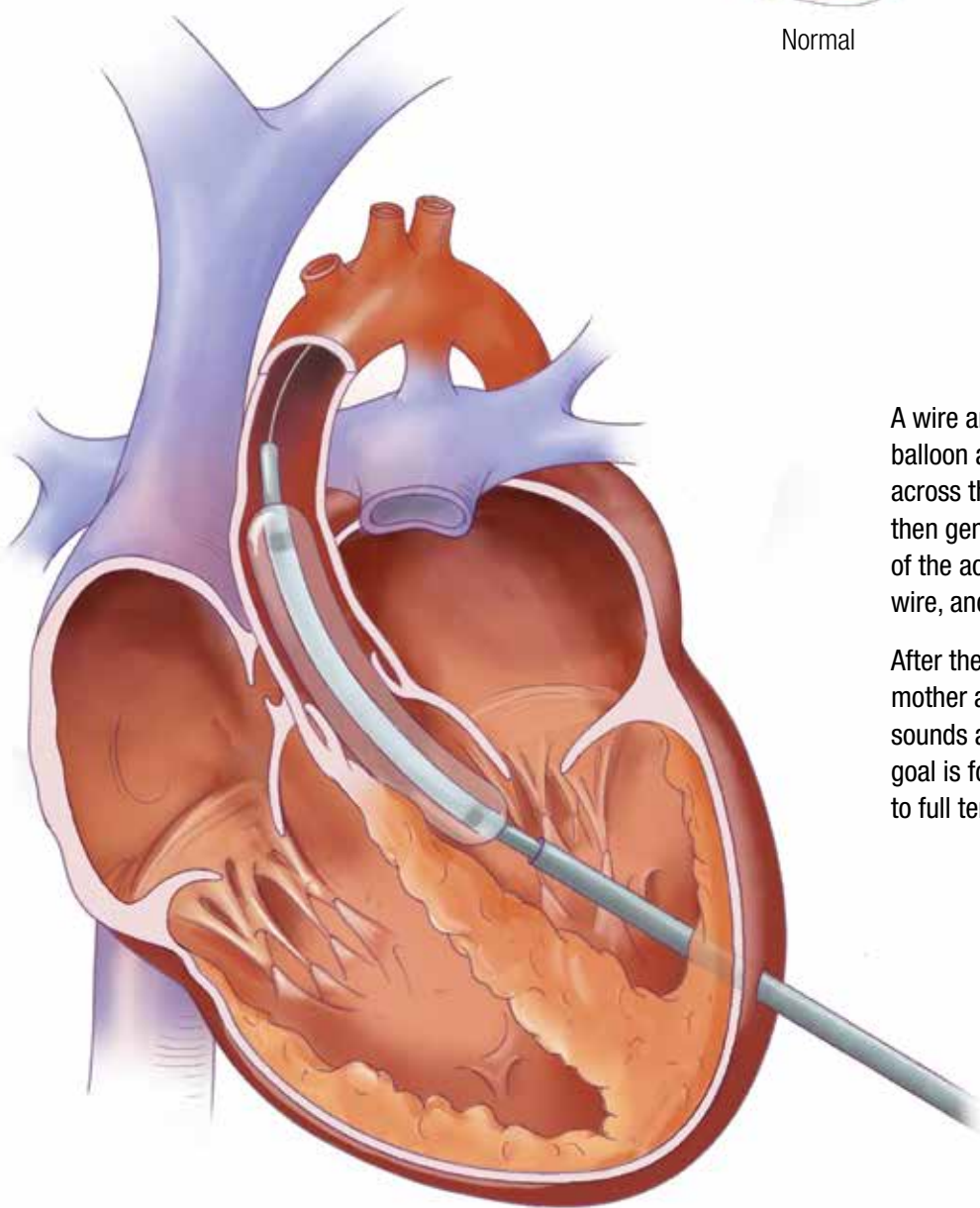
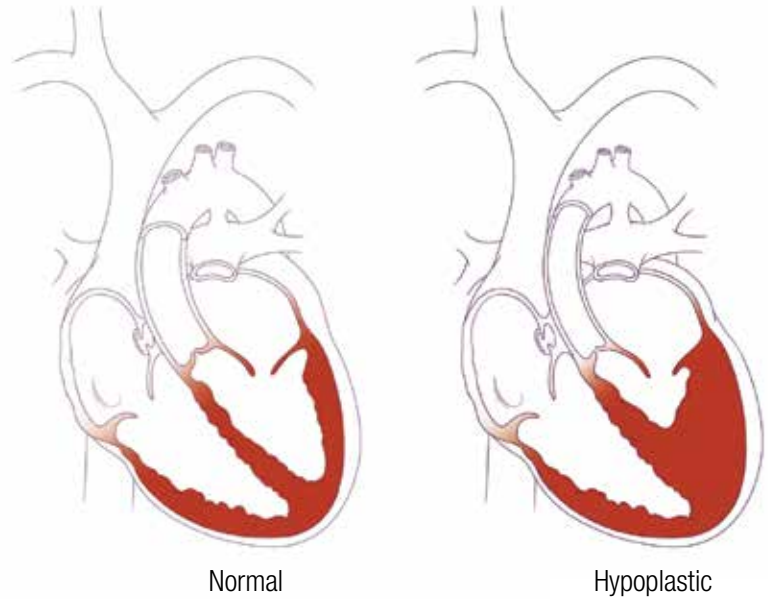
The Procedure

First, the mother has an epidural placed. Then, a needle is used to provide pain medicine to the fetus through an injection in the thigh.

Next, a needle is inserted into the mother's abdomen and uterus, through fetus's ribs and into the fetus's heart.



In HLHS, the left side of the heart is underdeveloped. Patients with HLHS have one pumping chamber that must send blood to both the lungs and body. This causes both short- and long-term problems, including many open-heart surgeries, catheterization procedures, and, eventually, heart transplantation.



A wire and a tiny coronary angioplasty balloon are placed through the needle across the aortic valve. The balloon is then gently inflated to make the opening of the aortic valve bigger. The balloon, wire, and needle are then removed.

After the procedure, doctors watch the mother and baby with many fetal ultrasounds and fetal echocardiograms. The goal is for the mother to deliver as close to full term as possible.

How Research Reinforces the Collaborative Culture of a Children's Hospital

AS HE RETIRES, THE CEO OF NATIONWIDE CHILDREN'S HOSPITAL REFLECTS ON THE LESS-OBVIOUS EFFECTS OF SCIENTIFIC DISCOVERY.



by Steve Allen, MD

Nationwide Children's Hospital has undergone a dramatic transformation in the last two decades, from an important regional resource into a nationally preeminent medical system. One of the clearest signs of our growth, and one that we're particularly proud of, is the expansion of our research program.

Like many of our academic medical peers, we are involved in the discovery of new knowledge, and our work is helping shape the future of health care. From my vantage point as CEO for the last 13 years, I have seen what may seem like a surprising effect of this research growth on Nationwide Children's itself: a powerful reinforcement of our collaborative hospital culture.

Children's hospitals across the country emphasize their institutional cultures and the effects on patients. Seattle Children's Hospital calls its operating principals "ART" for Accountability, Respect and Teamwork. Colorado Children's Hospital asks its staff to abide by a "Standards of Behavior Promise."

At Nationwide Children's, we have "One Team Values." Our values say that our primary goal is providing optimal care for children, and we can best achieve the goal by collaborating, supporting each other and holding each other accountable. We recruit employees and faculty who will uphold these values, and we train new hires to call out managers and senior leaders who act counter to them.

So what does an increase in the number of principal

investigators in our research institute from 111 to 195 since 2006, or a rise in National Institutes of Health research funding from \$23.9 million to nearly \$49 million, have to do with these internal values?

We have found that our increasing work to discover new knowledge, and the push to create new treatments and better outcomes, has actually driven collaboration, accountability and innovation, both at Nationwide Children's and far outside our walls. A growing research program:

- Allows us to make broader use of our personalized clinical work. The treatment provided to individual children at Nationwide Children's, in combination with knowledge about outcomes, can be used to better inform treatment practices here and elsewhere.
- Enables us to break through the fragmentation and regionalization of pediatric medicine. Pediatrics is often bound by geography and tradition – we do something because that's the way we've always done it. Through our membership in scores of national and international research consortiums and associations, we see in real time the successes and challenges of our peers, and they see ours. We all improve together.
- Motivates us to know what is new, and what is coming in the future. Because we are pushing the field of medicine forward, we must keep up with the ways others are pushing. We stay aware of the newest and best, and we change practice based on what we learn.



- Encourages greater cross-pollination between the bench and the bedside. Our clinicians increasingly turn to their research colleagues for help solving difficult problems, while our researchers increasingly focus on the translational aspects of their lab work. We also have more faculty members who identify as a “clinician-researcher” than ever before.
- Creates opportunities for technology commercialization, ultimately benefitting patients. A total of 13 startup companies are now based on the research of Nationwide Children’s staff. The companies can often take treatments to market more efficiently than we can, while we reinvest financial gains from our licensing efforts into our clinical and scientific endeavors.
- Continues to facilitate basic scientific discovery. An institution’s level of intellectual curiosity is raised when people push the boundaries of knowledge – when they learn something no one else knows about fundamental biologic mechanisms. This information forms the building blocks for others to pursue inquiries into disease.

There are countless examples in just the last two years of projects that have proven all of these points. Nathalie

Maitre, MD, PhD, a neonatologist and principal investigator in our Center for Perinatal Research, and Garey Noritz, MD, chief of our Section of Complex Care, helped develop new guidelines for early diagnosis and intervention in cerebral palsy as members of a multinational collaborative – then led Nationwide Children’s to be the first hospital in the world to fully implement them.

A child is typically diagnosed with cerebral palsy at 2 years of age or older; now, with the guidelines and as the coordinating site for the Cerebral Palsy Foundation’s Early Detection and Intervention for Cerebral Palsy network, our average age of diagnosis is 10.5 months. An earlier diagnosis allows for earlier interventions, and potentially better outcomes. Meanwhile, Dr. Maitre is using cutting-edge neural processing measurement technology to study how infants born preterm respond to stimuli in order to improve their neurodevelopment.

Lauren Bakaletz, PhD, director of our Center for Microbial Pathogenesis, and her colleagues are creating a vaccine for common otitis media, or middle ear infection, which can be delivered through a bandage on the skin. Some of the underlying basic research, though, has helped show how many bacteria survive typical treatments by forming resistant biofilms, and how those biofilms can be eradicated. This knowledge



On May 21, Nationwide Children’s will rename The Research Institute as the Abigail Wexner Research Institute. The renaming is in honor of long-time board member, former chair and research advocate Abigail Wexner.

PEDIATRIC RESEARCH GROWTH AT NATIONWIDE CHILDREN'S

2006

2018

STAFFING

725 EMPLOYEES
111 INVESTIGATORS*

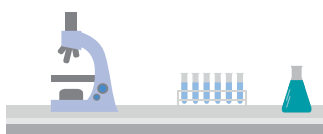


1,238 EMPLOYEES
195 INVESTIGATORS*

**with \$50,000 or more in research funding support*

PEDIATRIC RESEARCH SPACE

300,600
SQUARE FEET



600,000
SQUARE FEET

GRANTS AND AWARDS

\$41.7
MILLION



\$105.9
MILLION

has implications for researchers everywhere who study bacterial infection.

Perhaps most prominent is the work of Jerry Mendell, MD, a neurologist and principal investigator in our Center for Gene Therapy. Decades of basic science and clinical research led in 2017 to a publication in the *New England Journal of Medicine*, showing a gene therapy developed at Nationwide Children's was extending the survival of patients with spinal muscular atrophy type 1. The disease is caused by a mutation in a single gene and nearly always leads to death by 2 years of age.

Dr. Mendell and his collaborators have been able to insert a healthy gene into a modified virus, infuse the therapy into very young children and are seeing astonishing results. Children with SMA1 are typically never even able to achieve head control, but after this gene therapy, children have been able to walk. The technology has been licensed to a company now working to bring it to market.

This is not the only benefit of this line of inquiry,

however. To support gene therapy and other cell-based work, Nationwide Children's has built a Clinical Manufacturing Facility to produce pharmaceutical-grade biologics, such as the modified virus vector Dr. Mendell uses. We are now able to help other institutions with their own cell-based therapies as a result.

We have invested in these and many other projects for the good of children. That is Nationwide Children's Hospital's mission. But these projects have also proven important for our One Team culture, which helps us achieve our mission. They have deepened staff members' connections with each other. They have opened up lines of communication inside this institution that did not exist before. They have resulted in new infrastructure that will aid our discovery efforts for years to come.

In the end, our research growth has helped us remember that when it comes to better outcomes for children – whether here at Nationwide Children's or around the world – we're all on the same side. We're all One Team.

Stay informed. Keep up-to-date. Read more. Visit PediatricsNationwide.org for exclusive online content, physician commentaries and more.



A New “Rule” for Differentiating Stable Buckle and Other Distal Radius Fractures

by Jeb Phillips

Research over the last decade has shown that stable pediatric distal radius buckle fractures don't need to be immobilized in a cast. But some uncertainty about what a “definitive diagnosis” of stability might mean remained. After a joint study between the departments of Radiology and Orthopaedics at Nationwide Children's Hospital, the team developed and published what they call the “1-cm Rule.” Pediatric stable buckle fractures rarely occur less than 1 centimeter from the physis, a finding that may help radiologists and orthopedic surgeons better tailor treatments.

PediatricsNationwide.org/Radial-Fracture-Rule



“Learn From Every Patient” to Improve Clinical Care

by Lauren Dembeck, PhD

Hip displacement is a big problem for children with cerebral palsy, and most are screened annually with hip X-rays. So when physicians at Nationwide Children's Hospital questioned the necessity of yearly X-ray screenings for displacement, they went to the data. Using the Learn From Every Patient database, they were able to develop an evidence-based solution.

PediatricsNationwide.org/LFEP-Hip-Displacement



Algorithm Automates Coronary Flow Analysis for Early Detection of Coronary Microvascular Disease

by Kevin Mayhood

Aaron J. Trask, PhD, a principal investigator in the Center for Cardiac Research, and his team are focusing on transthoracic Doppler echocardiography (TTDE) to assess changes in blood flow patterns as a means to detect CMD. Their research, supported by an algorithm they developed and described here, suggests flow patterns correlate with coronary microvascular data.

PediatricsNationwide.org/Coronary-Flow-Analysis

Help us advance
the conversation
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NATIONWIDE CHILDREN'S

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