No Drugs for Neonates

Left out of clinical trials for years, preterm infants have very few drugs developed just for them. Regulators, industry, and neonatologists are teaming up to fix that.

Doctors typically treat preterm babies in the NICU with "hand-me-down" drugs that have only been tested in adults or children.

BY STEPHANIE DEMARCO, PHD

BEHIND THE DOORS OF THE Neonatal Intensive Care Unit (NICU) lie some of the smallest patients that doctors ever see. These babies can fit snugly in the palm of a hand, although they rarely leave their thick, clear-walled incubators to do so. Nestled in blankets with tangles of tubing linking them to monitors tracking vital signs, these patients sleep under the watchful eyes of their neonatal nurses and neonatologists.

Infants born prematurely — from about 23 to 36 weeks gestation — are often very sick. Thrust into the world before their organs and tissues have finished forming, these babies often develop preemie-specific diseases. They can develop necrotizing enterocolitis (NEC), which causes dangerous inflammation and infection in the gut, or experience intraventricular hemorrhage (IVH), leading to brain injury. These infants can also suffer from diseases common to adults such as infections and strokes, but because these conditions occur as these babies are developing, treatment is not at all straightforward.

Most of the drugs used in the NICU are "hand-me-down" drugs, meaning that researchers originally developed them with only adults or children in mind. Desperate for something to treat these fragile babies, neonatologists reach for what they have — even though these drugs have never been tested in clinical trials or approved for newborns or preterm infants.

"A lot of the efforts were really grassroots efforts," said Victoria Niklas, a neonatologist and the chief medical officer at the neonatal and rare disease company Oak Hill Bio. Neonatologists do their best with the drugs available to them, she added, "Let's just make it smaller, and let's get it to work for these babies."

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>
> *– Jonathan Davis, Tufts Medical Center*

To do this, neonatologists treat preterm infants like "little adults," said Eric Benner, a neonatologist at Duke University and cofounder of the neonatal care company Tellus Therapeutics. Doctors calculate how much of a particular medication to give a 500-gram baby based on the dosage recommendation for a 50-kilogram adult. But this calculated scale down does not directly translate to the right dose for premature babies because they may not have developed the enzymes needed to metabolize a particular drug, depending on how early they were born.

"When you get into the preterm population, they're really quite a bit different than adults," Benner said. "A lot of these drugs are the best we've got, but they're not very effective in some cases."

For a long time, drug regulators excluded infants from clinical trials of new drugs and devices with the intent of protecting them from potential harm. "But now we know that actually the best way to provide children with safe and effective treatment options is to include them in clinical research, while providing additional safeguards," said An Massaro, a neonatologist

in the Office of Pediatric Therapeutics at the Food and Drug Administration (FDA).

With recent encouragement from the FDA and regulatory agencies around the world, neonatologists and industry researchers are working together to develop new treatments specifically for newborns and preterm infants. With many of these new therapies in preclinical development and clinical trials already, it's only a matter of time until neonates get lifesaving treatments made just for them.

Regulating Change

The biggest success story in neonatal drug development provided a literal breath of fresh air for preterm infants. In healthy babies, alveoli — the air sacs in the lung — produce pulmonary surfactant, which is a combination of lipids and proteins that reduces the surface tension between the air-water interface inside alveoli. Surfactant ensures that as air leaves the alveoli during an exhale, the air sacs do not collapse.

In 1959, researchers discovered that infants born prematurely lack surfactant in their lungs, which leads to respiratory distress syndrome (RDS) (1). In many small clinical trials in the 1980s, scientists gave preterm infants artificial surfactant to see if replenishing the missing surfactant could both prevent and treat RDS, and by the end of the decade, they concluded that it did (2). The FDA approved this first surfactant replacement therapy for infants at risk for or with RDS in 1990 (3).

This was a great win for the neonatal field, but since then, drug development for newborns stagnated—not for lack of trying.

Around the same time as the surfactant clinical trials, Jonathan Davis, a neonatologist at Tufts Medical Center, was developing an antioxidant for babies with chronic lung disease. He and his colleagues had spent about 20 years working on the treatment.

The potential drug, Davis said, "appeared to make a huge improvement in their outcomes, and yet the project was not allowed to move forward by the FDA. They had certain concerns, and there weren't any pediatricians or neonatologists involved in those decisions." A pharmaceutical company that had expressed interest in the drug walked away. "It would have made, I think, a huge impact on survival, on outcomes, yet we'll never know. Based on that, I started working on advocacy types of efforts in Congress and at FDA to try to make sure those kinds of things never happened again," he added.

Some of Davis' and others' advocacy efforts led to important regulatory changes in the United States. In 2002, Congress passed the Best Pharmaceuticals for Children Act, which offered industry patent incentives to perform pediatric drug trials and allowed the National Institutes of Health (NIH) to sponsor clinical trials for off-patent drugs in pediatric patients (4). Through the support of this legislation, for example, the NIH and the National Institute of Child Health and Human Development teamed up with the Duke Clinical Research Institute to test off-patent drugs in neonates.

In 2012, Congress passed the FDA Safety and Innovation Act, which stated that if a company wanted to change the labeling of their drug, they were required to perform trials in children too. Companies would also need to provide a rationale for not doing neonatal clinical studies.

"The American Academy of Pediatrics just announced that since that legislation passed, there's been 1000 new drugs either approved for children or the labeling has improved for children. Yet, when you look at neonates, it really hasn't had much of an impact," said Davis.

Massaro at the FDA agreed: "Although we've made a lot of that progress, I would say that neonatal product development specifically is still lagging behind."

CREDIT: TUFTS MEDICAL CENTER

Jonathan Davis treats preterm infants in the NICU and works with the International Neonatal Consortium to develop new treatments and clinical trials for this fragile population.

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Some of the challenges stem from the fact that most researchers working in industry are not as familiar with diseases unique to preterm infants or neonatal development as neonatologists are. Additionally, studies in neonates take a long time, meaning that they are much more expensive to run than typical studies in adults. To determine if a drug leads to any adverse effects on a baby's development, researchers would need to follow them for years.

To invest in expensive trials in neonates, pharmaceutical companies need to know that there's a clear path to drug approval. But with the last major success in this sphere being surfactant more than 30 years ago, companies are wary of working with the neonatal population.

"The industry as a whole is largely unaware that there's a defined regulatory path in the FDA for developing drugs in babies," said Benner. "The perception is that, 'Well, there's a reason why nobody's doing it. It's probably really hard.' I would say that it's different and slightly more challenging, but not anything that can't be overcome."

To help spur neonatal drug development, the FDA helped establish the International Neonatal Consortium (INC) in 2015 as a part of the Critical Path Initiative, a public-private partnership that focuses on accelerating drug development in areas that need it.

"We started with four or five people. Now we have probably close to 400 members in 30 or 40 different countries. We also have all the regulators, families, [and] industry. We can all get together and talk about ways of improving clinical trials and product development for babies," said Davis, who is a codirector of INC.

INC has used these partnerships to develop a Neonatal Adverse Event Severity Scale (NAESS) and recommendations on how to design clinical trials for neonatal seizures. The FDA recently funded INC to collect real-world neonatal data to accelerate drug development and to better understand the risk factors for common preterm infant diseases. Davis estimates that so far, INC has collected data from 300,000 to 400,000 babies worldwide. The international nature of INC has also allowed regulatory agencies from different countries to communicate and agree on how to run neonatal clinical trials.

"The FDA has been quite good at helping to support some of these trials, even though they may come back and be the regulators to oversee them. They want to see babies getting more drugs and doing better," said Davis.

Encouraged by this regulatory support, a few research teams are already developing new treatments for this infant population, and many of them are using a familiar neonatal drug as a starting point: surfactant.

CREDIT: AIRWAY THERAPEUTICS

At Airway Therapeutics, Marc Salzberg hopes that treating preterm infants with surfactant protein D will prevent or reduce the severity of bronchopulmonary dysplasia.

CREDIT: VICTORIA NIKLAS

Victoria Niklas hopes that her Oak Hill Bio team's IGF-1 based drug will help treat and prevent bronchopulmonary dysplasia in preterm infants.

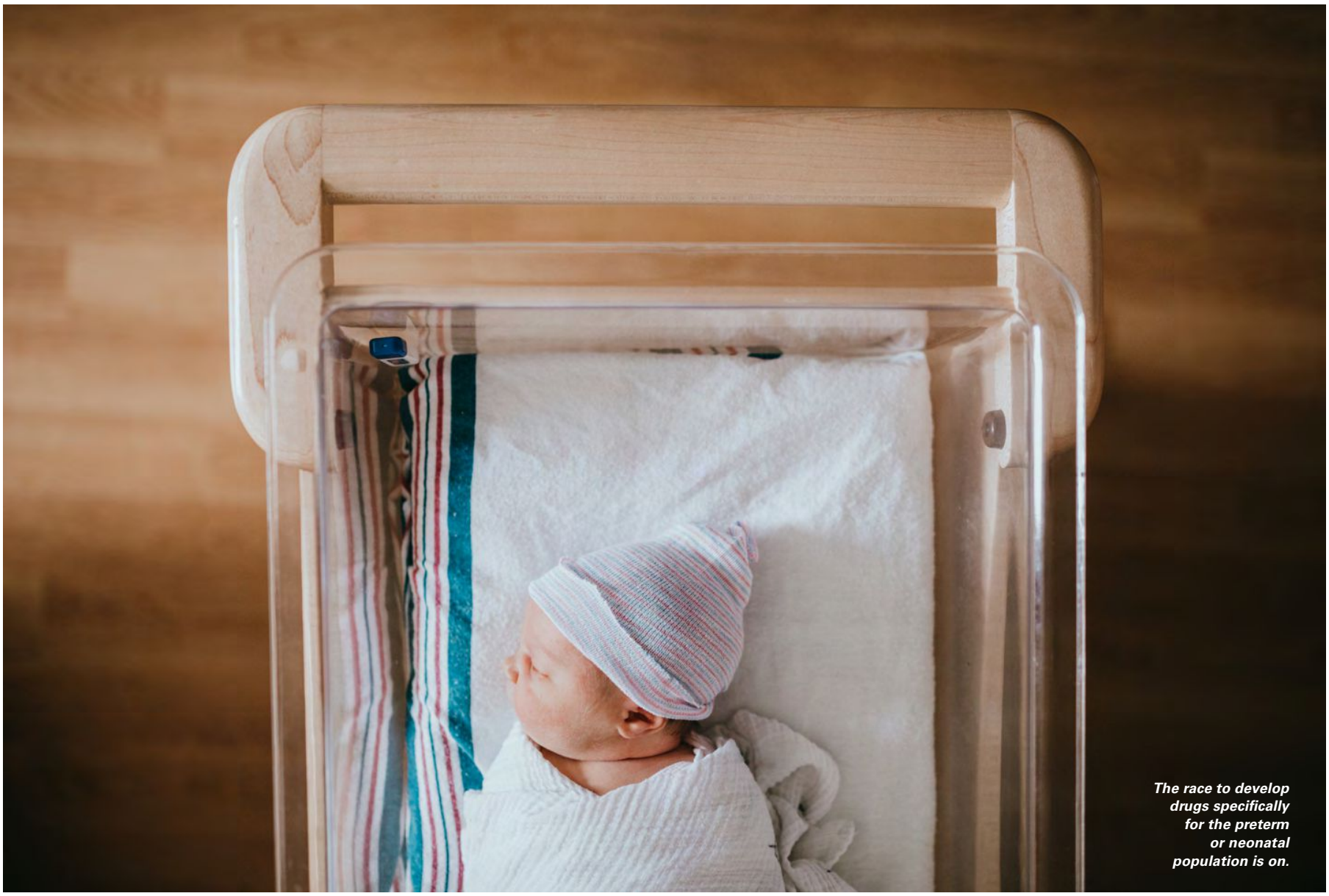
Replacing What's Missing

When Niklas walked into the NICU as an intern straight out of medical school, the FDA had just approved surfactant replacement therapy for preterm babies.

"I had the opportunity to see pre-surfactant infants and then surfactant infants — a huge difference in terms of acute as well as long term problems," said Niklas. While surfactant improved outcomes in the babies she treated, it didn't fix everything, she said. "These infants still developed blindness. They still developed hemorrhages in the brain. They still developed, most surprisingly to people, chronic lung disease or bronchopulmonary dysplasia."

Bronchopulmonary dysplasia (BPD) is common in preterm infants who need long-term oxygen support or mechanical ventilation. These supportive processes can overstretch the fragile alveoli in preterm lungs, damaging the lung tissue and leading to inflammation (5). Lung inflammation leads to further lung tissue damage, impairing proper lung development.

"This is a condition that's serious in terms of morbidity," said Marc Salzberg, the chief executive and chief medical officer at Airway Therapeutics, a biopharmaceutical company developing treatments for respiratory diseases including BPD. "Nothing really works to the extent that



The race to develop drugs specifically for the preterm or neonatal population is on.

the condition can be prevented or at least reduced in its severity, which would already have a major impact."

Surfactant replacement therapy consists of a mixture of phospholipids and either surfactant protein B or C, but natural surfactant contains these phospholipids in addition to surfactant proteins A through D. In typical surfactant replacement therapy preparations for preemies, surfactant proteins A and D get washed out in the purification process.

Salzberg and his team at Airway Therapeutics are particularly interested in surfactant protein D (SP-D). Researchers discovered that SP-D helps clear pathogens from the lung, regulates the lung inflammatory response, and maintains lipid homeostasis in surfactant (6). "It's like the immune police in the lung," said Salzberg.

The team at Airway Therapeutics developed a human recombinant form of SP-D, which also goes by the name zelpultide alfa. They figured out how to purify and stabilize SP-D into its proper functional form, which was not easy to do, Salzberg added.

Now, the researchers at Airway Therapeutics are conducting a Phase 1 study in extremely preterm infants (preemies born as early as 23 or 25 weeks of gestation) to evaluate the safety of zelpultide alfa. They recently completed the dose escalation part of their trial and reported no safety concerns at their highest treatment dose. Salzberg found the results encouraging, and he and the team should have preliminary results from the trial in July, and then they plan to assess how the babies are doing both six and twelve months after treatment.

"These babies with bronchopulmonary dysplasia are known to have repetitive, long-term respiratory and neurodevelopmental issues, so if we improve that, it's just going to make me very, very proud," said Salzberg.

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Like Salzberg's team, the scientists at Oak Hill Bio are also taking a replacement therapy approach to treating BPD, but their treatment centers on replacing a different biologic: insulin-like growth factor one (IGF-1).

During gestation, the placenta secretes IGF-1, which aids fetal development, but infants born prematurely have very low levels of the hormone. Researchers in Sweden and Boston discovered that these low IGF-1 levels correlated with the occurrence of multiple preterm infant diseases, including retinopathy of prematurity, IVH, NEC, and BPD (7). The researchers developed a therapeutic that contains human recombinant IGF-1 complexed with its main binding protein IGFBP3. They spun their drug out into the company Premacure AB in 2006 and assessed its safety in a Phase I clinical trial. In the midst of a Phase 2 study in 2013, the pharmaceutical company Shire acquired Premacure AB and completed the trial (8).

"Although it missed on its primary endpoint for a whole host of reasons, it showed very clearly a tremendous benefit in terms of reduction of bronchopulmonary dysplasia," said Niklas.

Soon after the researchers published their Phase 2 clinical trial data, Takeda acquired Shire and recruited Niklas to lead the development of this IGF-1 therapy further. Takeda originally started a Phase 2b trial of the drug in 2019 but paused it when the company's priorities shifted in 2022, much to the disappointment of many in the neonatology community who were following the drug's development.

"For us as neonatologists, this is totally unacceptable. There are major ethical issues with this kind of behavior from industry," said Bernard Thébaud, a neonatologist and stem cell biologist at Ottawa Hospital Research Institute. "Neonates are a specific population, but they deserve as much attention as other patients."

When Takeda decided to out license the IGF-1 therapy to Oak Hill Bio, Niklas decided: "I was going wherever that asset was going." She added, "It's a once in a lifetime opportunity. I knew that I could shepherd it through to its final outcome. Obviously, I'm planning for success."

Other neonatal drug development teams are also eager to see Oak Hill Bio's IGF-1 research move forward.

"It's an example of people believing in a molecule or an asset or an indication, and not taking no for an answer," said Jason Kralic, the cofounder and chief executive officer of Tellus Therapeutics.

Once Takeda finalized the out-licensing of the drug (now called OHB-607), Niklas joined the Oak Hill Bio team. They have taken over Takeda's planned Phase 2b study, made some modifications to streamline it, and are now raising funds to relaunch the trial. "We have an approved protocol. We've got sites that are engaged," said Niklas. "Everyone's ready to drop the 'go' flag."

Stem Cells and Breast Milk

While Airway Therapeutics and Oak Hill Bio are approaching neonatal diseases from the angle of replacing what's missing, other groups are instead adding something new. For Thébaud and his team, that's stem cells. In discussions with parents at his patients' bedsides, Thébaud sees the urgent need for new medicines for neonates firsthand.

"As a researcher with a wet lab, I have the opportunity to go back to the bench and try to answer some questions that we can't answer at the bedside. Our lab is focused on finding new therapies that could prevent lung injury or regenerate neonatal lungs," he said.

Prior research by his group and others has shown that mesenchymal stem cells (MSCs) could promote repair in organs including the heart and the brain, so Thébaud and his team wanted to determine whether these cells could benefit preterm infant lungs too (9). Their initial hypothesis was that the MSCs would establish themselves in infant lungs with BPD and differentiate into lung cells, healing the damaged lung tissue. But when they tested the cells in animal models, that is not what happened.

"They do not engraft. They don't replace the cells and become lung cells. Rather, they modulate the repair response, and they disappear very rapidly out of the lungs in three to four days," Thébaud explained. The MSCs attenuated inflammation in the lungs and released growth factors to stimulate tissue repair (10).

Their next step was to find a good source of MSCs. Thébaud and his team found that they could isolate MSCs from the umbilical cord tissue of healthy term infants who were delivered via C-section. "For a neonatologist, this is obviously a very clinically relevant source of these mesenchymal stromal cells, so we investigated them and got the same very promising results," he said.

To bring these therapeutic cells to the clinic, Thébaud and his team worked with an accelerator program at the Ottawa Hospital Research Institute. They wanted to give the trial the best chance of success, so they enlisted support from parents and neonatologists, first by assessing their interest through a survey and then by developing a video to educate parents in particular about the trial details (11).

"We tried to identify barriers and facilitators of clinical trial design, and ultimately, it led to a current Phase 1 trial testing the safety and feasibility of giving these mesenchymal stromal cells intravenously to preterm babies at risk of developing BPD," Thébaud said.

The team affectionately named the trial the Helping Underdeveloped Lungs with Cells or "HULC" trial after the superhero The Hulk. The babies in the trial are the real heroes, Thébaud added. They plan to enroll nine preterm infants in the trial and have enrolled four so far.

Thébaud hopes that these stem cells will decrease the incidence of BPD in preterm infants so that they can go home to their families sooner. "When they go home, this is the biggest event and the best event," he said.

Efforts to develop drugs specifically for preterm babies are entering clinical trials.

CREDIT: DUKE UNIVERSITY

At Tellus Therapeutics, Eric Benner and his team are working on a breast milk-based therapy for preterm infants with white matter injury.

CREDIT: MONICA IÑEZ

Jason Kralic, Eric Benner, and their team at Tellus Therapeutics hope that the success of a new drug for infants will forge a path for even more neonatal drug development.

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The team at Tellus Therapeutics is also developing a new compound for preterm infants from a familiar source: breast milk. Benner, Kralic, and their colleagues are targeting white matter injury — the most common brain injury in preemies.

"We have these kids with these really significant brain injuries. We know that their lives are going to be negatively impacted in very serious ways, and there's nothing we can do," said Benner.

They have identified a lipid in breast milk that has shown promising results in prematurely born animal models with white matter injury. Because the lipid exists naturally in breast milk, Benner explained, "everybody's a little more at ease with taking the most fragile patient population that we have in the hospital and enrolling them in clinical trials."

The Tellus Therapeutics team is developing their lipid-based drug to be delivered via an intravenous infusion. One of the major challenges they faced when starting their preclinical research was working with preterm animal models. If preterm babies are small, preterm rats are tiny.

"You can't give a postnatal day three rat an IV infusion. You just can't do it," said Austin Schwartz who leads operations at Tellus Therapeutics. "We're having to modify our studies in that respect."

As of right now, the research team continues their IND enabling studies, and they're eager to see new treatments for neonates being developed both by their team and other companies. A successful new drug for neonates will light the path for others to develop drugs for this population that desperately needs them.

"The idea that in hopefully a short period of time, we're going to actually have something that we can use to improve these outcomes is going to just completely change neonatal medicine," said Benner. "We're going to go from the Dark Ages to modern medicine." ■

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