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Widemann Recounts Journey Toward Developing First-Approved Treatment for NF1

BY ERIC BOCK

Five years ago, the Food and Drug Administration (FDA) approved selumetinib as the first-ever medical treatment for a rare condition called neurofibromatosis type 1 (NF1). This therapy wouldn't have been possible without Dr. Brigitte Widemann's research at the NIH Clinical Center.

"We were able to understand NF1 and, ultimately, come up with an effective treatment because we were able to learn from patients coming from all over the country to participate in clinical trials at NIH," said Widemann, a pediatric oncologist at NIH's National Cancer Institute.

NF1 occurs in approximately 1 in 3,000 people. About half of these patients will also develop tumors that grow along nerves called plexiform neurofibromas. The tumors can grow quickly and become very large. While these tumors are not cancerous, they can be disfiguring and painful and transform to become cancers. Surgical removal is often impossible because the tumors can be intertwined with nerves, blood vessels and tissue.


Dr. Brigitte Widemann

The disorder is caused by mutations in the *NF1* gene that codes for the protein neurofibromin. Neurofibromin is important in the signaling pathway called RAS. This pathway regulates cellular growth and development. In patients with NF1, RAS is overly active in tumor cells, which causing cells to grow uncontrollably.

Widemann started her career as a first-year fellow in pediatric hematology oncology in 1992. She chose to join the Pediatric Branch of the NCI for her fellowship because she could both care for patients and conduct research.

"I knew from the beginning my goal was to develop better treatments for kids with cancers," she said.

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Stories connect us with science. See p. 8.

ALSO THIS ISSUE

PERSEVERING FOR A TREATMENT

At Long Last, Drug to Treat AKU Gets Approved

BY DANA TALESNIK


Dr. Wendy Introne

Dr. Wendy Introne was not giving up. Despite initially disappointing study data, she knew a particular drug would work. The biochemical results were robust. It had to work. Now, 15 years after the small clinical trial, the drug in question was finally approved to treat the rare disease she studies.

Introne leads a team that studies alkaptonuria (AKU), a genetic, degenerative metabolic disease. In people with AKU, the body cannot fully break down an amino acid called tyrosine, which causes homogentisic acid (HGA) to accumulate.

"HGA is the culprit substance that binds to collagen and connective tissue and causes the damage we see," said Introne, a pediatrician who is a clinical and biochemical geneticist at NIH's National Human Genome Research Institute.

Degrading tyrosine is a multi-step process. In AKU, the third enzyme in the process is deficient. The one sign present from birth is black urine, due to the buildup of HGA that is excreted in the urine. When patients turn about 30, Introne explained, they begin to see other symptoms, notably musculoskeletal problems and joint damage that are extremely painful.

"But these patients are remarkably resilient," Introne said. "It's incredible to see the level of degeneration of their spine and joints and how they really continue to persevere despite all of that."

SEE **AKU**, PAGE 5

Symposium to Showcase Impact of Nursing Science

Sept. 17

NIH's National Institute of Nursing Research (NINR) is hosting an all-day 40th anniversary symposium on Sept. 17 in Masur Auditorium. The event will celebrate four decades of excellence in nursing research and showcase NINR-funded investigators who are leading scientific discoveries of innovative systems and models of care, breakthroughs in disease prevention and health promotion, and advances in population and community health.

The symposium will feature a keynote panel on NINR's scientific achievements; early-stage investigator highlights; scientific sessions on translating science to solutions and a voices of the community panel. To register, visit: bit.ly/4mYC7qA.

Crimmins to Speak on Geroscience

Sept. 24

The NIH Office of Behavioral and Social Sciences Research (OBSSR) is celebrating 30 years of advancing research to improve health outcomes.

OBSSR is continuing its celebration with a Director's Webinar featuring Dr. Eileen Crimmins on Sept. 24 from 2:00 to 3:00 p.m. ET. Her talk is titled, "Developing a Geroscience, Medical Science, and Social Science: Explanations for Differences in Aging Health."

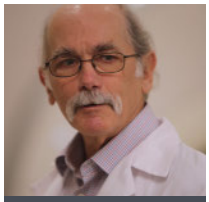
Geroscience hypothesizes that all age-related health outcomes are linked to a set of biological processes that collectively produce health deterioration with age. Medical science has identified an increasingly wide array of risk factors for age-related health outcomes.

Using insights from geroscience and medical science, Crimmins—professor at the USC Leonard Davis School of Gerontology—will discuss how the social environment affects biological processes to produce differential rates of aging.

To register for the webinar, see: obssr.od.nih.gov/30yearswebinarCrimmins. For a list of other 30th anniversary events, visit obssr.od.nih.gov/30years.

Toga Explores Real-World Data Sharing

NIH's Office of Data Science Strategy (ODSS) hosts a monthly seminar series on the second Friday of each month at noon ET. The series highlights researchers who take existing data and find clever ways to reuse the data or generate new findings.



Dr. Arthur Toga

On Friday, Sept. 12, Dr. Arthur Toga, director, USC Mark and Mary Stevens Institute of Neuroimaging and Informatics, will discuss his work on neuroimaging, informatics, AI applications in neuroscience and mapping brain structure and function.

This talk will cover challenges of incentivizing data sharing and will examine the impact of infrastructure on data sharing effectiveness, emphasizing the need for viable, affordable systems that support efficient data discovery, access and analysis.

To register, visit: bit.ly/45SrA9s.

Running Time: Get Set for NIH Relay, Community Day

Sept. 25

The beloved NIH Institute Relay is back, now in its 40th year. Whether you're a runner or a spectator, come join the fun on Thursday, Sept. 25. (The rain date is Oct. 9).

The rules are the same. The Relay consists of teams of five runners each who run a half-mile loop around Bldg. 1. All Institutes, Centers, Divisions, and contractors are invited to enter as many teams as they wish. Each team must have a mixture of male and female participants. The registration table will open by 10:30 a.m. Heat 1 will start at 11:45 a.m. following a brief warm-up.

Organizers are planning for three heats this year with a maximum of 50 teams per heat. So, gather your team and come up with a creative team name. Examples from last year include Urinary TRACK Infection, Septic Shockers, Lymph-Laugh-Love, Ignorance is Blisters, The Spore Losers, Easier Said Than Run and Baby Got Track.

The Relay is a great reason to set a new fitness goal while preparing for a fun event. However, the most important part of the race is to have fun and enjoy the company of your fellow NIHers.

To volunteer or for more information, contact David Browne at browned2@mail.nih.gov. Team registration is $30. To register, see bit.ly/45M8BNG.

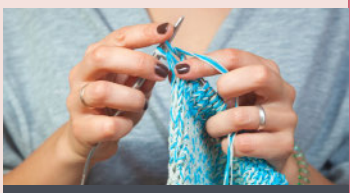
That same day will be NIH's first-ever Community Day. It will be a day of food, games, music and a chance to connect with colleagues from across NIH. Come build community and create lasting memories.

Teams gather at the 2023 Relay. **PHOTO: MARLEEN VAN DEN NESTE**

Have a question about some aspect of working at NIH? Use our feedback form (nihrecord.nih.gov/feedback) to post an anonymous query, and we'll try to provide an answer.

Question: If I wanted to start a club, are there rules or processes to follow? As an example, I've been thinking about starting an informal monthly lunchtime knit/crochet group that would meet in a corner of a cafeteria.

Response from Office of Research Services



EVERYONEPHOTOSTUDIO / SHUTTERSTOCK

Yes, there are criteria for starting a club at NIH. As for meeting space, it's preferable to identify a space outside of a cafeteria, such as the Wellness Room in Bldg. 31A (temporarily closed for repairs), in an effort to maintain cafeteria seating during mealtimes for staff.

As a starting point, here are guidelines for establishing a club at NIH:

Each club should have a mission statement or objective conducive to promoting recreational and/or physical activity programs that will benefit members who join. To see a list of existing clubs, see: bit.ly/4nTo5l1.

Initial applications to start a club are processed through NIH's Recreation & Welfare Association (R&W). To inquire about starting a club, contact the R&W's David Browne at browned2@mail.nih.gov.

Membership:

For most activities, a minimum of 10 people interested is required to start a club; however, this requirement may vary according to the type of activity being proposed.

At least 60% of the proposed members should be NIH staff; the activities should be open to all NIH staff, including contractors. All club members must be R&W members for a club to be eligible for approval. See: https://bit.ly/4lu6gNY.

Club leaders:

Each club should have an elected officer (leader, secretary and treasurer). Elected officers should contact the R&W for promotional opportunities, managing club membership and any finances. (Email browned2@mail.nih.gov)

Activities proposed should be as much self-sustaining as possible. Clubs are suggested to have scheduled meetings at least once a year.

A one-year probationary period will be established for all new clubs after which the R&W will evaluate whether the activity should be continued. Evaluation criteria would include sustained interest, participation, growth and finances.

After Texas Floods, NIH Swiftly Supports Health Research, Recovery

BY SAMANTHA EBERSOLD

When catastrophic flooding swept through central Texas in July, NIH's National Institute of Environmental Health Sciences (NIEHS) mobilized to address public health threats posed by rising waters, debris and health system disruptions. Institute leaders quickly activated the Disaster Research Response (DR2) program and the Worker Training Program (WTP) to aid in recovery and planning efforts.

The fast response to the flooding builds on longstanding efforts to reduce health risks and bolster preparedness in disaster-prone regions across the nation.

"NIEHS leads disaster research efforts through programs that provide critical support to improve response, recovery and preparedness for future disasters," said Dr. Aubrey Miller, senior medical advisor and director, NIH Disaster Research Response Program.

Such programs disseminate research tools to support robust data collection in the aftermath of disasters, in addition to providing health and safety training for response workers.

Coordinating a rapid response

NIEHS leaders called disaster health experts across the nation within days of the July 4 flooding to identify pressing concerns and facilitate research activities.

As part of this outreach, NIEHS shared resources to help support scientists' efforts to collect data rapidly. Researchers—many of whom are supported in part by NIEHS—identified safety issues, water quality monitoring, hazardous environmental exposures, and adverse socio-behavioral and mental health impacts as concerning areas warranting further investigations and long-term follow-up.

Floodwaters can result in mold, physical hazards, sewage, bacteria and contaminated debris, which pose significant health risks to responders and returning residents. The WTP provides free educational resources and mobile apps for safe cleanup and recovery.

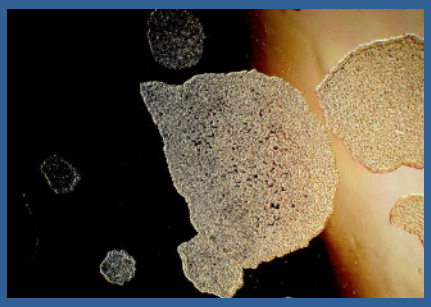
To explore these hurricane and flood training tools—including mold remediation, debris removal and respiratory protection resources—from WTP, see: https://go.nih.gov/mGfQzaT. All materials are available in English, Spanish and Vietnamese and are accessible via the WTP Disaster Preparedness app, which works offline for use in field research.

NIEHS researchers in Texas respond

The NIEHS Superfund Research Center at Texas A&M University (TAMU) will deploy a Community Assessment for Public Health Emergency Response (CASPER) in Kerr County, Texas, one of the areas hardest hit by the July flooding. The CASPER method provides rapid, household-based insights to inform local response and recovery and will help assess the health and infrastructure impacts of the flooding in Kerr County. TAMU's Community Engagement Core is also conducting research to better understand factors that affect community resilience during and after disasters.

For more information, the DR2 website highlights an extensive list of curated flood-specific resources available from NIEHS and other federal partners: https://www.niehs.nih.gov/research/programs/disaster.

Flooding of the Guadalupe River near Kerrville, Texas, July 5. NIEHS is leading efforts by NIH to bolster recovery and time-sensitive health research. **PHOTO: U.S. COAST GUARD**



ON THE COVER: *iPSC colonies captured using phase contrast microscopy. Derived from human umbilical cord blood, these iPSC colonies will give rise to regulatory B cells (Bregs) that suppress CNS autoimmune diseases. This research aims to generate human immune organoids that produce a hypoimmunogenic "off-the-shelf" source for Bregs for cell-based therapy.*

IMAGE: VIJAY NAGARAJAN / NEI

The NIH Record

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National Institutes of Health
Turning Discovery Into Health

NF1

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When she started working at NIH, researchers were starting to develop drug candidates to target RAS mutations. Although these drugs didn't work well against cancers, Widemann thought these drugs might be effective treatments for NF1 plexiform neurofibromas.

Widemann and her team have been studying NF1 for more than two decades. When they first started their natural history studies, no one knew how fast tumors grew, when they grew or if they ever shrunk on their own. And there were no effective treatments.

In the years since, they've a learned a lot about the growth patterns of plexiform neurofibromas. Widemann uses a method called "volumetric analysis" to measure tumor size, which allows her to precisely track a tumor's growth over time. They also tested patients' pain levels, hearing and physical abilities, and cognitive function.

"In the natural history study, we brought kids to the Clinical Center every four months to get an MRI," she said. "We learned tumors grow the fastest in young kids. In fact, they never shrink in kids. As they get older, tumor growth slows down and sometimes the tumors start shrinking a little bit by themselves."

Now that there was a target and a way to measure a drug's effectiveness, Widemann's lab started enrolling pediatric patients with inoperable tumors in clinical trials. They tested several candidate drugs over the years. None of them shrunk or delayed tumor growth.

After years of testing, Widemann and her colleagues decided to test selumetinib, a drug that blocks a protein in a RAS pathway called MEK. Selumetinib was originally created to treat melanoma, pancreatic cancer, colorectal cancer and non-small cell lung cancer.

The first studies of the drug were designed to find the correct dose of the treatment. After four months, the first patient who received selumetinib came back to the Clinical Center for a follow-up appointment.

When reviewing imaging scans of the tumor, Widemann noticed its size decreased. At first, she thought it was a fluke. In almost a decade of research, she never saw that occur. Then, Widemann saw it happen again.

"I then knew this wasn't a coincidence. It didn't happen by chance," she said. "This was the first time that we ever had a medicine that stopped the growth and shrank the tumors. It was really, really exciting."

Building on their initial success, she and her colleagues launched a larger clinical trial. Selumetinib shrank the tumors in 70% of participants and most of the tumors didn't grow again for more than a year.

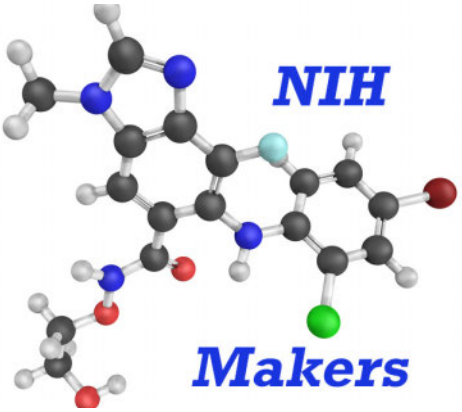
Based on the findings from the study, the FDA approved selumetinib for children two years and older with NF1 and symptomatic, inoperable plexiform neurofibromas.

Before there was an effective treatment, Widemann and her colleagues informally met with the FDA reviewers about designing clinical trials. Proving clinical benefit for drugs that target rare diseases presents unique challenges to researchers.

Traditional clinical trial endpoints focus on measurable, clinically meaningful outcomes such as survival. Fortunately, many children who have NF1 grow up to be adults so survival couldn't be an endpoint. Widemann developed alternative endpoints based off data from NF1 natural history studies. The reviewers could compare new findings with those from kids who weren't treated with selumetinib.

"I enjoyed working with the FDA. I was very impressed by their rigor," she said. "They understood they weren't dealing with straightforward standard populations."

Obtaining FDA approval was a group effort. Members of industry, NCI, the institute's Cancer Therapy Evaluation



Program, academic institutions and hospitals worked with patients, doctors, nurse practitioners and patient care coordinators and patient advocacy organizations. Patients, in particular, are central to the process. Some participated in six or seven clinical trials. They were committed to not only helping themselves, but others who might benefit in the future.

Although there's now an FDA-approved drug to treat NF1, Widemann's work continues.

"Ideally, I would like a drug that prevents the tumors from even establishing or from transforming to become more aggressive tumors," she said." There's lots of work that still needs to be done to identify better treatments."

Widemann is also applying the lessons she learned from NF1 to develop therapies for other childhood cancers and tumor-causing genetic disorders for which there are no effective treatments. Some of the diseases are so rare there are only 20 or 30 diagnoses per year in the United States.

This research would be difficult to conduct anywhere else, said Widemann. "The NIH Clinical Center is an exceptional place, where so many people are highly committed to science and research."

Widemann (r) with Travis Carpenter, who received selumetinib for NF1 at NIH. **PHOTO: NCI**

AKU

CONTINUED FROM PAGE 1

Other symptoms include aortic stenosis, due to HGA deposits in cardiac valves, as well as kidney and prostate stones.

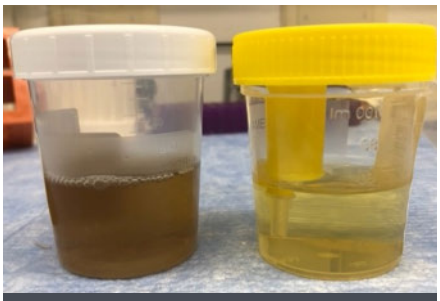
About 30 years ago, an unlikely compound began to be tested for a related rare disorder. The drug, nitisinone, was initially developed for the agricultural industry given its herbicide qualities. As toxicologists in England studied this drug to uncover its mechanism of action, they observed it inhibited the second enzyme in the tyrosine-breakdown process.

The toxicologists alerted researchers who were studying hereditary tyrosinemia type 1 (HT1)—in which a different enzyme in the tyrosine degradation pathway is deficient—about this finding. A decade later, nitisinone was approved to treat HT1.

"It completely revolutionized care of those individuals," Introne noted. "That's when we said we think this drug would be really helpful for AKU, because [the deficiency] is in the same pathway."

After acquiring permission to test nitisinone in their patients, Introne and colleagues launched a small clinical trial with 40 volunteers from 2005 to 2009 but despite dramatic biochemical results, the clinical results then weren't encouraging. Their primary outcome parameter did not prove clinical benefit.

The journey toward approval was fraught with challenges. As with any rare disease study, they were encumbered by the small number of patients in the trial.



Urine samples from a patient while not on nitisinone (l) and while on the drug (r)

Also, in this case, "AKU is a disease that progresses over decades so trying to identify a change that is measurable during a three-year clinical trial period is really difficult," Introne said. In addition, not everyone with AKU starts the same way or progresses on the exact same timeline.

"When you're trying to find something for a cohort that's changing, it's hard to identify just one measure that captures the entire cohort of patients," said Introne.

In the end, the answers they sought were in the original data. They knew a 2 mg dose of nitisinone reduced production of HGA by 95%. But they still had to link lower HGA to improved quality of life. The team kept looking, questioning and re-analyzing their data.

"We took a step back and looked at other objective numbers we could measure, such as cardiac function and radiographic changes," she said. "And some of this was the Food and Drug Administration (FDA) coming around to say they're interested in knowing how patients feel and function."

And they found plenty of evidence in the patient-reported outcomes from the initial trial.

"We saw statistically significant gains in their physical function and in their energy," as well as reduced pain levels, Introne said. "We saw improvements in terms of their activities, of daily living [after] starting the drug, and improvements in distance they're able to walk."

From l, Dr. William Gahl, Introne, Joy Bryant, RN; and Dr. Francis Rossignol pose in the Clinical Center. Other members of Introne's team (not pictured): Dr. Monique Perry, Kevin O'Brien and Kate Spears

Ultimately, persistence paid off. Introne's team submitted these measurable changes. "That was what convinced the FDA," she said. In June, the FDA approved nitisinone to treat AKU.

Introne's initial inspiration for studying AKU came from Dr. William Gahl, a senior investigator in the Medical Genetics Branch who runs NIH's Undiagnosed Diseases Program. Introne first met Gahl in 1998 when she arrived at NIH for a genetics fellowship. Gahl, her fellowship adviser, told her about a potential medication for a disease called AKU but first they needed to learn more about the disease.

Together, she and Gahl launched a natural history study for AKU and she soon began meeting with patients in the local area. "That was it. I was hooked," she said. "I've been really lucky because the patients are so dedicated."

In the early days, the first question was whether nitisinone, an herbicide, would be safe to consume.

"I think back to what a leap of faith [the study participants with HT-1] must have had in those investigators and that this medication would be safe for them," said Introne. "We had the advantage of already more than a decade of experience with nitisinone before we began giving it to our patients, because we knew how well-tolerated it was in the children who first tested it [for HT1]."

And it's the younger people, those who don't have symptoms yet, who stand to benefit the most from nitisinone. For them, the drug could be preventive.

"I have to sing the praises of all our patients who were so committed to this," she said, "because so many adults have told me, 'This medication may not change my life, but I really hope it will change the lives of young people with this disease.'"

Getting FDA approval of this treatment for AKU was a long time coming. "Sometimes the journey is not straightforward. Sometimes we have to be creative in how we get to the final endpoint," Introne said. "If you believe in it, just keep going. The biggest thing is to persevere."

NIH Remembers Cashel

Dr. Charles Michael Cashel passed away on July 15. He was a federal employee for 58 years, having retired in 2021.

Cashel had joined the laboratory of Dr. Ernst Freese at NIH's National Institute of Neurological Disorders and Stroke (NINDS) in 1963 while serving in the USPHS Commissioned Corps.

He moved to NIH's National Institute of Child Health and Human Development (NICHD) in 1971 where he was a member of the Laboratory of Developmental Biology. That laboratory merged with the Laboratory of Molecular Genetics (LMG) in which he was head of the section on molecular regulation. While still associated with NINDS, he was a graduate student in the Genetics Department at the University of Washington, completing his Ph.D. in two years. He'd previously earned his bachelor's from Amherst College and his MD from Case Western Reserve University.

Dr. Charles Michael Cashel

It was while earning his PhD that Cashel discovered a small nucleotide that is formed upon various types of stress, with ~60% of the cell's genes responding to the compound. He returned to NIH and determined the chemical nature of the compound was ppGpp, a guanine with di-phosphates on the 5' and 2' OH. His studies defined the roles of highly phosphorylated nucleotide secondary messengers in "rheostated" gene expression in bacteria.

Examining the many amazing cellular responses to ppGpp was the joy of his research for the remainder of his career. He also described transcription factors that bind directly to RNA polymerase and alter both transcription initiation and elongation. Notably, his lab generated a collection of over 20,000 bacterial strains that are an extremely valuable resource for ongoing and future research by many laboratories around the world.

Cashel was a giant in the field he founded and was an important contributor to LMG and the Division of Intramural Research. He was a true bench scientist, conducting experiments alongside his trainees up until his retirement.

NIH Mourns Passing of Neckers

Dr. Leonard (Len) Neckers, a renowned cancer researcher, passed away in July.

Neckers' 40-year career at NIH began in 1974 with studies at NIH's National Institute of Mental Health of serotonin turnover and serotoninergic pathways in the central nervous system. He joined NIH's National Cancer Institute in 1981 in the Laboratory of Pathology and later moved to the Urologic Oncology Branch.

Neckers worked tirelessly to develop molecularly targeted therapeutic approaches to modulate cancer cell growth and survival. His work put heat shock proteins on the map as potential targets for cancer therapy. He was regarded as an early advocate of the importance of translational research to bring laboratory findings into the world of patient care.

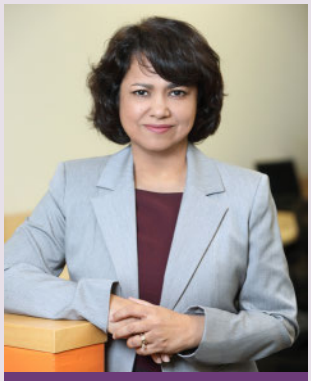
Dr. Len Neckers

Throughout his career, Neckers was known as a supportive mentor and a respected co-worker. He was described as kind, caring and thoughtful, always having time to stop and chat with a colleague.

The family posted a tribute wall (https://bit.ly/4fT2mwp) for sharing memories and photos. NCI published a celebration of his life and work last year at the time of his retirement: https://go.nih.gov/hurZG6q.

CSR Director Byrnes Retires

Dr. Noni Byrnes, director of NIH's Center for Scientific Review, retired from federal service on Aug. 31.



Dr. Noni Byrnes

Byrnes served as CSR Director since 2019, overseeing a majority of NIH's scientific peer review, which remains the gold standard for grant peer review around the world. Most recently, she oversaw the HHS and NIH effort to centralize peer review of all the agency's grants, cooperative agreements and research and development contracts— totaling approximately 100,000 per year.

During her tenure, Byrnes led the successful development and implementation of multiple initiatives to promote quality, integrity and fairness in NIH peer review. These include ENQUIRE (Evaluating Panel Quality in Review), CSR's systematic, data-driven process for the continuous restructuring of study sections to align with current and emerging science; NIH's new Simplified Review Framework for Research Project Grants, which simultaneously focuses reviewers on the important question of significance/innovation, reduces the inappropriate influence of the institution's reputation or the investigator's pedigree on the research project evaluation, and removes many administrative compliance items from the scientific peer review process; and NIH's revised fellowship application and review criteria, which identifies the most promising among the next generation of biomedical research scientists.

Byrnes also implemented many other changes to review practices and culture, designed to promote integrity, accountability and active management of undue influence in NIH peer review.

"Within CSR, Dr. Byrnes made strategic decisions to develop foundational capacity in technology, data analytics, and training, and significantly increased CSR's engagement with the broader extramural scientific community—all of which were critical for thoughtful implementation of the changes in peer review," said NIH Director Dr. Jay Bhattacharya. "She demonstrated her expertise in leading organizational change, evident by her prioritization of strengthening internal communications, increasing transparency within the center, investing in staff development and recognizing employee achievements."

Byrnes joined CSR in 2000 as a scientific review officer in the Chemistry and Biophysics Branch. Prior to becoming director, she took on a variety of leadership roles with increasing responsibility. Prior to joining CSR, she conducted research in bioanalytical chemistry in the pharmaceutical industry. Byrnes holds a Ph.D. in analytical chemistry from Emory University in Atlanta.

CSR Deputy Director Dr. Bruce Reed will serve as acting director while a search is conducted for Byrnes' replacement.

VOLUNTEERS

Trichuriasis Study Seeks Volunteers

NIH researchers are studying the immune response to *Trichuris trichiura.* Healthy volunteers in the Washington area are needed to identify the minimal number of eggs required to produce an infection without causing significant symptoms. Participants will visit the clinic 16 times over a period of up to 8 months. They will be screened, have a physical exam with blood tests and give stool samples.

Compensation will be available. If interested, contact the NIH Clinical Center Office of Patient Recruitment at 866-444-2214 (TTY users dial 7-1-1) or ccopr@nih.gov. Refer to research study #001706-I https://go.nih.gov/iyx4FNP.

Can Mother's Diet Prevent Early Sign of Food Allergy in Babies

PHOTO: MONTICELLO/SHUTTERSTOCK

An NIH-sponsored clinical trial is testing whether maternal consumption of peanuts and eggs during pregnancy and breastfeeding prevents babies from developing an early sign of allergies to these foods. The study is called Expecting Mother's Study of Consumption or Avoidance of Peanut and Egg (ESCAPE).

Peanut and egg are two of the most common early-childhood food allergens. The study will enroll non-allergic pregnant mothers whose babies are at high risk for food allergy because their mother has a close relative with allergies.

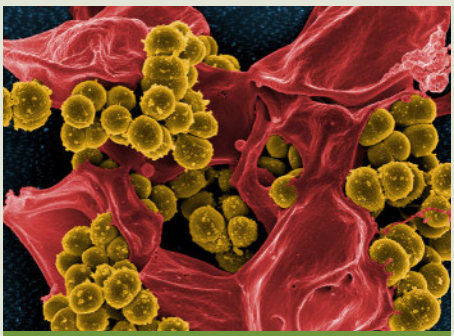
Studies have found that before some infants ever eat peanut or egg products, their immune systems have already produced an antibody called immunoglobulin E (IgE) against these foods. IgE is a precursor of food allergy. Early childhood food allergy prevention strategies may need to precede the introduction of solid foods.

The study team will enroll 504 mother-infant pairs. The mothers will be assigned at random to either eat or avoid peanut and egg, beginning in their third trimester and continuing through breastfeeding. Investigators will provide guidance on the amounts of peanut and egg to eat weekly or guidance on how to avoid eating them, as appropriate. The main goal of the study is to learn the proportion of infants in each group whose blood has IgE against peanut, egg or both at age 4 to 6 months, before they ever eat those foods. Mother-infant pairs will be followed until the children turn 1 year old.

More information about the trial, including contacts for people interested in participating, is available at ClinicalTrials.gov under study identifier NCT06260956.

Two-Dose Therapy for S. Aureus Bloodstream Infections on Par with Standard Treatment

An NIH-supported study has found that the outcome of treating complicated *Staphylococcus aureus* bloodstream infections with two intravenous (IV) doses of the antibiotic dalbavancin seven days apart is just as effective as daily IV doses of conventional antibiotics over four to six weeks. Nearly 120,000 *S. aureus* bloodstream infections and 20,000 associated deaths occurred in the U.S. in 2017.



Colorized scanning electron micrograph of MRSA bacteria (gold) interacting with a human neutrophil (red). IMAGE: NIAID

The findings were published in the *Journal of the American Medical Association.*

Standard therapy for complicated *S. aureus* bloodstream infections, or bacteremia, involves inserting a long IV line known as a peripherally inserted central catheter (PICC) into a vein to deliver antibiotics through the blood for many weeks. The PICC line remains in place for the full duration of treatment and can cause additional complications. Dalbavancin therapy requires temporarily inserting a short catheter into a vein twice for an hour at a time.

The Phase 2b trial enrolled 200 adults with *S. aureus* bacteremia. They were randomly assigned to receive either dalbavancin intravenously on days one and eight, or standard therapy for four to eight weeks.

The researchers aimed to capture not only the result of antibiotic therapy, but also participants' treatment-related experiences during therapy. The study team also compared the efficacy and safety of the two therapies.

Investigators found that a participant from the dalbavancin group was 47.7% likely to have a better overall treatment outcome than a counterpart from the standard therapy group, but the overall outcomes were similar for the two groups, suggesting that dalbavancin therapy and standard therapy were equally good. Study participants in the two groups reported a similar health-related quality of life.

As expected, the rate of side effects was greater in the standard therapy group than the dalbavancin therapy group. Yet the overarching similarities in the components of overall outcome diluted these differences.

Scientists Lay Foundation for Gene-Editing Therapy for Late-Onset Tay-Sachs

NIH scientists successfully reduced the severity of late-onset Tay-Sachs (LOTS) disease in human cell cultures and a mouse model using a novel gene-editing treatment. LOTS is a rare form of Tay-Sachs disease, with signs and symptoms such as muscle weakness, loss of coordination, muscle spasms and sometimes loss of mental function beginning in late childhood to adulthood.

LOTS is a genetic disorder caused by a mutation in the *HEXA* gene that causes a deficiency of an enzyme] critical to breaking down a fatty substance in the brain, known as GM2 ganglioside. GM2 buildup damages nerve cells in the brain and spinal cord. The amount of enzyme still being produced by the body affects the severity of the disease and the age of onset. By deploying the correction to the *HEXA* gene, scientists were able to increase the activity of the enzyme, known as beta-hexosaminidase A, delay symptom onset and significantly extend lifespan in the mouse model.

Scientists believe this work has laid the foundation for building testing in human participants. LOTS affects about 500 people worldwide. The human cells used in this study were donated by a study participant who is unique because they have two copies of the mutated gene.

While the current breakthrough is not a cure or viable treatment yet, researchers believe they are on the right path. Future studies will investigate the best ways to deliver the genetic edit to the central nervous system and brain.

Researchers have targeted LOTS for this research because other forms of Tay-Sachs disease occur more suddenly. The infantile form of the disorder is usually diagnosed within the first 3-6 months of life and is fatal by 4-5 years of age. Children diagnosed with the juvenile form of the disease often die in their teens.

Mutations in the HEXA gene that cause Tay-Sachs are found more often in certain populations—including Eastern and Central European Jewish communities (Ashkenazi Jews), certain French-Canadian communities in Quebec, the Cajun community of Louisiana and the Old Order Amish community in Pennsylvania.

In the United States, pregnant women and their partners are often given a blood test to identify carriers of the *HEXA* gene change that causes Tay-Sachs disease.

Stories Can Increase Connections with Science

BY ERIC BOCK

Storytelling can be an effective way to make science more relatable and memorable for the public, said Dr. Sarah Goodwin during a recent NIH Science of Science Communication interest group virtual meeting.

"We are primed as humans to engage with and appreciate stories," said Goodwin, executive director of the Science Communication Lab (SCL), a nonprofit that tells the stories of science through film. "Stories have been shown to enable audiences to take in new information more quickly and easily and retain that information."

Dr. Sarah Goodwin

Often, scientists communicate their research through scholarly journal articles and seminar lectures. They don't share their motivations or the range of emotions they experience during the research process.

Goodwin and her colleagues take a different approach to communicating scientific information. The lab has released three feature-length documentaries and several short, documentary-style videos. They emphasize the human side of science and the scientific process.

"When we're interviewing scientists about their research, we make sure we include their personal histories and what motivates their research and the research narrative, which is the sequence of events that led to a discovery or result," Goodwin said.

The SCL is measuring the effectiveness of storytelling in science communication, said Dr. Emily Howell, who conducts research and evaluation at the SCL.

In one study, the lab asked a representative sample of U.S. adults to watch one of four SCL-produced short documentaries. Each film relied on narrative storytelling, where the documentary's subject shared personal anecdotes about their research. Then, the respondents reported how engaged they felt with the narrative and the characters.

Dr. Emily Howell

Howell said respondents who reported higher levels of narrative engagement "had the highest levels of factual knowledge gain." They were more likely to report being interested in the topic.

The SCL has also found that their films help students understand how scientists see themselves and the nature and process of science, said Goodwin. In a survey of undergraduates, almost three quarters of respondents said the films "changed their idea of what it means to be a scientist or researcher." Students also reported the film showed them "science is a dynamic, iterative process that evolves over time."*Observer*, their most recent film, is about the power of observation and science. In the documentary, filmmaker Ian Cheney brings scientists, naturalists, artists and a hunter to locations around the world, often without telling them where they are going, and asks them to describe what they see.

★★★

"We are primed as humans to engage with and appreciate stories."

–DR. SARAH GOODWIN

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"We made sure that we didn't just pick beautiful, faraway places," Howell said. The goal was to convey, "Science exists everywhere, that many people can do science, that really anyone watching the film could do science."

At screenings across the country, they distributed activity kits, which included a watercolor paint set, journal and a paper microscope called a Foldscope.

Behind-the-scenes filming for Observer in Greenland

"Viewers enjoyed seeing the role of observation and being reminded of the child-like sense of curiosity that can be present in science," Howell said.

Those who watched the film remarked it inspired them to go out and do something, she said. They, for instance, wanted to travel, reconnect with nature or go back to school.

Science becomes much more relatable when it's human, Goodwin concluded. Stories "can give a greater understanding of how science works and shows the value."

For more information about the SCL, see: https://sciencecommunicationlab.org/. For more information about Observer, see: https://www.observerfilm.org/.