POTENTIAL COVID USE

Anderson Explains Role of Nanoparticles in Vaccines

BY RICH MCMANUS

If and when effective vaccines for Covid-19 are developed, some will surely rely on a nanoparticle delivery system whose origins lie in decades of painstaking groundwork.

Offering a tour of that effort on July 15 was Dr. Dan Anderson of MIT, who gave the ninth lecture in NIH’s Covid-19 scientific interest group lecture series.

The poster child for the talk was the mRNA vaccine that had just been reported on in the New England Journal of Medicine; the Moderna candidate, whose promising early results were described, relies on nanoparticle delivery.

“One of the heroes of this story is the nanoparticle,” said Anderson, professor of chemical engineering and of health sciences and technology at the MIT Koch Institute for Integrative Cancer Research.

“Encapsulating RNA in a package that can travel through the bloodstream and reach target cells is quite a challenge,” he explained. “Endocytosis is how it gets into the cell. Then it has to escape the endosome...”

NIDDK Research Shows Importance of Masks

BY LISA YUAN

As Covid-19 began spreading in the United States, scientists in NIDDK’s Laboratory of Chemical Physics (LCP) were already thinking about how to pivot their research to help end the pandemic. As the NIH campus emptied out, the LCP team, led by Drs. Adriaan Bax and Philip Anfinrud, began studying how people might be transmitting the virus through speech.

Their research in the weeks to follow found that normal talking disperses many...
NIH Holds Virtual Workshop on Reducing Inequities in Maternal Health

On Tuesday, Sept. 29 from 9 a.m. to 3:45 p.m., NIH will hold a virtual workshop on innovative models of care for reducing inequities in maternal health. The event will be streamed live via NIH Videocast (https://videocast.nih.gov/watch=38172) and registration is not required.

The workshop will explore how nurses, midwives and birth companions can improve maternal and infant health, specifically for women in U.S. communities affected by structural and health inequalities.

The workshop is co-sponsored by the National Institute of Child Health and Human Development, National Institute on Minority Health and Health Disparities and NIH’s Office of Research on Women’s Health and Tribal Health Research Office.

To learn more about the workshop, visit www.ninri.nih.gov/newsandinformation/events/maternalhealth2020.

Asian Pacific Islander Americans Discuss Health Inequity During Pandemic

The Covid-19 pandemic poses immense challenges to the Asian Pacific Islander American community, including the large health inequity that impedes their livelihood during this pandemic. To better understand the issue, the NIH chapter of the Federal Asian Pacific American Council recently held an online webinar titled “United to Fight Health Inequity During the Pandemic: What Can the AAPI Community Do?”

The event opened with remarks from Maryland’s First Lady Yumi Hogan, followed by a panel discussion on health inequity. Panelists included Dr. Yvonne Maddox, former NIH acting deputy director, Maryland State Delegate Lily Qi, Dr. Leana Wen, former Baltimore health commissioner, and Dr. Howard Koh, a professor at the Harvard T.H. Chan School of Public Health and former HHS assistant secretary for health.

The discussion centered around the issue of grave health inequities presented by the pandemic, lack of data collection on how the pandemic affects select groups and the importance of public health. Panelists shared their own personal reflections and experiences, as well as possible solutions on how to resolve the multitude of issues posed by the pandemic.

In many cases, panelists agreed on the need for a robust national strategy that will be effective during the nation’s vaccination phase, reinvestment in our public health safety net and a unified community that is devoid of racial discrimination. Panelists made it clear that there is more work to be accomplished despite the progress the nation is making. However, they are optimistic that the nation is heading in the right direction—united to fight the pandemic together.

For more information about the event, visit www.covid9teens.org.

A Call for Real Stories During Covid-19 Pandemic

Since January 2020, Covid-19 has had an impact on the NIH community in many ways—from researching and providing information about the disease, to developing therapeutics and vaccines, to caring for patients in the Clinical Center, to re-configuring the ways we perform our jobs.

To preserve this important period in NIH history, the Office of NIH History and Stetten Museum has initiated “Behind the Mask: Real Stories from NIH Staff About Life During the Covid-19 Pandemic.” The project is seeking personal reflections about how those who work at NIH have experienced the Covid-19 pandemic and is collecting documents, photos, objects and other types of media that will help narrate the story of Covid-19.

To learn more about the project and to participate, visit https://history.nih.gov/display/history/Behind+the+Mask.

NIH Lab Receives Chan Zuckerberg Initiative Award

The Chan Zuckerberg Initiative (CZI) has announced that a lab led by Dr. Michael E. Ward, an investigator at the National Institute of Neurological Disorders and Stroke, is part of one of 30 pairs of researchers to receive an award from CZI’s Neurodegeneration Challenge Network (NDCN). The NDCN is an interdisciplinary collaborative initiative that brings together experimental scientists from diverse research fields to understand the fundamental biology of neurodegenerative disorders such as Alzheimer’s and Parkinson’s disease.

Ward’s lab combines induced pluripotent stem cell technology and advanced molecular and genetic analysis techniques to study how cells from patients with inherited forms of dementia and other neurodegenerative disorders die and rewire the brain. For this project, his lab will work with researchers in the lab of Dr. Alessandro Ori at the Leibniz Institute on Aging-Fritz Lipmann Institute in Jena, Germany.

Ori’s team uses fish called killifish, which have very short lifespans, to study the molecular mechanisms of brain aging. Together, the labs will explore the role that aging plays in the neural damage caused by mutations in the gene TARDBP/TDP-43, which has been linked to some cases of frontotemporal dementia and amyotrophic lateral sclerosis.

Initially, each lab will receive $75,000 of first-phase seed funding for 18 months. If successful, the team may be eligible to apply for second-phase funding of $1.6 million over 4 years.

Director Offers Lunch Hour Serenade

On Friday, July 31, NIH director Dr. Francis Collins played a host of songs, from classical to standards, during the lunch hour in the Clinical Center atrium. It has been his custom in recent years to concertize in that spot when the spirit moves him.

Dr. Michael E. Ward
NCATS’s Virtual Poster Day May Have Found a New Home Online

The National Center for Advancing Translational Sciences held a very different Postbaccalaureate Poster Day recently, and its organizers think it might be the start of something new. Like the NIH-wide postbac poster day held the following week, this year’s NCATS event went online.

NCATS’s postbac poster events let fellows both share their teams’ findings and gain practice explaining their work. The fellows receive training and mentorship from NCATS scientists as part of the NIH Postbaccalaureate Intramural Research Training Award Program. NCATS also offers career development opportunities that give the trainees research experience, knowledge and skills needed to build the translational science workforce.

In recent years, these postbac events were lively yet crowded—they’ve taken place in a building that houses the NCATS intramural labs in Rockville. Dozens of postbacs would line up by their posters, ready to showcase their research, with their mentors close by.

This year, 21 postbacs participated onscreen through 3 concurrent Zoom sessions, with presentations in 15-minute intervals. One by one, each fellow described a research poster and took questions.

Attendees had the option of tuning in to any of the Zoom sessions. Judges and attendees also provided comments.

The format appears to have had many advantages. “We didn’t know what to expect,” said co-organizer Dr. Brittany Haynes of the NCATS Education Branch. “This year’s format seems to have allowed more people to attend and hear presentations in more detail than they might have otherwise in person.”

On virtual display were projects reflecting a range of expertise at NCATS, from new approaches for treating rare diseases to developing drugs that inhibit cancer growth to improving disease modeling.

Here are a few examples:

• Working with NCATS’s Office of Rare Diseases Research, postbac fellow Ainslie Tisdale wants to speed up the pace of diagnosing rare diseases, which often lags for years. She described a project looking at patient health care utilization patterns to better treatment options for dystonia, a group of rare neurological disorders. She and her teammates designed and synthesized a compound for a type of dystonia that will soon be tested further.

• Postbac fellow Alex Renn is working with a team to develop and test “nanobodies,” smaller versions of antibodies made by the body, to defend against invaders such as SARS-CoV-2. Such nanobodies might ultimately play a role in an anti-virus strategy.

Twenty NCATS postbac fellows also participated in the NIH 2020 Virtual Postbac Poster Day. Six postbac fellows, including Renn, received Postbac Poster Awards.

No one knows if an in-person NCATS poster day will be possible next year. Even so, Haynes said the remote format opens up new possibilities, and event organizers may consider using it again.
and release its payload. Decades of work have gone into this. It isn’t easy.”

Years of experiments on animal models have shown that injected nanoparticles usually end up in the organs that filter blood—liver, spleen, bone marrow and kidney.

But, as Anderson pointed out, “RNA or DNA is simply not a great drug. It does not cross cellular membranes. We need expression of these constructs to get function.”

An important precursor to nanoparticle vaccinology is basic research on small interfering RNA (siRNA), a breakthrough that won the 2006 Nobel prize. siRNAs can seek and destroy complementary strands of RNA. “In essence, we can turn off any gene we want,” Anderson said.

He described three key steps to turn nucleic acids into drugs: sequence selection, chemical modification and encapsulation.

“The first question with nanoparticles is, what do you build it out of?” Early biomaterials, such as the artificial heart, were made of material found in ladies’ girdles—polyether urethane. The tubing used for dialysis originated in sausage casing (cellulose acetate). The first vascular grafts came from the world of clothing—the synthetic fabric Dacron.

Since nothing off the shelf suggests a nanoparticle, scientists have engaged in what Anderson called the rational design of biomaterials. Biodegradable sutures, developed in the 1970s, are an example of this approach. “How do we build the perfect material if we don’t know the design criteria?” he asked.

Anderson and his colleagues believe the best approach is to test lots of options, using four basic building blocks: a helper phospholipid, cholesterol, polyethylene glycol lipids and immune lipids.

“Every nano vaccine manufacturer is focused on figuring out the structure of ionizable lipids,” he said.

Anderson has 15 years of experience with DNA delivery systems that harken back to such early compounds as DOTMA, DOTAP, DOPE and DOGS.

“The key question is, how do we increase the diversity of these compounds?” he said. “It’s a chemistry problem. The goal is a cationic lipid.”

One early success in developing RNA therapeutics was use of siRNA to silence the TTR gene, which, when misfolded, causes transthyretin-mediated amyloidosis, a serious liver disease.

The treatment was effective in primates, which Anderson said “surprised us. It was not as hard as we thought to make lipids that could do this.”

The first siRNA lipid nanoparticle was approved for human use in August 2018, in a drug called patisiran.

“This was proof to the field that these particles...actually can be translated and approved as medicine,” Anderson noted. “This inspired us...These types of particles could have broader use.”

They decided to take advantage of endogenous lipid-trafficking pathways in the body. These pathways feature chylomicrons, which is where the fats in the last Snickers bar you ate ended up.

While liver is a relatively easy target for nanoparticles, other targets include endothelium and perhaps even immune cells, including peripheral blood leukocytes. That would enable nanotherapy for some infectious diseases, Anderson said.

His team has been able to silence 5 genes in the lung in vivo using nanoparticles, and he cited a report of 20 genes being knocked down by a single particle.

At the moment, all cells within the liver in animal models can be targeted, as can the endothelium of many organs, including kidney, liver, spleen, heart, skeletal muscle and lung. Also amenable to nanotherapy are leukocyte populations including monocytes, macrophages and dendritic cells, along with a variety of tumors, and even some T and B cells in primates.

Anderson said his MIT colleague, Nobel laureate Dr. Phillip Sharp, has labeled the new technology “modular pharmacology.”

The Moderna vaccine described in the recent NEJM article uses mRNA to activate, not silence, a gene, as with siRNA. “It’s even more challenging than siRNA,” said Anderson. “It’s much bigger.”

It is not enough, he warned, to create an mRNA that encodes an antigen to SARS-CoV-2. “You also need to activate the immune system and have the antigen present for the correct amount of time in order to get the appropriate response.”

In a mouse study, mRNA led to large amounts of circulating protein produced in the liver, as modeled with the kidney hormone EPO. DARPA scientists have been investigating mRNA therapies that can produce antibodies against infectious agents used on the battlefield.

mRNA delivery is not limited to the liver, Anderson said. “Nanoformulations can be generated to express...
Chiang Named Next NEI Director

Dr. Michael F. Chiang, a practicing ophthalmologist and current Knowles professor of ophthalmology & medical informatics and clinical epidemiology at Oregon Health & Science University, has been named new director of the National Eye Institute. He is expected to assume his new role late this year.

Chiang, who is also associate director of the OHSU Casey Eye Institute, “brings extensive experience as a clinician, researcher and educator to NEI,” said NIH director Dr. Francis Collins, who made the appointment. “His work in biomedical informatics and telehealth research are particularly important for the future of vision research.”

Chiang will oversee NEI’s annual budget of nearly $824 million, most of which supports vision research through some 1,600 research grants and training awards made to scientists at more than 250 medical centers, universities and other institutions across the country and around the world.

Chiang’s own research involves telemedicine and artificial intelligence for diagnosis of retinopathy of prematurity and other ophthalmic diseases, implementation and evaluation of electronic health record systems, modeling of clinical workflow and data analytics. He has been a principal investigator on multiple NIH grants since 2003, and he and his research group have published more than 200 peer-reviewed journal papers. Chiang’s clinical practice focuses on pediatric ophthalmology and adult strabismus.

Chiang has mentored more than 50 postdoctoral fellows, medical students and graduate students. He co-directs an OHSU-wide, NIH-funded vision science training program for predoctoral and postdoctoral students, and co-directs an NIH-funded, mentored clinician-scientist program in ophthalmology.

Chiang is past chair of the American Academy of Ophthalmology (AAO) medical information technology committee and has served as an at-large member of the AAO board of trustees. He serves as associate editor for the Journal of the American Medical Informatics Association and has served as an associate editor for the Journal of the American Association for Pediatric Ophthalmology & Strabismus.

Chiang earned his bachelor’s degree in electrical engineering and biology from Stanford University; his master’s degree in biomedical informatics from Columbia University College of Physicians and Surgeons; and his M.D. and master’s in medical science from Harvard Medical School and Harvard-MIT Division of Health Sciences and Technology.

He completed residency and pediatric ophthalmology fellowship training at the Johns Hopkins Wilmer Eye Institute. He is board-certified in ophthalmology and clinical informatics and is a fellow of the American College of Medical Informatics.

Prior to joining OHSU in 2010, he spent over 9 years at Columbia University, where he was Anne S. Cohen associate professor of ophthalmology and biomedical informatics, director of medical student education in ophthalmology and director of the introductory graduate student course in biomedical informatics.

Until Chiang arrives, Dr. Santa Tumminia will continue to serve as acting NEI director, as she has since October 2019.

mRNA in different tissues.”

Nanoparticle mists could be inhaled, as with a nebulizer. “We can get very high expression in lung epithelium in animals,” he reported. One company is exploring this approach for patients with cystic fibrosis.

Anderson concluded with a discussion of genome editing using the CRISPR-Cas9 system, which permanently modifies DNA for some beneficial purpose.

“Can we permanently turn genes off in vivo?” he asked. Using chemically modified guide RNA to direct such editing, Anderson thinks better versions of the system can be developed, leveraging knowledge gained in studies of antisense molecules.

Scientists are currently trying to craft a nanoparticle that can permanently lower cholesterol; one candidate resulted in a 35 percent reduction in mice.

“I invite the creative scientists at NIH to propose gene targets, to either partially or fully knock them out, in infectious diseases,” Anderson said.

Already, a single-particle Ebola vaccine has been made whose payload targets three strains of Ebola, Anderson noted. “It offered complete protection in mice from a lethal dose of the virus.”

He imagines second-generation vaccines delivered by nanoparticle that will target cancer and Covid-19, as more is learned about lipid formulations and the best pathways to target.

The full talk is available at https://videocast.nih.gov/watch=37814.
“Although older studies have indicated that talking generates as much or more droplets than coughing or sneezing, visualizing this with newer technology was needed.”

-DR. ADRIAAN BAX

so aggressively there. He and his wife, who is a linguist, chatted about how people spit when they talk and how some words cause more saliva spray than others. Bax wondered if speaking could be a coronavirus pathway, particularly among asymptomatic people, for spreading harmful germs.

“Everyone was talking about washing your hands and coughing into your elbow to cover your mouth, which are important, but nobody was mentioning speaking,” said Bax. “Although older studies have indicated that talking generates as much or more droplets than coughing or sneezing, visualizing this with newer technology was needed.”

The challenge was that, unlike droplets released by sneezing and coughing, speech droplets are too small to detect without extremely sensitive scientific equipment. Bax turned to Anfinrud, who runs a laser lab normally used to study protein structural dynamics.

“Given our laser-related research backgrounds, it wasn’t much of a stretch to repurpose existing equipment to visualize speech droplets,” said Anfinrud.

Anfinrud painted the inside of a cardboard box black, cut slits in the sides and directed an intense laser light sheet through the slits. His idea was to speak into the box so that the speech particles would generate flashes of light as they passed through the light sheet. In just a few hours on a Saturday morning, he had an apparatus up and running. He called in Bax and Dr. Valentyn Stadnytskyi, a postdoctoral fellow in his lab with expertise in lasers and optics, and the scientists spent much of that weekend recording video clips with a smartphone and interpreting the data they recorded.

The video clips showed that saying simple phrases can generate thousands of potentially infectious speech droplets. Furthermore, wearing a homemade cloth mask blocked 99 percent of the droplets.
particles from being released.

The researchers, along with Bax’s daughter Christina, a medical student at the University of Pennsylvania and an NIDDK special volunteer, drafted the findings in a letter sent to the editor of the New England Journal of Medicine on Mar. 30 and also shared these findings with the CDC.

“We saw this as a call to action and took every step to get this to people quickly,” said Bax. “Our goal was not to get another publication; it was to use our data to help implement changes that we thought could help save thousands of lives.”

The letter was published on Apr. 15, shortly after the CDC began recommending the use of face coverings. But the researchers’ work was far from over. Their next project, already underway, aimed to quantitatively characterize the number and size of speech-generated droplets and determine how long these droplets can linger in the air.

The results, again captured on video, showed that loud speech produced several thousand droplets per second, and in a confined space of stagnant air, the droplets remained airborne for 8 to 14 minutes. The study, published in the Proceedings of the National Academy of Sciences on May 13, suggests that normal speaking in enclosed environments can carry a substantial risk of spreading infectious particles, if the speaker carries a virus such as SARS-CoV-2.

“How far might speech droplets travel before reaching the ground? Air convection and ventilation are factors, but anyone who has been in a room when someone lit up a cigarette may recall how quickly smoke permeates the space,” said Anfinrud. “Theoretically, a cell infected by just one SARS-CoV-2 virus particle can lead to a full-blown case of Covid-19. However, our findings suggest that if everyone wore a simple face covering, we could stop most transmissions.”

The results of the study were shared with the CDC and published in the Journal of the American Medical Association (JAMA) on May 13.

The researchers recommended that loud speaking in enclosed environments should be avoided, especially in this crucial period before we have a vaccine. They also recommended using face coverings.

**NINR Marks 20th Anniversary of Summer Genetics Institute**

This summer, NINR celebrated the 20th anniversary of its Summer Genetics Institute (SGI) with a virtual scientific symposium titled “Omnics to Advance Symptom Science Research.” Over the past two decades, SGI has provided nurse scientists with a foundation in molecular genetics appropriate for use in research and clinical practice. The anniversary symposium brought together more than 1,000 attendees from across the NIH community, academia and beyond to examine how omics methodologies are improving symptom measurement and characterization.

Then-acting NINR director Dr. Tara Schwetz opened the symposium by welcoming attendees and providing a brief background of the SGI, citing the program’s goal since its inception: “To ensure that nurse scientists have a comprehensive understanding of genetics and genomics, including state-of-the-art technologies and clinical applications to inform research programs.”

NIH director Dr. Francis Collins delivered opening remarks, highlighting the importance of genomics in nursing, reaffirming his belief that “through education, research and clinical applications, nurses can accelerate the pace of integrating genomics into options for care, thereby contributing significantly to reshaping and optimizing health care.”

The symposium featured presentations from leading nurse researchers including keynote speaker Dr. Christine Miaskowski of the University of California, San Francisco, discussed the use of omics to understand oncology patient symptoms. She also touched on the importance of genetics and genomics in nursing research as a catalyst for risk factor identification, providing fundamental knowledge about the mechanisms of disease and symptoms and identifying therapeutic targets.

Dr. Yvette Conley, professor and vice chair for research at the University of Pittsburgh, reviewed using omics to understand outcomes after neurological injury and Dr. Angela Starkweather, professor and associate dean for academic affairs at the University of Connecticut, described the genomics of the transition from acute to chronic pain. The speakers also discussed their involvement with SGI, their career trajectories and perspectives on the future of omics in translational programs of research and clinical care.

Acting scientific director Dr. Terri Armstrong closed the symposium and highlighted key papers that have helped build the framework for genomic nursing research and competencies.

She described a paradigm shift where approaches used in nursing and medicine are now interconnected. Genomic research can be used to study both the human response—a nursing approach—with the association with disease—an approach used in medicine.

Today, nearly 450 SGI graduates are making a difference in communities across the country—building programs of nursing research in genetics, disseminating the results of genetics-related research in peer-reviewed scientific publications and at scientific conferences and integrating genetics content in nursing school curricula and nursing practice.

Learn more about SGI at www.ninr.nih.gov/sgi. To view the videocast of the anniversary symposium, visit https://videocast.nih.gov/watch=37511.
Gene Therapy Program. “Over the last few years, the field has flourished.”

Hearing loss is one of the most common communication disorders in the world. Aging, exposure to loud noise, head trauma, genetic mutations, some medications and bacterial infections can all lead to hearing loss.

“As patients lose their hearing, they become more socially withdrawn because they don’t want to embarrass themselves in front of their family members and friends.

There’s a significant impact on the patient’s health as well as overall quality of life,” Chien said.

When a sound wave enters the ear, it travels through a narrow passage called the ear canal. There, it meets the eardrum. The sound waves strike the eardrum, which causes three tiny bones in the middle ear to vibrate. The vibrations travel to the cochlea, a fluid-filled structure shaped like a snail’s spiral shell, which activates the sensory cells in the inner ear called hair cells.

The hair cells translate the vibrations into electrical signals and auditory nerve fibers send the signals to the brain. The hair cells can detect a wide range of frequencies. Additionally, the vestibular organs in the inner ear help maintain a person’s balance.

For patients with mild to moderate hearing loss, hearing aids are one treatment option. However, only 14 percent of the U.S. population with hearing loss wears hearing aids. Chien thinks people are not aware of the problems that hearing loss causes, so they don’t appreciate the health benefits of hearing.

“It’s a very exciting time to be working on inner ear gene therapy. Through the collective effort of many investigators throughout the world, we hope to bring inner ear gene therapy from the bench to the bedside in the foreseeable future.”

-DR. WADE CHIEN

“Fortunately, this is rapidly changing” due to research, he said. “It’s my hope more and more people will realize the importance of treatment for hearing loss.”

Some people, particularly those with severe hearing loss, don’t find hearing aids effective. Many of Chien’s patients with severe hearing loss say hearing aids make sounds louder, not clearer.

For these patients, he said, cochlear implants are another treatment option. A cochlear implant is a device that stimulates the auditory nerve. The implant has external and internal parts. The external part includes a microphone, which relays information to the internal part, which transmits it to the cochlea.

“While hearing aids and cochlear implants are useful therapeutic options for patients with hearing loss, they are not perfect,” Chien said.

The lack of effective treatments inspired him to find new ones. His lab has focused on gene therapy as a potential treatment for both hearing loss and dizziness. Gene therapy is an experimental technique that modifies a person’s genes to treat a disease process.

Chien’s colleagues at NIDCD have helped to characterize a mutation found in the whirlin gene. Mutations in this gene are associated with Usher syndrome, a condition that affects hearing and vision. Deafness resulting from the syndrome is caused by the abnormal development of hair cells in the inner ear. The syndrome also causes balance problems.

To test the effectiveness of gene therapy at treating balance problems and hearing loss, Chien delivered normal copies of whirlin cDNA to the inner ear of mice with a mutation affecting the whirlin gene, which causes these mutant mice to be deaf and to spin around. The hope is to replace the mutated gene with a healthy copy of the gene. He found that gene therapy treatment caused these mutant mice to have longer stereocilia—the hair-like projections on the hair cells—than mice that didn’t get the gene therapy treatment. He found that the mutant mice that received gene therapy stopped spinning and started to walk in a straight line. In addition, he also found that these mutant mice could start to hear after gene therapy.

Chien said other researchers are also using gene-editing technologies, such as CRISPR-Cas9, to make changes in specific regions in the genome. In one study, Harvard University scientists prevented hearing loss in mice with hereditary deafness by using a gene-editing approach to disable a mutation that causes hearing loss. Research is ongoing.

“It’s a very exciting time to be working on inner ear gene therapy,” Chien concluded. “Through the collective effort of many investigators throughout the world, we hope to bring inner ear gene therapy from the bench to the bedside in the foreseeable future.”
Opioid Use May Be Linked to Pregnancy Loss, Lower Chance of Conception

Opioid use among women trying to conceive may be associated with a lower chance of pregnancy, suggests an NIH study. Moreover, opioid use in early pregnancy may be associated with a greater chance of pregnancy loss. The study appears in Epidemiology.

“Our findings indicate that women who are pregnant or planning a pregnancy should, along with their physicians, consider the potential effects opioids may have on their ability to conceive or sustain a pregnancy,” said Dr. Kerry Flannagan, primary author of the study and a postdoctoral researcher in NICHD’s Division of Intramural Population Health Research.

According to the authors, much of the research on prescription opioid use has focused on the effects of drug dependency. Little information exists on non-habitual, periodic opioid use around the time of conception and early in pregnancy.

The researchers analyzed data from the Effects of Aspirin in Gestation and Reproduction trial, which investigated low-dose aspirin as a treatment to prevent pregnancy loss. Participants were women from 18 to 40 years old with a history of 1 or 2 pregnancy losses. Women were followed for 6 monthly cycles if they did not get pregnant and throughout pregnancy if they did. The women provided urine samples, which were analyzed for various prescription opioids.

Of the 1,228 women in the study, 226 (18 percent) had used opioids while trying to conceive and 33 (5 percent) of 685 women who became pregnant had used opioids in early pregnancy. None tested positive for methadone or buprenorphine, typically used to treat opioid dependence.

Opioid use before conception was associated with a 29 percent lower chance of achieving pregnancy during a given monthly cycle, compared to women who had not used opioids. Among the women who became pregnant, those who used opioids around the time of conception were 1.5 times as likely to have a miscarriage as women who had not. Women who used opioids in the first 4 weeks of pregnancy were more than twice as likely to have a miscarriage. Women who used opioids in weeks 4 through 8 of pregnancy were 2.5 times as likely to have a miscarriage.

The authors called for additional research on how opioid use affects fertility and early pregnancy. They added that until more is known, patients and physicians should evaluate the potential risks and benefits of opioids for pain management among women who are pregnant or may become pregnant, including those undergoing assisted reproduction procedures that may involve opioid treatment to manage pain.

New Treatments Spur Sharp Reduction in Lung Cancer Mortality Rate

According to a new study, mortality rates from the most common lung cancer, non-small cell lung cancer (NSCLC), have fallen sharply in the United States in recent years, due primarily to recent advances in treatment.

The study was led by researchers at NCI. The findings were published Aug. 12 in the New England Journal of Medicine.

“Reduced tobacco consumption in the U.S. has been associated with a progressive decrease in lung cancer deaths that started around 1990 in men and around 2000 in women,” said Dr. Douglas Lowy, NCI deputy director and co-author of the study. “Until now, however, we have not known whether newer treatments might contribute to some of the recent improvement. This analysis shows for the first time that nationwide mortality rates for the most common category of lung cancer, non-small cell lung cancer, are declining faster than its incidence, an advance that correlates with the Food and Drug Administration approval of several targeted therapies for this cancer in recent years.”

In this study, researchers looked at data for both NSCLC, which accounts for 76 percent of lung cancer in the U.S., and small-cell lung cancer (SCLC), which accounts for 15 percent (other subtypes of lung cancer that constitute the remaining share of cases were not covered in this study).

In the last decade, new treatments for NSCLC have become available, including those that target genetic changes seen in some NSCLC tumors as well as immune checkpoint inhibitors that help the immune system better attack NSCLC. In contrast, there have been limited treatment advancements for SCLC.

The researchers found that, in recent years, deaths from NSCLC decreased even faster than the decrease in NSCLC incidence and the decrease in deaths was associated with a substantial improvement in survival.

“The survival benefit for patients with non-small cell lung cancer treated with targeted therapies has been demonstrated in clinical trials, but this study highlights the impact of these treatments at the population level,” said Dr. Nadia Howlader of NCI’s Division of Cancer Control and Population Sciences, who led the study. “We can now see the impact of advances in lung cancer treatment on survival.”

NIH’ers Generate Complete Human X Chromosome Sequence

Researchers at the National Human Genome Research Institute have produced the first end-to-end DNA sequence of a human chromosome. The results, published July 14 in Nature, show that generating a precise, base-by-base sequence of a human chromosome is now possible, and will enable researchers to produce a complete sequence of the human genome.

“This accomplishment begins a new era in genomics research,” said NHGRI director Dr. Eric Green. “The ability to generate truly complete sequences of chromosomes and genomes is a technical feat that will help us gain a comprehensive understanding of genome function and inform the use of genomic information in medical care.”

After nearly two decades of improvements, the reference sequence of the human genome is the most accurate and complete vertebrate genome sequence ever produced. However, there are hundreds of gaps or missing DNA sequences that are unknown.

These gaps most often contain repetitive DNA segments that are exceptionally difficult to sequence, and yet these repetitive segments include genes and other functional elements that may be relevant to human health and disease.

Because a human genome is incredibly long, consisting of about 6 billion bases, DNA sequencing machines cannot read all the bases at once. Instead, researchers chop the genome into smaller pieces, then analyze each piece to yield sequences of a few hundred bases at a time. Those smaller DNA sequences must then be put back together.

Senior author Dr. Adam Phillippy of NHGRI compared this issue to solving a puzzle.

“Imagine having to reconstruct a jigsaw puzzle. If you are working with smaller pieces, each contains less context for figuring out where it came from, especially in parts of the puzzle without any unique clues, like a blue sky,” he said. “The same is true for sequencing the human genome. Until now, the pieces were too small, and there was no way to put the hardest parts of the genome puzzle together.”

Of the 24 human chromosomes (excluding X and Y), study authors Phillippy and Dr. Karen Miga at the University of California, Santa Cruz, chose to complete the X chromosome sequence first, due to its link with myriad diseases including hemophilia, chronic granulomatous disease and Duchenne muscular dystrophy.
After grad school, when trying to decide what specific career path to travel next, Bilusic came across the Guyton-Coleman model of blood pressure homeostasis.

“This model was published in 1972 and was heavily criticized at that time as being very simplistic,” Bilusic said.

But 30-some years later—around 2002 or so—looking at the work in the same climate as the then-newly released draft Human Genome Project, he said he “found [the BP model] very exciting and I was thinking that it should be a perfect example of personalized medicine. Now we have a genome sequence. We have detected multiple genes. This is a polygenetic disorder. Maybe by studying this, by dissecting the genetics of hypertension, we can provide more personalized treatment for blood pressure.”

In 2002, Bilusic moved from his home in Croatia to the Medical College of Wisconsin, where he worked on the Family Blood Pressure Program, part of an NHLBI-funded Multi-Center Genetic Study of Hypertension that phenotyped and genotyped about 11,000 people in the U.S.

Nearly a generation later, in 2020, hypertension treatment is pretty much standardized across age, sex and racial and ethnic groups. Development of individualized therapies for the disorder appear to be moving at a crawl, Bilusic observed.

“All of us would agree that personalized oncology and precision oncology are much more advanced than precision medicine in hypertension,” he said.

“Why is progress so slow in one of the most commonly reported diseases such as hypertension?”

Bilusic suggested the answer may be one of economics. He pointed to a slide showing that cancer drugs—both prescription and over-the-counter—bring in the most pharmaceutical revenue, therefore there is a huge interest (and investment) by the industry in studying new oncology drugs. Average annual costs for oncology meds continue to trend upward, he said.

In 2018, a median yearly cancer treatment cost about $150,000. In addition, the FDA “breakthrough” designation—which expedites the approval process for highly promising therapies—in 2017 went to 2 percent of cardiology drugs versus 50 percent of cancer drugs.

“Currently we have about 850 molecules in late-phase development for oncology and it’s definitely moving toward targeted therapy and immunotherapy,” Bilusic said. “That’s why I think precision oncology is much more advanced than precision medicine in hypertension.”

He cited recent studies of advanced prostate and lung cancer to back up his argument that all patients with such metastatic tumors should be sequenced to identify possible genetic mutations for which successful treatments have already been proven.

Bilusic also talked about “exceptional responders,” or outlier patients who exceed expectations. “Most statisticians don’t like outliers,” he quipped. “Outliers can really mess up analysis. We oncologists really like them a lot. They are the patients we remember. They are our success stories and we love to share them with other patients and with our colleagues.”

In 2014, as an assistant professor at Fox Chase Cancer Center, Bilusic and colleagues wondered whether exceptional responders could help move precision oncology forward. The group studied 26 multi-year survivors who had battled one of several metastatic tumors including bladder, kidney, breast, lung, uterine and colon cancers.

“What was most striking was we found very high frequency of mutations in DNA damage response pathways, which suggests increased genomic instability in outliers,” Bilusic reported. So many outliers matched identical mutations across different tumor types.
Summing up, he predicted that one key advance for cancer precision medicine will be early detection via liquid biopsy, or sequencing of cell-free DNA (cfDNA). Perfecting liquid biopsy technology will propel precision oncology forward significantly because it also can detect cancer and recurrences 6 to 9 months sooner than imaging does.

“This still remains a challenge today because there is very low amount cfDNA found in patient blood,” Bilusic said.

“Precision oncology is running forward at a very fast pace,” he concluded. “Over the last 10 years, the overall cancer death rate has continued to decline and anti-cancer therapy has changed dramatically, particularly with development of immunotherapy and precision oncology. Despite all these accomplishments, clinical adoption of precision oncology has been very slow. As many as 60 percent of advanced-cancer patients are not receiving any form of genomic testing as of 2019.”

Why the slowdown? Bilusic suggested several theories: Oncologists’ lack of expertise with genomic data interpretation, costs of genomic sequencing remaining too high for many patients whose health insurance may not cover the process, and similarly, lack of insurance coverage of sequencing-derived drugs, which generally are expensive and not affordable when prescribed “off label.”

In terms of opportunities to move precision oncology into the fast lane, Bilusic recommended designing more innovative trials that enroll patients with different tumor types, but the same mutations, and pursuing further studies that involve outliers.

He also sees promise in developing personalized immunotherapy and vaccines; in exploring pharmacogenomics, which is in its early stages; and in artificial intelligence or machine learning—devising algorithms that could predict the best treatment sequence for a patient based on comparison with data found in historical patient profiles.

“Precision oncology is still growing,” Bilusic closed. “I don’t think we are there yet, but we are making dramatic progress every year. The future is very bright.”

Former NIGMS Director Cassman Mourned

Former NIGMS director Dr. Marvin Cassman passed away on Aug. 6.

He joined NIGMS in 1975 as a health scientist administrator in what was then the Cellular and Molecular Basis of Disease Program, advancing through the ranks to become NIGMS’s deputy director, acting director and, from 1996 to 2002, director. Cassman’s tenure as director coincided with the period of NIH’s budget doubling, and he ably led NIGMS’s establishment of key initiatives that have had a world-wide impact. These included the Protein Structure Initiative, the goal of which was to make the 3-dimensional, atomic-level structures of most proteins easily obtainable from knowledge of their corresponding DNA sequences. This enabled investigators to apply the new paradigm of high-throughput structure determination to study important biological and biomedical problems.

Furthermore, Cassman guided the establishment of the Pharmacogenomics Research Network, which promoted an understanding of the genetic contributions to drug responses and fostered the sharing of methods, data, knowledge and implementation strategies through resources for the research community, including PharmGKB. He recognized the need for basic research—particularly in structural biology—in the fight against AIDS and was strongly committed to ensuring that research instrumentation was available to the scientific community.

Cassman was well-liked and highly respected by NIGMS staff and the broader research community. He received the 1993 NIH Director’s Award and the 1991 Presidential Meritorious Executive Rank Award.

After leaving NIGMS, Cassman was appointed as first director of the Institute for Quantitative Biomedical Research at the University of California, San Francisco Mission Bay campus.

Upon his retirement from UCSF, he served on a number of national and international advisory committees.

Cassman enjoyed music, especially opera. He leaves behind his wife Alice, whom he married in 1972.

Cassman recognized the need for basic research—particularly in structural biology—in the fight against AIDS.

Healthy Volunteers Needed

NIDDK researchers seek healthy volunteers (18-45 years old) to participate in a study investigating how dopamine affects body weight and eating behavior. Participants must be able to visit the Clinical Center for 5 consecutive days to pick up food and then have a 5-day inpatient stay. For more information, call the Clinical Center Office of Patient Recruitment, 1-866-444-2214 or prpl@cc.nih.gov (TTY for the deaf or hard of hearing: 1-866-411-1010). Read more at https://go.usa.gov/xPTBn. Refer to study 18-DK-0132.

NHLBI Study Needs Patients

NHLBI researchers are testing two low doses of danazol on individuals with short telomere disease and bone marrow disease, lung or liver disease. For more information, call the Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Read more at https://go.usa.gov/xnPym. Refer to study 18-H-0004.
MORE VISUAL MEMOIRS
How I Spent My Quarantine

Below, find more evidence of the industrious nature of NIH’ers using their pandemic downtime well.

“The pandemic has given some people cabin fever,” said Keisha Shropshire, public health analyst at the Office of Disease Prevention. “For me, it has brought out my inner green thumb. Watching green (plants) grow is as beautiful as you think it is.”

“Thanks to my mother-in-law loaning me her old sewing machine, and to an amazing fabric store in town, I’ve taken up sewing as a new hobby,” said Wilma Peterman Cross, deputy director of the Office of Disease Prevention. “In addition to bags, I’ve made many face coverings for family and friends. It has turned out to be the perfect way to escape all of the craziness that 2020 has offered. I have ripped many mis-stitched seams, installed zippers backwards, and cut my pattern the wrong way countless times. Despite all of that, I couldn’t be happier.”

KUDOS GROW EVER MORE CREATIVE
Fauci Fans Amp Up Cultural Tributes

The salutes to NIAID director Dr. Anthony Fauci keep coming for his stalwart fight against covid. His fan base continues to expand as well, creatively presenting their appreciation via all forms of culture and couture. Joining the lawn signs, face masks, T-shirts, cocktails, baseball cards, bobbleheads and cupcakes seen in weeks past are recently noted performance art and fine art plaudits.

Stage and screen actor Bets Malone recorded Dear Dr. Fauci, a parody of the classic You Made Me Love You and released it via Facebook and YouTube (screenshots above), where it immediately went viral. A sampling of her show tune’s lyrics praise Fauci and exhort the rest of us: “The nation how you serve it, don’t know if we deserve it | Since ’84 you labor, protecting every neighbor | America, get a clue...Fauci is fighting for you!”

Another performer, folk singer-songwriter-musician-activist Joan Baez turned to another of her talents to show Fauci appreciation. She painted his portrait, accompanied by an open letter to the champion infection fighter. It reads in part:

“I’ve painted your portrait to honor you and all you are doing for us and for the world. It will be a part of my second art exhibit of ‘Mischief Makers,’ paintings of people who have made meaningful social change without the use of violence. I don’t imagine you’ve ever thought of it this way, but you are engaging in nonviolent resistance every time you stand in front of the cameras and attempt to educate the public on how to survive the Covid-19 pandemic.”

Also recently noted are several wearable items featuring Fauci’s visage—some created using fabric (shown, r) designed by Utah freelance graphic artist Kate Rhees.

Joan Baez
August 16

To Dr. Anthony Fauci

Dear Dr. Fauci,

I’ve painted your portrait to honor you and all you are doing for us and for the world. It will be a part of my second art exhibit of ‘Mischief Makers,’ paintings of people who have made meaningful social change without the use of violence.

I don’t imagine you’ve ever thought of it this way, but you are engaging in nonviolent resistance every time you stand in front of the cameras and attempt to educate the public on how to survive the Covid-19 pandemic. You cheerfully continue your task, surrounded by people who are dreaming up every way possible to discredit you and what you bring to us: common sense, scientific facts, some humor, a bit of humor, and towering moral fortitude. Telling the truth is out of favor with the rich and powerful, particularly these days. You speak truth to their dominion. You take a big risk in doing so.

Coraggio, Dr. Anthony Fauci!

If my friends and I can ever be of help to you, we need only let us know. We’ve got your back.

SEEN