

Research News Quarterly

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Letter from the Editor

The October Research News Quarterly continues our interview series with NIH institute and federal program heads with a conversation with the Acting Director of the Office of Rare Diseases Research (ORDR) Pamela McInnes, DDS. Dr. McInnes explains why ORDR is now housed at the National Centers for Advancing Translational Sciences (NCATS) and outlines the office's key programs and mechanisms for supporting research on rare lung diseases, including the Rare Diseases Clinical Research Network.

Moving to patient perspectives on clinical research, we feature an article from ATS Public Advisory Roundtable Past Chair Teresa Barnes on a recent meeting that the FDA held to involve and engage patients with pulmonary fibrosis, as two potential new therapies for the disease are under review by the agency. Moving to disease prevention, we provide an overview of the National Institute of Environmental Health Science's recent report identifying new carcinogenic chemicals.

Next, we shift to research funding advocacy efforts, with reports on the ATS leadership's annual meetings with NIH institutes and federal agencies including the NHLBI and VA Research program and on our Utah members breakthrough meeting with their local Congressman, a key member of the House subcommittee that funds health research—ATS member advocacy at its best! The October Quarterly is rounded out by quick updates from NCATS and NIGMS.

Sincerely,

Linda Nici, MD

Editor



INTERVIEW WITH PAMELA MCINNES, DDS, MSc (Dent.) Deputy Director, NCATS Acting Director, Office of Rare Diseases Research

Q: What is the National Center for Advancing Translational Sciences and what role does it play in rare diseases research?

A: NCATS is all about getting more treatments to more patients more efficiently. There are several thousand rare diseases affecting an estimated 25 million Americans, yet there are only a few hundred treatments available. Some obstacles to rare disease treatments include difficulties in diagnosis, geographically dispersed patients and scientific experts, a perceived high risk and cost of developing such treatments, and a lack of data from natural history studies. NCATS is directly addressing these challenges by developing ways to characterize, diagnose and treat rare diseases based on a modern understanding of relationships among disease mechanisms, genomics and drug action. By discovering new technologies and other approaches that can be used by all translational researchers, NCATS is addressing enormous unmet medical needs, and adding to the understanding of commonalities among diseases to improve the translational process.

Q: Would you give an overview of the Rare Diseases Clinical Research Network?

A: The RDCRN was established in 2003 by the NIH Office of Rare Diseases. NCATS now oversees the program, which is designed to advance medical research on rare diseases by facilitating collaboration, study enrollment, and data sharing. Since the program's launch, nearly 29,000 patients have been enrolled in network clinical studies. Currently, the network is comprised of about 2,600 researchers including NIH and non-government investigators and members of 98 patient advocacy groups; 91 studies are under way.

The real strength of the collaboration among RDCRN consortia is the power to obtain high-quality data. These data form an important base to better define patient populations, attract industry partners, share

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Pamela McInnes Interview *(Continued from page 2)*

information on best practices, and advance treatment options for the rare disease patient community.

Direct involvement of patient advocacy groups in operations and strategy also is a major focus, so each consortium includes relevant patient advocacy groups in partnership and research activities. Network consortia also establish training programs for clinical investigators interested in rare diseases research, provide information to the public on the rare diseases they study, and enable proof-of-concept in clinical research studies.

Q: How does NCATS' Office of Rare Diseases Research support rare lung diseases research?

A: NCATS focuses not on specific diseases, but on what is common among them and the translational science process. This said, we believe that problems are best solved in the context of particular scientific/medical problems, which includes efforts aimed at lung diseases.

The RDCRN, which is administered through NCATS' Office of Rare Diseases Research (ORDR), currently includes two consortia that focus on rare lung diseases. One is the Rare Lung Diseases Clinical (RLDC) Research Consortium at the Cincinnati Children's Hospital Medical Center. Designed to facilitate clinical research and education for rare lung diseases with a focus on the development of novel diagnostics and therapeutics, diseases under investigation include autoimmune pulmonary alveolar proteinosis, hereditary pulmonary alveolar proteinosis, Hermansky-Pudlak Syndrome, lymphangioleiomyomatosis, pulmonary alveolar microlithiasis, and secondary pulmonary alveolar proteinosis. In addition, the RLDC Clinical Research Network is comprised of 46 academic clinical centers worldwide that focus on diagnosis and support of patients with rare lung diseases.

There is also the Genetic Disorders of Mucociliary Clearance Consortium at the University of North Carolina at Chapel Hill School of Medicine. This

is a network of nine North American Centers that collaborate in diagnostic testing, genetic studies, and clinical trials in patients with impairments in mucociliary clearance, including primary ciliary dyskinesia, cystic fibrosis and pseudohypoaldosteronism. Other studies target related clinical conditions believed to be due to impaired mucociliary clearance, including idiopathic bronchiectasis and infection with non-tuberculous mycobacterial organisms. Ultimately, consortium researchers hope to better define the clinical pathogenesis of these airway diseases, improve or expand diagnostic testing, and develop new and effective treatments.

Q: What are some opportunities for collaborations with the National Heart, Lung and Blood Institute (NHLBI) on rare lung diseases?

A: There is a long history of ORDR and NHLBI collaboration. NHLBI supports the two consortia mentioned above, and also has supported 14 rare lung disease scientific conferences with ORDR over the past 10 years. The conferences have featured lymphangioleiomyomatosis, primary ciliary dyskinesia, lung surfactant research, as well as cellular and molecular biology advances in the areas of hereditary hemorrhagic telangiectasia type 2, sarcoidosis, and critical care for pediatric pulmonary issues.

Q: Since many adult diseases have their origins in childhood, what are some activities NCATS' ORDR supports in pediatric rare diseases?

A: It has been estimated that more than half of all rare diseases have their onset in childhood, and through ORDR, NCATS is quite involved in research efforts across NIH for many of those diseases. Staff and I work closely with the Eunice Kennedy Shriver National Institute of Child Health and Human Development, as well as the disease-specific institutes and centers to help coordinate efforts around childhood rare diseases. We also work closely with patient advocacy groups for childhood diseases, providing funding for small

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Pamela McInnes Interview *(Continued from page 3)*

research projects that can be the basis of a research portfolio.

In addition, many pediatric rare diseases are under active investigation through the RDCRN. The network supports a significant number of longitudinal natural history studies so that clinician-researchers can better understand the diseases and find ways to detect the diseases earlier when intervention may be more effective.

Q: What projects has NCATS supported to foster partnerships with industry to bring orphan lung disease treatments to the clinic?

A: One project we are particularly proud of is the development of a drug that treats patients who harbor a specific genetic mutation for cystic fibrosis. In 2012, researchers from 13 universities and hospitals, including 10 that have NCATS' Clinical and Translational Science Awards, partnered with the Cystic Fibrosis Foundation and the drug manufacturer Vertex Pharmaceuticals to conduct clinical trials and obtain FDA approval for the drug Kalydeco.

Kalydeco is an oral medicine that could greatly improve the lives of individuals living with a rare form of cystic fibrosis caused by a specific genetic mutation in the CFTR gene, G551D-CFTR, which occurs in approximately 5 percent of individuals with cystic fibrosis.

Q: Where can our members obtain more information about rare diseases?

A: NCATS has a wonderful patient resource called the Genetic and Rare Diseases (GARD) Information Center. GARD staff provides current and accurate information about genetic and rare diseases to patients, family members, healthcare workers, scientists and the general public. More information can be found at <http://rarediseases.info.nih.gov/gard>. ■

PATIENT VOICES

Idiopathic Pulmonary Fibrosis Takes Center Stage at FDA

Teresa Barnes, ATS Patient Advisory Roundtable, Past Chair, & Coalition for Pulmonary Fibrosis, Vice President

The U.S. Food and Drug Administration (FDA) has not yet approved a drug for idiopathic pulmonary fibrosis (IPF) but is listening closely to stakeholders at a time when the agency is also reviewing the first potential therapies.

The FDA held an IPF Workshop on Sept. 26 to insure patient, family member and caregiver voices are heard throughout the drug development process as potential therapies make their way to market both now and in the future. More than 100 people gathered in the Silver Spring, MD, offices—a crowd mostly made up of patients, family members, patient advocacy groups, medical professionals, and industry representatives. A few hundred also joined the event online, according to the FDA.

PF, which affects 200,000 Americans, is a lung disease characterized by progressive and irreversible scarring that renders the lungs unable to exchange blood oxygen. Patients die in an average 2.8 years and the disease claims as many lives as breast cancer.

During the meeting, patients and family members of deceased IPF patients spoke about the hardships of IPF, a disease that debilitates patients early in its course and produces a steady decline in quality of life and gradual worsening of symptoms such as shortness of breath, cough, and fatigue, as well as issues with anxiety and depression.

The patient stakeholders' experiences were paramount at the workshop that lasted four hours, with most of

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Patient Voices *(Continued from page 4)*

the time dedicated solely to hearing from them. FDA also heard from researchers, advocates, and others during the open public period at the end of the meeting, including ATS members David Lederer, MD, and Gregory Cosgrove, MD.

Two survivors of IPF spoke about their experience pre- and post-transplant and about how grateful they were to be part of the less than one percent of patients who survive the deadly disease.

One patient in the audience described his extreme shortness of breath during a particularly difficult episode of coughing as “knowing what it must be like to drown.” Others described the stress and anxiety related to fears around running out of supplemental oxygen and fear of suffocation.

Panelists thanked the FDA for giving the patients a voice in the drug development process. I had the pleasure of serving as a panelist at the meeting, and I encouraged the regulatory agency to include patients and advocates a decade or more earlier.

The FDA’s Banu Karimi-Shah, MD, agreed with the patients and advocates that the patient voice needs to be included in the process at an earlier stage “I learned so much today,” Dr. Karimi-Shah told the audience. “I know it wasn’t just a learning opportunity for me but all of us here at FDA.”

The only other public forum when the FDA has heard from IPF patients, family members, and caregivers was in 2010 at the FDA hearing on pirfenidone. During that meeting, patients and other stakeholders could speak for a minute or two each.

The FDA noted that the workshop’s purpose was for officials to hear directly from patients about the symptoms that matter most to them and current approaches to treating IPF.

The meeting was not held to review any particular drugs but rather to gather information that can aid the FDA in

reviewing drugs for the disease going forward. The FDA notes that a report will result from the meeting to guide the agency in future drug reviews and will be available publicly to the all stakeholders. The agency is holding 20 such disease-specific meetings in response to a congressional mandate that requires funding from the Prescription Drug User Fee Act to better understand the patient perspective.

The FDA is currently reviewing two drugs under breakthrough designation for IPF, Boehringer Ingelheim’s nintedanib and InterMune’s pirfenidone. Both drugs presented positive data during the ATS 2014 International Conference in San Diego in May.

The FDA is accepting comments from all stakeholders to also include physicians, researchers, allied health professionals, members of industry, and others via the public docket until Nov. 26. Submit your comments at <http://www.regulations.gov/#!docketDetail;D=FDA-2014-N-0865>.

To listen to the meeting’s webinar archive, visit fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm395774.htm. ■

RESEARCH ADVOCACY

ATS Leaders Engage with Federal Research Agencies

In late September, the executive committee of the American Thoracic Society held a series of meetings with key federal research programs, including the National Institutes of Health, the Environmental Protection Agency, Department of Veterans Affairs, and the ATS’s first meeting with the Food and Drug Administration’s Center for Tobacco Products. The purpose of the meetings was to urge federal programs

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Research Advocacy *(Continued from page 5)*

to continue to expand support for research on respiratory, critical care and sleep related illnesses.

The ATS leadership made a number of visits to key institutes at the NIH, including the National Heart Lung and Blood Institute, the National Institute of Allergy and Infectious Diseases, the National Institute of Nursing, the National Center for Advancing Translational Sciences, the National Institute of General Medical Sciences and the National Institute of Environmental Health Sciences.

“In each of the meetings, we made the case for continued and expanded support for respiratory, critical care and sleep related illnesses,” ATS President Tom Ferkol, MD, says. “Although the tone and details of the meetings varied by each institute and its particular area of research, all of the meetings emphasized our key message on the need for research and the many opportunities in lung, critical care and sleep in each institute’s purview.”

For several years, ATS leadership has met with federal research agencies. “As a result of these meetings and the other science-based activities of the ATS, NIH and other federal agencies view the ATS as a credible and informed partner.” ATS President-Elect Atul Malhotra, MD, says. “I really feel like we are making an important impact.” ■

ATS UT Members Advocate for Lung Research

In September, ATS members from the University of Utah’s divisions of pulmonary, and critical care met with their House Representative, Chris Stewart (R-UT), a member of the House Labor-Health and Human Services (L-HHS) Appropriations subcommittee, in his Salt Lake City office to urge his support for NIH and CDC funding. The L-HHS subcommittee determines annual funding levels for NIH and CDC proposed by the

House of Representatives. In this important position, Rep. Stewart is a key congressional target for ATS advocacy.

The meeting was a resounding success, with Rep. Stewart deeply engaged in learning about the innovative lung and critical care research at the University of Utah in areas such as cystic fibrosis, sepsis, and acute lung injury. He agreed that we must foster this and our national biomedical research enterprise through NIH. ATS members also discussed the need to support CDC funding through a discussion of tuberculosis and influenza. Lastly, the group also discussed their concern about air quality in Utah, highlighting the costs to both the people and the economy of the state of poor air quality.

State congressional visits are a key goal of the ATS’s advocacy network, the Breathing Better Alliance (BBA). District visits serve to strengthen our grassroots efforts across the country and enable ATS members and patients to engage in advocacy close to home without requiring travel to Washington, DC. The BBA will be holding additional state congressional meetings. The outcome of the November election will bring new targets for advocacy. Your Representative or Senator could be it: be ready! ■



From left, Samuel Brown, MD, Estelle Harris, MD, Matthew Rondina, MD, Rep. Chris Stewart (R-UT), Theodore Liou, MD, and Robert Paine, MD.

RESEARCH FUNDING

Congress Adjourns for November Election Following Passage of 2015 Spending Measure

Before adjourning for the November election, the House and Senate both passed a temporary spending measure, known as a continuing resolution (CR) during the week of Sept. 15. The CR provides funding for federal agencies and programs beyond the Sept. 30 end of fiscal year (FY) 2014 at current spending levels, minus a 0.0554 percent across-the-board cut in all discretionary spending to fund CDC and Biomedical Advanced Research and Development Authority (BARDA) efforts to respond to the Ebola outbreak. This placeholder bill keeps the government operating through Dec. 11, 2014. The president has signed the bill into law.

Control of the Senate is hanging in the balance until November. With a number of races expected to be extremely close, it is not known whether the Senate will remain in Democratic control for weeks following the election. Republicans must pick up at least six seats this year to win a Senate majority. The House of Representatives is expected to remain in Republican control. These last few weeks before election day is the perfect time to ask your members of Congress where they stand on NIH and CDC funding.

Congress is expected to return to Washington the week after the November election and top of their agenda will be to decide how to proceed on the FY2015 spending bills. The House and Senate Appropriations Committee chairs have both indicated their strong preference for an omnibus appropriations measure that wraps

some or all of the individually negotiated bills into a big spending package, but it is also possible that election dynamics dictate yet another CR which would extend programs at current levels through until early 2015 or for the entire fiscal year. ■

ENVIRONMENTAL HEALTH

HHS Releases 13th Report on Carcinogens

On Oct. 2, the Department of Health and Human Services (DHHS) released the 13th Report on Carcinogens (ROC). Released every two years as mandated by Congress, the ROC identifies chemical, biological, and physical agents that are considered cancer hazards for people in the U.S. It is prepared for the DHHS by the National Institute of Environmental Health Science's National Toxicology Program (NTP). The 13th report lists a total of 243 substances, with 56 substances as known carcinogens and a further 187 identified as reasonably anticipated to be carcinogens.

The report identifies one new substance as a known carcinogen and classifies three new substances as reasonably anticipated to be a known carcinogen. Two of these newly listed substances, ortho-toluidine and cumene, are chemicals found in tobacco smoke.

For each listed substance, the report contains a substance profile which provides information on (1) the listing status; (2) cancer studies in humans and animals and studies of biologic mechanisms and other data relevant to carcinogenicity; (3) the potential for human exposure to these substances; and (4) federal regulations to limit exposures. A listing in the report

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Environmental Health *(Continued from page 7)*

indicates a cancer hazard, but does not by itself mean that a substance will cause cancer.

The new substance now identified as a known carcinogen by the ROC is ortho-toluidine, used to make rubber chemicals, pesticides, and dyes. It is also found in tobacco smoke. The chemical was previously identified in the ROC as a potential carcinogen, but new research led the NTP to reexamine and reclassify ortho-toluidine as a known carcinogen based on human studies showing that it causes urinary bladder cancer.

Cumene, a flammable liquid and natural component of petroleum, is one of the three new substances identified as reasonably anticipated to be a carcinogen that can be inhaled through tobacco smoke. Exposure also occurs through the air, via auto emissions or gas spills and in workplace exposure through its manufacture as a paint solvent. Between 1990 and 2012, there were approximately 180 oil spill incidents in the U.S. in which cumene was released into the air. The NTP found that inhalation exposure to cumene causes lung tumors in both sexes of mice and liver tumors in female mice.

One of the two final chemicals identified as reasonably anticipated to be carcinogens, 1-bromopropane, has been found to cause lung and other organ tumors in animals. The chemical is used as a solvent in many commercial industries, including dry cleaning.

“This report provides a valuable resource for health regulatory and research agencies, and it empowers the public with information people can use to reduce exposure to cancer causing substances,” says Linda Birnbaum, PhD, director of the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP).

The 13th Report on Carcinogens is available at ntp.niehs.nih.gov/go/roc13. ■

RESEARCH OPPORTUNITIES

NCATS Opens CTSA Awards; Deadline Extended Until January 2015

In September, NCATS released its new funding opportunity for the Clinical and Translational Science Awards (CTSA). The CTSA program supports a national network of more than 60 medical research institutions aimed at advancing clinical and translational science and training. NCATS has also extended the original application deadline until Jan. 15, 2014.

Following a 2013 Institute of Medicine report that recommended changes to make the program more effective and efficient, the CTSA program is now incorporating these new goals into its operation:

- Greater alignment between the CTSA program and the NCATS mission of understanding and improving the translational process;
- Building a collaborative, national network to achieve strategic translational science goals;
- New initiatives to train a new generation of scientists with the special skills and knowledge required for clinical translation, including team science; and
- Accountability with evaluation using defined criteria for measurement, deliverables, and metrics.

The CTSA funding announcement can be found at: ncats.nih.gov/research/cts/ctsa/funding/funding.html. ■

NEWS FROM NIGMS

NIGMS Embarks on New Strategic Planning Process

The National Institute of General Medical Sciences (NIGMS) has recently begun a process to develop a new strategic plan for the institute to guide its work for the next five years, beginning in 2015, and respond to the changing biomedical research environment. NIGMS supports basic biomedical research aimed at advancing our knowledge of biological processes and research training. The institute has initiated the strategic planning process with the release of a draft statement of goals and objectives that it is inviting feedback on from the public. The five draft goals are:

- Support investigator-initiated biomedical research that drives fundamental scientific discoveries to advance our understanding of human health and disease.
- Support the development of a highly skilled, creative and diverse biomedical research workforce.
- Support the development of and access to essential research tools, resources and capabilities for biomedical research.
- Advance understanding of the NIGMS mission and its role in the biomedical research enterprise.
- Promote the efficient and effective use of human resources and business practices to advance the NIGMS mission.

The NIGMS will be releasing a full draft strategic plan for stakeholder review in the coming months. To view the strategic planning framework and news on the forthcoming strategic plan, visit: publications.nigms.nih.gov/strategicplan/. ■