TOMORROW'S MEDICINES:
Will Translational Science *Lead the Way*?

Translational science is an integral, innovative approach in which knowledge and information are seamlessly brought from the laboratory to the patient bedside and back again. This methodology enables researchers to convert medical findings into clinical practice quickly and efficiently to improve patient care, enhance decision-making and create the next generation of therapeutic breakthroughs.

On November 17th, a distinguished panel of government, regulatory and academic representatives, including members from the U.S. Food and Drug Administration (FDA) and National Institutes of Health (NIH) gathered at the New York Academy of Sciences to discuss the meaning, challenges and promise of translational science in guiding the future of medicine.

KEY QUESTIONS:

- How can industry, academia, and regulatory agencies begin to share data more effectively?
- What can the FDA do to promote translational science?
- What can be done to reduce the high cost of developing new therapeutics?
- How can patient advocacy groups contribute to translational science?
- What modifications to the intellectual property landscape could be made to encourage more sharing of information?
- What does the future hold for translational medicine?

Discussion panelists included:

- **Barbara M. Alving**, MD, Director, the National Center for Research Resources (NCRR) at the National Institutes of Health
- **ShaAvhree Buckman**, MD, PhD, FAAP, Director, Office of Translational Sciences, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- **Garret A. FitzGerald**, MD, Chair, Department of Pharmacology and Director, the Institute for Translational Medicine and Therapeutics, University of Pennsylvania
- **Laura K. Richman**, DVM, PhD, Vice President, Research and Development-Translational Sciences at MedImmune, the biologics unit of AstraZeneca
- **Ruth E. March**, PhD, Personalized Healthcare leader, AstraZeneca, UK
- **Orla Smith**, PhD, Managing Editor, *Science Translational Medicine*

CROSSING THE DIVIDE

Pharmaceutical companies have decades of expertise developing therapeutics through a multi-year process that includes toxicology studies, human clinical trials, drug formulation and other steps. This model has resulted in the development of thousands of therapies that help patients and satisfy company shareholders.

Yet for all the successes of this model, many new biological discoveries remain untapped as human therapeutics. Biotechnology and pharmaceutical companies face unprecedented marketplace pressures, multi-billion dollar costs for developing new drugs, and a drug development process that can last for 15 years or more, all of which allow for promising leads to be lost or delayed.

However, an emphasis on translational science focuses on providing funding, training and tools to bring basic discoveries through the formulation and testing stages to reach patients faster. Yet the feat is not as simple as it seems. At its heart, translational science involves convincing academic researchers, industry scientists and clinicians to change their very way of thinking. It also involves providing the right incentives for bench-to-bedside development while breaking down barriers to the sharing of information.

The translational effort is embraced by numerous companies, academic institutions, regulatory agencies, patient advocacy groups, health insurance companies and government funding agencies. All parties have an interest in reducing costs, improving efficiencies, and bringing medicines to patients in timely manner. "Translational science means always looking ahead to the next step," said Dr. Alving, "so that we can translate the richness that comes from basic discovery and basic research in which we invest so much."

TRAINING SCIENTISTS TO CROSS THE TRANSLATIONAL DIVIDE

One of the factors hampering the translation of biomedical discoveries has been the differing aims of scientists in academia, industry and patient care. For the academic scientist advancement comes from publication in prestigious journals – not from moving a discovery toward the marketplace. The academic scientist often has a five-year time commitment for each project since many grants last that long. In contrast, a scientist at a biopharmaceutical company may spend three times as many years working on a drug candidate. Clinicians, meanwhile, may not have the time or interest to follow biomedical research or to think about how their patients can participate in clinical research.

To help academic scientists, industry scientists, and clinicians bridge the gap, the National Institutes of Health, under former NIH-director Elias Zerhouni, stepped in to establish up to 60 Clinical and Translational Science Centers (CTSCs) across the nation. The NIH has committed $500 million annually to provide the infrastructure and personnel training to move basic science discoveries into animal models and clinical trials and then out into the community.

"We're developing better and more efficient ways to conduct clinical research to bring in participants in clinical trials and then to engage the community," Dr. Alving said.

An early leader in recognizing the importance of translational research was Dr. Garret FitzGerald, director of the Institute for Translational Medicine and Therapeutics (ITMAT) at the University of Pennsylvania. He noted that one important component is the cross-disciplinary approach, bringing in schools such as engineering, law, nursing, and the veterinary school. Another focus is integration of specialties across the pediatric and adult hospitals.

TRANSLATIONAL SCIENCE AND PERSONALIZED MEDICINE

Translational science is more important than ever in the era of personalized medicine, where therapeutics are matched to a person's genetic background or individual disease state. Personalized medicine can help increase the effectiveness of a therapy and reduce its toxicity. "The central paradigm here is ensuring that the right patient gets the right drug at the right time," Dr. March said.

Diagnostic tests and decision trees are an essential part of determining which patients need certain drugs. As only a subset of the population will respond to the medicine, the patient population and the market for a personalized therapeutic may be small. Translational science can help biopharmaceutical companies develop such drugs in a targeted, cost-effective manner. "Personalized medicine, if it's done properly, can be a win-win situation," Dr. March said. "Patients get the medicines that they need, and industry gets the return on investment that it needs."

THE PATIENT PERSPECTIVE

No factor could be more critical in drug development than the patient. Patient advocacy groups serve as resources for information and funding of translational research. Their members may donate tissue samples or serve as volunteers in clinical trials. These groups are vocal advocates for drug development. "They are driving personalized healthcare," said Dr. March. "They want drugs for their patients, their particular conditions – they want to know which medicines work, which don't, and they are really asking us why we are not going faster with this."

In the past, companies had little incentive to develop therapies for neglected and rare diseases. Patient groups have helped reshape this landscape so that companies and funding agencies are listening to patient needs. Often, developing a therapy for a disease that affects few can lead to basic insights that can help many.

"Patients are the most important component of the drug discovery process," Dr. Smith said. "Clinical observations in patients about disease progression and disease causes can inform researchers at the bench and help them to refine their experiments."

SHARING INFORMATION

Speeding up the transition to applied therapies also could be helped by greater sharing of data among scientists, more communication with regulatory agencies, novel reward structures, and a reconsideration of the incentives provided by intellectual property (IP) laws. "There are many unmet challenges but we are starting to address them," Dr. Smith said. "One of the biggest is breaking down the silos between the different stakeholders, such as the researchers in academia and industry, the clinicians, the patients, the patient advocacy groups, funding agencies, the people who coordinate clinical trials, and regulatory agencies at all levels."

"The intellectual property barrier can be overcome through novel agreements and consortiums," Dr. FitzGerald remarked, noting that the goal is "to expand what's called the precompetitive space – the space where we can pursue knowledge without impinging on issues relating to fundamental intellectual property. I think that is absolutely vital if we're going to permit industry and academia to interact in a more fruitful way."

A number of consortia have formed that have agreed to share information under novel IP agreements. In the area of neglected diseases, for example, parties have been willing to collapse their intellectual property barriers and to share information in a timely manner when given the incentive of obtaining funding contributed by governments, foundations, and companies. "There's a real need for partnership, not just among pharma and biotech and academia but also with the regulatory agencies. Because we're all quite interlocked in meeting this challenge," Dr. FitzGerald explained.

Breaking down the barriers to communication is an essential part of FDA's efforts to encourage translational science, Dr. Buckman noted. "One of the programs that we started in the Center for Drug Evaluation and Research a few years ago is a voluntary exploratory data submission program where companies, academics, sponsors, can come in the door to have open discussions with us outside of the regulatory review formal process to talk about data that they have that may have an impact downstream on drug development." Last month, the FDA released a guidance document on the use of drug development tools.

The sharing of information between industry and institutional partners is already underway at several biopharmaceutical companies, including AstraZeneca. "We have partnerships in AstraZeneca that have been progressing for many years," Dr. March said. "For example, we have partnerships with the Karolinska Institute in Sweden and with the Banner Institute in the U.S., which are about developing a new imaging technique for understanding what is going on in the early disease process for Alzheimer's disease. We are trying to understand what is going on with that disease process and develop imaging agents that could be potentially coupled with an early-acting, disease-modifying drug."

Dr. Richman noted that at the end of the day, "we realize we can't do it in isolation. We have to partner with the academic centers because they have expertise we don't."

NEW TOOLS

The basic tools of translational medicine have been *in vitro* studies, studies in animal models, and clinical trials in humans. Animal studies and clinical trials require highly-trained personnel and an enormous capital investment, so wherever possible, industry and regulatory agencies are working together to find viable replacements for resource intensive studies. Dr. Alving noted, for example, that the NIH is compiling a searchable database of animal models that researchers can use to avoid duplicating the efforts of others.

One way investigators can avoid duplication of efforts and increase accuracy is by identifying biomarkers – biological signatures that can be obtained from blood, urine, tissue or another biological sample from the patient. Biomarkers can be used to monitor a number of factors, including tracking disease progression, determining therapeutic efficacy and evaluating safety, or finding out whether a patient is likely to respond to a particular treatment.

For instance, MedImmune has developed a test to identify which patients are most likely to benefit from sifalimumab, an anti–interferon-α monoclonal antibody intended to treat Systemic Lupus Erythematosus (SLE). The test is based on a peripheral blood sample, and it looks for an interferon gene signature, which indicates patients who will likely respond to the drug. "What industry has realized is that it is really critical to develop companion diagnostics in tandem with the drug, rather than after drug development," said Dr. Richman.

Conversely, social networking and informatics will increasingly play a role in recruiting trial participants and in collecting and managing patient data. Informatics systems are needed to keep track of patient samples collected early in the disease process. "Rapid diagnosis at the bedside could help physicians select the correct medication before a dangerous infection or disease can progress. "There are many, very neat and exciting technologies that are being developed that are now being included in our clinical trials and that we feel are going to make a difference to patients," Dr. March said.

Clinical trial design also could be enhanced to capture better the therapeutic benefit of a novel drug. For example, the discovery that aspirin can reduce the risk of heart attacks was obscured for years because studies were done in the general population rather than in a population enriched in those susceptible to drug action – those suffering from a form of chest pains (unstable angina). "We design trials to test treatments assuming everybody's the same. Well, they're not the same," Dr. FitzGerald said.

In closing, the success of translational medicine will come from the new generation of scientists now being trained to "understand the pathways and to include community engagement," Dr. Alving said. Dr. Buckman added that, from the FDA's perspective, the biggest return will come from data sharing. "Human capital" should be at the top of the list of factors crucial to success of translational medicine, Dr. FitzGerald remarked. "I think we've allowed the number of people who understand how to integrate basic and clinical science and have an understanding of how drugs work, to drop to a critically low level," he said. "We've got to correct that."

The focus on personalized medicine will be essential in the future of translational science. "I strongly believe that we will have a dramatic increase in the number of drugs that are coming to market, which are tailored to specific patient populations using diagnostics and other types of tests," Dr. March predicted. Dr. Richman added that, "asking the right questions early on and then focusing those questions on the clinical trials and the patients is where we can win in bringing the right drugs to the right patients."

The new focus on translational science is essential for moving basic research discoveries from the laboratory to the patient. But, the panelists noted, patients need to remain front and center in the whole process.

– Reported by Catherine Zandonella, MPH

To access the webcast of the press forum "Tomorrow's Medicines: Will Translational Science Lead the Way?", please visit **www.nyas.org/tomorrowsmedicine**

For more information about the New York Academy of Sciences' Translational Medicine Initiative and upcoming events please visit **www.nyas.org/TransMed**

MedImmune

The New York Academy of Sciences