In medical, graduate education explored

BY BILL SNYDER

Diversity. Inclusion. Excellence. Innovation. You can’t have one without the others.
That was the take-home message from last week’s Flexner Discovery Lecture on the importance of diversity and inclusion to medical and graduate education and research.

“Diversity makes us more innovative,” said André Churchwell, M.D., Chief Diversity Officer for Vanderbilt University Medical Center (VUMC).

“Being inclusive is inherent to excellence,” added Linda Sealy, Ph.D., director of the Vanderbilt Initiative for Maxi-

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Study reveals new clues to cystic fibrosis ‘gender gap’

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A research team led by structural biologists from Vanderbilt University has come up with the first detailed molecular explanation for a factor that may contribute to the so-called cystic fibrosis (CF) “gender gap.”

There is evidence that women with CF die on average two to three years earlier than do men with the devastating lung airway disease. The researchers said their findings, which were published in Science Advances, an offshoot of Science magazine, may lead to improved treatments for CF.

“We think we may be illuminating an important mechanism that contributes to women succumbing earlier to cystic fibrosis,” said Charles Sanders, Ph.D., professor of Biochemistry and Medicine and the Aileen M. Lange and Annie Mary Lyle Professor of Cardiovascular Research at Vanderbilt.

A collaborative team of structural biologists and channel biophysicists that included Sanders and Vanderbilt post-doctoral fellow Brett Kroonke, Ph.D., the paper’s first author, focused on a potassium ion channel called KCNQ1, which in the lung is regulated by a protein called KCNE3.

Cystic fibrosis is caused by mutations in a gene encoding the CF transmembrane conductance regulator (CFTR), an ion channel that normally maintains proper salt balance in the lung. Both males and females can inherit mutations in the
Past research showed that centers performing fewer than 14 heart transplants or less than 20 lung transplants each year had increased patient mortality rates.

The study model used information from 12,594 heart transplant patients from 135 medical centers and 12,300 lung transplant patients from 67 centers in the United States.

The computer algorithm divided the continental United States into 11 regions as defined by UNOS and "began figuratively "closing" the center with the lowest number of transplants per year in each region," reads the study. "The algorithm essentially referred all patients from the 'closed' low-volume center to the largest one in that region and assigned those patients the largest center's reported mortality rate. This process was repeated until either five centers had been closed, or only one transplant center in a given region was left," the authors wrote.

The end result and the magnitude of the benefit surprised Shah:

"The conclusion of the study showed that closing programs would benefit patients and save lives," he said. "It brings key issues to the forefront, including how to have a very sober and candid conversation about how to deliver thoracic transplant care in the U.S. and how to delve into the elements that experienced centers utilize that are providing best patient outcomes.

"It's really a policy discussion that goes beyond individual transplant centers. We are trying to contribute to the larger conversation about best practices, policy and health care."

— Ashish Shah, M.D.

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CFTR gene, but the female hormone estrogen may make matters worse.

Normally CFTR function is supported by the potassium ion channel KCNQ1, when it is locked in its open position by its regulatory protein, KCNE3. But when estrogen stimulates attachment of a phosphate group to KCNE3, the protein can’t do its job.

"As a result, when the channel should be open, struggling to help restore an already disrupted salt balance, it doesn’t do that," Sanders said. "This may make an already unfortunate situation worse in a gender-specific manner."

The researchers used sophisticated techniques, including nuclear magnetic resonance (NMR) spectroscopy, electrophysiology and computational modeling, to create the first three-dimensional model for how estrogen, by interfering with the KCNQ3/KCNQ1 complex, disrupts channel function.

In the heart, mutations in the regulation of the same potassium ion channel are associated with long QT syndrome, which increases the risk of life-threatening cardiac arrhythmias.

"The model of the channel that we developed can now also be applied to long QT syndrome and other disorders that are associated with this channel," Sanders said.

Sanders, one of the paper’s three corresponding (senior) authors, said the paper "illustrates the power of the integrative approach to structural biology, which has been wholeheartedly championed by Vanderbilt’s Center for Structural Biology."

"It relies heavily on experimental work using NMR spectroscopy, biochemistry, electrophysiology and a very heavy dose of computational modeling," he added. "Without all of these things coming together, this project would not have happened."

The other corresponding authors were Wade Van Horn, Ph.D., of Arizona State University in Tempe, and Carlos Vanoye, Ph.D., of Northwestern University Feinberg School of Medicine in Chicago.

Other contributors included Jens Meiler, Ph.D., professor of Chemistry and associate professor of Pharmacology and Bio-medical Informatics at Vanderbilt, and Alfred George, M.D., chair of Pharmacology at Northwestern and former director of the Division of Genetic Medicine at Vanderbilt.

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