Circulation

CARDIOLOGY NEWS

From the Literature

Tracy Hampton, PhD

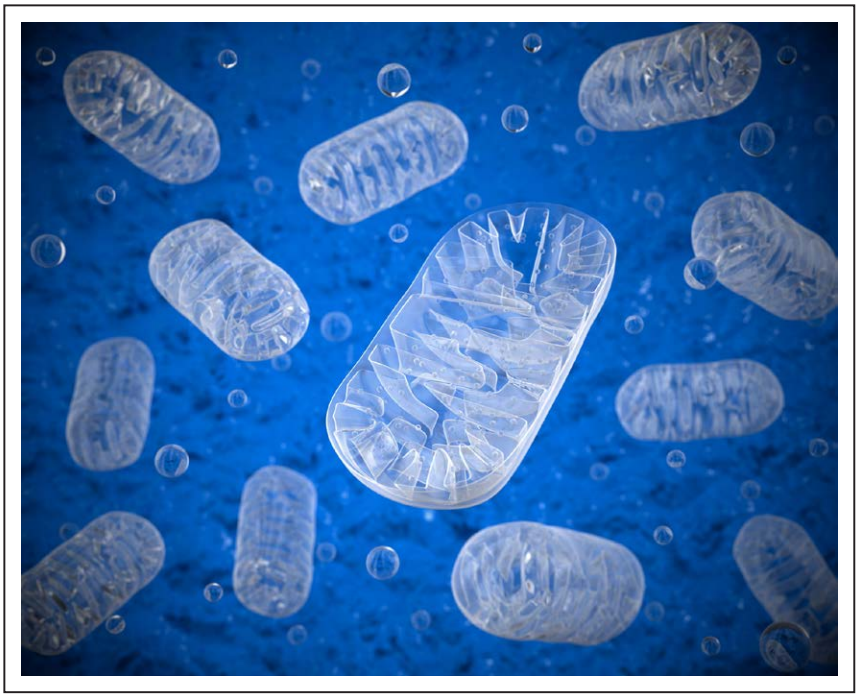
Semisynthetic Organism Creates Nonnatural Proteins

Researchers who previously developed a semisynthetic strain of the bacterium *Escherichia coli* with a genetic code containing 2 unnatural nucleotides in addition to the 4 natural nucleotides of DNA have now shown that the bacterium efficiently transcribes and translates both the natural and unnatural nucleotides to synthesize protein.

The use of organisms to make nonnatural proteins, as demonstrated in this latest research published in *Nature*, may pave the way for scientists to engineer novel therapeutics or protein drugs, plastics, and other materials that take on new functions such as the ability to degrade pollutants or toxic molecules or to target and destroy specific tissues or cell types in the body.

The research also offers new conceptual information that could change how scientists view biology. "Forever it has been argued that the molecules of life are somehow special and different from other types of molecules. This has often been based on religion, but also, the idea has remained common among scientists because it seems that biology is so complex and that evolution must have tailored them over billions of years," said senior author Floyd Romesberg, PhD, of The Scripps Research Institute, in La Jolla, CA. "We demonstrated, for the first time, that this may not be true. Our man-made part—the unnatural base pair—can function in what is arguably the most intimate of all biological processes: the storage and retrieval of information."

Dr Romesberg noted that it did so without hydrogen bonds, which are the forces that underlie the function of natural base pairs. "So our work would seem to suggest that not only are the natural alphabet and code not the only possible solutions, but they also suggest that the mechanisms and forces that nature uses are not the only ones possible," he said.



A new technique predicted cardiac arrest in rodents by measuring whether oxygen is reaching the mitochondria of heart cells.

Monitoring Mitochondria May Help Predict Cardiac Arrest

A new laser-based device may help determine whether the heart or other organs and tissues are receiving enough oxygen. In a study published in *Science Translational Medicine*, the technique predicted life-threatening cardiac arrest in rodents by measuring whether oxygen is reaching the mitochondria, the organelles that provide cells with energy.

Using laser light and resonance Raman spectroscopy, the device measures how light is scattered when the

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laser is shined on mitochondrial cytochromes and other proteins involved in the electron transport chain that generates energy. Under low-oxygen conditions, extra electrons accumulate, causing chemical bonds in the porphyrin rings of the proteins to bend and stretch, making the proteins scatter light differently. A complex algorithm produces a real-time metric that the study investigators call the resonance Raman reduced mitochondrial ratio (3RMR).

By monitoring the 3RMR of mitochondria in the cells on the surface of the heart, investigators could detect deficiencies in the electron transport chain and predict impending decrements in cardiac contractility. They found that a 3RMR value exceeding 40% predicted subsequent cardiac arrest in rodents with 95% sensitivity and 100% specificity, outperforming all current measures. In pigs undergoing cardiopulmonary bypass surgery, 3RMR increased progressively during the ischemic period and then dropped to baseline levels within minutes of reperfusion.

"I believe that this technique will, for the first time, allow us to examine the health of any tissue that we can see with our eyes. This will be useful in the resuscitation of patients with global disorders of oxygenation, including septic, hemorrhagic, or cariogenic shock, where it may represent a new target for resuscitation," said senior author John Kheir, MD, of Boston Children's Hospital and Harvard Medical School. "It may help us to monitor the health of the myocardium during an operation, knowing when to redose cardioplegia solution, for example, or may help us to understand ischemia-reperfusion injury in new ways. In the short term, this technique will help us to determine the health of the myocardium following congenital heart surgery, serving as an early warning sign of insufficient oxygen delivery to the heart muscle itself."

Research Examines Sex-Specific Cardiovascular Differences

In an effort to understand sex-specific cardiovascular variations that might help explain differences in the development, presentation, and outcome of cardiovascular disease in men and women, investigators from the University of Colorado recently analyzed contractility in the whole rat heart, adult rat ventricular myocytes (ARVMs), and myofibrils from both sexes.

As reported in a *Circulation: Cardiovascular Genetics* study, the researchers found that hearts and ARVMs from female rats displayed greater fractional shortening than male hearts and that female ARVMs and myofibrils took longer to relax.

RNA sequencing of ARVMs from male and female rats revealed ≈600 genes that were expressed in a sexually dimorphic manner, with many involved in various signaling pathways. At the protein level, female ARVMs exhibited higher protein kinase A activity, consistent with pathway enrichment identified through RNA sequencing.

"We found functional differences between the sexes in the whole heart all the way down to the basic cardiac contractile units of cardiac muscle cells. To understand how these functional differences came to be, we found that many genes were expressed differently in male and female hearts," said senior author Leslie Leinwand, PhD. "Even in the absence of any disease, the hearts of male and female animals exhibit fundamental differences that could easily influence disease development as well as the efficacy of drug treatments. We are encouraged by the recent National Institutes of Health initiative to make inclusion of both sexes required for basic research studies," added lead author Christa Trexler, PhD. ■

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