From Brain Imaging to Chemical Probes

Grants enable advanced technologies.

Looking at a photograph or tapping fingers to a tune sends signals to certain areas of the brain, increasing blood flow to those regions. Changes in blood flow and, more precisely, in the amount of oxygen, can be detected by functional magnetic resonance imaging (fMRI), an increasingly popular technique for probing the working human brain. John Gore, director of the Vanderbilt University Institute of Imaging Science in Nashville and world-renowned expert in the technology, has used fMRI to determine which parts of the brain "light up" when, for example, schizophrenic patients experience hallucinations or alcoholics have cravings.

John Gore, director of Nashville's Vanderbilt University Institute of Imaging Science, received a $2 million award to support the purchase of a 7-tesla human magnetic resonance imaging and spectroscopy system. It provides the highest magnetic imaging available for humans and is one of only several such instruments in the country.

Whereas fMRI gives insights into how the brain functions, another sophisticated technology tells researchers about the activities of tiny molecules. Nuclear magnetic resonance (NMR) spectroscopy exploits the magnetic properties of atomic nuclei to provide three-dimensional molecular structures. Maurizio Pellecchia of the Burnham Institute for Medical Research in La Jolla, Calif., has taken NMR spectroscopy to a new level by using it to study how proteins interact with one another and with other molecules. The information suggests how interactions among different molecules in the body generate signals necessary for biological processes and functions.

Both Gore's and Pellecchia's pioneering research recently got a boost through NCRR's High-End Instrumentation (HEI) Grant Program. Established in 2002, the HEI Program helps researchers purchase expensive equipment, such as imaging systems, high-end microscopes, supercomputers, and spectrometers, by providing anywhere from $750,000 to $2 million toward the cost. To date, NCRR has awarded 101 HEI grants and 2 supplements totaling $155.8 million. The most recent round of 14 awards, including those to Gore and Pellecchia, was announced in June. "Researchers can ask questions they could not ask before. They can do amazing experiments only possible with the new equipment," says Marjorie Tingle, director of the HEI Program. "The new instruments have much higher resolution and unsurpassed sensitivity."

Indeed, thanks in part to $2 million in support from NCRR, Gore's Vanderbilt University Institute of Imaging Science now houses a 7-tesla (7T) MRI scanner—the largest and most powerful MRI instrument currently available. Because of its greater magnetic strength, the new 35-ton scanner offers a more sensitive measure of changes in brain activity. It also provides higher resolution, giving researchers even more detailed pictures of the brain. Thus researchers can get a better idea of which areas of the brain are involved in complex behaviors or diseases.

PHOTO BY DANA JOHNSON, COURTESY OF VANDERBILT UNIVERSITY MEDICAL CENTER

The new 7T MRI scanner is bolstering the work of about 30 Vanderbilt researchers studying developmental disorders, learning disabilities, and psychiatric disorders such as schizophrenia, pathological gambling, and depression. In addition, through grants from NIH's National Institute of Biomedical Imaging and Bioengineering, the imaging institute provides training to graduate students, postdoctoral fellows, and medical residents in state-of-the-art imaging techniques. "We are training more than 50 people in imaging science," says Gore. "This new instrument will be a major flagship for a lot of their work."

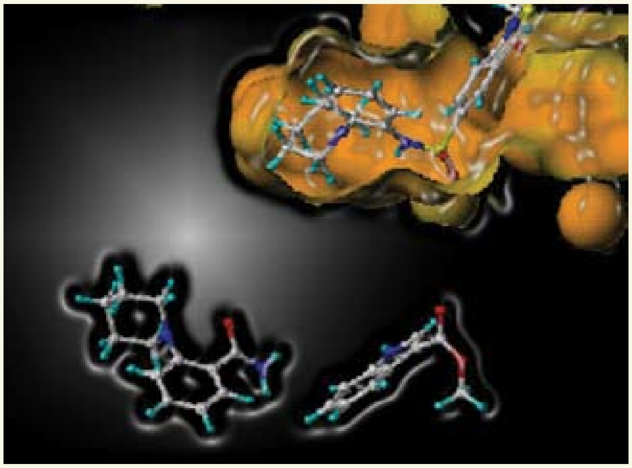
The new scanner will also serve the Meharry-Vanderbilt Alliance for Research Training in Neuroscience, a partnership that grew out of a broader, formal alliance, created in 1998 between Meharry Medical College—a historically black institution in Nashville—and Vanderbilt University Medical Center to foster collaboration on biomedical research, research training, and clinical care. Recent fMRI work within this Alliance has focused on identifying which brain circuits are active in chronic alcoholics and drug addicts during various stages of rehabilitation to understand the neuronal bases of these conditions.

Pellecchia's NMR instrument is also having a far-reaching impact on the work of researchers throughout the country. His group has pioneered using information collected by NMR spectroscopy to design small molecules, called chemical probes, to disrupt interactions among proteins. Doing so may reveal the importance of a particular interaction or pathway to disease and also give researchers a starting point for drug development.

Pellecchia and colleagues recently used the technique to identify chemical probes for the protein Bid, a molecule that causes neuronal cell death and is a suspected player in brain injury and neurological disorders, such as amyotrophic lateral sclerosis, also known as Lou Gehrig's disease.

Traditional drug discovery techniques often look for "downstream" targets of a protein—for example, in the case of an enzyme, the molecules the enzyme modifies. But because Bid is not an enzyme, it is not easily amenable to such approaches. Pellecchia used NMR spectroscopy to understand the structure of Bid and, in particular, the part of the protein that interacts with other molecules. He then used this information to design several chemical probes that stick to Bid, preventing it from finding its "partners." By preventing these interactions from occurring, the chemical probes also prevented Bid from inducing neuronal cell death. After further optimization, these chemical probes will be tested in animal models for their potential use in preventing nerve cell damage due to brain injury and other conditions.

One of the limitations of using NMR spectroscopy is that typically the technique can be used on only one sample at a time. In addition, the amount of sample needed for a single experiment can be substantial, depending on the instrument's signal-to-noise ratio, or its ability to distinguish a true signal from background noise. With the $1.45 million HEI grant, Pellecchia was able to purchase a 700-MHz NMR instrument with an accessory that generates a substantially higher signal-to-noise ratio, reducing the amount of sample needed for a study. The new instrument also comes with an automated sample changer, allowing it to test multiple samples automatically, greatly increasing the speed and efficiency of experiments.



Scientists at the Burnham Institute for Medical Research in La Jolla, Calif., are using nuclear magnetic resonance spectroscopy to probe interactions between small molecules and proteins as a first step in identifying potential drug targets. New instruments, supported by an NCRR High-End Instrumentation grant, will allow more researchers to benefit from the technology.

The new NMR instrument will support several multidisciplinary projects by Burnham Institute investigators focused on infectious diseases and signal transduction in cancer cells. It also will serve, in part, the San Diego Center for Chemical Genomics, as part of an NIH Roadmap Network to accelerate medical discoveries. All NIH-funded researchers can collaborate with members of the Network to identify small molecules that act in their favorite pathway. As Pellecchia points out, the San Diego Center for Chemical Genomics is the only center in the Network that will use NMR spectroscopy. "We are proud of that fact," he says. "And we are thrilled we've been awarded an additional instrument to support research in this area."

—FRANCES MCFARLAND HORNE

IMAGE COURTESY OF BURNHAM INSTITUTE FOR MEDICAL RESEARCH