

# A Timely Partner for SPECT

A new SPECT imaging pharmaceutical that captures the metabolic activity of cardiac cells appears to have the potential to dramatically improve the diagnosis of heart attacks in the emergency room and physician's office.

*By Tim Friend*

A Cambridge, MA, company, Molecular Insight Pharmaceuticals, has developed an imaging pharmaceutical for patients who are seeking care for symptoms related to acute coronary syndrome – which covers any ischemic condition from a heart attack to simple angina. Clinical studies conducted so far suggest that Zemiva™ can detect ischemia as it is evolving and for up to 30 hours after an ischemic event has occurred and normal blood flow has returned.

John Babich, PhD, President and Chief Scientific Officer of Molecular Insight Pharmaceuticals, says that Zemiva is designed to rapidly diagnose myocardial ischemia in the emergency room or in any clinical setting that has access to a conventional SPECT scanner. The SPECT tracer may be especially helpful for the many unwitting heart attack victims who have delayed seeking care at a physician's office or emergency room.

"We believe that there is a significant medical need for the triage of patients with acute coronary syndrome in the emergency department. Today, five to eight million people are admitted to the emergency room complaining of symptoms that may be suggestive of acute coronary ischemia, or myocardial infarction, or an evolving heart attack. Doctors obviously want to make a diagnosis as quickly as possible from the time a person starts having symptoms," says Babich. "For current procedures, a definitive diagnosis with three to four million of these patients can involve several days of tests and hospitalization, delaying critical time to intervention for individuals who require immediate treatment."

Coronary artery disease is the leading cause of death in the United States, responsible for nearly 700,000 deaths annually, according to the National Center for Health Statistics. More than 650,000 heart attacks are reported each year, accounting for more than \$350 billion in direct medical costs. About \$6 billion in hospital costs are associated with the time needed to rule in or rule out ischemia using current diagnostic procedures. In addition, approximately 40,000 patients who have just had a heart attack are sent home prematurely each year due to missed diagnoses.

## Faster Diagnosis Equals Cost Savings

Typically, patients admitted to the emergency room with current or recent chest pain are given a physical examination, a medical history, an electrocardiogram (ECG), and blood tests. The ECG can show whether a patient has experienced a previous heart attack, but the ECG will appear normal in about half of patients who are undergoing a current heart attack. Blood tests can reveal the presence of enzymes, such as troponin or creatine kinase, that are markers for heart cells damaged by ischemia, but they do not provide information about the presence or history of ischemia. Troponin test results also may appear normal at the time of a heart attack and for up to 12 hours afterward.

The usual symptoms that spur a patient to seek medical care – such as chest pain, indigestion, nausea, vomiting, or dizziness – are often nonspecific. And many times patients dismiss their symptoms and do not seek care immediately, making a



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diagnosis even more difficult at a later time. “When we are trying to determine the underlying cause of chest pain, it is challenging, because cardiac symptoms can be vague or mimicked by other conditions, such as gastrointestinal disorders,” says Vasken Dilsizian, MD, professor of medicine and radiology, and Director of Cardiovascular Nuclear Medicine and Cardiac PET at the University of Maryland in Baltimore, USA.

When symptoms and test results are equivocal, patients may be kept in the hospital for repeated blood tests and ultimately a thallium stress test or a perfusion study, using SPECT with one of the new blood flow imaging agents such as Cardiolite®. Babich says several published studies have demonstrated that SPECT imaging of chest pain patients submitted to emergency departments can yield meaningful medical and economic benefits. But conventional blood flow studies are limited by the inherent constraints of current imaging agents. For example, use of these agents is confined to a two-hour window after chest pain symptoms have gone away, he says. Blood flow studies are also limited by their ability to show only ischemia that is currently occurring, adds Dilsizian, who is leading the clinical trials of Zemiva.

### In an Energy Crisis, Time Is of the Essence

Zemiva looks directly at the status of cardiac fatty acid metabolism for the purpose of detecting the direct impact of ischemia on the heart. Fatty acids are the primary fuel that

hearts burn to make energy. Heart cells require a continual and adequate supply of oxygen to burn those fatty acids, Babich says. Oxygen is delivered to the heart by a steady stream of red blood cells via the coronary arteries. When the supply of oxygen-carrying red blood cells is interrupted by a clot or a spasm, or is insufficient to meet a sudden increase in demand through arteries that are narrowed by plaques, the heart will switch to a backup fuel system, namely carbohydrates.

As in any energy crisis, when the main source of fuel is lacking, an alternative fuel is needed. The alternative energy source for the heart is glucose, says Dilsizian. “Nature has put in place a safety valve so the heart can switch back and forth depending on conditions. When things are normal, it uses oxygen to burn fatty acids because they are a very efficient source of fuel. But in anaerobic conditions, the heart can switch to metabolizing glucose.”

Zemiva is the commercial name for beta-methyl-p-[123I]-iodophenyl-pentadecanoic acid (BMIPP). The compound mimics fatty acids and is coupled with the commonly used radioisotope Iodine-123. When it is injected, heart cells that are burning fatty acids will soak up the analog along with I-123, metabolize it, and release photons for the SPECT camera. Heart cells that have been starved of oxygen and are burning glucose do not take up the tracer and subsequently appear as dark or cold areas on the SPECT scan. Testing suggests that images can be taken as soon as ten minutes after injecting the tracer. For conventional perfusion agents, images

are typically not taken until one hour after the injection. Babich says ischemia-induced alterations in fatty acid metabolism persists for up to 30 hours after an ischemic event, even after blood flow is normalized, thus providing up to a 30-hour diagnostic window. If no ischemia has occurred, all the heart cells burn bright for the SPECT cameras and acute coronary syndrome can quickly be ruled out.

### Supportive Research and Clinical Trials

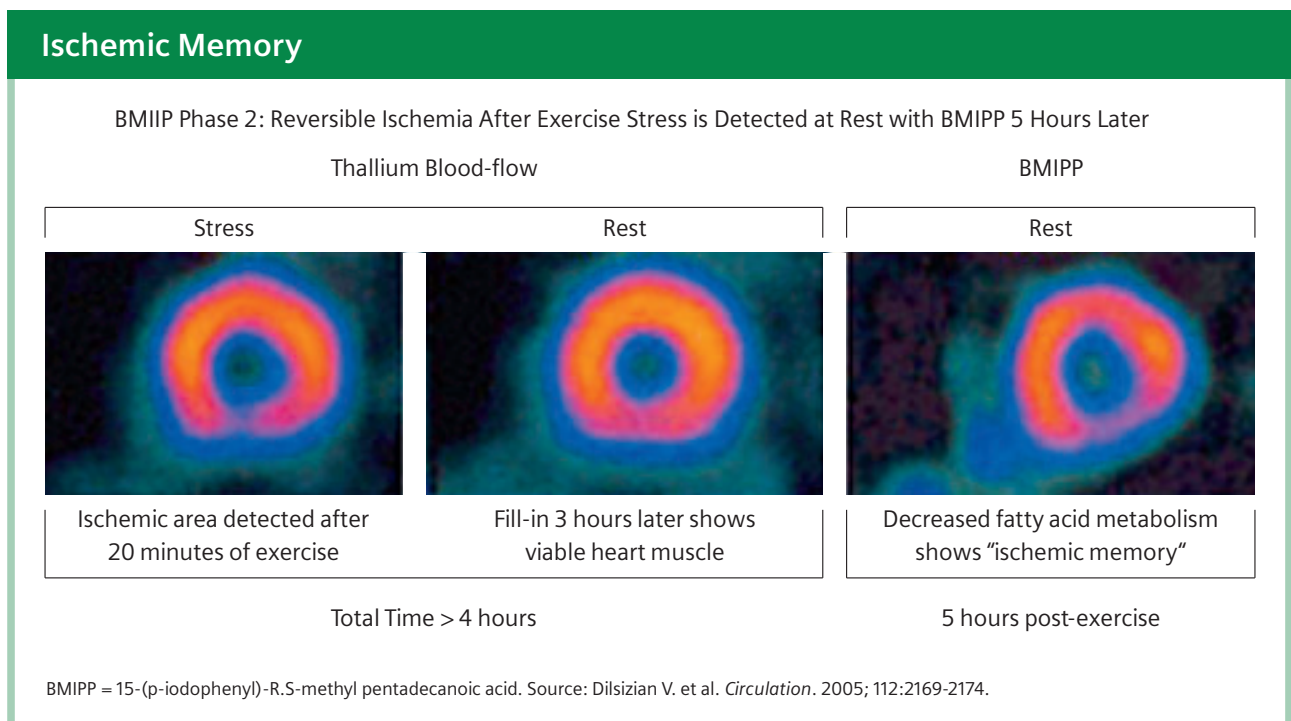
The proof of concept for metabolic imaging of the heart comes primarily from a Phase 2a clinical trial of Zemiva involving 32 patients, published in October 2005 in *Circulation* (2005; 112:2169-2174). Lead investigator Dilsizian and his colleagues performed thallium SPECT scans on 32 patients with exercise-induced ischemia and then conducted a single follow-up scan with Zemiva at different times on each patient over a 30-hour period. They found a close correlation between ischemic areas shown on the thallium scans and ischemic regions depicted by Zemiva scans.

Dilsizian and his colleagues, including Babich, who is a co-author on the paper, concluded that "Metabolic imaging with BMIPP identifies patients with recent exercise-induced myocardial ischemia. We believe these findings support the concept that BMIPP imaging can successfully demonstrate the metabolic imprint of a stress-induced ischemic episode, also known as ischemic memory."

Ischemic memory refers to the persistence of the metabolic signal, which Babich says is like leaving the forensic fingerprints of a heart attack.

"We believe the data demonstrate that Zemiva can detect areas of decreased fatty acid metabolism at rest that parallel defects in cardiac blood flow during stress. The correlation with stress perfusion imaging was noted for up to 30 hours after the stress study was completed and blood flow had normalized," Babich says.

The pivotal registration trials for the emergency department are currently under development and should be launched later this year. If the studies are successful, it will mean that Zemiva could be approved as early as 2009 for rapidly diagnosing myocardial ischemia in any patient complaining of chest pain, whether in the emergency room or physician's office. Babich and Dilsizian agree that a relatively simple 30-minute Zemiva SPECT scan could reduce the need for conventional diagnostic tests, shorten by hours or even days the time needed to make the diagnosis of a heart attack or any ischemic event, and reduce the number of unnecessary hospitalizations. Previous research published in the *Journal of the American Medical Association (JAMA, Dec. 4, 2002, Vol. 288, No. 21)* has stated that perfusion imaging with Tc-99 of patients admitted to emergency rooms with symptoms of cardiac ischemia can reduce unnecessary hospitalizations by 10 percent. Researchers have stated that



radiopharmaceutical cardiac imaging in the emergency room can reduce costly, unnecessary hospitalizations for those with no evidence of ischemia, and decrease the misdiagnosis of more severe cardiac events, allowing high-risk patients to be appropriately treated more quickly.

Other research, according to Babich, has suggested that perfusion imaging of the heart in patients presenting with ischemic symptoms can reduce the number of days in the hospital from 3.8 days to 1.4 days and reduce the cost of care from about \$9,000 per patient to about \$4,500.

## Putting Zemiva into Practice

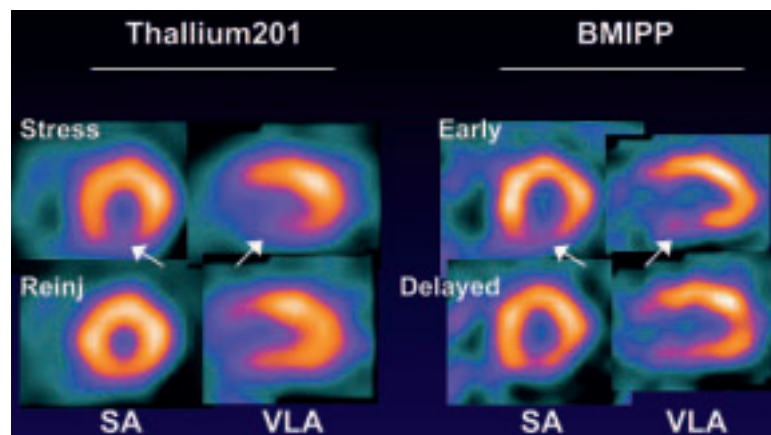
From an infrastructure perspective, Zemiva could be used in most clinics and hospitals without the need for new equipment purchases. Most hospitals and nuclear medicine outpatient clinics already have SPECT scanners that can perform the test. SPECT, like PET, allows direct visualization of various body tissues, such as the heart as it beats.

“Imaging with Zemiva is accomplished at rest, without the need for a stress test, through a 30-minute procedure with standard SPECT cameras. We estimate that the installed base of cameras is approximately 14,000 in the United States, with at least one in all accredited hospitals,” says Babich.

Adds Dilsizian, “Nuclear cardiology as a field has really grown. Almost every large cardiovascular practice now has a SPECT scanner. They’re available in a multitude of private offices.” Zemiva will be designed to be used with standard SPECT imaging cameras. In keeping with the current standard practice of utilizing a reference database of normal images, Molecular Insight Pharmaceuticals is currently developing a database of normal Zemiva heart scans that it plans to incorporate into a software package for the physicians who will be interpreting scans in the clinical setting.

“We have just opened a study to create a normal reference database for Zemiva,” Babich says. “We’re looking to create a database of normal images to allow physicians to see what Zemiva looks like in healthy hearts.” Babich says the project plan is to incorporate volumetric SPECT scans of 60 healthy men and women of different ages and ranges of normal function and size.

Babich, Dilsizian, and their colleagues are already looking toward additional applications for metabolic imaging of the heart. One of the most immediate areas of consideration is for heart failure, which is becoming an increasingly important issue for patients who have survived heart attacks. When blood flow to the heart diminishes slowly over time, the heart decreases demand by reducing its contractions and the amount of blood it pumps out to the body. Experts call this “hibernating myocardium”, because the tissue is still viable and heart function can be improved if blood flow is



A CLOSE CORRELATION between ischemic areas is shown on the thallium scans (left) and ischemic regions depicted by Zemiva scans (right).

increased. But with conventional methods, it is difficult to discern scarred or permanently damaged heart muscle from hibernating myocardium. Babich believes that a Zemiva SPECT scan of the heart could potentially allow physicians to determine whether the metabolic machinery is still functioning and to treat patients accordingly by revascularizing the heart with bypass grafts.

Babich also believes that periodic SPECT scans using Zemiva could be used to monitor drug therapies for heart failure patients and help physicians tailor therapies to the individual potentially more quickly and effectively than current methods. If a drug regimen is working, the heart should be able to resume at least a portion of its ability to burn fatty acids, which would be reflected by the scan.

Other future possibilities include the diagnosis of microvascular disease in women and perhaps screening in combination with perfusion studies for patients with symptoms of coronary artery disease. Dilsizian says he is excited about the potential, but especially for the most immediate application of diagnosing myocardial ischemia.

“Prompt and accurate diagnosis of cardiac ischemia is a national healthcare issue. There is a need for an imaging agent such as Zemiva that may have the potential to impact many levels of healthcare through rapid diagnosis, reduction of unnecessary hospital admissions, and savings in healthcare dollars,” says Dilsizian.

**Author:** Tim Friend is a freelance science and medical writer based in Alexandria, VA. He is the author of *Animal Talk: Breaking the Codes of Animal Language*, and is currently writing a second book on the discovery of a new form of life on earth, due out October 2006. He was a reporter at USA Today from 1987-2003.