

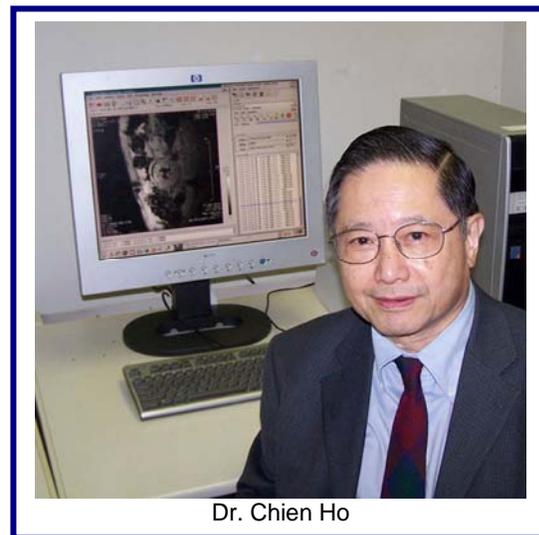


Organ transplants give patients a new lease on life. However, preventing their immune systems from rejecting the organ sometimes presents a challenge. Physicians must strike a balance between suppressing the immune system so that it does not reject the organ and maintaining enough activity to ward off infections. Tracking how well the body accepts the new organ is critical to this process.

The current “gold standard” for monitoring organ rejection is tissue biopsy, an invasive procedure in which a physician removes a small sample from the transplanted organ for testing. Biopsy has two drawbacks: patient discomfort, as the physician must perform the procedure multiple times, and poor selectivity since the biopsy removes tissue from only a limited number of sites, missing rejection starting elsewhere in the organ.

### Tracking Immune Cells

To overcome these limitations, researchers at Carnegie Mellon University are developing a new method to monitor organ rejection using magnetic resonance imaging (MRI). They inject polymer-coated nanometer- and micrometer-sized iron oxide particles into the blood where macrophages – immune cells that scavenge the body for foreign substances – ingest the particles and carry them to rejection sites in the transplanted organ. Because the highly magnetic iron particles can be clearly identified by MRI, researchers then use MRI to track the macrophages.



Dr. Chien Ho

“This technique may provide a way to optimize the administration of immunosuppressant drugs,” says Dr. Chien Ho, alumni professor of biological sciences at Carnegie Mellon University. “If we can detect acute rejection at an early stage, we can prevent irreversible tissue damage and the on-set of chronic rejection, which destroys the transplanted organ.”

### Larger is Better

In a recent experiment, Dr. Ho’s research group transplanted a living heart from one rat into the abdomen of another rat. Researchers injected the iron oxide particles into the host rat, and then performed MRI scans at regular intervals over the next several days as the rat’s body rejected the transplanted heart.

Previously, the researchers had studied mainly nanometer-sized particles, but in this experiment they also studied the effects of larger, micrometer-sized particles. They found that the larger iron particles allowed individual macrophages to be visualized by MRI.

The researchers also observed, for the first time, that the rejection process starts in the pericardium, the membrane surrounding the heart, and spreads inward to the endocardium, the inner lining of the heart.

Dr. Ho notes that the research has wider implications for tracking individual cells. “Tracking cell migration is not only very important in cell and developmental biology, but also in clinical medicine. This method is potentially useful for studying developing stem cells, the migration of cancer cells, inflammatory processes, and gene expression.”

### Potential for Clinical Use

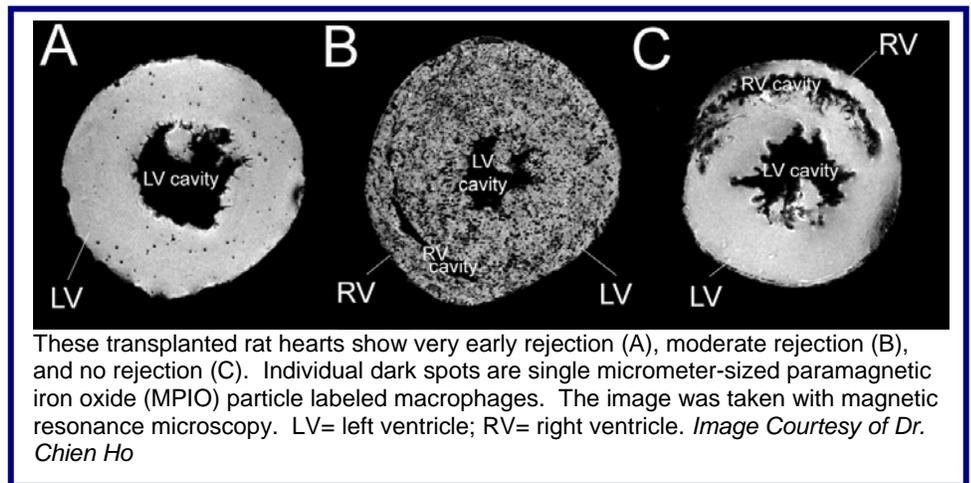
Echocardiography is used in heart transplantation as a screening tool for rejection, followed by tissue biopsy if actual rejection is suspected. But echocardiography lacks specificity. “All you can see by echocardiography is that the graft is not functioning well and that’s a subtle finding,” says Dr. Pedro del

Nido, chair of the Department of Cardiac Surgery at Children's Hospital Boston. "A number of other factors could explain the dysfunction."

The new iron oxide contrast agents may help solve this problem by allowing physicians to visualize actual rejection. "In essence," says Dr. del Nido, "this would give us a noninvasive biopsy. As a clinical tool, this has tremendous potential."

The new contrast agents could also allow investigators to follow the biology of transplantation over time. Currently, says Dr. del Nido,

biopsies provide only "spot checks." "There's a huge sampling problem. For example, we have never been able to look at foci where there is rejection and see how it evolves."



## Challenges to Overcome

Although iron-based MRI contrast agents have great potential, Dr. del Nido cautions that there are concerns about the build-up of iron in patients receiving multiple MRI studies using the specialized imaging agents. "The iron becomes part of the iron pool in the body, like taking an iron pill," says Dr. del Nido. "In adults this is less of an issue, but the question is, in children, will this be the case?"

Monitoring rejection in other organs, such as kidneys, livers, and lungs may also be possible. But using the contrast agents in the liver and lungs will be an imaging challenge. Iron found in the liver, the body's largest iron storage site, can drown out the contrast agent's signal. To use the agents in transplanted lungs, researchers must overcome imaging artifacts created by the organ's many air sacs.

Despite the technical hurdles researchers face, "it is becoming clear that the type of MRI experiment Dr. Ho's group has pioneered in rodents, will become clinically feasible," says Dr. Alan Koretsky, chief of the Laboratory of Functional and Molecular Imaging, National Institute of Neurological Disorders and Stroke, and director of the NIH Nuclear Magnetic Resonance Research Facility/Mouse Imaging Facility.

Koretsky notes that an iron particle contrast agent is being marketed in Europe to measure macrophage accumulation in atherosclerotic plaque, the waxy fat build-up found in blood vessels. "It will be an exciting time to test whether this new ability of MRI to detect macrophage accumulation can translate into useful clinical information. I suspect it will become an important addition to the wide range of parameters that MRI can measure."

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## Reference

Wu, YL et al., In situ labeling of immune cells with iron oxide particles: An approach to detect organ rejection by cellular MRI, Proceedings of the National Academy of Sciences 103: 1852-1857, 2006.