

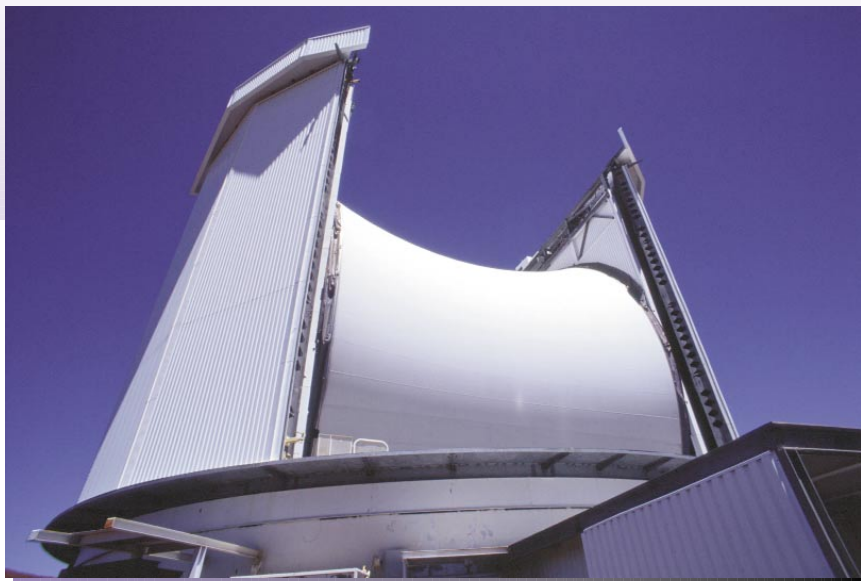


Figure 3. The James Clerk Maxwell Telescope on Hawaii's Mauna Kea. The 15-meter telescope detects radiation in the submillimeter band and houses SCUBA, the Submillimetre Common-User Bolometric Array. (Courtesy of Nik Szymonek.)

frequencies they considered; nonetheless, the researchers turned to the literature for typical emissivities of various kinds of dust. When they plugged in an emissivity appropriate to the diffuse interstellar medium, they estimated that the cold dust in Cas A weighs in at some $20 M_{\odot}$. That's roughly an order of magnitude higher than the maximum value theoreticians predict for a typical supernova.

The dust in Cas A, though, is younger than dust in the interstellar medium by a factor of about 10 000. So it may well be quite different from that material, which has endured numerous cycles of collisions, cloud formation, recycling in stars, and so forth. Emissivities appropriate to clumpy aggregates of dust, or dust in planetary nebulae, are more in line with Dunne and colleagues' best-fit value. Mass estimates based on those emissivities yield 2 to $6 M_{\odot}$ of cold dust. Still, says Edmunds, "It seems almost too much; it's an embarrassment of riches. Maybe the value should come down a bit."

In addition to Cas A, the Dunne team has also observed Kepler's supernova remnant, and hopes to report observations of Tycho's remnant be-

fore long. All three remnants are young and nearby. The group's analysis of its data from Kepler's remnant, to be published in *Astrophysical Journal*, indicates a quantity of cold dust comparable to, if somewhat smaller than, that of Cas A.

SCUBA-2, where are you?

Atmospheric water vapor is the main culprit that makes submillimeter observations difficult. The water absorbs submillimeter radiation and allows astronomers to peer only through certain wavelength windows. The window that includes $850 \mu\text{m}$ is relatively clear; observations through the window at $450 \mu\text{m}$ are considerably more challenging. To minimize the effects of atmospheric absorption, the SCUBA array is located at an altitude of 14 000 feet on Hawaii's Mauna Kea. It comprises more than 100 bolometers; with such a large quantity of individual detectors, the device can generate maps quickly. SCUBA operates at a temperature of 80 mK and its impressive sensitivity is a result of that low-temperature operation. The next-generation SCUBA-2 array, with its more than 10 000

bolometers, is already in the works. Scheduled for delivery to the Maxwell telescope (shown in figure 3) by the end of 2005, SCUBA-2 should provide a factor of at least 100 improvement in speed over its predecessor, along with increased sensitivity.

SCUBA's observations will soon be supplemented by additional measurements. Caltech's SHARC II camera, for example, views radiation at 350 and $450 \mu\text{m}$. Graduate students crafted the acronym to make clear that the Caltech team hopes to give SCUBA a run for its money. A number of cameras, planned or recently launched, will take submillimeter measurements from observatories borne above Earth's atmosphere. Perhaps the most ambitious mission is the European Space Agency's Herschel Space Observatory. Slated for launch in 2007, it should resolve supernova remnants in the 80 to $670 \mu\text{m}$ range.

The observatory was named for William Herschel (1738–1822), musician, telescope builder, and discoverer of the planet Uranus. He's also the discoverer of infrared radiation.

Steven K. Blau

References

1. I. Smail, R. J. Ivison, A. W. Blain, *Astrophys. J.* **490**, L5 (1997); D. H. Hughes et al., *Nature* **394**, 241 (1998); A. J. Barger et al., *Nature* **394**, 248 (1998).
2. S. C. Chapman, A. W. Blain, R. J. Ivison, I. R. Smail, *Nature* **422**, 695 (2003).
3. L. Dunne, S. Eales, R. Ivison, H. Morgan, M. Edmunds, *Nature* **424**, 285 (2003).

Nanoparticles Locate and Flag the Blood Vessels That Nourish Tumors

Ligand-coated droplets of oil can travel through the bloodstream to attach themselves to malignant cells.

Cancer kills its victims when the tumor burden in their bodies reaches about 10^{13} cells. Before then, when a tumor comprises about 10^{10} cells and is the size of a sugar cube, a physician can usually find it in an x-ray

or MRI scan. At that stage, if treated promptly, a victim may survive.

Too often, however, cancer lurks unnoticed until it's past curing. Lack of resolution isn't what frustrates early detection. Clinical MRI and x-

ray machines can resolve features a few hundred micrometers across. Rather, the difficulty lies in identifying a small blob of cells whose combined malignancy is too weak to signal where to look and whose appearance in an MRI or x-ray image is too similar to the surrounding, healthy tissue.

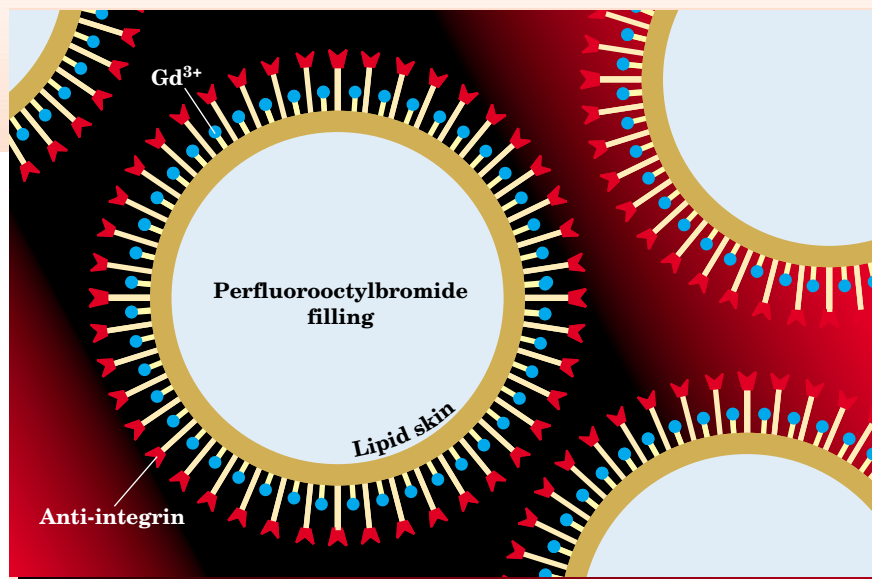


Figure 1. Targeted nanoparticles, shown in schematic cross section, contain liquid perfluorooctylbromide encased in a functional lipid skin.

But at the molecular level, cancer cells look and behave quite differently from healthy cells. They reproduce faster and, as they do so, manufacture certain molecules in far greater numbers.

Among a cancer cell's molecular output are transmembrane proteins called integrins. Integrins take part in angiogenesis, the process by which tumors build networks of blood vessels

that tap into the host's blood supply. Without siphoned nutrients, a tumor can't grow beyond a few tens of cells.

Like some other proteins, integrins can be disabled when antibodies of just the right shape lock on to them. In 1998, Dorothy Sipkins and her collaborators at Stanford University and the Scripps Research Institute exploited integrin's role in angiogenesis and the specificity of its antibodies to create a

new method for flagging tumors.¹

Sipkins's idea was to coat liposomes (artificial, cell-like capsules of fluid) with integrin antibodies and MRI contrast agents. Thanks to the antibodies, the liposomes would attach to the sites of angiogenesis. The contrast agents would act as beacons, boosting and sharpening the MRI signal.

At 300–350 nm across, the coated liposomes qualified—metrically speaking—as nanoparticles. To test them, Sipkins implanted small tumors into the hind legs of rabbits. After giving the tumors time to form new blood vessels, she injected the liposomes into the rabbits' bloodstreams. Twenty-four hours later, the angiogenesis sites showed up in MRI scans.

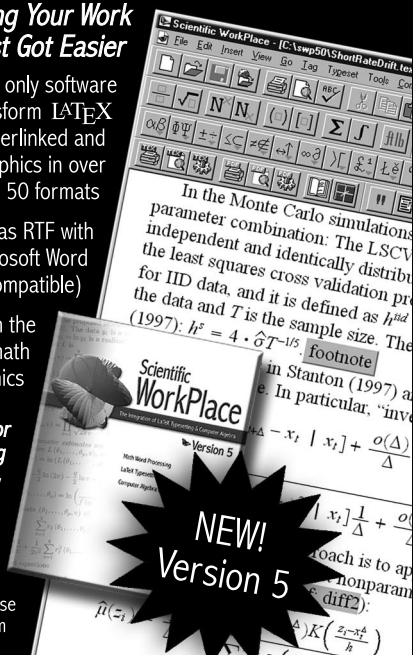
Now, a team led by Greg Lanza and Sam Wickline of Washington University in St. Louis (WUSTL) has extended the technique.² Like the Stanford–Scripps team, the WUSTL researchers coat nanoparticles with integrin antibodies and MRI contrast agents, but instead of liposomes, they

Mathematical Word Processing • L^AT_EX Typesetting • Computer Algebra

ScientificWorkPlace®

*Sharing Your Work
Just Got Easier*

- Typeset PDF in the only software that allows you to transform L^AT_EX files to PDF fully hyperlinked and with embedded graphics in over 50 formats
 - Export documents as RTF with editable math (Microsoft Word and MathType compatible)
 - Share documents on the web as HTML with math as MathML or graphics
- The Gold Standard for Mathematical Publishing**
- Increase productivity
 - Produce stunning documents quickly & easily
 - Typeset documents with L^AT_EX
 - Work with the easiest-to-use computer algebra system



MacKichan
SOFTWARE, INC.

Toll-free: 877-724-9673 • Email: info@mackichan.com
www.mackichan.com/pt
Visit our website for free trial versions of all our products.

Screen text is reprinted from an article in the Journal of Finance.

Circle number 14 on Reader Service card

RGA+Ion Gauge+Pirani
Residual Gas Analyzer Plus.....

Extorr



**Booth
647
Baltimore
AVS**

- *Three gauges on a single probe with a 2 3/4" flange.
- *A small, powerful control package drives the probe.
- *RS232 connection to your computer.
- *Complete operation under Extorr windows software.
- *Immediate startup using the built-in Pirani gauge.
- *Automatic ion gauge operation.
- *Automatic residual gas analyzer operation.
- *Continuous monitoring protects the filament.
- *All is recorded. All is protected. All is monitored.
- *Autoranging, high stability, and high sensitivity.

Three gauges in one extraordinary package.
Extorr is an outstanding vacuum measurement value.

100 amu for \$3450

Extorr Inc.
307 Columbia Road
New Kensington, PA 15068
724-337-3000

Our Website is
www.extorr.com

Circle number 15 on Reader Service card

use an emulsion of nanoscale droplets, which are easier to make and carry more contrast agents. Testing their nanoparticles on rabbits, they see significant MRI enhancement after just two hours.

Lanza and Wickline intend to register the nanoparticles with the US Food and Drug Administration as what the agency calls an investigational new drug. Clinical trials should begin in 2006.

Oil, water, and lipids

Making nanoparticles the WUSTL way is a bit like making salad dressing. Instead of olive oil and balsamic vinegar, Lanza and Wickline use water and an octane derivative called perfluorooctylbromide (PFOB). And instead of a whisk, they use a microfluidizer, a device that forces mixtures through a fine sieve to create an emulsion of nanoscale droplets, shown schematically in figure 1.

The immiscibility of PFOB and water also provides a way to coat the droplets. When mixed with PFOB and water, lipids seek the interface between the two liquids. At the interface, the lipids' hydrophilic heads point into the water, while their hydrophobic tails point into the PFOB. Coating a droplet with functional groups is simply a matter of binding the groups to the lipids' hydrophilic ends, a task that can be done before mixing and emulsification.

For the antibody, Lanza and Wickline use a synthetic peptide. For the MRI contrast agent, they use gadolinium ions. Thanks to their seven unpaired electrons, Gd^{3+} ions are extremely paramagnetic and, following an MRI pulse, can help protons in their vicinity regain equilibrium faster than distant protons. This difference in recovery time (T_1 relaxation time to cognoscenti) shows up as enhanced contrast. The 90 000 Gd^{3+} ions that cover a typical WUSTL nanoparticle speed up T_1 relaxation rates by a factor of a million.

The WUSTL nanoparticles are about 250 nm in diameter. If the particles were much larger, lungs would trap them. If the particles were smaller, they couldn't carry enough contrast agents to enhance images.

Twelve rabbits

During angiogenesis, proliferating cancer cells break through the walls of the host's blood vessels and create holes. The blood that feeds the growing tumor leaks through the holes and through the newly forming vessels.

Because of this leakiness, any nanoparticles, whether studded with

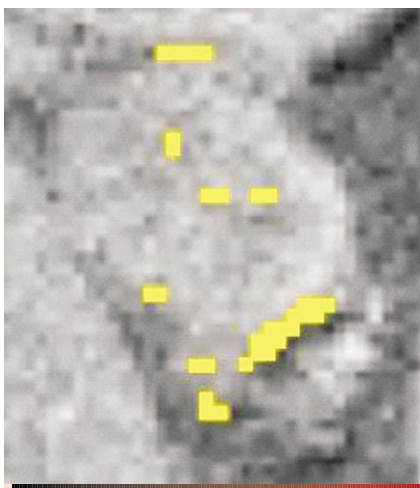


Figure 2. Nuclear magnetic resonance image of a tumor implanted in the hind leg of a rabbit. The yellow patches in this 9×10 mm² image indicate regions of enhanced NMR emission and correspond to the sites of angiogenesis. (Adapted from ref. 2.)

sticky antibodies or not, can make their way out of the bloodstream and pool temporarily around the tumor. To verify that their nanoparticles adhere to the sites of angiogenesis, Lanza and Wickline divided their experimental subjects—12 rabbits—into three groups of four.

The targeted group received integrin-targeted, gadolinium-covered nanoparticles. The control group received nontargeted gadolinium-covered nanoparticles. The competitive blockade group received a dose of targeted, uncovered particles two hours before imaging began. That group then received a dose of targeted, covered nanoparticles.

All 12 rabbits were implanted with a tumor, each about $2 \times 2 \times 2$ mm³ in size. The WUSTL researchers then waited for 12 days before injecting the rabbits with the nanoparticles. That's enough time for a tumor to initiate angiogenesis, but not enough time for it to grow significantly. If physicians could catch such small tumors in humans, the chance of a complete cure would be high.

After a dose of anesthetic, each rabbit was placed in a 1.5-tesla MRI chamber and imaged six times: 30 minutes before dosage, immediately after, then 30, 60, 90, and 120 minutes after. To quantify any image enhancement, the team used the predosage image as a baseline.

At first, the targeted and control groups showed similar enhancement, which the WUSTL team attributes to the leakiness of the blood vessels

around the tumors. But by two hours, as more and more nanoparticles stuck to the tumors, the targeted group had moved ahead to exhibit an average enhancement of 125%.

The competitive blockade group had the lowest enhancement. As Lanza and Wickline anticipated, the first wave of targeted, uncovered particles stuck to the sites of angiogenesis and partially blocked access for the second wave of targeted covered particles.

Under the microscope

Figure 2 shows a typical MRI image from one of the rabbits in the targeted group. In this example, the patches of enhanced contrast appear on the edges of the tumor. In other examples, patches appear close to, but not on, the tumor, as if the tumor were in the process of establishing a vascular bridge.

To confirm that the patches correspond to angiogenesis, the researchers cut out the tumors, then stained, sliced, and examined them under the microscope—a process called histology. The histology provided confirmation.

Proving that targeted nanoparticles can locate and stick to the sites of angiogenesis is important not only for diagnosing cancer, but also for potential therapies. In 1971, Harvard University's Judah Folkman hypothesized that stopping angiogenesis would contain cancer.³ Now, several angiogenesis inhibitors, among them the drugs endostatin and angiostatin, are in clinical trials. And last year, David Cheresh of Scripps and his collaborators showed that integrin-targeted nanoparticles can deliver therapeutic genes to cancer cells.⁴

Testing any anticancer drug involves assessing its effect on tumors. Targeted nanoparticles could do the job without the need for a biopsy. And they don't need MRI. Lanza points out that PFOB is twice as dense as water, which makes it an x-ray contrast agent, and has a sound speed one third that of water, which makes it an ultrasound contrast agent, too. Not bad for salad dressing.

Charles Day

References

1. D. A. Sipkins et al., *Nat. Med.* **4**, 623 (1998).
2. P. M. Winter et al., *Cancer Res.* (in press).
3. J. Folkman, *N. Engl. J. Med.* **285**, 1182 (1971).
4. J. D. Wood et al., *Science* **296**, 2404 (2002). ■