

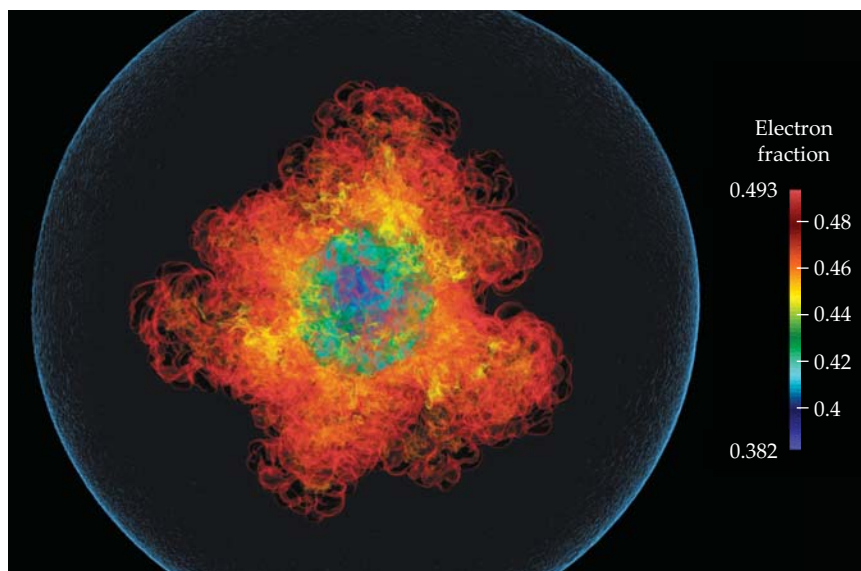


FIGURE 3. NUMERICAL SIMULATIONS SHOW THE SUPERNOVA that results from an oxygen–neon stellar core after the newly measured neon-20 electron capture triggers a thermonuclear explosion. The color key shows the explosion’s electron fraction, which describes whether isotopes tend to be richer in protons or neutrons. For example, iron-56 has 26 protons and 30 neutrons, so its electron fraction is 26/56 or 0.464 and corresponds to the orange regions of the explosion. Iron-60 has an electron fraction of 26/60 or 0.433, corresponding to the turquoise region. The lowest electron fraction achieved in the simulation (blue) is below 0.40, which is 12% lower than regular supernovae. (Adapted from ref 5.)

considering stellar plasma densities of 10^9 g/cm³, electron capture on ^{20}Ne was determined to occur eight orders of magnitude more often than assumed by previous calculations.

Stellar implications

Numerical simulations of stellar evolution that take into account the newly measured Ne–F transition rate suggest that the star’s core begins to generate heat earlier than previous models predicted.⁴ Once the core reaches 1.5×10^9 K, oxygen can fuse with itself; the earlier ignition happens, the higher the likelihood of a thermonuclear explosion.

The resulting supernova, like the one simulated in figure 3, differs from the type II supernova that ends the life of a star more massive than 11 solar masses.

It also differs from the type Ia supernova in which a carbon–oxygen white dwarf fully explodes. It ejects more mass and it leaves behind an iron-rich white dwarf, as opposed to a neutron star or black hole.⁵ The proportion of ejected elements also differs from both other supernova types; it is richer in calcium-48, titanium-50, chromium-54, and iron-60.

By itself, a high Ne–F transition rate isn’t enough to preordain the explosion of a 7- to 11-solar-mass star. The energy released by electron capture on ^{20}Ne may trigger convection in the stellar core. Convection leads to mixing and could delay the onset of oxygen ignition, so that gravitational collapse would be the end of the star. Improved models of convection in the stellar core are needed.

The observation of iron-rich white

dwarfs would clinch the case that the Ne–F transition drives a thermonuclear explosion. Several candidates have already been detected through observations of their atmospheres.⁶ The associated explosions are expected to be characterized by specific spectral features that could, in principle, be observed.⁵

Rachel Berkowitz

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Doubt is cast on a mechanism of cancer nanomedicine

Leaky blood vessels seemed like the perfect conduit to deliver cancer-fighting drugs selectively to tumors. But the reality is starting to look more complicated.

Cancer is a disease of tissue growth gone wrong. Tumor cells proliferate uncontrollably and don’t die as they should. When a solid tumor grows large enough to need to sprout its own blood vessels, those vessels, too, grow irregularly. The tumor vessel networks are tortuous and disorganized (see PHYSICS TODAY, Febru-

ary 2016, page 14), and the vessels’ lining, or endothelium, is riddled with gaps hundreds of microns wide between cells.

The challenge of chemotherapy is to kill off the tumor cells without doing too much harm to healthy ones. The inter-endothelial gaps promised a way to do that. Nanoparticles up to 300 nm in diameter can fit through the gaps, and they can’t permeate normal blood vessels the same way. So nanoparticles loaded with a drug should, it stands to reason, selectively enter and attack tumor tissue but leave healthy tissue alone. An inherently biomedical challenge was seemingly

transformed into one of nanotechnology and fluid dynamics.

A quarter century of nanomedicine research has indeed yielded a few nanoparticle drug formulations that offer better performance or fewer side effects than their molecular counterparts. (See the article by Jennifer Grossman and Scott McNeil, PHYSICS TODAY, August 2012, page 38.) The mechanism of their action, however, has never been fully verified. No technique exists that can image nanoparticles *in vivo*, in real time, and with sufficient resolution to observe the particles slipping through the inter-

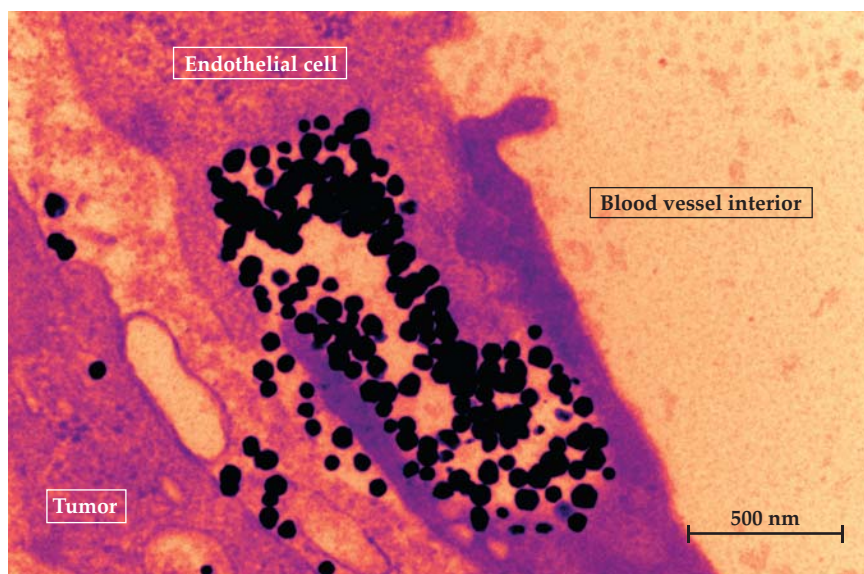


FIGURE 1. GOLD NANOPARTICLES (black) injected into the blood of a tumor-bearing mouse appear in the cytoplasm of the endothelial cells that line the tumor blood vessel; a few have been expelled into the tumor. Nanoparticles have been assumed to enter tumors through large gaps in the endothelium, but no such gap is visible in this transmission electron microscopy image. (Courtesy of Shrey Sindhvani.)

endothelial gaps in a tumor's blood vessels. The idea that they do has always been an assumption.

New research by Shrey Sindhvani, Abdullah Muhammad Syed (both with Warren Chan's laboratory at the University of Toronto), and their colleagues suggests that that assumption might not be correct. Most nanoparticles that end up in tumors, the researchers found, get there by passing through the endothelial cells, not between them.¹

The underlying biological details are still murky. Several possible mechanisms fall under the umbrella of trans-endothelial pathways, and the researchers don't yet know which one predominates or why. For example, individual endothelial cells might engulf the nanoparticles and then expel them into the surrounding tumor, or the nanoparticles might pass through small intracellular pores that open up to exchange nutrients across the endothelium.

What the possible mechanisms have in common, however, is that they're all active cellular processes, so they're sensitive to nanoparticle surface chemistry and composition in ways that a passive physical mechanism isn't. The task of getting nanomedicines into tumors may therefore be a biological one rather than a physical one after all.

Mind the gaps

Chan and his colleagues have been testing the foundations of cancer nanomedicine for several years. In a controversial 2016 analysis of the literature, they found that among all published experiments in

the field, a median of just 0.7% of the injected nanoparticles were delivered to the tumor.² Critics countered that some nanomaterials are delivered in quantities much greater than the median, that even 0.7% of the injected dose might be enough to treat a tumor, and that the amount of nanomaterial detectable in a tumor isn't necessarily the best measure of a drug's effectiveness.³ But as Sindhvani explains, the Toronto researchers had their minds on a more fundamental question: "If there are all these gaps in the blood-vessel lining, why is the tumor accumulation so low? What are these gaps, and how many are there?"

Meanwhile, Sindhvani was also learning about Harold Dvorak's work on trans-endothelial mechanisms that can carry proteins as large as 5 nm into tumors. "That work is relatively unknown in the nano community," he says, "and nobody had looked at its relevance to nanoparticles."

It's relatively straightforward to show that trans-endothelial delivery of nanoparticles to tumors is possible. The researchers injected gold nanoparticles into a tumor-bearing mouse, allowed them to circulate, then extracted slices of the tumor and imaged them with transmission electron microscopy (TEM). Some of the images, including the one in figure 1, showed large caches of nanoparticles trapped in the endothelial cytoplasm, caught in the act of passing through an endothelial cell.

But which of the possible mechanisms predominates? That's a statistical question, and answering it required a lot of data—and a combination of methods.

"It is really challenging to design experiments for looking at what nanoparticles are doing in the tumor," says Syed.

The first step was to determine how many inter-endothelial gaps there really were. The researchers took TEM images of hundreds of blood vessels from both mouse and human tumors, and they trained a team of nine colleagues to identify the inter-endothelial gaps. To reduce bias, they had each image independently evaluated by three randomly chosen team members who didn't talk to one another.

As it turned out, inter-endothelial gaps were surprisingly rare: Images of 313 blood vessels from mice showed just seven gaps in total, or about one per 20,000 square microns of endothelium. Human tumor vessels showed gaps in similarly small numbers. In a fluid-dynamical simulation of 50 nm nanoparticles, the observed density of gaps could account for just 1–2% of the already small number of nanoparticles known to reach the tumors.

Zombie mice

The researchers also wanted an experiment that could distinguish passive from active nanoparticle transport. For that, they developed a mouse model they called Zombie. Tumor-bearing Zombie mice, as the name suggests, are effectively animated corpses: dead, chemically treated to halt all cell activity, and hooked up to an external pump to keep their blood circulating. If nanoparticles enter tumors by passively flowing through inter-endothelial gaps, then just as many nanoparticles should reach the tumors in Zombie mice as in control, or live, tumor-bearing mice.

But that's not what happened. Fluorescence images in figure 2 show blood vessels in red and nanoparticles in green. Nanoparticles in the control mouse spread throughout the tumor, and some

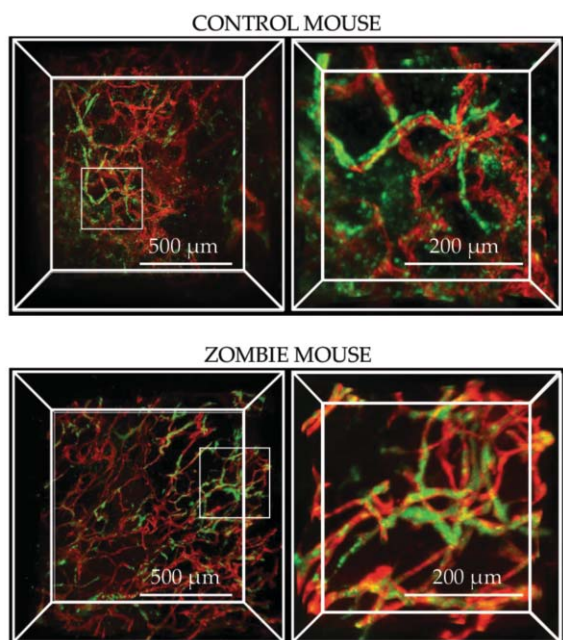


FIGURE 2. FLUORESCENCE IMAGES show the propagation of nanoparticles in the tumors of control tumor-bearing mice, which were alive, and Zombie mice, all of whose cells were dead. In the control mouse, nanoparticles (green) are able to escape the blood vessels (red), but in the Zombie mouse they can't. (Adapted from ref. 1.)

appear far from any blood vessels. But in the Zombie mouse, they remained confined to the tumor blood vessels. In other words, most nanoparticles escape the tumor blood vessels only when the cells in the vessel walls are alive.

Analysis of the Zombie experiment

implies some confirmation of both methods. "That was a pleasant surprise," said Sindhvani, "and it gave us confidence."

All lines of the Toronto researchers' reasoning point to active trans-endothelial pathways as the primary means by which nanoparticles are delivered to tu-

mors. But there's still work to be done. All their experiments so far used nanoparticles made of gold, which are easy to image but may not be representative of all nanomaterials. It's possible that passive transport doesn't work in exactly the same way in Zombie mice as in live ones. And the experiments don't reveal anything about what the predominant active molecular pathways are, what biomolecules are involved in regulating them, or—crucially for nanomedicine—how they compare to similar pathways at work in healthy tissue. "While we've made a first step," says Sindhvani, "we need a major collaborative undertaking to figure this out."

Johanna Miller

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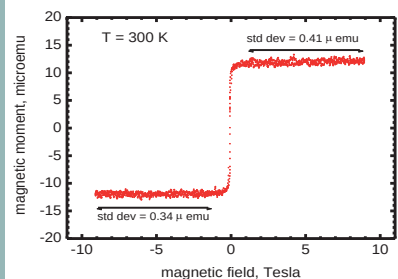
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