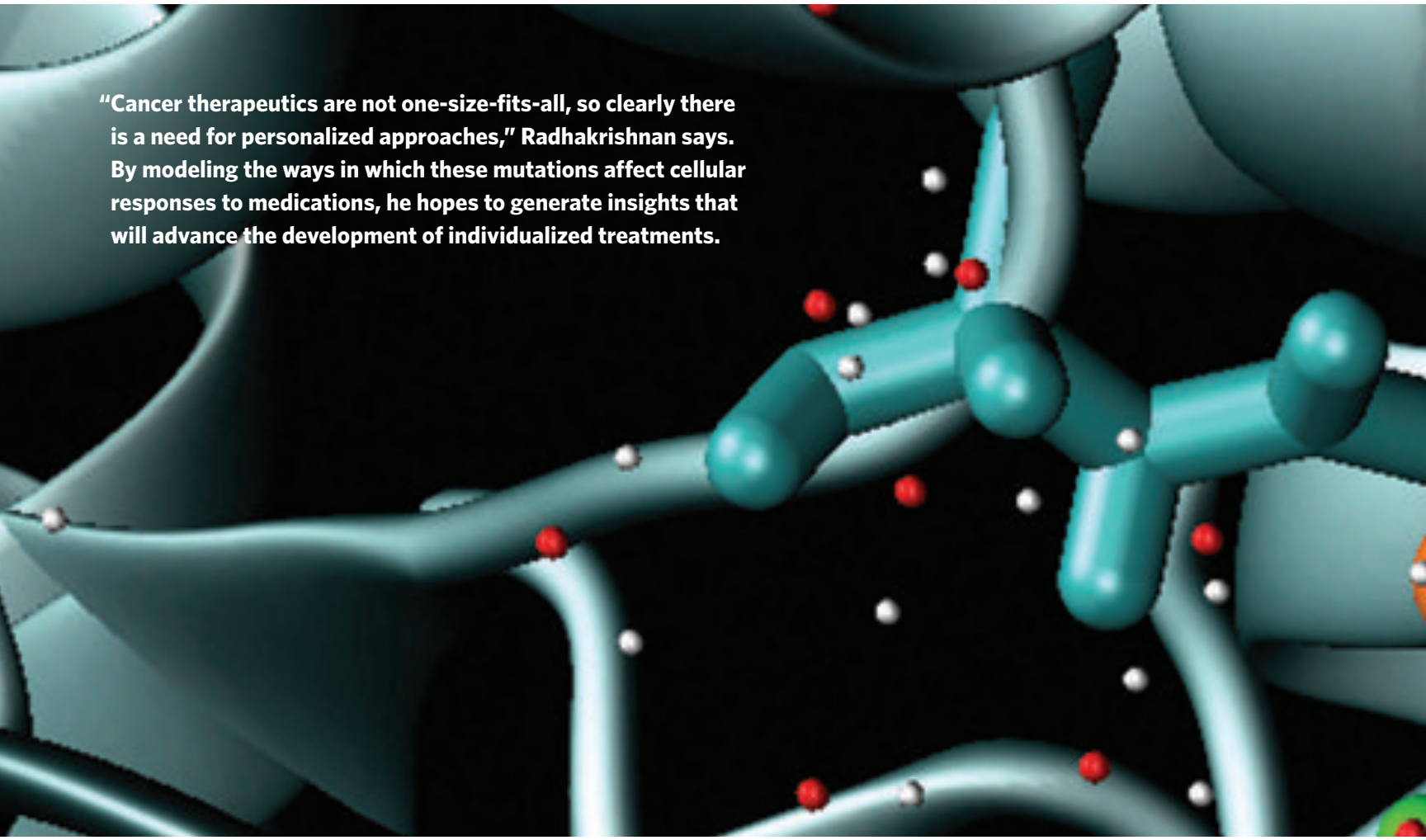
A United Front Against Cancer

By Janelle Weaver

Cancer accounts for nearly a quarter of all deaths and is the second most common cause of mortality in the United States. Since President Richard Nixon declared a "War on Cancer" by signing the National Cancer Act 40 years ago, five-year relative survival rates have risen, but the proportion of the population that dies from cancer each year has grown by about 13 percent. Billions of dollars worth of cancer research has produced fragmented knowledge about the causes of the disease, and relatively few breakthrough therapies.

In response to this crisis, the National Cancer Institute has recently turned its attention to mathematics and the physical sciences to foster a more comprehensive and quantitative understanding of the complex disease. In 2009, the agency launched a dozen Physical Sciences-Oncology Centers to encourage interdisciplinary initiatives. "We need to bring in new approaches and perspectives from other disciplines," says Ravi Radhakrishnan, associate professor of Bioengineering. "That's where my lab fits in."

Since joining the Penn faculty in 2005, Radhakrishnan has been developing mathematical models that integrate multiple spatial scales, from molecules to tissues, to examine how cells become malignant. Understanding cancer at these diverse levels is crucial for accurately predicting disease progression and treatment success, he says.



"Cancer therapeutics are not one-size-fits-all, so clearly there is a need for personalized approaches," Radhakrishnan says. By modeling the ways in which these mutations affect cellular responses to medications, he hopes to generate insights that will advance the development of individualized treatments.

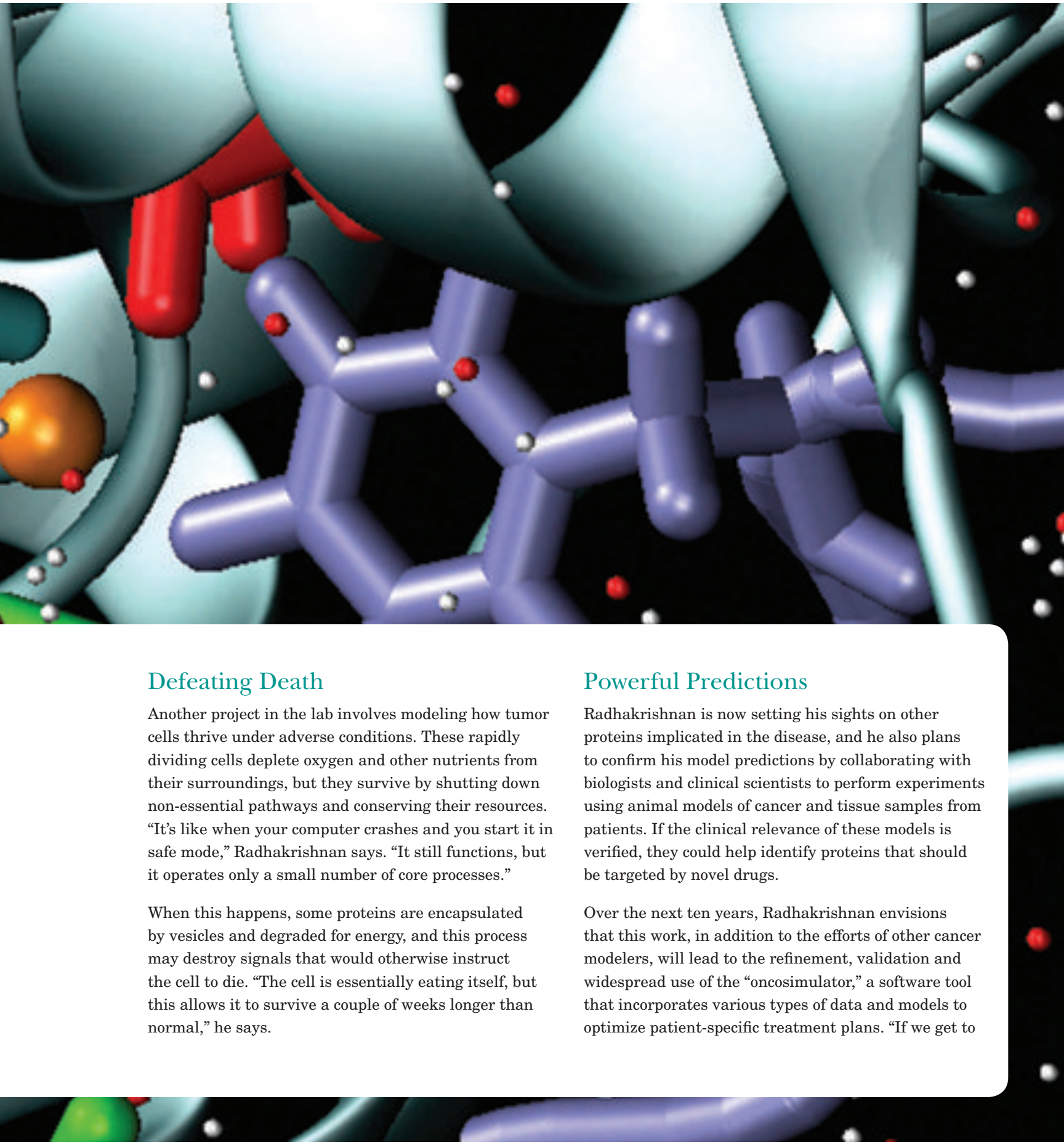
Given that cancer is so complex, a multi-pronged strategy is needed to combat the disease. Instead of using theoretical means to probe the molecular underpinnings of cancer, Andrew Tsourkas, associate professor of Bioengineering, develops innovative diagnostic tools. "Because Ravi and Andrew cover different parts of this broad research area, their concerted research effort is that much stronger," says David Meaney, Solomon R. Pollack Professor and Chair of Bioengineering.

Tailored Treatment

A variety of cancers are associated with mutations in genes that code for the ErbB family of proteins, which activate a chain of chemical reactions within the cell when certain molecules bind to them. Radhakrishnan models how these mutations can result in excessive signaling that causes cells to survive longer and divide uncontrollably.

Several approved drugs inhibit ErbB activity, but their effectiveness depends on the specific ErbB mutations patients have. "Cancer therapeutics are not one-size-fits-all, so clearly there is a need for personalized approaches," Radhakrishnan says. By modeling the ways in which these mutations affect cellular responses to medications, he hopes to generate insights that will advance the development of individualized treatments.

"The most immediate contribution of Ravi's work will be to help us understand why drugs work for some but not all people," Meaney says. "This information could then be used to figure out the best ways to design a drug or therapy from scratch."



Defeating Death

Another project in the lab involves modeling how tumor cells thrive under adverse conditions. These rapidly dividing cells deplete oxygen and other nutrients from their surroundings, but they survive by shutting down non-essential pathways and conserving their resources. "It's like when your computer crashes and you start it in safe mode," Radhakrishnan says. "It still functions, but it operates only a small number of core processes."

When this happens, some proteins are encapsulated by vesicles and degraded for energy, and this process may destroy signals that would otherwise instruct the cell to die. "The cell is essentially eating itself, but this allows it to survive a couple of weeks longer than normal," he says.

Powerful Predictions

Radhakrishnan is now setting his sights on other proteins implicated in the disease, and he also plans to confirm his model predictions by collaborating with biologists and clinical scientists to perform experiments using animal models of cancer and tissue samples from patients. If the clinical relevance of these models is verified, they could help identify proteins that should be targeted by novel drugs.

Over the next ten years, Radhakrishnan envisions that this work, in addition to the efforts of other cancer modelers, will lead to the refinement, validation and widespread use of the "oncosimulator," a software tool that incorporates various types of data and models to optimize patient-specific treatment plans. "If we get to

the point where these models become very predictive, I can't even imagine how that will change the way we think about therapies."

Tracking Down Tumors

While Radhakrishnan studies molecular events that underlie a range of cancers, Andrew Tsourkas is focusing on prostate cancer, the second most common cancer among men in the United States. It is often detected based on rising blood levels of a protein called prostate-specific antigen (PSA), which does not provide enough information to distinguish cancer from benign conditions, such as inflammation or infection. The benefits of PSA screening may not outweigh the risks associated with follow-up tests and treatments, and it might not save lives.

To address this problem, Tsourkas is devising new methods to improve the detection of cancer using non-invasive, high-resolution magnetic resonance imaging (MRI). This approach can be useful for discovering tumors, which produce a distinct MRI signal compared with healthy tissue. During exams, patients are sometimes injected with a metal called gadolinium because it accumulates in tissue with abnormal vasculature and has magnetic properties that amplify the signal in these areas. Still, either the metal doesn't specifically mark tumors or the signal is too weak to result in a reliable diagnosis. "That has been a huge limitation, and I think we've taken a big step toward eliminating the problem," Tsourkas says.

Tsourkas is further tailoring these nanoparticles to detect prostate cancer by coating them with F77, a unique antibody that selectively binds to molecules on the surface of prostate cancer cells at both early and late disease stages.

Brighter Future

To strengthen the signal enough to notice small tumors, Tsourkas has designed nanoparticles that carry a large amount of gadolinium. In most cases, gadolinium is attached only to the outer layer of the nanoparticle because the signal is stronger when the element is in contact with water. By contrast, Tsourkas' nanoparticle has a highly porous outer shell that allows water to flow through and surround extra gadolinium on the inside. Because these nanoparticles intensify the signal, they could facilitate the early detection of cancer.

Tsourkas is further tailoring these nanoparticles to detect prostate cancer by coating them with F77, a unique antibody that selectively binds to molecules on the surface of prostate cancer cells at both early and late disease stages. This protein was identified and characterized by his collaborators, Mark Greene, John W. Eckman Professor of Medical Science, and Hongtao Zhang, research assistant professor of Pathology and Laboratory Medicine, both of the Perelman School of Medicine.

The next step is to test the safety of this technology in animal models of cancer, and then possibly in human clinical trials. If approved, the nanoparticles would help clinicians make accurate diagnoses, select appropriate therapies and monitor their efficacy. Tsourkas hopes that clinicians will be able to choose from a variety of nanoparticles targeted for different types of cancer, or even other categories of diseases.

"It's well known that one of the best ways to treat cancer is to find it when it's just beginning to form in the body," Meaney says. "A lot of what Andrew does really focuses on this general area of early detection, and that's one way I think he'll create an impact."