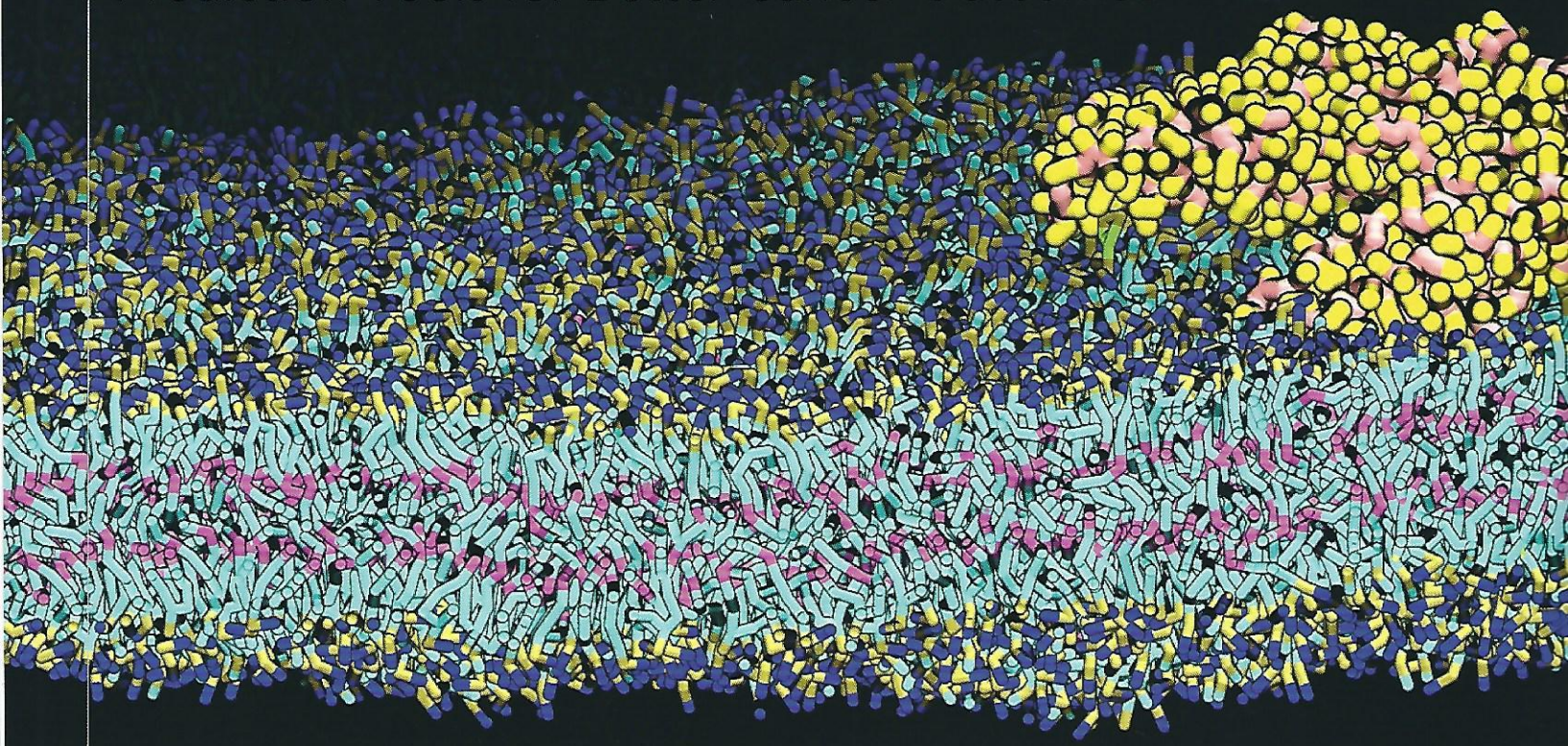
Why Cells Go Rogue

Prediction Tools for Better Cancer Outcomes



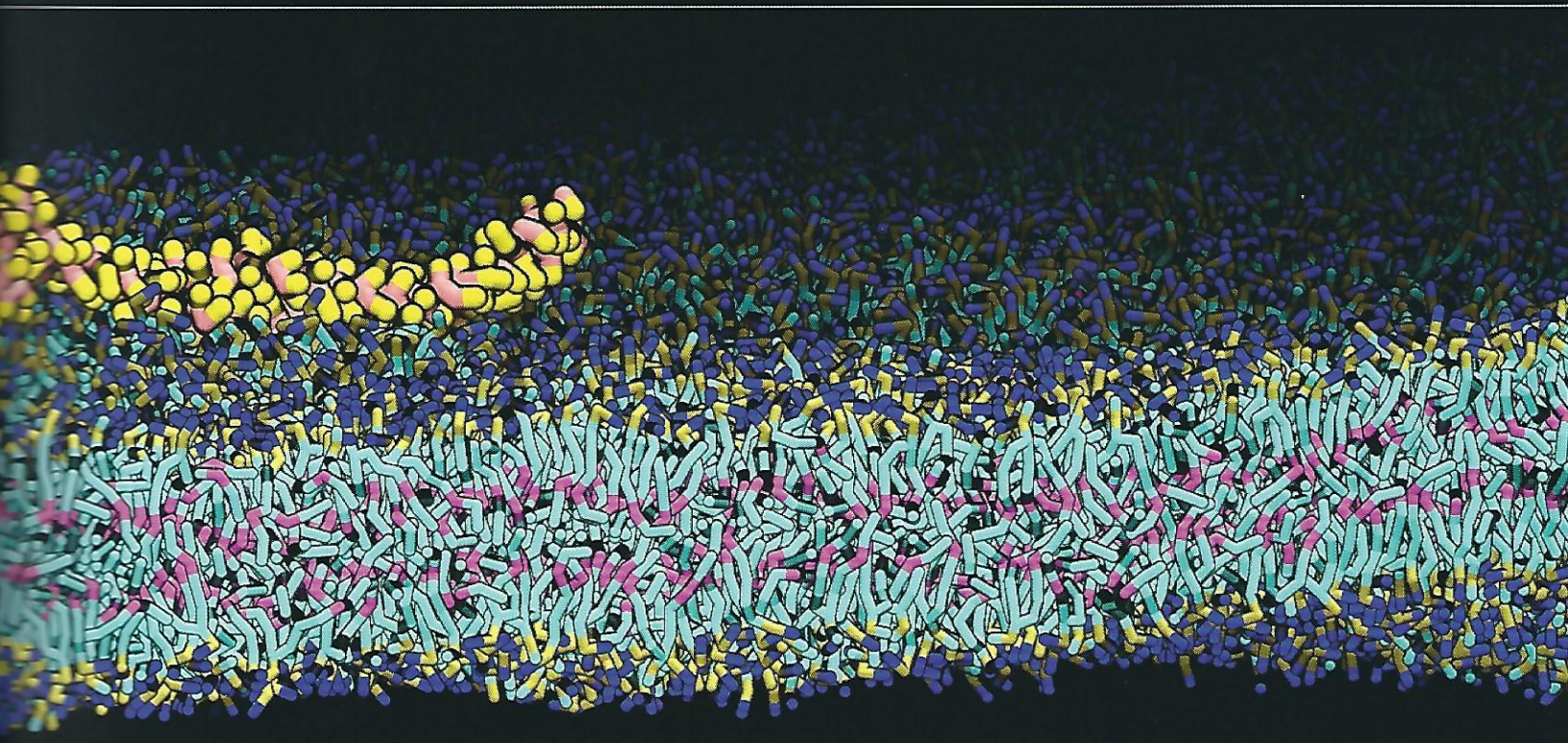
Ravi Radhakrishnan designs and continually refines computer models, illuminating fundamental mechanisms of central importance in biological engineering relevant to cancer research.

On a daily, often hourly basis, at a pace that reflects the urgent need for this information, his lab integrates new data and poses questions to chemists, cell biologists, pharmacologists and oncologists. "I am continually engaging with these communities of researchers," says Radhakrishnan, professor in Bioengineering and in Chemical and Biomolecular Engineering. "The most central paradigm in our lab is to make sure that the theory and models that we construct actually interface with all of these collaborators and different scales in a meaningful way."

Radhakrishnan, a member of the National Cancer Institute's (NCI) Physical Sciences Oncology Center at Penn, works at the interface of chemical physics and molecular biology. His lab develops computer models that synthesize fundamental laws of physics and biology with *in vitro* experimental and patient-specific genomic data. As data is continuously added, these computer models have become increasingly more quantitatively accurate and useful for cancer screening and diagnostics, clinical decision-making about therapeutics, and development of next-generation therapeutics (such as nanocapsules that can deliver cancer medication to diseased cells only, without harming adjacent healthy cells).

RADHAKRISHNAN AND HIS TEAM UNDERSTAND THE FUNDAMENTAL BIOPHYSICS AND MATHEMATICS AND HOW TO INTEGRATE THESE INTO PREDICTIONS AND INSIGHT FOR LEADING-EDGE EXPERIMENTS.

A molecular simulation of a protein (yellow) using thermal waves to help bend a cell membrane into different shapes.



Dennis E. Discher, Robert D. Bent Professor in Chemical and Biomolecular Engineering and principal investigator of the Oncology Center, notes that, "NCI realizes you're not going to answer everything with genetics, even when doing all the sequencing you want. Other scientists in our center are experimentalists with strong theory backgrounds, so there's a robust interplay with Ravi's group. Ravi and his team understand the fundamental biophysics and mathematics and how to integrate these into predictions and insight for leading-edge experiments."

INTEGRATING DATA

"I see the potential of our approach to be truly transformative and to touch a large class of people and patients," says Radhakrishnan, whose lab may well be the first to design computer models that integrate data at the scale of individual atoms and electrons, utilizing data sources ranging from membranes, proteins, cells, tissues, organs, mice, individual patients and large cohorts of patients with cancer.

"Ravi's methods have made people sit up and take notice," says Mark A. Lemmon, co-director of Yale University's Cancer Biology Institute. His ongoing collaboration with Radhakrishnan and Yael Mossé, a pediatric oncologist at The Children's Hospital of Philadelphia, has generated a comprehensive computational model of key gene mutations of importance to the treatment of neuroblastoma, a childhood cancer.

"We routinely get urgent requests from clinicians around the world who need to know whether their patient's specific mutation would respond to a drug targeting that mutation," says Lemmon. "The dream is that a clinician would pick up an iPhone and plug in the neuroblastoma mutation. With what Ravi has developed, in principle it could be that simple."

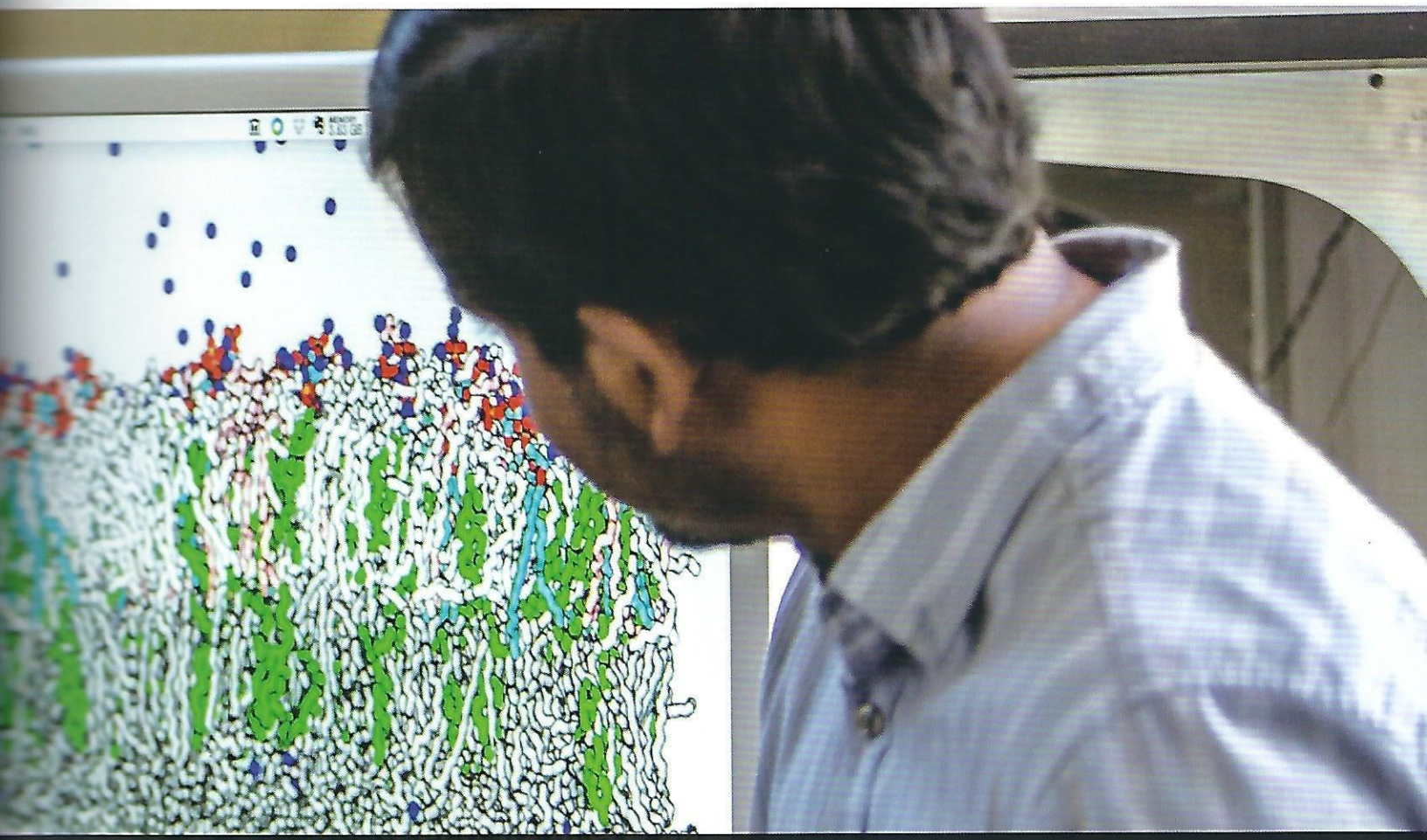
WHALE SOUNDS

Even as he generates insights relevant to patient care, Radhakrishnan's lab also investigates cancer-relevant properties in proteins that are a thousand times smaller than a single cell. Radhakrishnan and recent doctoral graduate Ryan Bradley co-authored a paper in July's *Proceedings of the National Academy of Sciences (PNAS)* in which they explain their crucial new insights about the mechanisms that individual proteins use to signal each other across long distances: They use undulations of thermal waves to spur proteins on faraway cell membranes to form capsules that perform basic necessary cellular functions such as metabolizing, migrating and proliferating.

"A cell starts to become a 'rogue' cell as these capsules malfunction," says Radhakrishnan. A cancer tumor is a cluster of these rogue cells. "Just as whales talk to one another through sound waves in the ocean, similarly proteins can feel the presence of neighbors from fairly far away via these elastic waves. Such learnings of fundamental biophysical interactions can be carried forward and applied to future technologies for cancer diagnostics and could also inform drug design. For example, can we artificially create nanocapsules filled with drugs using small molecules to shut off certain proteins, and also shuttle those drugs to where you need them the most? That's something we can start designing based on these findings."

THESE FUNDAMENTAL SCIENTIFIC INSIGHTS MAY BE THE UNDERPINNING FOR A NEW FORM OF CANCER DIAGNOSTICS.

Radhakrishnan's lab is now working to design and optimize "nanocarriers" to potentially deliver cancer medication to diseased cells only. "Our platform takes into account all of the chemical or physical aspects that determine whether a nanocarrier will go to a particular location or not," says Ramakrishnan Natesan, postdoctoral fellow in Radhakrishnan's lab



Ravi Radhakrishnan (center) and doctoral students Ryan Bradley (left) and Ramakrishnan Natesan (right) discuss results from a simulation of highly charged signaling molecules moving in a cell membrane.

and first author of a paper published in May in the journal *Royal Society Open Science*. "Proof of concept is in that paper. Now we're exploring the relevance of this finding to many different therapeutic drug-delivery scenarios."

SCREENING CELLS

Over the past decade, patient- and tumor-specific genetic screening and cell-based immunotherapy have dramatically changed and improved cancer treatment outcomes. "Yet for certain cancers, notably pancreatic and liver cancer, there aren't 'smoking gun' mutations like you see in lung cancer and neuroblastoma," says Lemmon. "Another approach is to look at the physical state of the organ, the injury to the pancreas and structure of the liver, for a predisposition to cancer. We're trying to understand how variations in cellular stiffness change the biochemistry of gene regulation. These fundamental scientific insights may be the underpinning for a new form of cancer diagnostics."

"We've shown that we can predict conditions for membrane bending with high accuracy based on the exact chemistry and presence of proteins," says Bradley. "Now we're trying to understand how physical forces such as stiffness of the environment outside the cell can modulate the cell's behavior."

"We're still a ways away from the goal of measuring cellular stiffness in every cancer patient, an experimental technology not yet approved for clinical use," adds Radhakrishnan. "We are building the case that this might be what we have to do. Our research indicates that genetic sequencing and cellular stiffness screening may be equally important, especially in cancers of the soft tissue. The real questions now are whether measuring stiffness at a cellular level is economical and can lead to precise diagnosis. That remains to be seen. But there's promise."

By Jessica Stein Diamond