The Nanobiology Institute at Yale’s West Campus

Nanobiology  Cancer Biology  Chemical Biology  Energy Sciences  Microbial Diversity  Systems Biology
In 1665, the English natural philosopher Robert Hooke turned his eye to the microscope and rendered what he saw in *Micrographia*, revealing for his fellow naturalists—and a riveted public—tiny marvels just a fraction of a millimeter wide: the hairs on a flea’s leg, a fly’s eye, a bee’s stinger.

Within the next two decades, with improved instruments that could resolve details as small as one micrometer across, Dutch scientist Antonie van Leeuwenhoek glimpsed bacteria and protozoa in water droplets. These discoveries dramatically reframed the seventeenth-century understanding of life, and affirmed the paramount importance of basic scientific research: Where discovery leads, explanations and applications follow.

In 2011, Yale founded its Nanobiology Institute at West Campus to advance another paradigm shift. Using instruments a thousand times more powerful than Hooke’s, Yale scientists are exploring a new frontier within living cells, observing and describing structures as small as 20 nanometers, or just 20 billionths of a meter across. Today’s most sensitive microscopes allow real-time observations of proteins at work within a living organism. Equally important are tools and techniques that enable them to actually manipulate matter at the nanoscale: optical tweezers that can grab single molecules, and DNA strands that can self-assemble into artificial shapes.

These are not mere curiosities. Among the most profound insights of the past decade is the discovery that proteins assemble themselves into molecular machines—10 to 150 nanometers in size—that control the principal processes of life: replicating DNA, making and distributing new proteins, controlling cell division, or enabling cell-to-cell communication. The interdisciplinary Nanobiology Institute will supply the tools and theoretical framework that cell biologists need to illuminate molecular machines and their workings in exacting detail.

Fundamental research at the Nanobiology Institute promises a new understanding of cellular processes and the miscues that lead to human disease. Future applications may one day rival today’s science fiction: nanomachines that enter cells and perform corrective actions, engineered genes that better respond to drug treatments, or biofuels that provide renewable energy. The potential for discovery is extraordinary.
Truly a pioneering venture, the Nanobiology Institute is one of a handful of U.S. programs at the forefront of this still-nascent field. And like its fellow institutes at Yale’s West Campus, it is founded on a commitment to integrated, interdisciplinary science. By definition, the study of cellular nanomachines requires teamwork among cell biologists, engineers, physicists, computer scientists, chemists, and other experts. The Institute is designed to unite these scientists and to support their work in the most cutting-edge laboratories.

Under the leadership of James E. Rothman ’71, the Fergus F. Wallace Chair in Biomedical Sciences, the Nanobiology Institute will build on Yale’s globally recognized expertise in the area of biological membranes—particularly, the understanding of how a tiny sac-like structure called a transport vesicle fuses with another membrane, releasing hormones or chemicals that drive a range of processes implicated in both health and disease. In parallel with this research, the Institute will engage in the ongoing development of tools for imaging and manipulating materials at the nanoscale. Collaborative work of this nature is already enabling the Institute’s core faculty to mimic cellular activity using specialized nanoscale machines, providing novel approaches to exploring basic life processes.
Building a powerful, far-reaching institute

When it is fully staffed, the Nanobiology Institute will house eight principal investigators and their laboratories, with teams of post-docs, visiting scholars, and graduate students drawn from Yale’s Graduate, Engineering, and Medical schools. As nanobiology and its related subfields are highly specialized, competition for the best scientists will be keen as the Institute grows.

A major draw is the West Campus’ top-end facilities and equipment, including today’s most sophisticated imaging tools and ultra-powerful computing systems. Researchers will have access to instruments located within the Institute, as well as advanced equipment and support staff in the West Campus’ four core facilities – the Yale Center for Molecular Discovery, the Yale Center for Genome Analysis, the High Performance Computing Center, and the West Campus Analytical Chemistry Core.

During the Institute’s first two years of operations, broad support is critical to sustaining its ambitious growth trajectory and helping its leaders attract and retain the best scientists. Already the Institute is publishing groundbreaking research through the partnerships of newly hired specialists and Yale’s proven leaders in cell biology. Their highly complex, interdependent work requires both short-term support to keep laboratories at the cutting-edge and long-term, visionary support to keep pushing the boundaries of discovery — and further our understanding of life itself.
Yale Innovators in Nanobiology Research
Learning how cells communicate

During his internationally acclaimed career, James Rothman ’71 has rarely taken his focus off what he calls his “favorite molecular machine”: the transport vesicle. Understanding this infinitesimal, sac-like structure brings him to a level of detail so small—just 10 or 15 nanometers—that it is almost beyond comprehension. And yet here lie the secrets to how our nerve cells communicate and how cells secrete hormones and other chemical messengers. By understanding these processes in detail, researchers can also understand why they go wrong, providing insights into brain disorders, diabetes, and other diseases.

In 2002, Rothman received an Albert Lasker Basic Medical Research Award for elucidating how cells transport proteins and direct their assembly; in 2010, he was one of three scientists to receive the Kavli Prize in Neuroscience for discovering the molecular basis for the release of neurotransmitters. Today, he continues to investigate the precise dynamics of transport vesicles— their underlying biochemical and biophysical mechanisms and the systems by which cells and tissues regulate their activity.

Rothman also has his eye on designing vesicles using nanomaterials—that is, using nano-DNA principles to make vesicles of defined size and content. Already he and fellow scientists have managed to use a tiny ring of DNA to “template” a vesicle and determine its contents. Nanotemplating, Rothman explains, is basically “a whole new field,” one that conjures a host of exciting applications. But for Rothman, its significance as a major step forward in basic science is what appeals most. “This is a biological problem we are trying to understand,” he says. “It’s very foundational—and very important—work.”

Tiny molecules, major findings

Yongli Zhang ’03 Ph.D., a cell biologist and frequent collaborator with Rothman, makes his work sound simple: “Optical tweezers basically extend our hands, so we can grab a single molecule and play with it,” he says.

Optical tweezers are, of course, more complex than their splinter-pulling forebears. They use the momentum carried by light to trap a micron-sized bead and then guide the bead as a force probe to manipulate molecules. Paired with an imaging technique called single molecule fluorescence, optical tweezers allow the user to “see” a single molecule while manipulating it. Zhang is primarily interested in how proteins fold or misfold. “When a protein misfolds, it can lead to all kinds of health problems, including neurodegenerative disease, diabetes, and even cancer,” he explained.

Using optical tweezers, Zhang recently arrived at a major breakthrough: Working with Rothman and other scientists, he was able to observe for the first time how a single SNARE complex, the molecular machine for membrane fusion, folds like a zipper to produce the energy needed for that fusion. The zippering process in neurons is extremely fast, energetic, and efficient, and it is critical to understanding how neurons communicate in the brain.

“People had tried all the available traditional approaches to study how SNAREs fold,” Zhang said. “With optical tweezers, we can chart the kinetics and intermediates of SNARE folding in real time at the single-molecule level.”
Karatekin has trained in chemistry and physics allows him to look at nanostructures from several perspectives. Not only does he deconstruct cellular materials to understand how they fit together, he also builds them. “You need to both break down and build, because both methods have their limitations,” he says. “If you start with an intact cell, it’s hard to isolate a single protein. But if you build with single proteins, suddenly you have hundreds of components, and you end up missing certain things. So we go both ways and try to control the environment by using naturally occurring vesicles and fusing them with artificial materials.”

Like Rothman, Karatekin seeks the fundamental explanations for cellular processes, but his work has many implications for the understanding and treatment of disease. Cells that secrete adrenaline, for example, have a pore that opens and closes slowly, but in an emergency it dilates instantly and releases its hormone in bulk. “This action seems reasonable, and people are coming up with reasonable explanations from a physical point of view,” he says. “But the molecular mechanisms governing this process are not yet understood. This is the sort of thing we hope to discover.”

Zhang draws on his expertise as a biophysicist and research interests that cross chemistry, engineering, and mathematics. “In nanobiology we have to combine cutting-edge technology with knowledge in different disciplines,” he said. “We have to use optics, instrumentation, and computer control. We typically acquire a few gigabytes of data per day and need sophisticated mathematics to analyze it.

“Fortunately, we have top scientists. We can find the biggest scientific problem and then apply the best technology to solve it.”

Breaking down cells to build them again

Erdem Karatekin is formally trained as a physicist and chemical engineer, but in the past decade he has become fascinated by cell biology, in particular membrane fusion—a fundamental process required for the trafficking of proteins and the secretion of hormones and neurotransmitters. Today, in close collaboration with Rothman and others, the assistant professor of cellular and molecular physiology is developing new methods to detect membrane fusion events with unprecedented detail.

“We can now see single molecules that transfer from one membrane to another during the fusion of two membranes,” he explains—no small feat, as such molecules are less than a nanometer in size.

There’s a good reason traditional light microscopy doesn’t work at the nanoscale: Most sub-cellular features are smaller than a half-wavelength of light (about 250 nanometers), and refracted light can only yield blurry images.

Joerg Bewersdorf, assistant professor of cell biology and biomedical engineering, applies his expertise in both optical physics and biophysics to the emerging field of novel super-resolution light microscopy. “With our new tools, we can investigate the dynamics of a cell at the nanoscale... and resolve questions that have been disputed for decades.”
of a cell at the nanoscale, looking into subcompartments of organelles for the first time,” he explains. “We can resolve questions that have been disputed for decades.”

At Yale, Bewersdorf has access to one of the first Leica TCS Stimulated Emission Depletion microscopes in the United States, among other tools, and he adds to the toolkit by developing new technology of his own. He has been collaborating with Rothman to visualize dynamic nanostructures at the sub-cellular level, actively engaging in the sort of symbiotic research that is both a signature of the West Campus and essential to its ongoing work. Bewersdorf’s colleagues are quick to say that their observations would be impossible without his tools.

“Yale is a great place for me to perform my research because of the high concentration of world-class biomedical scientists, and for its traditional strength in applying new microscopes to tackle problems,” Bewersdorf says. “This environment assures that my instruments are applied to some of the most pressing questions in biomedical research today.”

**Understanding life through its building blocks**

A chemist by training, Chenxiang Lin talks more like an engineer — albeit one who constructs what might be the world’s tiniest man-made structures. “We use DNA as a building material,” he explains. “We customize its shape and size, which allows us to put nanoparticles or proteins or other things on a surface in a pre-arranged manner.”

Lin is an expert in DNA origami, so-called because it involves folding DNA to make pre-determined shapes — everything from simple squares and circles to working biological tools. Lin uses chemistry, computer science, engineering, and physics to make his DNA shapes, and then works alongside cell biologists to understand what he’s seeing and consider how to translate it into applications. A recent Yale recruit who formerly worked at Harvard’s Wyss Institute, Lin now partners closely with Rothman and other Yale scientists to better understand cell processes and identify the actions of specific proteins, especially in membrane fusion.

DNA origami has numerous potential long-term applications, particularly in diagnostics and drug delivery. “We have the power to design the shape and the surface of these nano-structures, and I am optimistic that we will be able to design particles and drug carriers to have superior performance,” Lin explains.

“For a long time cell biologists were in many circumstances limited by what nature gives them,” he adds. “We deconstruct what nature gives us and arrange it in the way we want.”

**The 136-acre West Campus is home to an integrated cluster of research institutes in the areas of chemical biology, cancer, nanobiology, systems biology, microbial diversity, and energy sciences. Supporting this work are four core facilities shared by Yale’s science faculty:**

- Yale Center for Molecular Discovery
- Yale Center for Genome Analysis
- High Performance Computing Center
- West Campus Analytical Chemistry Core

These interrelated institutes and core facilities sustain a multidisciplinary approach to today’s most pressing questions of human sustainability — health, the environment, and energy — and advance Yale University as a national leader in scientific teaching and research.
To learn more
For more information about Yale’s West Campus, please visit:
www.yale.edu/westcampus

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