

The Yale Center for Molecular Discovery



A Core Research Facility at Yale's West Campus



“This is one-stop shopping for scientists who are looking to take the next step in advancing their research.”

Scott Strobel, vice president for West Campus
planning and program development

Making sense of life's complexity

The adult human body contains more than 60 trillion cells, organized into 300 distinct cell types that carry out the many processes of life—replicating DNA, distributing new proteins, controlling cell division, or enabling cell-to-cell communication. Yet within this complexity, a single molecule can have a profound impact. Scientists have long known that mutations in specific genes can cause devastating diseases like sickle-cell anemia, hemophilia, or cystic fibrosis. Equally important, small molecules can attach to the surface of a cell or even pass through membranes to impact the cell's inner workings, with profound implications for human development and health.

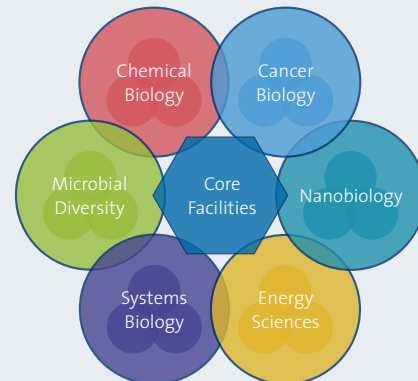
This is the province of the Yale Center for Molecular Discovery (YCMD). A core facility on Yale's West Campus, the Center is uniquely equipped to study how chemical compounds drive cellular machinery and to ask what happens to the cell when specific genes are switched off. The answers not only expand our basic knowledge of biology, but also may lead to new treatments in the fight against hereditary diseases, drug-resistant bacteria, and cancer.

Accelerating the pace of discovery

At the heart of the Center is the ability to scale up a laboratory investigation, moving from a handful of samples per day—typical for academic laboratories—to tens of thousands per day, a level once associated only with big pharmaceutical companies. This scale-up, so critical to the translation of basic research into new medicines, requires an innovative organizational model as well as state-of-the-art equipment.

The YCMD is staffed with experts drawn from both academic laboratories and biopharmaceutical companies, bringing in-depth knowledge of tools and techniques not usually found in a university setting. Further, the Center is the only core service facility of its kind to select its projects through a peer-review process, ensuring that the most promising ideas are given top priority. Once a project is selected, the Yale faculty researcher is paired with a YCMD staff member, and research proceeds collaboratively. The team uses a suite of automated liquid dispensers, plate readers, and microscopes to rapidly process large numbers of samples, while retaining the high level of quality that is the hallmark of Yale's scientific research.

Taken together, the capabilities of the YCMD open an extraordinary window into the living cell, with implications across the areas of natural science, human health, and the discovery of novel medical treatments. Only a handful of universities around the world have access to this combination



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.



The Yale Center for Molecular Discovery has a major educational mission, preparing undergraduates, graduate students, and postdoctoral fellows for leadership positions in tomorrow's research laboratories. The Center is staffed by researchers who are well-versed in the approaches used in the pharmaceutical industry. At the same time, it draws from Yale's leadership in basic and applied biology, chemistry, and engineering departments and helps to sustain a growing program of clinical research. This high-tech, multidisciplinary setting supports the cutting edge of biomedical education as well as research. The Center conducts more than eighty projects per year, each involving students, and it sponsors a summer internship to provide undergraduates with a meaningful research experience. A series of "nanocourses" helps students and faculty navigate the challenges of translating basic research results into candidates for drug discovery.

of expertise and technology, and at West Campus, Yale is determined to sustain and expand the YCMD at the absolute cutting edge. Donor support will play an essential role in this mission, not only enabling new discoveries but also distinguishing Yale in the top echelon of research institutions.

A focus on tomorrow's drug pipeline

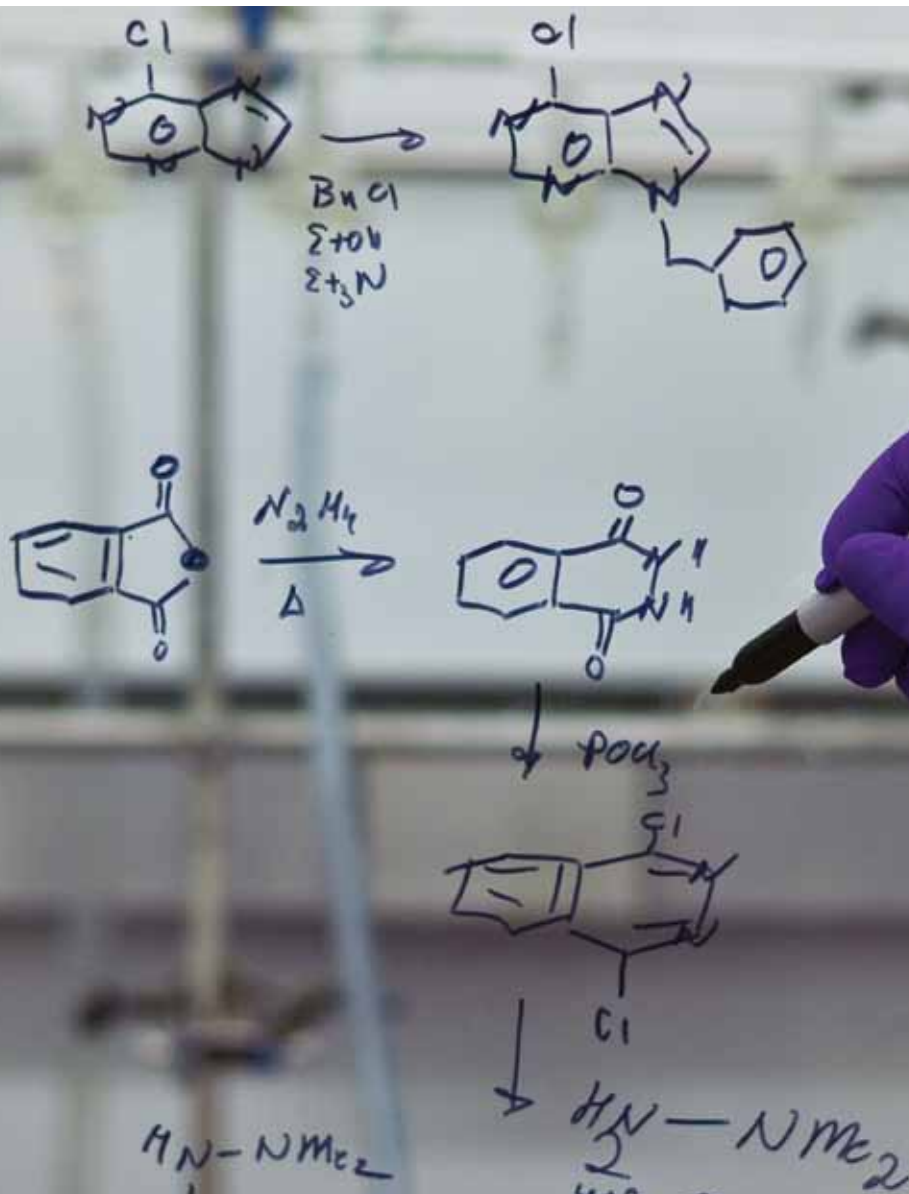
What makes a good candidate for drug research and development? Yale's Center for Molecular Discovery has been designed to answer this question, with tools to not only find active compounds, but also map out how they work, so that the most promising can be advanced to clinical trials.

For Yale, this early-stage research and development work is more essential than ever. A pharmaceutical company needs a solid foundation before it will commit a compound to the drug discovery pipeline: What is the structure of the chemical compound, how does it interact with the cell, and what will it do in the body? Today, just a few hundred compounds are well understood. There remains a vast knowledge gap that must be filled—what drug companies call "the valley of death"—that distinguishes our expanding knowledge of how the body works from our ability to intervene and correct known defects.

Increasingly, the ability to bridge this divide is something that only the nation's top academic institutions can accomplish. Large pharmaceutical companies facing new economic constraints have dramatically curtailed their funding of major research and development efforts. Leading universities like Yale must build the capacity to conduct translational research on a new scale, or the pipeline of critical new medicines will begin to run dry.

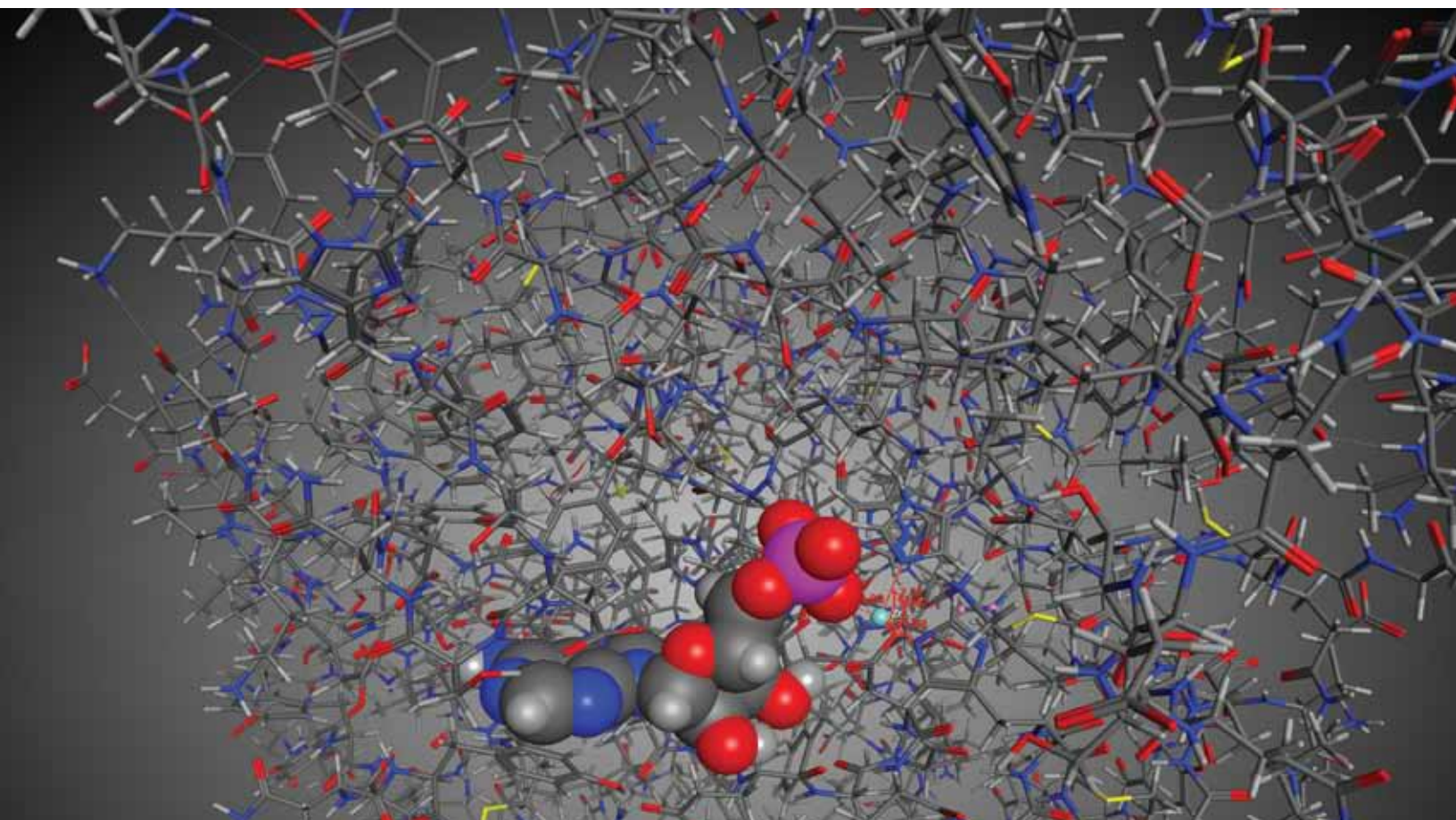
Yale biologist Craig Crews, director of the YCMD, has a deep understanding of this landscape. In July 2012, Crews completed the goal of successfully shepherding a compound from the lab bench into the clinic. His cancer drug, Carfilzomib (Kyprolis), was approved by the US Food and Drug Administration to treat recurrent multiple myeloma, a blood disorder, without the painful complications that often accompanied earlier therapies.

Building on this expertise, Crews now helps fellow researchers find their own paths to drug discovery, using high-throughput technologies to characterize a novel chemical, learn how that chemical affects cellular processes, and envision how it might be repurposed to cure disease in the human body.

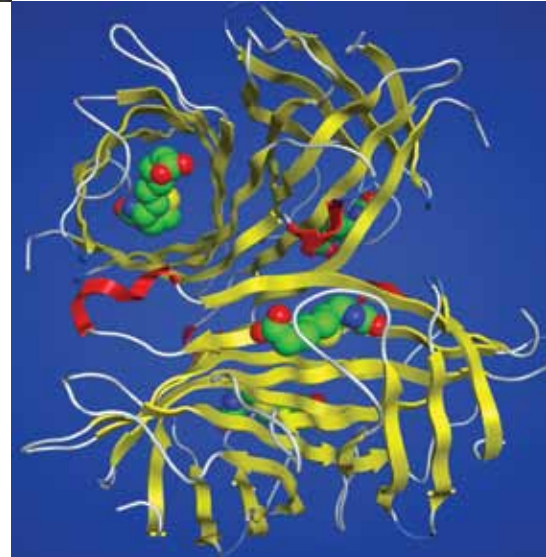
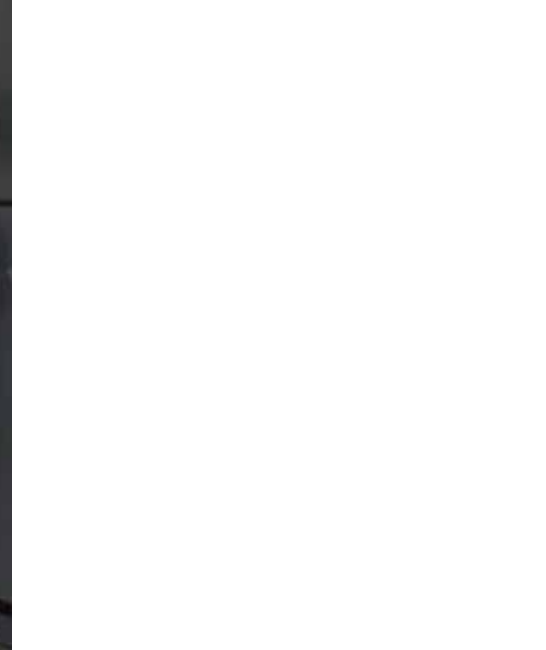


Only a select few compounds have the potential to impact disease in a way that is targeted, safe, and affordable, and fewer still will actually survive the long and expensive path to becoming an approved drug.

Leaders in Discovery



Above: Advanced molecular modeling graphics allow the detailed examination of Adenosine monophosphate (AMP) interacting with a new target protein. Opposite page, top: A researcher prepares copies of master assay plates using the TECAN liquid handler. Opposite page, right: The molecular interaction of Streptavidin with its natural ligand Biotin serves as the basis of many biochemical techniques at the Center.

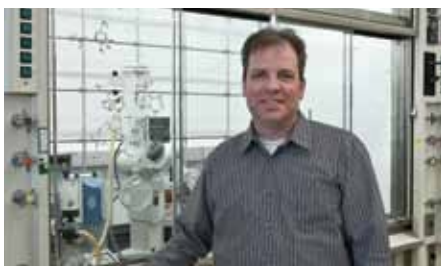


Yale is widely known for its strength in the life sciences, spanning basic biology, biomedical engineering, and medicine. In labs across the University, scientists are now turning to the Yale Center for Molecular Discovery, illustrating the promise of high-throughput screening technologies in solving urgent problems in areas from the environment to human health.

Neuroscientist **Stephen Strittmatter** studies key genes and proteins implicated in devastating neurological conditions. With the support of the YCMD, he is searching for drug candidates that can arrest the progress of Alzheimer's disease, and he hopes to understand the action of compounds that prevent the regeneration of adult neurons—research with promise for victims of stroke or traumatic spinal cord injury.

Diane Krause seeks to pinpoint the molecular mechanisms that regulate the formation of blood cells. Her work at the YCMD, screening stem cells derived from bone marrow, is shedding light on the processes of self-renewal and differentiation—findings that may lead to improved strategies for bone marrow and stem cell transplantation as well as novel therapies for treating leukemia and lymphoma.

What new functions can be found for engineered RNA and DNA? And can the ancient functions of dormant nucleic acids be discovered and put to use? These are the big questions that inspire **Ronald Breaker's** research. Of special interest are ribozymes and riboswitches—RNA molecules that catalyze chemical reactions or that serve as chemical sensors and gene control elements. With help from the YCMD, the Breaker lab is investigating the potential use of riboswitches in a new class of antibiotics that circumvent bacteria's ability to develop resistance.



Michael Kinch, managing director of the YCMD, leads a scientific team of ten investigators spanning academia and the pharmaceutical industry. Their mission is to assist Yale faculty members who want to use high-throughput screening tools not found in conventional academic labs. These include extensive compound libraries, cutting-edge robotics, high-resolution imaging, and state-of-the-art computational approaches that dramatically accelerate the discovery process.

“We want to provide to the Yale faculty the advice and equipment they need to begin the journey from discovery to development of new drugs,” says Kinch.

“This work can speed the translation of basic research and broaden the attractiveness of Yale as a partner of choice for biopharmaceutical companies.”

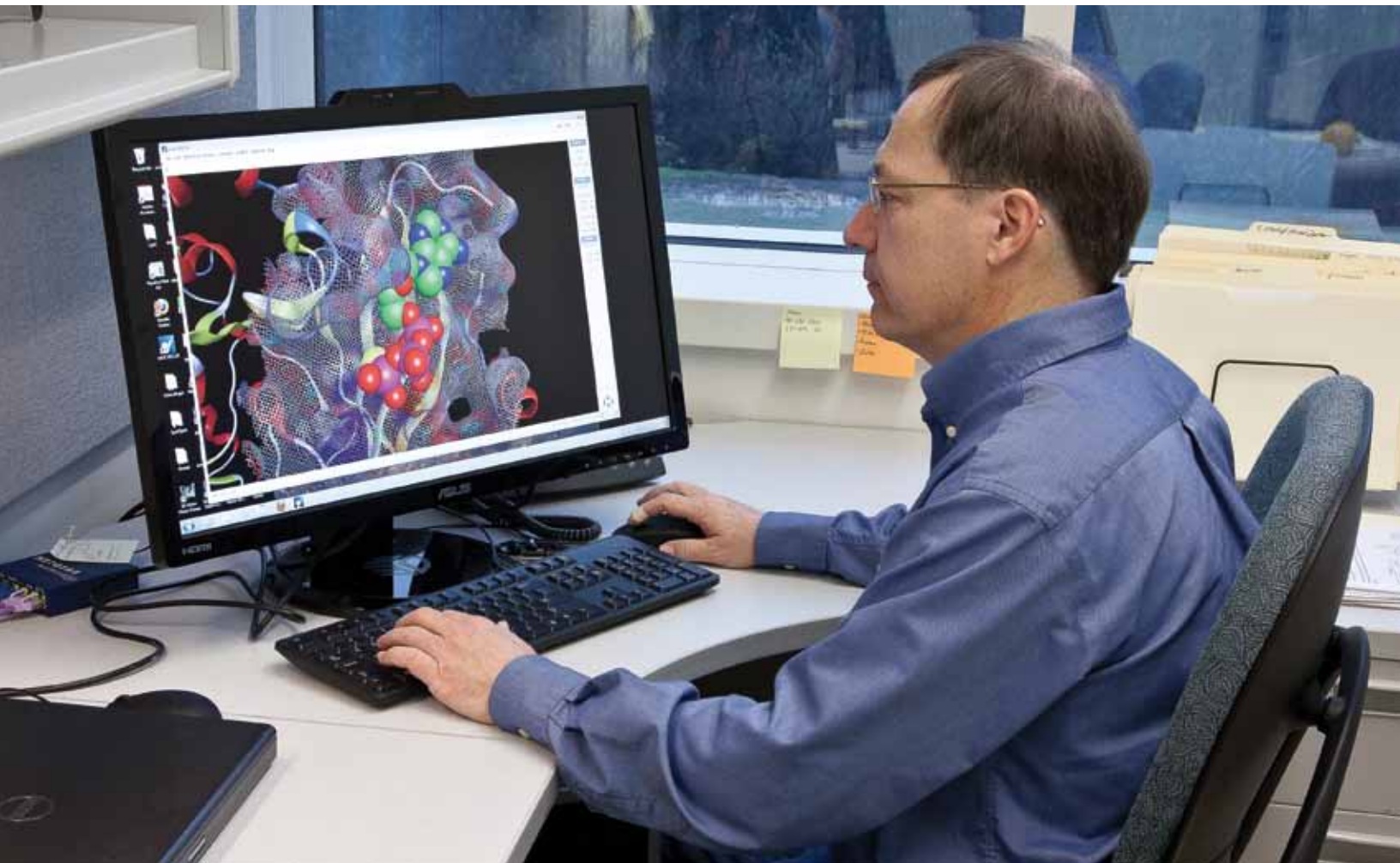
Kinch has a background well suited to his leadership role. From 1996 to 2001, he was a tenured professor at Purdue University, where he focused on cancer research. In 2001, he was recruited to lead the departments of cancer biology and translational sciences at MedImmune, a successful biotechnology company. He later served as chief scientific officer at Functional Genetics, which pioneered new approaches for treating infection by HIV, influenza, Ebola, and other viruses. He came to Yale in 2010 to help advance Yale’s West Campus initiatives.

David F. Stern and **Marcus Bosenberg** investigate ways to combine the actions of different chemotherapeutic drugs to provide a more safe and effective means of combating cancer. Their research uses tumor samples and treatment models taken directly from the Yale Cancer Center, advancing our knowledge of combination therapy while having immediate clinical impacts.

Susan Baserga is interested in the nucleolus—a structure within the cell’s nucleus composed of proteins and nucleic acids. A healthy cell has two or three of these structures, which act as essential ribosome producing machines. In contrast, a cancer cell may have too many nucleoli, or perhaps a single, oversized one. Baserga is using the tools of the YCMD to identify proteins that lead to these unhealthy nuclear formations, in hopes of finding a druggable target in the fight against melanoma and other cancers.

Jo Handelsman takes a big-picture view of biology as a pioneer of metagenomics, an emerging discipline that looks at the diversity of genes found in specimens across a whole ecosystem. Opening a window on a vast microbial world that was previously inaccessible, metagenomics has both theoretical and practical applications, allowing Handelsman to look for new antibiotics, for example, or to explore the genetic basis of antibiotic resistance.





Above: The novel protein NPP4, discovered at Yale, is examined in preparation for molecular docking. Opposite page, bottom: Natural products are extracted from a variety of cultured organisms and tested in novel drug target screens.



To learn more

For more information about Yale's West Campus, please visit:
www.yale.edu/westcampus

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Michael Marsland: page 8



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