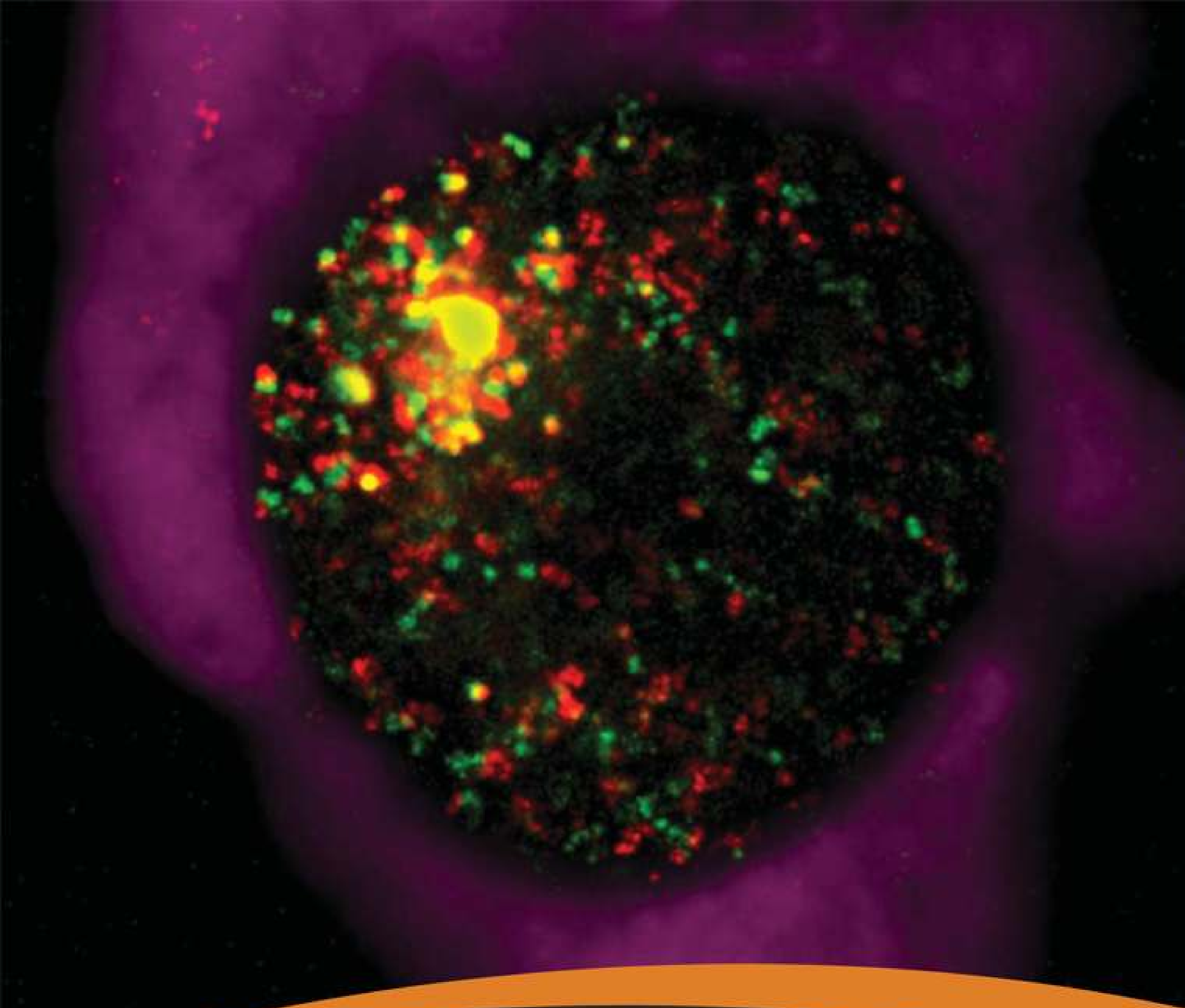


Science & Technology Series

Systems Biology and Bio-Medicine

Life in its Marvelous Complexity

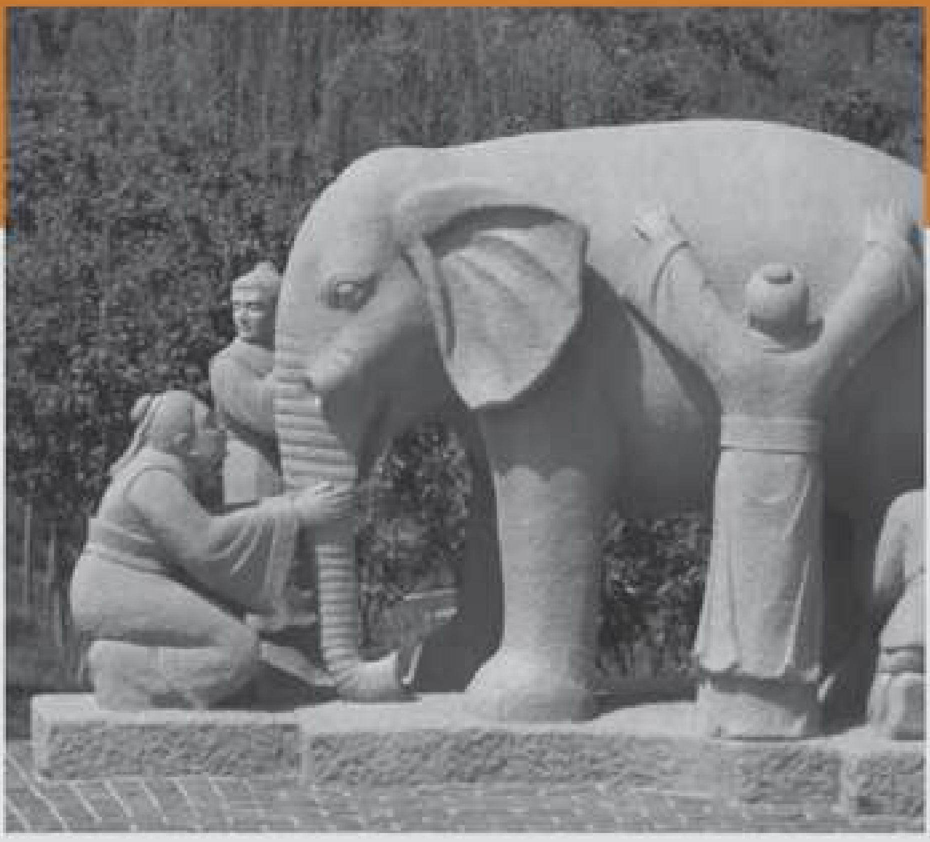
Tradition of Excellence
Bar-Ilan University

The goal of the BIU Systems Biology team is as practical as it is visionary: to perform the basic research that – someday – will give doctors the same control over cells that electronic engineers have over their circuits.

Pictured from left to right:
Dr. Sol Efroni
Dr. Yanay Ofran
Dr. Erez Levanon

Biology Marvelous

Complexity



An old folk tale tells of three blind men and an elephant. The first pats the elephant's leg. "An elephant," he announces, "is very like a tree. The second grasps the elephant's trunk. "You are wrong," he says. "An elephant is very like a snake. "The third man, touching the elephant's ear, declares, "An elephant is very like a fan."

To really understand something, it is important to integrate different points of view. Systems Biology is "network" science, in which different levels of bio-based activity – from molecules to cells to tissues – are examined as part of the same larger puzzle.

More than just an attitude about basic research, Systems Biology is transforming medical practice. Systems Biology has the potential to replace today's "reactive" treatments with medicine that is predictive, personal, participatory and ultimately, preventative.

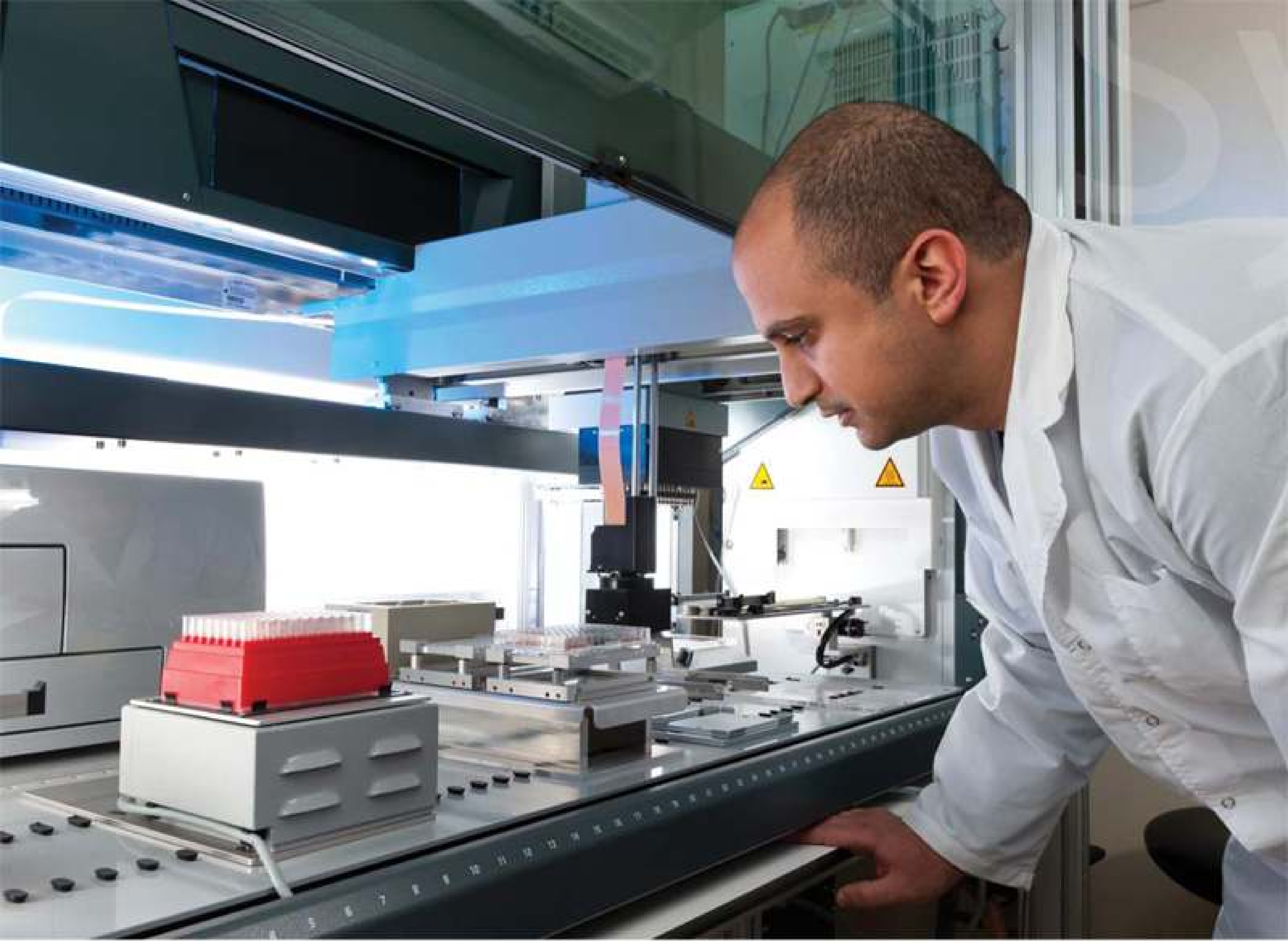
At Bar-Ilan University, a core group of systems-based researchers are revolutionizing our understanding of complex biological processes, and creating new tools that may hold the key to conquering health problems such as cancer, diabetes, and AIDS. They are elucidating the "design principles" of biological networks, applying new experimental and computational techniques to the study of disease, creating new technologies, and devising new methods for modeling network-based activity. Connecting the dots between every aspect of a fully functioning organism, the goal of the Bar-Ilan Systems Biology team is as practical as it is visionary: to perform the basic research that – someday – will give physicians the same kind of control over cells that electronic engineers have over their circuits.

Life's Design Principles

When a body cell replicates itself, a copy of its genome – the sum total of its genetic material – is passed down to the next generation. But in the case of cancer, cell replication is unstable. Dr. Shay Ben Aroya is mapping out the network of complex interactions that ensure genome maintenance and stable chromosome transmission both in yeast and in human body cells. His studies will allow him to identify specific genes that promote a predisposition for cancer, as well as molecular targets for novel anti-cancer therapies.

In another systems-based study with implications for cancer treatment, Prof. Doron Ginsberg is examining a family of genetic factors that play a critical role in cell proliferation and the cessation of cell growth – processes that are vital for any cell, but proceed abnormally in the presence of cancer. Ginsberg's recent work indicates that one member of this family of factors is involved in autophagy – a normal process in which a cell destroys proteins and other substances inside the cell. Autophagy may protect cancer cells from the effects of chemotherapeutic drugs, and Ginsberg is examining this possibility by studying the way this genetic factor interacts with drug-based cancer treatments.

Aging is another natural process controlled by network-based signaling. Building on a recent discovery that yeast cells with two copies of a gene called SIR2 live significantly longer than cells with only one, Dr. Haim Cohen has shown how, in mammals, an overabundance of SIR2-type genes "tip" the intra-cellular message away from cell death. In another project, Cohen found a link between severe calorie restriction – known to increase life expectancy in laboratory animals – and SIR2-type genes. Cohen is currently examining libraries of small molecules that could potentially elevate SIR2 levels in humans – research that could possibly speed the design of drugs that would mimic calorie restriction's anti-aging effects, without dieting.



Bar-Ilan scientists are developing computational tools that help identify specific targets for drug-based intervention.

When the "System" Breaks Down

What happens to biological networks when cells or tissues transition from a normal to a diseased state? Dr. Sol Efroni, head of BIU's Systems Biomedicine Lab, is quantifying the network-wide changes that occur when normal tissue becomes malignant. Using high throughput techniques that allow him to identify a broad range of simultaneous interactions, Efroni also develops computational tools that help identify specific targets for drug-based intervention.

An expert in the complex give-and-take that leads to the control of gene expression, Prof. Uri Nir has discovered a molecular factor that triggers network-level processes that, in several tissue types, lead to cancer. Nir's work focuses on an enzyme that plays a pivotal role in the onset of colon, prostate and breast cancers. The fact that this same enzyme-based mechanism appears in all these cancers indicates that Nir may have found an important molecular junction where normal tissues turn cancerous. Currently Prof. Nir is engaged in developing new anti-cancer drugs that will target this key regulatory enzyme.

Dr. Yanay Ofran also takes a systems-based approach to cancer – or more specifically, to cancer patients. Seeking to understand why patients with identical diagnoses often respond differently to treatment, Ofran is examining tiny genetic variations referred to as Single Nucleotide Polymorphisms, or SNPs. Ofran is looking at how SNPs – which usually do not produce physical changes – may predispose people to disease and influence their response to drugs. He is also examining how certain SNP combinations are linked to specific tumors and treatment outcomes. Ofran is also using genomic data to predict how patients will respond to various combinations of chemotherapeutic medications.

An expert on "silencing" RNA – genetic material that prevents the expression of specific genes – Dr. Shulamit Michaeli designs and synthesizes RNA-protein complexes that inhibit the function of a variety of genes involved in the onset of cancer. Michaeli's silencing RNA is delivered by a nanosized inorganic particle created in collaboration with Prof. Jean-Paul Lallouche. In another area of her research, Michaeli has parleyed her systems-based understanding of diabetes into a biotechnological breakthrough: an implantable bio-sensor – developed together with Dr. Benny Motro – that continuously measures levels of glucose in the blood, and transmits the results in real time to a monitor outside the body.

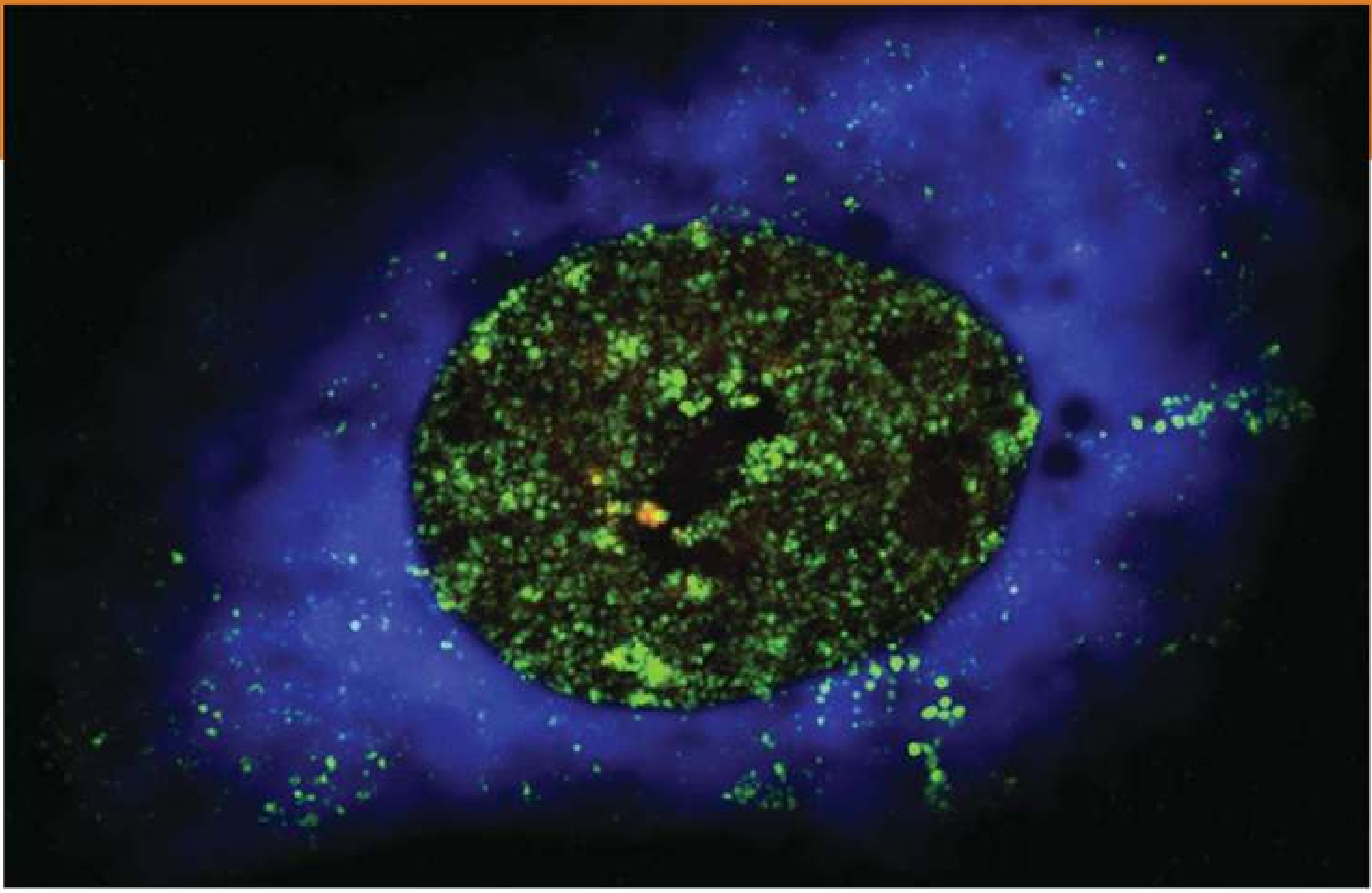
Creating New Tools of the Trade

Genetic signaling begins inside the cellular nucleus. But what exactly are these signals, and what happens to them in the case of disease? Using techniques taken from the world of molecular cell biology in combination with time-lapse microscopy, Dr. Yaron Shav-Tal has created a unique experimental set-up that quantifies the rate at which individual genes are switched "on" and "off" in the nucleus, and – for the first time in any lab – reveals the path that genetic signals follow on the way to protein production. Shav-Tal is also looking at how these processes differ in the case of cancer.

When body cells replicate and pass down their genetic content, certain well-preserved families of proteins sometimes "edit" DNA and RNA. While until recently such events were considered rare, it is now known that there are a wide range of subtle changes that have a significant impact on human health, and can be associated with several neurodegenerative diseases as well as cancer. Bioinformatics expert Dr. Erez Levanon uses computer "libraries" of sequenced genes to quantify the prevalence of this editing activity, and has discovered numerous such DNA and RNA editing sites. One change that appears more than any other is an "edit" in which the genomic encoded nucleotide Adenosine (A) is transformed in the RNA into Inosine (I) – which in turn, is read as a G (Guanine) by the cell's internal machinery. In another area of his work, Levanon has created an inexpensive, high-throughput technique that screens hundreds of RNA sites for editing changes – information that may someday be parleyed into new drugs designed to control editing activity.

➔ Mathematical models, computer simulations and bioinformatic techniques help BIU researchers understand how the immune system behaves in the presence of cancer.

Another BIU scientist who uses high throughput techniques to study disease – in this case, viral disease – is Dr. Doron Gerber. Gerber has created a new technology that addresses a vexing biomedical "bottleneck"– the fact that traditional protein replication techniques produce inactive viral proteins, or, if active, produce them in insufficient quantities for the many experiments needed to isolate important protein-protein interactions. Searching for a way to do more with less, Gerber designed a tool etched with thousands of "microfluidic" channels. Inside these channels, thousands of experiments – each consisting of a unique protein-protein interaction – can be performed simultaneously.



Fighting cancer requires a strategy, and strategy is the specialty of Prof. Ramit Mehr, a computational immunologist who uses mathematical models, computer simulations and bioinformatic techniques to understand immune system dynamics. Mehr has created models for how the immune system will behave in the presence of cancer and other diseases. In a recent project, Mehr devised a novel method for analyzing the genetic mutations in lymphomas, which are cancers of antibody-forming cells. Her work has demonstrated that the molecular factors triggering cell death or promoting survival in lymphoma cells – as well as those cells involved in the chronic inflammation that can lead to cancer – are different from the factors that determine cell death and survival in normal, non-cancer-related cells.

Another researcher who is modeling the body's response to pathogens is Prof. Avidan Neumann. Using computational techniques as well as tools of bioinformatic analysis, Neumann examines the evolution of the viruses that cause malaria, hepatitis, AIDS and other infectious diseases. Neumann is now applying his modeling techniques to the search for a clearer picture of how the human immune system responds to cancer.

Prof. Ron Unger is another BIU researcher working in the areas of bioinformatics and computational biology. In a bid to bridge the gap between biology and computer science, Unger's work involves adapting algorithms to specific biological questions, while framing biological concepts – such as neural networks and genetics – in computational terms. His work is revealing important data related to the three-dimensional structure of proteins and protein folding. He is also examining the controlled flow of genetic information on the genome-wide level, with particular focus on the function of non-protein-producing RNA elements.

Progress on Every Level

At Bar-Ilan University, scientists are incorporating systems-level data into new strategies for fighting disease. By advancing integrated research that examines life in all its marvelous complexity – from the molecular level to the level of the living organisms – Bar-Ilan researchers are leading the way toward the effective – and personalized – medicine of tomorrow.

For more about the research of BIU faculty listed in this brochure go to: www.biu.ac.il and click Research.

The Gonda (Goldschmied) Medical Diagnostics Research Building

Bar-Ilan University

Science and Technology

Bar-Ilan University stands at the forefront of cutting-edge research. Bar-Ilan researchers are making breakthroughs that improve life around the globe in areas such as drug-development, nanotechnology, medical research, bio-engineering, microscopy, optics, communications, energy, security, and more. As part of a national program to combat Israel's brain drain, BIU has taken the lead by committing to absorb dozens of returning experimental scientists within its world-class research infrastructure, and has added state-of-the-art physical facilities in engineering, brain sciences and nanotechnology to house these innovative initiatives. The Science and Technology Series highlights some of the University's most exciting research endeavors.

Tradition of Excellence
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