Science & Technology Series

Infectious Disease Research

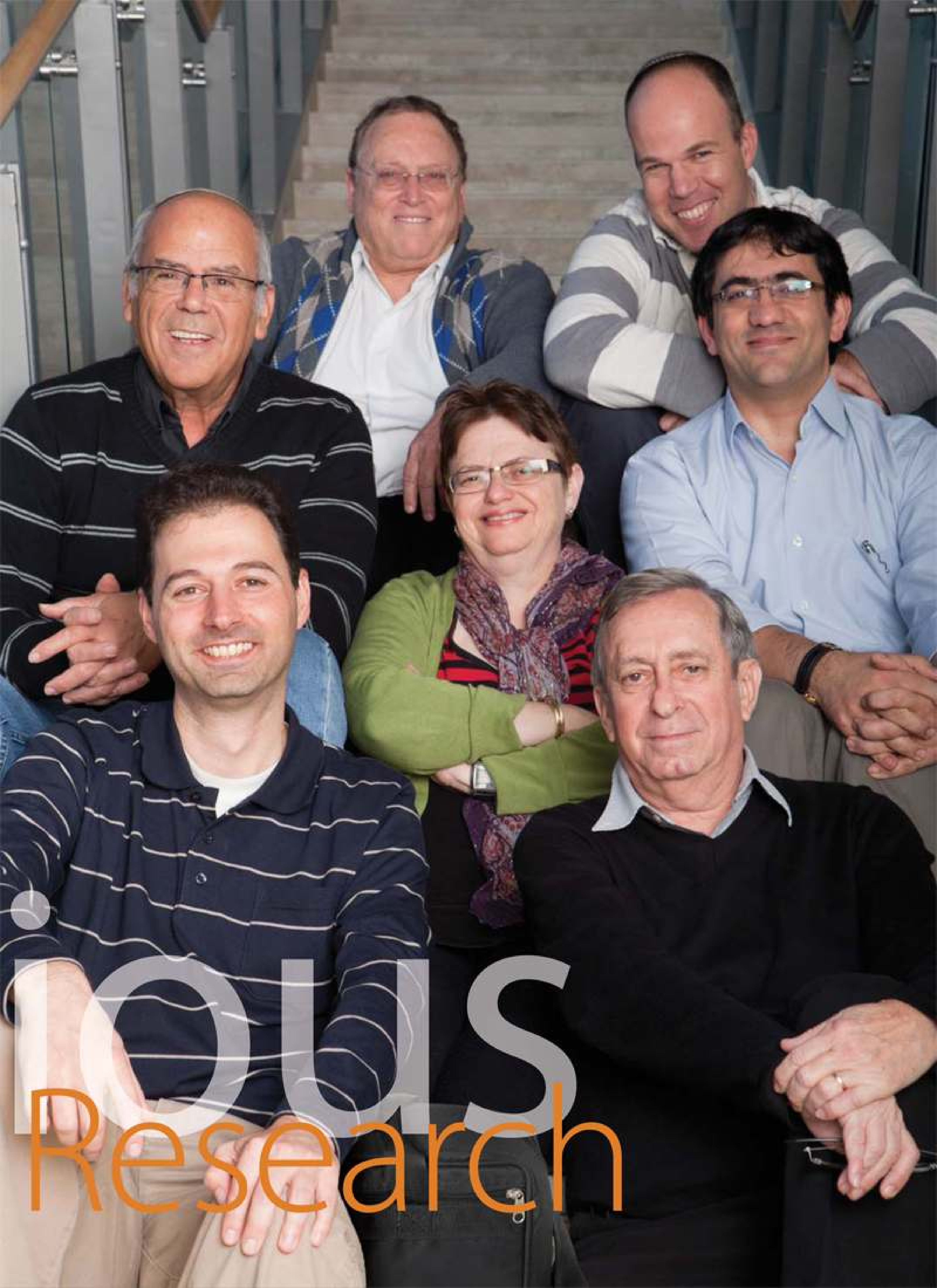
Stopping the Scourge

Bar-Ilan University
Tradition of Excellence

At Bar-Ilan University, scientists from a wide range of disciplines are working together to forge a better understanding of infectious diseases and to create a new "toolkit" for clinical treatment.

Pictured from left to right:
Top:
Prof. Shlomo Margel
Dr. Ehud Banin
Middle:
Prof. Aharon Gedanken
Prof. Shula Michaeli
Dr. Shai Rahimipour
Bottom:
Dr. Doron Gerber
Prof. Benjamin Sredni

Infect
Disease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Research

Alexander Fleming

Eighty years after Sir Alexander Fleming first observed the bacteria-killing action of the mold *Penicillium notatum*, the fight against infectious diseases is far from over. While mankind survived the Black Death – a plague that claimed the lives of over 25 million Europeans during the Middle Ages – and the influenza pandemic of 1918 may seem like a distant memory, the modern world is still threatened by the scourge of infection. In fact, malaria, a disease that has caused more deaths than any other illness in history, still kills 1.5 to 2.7 million people annually – and another child every thirty seconds.

Despite intensive efforts, science has not yet found a way to stop infectious disease. This is because the microorganisms that carry infection are moving targets, constantly evolving and becoming impervious to existing medications. Misuse of antibiotics is adding to the problem, with incomplete treatments killing only the most susceptible bacteria while helping the most drug-resistant strains to achieve dominance.

Another serious issue is clinical treatment. Viruses wreak their havoc by integrating into cells and taking over their genetic machinery. Parasites are similar in many ways to the cells they attack. As a result, drugs designed to fight these invaders frequently damage healthy tissues as well.

At Bar-Ilan University, scientists from a wide range of disciplines are working together to forge a better understanding of infectious diseases and to create a new "toolkit" for clinical treatment. Partnering with colleagues trained in nanotechnology, materials science and computers, Bar-Ilan's bacteriologists, virologists and parasitologists are creating new strategies for "cornering and conquering" the agents of infection.

Know Your Enemy

Dr. Ehud Banin is examining how bacteria "team up" to form an antibiotic-resistant collective called a biofilm. Not only do these collectives help individual bacteria survive – their architecture includes channels that allow nutrients to come in and waste to go out – biofilms serve as "safe havens" for disease-causing pathogens. By revealing the specific pattern of gene expression that allows harmful bacteria to band together and survive, Banin's work is defining an important target in the ongoing fight against antibiotic resistance.

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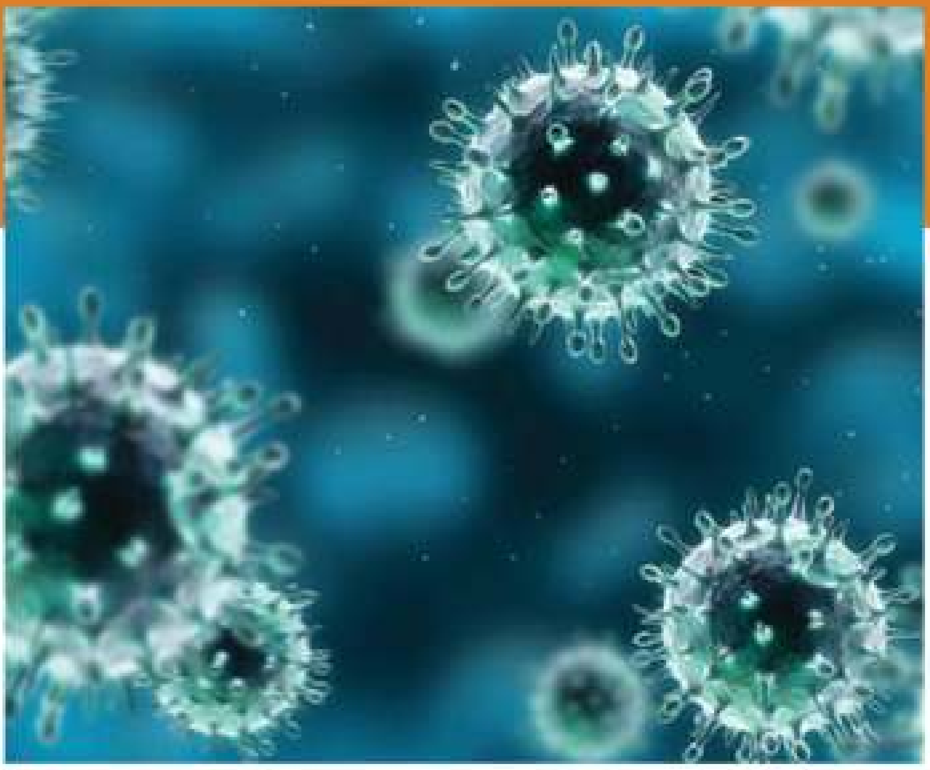
Another weapon in the bacterial "arsenal" is being studied by Prof. Nechama Gilboa-Garber. In 1972 Gilboa-Garber was the first to discover bacterial lectins – a class of proteins that, owing to their attraction to sugars, allows bacteria to attach to the surface of host cells. Since then, she has identified nine additional lectins. Her work has provided important data about how the lectins of virulent bacteria contribute to the establishment of their infectious diseases. In animal models, Gilboa-Garber has proven the efficacy of lectin vaccines and drug treatments for blocking bacterial lectin activity. She has also demonstrated how sugars from common nutrients can prevent these proteins from helping bacteria adhere to host cells.

Bacterial adhesion is also being examined by Prof. Yeshayahu Nitzan. Focusing on the external "loops" of proteins located on the surface of a pathogenic bacterium, he characterized how these loops contribute to adhesion and infection. Nitzan and his collaborators are examining strategies for blocking the adhesion of bacteria to fractured bones.



Looking for the Big Picture

In the area of virology, Dr. Doron Gerber is mapping the complex interactions that allow viruses to "hijack" healthy cells and take over their genetic machinery. Gerber's studies – based on high-throughput tools that Gerber himself designed – tease an enormous amount of network-based information out of a very tiny liquid sample. Using this platform, Gerber has characterized a new function for a membrane protein from the Hepatitis C virus. He has also identified a compound for combating this function that has successfully passed preliminary clinical tests.

Prof. Avidan Neumann is another BIU scientist who is looking for the big picture on viral infection. An expert in bio-mathematical modeling, Neumann uses the tools of bioinfomatics to simulate the evolution of infectious agents including HIV – the virus that causes AIDS – as well as hepatitis, Ebola and influenza. By modeling the activity of these viruses – as well as the immune system's response – he is helping to define targets for more effective anti-viral therapies.

Cancer is usually not associated with infectious disease, but there are some viruses that trigger the growth of malignant tumors. One of these is Kaposi's sarcoma-associated herpesvirus, or KSHV. Prof. Ronit Sarid is a noted authority on this virus, which – in a minority of infected individuals – triggers malignant skin lesions. Sarid has identified a number of factors that can cause a "sleeper" virus like KSHV – which often remains dormant in the body for many years – to "wake up" cancerous processes. In another project, Sarid is investigating the role of selected viral proteins in infection-related tumor growth. Using the genes that code for these viral proteins as probes, Sarid is helping to clarify the cellular interactions involved in cancer onset.

Pinpointing Genetic Differences

Parasitology research at Bar-Ilan is centered firmly in the lab of Prof. Shulamit Michaeli. Michaeli's pioneering work focuses on trypanosomes, parasitic protozoa that cause sleeping sickness, as well as other devastating diseases. Early in her career, Michaeli demonstrated how the genetic code of trypanosomes periodically undergoes fundamental changes. This led to seminal discoveries about trypanosome RNA – the genetic "messenger" molecules that mediate protein synthesis. Based on these discoveries, Michaeli was able to pinpoint fundamental genetic differences between parasites and the host organism, creating a clear target for anti-parasitic gene therapy.

➔ Bacterial biofilms that develop on the surface of medical implants are responsible for fully 60% of infections acquired in hospitals. A number of BIU teams are working on new, nano-technology-based strategies for combating this phenomenon.

BIU Fights Back

Drugs that target bacteria are distributed uniformly throughout the body, creating toxic effects that cause damage to healthy tissues. That's why a new nanotechnology-based approach from Prof. Jean-Paul Lellouche's group is a step in the right direction. Lellouche has engineered a silica-based nanoparticle that can carry a "payload" of various types of bacteria-killing medication. The nanoparticle's inorganic shell prevents the medication from leaking into the inter-cellular environment and damaging healthy cells.

Once a bacterium engulfs the nanoparticle, however, the shell is destroyed, releasing the bacteria-killing medication at full strength, right on target.

Profs. Yeshayahu Nitzan and Zvi Malik are "photokilling" bacteria by exposing them to light in the presence of a photosensitizer. This process – which employs a class of light-sensitive compounds called porphyrins – may be used for treating infected burns and skin wounds. Nitzan and Malik have also created a chemical technique that increases the number of light-sensitive porphyrins generated inside bacterial cells – a process that renders these bacteria susceptible to photodynamic therapy and has been successfully used for treating acne. With Dr. Rachel Lubart, Nitzan has shown that visible light at high intensity can kill bacteria in infected wounds, resulting in faster healing.

Prof. Aharon Gedanken and Prof. Yeshayahu Nitzan have demonstated that nanoparticles can kill pathogenic bacteria on direct contact. Working together with Dr. Ehud Banin, Prof. Gedanken is also developing antibacterial nanoparticles for coating the surface of catheters and other implanted medical devices.

Other BIU researchers working in this area include Prof. Shlomo Margel, who is developing techniques for anchoring molecular "brushes" primed with anti-microbial agents onto the surface of polymeric materials, and Dr. Shai Rahimipour, who has successfully discovered a general approach that converts a wide variety of substrates into self-disinfecting surfaces that kill bacteria on contact.

Finally, in research that may help clinicians overcome the problem of mutational drug resistance, Prof. Amnon Albeck and Dr. Michael Shokhen are developing computational tools for the design of new antibacterial and antiviral drugs based on enzyme inhibitors.

the Scourge

Combating Diseases

Viral infections are notoriously difficult to treat because, as German biophysicist Max Delbruck once quipped, viruses "make themselves known by the cells they destroy, much as a small boy announces his presence when a cake disappears." But here again, nanotechnology may hold the key to a cure.

In the laboratory of Prof. Ronit Sarid, gold- and silver-capped nanoparticles have been shown to inhibit viral infection in culture. The nanoparticles, synthesized through a microwave-based technique pioneered by Prof. Aharon Gedanken, mimic heparan sulfate (HS), a molecule that serves as a cellular receptor for a number of viruses, including HIV. So far, Sarid and Gedanken's HS-like compound has been shown to block infection by herpes simplex, as well as five different viruses that trigger influenza.

➔ Nanotechnology may hold the key to curing viral infections.

Another BIU project is using nanotechnology to enhance the immune system's ability to fight both viral and parasitic threats. Prof. Benjamin Sredni, former Chief Scientist of the Israeli Ministry of Health, was the first to develop a method for producing large numbers of lymphocytes – important players in the immune response – from a single cell. This led to the synthesis – with Prof. Michael Albeck – of a compound called AS101, which significantly stimulates immune function. AS101 has been shown to be effective against the herpes virus CMV, and a malaria-like parasitic disease called Babesiosis. Working with Prof. Nitzan, Prof. Sredni has also demonstrated that AS101 can efficiently destroy antibiotic-resistant bacteria.

➔ Bar-Ilan researchers are creating new approaches to combating parasitic diseases.

Enhancing the Immune System

Prof. Shulamit Michaeli is pursuing a number of projects that are creating new approaches to combating parasitic diseases. Building on her research about how RNA helps parasites survive inside a host cell, Michaeli is now exploring RNA "silencing" as a potential parasite-killing therapy.

In collaboration with Prof. Jean-Paul Lellouche, Michaeli is fabricating hybrid nanoparticles in which "silencing" RNA – genetic material that prevents the expression of specific genes – is bound to the surface of various types of inorganic nanosized carriers. In another project, conducted together with Prof. Aharon Gedanken, Michaeli is employing microwave-based techniques to create nanoparticles from RNA itself. She is also working with Dr. Yaron Shav-Tal, whose unique imaging techniques allow her to track parasitic protein production on the molecular level.

Saving Lives

Ever since the dramatic discovery of penicillin, science has been trying to keep one step ahead of infection, as infectious agents develop new forms of resistance to tried-and-true medications. By pursuing multi-disciplinary research that links teams based in the biological sciences with experts in nanotechnology, chemistry and computers, Bar-Ilan University is pioneering new ways to close in on this elusive target.

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

A peek into a lab at BIU's Leslie and Susan Gonda (Goldschmied) Nanotechnology Triplex

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.

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