

BIOTECHNOLOGY Takes Center Stage

by Shimmy Carlebach

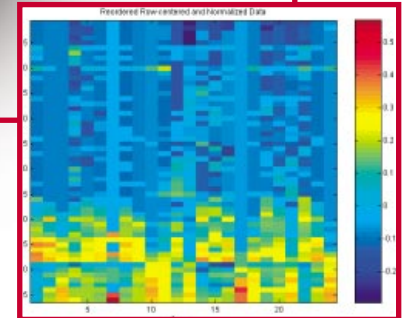
New approaches and technologies have broadened the scope of biotechnology

In zero gravity, aboard the space shuttle Columbia's upcoming flight, Air Force Colonel Ilan Ramon – Israel's first astronaut – will carry out experiments on adult stem cells that have been genetically engineered to grow into bone tissue by his old friend, Professor Dan Gazit of the Hebrew University's Faculty of Dental Medicine.

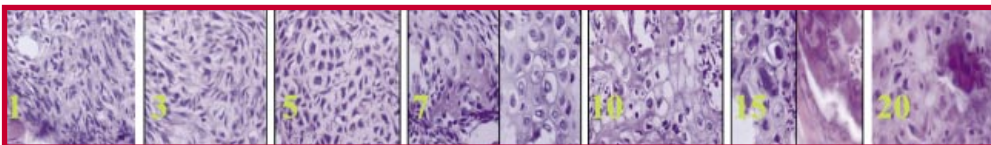
The underlying motive for Gazit's research, however, is firmly grounded on earth. By comparing the behavior of the genetically altered cells in space and on earth, Prof. Gazit hopes to discover the molecular mechanisms involved in loss of bone mass (which occurs among some elderly people and all astronauts) and how to forestall it. His main aim, in the long-term, is to provide bone-damaged patients with transplants of new bone tissue grown from their very own marrow.

Gazit was one of the first researchers to genetically engineer adult, as opposed to embryonic, stem cells for therapeutic use, an approach that addresses the concerns and resolves the ethical dilemma surrounding embryonic stem use. His novel skeletal regenerative therapy – which works for cartilage, tendon and ligament tissue as well as bone – is also the basis for a new biotechnology company, SBT (Skeletal Bio-Therapy) Ltd., established last year by Yissum, the Hebrew University's research development company.

Gazit's research typifies biotechnology, a term that is broadly defined as the elucidation of basic mechanisms of living organisms and the development of methods that utilize or apply these mechanisms. Biotechnology also includes the development of tools to support such research through fields such as biophysics, bioinformatics and bioengineering, and related research can stretch to such seemingly far-off fields as law, ethics, philosophy and economics. In recognition of the growing importance of the academia-biotechnology relationship, University Rector Professor Haim D. Rabinowitch



Left: University Vice-President for Research & Development Prof. Hillel Bercovier, right: University Rector Prof. Haim D. Rabinowitch
Opposite, top: Computerized reading of novel gene expression in bone formation, below: computer and x-ray images showing fracture (left) in forearm bone and healed fracture (right) after skeletal regenerative therapy



Sequence shows development of genetically engineered adult stem cells into cartilage and bone cells

Prof. Danny Gazit



last year set up a steering committee, chaired by Gazit, to evaluate and advance all University research and teaching activities in biotechnology.

Although biotechnology led the worldwide love affair between industry and academia in the 1980s, it quickly took a backseat to the emerging hi-tech ventures that yielded quicker profits. Now, says Rabinowitch, biotech is back – and not because the hi-tech bubble burst.

“There is a new approach to doing science,” he says. “Whereas biological discovery in the 20th century was about breaking down processes to their elemental parts like mitochondria in cells and a gene in DNA, that in itself could not lead to practical solutions for, let’s say, the farmer.”

Current scientific approaches such as genomics, proteomics or cellomics, however, offer an overall picture of the DNA or protein activity of an organism expressed in a cell and that control specific developmental processes, thus helping make practical manipulations more feasible. Such research has become possible thanks to genome projects, such as the human genome, which map the entire genetic blueprint of a species and produce vast databanks of informational material.

The databanks are “like a dictionary of words,” says microbiologist Professor Hillel Bercovier who is Vice President for Research and Development. “But you need to create a language and construct sentences which relate the data to functional processes.” Indeed, it was just such a process, he notes, that led Faculty of Agricultural, Food and Environmental Quality Sciences scientists in physiology, analytic chemistry, breeding, genomics, proteomics and bioinformatics – the last of which harnesses computer science with life sciences – to discover how flower genes function with regard to fragrance.

“Once we had acquired that knowledge,” recalls Prof. Rabinowitch, a plant physiologist and former dean of the Faculty of Agricultural, Food and Environmental Quality Sciences, “it allowed plant biologist Dr. David Weiss to restore fragrance to flowers whose scent was lost over decades of breeding for color, ornamentation, size and long shelf life.

“An analogous approach by a team headed by another Faculty plant scientist,

‘THE LINK BETWEEN BASIC AND APPLIED SCIENCE IS NOW CLOSER THAN EVER’

Professor Oded Shoseyov, led to the establishment of one of Israel’s top start-up companies, CBD-Technologies Ltd.,” adds Rabinowitch. “The company genetically engineers plant growth enhancers that promise to play an important role in increasing world

production of cellulose, a plant-derived polymer that is ubiquitous in everyday products such as paper, packaging and clothing,” says Shoseyov.

“WITH half of the Israeli biotech industry now centered around Jerusalem and Rehovot – the cities where we have our campuses – the relationship between the Hebrew University and biotechnology is flourishing,” says Rabinowitch.

“We are the country’s leading producer of graduate students and research in biotechnology-related fields,” reports Prof. Gazit. “We enroll close to half of the country’s masters and doctoral students in biotechnology.”

“Our hidden strength,” says Prof. Bercovier who oversees all aspects of the University’s research funding “is that some 75 percent of our research grants are allocated to basic science. The link between basic and applied science is now closer than ever – and our unique approach is to train scientists who can switch focus at ease.” In addition to the University’s many programs in biotechnology-related fields, the faculties of Medicine, Dental Medicine, Science, and Agricultural, Food and

Environmental Quality Sciences run a joint graduate program in biotechnology. And outside science, notes Prof. Rabinowitch, programs and courses that address specific



Clonal plants (above) are genetically engineered and undergo several stages of development such as callusing (top) and elongation (right) to enhance their growth

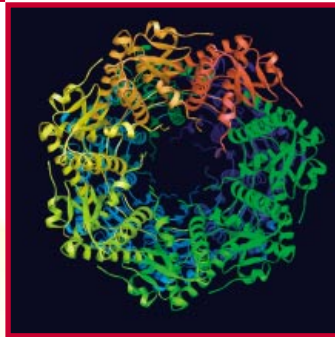
Prof. Oded Shoseyov





When a new protein (right) is discovered in a cell (above), the genetic analysis of its structure and function is aided by mapping (below) its components and comparing them with protein and protein clusters whose structures are known

Prof. Michal Linial



aspects of biotechnology are up-and-running or at the planning stage at the Jerusalem School of Business Administration, and the faculties of Law, Social Sciences and Humanities.

More recently, in June 2002, the first class of the flagship undergraduate program in computational biology graduated. The program – which, since 2001s, has provided scholarships to its top first-year students through a gift from the Goldie-Anna Charitable Trust and trustee Kenneth L. Stein – brings together computer science and life sciences, says program director Professor Michal Linial. “This ensures that we produce graduates who are both highly trained biologists and computer engineers, not just a bit of both. Whatever the field they choose,” she says, “we want to prepare our graduates for the top jobs.”

Linial, a biochemist who employs genomics and proteomics technologies in her work at the Alexander Silberman Institute of Life Sciences, is excited about the technological breakthroughs that underlie the new approaches to research: “Within the last five years or so, new ‘DNA arrays’ chip technology has allowed us to fit on one tiny slide all the genes being expressed in, say, a tumor cell and compare it with a slide of all the genes of a neighboring, healthy, cell. This means that we can identify the genes that specify the cancer in that individual.”

Such technology narrows the gap between academic research and medical diagnosis. “Very soon,” says Linial, “clinics should be able to compare levels of gene expression in a family with a history of cancer and ascertain the varying levels of susceptibility in each member.”

In her own research in neurobiology, Linial compares the dying and normal brain cells of Alzheimer’s patients in order to uncover the network of genes connected to the disease. “Cell function is determined by gene-coded proteins. It used to take ages just to isolate and identify single proteins. Now, we can take a snapshot of thousands of functioning proteins in diseased and healthy cells and use it to track down the candidate genes for the disease.

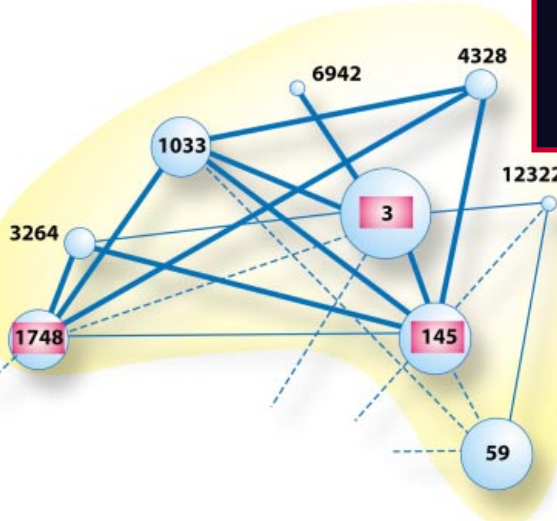
“With vast amounts of data generated by such experiments, the major thrust in bioinformatics today,” says Linial, “is the development of methods to eliminate results that are not directly relevant.” The Hebrew University is considered a world leader in this field, called ‘gene expression analysis’, which brings together computer scientists, mathematicians and biologists. Their efforts are coordinated by the Faculty of Medicine’s bioinformatics laboratory established by molecular geneticist Professor Hanah Margalit who chairs a University committee on bioinformatics.

AS part of the renowned Canada-based team that discovered and cloned the cystic fibrosis gene some 13 years ago, geneticist Batsheva Kerem is a veteran genomics expert and Scientific Director of the national Center for Genomic Technologies. The Center, which serves academics, hospitals and the biotech industry, was established at the Hebrew University in 2001, with the support of the Ministry of Science and the Israel Academy of Sciences and Humanities.

“This is the only center in Israel providing whole genome scans,” says Professor Kerem. “We serve as a research and service laboratory for whole-genome analysis of mammalian, plant, or bacterial DNA. Last year we helped identify regions in the human genome associated with schizophrenia, asthma and deafness. We have also helped search, for instance, for regions associated with low fat in chickens.

“We use a state-of-the-art automated DNA sequencing machine to identify the genes that code for an organism. We also provide DNA microarray technology whereby hundreds of thousands of genes are printed on to a small surface and their expression

'WE PRODUCE GRADUATES WHO ARE BOTH HIGHLY TRAINED BIOLOGISTS AND COMPUTER ENGINEERS, NOT JUST A BIT OF BOTH...'

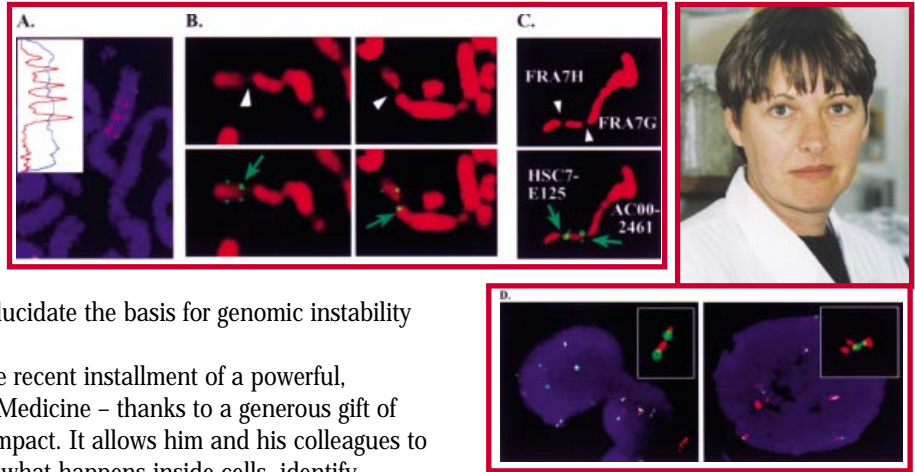


levels evaluated. This past July, we ran the country's first graduate course on microarray technology."

In her own research at the Silberman Institute of Life Sciences, Professor Kerem makes full use of these new technologies to investigate the role of other genes in determining the severity of cystic fibrosis, while also working on therapies for the disease. Her research team is also seeking to elucidate the basis for genomic instability in cancerous cells.

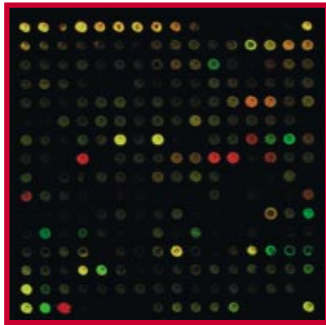
For cancer researcher Yinon Ben-Neriah, the recent installment of a powerful, advanced mass spectrometer at the Faculty of Medicine – thanks to a generous gift of the Horowitz Foundation – has had a similar impact. It allows him and his colleagues to see “exactly what happens inside cells, identify proteins, determine their sequences and, thereby, track previously hidden biological transformations.” It also provides the basis for a new center in proteomics that he will head.

“It is not just a matter of providing the right tools,” says Professor Ben-Neriah, the incumbent of the Blumenthal Chair in Basic Cancer Research. “In addition to providing help to the broad range of protein-based research carried out at the University, we will also train students to work in this new field,”



Prof. Batsheva Kerem

Above: Microscopic images showing genomic instability in cancerous cell: the breaks in the gene cause it to replicate itself 10 times, thus triggering cancer, left: DNA microarray technology allows for the evaluation of the expression levels of hundreds of thousands of genes



'LAST YEAR WE HELPED IDENTIFY REGIONS IN THE HUMAN GENOME ASSOCIATED WITH SCHIZOPHRENIA, ASTHMA AND DEAFNESS'

he says. “Next year, we plan to open a master’s program in proteomics, in collaboration with the University’s Wolfson Center for Structural Biology and the School of Engineering and Computer Science. The program will include Israel’s first mass-spectrometry protein analysis course for research students, given by Dr. Dan Gibson of the School of Pharmacy and which began this year.”

Ben-Neriah himself, in collaboration with Technion and Weizmann Institute scientists, is part of an Israel Academy of Sciences and Humanities National Center of Excellence team that is pioneering research on ‘ubiquitination’, a highly common mechanism of protein destruction whose prize-winning discovery was made by his Technion collaborators Professors Aaron Ciechanover and Avram Hershko.

The research team’s papers have been widely cited – and, in keeping with the academia-industry alliance that characterizes biotechnology in the 21st century, many biotech companies have already jumped onto the ubiquitin bandwagon as they strive to develop revolutionary cancer therapies.

Prof. Yinon Ben Neriah

Proteomics work shows changes and interactions of proteins in cells: radiogram (left) identifies site of protein activity, mass spectrometer readings (right) allow for identification of a specific protein whose activity is then illustrated in schematic diagrams (below)

