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R&D
in Israel

The New Frontier:
ISRAEL'S BIOTECHNOLOGY

Israel's hi-tech industries are in the doldrums, owing to the slump in this sector throughout the Western world and to the Palestinian war of terror against Israel, which has deterred investors and helped stall the economy. Nevertheless, biotechnology companies here seem to be alive and kicking.

The number of biotech companies – defined as enterprises that synthesize copies of substances found naturally in minute quantities in humans, animals, and plants and study their genetic makeup to produce drugs that treat diseases – has been growing at an estimated 17 percent annually, despite the serious decline in the economy. The country's 160 biotech firms (compared to only 30 a decade ago) employ some 4,000 workers and show annual sales of nearly $1 billion. If all goes well, according to Industry and Trade Ministry chief scientist Dr. Carmel Vernia, Israel could control one to three percent of the world's biotech market by the end of this decade.

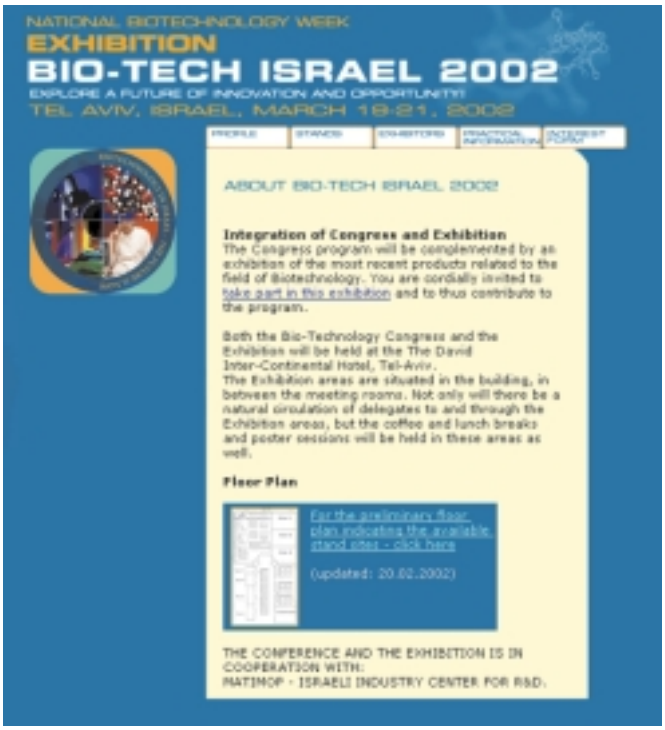
A report recently released by the investment firm Ernst & Young reflected this impressive growth in Israel's life-sciences industries. Last year, investment in Israel's life sciences sector increased by 43 percent, reaching $293 million. The number of individual investments has doubled since 1999. Israel now ranks second in the world in the number of life-science startups launched each year.

Prof. Yosef Yarden, a biotech expert at the Weizmann Institute of Science in Rehovot, has predicted that by 2010, there could be between 12,000 to 15,000 workers in 500 biotechnology companies, producing $5 billion worth of products a year. Local biotech firms' sales are less affected by the political situation than computer companies because the majority of them are global enterprises, with offices, management, and strategic partnerships outside the country.

On the other hand, experts note that it's become harder to obtain venture capital funds for advancing biotech developments. Dr. Haim Aviv, chairman of the Pharmos biotech company in Rehovot, said recently: "Let's face it, we are at war, and despite that, there is so much building going on in biotech, so much hope. Against the background of all the killing, we are developing drugs to save lives and treat people. Right now the money is still flowing, but at a much slower pace, and the longer this situation keeps on, the more difficult it is becoming."

Although foreign tourism has seriously declined in the past year for obvious reasons, representatives of about 25 companies and venture capital funds from eight countries did come to Israel to staff booths or lecture at Bio-tech Israel 2002, the first-ever government-sponsored biotech convention and exhibition, in conjunction with the newly launched annual National Biotechnology Week.

The organizers of the event, held March 19 - 21, were as pleased to see them as they were disappointed by the absence of the 75 foreign representatives who did not attend. "We are happy with those who came and understand those who did not," said David Haselkorn, CEO of Clal Biotechnology Industries Ltd., and one of the convention officials.



But Bio-tech Israel 2002 organizers were buoyed by the news that heads of the largest international biotech convention and exhibition in the world, Bio 2003 in San Diego, will hold a special session on the Israeli biotech industry. In addition, even if foreign attendance was disappointing, news of the Tel Aviv convention increased awareness among the Israeli public about the importance and promise of biotechnology. Jerusalem, which has long been regarded as a city of as many government bureaucrats as yeshiva students, is becoming the center of the country's biotech industry, along with Rehovot (home of the Weizmann Institute and Weizmann Science Park). The Israel Manufacturers Association reported last year that biotech has grown by 50 percent in the capital over the previous three years, with some 750 employees in 50 firms, most of them small. About one-third are young startups in existence for less than three years. But the number of firms and employees here is expected to double by the year 2007. Fully one quarter of all biotech companies are in Jerusalem (largely thanks to the capable graduates of the Hebrew University's life-sciences programs), compared to 27 percent in Rehovot and about 14 percent each in Tel Aviv and Haifa.

For decades, university scientists preferred to carry out basic research mainly to increase scientific knowledge and looked down on colleagues who left their ivory towers to pursue their professional interests by establishing or joining profit-making businesses. But things have changed: with the dearth of research funding for universities and the relatively rapid transfer of know-how from basic to applied science, many in the field have chosen to work in private industry.

Weizmann's Yarden advocates the establishment of strong links between academia and industry, but adds that once scientists in the universities complete the research phase, they should move off campus to complete their professional development. If not, there will be considerable tension, he says. "And we don't teach students in biotechnology the basics on how to raise capital, or business administration. They should at least learn the basics in order for them to set up their own businesses."

Among the first and most successful product to be sold to industry was Copaxone, the multiple sclerosis drug developed over a quarter century by Weizmann Institute researchers and sold to Israel's Teva Pharmaceuticals. This major intellectual property, also licensed in the U.S., Britain, and other countries, is an important weapon in the effort to reduce the frequency and severity of neurological attacks in patients with relapsing-remitting MS.

Octogenarian Prof. Ephraim Katzir, a one-term president of Israel in the 1970s and an outstanding biochemist, still doing research at the Weizmann Institute, says the country has a huge potential in the field, but that more funds must be invested in basic and applied scientific research, education, and developing industries to keep highly qualified young people from emigrating in search of good jobs.

When Katzir was a Defense Ministry chief scientist nearly four decades ago, he persuaded then-Prime Minister Levi Eshkol to appoint chief scientists to other ministries, even though the premier "didn't know what a chief scientist was or did." Katzir was also a leading member of several committees aimed at promoting Israeli biotechnology, and while some of their reports were ignored, research and development in the field were boosted as a result of his efforts.

"We must stress agricultural biotechnology," insists Katzir, "because while the country is cutting down on [conventional] agriculture, ways must be found to feed the growing number of mouths in the world. And biotechnology [in pharmaceuticals and medicine] is needed to provide medical care for the growing number of elderly."

At a recent symposium on medical physics and medical instrumentation at the 32-year-old Jerusalem College of Technology, a prestigious four-year engineering school for Orthodox Jewish students (men and women separately), medical engineer Prof. Yona Maller said that doctors "don't like theory. They are practical and are eager to use products that help their patients. Israeli researchers have very fertile, innovative minds. But investors have to be patient, because it takes some time and a lot of funds to get all the necessary approvals and prove safety and efficacy through many rounds of clinical trials."

THE FOLLOWING ARE SOME OF THE MOST CUTTING-EDGE BIOTECH COMPANIES IN ISRAEL:

IDgene Pharmaceuticals Ltd.

A passerby, the old story goes, was amazed to see a series of arrows stuck in the exact center of a series of bulls' eyes. Seeing a boy with a bow and arrow, the passerby asked him how he accomplished such a feat. "It's easy," explained the youth. "First I shoot the arrow at the wall and then I draw the circles around it." Researchers at IDgene Pharmaceuticals Ltd., a three-year-old Jerusalem genomics startup, have taken a similar approach. They have targeted the major chronic disorders that shorten lives and cause misery among the world's population both in the West and even in the developing world: diabetes, cancers, hypertension, atherosclerosis, Alzheimer's, Parkinson's, osteoporosis, psoriasis, schizophrenia, and rheumatoid arthritis. Instead of working at the gene level to discover what diseases they help cause, IDgene researchers are collecting blood samples from disease sufferers in a genetically homogeneous population. They are examining what gene forms these patients have in common, and plan eventually to zoom in on which of the mutations contribute to these disorders. The ultimate aim, whose achievement is still many years away, is the creation of a customized computer design of unique and specific medications to treat or even cure these diseases by homing in on the malfunctioning genes. IDgene has, for the first time ever, identified genes that are risk factors for schizophrenia. The company also wants to optimize existing treatments, enhance accurate diagnostics, and promote ways of preventing these disorders in genetically susceptible people. The homogeneous ethnic population that the company, based in ultramodern rented quarters in the capital's Givat Shaul quarter, is targeting Israel's Ashkenazi Jews. This sub-group, which comprises 2.5 million residents in Israel alone, displays significant genetic similarity, says Dr. Ariel Darvasi, IDgene's president and chief scientific officer. "Israel is also ideal for this research thanks to its highly developed Western-style medicine and well-trained researchers." Darvasi, a senior lecturer at the Hebrew University's Life Science Institute, is an internationally recognized geneticist who has published numerous articles in leading scientific journals. Before he established IDgene, he was associate director of human genetics and head of statistical genetics at the giant British pharmaceutical company, SmithKlineBeecham (now the world's largest pharmaceutical company, Glaxo SmithKline), where he introduced several of the genetic strategies that are applied in Britain today. Darvasi has received several awards for his work, including the prestigious Landau Prize.

IDgene's 40 geneticists, molecular biologists, computer experts, and others know that their work will not bear fruit overnight. But they are convinced that their population-based approach is an extremely promising one – used by only half-a-dozen other companies in the world. They involve such companies as Decode in Iceland (where the population is also highly genetically homogeneous and where there is a major library of family records); Gemini in England; Genomics Collaborative in Boston; and Signal Gene in Canada (with French Canadians as the study population).

But studying Jews of European origin, who today constitute more than 80 percent of all world Jewry, has unique benefits beyond their traditional endogamy (marriage within the community), Darvasi says. The early founders of the Ashkenazi community who left the land of Israel after the destruction of the second temple made their way to Europe during Roman rule. But the majority came more recently from the region of present-day Israel, moved to Spain, France, and Italy and then in the 10th century to the Rhineland valley in Germany. Prior to the first Crusade in 1096, it is estimated that the entire Jewish population of Germany numbered 20,000. The Crusades in the 11th to 13th centuries and the charters of protection granted to the Jews in 1264 in order to rebuild the Polish cities encouraged the migration of many Jews to Poland and Lithuania. The early Jewish settlements in these areas often consisted of only a few families that were isolated genetically, not only from their non-Jewish neighbors, but also from other Jewish communities.

Until the end of the Middle Ages, the Jewish population of Eastern Europe was very small, Darvasi says: There were only about 5,000 Jews in all of Poland and Lithuania seven centuries ago, and by 1490 their number had increased to between 10,000 and 30,000. In the mid-1600s, the Cossack uprising led to the massacre of many of the Jews of Poland and the Ukraine. In the 18th century, there was a large growth in the number of Ashkenazi Jews to about 750,000, but persecutions and economic difficulties in the 19th century caused many to emigrate to the U.S. and Palestine. The Holocaust wiped out one-third of the Jewish people, most of them Ashkenazi, and many of the survivors immigrated to Israel. In the last decade, 800,000 Russian Jews have reunited with their people here.

"The Ashkenazi Jewish population is unique in terms of its demographic history and genetic architecture. The history of the Ashkenazi population includes emergence from a limited number of founders, exceptional expansion and contraction of the population, and a long history of marriage within the family and within the faith. In addition, the unequal reproduction rate among the social classes of the Ashkenazi Jews made the effective population size much smaller. This means that the current Ashkenazi population did not originate from all of the founders living many centuries ago, but selectively from a small fraction of wealthier people," he continues.

The consequence of the unique demographic history of the Ashkenazi Jews is their similar genetic makeup and the retention at large distances of the correlation among polymorphisms. Inbreeding has

resulted in a number of genetic diseases that occur with a particularly high incidence among Ashkenazi Jews – but are rare among other populations – such as Tay-Sachs, Gaucher disease, Canavan disease, Bloom syndrome, idiopathic torsion dystonia, and familial dysautonomia. A specific, single genetic mutation resulting from a single "founder" for each disorder in Ashkenazi Jews has been identified for many of these disorders, with all of the known mutations dating back to the 9th and 14th centuries, when Jews migrated to Western Europe and the Jewish communities in Eastern Europe were founded.

"The high frequency of some genetic disorders among the Ashkenazi Jews (with a carrier rate of fewer than one per 100) indicates that the founder chromosome carrying the disease allele was introduced into a small population, probably on the order of about 100 unrelated individuals. Chronic diseases that affect all of mankind are due not to a single mutation like Tay-Sachs, but are polygenic, influenced by a relatively large number of genes, as well as by environmental and lifestyle factors. Identifying slight variations and targeting these shared mutant genes in a homogeneous population here can tease them out of the genome," Darvasi explains.

Thus, with Health Ministry permission, IDgene has asked suitable patients in all Israeli general hospitals who suffer from the major chronic diseases and have four Ashkenazi grandparents to donate a single blood sample for genetic testing; patients must give their written consent, and the resulting data are blind.

The company, which has a goal of collecting several thousand vials, gathers blood samples from Ashkenazi Jewish patients in the U.S. as well. Idgene's premises have several computerized polymerase chain reaction (PCR) machines and other devices to speed up genetic analysis of the samples. "Once we find these genes, we wouldn't necessarily develop the customized drugs ourselves but sign cooperation agreements with pharmaceutical companies that will do this and help finance our work," says Darvasi.

Last year, IDgene had its first success, completing a "proof-of-concept" experiment published in the journal *Nature Genetics*. "The results," declared Darvasi, "establish strong evidence supporting the superiority of the company's scientific approach to gene discovery. The study proved that the use of isolated populations such as Ashkenazi Jews can significantly increase the ability to identify genes affecting common diseases."

Although a young startup, ID gene has collected more than $8 million in funds, invested by APAX Partners (a London-based venture capital firm), Israel Seed Partners, and the Wellcome Trust (a charitable organization that funded a major part of the Human Genome Project along with U.S. government supporters).

"Life expectancy about a century ago was barely 50, because of the many deaths from infectious diseases that are now treated with antibiotics and other drugs," Darvasi concludes. "In the coming decades, people will live longer. But we want not only that they live longer, but that they enjoy a better quality of life. For this, we have to work on the aging process itself. If people age more slowly and suffer from fewer diseases, this will be a positive thing; there will be more contributing members of society and fewer will be sick and need help."

Compugen

Early diagnosis of prostate cancer is very difficult. For some years, urologists have used prostate-specific-antigen (PSA) screening, as PSA levels may be higher in men with prostate cancer; however, they can also be high in those who are free of cancer but have only benign prostate hyperplasia. Now Compugen, a computational biology company, has discovered two novel prostate-specific proteins encoded by the PSA gene, which may serve to improve diagnosis of the tumor. These proteins are encoded by alternative mRNA splice variants of the genes for PSA and its related protein, human kallikrein 2 (hK2). Compugen's findings were recently published in the *Journal of Biological Chemistry*.

The PSA and hK2 proteins could have important applications in developing new diagnostic tools for prostate cancer and for understanding the pathobiology of the disease, says Dr. Mor Amitai, Compugen's CEO. The company believes the novel proteins may provide additional tumor markers for the development of prostate-cancer diagnostic tools aimed at helping doctors to differentiate between the benign disease and malignant ones.

Bio-Technology General

In the U.S. alone, there are about 32,000 patients who suffer from severe, untreatable gout. The disease, which occurs mainly in men, causes swollen toes and severe pain and may lead to kidney stones, as well as joint damage. Bio-Technology General (BTG), based in Rehovot, has commenced a Phase I clinical study of Puricase, a polyethylene glycol (PEG) conjugate of uricase (urate oxidase), for the treatment of severe gout. The Phase I study, conducted at Duke University Medical Center, will evaluate the safety, tolerability, and pharmacokinetics of Puricase following a range of single doses taken by patients with symptomatic gout that does not respond to conventional treatment. Uric acid is a breakdown product that is normally excreted by the kidneys, but if an excessive amount accumulates, it can crystallize in the joints and cause gout. Current treatments for

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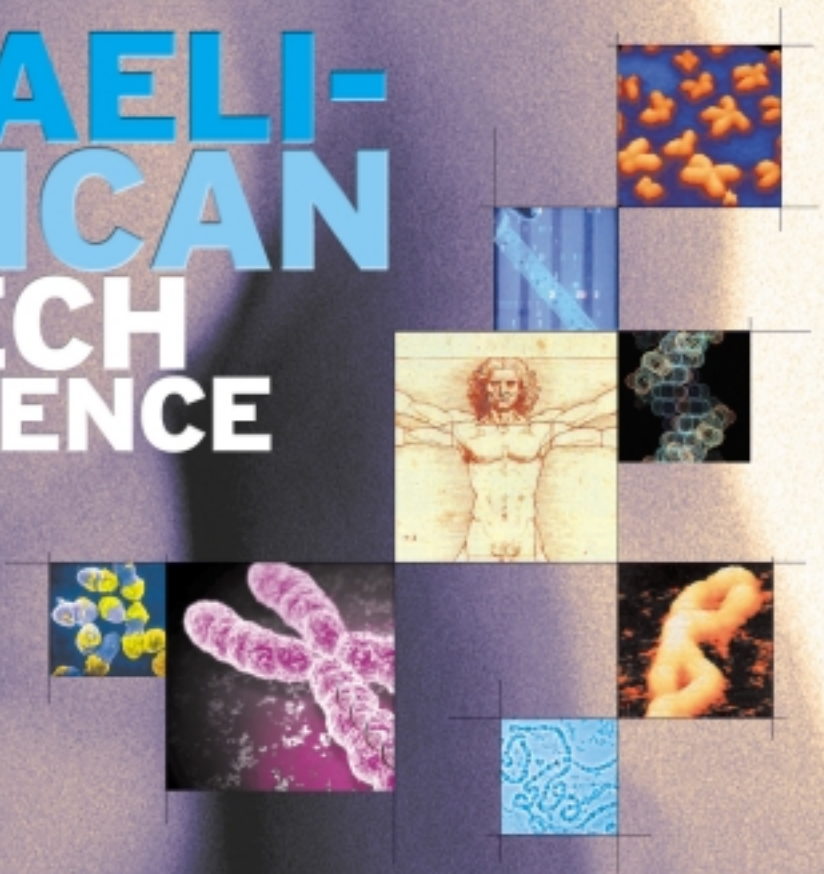
ISRAELI-AMERICAN BIOTECH CONFERENCE



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gout are sometimes ineffective and may even cause life-threatening allergic reactions.

Uricase, an enzyme produced by most animals but not by humans, converts uric acid into allantoin, a highly soluble and easily excreted product. Puricase is a chemically modified form of recombinant uricase, based on mammalian sequences, that is being developed by BTG. Compared to unmodified uricase, the PEG-modified enzyme is expected to circulate longer in the bloodstream and be less likely to induce immune reactions in humans. In February 2001, BTG received "orphan drug" status (drugs for diseases with a relatively small number of sufferers) for Puricase to treat gout patients for whom conventional therapy is contraindicated or has been ineffective. BTG licensed worldwide rights to the technology from Duke University and Mountain View Pharmaceuticals, Inc.

Other genetically engineered drugs previously developed by BTG include Bio Hep-B, an improved hepatitis B vaccine; Oxandrin, an anabolic steroid relative of testosterone that doesn't pose a risk of liver damage or cause androgenic effects in women, and that has been helpful for muscle-wasting cachexia in AIDS patients and others suffering from unexplained weight loss; Biotropin, a recombinant growth hormone; and BioLon, hyaluronic acid to enhance the results of cataract surgery and *in-vitro* fertilization.

Lapid Pharmaceuticals

Numerous drugs can lose their efficacy when the active ingredient is destroyed by gastric juices but are effective when given by injection. Lapid Pharmaceuticals has developed a technology that retains the efficacy of the active ingredient when some of these medications are ingested orally. The technology incorporates the Fmoc (9-fluorenylmethoxycarbonyl) moiety, which is attached to certain drugs that cannot be absorbed in their native form, enabling the drugs to be taken orally with sustained effect and reduced toxicity. With this technology, which was originally developed at the Weizmann Institute, the company has achieved preclinical evidence of oral availability and long-lasting effects.

Lapid Pharmaceuticals defines a ProDrug or a "prolonged-acting" drug as a compound that undergoes a chemical conversion to become an active drug when metabolized by the body.

"We have compared *in vivo* the ability of native anti-cancer drugs to be absorbed orally with our ProDrug," says company CEO Stanley Fass. "When the ProDrug is administered orally, it is found in the urine after one hour, meaning the drug was absorbed, while the native drug was not." Lapid is developing orally ingested ProDrugs based on doxorubicin, a treatment for hard tumors, GnRH for prostate cancer, and met-enkephalin, a naturally occurring pain reliever.

Oral availability is achieved through binding of the Fmoc moiety to an open amino, hydroxy or carboxy or other specific chemical group in the native drug compound. "The reaction is performed at room temperature, and the drug is protected as long as the Fmoc derivative is bound," says Fass, whose company was established in late 1998. The drug is cleaved from the Fmoc molecule only in a high-temperature (i.e., body temperature) environment with a pH of 7 or greater. As a result, drugs that would normally be broken down in the acidic environment of the stomach are protected, while the ProDrugs created by Lapid have shown the ability to penetrate the intestinal walls into the bloodstream.

Fass maintains that no one else has developed an oral version of these drugs. "The result will be improved compliance, fewer side effects, and less expensive treatments overall."

Ester Neurosciences

Post-traumatic stress disorder (PTSD) is clearly a psychological disease, but it now has been shown to have biological aspects. A new study on the connection between PTSD and the AChE-R protein helps corroborate Ester Neurosciences' drug-discovery program. The study, conducted by company chief scientist and Hebrew University Prof. Hermona Soreq (and published in the January 18 edition of *Science*), provides evidence that the otherwise rare protein accumulates in the body as a result of a psychologically traumatic event. Work carried out by Ester scientists suggests that there is an underlying common denominator to a wide variety of neurological diseases such as PTSD and the AChE-R protein. Now the company is focusing on developing drugs that will control this protein. The company's lead product, EN101, is currently undergoing human Phase Ib/II trials for myasthenia gravis, a debilitating autoimmune neuromuscular disease. Ester scientists say that a mechanical, chemical or psychological event can cause a "detrimental cascade of events" leading to accumulating levels of a pathological variant of acetyl cholinesterase, an enzyme involved in the degradation of neurotransmitter acetylcholine.

"The accumulation of AChE-R provides a unifying pathological mechanism common to a wide range of conditions, including post traumatic stress, Alzheimer's disease, head injury, as well as others," said Ester president Dr. Oded Ben-Joseph. "In this regard, we believe that the control of this stress-induced protein will provide a desperately needed disease-modifying therapeutic window."

These and dozens of other Israeli discoveries and developments have aroused much interest around the world. This is a country not only of terror victims, funerals, crises, and sadness, but also of unbridled curiosity, dedicated research, and hope for a better and healthier tomorrow.


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BIOTECH: REPAIRING the "irreparable"

Spinal-cord injury often means irreversible paralysis. A new therapy developed by Israel's Proneuron Biotechnology -using the body's natural immunobiological defenses- brings some hope.

From the moment on that cursed afternoon in June 2000 that 18-year-old Melissa Holley suffered a severely injured spinal cord in a car accident on a treacherous highway in Colorado's Rocky Mountains, the clock began to tick: she had to get to Israel within two weeks if she was to have a chance to participate in an experimental procedure that would restore some of her neural functioning. As it happened, her father, Roy, rounded the road soon after the accident and came upon his daughter and her crumpled car. He rushed her to the nearest hospital, where he was informed that she was completely paralyzed and without feeling below the middle of her chest, and that she would never walk again. Frantic, knowing nothing about spinal-cord injury and treatment, he turned to the Internet to search for help and learned of an experimental immune-system treatment about to be clinically tested at Sheba Hospital in Ramat Gan, near Tel Aviv. The treatment is based on years of research by Prof. Michal Schwartz, a veteran immunobiologist at the prestigious Weizmann Institute in Rehovot.

This therapy, which uses the body's own natural defenses to heal neural damage, has been approved for its Israeli trials by the U.S. Food and Drug Administration and Israel's Helsinki Committee on Human Medical Experimentation. Proneuron Biotechnology Ltd., which is located at the Rabin Science Park in Rehovot since it was established nearly six years ago, owns the rights for the treatment and agreed to accept Holley as the first patient. Dr. Valentin Fulga, director of the company's medical arm, along with some three dozen other employees, has achieved much with a relatively small financial investment.

Now back in Colorado, Holley has regained all feeling below the injury, as well as the ability to move her toes and some leg muscles, and she's fit enough to learn how to get around with crutches and braces. Although she is unable to walk independently, she is definitely better off than she would have been without the Proneuron treatment, and there is hope for further improvement. Holley's "miracle" was broadcast on NBC's "Nightly News," sparking much interest throughout the U.S. About one in 10 paralyzed patients regains some feeling following a spinal-cord injury after undergoing physiotherapy and steroid treatment. Proneuron's efficacy will be scientifically validated if three more paraplegics show improvement with the treatment. If such a result can be shown, then it can be determined with certainty if Schwartz's immune-system treatment was responsible for Holley's improvement or whether some of her spinal-cord tissue remained unharmed. After the current trials at Sheba Hospital, the Proneuron treatment is expected to be offered to several dozen patients in the U.S. and Europe, and if results are successful, it could earn FDA approval in two or three years.

Prof. Michal Schwartz

Luba Vikhanski,
Weizmann Institute of Science's publications department

The Proneuron treatment – which costs some $50,000 – has the potential to save money by greatly reducing the costs of caring for paraplegics. The life expectancy of paraplegics is much shorter than it is for healthy, ambulatory individuals. In the U.S. alone, between 10,000 to 12,000 people are paralyzed, mostly as the result of car crashes, jumping carelessly into swimming pools, or falling from horses. To date, there has been no effective treatment or cure. Schwartz, a slender mother of four with a seemingly limitless supply of fiery energy, is Proneuron's chief scientist. She has spent 20 years studying the impact of the immune system and inflammation on the nervous system. She and her team studied the optic nerve, which regenerates in fish but not in mammals, in the hope of finding a strategy for effectively regenerating nerves in higher animals. Her experiments were conducted on ordinary carp (the basic ingredient for gefilte fish!). Schwartz dipped the live fish in a bucket of diluted sleeping pills so they would not suffer when she and her team crushed their optic nerves. A fish-nerve extract obtained from this procedure produced regrowth in the optic nerves of rabbits, but the team was not able to explain the mechanism. By the mid-90s, they thought the neurons' inflammatory response was the answer.

When most tissues are damaged, writes Luba Vikhanski of the Weizmann Institute of Science's publications department, evolution sees to it that the immune system cleans up the debris of damaged and infected cells. In the simple CNS (central nervous system) of fish, which have little brain power, regeneration can occur, but in mammals, the advanced CNS is protected from invasion by the immune system, thereby losing the ability to regenerate injured nerves. So Schwartz's team enlisted macrophages (the immune system's vacuum cleaners), incubated them in the presence of damaged peripheral nerves (which can naturally regenerate, unlike those in the spine) to activate their healing mechanism, and injected them into the damaged spinal cords of rats. Although unable to walk normally, the rodents were able to move their legs and put weight on them – an amazing achievement. "The results of our experiments are promising," said Schwartz in 1998, after publication of her research in the prestigious journal *Nature Medicine*. "However, for the moment, they have been achieved only in rats, and much additional research still needs to be done before the new treatment is available to humans." But in the case of Holley, Schwartz overcame that barrier. Her ingenious immunological treatment is highlighted in a new authoritative and highly readable book, *In Search of the Lost Cord: Solving the Mystery of Spinal-Cord Regeneration*. Written by Vikhanski, the book reads like a scientific detective story, covering the painstaking research efforts of dozens of scientists around the world over the past few decades to cure spinal-cord injury – which for the last 3,500 years has been deemed irreparable. Vikhanski interviewed more than 150 scientists, researchers, and spine-injured patients in eight countries and attended numerous neuroscience conferences before sitting down to write the book. The $27.95 volume, 269 pages long, was published by Dana Press and Joseph Henry Press (an imprint of the National Academy Press affiliated with the U.S. National Academy of Sciences). Aimed at the intelligent layperson, it has also been made available free of charge as a public service on the academy's Web site (at www.nap.edu/books/0309074371/html). The book came to the attention of Christopher Reeve, the "Superman" movie actor who broke his spine in 1995, when he fell from a horse, leaving him paralyzed

A number of treadmill programs are currently operating in North America and Europe.

from the neck down and unable to breathe normally without help from a respirator. "Poignant and exciting...what an incredible story it is," said the wheelchair-bound actor, whose Christopher Reeve Paralysis Foundation raises money for funding spinal-cord regeneration research. Although Reeve's injury is much too old to have a wisp of hope that Proneuron's treatment can help him, he nevertheless believes that one day he will be able to walk again.

The nervous system comprises the central nervous system (the brain and spinal cord) and the peripheral nerves, which can grow and become operational again. When a person's body suffers injury, it causes inflammation, which, however, cannot reach the brain. Otherwise, inflammation would cause damage to synaptic connections that make up brain tissue and control body functioning. But the disadvantage is that microphages, which are involved in the inflammatory process, are needed to heal wounds and regenerate damaged tissues. If a spinal cord is severed or even pinched, the victim can remain paralyzed in two or four limbs for life. Schwartz's idea was to trigger regeneration of spinal cord tissue by taking activated T-cell macrophages from a patient's peripheral nerves and injecting them into the spinal cord to cause a healing inflammation. Since the person's white cells are recognized by the immune system as "friendly" rather than as "foreign," there is no rejection, and they can be inserted precisely into the part of the body where they are needed.

The main problem is that the treatment has been shown to be effective only during a short window of opportunity – within 14 days of the injury. When the spinal cord is initially injured, nerve cells die. But subsequent cascading rounds of cell death follow, with the dead cells emitting chemicals that damage remaining cells and close down synapses. This time limit naturally reduces the number of patients around the world who can be admitted for treatment, as it takes time for patients to learn about the possibility, but the costs are no barrier, as Proneuron covers the airline tickets and all treatment expenses. Beyond the Proneuron story, Vikhanski devotes a whole chapter to discussing worldwide efforts to "teach" partially damaged spinal cords how to recover some of their ability to transmit neural messages. Paralyzed patients whose spinal cords have not been totally destroyed are being put in parachute-like harnesses and onto treadmills. The aim of this promising but controversial technique is to "teach the spinal cord to interpret sensory information coming from the feet in the hope that nerve circuitry in the injured cord will take control of walking in its new situation." A number of treadmill programs are currently operating in North America and Europe, not only for partial spinal-cord injury but also for stroke patients. Vikhanski concludes her book on an optimistic note: "In writing about spinal-cord regeneration and repair before the search has culminated in a happy ending, I yearn to know how this story will unfold. In a way, writing about the field now is much as it must have been writing about DNA and heredity in the years preceding the discovery of the double helix. Only after a great scientific discovery is made does the newly revealed truth appear amazingly obvious; today it seems as if the role and structure of DNA should have always been known to researchers, rather than uncovered only some 50 years ago.... It is possible that one day, this is how we'll be talking about recovery from spinal cord injury... For the time being, the suspense is still there. Will any regeneration therapies work for humans? If so, which ones? ... The feat still sounds like a miracle, but now there is real hope that eventually they will; and then medical textbooks -- and this book too – will have to be rewritten." Melissa Holley, Christopher Reeve, and millions of others will undoubtedly look forward to such an updated version.