

Jerusalem of Biotech



Jenny Hazan

The medical establishment had given up on Adam C., who was suffering from bladder cancer and had been treated with chemotherapy and radiation, to no effect. The last course available to him: bladder removal. He was booked for surgery. Then, a week before his appointment, the opportunity arose to try out BC-819, an experimental therapy that was in the second phase of testing by the US Food and Drug Administration (FDA). He did what most of us would do — grabbed the opportunity with both hands and prayed that it would work.

After just a few weeks of treatment with BC-819, Adam began to show improvement. Six years later, he is living life cancer-free, with a healthy and fully functioning bladder.

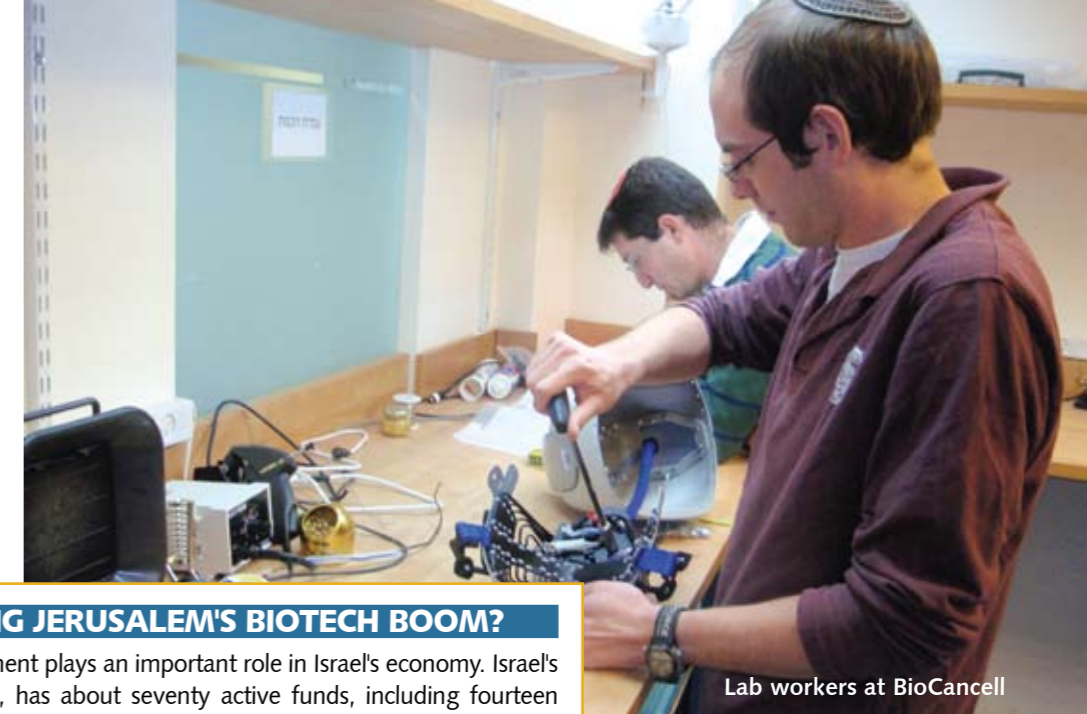
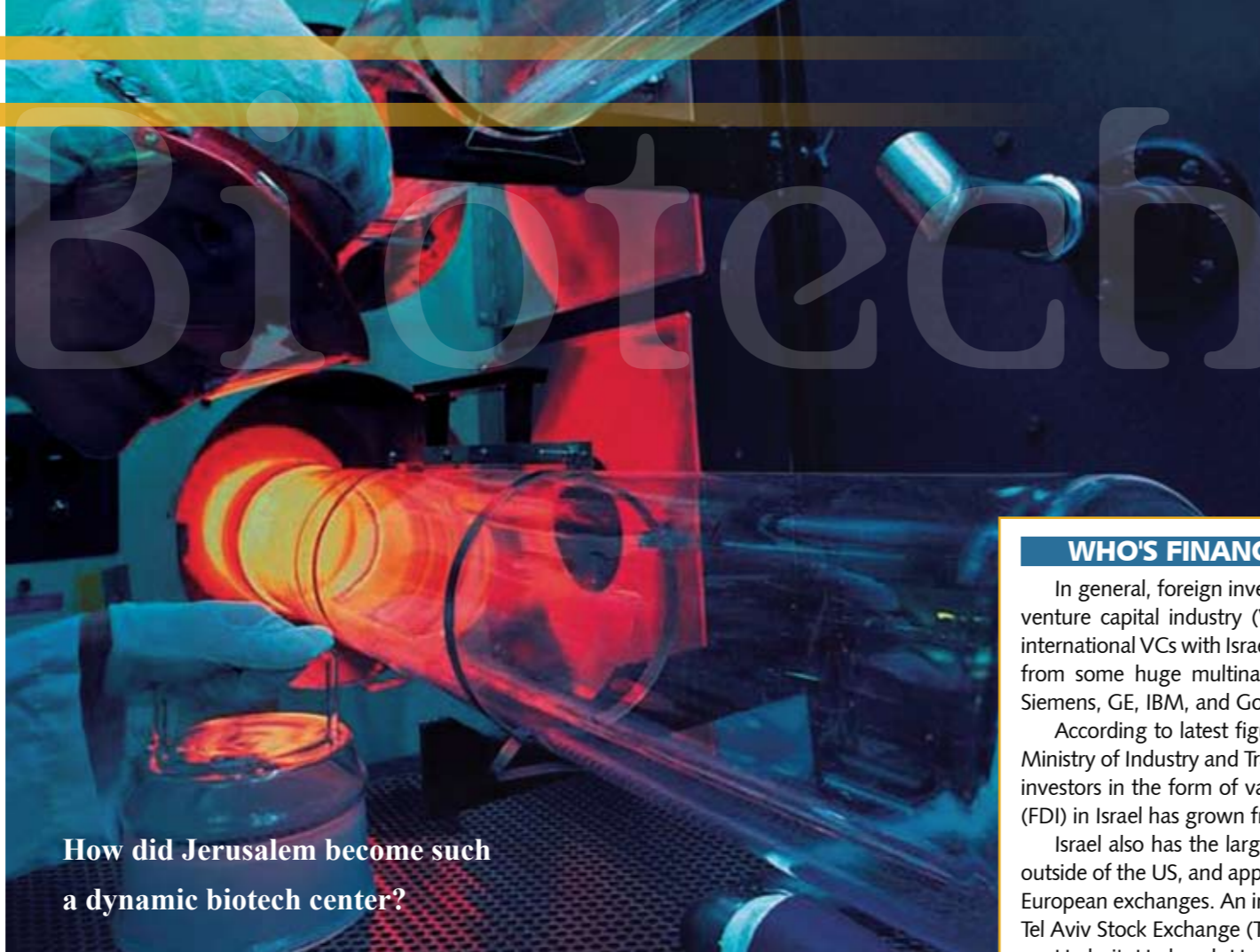
The miracle drug behind his miraculous recovery was developed by Har Hotzvim-based start-up company BioCancell Therapeutics Inc., which came into being in 2004 to develop and market the new drug, invented by researchers at the Hebrew University of Jerusalem.

Professor Avraham Hochberg, chief scientist of the start-up, explains how it works. After discovering that the common denominator that appears in almost all cancers is a gene (dubbed “H19”), he and his team designed a new diagnostic technology to determine the presence of the gene in the cancer cells of patients. If detected, the patient is eligible for treatment. The therapy — in the form of a shot — is a harmless substance that only turns into a drug in the presence of expressed H19. It is designed to destroy only cells expressing this gene, by a sort of “search and destroy” method that has no effect on surrounding tissue and no observed side effects.

A drug that destroys cancer cells and leaves healthy ones alone? A helmet that can cure brain disorders? A replacement for bone marrow transplants? A handheld laboratory? Sound like science fiction? It's not. It's just a list of a few of the extraordinary life science advances coming out of Jerusalem's vibrant biotech industry

Har Hotzvim, in north Jerusalem, is the largest of the city's three major biotechnology parks

Photo: Flash 90



Lab workers at BioCancell

“The problem with current treatments for cancer, such as chemotherapy and radiation, is that they are blunt tools; they attack both cancer cells and healthy cells,” says Professor Hochberg, who has been working on cancer research for forty years, the last twenty-two of which have been dedicated to the study of H19. “A drug that only attacks cancer cells is a completely novel approach.”

The drug is currently being tested in trials with ovarian cancer patients. The technology has shown excellent potential for the treatment of other fatal cancers, such as those affecting the liver and pancreas, as well as high-incidence cancers including lung and colon. “It actually has the potential to work on most cancers,” says Prof. Hochberg, “as long as they involve the expression of H19.”

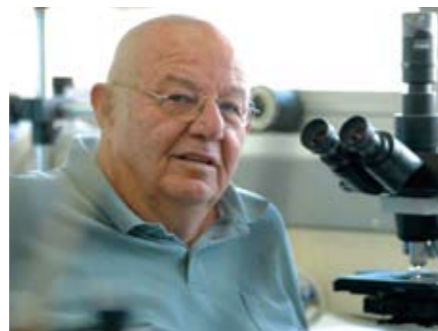
An Industry is Born BioCancell is one of 110 pharmaceutical, biotech, medical-device, and health-care companies spanning Jerusalem’s three major biotech parks: the Har Hotzvim Industrial Park, the Malcha Technology Park, and the newly inaugurated Jerusalem BioPark (JBP) in Ein Kerem.

Together, these companies, which range from multinationals like Teva Pharmaceuticals, the largest generic pharmaceutical company in the world, to early-stage start-ups, employ more than 3,250 people, among them more than 2,000 scientists and physicians. Jerusalem accounts for some 35 percent of Israel’s national biotech industry, one of the largest hubs of biotech activity in both Israel and the world.

How did Jerusalem become such a dynamic biotech center? The answer is multifold and starts with the Hebrew University of Jerusalem, a research powerhouse, with more than 1,800 graduates from life science programs annually and the highest number of life science PhD students in Israel. Ranking twelfth in the world (Harvard ranks eleventh) for production of biotechnology patents, some 43 percent of all biotech research in Israel is performed at the Hebrew University.

The University’s School of Pharmacy, which has long been a strategic pharmaceutical industry partner (it was recently converted to an institute for drug research and development), gave rise in the late 1980s to Israel’s top pharmaceutical success stories: Doxil (Johnson & Johnson), a very successful ovarian cancer drug, and Exilon (Novartis), a patch for easing symptoms of Alzheimer’s and

How did Jerusalem become such a dynamic biotech center?



Professor Avraham Hochberg of BioCancell

dementia. These drugs alone generate more than \$1 billion in annual sales.

The city’s hospitals are another key ingredient to the city’s biotech success. The Hadassah Medical Center and its affiliate Clinical Research Center (HCRC) provide an extensive clinical research resource, replete with labs, equipment, doctors, and patients. The only private hospital in Israel, Hadassah’s lack of affiliation with the Ministry of Health or any HMO puts it in a unique patent-friendly position, free of complications regarding intellectual property. Hadassah is responsible for about 50 percent of the clinical research conducted in the country, and generates more patents than any other hospital in Israel.

The government of Israel, recognizing the extraordinary potential of these intellectual resources for economic

growth, came on board. Based on Harvard University Professor Michael Porter’s economic-cluster theory — the idea that placing similar companies, suppliers, and service providers in one geographic area will stimulate competition, cooperation, innovation, and increase efficiency and productivity — the government began offering significant financial incentives to open biotech companies in the capital.

Not only did the government designate Jerusalem as a National Development Zone A—which entitles companies to top public grants and tax incentives—but the Office of the Chief Scientist (OCS) in the Ministry of Industry, Trade, and Labor recently boosted its grants both to biotech (now accounting for 25 percent of the total OCS budget), and to Jerusalem start-ups, which are now eligible to receive up to 85 percent of their budget from the OCS. This latter figure contrasts with the 60 percent available for companies founded outside the city (and 60 percent, as opposed to 50 percent, for later-stage companies).

In 2004, the government also launched the country’s first and only biotechnology incubator in Jerusalem, dedicated to drug development. BioLine Innovations Jerusalem (BIJ) received an unprecedented government grant of \$21 million over six years. Projects can receive early-stage development funding

WHO'S FINANCING JERUSALEM'S BIOTECH BOOM?

In general, foreign investment plays an important role in Israel's economy. Israel's venture capital industry (VC), has about seventy active funds, including fourteen international VCs with Israeli offices. In addition, Israeli start-ups have won investment from some huge multinationals, including: Microsoft, Cisco, Motorola, Intel, HP, Siemens, GE, IBM, and Google — just to name a few.

According to latest figures reported by the Israel Investment Center (IIC) of the Ministry of Industry and Trade, which offers special incentives to both companies and investors in the form of various tax incentives and grants, foreign direct investment (FDI) in Israel has grown from \$600 million in 1993 to \$10.5 billion in 2008.

Israel also has the largest number of companies listed on the NASDAQ that are outside of the US, and approximately seventy Israeli companies are traded on various European exchanges. An increasing number of biotech start-ups can be found on the Tel Aviv Stock Exchange (TASE).

Hadasit, Hadassah Hospital's Technology Transfer Office (TTO), which generates more patents than any other hospital in Israel and has given life to forty start-ups, wrapped up nine of these companies in a public "basket" on the TASE via the world's first-ever research hospital public arm, Hadasit Bio-Holdings Ltd. (HBL), which went live in January 2006.

"Now, Joe Public can call his broker and buy Hadasit stock and become a partner in the best and brightest innovations coming out of this leading center," says Ophir Shahaf, CEO of HBL.

How has this sector been influenced by the global recession?

According to a report published in Israel's business daily *Globes* last week, "Israeli venture capital-backed start-ups raised around \$178 million in the third quarter of 2009, 10 percent more than in the \$162 million raised in preceding quarter, but 55 percent less than the \$393 million raised in the third quarter of 2008, according to the MoneyTree Report for the Third Quarter by Kesselman & Kesselman Pricewaterhouse Cooper Israel."

The report noted that while VC investment in software plummeted to a ten-year low, investment in life sciences start-ups, especially those in medical devices, reached its second highest level in the past four years, demonstrating the great strength and importance of the industry in Israel and its soundness even in hard times, according to Rubi Suliman, a high-tech practice partner with Kesselman & Kesselman.

from the incubator for up to three years (up to \$1.5 million).

“Jerusalem has the right people and the right infrastructure to make the project successful,” says Dr. Ora Dar, head of the life sciences section at the Office of the Chief Scientist. “The industry in Jerusalem is undergoing huge growth. It is getting bigger and stronger.”

The Jerusalem Development Authority (JDA), a statutory authority charged with stimulating the city’s economic development, also came on board; and, since October 2008, started offering grants of 30,000 shekels per year for each biomed employee in Jerusalem, up to a total of 600,000 shekels per company over a period of two years. Then in May, the JDA announced an unprecedented 2.4 million shekel grant for life science companies that choose to launch or expand their business in the capital.

In 2007, the JDA also launched BioJerusalem, a comprehensive web portal aimed at connecting life science companies with resources, offering guidance to companies, facilitating investment in the city’s start-ups, encouraging the creation of new enterprises in the city, and strengthening the ties between local and global life science industries.

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Brainsway has developed a magnetic helmet that is being tested on a wide array of brain disorders

All of this effort and support has given rise to a thriving pool of biotech companies in the capital. Shirley Kutner, PhD, outgoing executive director of BioJerusalem, notes that despite the recent economic downturn, there has been a 34 percent growth in the number of biomed employees in Jerusalem since 2006, and a 20 percent growth in the number of companies. Some are on the cusp of truly incredible and potentially life-altering discoveries.

Here's a taste of this year's top innovations.

A New Way to the Brain Mood disorders such as schizophrenia, bipolar disorder, and depression, and neurological diseases like Parkinson's and Alzheimer's, are typically treated with a range of drugs meant to stabilize the amount of chemicals being released by the brain. In some cases, like Parkinson's,

the brain releases too much; in others, like depression, too little.

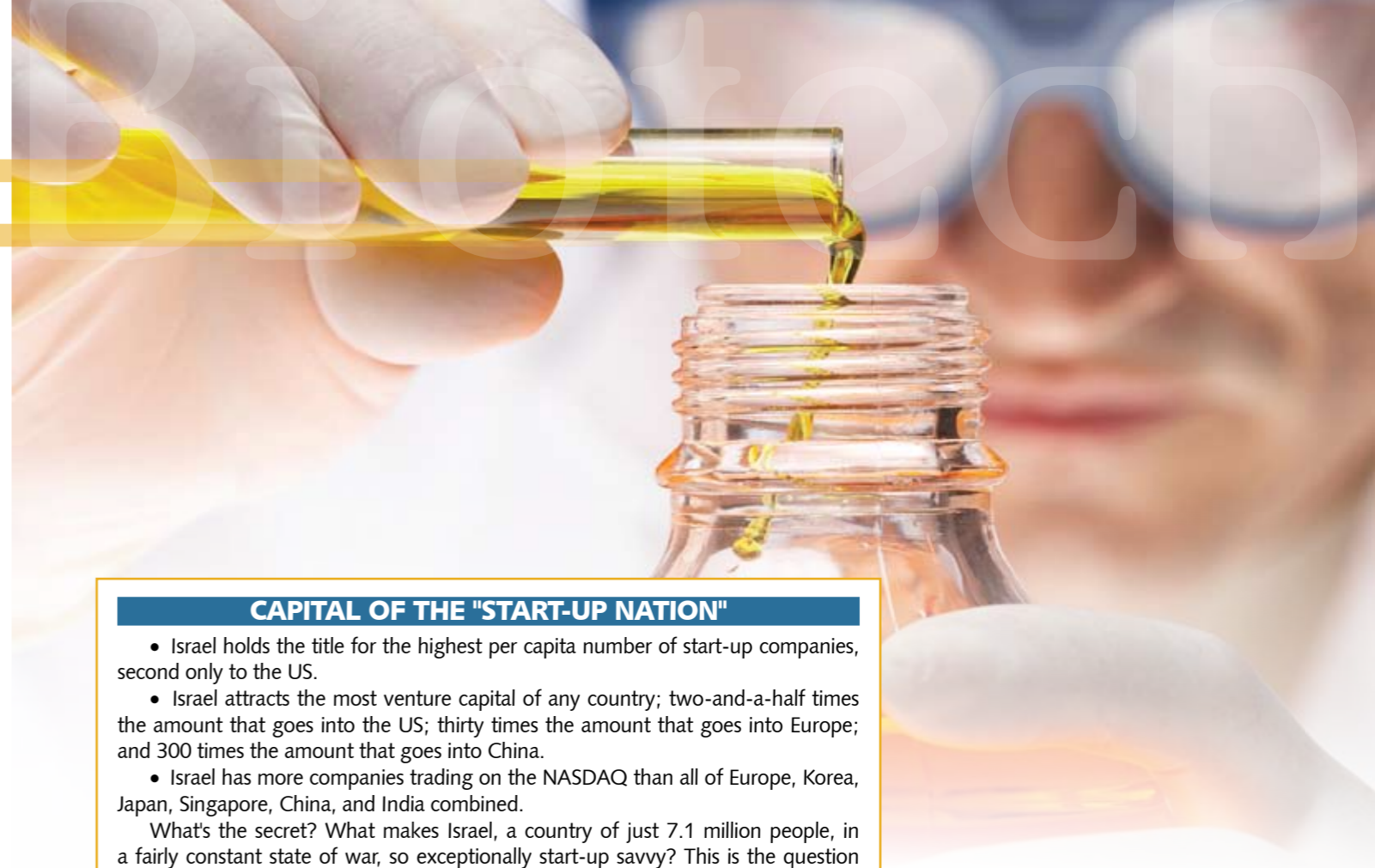
There are a lot of potential problems with drugs, however: some patients don't respond to drugs; some drugs come with a gamut of unpleasant side effects; with time, some patients become drug resistant; and psychiatric patients often go off their medications and are prone to relapse.

Har Hotzvim-based start-up Brainsway Ltd. has come up with an alternative to avoid these problems. Their technology, which has already been released in Europe (it is currently in the final phase of FDA approval), is called Deep TMS (Transcranial Magnetic Stimulation). Deep TMS uses a completely noninvasive piece of medical equipment — a helmet — that harnesses the power of magnetic fields to stimulate deep regions of the brain (up to 6–7 cm) known to be involved in disorders.

Brainsway CEO Uzi Sofer, one of the company's five founders, explains. "Whenever you think, feel, or do anything, these actions are preceded by activity in electric fields in the brain, which cause the release or inhibition of neurochemicals, which in turn cause the thought, feeling, or behavior. Brain disorder problems start with problems in the brain's electric fields.

"With our technology, we can penetrate a region of the brain and change the electric field to either excite or inhibit stimulation, depending on the problem," says Sofer.

Patients are treated for fifteen



CAPITAL OF THE "START-UP NATION"

- Israel holds the title for the highest per capita number of start-up companies, second only to the US.
- Israel attracts the most venture capital of any country; two-and-a-half times the amount that goes into the US; thirty times the amount that goes into Europe; and 300 times the amount that goes into China.
- Israel has more companies trading on the NASDAQ than all of Europe, Korea, Japan, Singapore, China, and India combined.

What's the secret? What makes Israel, a country of just 7.1 million people, in a fairly constant state of war, so exceptionally start-up savvy? This is the question authors Dan Senor and Saul Singer have answered in their new book, *Start-up Nation: the Story of Israel's Economic Miracle*, officially released November 4.

The book, which includes interviews with more than 100 geopolitical experts, government reps, business people, historians, start-ups, and venture capitalists, tries to tackle the question from a cultural perspective. "We are asking why this happened in Israel, as opposed to anywhere else," says Singer, a columnist and former editorial page editor at the *Jerusalem Post* and the author of *Confronting Jihad: Israel's Struggle and the World after 9/11*.

The answers are manifold. To start, says Singer, there's the military. "I'm not just talking about the high-tech units within the military that have produced civilian spin-offs," he says. "I am talking about the impact of the military experience on Israeli culture, and what people learn there about leadership, teamwork, and initiative."

Another major factor, he says, is that Israel is a country of immigrants. "Immigrants take risks," says Singer. "They are natural entrepreneurs."

The pervasive atmosphere in Israel is one of the pioneering spirit, of the drive to build something, says Singer. "The country as a whole is a start-up. That's where the title [for the book] comes from. It's not just because of the extraordinary number of start-ups in Israel, but also because the country itself is a start-up," he says.

Nowhere is this culture more evident than in Israel's biotech industry, which is the world's number-one producer of medical device patents. Singer suggests this sub-sector of biotech might be the most popular because of its potential for quick turnaround, as opposed to drug development, which is a very long process.

"I also think [medical devices] are the perfect expression of two Israeli specialties: out-of-the-box thinking and, what we call 'mash-ups,' the combination of different technologies from wildly different areas that produce incredible inventions."

Singer gives the example of Israeli company Given Imaging's PillCam, a swallowable disposable video camera that weighs just four grams (about an eighth of an ounce) and sends a live wireless feed back to the doctor. This technology, which came from the nose cone of fighter jets, represents a "mash up" between medical and military science. "This is a classic Israeli invention," says Singer.

The book, which represents two years of research, will also be released in Hebrew. "I'm very happy about this," says Singer, an immigrant to Israel from the US who lives with his wife and three daughters in Jerusalem. "There's a tendency when you are in Israel to look at all the problems and all the things that need to be fixed. Israelis don't always realize how amazing the country really is. Sure, they know Israel is good in high-tech, but I don't think they appreciate how unusual [the industry here] is."

minutes, five times a week, for a period of four weeks, followed by a maintenance period involving sessions once or twice a week. Eventually, explains Sofer, the brain learns the new electric field and it works on its own, without the assistance of the helmet, through a process of Long-Term Potentiation (LTP).

To date, Deep TMS has been tested on patients with depression, schizophrenia, and bipolar disorder. More than half have been cured completely, with a 60 percent response rate. The company is in the midst of clinical studies involving patients with Parkinson's, Post-Traumatic Stress Disorder (PTSD), and Alzheimer's.

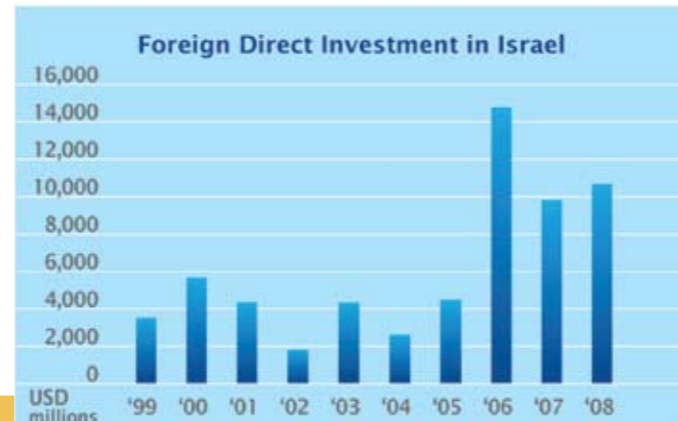
Sofer says the technology may also help with autism, impulse disorders, and addictions, as well as improve memory.

No More Waiting for a Match

According to Dr. Yael Margolin, president and CEO of Givat Shaul-based Gamida Cell, about half of the people with leukemia or lymphoma never find a life-saving bone marrow donor match. "This is a potential cure for these patients; it doesn't just extend their lives," she says.

Her company, which came out of research conducted by Dr. Tony Peled at Hadassah Hospital, has come up with a much more accessible alternative, based on stem cells.

Israel's Competitiveness				
Country Rank	1st	2nd	3rd	4th
Entrepreneurship	Israel	Hong Kong	Brazil	Malaysia
Total Public Expenditure On Education - % Of Gdp	Israel	Portugal	Mexico	Denmark
Business Expenditure On R&D - % Of Gdp	Israel	Sweden	Japan	Finland
Qualified Engineers	Finland	Israel	Ireland	India
Venture Capital	Hong Kong	Singapore	Israel	Malaysia



Tables courtesy of Israel's Ministry of Industry, Trade, and Labor

The therapeutic potential of stem cells, the cells that come from umbilical cord blood, for cancer and autoimmune diseases has long been known. Unlike bone marrow, for which recipients need donors with a total tissue match, stem cells can be used in almost any patient.

However, explains Dr. Margolin, there are two problems with stem cells: first, they are not plentiful enough (you need a large number of cells for transplantation, calculated based on the body weight of the patient); and second, all attempts to generate them in a lab have failed, since they automatically mature through a normal cell cycle, and don't remain in the "stem" stage.

StemEx, Gamida Cell's flagship technology, developed in a joint venture with Teva Pharmaceuticals, is currently in phase-III advanced clinical trials in the US. It uses small molecules to stimulate stem-cell renewal, with "limited differentiation."

"Our technology enriches the umbilical cord blood with stem cells; and, while allowing them to proliferate, prevents them from maturing," says Dr. Margolin. The technology brings the average percentage of stem cells in one unit of umbilical cord blood up from 0.25 percent to a whopping 20 to 25 percent.

"This graft can then be transplanted into patients as an alternative to bone marrow



Uzi Sofer, Brainsway CEO

transplantation for those who don't have a donor," she says. Dr. Margolin expects the technology to hit the market by 2011.

Testing, Testing, 1-2-3 Har Hotzvim-based LeukoDx's flow cytometer, a handheld device for quick diagnosis of life-threatening conditions, was originally designed for NASA astronauts. "The idea was to give astronauts a small instrument for testing themselves for infection while in space," explains Walter Drimer, chairman of Jerusalem's Cardio Ventures business accelerator, from which LeukoDx emerged as an early-stage spin-off.

In the end, the inexpensive portable blood analyzer, which functions much like

a glucometer used by diabetes patients, complete with finger prick and disposable cartridges, never went to Mars. It does, however, have a wide range of potential applications this side of the stratosphere, where the ability to detect diseases quickly, rather than having to wait several days for a lab culture diagnosis, can be a huge advantage.

According to Drimer, its first and widest application will be in emergency rooms, for the quick detection of sepsis. More than 250,000 people in the US died from the hospital-acquired infection last year. "It has been demonstrated that the earlier you catch it, the greater chance you have of avoiding severe sepsis," he says.

In addition, the technology stands to save hospitals millions of dollars, since their first line of defense against sepsis is to administer a broad spectrum of antibiotics without waiting for positive test results. "This technology can give results in fifteen to twenty minutes," says Drimer.

The cytometer may also prove useful in HIV testing and for the self-monitoring of AIDS patients, who can determine and alter drug cocktail levels in their blood without the need for frequent doctor visits. This could be especially important for parts of the developing world, where

the population of AIDS patients is high and access to doctors is limited.

The company is also working on an application for detecting and monitoring heart problems. "The device may be able to identify if someone is about to have a heart attack," says Drimer, who estimates that this application is two to three years away.

A Promising Future By all counts, it seems it is just the beginning for the Jerusalem biotech industry. This summer, the government announced the establishment of a 250 million shekel biotech fund, which it hopes to turn into 1 billion shekels by attracting private investors.

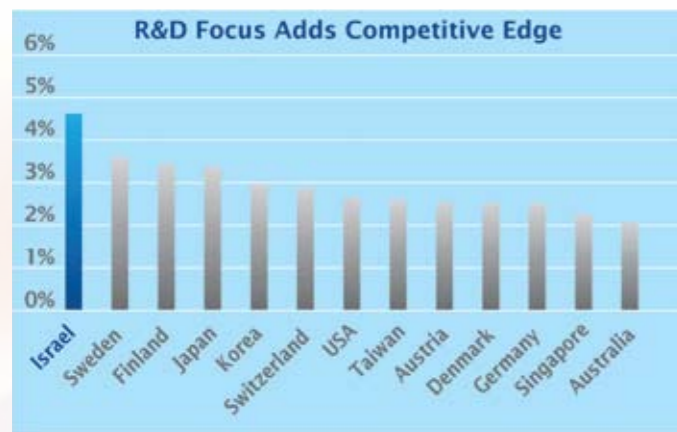
At the ILSI Biomed 2009 conference in Tel Aviv this past June, Jerusalem mayor Nir Barkat announced his intention, in collaboration with the JDA, to raise an additional 100 million shekels over the next five years to promote growth of the capital's life science cluster, aimed at creating jobs and attracting multinationals to the city.

At the same time, companies have begun to populate the new Jerusalem BioPark (JBP) at Ein Kerem.

"We project that the growth trend will significantly increase in the near future," Dr. Kutner said in a BioJerusalem press release, distributed in June. "The investment on behalf of biomed companies is expected to top \$350 million over the next five years. This growth will be accompanied by an addition of some 2,000 employees with academic degrees in biology, biotechnology, chemistry, pharmacy, and engineering."

This growing "hub" of biotech activity is what attracted LeukoDx to the capital. "Jerusalem has a growing and emerging biotech center. There are lots of rich resources here. Being here gives you access to a variety of potential strategic relationships and talent, and there is a sense of common purpose. These are the luxuries of being part of a larger community," says Drimer.

"The effort to make Jerusalem not only the capital of the state, but a capital of biotech in Israel, has been great," says Michal Kainan Koren, director of marketing at Yissum, the Hebrew University of Jerusalem's Technology Transfer Office (TTO). "This growth is causing more growth. It is making work in the biotech field easier, with everything and everyone closer and more reachable." ■



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