Is Small

Israeli researchers are on the cutting edge of the emerging discipline of nanoscience, pushing the boundaries in everything from drugs and diagnosis to fuel, semiconductors and cosmetics. The potential for revolutionary innovation is immense. Will the financial rewards match up?

Hanan Sher

THE ANNOUNCEMENT CREATED AN understandable world-wide stir. A team of Israeli scientists, led by Prof. Ehud Shapiro of the Weizmann Institute, recently disclosed that they have created the prototype of a revolutionary medical computer — one that can pick up molecular signals of 15 types of cancer in the human body. This "doctor in a cell" is so small that it can fit into a single drop of water... a trillion times over; its creators say that, when development is completed, it can be deployed inside the human body to spot cancer, and to react by harnessing a single strand of DNA, the material of genes, to destroy the malignancy.

This amazing microscopic medical kit, still in the test-tube stage, has already been programmed to work against prostate cancer and one form of lung cancer. It's one of the first practical applications of a "molecular computer" developed in Shapiro's lab three years ago and recognized in the 2003 "Guinness Book of Records" as the world's smallest biological computer. And it illustrates the potential of nanoscience — and Israel's leading role in the emerging discipline. Spanning the recognized fields of chemistry, physics, biology and computer science, nanoscience aims to revolutionize medical science, space travel, communications, computing — creating new materials stronger and more flexible than anything available today and, perhaps, astoundingly, begetting machines that operate outside the limitations imposed by the physical laws that govern the universe as we know them.

The common denominator is the size of the subject matter, and the discovery that at a small-enough scale of between one and a few thousand atoms, carbon and many metals can be manipulated so that their basic properties are changed, creating new super-strong ma

Beautiful?

COURTESY WEIZMANN INSTITUTE OF SCIENCE

MINI MEDIC: Ehud Shapiro, second from left, and his Weizmann Institute team are developing an anti-cancer nanocomputer

terials and ultra-small devices. To get an idea of how small small can be, consider that a nanometer (nm), the standard measure of nanoscience, amounts to the size of barely three atoms or one billionth of a meter; a human hair is typically 200,000 nm in diameter.

The notion that nanoscience, and its practical twin nanotechnology, have a colossal future is now conventional wisdom. Respectable scientists speak matter-of-factly about creating things once straight out of sci-fi, with implications from the marginal to the earth-shaking:

- cameras, with transmitters, no bigger than a speck of dust;
- "smart drugs" able to fight specific diseases by honing in on diseased cells and destroying them;
- intercept-proof secure communication, with single components of a message transmitted on single molecules;
- the harnessing of single molecules to create new fuel cells, which can free the world from the tyranny of petroleum, and to clean pollutants and thus assure the world's endangered supply of pure, fresh water;
- sensors that can be stationed in orbit to spot mineral deposits, or to detect the movement of magma or tectonic plates miles below the earth's surface and predict an impending eruption or earthquake;
- carbon-based materials 70 times stronger than steel, that can be used in armor for soldiers and public figures and yet are no thicker or heavier than an ordinary shirt;
- even the elevator running from the Earth's surface thousands of miles into space predicted four decades ago by sci-fi guru Arthur C. Clarke.

The field's immense potential is causing a rush of global interest, with governments and research institutions pouring hundreds of millions of dollars into attempts to gain a foothold in what could be the technology of the future. The U.S. invested about $2 billion in nanotech research between 2000, the year president Clinton announced the National Nanotech Initiative, and 2003, and allocated an additional $800 million for 2004; investment last year from the European Union and EU member states amounted to 1.15 billion euros (about $1.4 billion), and EU leaders recently called for another 6.3 billion euros in R&D spending. Japan is looking to spend billions as well.

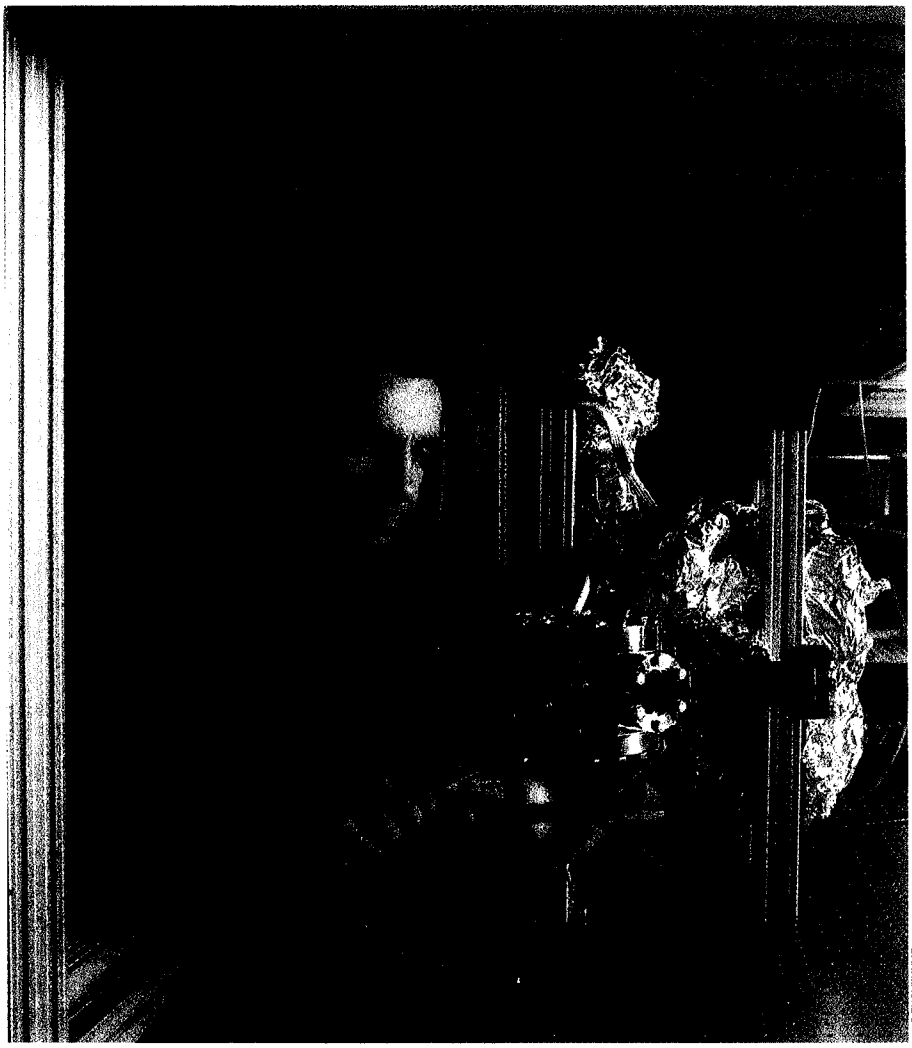
Israel, relatively speaking, is spending big, too, and is on the cutting edge of nano-development. The Israel National Nanotechnology Initiative (INNI), created by the government in 2002, has funding of $150 million to develop the necessary scientific research and educational infrastructure. The Israel Nanotechnology Trust (INT), the INNI's fundraising arm whose driving force is Labor party leader Shimon Peres, is currently trying to raise $300 million from Jews around the world. "There are no discounts for being small, and everyone needs the same expensive equipment," notes INT managing director Einat Wilf. "As Peres says, small countries can't get by on small microscopes."

Adamant that Israel must play as dominant a role in nanotechnology as it has done in high-tech, where it is a recognized world leader, Peres speaks of the challenge in dramatic, strategic terms, as nothing less than the "next great national task": If in the 20th century, the Jewish people reclaimed the land and afforested it, he says, in the 21st it will build nanotechnology laboratories.

Peres heralded the global future of nanotech in September 2003, as the keynote speaker at the World Nano-Economic Conference held in Washington. "We can use smallness to become great," he told an audience that included executives of many of the world's largest corporations, representatives of most Western governments and top scientists.

All six major Israeli academic institutions — the Technion, the Weizmann Institute, and Haifa, Tel Aviv, Ben-Gurion and the Hebrew universities — now have their own nanoscience institutes, seeking to build on Israel's world-class scientific base: According to a recent European survey, the number of scientific papers published by Israel on a variety of topics, including nanoscience, is 109 per 10,000 people, the highest in the world. Israel is also near the top, per capita, in number of patents filed.

ALTHOUGH MOST PIONEERING nano-work is, obviously in a field still so young, going on in academic labs — Shapiro, at the Weizmann Institute, for instance, says his breathtaking computer kit may only be readily available a



DANNY MACHLIS

CHIPMAKER: Ron Folman of Ben-Gurion University, with part of the vacuum chamber used in his work on the 'atomic chip'

decade or two from now — a few Israeli companies are already creating real products. One of them is Solubest, founded by three immigrants from the former Soviet Union, which has developed ways to enhance the delivery of drugs and increase their solubility by mixing them with other compounds, at the scale of a few nanometers. In Solubest's development pipeline are a more soluble form of Azithromycin, used to fight bacterial infections in various parts of the body; a version of the anti-fungus drug Itraconazole, used particularly by patients whose immune systems have been compromised; and a more soluble Taxol, a drug found in the bark of California yucca trees which is used to treat breast cancer and ovarian cancer. Greater solubility of all these drugs means a radically reduced dosage and, crucially, fewer potential side effects. Irene Jaffe, Solubest's director of technology, says the firm has also signed major agreements to conduct feasibility studies on drug development for several international pharmaceutical firms, including a leading American generic manufacturer, as well as Israel's own Teva and Agis.

ApNano Materials, based near Solubest in the Kiryat Weizmann tech park at Nes Tzionah, south of Tel Aviv, is about to launch NanoLub, nano-sized bits of various metals that can increase the efficiency of lubricants now used for automobiles and industrial machines, in aeronautics and even space flight.

The scientific base for ApNano's technology — tiny super-strong metal structures known as fullerenes — was discovered in the materials lab of Weizmann Institute Prof. Reshef Tenne, where company founder Menachem Genut was a researcher 10 years ago. ApNano says its first lubrication products will be launched within months, and that it is working with Volkswagen on the development of materials that will eliminate the need for grease in automobiles. While many other nanocompanies are a long way from solid sales, Genut says, "We're definitely not a bubble, or based on hype."

There are environmental benefits, too. ApNano's Niles Fleischer notes that "the oil and grease you buy for your car is fortified by a large cocktail of additives to enhance its performance," including many that are unfriendly to the environment.

Haifa-based NanoPass (*see "Small Needles, Big Deal," November 18, 2002*) has signed an agreement with GlaxoSmith-Kline, a leading pharmaceutical multinational, to complete development of its patch containing tiny needles that can be placed on the skin to deliver small quantities of drugs, over time. CEO Alon Seri-Levi of Sol-Gel Technologies of Beit Shemesh, about halfway between Jerusalem and Tel Aviv (*see "Made in the Shade," September 25, 2000*), says his firm, in cooperation with Merck of Germany, has been marketing a sunscreen enclosed in tiny bubbles of glass in Europe and North America for the last two years. And NanoPowders, based in Caesarea, has used nanotechnogy to develop metallic inks that can be used with ink-jet printers, and a transparent coating material that can conduct electric current for use in ultra-thin transparent moving displays.

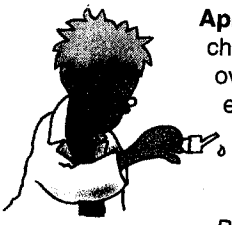
Exciting though such developments and products may be, they do not, at this stage, amount to evidence that nanotechnology can transform, or even play a central role in boosting, the Israeli economy. Indeed, very few companies, in Israel or elsewhere, are selling nano-products as yet, notes Bob Rosenbaum, who publishes Nanotech Advantage, a newsletter covering the Israeli industry, and acts as a consultant to several nanotech firms and institutions. "In spite of the tremendous amount of talk, publicity and expectation," says Rosenbaum, "there are really very few applications on the market that you can really call nano. That's true in Israel and in the rest of the world."

Beyond the rosy predictions, the huge investments and the massive hype that have surrounded nanotechnology, therefore, central questions remain unanswered, and may be unanswerable for years: Will the discoveries being made now and over the coming decade constitute a scientific revolution that affects technology in the same way as, say, the transistor and silicon chip did in the mid- and late-20th century? Or will they turn out to be merely interesting experiments that work in a test tube, but are too expensive — or too complicated — to turn into products that can be consumed by a changing society? And if nanotechnology

The Tiny Pioneers

...at the forefront of the hoped-for nanotech revolution

Advanced Nanoparticles: Makes "contrast agents" — dyes used in MRI body-imaging scans — which are currently being tested in Israeli hospitals. Founded by chemistry Prof. Shlomo Margel of Bar-Ilan University. *Based in Jerusalem*



ApNano: Its solid lubricant for car engines and industrial machines, using organic nanoparticles to improve performance over petroleum-based products, is due soon on the market, employing technology developed at the Weizmann Institute. *Kiryat Weizmann, Nes Tzionah*

BG Polymers: Researches nanotechnology to improve its conventional line of sealants, coatings and paints. *Kibbutz Beit Guvrin, in southern Israel*

El-Mul Technologies: Incorporates nanotechnology in the development of precision instruments; its first nano-based product is due to be released later this year. *Yavneh*

Jettable Ltd.: Specializes in nano-based inks that can be applied by inkjet on non-porous substances such as ceramics and glass. *Netanyah*

NanoCyte: Specializes in nano-based drug-delivery systems. *Tzemah, Jordan Valley*

Nanolayers: Uses molecular nanotechnology, pioneered in the laboratory of Dr. Shlomo Yitzchaik at the Hebrew University, to develop semiconductor material a few nanometers thick. *Jerusalem*

Nanonics Imaging: Develops nanoinstruments, including microscopes. Headed by Hebrew University Prof. Aaron Lewis. *Jerusalem*

NanoPass: Develops painless microneedle devices for drug delivery. Insulin delivery tested on rats. *Haifa*

NanoPowders: Produces nano-based metal powders to be used in inks for digital inkjet printing of microcircuits and transparent conductive coatings for electronic displays. *Caesarea*

Nanosize: Grinds metals to nanosize for use in cosmetics, electronic devices, magnetic materials, pigments and coatings, structural ceramics and inks. *Migdal Ha'emek*

Newgal: Makes diamond dust 4-8 nm in size for industry, medicine and cosmetics. *Ashkelon*

Sol-Gel Technologies: Makes nano-based encapsulated agents for cosmetic, oral care and consumer products. *Beit Shemesh*

Solubest: Uses nanotechnology to re-engineer drugs and make them more soluble. *Kiryat Weizmann, Nes Tzionah*

does turn out to be, as some predict, the "engine" driving the world economy into the second decade of the 21st century and beyond, is Israel positioned to be part of that revolution?

NANOSCIENCE AND NANOtechnology are hard to define because they cross the lines of many disciplines. "Even ordinary chemists, who put various materials into a test tube and mix them, can call themselves nanoscientists if, at the end of the day, they can control what happens in the tube down to the single atom," says Ron Folman, a Ben-Gurion University researcher whose main field of interest is the nano-sized "atom chip."

It's not just a matter of small size. "The great promise of the field is in its complexity. Once we are able to manipulate single atoms and molecules, we can build things that we never had before," Folman says. "It's like Lego — with its red, yellow and blue pieces. When we can manipulate molecules and atoms in the way that a child can assemble Lego, the variety is infinite, the possibilities limitless. We'll be able to create a robot that delivers a drug inside the body, or one that can clean up the oil spill from a tanker. Or create new materials that are extremely strong and light, for aeronautics."

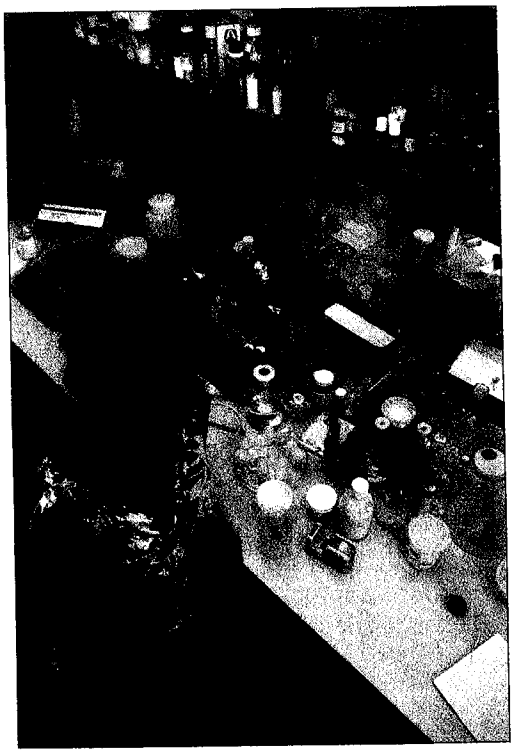
Underlining the limitless potential of his field, Folman now departs into spy-thriller territory, raising the possibility of super-miniaturized electronic, communications and optical systems — combing into "smart dust." "At the size of a grain of dust, which is slightly larger than the nano scale but still very small," Folman says, "you may be able to build an entire intelligence-gathering system with a sensory device that detects electronic fields, a camera, recording device and transmitter, and all the electronics needed to control them."

Such a development would, obviously, revolutionize the way governments — and their espionage agencies — gather information. But it has dangers, says Folman, departing still further into the realm of what was hitherto science fiction. What would happen if somebody breathed in one of these electronically packed micro-dust grains? How would the body cope? Unsurprisingly, he has no answer.

Folman's specific research — parallel to that done in 25 other places around the world — is on an "atom chip" for computing, which because it operates in a vacuum with no air around it can be exponentially more efficient than the current silicon chips. The super-fast, super-smart atom chip, Folman says, could be the basis for much-improved, ultra-precise navigation systems for space travel ("if we are ever going to send a man to Mars," Folman says, "we'll need a much better guidance system than the ones they use now"), for new levels of encryption or, most of all, for quantum computers that could perform in a single day tasks that even today's supercomputers could never complete. "They could be an infinity faster, at least in theory," he says.

As with Shapiro's work at the Weizmann Institute, much of what is going on in Folman's university labs has immense potential practical application — but only years from now. In the same vein, Prof. Ehud Gazit thinks that the peptide nanotubes discovered in his Tel Aviv University microbiology lab could, some day, be a key to the development of complex nano-size electronic systems, like those in "smart dust."

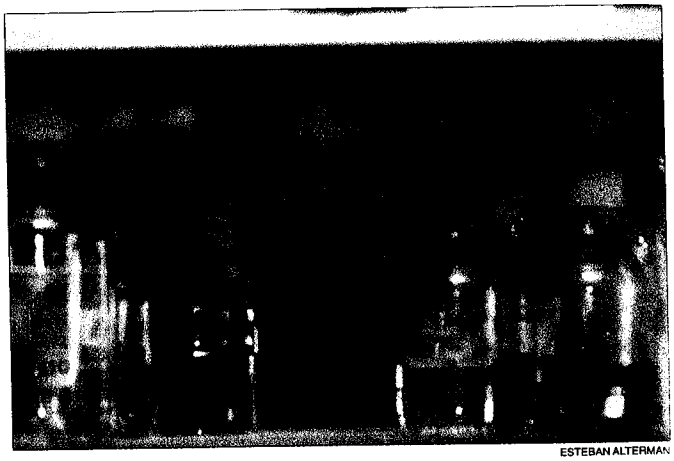
Peptide nanotubes were found almost by accident. Gazit and a graduate student were studying the plaque that forms in the brain cells of Alzheimer's patients, when they discovered a minuscule chain of protein molecules that assemble themselves into tiny hollow tubes about 20 nm in diameter. They devised a way to fill these tubes with silver, then dissolve the protein



ESTEBAN ALTERMAN

PASS ON THE BROCCOLI: Lutein researcher Irit Yuli Amar, left

THINKING SMALL: Ehud Gazit, right, discovered peptide nanotubes while studying Alzheimer's



ESTEBAN ALTERMAN

to leave ultra-tiny nanowires. The ability to build such nano-sized electrical components could be a key to great advances in computing, Gazit believes. After all, developing nano-sized chips is no use unless you have nano-sized wires to connect them to each other and the outside world. "The first computers, they were as big as a building," he points out. "And they did far less than the Casio calculator on my desk."

At Prof. Nissim Garti's Hebrew University chemistry lab, doctoral students are looking for ways to utilize the healing properties of the antioxidants found in the body and in fruits and vegetables. There is evidence that one of these, phytosterol, found in edible vegetable oils, slows the absorption of cholesterol in the small intestine. Another, lutein, protects the retina and prevents the formation of cataracts. The problem is how to deliver these natural healers. "They are not soluble in water, and are barely soluble in oil," says Idit Yuli Amar, 28, a graduate student in the lab, "so they cannot be easily inserted into various liquids. And you'd have to consume 2 kilos (4.4 lb) of broccoli a day to get enough lutein in you," she adds.

At the nano-level, however, delivery seems possible. Together with another grad student, Aviram Spernath, she has now created nano-sized droplets which contain water, oil and an emulsifier to combine them. "One side of the droplets likes water and one side likes oil," she explains. And the antioxidant enters at the interface between them. "Since there are billions of these tiny interfaces, we can get a lot of the material into the system." In much the same way as fluorides in toothpaste combat tooth decay, therefore, delivery of lutein by her method in soft drinks, water or milk, could, she says, help avoid cataracts; delivery of phytosterol, similarly, could block cholesterol.

EVEN THOSE DIRECTLY ENGAGED in the field can't promise that nanotechnology is going to trigger an economic bonanza for Israel, or any other country. "You will not get a commitment from me that nanotech is not going to be a bubble," says Folman. "But the dream of those of us involved in nanoscience is for Israel to become a center of excellence, which would affect Israel's place in the world economy. Look at what happened with fields like communications, optics and computers," Folman urges. "When they got started no one was able to estimate their impact on the world economy. Under the right conditions, Nanotech could create an infinite number of jobs" — albeit mainly in science, rather than in semi-skilled manufacturing.

The pessimistic scenario, which Folman readily admits, is that the technology will not, ultimately, hold water — "that the ideas will be nice but unfeasible, just too expensive to develop into businesses. The problem is we'll only know that in 10 years. Or maybe in 20."

Nir Belzer, whose Tel Aviv-based Millennium Materials Fund is the only Israeli venture capital outfit to have made an appreciable investment in nanotech so far, shares the wariness. "Nanotech is an enabling technology, not a product in itself," he cautions, "so you have to come up with what is being enabled." Then traditional business strategies must be applied. Production costs must be assessed.

"You can make two grams of something wonderful in a lab, but it's another story entirely if you want to scale up into industrial production." Market research has to be carried out. "You have to ask whether John Smith will buy it, why it's better than what's already available, what edge, if any, it gains by being. And even if all the answers are positive, Belzer foresees long delays before nano-products are adopted by at least some mass-production industries. In computer chips, for example, "the Intels and other manufacturers have invested hundreds of millions of dollars in production lines. Replacing them will be a very slow process."

In short, Belzer sums up, "if someone comes to us with a nanotech idea today, we ask when it will be on the market." He doesn't expect his fund's first nanotech investment, made in 1998, to bear fruit before 2008, at the earliest.

Other venture capitalists, even warier, have refrained from putting any money into nanotech start-ups. One of them, whose fund concentrates on information technology and semiconductor investments, explains why: "Some day, perhaps, nanomaterials will rival the silicon materials currently used to make semiconductors. I should live so long."

Folman, who helps raise money from private individuals, foundations and governmental agencies for the Ben-Gurion University nanocenter, is more upbeat. "Nanoscience is a thing of the future, not of tomorrow," he tells potential donors. "But you must invest now. If you don't, you're not going to lose anything — but you won't gain anything either." ●