The Canaries of the Future

Yissum, the Hebrew University's technology transfer company is located at the juncture between basic research and industry

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EARLY WARNING: Biosensor bacteria, 'tailored' to fluoresce in green or in red when in the presence of toxic chemicals, growing on an agar plate

COAL MINERS ONCE USED canaries to warn them of the imminent danger of gas build-ups in mines. Now, a Jerusalem biologist has devised an early warning system for polluted water reservoirs, also based on nature's monitoring abilities.

Instead of the canary, however, it's bacteria, genetically engineered to respond to various chemicals, that Shimshon Belkin, professor at the Hebrew University's Silberman Institute of Life Sciences is harnessing to serve as reliable, real-time indicators of water quality. Attached to polymers and immersed in a body of water, they literally glow in response to the presence of pollutants.

The system, developed into monitoring technology by fusing biology with electronic hardware in collaboration with Prof. Aharon Agranat of Hebrew University's Applied Physics Department, provides a quick alternative to the traditional and more tedious method of analyzing water samples in laboratories, which can often take up to a week.

The Belkin-Agranat biosensor project was recently selected as one of five novel technologies receiving financing from the CleanTech fund, which supports the development of inventions with commercial potential in environmentally-friendly industries. Established by Yissum, Hebrew University's technology-transfer company, the CleanTech fund is an expression of Yissum's identification of environmental technologies as a fast emerging global megatrend.

Yissum – the name means "application" in Hebrew – and its staff of 24 are located at the juncture between basic research and industry – a crossroads that is increasingly important as the world's wealth becomes ever more dependent on what is being termed a "knowledge economy." Owned by the university but registered and run as a fully for-profit corporation, it earned revenues of $55 million last year.

It was originally founded on a classic technology transfer business model – registering patents based on research conducted by university scientists and making profits from the licensing royalties generated by those patents. But over the years Yissum has expanded in a more aggressive direction of actively seeking partnerships with business, working with industry leaders for the commercialization of inventions. It also has the authority to create its own spin-off companies, and has over the years created 65 of them, including successful start-ups such as Chiasma, a biotechnology company, and MobileEye, which produces a vehicle vision system for on-board driving assistance and recently signed a $150 million contract with Italy's Cobra Automotive Technologies.

"WE NEED TO REMAIN ON top of emerging megatrends as much as any technology or investment company," Yehuda Yarmut, vice president for licensing and intellectual property (IP) and currently serving as the acting CEO of Yissum, tells The Jerusalem Report. "We are now in the process of expanding the model by asking companies what their future needs might be, even before the research has been conducted and the patents registered. We are asking them to peer ten years into the future, and then matching them with appropriate researchers."

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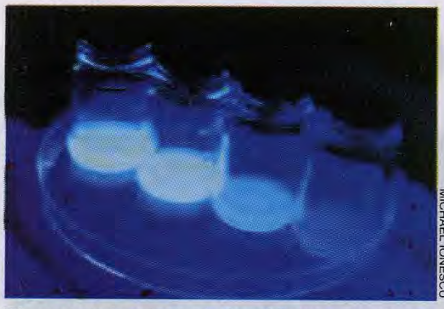
Yarmut explains that "corporate funding pays for experiments and the support of researchers and graduate schools; patents are registered on the discoveries; and the company putting up the money gets the technology it needs." Yissum is in advanced stages of negotiating deals structured around this model with several large European corporations, says Yarmut, the holder of a masters degree in agricultural sciences from Hebrew University and an MBA from Erasmus University in the Netherlands. He worked in management positions at computer start-ups before taking a marketing position at Yissum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Biosensor bacteria derived from a medusa

seven years ago.

Patents royalties are a very big business. Yissum has over 5,500 listed patents covering 1,600 inventions, and it has signed deals for 480 technology licenses that have commercialized an array of successful products generating over $1 billion in worldwide sales every year. Some of the big hits Yissum has scored include its patents for Doxil, a cancer treatment drug licensed by Johnson & Johnson, and Exelon, used in Alzheimer treatment, purchased by Novartis. Its licensing partners include 3M, Bayer, Intel, Merck, IBM and Dupont. Its in-house legal staff works on over 100 patents a year, making it one of the leading IP legal teams in Israel.

The Weizmann Institute's counterpart to Yissum, Yeda, reportedly has sales that are twice as large as Yissum's. Both are among the top 15 university technology-transfer companies in the world.

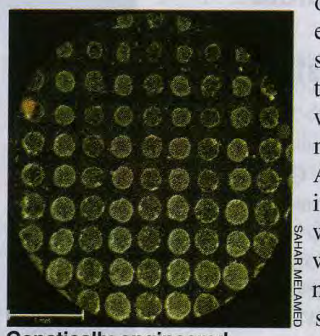
"Basic research is always going to be in high demand," says Yarmut. "Last year, when everyone in the business world was going through the worst year in memory, Yissum had its best year," he says glowingly. "We are like a huge ship that will always glide its way through the waters, even under the stormiest of conditions."

The range of technologies covered by Yissum's portfolio is vast, and includes medicine, the life sciences, the natural sciences (physics and chemistry), ecology, applied mathematics, computer science, engineering and agriculture – one of its substantial revenue sources is from long-shelf-life tomatoes. It has recently branched out to tap into revenue sources from IP assets produced by humanities departments, such as dictionaries, databases and film rights. "We're going to expand to social science IP rights next," says Yarmut. "Knowledge is a major asset, and there is no reason that the knowledge created and stored in educational institutions should not be adequately remunerated at its market value."

Some of the recent megatrends that Yissum has identified as worthy of increased attention include renewable energy, biomedical engineering and green technologies. "Green technology has been underfunded over the past 20 years, because it was overshadowed by other technology trends," says Yarmut. "But it is now attracting enormous attention."

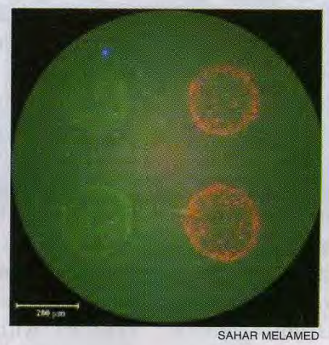
"In green technology, if you solve one problem, you might create another," he continues. "Take, for example, desalination. We've got researchers who are experts in desalination technology. By providing a source of drinking water, it has enormous environmental importance, but it also produces brine as a side effect – brine that could be a source of ocean pollution. Fortunately, we also have chemists who are developing methods for brine treatment. Systemic thinking is needed, which is why the university is the best place for green R&D – there is no company that includes an R&D department that is so multidisciplinary."

The CleanTech fund was created in December 2008 by Yissum from income generated by sales of shares in MobileEye. The first research efforts to benefit from its support include a novel method for the effective clearing of poisonous mercury from gases emitted into the atmosphere by coal-fired power plants, research into developing accelerated photoreactions as a way to harness solar energy, as well as the Belkin-Agranat project of microbial biosensors.


SAHAR MELAMED

Genetically engineered bacteria arrayed in tiny dots


SAHAR MELAMED


SAHAR MELAMED

BELKIN'S WORK ON THE SUBject began over ten years ago. Working with Yossi Shacham and other scientists at Tel Aviv University, Belkin created panels composed of four to six different types of bacteria, embedded in polymers placed in water environments. Using the panels added the bonus of uncovering changing patterns that could be "read like fingerprints, notes Belkin. "By using live cells we are able to detect complex series of reactions that can exist only in an intact, functioning cell," he says. To promote the commercial application of this research, he founded a company – appropriately called Canarius.

But why stop at only six types of bacteria? Why not create panels of hundreds or even thousands of different bacteria, capable of sending signals read by electronic devices, for a very wide range of readings and monitoring? That is where Agranat comes in. Agranat's interest in Belkin's work was piqued two years ago when his wife mentioned a newspaper article on the subject to him. "I kept thinking about it for three straight days," he relates. "And then I contacted him with the suggestion that we collaborate on the project. Patents can often follow such chance events."

Agranat is no stranger to innovation, both in basic research and business-applicable patent work. After earning a series of degrees in physics and mathematics at Hebrew University, culminating in a PhD in physics in 1986, he worked as a research fellow at Caltech in California. He returned to Israel in 1991 to found the opto-electronic computing laboratory at Hebrew University and, in 2001, was awarded New York-based Discover Magazine's Innovation Award, a major engineering prize, the only Israeli to have been so honored, for his invention of an optical switching method based on holograms.

Israeli-born Agranat, 57, married and a father of four, son of Shimon Agranat, who was Chief Justice of the Supreme Court, is a man with unmistakable presence in a room, capable of patiently explaining complex ideas while exhibiting a fast-moving, inquisitive mind fascinated with science and technology. In conversation he is always

seeking the "larger picture," drawing on examples ranging from Thomas Edison's laboratory experiences to the Manhattan Project. Biosensors, he explains, also fit into a larger trend that will form the next stage of the Web.

"Ten years ago the nodes of the Internet consisted almost entirely of computers, monitors and a cable connection," notes Agranat. "Today every mobile phone and iPod can potentially be a node in the Internet. Eventually, everything – and I mean everything – will be an Internet node: every quart of milk in the supermarket and every part in your car. There is no reason for you to take all the items out of the trolley at the check-out aisle of the supermarket – only to put it all back in the trolley."

The revolution, he says, will come about when sensors are added to the existing computer-communications networks. A mobile telephone equipped with a camera (a form of sensor), a GPS (self-knowledge of its location) and a connection to the Internet already exhibits a rudimentary form of this, in his opinion. "Some fear this means that Big Brother is here, but the opposite may be true," he is quick to reassure. "People with mobile telephones are taking photographs of policemen overstepping their bounds. With sensors everywhere, Little Brother may prove stronger than Big Brother."

He even foresees a future in which people themselves can be Internet nodes. In recent work with Hebrew University Prof. Uri Feldman, an expert in spectroscopy, Agranat noticed that human sweat glands have a shape that bears a suggestive resemblance to helical-shaped antennae used, for example, for naval communications 30 years ago – leading him to suspect that the human body could be broadcasting internal information in a way that can be detected. That observation led to a discovery that should make it possible to measure physiological markers in people, such as heart rate and blood pressure, from a distance without direct contact – enabling human health to be monitored over the Internet.

Agranat's work with biosensors fits in naturally with the theme of merging sensors with networks – and carries it a step further by marrying biology with the world of electronic communications networks. "Consider a pollutant entering the water system of an agricultural settlement in Israel," he says. "It takes time for the local residents to suspect something is amiss, then perhaps a week until an agent from the Environmental Protection Ministry comes by to take a sample back to a lab, and so forth. If we could implant a networked sensing environment directly in place, this wouldn't happen. I foresee networked sensors shrunk down to the size of dust motes, in what is being termed "smart dust," that could then be scattered wherever there is a need to keep track of environmental conditions."

Belkin, in contrast to Arganat's exuberant style, speaks in calm, measured sentences. Also a native of Israel, Belkin completed his doctorate in oceanography at the Hebrew University in 1975 and went on to do a post-doctorate at the Woods Hole Oceanography Institute in Massachusetts. This was followed by two years of research at University of California, Berkeley before he returned to Israel, taking a position in the desert research institute at Ben-Gurion University in Beersheba. "Does it sound strange that an oceanographer went on to study the desert?" he asks with a smile. "Yes. I've done many different things."

Despite their differing personal styles, the two researchers have been successful in their joint work. "If you want to spot a specific chemical," says Belkin, "there are very good existing tools for chemical analysis for that. But what if you don't know exactly what you are looking for, but you need to know if there is 'anything out there' that may be harmful? Exposing a living organism to the environment is then a good idea, and if you want real-time indications, use bacteria. A chemically threatening environment triggers a reaction in the bacteria, and by using genetic engineering we can bring about a situation in which those bacteria give off fluorescent or luminescent light, with the intensity of the light increasing along with the concentration of the chemicals involved."

Agranat continues the explanation. "A bacterium is, in a sense, a very small biochemical factory, but it has advantages over standard chemical factories. Its small size makes it portable. It can not only be grown, it can be programmed, genetically, to recognize specific molecules, even very complex molecules. And it lives, and dies, which gives us important indications regarding hazardous conditions."

Agranat tells The Report he is confident that, with the support of Yissum, commercially viable applications of his project with Belkin can be produced within three years, making bacteria the canaries of the future.

TICKER

• Ratings agency **Standard & Poor's reaffirmed its appraisal of Israel's credit rating as stable** after concluding that the recent Gaza conflict would have only short-term impact on the economy, despite an expected widening of the country's fiscal deficit to pay for conflict-related expenses.

• Teva Pharmaceutical Industries Ltd. and Lonza Group AG, a major Swiss pharmaceuticals company, signed an agreement in late January to cooperate in the **burgeoning market for biotechnological medicines**, making lower-priced generic equivalents to branded biological medicines. Biotechnology drugs, made from living cells, are more complex and, difficult to make than traditional pharmaceuticals, and are expected to have a market potential of $71 billion.

• The Bank of Israel lowered its interest rate to 1% on January 26, **the lowest level in Israel's history**. The move came on the heels of the bank's estimate that the economy will contract by 0.2% this year, the first contraction in the economy since 2002. Growth had averaged about 5% over the past five years. The bank also predicted a consumer spending growth of only 1.1% in 2009, the slowest pace since 2003. The unemployment rate is expected to rise to 7.6%, while investment in machinery and equipment will decline 5.9%.

• Trading of shares of Bank Hapoalim on the Tel Aviv Stock Exchange ceased for 30 minutes on February 3 after the announcement that Israel's largest bank suffered **losses of 250 million shekels ($62 million) in the fourth quarter of 2008**. Bank Hapoalim has not posted losses since the early 1980s.