

# The Existential Dilemma of Israeli Biotech

## ISRAELI BIOTECH

*Maybe they had all been smoking something.*

By January 2007, when Israel's most watched biotech, **Pharmos Corp.**, announced that its cannabis-derived IV cannabimimetic against postoperative pain had failed to work in its higher doses—the company's second major clinical disappointment—Tel Aviv Stock Exchange investors had already begun to sour on the public venture experiment they'd been conducting for the previous two years.

Israel's biotech industry—a scientific and entrepreneurial dynamo but starved for capital, infrastructure, and managerial experience—had figured these investors were at least a partial solution to its financial needs. Since 2004, when investment rules loosened up, a few dozen pharma-focused groups had gone public on the Tel Aviv Stock Exchange, generally with packages of shares and warrants and sometimes debt. Several of the companies, like **Clal Biotechnology Industries Ltd.** and **Hadasit Bio-Holdings Ltd.**, were in effect collections of projects in the guise of companies, doling out management services and a little cash to their portfolio businesses.

Few of the companies raised much money. Indeed, the minimal investments seemed like a kind of compromise. Most successes would only be incremental but the downsides wouldn't be too steep either. Failures would be learning experiences, **BioLineRx Ltd.**'s CEO Morris Laster, MD, told *START-UP* a year ago. (See “Public Venture Capital for Israel's Biotech Industry,” *START-UP*, June 2007.) They will “create people who will know how to run biotechs,” he said. “They'll learn from their mistakes. And that's how you develop an industry.”

Perhaps. But Israeli investors haven't wanted to give the industry a second chance. Biotech stocks have been crushed—**BioLineRx** is now trading at a market cap roughly equal to the \$50 million it raised a year ago. Stock in **Clal**, whose market cap of about \$140 million makes it Israel's most valuable biotech listing (it comprises investments, most of them shareholdings of 25% or more, in some 16 companies) has lost 40% of its value. **Hadasit**, essentially a public vehicle for medical start-

ups from **Hadassah Medical Organization**, has a market cap of about \$13 million, less than a third of its year-ago price. The median market cap for the 14 publicly traded Israeli biotechs in TASE's Biomed group is \$26 million.

“Knowledgeable funding is a bigger issue than ever” in Israel, says Nava Swersky Sofer, president and CEO of **Yissum Research Development Co.**, the tech-transfer arm of the **Hebrew University**. The already small universe of Israeli VCs—largely investors from the device world—seems to be shrinking, since one, **Medica**, is reportedly at the end of its capital commitments. “By and large,” she says, “we're not creating an industry. There are too many holes.”

Of course, biotech stocks are depressed worldwide—Israel is exceptional only in the extremity of its market decline. Which therefore leads to the industry's basic existential question: can it flourish on a worldwide stage?

“Look,” says Laster, “there's a process of natural selection going on. To a large extent, Israel got a window of opportunity. Whoever managed to [go public] did—and they've now got a responsibility to deliver.” And if none of those companies deliver, he says, “maybe there's not an industry.”

But Laster's faith in the justice of economic Darwinism is by no means typical—and with more than 18 months of cash, it's a bit easier for him to cast a cold eye on his poorer compatriots. Most of the other executives and investors we spoke with, however, believe the industry is starting with too many disadvantages to give it a fair chance.

The majority look to the Israeli government, which has so far not done much for biotech. The Office of the Chief Scientist, the main source of federal monies, has a total budget of about \$250 million of which perhaps 20% is earmarked for life sciences, says Raphael Hofstein, PhD, chairman of **Hadasit Bio**. Half of that \$50 million goes to devices, leaving \$25 million for biotech. And while the biotech industry gets the theoretical benefit of university patents—about 80% of which focus on the area—the device world gets the far more finance—able boost of Israeli defense spending, a constant source of spin-off ideas (such as

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**Given Imaging Ltd.**'s tiny *PillCam* endoscope—a byproduct of missile technology).

Meanwhile, there are few openings for young life-science academics, many of whom do their post-docs in the US, where NIH funding is plentiful—and where, after finishing up, they can join American biotechs. Local heroes Aya Jakobovits, PhD, a scientific founder of **Cell Genesys Inc.**, Abgenix and Agensys, the latter two acquired in high-value deals by **Amgen Inc.** and **Astellas Pharma Inc.**, respectively, and Arnon Rosenthal, PhD, a founder of Rinat (bought by **Pfizer Inc.**), both remain in the US. Could Rinat have been created in Israel? Not likely, says Rosenthal.

The brain drain is now an officially recognized problem—the government's Immigration & Absorption Office tries to entice expat Israelis to come home. But its program is a small step in a very long journey.

Indeed, the government hasn't yet decided that biotechnology is a strategic investment area—and won't until the industry proves its bona fides as an employment center. The financial community isn't providing much credibility, notes Zvika Rubinstein, CEO of the Meytav Technological Incubator, like Clal, a collection of investments in start-ups to which it provides management services and some funding. Israeli investors want “quick returns,” which is why they vastly prefer device opportunities (indeed, device companies fill roughly two-thirds of Meytav's own portfolio).

The alternative: attract Big Pharma, he says, which would in turn lead the government to “understand that there's a big potential” in the biotech industry.

Judging from the attendee list at the late May ILSI-Biomed conference, Israel's annual biotech show, Big Pharma hasn't exactly been ignoring Israel. Plenty of the larger companies were in evidence. But Rubinstein is right: deal-making has been sparse.

It's a chicken-and-egg problem, says Hofstein. Big Pharma won't come because companies in Israel don't have the infrastructure they need to present complete preclinical packages—and Israel doesn't have the infrastructure because it doesn't have the funding—government funding. “We've got to go to Romania, to China, do the dog tox in Ireland—and then do a little bit of work in Rehovot. If Pfizer has to go all around to collect this package, they won't come here,” he argues. “We claim a leadership position in stem cells,

but we don't even have the infrastructure for a bank of stem cell lines.”

Not that Hofstein expects the government to suddenly change its way, but he is trying to create a “revolutionary” new financing tool—a not-for-profit \$2 billion fund, a complicated combination of investment and loan guarantees from venture philanthropies (he mentions the Milken Institute), European investment banks, some foreign governments looking for spillover from technology developed in Israel—and the Israeli finance ministry, without whose “meaningful [investment] commitment” the idea simply sputters.

Hofstein's idea isn't so strange in this country: surrounded by enemies, Israel has always depended on the kindness of strangers, particularly North American strangers. But most Israeli biotechs and their investors are pursuing more immediately practical, make-do solutions. Nava Sofer is planning to put together a small pool of capital to jumpstart new companies. “There isn't anyone else to partner with to do this—except the incubators, and they've got limited capital with too many strings attached to it.”

Indeed it is those strings which allow the incubators to, theoretically, make money in an industry with precious few exits. Clal's strategy, for example, relies on what CEO Ruben Krupik calls the “flexible exit”—a way to cover the bet without badly cutting the upside. Take **MediWound Ltd.**, which has a Phase III biological agent for debriding wounds. With Clal co-founding and funding the company, and starting with an 80% shareholding, Krupik says he rejected a “lousy” deal on the agent from an American medical device company, opting instead to sell \$30 million worth of MediWound's shares, at a \$100 million pre-money value, to **Teva Pharmaceutical Industries Ltd.** (already a 16% shareholder in Clal) and institutional shareholders—recouping its original investment, with Teva taking a license to the drug. Clal still owns 56% of the company with the right to put more shares to Teva—at a \$250 million valuation on approval in Europe and a \$310 million valuation on US approval. Even after those sales, says Krupik, Clal will own 30% of MediWound's shares—and can still trigger an IPO. That said, MediWound is hardly the kind of investment likely to be attractive to ex-US investors or Big Pharma partners, who want to see their money go into product development, not reward other investors first.

Or **Andromeda Biotech Ltd.**—“my masterpiece,” says Krupik. The company's technology, created at the **Weizmann Institute of Science**, was acquired [as Peptor] by the German biotech **DeveloGen AG**. DeveloGen funded Peptor's lead product, for Type I diabetes and latent autoimmune diabetes, through part of Phase III—and then stopped. Not that the drug didn't work, says Krupik—but it was burdened with a 45% royalty obligation. In return for the product, Clal agreed to fund the rest of the trial with \$7 million and would pay two larger milestones as the drug progressed. Meanwhile, it had negotiated with its royalty holders, Weizmann and Teva, to reduce the royalties to 9%, giving Teva an option on the product. “If it doesn't work, we're out \$7 million,” says Krupik. “And we'll know in just a few weeks.”

Clal, like all of Israel's major biotech players, has had to make a virtue of being a big fish in a small pond—of being able to buy cheap. BioLineRx has done the same thing—getting first dibs on a wide variety of preclinical Israeli university programs on which it moves quickly and inexpensively to go/no go decisions. BioLineRx even has a separately funded program—via a group of apparently philanthropically inclined Canadian investors and a small contribution from BioLineRx—for working on very early, *in vitro* stage university projects.

But it is Teva which has taken most advantage of the Israeli biotech industry's weakness and the lack of competition for its innovation. The company is everywhere in Israeli biotech—a shareholder in Clal and several of its portfolio companies; in BioLineRx; in dozens of other start-ups. And it will be doing more. Roughly \$200 million of its \$700 million annual R&D budget—7% of revenues—goes to innovative research. The rest is targeted to generics. But notes Aharon Schwartz, PhD, VP, Innovative Ventures, for Teva, “there's a limit to how much money you can throw into generics R&D,” particularly as the company projects a doubling of sales to \$20 billion by 2012. Teva will still be spending 7% of its sales on R&D but the growth rate for the generic share will slow, he says, and its innovative R&D spending will grow disproportionately. “I can assure you,” he continues, “if Lilly, Bayer or Merck want a product, we can't compete. But they're not even looking very hard in their own backyards, in the American academic centers, let alone here.”

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—ROGER LONGMAN