

# Israel's Biotech Businesses See Promise of Profits

After years of investment, some Israeli biotech firms are beginning to see the prospect of significant returns.

Israel has a strong pipeline of promising new biotech projects at a time when global pharmaceutical companies have a severe lack of new drugs in development. Investors in Israeli companies are finally beginning to see some profitable light at the end of the tunnel. In particular, Israeli investors are realizing that though biotech ideas may take longer to develop into marketable products than in other high-tech sectors, the rewards are bigger and last longer.

## Copaxone Sets a Profitable Example

Teva Pharmaceuticals (Nasdaq: TEVA; TASE: TEVA) has proven this point in Israel. During 2010 Teva saw sales of its branded drug – Copaxone® reach \$3.3 billion, up 17% from \$2.8 billion the previous year. Accumulative sales of Copaxone® for the period 2002-2010 have totaled more than \$14 billion.

Sales of Copaxone® helped Teva raise its total sales

by 16% to \$16.1 billion in 2010 with profits of \$4.1 billion, up 36% from 2009, easily making it Israel's largest company. Though most of Teva's income is generated from generic drugs – it is the world's largest generic drug manufacturer - there is also the promise of more branded ethical pharmaceutical income in the not very distant future. In 2007 Teva received FDA and EU approval for Azilect for the treatment of Parkinson's Disease and worldwide sales reached \$318 million in 2010 up 31% from \$243 million in 2009.

Other new drugs in the Teva pipeline are led by Laquinimod for the treatment of Multiple Sclerosis, which has the advantage of being taken orally. Teva recently reported

favorable results from its Allegro Phase III trial including a 23% reduction in the annualized multiple sclerosis relapse rate, a 36% reduction in the risk of confirmed disability progression and a 33% reduction in progression of brain atrophy. Teva expects to

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receive FDA approval to market the drug in the final quarter of 2012 or first quarter of 2013. Teva's recent acquisition of US branded drug developer Cephalon for \$6.8 billion, has greatly increased Teva's branded drug sales and development pipeline.

Teva also has a portfolio of promising new drugs through its partnership with Clal Biotechnology Industries (CBI) (TASE:CBI). Teva has invested \$69 million in CBI and holds a 15% stake, while Clal Industries and Investments of IDB Group (Israel's largest holding company) holds a 59% stake in CBI, which is managed by Arte Venture Group. CBI's portfolio includes 17 life science companies and manages over \$600 million in capital.

### Successful Trials

CBI's portfolio companies include MediWound, in which CBI owns a 55.2% stake, and which has successfully completed a Phase III trial for its burn and wound treatment product. MediWound also owns the commercialization rights for PolyHeal (38%) which recently received CE approval for marketing in Europe, and is close to FDA approval for its wound management treatment. CBI has a 38% stake in Polyheal. Andromeda Biotech, in which Clal Biotech owns a 84% stake, has reported good interim results in the Phase III clinical trial of its type 1 diabetes drug. CureTech (37%) reported progress in its Phase IIb clinical trial of a cancer treatment, and The company has also received a CE mark.

CBI also has stakes in three companies traded on the TASE: D-Pharm (46%) is pioneering the development of lipid-like therapeutics for treating strokes; Biocancell (15%) is developing cancer treatments and its lead product for the treatment of bladder cancer is in a Phase IIa clinical trial; and Aposense (4%) whose lead compound ML-10 for PET imaging of apoptosis is in Phase II clinical trials for early visualization of the effect of anticancer therapy.

Other CBI portfolio companies include Transpharma Medical (12%) whose products include ViaDerm-hPTH (1-34), to treat osteoporosis, developed in collaboration with Eli Lilly and undergoing Phase

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IIb clinical trials. Two additional products have completed Phase I testing, one of which is ViaDerm-GLP 1 agonist for the treatment of type 2 diabetes. Thrombotech (42%) has developed THR-18, a peptide administered alongside existing stroke treatments. THR-18's unique mechanism of action and experimental evidence suggest that it may also

be effective against heart attacks, traumatic brain injury, lung embolisms, and occluded arteries and veins in the legs and arms. Recent findings suggest THR-18 may have other clinical indications such as treatment of asthma and hypertension.

Earlier stage CBI portfolio companies include Braintact (38%), which is developing an innovative, proprietary blood glutamate scavenging platform for the treatment of acute and chronic neurodegenerative diseases, and ProtAb (15%),

which is developing novel therapeutic agents that modulate cytokine regulation, tipping the balance toward anti-inflammatory signaling pathways in the treatment of autoimmune and inflammatory diseases. There are about 250 biotech, pharmaceutical and agbio companies in Israel. The country's veteran biotech firm Bio-Technology General (BTG) is fully owned by Ferring Pharmaceuticals, which acquired the company from Savient Pharmaceuticals of the US in 2005 for \$80 million. Operating from its cGMP plant in Beer Tuvia, BTG acts as one of Ferring's R&D centers focusing on Development and manufacture of recombinant bacterial and mammalian cell based products for the pharmaceutical and medical device industries. Sales amounted to about \$50 million in 2010.

### Veteran Companies

Other veteran Israeli biotech firms that are further down the development road include Peptor, which during 2003 merged with the German firm Develogen. Peptor has also signed strategic agreements with major international players in developing its synthetic peptide-based pharmaceuticals. This includes a licensing agreement

with Aventis for its diabetes drug and cooperation with Roche in the field of cancer treatment.

Compugen (Nasdaq: CGEN; TASE: CGEN) has an agreement with Diagnostic Product on its newly discovered prostrate linked antigens and with Teva on biomarkers for early detection of drug-induced kidney toxicity. Compugen has more recently moved into drug development and its lead products are CGEN-15001, a protein for autoimmune diseases, and its counterpart, a drug target candidate for mAb therapy in oncology.

Other Israeli firms developing new chemical entities include Proteologics (TASE: PRTL), which specializes in the ubiquitin system. Based on research by Nobel Prize winner Prof. Aaron Ciechanover of the Technion, Israel Institute of Technology, the company develops a new class of small molecule drugs against major diseases based on ubiquitin ligase inhibitors. Proteologics has signed a commercialization deal with GSK to develop its promising cancer treatment molecules and recently reported positive results in animal trials on two anti-inflammatory treatments.

Another Teva portfolio company which is developing a new chemical entity is Vascular Biogenics (VBL). VBL is dedicated to the development of innovative therapies targeting the vascular wall and its extensive vascular expertise is utilized in addressing the cardiovascular and cancer drug markets.

### **Promising Developments**

Other promising Israeli biotech companies traded on the TASE include Can-Fite BioPharma (TASE: CFBI), which is developing novel treatments for autoimmune and liver diseases, and cancer. Can-Fite's lead drug CF101 successfully has progressed through Phase IIa trials for the treatment of rheumatoid arthritis, psoriasis and glaucoma. Another drug CF 102 for the treatment of liver diseases is currently in Phase II clinical trials.

Kamada (TASE: KMDA) is another of the few Israeli biotech companies to successfully complete Phase III clinical trials. The company received FDA approval in

July 2010 for Glassia, its intravenous AAT treatment for congenital emphysema and has a distribution agreement with Baxter International. Kamada had sales of \$36 million in 2010. Intec Pharma (TASE: INTP) is conducting Phase II trials for its sleep disorder treatment. Prolor Biotech (AMEX: PBTH; TASE: PBTH)

is holding a Phase II trial for hGH-CTP, which treats growth hormone deficiency. XTL Biopharmaceuticals (Pink Sheets: XTLBY; TASE: XTL) is developing a drug for the treatment of blood cancer, while RedHill Biopharma (TASE: RDHL), which buys the rights for drugs in advanced clinical trials, raised over \$15 million in an IPO in February.

Cell therapy offers the world much hope in pioneering new treatments. In Israel Gamida-Cell, subsidiary of Elbit Medical Technologies (TASE: EMTC)

(31.6%) and a CBI portfolio company (20%) is a leader in the expansion of stem cell therapeutics. The company's lead product, StemEx, is now being tested in an advanced, Phase II clinical trial for hematological malignancies. The company is also developing NiCord, a therapeutic derived from the Gamida-Cell's second platform technology for stem cell expansion for the treatment of autoimmune and hematological diseases.

Pluristem Therapeutics (Nasdaq: PSTI; TASE PSTI) is developing stem cell therapy to treat severe obstruction of arteries that can lead to amputation, and plans to start a Phase II/III trial to treat critical limb ischemia in the second half of 2011..

Biokine Therapeutics (CBI holds 31%) develops novel anti-cancer and stem cells mobilization drugs. Biokine's lead molecule, BKT140, a CXCR4 antagonist, recently finalized a Phase I/IIa clinical trial on 16 multiple myeloma patients

Protalix Biotherapeutics (AMEX: PLX) is capitalizing on its proprietary biomanufacturing plant cell culture platform to develop biopharmaceuticals and biogenerics or biosimilar pharmaceutical proteins. Protalix has successfully completed Phase III trials on a Gaucher's Disease treatment and sold commercialization rights to Pfizer although FDA approval has been delayed until at least 2012.

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### **Innovative Business Structures**

Among innovative business structures, which are designed to overcome Israeli biotech's difficulties in raising capital and lack of management know-how, is BioLineRX (TASE: BLRX). The public owns 73% of BiolineRX, Teva (10%) and other partners 17%. Billed as a drug development company, BioLineRx is bridging the gap between Israel's enormous innovative R&D potential and global pharmaceutical marketing. The company has an agreement with Cypress Bioscience to develop one of its two leading drugs, BL 1020 for the treatment of schizophrenia. The company's second leading drug is BL 1040 for rebuilding heart tissue for heart attack sufferers is being developed in partnership with Ikaria Holdings.

BioLineRx was also selected as the sole recipient of a \$21 million grant for the development of pre-clinical compounds as part of the Office of the Chief Scientist's (OCS) policy of funding incubators dedicated to biotech.

ProCognia (TASE: PRCG) has developed a protein-based technology for analyzing blood sugar molecules (glycoanalysis), while Medgenics (AMEX: MDGC AIM: MDGC) has developed a proprietary biological platform, the Biopump, which allows patients to produce, within their bodies and on a long-term basis, their own natural human protein therapy for the treatment of a range of chronic diseases, such as anemia and hepatitis C. Nasvax (TASE: NSVX) has an agreement with Novartis to develop a family of improved vaccines.

### **Industrial Biotech and Agro-Bio**

In industrial biotechnology, Bio Dalia Technologies manufactures and markets *Bacillus thuringiensis* bioinsecticides and is active in contract manufacturing of biochemicals by fermentation, industrial bioprocess development and R&D. Enzymotec develops special stable enzyme for research and industrial use. Furthermore, the company is developing new and improved products by means of a biosynthesis technology.

In Agro-Bio Hazera and Zeraim Gedera are world leaders in seed technology, while Rahan Meristem

has developed tissue culture plants for the diagnosis of plant pathogens and recombinant vaccines for veterinary purposes. Among promising projects being developed by Gavish Bio Applications in the Galilee is a post-harvest preservation and protection of fruits and genetically modified plants, which raise the nutritional quality of animal feed and food for human consumption.

AgroGreen, a member of MINRAV GROUP, provides "green" and friendly solutions for agricultural problems and demands. AGROGREEN focuses its development efforts on biological pesticides. BioFeed has developed a device that is an environmentally safe for controlling the Mediterranean fruit fly (Medfly), in which no chemicals come into contact with the fruit, while Biomor is devoted to developing a biocide

based on Tea Tree Oil extract.

Evogene (TASE: EVGN) is a crop genetics company, a spin-off of Compugen, which is focused on the improvement of high commercial value key traits in important crops through gene discovery, genome remodeling and advanced breeding techniques. Evogene and French biotech firm Biogemma SAS recently reported success in the first year field trial of high-yield drought resistant corn developed with genes located by Evogene.

FertiSeeds is an agro-biotechnology company offering a novel, universal solution for low cost production of hybrid seeds based on molecular genetic technology, while Virumar develops an innovative platform technology and vaccine against Marek's disease in poultry. Rosetta Green (TASE: RSTG), which uses unique genes named microRNAs to develop plants and algae with improved traits recently raised \$6.4 million on the TASE.

### **VC Boost**

Israeli biotech was recently given a boost by the establishment of a \$203 million VC fund which will be managed by Orbimed Advisors, the largest healthcare investment fund in the world. The fund was initiated by an Israeli government tender and investment of \$40 million and reflects the feeling that the country's biotech industry is only scratching the surface of its potential.

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