NEWSLETTER OF THE FRIENDS OF THE ISRAEL HEART SOCIETY

Editor's Note: Welcome to the Winter 2009 issue of the Newsletter. Due to the overwhelming support we have received in the form of emails for this project, this will be an expanded Newsletter that I think you will enjoy.

In this issue: Amir Lerman and the Fellowship Committee in conjunction with the Israel Heart Society developed its first travel grant for an Israeli fellow to fly to AHA this past November- we have a letter from the awardee Dr. Roy Beigel.

We have a book review by Dr. Peter Fitzgerald and a reprint from In Vivo Magazine reviewing the state of Medical entrepreneurship in the State of Israel.

On Page 4 of our newsletter, please note an announcement for the Annual FIHS/HIS Reception at the ACC meeting in Atlanta Sunday, March 14.

Finally, we have our usual features highlighting Israeli research, introducing a leading Israeli Cardiology Center, Tel Aviv Heart Center and announcements for upcoming meetings in the Holy Land.

Remember, this Newsletter belongs to the membership. Please feel free to email us with questions, advice, anything we inadvertently left out, or to just tell us we did a good job. We look forward to working with you to make this Newsletter and the connections between Israeli and foreign cardiologists and their institutions grow and prosper!

Meet and Greet: The first "Meet and Greet" for FIHS took place November 10 in Skokie, Illinois. Featured guests were our own president Jeff Goldberger, Dr. David Gutterman- dean of Clinical Research at the Medical College of Wisconsin, and Ms. Noa Asher- Consul for Economic Affairs to the Midwest, Government of Israel. This program succeeded in raising awareness of our Society and increased membership. More to come!

NEWSLETTER OF THE FRIENDS

OF THE ISRAEL HEART SOCIETY

Message from the President:

It has been a great year for the Friends of the Israel Heart Society. I want to thank all who have contributed to our efforts and growth this year. We look to further growth and development next year. I want to make you aware of several items:

1) **FIHS reception at ACC** - as we have done in the past, we will be having a reception at ACC on Sunday, March 14, 2010 beginning at 5:30 PM. We look forward to seeing you there! An RSVP form is in the newsletter.

2) We acknowledge Dr. Roy Beigel, the FIHS awardee for a traveling fellowship to AHA – see his letter and photograph of fellowship presentation.

3) We also acknowledge the winners of the 10th International Dead Sea Symposium Fellow's Case Competition, a program that provide stipends to fellows in accredited North American cardiovascular training programs to attend the meeting. They are:

Mohammad M. Ansari, MD

St. Elizabeth Medical Center, Tufts University School of Medicine

A Novel Imaging Technique to Facilitate Radiofrequency Catheter Ablation of an Accessory Pulmonary Vein

Alejandro Jimenez, MD

University of Maryland Medical Center

Multimodality Imaging for Ablation of Idiopathic Ventricular Fibrillation: Use of Electroanatomical Mapping to Guide Radiofrequency Ablation and Computer Tomography to Assess Endocardial Lesion

Keila Lopez, MD MPH

Texas Children's Hospital, Baylor College of Medicine

Atrial Quiescence and Recalcitrant Ventricular Arrhythmias: An Unusual Presentation of SCN5A Mutation

Michael J. Mazzini, MD

Boston Medical Center

Ventricular fibrillation in a 22-year-old woman with primary carnitine (OCTN2) deficiency: a novel mutation and in vivo evidence of increased oxidative stress

Michael R. Weber , MD

Montefiore Medical Center

Failure to Deliver Appropriate ICD Therapy During Sustained Ventricular Tachycardia – an Illustration of Current Limitations of Arrhythmia Algorithm Classification

4) As 2010 rolls in, and we plan for further growth, we need your support for membership – both financially and in recruiting some colleagues and friends who are inclined to be members but are not aware of the FIHS – please reach out with this newsletter. Annual membership can be paid through the FIHS website at: http://www.friendsihs.org/index.html or by mailing a check made out to the Friends of the Israel Heart Society to:

FIHS

c/o Debbie Burg

8626 Central Park

Skokie, IL 60076

5) Thank you to all who helped support the campaign against the Norwegian boycott! The Board voted against the proposal to boycott.

6) Finally, many thanks to our Silver, Gold, and Platinum members for 2009 - we could not have succeeded without your support.

Thank you for your continued support!

Jeff Goldberger

President, Friends of the Israel Heart Society

Upcoming Meetings in Israel

The 10th International Dead Sea Symposium on Cardiac Arrhythmias and Device Therapy (IDSS)

February 8-10, 2010, Tel Aviv

http://www.paragon-conventions.com/arrhythmia2010

Dear Colleague,

We are writing to provide you with a brief summary of the 9th IDSS meeting and to announce the 10th IDSS, which will be held in Tel Aviv, February 8-10, 2010 at the David InterContinental Convention Center.
The 9th IDSS proved to be a very successful meeting, exceeding all expectations of the organizers. Once again, attendance exceeded previous years (696 participants), with a remarkable attendance from the Russian Federation and USA. Representation from Europe, including Germany, France, Hungary, Italy, Poland, Serbia, the Netherlands and others, was also impressive. It was truly an international gathering with active participation of representatives from 32 countries from Europe, North America and Israel, including several physicians from South America and the Asian-Pacific area.

The CME accredited scientific program was presented by leading experts from Europe, the USA, Canada and Israel, and included various topics of clinical and basic electrophysiology and pacing, satellite symposia, training courses, and an industry exhibition which ran throughout the meeting and drew a lot of interest of participants. Of particular interest was the high attendance at educational courses, such as 2-day courses for fellows in EP and internal medicine, pediatric sessions and sessions dedicated to arrhythmias in athletes. In addition, there were two sessions dedicated to surgical treatment of cardiac

arrhythmias and full-day sessions for family physicians concentrating on 'hot' topics, such as non-pharmacological treatment of AF and CHF. Satellite symposia sponsored by the industry, dedicated to the monitoring of implantable devices, ICD/CRT-D innovations leading to improved patient outcome, and lead extraction, were very successful and particularly well attended.

Next year the IDSS celebrates its 20th anniversary. The program will be modified according to feedback received from participants in the 9th meeting, with further emphasis on educational activities and on increasing the number of satellite sessions. We intend to provide more space for the exhibition and welcome earlier involvement of the industry in planning the industry – sponsored scientific activity.

On behalf of the Organizing and Executive Scientific Committees, it is my pleasure to invite you to participate in the symposium. We hope that you will accept our invitation and take an active part in what promises to be an outstanding international scientific and social event within Tel-Aviv, Israel's largest city, which offers an exciting and cosmopolitan mix of outdoor cafes, ethnic restaurants, cultural centers, open markets and of course the Mediterranean shore and its golden beaches.

With best regards,
Sincerely Yours,
Prof. I. Eli Ovsyshcher, MD, PhD, FESC, FACC, FHRS, MAHA
President of the Symposium
eliovsy@bgu.ac.il

See you at the FIHS/ACC

Meeting at ACC!

The Friends of the Israel Heart Society (FIHS) and the Israel Heart Society (IHS) take great pleasure in inviting you to the Friends of the Israel Heart Society Reception at ACC

Location: Atlanta Marriott Marquis

265 Peachtree Center Avenue, Atlanta

Hall: Marquis room L401-L403
Date: Sunday, March 14, 2010
Time: 5:30 pm - 7:00 pm
It will be a great pleasure to meet and host you at our event. Please reply using the form below.

We also remind you to make your annual contribution, which can include the annual $50 dues, through the FIHS website at: http://www.friendsihs.org/index.html

Alternatively, mail a check made out to the Friends of the Israel Heart Society to FIHS, c/o Debbie Burg, 8626 Central Park, Skokie, IL 60076
All contributions will be greatly appreciated and are tax-deductible.

With best wishes

Yours sincerely,

Jeffrey Goldberger, MD, FACC

President, FIHS

[ ] I will be pleased to participate in the event

[ ] I regret that I cannot participate

First &Last Name: _____

Please return your confirmation to the

FIHS Secretariat at:mailto:: debbie@virtual9to5.com

NEWSLETTER OF THE FRIENDS

האיגוד הקרדיולוגי בישראל
ISRAEL HEART SOCIETY

OF THE ISRAEL HEART SOCIETY

57th Annual Conference of the Israel Heart Society/Israel Society of Cardiothoracic Surgery in association with the European Society of Cardiology, American College of Cardiology, and European Heart Rhythm Association

April 14-15, 2010, David Intercontinental Hotel and Convention Center, Tel Aviv, Israel

Guest speakers:

Steen Dalby Kristensen, MD, FESC
Vice President European Society of Cardiology (ESC)
Aarhus University Hospital, Denmark

Patrick Serryus, MD, PhD, FESC
Erasmus University Medical Center, Netherlands

Robert A. Harrington, MD, FACC, FAHA
Duke University Medical Center Durham, NC, USA

Robert O. Bonow, MD, FACC, FAHA
Immediate past-President of the American Heart Association (AHA)
Northwestern Memorial Hospital, Chicago, IL, USA
http://www.israelheart.com/

Featured Research:

N Engl J Med 2008;359:229-41.

Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet

Iris Shai, R.D., Ph.D., Dan Schwarzfuchs, M.D., Yaakov Henkin, M.D., Danit R. Shahar, R.D., Ph.D., Shula Witkow, R.D., M.P.H., Ilana Greenberg, R.D., M.P.H., Rachel Golan, R.D., M.P.H., Drora Fraser, Ph.D., Arkady Bolotin, Ph.D., Hilel Vardi, M.Sc., Osnat Tangi-Rozental, B.A., Rachel Zuk-Ramot, R.N., Benjamin Sarusi, M.Sc., Dov Brickner, M.D., Ziva Schwartz, M.D., Einat Sheiner, M.D., Rachel Marko, M.Sc., Esther Katorza, M.Sc., Joachim Thiery, M.D., Georg Martin Fiedler, M.D., Matthias Blüher, M.D., Michael Stumvoll, M.D., and Meir J. Stampfer, M.D., Dr.P.H., for the Dietary Intervention Randomized Controlled Trial (DIRECT) Group

Background

Trials comparing the effectiveness and safety of weight-loss diets are frequently limited by short follow-up times and high dropout rates.

Methods

In this 2-year trial, we randomly assigned 322 moderately obese subjects (mean age, 52 years; mean body-mass index [the weight in kilograms divided by the square of the height in meters], 31; male sex, 86%) to one of three diets: low-fat, restricted-calorie; Mediterranean, restricted-calorie; or low-carbohydrate, non–restricted-calorie.

Results

The rate of adherence to a study diet was 95.4% at 1 year and 84.6% at 2 years. The Mediterranean-diet group consumed the largest amounts of dietary fiber and had the highest ratio of monounsaturated to saturated fat ($P<0.05$ for all comparisons among treatment groups). The low-carbohydrate group consumed the smallest amount of carbohydrates and the largest amounts of fat, protein, and cholesterol

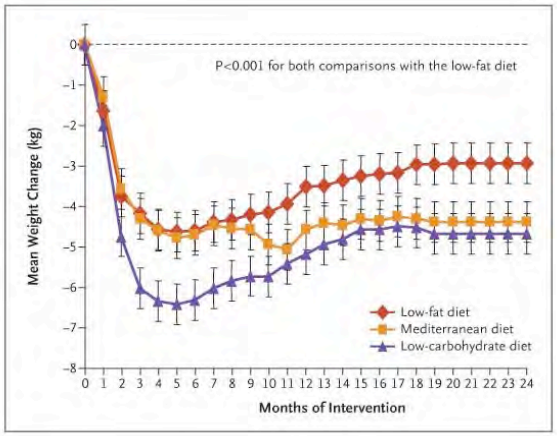
and had the highest percentage of participants with detectable urinary ketones (P<0.05 for all comparisons among treatment groups). The mean weight loss was 2.9 kg for the low-fat group, 4.4 kg for the Mediterranean-diet group, and 4.7 kg for the low-carbohydrate group (P<0.001 for the interaction between diet group and time); among the 272 participants who completed the intervention, the mean weight losses were 3.3 kg, 4.6 kg, and 5.5 kg, respectively. The relative reduction in the ratio of total cholesterol to high-density lipoprotein cholesterol was 20% in the low-carbohydrate group and 12% in the low-fat group (P=0.01). Among the 36 subjects with diabetes, changes in fasting plasma glucose and insulin levels were more favorable among those assigned to the Mediterranean diet than among those assigned to the low-fat diet (P<0.001 for the interaction among diabetes and Mediterranean diet and time with respect to fasting glucose levels).

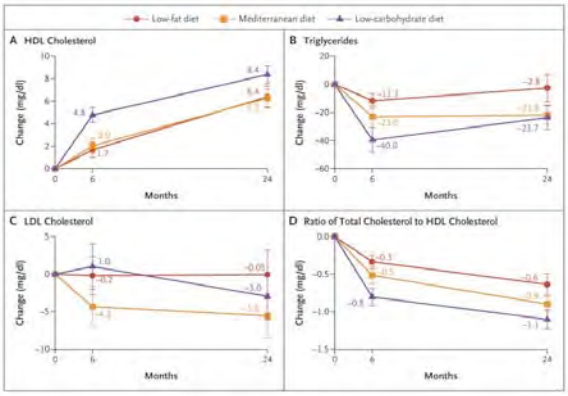
Conclusions

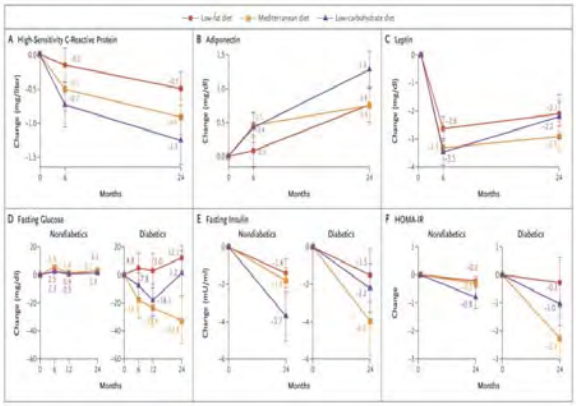
Mediterranean and low-carbohydrate diets may be effective alternatives to low-fat diets. The more favorable effects on lipids (with the low-carbohydrate diet) and on glycemic control (with the Mediterranean diet) suggest that personal preferences and metabolic considerations might inform individualized tailoring of dietary interventions. (ClinicalTrials.gov number, NCT00160108.)

From the S. Daniel Abraham Center for Health and Nutrition, Ben-Gurion University of the Negev, Beer-Sheva (I.S., D.R.S., S.W., I.G., R.G., D.F., A.B., H.V., O.T.-R.); the Nuclear Research Center Negev, Dimona (D.S., R.Z.-R., B.S., D.B., Z.S., E.S., R.M., E.K.); and the Department of Cardiology, Soroka University Medical Center, Beer-Sheva (Y.H.) — all in Israel; the Institute of Laboratory Medicine, University Hospital Leipzig (J.T., G.M.F.); and the Department of Medicine, University of Leipzig (M.B., M.S.) — both in Leipzig, Germany; and Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, and the Departments of Epidemiology and Nutrition, Harvard School of Public Health — all in Boston (M.J.S.). Address reprint requests to Dr. Shai at the S. Daniel Abraham International Center for Health and Nutrition, Department of Epidemiology and Health Systems Evaluation, Ben- Gurion University of the Negev, P.O. Box 653, Beer-Sheva 84105, Israel, or at irish@bgu.ac.il.

http://content.nejm.org/cgi/content/full/359/3/229







NEWSLETTER OF THE FRIENDS OF THE ISRAEL HEART SOCIETY

Fellow Travel Grant Letter:

Amir Lerman MD and the Fellowship Committee in conjunction with the Israel Heart Society developed its first travel grant for an Israeli fellow to fly to AHA this past November- the awardee, Dr. Roy Beigel, wrote the following letter:

This November I had the opportunity to attend the AHA scientific sessions held in the orange county convention center at Orlando, Florida. The sessions provided me with a unique learning opportunity, as I became familiar with the latest clinical trials results such as the Arbiter-6, PLATO-STEMI, Record-AF and many other new studies that were first introduced during these sessions. I also had the chance to attend various sessions regarding new ongoing research in different topics and fields such as interventional cardiology, non invasive imaging and electrophysiology expanding my horizons and giving me further insight towards novel issues and technologies.

The sessions were truly a learning experience on my behalf and I recommend that every fellow attend these sorts of meetings at least once during his or her fellowship in order to receive better understanding of the research "industry" behind the world of cardiology.

Roy Beigel MD

The Leviev Heart Institute, Sheba Medical Center, Tel Hashomer, Israel

Traveling fellowship award to attend 2009 AHA Scientific Sessions presented by Drs. Goldberger, Zipes, and Lerman (right to left) to Dr. Beigel from Sheba Medical Center with Dr. Zahger from the Israel Heart Society (left) in attendance (photo compliments of Cardiology Today).

TEL AVIV HEART CENTER

Tel Aviv is a vibrant city, and is the business and cultural center of Israel. It is full of atmosphere, wonderful seashore, parks and boulevards. In the middle of all this is the Tel Aviv Medical Center. The hospital is an 1100 bed tertiary care center affiliated to the Sackler School of Medicine with very active clinical and research programs.

Tel Aviv's population is growing older, and thus cardiovascular disease is a leading cause of morbidity of mortality. This was the reason for the development of the large the department of cardiology at the hospital in order to provide medical, interventional and surgical care. All services of cardiology are provided within the department including intensive care, cardiac catheterization and interventional procedures, electrophysiology and device implantation, non-invasive cardiac imaging including echocardiography, radionuclide angiography, exercise testing and physiology, CT and MR imaging in collaboration with radiology, and a very active rehabilitation center.

The department of cardiology is currently undergoing significant changes as we are currently building a new Heart Center (The Sami Ofer Heart Center) with larger facilities and different level of comfort and sophistication. In the new Heart Center, the department of cardiology, cardiac surgery, and the corresponding research laboratories will be under the same roof thereby facilitating communication and collaboration. Importantly, we have a large training program with 8-10 cardiology fellows. Our affiliation with the Sackler School of Medicine offers intense involvement in educational activities for students in all stages of their medical studies and mainly during rotations in the 4th to 6th years of studies.

Tel Aviv Medical Center has a very active intensive care unit, currently with 8 beds that will expand to 12 beds in the new building, hoping to assure that every patient with acute MI and every complex cardiac patient admitted will be treated during the initial period of hospitalization under the intensive monitoring of our staff. The intermediate cardiac care unit has in its current form 29 beds and is dedicated to caring for patients after the initial phase in the ICCU, patients with arrhythmia, heart failure, or complex cardiac clinical problems in need of extensive cardiac evaluation. Within this unit we follow patients after EP guided therapies, arrhythmia ablation, or device implantation. Twenty-one of these beds are fully monitored and another 8 are dedicated for patients after cardiac catheterization and interventional therapeutic procedures. Within the new Heart Center this part of the department will expand to 38 beds so that the new department will include 50 inpatient beds.

Our interventional cardiology unit currently has 3 laboratories that will expand to four in the new Heart Center. Two of the laboratories are involved with coronary and structural heart disease interventions and 2 labs will be dedicated to electrophysiology and device implantation. We perform yearly about 4000 cardiac interventions, 400 EP studies and ablations, and we implant 300 pacemakers and more than 120 ICD or CRTDs.

The interventional cardiology center within our department provides primary PCI to the Tel Aviv population 24/7. The team engages in complex PCI procedures and in structural heart disease

interventions. These include ASD and PFO closure, balloon dilatation of stenotic aortic valves and more recently our Percutaneous Aortic valve implantation program has been launched.

The Arrhythmia and Electrophysiology service provides medical care for patients from all around Israel. EP investigations of ventricular, supraventricular arrhythmia are routine activities including ablation of complex arrhythmias and atrial fibrillation. Investigation of populations prone to sudden death is in the core of our clinical service and research activities. Our younger generation of electrophysiologists travelled abroad to expand their knowledge and returned home to help us in leading the way in this rapidly expanding field.

Our non-invasive laboratories are high volume centers with thousands of echocardiograms performed to service the large 1100 bed hospital, and the active surgical program to help plan and monitor sophisticated surgical interventions and mainly corrective valve surgery. We perform transthoracic echo, TEE, 3D imaging, and stress echo on a routine basis. Within the non-invasive laboratories, exercise testing, holter monitoring, and radionuclide perfusion scans of the heart are performed.
Ten years ago we have added 2 important centers, namely the heart failure center and a rehabilitation center. The heart failure center is organized as clinics around a 10-bed day care where severe heart failure patients are monitored, examined and treated. These patients rarely need full hospitalization in our department to stabilize their condition. In the rehabilitation center, more than 300 patients are trained and undergo a full rehabilitation program after myocardial infarction, cardiac surgery, device implantation, or as part of rehabilitation for heart failure.

Cardiac research in the department is intense both clinically and in the basic science laboratory. Our clinical programs are vast with applied research via connection to the industry in the fields of intensive care, cardiac interventions, pharmacology of heart failure, rhythm disorders and original research in cardiac imaging.

The basic laboratory has collaboration with the Weizmann Institute and Tel Aviv University on stem cell research, inflammation and mainly regulatory T cell research within the context of acute MI, HF or vascular injury and atherosclerosis. Research is performed in the molecular lab, in small animal models and in human clinical protocols. Significant innovations and original contributions were published based on work done by students who performed their research within the laboratory.

Within the new Heart Center with the spirit of collaboration and multidisciplinary teamwork we hope to continue and provide the best possible care for our patients, and promote excellence in clinical practice and scientific progress of our department.

Contact Information

Director – Prof. Gad Keren

kereng@tasmc.health.gov.il

ICCU

Prof. Arie Roth

arieroth@tasmc.health.gov.il

Dr. Yehuda Levy

ylevy@hotmail.com

Intermediate coronary care and EP

Prof. Sami Viskin

saviskin@tasmc.health.gov.il

Interventional Cardiology

Prof. Shmuel Banai

shmuelb@tasmc.health.gov.il

Dr. Arik Finkelstein

afinkel@tasmc.health.gov.il

Dr. Amir Halkin

ahalkin@netvision.net.il

Dr. Itzhak Herz

isach@tasmc.health.gov.il

Electrophysiology

Prof. Bernard Belhassen

bblhass@tasmc.health.gov.il

Dr. Aron Glik

glikaron@tasmc.health.gov.il

Dr. Moty Hochenberg

mirimoty@inter.net.il

Heart Failure

Dr. David Sheps

davidsh@tasmc.health.gov.il

Dr. Dov Wexler (+Echocardiography)

wexlerd@tasmc.health.gov.il

Thallium Cardiac Scan

Dr. Shimon Braun

brauns@netvision.net.il

Dr. Genady Chausovsky

enady_chau@yahoo.com

Echocardiography

Dr. Bella Koifman (+ Women's Heart Clinic)

bellak@tasmc.health.gov.il

Dr. Lev Mendelevich

levm@tasmc.health.gov.il

Dr. Simon Biner

simon.biner@gmail.com

NEWSLETTER OF THE FRIENDS OF THE ISRAEL HEART SOCIETY

MEMBERSHIP DRIVE

At this time we would like to acknowledge the generous support provided to the FIHS. It is only through the support of all of our members that we can meet our goal of forming a worldwide network of cardiologists and associated professionals dedicated to furthering relationships with our Israeli counterparts.

To our Platinum, Gold, and Silver patrons - we thank you from the bottom of our hearts. Please spread the word!

Platinum Members

Dr. Jeffrey S. Borer
Dr. Eugene Braunwald
Dr. Michael J. Wolk
Dr. Douglas P. Zipes

Gold Members

Dr. Jeffrey Goldberger
Dr. Amir Lerman
Dr. Charles J. Love

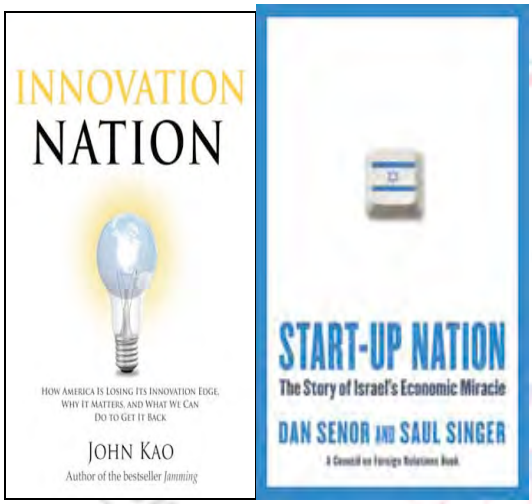
Silver Member

Dr. Charles Antzelevitch
Ms. Kathy Binder, RN
Dr. Robert Bonow
Dr. David S. Cannom
Dr. Robert L. Frey
Dr. Samuel Goldstein
Dr. Nina Charnoff
Dr. Zev Jacobson
Dr. Michael Jaff
Dr. Helmut U. Klein
Dr. Morton Leibowitz
Dr. Arthur Moss
Dr. Stanley Nattel
Dr. Richard L. Popp
Dr. Joe L. Rod
Dr. Stacey Rosen
Dr. David Rosenbaum
Dr. Gregory Schwartz
Dr. Jack Stroh
Dr. Giora Weisz

Thank you!

Entrepreneurship In Israel:

We have a book review by Dr. David Fitzgerald and a reprint from In Vivo Magazine reviewing the state of Medical entrepreneurship in the State of Israel.



Israel faces Silicon Valley:

Medical Technology

For the Heart

Peter J. Fitzgerald, MD, PhD

Stanford University School of Medicine

The new best seller, "start up nation, represents only a glimpse into the ground swell of the restlessness, curiosity, and intellect that makes up the innovative spirit in Israel today. I have been involved in medical technology companies for 20 years in the Silicon Valley, and Israel feels to me like the Bay Area in the mid nineties. From the coffee houses to the university animal labs, a plethora of start ups in the life sciences exists in a small country whose population of 7 million, is equivalent to Silicon Valley and equal in land mass to that of Vancouver Island. Yet there is over 800-life science start ups (a large majority in the cardiovascular arena) compared with 525 in Silicon Valley. Israel is number one in patents per capita in the world.

I am involved in a small venture fund, named TriVentures, in Herzlyia founded by Michal Geva. It is sort of a cross between a venture fund and an incubator working on new technologies focused in Cardiovascular Medicine. Marty Leon and I work with TriVentures identifying and sometimes founding early start up companies focusing simple device concepts for complex cardiovascular disease states. Identifying and understanding the needs of patients together with the amazing innovative "edge" on the soils of Israel is a unique combination. From the rapid prototyping facilities to the superb preclinical validation, the streets of Tel Aviv, Herzlyia, Caesarea, Rehoboth and may other towns buzz with the next disruptive innovation to improve the care of patients with Heart disease.

For me, an Irish guy, it's amazing to be part of such an electric milieu. One of the important things in my life has been the opportunity to participate in the world bridged between engineering and medicine. The identification of a clinical need and the realization of a device that may help such a patient is a world I am proud to participate being able to contribute within such an endeavor, from San Hill Road in Palo Alto to Rothschild Avenue in Tel Aviv remains, for me, a fascination of the heart.

<u>Further reading</u>

1. Start Up Nation (Senor & Singer)
2. Innovation Nation (Kao)
3. In vivo Magazine (October, 2008)

IN VIVO

THE BUSINESS & MEDICINE REPORT

Windhover Information Inc.
windhover.com

OCTOBER 2008
Vol. 26, No. 9

Pharmaceutical Strategic Alliances

What We Have Here is a Failure to Innovate

BY FDC-WINDHOVER'S BIOPHARMA TEAM

Pharmaceuticals

Credit Woes Hit Pharma

BY WENDY DILLER

Medical Devices

Israel's Device Community: Finding New Models as Medtech Matures

BY DAVID CASSAK

Pharmaceutical Marketing

Blow the Launch—Doom the Product

BY SARAH RICKWOOD

Cardica: REBUILDING THE CARDIAC SURGERY MARKET

BY STEPHEN LEVIN

Lilly's Oncology Focus • Is Integra's Growth Sustainable?

ISRAEL'S DEVICE COMMUNITY: FINDING NEW MODELS AS MEDTECH MATURES

One of the most successful centers of medical device innovation, Israel is wrestling with that success and adopting new models to build on it.

- Over the past decade or so, Israel has clearly emerged as a leader in producing innovative device technology, often stemming from its expertise in military technologies.
- But even as innovative devices continue to pour out of Israel, some industry executives worry about a funding gap—too few dollars to support all of the innovation efforts.
- On the other end of the spectrum, as the Israeli device industry matures, executives are also asking why Israel has never developed a large commercial powerhouse—the device equivalent of Teva, the large Israeli drug company—and some are working on new models to enable that.
- To deal with the growing concerns, new models are emerging. TriVentures, a new firm that is part incubator, part VC fund, is focusing on companies at the very earliest stages of their development; Ofer Hi-Tech, at the other end of the spectrum, is looking to roll up companies and create the next Kyphon.

Executive Summary >> 90

BY DAVID CASSAK

Few medical device industry executives would quarrel with the notion that Israel has been one, if not the leading, sources of new device technology over the past decade or so. Anecdotally, some large US device companies now say that one-third to one-half of the new companies and devices they look at either come from Israel or originated there. Today, Israel ranks number-one in the world in patent applications for medical device technology and first in patents per capita, and the list of innovative devices that have come out of Israel would cover all therapeutic areas and all technological fields—including some where Israeli companies seem to have a particular affinity or expertise such as innovative imaging devices and robotics—and would be simply too long to list. So why are so many Israeli device executives, both company types and investors, so anxious these days?

Indeed, even when acknowledging the robustness of the Israeli device industry, one VC adds plaintively, "The problem is, no one's making any money." In large part, the very success of the device industry has led to a growing appreciation of the limits of that success or, perhaps better, of what more could be done. If there's one criticism fairly leveled at the Israeli industry, it's that it's great at developing new technologies, but not so good when it comes to developing companies to realize the full commercial potential of those technologies. **Elscint Ltd.**'s story is long told, and the few clear successes of more recent times, such as **Given Imaging Ltd.**, seem like outliers. Ask many device industry executives where the Israeli equivalent of **Boston Scientific Corp.** or Guidant Corp. is, and they point to **Teva Pharmaceutical Industries Ltd.**, the world's largest generics company that has successfully created a branded pharmaceutical unit, albeit a relatively small one. Hardly a ringing endorsement of the commercial—as distinguished from the technical—success of the Israeli device industry.

Instead, much of the Israeli model has rested over the past decade on a kind of quick-flip mentality: find an innovative device or novel approach to a clinical problem, develop it just so far, and then try to find a buyer or, in a relatively few number of cases, move the company offshore, most often to the US.

Political concerns certainly weigh on Israeli companies and may in some ways make long-term trajectories unrealistic. But, interestingly, talk to Israeli device executives and few point to the political scene as a fundamental impediment to robust company creation. Rather, many point to a kind of financing gap—or, more properly, a couple of financing gaps—that inherently limit the way Israeli device companies have been funded and has led to the current undercurrent of concern.

To a degree, the financing issues have

always been there in Israel. But as the Israeli device community continues to grow and turn out more companies and, just as importantly, as Israeli device start-ups begin to face many of the same issues that US device start-ups face—longer, more complex clinical trials, a more difficult regulatory environment, and a more conservative M&A environment—a financing climate that once seemed entirely sufficient to bring forth new technologies now seems inadequate to bring to market the next generation of Israeli companies. Perhaps most importantly, as the industry matures and Israel more firmly establishes itself as a leading source of medical technology, there's a growing sense that a financing model best suited to serve early-stage companies may fall short as the industry and its companies evolve.

Indeed, there seems to be a growing chorus of device industry executives and investors in Israel who, while acknowledging the powerful innovation engine that Israel has been and continues to be, are calling for new approaches and new models—approaches that focus on providing adequate funding for the rich pool of technologies being created in Israel, on one end of the spectrum and, on the other, on creating strong companies, not just novel technologies, with deeper financial resources, longer trajectories, and that tap into a more international resource pool as Israel's technology innovators capture the imaginations of industry executives and investors all over the world.

A BIAS TOWARD DEVICES

The sense that there's something broken or flawed about the Israeli device industry is far from universal; if anything, the extraordinary success of the industry over the past decade certainly encourages an "if it ain't broke, don't fix it" mentality on the part of many. And there seems little sign that that rich technology flow is likely to abate soon—indeed, the success of the Israeli medtech community encourages ever more innovation and attracts ever more creative minds.

But, in part, that very success is also a source of much of the brewing anxiety. By any measure, the Israeli device industry is amazing, even when compared with the US. Even with the recent surge in interest in medtech venture investing in the US, the US remains a market in which medical devices play second fiddle to biopharma. In the US, significantly more venture dollars pour into the biotech sector than medical devices—by some estimates as much as 70 to 75% of all venture dollars fund biotech start-ups and, even with a recent record surge in US device investing, it's still routine to find VC firms with a portfolio balance that has two-thirds or even three-quarters of its investments in biotech. In Israel, the balance is reversed and strikingly so. Devices dominate both the dollars invested and number of companies in most VC's portfolios. Devices tend to be viewed as a well-established, stable industry—it's not unusual to talk to VCs whose portfolios are 75% device plays—while biotech is seen as the promising, but still up and coming sector.

One major reason is economic: in a capital-squeezed Israeli start-up world, the amount of money it takes to develop a device and start a company is much smaller than would be required for a drug. In turn, the heavy emphasis on devices creates a kind of self-fulfilling prophecy: Israeli entrepreneurs tend to come more from the ranks of engineers than chemists and biologists, and for that reason, many industry executives insist that the infrastructure and expertise needed for devices is much stronger than that for biotech, where, notwithstanding a strong grounding in basic science and robust IP in universities and research institutes, there tend to be fewer investors and industry executives with the know-how and expertise in biopharma to take products beyond the research phase into full commercialization. (*See "Rainbow Medical: Entrepreneurial Efficiency in Medical Devices,"* START-UP, *September 2008.*)

In addition, some Israeli device executives point to the important role that the military and defense industries play in Israeli society and the close link, particularly in areas such as imaging and robotics, between medical device and military technology as a factor in building the device industry's infrastructure. It has also helped to create a pool of seasoned executives and investors. In contrast, the complexity of the technology and the lack of infrastructure in biotech are major reasons why, in a kind of vicious cycle, biotech in Israel both requires more money and lacks seasoned management. It's also why many Israeli biotech investors and companies also see a lack of sufficient capital as another major problem for the sector.

AN INCUBATOR AND VENTURE FUND

Not so in medical devices, industry executives have long held. Devices, in contrast, usually take less money to develop, not just because development costs of a device tend to be lower than those of a biotech drug generally speaking, but also because, at least in the case of Israel, devices in large part draw on many of the same technologies and skill-sets that are critical in high tech and software development, another area of strength in Israel's technology community, and in the defense industry. (Also contributing to the greater efficiency of device start-ups: particularly in their earliest stages: you can still run a device company with three or four people and get to proof-of-concept and expand from there—something you can't do in biotech.) But increasingly, at least some Israeli device executives see a similar worry about a lack of sufficient capital. And it's beginning to make some device executives think about new ways of funding medical device start-ups in Israel.

Michal Geva is one of three principles in a new Herzlyah, Israel-based device accelerator called **TriVentures**. She spent the past decade working for a number of US and Israeli device start-ups, most recently, Advanced Stent Technologies Inc. (AST; now part of Boston Scientific Corp.), before returning to Israel five years ago to work at GI View Ltd., an Israeli company founded by Yossi Gross, developing a device to do colorectal screening.

After several years at GI View, Geva decided she was ready for a change. "Working with several US companies that have R&D centers here [i.e., in Israel], as well as with some venture capitalists, it was clear that there is a huge amount of creativity here," Geva concluded. But much of the efforts around technology development and investment are focused on the very earliest stages of product development. "We know how to do things quickly and at a very early stage," she goes on. "But if you look at the bottom line in terms of number of products that get to market and the number of exits, it's clear we have a long way to go," she explains.

To Geva, the problem is economic. She notes that there are now about 750 Israeli life science start-ups, backed by an Israeli VC community with about $700 million to invest. (Of those 750, just over 50%

are medical device companies, with the rest spread among biotech firms, medical IT, and others.) "It now costs $50 million just to bring even a bare-metal stent to market," she says. "One million dollars per company just isn't enough." Non-Israeli VCs do sometimes invest in Israeli companies, but mostly in later stages. Hence the financing gap: for those companies that have a promising technology but are nowhere near a commercial launch, there's simply not enough capital to get started.

Geva notes that it's not all that difficult for an Israeli start-up to get its first $500,000 to $1 million dollars—if traditional VCs don't want to invest, there's always the government-sponsored incubator program (*see sidebar "Israeli Incubators: We're from the Government and We're Here to Help (No, Really)"*). But she goes on, "what the first half million gets you isn't all that much." Often, the initial money helps to kick off the efforts of "skilled doctors or engineers who've come up with an innovative solution to a clinical problem." But in such inexperienced hands, the initial capital doesn't go very far in helping to launch an actual company.

That's where TriVentures comes in; Geva describes it as "a cross between an incubator and a venture fund." Like a traditional venture fund, it has limited partners and provides capital. But what it most importantly brings to the table is the experience to "guide and develop, invest and transition early-stage device companies," she goes on, in everything from product development to clinical development to business development—that is, the operational aspects of running an actual business. The idea: with limited capital available, what Israeli companies need is to select just the right projects to pursue and then develop them with a plan that stresses speed, agility, and the highly efficient use of capital.

AVOIDING THE POTHOLES

It was at Pleasanton, CA-based AST, where she ran clinical and regulatory affairs, that Michal Geva met Peter Fitzgerald, MD, and Martin Leon, MD, two leading interventional cardiologists who served as advisors to AST and who would eventually join her in launching TriVentures.

For Fitzgerald, the heart of Israeli innovation lies in those engineers and physicians, working in prototyping labs and even their garages, turning out new products by the dozens. "It's like the Bay Area in the early 1990s," he says. "Young guys working day and night on really interesting projects." But over time, such a model becomes hard to sustain if only because, insists Fitzgerald, the process of creation—if not the technology itself—has become "too complex, too complicated." In a funny way, he adds, "it's just not simple enough anymore."

In addition, funding device companies increasingly takes longer, as regulatory and reimbursement hurdles rise and time-to-market lengthens, meaning that larger VCs are increasingly focused on downstream challenges. Those large VCs play a valuable role, Fitzgerald notes, "but they don't really have the time to go into these garages and work with the engineers." Noting "the exponential rise in device start-ups in Israel over the past three or four years," Fitzgerald adds that on the company side, too often the people launching those start-ups don't really know how to create real companies. "They don't understand the market and they don't understand the next phase [beyond technology development], which is execution," he says. TriVentures' principals, he goes on, "have seen a lot of companies and made lots of mistakes; we know the potholes that you run into on the way from concept to patient integration."

The mentoring that comes from such experience is critical to what TriVentures is trying to do as its principals look for people who have exciting new ideas but who haven't thought through the market implications. By way of example, Fitzgerald notes, "Someone comes to you with a great new drug-eluting stent, using nanotechnology. But what they don't realize is that window closed two years ago." Rather than fumble around and, most likely, fail to bring that technology to market, what the developers of that technology need is "coaching," he says. "They need someone who can help them to apply that nanotechnology to other devices and, at the same time, to be ready if the window opens up again."

A CLINICAL—AND INDUSTRIAL—NEED

Most importantly, they need the discipline not to lose sight of the ultimate goal. "They need funding, but it has to be tied to specific milestones," Fitzgerald says. As Fitzgerald's comments suggest, TriVentures is more than an investment vehicle and, with its emphasis on coaching young companies, more than a traditional incubator, with its focus on shared resources. TriVentures' plan is to focus on companies with what Michal Geva calls "maturing technologies in their early stages," for which its principals can help accelerate both product development and company creation. The goal: to bring some initial funding to a project, up to $2 million, and, more importantly, to provide expertise and guidance so that the company can mature quickly and then be handed off, either to a large buyer or, more likely, a more traditional VC, to pursue a more conventional financing strategy. Rather than playing the role of a VC *per se*, says Geva, TriVentures sees itself almost as a nurturing force, "making [the companies] more attractive to venture capitalists later on."

Indeed, Geva describes TriVentures as "more synergistic than competitive" with traditional VCs. Peter Fitzgerald calls TriVentures "a transitional bridge." "We start with a small amount of money, heavily tranched, to get them to the next stage, when we bring in the big VCs," he says. (Indeed, some of the limited partners in TriVentures II will likely be venture capital firms, such as Michigan-based BioStar and 20/20 of Boston.) "If we're really going to do what we want to do, we have to provide support not just at the seed level, but at the next stage, when we envision that we'll syndicate with the big Israeli VCs like Pitango and Giza," says Fitzgerald, who has been involved for years with San Francisco-based Latterell Venture Partners (LVP) a venture fund that does early-stage investing in both medical devices and biotech. In turn, Fitzgerald believes this TriVentures represents "an ideal formula to source deals for LVP and provide significant capital and bay area experience to form successful medical device companies." "As the Israeli start-ups mature and transition to the US, we anticipate that they'll be syndicated and cradled by Eastern VCs like Accelerated Technology Partners and BioStar and West Coast firms like LVP," he says. (Accelerated Technology Partners is a venture fund that grew out of device accelerator Accelerated Technologies Inc., which was founded by venture capitalist Yuval Binur and Marty Leon. For more on ATI, *see, "ATI: Is This the Device Development Model?,"* IN VIVO, *February 2005.*)

More specifically, says Fitzgerald, "We need to get good IP, good proof-of-concept, and good prototypes. If we can't do that, we don't continue. We can't afford to dribble money into projects hoping something will turn up." TriVentures also hopes to be in its first clinical studies within

18 months, in preparation for follow-on financing from traditional VCs. Beyond that, it looks for relatively simple devices, those without a lot of complex science and engineering behind them—"more 510(k)s than PMAs," says Michal Geva. "It's actually all about the simplicity or complexity of the devices," she goes on. "We look for technologies with a clear path to market in terms of the reimbursement and regulatory strategy and before we even start a project, we want to have three potential buyers [of the company] identified." Too often in a start-up, she adds, the company starts out with engineers with a promising technology, "looking for the killer application. What we want to do is to start with a clear clinical need"—and just as importantly, what Geva calls "an industrial need," that is, an appeal to one of the large device companies.

ISRAELI INCUBATORS: WE'RE FROM THE GOVERNMENT AND WE'RE HERE TO HELP (NO, REALLY)

Notwithstanding all of the interest in the Israeli device community, there are those start-ups that have trouble getting funded. Maybe it's the financing gap, maybe it's a function of the evolution of the VC community—whatever the reason, in Israel, when a would-be entrepreneur hits a wall, the government is there to help.

Rina Pridor runs the Israeli incubator program on behalf of the Israeli government, part of the Office of the Chief Scientist, which is part of the Ministry of Industry, Trade and Labor. In fact, it has the largest budget within the Ministry, part of a concerted effort on the part of the Israeli government to aggressively promote high tech industries, of which health care is clearly one.

Israel's incubator program is one of three programs under the Office of the Chief Scientist. (Of the other two, one provides R&D grants to companies with innovative technology and the other is a magnet program to bring together academia and industry in a series of consortia that are created with the mandate of launching an innovative new technology within five years.) With an annual budget of just $35 million, the incubator program provides funding to companies in what Pridor calls "the first phase of technological initiative, which is a very fragile and problematic phase, a phase where private money really doesn't want to invest."

Indeed, Pridor notes that most often the Israeli incubator program invests "pre-pre-seed." "These are individuals," she says. "They aren't really companies yet." Most of them are university researchers, professors, and engineers who have worked for other companies and suddenly come up with an idea of their own for a promising new technology.

The large influx of émigrés into Israel, mostly from Russia, in the early 1990s has been the source of many of the new ideas, and the goal of the program is to realize, to the extent possible, the practical goods of this font of inspiration. Notes Pridor, "We, Israel, do not want to see potential good ideas just disappear because they were not given a chance to prove themselves, because human capital is our only natural resource."

Though Pridor describes the incubators' stage as "pre-pre-seed," they represent a funding source for people who have on their own failed to get venture funding. Israeli incubators are still making judgment calls as to the viability and value of the technology ideas, but their mandate is clearly to fund things that conventional VCs won't, most often because it is too early in its development, and in all cases, the would-be entrepreneurs who come to the incubator program have tried, and failed, to raise money on their own. (In select cases, the incubators will determine that an idea is so early in its conception, the scientist needs to go back to a lab to vet it some more; still, Pridor calls most of the ideas brought to the incubators "very, very immature.") In turn, the goal of the incubator program is to help the would-be entrepreneur develop his or her technology—and the company that will come of it—to the point that, after two to three years, venture capitalists will back it. "We give them the chance to prove themselves," says Pridor.

In fact, Pridor notes that one of the misconceptions of the incubator program is that the incubators compete with traditional venture capital. "If a project comes to our committee for final approval, and the committee is too mature, as tempted as we might be, we won't approve it," she says.

Around 60% of the projects that come into the incubator program are life science plays, of which around two-thirds (or 40% of the total) are medical device projects, one-third (20%) are biotech. (Though biotech projects are fewer in number, they're growing much faster; seven years ago, only 5% of the incubator projects were biotech.)

Pridor notes that life science projects dominate, in part, because they're riskier than other tech projects, and thus, "private money is more reluctant to invest in them," as she puts it, though the heavy emphasis on medtech versus biotech is a kind of risk-hedging of its own. The government funding is channeled through 24 incubators that operate, geographically, all over Israel, from Kiryat Shmona in the far north to the Negev in the far south. In fact, the Israeli government specifically structured the program to reach would-be entrepreneurs who weren't necessarily located in popular central cities such as Herzlya, Tel Aviv, and Jerusalem, and Pridor notes that the remote locations of the incubators also help the local economies.

Six years ago, to attract strong, experienced managers, the Israeli government began a process of privatization of the incubators, offering what Pridor calls "a large upside" if and when the companies they help develop become successful; today 22 of Israel's 24 incubators are in private hands and the other two are expected to be private soon. The money for each project comes in the form of a loan to the incubator; if it is paid back within seven years—a payback that assumes that the incubator has been able to vet the technology, launch a company, and raise the next round of capital—the incubator's owners and managers receive a portion of the money invested in the form of equity in the company. The company's founder, the person who brought the idea to the incubator, typically retains about 50% of the equity by the time the first professional venture capital is invested and, because the

Thus, TriVentures officials believe it's as important to keep up with what's going on in the business development departments of Boston Scientific and **Stryker Corp.** as it is the small labs and workshops of Israeli engineers and designing physicians. The idea is to find innovative technology or launch new companies based on unmet clinical needs, but only if they match with where the large device companies will be placing bets in two to three years. That's a perspective start-up CEOs, particularly first-time CEOs, often lack and it's why, says Peter Fitzgerald, the discipline of milestones are so important. Start-ups "have to be oriented to the right commercialization pathway, and it has to be a congruent pathway," he goes on.

Indeed, says Fitzgerald, often TriVentures will come across an innovative device and "it's phenomenal technology, but the landscape has already moved away." Given the backgrounds of TriVenture's founders, cardiovascular devices are a natural sweet

government funding is provided directly to the incubator, has no obligation to pay back the money. (Because the privatization program is only six years old, and the time period for payback is seven years, there are no indications, broadly, of whether the payback program is working, though Pridor notes that several incubators repaid their loans within two years.)

Even with the strong government support, the incubator program must be selective—each incubator gets at least 100 applications a year, of which only five or six become incubator projects. Incubators can offer different terms to potential projects and applicants are allowed to apply to more than one incubator to get the best terms. Pridor prefers the word "screen," insisting that the process is not intended as a competition to find the best projects. If a project complies with some basic criteria for inclusion and passes a professional assessment, the incubator then gets funding of around $500,000 from the Israeli government to help develop the technology, constituting 85% of the initial funding, with the founders providing the other 15%.

Pridor notes that the incubator then becomes a "partner" of the entrepreneur, providing not just money, but all kinds of assistance and ancillary services needed to develop the technology, write a business plan, recruit the right people, etc. Pridor notes that the entrepreneurs who turn to the incubators are "very bright, clever people, very creative," but for those very reasons they often lack the experience and expertise to actually launch a company. The people who come to the incubator "don't come as a company, they come as individuals," she says. "And they need to start behaving like a company and building value in the company," which means proving that the technology is viable, that there's a clear market, that the regulatory path is anticipated, and, perhaps most of all, securing the IP behind the device.

The Israeli incubator approach seems well-suited for devices—most device start-ups can, within two years and with $500,000 to work with, get a working prototype and even do some early clinical studies. But what about biopharma projects—as noted, an increasingly important portion of the life science ideas coming out of Israel? Pridor insists the model works, though Israel did establish only one of the 24 incubators as a specialist in biopharma projects, which is allowed to invest more (up to $1.8 million), spend an additional three years, and work with slightly older ideas, though still preclinical. It can also take projects that, after two years, come out of other incubators but aren't ready yet for initial funding. Pridor points to **Protalix BioTherapeutics Ltd.**, which has a Phase III drug for Gaucher's disease, and which is already trading on NASDAQ, and **D-Pharm Ltd.**, which has a drug for ischemia, as examples of successful biopharma companies that have come out of the Israeli incubator program.

On the device side, Remon Medical Technologies Ltd., a neurostimulation company acquired in 2007 by Boston Scientific, and Sightline Technologies Ltd., an orthopedics visualization company acquired by Stryker Corp. in 2006 for $150 million, may be the incubator program's highest profile graduates. (In turn, five of the companies that emerged from Israeli incubators are now public, traded on the Tel Aviv stock exchange, including Maaryan and Biomedics.)

Now nearly 20 years old, the Israeli incubator program has clearly been a success. Pridor notes that since about 1997, the ratio of private money to government money in the incubator-spawned companies has soared—private investments are now five times the initial government stake, some of that due to private investors putting money into later stages of the companies that have launched.

But with that success, the incubator program also faces some challenges. In the early 1990s, the influx of scientists who came with the large waves of Russians immigrating to Israel dramatically increased Israel's population—by more than 10%—and brought a tremendous surge in intellectual capital; in its first five years, 70% of the incubator programs came from these scientists.

Absorbing such a large group of highly trained, highly specialized people presented challenges of its own for Israeli society, and the incubator program was one of the tools developed to help cope. Today, that wave of scientists is long past and one of the challenges that Israeli incubators face, Pridor notes, is keeping the flow of ideas coming. "The deal flow has changed," she says. At the same time, as the Israeli life science industry, broadly speaking, has matured, the incubators are finding more sophisticated entrepreneurs and follow-on investors more willing to provide the next stage of capital.

The Israeli program assumes a company will spend about two years in the incubator before launching on its own, and Pridor notes that over the past four or five years, more than 60% of the incubated companies have found success, that is, they've been able to raise a first round of financing. Indeed, Pridor sees the incubator program serving Israel's VC community every bit as much as its would-be entrepreneurs. "That's what we're trying to do," she explains. "Take ideas that no one wanted to invest in before and turn them into companies people will invest in."

spot, but TriVentures officials insist they'll look broadly at devices in all therapeutic areas. To date, the firm, which was launched earlier this year, has raised an initial fund of less than $1 million, which it used to launch its first five companies, and just now it is closing on its second fund, which will have a war chest of $15 million.

Having looked at nearly 70 companies, TriVentures has committed to five companies to date. Of the five, four are cardiovascular companies, including a CTO company, a developer of a stent locator device, and two companies with technologies "that are aiming at a new emerging market," says Michal Geva. "Part of TriVentures' model is to spot future clinical trends and innovate ancillary devices for the 'next play,' for example the minimally invasive, catheter-based AAA device or percutaneous valve replacement procedures." In addition, TriVentures is working on an innovative device for femoral artery closure designed not for conventional angioplasty, but for the devices that will increasingly be used in procedures that require larger insertion spaces, such as percutaneous valve and AAA procedures. (The non-cardiovascular company is in robotics, a company called MST, and is developing a technology that enhances visualization during laparoscopic procedures.)

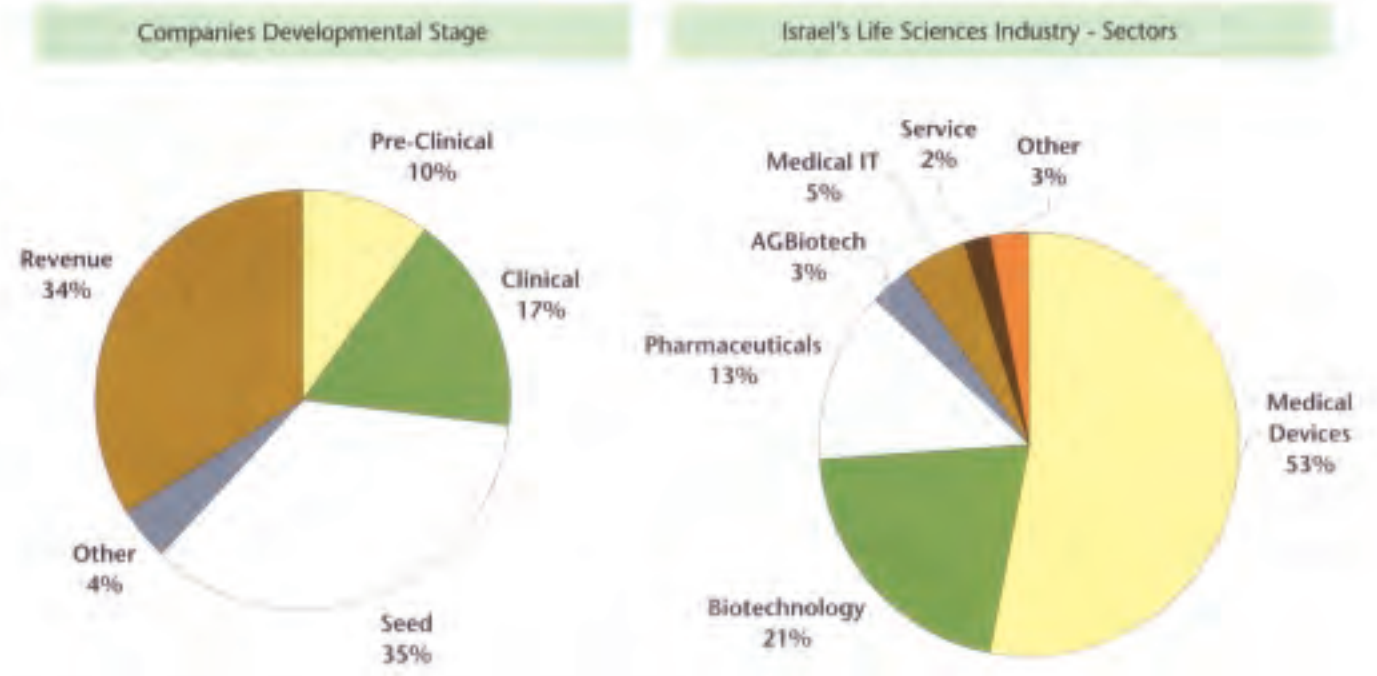
About the femoral artery closure company, Michal Geva notes, "We're not talking about 6 French devices anymore, but about devices with an inner diameter of 24 French and an outer diameter of 28 French. For those procedures, you can't use the closure devices on the market because they require more of a skin-to-skin approach." The femoral artery closure device offers an example of the kind of market-savvy coaching that TriVentures hopes to provide its portfolio companies. All three of TriVentures' founders have extensive backgrounds in femoral artery closure start-ups, and both Peter Fitzgerald and Marty Leon were also instrumental in developing the first-generation percutaneous heart valves. Says Fitzgerald, "Percutaneous valves are important, but I don't want to just come up with a new valve."

Rather, as percutaenous valves catch on, there will be a host of ancillary devices needed that address what Fitzgerald calls "the infrastructure" of percutaneous procedures. "We're looking at a revolution in valve procedures and we're using 15-year-old valvuloplasty equipment," he says. "We need to have smart balloons that offer us the perfect angle, whether we're using a PVT or CoreValve valve, and we need, of course, to close the groin." Similarly, Fitzgerald acknowledges Israel's reputation for developing novel technology in areas such as robotics, imaging, and guidance, but, he notes, companies have to understand how and when those devices will be used in actual clinical practice. "They need to be developed in a way that is really focused," he says. "You can bring a great guidance technology from the military into a minimally invasive robotics play, but you have to know where it's going to go."

More to the point, as TriVentures looks not just at clinical applications, but corporate direction as well, Fitzgerald argues that the largest CV companies increasingly find it hard to focus a lot of time and attention on the kinds of devices TriVentures hopes to bring to market. TriVentures, he says, is trying to build companies that address gaps in the R&D efforts of large companies and that are "complementary to the pathway to improving care for patients." But, he says, big companies "spent so many resources on developing drug-eluting stents, they can't do a CTO device, but they know they need one to offer something synergistic and complementary to those products." Such an approach, in turn, gives TriVentures an exit alternative: the

Exhibit 1

Israeli Medical Device Landscape



SOURCE: TriVentures

firm's first hope is to develop companies that larger VCs will want to invest in; but if it turns out that a quick flip to a large corporate buyer appears, well, that's not so bad an exit either.

Having started five companies, TriVentures estimates it will do four or five more a year, each starting with an investment of around $500,000, and a goal of being in its first human clinicals in 12 to 18 months. With a successful track record and a deep network, TriVentures could in the future raise ever larger funds. But, Geva cautions, "When we got to [a] $50 million [fund], we'd be just like a regular venture capitalist, and we don't want to do that."

PRETZELS FOR LUNCH

Not everyone believes there's a funding crisis for very early-stage companies in Israel. Says one industry executive, "It's the same old story: people who can't get their company funded always claim there's something wrong with the system, not with their technology. Trust me, if you have a really important technology, you're going to get it funded."

Still, in some ways, the Israeli device industry turns on its head the typical venture climate: in frothy, vibrant markets, success generates higher returns for venture capitalists and ever larger follow-on funds, leading often to investors with large amounts of money looking for quality deals. In Israel, notwithstanding all of its success, the device industry faces just the opposite: instead of too few quality companies and lots of capital available, many Israeli device execs see too many companies, with too few venture dollars available. Industry observers note that just a decade ago, there were only about 50 or 60 Israeli life science companies, with device companies the largest subgroup; given a population of life science companies over 750 today, that means that the vast majority are, almost by definition, start-ups and early-stage start-ups at that. And the Israeli VC community hasn't grown in proportion.

As noted, for Peter Fitzgerald, in some respects, Israel represents something of a throw-back. "It's like the Bay Area 20 years ago," he says. "We sit in garages in Israel from morning to night, eating pretzels for lunch, talking about technology." But if TriVentures represents a solution to one kind of financing gap—that facing the earliest-stage companies that are under increasing pressure to be capital efficient—there's another financing gap that's emerging as Israel's device industry evolves and matures, one that addresses later-stage company creation issues more than technology development or company launch.

Lihu Avitov is an EVP of **Ofer Hi-Tech**, a large, diversified fund backed by the Ofer Brothers Group, one of a small group of family-driven investment vehicles that represents the backbone of the Israeli investment community. In addition to its portfolio of direct investments, Ofer Hi-Tech owns its own incubator, Naiot, but it is perhaps best known for its private equity fund, where it puts large amounts of money, often $50 to $100 million, in later-stage companies, those with $100 million or more in revenues. Around 80% of Ofer's portfolio is in medical devices (11 of its 14 health care companies), with the rest in biotech. The firm's preference in devices leans toward interventional technologies (cardiology, radiology, oncology) and laparoscopic surgical devices, with only a few investments in implantable devices.

If there's a common theme to Ofer's investment approach, says Avitov, it's less clinically than economically driven: "Our preference," he says, "is for devices where the cost of development is not very high." Even a fund as deep-pocketed as Ofer points to the broader limitations of capital investment in Israel, as the Israeli device industry matures. "If you look at Israel, one of the things we are missing is the large sums of money needed to really grow companies," he goes on. "I don't think we can afford to build a company in Israel if it takes $50 to $100 million." That's one reason why Ofer prefers less complex devices. "If the technology is complicated, you can assume the marketing will be complicated, and you end up needing $50 to $70 million," says Avitov. "And for small investors—and everyone in Israel is a small investor—it's a big problem."

Among Ofer's device companies: **Angioslide Ltd.**, with a combination angioplasty balloon and embolic protection device, which received CE mark earlier this year and which has just completed a multi-center trial that, it is hoped, will lead to FDA approval relatively soon. In many ways, Angioslide is a typical Israeli start-up. Founded from an idea developed by an engineer and a physician, "there's tons of engineering to be done, but the technology itself is simple," says Avitov. More to the point, the company has reached CE mark with relatively little invested: as of mid-2008, the company had raised just over $12 million, and it has been able to get to its initial human clinical trials spending just $2 million in a relatively short period of time. That kind of capital efficiency is, says Avitov, "something you'd see only in Israel."

A ROLL-UP STRATEGY

But Avitov is also part of the growing chorus that believes the Israeli device industry is changing, and Angioslide may in this regard be typical of the kind of device companies that Israel turns out in the future. Angioslide is, he says, "one of the few companies we believe that can actually get to market and generate sales," particularly because, targeting the peripherals, it will face relatively little competition from the big CV giants, Avitov claims. Angioslide may even begin to look around, in Israel and other places, for additional products to add to its portfolio, and "build a franchise in this business," says Avitov, who notes that at that point Angioslide could even go public.

"This is one of those areas where there are so many innovative technologies, and the only question is whether you can build a company around it," says Avitov. But if it does, Angioslide will depart from the traditional Israeli start-up path: develop an innovative technology efficiently but only so far, and then look for a corporate buyer. Indeed, Avitov believes that the criticism that Israel has been great at developing devices, but not companies, is a fair one, and he says that has to end. "We cannot sustain this industry purely as inventors of technology," he says. Avitov points to a change, happening more broadly throughout Israeli industry, where small companies are looking to create more lasting, sustained value. "I see more and more start-ups building their own marketing and sales networks—not building the company to sell, but building to sell products, and this is something that as investors we should all support."

And Avitov believes he is seeing a change in attitude among Israeli VCs, particularly those who are managing larger and larger funds—"not the size of some US funds, but still large," he notes—and who are thinking about the implications. "I think we're seeing VCs in Israel now that have enough money to support both early- and later-stage deals," he says. Of course, simply having more money on hand may not be enough. There are other issues, besides the financial

constraint of the indigenous venture community, confronting Israeli device start-ups as they seek to grow from technology developers to company creators.

For one thing, because the financial constraints have channeled much of the technology development into capital-efficient, basic technology areas where there are ample predicates, much of the technology development in Israel has focused on cardiovascular and orthopedics, two clinical spaces where large companies dominate. Reflecting on Angioslide's prospects, Lihu Avitov notes that "if you look at coronary interventions, four players hold almost 100% of the market." That's one reason Angioslide has targeted peripherals; although most of the big CV companies do have peripheral programs, they remain secondary—one is tempted to say, peripheral—to their core coronary businesses.

CREATING THE NEXT KYPHON

The presence of device giants creates a kind of twofold barrier for Israeli start-ups. Not only do such competitors erect obstacles to market as they get bigger, but trying to create anything similar from a company-creation point of view becomes so much harder. "Will we ever build a Medtronic in Israel?" Avitov asks rhetorically. "I seriously doubt it."

Just as importantly, as the big companies get ever bigger, their ability to find value in single-technology start-ups becomes more limited. Avitov notes that a few years ago, companies could plan for an early sale to one of the large cardiovascular companies because those companies were "looking to add technologies to their pipeline," and with that came an appetite for early-stage companies. But today, big companies have become much more selective about what Avitov calls "technology deals," for early-stage companies. Rather, he goes on, "they are looking for market traction, even with innovative products." Some of the mid-tier companies are stepping up, Avitov notes, but even they like companies with revenues.

And that's leading more Israeli companies "to build fully integrated businesses, opening alternative exit strategies," says Avitov, and providing a rationale for a roll-up strategy. If building a **Medtronic Inc.** or Boston Scientific is unrealistic, Avitov thinks it isn't unrealistic to think in terms of an Israeli Kyphon Inc. or, in Angioslide's competitive space, **ev3 Inc.** and **Spectranetics Corp.**: companies that find clinical and technology niches and roll up other companies to create valuable commercial and clinical franchises. "It's all about owning your channel," he goes on. "If your channels are strong, you can start infusing more and more technologies into them."

Of course, Kyphon resonates in Israel, in part, because one of its roll-ups was Disc-O-Tech Medical Technologies Ltd., an Israeli spine company. "I think that in time, if we work hard enough, we can build companies like Kyphon in Israel," says Avitov, who cites **Lumenis Ltd.** and Given Imaging Ltd. as two Israeli companies that have built major franchises.

The fact that Kyphon was itself recently taken out by **Medtronic Sofamor Danek** adds additional context to the debate going on in Israel; still, there is a growing chorus in Israel calling for more focus on company creation. Certainly, Ofer has its share of companies in its portfolio that will likely look like more conventional, single-technology plays—it's an investor, for example, in **CorAssist Cardiovascular Ltd.**, a cardiovascular start-up with a promising technology focusing on systolic heart failure, and in **EndoCross Ltd.**, which has a CTO crossing solution. But neither is Angioslide unique in its portfolio. Another Ofer investment, **EZsurgical Ltd.**, is developing what Avitov calls "smart laparoscopic devices" used in surgery. Just two years old, EZsurgical already has six products in its pipeline and is selling one of them in the US and Europe. EZsurgical's goal: "to build a cluster of medical products, all of them focused on the business of laparoscopic and general surgery." And although Avitov isn't promising another **United States Surgical** (part of **Covidien Ltd.**), Ofer is, he says, "building a company that can sell multiple products on multiple technology platforms." Five years ago, he goes on, "you never would have done that in Israel, but right now there are many VCs here thinking about clustering technologies and building bigger companies, not just investing in a one-trick pony and then selling off their technology."

A CONTRARIAN TRADITIONALIST

Lihu Avitov notes that the capital constraints of the Israeli device industry have always meant that, notwithstanding their reputation for capital efficiency, Israeli companies tend to take longer to find an exit. "Because they have less cash to begin with, [Israeli companies] tend to take longer," he says. A change in strategy that would fund companies all the way to commercialization and sales would likely only make time to exit longer. But that's fine with Ofer: Israel has clearly emerged as "one of the major hubs for medical technologies in the world," says Avitov. "We need to maintain this, but we should start growing companies, not just technology."

Of course, for TriVentures, with its much smaller fund, finding and growing promising technologies is just fine. Indeed, it goes without saying that the specific characteristics of the different players you talk to in Israel influences the way each sees the evolution of the Israeli device industry. TriVentures, with its focus on the very earliest-stage companies and on the need for capital efficiency, tends to see a financing gap largely in the difficulty that promising early-stage companies find in attracting sufficient capital to grow. "The companies we're working with aren't going to be the next Kyphon," says Peter Fitzgerald. Still, even Michal Geva sees an important role for the kinds of commercially driven—as opposed to technology-driven—companies that will benefit the entire Israeli device industry. "More and more people in Israel appreciate that fact that we don't have any real corporate [players] in devices," she says. "And it influences the entire industry. I think it makes a lot of sense to try to build the equivalent of Teva in devices."

Ofer, for its part, with the resources of a private equity fund, tends to see the challenge for Israel in its ability to grow companies and create larger, more global device players. (Ofer recently led a $120 million financing to turn around Lumenis, a large laser company, doing more than $250 million in revenues a year] with applications in urology, surgery and aesthetics, a firm that had gone public, but that ran into financial difficulties and wound up being de-listed by NASDAQ two years ago.)

Of course, it should be pointed out, neither Ofer nor TriVentures are venture capitalists in the conventional sense of the term, and that certainly influences how they see the market. Ruti Alon, a General Partner at Pitango Venture Capital, Israel's largest VC fund with around $1.3 billion under management (around 20 to 25% of which is in life sciences), tends to take more of a middle ground. (Of Pitango's recent

funds, Pitango III was, Alon says, primarily medical devices; the more recent funds include a higher proportion of biopharma companies, around 50%.) Among the medical device companies that are now or were once in Pitango's portfolio: **Medinol Ltd.**, **BrainsGate Ltd.**, **BioControl Medical Ltd.**, **VisionCare Ophthalmic Technologies Inc.**, Cadent Medical Corp. (now part of **Cardiac Science Corp.**), **ColBar LifeScience Ltd.**, **Ventor Technologies Ltd.**, **Atria Medical Inc.**, **superDimension Ltd.**, Disc-O-Tech, **Odin Medical Technologies** (part of Medtronic), and **TopSpin Medical**, to name just a few.

If there are changes coming and new models emerging, she says, it's less because of specific features of the Israeli device industry than because of a kind of a natural evolution of the global medical device industry—an evolution, if anything, that may be accelerated because of Israel's amazing fecundity when it comes to developing new device technologies and companies. Devices are, she notes, "an area of strength in Israel," in part because of expertise in underlying skill-sets, such as engineering, miniaturization, materials, and optics—all of which, combined with strong medical institutions and physicians, make for Israel's strong industry infrastructure.

BUILDING THE FOUNDATION

But Alon, for the most part, argues against a kind of Israeli exceptionalism in devices. Yes, the industry is remarkably fertile and strong, but almost for that, she says, it makes more sense to see Israel in the context of the global industry. Thus, to the charge that Israeli companies have historically developed technologies quickly and then sold them just as quickly to large companies, particularly US companies, Alon notes that the same thing is true of device companies all over the world.

Similarly, the question whether Israel will ever create its own Boston Scientific or Guidant is, she says "irrelevant." Yes, device start-ups in Israel tend to be bought up early. But she goes on, "Companies are being bought in the US and Europe as well." It may very well be that we'll begin to see smaller Israeli companies come together in order to create larger entities with broader product lines and a larger enterprise value. But, she goes on, "I don't think that's unique to Israel."

Rather, if there is something unique about Israel, says Alon, it lies in the sheer number and force of entrepreneurship. And in such an environment, companies with compelling technologies and strong prospects can always find sufficient capital to grow. A financing gap exists, she goes on, when companies with good technology and promising clinical trials still can't get the funding they need. "That's not what's happening in Israel today," says Alon.

Still, Alon acknowledges that the Israeli start-up world is still young and growing. "You don't see a lot of people with grey hair here," she says. Every industry takes time to build, to develop the infrastructure to finance companies, accelerate technology development and train experienced managers. "The whole Israeli industry is barely 10 years old; how many US companies with PMA products get to market in 10 years? Very few."

Those who are critical of the Israeli device industry "have to be patient," Alon goes on. "They need to understand that when you build a business, you start with the foundation and then build rows and rows of bricks until you have a house." Moreover, s noted, there are broader pressures on the device industry that are affecting all start-ups, not just Israeli. "Look at the US," she says. "The regulatory environment has gotten much harder. Six years ago, there were 60 PMAs approved; last year it was 21." More to the point, six years ago, you could get a PMA product to market after an investment of $10 to $20 million; today, it can cost $60 to $100 million. "Forget about Israel," she says. "How many companies in the world today can easily raise $60 to $100 million?"

Similarly, in such an environment, a roll-up strategy—as opposed to a quick flip—is "a natural development," Alon goes on. But, she adds, rolling up companies isn't easy either and isn't just a function of having more money. "How many ev3s are there or Volcanos?" she asks.

In any event, Alon insists that the need to fund companies' over longer time frames or to roll up technologies stems more from the global forces than from any kind of financing issues inherent to the Israeli industry. If there is to emerge an Israeli equivalent of Boston Scientific or a device counterpart to Teva Pharmaceutical, says Alon, it will happen as the result of the maturing of the industry, not because someone comes up with a fix for the current model for funding Israeli companies. "I can't promise that it will happen," she says. "But I know it's not going to happen overnight." And if and when it does, it will only reinforce that Israel remains an important font of new device technologies.

LOOKING ABROAD

Pitango's view of the Israeli device industry may, as noted, be a function of its unique position as Israel's largest device investor. The extent to which new models such as TriVentures or new approaches such as the roll-ups that Ofer and others talk about emerge may result from the fact that each of these firms is looking for a specific role or niche in the vibrant Israeli community. But none of these different approaches or perspectives is mutually exclusive; if anything, one indication of the industry's maturation and evolution may be precisely the emergence of different entities experimenting with different models, all of which, ultimately, fit, sometimes synergistically, in some kind of larger, well-rounded industry. Thus, rather than the stark opposites they seem to represent, TriVentures and Ofer may on some level co-exist nicely, as TriVentures comes to represent something of a solution to the early-stage financing gap, creating the kinds of strong Israeli start-ups that can be rolled up into an Israeli version of Kyphon or ev3.

As noted, not everyone buys into the notion that the Israeli device industry is in need of new models. But nearly everyone agrees that there's something of an evolution going on, an evolution driven both by internal dynamics and larger, global forces. In such an environment, Israeli device companies and foreign investors, from both the US and Europe, are increasingly finding each other—Israelis as they look for new sources of capital, and foreign investors who, in a re-invigorated device investment community, are looking for more good opportunities.

But for every VC firm that will take a chance on an Israeli company, there are a dozen that are uncomfortable, primarily for geographic reasons. Says one US VC, who actually has invested in Israeli companies, "I like to be close enough to my portfolio companies that I can go down and yell at them at lunch time." Hence the interest by foreign investors in mostly later-stage Israeli companies, rather than the early-stage companies that dominate the Israeli landscape.

Indeed, the parochialism, both geographic and cultural, that seems to so much benefit Israeli companies at the early stages becomes something of a liability as the individual companies grow. That's

why the US is so important for the Israeli device industry. Even Pitango's Ruti Alon believes, notwithstanding her fund's vast resources, that Israeli VCs will increasingly invest along with non-Israeli investors in the technologies Israel produces. Israel's reputation for innovative technology has, she notes, "put up a large stop sign" for investors, both venture firms and strategics, from outside. Broadly speaking, she says, across high tech and life sciences about half of the funding of Israeli start-ups comes from abroad. In fact, Alon notes that while it was rare several years ago for foreign VCs to fund an Israeli company, today the practice is routine, particularly for large, well-established funds like Pitango. "I don't think we have one investment that doesn't have international investors," she says. "And it's now become relatively easy to bring international investors into our companies."

Moreover, Alon points out that Israeli companies find themselves dependent on outsiders for another reason: it's hard to build a significant business within Israel, if only because of the country's small market size. Thus, whether it's with an eye to a quick flip of the technology or, increasingly, toward building a commercial operation, Israeli device start-ups have to, at some point, engage the outside world. "We are a very small country in a world of global markets," says Alon. "We aren't in that sense self-sufficient; we can't create a business just around Israeli markets, not in the life sciences. We have to look at the whole world."

For a group like TriVentures, with its early-stage focus, the US is even more important; in fact, TriVentures' principals see themselves explicitly as "building a bridge" to the US for the Israeli companies they back. Michal Geva notes that one difference between TriVentures and the kind of incubator sponsored by the Israeli government is that TriVentures will have the freedom to move its companies, as they grow, elsewhere, most notably to the US, if need be. "I think we're great at innovating and developing new technologies, and we know how to do things fast at the early stages," she says. "But we also want to make sure that we'll potentially be able to transition them, even before an M&A exit, to the US, for example, if that's what's required in order to build a more global company."

A related issue: the difficulty of finding an indigenous stock market on which to float IPOs. Ofer's Lihu Avitov notes that five years ago, virtually the only exit an Israeli device company seriously contemplated was a sale to a larger company. As companies grow and begin to generate sales on their own, IPOs become a viable alternative. The problem: today, Israel's Tel Aviv Stock Exchange (TASE) can't really support the mid-sized companies that are the best candidates for public offerings. That means that Israeli companies have to look to foreign exchanges for an exit via IPO, if not now, soon, when the IPO window opens again.

But as the Israeli device industry matures, it will increasingly become more opportunistic in the way it reaches out to other markets. Interestingly, anecdotally at least, it seems as if more and more Israeli companies are looking to China, another country attracting attention as a source of new medical technology. Lihu Avitov has visited the Far East a number of times recently, looking for opportunities for his portfolio companies. "I think we're going to see clusters of innovation in China," he says. "It may take five or 10 years, but China is going to be a dominant player in terms of innovation and technology." (*See "China: The Wild, Wild East for Medical Devices"* START-UP, *May 2008.*)

TAKING COMPANIES TO THE NEXT LEVEL

The relative youth of the Israeli device industry and, more importantly, the lack of Israeli equivalents of BSC or Guidant raises another issue: the lack, perceived by some though not all, of a sufficient pool of seasoned managers to run companies beyond an early technology development-oriented stage. Indeed, one powerful rationale in the TriVentures model is that the expertise of the principals is critical to guiding freshly minted entrepreneurs in company creation as much as technology vetting. As Michal Geva puts it, Israel has "lots of entrepreneurs, but not enough corporate executives," managers who are able to take companies at the early stage of technology development "and take them to the next level."

Ofer's Lihu Avitov believes there's plenty of management talent for start-ups, if only because so much of the industry is made up of early-stage companies. But he does agree that there are fewer managers able to help companies grow to the next stage. "I think that the early-stage entrepreneurs in Israel are superb, maybe the best in the world in terms of capital efficiency," he says. "Our biggest concern is for the later-stage companies; I still don't think we have enough managers who know how to help a company on the sales ramp." Avitov notes that in the US, small companies can tap seasoned executives form companies such as Medtronic or Boston Scientific as companies mature, but there just aren't similar pools of executives with like experience in Israel.

The concern over a lack of seasoned managers—or more properly, a lack of managers with experience running larger, later-stage companies—speaks to the criticism that Israel has been good at developing technologies, not so good at developing companies. But that may be a misplaced criticism. Creating an Israeli equivalent of Kyphon or ev3 may be a natural evolution for some companies, but it's not a necessary evolution for all.

Rather, the criticisms seem to be, if anything, further proof of the extraordinary vitality of the Israeli device industry. Still, there is growing evidence that new pressures are transforming the Israeli device industry. Some of those pressures are external and global, affecting all device companies—pressures such as ramping regulatory hurdles and reimbursement squeezes, increasing clinical trials burdens, and the shifting nature of the M&A world. Some are more local—such as the inherent limitations of an Israeli VC community to bring to fruition all of the device technology the country's scientists, engineers, and physicians can dream of.

Indeed, although there are still voices for a more conventional or traditional investment model in Israel, even traditionalists acknowledge that, as the Israeli industry matures and evolves, new challenges are arising that require new approaches to financing and, ultimately, company creation. No worry. Who says Israel has ever been anything but creative and resourceful? IV

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