Israeli Biotechnology Strategy Project

***

Realizing Our Potential

Final Report

Tel Aviv, March 2001

Submitted to

The Chief Scientist, Ministry of Industry and Trade

The Ministry of Finance

The IBO

by

MONITOR COMPANY

Content

Introduction

Biotechnology is one of the fastest growing sectors worldwide and is reshaping the life science and agriculture industries. The key question addressed by this project is: *What is the real potential for Israeli biotechnology and what must Israel do to realize it?*

The initial diagnostic phase of this project comprised two aspects: the first was to identify the worldwide potential of biotechnology by sector and to assess Israel's unique capabilities in this industry; the second was to identify potential bottlenecks or sources of inefficiencies within the biotech industry in Israel and to benchmark successful biotech clusters abroad. The strength and dynamic of the relationship between the industry participants (e.g., academia, Government, companies…) were analyzed using the Cluster Analysis[1] approach in association with the 7 Forms of Capital[2]. Over 100 detailed interviews were conducted in Israel, the UK, US and Canada *(sections C and D)* to identify the key success factors of the most prominent biotech clusters in the world and draw the lessons for Israel.

The second phase of the project consisted of developing a set of specific recommendations, initiating the implementation process and providing a detailed action plan (*section E).* These recommendations are not company-specific but rather relate to Government policy and broad industrial development. The estimated cost of implementing each recommendation is also provided with a suggested timeline.

Finally, a set of long term objectives that could be reached by the Israeli biotech industry are presented in the conclusion. They are ambitious but achievable if all the participants of the biotech sector join in coordinating their effort towards achieving a common goal: "to create in Israel a world-class Center of Excellence in Biotechnology"

[1] "*The Competitive Advantage of Nations"*, Michael Porter (Monitor Company)
[2] "*Plowing the sea"*, Michael Fairbanks and Stace Lindsay (Monitor Company)

B. Executive Summary

I. Biotechnology Global Trends And Potential For Israel

The biotechnology market is expected to grow by 12% annually and to generate over $40Bn revenues in 2004 (potentially $100M by 2010). Market capitalization of US companies reached over $250Bn in 2000 (more than 25% growth per year since 1996) with revenues above $22Bn[3]. Growth is both driven by structural demand factors such as aging populations and the need to control costs of drugs, as well as by technological and marketing evolutions.

Bio-therapeutic drugs sales are expected to be around $28Bn in 2004, growing by 10% annually (i.e., sales projection of existing drugs). The aging population in the Western world, the existence of large markets with sub-optimal treatments or no cure, and the emergence of new protein-based drugs drive the growth in this sector - mainly in cancer, auto-immune and CNS therapeutic areas. Around 50% of University research projects in life science therapeutic conducted in Israel are in those therapeutic areas and biotech firms have 2/3 of their product pipelines in those areas.

Platform technologies should generate around $7Bn revenues in 2004 (+35% growth per year). Their specific demand factors are the pharmaceutical companies' need to fill their product pipelines, the requirement to reduce research and testing costs, and the broad applicability of those technologies. The key areas of growth will most likely be functional genomics, pharmacogenomics and proteomics, with other areas such as bio-nanotechnology and bio-catalysis also emerging. Israeli companies are not yet present in these key area (with only 19% of the employees in this sector devoted to post-genomic technologies), and the University applied research is focused on drug discovery and bioinformatics (37% of all research in this field), and less on proteomics and pharmacogenomics. However, Israel has a comparative advantage thanks to the potential synergies with other disciplines such as computer science and physics.

Diagnostics sales are forecast to reach $3Bn in 2004 (growth of 22% annually). There is a need for tests that increase drug efficacy and for products that reduce costs related to adverse drug reaction. Traditional diagnostics will tend to be replaced by theranostic technologies such as Nucleic Acid Probe Testing (NAT) and Point of Care (POC) assays. Israeli diagnostic firms are mostly involved in traditional tests.

Agricultural biotechnology revenues are forecast to be $4Bn in 2004 (15% annual growth). Demand has been driven by farmers' need to improve crop yields at lower costs to serve a population with increased life expectancy (input traits). Focus has now shifted towards satisfying consumer demand for healthier diets such as foods with higher protein, starch or vitamin content (output traits). This sector is suffering from negative publicity over GMOs and limited exit opportunities for investors. However, agrobiotech companies in Israel are involved in seed development and veterinary products (50% of their activities).

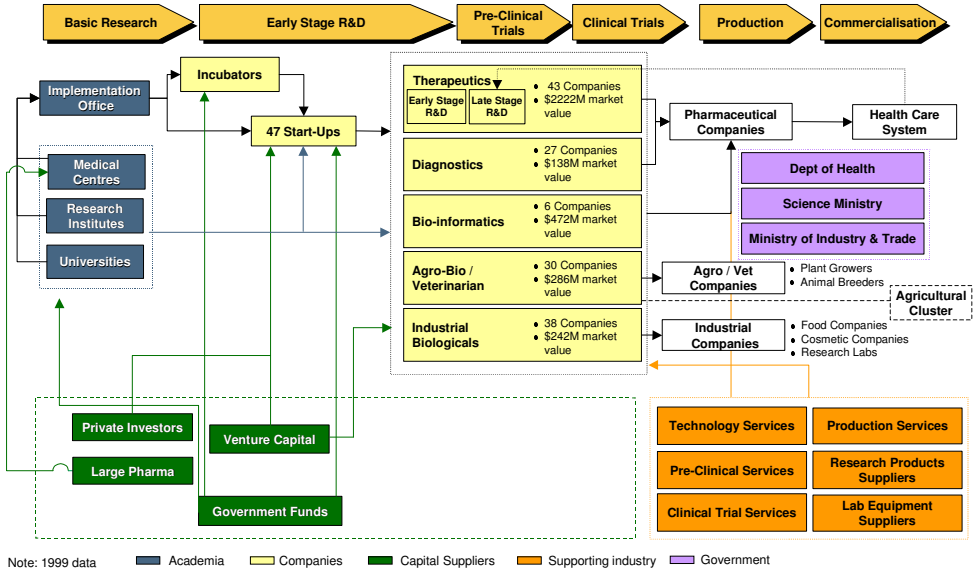
Bio-industrial and biological products sales are too small to offer a global market size for this segment. However, biotechnology is now being adopted by a wide variety

[3] Source: Ernst & Young and Recombinant Capital

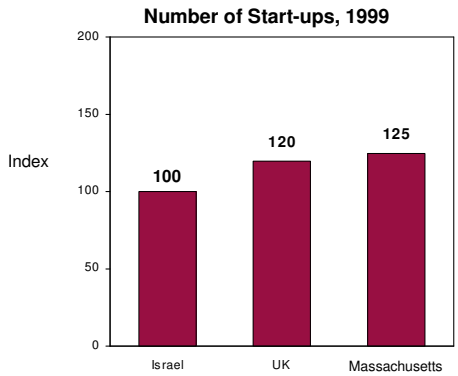
of industries for improving productivity, gaining energy efficiencies and developing ecologically-friendly processes. For example, bio-pulping could reduce the electrical energy required in the wood pulping process by 30%. As in other countries, several Israeli companies (24) focus on this segment, and they are mainly in food, cosmetics and environmental products. In biologicals, Israel's sector is also small, but in line with the low market size for biological products.

II. Key Issues Identified In The Israeli Biotech Cluster And Benchmark Of Foreign Clusters

Using cluster analysis, this project has comprehensively mapped and analyzed the main constituents of Israel's biotechnology cluster. These include: academia, incubators, hospitals, start-up companies, VC companies, biotech companies, pharmaceutical companies, service companies and the Government sector.



The picture revealed is one of an emergent industry with relatively many small companies. The challenge for the industry will be to move to the next phase of growth in which it nurtures more broadly based companies, supported by physical, regulatory and scientific infrastructure which will produce the environment for long term growth.



The main challenges to the development of a strong industry were identified as:

- A lack of clear national vision and focus
- Insufficient industrial infrastructure
- Limited coordination of private sector and Governmental efforts, (all the more as the local industry is highly dependent on foreign market resources and demand)
- Key bottlenecks and challenges primarily in the early commercialization stage:
  - Lack of "smart" pre-seed funding for late stage applied research
  - Weak academia-industry links
  - Lack of managerial skills
  - Need to strengthen the regulatory infrastructure
  - Lack of data on the industry (that can reveal opportunities for collaboration and scaling-up, both at pre and post-commercialization stages)

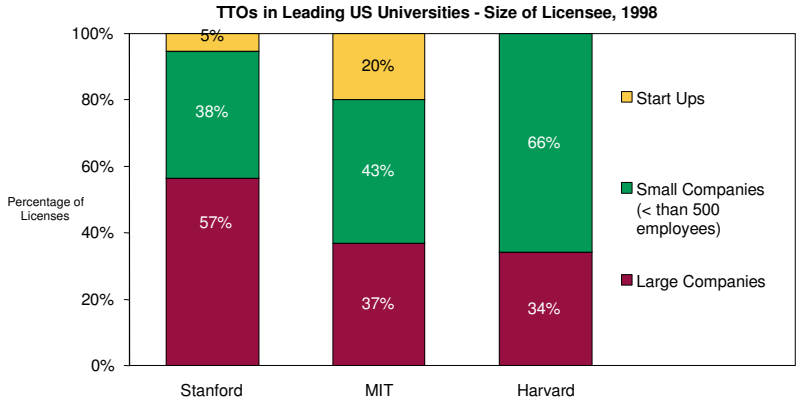
There is a distinct absence of high level interaction in Israel, which is required to generate an effective cluster dynamic. The biotech cluster suffers from low levels of interaction and communication between the companies themselves, the academia, the Governmental bodies and the VC community. Cooperation and collaboration in this industry is essential. For example, some start-ups would grow faster with more cross-company collaboration or alignment of strategic efforts with other players in related business areas to create larger and stronger companies.

The emerging biotech companies suffer from the lack of infrastructure with an integrated service offering. Local services offered at the drug discovery stage and for early pre-clinical, GLP pharmacology & animal testing, GLP analytical services and GMP batch manufacturing are not comprehensive. There are a few companies that offer services to the industry (e.g., Harlan, Analyst..), but their offering does not cover the full spectrum of services. In consequence, local biotech firms tend to work with US or European suppliers, increasing their costs and losing efficiency in the research process (e.g., loss of control of the compounds and its potential).

The transfer of technology from the academia and hospitals to the private sector is critical to the industry as biotechnology depends heavily on the innovations

from the academia. Israel's Technology Transfer Companies (TTCs) have relatively few resources to carryout commercial activities (as compared with leading TTCs in the US) and play a more important role in terms of funding the institution (as again compared with their US peers), while Israeli Universities have relatively low research budgets - which often inhibits efforts to advance the research to a level where it can be commercialized. TTCs in Israel have significantly more scientists per transfer agent than their US peers, they do not have resources to develop the innovations further to make them more attractive for licensing and have limited budgets to conduct IP work. Israeli TTCs are licensing, on average, up to 70% of their intellectual property to companies overseas. In many cases, the young nature of Israeli companies implies that they cannot yet absorb or develop these technologies. Still, the Israeli TTCs are an important source of funding for their institutions, generating anywhere between 25% and 40% of the University's total research budget.

In the US, primarily in leading institutions who have significant resources to support their research activities (from NIH, alumni and other contribution), TTCs strictly focus on commercialization of technology. TTCs' officers, who typically hold experience within the industry as business developers, patent and license out relatively more technologies than their Israeli counterparts. Their focus is to provide the best service to the scientists and support the local industry, especially small and medium size companies. The TTCs in the UK stand somewhere between the Israeli



and US ones in terms of mission and resources.

Scientists in Universities and research institutes also face a lack of financial resources and infrastructure to develop their technologies (e.g., up to proof of concept). This results in technologies being licensed to the industry at premature stages for limited financial compensation, or, in many cases, not licensed at all.

There is an emerging trend among TTCs to create start-ups rather than license-out innovations. However, they struggle to attract VC funds or other investors at such an early stage where the risk is high and the exit (e.g., IPO or sale) distant.

Israeli biotech entrepreneurs face the challenge of developing a start-up with limited funding, managerial and commercial support over a long development time. Scientists usually have limited marketing knowledge and drug development experience to manage a biotech start-up. They face limited access to specialized support: incubators and TTCs lack adequate resources to provide them with high

quality advice and there is limited alternative sources of support. Entrepreneurs also face increasing but still limited VC or angel investor funds to support their companies in very early stages of development.

Almost 50% of the projects out of incubators fail to raise funds after two years in the program. However, specialized incubators in life science which are backed by private investment groups are more successful, with over 85% of projects developing into viable start-ups.

Israeli Biotech Companies, 1999

Sector	Projects within incubators	Companies that graduated from incubators	As % of total companies	Non-incubator start-ups *
Therapeutics	7	4	26%	9
Diagnostics	12	2	50%	0
Agrobiotech	16	6	39%	1
Industrial *	10	3	59%	2
Biologicals	4	2	38%	1
Bioinformatics	1	1	33%	1
Total	40	18	40%	14

Young entrepreneurs also have to deal with incompatible policies between the incubators and the TTCs, especially regarding intellectual property clauses and equity ownership. This prevents them from fully leveraging all the resources offered through Government programs.

US and UK incubators have a very different profile: they are private entities specialized in specific areas and usually associated with a research institute through which they can provide access to specific infrastructure and high quality management support (e.g., Boston University Photonic Center in the US and the Babraham Bio-Incubator in the UK). They do not provide financial support to the projects, which will have to raise private funding on their own.

The regulatory infrastructure is suffering from a lack of resources. The Institute of Standardization and Control of Pharmaceuticals within Ministry of Health developed a unit dedicated to the biotechnology industry, however, the resources it currently has are not sufficient to provide the expected needs of the industry. Also, it is difficult for the Health Ministry to deal with approval of phase I clinical trials, if the applicant does not have FDA or EMEA approval. This is primarily important during the early phase of development where the failure rate is high.

III. Recommendations

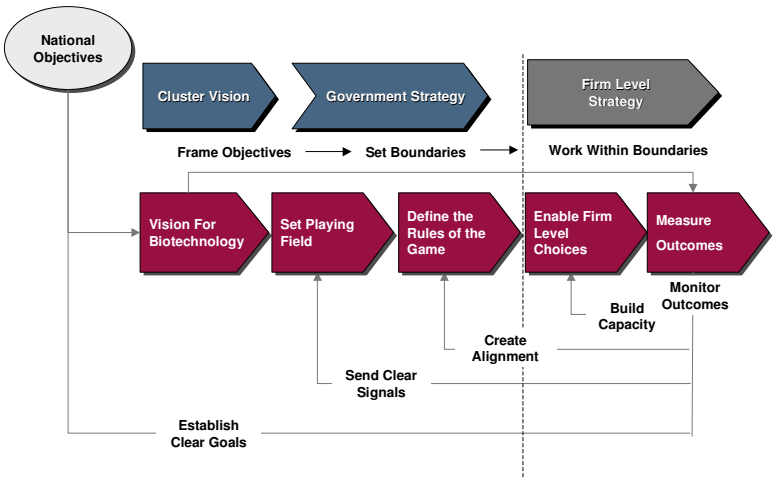
Define a set of recommendations aligned with a clear vision:

The proposed set of recommendations were developed according to a clear vision and were articulated around three key parameters:

- Knowledge creation
- Infrastructure development
- Commercial growth path

These recommendations provide the platform which will allow the firms to realize their own individual strategies.

Key areas of recommendations:



The cluster strategy should be focused on removing the obstacles slowing the development of the industry and building the platform to allow all participants (i.e., academia, industry, investors…) to realize their maximum potential. The seven main areas for actions are:

- ***Define a private sector leadership headed by the IBO to work with the Government***:
  - Firstly, ensure biotechnology is on the national agenda with a clear signal sent to the market through the statement of a national vision delivered at a governmental level
  - Secondly, form an intergovernmental

task force in cooperation with the private sector and the academia/hospital community to coordinate all Government policies, private sector initiatives and public activities. This effort should be led by the private sector to ensure the recommendations are implemented and all the incentives/signaling are aligned with the vision

- ***Upgrade the physical infrastructure supporting the industry****:* Attract an international company and support local companies which provide integrated services and equipment in pharmacology and animal testing, analytical services and GMP pilot batches manufacturing facilities. Examine the needs of the biotechnology centers to preserve their capabilities to provide contract services to the industry in the specific areas where the industry utilizes the centers.
- ***Support technology transfer processes*****:**
  - Establish a pre-seed fund to support promising applied research in the academia and medical institutions
  - Set pre-agreed guidelines for the commercialization of these projects (if indeed a commercial application arises from the academic research).
  - Provide resources to TTCs to patent innovations and deliver services to scientists, the

academic institution and the industry

- Create a dedicated fund to enable TTCs to outsource highly specialized services as and when necessary
- Align the IP and equity ownership rules with the incubators

- ***Improve early commercialization:***
  - Create two world-class incubators with first-rate business and management support which will work in cooperation with a state-of-the-art scientific service center.

    It is important to recognize the specific needs of biotech projects and adapt the incubation rules accordingly. Through these incubators the promising projects in biotech will have access to adequate pre-seed funding, as well as to the necessary supporting infrastructure described above.
- ***Reinforce the regulatory infrastructure***:
  - strengthen the resources at the Ministry of Health dedicated to serve the industry (GMP certification and clinical trials).
  - Evaluate two options to facilitate an easier process of approval of phase I clinical trials: a) creating closer links with the FDA (e.g. through an FDA affiliate office) b) add resources to the Ministry of Health to approve phase I clinical trials.

- ***Implement a tracking system for industry data and performance matrix*:** Ensure relevant data are collected on a regular and efficient basis to provide information on the cluster's development, reveal opportunities for cooperation and networking, assess the efficiency of the programs implemented and facilitate communication with foreign interlocutors (e.g., investors, pharmaceutical companies, support industry…).
- ***Map the infrastructure requirements for basic research in academia:*** The academic infrastructure provides the knowledge capital underpinning the biotechnology industry. However, assessing the strengths and weaknesses of this infrastructure went beyond the scope of this project. Therefore, the equipment requirements and educational programs available at each institution

should be mapped to ensure that Israel's knowledge creation and human resource training remains competitive.

Estimated budget to implement the proposed recommendations

Recommendations	One time cost	On-going cost per year	Total cost over 4 years
• Task forces creation with private sector leadership	_	$0.3M-$0.5	$1M- $2M
• Support selective applied research projects and technology transfer	$0.25M -$0.5M	Govt $8M	Govt $32M
		Non gov't $5M	Non gov't $20M
• Establish two bio-incubators	$5M	$10M	$45M
• Provide incentives to upgrade industrial infrastructure	$6M	_	$6M
• Reinforce regulatory infrastructure		To be assessed	To be assessed
• Implement tracking system	_	$0.05M	$0.2M
Total cost	**$12.5M**	**$23M***	**$105M****

* Government's share is $18M; ** Government's share is $84.5M

Conclusion:

Biotechnology is one of the fastest growing industries, reshaping the structure and dynamic of the traditional pharmaceutical industry, and improving efficiencies of many others. Investing now in biotech will give Israel the option of pursuing this opportunity in the future, in which it has the capabilities to succeed.

The expected outcomes of the recommendations presented in this report are several:

- Israel should aim to create 5 multi-billion value biotech companies by 2010 within an industry generating $2B - $3Bn in revenue. At the same time, the supporting industry should see its revenues multiply by 5, compared to their current level, due to the increased business.
- Productivity will increase, but the total employment in the sector should be 10,000 - 14,000 by 2010 (versus 3,500 today across all biotech firms). Other industries will also benefit from this set of recommendations as some of them positively impact other knowledge-based industries.

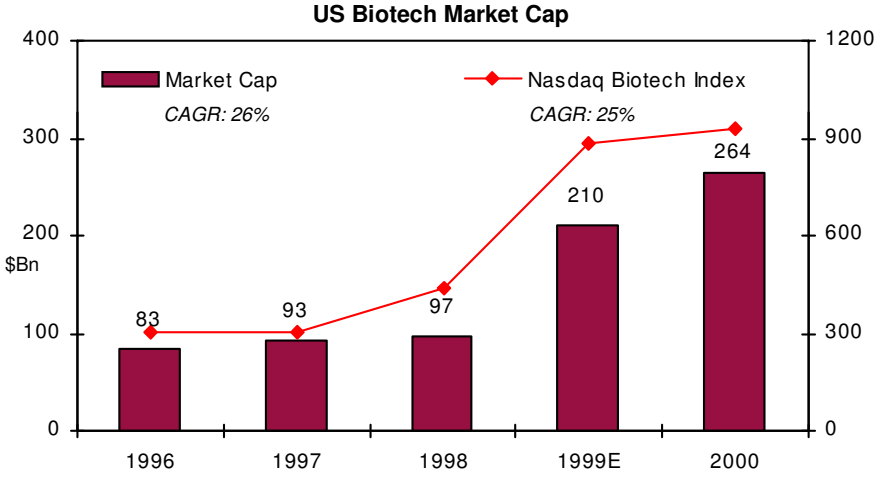
C. Global Trends and Potential for Israel

I. Global Biotechnology Market – Overview

The worldwide biotechnology market is expected to enjoy an annual growth of 12% with over $40Bn revenues by the year 2004 (potentially $100M by 2010). The development of this sector is driven both by structural demand factors such as an aging population, the need to control the costs of drugs, and by technological and marketing changes.

This market is mostly dominated by bio-therapeutic and platform technologies (80% of the market) with the development of new age therapeutic products. Post-genomic technologies are laying the foundation for a new era of therapeutic products with many of the conventional drug therapies being replaced by safer and more effective ones over the next decade.

One indicator of the high expectations for biotechnology in the future is the accelerating market capitalization of US biotech companies which have more than tripled during the last 4 years. With on average 25% annual growth rate, their market capitalization has reached over $250Bn in 2000 with total revenues above $22Bn.



II. Israeli Biotechnology Industry – Overview

The biotechnology industry in Israel is still in his infancy with 144 companies, including 40 incubators projects, and about 3500 employees. Most of the companies are small start-ups with less than 20 employees (75% of the companies), while a dozen companies represent 80% of the total market value of the industry, generate 2/3 of the sales and employ about 50% of the industry's human resources[4].

[4] Include BTG, Compugen, D-Pharm, Interpharm, Keryx, Omrix, Peptor, Pharmos, QBI and three companies with limited biotech activities (Abic, Hazera, Sigma Israel) but still significant player in their biotech specialty; Estimated market value as per August 31, 2000

In the last decade, the number of companies increased, by an average of 17% per annum, while the sales generated by the sector grew by 27% per annum over the same period[5]. However, over the last 5 years the annual growth in the number of companies slowed to 13% with only 14% annual growth in sales.

The estimated market valuation of the entire biotech industry in Israel is about $3.5Bn in 2000, including 7 public biotech companies capitalizing $2.1Bn[6]. The large majority of the valuation is driven by bio-therapeutic and bioinformatics companies (80% of total market cap) following worldwide market trends. These sectors are expected to generate higher returns than any others, as indicated by their ratio of market valuation per employee which is 5 times higher then that for other industry sectors, such as agrobiotech.

The sales of the biotech sector in Israel, reached $376M[7] in 1999 (close to $600M including Copaxone sales by Teva) of which 92% was generated by less than 10% of the companies. This low revenue stems from the fact that most biotech companies' products are still in the R&D phase. An estimated 21 therapeutic products are currently in clinical trials phase I, II and III with at least 51 products still in pre-clinical development. In the therapeutic sector, it may take 10 to15 years before a company can enjoy any revenue. Even in the sectors of diagnostics and agrobiotech it can take over 5 years.

Israeli Biotech Companies Statistics

Segment	Companies	Employees	1999 Sales $M	2000 Market value $M
Therapeutics	43	1,280	166	2,222
Diagnostics	27	471	28	138
Agrobiotech	30	830	114	286
Industrial[7]	24	191	39	93
Biologicals	14	492	79	149
Bioinformatics	6	231	3	472
Total	**144**	**3,495**	**429**	**3,360**
Adjusted Total[7]	144	3,276	376	3,238

In 1999, venture capital funds have invested $28M in biotech firms and are becoming increasingly interested by this sector. Since the beginning of 1999 four additional Israeli biotech companies have gone public, increasing the total to seven. This provides more exit opportunities for VC funds.

The biotech industry in Israel is still emerging with no backing from large ethical pharmaceutical companies. Therefore, the companies lack the appropriate experience to fully develop a therapeutic drug. On the other hand, Israel has a comparative advantage and synergy opportunities with its strong related industries in computers & physics to develop platform technologies, bioinformatics and diagnostic tools.

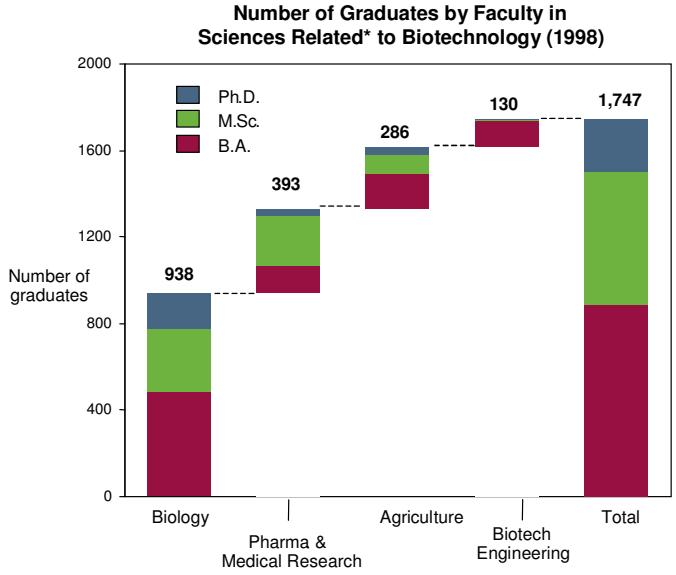
[5] In 1990, there were 30 companies with 600 employees and $50M sales
[6] By August 31, 2000
[7] Adjusted for Hazera biotech activities which are estimated to represent only 20% of their total activity; Industrial includes food, cosmetics, environment and chemical industry

III. Israeli Biotech-Related Research in the Academia

The seven Universities and research centers involved in biotech in Israel host over 800 research projects in the field, with additional research projects conducted in hospitals. Two thirds of the academic research is related to therapeutic drugs (of which 75% are in a basic research phase), one quarter to agrobiotech, and a further 10% to bioinformatics. The last two are by their nature considered applied research.

When comparing the sectoral focus of the academia and industry there appears to be considerable alignment. For example, both show limited activity in genomics and post-genomics reflecting Israel's relative absence from the original genome research project.

There is a large reservoir of science-skilled human resources in the academia. There are about 900 senior faculty members in the biotech-related departments in the Universities, including biology, biotechnology engineering, agriculture, pharmaceutical & medical research. In the 1998/1999 academic year, a third of all Ph.D. graduates were in biotech related programs (210 graduated), and there were about 650 graduates with a biotech related M.Sc. (10% of all Master's graduates)[8].



The level of research conducted in Israel is of a high quality, as measured by the number of publications in leading professional periodicals. When corrected for the population, Israel's publication level is very similar to the UK, while the US is holding the lead in research intensity and quality worldwide.

[8] Source: VATAT (Council for Higher Education - Planning and Budgeting Committee)

IV. Analysis by Sector:

Bio-Therapeutic

a) Global Trends

Biotech products are the future of the pharmaceutical industry, as companies struggle to develop new drugs to fill their pipelines and ensure future revenue flows.

> *"Today biopharmaceuticals account for only 5% of world prescription drug sales, but by 2005 they are expected to account for 15% of world prescription drug sales"* —Industry Canada, Bio-Industry Group

Worldwide bio-therapeutic drug sales are expected to be around $28Bn in 2004, growing by 10% annually (i.e., sales projection of existing drugs). As aforementioned, this growth is being driven by an aging population in the developed world, the existence of large markets with sub-optimal treatments and incurable conditions, and the emergence of new protein-based drugs. The three key therapeutics areas are cancer, auto-immune and CNS, with cancer being the most significant.

In 1999, the NIH allocated 19% (or $3.3Bn) of its grants to cancer research. Cancer therapies account for 47% (175 drugs) of all the compounds currently in clinical trials. There are at least 49 biotech cancer products on the market, which together generated sales of $2.7Bn in 1998 (already 15% of the entire market for cancer therapeutics). These sales are expected to reach $8.8Bn in 2005, growing by 18% annually. At the same time, the total cancer therapeutic market is expected to be around $34Bn in 2002 (17% annual growth).

Auto-immune diseases cover a wide spectrum of illnesses including Diabetes which is the most prominent one. There are currently 16 biotech products on the market for auto-immune disorders with an additional 19 in clinical trials. Their expected sales for 2005 are around $5.5Bn, a 12% compound annual growth rate.

Central nervous system (CNS) disorders include a number of common old-age conditions like stroke, Alzheimer and Parkinson diseases. CNS is the third largest therapeutic market with total sales of $31Bn in 1999. The sales of biotech products were still limited to $672M in 1998 but they should be over $1.6Bn by 2005 (13% compound annual growth).

Infectious diseases, especially viral diseases, are still the subject of intense scientific investigation. Modern medicine still lacks effective cures for many viral infections, from simple flu to the most deadly infections such as AIDS. The market for protein-based drugs in infectious diseases is expected to reach $1.2Bn by 2005, a growth of 17% annually. Currently there are over 50 biotech drugs in clinical trials.

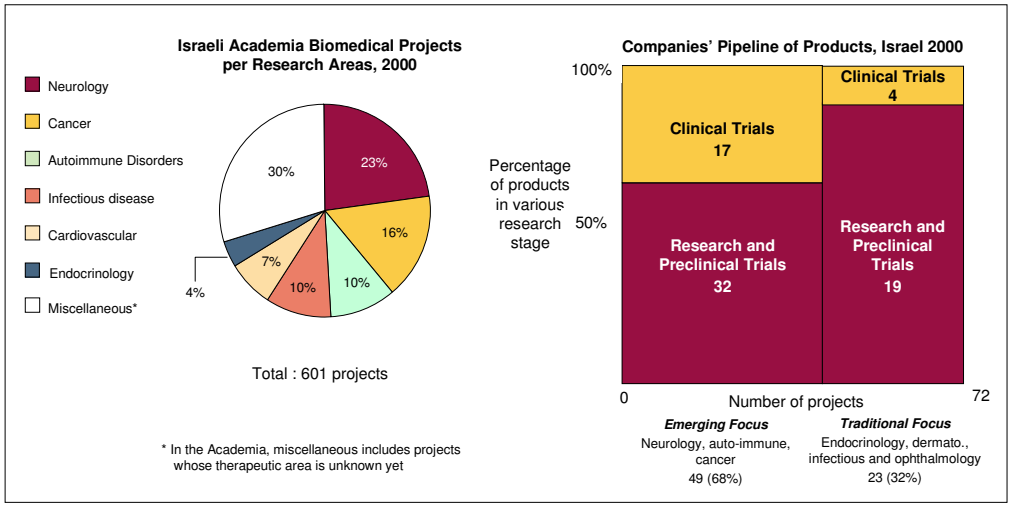
Cardiovascular diseases are still one of the main cause of death in the modern world. However, the market is fairly mature and should remain stable. By 2005, the market for cardiovascular products is estimated to be $1.3Bn, enjoying an annual growth of only 4%. Currently, there are 19 biotech drugs in clinical trials.

b) Israel's Position

The industry and academia have similar areas of interest, based on the number of products in the pipeline and the research conducted in the academia. The top three

therapeutic areas in these two sectors are neurology disorders, cancer and auto-immune system disorders. This is consistent with the fastest growing markets worldwide. About 50% of University research projects in therapeutic and 2/3 of biotech drugs in the pipeline are in these therapeutic areas. In fact, in these three therapeutic areas the academia published more papers per capita than the UK or US in 1999. They accounted for over 35% of all the papers published by Israeli institutions in bio-related research.

Traditionally, the products in the market were in endocrinology, dermatology, infectious diseases and ophthalmology. These therapeutic areas still dominate with about 80% of the products in the market, but represent only 21% of the academia research projects. The focus of academia research and company R&D efforts has shifted towards neurology, auto-immune disorders and cancer. These areas still represent only 21% of the products in the market but account for about 70% of all the products in the pipelines, (even 80% of products in clinical trials).



The technological focus in the therapeutic sector is on recombinant proteins, drug delivery systems and bioinformatics. In the academia the applied research is centered around drug discovery and bioinformatics. These technologies can help in the future development of the therapeutic sector, especially in drug discovery.

Platform Technology

a) Global Trends

Platform technologies should generate around $7Bn in revenues by 2004, with a growth of 35% per year. They are driven by pharmaceutical companies' needs for new tools to help them fill their product pipelines and reduce both their R&D time and cost (due to increasing efficiencies throughout the development process). Most of the successful companies in this area developed privileged relationships or forged alliances with major pharmaceutical companies. It is an intensive knowledge-content sector of this industry that requires close contact with the customers.

The platform technologies being developed have a broad applicability across the research and the commercial sectors. The key areas for the future will most likely be in functional genomics, pharmacogenomics and proteomics.

"The major movers in the industry see the new fields of DNA chips and genomics as offering the greatest growth in the next 5-10 years" —Merrill Lynch

Functional genomics, including bioinformatics and biochips, is a leading technology area that will drive discovery in the field of human health. In the "post-genomic" era, the challenge is to organize biological data and discover the biological function of particular genes. The market for bioinformatics is expected to grow rapidly (43% annually) and reach $1Bn in 2004. The market for biochips is similarly expected to enjoy a high growth rate (36% a year) and generate around $800M in sales in 2003.

In future, pharmacogenomics will allow the design of drugs tailored to specific sub-populations based on the genomic information. This area will revolutionize the markets of diagnostics and therapeutics. The market of pharmacogenomics is expecting to grow rapidly with a 108% growth rate a year and sales of $1.4Bn in 2004.

Another recognized emerging technology is proteomics, the business of mapping and studying protein function, which is relatively new and should grow several-fold over the next few years.

However, the areas mentioned are not exhaustive, with other areas such as bio-nanotechnology and bio-catalysis also under development.

b) Israel's Position

Israeli companies have limited activities in post-genomic technologies with only 19% of the employees in this sector devoted to bioinformatics or drug discovery. In the same time, research in the Universities is focused on drug discovery and bioinformatic with about 37% of all therapeutic research conducted in these fields.

However, there is limited research conducted in advanced post-genomic technologies, such as proteomics and pharmacogenomics, even in the academia. This is partially an inheritance from the low level of activity in the Human Genome Project. Many people in the industry and the academia regret that Israel lost out on the global genomic effort, but they still believe Israel can build a position in the post-genomic era. To do so, it will be important for Israel to support academic research in those areas which represent the future growth of the biotech industry.

Diagnostics

a) Global Trends

Traditional diagnostics, mostly based on immunoassays, will tend to be replaced by theranostic technologies based on DNA assays. The growth in medical diagnostics will come from the development of these new technologies which link the diagnostic to the therapeutic process. They will be used for preventive testing, predisposition testing, disease diagnostics, therapy selection and therapy monitoring.

Diagnostics sales are forecast to be around $3Bn in 2004, with an annual growth of 22%. There is a need for tests which increase the efficacy of drug therapy and for products that reduce the cost related to adverse drug reaction. The growth of traditional diagnostic products will slow down to around 1% or 2% per annum.

Another technology, the Nucleic Acid Probe Testing (NAT), is used to:

- Test for infectious diseases by detecting the pathogens DNA.
- Test a patient's susceptibility to different diseases by mapping their specific genetic composition.
- Determine therapy responses based on the patient's genetic make-up.

The market size for NAT products is expected to be about $1.4Bn by 2002 (a 25% CAGR[9]).

Point of Care assays (POC) are products that can be used in the physicians' offices, at the patient's bedside and by the patient himself. These products will gradually replace many of the traditional assays that can be performed only in the diagnostic labs by professional technicians. The market size for POC products was $5.6Bn in 1996 and only 30% of the total diagnostic market. By 2002, the POC market should be $7.9Bn, representing a 41% share of the total market.

"The best is that genomics and bioinformatics can be used to develop … diagnostics from a relatively uninteresting low-margin commodity business into one that justifies stand-alone companies with high margins" —Ernst & Young, Biotech 1999

b) Israel's Position

Israeli diagnostic firms are mostly involved in traditional tests based on immunoassay kits. The major segment is diagnostic kits for infectious diseases, based on the number of employees in this segment (50% of the sector). Only a very small portion, 3% of the employees, are involved in developing DNA-based diagnostic products. For the development of future products in diagnostics, like in therapeutics, there is a need for a strong foundation of post genomic technologies.

Agrobiotech

a) Global Trends

"With increasing competitiveness, globalization of prices, & consumer demands for food that is safe & produced in a sustainable way, biotechnology is arguably the only technology that can seriously address these challenges" —Irish Government's Agricultural & Food Biotechnology Group, 1999

The market for agricultural biotechnology products is expected to continue growing, with sales of transgenic seeds and biopesticides forecast to reach $4Bn by 2004 (15% annual growth). This figure excludes sales of veterinary biotech products or expected sales from biotech-derived nutraceutical & functional food products, which are beginning to emerge.

Traditionally, demand in this sector has been driven by farmers' needs to improve crop yields at lower costs. However, today, agrobiotech companies have shifted focus towards satisfying consumer preferences for healthier diets. This is, in large part, driven by a desire to win public opinion over agricultural biotechnology given the

[9] Compound Annual Growth Rate

continuing adverse publicity in Europe over Genetically Modified Organisms (GMOs).

The agricultural biotechnology industry can be divided into three major sub-sectors: plant biotechnology, biopesticides and veterinary biotechnology. In plant biotechnology, plants can be modified to:

- Satisfy farmers' needs for higher yield, pest-resistant, stress-tolerant crops (input traits). This market is expected to grow by 13% annually from $1.6Bn in 1999 to $2.9Bn in 2004.
- Satisfy consumer demand for healthier, vitamin rich and flavorful foods (output traits), as well as medical needs for pharmaceutical products, such as edible vaccines. While there are very few biotech food products of this type currently on the market, in future companies can hope to win a sizeable share of the market for functional foods, projected to reach $51Bn by 2004.

Overall, the total market for plant biotechnology products is projected to reach $40Bn in 2009. It is not surprising, therefore, that Germany's BASF has chosen to invest $600M over the next 10 years in developing plant biotechnology, both for input and output trait products.

The biopesticide market had sales of $130M in 1999 and is growing by 15% a year. This constitutes only a tiny proportion of the total chemical pesticides market of $39Bn. It can be expected, therefore, that biopesticides will grow as it takes an increasingly large share of this market.

In veterinary biotechnology, companies develop and produce therapeutics, vaccines and diagnostics for disease control in livestock and pets. As in the other segments, biotech products can also expect to win a share of this market, valued at $12Bn in 1999.

However, start-ups entering agricultural biotechnology face a difficult financial situation, as the industry is dominated by a handful of giant corporations, like Monsanto, which limits the exit opportunities for investors.

b) Israel's Position

Agricultural biotechnology in Israel includes two major sub-sectors: plant biotechnology, with over 80% of the industry, and veterinary biotechnology.

The plant biotech industry is dominated by one large company, Hazera, which develops seeds. Hazera has no transgenic seeds on the market yet, but it heavily invests in biotech R&D in this field. Two plants have been registered so far in the genetically modified category (flower vase life expectancy and petal color) and 4 projects are in field trials in Israel. At the industry level, about 67% of the agrobiotech sector R&D effort is devoted to the development of seeds and transgenic plants (including companies that produce plant tissue culture for seed-developing companies).

The largest number of start-ups in the sector are in bio-pest control, but they only employ 11% of the sector's work force. When comparing the activity of the academia and the industry, there are similar areas of interest. Both have very broad focus with no clear concentration on any specific area or niche opportunity.

Bio-industrial & Biological Products

a) Global Trends

For most of its 20-year history, biotechnology has focused on treating diseases. Today, biotechnology is being adopted by a wide variety of industries for improving productivity, gaining energy efficiencies and developing environmentally-friendly manufacturing solutions.

The industries most receptive to biotechnology are: paper and pulp, chemicals (biocatalysis, plastic, detergents, etc.), textiles, energy (oil production, oil degradation, new energy forms etc.), Governments (waste disposal, bioremediation etc.), cosmetics, computer hardware, information technology.

At the moment, the biotech involvement in these industries is limited and so it is difficult to estimate the current and projected size of this market. Nevertheless, large companies like Dow Chemical, DuPont, Motorola, IBM and Compaq are investing heavily in biotech and some experts believe that the major impact of bioscience will be felt in these vast and diversified industries.

The American Biotechnology Industry Organization (Washington DC) has made the following projections for some existing industrial applications:

- Detergent enzymes account for the largest portion of the total enzyme market revenues. It is estimated that detergent enzymes constitute between one-third and one-half of the estimated total enzyme market of $624 million to $1.6 billion.
- Some agricultural crops, such as corn, can be used in lieu of petroleum to produce chemicals. The crop's sugar can be fermented to acid, which can then be used as an intermediate to produce other chemical feedstocks for various products. It has been projected that up to 30 percent of the world's chemical and fuel needs could be supplied by such renewable resources in the first half of the next century.
- It has been demonstrated, at test scale, that biopulping reduces the electrical energy required for the wood pulping process by 30 percent.

In the biological sector - companies producing biological and biochemical products for research in the academia and industry - the total market for research products is estimated at about $1Bn-$2Bn. This market is highly competitive with low barriers to entry.

b) Israel's position

The sector of bio-industrials in Israel is very small, with less than 5% of the industry employees. Although 24 companies can be listed as involved in this sector, most of them are small with on average only 8 employees. The time to market is considerably shorter than in human health and agriculture. However, at the present the market value per employee is low.

The bio-industrials sector in Israel includes food, cosmetic and environmental products. Food supplement and food technology involve 3/4 of the employees in this sector.

The biologicals sector in Israel represents 14% of industry employees. Of the 14 companies that can be listed in this sector, only Sigma Israel and Gadot Biochemicals are relatively large corporations.

D. Key Issues Identified In Israel And Benchmark Of Foreign Clusters

I. Lack of a National Vision for the Industry

One of the leading entrepreneurs this century once commented that "capital isn't scarce; vision is"[10]. This statement is largely applicable to biotechnology in Israel, with several interviewees commenting on the absence of a strategic vision for the industry.

Creating a national vision for biotechnology and *communicating* that vision across the cluster is a necessary instrument that will help to:

1. Align policies across Government departments so that a logical and comprehensive platform for the cluster's development can be put in place, covering everything from basic research funding to clinical trials' regulation
2. Mobilize & focus biotech companies on creating an active cluster dynamic, thereby facilitating more rigorous competition but also cooperation between companies
3. More closely align the missions and objectives of all actors involved in knowledge creation and its commercialization with the objectives of the cluster
4. Secure greater interest and involvement from the financial community (e.g., venture capitalists & business angels) and potential customers, at home and overseas, (e.g., pharmaceutical companies and industrial manufacturers) in the cluster
5. Identify performance measures by which the Government and cluster members are able to judge the cluster's development and address new challenges as they emerge

International biotech clusters have all acknowledged the importance of defining a long term vision for their clusters as part of their overall policy framework. In 1993, the industry-Government business network in Silicon Valley, USA, declared its vision for the region's biotech cluster:

"Silicon Valley and the Bay Area will remain the leading concentration of bioscience companies in the world. Over the next decade, the industry will grow to five times its present size in the Bay Area. Relying on the high quality of local education and research institutions, job growth primarily will be in high-end research, development and production activities. Collaboration between local governments and the industry will facilitate business expansion, and collaboration between Universities and companies will support education, research and technology exchange. The industry will continue to grow in its mainstream areas such as therapeutics…"[11]

Similarly, in Scotland, the Scottish Enterprise Network Biotechnology Group set its vision to "*strengthen Scotland's position as a world center for leading edge biotechnology research and commercialization"* by building a critical mass of robust

[10] Sam Walton, Founder and CEO of Wal-Mart
[11] Joint Venture Silicon Valley Network, in San Jose, CA, USA, June 1993

companies, commercializing the research in Universities, developing critical linkages within the cluster, and promoting Scotland as the hotbed of biotech activity.[12]

It is equally important that Israel defines its vision for biotechnology and creates a sense of purpose that can stimulate new initiatives both from within the Government and from the private sector to drive the industry forward.

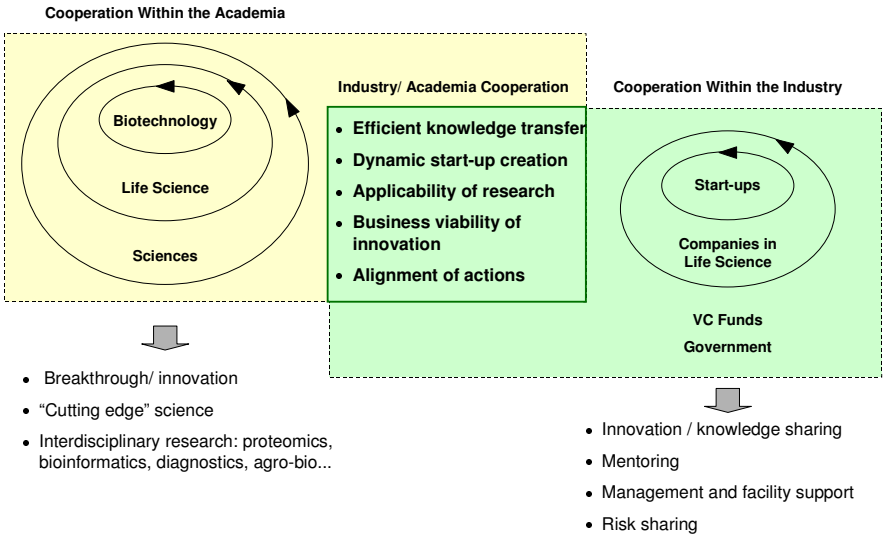
II. ***Weak Linkages between the Actors inside the Cluster***

Strong Linkages are Critical for the Development of Clusters

A common thread running through all research into systems of innovation in national economies is the requirement for increasing levels of interaction between companies and other actors in the value chain. The Organization for Economic Cooperation and Development (OECD), in its study on innovation systems, argued forcefully that:

"The competitiveness of companies is becoming more dependent on complementary knowledge acquired from other firms and institutions. Increasing complexity, costs and risks in innovation are enhancing the value of inter-firm networking and collaboration in order to reduce moral hazard and transaction costs, spurring a multitude of partnerships between firms of complementary assets….Interactions are also intensifying between firms and a number of other institutions in the innovation process, such as Universities and other institutions of higher education, private and public research labs, consultancy and technical service providers and regulatory bodies" (OECD, 1999)[13]

Strategic Importance of Cooperation



The primary function of these interactions is information exchange, which will only flourish under the right social conditions, specifically social interaction among

[12] Biotechnology – A Framework for Action, Scottish Enterprise Network, Nov 1999
[13] Boosting Innovation: The Cluster Approach (OECD Publications, 1999)

members of the cluster, mutual trust between those members and a shared vision for the cluster. (Rosenfeld, 1996)[14].

For any cluster, the key benefits of these interactions (which create an effective cluster dynamic) should be to:

1. Foster "scaling-up" within the industry - the growth of alliances, partnerships or mergers between companies which may increase their chance of survival & make them more competitive globally
2. Facilitate a higher level of mentoring support for start-ups by giving them access to a wide and supportive network of contacts who can offer business advice and technical information
3. Encourage greater specialization among support service providers who may better cater to the specific needs of companies in their formative stages of development
4. Facilitate the creation of a strong and effective cross-industry body, that brings together the key actors in the value chain & the Government to determine the needs of the industry
5. Create an active and well-supported trade association which can publicize the opportunities for partnership with overseas companies and help market its members' technologies to overseas customers and clusters
6. Improve the likelihood of generating new and commercially valuable innovations and strengthen the processes around the commercialization of those innovations

In Israel, there is a distinct absence of a high level of interaction required to generate an effective cluster dynamic.

Interviewees from all sections of the biotech value chain concurred that the industry can benefit from a greater degree of cooperation and knowledge sharing. Culture and a general lack of trust among companies and entrepreneurs, unaccustomed to sharing any knowledge with potential or actual competitors, were cited as limiting factors.

The low level of collaboration between companies is proving to be an obstacle both to the creation of new companies and the construction of more robust companies established through alliances or mergers. In the case of new companies, managers of incubators have signaled their difficulty in soliciting objective information about the quality of projects in their facilities:

> *"It is difficult to solicit honest opinions of others about the scientific / business potential of a project because there is lots of envy and politics"* (Incubator)

Even when it comes to collaboration between existing companies, both the companies and organizations promoting collaboration admit that it is low and is thereby reducing the level of investment in the sector:

> *"There is low collaboration between companies in Israel, we in Israel tend to collaborate less, since it is a small place and everyone knows everyone else - we are concerned that information will leak"* (Biotech Company)

[14] Rosenfeld, Stuart A. 1996. Overachievers, Business Clusters that Work: Prospects for Regional Development. Chapel Hill, NC: Regional Technology Strategies.

"Enhancing collaborations is a way to answer a market failure : the lack of interest from investors for technologies that will not be profitable in the near term – this is particularly true for biotechnologies". (Government-supported Program)

This problem extends into the relationship between the academia and the biotech industry, where both doubt the motives and utility of interaction with the other:

"We do not have access to Israel's greatest strength – the science base. One institute is so secretive you can't even get access to its grounds" (Biotech company)

"The industry likes to tap into the knowledge in the University without paying" (Academic institution)

This suspicion between the academia and the industry is limiting the development of an effective and continuous system of knowledge transfer between them. Both sides are losing:

1. The industry is losing out by failing to acquire knowledge about the new technologies and processes emerging from the academic and hospital research base
2. The academia may be missing out on the financial and knowledge flow benefits which a strong industry can provide

Nevertheless, there is clearly a need to foster the kind of collaboration required to generate a more robust cluster dynamic. Part of the way has been paved already simply by conducting this analysis and bringing some of the main actors in the biotech industry together to consider the future of the sector. In addition, testimonials from the heads of existing Government programs suggest that once firms are forced to collaborate "*they finally like it"*.

The importance of creating a powerful cluster dynamic has been borne out by the experience and activities in the UK and US biotech clusters.

In Cambridgeshire, UK, the private sector has created the Eastern Region Biotechnology Initiative, which has brought together representatives of the academia, service companies (including patent lawyers, accountants, stockbrokers and banks), customers (GlaxoWellcome), biotech companies and regional government to consider strategic issues facing the industry and promote activities to foster greater interaction, knowledge-sharing and awareness of business development opportunities.

In Massachusetts, USA, the private sector formed a Biotechnology Council which has brought together the biotech companies and MIT's Technology Transfer Office, local venture capitalists, local service providers, hospitals and others to: 1) address the issues facing the cluster; 2) promote networking; 3) lobby the State and Federal Governments on important issues; 4) offer valuable cost-saving or business development opportunities to biotech companies.

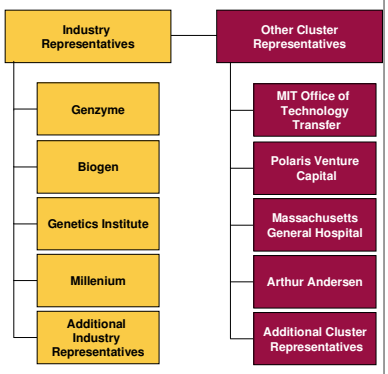
Create Cluster Dynamic - Industry Leadership
Massachusetts Biotechnology Council

The council provides a forum for networking between the various parts of the cluster, improves the business environment and interfaces between the industry and government

Activities and Mechanisms

- **Policy:** Addresses issues related to policy, clinical trials, regulatory etc..
  - The Council regularly lobbies local, state, and federal government officials on issues related to biotech (e.g. regulatory affairs)
- **Networking:** Separate committees are also established to develop networks among professionals in specific areas of biotech activity (e.g. bioinformatics, business development, purchasing etc…)
  - Committees may also include pharmaceutical companies and other interested parties (e.g. Compaq and Pfizer)
- **Purchasing:** The Council negotiates broad based agreements with scientific suppliers as a cost saving mechanism for its members
- **Conferences:** Local and international conferences are organized on broad issues (e.g. BIO2000) or on a specific topic (e.g. financing)

Board of Directors



III. Weak Process of Technology Transfer

The Importance of Technology Transfer for Cluster Development

Globally, the public sector research base is a key source of innovations in biotechnology and medicine. During the early development of a national biotech cluster it is, in fact, *the* source of innovations and consequently the root of the majority of new companies. Even for developing and developed clusters, it continues to play a significant role in building the critical mass of companies required for a cluster's competitiveness, as well as acting as an important potential research partner for existing companies.

Therefore, it is critical that a system is in place to transfer efficiently the knowledge and intellectual property generated from the academic and hospital research base to the locally-based private sector, a conclusion shared by governments in other industrialized countries:

"Against the background of a growing significance of knowledge-based technology, an acceleration of product life cycles and a rise in the costs of modern research, the debate on the status and possibilities of improvement [of technology transfer from academia] has recently been revived." (Germany's Federal Ministry for Education & Research, Oct 2000)[15]

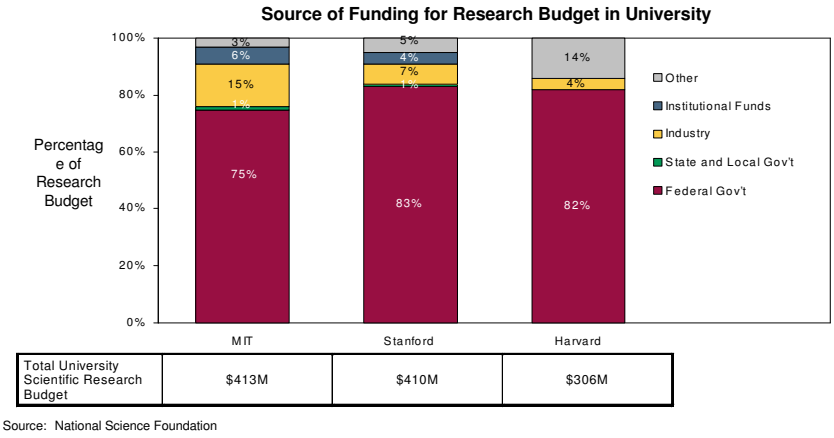
The leading technology transfer offices in the US (and to a lesser extent in the UK) serve the researchers & industry by ensuring the commercialization of researchers' intellectual property.

[15] Knowledge and Technology Transfer in Germany. Report commissioned by the Federal Ministry for Education and Research, October 2000

Our research into the leading technology transfer offices (TTOs) in the US & UK[16] identified several common features:

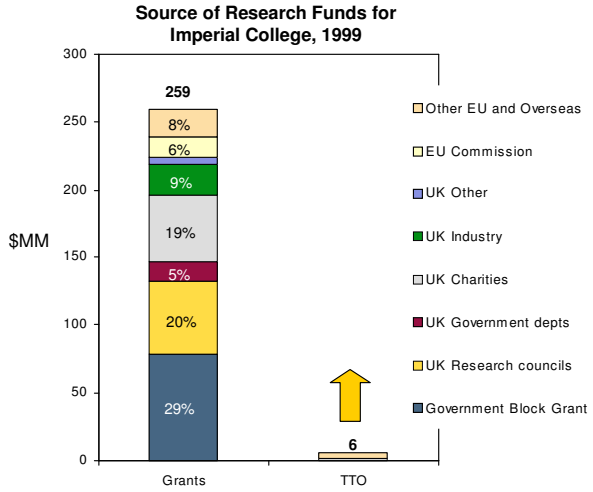
Mission to Commercialize Research

- The mission of US leading TTOs (e.g., MIT, Stanford and Harvard) is to serve the researchers by providing information on, and assistance with, the commercialization of their innovations, while making acceptable returns for the University[17]. Consequently, they are independent companies dedicated to licensing and spinout with 3rd parties, which excludes corporate research sponsorships.



Source: National Science Foundation

- Researchers are given incentives to create start-ups through a lucrative equity share (~45% before the dilution of a 3rd party) and permission to spend time throughout the year running their start-ups
- Their licensing deals make relatively modest contributions to the total University research budget (between 1% & 10%), which gives them the flexibility to meet industry needs.



Note: Block Grant includes research infrastructure costs
Source: Imperial College 1999/2000 Annual Report

[16] MIT, Stanford, Harvard in the US; Imperial College (London) and Oxford University in the UK

Skilled and Sufficient Resources

- They are numerically well staffed, with the ratio of senior faculty members to technology transfer officers averaging 66 in the US (UK data not available), facilitating short transaction times which meets the demands of both the industry and researchers
- Negotiations are handled by highly skilled businesspeople, with MBAs or strong business development experience, who also possess Masters or Ph.Ds in life sciences. Such staff are attracted by the career opportunities available and the increasingly generous compensation schemes on offer
- Technology transfer officers have the capacity to secure further investment in research to develop an innovation before patenting, licensing or spinout negotiation
- Their patent budgets are relatively large (e.g., around $1.5m per annum for Oxford University), enabling them to hold a broad portfolio of patents and/or hold patents for a longer duration

Supportive of the Local Economy

- A majority of their licensing agreements are made with domestic companies (*~90% for US TTOs; ~ 50% for Oxford University's TTO)* [18], and some have large portfolios of spinout companies (e.g., 53 for MIT; 36 for Imperial College)

The features above largely conform to the recommendations of the National Governors' Association for technology transfer practices:

"For University-industry technology transfer to thrive, it must rest on a foundation of effective University-industry research partnerships, appropriate staffing, flexible policies, and a supportive culture and mission orientation. For technology transfer to have a positive impact on state and local development, it must be oriented toward fostering state-based, University-industry R&D partnerships and licensing arrangements and toward commercialization through local start-up companies".(NGA, 2000)[19]

Israel's Technology Transfer Companies (TTCs) have relatively few resources to carryout commercial activities (as compared with leading TTCs in the US) and play a more important role in terms of funding the institution (as again compared with their US peers), while Israeli Universities have relatively low research budgets - which often inhibits efforts to advance the research to a level where it can be commercialized.

[17] In the UK, the mission is to support the funding of the academia, in a manner that is profitable for the industry

[18] However, Imperial College only licensed ~25% of its Intellectual Property to UK-based companies

[19] Building State Economies by Promoting University-Industry Technology Transfer. National Governors' Association, USA, 2000

Inadequate Resources:

- The staffing in the Israeli TTCs is not sufficient to perform the commercialization & internal marketing functions as efficiently as in the US & UK TTCs. In some cases, technology transfer companies in Israel have twice as many scientists per agent to manage as their leading counterparts in the US
- TTCs do not have the resources nor the mandate to develop innovations to a level where the potential for the technology can be proven. Such a development stage would reduce the risk of licensing for small & medium-size Israeli companies. However, some TTCs, like NG Negev, are trying to create an internal fund to address this issue (*see next chapter on lack of pre-seed funding)*
- Some TTCs do not have substantial budgets at their disposal to retain IP rights for technologies that they believe have strong commercial potential

TTCs are an important source of funding

- Their mission is principally to raise money for the University from the private sector and protect the interests of the University, (and in this they outperform foreign TTCs benchmarked). This mission results in the TTCs being entrusted with all negotiations with the private sector, including frame agreements, instead of being dedicated to technology transfer
- Licensing is a critical source of funds, generating anywhere between 25% and 40% of the University's total research budget[20]
- Protecting the University's interests also means scientists are sometimes given little incentive to participate in spinout companies, receiving in some cases less than 15% equity stake, and facing the prospect of losing their tenure at the University if they participate beyond one year. In hospitals, researchers are not entitled to any equity in a start-up or income from licensing their IP

"The scientists are not permitted to be major owners or managers in an established start-up, our policy attempts to keep the scientist in basic research in the institute/University" (TTC)

Domestic versus foreign activity:

- TTCs are licensing, on average, up to 70% of their intellectual property to companies overseas. In many cases, the young development stage of Israeli companies means they cannot absorb or develop these technologies. Also, multinational companies that support research in Israel can afford to acquire technologies in early, unproven stages

Overall, the resources dedicated to technology transfer in Israel do not adequately support cluster development in biotechnology, as the resources of the TTCs and the University are insufficient to support an effective commercialization of technologies in Israel.

[20] Based on information provided in interviews with TTCs, but percentages vary by institution

IV. Lack of Pre-Seed Funding

Pre-seed or development funding is the necessary capital required to turn good research into good business. In many Universities across Europe and the US, innovations are discovered but are not sufficiently advanced to be patented and licensed to the private sector immediately. Without additional research, these innovations will simply lay idle in laboratories until eventually becoming outdated as the same or newer innovations emerge elsewhere.

In Israel, there is a lack of pre-seed funding which restricts the amount of innovations accessible to the biotech SMEs in the national economy:

"Foreign companies are buying technology for nickels and dimes from Universities, as they are desperate for cash" (VC Company)

In many cases, the absence of development funds means that TTCs license their technologies to major foreign multinationals who have the resources to invest in developing the technology, even with doubts about its ultimate application. This is not true for most Israeli biotech companies, who are too small to license technologies at a stage when its application is unclear.

In the US, this problem is not acute, but in the UK this issue is referred to as the "development gap" and is being addressed through targeted Government programs

For example, the UK Government established the University Challenge Fund in 1998, providing several Universities with pre-seed or "proof of concept" funds to test the commercial application of a technology (see Appendix A). The funds available range from $1.6m to $7m per University for all disciplines.

V. Early stage incubation in Israel does not fit industry needs

Most start-ups in biotechnology face similar constraints on their development: finance, business development experience, managing IP, marketing expertise, technical expertise, office and laboratory space, and specialist equipment. Incubators offer a potentially comprehensive solution for start-ups, providing a medium for all these issues to be addressed simultaneously.

Israeli incubators, however, were not intended and not equipped to meet the specific needs of biotech start-ups

Currently there are 24 incubators in Israel, each operationally independent but funded jointly by the Chief Scientist Office, royalties from successful projects and private sector sponsorship. To date, their contribution to the number of biotech companies is impressive (40%), but many of these are weak, single-product companies that contribute only modestly to the strength of the cluster. This is primarily because:

1. Only a minority of projects being accepted are biotech - only 15%-20%; and
2. The average failure rate for all incubator projects is 48%, a figure that worsens after adjusting for the low failure rate of one incubator[21].

[21] One incubator has a success rate of 85%, which raised the average success rate quite significantly

The drivers of these two factors are:

Inadequate resources supporting the Incubator

Incubators have limited financial resources with which to support their projects. Therefore, projects only receive $150k per annum over 2 years, which is insufficient to advance them significantly, especially in biotech.

The current managerial support available, while albeit useful, is not sufficient to provide:

- The necessary expertise in all fields of biotechnology to select strong projects, and have difficulty obtaining impartial expert advice to assist them
- The level of business or technical mentoring required by each project

There are limited networking opportunities provided by incubators from which specialized business or technical mentoring support might be made available.

An absence of specialization

Incubators do not provide the specialist equipment, facilities and technical expertise that are needed by biotech projects. This forces projects to rely on their own limited budgets to gain access to the necessary equipment and technical support.

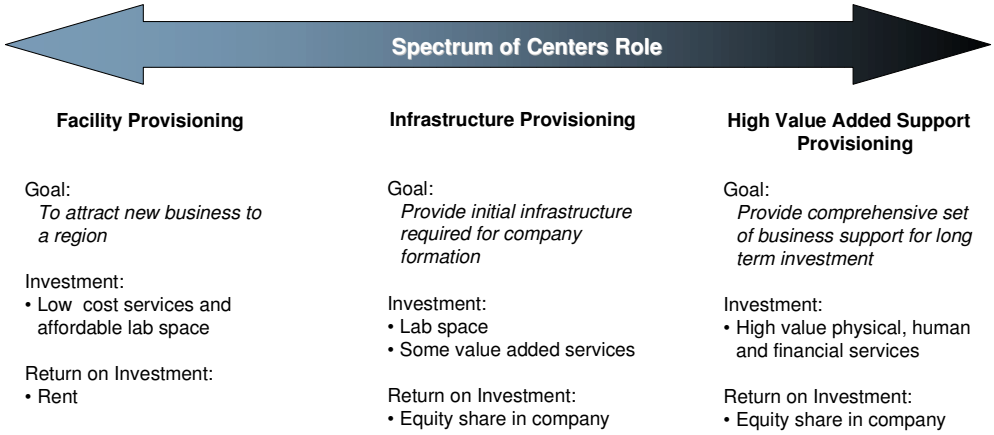
Furthermore, biotech projects require several years to bring their technologies to maturity. However, under the current rules, projects must leave the incubators within 2 years.

Finally, under current arrangements, different biotech projects can be working in complementary areas but not know of each other's existence. This limits the opportunities for collaboration and mergers, which might produce more robust technologies and companies.

"*…there is much duplication of research as incubators do not specialize in biotech and so people do not know who is doing what*" (Government Program)

Incubators in the UK and the US do possess specialist incubators which provide business and technical mentoring according to the requirements of each project.

Research into the UK and US revealed that there are different types of incubators operating more like service centers. At one end of the spectrum, there are centers that offer just the basic facilities and equipment for the projects; while at the other end, they provide specialist and highly value-added services that will give projects a competitive advantage in the marketplace.



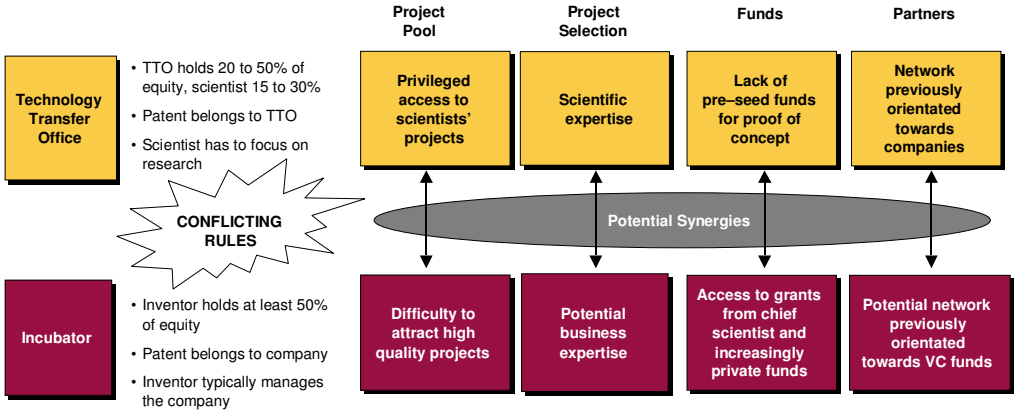
One example of the latter is the Babraham Bio-Incubator in the UK, an incubator that is linked to the Babraham Institute - a leading UK institute dedicated to functional genomics. This incubator provides projects with access to the technical support of the Institute (equipment, samples, technicians and scientific advice from peers) as well as business and networking support from the incubator's management team, which is well connected to the biotech service sector (see Appendix B).

There are initiatives underway in Israeli incubators that will address some of the issues identified above

- Some incubators are bringing independent investors in to provide financial backing to both the incubator itself and individual projects in exchange for equity (e.g., Naiot, LN Innovative Technologies)
- Some incubators are creating a fund with VCs to jointly invest in a project (e.g., HiTec)
- A number of incubators are choosing to specialize (e.g., Rad Ramot and Naiot in Biotechnology)
- Agreements have been reached between a hospital TTC and Incubators on aligning their IP policies to enable cooperation (see next section)
- Private initiatives to increase collaboration or provide high value-added services to projects are being developed

VI. Incompatible Intellectual Property clauses between Incubators and TTCs

One issue that emerged from the study of the TTCs and Incubators was the incompatibility of their respective policies concerning the scientist's equity stake in a start-up. This disparity means that cooperation between the two institutions is difficult, if not impossible, further hampering the development of new businesses emerging from the research base.



"Conflicting polices prevents us from work with the incubators" —TTC

This issue is currently under discussion between the Chief Scientist Office and the VP or research of the universities.

VII. A shortage of skilled managers/entrepreneurs in biotech

From all sections of the biotech-interested community, the lack of experienced management personnel is regarded as a major obstacle to the growth of the sector:

"There is a serious lack of managers and entrepreneurs in the biotech industry" (Biotech Company)

"Several scientists come in and ask me if there are any good managers they can be put in touch with. But it is difficult as there aren't many" (Government Program)

"Management capability is scarce in Israel" (VC Company)

"I see no managerial skills whatsoever. In the biotech it is impossible to find a manager – while in the high tech they find them in the army" (TTC)

This issue is not peculiar to Israel, with the UK and others identifying it as a major problem which they are seeking to address through different initiatives. However, in Israel, the situation is more acute, with not only a shortage of skilled managers but also people with experience in drug development.

This issue has been identified by the private sector, and some initiatives like TIM[22] or a new management program at the Tel Aviv University are being organized to provide mentoring and training to future or existing managers of biotech companies.

[22] Technion Institute of Management is a new, independent institution, created by the Technion, international business and academic leaders providing management education, information and expertise (see www.TIM.co.il)

VIII. Infrastructure for the industry is not comprehensive

The infrastructure for the industry is the platform which will allow biotech companies to take their technologies from the initial lead generation through to late stage clinical trials. It would, therefore, include services such as contracted research which can provide analytical and pre-clinical trial laboratories which are accredited and GLP[23] recognized.

In Israel, a platform exists to provide support up to phase II clinical trials, but even in some of these areas it still remains extremely limited.

Our research identified several weaknesses in the existing infrastructure for the biotech industry:

- There is a shortage of laboratories that can provide:
  - *GLP Pharmacology and Animal Testing*: Identification of structural lead (biological evaluation); in vivo activity & activity acute; acute & sub-acute genetic reproduction; pharmacology & pharmacokinetics; metabolism; toxicology
  - *GLP Analytical Services*: Analytical support; bioanalytical research; physical and chemical properties; physiological properties
  - *GMP[24] Chemical Synthesis and Biopharmaceutical Development*: Rational synthesis; formulation and stability; dosage forms (manufacturing of pilot batches)

Israel only possesses 3 GLP recognized independent laboratories (Harlan, Analyst, Makteshim Agan), but none are able to offer a comprehensive, integrated service to take a product through analytical and pre-clinical trials. So, for example, in the case of toxicology studies, companies must seek support abroad, adding an additional expense on Israel's biotech companies. It also increases the risk of losing control over the compound or missing new application opportunities by knowing more about the compound.

IX. The regulatory system for certification and clinical trial approvals needs reinforcement

The regulatory system is the necessary legal framework by which a company's products can be evaluated to ensure that they conform to the most rigorous safety standards for sale in national and international markets. These regulations will concern both the biotech companies and the Contract Research Organizations (of which there are 15 in Israel)[25] since they conduct most of the research and make the necessary applications to the national authorities.

In Israel, the regulatory system for laboratory accreditation and GLP recognition is making progress, while more resources are required for regulation for clinical trials and GMP accreditation.

GLP Accreditation and Recognition

[23] Good Laboratory Practice
[24] Good Manufacturing Practice
[25] Most of these CROs are international offices of foreign companies

Pre-clinical tests must be performed under GLP standards in GLP accredited laboratories in order to be recognized by the FDA or EMEA[26] for phase I clinical trial approval.

Under the auspices of the ILAA[27] (Ministry of Industry & Trade), the system for regulating laboratory accreditation and GLP recognition is being developed in Israel in accordance with international standards. The ILAA is set to become a signatory to the International Laboratory Accreditation & Cooperation (ILAC) Authority, and will secure recognition from the accreditation authorities of the EU and US in due course[28].

The one limitation on GLP in Israel is, therefore, purely a supply/demand issue: very few laboratories want to secure GLP recognition (possibly due to the cost of upgrading a laboratory to meet those standards) as they do not perceive a strong local demand. On the other hand, most companies go abroad to secure their entire toxicology tests from one integrated service supplier.

Clinical Trials Approval

Clinical Trials regulation falls within the auspices of the Ministry of Health's Pharmaceutical Division. For a biotechnology drug candidate, approval for a clinical trial at any phase (I-IV) must be obtained from the National Committee for Clinical Trials (NCCT) of the Ministry of Health. In most cases, biotech drugs do not have access to the special clinical trials track (available for "known risk" drugs at phases III & IV in which the approval can be obtained from hospitals' Institutional Review Boards (IRB)[29]) as they are still considered "high risk" drugs.

We identified few areas in the clinical trials process that require strengthening:

1. Application & approval procedures for clinical trials of biotech drugs
   - There is no pre-submission process between the investigator and a committee or individuals representing the NCCT, in which issues such as reviewing the required documents to submit, the additional tests to conduct prior to application, etc. are being discussed. This process can improve the chances of a successful application process.
   - The Ministry of Health find it difficult to handle approval for Phase I & II clinical trials without prior FDA or EMEA approval, and then approval takes a

[26] Europe
[27] Israeli I
[28] The EU
operations and auditors. The final evaluation is in April 2001
[29] See "*Regulation of clinical trials in Israel - recent developments*", ICON and Ministry of Health, 2000 (Israel)

Distribution of Applications for Drug Clinical Studies in 1998

Type of Trial	% of Applications
Phase I	2%
Phase II	14%
Phase III	44%
Phase IV	12%
Bioequivalence Studies	6%
Others*	22%

* Individual investigators, not companies, where the phase is not defined, such as studies comparing registered drugs

Source: Regulation of Clinical Trials in Israel, Drug Information Journal, Vol 34, 2000

further two months. Therefore, companies tend to conduct the phase I clinical trial in the US or Europe, where they get the approval, rather than to wait for further approval in Israel

2. Regulation & enforcement of clinical trials' procedures and standards (GCP[30])

There are currently no formal regulations covering clinical trials[31], only guidelines which are open to individual interpretation. Consequently, there is a lack of standardization across hospitals in the process followed for approving new clinical trials or conducting such trials.

Additionally, there is no formal audit conducted in hospitals carrying out clinical trials, either to verify adherence to the guidelines or to GCP standards in their laboratories to guarantee a high quality of service. Not surprisingly, there is also a lack of experts to conduct such audits in Israel.

As a side, but related issue, there is no formal accreditation available for clinical investigators managing the trial in the hospitals (in the US, private organization can certify the GCP practice).

Scientific Review and GMP certification procedure

The authority in charge of GMP certification is the Institute of Standardization & Control of Pharmaceuticals from the Ministry of Health. Five years ago the institute set up a unit dedicated to the biotechnology industry.

The Institute conducts detailed scientific review of the biological material and the manufacturing process and has capabilities to provide GMP accreditation. Globally there is no mutual GMP recognition between different countries, however, initial discussions have started to facilitate mutual recognition of GMP certification.

There are currently an estimated 65 new drugs in various clinical trials phases developed by Israeli companies. These drugs could potentially require scientific evaluation and GMP certification for small batches' manufacturing in view of these clinical trials. The institute does not have the sufficient human resources to address this need, given the expected demand from the industry (particularly if a system of mutual recognition of GMP is established).

Products in Israeli Therapeutic Companies by Therapeutic Area and Stage of Development, 2000

Sector	Area Portion	Total Projects	Stage of Development					
			Research	Pre- clinical	Phase I	Phase II	Phase III	On Market
Neurological	21% (24%)	16 (21)	10	1 (2)	3	1 (3)	1 (3)	
Autoimmune disorders	17% (19%)	13 (16)	4 (5)	3	1	3	1 (2)	1 (2)
Cancer	19% (17%)	15	10	2	2			1
Endocrinological	8% (7%)	6	2		1			4
Dermatology	8% (7%)	6	4	1				1
Infectious diseases	6%	5		2				3
Ophtalmological	6%	5		1			1	3
Cardiovascular	4% (3%)	3	1	1			1	
Miscellaneous	12% (10%)	9	6	1		1		
Total	100%	78 (86)	37 (38)	12 (13)	7	5 (7)	4 (7)	13 (14)
Percent		100%	47%	15%	9%	6%	5%	17%

[30] Good Clinical Practice

[31] The highest legal framework is the Public Health Regulation

General lack of resources

The interviewees have indicated that the resources available to the relevant Ministry of Health units are inadequate to provide a smooth and comprehensive regulatory system. There are simply not enough agents to approve new clinical trials in an efficient manner. The new guidelines have improved the situation, with the transfer of authority to the local IRB for "known-risk" trials easing the bottleneck. However, it is questionable whether Israel, given its size, can justify a fully fledged FDA-style authority, possessing wide-ranging expertise, to be able to review all the phase I and II applications.

Agricultural Biotechnology

Plant biotechnology is regulated by the Ministry of Agriculture under the National Committee for Transgenic Plants. This committee has only scrutinized 12 projects since 1995 and approved 2 GMOs from such trials, since the number of companies developing them is small and openness to GMOs in Europe remains low. However, if the industry develops in the future, both the resources and the system for plant biotechnology trials will need to be reviewed.

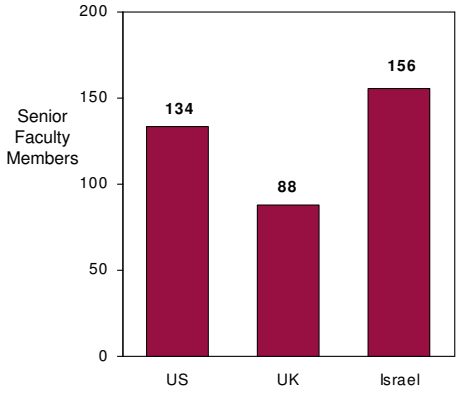
X. Infrastructure in the academia needs to be internationally competitive

As the source of the innovations for the cluster, the importance of ensuring a strong, focused and well-equipped academic research base is paramount for the long term future of the sector.

Israel has the volume of scientists and good quality science, but it needs to consider the level and type of investments required to keep pace with other leading countries in biotechnology.

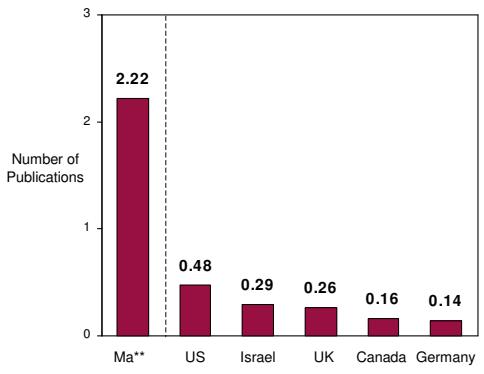
Although accurately assessing the strength of Israeli life science research on a macro level is difficult, the indicators below suggest that Israel is performing quite well relative to other industrialized nations.

Senior Faculty Members per Million Inhabitants, 1999



*Source : UK's HESA; NSF survey on research grants; American Assoc. for the advancement of science, Bureau of Labor Statistics (US) , VATAT

Publications in Leading Life Science Magazines* per 100,000 Inhabitants, 1999



* Leading magazines; Nature, Science, The Cell; ** Massachusetts
Source: Pubmed; Monitor Analysis

However, a number of concerns still remain over whether the existing research quality will endure and spread into new disciplines in the future:

- The amount of interdisciplinary research within life sciences and between life science and computer science is neither high nor organized. In an industry where interdisciplinary research is becoming increasingly important (and being promoted by foreign governments[32]), this issue needs to be addressed.

  "We (in physics) work with biologists on co-programs here because they came to ask us for help. Its all based on personal relationships. There is no support or structure to provoke it." (Academia, Israel)

- There needs to be a critical mass of scientists in a particular field to compete with scientists globally

  ". . . Post-doc scientists go to the U.S. to join labs of 30–40 specialists in their fields who are part of a network of researchers across the country. We don't have the scale for this here." (Academia, Israel)

- The level of funding for Israel's top laboratories is not comparable to those in leading industrialized countries

  "…in Israel, every researcher gets funding, but not enough. There are several stars in Israel but they don't have the infrastructure." (Academia, U.S.)

  "The research groups in the academia are too small" (Academia, Israel)

- Israel needs to ensure it is well-equipped to compete in the post-genomics era

  "*Genomics research in Israeli research institutions is in its infancy and there is a need to unite our efforts at a national level*" (Academia, Israel)

XI. Attracting foreign business investment and strengthening demand for Israeli biotech

Attracting investments from overseas pharmaceutical, biotechnology, agrochemical or other industrial companies with a need for biotechnology R&D would bring additional capital (financial and human), knowledge on management of drug development and information about customer needs to Israeli companies.

In European countries, governments have adopted several approaches to increase the attractiveness of their countries as a location for industrial R&D

Such measures have included:

- Creating focused initiatives to attract investment from foreign pharmaceutical and biotechnology companies
- Establishing call centers and providing consultants for potential users to know whether biotechnology can be applied in their manufacturing processes
- Providing grants for companies to adopt biotechnology in a novel way that could be used as a demonstration to other companies in that industry

[32] The UK's Medical Research Council has set up "Discipline Hopping Awards" – One year grants of $75k to provide short-term support to pump-prime interdisciplinary research with a view to further collaborations

E. Areas Of Recommendations

We propose to implement a 7 point program to address the challenges outlined above:

I. Define a private sector leadership headed by the IBO to work with the Government on implementing cluster initiative
   - Bring biotech on the national agenda and declare a clear vision for the industry
   - Appoint a full time project leader or executive director to lead the implementation effort
   - Form an intergovernmental task force to coordinate Government policy

II. Upgrade the physical infrastructure supporting the industry
   - Attract an international service company and support local service companies to develop integrated services and equipment in pharmacology and animal testing, analytical services and GMP pilot batches manufacturing facilities
   - Examine the needs of the biotechnology centers to preserve their capabilities in providing contract services to the industry in the specific areas where the industry utilizes the centers.

III. Support technology transfer processes in the Universities and Hospitals:
   - Increase financial and human resources to improve commercialization activities
   - Create a pre-seed funding to support final development of innovations with commercial potential to improve the odds of a successful technology transfer
   - Align IP and equity ownership rules of commercialization companies in the Universities with incubators

IV. Improve early commercialization: create a world class incubator with state of the art physical infrastructure:
   - Adapt the incubation rules to specific needs of biotech project
   - Provide access to pre-seed funding for promising projects and excellent business and management support

V. Reinforce regulatory infrastructure:
   - Provide additional resources at the Ministry of Health dedicated to serve the needs of the industry – clinical trials, evaluation, and GMP certification

VI. Implement a tracking system for industry data and set up a performance matrix, as well as map research in the academia, which may open up opportunities for enhanced collaboration between industry participants (and possibly academia)

VII. Map the infrastructure required to support research in academia:
   - Identify the resource and equipment requirements of Universities
   - Ensure educational programs are offering training to facilitate cutting-edge research in post-genomic fields

I. Define a private sector leadership headed by the IBO to work with the Government

Initiate the process by sending clear signals:

The development of a successful biotechnology sector in Israel will be complex and will require significant commitment and resources from all parties involved, industry, Government, and academia. This is the reason why the highest authorities in Israel, the Prime Minister and key Ministers, need to declare biotechnology a national priority.

This declaration could be achieved through the statement of a national vision for biotechnology, as follow:

"Create in Israel a world-class Center of Excellence in Biotechnology"

This Center of Excellence will provide access to a world-class biotech incubator with state-of-the-art infrastructure; It will benefit from the advice of an internationally recognized Scientific Advisory Board and the efficient flow of technology transfer from the academia and the hospitals

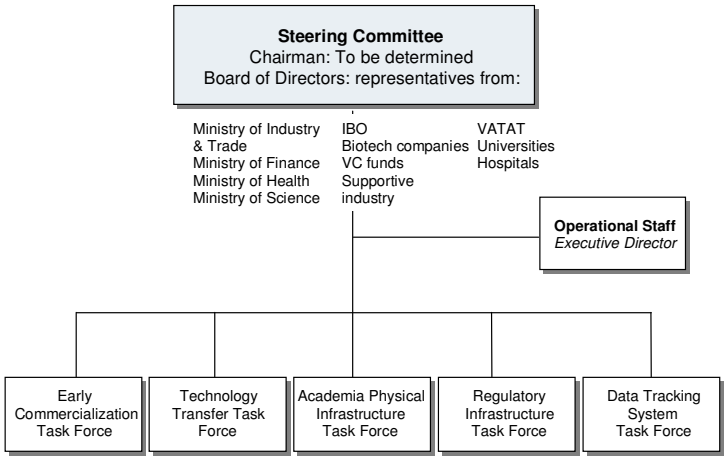
The overall objectives are to drive economic development, create jobs and position Israel in this new technology. The more detailed targets are to:

- Create 5 multi-billion value companies by 2010
- Generate $2B-$3Bn revenues from biotech companies by 2010 (and multiple by 5 service companies revenues)
- Increase employment in the sector to 10,000 - 14,000 by 2010 (versus 3,500 today)
- Position Israel as a recognized world-leader in specific biotech markets
- Provide Israel with an option to pursue future opportunities in this fast growing industry
- Enhance deal flow from the academia to the industry (x2 within 4 years)
- Develop the physical and regulatory platform to allow companies to grow

Ensure the implementation of the recommendations:

The current steering committee for the Biotechnology Strategy Project does not have the mandate to implement the above proposed 7 point program. It is critical to establish an organization that will integrate within one arena the political initiatives, the private sector leadership and other key parties involved (e.g., Universities, Hospitals).

The suggested structure is to create 5 task forces (see Appendix C for detailed organizational chart), each responsible for the implementation of a key recommendation, which would gather representatives from key leaders in their area.



All the task forces will report to a board of directors composed of representatives from the Government, the private sector (including VC funds) and other parties. The chairman of this group should be a high governmental figure.

The operational tasks (coordination and integration) should be under the responsibility of an executive director from the private sector (see Appendix D for profile).

- *Early commercialization task force (incubation and physical infrastructure)* (chairman: Chief Scientist): IBO, Chief Scientist, VC funds
- *Technology transfer task force* (chairman: University representative): IBO, Chief Scientist, VC funds, Ministry of Finance, VATAT, head of Universities, Hospitals
- *Academia physical infrastructure task force* (chairman: University representative): ministries of science, finance, industry & trade, head of Universities and Chief Scientist
- *Regulatory infrastructure task force* (chairman: Ministry of Health): IBO, ministries of health and industry & trade
- *Data tracking system task force* (chairman: Ministry of Industry & Trade): IBO, ministries of industry & trade and of finance

As new issues may arise in the process of implementing the recommendations, such as tax and legal environment or regional development, an additional task force could be created if needed.

II. Upgrade physical infrastructure supporting the industry:

Objective:

The objective of this task force is to implement the set of measures required to upgrade the research development and production infrastructure required for the industry.

Active participants:

Representatives from the following organizations have to be actively involved in the activities of this task force:

- IBO
- Ministry of Finance
- Chief Scientist of the Ministry of Industry & Trade
- Ministry of Science Culture and Sport

Recommendations

The gaps in the current infrastructure for the industry need to be filled by:

- Attracting an international service company such as Quintiles, Parexel or Phoenix International, to set up an integrated resource center, (co-located with the biomedical incubator(s)). The services should include (non-exhaustive list):
  - Pharmacology and animal testing (GLP)
  - Analytical services (GLP)
  - Chemical synthesis and biopharmaceutical development (GMP)
- Providing grants to help existing labs to update their equipment and facility (e.g., GLP accreditation) and offer fully integrated services. This could be done through existing schemes
- Examining the needs of the biotechnology centers to preserve their capabilities to provide contract services to the industry in the specific areas where the industry utilizes the centers. Some of these center provide contract services to the industry (such as the protein center in the Technion), these services and the budgetary requirements for providing them need to be specified jointly by the industry and the science ministry.

Cost for industrial infrastructure (Chief Scientist share)	**Total Cost***
One time cost: • Attract an international service company • Provide grants to upgrade existing service companies	 $5M (25% of $20M) $1M (20% of $5M)
Total one time cost	**$6M***

- The cost does not include the resources required for the biotechnology centers.

III. Support technology transfer process in the Universities and Hospitals:

Compared to the high-tech sector, Universities' and Hospitals' technology transfer companies (TTCs) are a major source of innovations for the biotechnology industry. They are also a significant source of research funding for some Universities. From the perspective of the development of a local biotech industry, it will be important to align and manage these objectives.

Objective:

The main objective of this task force is to ensure the implementation of a program to improve the resources available and the process of technology transfer.

Active participants:

Representatives from the following organizations have to be actively involved in the activities of this task force to ensure a balance of interests:

- Heads and VPs of research of Universities
- VATAT
- Hospitals conducting research
- Technology transfer companies (Universities and Hospitals)
- IBO
- VC funds
- Ministry of Finance
- Chief Scientist of the Ministry of Industry & Trade

Recommendations:

Establish a pre-seed fund to further support the development of innovations with promising commercial potential. Like most of the Universities across the world, the Israeli Universities face difficulty in commercializing under-developed technologies or products. This issue could be partially solved by the creation of a pre-seed fund dedicated to supporting late stage applied research of highly attractive projects, along with product development support.

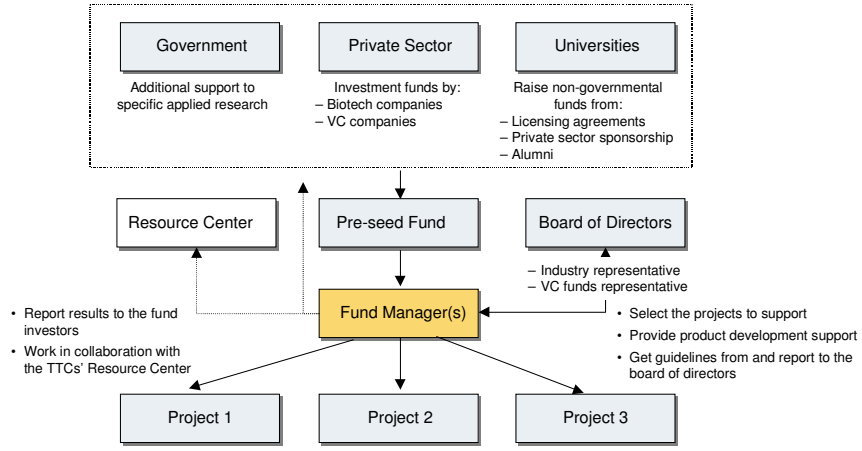
The pre-seed fund would be an additional source of funding for applied research, to conduct further analysis or final proof of concept testing, to increase the chances of patenting an innovation. Depending on the project, the financial support could range from $25,000 to $200,000 per year for exceptional projects.

The product development support should be provided by an expert in the field, who could also be the manager of the fund. He or she will provide the scientists with details on the necessary steps to follow in order to bring their innovations up to the commercialization phase (see below).

The pre-seed fund should follow the structure of the University Challenge Fund in the UK (see Appendix A for details) with some adjustment to suit the needs of the academic community in Israel. The fund will be available to life science scientists who apply for the grant to bring their innovations to the commercialization phase. The University will have to provide the equivalent of 25% of the grant and the scientist will have to respect some rules, such as the technology or product developed has to be licensed to an Israeli company or the grant will have to be reimbursed by the foreign licensee.

The pre-seed fund should be financed by the government (up to 50%), the private sector for at least 25% (industry, VC community, donators…) and the University with a matching fund up to 25% of the grant (from non-governmental funds).

The administration of the pre-seed fund and the development support provided to the scientists should be performed by an experienced product developer with strong management skills, who will report to a board of directors composed of representatives of the industry, the Universities, the government and the Ministry of Industry & Trade. This manager will work in cooperation with the TTCs to identify the most promising projects and the required additional development steps to be performed in order to commercialize the innovation.



Some Universities / TTCs are currently working independently on raising such pre-seed funding like NG Negev for the Ben-Gurion University.

Increase budges to recruit transfer agents and experts: It is critical for the TTCs to improve their internal and external marketing, the intellectual property work and licensing procedures. The government should support the Universities' TTCs to allow them to invest more resources in the following critical commercial activities:

- Internal marketing: Inform the scientists on the commercial potential of their research, support them with the procedure to patent their innovations, the potential trade-off to make and the necessary steps to go through in order to commercialize their innovations (e.g., proof of concept, number of experiments…)
- External marketing (see shared resource center below): Conduct international marketing research, identify potential partners in Israel and abroad, assess opportunity to create a start-up…
- Intellectual property protection: Use experts to prepare and submit the applications to the Patent Office in Israel or abroad
- Licensing negotiation: Conduct negotiation in the best interest of the scientist and the community

Provide financial incentives to TTCs to license technologies to Israeli companies: In order to support the development of the cluster in Israel it is critical to encourage commercialization to Israeli companies. However, it would be damaging and inefficient to impose constraints on the TTCs in this matter. The Universities, VATAT and the Chief Scientist have to develop a set of financial incentives, like the partial payment of the IP cost, to encourage licensing to local companies. They should also agree on targets for commercialization activities in Israel.

Create a dedicated fund to enable TTCs to outsource highly specialized services as and when necessary: This fund will be provided to enable TTCs to hire external companies for expert IP management or market & business assessment services for different biotech projects (see appendix E for fund overview)

Harmonize procedures and increase transparency: Ensure the procedures to license out or sign a frame agreement are harmonized and transparent across the TTCs. This will better facilitate dialogue and negotiations with potential partners.

Align equity and intellectual property ownership rules with incubators and other private sector initiatives: In order to effectively integrate the various schemes and programs and leverage their activities, the rules of the TTCs and the incubators should be consistent, especially regarding scientists or MDs' equity ownership. There are great potential synergies between the two entities (e.g., access to knowledge versus access to funding, management support, connection with VC community) but their current divergence in operational rules do not allow potential start-ups to capture them.

Furthermore, the ownership rules should be revised at a national level for all public or semi-public scientists, professors and MDs, in order to retain the most creative ones and attract new commercially-minded scientists into academic and hospital research. As it stands today, MDs cannot by law own equity in a start-up based on their research and discovery, thereby limiting innovation and pushing some of them to quit their institution.

Implement a national tracking system to assist TTCs' commercialization activities: In cooperation with the data tracking system task force, the Universities, VATAT, the Ministry of Finance and the Chief Scientist need to ensure proper indicators are defined (see Appendix I for examples) and data is available on a consistent basis for all TTCs over time. This is necessary to monitor performance, assess the impact of new measures and incentives (and to adjust them if required).

Estimated budget to improve technology transfer process:

The additional budget required to finance the pre-seed fund should be $10M per year, of which the financial incentives for the TTCs to license out to local companies should be around $1M a year.

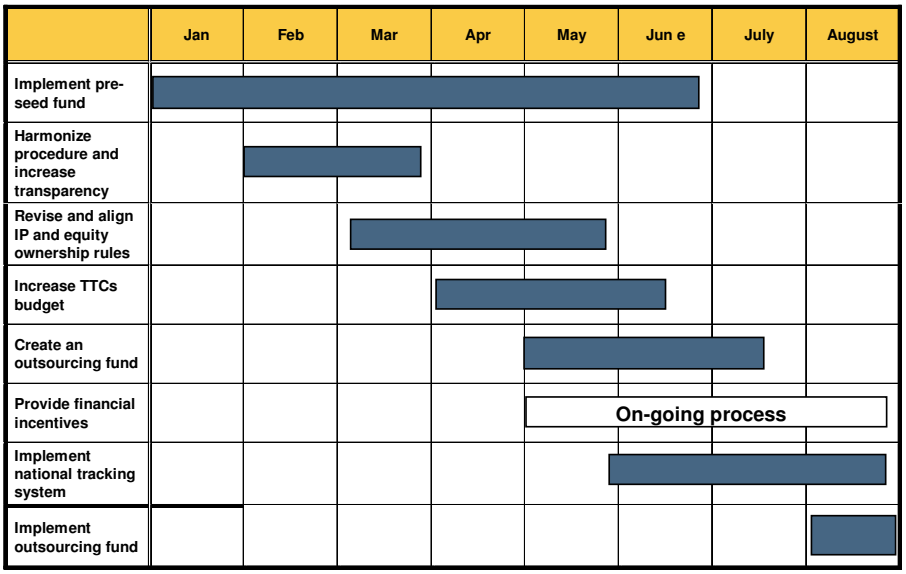
The amount to be made available to the TTCs to upgrade resources and outsource key activities will range between $2M to $3M per annum, based on TTCs using external agents for the majority of the current life science patents filed and projects screened.

	Cost per year	Total Cost over 4 years
• Pre-seed funding		
• Government share	$5M	$20M
• Matching funds from Private Sector & Universities	$5M	$20M
• Upgrade resources and outsourcing Fund	$3M	$12M
Total	**$13M***	**~$52M****

* Government's share is $8M; ** Government's share is ~$32M

Suggested timeline:

Technology Transfer Task Force: Implementation Planning



IV. Improve early commercialization: create a world class incubator:

The concept of the incubation of emerging start-ups was adapted in various countries and turned out to be very successful, especially for internet companies. However, it has to be reformed to serve the specific needs of the biomedical industry, including a long development phase and expensive equipment requirements.

Objective:

Create two world-class incubators specialized in biomedical projects, with access to a state-of-the-art scientific service center with dedicated equipment, labs, technicians and a full range of pre-clinical services. These incubators will be privately owned (by one or several VC funds and/or industry companies) to ensure proper financing and access to adequate business support. The private investors will co-invest with the Chief Scientist in a fund dedicated to biomedical projects. The main objective is to establish a highly selective process to identify the most promising projects and provide them with the best financial, managerial, technical and networking support possible in order to cultivate several highly successful companies.

Active participants:

To develop these two incubators supported by a scientific service center (industry infrastructure), the following organizations need to be involved: the Chief Scientist, the Ministry of Industry & Trade, the Ministry of Finance, the IBO and the VC community.

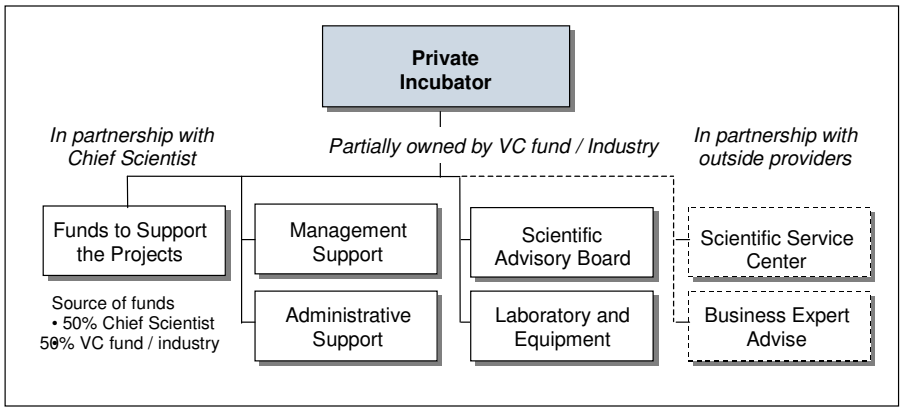
Recommendations:

Convert or create one or two new incubator(s) dedicated to biomedical projects operating at world-class standards: The Chief Scientist will need to organize a selection process to identify the best private incubator programs, from existing ones (private or public) or new ones to be created. The incubators will need to partner with one or several VC funds, and provide as a minimum the type of support described below. The public sector will then financially support the upgrading or creation of these two biomedical incubators for a maximum of 4 years (till the first wave of projects graduate) and will finance the projects run by the incubators up to 50%.

Define new operational rules and provide adequate support for biomedical projects to allow them to become viable start-up companies at the end of the incubation period (see Appendix F for details on budget breakdown).

- New operational rules:
  - Lengthen incubation period to 4 years with clear milestones every year. Companies that do not meet the pre-defined milestones have to leave the incubator
  - Increase financial support to $500,000 per project for the first two years, then $1M/year for year 3 and 4 (with 50% financed by the private sector)
  - Remove salary caps, and allow flexibility in the timing of expenses (however, salaries and expected expenses should be done according to the approved business plan)

Proposed Structure for the World-class Incubator



- Relax the operational constraints to allow the project to run as an independent company

- There will be no royalties paid to the Chief Scientist since he will own up to 10% equity in the project. Conflict of interest could raise from a dual source of revenues.

- Adequate support:
  - Create a first rate Scientific Advisory Board with business managers and academic experts in biotech from Israel and abroad. This board will:
    - Screen and select the projects eligible for the incubator(s), based on management capabilities, strength of the innovation and commercial opportunities
    - Provide mentoring and networking support to the projects, and technical advise when required
    - Review the annual report submitted by each project about its scientific progress and assess its ability to meet its milestone for the year

    The Scientific Advisory Board members should be compensated by the incubator for their time spent with the projects (financed by the management fee paid by the projects) but not by the projects directly, to avoid any conflict of interest (i.e., members would select the projects and then get paid by them). The Advisory Board should be common to both incubators to share the cost.
  - Establish within the incubators high quality management support in marketing, business, and networking, and help the projects identify opportunities to partner, merge or structure license agreements with other projects to scale-up their company
  - Provide projects with access to a business center offering advise from local and international experts in legal, tax, IP management and strategic issues
  - Invest in a GLP lab with equipment commonly needed by companies in the biomedical sector, and staffed by 1 or 2 technicians. This will reduce the individual investment required for each project and avoid duplicate investment in common equipment
  - Co-locate the biomedical incubator with a Scientific Service Center dedicated to the sector (see details below)

Define new rules and objectives for the two incubators themselves:

- They should be privately owned: up to 10% equity should be reserved for the incubator management and up to 10% to the Scientific Advisory Board
- Up to 4 new projects are to be financed by the co-fund each year
- Approximately 16 companies can be housed by one incubator at a given time
- If an incubator is not fully utilized by new projects, spare space can be rented to outside start-ups to provide them with access to management services and shared equipment. They will pay a service fee, like other projects, and give 10% equity to the incubator
- The management (at least 2 managers for 16 projects) will need a relevant science background and experience in the industry. They will receive 2% equity in the project they support plus part of the 10% incubator equity reserved for management (see above)
- Agreements should be negotiated with the TTCs from Universities and Hospitals about IP ownership and the scientist's involvement in the event of a start-up

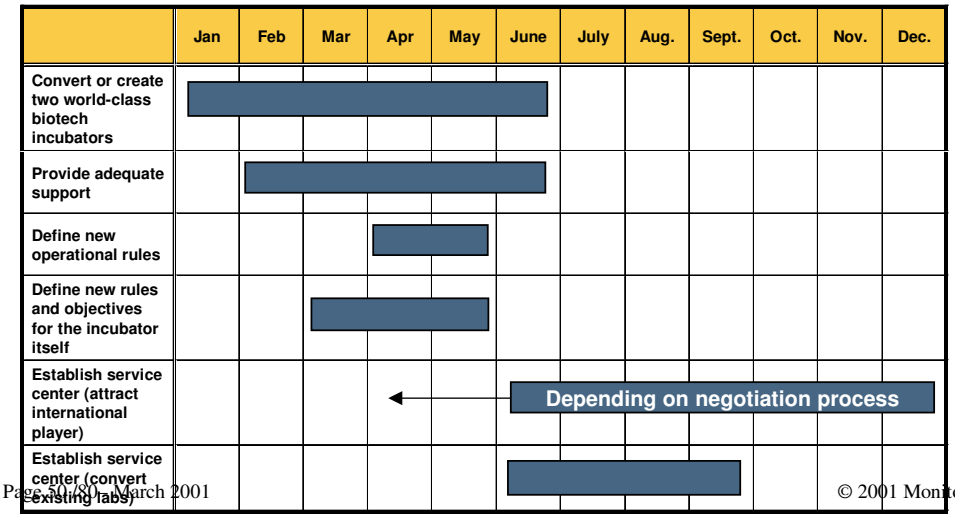
Provide subsidized access to a scientific service center located nearby the incubators to offer highly specialized services to the incubator projects.

Estimated budget to improve early commercialization

Cost for two incubators (Chief Scientist share)	**Cost per year**	**Total Cost over 4 years**
One time cost: • Establish the incubator (facility, equipment, operational cost) in cooperation with the VC fund • Recruit and finance the advisory board		2 x $2M $1M
Total one time cost		**$5M**
On-going cost: • Grants to projects (assume 4 new projects per year per incubator)	2 x $5M	2 x $20M
Total on-going cost	**$10M**	**$40M**

Suggested timeline

Early Commercialization Task Force: Implementation Planning



*V. **Reinforce regulatory infrastructure:***

Objective

The main objective is to strengthen the resources dedicated to serve the needs of the industry, for clinical trials, evaluation and GMP certification.

Active participants:

The task force should regroup representatives from the Ministry of Health itself, from the Pharmaceutical Department and from the Institute for Standardization and Control of Pharmaceuticals (ISCP).

Representatives from the ethical committees of the hospitals (IRB) and from CROs in Israel should be invited to participate as well

Finally, it should include representatives from biotech companies and, if possible, observers from the FDA/EMEA.

Recommendations:

Add resources to the ICSP to allow it to meet the expected demand for GMP certification. The task force should study the opportunity to increase the resources of the Institute for Standardization and Control of Pharmaceuticals dedicated to serve the needs of the biotechnology industry.

Provide information of the various certification processes related to pharmaceuticals and biotech products, mostly GLP and GMP. The two authorities responsible to the different types of certifications should be able to allocate resources to educate and communicate with the industry on the needs and the process to obtain GLP certification for their research labs and GMP certification for their production processes.

Revise and clarify the guidelines and requirements for the hospital ethics committees that manage the clinical trials. Since end of 1999, the new regulatory guidelines delegate the responsibility of clinical trials authorization to local Institutional Review Boards (IRB) for "known risk" products. They transmit any other applications to the Ministry of Health for approval by the National Committee (see section D: Key issues and benchmark). However, there are still gaps in the new regulations regarding:

- Clear guidelines to be followed for the IRB to authorize and manage clinical trials – there is a need for greater national standardization across local IRBs to avoid discrepancies in the recommendations' application
- Obligation for hospitals' internal GLP labs to conduct the required tests in accordance with the GCP standards and the FDA or EMEA requirements
- Capacity to audit the compliance with GCP standards to enforce their application

For the phase I clinical trial, study the opportunity to create a special bridge with the FDA or to add resources at the Ministry of Health, to facilitate the approval of clinical trials. Due to the size of the market here in Israel and lack of resources, it is neither possible nor desirable to duplicate the FDA's activities locally. However, the task force should study the opportunity to either develop in coordination with the

FDA and the EU a fast track for Israeli products in the context of international cooperation, or add dedicated resources at the Ministry of Health for this task.

Increase the communication and the transparency around the procedures to obtain clinical trials or new drug approvals and to secure accreditation. The task force should ensure the various institutions increase the communication regarding their activities:

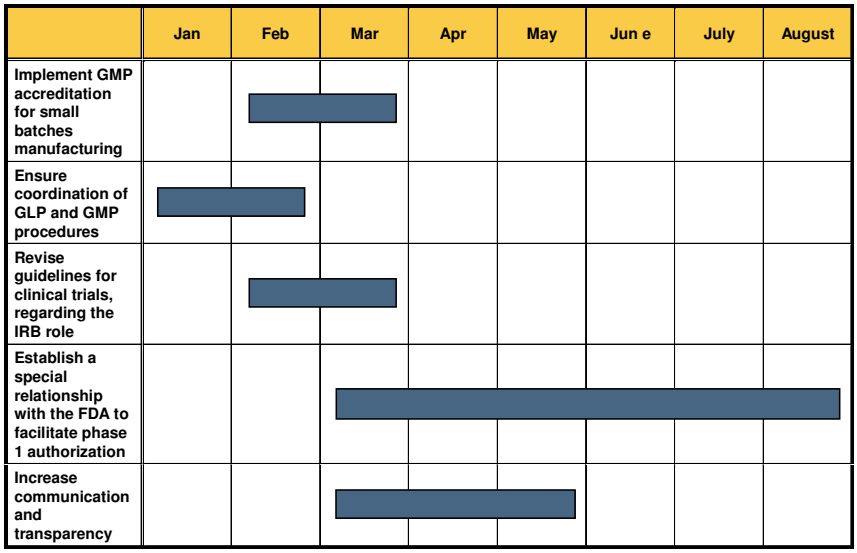
- The biotech companies or their representatives (CROs) would benefit knowing from the department of pharmaceuticals in the Ministry of Health the meeting schedule of the National Committee for Clinical Trials (NCCT), and the requirements to approve a clinical trial. The new communication plan could include the establishment of a pre-meeting between the applicant and the NCCT to discuss its requirements to approve the application
- Another source of transparency would be to explain the requirements and procedures to obtain GMP accreditation for new drugs manufacturing when conducting clinical trials, as this is not well-known among scientists and new entrepreneurs

Even if budget are allocated, the Ministry of Health may find it difficult to hire the highly skilled personnel it needs without being able to offer competitive compensation. The task force should examine the options open to the Ministry to increase its flexibility in setting competitive compensation levels to attract the personnel it needs.

Estimated budget to reinforce regulatory infrastructure

The cost of reinforcing the regulatory infrastructure should be determined following a dialogue with the industry and the selection of the preferred option for phase I approval. ***Suggested timeline***

Regulatory Infrastructure Task Force: Implementation Planning



VI. Implement tracking system for industry/academia data & performance matrix:

A key aspect of implementing new programs and policies is to assess their real impact and performance on the wealth creation and well-being of people. This requires a systematic process to collect, analyze and transmit information on various indicators. Such a system does not exist in Israel, especially for a knowledge-based economy.

> *"The system-wide view of the Innovation Economy* [set of indicators in various sectors in Massachusetts] *enables stakeholders to look at the performance of the economy and its underlying structure and dynamics. The Innovation Economy indicators tell a story about how well innovation resources are being turned into tangible results for people and business. This approach makes it possible to identify early warning signs of weakness in the innovation process and in the resources that this process translates into high-performance results*" — The Massachusetts Technology Collaborative, 1999

In addition, by tracking and mapping the research interests of the industry, new opportunities for networking and collaboration could be revealed and then exploited.

Objective of the task force:

Define the objectives and the needs of such a tracking system to identify the scope and type of system to implement.
Audit and benchmark various ministries and industry institutions to identify what matrices need to be measured, which entity can measure them, how and with which frequency to collect data and finally what is the most appropriate delivery vehicle.

Active participants:

- IBO
- VCs
- Ministry of Industry & Trade
- Ministry of Finance
- Bureau of Statistics

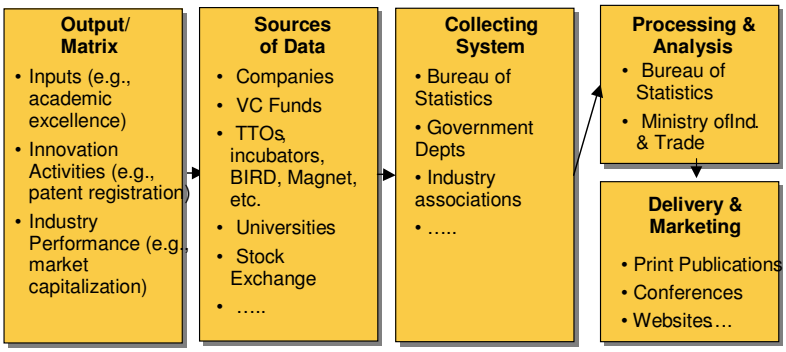
Recommendations:

Conduct working sessions, internally and with members of other task forces, to identify the following information:

- The relevant matrices to be measured in each area of the recommendations (see appendix I for examples)
- The institutions or organizations generating the raw data (or not if they do not exist yet)
- The organizations which are best positioned to collect the data and create the matrices. They should also define the frequency with which to collect the data (every month, twice a year, annually…)
- The type of systems to be implemented in order to collect the data and ensure the flow of information (e.g., create a reporting system or a database, conduct surveys, sample several companies…)
- The audience and users of the matrices for which they need to be made available

Process of Collecting, Collating and Analyzing Data

Define Why & For Whom is the Data Being Collected



Review the technical feasibility and estimate the cost of implementing new systems to collect the data. The cost can include marketing agency fees to conduct survey, computational time, edition of reports…

Design the systems to collect the data and implement them.

Form a group (potentially from the members of the task force) that will be responsible each year for:

- Collecting the data and analyzing them
- Producing a report on the trends and evolution of the indicators/matrices

Using the matrices, and other sources of information, the members of the Industry Leadership Organization should adjust the policies and the recommendations to continuously improve the processes in the biotech cluster.

Estimated budget to implement tracking system

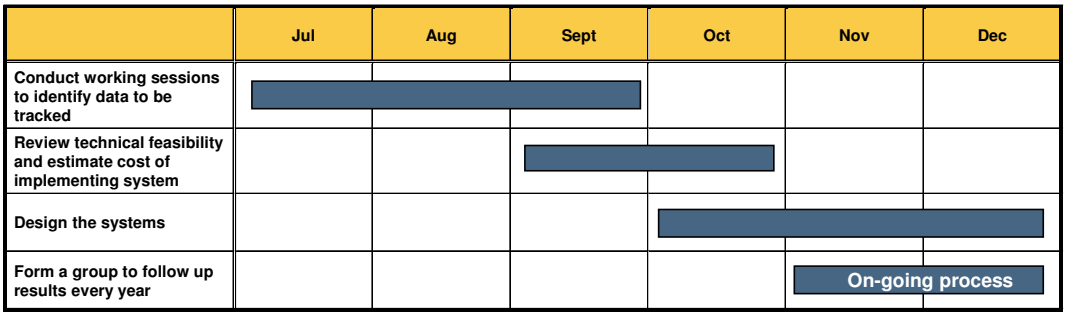
The cost of implementing a tracking system is directly correlated with the number and type of matrix and the complexity of the systems required. It is, clearly, also dependent on the matrices already in existence.

Due to the necessity of tracking the data that will be identified by the task force, each organization or institution responsible for generating the data should bear the cost of producing the data as it should be part of their tasks to do so.

The operating cost of the task force itself should be fairly low (around $50,000) and only cover the logistics expenses of the participants.

Suggested timeline

Tracking System Implementation Task Force: Implementation Planning



VII. <u>Map infrastructure needs to support research in academia:</u>

The analysis of the infrastructure needs in the academia was not within the remit of this study, which focused on industry needs. However, this issue is an important and complex one that requires the work of a fully dedicated study to clearly identify the gaps and their impact on knowledge creation and the future position of biology science in Israel (see Appendix H for abstract of the UK study). Without an adequate infrastructure dedicated to state-of-the-art academic research in biotechnology, Israel will risk losing its position in the future of this industry.

Objective:

Assess the future infrastructure needs for life science research in each institution and from a national perspective, in order to formulate an investment plan to maintain Israel's academic excellence.

Recommendations:

The study should aim to identify:

- The specific equipment needs of laboratories for each University and from a national perspective, to ensure scientists have the appropriate resources to conduct post-genomics and cutting-edge biotech research, both basic and applied. It is critical to maintain the excellence of research conducted by Israeli life scientists
- Areas for modifying existing educational programs to provide the human skills needed for post-genomics basic research, including:
  - New academic positions in post-genomics
  - New curricula for life science students in genomics
  - Fast track Ph.D. programs
  - Inter-disciplinary programs
  - Student/researcher placements in the industry

Active participants:

All the parties involved in the financing and management of the Universities should be part of this task force. The major aspects of the future research conducted in life science by the academia have to be reviewed and actions have to be taken by this task force. The proposed members are:

- VATAT

- Ministry of Science
- Ministry of Finance
- Head of Universities
- The Israel Science Foundation
- Chief Scientist

The budgetary requirements for improving the academic infrastructure should be determined once the study has been completed.

Overall budget of the proposed recommendations:

Recommendations	On time cost	On-going cost per year	Total cost over 4 years
• Task forces creation with private sector leadership	_	$0.3M-$0.5	$1M- $2M
• Support selective applied research projects and technology transfer	$0.25M -$0.5M	Govt $8M	Govt $32M
		Private $5M	Private $20M
• Establish the bio-incubator	$5M	$10M	$45M
• Upgrade industrial infrastructure***	$6M	_	$6M
• Reinforce regulatory infrastructure	$1M	To be assessed	$1M
• Implement tracking system	_	$0.05M	$0.2M
Total cost	**$12.5M**	**$23M***	**$105M****

* Government's share is $18M; ** Government's share is $84.5M; *** Excluding investment required in biotechnology centers

F. Conclusion- Long term Objectives For Israel

Biotechnology is one of the fastest growing industries which is reshaping the structure and dynamic of the traditional pharmaceutical industry. Israel has unique capabilities, particularly a large base of academics and a strong entrepreneurial spirit. Although only a small country, the quality of its science is recognized worldwide in such areas as computer science, physics and life science. All these disciplines have strong synergies for the development of new tools and platform technologies which will lead to the discovery of tomorrow's therapeutic treatments.

Investing in biotech now will benefit Israel by giving it the option to pursue these opportunities in the future and reduce its industrial risk by diversifying into other sectors. Israel must invest today in the essential infrastructures to compete in the post-genomic era, especially basic research infrastructure and early stage commercialization.

The expected outcome of the recommendations listed above are several: assuming the deal flow from the academia to the industry will double within the next four years due to the improvement in the technology transfer system and greater support to research, Israel should aim to create 5 multi-billion value biotech companies will emerge by 2010 within an industry generating $2B - $3Bn revenues. In the meantime, the supporting industry should see its revenues multiply by 5, compared to their current level, due to the increased business. The productivity will increase, but the total employment in the sector should be 10,000 - 14,000 by 2010 (versus 3,500 today across all biotech firms).

Other industries will also benefit from this set of recommendations as they affect global sectors like the technology transfer companies and the regulatory infrastructure.

Finally, and with any luck, governmental, public and private entities will appreciate the value of strong communication and coordination of policies/initiatives, and will apply them in other industries.

G. Glossary of Terms

CAGR: Compound Average Growth Rate

CNS: Central Nervous System

CRO: Contract Research Organization

EMEA: European Medicine Evaluation Agency

FDA: Food and Drug Administration (USA)

GCP: Good Clinical Test Practice

GLP: Good Laboratory Practice

GMO: Genetically Modified Organism

GMP: Good Manufacturing Practice

IBO: Israeli Biotech Organization

ILAA: Israeli Laboratories Accreditation Authority

ILAC: International Laboratory Accreditation & Cooperation

IP: Intellectual Property

IPO: Initial Public Offering (first introduction on the stock market)

IRB: Institutional Review Board (hospital ethic committees)

NAT: Nucleic Acid Probe Testing (diagnostic tool)

NCCT: National Committee for Clinical Trials

PDA: Parental Drug Association

POC: Point of care(diagnostic tool)

TIM: Technion Institute of Management (Israel)

TTC: Technology Transfer Company of Universities or Hospitals

TTO: Technology Transfer Office of Universities or Hospitals

VATAT: Planning and Budgeting Committee (Council of Higher Education)

VC funds: Venture Capital funds

H. List of interviewees

Companies:
- Agis, Mory Arkin
- CellStain, Dr. Dan Gelvan
- Compugen, Lior Ma'ayan and Dr. Ron Pinter
- D-Pharm, Dr. Yaffa Beck
- Harlan Biotech Israel, Dr. Nathan Ezov
- Harrison Clinical Research Israel, Dr. Nira Garty
- Icon, Ran Frenkel
- IMBM, Zvia Agur
- IMI (TAMI), Gilead Fortuna
- Insight, Naim Tamari and Deror Melamed
- Interpharm (Serono), Dr.Ezra Ouziel
- Makhteshim Agan Industries, Alex Mogle
- Merck, Sophie Kornowski
- Millennium, Dr. Yigal Koltin
- Orgenics, Emanuel Hart
- PCI, Karen Ginsbury
- Peptor, Dr. Yoram Karmon
- Pfizer, Dr. Ella Tenenbaum-Koren
- Pharmos, Haim Aviv
- Sigma-Aldrich, Dr. Charles Hexter and Dr. Moshe Rashi
- Teva, Anat Eitan and Dr. Irit Pinchasi
- Teva, Dr. Aaron Schwartz
- Teva, Dr. Yehudah Liveneh (legal issues)
- XTL, Dr. Martin Becker

VC funds:
- Apax, Amos Goren
- Biomedical, Prof. Benad Goldwaser, Dr. Rosette Becker and Ram Waisbourd
- Biotech HAM, Prof. Tolo Friedlander
- Evergreen, Dr. Ronit Bendori
- Koor, Einat Wilf (venture capital)
- Medica Venture Partners, Prof. Eli Hazum and Dr. Ehud Geller
- Medabiotech, Jeremy Lok and Willem Hazenberg
- Mor Yisumm, Prof. Pnina Fishman
- Nesua Zanex, Ag-tech, Yoav Millet
- Pamot, Ariel Landau
- Rad data communication, Zohar Zissapel
- Yozma Management, Yigal Ehrlich

Other private sector:
- Reinhold Cohn & Partners, Dr. Ilan Cohn, patent attorney
- Mark Friedman, patent attorney
- Ernst and Young, Yoran Wilamowski and Yifat Adoram
- Ilan Kuziatin

- EagerBio, Prof. Max Herzberg

Academia:

- Ben-Gurion University, Prof. Avishay Braverman (President)
- Ben-Gurion University, Prof. Shoshana Arad (instit. for applied bioscience)
- Ben-Gurion University, Prof. Zamik Rosenwaks (VP and Dean for research)
- Hebrew University, Prof. Dani Zamir (facult. of agriculture)
- Hebrew University, Prof. Dan Gazit
- Hebrew University, Prof. Hermona Soreq (Molecular Biology)
- Hebrew University, Prof. Ilan Chet (VP for research)
- Tel Aviv University, Prof. Yair Aharonovitz (VP and Dean for research)
- Weizmann Institute, Prof. Benny Geger (Dean)
- Weizmann Institute, Prof. Doron Lancet (Human Genome Center)
- Weizmann Institute, Prof. Elisha Mozes (Department of Physics)
- Weizmann Institute, Prof. Michal Schwartz (Chief Scientist of Proneuron)
- Weizmann Institute, Prof. Michel Revel (Chairman of NBC)

Technology transfer companies :

- Kidum (Volcani Institute), Dr. Itamar Glazer
- NG Negev, Reuven Sadeh and Dr. Ora Horovitz
- Ramot, Dr. Ben-Zion Rubinfeld and Shmuel Orenbuch
- Technion, Avishai Tzur
- Yeda, Prof. Orgad Laub
- Yissum, Reuven Ron

Public sector:

- Council for Higher Education, Prof. Nehemia Levtzion
- Israel Academy of Science and Humanities, Prof. Jacob Ziv
- Israel export institute, Yaachov Nadborny
- Israel Science Foundation, Prof. Paul Singer
- Israeli Biotech Organization (IBO), Zachi Berger and Limor Lastigzon
- Israel Lab Accreditation Authority, Dr. Orna Dreazen
- Manufacturers Association, Yossi Arie
- Ministry of Agriculture, Arieh Maoz (transgenic plants)
- Ministry of Agriculture, Prof. Dan Levanon
- Ministry of Finance, Yoel Naveh and Gadi Levin
- Ministry of Health, Institute of Inspection and Regulation, Dr. Rachel Karpel and Dr. Ofra Exelrod
- Ministry of Health, Osnat Luxenburg
- Ministry of Industry and Trade, Tal Govrin
- Ministry of Science, Prof. Hagit Messer-Yaron
- NBC, Dr. Talia Ben- Neria
- Patent office, Moshe Goldberg and Bernard Crammer
- US/Israel Science & Technology, David Wapner
- VATAT, Shlomo Herskovic and Shlomo Grossman

Hospital:

- Hadasit, Dr. Raphael Hofstein
- Hadassah Hospital, Marta Rosen
- Hadassah Hospital, Prof. Eathen Gallum (The Institute of Gene Therapy)

- Sheba Medical center, Dr. Arie Orenstein

Government programs:
- Incubator program, Rina Pridor
- Bio Tech at HiTec, Yirmi Egert
- Naiot, Limor Sandach
- LN Innovative Technologies, Eyal Zioni
- Rad Ramot, Dr. Jacques Peretz
- Magnet program, Ilan Peled
- Bird Foundation, Dov Hershberg

Foreign interviews:
- "Prescribe UK" Initiative, Invest in Britain Bureau, UK
- Babraham Institute, David Hardman (head of commercial affairs), UK
- Biotechnology & Biological Science Research Council, Mary Hutchinson, UK
- BioWise, Karen Folkes, Deputy Head, Dept of Trade & Industry, UK
- Cambridge University, Dr Richard Jennings (CEO - TTO), UK
- Imperial College Company Maker Ltd, Dr David Holbrook (CEO -TTO), UK
- Imperial College Innovations, Patricia Latter (technology executive & head of marketing -TTO), UK
- Oxford, Dr David Baghurst (managing director of BioBusiness Centre and Oxford BiotechNet), UK
- Oxford, Pete Hotten (life science executive of Isis Innovations - TTO Oxford), UK
- Southern Bioscience Initiative, Margaret Parton, Project Leader, UK
- UK Biotechnology Financial Advisory Service, Dr Barry Burles, Director, UK
- Harvard Medical School, Jeffrey Labovitz (head of technology transfer office), USA
- MIT, Tom Ittleson (biotech technology transfer officer) and Karen Rivard (Counsel), USA
- Photonic center in Boston University, Dr. Robinson (head of corporate relations), USA
- Stanford, Katherine Ku (head of technology transfer office), USA
- Prof. Yossi Schlezinger, USA

I. Bibliography

Market Review:

- A developmental German state? Explaining growth in German biotechnology and venture capital, K. Adelberger, 1999
- Benchmarking the competitiveness of biotechnology in Europe, EuropaBio, June 1997
- BioBusiness trends, Eastern region biotechnology initiative, UK, 1999
- Biopesticides, BioPortfolio 1999
- Biotech index and Nasdaq index, Nasdaq, www.nasdaq.com
- Biotechnology industry annual report for 1998 and 1999, Ernst & Young,
- Biotechnology state of the industry report, BioWorld, 2000 (USA)
- Developments in new biotechnology firms in Germany, M. Sharp, Technovation, 1999
- European life science 6th annual report, communicating value, Ernst & Young, 1999
- European life science 7th annual report, evolution, Ernst & Young, 2000
- Genome valley report, DTI, 2000
- Germany's biotechnology takes off in 1998, Ernst & Young, 1998
- Global review of commercialized transgenic crops, ISAAA, 1999
- Impact of industry concentration on innovation in the US plant biotechnology industry, M. Brennan et al., 1999
- IMS Health, Data: www.imshealth.com
- Industry Canada, data on Canadian market: www.strategis.ic.gc.ca
- Journal of commercial biotechnology, volume 6, 2000
- Market potential of agriculture markers, BTG Plc, www.btgplc.com
- Massachusetts biotechnology directory, 2000 edition (USA)
- Merrill lynch, analyst reports
- North West biotech development study, Government Office for the North West, UK, June 1998
- Report on functional food, Euromonitor international, June 2000 (USA)
- The future role of pesticides in US agriculture, The National Academy of Sciences, 2000 www.pnas.org
- The genomics industry, Dan Rauscher Wessels, 1999 (USA)
- The market for biopesticides, BioAnalysis, 2000
- The pharmaceutical industry into its second century: from serendipity to strategy, Boston Consulting Group (BCG), 1999 (USA)
- Therapeutic product markets, Frost & Sullivan
- Therapeutic proteins 1999, Datamonitor, (June 2000)
- World agriculture biotechnology, GMOs to 2004, Freedonia, 2000
- Biotechnology for Clean Industrial Products & Processes, Organization for Economic Cooperation and Development Report, 1998 (USA)

Academia:

- Senior faculty members, research expenses, number of students, Committee of Higher Education, (1998/1999)
- The Israeli Bureau of Statistics (1999), www.cbs.gov.il
- Science publications by country, PubMed,www.ncbi.nlm.nih.gov/entrez/query.fcgi
- Biotechnology and Biological Sciences Research Council (BBSRC), UK
- European comparison of public sector research systems, J. Senker, University of Sussex, Sept 1999
- Higher Education Funding Council, UK
- Higher Education Statistics Agency, UK
- Imperial College annual report 1999-2000, Imperial College London, 2000, UK
- Manchester University's School of Biological Sciences, UK
- Oxford University annual review 1998-9, Oxford University, 1999, UK
- Oxford University's Institute of Biochemistry, UK

Israel Company data:

- Biotechnology in Israel 1999 & update for 2000, National Biotech Committee Israel
- Company database, Harry Langbeheim, Private biotechnology consultant (1999/2000)
- Company press releases (2000), Haaretz, Globes, TheMarker
- Company Websites
- Incubator program, rules and overview: www.incubators.org.il

Regulatory environment:

- FDA data:
  - General site (new drug approval, GMP accreditation, GCP standard…): www.fda.gov
  - Center for biologics evaluation and research: www.fda.gov/cber/ind
- Laboratories compliance for GLP and GMP, PDA, (USA) www.labcompliance.com
- Patent office statistics, Ministry of Justice (Israel)
- Patent statistics worldwide, World Intellectual Property Organization,: www.wipo.int
- Regulation of clinical trials in Israel - recent developments, ICON and Ministry of Health, , 2000 (Israel)

Technology Transfer Offices:

- AUTM (Association of University Technology Managers) www.autm.net
  - Licensing survey 1998
  - Licensing survey 1999
  - Technology transfer offices websites

- A tutorial on technology transfer in US colleges and Universities, Council on Governmental Relations (COGR), 2000 (USA)
- Building State Economies by Promoting University-Industry Technology Transfer, National Governors' Association, 2000
- Industry-Academia Links in the UK, Higher Education Funding Council for England, December 1998
- Knowledge & Technology Transfer in Germany, Federal Ministry for Education & Research, Oct 2000
- Technology Transfer in the UK Life Sciences, Arthur Andersen, Oct 1998

Other Sources:

- Bioguide – Regulation, information and support for biotechnology in the UK, DTI (No date of publication)
- BioIndustry Association (UK's Biotechnology Trade Association)
- Biotechnology mentoring & incubator challenge guidelines, DTI, August 1999
- Boosting innovation – The cluster approach, OECD Publications, 2000
- British Venture Capital Association, UK
- Contact Canada, www.contactcanada.com
- DTI (& Office of Science & Technology), UK
- Foresight
- House of Commons select committees on science & technology, UK
- Innovation, UK Department of Trade & Industry, 2000
- Inventory of public biotechnology R&D programmes in Europe, national reports, EU Commission, 1999
- Manufacturing for biotechnology, early stage biopharmaceuticals manufacturing, a report to the department of trade and industry,1999 (UK)
- Medical Research Council, UK
- Money for Growth: The European technology investment report, 1999, PwC
- Pharmaceutical researchers & manufactures of America, http://www.phrma.org
- Recombinant Capital: www.recap.com
- Reuters
- Scotland's biotechnology – A framework for action, Scottish Enterprise, 1999
- Theta Corp (July 1997)
- UK biotech cluster, Lord Sainsbury's report, August 1999
- Wellcome Trust, UK

APPENDIX

Appendix A

University Challenge Fund in the UK

Objective

"To enable Universities to access seed funds in order to assist the successful transformation of good research into good business". Funds are used for: financing access to managerial skills; securing or enhancing intellectual property; supporting additional applied R&D; construction of a prototype; preparation of a business plan; covering legal costs, etc.

Main Success Criteria for the Funds given to Universities

To increase the number of ideas, originating in Universities, which are developed to the stage that they warrant or are able to attract funding through existing channels (e.g., VCs). Success is measured by: (a) an increase in the number of deals with venture capitalists or business angels; (b) a larger number of licenses with existing companies.

Applying and Rules for the Funds

Universities apply through an application form to the Department of Trade and Industry, detailing the fund size and their qualifications for UCF funds (see Annex B). Universities must be able to raise 25% of the total fund from external contributors (e.g., industry). There was no maximum UCF grant size, but nothing above $7.5m was expected (nor given) by the UCF. Minimum UCF grant was $1.5m.

Operation of a University Challenge Fund

Each University is free to devise its own operational procedures and investment levels, within specified government guidelines (see Annex A for Cambridge University's UCF). These guidelines are:

- The fund is administered by an experienced fund manager, who must report to a board comprising members of relevant experience (preferably from venture capital and local business orgs). No more than 1/3 of board members can be from academia.
- A fund is free to invest more than once in a project, but the total investment must not exceed $375k
- An annual report and audited accounts must be presented to the Government's UCF Steering Committee to assess the investments, nature of projects supported, licensing & spinout income, etc.

While these funds are operated independently from TTOs, they liaise closely with them, and in one known case, the CEO of a TTO can secure up to $37k for a project if he believes in its potential.

Annex A

Cambridge University's UCF

Cambridge's University Challenge Funds can offer:

- **PathFinder** funding up to £10K to carry out market and IP assessments, plan marketing strategies..
- **Applied research funding** up to £60K to prove a concept, assess the market etc. This could lead to a licence or to:
- **Seed funding** up to £250K to set up a new company, joint venture or partnership
- Close liaison with the Wolfson Industrial Liaison Office (Cambridge University's TTO) and the Cambridge Entrepreneurship Center to ensure you get the best and **fullest support**
- **Competitive terms**, since most of UCF's funds do not have to be repaid

Cambridge University's Challenge Fund Board & Management Team:

Executive Board:

- Chairman: Sir Alistair Morton, Chairman, Shadow Strategic Rail
- Amadeus Capital Partners
- Director, Institute of Biotechnology
- Microsoft Research
- Treasurer of Cambridge University
- Director, Babraham Institute

Advisory Board:

- Chair: Professor Air Alec Broers, Vice Chancellor of Cambridge University
- Senior VP of Discovery, SmithKline Beecham
- Director, Ogden Securities
- Senior City Trust & Charity Lawyer
- Chairman, Glaxo-Wellcome
- Executive Chairman, Morgan Stanley Group

Management Team

Manager of Fund: William John Matthews FCA BA(Econ)

Fund Manager of the Cambridge Quantum Fund (1998-1999); Director of Team Consulting (1988 to present); Finance Director TI Research at Hinxton (1987-1988); Director of Sinclair Research (1982-1987); Management Consultant Price Waterhouse in Canada and the USA (1975-1982)

Technology Manager: Dr Nick Slaymaker

After reading Natural and Electrical Sciences and gaining a First Class Honours…, he held several marketing and management jobs in industry before being a founding

member of a Venture Capital backed technology transfer company that had special rights to MOD research……

Example investment by Cambridge University's UCF

The Challenge Fund is making a Pathfinder investment of £10,000 in a project to take forward a promising advance in integrated circuit technology. The ideas have been developed by a professor and a lecturer in the University of Cambridge Engineering Department. The devices as envisaged could have wide ranging application in micro electronics . The Challenge Fund money will be used to protect the intellectual property and to fund a technical and market study. If these prove out, the project should proceed more rapidly than would otherwise have been the case. As Nick Slaymaker, the Challenge Fund Technology Manager said " We can back promising ideas at a very early stage. We hope to continue to support this project with more substantial funding in the coming months. This could prove to be an exciting development of which the Challenge Fund is proud to be part."

Annex B

Portion of Entry Form to Government's UCF Competition, UK

This part of the entry form should not exceed six sides of A4 using a normal, easily legible typeface. It should describe your proposals for a seed fund. Part 2 should include sections with the following headings (in the order shown) and content. Each section should start on a new side.

6. Strategy (one side)
Overview of the strategy to be adopted by the seed fund - flow and selection of projects for funding, decision process, types (e.g. loan, equity stake), uses (e.g. research, prototyping, IP protection) and sizes of investments, monitoring of investments, exit strategy, etc.

7. Management and Resources (two sides)
Explain the proposed arrangements for the following aspects:

- relationship between the seed fund and the University (Universities and other partners
  in the case of a collaborative bid);
- expected membership of boards/committees/advisors and advisory groups/etc;
- fund manager; (profile of person who will be sought, objectives to which
  he/she will work, full/part-time. It is not necessary to name an individual at the
  outline bid stage)
- process for deciding on investments;
- resources available, e.g. IP expertise, contacts relevant to gaining funding beyond
  the "seed stage"
- financial control.
- reporting

8. Projects for funding (one side)

Give examples of projects which have arisen within the University(ies) within the last three years and which would have been candidates for University Challenge seed funding had the fund existed. Indicate which of these projects are still candidates and, if not, what happened (e.g. they were funded from another source, or they were not funded at all).

9. Experience of commercialization (one side)
Give examples of research originating from the applicant(s) which has been exploited to illustrate the applicant's case for having a seed fund - quality of research ideas, understanding of the commercialization process, etc.

Discuss the approach which will be taken in the case of successful projects which need investment beyond the seed stage. For example provide evidence of established contacts with sources of further investment, e.g. venture capital funds, business angels, existing companies.

10. Funds flow (one side)
Explain the proposed arrangements for the following aspects;

- investment of seed funds prior to use for the objectives of the fund; and
- estimated number and size of investments which it is expected will be made each year.

PART 3 - This part of the entry form is designed to help evaluate the effectiveness of the University Challenge Fund by collecting baseline data on the exploitation of University research outcomes.
Separate sheets should be completed for each institution if the entry is a collaboration.

Licences/sales/options - numbers

	Number of licences/options executed	
	1995/96	1996/97
Excluding software		
Software		

Licences/sales/options - income

	Gross income to institution from all licences, sales, options	
	1995/96	1996/97
Excluding software		
Software		

Patents - filed by institution

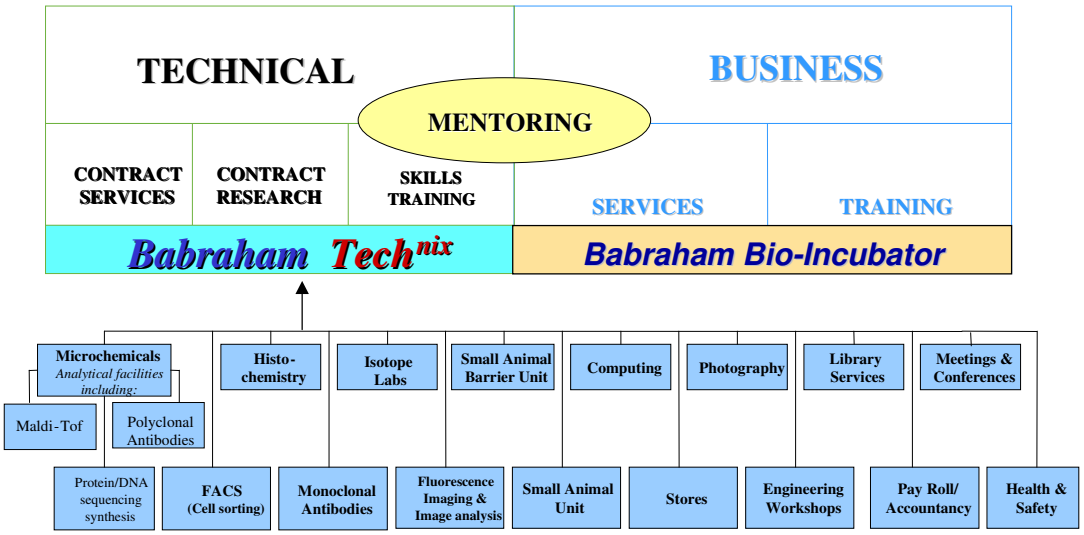
	Total UK patent applications filed[1]	**New UK patent applications filed[2]**	**UK patents granted**
1995/96			
1996/97			

Patents - filed by others with institution staff named as inventors

List of Spin out companies

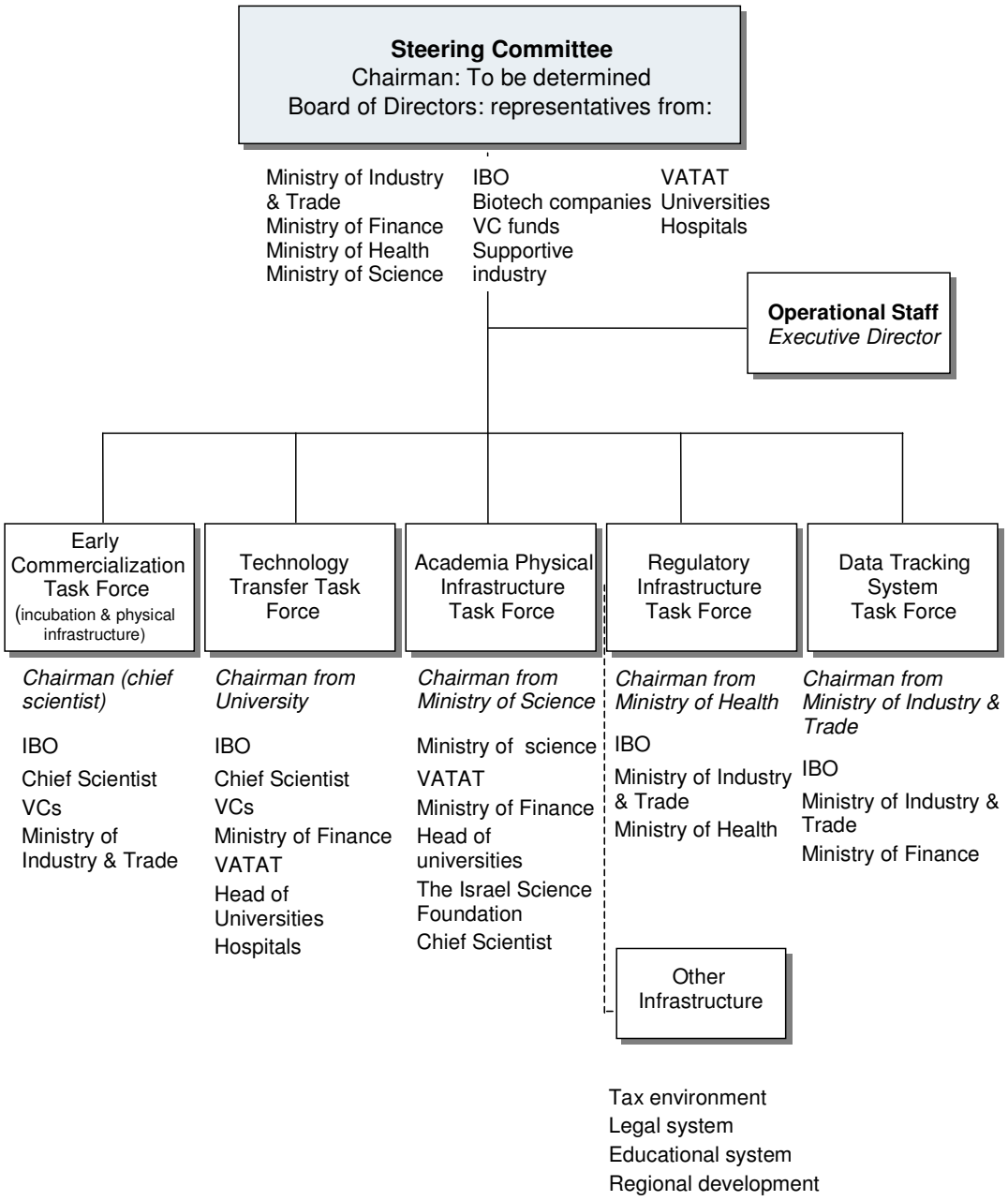
Appendix B

Babraham Bio-incubator in the UK



Appendix C

Implementation Task Force – Proposed Organizational Structure



Appendix D

Profile of the Executive Director

The Executive Director will serve for a maximum of two years, when all the recommendations should be implemented.

The responsibilities and duties of the Executive Director shall be:

Main Functions

- To see, on behalf of the Steering Committee, to the faithful execution of the decisions and recommendations, and report thereon to the Steering Committee on a regular basis or when required
- To be the official spokesman for the Steering Committee in:
  - Interaction with the various task forces' members
  - Other Government entities
  - Industry fora (including with major pharmaceutical companies)
- To set up ad hoc working groups to support the objectives of the Group
- To manage the interactions with the Scientific Advisory Board
- To act as or appoint a Steering Committee observer in the committees and other organizations where it is granted observer status
- To determine the use and expenditure of funds of the Steering Committee, in accordance with the initiatives and purposes approved by the Group (e.g., commissioned research, consultant salaries/fees)
- To present the budget estimates for the Group

Administrative Functions

- To make decisions relative to the administrative and logistical support services for the Steering Committee
- To call the Task Forces together to perform its functions
- To preside over meetings of the Task Forces if necessary
- To prepare or supervise the preparation of reports
- To have custody of all papers referred to the Steering Committee

Profile of the Executive Director

To carryout the aforementioned responsibilities successfully, the candidate would need to have:

- At least 5 years senior managerial experience in the private sector
- Relevant business development experience, abroad preferably
- Experience in government relationship management
- Strong negotiating skills
- Previous experience as managing director of a company or not-for-profit organization
- Fluency in English and Hebrew

The Financial or Budgetary Issue

- The Executive Director will have responsibility for determining the use and expenditure of the Steering Committee and Task Forces' funds, and be accountable for the allocation of the funds to the Steering Committee Board of Directors.
- This responsibility assumes that funds will be at the disposal of the Steering Committee. The level of funding will, however, need to be determined according to the potential costs incurred by the Steering Committee.
- Such expenses might include:
    - Salary of the Executive Director
    - Contributions to all administrative support provided by the IBO Secretariat (labour & materials)
    - Employment of external agencies for market research, printing & publishing, etc.
    - Payments for logistics (e.g., international travel for Group members)

<u>The issues that remain to be addressed are:</u>

- What costs that are likely to be incurred through the Steering Committee and Task Forces' activities
- Who will meet these costs (what are the relative contributions of the IBO and the Government)

Appendix E

Recommendations: Technology Transfer Process

- Outsourcing Fund for TTCs:

  The budget allocated to this fund will be regulated to:
  - Ensure they are spent correctly; and
  - Measure the value they have added to TTCs' commercialization performance

  Funds might be allocated according to each University's record of commercialization in biotechnology, but only on condition that annual reports are submitted to the Government accounting for its expenditure, which would describe for each project the:
  - Services utilized for each project
  - Vendor used
  - Cost of the services
  - Status of the project subsequently

- Data tracking system: examples of indicators to be followed in each TTC:
  - Number of licensing agreements with Israeli companies, by sector of activities (e.g., biotech, software developers, medical devices…)
  - Number of licensing agreements with foreign companies, by sector of activities and by country
  - Level of satisfaction of scientists with services provided by TTC (survey)
  - Number of projects submitted by scientists, by discipline
  - Number of projects filing for a patent application, by discipline
  - Number of patent granted, by discipline
  - Number and cost of marketing research conducted, by discipline
  - Time to negotiate licensing agreements
  - Number of conference/formal communication engaged with scientists on patenting issues and commercial potential of research
  - Number of start-up created, by sector
  - Average amount of investment by third party in start-up creation, by sector

Appendix F

Incubator

Projected expenses to support the projects:

One incubator Grant (million$) Year	1	2	3	4	5	6	7	8
Project 1	$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00	$1.00
Project 2	$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00	$1.00
Project 3	$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00	$1.00
Project 4	$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00	$1.00
Project 5		$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00
Project 6		$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00
Project 7		$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00
Project 8		$0.25	$0.25	$1.00	$1.00	$0.25	$0.25	$1.00
Project 9			$0.25	$0.25	$1.00	$1.00	$0.25	$0.25
Project 10			$0.25	$0.25	$1.00	$1.00	$0.25	$0.25
Project 11			$0.25	$0.25	$1.00	$1.00	$0.25	$0.25
Project 12			$0.25	$0.25	$1.00	$1.00	$0.25	$0.25
Project 13				$0.25	$0.25	$1.00	$1.00	$0.25
Project 14				$0.25	$0.25	$1.00	$1.00	$0.25
Project 15				$0.25	$0.25	$1.00	$1.00	$0.25
Project 16				$0.25	$0.25	$1.00	$1.00	$0.25
Total per year	**$1.00**	**$2.00**	**$6.00**	**$10.00**	**$10.00**	**$10.00**	**$10.00**	**$10.00**
50% Chief scientist	$0.50	$1.00	$3.00	$5.00	$5.00	$5.00	$5.00	$5.00

Potential activities:

- Define the type of projects eligible for the Biomedical Incubator (i.e., type of technology or product developed)
- Prepare the tender to select the best partner for the Chief Scientist to run the incubator. It has to be accessible for existing public or private incubators who wish to apply for the program[33]
- Identify the best location for it: close to a University, attractive for an international service company and a VC company, potentially providing access to Government programs

[33] If existing incubator is selected, the new operating rules will be applied to it and the status of the incubator will need to be revised to become a private entity

Appendix G

Centers for Technologies

- The seven Technology Centers are:
    1. Protein micro-sequencing (proteomics) – The Technion
    2. Transgenic animals (including knock-outs) – Weizmann Institute
    3. Plant genomics – Weizmann Institute
    4. Human genomics – in two locations:
        - DNA sequencing, bioinformatics & biochips in Weizmann Institute
        - Mutation analysis in Hebrew University
    5. Screening for bio-active chemicals from the nature – Tel-Aviv University
    6. Gene Therapy Center - Hebrew University
    7. Bioinformatics Center - Weizmann Institute (free access to information)
- The budget for the technology centers is $270,000 a year financed by the Ministry of Science

Appendix H

Abstract of recommendations and comments from the Dearing report[34], the SBS[35] comments and the UK Life Science Committee on a similar study conducted in the United Kingdom

- *Labs and equipment:* An excellent science base is the master piece of an innovation strategy plan. The critical aspects are the funding level and the structure of this science base. The UK has suffered from a relatively poor performance at turning ideas from the science base into useful, innovative products and services that could increase the living standards and quality of life of its citizens.
  - The Government should establish as soon as possible a revolving loan fund of £400 to £500 million, financed jointly by public and private research sponsors, to support infrastructure in a limited number of top quality research departments which can demonstrate a real need
  - An adequate funding for infrastructure to support high quality research should be provided to Universities
- *Educational system:* The scientific research base is actually made up of the people who work in it. That set of individuals overlaps extensively with the set of people charged with teaching, training, lecturing and examining in the higher education system. It is thus impossible to divorce any consideration of how to sustain an excellent research base from the details of sustaining excellence in teaching and training:
  - An improvement in the career structure for research scientists, particularly for younger ones, is the single most important way in which the science and engineering research base could be enhanced
  - The institutions of higher education should, over the next two years, review their postgraduate research training to ensure that they include, in addition to understanding of a range of research methods and training in appropriate technical skills, the development of professional skills, such as communication, self-management and planning
  - The funding policies to support research should promote as far as possible, not devalue teaching
  - The improvement of the flow of skilled scientists and engineers to industry is important but facilitating communication between industry and academic institutions, for the benefice of both, is equally important. The Teaching Company Scheme works well at a junior level and might be used as a model to enable senior staff to move between academia and industry and vice versa.
- *Supporting research:* In case of research grants, the full indirect costs should be funded as an element of the grant. Where the overall budget is limited, as it always will be, a smaller amount of higher quality research is preferable to a wider spread of resources producing a larger volume of less valuable results.

[34] National Committee of Inquiry Into Higher Education report which was submitted to the Secretaries of State for Education and Employment, Wales, Scotland and Northern Ireland in July 1997
[35] SBS (Save British Science) response to the Government's consultation on science and innovation strategy

- The Funding Bodies and the Research Councils should commission a study to evaluate the funding of interdisciplinary research, including the incentives and disincentives
- The key is to facilitate movement between disciplines
- The Government should establish an Industrial Partnership Development Fund immediately to attract matching funds from industry, and to contribute to regional and economic development
- Funding for research is presently spread too thinly across many Universities. Whatever funding system is adopted should aim to place research money with the best people, wherever they may be located. Keeping the balance between core funding and grants is key.
- Public funding for research of national and international standing should continue to be available on a competitive basis

Over the last few years, the UK Government has acknowledged its neglect of the research infrastructure and set up two major infrastructure funds to address the problem:

- The Joint Infrastructure Fund ($1.2Bn over 3 years) which has been extended by the Science Research Investment Fund ($1.65Bn over 2 years)

- The Joint Research Equipment Initiative (allocated $50m in 1997)

Appendix I

Examples of Indicators by Sector that Could be Tracked

Government Support

Collected by Government

- Total funding for biotechnology R&D in academia (basic/applied)
- Total funding for biotechnology R&D by priority area
- Total funding for biotechnology programs
- Assessment of efficiency and performance of programs against expected targets
- Total grants for biotechnology companies (by therapeutic area)

Academic Excellence

Collected by Government

- Total number of scientists in life science
- Total number of research projects by genre
- Total budget of Israeli research groups
- Total number of publications in leading life science magazines

Innovation

Collected by Government

- Total number of biotech projects screened (by TTOs)
- Total number of biotech patents filed (by TTOs and nationally)
- Total number of licensing deals by TTOs
- Total number of spinouts from research institutions
- Total number of projects entering incubators
- Total number of projects graduating from incubator

Industry Performance

Collected by Industry

- Total number of companies by segment
- Total number of employees by segment
- Total sales by segment
- Total products on market and in trials
- Number of publicly quoted Israeli companies and combined Mkt Cap