FINAL REPORT

ON BIO-LINK

PROJECT

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BIO-LINK

FINAL REPORT:

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Introduction

The quality of scientific research in Europe is undisputed, but turning academic research into viable businesses requires considerable support. The entrepreneurs in the biotechnology industry are mostly scientists and researchers from academic institutions and as such, lack the business skills and experience necessary to succeed. Realizing this need, many regions have implemented specific measures to support biotechnology start- up companies. Technology incubators specializing in biotechnology (bioincubators) have become a key instrument in the fostering of the biotechnology industry.

Bioincubators offer companies the expertise and know-how they often lack. The proximity to research and academic institutions has been noted as a characteristic of the biotechnology industry, since it is very dependent on a strong scientific base. The regional dimension of the biotechnology industry is therefore very dominant and the bioincubators act as an integral unit of this regional innovation system. The experience of the incubators is mostly with regional actors. The development of companies operating within one of these incubators is therefore more dependent on regionally-based capabilities. However, in today's global economy, especially in knowledge-based fields such as biotechnology, start-ups are required to operate internationally from their very early stages in order to succeed.

The proposed scheme of the Bio-Link project was based on cooperation between five successful bioincubators across Europe including one from a developing region. The basic concept was that cooperation between successful incubators will allow start-ups to benefit from the expertise of the different incubators, thus increasing the array of services available. This included exposing the start-ups to leading VCs and other financing sources, access to leading scientists and experts, direct channels to leading IP and regulatory consultants, exposure to potential strategic partners, access to specialized equipment, etc. In addition, the international dimension of the scheme was intended to motivate the firms to operate in an international context from their very early stages while getting in touch with other client companies.

1. Literature review:

This section is intended to provide an overview of the current fairly small body of research conducted into incubators in the US and to provide some comparative analysis with European incubators. It is intended to complement the findings of our qualitative findings gained through face-to-face interviews with incubator managers in North America conducted in September 2003 and reported in Bio-Link WP1 and the Survey of European Incubators conducted during 2004.

There is a paucity of research in the specialist area of biotechnology incubators, both in the US and Europe. Tornatzky, Sherman and Adkins (2002) benchmarking study of 79 business incubators is one of the most relevant biotechnology-related studies carried out in the US to date. The study includes a survey of 19 biotechnology/biomedical incubators representing 24% of the total survey sample and therefore the study has validity and its key findings are reported here.
The Centre for Strategy & Evaluation Services (2002) Benchmarking of Business Incubators report is probably the most relevant study of business incubation conducted in Europe to date. While this study included an examination of 201 biotechnology/pharmaceutical incubators, this represents just 14% of the total survey sample and the analysis is not disaggregated by incubator type, thus it only provides partially valid comparative findings.

1.1 Incubator history:

Incubators were initially constructed in an attempt to revitalize declining manufacturing areas. The first incubator was founded in the 1950's in New York in response to plant closures, offering services to all kinds of enterprises from lo-tech service providers to high-tech manufacturers. In Europe, incubators started up for the same reason with British Steel forming a subsidiary named British Steel Industry in 1975 to create jobs in areas where the steel industry had closed.
As the industry developed, the focus of incubators shifted from the development of sites, space and subsidies to the provision of value added business services. In addition, technology entrepreneurs are seeking the managerial expertise that is imparted via entrepreneurial training programmes and networking opportunities (Lichtenstein, 1992).
The development of business incubators has become a key element of local economic development strategies aimed at boosting company formation, developing technology clusters and raising the innovation levels.

Until the 1980's, incubators were still reasonably scarce (approximately 200 worldwide), but the technological boost of the 80's and 90's caused a rapid growth in the incubation programme resulting

in over 3000 incubators worldwide by the year 2000 (United Nations, 2000). In addition, incubators evolved from job creators into an instrument for improving regional competitiveness by fostering the emergence of technology based firms.

1.2 What is an incubator?

The rapid growth of the incubator programme together with the adaptation of the programme by different cultures resulted in a varied number of definitions for what an incubator is and what it aims to do.

1.2.1 The European Commission defines a business incubator as "a place where newly created firms are concentrated in a limited space. Its aim is to improve the chance of growth and rate of survival of these firms by providing them with a modular building with common facilities (fax, computing facilities, etc.) as well as with managerial support and back-up services. The main emphasis is on local development and job creation. The technology orientation is often marginal."

1.2.2 The United States National Business Incubation Association (USNBIA) defines the business incubator as "an economic development tool designed to accelerate the growth and success of entrepreneurial companies through an array of business support resources and services. A business incubator's main goal is to produce successful firms that will leave the programme financially viable and free-standing."

Researchers are also in disagreement regarding the definition of business incubators.

1.2.3 Smilor and Gill, (1986): "The incubation concept seeks to link effectively talent, technology, capital and know-how to leverage entrepreneurial talent, accelerate the development of new companies, and thus speed the commercialization of technology".

1.3 Types of business incubators:

Along with the differences in the definition of an incubator come the differences in their business models, whether due to differences in objectives or due to the incubator stakeholders.

1.3.1 Rudy Aernoudt (2004) divides incubators into 5 business models according to their objectives and clients but does not take into account the financial model of the incubator.

- Mixed incubators: main objectives are creating start-ups and employment. Function in all sectors.
- Economic development incubators: main objectives are regional development and business creation. Function in all sectors.

- Technology incubators: main objectives are entrepreneurship creation and stimulating innovation, technology start-ups and graduates. The sectors they focus on are recently targeted technology sectors, e.g. IT, biotechnology, etc.
- Social incubators: main objectives are integration of social categories and creating employment. Function in the non-profit sector.
- Basic research incubators: main objectives are Blue-Sky research and spin-offs. Function in the high-tech sector. Some of them (eg Genopole) start operations from the bench and thus integrate the functions of a technology transfer office.

1.3.2 Peters, Rice and Sundararajan (2004) determine that incubators are divided into 3 models according to their stakeholders. They also take into account the services given by an incubator (coaching, networking and infrastructure) but do not refer to the incubatee level at all.

1. Non-profit models, which include government, community based incubators.
2. University based incubators.
3. For profit incubators

1.3.3 Hackett and Dilts (2004) taxonomy of business incubators is perhaps the most relevant to our study, though it too, does not take into account the location of the incubator (Metropolitan, Intermediate, and Peripheral).

- **Incubator level: primary financial sponsorship**:
  - Publicly sponsored
  - Nonprofit sponsored
  - University sponsored
  - Privately sponsored
- **Incubator level: business focus**
  - Property development
    1. Single tenant
    2. Multi tenant
  - Business assistance
    1. Shared space
    2. Low rent
    3. Business support services.
- **Incubatee level: business focus**

- Product development
- Manufacturing
- Mixed-use

- **Type of Incubatee**
  - Spin-off
  - Start-up

1.3.4 In addition to the above taxonomy, Hackett and Dilts (2004) describe a new business model that has developed in recent years; the virtual incubator. This is an incubator without walls that endeavours to deliver business assistance services to clients not co-located within the incubator. The emergence of virtual incubators is problematic, concludes Bearse (1998), because it is questionable whether they can be considered "bona fide" incubators. If they can be considered incubators, then implicitly, any entity that provides business assistance services can also be considered an incubator.

On the other hand, Nowak and Grantham (2000) focus on flows of knowledge in the software industry and contend that because leading-edge software industry knowledge is geographically distributed and embedded within practices, a virtual incubator is needed to foster the development of information-intensive new software ventures through information dissemination (Nowak and Grantham, 2000).

1.4 US Incubator Management Practices

Managerial Attributes of Incubator Managers/ Embeddedness

In their benchmarking analysis of 79 US technology business incubators, Tornatzky, Sherman and Adkins (2002) report that managers of top performing incubators identify two attributes as critical to their success, both of which relate to the incubator's location within or adjacent to a major research university, medical institution, or federal laboratory, or in an otherwise resource-rich environment. Incubators use these research institutions to provide start-ups with networks of highly specialized technical assistance providers, qualified workforces, specialized laboratories and equipment. Furthermore, these environments provide start-ups with credibility and reputational benefits resulting in the attraction of highly qualified employees, ability to access venture and angel financing and have credibility with customers and suppliers.

In their study of successful incubator managers, Rice and Andrews (1995) discuss the need to embed an incubator programme into the host community, and they argue for the involvement of a broad spectrum of community stakeholders acting as "champions". In the development phase, stakeholders should form a Community Advisory Team (CAT) to mobilize financial resources and subsequently form the nucleus of an incubator advisory board.

Local embeddedness is also seen by Rice and Andrews (1995) as critical in the technology transfer process by developing positive relationships with technology generators in the region which facilitates access to marketable technologies and technical expertise as well as building a stronger potential client base.

Organizational Attributes

The organizational attributes associated with successful US incubators include: an advisory board with representation from local government, local professional service providers network (including a general practice lawyer, patent attorney, accountant, and the investment community), host institution, local entrepreneurial community, tech-commercialization specialist, and a graduate firm. In addition, incubators should have a well-developed mission statement and goals. The manager should be carefully selected and have local knowledge, be motivated, able to multitask, be a team player (Hayhow 1999).

Entrance and exit criteria for client firms designed to lead the enterprise to self-sufficiency and an ongoing evaluation of incubator performance.

In his 2001 Review of Technology Incubation, Lewis found that business assistance services may be supplied to client forms through a variety of mechanisms and through various cost structures including incubator manager and staff; advisory board or host institution (such as university's faculty); local Small Business Development Centre; and/or arrangements with area professional service firms.

Organizational Structure

US business incubators have six main sponsoring bodies according to NBIA statistics (2002), which account for the following percentages of the sector: academic institutes, 25%; no sponsoring entity (19%); government (16%); economic development agencies (15%); for profit entities (10%); hybrid more than one sponsor (6%). In the specific case of technology incubators, the majority are hosted by academic institutions (McKinnon and Hayhow, 1998).

Lewis (2001) has found that revenue streams that support an incubator vary over time and this is related to three factors. First, the revenue from rent and fees for services increases as a percentage of total revenue over time, eventually becoming the largest portion of revenue. Second, the level of private and public grants received fluctuates over time. This fluctuation forces a manager to devote considerable effort to fundraising and may compel an incubator to relax entrance criteria or extend tenancy to a firm ready to graduate in order to increase rent revenue.

Networking

Research by Shahidi (1998) tested the hypothesis that there are more networking opportunities for technology incubator client firms than for similar non-incubated firms and that these networks enhance the performance of technology incubator client firms. Shahidi concluded that these networks had demonstrable positive impacts on client firms. The opportunity to access customer networks offered incubated firms more informal sales contacts. Also, the range of consultants and advisors associated with incubators provided client firms with an advantage. These benefits led to statistically higher rates of equity capital, grants, and seed fund financing for incubated firms than for similar non-incubated firms.

Incubator-Research Institution Partnership

Research sponsored by the Council for Urban Economic Development in 1985 concluded that university partnerships can make technology incubators more effective because the association of the client firm with a university is valued by the client firm and potential customers, partners, and suppliers. Mian (1994, 1996, and 1997) has tested this argument in some detail and concluded that university image, laboratories and equipment, and student employees add the greatest value to client firms and make universities a viable location for nurturing new technology-based businesses. Furthermore, he concluded that the incubator provides opportunities for university faculty and students, as well as the potential for generating revenues for the university. DiGiovaima and Lewis (1998) found similar evidence in the case of some university-hosted technology incubators in New Jersey. These results also confirm Smilor and Gill's (1986) research, which indicates technology incubators associated with universities generally focus on commercializing university-developed technologies and that the advantages of being associated with a university include (1) access to library facilities, (2) access to student labour, (3) a creative environment, and (4) exposure to state-of-the-art facilities and expertise.

Regional Characteristics

Wolfe et al. (1999, 2000) argue that the following regional characteristics will increase the likelihood of successful incubation of start-up technology firms.

Some necessary, but not sufficient, regional characteristics for successful incubation include:

(1) Presence of one or more technology generators. A technology generator is an institution—such as a university, national laboratory, or private research and development laboratory—that ensures a sufficient concentration of human capital and engages in an adequate amount of R&D to produce numerous opportunities for new commercialization ventures.
(2) A sufficiently skilled labour force that can provide potential clients with employees who have the critical skills to fill the newly created technology-oriented jobs.
(3) A technology culture in the community, that is, a location where failure at one new technology venture is not considered the final opportunity for an entrepreneur. In other words, investors and the community-at-large understand the risk of technology ventures and thus applaud the attempt and encourage second chances.
(4) Sufficient investment capital activity in the region, including angel investors, venture capital, traditional financial markets, SBIR grants, state-funded seed and venture funds, and corporate partnership money.

Campbell et al. (1988) provide evidence that the host region will affect outcomes. They found that the exact cost per job varies based on some regional characteristics and the type of firm incubated. Client firms in regions that have large corporations that purchase from them appear to have higher growth rates.

Similarly, the presence of a university has been demonstrated to have positive correlation with client firm success (Peterson et al. 1985; Mian 1996; Smilor and Gill 1986). The host region may determine the types of services provided by an incubator programme (Peterson et al. 1985; Tornatzky et al. 1996).

Strategic Framework

The CSES European study (2002) recommends that "Business incubators should be designed to support and be part of a broader strategic framework – either territorially orientated or focused on

particular policy priorities (e.g. development of clusters), or a combination of these factors. Incubators should not be standalone entities but rather work alongside other organizations and schemes to promote broader strategies. Examples could involve incubators acting as a link between centres of R&D excellence and business, commercializing R&D, helping to develop the supply chains for industrial clusters, promoting SME competitiveness, and in some cases, a more specialized role, e.g. addressing social inclusion by helping disadvantaged, communities to engage in entrepreneurial activity or promoting other territorially focused priorities".

Management Structure

According to Hayhow (1997), most US incubators have a fairly common management structure comprising a manager in charge of day-to-day operations, delivery of complementary services, co-ordination of support staff, and some of the marketing activities. In most cases, incubators have an advisory board that acts as the board of directors and supervises the manager and assists in decision making - for example, to evaluate potential incubator clients or establish entry criteria. The board will comprise representatives from the host organization, state or local economic development organization, local professional services network and various community leaders.

Equity Investment/Royalties

A growing number of US incubators make equity investments or receive royalty payments from client companies. The NBIA Study (NBIA, 2002) reported that "31% of university sponsored incubation programmes take an equity stake in client companies signalling a change in university culture that has grown since the passage of the Bayh-Dole Act in 1980 which allowed universities to transfer intellectual property rights to private companies. The study also found that incubation programmes taking equity stakes were five times more likely to be technology incubators than mixed-use programmes. Bray and Lee (2000) in a small-scale study found that US universities taking an equity stake in spin-off companies realized a greater return in the long run, relative to the average revenues.

Occupancy Rates

According to the CSES study (2002), there is little variation in occupancy rates across EU Member States. France and Sweden have occupancy rates within 0.5% of the EU average of 85%. Occupancy

rates in the North America are reported to be somewhat lower than EU rates with the latest NBIA survey (2002) reporting a rate of 75%.

Exit Rules

The vast majority of both US and European incubators have graduation policies for their maturing companies. US incubators have a range of formal and informal policies that guide how long a client stays in the incubator. Growth is the most common reason with clients leaving when they have outgrown their incubator's available space (National Business Incubation Association NBIA 2002). Policies that limit time periods of occupation are also key reasons for a company's exit. A reason not evident in our survey of European incubators is that the client left because they failed to reach certain mutually agreed milestones.

Tax Status

Technology based incubator programmes were found to have the highest percentage of for-profit programmes: 46% compared to 30% of mixed-use incubators, 13% of service incubators and only 4% of manufacturing incubators (National Business Incubation Association NBIA 2002). Non-profit technology incubators in the US account for 35% of US technology incubators.

Anchor Tenants

In the US anchor tenants - companies that reside in an incubator but do not receive business assistance services - are an integral part of incubation programmes (NBIA, 2002). NBIA's study found that only 15% of programmes had no anchor tenants. Anecdotal evidence suggesting that they provide a number of benefits to an incubation programme, such as offering incubator companies synergistic business opportunities, a good business model, or a ready source of services. They can also provide a stable source of income to a programme

Product/Service Focus

Of the 79 incubators studied by Tornatzky, Sherman and Adkins (2002), 19 were biotechnology or biomedical focused. Of these incubators, 57.9% were focused on developing a product while 10.5% had a service focus with 31.6% having a mixed product/services emphasis.

Performance Comparisons US/EU Incubators

The CSEL Benchmarking study (2002) provides a brief comparison of US and EU incubators on a range of performance characteristics and indicators. The larger proportion of US incubators taking an

equity stake in the companies is one of the key differences between US and EU incubators. However, our survey of European incubators found that there is an increasing trend for EU based incubators to take equity or royalty stakes in their companies. On the basis of this study, there are rather surprisingly almost twice as many for-profit incubators in the EU compared to the US. The size of US incubators is larger and the related average number of tenants accommodated at incubators is substantially higher in US incubators than those in the EU.

1.5 Incubation statistics

Differences between the incubator programmes in different countries can be demonstrated further in light of the following statistics:-

1.5.1 Europe (CSES 2002)

- Today there are approximately 900 business incubators operating in the 15 EU countries, 300 of them in Germany alone.
- Ratio of incubators per SME's is on average 1:19,000. Austria has the highest density of incubators with 1:3,000 SME's and Greece has the lowest density standing at 1:106,000.
- The average graduation rate of European incubator clients is 85%.
- Some 40,000 new (net) jobs are generated each year by incubators in the EU, at an average gross cost per job to public authorities of around €4,500 (€4,000 net).
- Public funding accounts for a high proportion of the setup costs of most incubators (which average around €4 million) and for around 37% of operating revenue.
- Incubator operating costs average around €500,000 per annum, the highest proportion of cost relating to staff (41%) followed by client services (24%), maintenance of buildings and equipment (22%), and other costs such as utilities (13%). Whilst many incubators are able to recoup a significant proportion of these costs (averaging around 40%) from tenants, the element of public subsidy remains high in most cases. At present, some three-quarters (77%) of European incubators operate on a not-for-profit basis.
- European incubators typically have around 5,800 square metres of space for tenants, sufficient to accommodate some 18 firms at any one time in a variety of units.

1.5.2 North America (statistics are from the NBIA website)

- Today there are approximately 950 business incubators in North America, up from 587 in 1998 and just 12 in 1980.
- In 2001 alone, North American incubators assisted more than 35,000 start-up companies that provided full-time employment for nearly 82,000 workers and generated annual earnings of more than $7 billion.
- NBIA member incubators report that 87 percent of all firms that graduated from their incubators are still in business.
- Startup firms served by NBIA member incubators annually increased sales by $240,000 each and added an average of 3.7 full- and part-time jobs per firm.
- For every $1 of estimated annual public investment provided to the incubator, clients and graduates of NBIA member incubators generate approximately $30 in local tax revenue alone.
- NBIA members report that 84 percent of incubator graduates stay in their communities and continue to provide a return to their investors.
- Publicly supported incubators create jobs at a cost of about $1,100 each, whereas other publicly supported job creation mechanisms commonly cost more than $10,000 per job created.
- Every 50 jobs created by an incubator client generate another 25 jobs in the community.
- 60 percent of business incubators are either self sufficient or could be self sufficient if subsidies ceased. In 1997, only 13 percent believed they could continue at current levels without subsidies.

1.5.3 Israel

- The incubation programme began in Israel in 1991. Between the years 1991-1993, 28 incubators were established. Today 24 incubators remain.
- The Office of the Chief Scientist of the Ministry of Industry and Trade grants up to $175,000 per annum to each incubator and up to $150,000 per year to each project for a maximum of two years. The level of the grant is up to 85% of the approved budget of the project.

- Each incubator is a not-for-profit entity, usually sponsored by a university, a municipality, or a large firm. There is no sector limitation, and an incubator can support between 8 and 12 projects.
- The graduation rate in 2002 in Israel was 86.4%. The highest rates of success were recorded for projects belonging to drugs (90.0%); hardware, communication, and electronic components (95.5%); and biotechnology (90.3%). On the other hand, the highest rate of failure was found among projects belonging to the energy and ecology area (31.3%).

Best Practices

In their study of US business incubators, Tornatzky, Sherman and Adkins (2002) identify the individual skills of the incubator manager as a prime predictor of incubator performance. Interestingly they found that the clients of incubators with a greater biotech/biomedical client focus had raised more money, obtained more research support, held more patents and in-licensed more technology than clients of non-biotechnology incubators . Furthermore, they found that biotech/biomedical focused incubators' clients had slower revenue growth than IT/electronics and mixed technology incubators' clients and fell behind mixed technology incubators in employment growth. Essentially the biotech/biomedical incubators grew but growth was based on investment capital.

Although the research found no strong relationships between incubator business assistance practices and primary outcomes (e.g., sales and revenue growth), it did reveal a predictive relationship between the business assistance practices and the secondary business outcomes (e.g., equity investment, patents, research grant support, copyrights, and licensed intellectual property) that are important precursors to the primary outcomes. The reason for this, the researchers proposed, is that individual business assistance practices of incubators will have greater predictive relationships with performance outcomes only if most clients utilized certain practices. This was assumed to be unlikely, however, as every company has a different needs profile to be addressed. Instead, the researchers proposed that the strength of ties to community technology generators, as well as the

individual skills of the incubator manager, are greater predictors of performance than whether the incubator provides mentoring relationships or loaned executives for use by client firms.

The key importance attached to incubator managers' personal and professional attributes is evident in the US literature with entrepreneurial qualities at the forefront. Pro-active involvement in the provision of services and careful monitoring and involvement in company development are other key requirements of the successful incubator manager.

The location of an incubator within a university setting has been found to be a key driver of successful incubators. A key factor is the reputation benefits that accrue and help to attract funding, customers and partners. The availability of technological expertise and facilities is another key benefit of a university-incubator linkage.

1.6 The importance of networking

Kaufmann et al., 2003 attempted to map out the role location and regional networks play in developing biotechnology firms in Israel.

Many researchers have stressed the need of new firms to gain access to complementary assets and knowledge as a main motive for forming different types of strategic alliances (Teece, 1986; Nohria and Garcia-Pont, 1991). This is specifically true in fields where new knowledge emerges frequently, as is the case of the biotechnology industry (Cohen and Levinthal, 1990; Powell et al., 1996).

As a result, it is expected that firms are formed where knowledge spillover exists and where transaction costs are expected to be low (Baum et al., 2000; Dyer, Kale and Singh, 2001; Gautam, 2000). Furthermore, networks can provide firms with an advantage when the relationship between a firm's competitive advantage and the resources it uses is not transparent (Lippman and Rumelt, 1982). This may increase when tacitness, complexity and specificity characterize the resources. Zucker and Darby (1997) as well as Zeller (2001) and Kaufmann and Levin (2002) argued that the tendency of New Biotechnology Firms (NBFs) to locate around leading academic institutions stems from the need to increase the flow of knowledge from academic institutions, knowledge that in large part contains tacit elements. Deeds et al. (1999) found that continuous flow of new products (pipeline) and the location of a firm are strongly correlated with NBF performance. The need to maintain a pipeline of new products stems from both the risks and costs associated with the

development of biotechnology products. The high risks deter investors from investing in 'one-product' companies, as failure of this single product means their investment will be lost. The high development cost of biotechnology products, which are highly influenced by the regulation process, create a specific financing model, where new products are sold or out-licensed at a relatively early development stage (e.g. Phase II in drug development) in order to finance the development of the next product. This process repeats itself a number of times until the NBF succeeds in generating sufficient financial strength to 'go it alone' through the entire regulation, production and marketing processes. This is another explanation for the importance of having a pipeline of new products. Analyzing many Israeli firms such as Biotechnology General, Pharmos and D-Pharm, as well as other American firms such as Genentech and Genzyme, reveals a development path based on several different agreements with big pharmaceutical firms until the firm gains the ability to vertically integrate the required assets needed to develop, produce and market a new drug independently. This development path reflects the requirement for the firms to balance their short-term financing needs and long-term value creation.

Autio et al. (1999) emphasized the importance of the entrepreneur's social capital in gaining access to different complementary assets and in forming strategic alliances. Accordingly, as the firm develops, the entrepreneur's social capital is merged with the firm's social capital, which gradually expands to include links to investors, suppliers, customer research centres and more. These new links, in turn, expose the firm to new networks, creating, for some period of time, an exponential type of networking expansion process. The positive influence of the entrepreneur's social capital on entrepreneurial success was supported by Jenssen, and Koenig (2002) in their study of Norwegian entrepreneurs and by Cooke and Wills (1999) in their study of the influence of public programmes for building social capital in Denmark, Ireland and Wales. For broad discussion on the influence of social capital on economic and business dimensions of firms, readers are referred to Cooke (2002b).

The fact that most biotechnology entrepreneurs come directly from academic or research institutes provides sufficient reason to assume that their social capital is based predominantly on their relationships with people from these settings, giving them a strong regional dimension. This is unlike other sectors where the social capital of the entrepreneurs, as a result of their former business experience, includes links to different types of business agents such as investors, firms and suppliers, and thus tend to be less regional.

Most of the literature on networking deals with the phenomenon of networks and cluster formation (Harrigan, 1988) or analyses of the influence of networks on firm performance (Baum et al., 2000;

Dyer, Kale and Singh, 2001; Ahuja, 2000; Deeds et al., 1999). Some of the literature is focused on describing the basic conditions for network formation (Ahuja, 2000) and the role such networks have on firm success. Other researchers refer to the geographical dimensions of networks (Zeller, 2001; Storper, 1997) and highlight the importance of concentration around research institutes (Swann et al., 1998; Prevezer, 1997). However, most of these research studies have focused their attention on the advantages of networking and clustering.

Kaufmann et al., 2003 hypothesize that biotechnology entrepreneurs encounter more difficulties in the process of business networking, given that they have relatively less business experience than do their counterparts in other sectors. This is attributable to the fact that most biotechnology entrepreneurs gain most of their work experience in academic and research institutes. As a result, their need to turn to external business assistance is expected to be higher than that of entrepreneurs in other sectors, a fact that may justify the implementation of specific policy measures.

The study found that despite the small geographic size of Israel, its biotechnology industry does tend to cluster around leading academic or research institutes. High correlations were found between the relative strength of the academic institute in biotechnology-related fields (measured in terms of senior staff members, number of students and number of registered patents) and the number of biotechnology firms in the region. It was shown that in regions with strong biotechnology academic departments, there is substantial biotechnology industrial activity. There was a strong tendency for biotechnology entrepreneurs to locate in close proximity to research institutes that were commonly their former workplaces.

Findings also point to the relative importance of networking-related activities in the biotechnology industry. The high importance biotechnology entrepreneurs ascribe to networking has been shown to be high both at the incubation level and at the more advanced stages.

Significant differences were found between biotechnology entrepreneurs and other entrepreneurs in regard to the importance of choosing an incubator that is in close proximity to academic institutes, cooperates with research institutes, supports similar projects in the incubator and succeeds in attracting well-developed firms. All of these factors point to the relative high importance biotechnology entrepreneurs ascribe to networking and clustering-related issues.

Furthermore, entrepreneurs in the field of biotechnology tend to have more advanced academic degrees, less business education and less industrial work experience than entrepreneurs from other fields. This is particularly true for European bio-entrepreneurs, a cultural gap. This led us to

conclude that in general, biotechnology entrepreneurs are more dependent on external sources of assistance, primarily in regard to business and networking factors. This assumption received support from both the incubator survey and the study of the Jerusalem biotechnology cluster.

NBFs show great dependency on regional networks that centre around strong academic and research institutes. During their development, they begin focusing on expanding their business networks. Interestingly, it was found that although the centre of gravity of their networking may shift from the local to the international level, the regional scientific network remains important.

The research findings shed new light on the specific difficulties associated with NBFs and emphasize the importance of implementing specific policies to assist the development of the biotech industry.

2. Building Co-incubation: the Bio-Link Project :

2.1 Objectives

The Bio-Link project started to operate in January 2003. The concept of co-incubation was new to all of the participants in the project and therefore a need to define and adjust the expectations was essential. Since the very first consortium meetings, it was clear that the project should focus on two main tasks:-

1. Exposing incubator managers to other incubation practices. This was achieved through exchange of experience between leading incubators that implement different methods. The result of this process is presented in the Best Incubation Practices (BIP-Toolkit) report.
2. Increasing the level of networking of the client companies by means of exposure to: a. other client companies having complementary assets; b. companies and organizations outside the Bio-Link consortium such as big pharma, venture capital, CROs (contract research organizations), etc.

During the progress of the project, it became clear that the expectation of achieving real advancements in companies' performance in terms of number of patents, number of employees, capital raised, etc. were unrealistic, mainly due to the relatively limited duration of the project. The actual co-incubation period for a company (after reducing the time for selection, contacting the manager, analyzing the needs, finding potential matches for co-incubation, etc.) was between 12-18 months. Moreover, it must be taken into account that forming actual contracts with

partners is a process that can take 6-12 months from the very first contact. Therefore, it is strongly recommended to continue and follow the project and to re-measure these factors within 12-24 months from the project end.

As a result of these difficulties, the project evaluation team decided to add to the evaluation further issues that will provide knowledge on:-

- **The needs of client companies for services aimed at extending their network**. This part compared the need for networking services on the one hand, and on their level of satisfaction from the related services provided by their incubator.
- **Assess the direct influence of the scheme on the level of networking of the companies.** This evaluation is important since we assume that an increase in the networking level of a firm will positively influence its performance. This assumption receives strong backing in the literature. Networks and network capabilities have been found to be correlated to many dimensions of firms' performance. Firms with strong networks received higher values, reached IPO faster, showed higher growth rates, were more innovative and demonstrated better abilities to overcome periods of economic crisis. Moreover, it has been proved that networks are of specific importance in fields that are facing frequent technological changes, such as biotechnology. Some studies even attributed the difference between the US and the European biotech sector to the fact that companies in the US have stronger network capabilities. (For more details see for example: Cohen and Levinthal, 1990; Powell et al, 1996; Prevezer, 1997; Kaufmann et al, 2003).
- To assess the importance of the co-incubation concept as a service provided by the incubator
- To assess the influence of the Bio-Link scheme on the level of satisfaction of client companies from their incubator.
- To assess the influence of the Bio-Link project on the management capabilities of the incubator manager.

In addition, we analyzed the international dimension of the scheme with specific attention to the ability of this scheme to assist developing regions. It is anticipated that since many of the services in those regions are limited and companies are, by definition, far from the main markets, the Bio-Link scheme will be of significant importance.

2.2 Project Description:

In January 2003, an international consortium of five biotechnology incubators, implementing different incubation methods, was formed. Their complementary advantages as well as their experience in different incubation processes were analyzed and a co-incubation scheme was tested on 20-30 start-ups.

The formation of the team working on this research was carefully constructed, taking into consideration the complementary skills and experiences of the partners and the desired research objectives.

Oxfordshire BiotechNet, **Bio^{M} AG**, **Genopole** and **Hadasit** provide the proven expertise in hands-on incubation of technology based start-ups. Through various models, each organization has pioneered nationally the development of bio-business incubation principles and extensive company support networks. The projects vary in the precise mix of support mechanisms utilized e.g. **Oxfordshire BiotechNet** provides fully serviced laboratory facilities but does not have its own investment fund while **Bio^{M} AG** manages its own post-seedcorn investment fund but does not provide premises. At the same time both **Oxfordshire BiotechNet** and **Bio^{M}** are actively involved in consultancy activities leading to the creation of bioscience firms. Similarly, while **Hadasit** offers accommodation and support to companies, **Genopole** offers premises to both academic research groups and companies. Further similarities and differences exist in the regulatory environment and government policies surrounding each project.

Having begun the process of implementing support services and providing premises to technology companies, **Consorzio Ventuno** provides the most challenging testbed for models developed during this project.

The suppliers to this project, **The Centre for Advanced Studies** and the **Jerusalem Institute for Israel Studies**, provide research expertise which put the project on a sound applied academic foundation. Both organizations have considerable experience in carrying out Europe wide research projects and both have considerable influence on innovation support policy.

The project was constructed as follows:

Bio-Link partner incubators:

- Bio^{M} AG (Munich, Germany)
- Genopole (Evry, France)
- Hadasit (Jerusalem, Israel)
- Oxfordshire BiotechNet Ltd (Oxford, UK)
- Polaris Consorzio 21 (Cagliari, Sardinia)

Oxfordshire BiotechNet Ltd, represented by Mr. Nigel Wild, were appointed as the coordinators of Bio-Link. An important development in the project was the nomination of Dr. Avri Havron from Operon Consultants Ltd., Israel who acted as a professional manager to the project. He was nominated 14 months after the start of the project and after it became clear that the incubator managers lacked the managerial capabilities and time to run such a complicated scheme. The fact that the incubator managers come from different backgrounds (not all them have expertise in biotechnology), the different incubation model used by them and severe time constraints created a need for a professional manager. This decision was, in our opinion, crucial to the success of the project and can serve as a general important conclusion to any co-incubation project in the future.

The following table classifies the different Bio-Link participants according to the main three scholars of incubation:

Table 1 Typology of Bio-Link Incubators

Incubator	Rudy Aernoudt	Peters, Rice and Sundararajan	Hackett and Dilts
Oxfordshire BiotechNet	Technology incubator	For profit	**Incubator level:** privately sponsored, multi client, all types of business assistance. **Incubatee level:** Product development from university and industrial spin-offs.
Genopole	Technology incubator	Non-profit (governmental)	**Incubator level:** publicly funded, multi client, all types of business assistance. **Incubatee level:** product development from the bench, start-ups and spin-offs.
Hadasit	Technology incubator	For profit/university	**Incubator level:** privately sponsored, multi client, all types of business assistance. **Incubatee level:** Product development from hospital spin-offs.
Consorzio Ventuno	Technology incubator	Non-profit (governmental)	**Incubator level:** Publicly funded, single client , low rent **Incubatee level:** Mixed use start-ups.
Bio^{M}	Technology incubator	For profit	**Incubator level:** publicly sponsored, multi client , business support service **Incubatee level:** Mixed use start-ups

3. Description of the Co-Incubation (CI) Model

A. Company Level

3.1 Selection of CI candidates within each of the partner incubators.

In order to select the best candidate companies in each incubator, the following selection plan was implemented in each of the 5 participating incubators:-

- Internal peer review in each incubator regarding the most suitable candidate companies for CI. This selection was done according to the selection criteria decided and agreed by the partners (please refer to D4).
- Each of the managers of the partnering incubators met the managers of the potential selected clients in order to present the Bio-Link concept to them and to interest them in the CI concept and opportunity.
- Exchange of information regarding the selected CI candidates between the partners by emails & telephone. The main objective of these communications was to:
  a) Find potential matching between companies with complementary technologies or business concepts.
  b) Find potential candidates which can be assisted by the other incubator, by its infrastructure, core expertise or by its professional network.

Based on the above points, the final list of candidate companies for CI was refined and brought to the incubator's management and to the candidate company for approval.

The outcome of this procedure was the final list of candidate companies for CI. This list was the basis for the meeting held in Sardinia between September 30 and October 1, 2003.

At that meeting, parallel face to face meetings between the incubator managers were held. In each of the meetings, managers of two incubators discussed the potential co-incubation projects. A total of 10 such sessions were held in which all aspects of the co-incubation process were considered.

The outcome of these meeting was as follows:-

a) Decision regarding the CI model of each of the candidate companies namely, company-company, company-incubator.

b) Selection of candidate companies for CI with companies outside the Bio-Link consortium.

c) General implementation plan including action items and leading incubator.

As the meeting progressed, it became clear that the CI process required managerial and technological attention that was beyond the Bio-Link management's professional expertise. It was agreed that an external expert specializing in Biotechnology should be recruited. The expert was expected to meet each of the partners including each of the potential CI candidate companies in order to analyze their

specific capabilities and needs, assess the proper CI model, construct a detailed workplan for each project and follow its implementation. In addition, it was expected that the expert would contribute his own knowledge and links to the CI process.
The candidacy of some potential experts was raised and finally Dr. Avri Havron was selected. Dr. Havron has more than 20 years experience in Biotechnology including senior managerial positions in multi-national biopharmaceutical and investment companies (Serono, BioTechnology General Corp. and Clal Biotechnology Industries).

Selection criteria for the Bio-Link project

The client companies belonging to the five participating bioincubators in the Bio-Link project can be divided into 3 major categories:

a) Companies developing platform technology (for example: new method for identifying drug targets on cell surface, on-line bioinformatics software solutions))

b) Service-providing companies (for example: analytical services, animal toxicology, clinical trial services)

c) Product-developing companies (specific drugs – small and large molecules, medical devices)

The selection of a company for a successful co-incubation should meet the following criteria:

a) For companies developing platform technology:

- Post proof of concept. Has the method been tested in an actual experiment and has the results been recorded in a satisfactory and well documented manner?
- Suitable for a wide range of collaborations. Can the platform be used by many potential partners without granting exclusivity to any of them? In the case of on-line bio-informatics software this is clearly obvious.

b) For service-providing companies:

- Meeting a defined need. Does the service meet a real need for a wide range of customers? Is it unique in any way in comparison with existing competitors?
- Existing solution. Is the service in-place in terms that it can be provided in a short time to potential customers? Or, how long will it take until the company reaches this status?
- Certified. Has the company obtained all the required certificates from regulatory services or other authorities to provide the service (EMEA, EU notified bodies, FDA etc.)

c) For product-developing companies (diagnostic kits, medical devices or therapeutic molecules):

- Proof of concept (alpha-site, animal model). Has the product been tested in an acceptable experimental model whether in animals or in the lab, to enable potential partners to evaluate it using consensus scientific tools?

- Fast implementation. How long will it take to transfer the technology to a potential co-incubation partner? Are standard operating procedures in place? Have they been validated in-house prior to their being transferred to a potential partner?
-Short time to realization. New therapeutics require an extremely long development time. The co-incubation process should take just one aspect of the development – for example the development of an assay in cells to test the efficacy of the molecule. This is a task that can be accomplished within a short period (12-24 months).

In addition, the following parameters should play a major role in the selection of a company for co-incubation:-
Maturity – companies which are in their seed phase (conception) are not ready for collaboration due to their need to focus and accomplish significant milestones in a short time and under considerable budgetary restraints. Therefore companies which are ready for co-incubation should be 2-3 years old. This age will also result in internal clarification and understanding of the needs for co-incubation in terms of the benefits that the company can obtain with such potential collaborations.

Critical mass – the need to allocate well-trained scientific and technological staff for the co-incubation with a potential partner is impossible for a company with less than 8 employees. Co-incubation requires a dedicated scientist/engineer who can devote most if not all his time to the project.

Proposed Modes of Co-Incubation
Six potential modes of co-incubation were examined during the Bio-Link project:-

a) Shared R&D
b) Provision of services
c) Technology transfer
d) Material transfer/sale
e) Joint projects/products
f) Joint application for R&D funding

a) Shared R&D requires defined splitting of tasks between the parties, lots of exchange of information and travel, a dedicated budget, and hence intensive managerial attention – this as we found is an unfavoured mode of collaboration.

b) Provision of services. This mode of co-incubation is easy to implement if the service-providing company has everything in place. It provides the company with income whilst it provides the co-incubation partner with a solution to a defined problem, (for example a validation of a difficult to validate Bioanalytical assay). We found this mode as the most favoured mode of co-incubation

c) Technology transfer/sale. This is also an easy to implement mode of co-incubation. Companies which are ready for technology transfer are usually prepared to do so in terms of their procedures and certification. For example, this is the case for companies providing bio-informatics on-line software solutions. We found this mode of collaboration was favoured by the relevant participating Bio-Link portfolio companies.

d) Material transfer/sale. This mode of co-incubation does usually not apply to young companies which do not have ready products. Products under development are usually not shared with other companies due to IP considerations. We found this mode of co-incubation unfavoured by the participating portfolio companies.

e) Joint projects/products. Young companies do not have the resources to share projects with other companies. These resources refer to financial ones, management attention, legal aspects related to the joint project and lack of personnel in the young companies. For these reasons, this mode of potential co-incubation was rejected by Bio-Link portfolio companies.

f) Joint application for R&D funding. This co-incubation mode requires strict definition of the IP sharing . Since the IP of young incubator companies is their most valuable asset, this mode of collaboration was not favoured.

3.2 Portfolio companies selected and reviewed for co-incubation

The following table lists the 37 companies which were visited and reviewed during the course of the project

	Location	Company Visited and Reviewed
	Oxford	Oxfordshire BiotechNet
1	Oxford	BioAnaLab
2	Oxford	Hybrid Systems
3	Oxford	Oxford Immunotec
4	Oxford	Ludger
5	Oxford	Caretek Medical
6	Oxford	Green Biologics
	Evry	Genopole
7	Evry	Nokad
8	Evry	Nautilus Biotech
9	Evry	Genosafe

10	Evry	Nanobiogene
11	Evry	Genodyssee
12	Evry	Genewave
13	Evry	Cryozootech
14	Evry	Genoplante Valor
15	Evry	Vaxon Biotech
16	Evry	Biomethodes
	Sardinia	Consorzio 21/Polaris
17	Sardinia	Sardinia Genomics
18	Sardinia	Pharmaness
19	Sardinia	SharDNA
20	Sardinia	Bioker
21	Sardinia	bcs Biotech
22	Sardinia	Centre for Advanced Studies
	Munich	Bio^{M}
23	Munich	Aurigon Life Science
24	Munich	NascaCell IP
25	Munich	Genomatix Software
26	Munich	Nanion
27	Munich	BioNetWorks
28	Munich	conoGenetix biosciences
29	Munich	Xerion Pharmaceuticals
30	Munich	4SC
31	Munich	Pieris Proteolab
32	Munich	Apalexo Biotechnologie
	Jerusalem	Hadasit - see remark below marked with*
33	Jerusalem	InCure
34	Jerusalem	GVT
35	Jerusalem	Hapto Biotech
36	Jerusalem	Priosense
37	Jerusalem	Hadassah Clinical Services

***Hadasit affiliates**

BiolineRx

Hadasit, the Israeli partner of Bio-Link, is the technology transfer arm of the Hadassah Medical Centres (Jerusalem, Israel). Hadasit's business model is also based on investments and equity holding in other Israeli-based biotechnology and pharmaceutical development organizations.

Hadasit is a partner in a young Israeli drug development company called BiolineRx (www.biolinerx.com). BiolineRx takes projects from Israeli academia, industry and government research institutes with the aim of developing them to an advanced stage to enable a strategic partnership with a global pharmaceutical or biotech company.

BiolineRx began its operations in 2004. In terms of the Bio-Link project, BiolineRx should be considered as an "affiliate member" due to its affiliation with Hadasit. The manager of BiolineRX participated in the Maastricht meeting and presented his company's model and discussed possible cooperation.

Meytav Incubator
Meytav is an incubator specializing in healthcare. It is part of the Israeli national incubator programme and is located in Kiryat Shmona in the north of Israel. It comprises currently 15 young companies. Meytav is a private incubator financed by private investors in addition to the government basic funding.

BioLineRx is one of the private investors in Meytav. The philosophy behind this investment is to offer BiolineRx direct access to projects and products which will be developed during their early stages in Meytav. As such, Meytav is also considered as an affiliate member of Bio-Link. The manager of Meytav will take part in the summary meeting in Sardinia and will analyze the special conditions required for incubation in developing regions..

3.3 Summary of the technological and the commercial status of the selected Bio-Link portfolio companies approached (as at November 30, 2004)

Company	Technology	Status
Oxfordshire BiotechNet		
BioAnaLab	Development & validation of immuno-assays	Operational service provider for diagnostics
Hybrid Systems	Gene-therapy using coated viral vectors, mainly adenovirus	Platform technology ; early stage bio-pharma
Oxford Immunotec	Detection of long term incubation diseases	Diagnostics, first product (TB) being launched
Ludger	Biochemical analysis of glycosylation chains of proteins	Operational service provider for biotech companies
Green Biologics	Waste treatment by selected bacteria	Advanced stage development and service company
Caretek Medical	Needle free drug delivery device	Early stage start-up
Genopole		
Nokad	Single protein immuno-inactivated animal models	Platform technology.; early stage animal model provider
Nautilus Biotech	Enhance activity/longevity of therapeutic proteins	Mezzanine stage bio-pharma with platform tech.
Genosafe	QA/QC services for gene-therapy	Service provider; to become operational within 1 year
Nanobiogene	Miniaturization of Lab equipment for High Throughput Screening	Manipulation of liquids of minimum volume
Genodyssee	Therapeutic proteins – natural according mutants of known drugs	Platform technology, advanced stage start-up
Genewave	Fluorescence signal amplification for diagnostics	Platform technology, early stage technology

		developer
Cryozootech	Cloning of sport horses	Service provider
Genoplante Valor	Genetically modified plants	Developer and provider of patents for improved plant strains
Biomethodes	Improved industrial enzymes by genetic engineering	Platform technology, service provider
Consorzio 21/Polaris		
Sardinia Genomics	r-h-protein fragments for treating patients with genetic disorders	Early stage bio-pharma
Pharmaness	Animal facility specializing in neurological & psychotic drugs	Service provider; to become operational within 6 months
SharDNA	Access to genetically homogenic population database	Service provider (recruiter) for specific clinical genetic trials
Bioker	r-h-proteins for generics & special formulations	Early stage; generic bio-pharma & formulations
bcs Biotech	Diagnostic kits	Manufacturer, seller & developer of diagnostic kits
Centre for Advanced Studies	Computational analysis & surgical procedures simulation	Computational solutions to clients from healthcare industry.
Bio^{M}		
Aurigon Life Science	CRO - preclinical studies	Service provider
NascaCell IP	Aptamers as research tools	Platform tech.; early stage provider of research reagents
Genomatix	Bioinformatics: Eukaryotic prompters	On line bio-informatics service provider
Nanion	Electrophysiology of ion channeling	Manufacturer, developer & seller of equipment
BioNetWorks	Drug for rheumatoid arthritis & hormone diseases	Pre-clinical stage of 1 drug candidate
conoGenetix biosciences	Isolation of drugs from snails for ion-channels	Early stage start-up
Xerion Pharmaceuticals	Therapeutic monoclonal antibodies against cellular targets	Platform technology advanced service provider
4SC	Drug developer based on 3D structure of the target protein	Drug and technology developer
Pieris Proteolab	Computer integration tools based on Eclipse	Developer of therapeutics and reagents
Apalexo Biotechnologie	Cancer vaccines	Developer post feasibility studies in humans
Hadasit		
InCure	Early detection of solid tumours	Early stage developer of cancer diagnostic kit

GVT	Viral vectors	Platform technology, early stage gene-therapy
Hapto Biotech	Tissue engineering	Advanced start-up
Priosense	Diagnostics – detection of prions	Early stage
Hadassah Clinical Services	Vertical clinical services by Hadassah Medical Centres	Phase I-III trials + beta sites for medical devices

3.4 Company analysis in view of their CI potential

***Maturity and business status*:**

Out of the **37** reviewed portfolio companies:

- **16** are already in commercial phase providing services or products (BioAnaLab, Oxford Immunotec, Ludger, Pharmaness, SharDNA, CRS4, Genosafe, Cryozootech, bcs Biotech, Aurigon, Nanion, Genomatix, NascaCell, Pieris, 4SC, Xerion pharmaceuticals and Hadassah Clinical Services)

Five of these companies became commercial during 2004 (Pharmaness, Genosafe, NascaCell, CRS4, Oxford Immunotec)

- **1** has the potential to immediately be involved in clinical trials of Large Pharmaceutical companies (SharDNA).
- **20** companies (all the rest) are either in early incubation phases or few years away from commercialization.

***Field of expertise*:**

The above 37 portfolio companies are split as follows:

- 12 are in bio-pharmaceuticals
- 7 are in diagnostics
- 3 are developing molecular or animal based research tools
- 3 are CROs providing pre-clinical studies in animal models
- 2 are developing laboratory equipment
- 1 is in bioinformatics
- 1 is providing computation solutions (tools) for bio-information
- 1 is service provider of genetic data base
- 1 is providing computational solutions related to medical research
- 1 is providing cloning services for sports horses
- 1 is providing vertical services for clinical trials
- 1 is a developer of waste treatment solutions
- 1 is a developer of drug delivery medical device
- 1 is a developer of improved industrial enzymes

- 1 is developing and commercializing genetically modified plants

3.5 Analysis of Co-Incubation Potential

Analysis was made of the 37 candidate companies in terms of their co-incubation potential with Bio-Link portfolio companies as well as with non Bio-Link portfolio companies. The results are shown in the following table:

Company	Potential Co-Incubation within Bio-Link	Potential links outside Bio-Link
Oxfordshire BiotechNet		
BioAnaLab	InCure,	NasVax, CureTech, and other
Hybrid Systems	GVT, Nokad	VBL
Oxford Immunotec		XTL
Ludger	4SC, Xerion, Nautilus, Genodyssee	Bio-pharmaceutical companies
Green Biologics		Farming organizations
Caretek Medical		Pharmaceutical companies having injectable drugs
Genopole		
Nokad	Hybrid Systems, GVT	VBL, Harlan, Sigma
Nautilus Biotech	Pharmaness, BioAnaLab, Ludger	
Genosafe	GVT, Hybrid Systems	VBL, Ester
Nanobiogene		Zephyr, Israel's "Nano project"
Genodyssee		Bio-pharmaceutical companies
Genewave	Nanobiogene	Diagnostic companies
Cryozootech		
Genoplante Valor	Pieris, Genomatix	Large GM companies
Biomethodes		Enzyme based biochemical companies
Vaxon Biotech	BioAnaLab, Ludger	Cancer immunotherapy companies
Consorzio 21/Polaris		
Sardinia Genomics		
Pharmaness	Aurigon, Nanion	Phytomedics (US), Teva
SharDNA		Compugen, Teva
Bioker		Teva
bcs Biotech	InCure, Hadasit's BSE project	Zephyr
Centre for Advanced Studies		Airler
Bio^{M}		
Aurigon Life Science	Pharmaness, Nautilus	Teva (Bioline) + other
NascaCell IP		Compugen, Teva (Bioline)
Genomatix	Access package to Bio-Link	Evogene, Protalix, CBD,
Nanion	Pharmaness	Harlan, Teva
BioNetWorks		Teva
ConoGenetix biosciences	Nanion (existing!)	

Xerion Pharmaceuticals	BioAnaLab, Ludger, Aurigon	Biopharmaceutical companies
4SC	BioAnaLab, Ludger, Aurigon	Pharmaceutical companies
Pieris Proteolab	Genomatix, Genoplante	Academic & research institutes
Apalexo Biotechnologie		Biopharmaceutical companies
Hadasit		
InCure	BioAnaLab, bcs Biotech	
GVT	Genosafe, Nokad	
Priosense	Bcs Biotech	Veterinary diagnostic companies
Hapto Biotech	Aurigon	Tissue engineering and wound healing companies
Hadassah Clinical services	Oxford Immunotec, 4SC, Nautilus	Pharma, biotech and medical devices companies

3.6 Actual Links made aiming at co-incubation (As at May 30, 2005)

Type of contact made for Bio-Link	**Number of contacts**	**Remarks**
Within Bio-Link portfolio companies	41	Including Hadasit subsidiaries
Non-member bio or pharma startups	33	
European biotech	37	
Global pharma	16	
Israeli biotech or pharma	43	
Israeli technology representatives & service	5	
Israeli academia (research groups)	11	
Global bio-investment & management funds	5	
Opinion leaders	3	
Global CRO	1	
Equipment company	5	Nano technology
Ecology & waste treatment company	2	
Staff recruitment for Bio-Link companies	1	Business development
Total	**203**	
Responses		
Negative	63	
Positive	99	
No response	41	
Meetings between parties	31	Including Evry road show
NDA (signed)	6	

Exchange of written information	14	

3.7 Contact analysis per company (May 30, 2005)

	Bio-Link Company	Incubator	Business model	Status	Number of contacts
1	Genomatix	Bio^{M}	On line bio-information	Commercial	4
2	Pharmaness	Consorzio 21	Service provider	Commercial	15
3	BioAnaLab	OBL	Service provider	Commercial	15
4	Aurigon Life Science	Bio^{M}	Service provider	Commercial	26
5	Bcs Biotech	Consorzio 21	Diagnostics	Commercial	5
6	Nanion	Bio^{M}	Laboratory equipment	Commercial	9
7	SharDNA	Consorzio 21	Genetic data base	Commercial	5
8	CRS 4	Consorzio 21	Simulator developer	Commercial	1
9	Genosafe	Genopole	RA service provider	Commercial	10
10	Ludger	OBL	Bioanalytical services	Commercial	15
11	Pieris Proteolab	Bio^{M}	Therapeutics and reagents	Commercial	3
12	Cryozootech	Genopole	Cloning of sport horses	Commercial	1
13	NascaCell IP	Bio^{M}	Aptamers for molecular R&D	Commercial	10
14	4SC	Bio^{M}	Small molecule synthesis targets	Commercial	12
15	Xerion	Bio^{M}	Mab developer by phage display	Commercial - bankrupt	13
16	Nanobiogene	Genopole	Equipment for HTS	Development - advanced	2
17	Nokad	Genopole	Platform for research	Development - early	9
18	InCure	Hadasit	Diagnostics + pharma	Development - early	1
19	Hapto Biotech	Hadasit	Tissue engineering	Development	2
20	Priosense	Hadasit	Veterinary diagnostics	Development	1
21	GVT	Hadasit	Gene therapy vectors	Development - early	4
22	Oxford Immunotec	OBL	Diagnostics	Development - advanced	3
23	Hybrid Systems	OBL	Platform gene-therapy	Development - early	4
24	Switch biotech	Bio^{M}	Wound care	Development - bankrupt	1
25	Bioker	Consorzio 21	Pharma bio-generic	Development	3
26	BioNetWorks	Bio^{M}	Pharma	Development	3
27	Apalexo	Bio^{M}	Bio-Pharma	Development–bankruptcy	4
28	Green Biologics	OBL	Ecology & waste treatment	Development	4

29	Genoplante Valor	Genopole	Genetically modified plants	Development - advanced	2
30	Nautilus Biotech	Genopole	Extension of T1/2 of therapeutic proteins	Development - advanced	8
31	Genewave	Genopole	Amplification of fluorescence for Dx kits	Development - advanced	1
32	Genodyssee	Genopole	Natural mutations of therapeutic proteins	Development	7
	Total				**203**
	Bio-Link - general presentation		Presentation: general overview + presentation of portfolio companies incubation concept		15

3.8 Bio-Link companies actually taking part in the project

Definitions – A Bio-Link portfolio company took part in the project if its technology met the criteria set for co-incubation by the Bio-Link consortium management. Companies meeting those criteria but which refused to take part in the project or ignored repeated approaches to consider joining it, are also regarded as non participants.

	Bio-Link Company	Incubator	Business model	Status
1	Genomatix	Bio^{M}	On line bio-information	Commercial
2	Pharmaness	Consorzio 21	Service provider	Commercial
3	BioAnaLab	OBL	Service provider	Commercial
4	Aurigon Life Science	Bio^{M}	Service provider	Commercial
5	Bcs Biotech	Consorzio 21	Diagnostics	Commercial
6	Nanion	Bio^{M}	Laboratory equipment	Commercial
7	SharDNA	Consorzio 21	Genetic data base	Commercial
8	Genosafe	Genopole	RA service provider	Commercial
9	NascaCell IP	Bio^{M}	Aptamers for molecular R&D	Commercial
10	4SC	Bio^{M}	Small molecule synthesis targets	Commercial
11	Xerion	Bio^{M}	Mab developer by phage display	Commercial - Insolvent
12	Nanobiogene	Genopole	Equipment for HTS	Development - advanced
13	Nokad	Genopole	Platform for research	Development - early
14	InCure	Hadasit	Diagnostics + pharma	Development -early
15	Hapto Biotech	Hadasit	Tissue engineering	Development
16	GVT	Hadasit	Gene therapy vectors	Development - early
17	Oxford Immunotec	OBL	Diagnostics	Development - advanced
18	BioNetWorks	Bio^{M}	Pharma	Development
19	Green Biologics	OBL	Ecology & waste treatment	Development

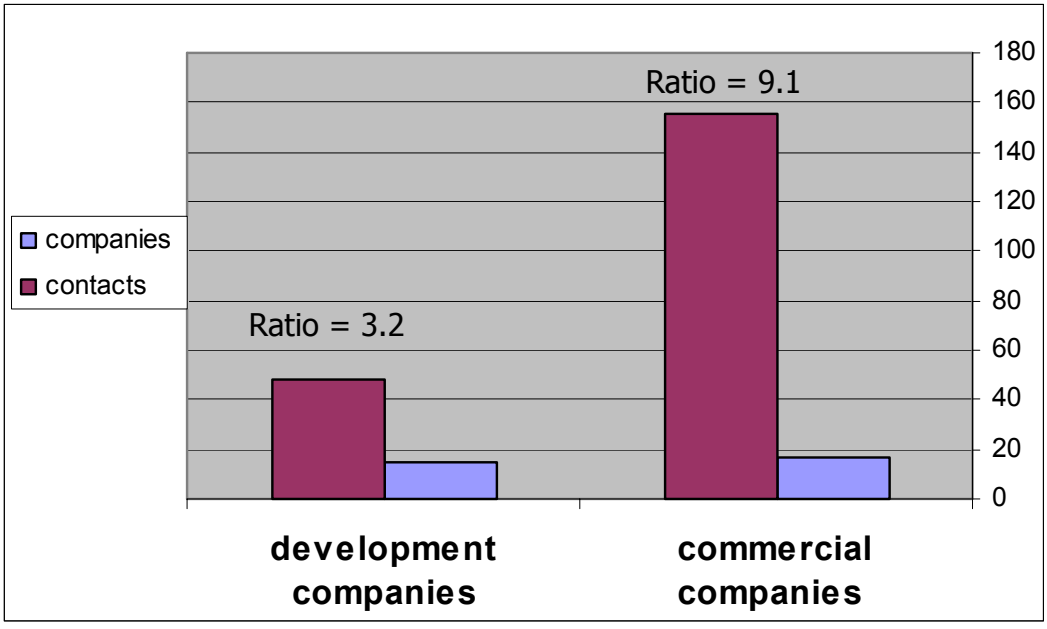
20	Nautilus Biotech	Genopole	Extension of T1/2 of therapeutic proteins	Development - advanced
21	Genodyssee	Genopole	Natural mutations of therapeutic proteins	Development
22	Hadassah Clinical Services	Hadasit	Provider of vertical services for clinical trials	Commercial
	Total			
	Bio-Link General		Presentation: general overview + presentation of portfolio companies incubation concept	

3.9 Analysis of the contacts made for Bio-link portfolio companies

The first conclusion of the Bio-Link project was that companies which have already reached the commercial phase have a higher interest in collaborating and co-incubating. In addition, as a result of the value of their services/products and technologies, these companies are more attractive to collaborators from both the Bio-Link circle as well as from outside it.

The following figure shows the advantage that more advanced companies have over the less advanced ones in terms of the number of contacts made for each of them . For the 15 advanced Bio-Link portfolio companies 155 contacts were made, an average of 9.1 contacts per company. For the 17 less advanced Bio-Link portfolio companies 48 contacts were made, an average of 3.2 contacts per company or 3 times less.

This result is shown in the following figure:



3.10 Modes of contacts made in order to explore potential co-incubation

Three modes were used in order to explore the co-incubation potential within the Bio-Link consortium as well as with companies outside it. Whenever possible, a personal meeting of the advisor with the candidate collaborator was attempted. The two other routes of contact (telephone and electronic mail) were the second choice.

The following table shows the number of contacts made:-

Communication mode	**Number of contacts**
Meetings	77
Email	84
Telephone	42
Total	**203**

In addition, it should be emphasized that Dr. Havron held several seminars and working meetings in which the Bio-Link consortium was presented as a whole. In addition, these seminars and meetings included presentations of specific portfolio companies according to their level of compatibility to the area of activity of the organization to whom the presentation was made. Seminars such as these were presented to Teva Pharmaceutical Industries, Meytav biotech incubator, to the Head of the Department of Biochemistry at the Weizmann Institute of Science and Clal Biotechnology Industries

3.11 Time required for creating a successful link

Forming a successful link between two Bio-Link portfolio companies or between a Bio-Link company and a non Bio-Link one is a time consuming process. 3-4 months are needed from the time that a company has been introduced to Bio-Link's technology advisor until an initial actual exchange of information between the company and a potential partner takes place. From this point onward, the progress of the link depends on the need and on the priorities that both parties give to the mutual project.

The following table lists the average time-lines for creating a link between two parties:

Task	**Months**	**Remarks**
Introduction of the technology to Bio-Link 's advisor	1 – 1.5	Requires travel to the various incubators
Introducing the candidate company to a potential partner + initial	1 - 2	

response		
Exchange of basic information between the parties	1 - 2	
Exchange and signing of a Non Disclosure Agreement (NDA)	1- 2	
Exchange and signing of term-sheet or RFQ (request for quotation)	3 - 6	
Total	7 – 13.5	

3.12 Presenting Bio-Link to multi-disciplinary organizations

In order to expand the exposure of Bio-Link to potential collaborators outside the consortium, a new approach was adopted from the second half of 2004. Within this approach, an attempt was made to attract the attention of vertical pharmaceutical companies which have multi-disciplinary in-company activities such as drug screening, drug development, drug delivery and pharmaceutical development. In addition, companies with specific strengths in certain medical fields such as cancer, central nervous system, circulation/coagulation, cardiology and gastroenterology have been approached. These companies are attractive potential collaborators for the Bio-Link consortium due to their need to find new technologies and products for their pipeline. The approached organizations include pharmaceutical companies, drug-development companies, biotech incubators and venture capital funds investing and managing a large biotech portfolio.

The presentation of Bio-Link to these organizations included the following activities:-

a) Presentation of 60-75 minutes about the Bio-Link consortium and its portfolio companies with a short description of the portfolio companies and their technology.

b) Forwarding the detailed technical material of each company to the hosting organization including contact details for each specific company.

c) Notifying the Bio-Link company about the link formed

The following table lists the organizations to which Bio-Link was presented:-

Organization (state)	Field of activity
Teva - Division of Innovative Research (IL)	Global big pharma (generics, cancer, CNS)
Teva – Strategic Business Planning & New Ventures	Global "newcomer" of generic biotechnology
Johnson & Johnson Development Corp.	Global Investment arm of J&J looking for new products
BiolineRx (IL)	Israeli Drug development company
Medica VC	International VC fund managing a wide biotech portfolio

Compugen	US based bio-informatics and drug development company
Wales Gene Park (UK)	Government affiliated institute to promote bio-business in Wales
Biopartner Incubator Maastricht (NL)	Bioincubator which will house10-12 biotech companies
Innomed	International VC fund managing and holding a wide biotech portfolio
Rad Biomed (IL)	Privatized healthcare incubator in Tel Aviv, Israel
NGT (IL)	Privatized healthcare incubator in Nazareth, Israel
Meytav (IL)	Privatized incubator in Kiryat Shemona, Israel

3.13 Road-shows

First road show January 8-9, 2004

As part of the Bio-link effort to promote co-incubation, a road-show for GVT (Hadasit, Jerusalem) was held on January 8 and 9 in Genopole (Evry, France). During this road-show, the company and its novel gene-therapy technology were presented to Genopole's management and to several of its portfolio companies including Nautilus, Genosafe and Genotone. All expressed an interest in GVT's technology. It was agreed that the contacts will be continued once GVT have proof of concept in an animal model for one genetic disease.

Second road show January 31, 2005

The Evry road-show seminar was held on January 31 and was hosted by Genopole in Evry. 14 Bio-Link portfolio companies took part in the event which included a half day of short presentations from each of the participants and then one-on-one meetings.
In addition, managers from 3 big-pharma – Sanofi Aventis, Eli-Lilly and Teva and from the French VC fund Sofinnova took part in the event.

The objective of the road-show seminar was to enable the participating companies to present their technology and meet representatives from pharmaceutical and biotech companies as well as from VC funds.
Another objective was to enable interaction between the companies from the 5 member bioincubators of the Bio-Link consortium in order to extend their networks for potential collaborations and business development.
Two types of companies that belong to the Bio-Link consortium took part in the event:
a. Companies involved in molecular-targeting.
b. Service-providing companies to early stage and more advanced drug development projects.

Bio-Link portfolio and invited companies participating in the Evry Biz-Dev Road-Show Seminar

No	Company	Incubator	Field of activity	website	Contact person
1	4SC	Bio^{M} Munich, D	New drug candidates for inflammation, cancer and infectious diseases	www.4sc.com	Dr. Sven Harmsen, B. Devel. sven.harmsen@4sc.com +49 89 7007 63-0
2	NascaCell IP	Bio^{M} Munich, D	Aptamers for drug development and research	www.nascacell.com	Dr. Andreas Jenne a.jenne@nascacell.de +49 (0)89 54 7272-0
3	Aurigon Life Science	Bio^{M} Munich, D	CRO- pre-clinical research & development	www.aurigon.de	Mr. Alexander Werner alexander.wernerl@aurigon.de +49 (0) 8158 2597-0
4	Bioker	C21 Cagliari, It	Drug delivery & bio-generics		Dr. G. Tonon, VP Biotech g.tonon@Keryos.itt +39 0252778.1
5	Pharmaness	C21 Cagliari, It	CRO pre clinical + animal models for psychotic drugs	www.pharmaness.it	Dr. Luca Pani, CEO +39 (0)70-924 2025 20 luca.pani@pharmaness.it
6	Genodyssee	Genopole Evry, Fr	Exploiting genetic mutations that confer super therapeutic indexes of natural cytokines	www.genodyssee.com	Dr. Jean-Louis Escary, CEO escary@genodyssee.com +33 (0) 1 69 29 80 55
7	Nokad	Genopole Evry, Fr	"knock-out" like animals by in-vivo deactivation of circulating proteins using viral vectors	www.nokad-technology.com	Dr. Aymeric Dugray, CEO Dugray@nokad.net +33(0) 6 24 20 80 59
8	Nautilus	Genopole Evry, Fr	Cell line& protein improvement for the manufacture of vaccines rec. proteins & antibodies	www.nautilusbiotech.com	Dr. Manuel Vega, CEO mvega@nautilusbiotech.com +33 (0) 1 687 69 56 38
9	Genosafe	Genopole Evry, Fr	Service company dedicated to gene transfer& cell therapy safety evaluation	www.genosafe.com	Dr. Patricia Noguiez-Hellin, CEO contact@genosafe.com +33 1 69 36 07 57
10	Bio-methodes	Genopole Evry, Fr	Molecular Evolution for improving enzymes and therapeutic proteins	www.biomethodes.com	Dr. Marc Delcourt, CEO Marc.delcourt@biomethodes.com +33 (0) 1 60 87 89 39

11	Asilomar	Woodside, California, USA	Development of off-marketed drugs to improve treatment of the nervous system.	www.asilomarpharma.com	Ms Constance McKee, founder constance@asilomarpharma.com +1 408.872.1094
12	Cellectis	Biocitech Romainville, Fr	Rational genome engineering using Meganucleases and DNA recombination for targeting unique DNA break at a specific location within living cells.	www.cellectis.com	Dr. André Choulika mail@cellectis.com +33 (0) 1 41 83 99 00
13	TK Signal	Hadasit Jerusalem, Il	Development of targeted radiopharmaceuticals for cancer diagnosis, treatment selection, disease monitoring and therapy	www.hadasit.co.il (go to portfolio companies)	Kobi Inbar, Ph.D CEO kobi@tksignal.com Tel: 972-3-643 8890
14	GVT	Hadasit Jerusalem, Il	Novel viral vector for gene-therapy	www.hadasit.co.il (go to portfolio companies)	Sorin Teich, CEO +972-8-6713658 g.v.t@ati.co.il
15	Ludger	OBL Oxford, UK	Products for glycobiology, glycomics & glycotechnology for therapeutic glycoproteins	www.ludger.com	Dr. Daryl Fernandes, CEO daryl.fernandes@ludger.com +44-(0)870 085 7011

Two months after the event – in April 2005 - a follow-up questionnaire was sent to the attendees of the seminar . The results of the questionnaire are shown in the following table:-

Contacts made between Bio-Link portfolio companies	18
Contacts made between Bio-Link portfolio companies and non bio-Link companies	4 All with Teva
Exchange of information after the seminar	12
NDAs signed	2
Collaboration initiated	2 (pending funding)

3.14 Business development visits of portfolio companies organized through Bio-Link

One of the objectives of the Bio-Link project was to promote exchange of information and to promote networking and business development.

Delegates from three Bio-Link portfolio companies decided to use their membership of the consortium to take a business trip to other incubators.

a) Apalexo's (Bio^{M}) CEO Dr. Freier made a visit tour to Consorzio21 in Sardinia and was introduced to several of the portfolio companies by Mr. Songini

b) Genodyssee's (Genopole) CEO Dr. Escary visited Israel and was introduced by A. Havron to 4 potential collaborators from the Israeli biotech and pharma industries as well as VC fund.

c) Aurigon's (Bio^{M}) Business Development Manager Dr. Werner visited Israel and was introduced by A. Havron to 8 potential clients.

B. Incubator Level

3.15 Partners meetings

Four partners meetings were held in 2004:

Location	Date
Evry	January 12-13
Jerusalem	May 9-10
Cardiff	July 5-6
Maastricht	November 4-5

Two partners meetings were held in 2005:

Location	Date
Evry	January 31– February 1
Cagliari	June 6-7

The major discussion topics during those meetings were the following:

a) Co-incubation efforts at the level of the incubator and the company level.

b) Report and follow-up regarding the progress of the project in terms of links, level of responsiveness, success and failure and conclusions to be drawn from them.

c) New recommended contacts proposed by the various participants.

d) Major hurdles encountered in the project and ways to overcome them.

e) Financial issues

f) Proposals for next seminars and meetings

g)) Lessons learned during the project

h) Recommendations for future activities

3.16 Bio-Link Seminars

Four Bio-Link seminars were held during 2004

Location	Date	Seminar key-speaker	Main Topic of Seminar
Paris	January 12	Prof. Phil Cooke, School of Social Sciences, University of Wales, UK	Assessment of European and North American incubators
Jerusalem	May11	Dr. Rina Pridor Israel's head of national incubator programme	Israel's incubator programme accomplishments and lessons for future
Cardiff	July 6	Dr. Nick Lench, Director the Wales Gene Park	Programmes and means for promoting biotechnology in Wales
Maastricht	November 4	Mr. Patrick Klein, Enterprise Directorate General, SME Financing Policy Unit, EC	Access to finance by SMEs and EU financial instruments

Two Bio-Link seminars were held during 2005

Location	Date	Seminar key-speaker	Main Topic of Seminar
Evry	January 12	Dr. Rafaele Tordjman, Sofinnova	Early stage financing
Cagliari	June 6	Mr. Zvi Rubinstein, CEO of Meytav incubator, Kiryat Shemona, Israel	Managing a bioincubator in development area - the Israeli experience

Details regarding Bio-Link seminars can be found in www.biolink.org.il *under Seminars*

3.17 Other events

a) ***Partnering event*** was held as a satellite seminar of Bionale in Maastricht on November 4, 2004.

b) Road show seminars

Please refer to section 1.13 of this report

4. Analysis of impact indicators

4.1 Success Factors

Five major factors were identified as key for co-incubation between young biotech companies in the participating incubators.

a) Technology
b) Incubator's support
c) Company's management
d) Budget
e) Time

a) **Technology**. A company is ripe for co-incubation if and only if its technology has reached beyond the proof of concept phase. This means that it has been tested successfully in applicable models several times and has been reviewed both internally as well as by outside experts. In addition, the technology must be transferable. This refers to procedures that are well documented in the form of scientific papers or in the form of industry style Standard Operating Procedures.

b) **Incubator's support**. Being a complex task, co-incubation requires the involvement of the host bioincubator. This involvement includes several important tasks:-
- Networking with other incubator, biotech and pharma companies.
- Follow-up of the activity
- Administrative support (legal, IP, etc.)
- Involvement of experts and consultants to assist in accomplishing the co-incubation objectives.

c) **Company's management**. The management of a start-up company must be devoted to success of the co-incubation. Unless this happens, the driving force of the process is lost. The involvement should be of both the CEO and the R&D manager at a level of the results and the problems encountered during the mutual work. In particular, a manager for the co-incubation project should be appointed. Without a project manager the project is bound to fail!

d) **Budget**. Co-incubation requires an allocated budget. This budget should support materials, labour and overhead and should allow travel between the co-incubation partners. Without a

special co-incubation budget, in a company with limited resources, the project will fail since it will take financial resources from the company's ongoing activities. It is recommended that a minimal annual budget of € 50,000 per company be reserved for co-incubation.

e) **Time**. The basic time unit in the bio-business world is 6 months. Therefore co-incubation demands patience. Just the mutual review of the technology may take 6 months and the signing of the agreements another 6 months. Results from a co-incubation project can **therefore** be expected after 2 years or even 3. The co-incubation process is aimed at strengthening the companies R&D capabilities to support future business development. It should be viewed within the long term scale which is required to develop a new drug, device or method in the healthcare industry.

4.2 Level of interest and motivation for co-incubation

We found that the expected level of motivation for co-incubation of young incubator companies is directly related to their field of activity:

For companies within the Bio-Link consortium, the level of interest and motivation in co-incubation was as follows:

- High for service-providing companies
- High for start-ups in commercial phase
- Moderate for platform technology start-ups
- Low for all companies in early development stage

As for the motivation for young Bio-Link portfolio companies to co-incubate with companies outside the Bio-Link consortium, we found the following:

- High for service-providing start-ups
- High for start-ups in commercial phase
- Moderate for platform technology start-ups

Low for all companies in early development stages

5. Relevance to other technological areas

The portfolio of companies which took part in the Bio-Link project was quite diverse. Although most of the companies in the project can be classified as biotech companies focusing on bio-pharmaceuticals, diagnostics or molecular tools for supporting such activities, the list included companies from quite diversified areas, all of which are linked to the healthcare industry:

- Bio-informatics software services provided through the internet (Genomatix, Bio$^{M)}$
- Software solutions for simulation of various medical procedures (CRS4, Consorzio-21)

- Genetic database for various clinical and diagnostic applications (SharDNA, Consorzio-21)
- Genetically modified plants (Genoplante, Genopole)
- Biophysical laboratory equipment - manufacturing & marketing (Nanion, Bio^{M})
- Manufacturer of medical device (Caretek Medical, Oxford BiotechNet)
- Waste treatment and ecological solutions (Green Biologics, Oxford BiotechNet)
- Animal model experimentation service providers (Pharmaness, Consorzio21; Aurigon, Bio^{M}; Nokad, Genopole))
- Analytical services (BioAnaLab and Ludger, Oxford BiotechNet; Genosafe, Genopole)
- Clinical trials services (Hadassah Med. Centre, Hadasit)

On the basis of this list, we claim that the conclusions drawn from the Bio-Link project have a significant level of relevance to other technological areas.
The relevance of the conclusions of the Bio-Link project in terms of the co-incubation model and BIP (Best Incubation Practice) Toolkit to other areas should be examined at three levels: Company's maturity, its business model and the technological need and solution it provides.

5.1 Company's maturity

Early stage incubator companies in any technological area are defined as companies which are less than 3 years old and have no more than 6 employees. This applies to companies which belong to all the incubation models analyzed in the Bio-Link project. These companies are reluctant to commit themselves to collaboration with similar entities for the reasons analyzed in detail in this report: need to focus on short term objectives, limited managerial attention, limited human resources, need for IP protection, lack of financial resources and lack of support at the incubator level. In addition, these companies have a difficulty in pinpointing and focusing their collaboration. Co-incubation requires allocated budget which should be provided by the host bioincubators, especially for young companies that cannot afford it (labour, travel, materials etc.). These parameters were common to all the early stage companies in the Bio-Link project regardless of their field of activity.
More mature companies, especially those that focus on providing services, are by definition customer oriented and thus seek collaborations at a relatively early stage. Mezzanine companies which are beyond the conception phase were in general found to be more open to collaborations, mainly to increase awareness and to find solutions to existing needs which can be treated by collaborating with other companies.

Thus, for some technological areas which mature faster than biotechnology such as IT, the co-incubation model may be even more relevant. This is due to the earlier need to reach the proof of concept stage which requires co-incubation and collaboration as described in the next paragraph.

5.2 Business model

Regardless of their field of activity, companies in the Bio-Link project could be split into three types: service-providing companies, product-providing companies and a mixed model combining service and product.

Service-providing companies are actually ready for co-incubation once their facility and certification are in place. These goals can be achieved within a relatively short time. The type of co-incubation these companies seek is aimed at promoting their business. To do so, they need to focus on introducing themselves to potential clients. The co-incubation model provides an ideal framework for such "market-penetration", since it enables the service provider to run a pilot "service" while the customer receives the service at an introductory cost for the provision of the feedback from the study.

This type of collaboration is relevant to any field. If successful, it may pave the way for both companies to promote their business. On the other hand, the main drawback of this model is that the "service receiver", which is usually a young company, cannot afford too many failures with an inexperienced service provider. Within the Bio-Link project, the product-developing companies were the major customers of the "service providers". Most of the services are part of the regulatory package which is required to take a pharmaceutical product or a medical device through the approval process in the EU or the US.

Most of the product-developing companies in the Bio-Link project were relatively young and therefore were not in a position to promote their products. On the other hand, some of them, especially the more mature ones, were already at the stage of looking for certain service providers. On this basis, several successful co-incubation projects were initiated.

According to the above analysis, the implementation of the co-incubation model to other technological areas is highly dependent on the financial support that the co-incubation activity is receiving. In our opinion, the success of the process can be enhanced by providing the partnering companies with a dedicated budget for the co-incubation. Thus, the "pilot" run of the "service" will be financed by an external grant which will reduce the risk that both parties are taking by implementing a new technology or service for the first time. In addition it will provide the financing entity (EU or other) to provide "mentoring" activities to the young companies and guide them accordingly.

A co-incubation model does not necessarily call for the involvement of two young companies. Based on the Bio-Link experience, such a co-incubation model is ideal when the partner of the young start-up company is a more mature firm whose needs are well defined and who can "afford" the risk of collaborating with the young company. In the Bio-Link case, many of the "service-providing" companies collaborated with companies which were not part of the Bio-Link project. Good examples are several collaborations with Teva, the world's largest global generic pharmaceutical company. This type of collaboration is highly recommended as a model for other technological areas. Namely, a leading company in a certain field uses the services/products of young companies in order to solve a specific problem in a "niche" in which the young company has an advantage. Beyond the specific technical collaboration, this relationship has other incremental benefits such as exposing the young companies to the business culture of big firms and to their managerial and planning activities.

5.3 The technological need and solution.

Few of the portfolio companies in the Bio-Link project provided a unique solution to a problem which concerned many companies. Three examples are worth mentioning. The first is Nanion (Bio^{M}, Germany) that developed new bench-top equipment to measure the effect of various potential drug candidates on ion-channels. The regulatory authorities in the EU and the US have made this test mandatory.. Nanion has therefore introduced a solution to an unmet need which prior to its invention, was carried out in few places around the world using a cumbersome and very expensive experimental setup. The other example is Genosafe (Genopole, France), that established a regulatory service specializing in gene-therapy. Gene-therapy has become a controversial field due to the need to use viral vectors to carry the gene to the target cells. There have been some successes, such as the treatment of 'bubble babies' by A Fischer's team at the Necker Hospital in Paris. Several clinical trials ended with the death of a few patients. However, it is obvious that for some severe genetic disorders, gene-therapy will be the only solution. Hence there is a real need for a company that can guide and take gene-therapy companies through the complex regulatory process they face.

The third example is Green Biologics (Oxford BiotechNet, UK) which develops special bacterial strains to expedite the processing of domestic and plant derived waste and turning it to compost. Obviously, many organizations and industries have to cope with this problem, which until now was solved by standard "compostation" methods which require long incubation periods and therefore substantial storage areas.

These three examples are applicable to any technological area. It seems that in fields such as IT, engineering and industrial chemistry, there is a lot of scope for companies providing "niche"

solutions. These companies are excellent candidates for co-incubation with well established companies.

General lessons which were gained during the Bio-Link project and can be applied to other technological areas include:-

1. The appointment of a technology and business advisor to the co-incubation project who maps the needs, the solutions and the matching companies for a specific technology. Incubator companies need to be “taken by the hand" for the purpose of exchanging information and meet potential collaborators. This can be accomplished only by an expert in the field who understands both the technology as well as the business environment within which these companies operate.
2. Dissemination. From all the dissemination activities which were carried out during the 30 months of the project, the most significant and fruitful one was a technology road show seminar in which 14 portfolio companies of the Bio-Link project met and presented their technology. Among the invited companies to this event were "big-pharma" and venture capital funds. One of the main conclusions from the Bio-Link project is to make such meetings an annual or even semi-annual event. One-on-one meetings between companies are the best opportunity to create fruitful co-incubation collaboration.

5.4 Summary

In spite of the fact that the Bio-Link project focused on life-sciences, healthcare and biotechnology, its relevance to other technological areas is high. The conclusions drawn during the project are applicable to other areas, especially when points such as company maturity, company's business model and the unique solution provided by the company are being considered. Service-providing companies have a better starting point to create a successful co-incubation project than companies which are developing a product. Young companies (less than 3 years old and less than 6 employees) are unlikely to be involved in co-incubation projects. A unique technological solution increases the chances for co-incubation even at an early stage. A co-incubation project is more likely to succeed when one of the partners of the incubator company is a well established organization that on the one hand can "bear" the risk of collaborating with a young company and on the other hand, can bring to the collaboration its technology and business culture.

General recommendations which are applicable to enhance co-incubation in any technological area refer to the need for an allocated co-incubation budget, the need to appoint a business and technology

leader and the need to carry out many dissemination events in which companies will get the opportunity for exposure.

We believe that the Bio-Link project served as a successful model for co-incubation and industrial collaborations between young companies and more mature companies in any technological area.

6. Relevance to other regions

The Bio-Link project comprised five partners from five regions from the EC and AC. The only common denominator between the five regions was their role as centres for biotechnology. The co-incubation scheme is very relevant to other regions, as the logic behind it is enhancing customer performance by creating a network of links between a number of incubators from different regions. In addition, the experience gained by the project showed that big-pharma companies have few limitations in cooperating with companies outside their region due to their global operations.

In our research, we did not find many cultural differences between the regions. This was because the field of bio-technology is dominated by regulation and therefore there is little room for individuality in the research process. Other fields in which the regulation does not dominate the process might expect an increase in cultural differences. Still, there are certain regional attributes required for applying the scheme successfully to other regions:-

a) Each region participating in the scheme must have a strong centre focused on the technology being co-incubated (IT, Biotech, engineering, etc.)

b) The region must have sufficient infrastructure for technology development including Universities, Hospitals (important for Biotech) and advanced industry.

c) Developing regions: The project can be especially productive for developing regions, as shown in the relevant chapter of this report, but for every developing region participating in the project, there must be at least four other partners from regions that are considered leaders in the industry.

d) One of the main lessons gained from the project was that a dedicated manager is required to work full time on creating the links between the incubators and between their customers. A full time manager can only deal with 5-6 regions at a time. Any scheme involving more than 5 regions will require an additional manager.

e) Language barriers: Though in today's global village most managers have quite a strong grasp of English or French, it is essential to make sure all the incubator managers from the participating regions have at least one common language of communication.

7. Transferability to Developing Regions

An important aspect of the Bio-Link project was to evaluate the success of the scheme in developing regions. The Consorzio Ventuno incubator in Sardinia was chosen as the fifth partner in the project. Created by the Autonomous Region of Sardinia with Law n. 21, Consorzio Ventuno has been working side by side with operators since 1989. It is the first public company in Sardinia to receive ISO 9001 quality certification.

Consorzio Ventuno has two missions: the first is to supply real and technological services to the island's enterprises to facilitate their integration into the global market; the second is to promote, implement and manage POLARIS, the scientific and technological park of Sardinia.

Consorzio Ventuno offers two kinds of services to Sardinia's small and medium enterprises:-

- **Real services** consisting of specialized consultancy in all stages of company activities, from drawing up business plans to financial, technical and organizational assistance, including marketing services and quality certification.
- **Technological innovation services**, with the aim of introducing innovation in products and processes into companies.

  Consorzio Ventuno manages vocational training classes and information initiatives on new entrepreneurial and technological trends.

Activities in support of applied research:

Polaris – Poles of Advanced Research in Sardinia

Consorzio Ventuno participates in the share capital of the following research consortia and companies, which are also partners of Polaris: CRS4 (Information & Communication Technologies); Porto Conte Ricerche (Biotechnologies applied to agribusiness and environment); Società Parco Scientifico e Tecnologico della Sardegna; Promea (Materials); Pharmaness (Pharmacology of the central nervous system); AILUN (optical technologies); Parco Genos (Molecular genetics; Biomedicine; Bioinformatics).

Incubation, prototyping and experimentation services

Within the Polaris network, Consorzio Ventuno manages:-

- A prototyping and vocational training centre (Proto 21) and a technological incubator for enterprises operating in the Information & Communication Technologies (Internet Farm) in Cagliari-Pula;
- A technological incubator, a pilot plant and a large equipment centre for biotechnologies applied to agribusiness and environment in Alghero-Tramariglio;
- A technological incubator in Nuoro
- A service centre for enterprises of the textile sector in Oristano (Officina Tessile).

7.1. Conclusion Gained from the Participation of C-21 in the Bio-Link Project

Four portfolio companies from C21 were selected for the Bio-Link project:-
Pharmaness (Pharmaness)
Bioker
SharDNA
Bcs biotech

Of the four, Pharmaness is a service-providing company in the area of pre-clinical trials, whilst Bcs – biotech is a commercial diagnostic company selling kits for the human and veterinary markets.
The two other companies, Bioker and SharDNA, are development companies, one in the field of generic therapeutic recombinant human proteins and the other in genetic databases provided through the unique genetic homogeneity of part of the Sardinian population.
In comparison to the other 4 partners of the Bio-Link project, C21 was significantly less responsive at both the incubator management level as well as at the company level (Pharmaness being an exception). As a result, no significant co-incubation ties were formed between the C21 portfolio companies and other portfolio companies of the Bio-Link consortium or with companies outside the consortium. Pharmaness being a service-providing company was an exception and created several fruitful links during the project.
The reasons for that are attributed to the following:-

1. Language – most of the managers in the Sardinian incubator as well as those in its portfolio companies do not speak fluent English. This results in hesitancy to communicate both in writing and also in presentations.
2. Maturity – most of the portfolio companies of C21 were relatively young and as such, had to focus on short term objectives such as their establishment, fundraising and recruitment of professional staff – a quite difficult task in Sardinia. In addition, during the two years of the

project, all the portfolio companies were involved in planning the new facility in Pula which was recently officially opened. This has drawn a lot of managerial attention and other resources from the companies, not allowing them to dedicate time to collaborations.

3. Tradition of collaboration - since the Sardinian companies are relatively young (Bioker being an exception) their management was either unaware or not experienced enough to appreciate the benefits that co-incubation can provide.

However, the Bio-Link project had some important contributions to C21 managers and their client companies:-

1. **Increased management capabilities**- As Consorzio Ventuno is not an incubator in the strict sense of the word but more a science park, the local management lacked certain expertise and skills in the field of Bio-Incubation management. The close connections with four experienced managers and the participation in five seminars focused on management capabilities greatly enhanced the abilities of the managers of Consorzio Ventuno.
2. **Exposure to the European Bioincubator network**-As detailed above, Consorzio Ventuno houses a number of unique and attractive companies. Exposing the Biotechnology abilities of Consorzio Ventuno is a difficult and expensive process due to the isolation of the area. Therefore, the Bio-Link project, which enabled the other four incubators to get acquainted with these companies on a level which would not have been possible otherwise, was of great importance.
3. **Co-Incubation success-** The Bio-Link co-incubation scheme created 22 contacts for five companies within Consorzio Ventuno. (As seen in Table 5). These connections contribute not only to Sardinia but to all players in the European Biotech industry who were previously unaware of the area's strengths in fields such as pharmacogenomics or the strong knowledge base and genetic skills on endogamy and consanguinity in firms and institutes like SharDNA, Pharmaness, CRS4 and Parco Genos.

The Bio-Link co-incubation scheme has proved its potential in enhancing the learning curve of managers in developing areas by helping them avoid repeating mistakes of newcomers to the industry. The scheme can potentially promote the region's entry into the European market and increases the exposure of the companies in such regions.

7.2 Conclusion regarding participation of incubator in less developed biotech areas.

Based on these observations, some recommendations should be adopted.

Bioincubators from less developed areas should participate in a co-incubation process if they can meet the following criteria:-

- No language hurdles (English!)
- At least 3 years post establishment.
- Previous experience of the management of the portfolio companies in international technological collaboration.
- Higher level of involvement and commitment of the incubator's management in the co-incubation process of its portfolio companies.
- Our general conclusion regarding the relevance of service-providing companies to a co-incubation process is even more relevant to bio-development areas.

Pharmaness, which as previously stated, was an exception in C21 portfolio companies, stresses these conclusions even more. Its relative success in the Bio-Link project can be attributed to the fact that its management had a wide previous international exposure and a strong need for collaboration.

8. Experience gained by the start-up companies as well as by the incubators during validation

8.1. Level of responsiveness and need for follow-up

The level of responsiveness of some of Bio-Link's portfolio companies is insufficient.

Out of the 32 companies approached:
17 responded after the first approach
10 responded after the second or third approach
5 did not respond

Intensive follow-on efforts were made in order to convince the selected portfolio companies (which agreed to take part in the projects) that they can benefit from it.

8.2. Lack of background material

During the second half of 2004, four Bio-Link portfolio companies opened a website. This made the effort to link them to a potential partner much easier. There are still a few companies that do not have a website which as we can conclude today, is an essential tool for co-incubation.

8.3. Lack of resources

During his contacts with several Bio-Link portfolio companies, it was made clear to the project's technology advisor (Dr. Havron) that most of the young companies in the development phase (not those in the commercial phase) cannot devote resources to explore the co-incubation opportunity offered by Bio-Link. The reasons given are the need to focus on the activities to which they are committed, lack of scientific or technological personnel and lack of budget. Dedicated co-incubation budget will allow turning some of the initial links into practice, especially between young Bio-Link portfolio companies.

8.4. Lack of time to follow the actual results of the project

Based on the experience gained so far in the project, the average time to create a link is 3-4 months while 6 more months are needed to start operating the main science and technology activities of the co-incubation process. According to these interim results, it is estimated that by June 2005, the number of links will reach approximately 200. The creation of a successful co-incubation out of these links will extend beyond June 2005 and is expected to last through 2005 and 2006. By that time, the fruits of some of the co-incubation projects may become available, providing the final and most significant results of the Bio-Link venture.

8.5. Business development.

Co-incubation is primarily aimed at business development. Since all the participating incubators lack a position of "incubator business development manager", it is strongly recommended that per each co-incubation initiative, an accompanying expert in business development should be appointed. This refers mainly to the 3 major professional disciplines: drugs, medical devices and platform technologies. The responsibilities of the business development advisor will include the review of the business impact of the co-incubation in terms of its relative contributions to both parties. A business development "mentor" can also explain and clarify the benefits of the co-incubation to the management of young start-up companies, which in most cases lack the necessary business experience. Once an agreement or a term sheet has been issued, his role will be to review it and adjust it to the actual needs of both partners. In most cases, this assistance refers to simplifying the agreement.

8.6. Need for Consolidation.

Bioincubators should try to consolidate their co-incubation efforts. This refers mainly to their portfolio companies in a specific field such as new drugs for cancer. In this case, the desired co-incubation model will aim at collaborating with one major partner with all the portfolio companies

dealing with cancer in that specific incubator. This model has several advantages as compared to the one-on-one model. In the first place, it reduces the risk for the partnering company. Then, it enables the interested biotech or pharma company to save time and resources by reviewing several companies in "one glance". Such collaboration creates a lot of motivation and drive for the incubator client companies and will also enable the incubator to attract better new companies which are active in a specific field and create a selection among the candidate companies. It also affords the opportunity to create group of SMEs involved in one theme or topic, which would allow better access to national and European funds, to become a one-stop shop for end users and better respond to the needs of the clinical professionals.

9. Bio-Link Project Evaluation including advantages and limitations of the co-incubation scheme

9.1. **Strengths:**

The relative strengths of the Bio-Link projects are the following:-

1.1 ***Academic environment*** – each of the five participating incubators is one of the leading incubators in its country. Each of these incubators has a strong interaction with the adjacent academic institutions, some of which are among the leading ones in the world. Many of the portfolio companies in each of the participating incubators actually came out of the "next door academic institute". This applies to Oxfordshire BiotechNet and Oxford University, Bio^{M} and three Max Planck Institutes in Munich as well as the University of Munich, Genopole and the adjacent French Research Centres, Consorzio 21 and the University of Cagliari and Hadasit with the Hebrew University of Jerusalem and the Hadassah Medical Centres. Each of the incubators has board members from the local academic community. In some cases, the scientists from academia serve on several of the incubator committees and assist in selecting projects and in solving scientific and technological problems. In most cases, we found that the incubator actually sees itself as the default organization for the commercialization of projects coming from the neighbouring university. In addition, the incubator identifies itself in many cases as an affiliate of the University.

1.2 ***Science and Technology*** - The portfolio companies of all five participating incubators deal with very high levels of technology which are in the "front-line" of the innovation in their field. In addition, the companies selected for the Bio-Link project in each incubator covered a wide scope of technologies from genomics, proteomics, drug delivery, pharmaceutical technology, analytical methods and animal services. This fact enabled each incubator to provide co-incubation potential

to a wide scope of potential partners. In addition, the internal interaction within each incubator enabled a lot of fertilization and exchange of know-how.

1.3 ***Infrastructure*** **–** All the five participating incubators in the Bio-Link project have facilities which are very supportive for biotech start-up companies. The services provided include not only physical items such as space, utilities and scientific equipment but also administrative support and access to service providers such as law offices, patent attorneys, accounting etc. In some cases, like Consorzio 21 in Sardinia, state of the art facilities were built for the client companies. Hadasit in Jerusalem is an incubator that provides its client companies with vertical services starting from basic science and ending in clinical trials in human beings.

1.4 ***Location*** **–** 3 out of the participating incubators in the Bio-Link project (Bio^{M}, OBL and Genopole) are located in the centre of the European Biotech Circle and as such are accessible for visitors and enable their clients to take part in the major European biotech events. Two partners (C21 and Hadasit) are more on the periphery and thus travel from and to their locations is more expensive and time consuming.

1.5 ***Networking*** **–** The Bio-Link project expanded the networking of each of the participating portfolio companies. According to the project's reports, more than 240 links were made for the 22 portfolio companies which were selected as best candidates for co-incubation. The networking was provided by the Bio-Link project through personal contacts of the Technology Advisor (who has 25 years of experience in the global bio-pharmaceutical industry), by mutual meetings between the companies, by articles, lectures and other dissemination activities. In fact, the contribution of Bio-Link to the networking of the portfolio companies was mentioned by them as the major contribution of the project.

9.2 Weaknesses:

The major weaknesses which were identified in the project are as follows:-

1. ***Awareness to the need for co-incubation*** – most of the entrepreneurs that founded the Bio-Link portfolio companies came directly from academia and for most of them, this was their first business experience. As such, they were very focused on their invention and lacked the business culture of "openness and sharing" which is the basic essential for co-incubation. This refers mainly to the early stage product developing companies (75% of the Bio-Link portfolio companies) and not to the service-providing companies. In those cases where the managers of a certain portfolio company had already worked for a biotech or pharmaceutical company, they were much more open to the co-incubation process. A unjustified fear for their

IP also prevented some of the companies considering a co-incubation and collaboration with another young company.

2. ***Maturity*** – companies which are in their seed phase (conception) are not ready for collaboration due to their need to focus and accomplish significant milestones in a short time and under considerable budgetary restraints. Therefore companies which are ready for co-incubation should be 2-3 years old. This age will also result in internal clarification and understanding of the needs for co-incubation in terms of the benefits that the company can obtain with such potential collaborations.
3. ***Critical mass*** – the need to allocate well-trained scientific and technological staff for the co-incubation with a potential partner is impossible for a company with less than 8 employees. Co-incubation requires a dedicated scientist/engineer who can devote most if not all of his time to the project.
4. ***Management*** – inexperienced management of the founding scientists usually lacks the required view to understand the need for collaboration and co-incubation. Again, this applies mainly to the product-developing companies rather than to the service-providing portfolio companies which are much more business-oriented.
5. ***Business model*** – Young biotech product-developing companies are not ready for co-incubation due to their need to focus on short term tasks and accomplish the milestones set in their business and working plans. Co-incubation requires the allocation of personnel, time and material which these young companies simply cannot afford.
6. ***Lack of dedicated co-incubation funding*** – Co-incubation requires dedicated funding since collaboration between scientific or technology developing groups means travel, use of material, use of legal services to set the terms of the collaboration, considerations related to sharing IP etc. The Bio-Link project did not take these expenses into consideration. Budget to support co-incubation between portfolio companies did not exist, so any co-incubation was financed by the portfolio companies themselves. This limitation enabled only more established, advanced companies to take part in the co-incubation process while the young companies which may have needed co-incubation were unable to afford it.
7. ***Lack of financial resources dedicated to the main Incubation Stage purpose***: Industrial Proof of Concept.

Genopole, since inception, has promoted and put into operation an incubation system including a pre-seed fund: Genopole 1er Jour (G1J). This very small fund (1.2 M€ and recently an additional 2.2 M€) was intended to finance the preparation of a business plan (BP) to be used by start-up companies to more consistently and credibly approach venture capitalists.

Genopole's experience over the first months of incubation activity indicated that projects in the incubation-seed stage could be classified into two well-defined categories:

Category A: projects that raise more than €5m within 6 to 12 months,
Category B: projects that raise between €1.5m and €2m after a period of 18 to 24 months

Note that both categories benefited from the same model of financing and follow-up from Genopole.

The reflections derived from that situation have led Gabriel Mergui, the first designer of G1J, to propose a project for a Local European Seed Fund (LESF) which could address the need for an incubator, for example Genopole, to have access to seed funding as well as the pre-seed funding provided by G1J. This document is attached to this Final Report as an Appendix .

Analysis:

It is likely that the excessive length of the fundraising period for the companies in category B resulted from a lack of visibility of these companies to the venture capital community ("VCs"). Where projects were not considered, it was because they had not achieved their **industrial proof of concept**.
Genopole observed that if the duty of an incubator was to accelerate achieving such proof of concept, it was similarly the duty of the incubator to avoid wasting one of the major assets of the future company, namely the start-up company's **lead on competitors**.

For a number of reasons discussed in the attached document, VCs are increasingly reluctant to invest in pre-seed and seed-stage companies. The current reluctance of VCs to invest in early stage rounds of financing confirms our thinking that an incubator must play a stronger role in a start-up's success. The presence of a seed fund connected to an incubator would be powerful leverage in helping start-up companies complete rounds of finance more quickly.

The objective of the LESF project is ambitious and twofold:
Describe a model for a seed fund linked to an incubator: LESF. This seed fund would specialize in biotech and would make 80% of investments in the local area and 20% in other European bio-clusters.

Convince several European financial players to create similar funds which would work .2 together in a **network**.

It is likely that the level of solidarity which is presumed in a complete co-incubation would be much more easily achieved when a co-investment takes place.
Building Europe may very well take this path.

9.3 Opportunities:

The main opportunity for the Bio-Link project refers to the business potential it opened for the participating portfolio companies. These include:-

1. ***Exposure*** – some of Bio-Link portfolio companies made as many as 20 links to potential collaborators and thus were exposed to a variety of companies in their field. The links made for these companies were not only within the Bio-Link circle but also to companies outside it, including other biotech incubators, biotech companies, big-pharma, academic institutions and commercial representatives.
2. ***The Bio-Link service model for early stage biotech companies*** – service providing companies such as BioAnaLab, Ludger, Aurigon, Pharmaness, Hadasit Clinical Services, Genosafe and Nokad should become a core "mini-consortium", whose main objective should be to provide services to young biopharmaceutical companies who are in the development stages to submit an IND (Investigational New Drug) application in the EU or the US. The submission of this document requires process development, analytical development, pharmaceutical, pre-clinical development and clinical development. All these are provided by the companies in the above list – each in its field of expertise. Bio-Link's major opportunity could be in establishing a service-providing consortium to enhance and expedite the ability of young biotech companies to reach the IND phase and by that increase their valuation and their ability to raise additional funding.
3. ***Developing areas*** – we believe that the Bio-Link model is a good one to be adopted by developing areas in the field of biotechnology and the healthcare industry. A prime example is Consorzio 21 in Sardinia, which is considered a developing area, since biotechnology began its rise there only a few years ago. The co-incubation with more advanced incubators located in the core of the European biotech community can be very beneficial both from the academic aspects as well as from the business development ones.

4. ***Best Incubation Practice (BIP-toolkit)*** – As part of the Bio-Link project, we devised the BIP-toolkit. We see the adoption of this toolkit as an opportunity for policymakers in the EU, and at national and regional level, to improve the incubation practice for young biotech companies in the EC and the affiliated countries. The toolkit is actually the direct outcome of the whole project and included in it are recommendations which refer to the advantages and weaknesses of the Bio-Link project which are set out in this report . The major recommendations of the BIP-toolkit are summarized below:-

Best co-Incubation Practice Tool Kit

Optimal incubation model	*'All in one' model:* - In house biotech technological infrastructure - Access to and collaboration with industry - Access to business development experts - Networking - Access to VCs & financial community - Access to service providers (legal, IP, accounting) - Collaboration with local academic institutes - In-house science & technology guidance - Synergy with next door neighbour - Public relations
Selection criteria for co-incubation	*a)Technology developer* Wide scope Ready for implementation and/or technology transfer *b)Service provider* Certification Technological background material + website Fast response Accessibility *c) Maturity* Post "creation hassle" – 2-3 years old *d) Critical mass – not less than 8 employees*
Key Success Factors for Co-incubation	1. *Technology* Beyond proof-of-concept "Transferable" – at "operating procedure" level 2. *Incubator* Co-incubation oriented and supportive Business development guidance – from day zero Administrative assistance (TT and MTA template documents in place) 3. *Company's Management* Willingness and openness to collaborate and share (language &

	culture gap) Managerial awareness and attention Co-incubation project manager 4. *Budget* Financial resources allocated for co-incubation – labour, material, travel 5. *Time* A successful co-incubation requires at least 2-3 years from conception.
Likelihood of co-incubation success	High for service-providing companies Medium for platform technology companies Low for developers of molecules High for companies in commercial stage Medium for companies in transition (pre-commercial) Low for early stage companies

5. ***BizBioLink*** - A continuation programme for Bio-Link named BizBioLink was submitted by the five participants in the Bio-Link project to the FP6 programme. It focuses on business development assistance for young companies in the five incubators and in addition, incubators in Spain and Eastern Europe. We hope to implement our recommendations from the Bio-Link project and take them one step further to actual business ties and agreements.

9.4. Threats

The major threats for the Bio-Link project may arise if the recommendation outlines in our reports and conclusions are ignored by others who intend to implement a co-incubation model. Co-incubation is a promising tool to enable young companies to reach their milestones and bring their products/technology to maturity. This will increase their value and their chances of additional funding. Without significant achievements that are at least partly nourished by co-incubation, many of these companies will return their intellectual property to the academic institutes from which they originate, be acquired for an insignificant sum of money or relocate, mainly to the US.
An additional threat to the EU entrepreneurial biotech comes from US-based companies which are looking to purchase attractive, advanced, innovative European technologies. Co-incubation can deepen the roots of the European companies and avoid the early transfer of their technologies across the Atlantic.

10. Success stories

Overall during the project 6 NDAs were signed and 14 exchanges of written proprietary information have been made.

10.1 Bio-Link Service Providing Companies

	Name	Incubator	Field of activity
1	**Aurigon Life Science**	Bio^{M}, Munich	CRO pre-clinical & animal models
2	**BioAnalab**	Oxfordshire BiotechNet, Oxford	Validation of immuno assays
3	**Genosafe**	Genopole, Evry	Regulatory and strategy for gene-therapy and other bio-molecular agents
4	**Ludger**	Oxfordshire BiotechNet, Oxford	Analysis of glycosylated side chains
5	**Nanion**	Bio^{M}, Munich	Monitoring the effect of new chemicals on ion channels
6	**NascaCell IP**	Bio^{M}, Munich	Custom designed Aptamers for R&D
7	**Pharmaness**	Consorzio 21, Cagliari	CRO pre-clinical & animal models with specialty in mental disorders/psychotic drugs
8	**Nokad**	Genopole, Evry	Autoimmune (non-genetic) knock-out animals for biological studies

A total of 109 links out of the 203 links made during the project were for the 8 service-providing companies listed above. The success of the Bio-Link project regarding these companies can be split into two parts:-

1. Exposure to consumers:

The Bio-Link project includes more than 15 companies that develop products. These products are either drugs (molecules), diagnostics, medical devices or various methods used to assist in the development process of these products. The regulatory registration process of each type of product requires the services of one of the "service-providing" companies. For example, pre-clinical trials in animals are required for medical devices and for drugs. Aurigon, Nokad and Pharmaness provide them. Regulatory assistance is provided by Genosafe while analytical services and method validation are provided by

Ludger and BioAnaLab. NascaCell provides a molecular method to assess the activity of a candidate drug.

This battery of service-providing Bio-Link portfolio companies was presented as a potential IND package to many potential collaborators. The IND package is the application submitted to the EMEA and /or FDA to initiate clinical trials in human beings. The application includes data provided by the above 8 companies. As a result of the Bio-Link project, all of the portfolio companies are now aware of the capabilities of the service-providing companies which will be approached by them once they are ready to begin the compilation of their IND package. In addition, the battery of service-providing Bio-Link portfolio companies was presented to many biotech and pharmaceutical companies to encourage them to use these services in the future.

2. Specific success stories for the service providing companies include:-

a) Ongoing business relations of Aurigon, Ludger and BioAnaLab with 4 biotech incubators in Israel (Rad-Biomed, Meytav, NGT and BiolineRx) and with 4 Israeli companies (Teva, Protalix, Target-In and CureTech). These types of relations refer mainly to the fact that the Bio-Link service providing members are included in the list of approved sub-contractors of their client companies who will approach them whenever required.

b) The following business relations were formed between Bio-Link service-providing companies and other Bio-Link portfolio companies:-

Company	Genosafe	NascaCell	Aurigon	Ludger	Pharmaness
Incubator	Genopole	Bio^M	Bio^M	OBL	C21
Contacts established with:	Nokad GVT Aurigon	Pharmaness Ludger 4SC	Nokad Nautilus TK Signal Ludger	NascaCell Aurigon	NascaCell Nokad GVT
Exchange of information after first meeting	Nokad	Pharmaness Ludger 4SC	Nokad		Nokad GVT
Ongoing collaborations	Nokad	Pharmaness (expected)			Nokad

c) Contacts of service providers to other companies:

Ludger (OBL) – Protalix (Israel): Analysis of glycosylated human therapeutic recombinant proteins expressed in plant cells.

BioAnaLab (OBL) – Protalix (Israel): Development of test for monitoring levels of product in blood

10.2 Bio-Link product-developing companies

All the success stories related to Bio-Link product-developing companies are with external companies which do not belong to the consortium:

Green Biologics (OBL) – Hazeva R&D unit (Israel) Collaboration and exchange of material are ongoing in order to implement Green Biologics bacterial technology to expedite the processing of agricultural green debris and turning it into compost which can be used to fertilize the plants for the next season. The feasibility of the technology will be assessed next season pending funding by the Israeli Ministry of Agriculture.

4SC (Bio^{M}) – *Teva (Israel)* Teva is exploring several molecules of 4SC in order to use them as drug candidates in fields like CNS, cancer and inflammatory diseases.

Oxford Immunotec (OBL) – Hadassah Medical Centre (Israel) Hadassah will serve as beta-site to run a trial with Oxford Immunotec's innovative Tuberculosis test.

Genodyssee (Genopole) – Protalix (Israel) Protalix will explore one of Genodyssee's new molecules using their plant cell based expression system.

*Nanion (*Bio^{M}*)* – contact was made with two Israeli technology agencies in order to implement Nanion's ion-channel testing technology in the Israeli Academy and Industry.

Genomatix (Bio^{M}) – Israeli academic institutions Exposure of Genomatix on-line genomic services in order to encourage its use for research.

11. Policy implications including basic conditions for success

We propose that the optimal bioincubator should be based on the "all in one" model. Co-incubation is dependent on the services and the surrounding business environment provided by the host incubator. The analysis of the 5 participating incubators in Bio-Link (described in a separate part of this report) has clearly demonstrated that portfolio companies belonging to bioincubators which provide vertical services have better chances for co-incubation than those belonging to incubators that provide only part of these services.

The ten "pillars" for the "all in one" models include:-

1) In house biotech technological infrastructure
2) Access to and collaboration with industry
3) Access to business development experts
4) Networking

5) Access to VCs & financial community
6) Access to service providers (legal, IP, accounting)
7) Collaboration with adjacent academic institutes
8) In-house science & technology guidance
9) Synergy with next door neighbour
10) Public relations

1. *Technological infrastructure*. The bioincubator should be able to provide space and infrastructure for a variety of technologies. This includes upstream and downstream technologies related to products derived form various hosts such as bacteria, yeast and mammalian cells. The incubator should be able to support synthetic chemistry activities. An attractive option is that the incubator should own part of the expensive equipment and enable the clients to use it.
2. *Access and collaboration with Industry*. The bioincubator should establish relations and collaborations with the healthcare industry. The projects in the bioincubator should be presented on a periodic basis to companies in the sector. In addition, the technical support of these companies can be very beneficial (use of equipment, materials, animal facilities etc.). It is the responsibility of the bioincubator manager to make sure that his projects will get a high level of exposure to the healthcare industry. Bioincubators with strong relations with the industry have a clear advantage in promoting co-incubation and business development as compared to those which do not give enough emphasis to relations with industry.
3. *Access to business development experts*. Each bioincubator should have a director of business development whose responsibilities will include partnering, preparation of presentations, deal structuring and analysis assistance in the preparation of business plans. The lack of this function in most of the partnering bioincubators in Bio-Link was the main reason for the lack of co-incubation deals in the first year of the project. The function of business development can also be split between several experts in their own particular fields. It should be remembered that most if not all of the entrepreneurs are scientists that lack the experience and the culture of the healthcare industry and can tend to make many mistakes during the early years of their incubation.
4. *Networking*. This is a joint task of all the management members of the bioincubator. Networking can be split into personal networks which are the result of the relations created during the years between the members of the bioincubator to external organizations, industry, academia, financial community etc. Another form of networking is the virtual one, which is based on databases provided on the internet. Access to literature and reports issued by expert companies are part of this virtual networking. We found out that some of the incubators are unfamiliar with the current publications

related to bio-business such as Bio-World Today etc. Networking was found to be the major parameter appreciated by client companies in all the five partner incubators of the Bio-Link project.

5. *Access to VCs and financial community*. This is clearly a key factor for the success of each entrepreneurial organization. Connections to the financial community refer to angels and private investors, local banks, global VCs, local VCs and also to the healthcare industry. A basic business model is an essential tool for each company in a bioincubator to enable it to present its business concept to these potential investors. The incubator should arrange periodic meetings with potential investors and be able to sell the 3 basics of a bio-start-up: Technology Networking and Dream (Profit).

6. *Access to service providers*. The bioincubator should be able to take care of all the administrative tasks which a young client company has to undertake. This includes accounting and book-keeping, legal services, intellectual property services and personnel recruitment agencies. Provision of these services to the client companies should enable the CEOs of the young entrepreneurial companies to focus on their technology objectives.

7. *Collaboration with local academic institutes*. The relations with academia are an essential service that should be provided by the bioincubator. Such relations contribute to the flow of projects that are forwarded from the bioincubator. They also are essential as a source for scientific experts who can serve as consultants and as members of the Scientific Advisory Boards of the client companies. A relationship with a prestigious academic institute is also a key success factor in fundraising and for the public relations of the bioincubator. The relations between the bioincubator and the academic institute should be almost symbiotic so that the bioincubator is the default address to which young entrepreneurs from the university are referred by their Technology Transfer Offices. On the other hand, the university should be able to present the bioincubator as its window for the "applicative world".

8. *In-house science and technology guidance.* This guidance refers mainly to technological aspects which are part of the development process in the healthcare industry. Pharmaceutical development, clinical development and regulatory affairs are just part of the guidance required by young biotech and pharma companies. Guidance in these fields which are usually part of the more advanced stages of a project are essential from day zero since they have a cardinal impact on the company's development plans, business model, likelihood of registration and hence on fundraising.

9. *Synergy with next door neighbour*. Bioincubators should try to form an internal technological cluster. This recommendation refers mainly to basic technologies such as genetic engineering, monoclonal antibodies etc. Internal clustering can contribute to real sharing of expertise and resources. However, its main advantage is in business development and accumulation of internal

expertise in a certain field. Companies with similar technologies can use the same basic development equipment which is usually quite expensive and cannot be justified for one company, especially if it is not routinely used.

10. *Public relations*. Young biotech companies are "selling dreams". It is within this scope that the bioincubator must provide them with an optimal exposure to the printed and electronic press. Public relations have a major influence on the financial community especially on fundraising which is so essential for any young company. Therefore the bioincubator should hire the services of a professional public relations firm as part of its service package to its client companies.

12. Summary

During the 30 months of the project, the incubation models of 5 different bioincubators were compared. In addition, extensive co-incubation efforts were made to link the Bio-Link portfolio companies and create technological ties as well as business ties between them. The following table summarizes the strength, weaknesses, opportunities and threats of the project:

Optimal incubation model	*'All in one' model:* - In house biotech technological infrastructure - Access to and collaboration with industry - Access to business development experts - Networking - Access to VCs & financial community - Access to service providers (legal, IP, accounting) - Collaboration with adjacent academic institutes - In-house science & technology guidance - Synergy with next door neighbour - Public relations
Selection criteria for co-incubation	*a)Technology developer* Wide scope Ready for implementation and/or technology transfer *b)Service provider* Certification Technological background material + website Fast response Accessibility *c) Maturity* Post "creation hassle" – 2-3 years old *d) Critical mass – not less than 8 employees*
Key Success Factors for Co-incubation	1. *Technology* Beyond proof-of-concept "Transferable" – at "operating procedure" level 2. *Incubator* Co-incubation oriented and supportive Business development guidance – from day zero

	Administrative assistance (TT and MTA template documents in place) 3. *Company's Management* Willingness and openness to collaborate and share (language & culture gap) Managerial awareness and attention Co-incubation project manager 4. *Budget* Financial resources allocated for co-incubation – labour, material, travel 5. *Time* A successful co-incubation requires at least 2-3 years from conception.
Likelihood of co-incubation success	High for service-providing companies Medium for platform technology companies Low for developers of molecules High for companies in commercial stage Medium for companies in transition (pre-commercial) Low for early stage companies

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Guidelines Proposal for the construction of a Local & European Seed Fund (LESF)

(Code name)

Gabriel Mergui

Warning: This document is derived from the experience of Genopole incubation system and that of Genopole 1er Jour, a private pre-seed fund co-managed by Genopole.
The experience of Genopole occurs within the framework of Bio-Link, an EU 5FP consortium dedicated to the study of best incubation practices.
However, the views expressed herein represent the sole personal opinion of Gabriel Mergui. They are meant to foster discussions between individuals concerned with the problem of seed funding of biotech start-up companies in Europe.

Gabriel Mergui
Nov 02 through Dec 04

Project for a Local European Seed Fund. (LESF)

Preamble.

In May 1998, Genopole[1] was created with the dual ambition to establish an academic research campus and an incubator. Genopole promoted and put into operation an incubation system including the pre-seed fund Genopole 1er Jour (G1J). This very small fund (1.2 M€ and recently an additional 2.2 M€) was intended to finance the preparation of a business plan (BP) to be used by start-up companies to more consistently and credibly approach venture capitalists.

Genopole's experience over the first months of incubation activity indicated that projects in the incubation-seed stage could be put into two well-defined categories:

Category A: projects that raise more than 5 M€. within 6 to 12 months,
Category B: projects that raise between 1.5 M€ and 2 M€ after a period of 18 to 24 months

Note that both categories benefited from the same model of financing and follow-up from Genopole.

The project described below as the Project for a Local European Seed Fund (LESF) addresses the need for an incubator, for example Genopole, to have access to seed funding as well as the pre-seed funding provided by G1J.

Analysis:

It is likely that the excessively long fundraising period for the companies in category B resulted from a lack of visibility of these companies to the venture capital community ("VCs"). Where projects were not considered, it was because they had not achieved their **industrial proof of concept**.
Genopole observed that if the duty of an incubator was to accelerate achieving such proof of concept, it was similarly the duty of the incubator to avoid wasting one of the major assets of the future company, namely the start-up company's **lead on competitors**.

For a number of reasons discussed below, VCs are increasingly reluctant to invest in pre-seed and seed-stage companies. The current reluctance of VCs to invest in early stage rounds of financing confirms our thinking that an incubator must play a stronger role in a start-up's success. The presence of a seed fund connected to an incubator would be powerful leverage in helping start-up companies complete rounds of financing more quickly.

The objective of the present document is ambitious and twofold:

[1] Genopole is a technopole specialized in Genomics, other biotechnologies and related disciplines, located 30 Km south of Paris. In 6 years it has hosted 24 academic labs and help to create 50 companies through an incubator and a pre-seed fund: "Genopole 1er Jour" (Genopole First Day).

Describe a model for a seed fund linked to an incubator: LESF. This seed fund would 1. specialize in biotech and would make 80% of investments in the local area and 20% in other European bio-clusters.

Convince several European financial players to create similar funds which would work 2. together in a **network**.

There are many aspects of the LESF concept that already exist and whose industrial value has already been proven. Best practices for both biotech incubators and seed funds have been established in the past fifteen years: LESF relies heavily on proven practice. However, LESF represents an intensification of all the key factors to strongly enhance the efficiency of the financial concept proposed.

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TABLE

1 – Economic Value of the Biotechnology Industry

11 – Biotechnology Industry as Regional Economic Asset[2]

For every one dollar invested in or spent in the US on biotech R&D, another 5.7 dollars are created in the local economy. From its beginnings in 1980, the biotechnology industry now represents less than 2% of US GDP. However, the industry's relative economic impact (1:5.7) makes it the most valuable in the US: 406 700 employees, $ 64 billion real output. This high economic value is the reason that key US states and regions are increasing their support in the biotech sector.

However, the future of the biotech industry in the US looks less attractive. The biotech sector is predicted to grow by 11.4% over the next decade.(3) This is a slower rate of growth than in the past two decades. Federal funding support since 2000 in key programmes such as SBIR (Small Business Innovation Research) and ATP (Advanced Technology Programme) has decreased markedly. Capital markets continue to struggle following the economic downturn of 2001-2002, confounding the efforts of companies looking for financing. The outlook in the US through 2008 sees a continuation of current policies, with similar results.

12 – The Time is Now: An Opportunity for Europe.

The next five years probably represent a unique period of time when Europe must take risks while the US continues to recover and before Asian countries reach their full speed of development.

The tool proposed herein offers a strong competitive response, and builds on the strengths of European sciences, and European industrial track record and experience.

[2] This Chapter is derived from data brought by and discussions held with Ms Constance McKee, CEO of Asilomar Pharmaceuticals and former Chief Executive of a seed venture fund at Cambridge University, Cambridge Quantum Fund I (CQFI).

[3] US data for 2003, from Milken Institute October 2004 Report

2 - Creation of a network of Local European Seed funds LESF

21 - Proposal

This document proposes that several European Bio-Clusters promote seed funds within their local operating environment. The code name of this group of seed funds will be: "Local & European Seed Fund – LESF." These funds will **specialize in genomics and other biotechnologies**. They will make 80% of their investments in their immediate vicinity and 20% elsewhere in Europe.

The aims and practices of this proposal are derived from the experience of Genopole after five years of operating the Pre-seed Fund Genopole 1er Jour. Genopole reports statistics on the first 33 companies incubated by it. After the first six to nine months, following preparation of a Business Plan (BP) and first presentation to Venture Capitalists, the Genopole companies received the following responses:

- The VCs invested immediately (5 projects)
- The VCs declined to invest (5 projects)
- Twenty-three (23) projects fell in the "Grey Zone" where the VCs declared:

"This is good, but we can't invest now[4]. We need a convincing "Industrial Proof of Concept" (IPoC) before we invest."

The time and cash requirements for the average IPoC were about

- 18 to 24 months,
- 1.5 M€ to 3 M€ of direct costs

A company must raise 1 M€ to 2 M€ of equity finance. The challenge was to find investors willing and able to invest between 0.3 M€ and 1 M €. Such investors are too scarce in Europe.

Hence the principal characteristic trait of the LESF: it must be small in size, since big funds do not invest in early stage. In the model given in Tables 1-6 in the Appendix, the average initial investment would be 330K€.

Sections 1.2 – 1.6 give the other main characteristics and investment parameters of the LESF.

22 - Technical chart

The technical aspects of the LESF proposal are detailed in Tables 1 to 6 in the Appendix.

[4] A research paper by Philip Auerswald and Lewis Branscomb (George Mason and Harvard Universities-2003) shows that in the process of financing what they call "the Darwinian sea of innovation", the VC community brings only 5% of the total. The rest is distributed as follows: Corporations and Corporate Venture: 40%, Angel investors: 26%, Federal Govt: 23%, State Govts: 3%, University's own funds: 3%. **It is clear that financing companies in their early stage is not, or is no longer, the job of the VC's.**

- **Duration of the fund**: 8 to 10 years
- **Legal status**: to be optimized
- **Operational structure:** structure with two tiers: the fund itself (LESF) and its management entity. Code name for the management entity is: "LESF-Partners" (LESF-P).

Investments: to be made only in companies less than 3 years old, in their seed stage, defined as follows:

- With a Business Plan.
- Able to achieve the milestone of an "Industrial proof of concept" over a period of approximately 18 to 24 months.
- Operating in the area of Genomics, post-genomics and Biotechnology related techniques.

Thus, LESF is intended to be a **highly specialized** fund.

Investment amounts (Table 2)

- Between 200 K€ and 600 K€ by project. **Average 330 K€.**
- Not exceeding **40 % of the current round of financing**, for investments made in the Local Area and 25 %, for investments made in the rest of Europe.
- The investment round will include at least one (and preferably two) other investors. Each of them will carry out **due diligence independent** of LESF.
- Limited to **less than 6 %** of the fund for any one company.

Number of projects:

The investments will be made over the first five years of the duration of the fund.

The goal is to invest in a total of 30 Companies.
As an example, assuming a possible Genopole LESF, the geographic distribution of investments, and their relative weight in the LESF portfolio might be:

- 10 in Genopole Evry Bio-Technopole (33.3 %)
- 8 in the rest of Paris Region Bio-Cluster (26.67 %)
- 6 in France except Paris Region (20 %); and
- 5 in Europe (20 %).

Financial programmes likely to be approved (Table 2)

- The fund may invest in projects that require longer-term funding ranging from 1.5 M€ to 3 M€. The model in Table 2 indicates three levels of total investment: low (1.5 M€), medium (2.2 M€) and high (3 M€).
- These projects can logically benefit from **public grants** at the level of approximately 30 % of the total (*cf* the ANVAR grants in France)[5].
- Of the total capital required per investment, LESF could contribute 200 K€, 300 K€ and 600 K€ respectively. This level of participation would represent 19 % of stockholders' equity for the first two levels of investment, and 29 % for the highest level of investment.

[5] This assumption is conservative. It is of the utmost importance that public grants, originating either from local or national authorities or from the EU, must not go below this figure, considering the incentives brought by other countries to their Biotech.

Distribution of investments by size

The model distributes these three levels of investment over the portfolio as follows:

- 200 K€ in 9 deals
- 300 K€ in 15 deals
- 600 K€ in 6 deals

Thus a total of 9900 K€ on 30 investments, at an average investment of 330 K€.

Follow-on Seed Investments.

The higher level of risk in a seed stage company, plus disappointing market conditions for follow-on rounds, may lead to a situation where VCs could take advantage of a bad financial situation to destroy existing share value and invest at a lower price than that of the seed stage. This describes the current situation in the US (BioCentury review, October and November 2004).

In order to protect its investment in a given portfolio company, LESF must be able to reinvest in follow-on rounds alongside VC rounds of finance to preserve its equity position. The model takes this eventuality into account by creating a special compartment of 5 M€ dedicated to 10 follow-on-seed investments of 0.5 M€ of average investment.

23 - Size of the Fund: 18.3 M€ (Table3)

The size of LESF is determined arithmetically, by adding the average amount investments:

- 330K€ for the first 30 investments: 330K€ x 30 = 9900 K€, management fees not included.
- 500K€ for the following 10 investments: 5000 K€, management fees not included.

The amount dedicated to direct investments, exclusive of management fees, is 14,900 K€

23-1 Management Compensation.

- Management fees of 419,9 K€ per year: 2.3 % of the amount of the Fund during 8 years (5 years of investments + 3 years of Exit)
- 20 % of the carried interest

The arithmetical formula gives a value of the fund of 18.259 M€ with management fees of 419,98 K€ per year during 8 years: 5 years of investments and 3 years of harvesting and exit.

23-2 Selection Criteria for Investment

During the pre-seed stage (first nine months' preparation of Business Plan), each project that has <u>not</u> attracted a first VC round of finance will automatically be presented to the Expert Committee

(EC) of the Incubator. The EC will reassess the project and consider the following criteria, with the possibility for further funding support from LESF:

- The technical effort undertaken and results achieved,
- The quality and opportunity of the completed business plan,
- The experience and commitment of the team, and
- The feedback of the first VCs consulted

In the event of a decision to invest, the project will be presented to an **Investment Committee** to obtain a financing.

Investment Committee

The Investment Committee would represent both the shareholders and the Management team of the fund as well as the Incubator and its Expert Committee.

The presence of financial analysts representing shareholders is, at this stage, useful and necessary because a Business plan exists and can and should be reviewed and analyzed.

Possible composition of the LESF Investment Committee:
2 academics
2 industrialists
2 financiers
1 representative of the Incubator
The decision of the Investment Committee is normally ratified by the Board of Directors of LESF.

Management of the Fund: It will be entrusted to a management company.
Code name: LESF-Partners (LESF-P)

The Management team shall be composed of two individuals: one Senior Officer and one Junior Officer[6]. Their roles will be to:

1 °) **Validate** projects by carrying out due diligence directly or by subcontracting due diligence to appropriate bodies for example clinical experts within Genopole.

2 °) **Follow up** the investments made, either as lead investor, or as simple investor.

3 °) Complete the **fundraising** for future rounds, either alone or in syndication with other consultants in fundraising.
4 °) Achieve, as far as possible, the **final exit** and sale of portfolio at the end of the fund period.

23-3 Operating costs coverage LESF-P. (Table 5)

[6] It is of utmost importance that Junior Officers should be trained and gain experience in the process of managing Venture Funds like LESF throughout Europe. The lack of such skills is a major handicap within the EU VC community.

Expenses
Operating costs have three main items: salaries, management costs and direct costs of due diligence.

Salaries.

The tasks outlined above require hiring the most experienced professionals, implying commensurate salary levels.
The team will be assisted by trainees and one secretary.
A total of 362 K€ is dedicated every year to salaries (60.5 % of expenses of LESF-P)

Management costs

This is the second biggest item (22.5%). It is composed of 75K€ of management costs and travel and 60 K€ of legal expenses.

Due Diligence (DD).

Costs of due diligence are further divided into two parts.

- **The first one is achieved directly by the Management team,**
- **The second one would be supervised by the team of LESF-P, but carried by the Incubator team or by relevant clinical or industrial experts.**

The second part would be accounted for as a loan made by the Incubator, the counterpart of which would be paid by the Management Company in the form of a percentage of the Carried Interest.

An average of 5 deals per year will incur DD expenses of 20 K€, of which 50% would be paid from a special account within the Incubator.

The total estimated annual expenses of the LESF management is: 598.4 K€,

Revenues

Management fees.

For small VC Funds, market data suggests that Management Fees lie between 2 and 3 % of the total funds raised. According to the model proposed here, LESF-P will take 2,3 %. The cash value of these fees is 420 K€ per annum, or 70.2 % of total capital.

Subsidy from National or local Authorities (Example in France: the DRIRE - Ministry of Industry Regional Office).

The DRIRE grants a subsidy of a maximal amount of 75K€ to management teams of VC Funds investing in small capitalization companies. Such grants could be provided by national or local authorities to LESF to assure hiring top management talent.

Subsidy from the European Investment Bank

Similarly, the EIB grants a subsidy of a maximal amount of 100 K€ to management teams of VC Funds investing in small capitalization companies.

Combined, these subsidies could reach 150 K€ in France. The model assumes a conservative amount of 100 K€, 50/50 contributed from local and EU institutions. This assumption means that 16.7% of total expenses of the management team would be thus covered by such subsidies. This seems a fair compensation for duties involving:

- Investing in seed stage companies; and
- Investing all other Europe 20% of all investments.

N.B.: One might consider that such subsidies could legitimately go up to 20% of all expenses.

Fundraising Fees
By a legal mechanism to be optimized, LESF-P team can also participate in success fees earned by fundraising for portfolio companies, either as lead or simple fundraiser.

The model assumes a performance only in the linked incubator portfolio, with fundraising for ten projects, or a cash value of 43 M€ raised over a period of seven years.

NB: This assumption is benchmarked to the performance achieved by G1J in 3 years: 17 investments, 8 rounds of financing achieved, 32M€ raised.

For 1.5 % of success fees obtained, LESF-P would receive 25% from it, whereas the Incubator would receive the 75% in return for the due diligence achieved with LESF-P. Of the 43 M€ success fees assumed, 28.4 K€ would be collected by the Incubator.

The Profit & Loss sheet reaches break-even using these assumptions.

23-4 Sources of Fund for LESF (Table 4)

Table 4 recaps the capital needs for LESF of 18,26M€.

Origin of Funds.

1 - The European Union and/or the National State[7] bring 25 % of this total. Thus 4.5 M€.
2 - It is likely that the BigBank1 can take 15 % of the fund (that is 2.7 M€), its maximum being 20 %.
3 - The X.... company undertook verbally to invest 1 M€
4 - The BigBank2 could do the same

It is likely that 5 M€ of LESF capital can be raised from ten local institutional investors or business angels with an average investment of 500 K€.

[7] France has a fund of funds dedicated to such task.

A soft loan of 4M€ could leverage this investment for private investors, provided that a lower part of the carried interest could be dedicated to bring an interest to the loan.

Financial results.

Given all the above assumptions, the model suggests that the IRT of LESF, assuming that LESF's capital is drawn down in two payments (in years 1 and 3), but without taking the soft loan into account, would be 18.52 %. In case of such a soft loan, the IRT is higher.

3 - Promotion of a European network of Local & European Seed Funds specialized in Biotech

31 - Number of operators

The European requirement for seed-stage investment in biotechnology companies can be estimated as follows:

- In France, based on historical deal flow, 25 start-up companies would require seed stage investment. One LESF (supposedly that of the Paris Region operated in the environment of Genopole) would cover one-third of the capital needs, and 100% of the local hands-on assistance provided by the local LESF management team. This analysis suggests that two additional seed funds of the same size should be created in France or, if need be, reformatted.

- In Europe, based on historical deal flow, the French figure can be multiplied by five, or about 125 companies in Europe.

- This suggests that a maximum of 15 seed funds in the LESF format could prospect, share due diligence and co-invest throughout Europe.

The format proposed here is only one possibility. Other formats are possible, for example, a network of LESF funds could be composed of between 10 and 15 operators, among which some would be "Business Angels" (BA) and some might be "additional" unspecialized Seed Funds.

32 - Modalities of investments

What factors and legal provisions would persuade a British or German LESF to invest in France, say, alongside a Genopole LESF, and conversely? What guarantees would foreign investors, ready to invest at a geographic distance from their base, require to give assurance and confidence to their investment?

NB: documents deciding an investment and then moving to definitive documentation can be standardized to keep costs and effort at a minimum. Many of these documents and steps are already standardized within the industry. Standard documents are indicated below with an asterisk (*).

32-1 The Decision-Making Process.

Decisions will be considered only after the following basic information has been obtained and confirmed:

- Statement of a "Lead investor", committing to managing the communication and to drafting the legal terms of the investment ("closing"). Such documents (the famous "Bible", Business Plan, Investment agreement, Shareholders' agreement, etc.) (*) will be « simple and robust » and drafted in English.

- The BP (*) will be drafted in English and will conform to normal forms of presentation. The same will hold true for Appendices. (Scientific Publications, IP documentation, Key persons Resumes, etc.)
- Due diligence made **independently by at least two specialized entities.**

32-2 The follow-up: Reporting

Very strict standards of follow-up and reporting must be exercised so that the foreign investors can follow their portfolio companies without excessive cost or effort.

For each portfolio investment, the start-up team and LESF will adopt a management style and process to include monthly meetings of its executive authority: board of directors (American style « Board meetings ») or Executive committee. The foreign investor will be regularly invited to these formal Board meetings.

A rigorous Reporting system(*) will be defined and sent by secure e-mail several days before each meeting.

Each foreign investor will be required to make at least 2 visits a year to the portfolio company. In the interval, he will be informed every month, by a short note from the Lead Investor on the Reporting and the meetings of the Executive Committees held.

All these rules of follow-up (that have to be clarified and completed), should be a part of a "General Agreement" to which the members of the network would adhere and that would represent a quality standard likely to reassure the unspecialized investors.

32-3 The exit

This would logically happen at the time of an initial public offering or when the company is acquired by or merged into another industrial entity.

If there is no spontaneous exit, the management team will undertake to sell all the remaining securities in the portfolio in the final eighth year. Any unsold and still illiquid securities will be distributed to the shareholders in proportion to their stake in the LESF.

4 - Accompanying measures

Additional measures can further support the creation of and ultimate success of the proposed network of Local & European Seed Funds. Most of them exist already. This proposal suggests that they be strengthened and re-oriented to be more effective.

41 - Mobilizing Research Institutes

We suggest the creation of a think-tank to include agents close to the decision-making level of:

- Incubator,
- Academia (Research institutes and Universities) where most of the projects are originated, and that usually develop and hold the portfolio company IP.
- In addition to Experts

Mission: to define a framework procedure of shared incubation (that should lead to a tripartite agreement: Creator - Academia - Incubator) which would define:

The contributions of the Academic institution where the Start-up Co originated A.

- Grants
- Salaries (in France within the framework of the Law on Innovation -Art. 25-1),
- Use of Academic premises and equipments,
- Filing and maintenance of leading patents and depending patents
- Use of internal **pre-seed funds** to complete the R/D.

The Incubator's contribution B.

- More active prospecting and faster and more complete validation (due diligence expenses revalued)
- Human assets: follow-up by Incubation team + trainees + Interim management
- Logistics facilities in addition to those provided by the Academic institution (e.g.: lab available in the Institute + office in Incubator)
- Accounting taken care of by consultants.
- Financial means: raise the loans provided by Incubator at a correct level.
- More selectivity in the choice of the consultants and closer follow-up of their work

The rights and obligations of the Company leader. C.

- Information for the Incubator and Seed Fund,
- Respect for the current regulations including an Ethical Chart.

42 - Better use of the Tech Transfer Govt Agencies (TTO) soft money (In France: ANVAR)

Once the result above is achieved, it will be advisable to turn to the TTO's to ask for a positive response:

Revise the Innovation soft loans programmes (*cf* in France: "Aide à l'innovation")

- Higher amounts granted and percentage of programmes financed.
- Accelerate implementation so that due diligence costs can be covered rapidly

Boost the grants to academic labs (*cf* in France: "Aide aux laboratoires").

These grants are intended to finance the pre-development phase, that is the phase mostly "orphan", (neither Research nor Industrial development) which should allow a project to acquire the maturity which may lead to opening a phase of industrial development.

In the current situation, it is advisable to boost them by negotiating pre-development budgets **co-financed** by the Government TTO's and the **Pre-Development Funds of the Research Institutes**. If the amounts of pre-development funds are increased, they can work closely and effectively alongside LESF and other capital sources to accelerate start-up growth and accelerate bringing new products to the market. This complements the existing goal of this initiative.

43 - Mobilize EU Resources

Numerous documents emanating from the EU describe these grants, and no further description is provided here. The "Marie Curie" scholarships are perhaps a good example, since their evolution offers lessons and perspectives for start-ups in their seed stage.

Initially Marie Curie scholarships in the 5FP were:

- Of short duration
- Reserved solely for members of the EU.
- Reserved for academic Research

This was neither very interesting nor successful in generating start-up companies. Now, however, in the 6th FP, with key changes, the effect is positive and dramatic. Criteria for these scholarships have expanded and become much more attractive for start-up companies: Now they are:

Of **short or long-term duration (maximum: 24 months)** ·
Reserved for the members of the EC **and in associated countries (Ex: Russia)** ·
Reserved for academic research **and for start-up companies.** ·

Many other European grants can be mobilized.

Conclusion: Next Steps 2005

Next steps to achieving LESF in 2005 are:

1 – Finalize the operating model, to include geographic area, number of investments, thematic fields covered, co-investments, cooperation with Lead and the other Incubators.
2 - Meet and discuss common objectives and needs with,
Other EU incubators ·
Other similar pre- and seed funds in Europe ·
Potential private and public sources of EU capital for LESF ·
3 – Locate a CEO
4 – Write a comprehensive business plan-memorandum for LESF
5 - Launch the fundraising effort in late 2005, with target completion for early 2006

APPENDIX

Table 1 **Distribution of investments for a LESF launched in the environment of Genopole**

Year	Genopole Evry	Paris Bio-Cluster	Others in France	Europe	**Total**	Total cumulated	% invested cumulated	
1	3	2	2	1	**8**	8	26,7%	
2	3	2	1	2	**8**	16	53,3%	Usual :
3	2	2	1	2	**7**	23	**76,7%**	70% in 3 years
4	1	1	1	1	**4**	27	90,0%	
5	1	1	1	0	**3**	30	100,0%	
6								
Total	**10**	**8**	**6**	**6**	**30**	**30**		
	33,33%	26,67%	20,00%	20,00%	100%			
	60,00%							

Table 2 **Seed stage program financed (K€)** **Distribution by scale (K€)**

	Low	**%**	**Medium**	**%**	**High**	**%**	Nb of deals	Invest/deal	Total
Total charges	1500		2200		3000		9	200	1800
Equity : LESF	200	13,33%	300	13,64%	600	20,00%	15	300	4500
Other seed funds	850	56,67%	1200	54,55%	1500	50,00%	6	600	3600
							10	*500*	*5000*
Public Grants	450	30,00%	700	31,82%	900	30,00%	30		14900
Total ressources	1500	100,00%	2200	100,00%	3000	100,00%		Average>>	496,67
Stake of LESF in the							10	"follow on Seed"	
Seed round >>>	*19,05%*		*20,00%*		*28,57%*		investments during the VC round		
							Average "follow on seed" investment :	500	K€
							Average investment before "follow on seed":	330	K€

	Table 3	**Size of the Seed Fund and distribution between investments and Management fees**							
	Average Investment		496,67	K€					
	Total invested		14900	K€		Duration			
	Management Charges		2,30%	per year during		**8**	years, as of :		
		As of:	18,40%	of fund size		5	years with investments and		
	Overall amount of Seed Fund		18259,80	K€		3	years of liquidation		
	Annual management fees		419,98	K€					
	Tableau 4	**Fund Raising**							
Status				K€	%				
"Automatic"	French Gov or EU Fund of Funds			4 564,95	25%				
Lead	BigBank1			2 738,97	15%				
	Investor X			1 000,00	5,48%				
	BigBank 2			1 000,00	5,48%				
	Small shareholers		**10**	**5 000,00**	27,38%				
			500						
					0,00%				
	Soft loan (leverage)			**4 000,00**	21,91%				
	To be found			-44,12	-0,24%				
		TOTAL		18 259,80	100,00%				

Table 5 Annual Expenses and Revenues sheet of "LESF Partners" (LESF-P) Management team

Expenses					Revenues			
Salaries			K€	%				%
Salary Senior	Net/Mth (K€)	Net/Mtf (KF)			Management fee		419,98	*70,19%*
Annuel Salary	8	52,48	172,8	*28,88%*	*Base managt fees*	***2,30%***		
Salary Junior								
Annuel Salary	5	32,8	108	*18,05%*	Gvt Grant (France: Max 75K€)		50,00	*8,36%*
	Net/Mth (K€)	Number			EU Grant Max 100 K€		50,00	*8,36%*
Training periods (LT)	1,5	1,5	48,6	*8,12%*				
Secretary	1,5	1	32,4	*5,41%*				
p.m. : sub total salaries			*361,8*	*60,46%*	Success fees/Fund raising		28,39	*4,75%*
Management Costs								
Management expenses and Travels			75	*12,53%*				
Legal			60	*10,03%*				
Due Diligences	Nb Deals	K€/deal						
Made by Management team	5	10	50	*8,36%*				
Contracted to Incubator	*5*	*10*	*50*	*8,36%*	*Contracted to Incubator*		*50*	*8,36%*
Sub total			596,8	*99,7%*	Sub total		598,37	*100%*
Benefit			1,57	*0,26%*	Loss		0,00	*0,00%*
Total			**598,37**	***100%***	**Total**		**598,37**	***100%***

Table 6	Simulation financial output								
						Fds raised p/Y	Success fees	Out of which	
		Revenue for	As of for	Total funds raised	Total funds raised	by Portfolio Cies	from Fd Raisg	to Incubator	to LESF-P
		30	18 259,80	for 10 Cies	30	7	(K€)	(K€)	(K€)
Out of 10 deals	= invest X by	deals	K€ invested	in M€	Cies	years in M€	1,50%	75%	25%
1 outstanding	20	60		20	60	2,86	42,86	32,14	10,71
1 medium success :	10	30		15	45	2,14	32,14	24,11	8,04
1 low success :	5	15		8	24	1,14	17,14	12,86	4,29
1 mediocre success :	3	9		5	15	0,71	10,71	8,04	2,68
2 simple pay back	2	6		5	15	0,71	10,71	8,04	2,68
4 failures			Gross rev K€						
Total	40	120	59 600,00	53	159	7,57	113,57	85,18	28,39
	Carried interest		41 340,20	M€	M€	M€	K€	K€	K€
Share of Management Team			20,0%						
		as of:	8 268,04						
Balance due to Investors :			51 331,96						