

FIZ & Friends

Network of Excellence in
Innovation and Entrepreneurship



Frankfurter Innovationszentrum
Biotechnologie



>> It takes many intelligent minds to turn a bright idea into a success. FIZ unites such minds to form a powerful network. We invite you to take a peek at the dense web of competence at FIZ & Friends. >>



Frankfurter Innovationszentrum
Biotechnologie

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Welcome Address

by Roland Koch, Premier of the State of Hesse

The Frankfurt Innovation Centre for Biotechnology forms a bridgehead into the future. This center is further proof that Hesse is well on the way to becoming the top location for biotechnology in Germany and Europe. Thanks to Hesse's thriving economy, scientific expertise and cosmopolitan outlook, we can offer excellent advantages to companies and businessmen wishing to locate in our region, especially when it comes to the field of biotechnology.

The Innovation Center, which oversees the successful development of growth technologies from Germany and abroad, is an important landmark in this respect. It will become the nucleus for the combined forces of the pharmaceutical and chemical industries as well as the world of finance and biotechnology as they all work together to develop new market products. Hesse is the state for entrepreneurs, ranking among the best in Germany with 78 registered businesses per 10,000 inhabitants. Moreover it is these technologies of the future, such as biotechnology, that open up new horizons for companies' financial success, thereby benefiting employ-

ees and contributing to the economic prosperity of the country as a whole.

Hesse, which is situated at the heart of Europe, has one of the strongest regional economies on the European continent. Located in the center of Germany, it is the country's most dynamic state, setting the economic pace nationwide. The state of Hesse has an excellent reputation both at home and abroad, mainly due to its open-minded approach to new developments. Both small and medium-sized firms – the backbone of our economy – as well as big international companies profit from the favourable economic conditions the state has to offer. New financial advantages such as "bank-free guarantees" from the Bürgschaftsbank Hessen, actively support small and middle-sized firms as well as in particular those setting up their own businesses by issuing guarantees which enable people to obtain credit with their own bank.

Hesse offers all companies many excellent location advantages, including Frankfurt airport, the largest in Europe and an international air hub which provi-

des first-rate connections to virtually any destination worldwide. In addition to the high priority accorded air transportation, the Rhine-Main area is of course also connected with Europe's high-speed rail networks. An extensive motorway system also links Hesse to all major European cities in North, South, East and West. More and more companies are taking advantage of Hesse's ideal central European location to expand their markets, particularly in Eastern European countries. The state of Hesse is also becoming increasingly important as a major center for information technology in Europe.

And the state has still more to offer, particularly with regard to its young people. Equipped with a high level of expertise and competence provided by Hesse's schools, universities and training centers, they are an asset to all companies marketing highly sophisticated products in international fields. Young people in Hesse receive an excellent education on a professional level and are encouraged to be tolerant and have an open mentality since skills and expertise no longer suffice in to-

day's global economy. People must also understand and respect one another as well as being aware of different ways of life and a variety of political and economic situations.

The Frankfurt Innovation Center for Biotechnology provides marvellous opportunities for highly specialized companies and their trained staff to do successful work. One major advantage in this respect is the physical proximity to the city's university and the Max Planck Institute for Biophysics as well as the chance to work together with the University Teaching Hospital. Hesse has maintained its reputation as the "Pharmacy of Europe" thanks to its thriving chemical and pharmaceutical industries. The Innovation Center will help to strengthen this position and enhance the state's reputation in this regard.

Numerous surveys have confirmed Hesse as a prominent example of an outstanding economy in comparison with other regions throughout Europe and the rest of the world. Accordingly, two Hessian cities – Frankfurt in second place and Wiesbaden in sixth place – rank among the Top Ten

list of Germany's most economically vibrant cities. This confirms the fact that Hesse is an attractive business location whose promotion is a major priority for the regional government. A thriving economic climate, high-profile location and increasing economic prosperity combine to form the dynamic economic power of the Rhine-Main region and we must continue to expand these strengths.

The inauguration of the Innovation Center is a big step towards achieving this goal since biotechnology is an important sector which makes a vital contribution towards ensuring the economic prosperity of the future. Other areas where the regional government is active in this regard include for example strengthening Frankfurt's position as a leading financial center as well as expanding Frankfurt Airport with the construction of a new landing strip while maintaining a ban on night flights.

The basis for Hesse's international reputation and the success of its economy worldwide is a tribute to the innovative strength of its companies and the skill and hard work of their employees. The

Hessian government has undertaken a firm commitment to maintain these standards and, where possible, to expand them. We have established a framework which allows companies and their employers to operate successfully and I am sure that the Innovation Center will open up new possibilities in this area, too. So I would like to take this opportunity to extend my best wishes to all those working at the Frankfurt Innovation Center. I wish you all every success.

Roland Koch
Premier of the State of Hesse



FIZ shareholders:
ICC President Dr. Joachim von Harbou, Mayor Petra Roth and Premier Roland Koch





FIZ
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Friedrichshöferallee 3

>> FIZ is a business incubator that promotes the development and marketing of innovative products, creates jobs, and helps the region extend its lead in the world economy. The Institute strengthens Frankfurt's biotech sector and supports the growth of the Frankfurt-Rhine-Main economy. >>



Frankfurter Innovationszentrum
Biotechnologie

FIZ – Center for Innovation and Entrepreneurship

Analysis – Strategy – Prospects

Frankfurter Innovationszentrum Biotechnologie GmbH (FIZ) was founded in June 2002. A lot has happened since then: The FIZ Team has analyzed current trends, discussed their significance, evaluated them, planned future activities, and, most importantly, developed the following three-pronged strategy:

1. Take advantage of new opportunities through international cooperation
2. Identify new sources of profit on the global market
3. Strengthen the region's innovativeness and entrepreneurship.

Taking Advantage of New Opportunities through International Cooperation

Hesse has established itself as a location for a large number of biotech companies and is thus considered a fast-growing indus-

trial area in the fields of pharmaceutical and biopharmaceutical research, engineering and production, protein research, biotech IT, clinical research, and products in the field of medical technology. To survive in the face of global competition, the industries that drive our growth must cooperate on a global scale. They must find the best location for the various parts of their business, work in partnership with local providers, and keep their fingers on the pulse of international customers. This also means hiring people and expanding operations in a variety of regions. As it lacks boundaries, the New Economy causes firms to spread departments and highly qualified staff across many regions the world over.

Companies that have joined the FIZ network, including medicament and diagnostic systems manufacturers and clinical research institutes, are expanding their value chains via global partnerships.

FIZ's key competitive edge is innovation and entrepreneurship in the early stages of the value chain, covering incubation, research, development and prototype production. While other regions act as innovators in these early phases as well, most of them lack the possibility to go into mass production and sales later on in the game. FIZ looks for regional and global partners to achieve success in both stages, with a view to promoting innovativeness and entrepreneurship in our region and creating value chains that can compete on world markets. Individual firms set up departments that complement each other across divisions. They fall into the four generic categories depicted in the figure on the next page:

- Company management
- Research & Development
- Production
- Marketing & Sales.

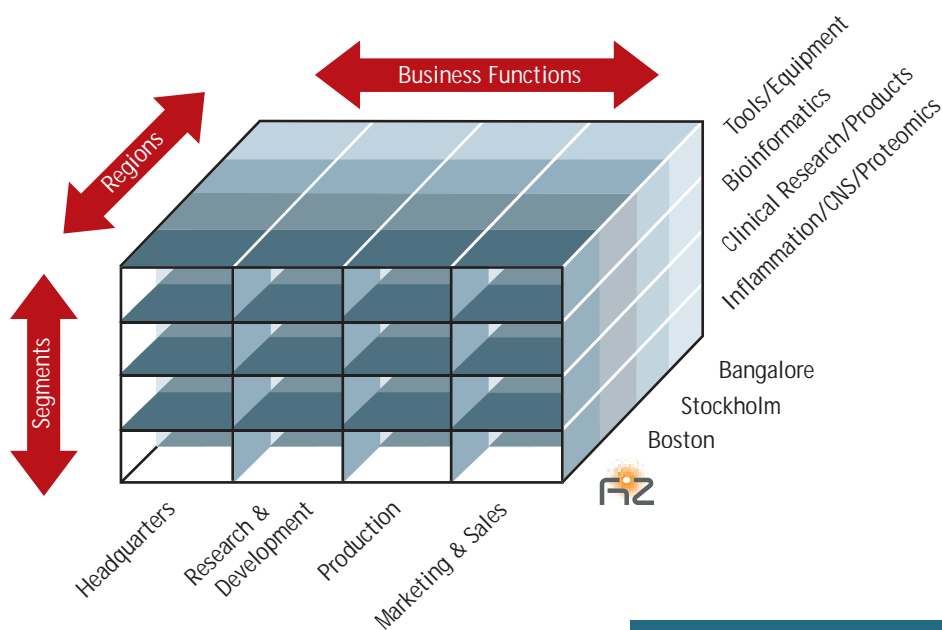
Companies decide where best to locate their divisions based on criteria such as cost, business risk, proximity to qualified staff,

and market access. In the global economy, these factors differ from one region to the next. This is why it is rare for all of a company's divisions to be located in the same region. Multinational enterprises become competitive by combining the best each region has to offer and relocating divisions to areas with an optimum mix of cost, quality, and other beneficial factors on a case-by-case basis.

Going above and beyond companies and divisions, areas of complementarity also exist between segments and regions that form part of the global economy.

Complementarity is a global reality – one that can prove profitable for regions that cooperate in order to compete. Therefore, every region must look for areas of complementarity that help

make it more competitive. This can happen within one and the same company as it spreads its functions geographically, among two or more enterprises by establishing joint ventures, or between segments that forge partnerships. Cooperating across regions can make companies, branches of industry and regions more competitive. Naturally, such collaborative efforts differ from each other considerably, because:



Business Functions

- the skills and networks of interest to firms offered by regions throughout the world differ from one another substantially. Businesses require very specific blends of regional competence, depending on their functions, products, and services. (For example, the needs of a pharmaceutical company in R&D are entirely different from those of a pharmaceutical firm in the field of production.)
- sectors have varying needs and unique “value chains,” each demanding its own specific mix of competence. (For example, the value chain of biopharmaceutical products is fundamentally different from that of bioinformatics.) Companies locate functions in specific areas for complex reasons, based on a number of factors, which differ depending on the company's lifecycle and the requirements unique to the sector. Businesses choose to operate under the umbrella of FIZ primarily because we offer them:

1. a pool of scientists active in business along with our proximity to the university system and other research institutions (this accelerates the convergence of biotechnology, nanotechnology, and information technology)
2. an entrepreneurial business climate with access to capital (FIZ Fund)
3. an established infrastructure and access to Europe's largest markets, and



Photo: Ulf Kreifels

4. transfer of technology (creation of a global scientific and company network).

Furthermore, companies affiliated with FIZ generally choose to be a part of our international network, because it allows them to

1. take advantage of comparative cost benefits
2. benefit from a growing pool of skilled workers (e.g. in China and India), and
3. gain access to growth markets, with Asia leading the way.

With all this complexity, there is one certainty: continuous innovation and entrepreneurship make complementarity among regions a dynamic process, which, in turn, stimulates the perennial structuring process among companies, industries and regions. The new global economy forces companies to constantly make decisions on where to locate the various parts of their business. Regions need to understand and then maximize their own unique advantages while recognizing that companies have an increasing number of choices

and competitive requirements that they must meet by distributing their operations around the globe. Global partnerships enable several regions to benefit from complementarities.

Identifying New Sources of Profit on the Global Market

FIZ is one of many nodes in a growing network of regional economies (see figure below). We set ourselves apart from other regions by combining the four following key location factors:

1. Universities and research institutes in our immediate surroundings
2. Traffic infrastructure serves as an international hub
3. International finance center, offering access to funding, including venture capital, private equity, and initial public offerings
4. Existing human capital, workers with outstanding qualifications as well as pharmaceutical, biotech, and chemical production plants.

These location factors give us visionary potential. We are capable of translating promising ideas into sustainable products and companies. This explains why many successful innovations in technology and business models originate in the Frankfurt-Rhine-Main region. As it operates on the global market, FIZ takes on the role of innovator and entrepreneur, creating new sources of profit for the region. FIZ believes creating value involves identifying a region's most favorable characteristics, tapping into them, and coupling them with the most beneficial features of other regions in order to serve the world's growing markets.

The FIZ within a Global Network of Regions



FIZ's Role Within a Global Network

FIZ benefits from the potentially powerful combination of these technologies and the emerging applications. Growing opportunities for new products, companies and employment could arise from such areas as bioinformatics (e.g., processing large amounts of complex biological data in product development), biomaterials (e.g., new applications for manufacturing), biopharmaceutical therapies against inflammation, cancer, and central nervous system diseases, and biochips (e.g., a convergence of microelectronics and molecular biology that can help diagnose illnesses).

Along with the new reality of globally dispersed business functions comes a new opportunity for FIZ to play a unique "interface" role, offering tailor-made services and expertise to business operations worldwide. FIZ is capable of adding value at each stage of the global supply chain in our rapidly growing industries. This enables firms to make use of FIZ's excellence in high-end research, engineering, design, and prototype production. They can also benefit from our support in production, marketing, logistics, and sales as we interface with regional industrial parks and the growing number of regions playing a role in the pharmaceutical, chemical, and biotechnological industries.

The biomedical industry is an emerging sector with a strong R&D element. Partnerships are beginning to develop, primarily within Asia, Europe and North America, as large pharmaceutical companies acquire smaller biotech firms or cooperate with them. The application of new technologies – applying nanotechnology to biotech and information technologies, for example – will create new opportunities for FIZ in the years to come.

As industrial segments move into mass production, it makes economic sense to shift these activities to other regions to optimize cost. At the early stages of research, design, and prototype production, innovation takes center stage, which makes FIZ the perfect place to be. At later stages, cost becomes more important, and by consequence, other locations may then prove more ideal. However, this shift does not signal the end of manufacturing in the Frankfurt-Rhine-Main region. Today, innovative manufacturing encompasses the entire value chain from research and design to production and distribution in every segment of our industry, whether pharmaceutical, chemical, biopharmaceutical research and engineering, proteomics research, bioinformatics, clinical research, or medical devices. In short, manufacturing in these sectors is a process that can hardly be compared to mass production. It can be located in nearby industrial parks such as InfraServ Hoechst, or Wolfgang in Hanau. While

FIZ's core competencies are its focus on highly qualified staff and intellectual capital in the research and engineering of life science products, it is important to remember that the real FIZ advantages are innovation and entrepreneurship rather than one particular industry or technology.

The future of manufacturing in the Frankfurt-Rhine-Main region is less about large factories. It is more about smaller, customized production operations and increasingly about production support services delivered to partners throughout the world.

Strengthening Our Region's Innovative and Entrepreneurial Power

To play this role, FIZ must set its expectations high and strive to deliver outstanding performance. To find new ways of adding value within the context of the global economy and to change the role we play with other regions, we must strive to be a world-class community in all respects, from education and infrastructure to quality of life. Instead of taking our flexible, fertile environment for innovation and entrepreneurship for granted, we must continuously improve it by investing in training and infrastructure.

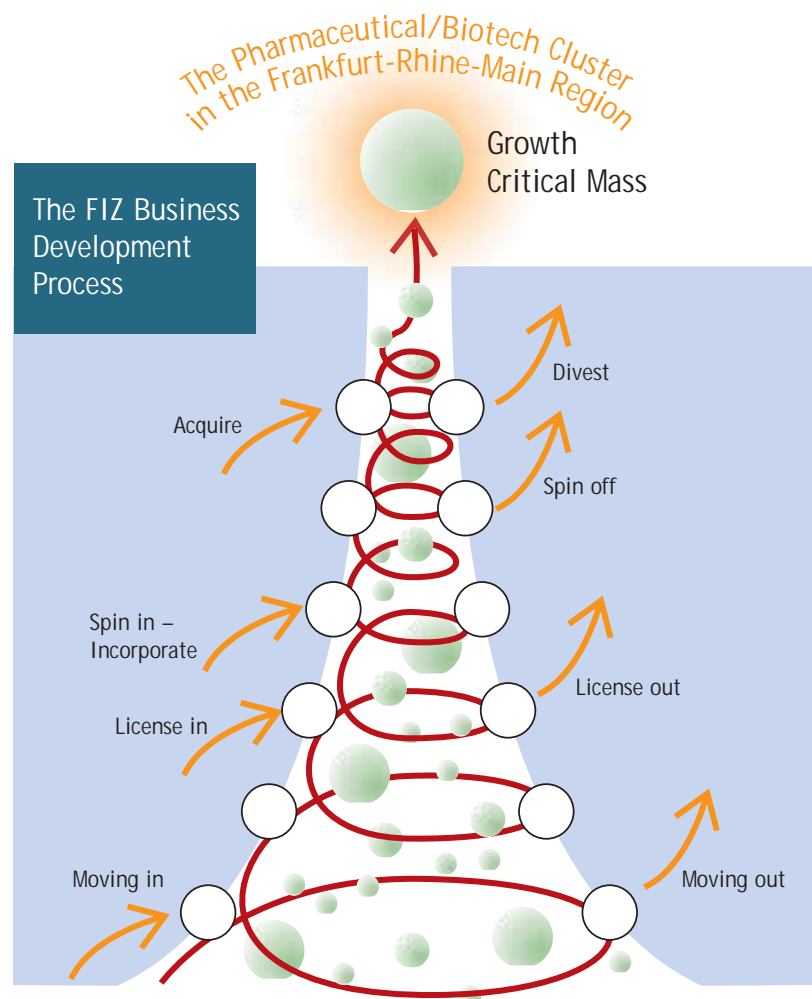
The challenge is clear: FIZ must provide one of the world's best centers, where people, capital and technology come together to fuel innovation and entrepreneurship.

While several regions have made a name for themselves in innovation and entrepreneurship, the Frankfurt-Rhine-Main region looks back on a remarkable history of transforming technolo-

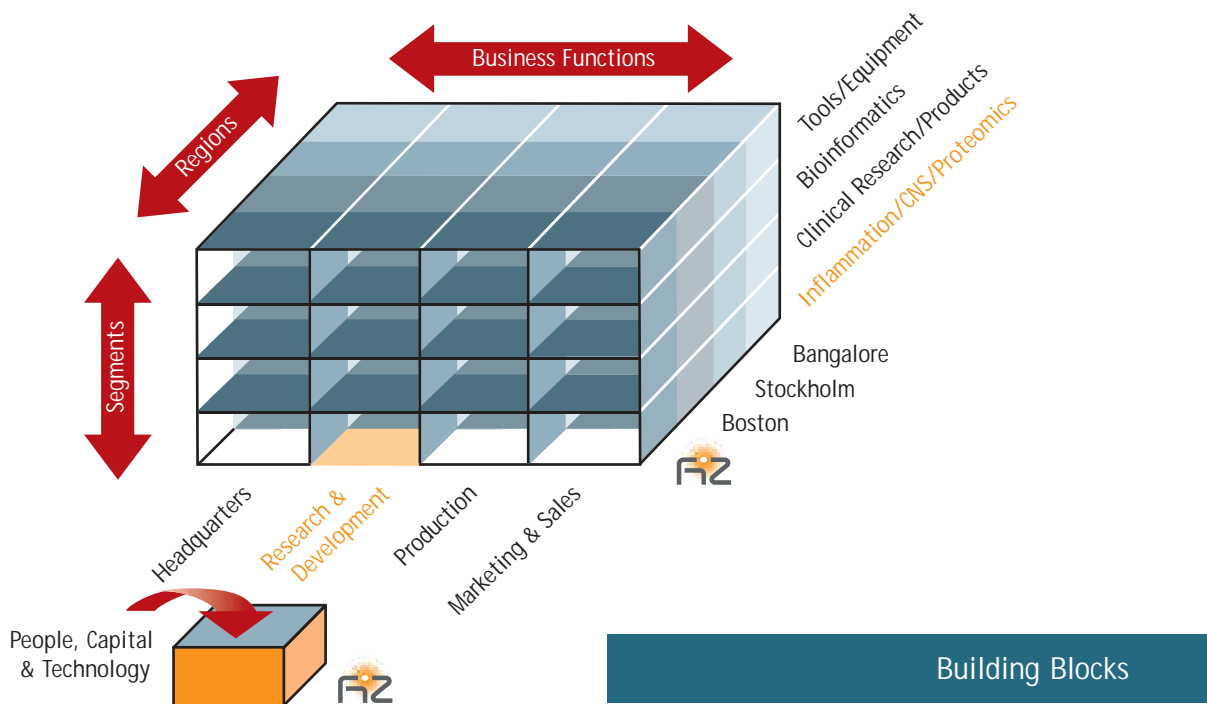
gical innovation into commercially successful companies and products¹. Potent venture capital networks promote the commercialization of technology through frequent forums and get-togethers where scientists and investors meet to exchange ideas.

FIZ will be a strong incubator of new companies based on the commercialization of innova-

tive ideas. The majority of economic activity occurs within the rapidly churning incubator, inside of which processes are marked by company start-ups and liquidations, with firms permeating in and out of the incubator's "membrane," aiming to achieve critical mass and long-term growth (see figure below). Globalization plays an important role in this "churning" of companies in FIZ.



¹ A study carried out by the Oxford Research Group in cooperation with Inside Consulting for the Danish Ministry of Science came to the conclusion that Boston, Hesse and Stockholm are among the strongest regions in the world when it comes to commercializing technological research.



Systematic and constant renovation within the FIZ organization is essential for growing the region's value-added as well as for creating new companies and jobs in the face of new global realities.

To be a strong player in today's global economy, FIZ must position itself at the cutting edge of innovation and be home to companies that commercialize new ideas. While members of the FIZ Scientific and Business Advisory Boards have several years of experience in both innovation and entrepreneurship, FIZ's future is not a foregone conclusion. It requires continued attention, reinvestment and adaptation. FIZ will focus on its

core assets – people, capital, and technology – that provide the foundation of our competitive advantage in the global economy (see figure above).

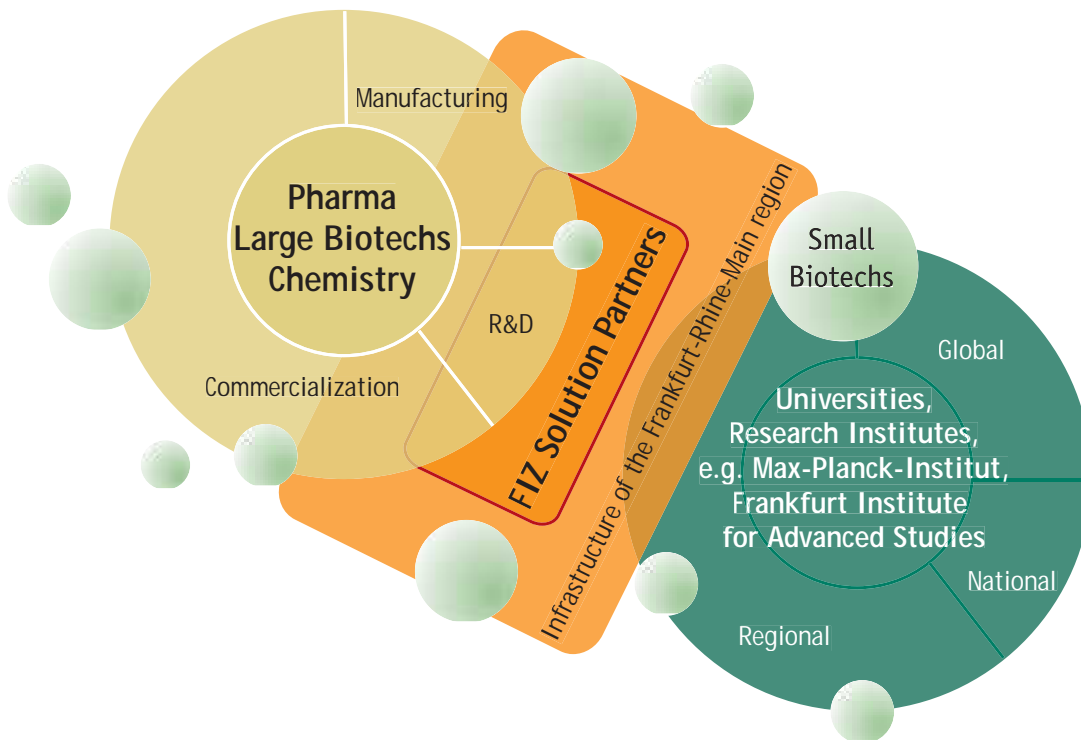
Besides providing these key elements, our region must connect and leverage them to fuel innovation and entrepreneurship, which in turn produce economic prosperity.

A web of local and regional institutions, guidelines, and practices, can connect people, capital, and technology. Running the gamut from research conducted by universities to local government approval processes to business financing to the education and training of specialized workers, everything converges to

enable the key factors to build on each other and thus turn into competencies. These competencies are at the heart of the center for innovation and entrepreneurship called FIZ.

The center participates in projects focused on research in the fields inflammation, cancer, diseases of the central nervous system, and proteomics. It is also active in areas that have a broader impact (e.g., lobbying for greater federal research funding, or for the support of startups). Regional and local institutions, policies and practices must continually adapt to changing global conditions to ensure that people, capital, and technology are connected in ways that cre-

The FIZ Business Incubator Model



ate a dynamic competitive advantage through innovation and entrepreneurship. Thus, the challenge facing FIZ is to determine what actions will strengthen and connect our competencies to achieve the desired results for the region.

Efficiency is gaining importance in both research and development. Large pharmaceutical enterprises often benefit from scientific achievements through collaborative endeavors or by acquiring small innovative businesses. Many fledgling biotech

firms thus serve as intermediaries between research departments in universities and other institutions as well as among the pharmaceutical, chemical, and biotech industries. Groups of companies in these sectors handle the sales and marketing of products and services created by innovative academic ventures. FIZ provides the infrastructure required to refine this process in an efficient manner to enable universities and other research institutions to license or sell their inventions strategically.

This business model continues to gain in importance because resources are becoming ever more scarce, with capital costs increasing to boot (see figure above).

What Does FIZ Have to Offer?

The nucleus of any attractive environment relies on effective interplay among people, companies and institutions. FIZ constitutes exactly this type of nucleus, marked by complex, dynamic interdependencies.

More specifically:

- *Favorable conditions for new ventures* – The FIZ system gives start-up founders from scientific institutions a professional entry into the business world.
- *Knowledge intensity* – FIZ is a bubbling cauldron of ideas for new products, services, markets and business models.
- *Open business environment* – Individuals and companies are open to win-win exchanges of knowledge and alliances.
- *Result-oriented action* – Large numbers of domestic and foreign companies have succeeded in the region, as has a diverse workforce, thanks to their willingness to assume responsibility.
- *Specialized business infrastructure* – There is a wide array of support services for upstarts, including venture capitalists, bankers, lawyers, headhunters, accountants, and consultants.
- *VC interest is essential for consistent entrepreneurial success* – By improving technology transfer policies and

taking steps to increase collaboration in research between institutions and the industry (for example, by building dedicated physical space for these partnerships), FIZ can create a more attractive environment for capital investment.

- *Highly-qualified, mobile workforce* – FIZ is a magnet for talent, including entrepreneurs, whose ranks are continuously replenished, ushering in new prospects and stimulating innovations.
- *Universities and research institutes interacting with industry* – Two-way street for

ideas and knowledge, shared in various ways, creating mutually powerful spill-over effects.

- *Collaboration among business, government and non-profit organizations* – Working relationships among companies, governments, associations, and others provide the means to address key issues and community needs.
- *High quality of life* – The natural, cultural, historical, and intellectual qualities of the region have long been major attractions for talent and companies.





Prof. Dr. Gerhard G. Steinmann,
Speaker of the
Scientific Advisory
Board

Department Head at
Boehringer Ingelheim
Pharma GmbH & Co. KG
in Biberach.

In addition to his management position, Steinmann holds a professorship in pathology in Kiel. He has also successfully applied his expertise at Immunex in Seattle, Washington. At Boehringer Ingelheim he leads teams of researchers working in drug discovery, immunopharmacology, clinical oncology, immunology, and virology. He takes credit for having developed three cytokines to market maturity, and has initiated a global network of experts in industry and science.



Frankfurter Innovationszentrum
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Incubation of Biotech Business

between Science and Industry in Germany

Biotechnologically produced pharmaceutical drugs for the treatment of diseases have been around for almost 20 years and today are contained in about 10% of all approved medications. Among drugs currently in late stages of their clinical development (phase III), their share is even twice as high, namely 20 %. In early clinical and pre-clinical stages of development they account for 26 % of compounds. Regarding the number of patent applications in this field, in 2002 Germany was second only to the United States, submitting 12 % of all applications.¹

These figures illustrate two points:

- The productivity of biotechnological methods continues to grow with unchanged dynamics in Germany, too
- Science, industry and politics in Germany are facing the important task of translating their high share of good quality biotechnological ideas into a commensurate share of successful companies.

The BioRegio competition of

1995/96 triggered an impressive boom of companies being founded in Germany. Between 1997 and 2000, 283 of the so-called biotechnology core enterprises were created, i.e. enterprises that, according to the OECD definition of this term, employ primarily biotechnological processes. According to the Federal Statistical Office's (Statistisches Bundesamt) second survey on biotechnology in Germany,² the upswing has entered a consolidation phase which will not only differentiate the market, but also have a stabilizing effect.

In 2002 only 11 core enterprises were founded – the same number as in 1990. Yet, the number of employees in this sector rose by 20 % between 2000 and 2002, with the number of small companies decreasing and with larger companies gaining stability and increasing their revenues by 90 % on average. The past two years have also seen only a few new German companies that primarily work with biotechnological methods.

Since research is the basis for innovation, it is not surprising that employees in newly founded

companies essentially work in research and development (R&D). The younger and smaller the company, the higher the R&D share. In small companies R&D typically make up between 60 % and 100 % of the company's activities. The extent to which biotechnology core enterprises have increased their spending on R&D, especially during the competitive consolidation period in recent years, is truly noteworthy. R&D spending increased overall by 109 % between 2000 and 2002; however, at the same time R&D spending in smaller companies decreased, in some cases significantly.³

In the aftermath of the founding boom of biotechnology core enterprises, a somewhat delayed wave of both non-profit and profit-oriented business incubators has swept across Germany. In 1999 and 2000, the number of profit-oriented incubators grew as quickly each month as it had previously done in an entire year. Incubators for young biotechnology companies accounted for 13 % of the market.

The concept of business incubation through public or private

organizations has been in circulation for more than forty years and is successfully established worldwide. In addition to “incubators,” these institutions have also been labeled “seed capitalists,” “growth accelerators,” “venture catalysts” and the like, terms that invoke associations with biological processes, thereby making these institutions more accessible and promoting trust not only in life scientists.

Biotechnology founders are well aware of the biological meaning of incubation and of the benefits of incubators in the laboratory. Life scientists rely on these incubators when certain physical and chemical parameters have to be kept constant and when the atmosphere has to be free from harmful influences. However, no matter how optimal the growth of an organism in a controlled environment or – applied to the business of biotechnology – how well a good idea can be developed under the wings of the business incubator, answers to essential questions such as the following cannot be found that way:

- Are my scientific data accurate?
- Do I have sufficient intellectual property protection?
- Do I need more licensing?
- Does my idea meet a true need of economic importance?
- Do others understand my plan?
- How far will funding carry me?

- Where are my partners for continued development?

The incubator market, adapting to the changes in the founding market and the increasingly conservative attitudes of investors, has also been consolidated:

- Incubators without clear core competencies have lost their influence or are no longer in the market
- Incubators were able to develop their core competencies more quickly when they focused on a certain branch of biotechnology or on a certain type or phase of founding
- It was possible for the competency of an incubator to improve during incubation, resembling training on the job, so to speak, but an incubator could not afford to wait until after the start of incubation to develop its competency.

That is because there are high demands on biotechnology founders. They usually cannot provide the required resources in terms of capital and consultation on their own. Depending on the developmental stage of their businesses, they will need one or the other, and sometimes more, sometimes less of it. Founders usually learn their business the hard way, at the latest they do so when they understand that there is always one responder among the very first patients in

a clinical study. During the boom days, good marketing of research alone was sufficient to attract investors, but today the start-up management needs to be able to present valid research results exhibiting due-diligence resistance, substantial industry experience and a bullet-proof business plan to avoid pessimistic or even cynical comments from investors.

During the past consolidation battle, some lessons for biotech founders have been tested and found to be essential for survival. The following three should be written in stone:

- Stay away from one-product miracles. They are in big danger of being ridiculed. Investors will prefer technology platforms capable of yielding multiple product lines.
- There is no such thing as an overcapitalized biotech start-up. The primary concern needs to be that the finance plan ensures the success of the start-up, not the founder’s share in the business.
- Even when sufficient scientific, business, and legal expertise is present, the start-up management can bring experience to the team only by getting experienced veterans on board.

Following the role model of traditional incubators in the USA, German biotech incubators have often limited themselves to pro-

viding laboratories, offices, and infrastructure right outside a university campus – just as the image of a temperature- and humidity-controlled laboratory incubator suggests. This image, however, also reflects the belief that business people are born rather than made. There are examples of such cases, but experts are no longer so sure. The public question remains whether people are not, after all, capable of learning how to turn good ideas into great enterprises. The answer to that question will be decisive for the unemployment-ridden German national economy and its fate over the coming decades.

The services offered by traditional incubators, therefore, are no longer sufficient for young biotech companies. The incubator concept needs to alter its passive message. It is no longer suitable if the incubator orients itself towards the potential biotech founder as a client. Biotechnology itself has long since moved beyond the traditional passive incubator to modern, actively supplied culturing systems with harvesting devices, and it knows of bioreactors that will work even in space. Does a reactor also make a better image for business incubation with a future?

Towards the end of the biotech start-up boom, successful incubators already began turning to questions and specific needs of the founders and offered them



more. Today, at the end of the consolidation phase, the full spectrum of outsourceable business functions has to be provided, such as scientific, business and legal expertise, funding, contacts and networking, media and public relations, operational support, controlling, marketing, sales, human resources, and business development.

A successful incubator of biotech start-ups must meet these needs in order to increase the chances of survival for its “incubatees” in the world between science and industry. The Frankfurter Innovationszentrum Biotechnologie will fulfill this task. It will be a business reactor.

1 Verband Forschender Arzneimittelhersteller, Statistics 2003

2 J. Hahlen, Statistisches Bundesamt, Oct. 21, 2003

3 A.K. Achleitner, R. Engel, Der Markt für Inkubatoren in Deutschland, Jan. 2001



Dr. Wolfgang Berthold

Senior Vice President of Biogen Idec Inc., San Diego/Cambridge.

At Biogen Idec Inc., Wolf Berthold is responsible for biotech manufacturing operations and development. He was already in charge of this area for IDEC

Pharmaceuticals Corp. and earlier at Hoffmann La Roche Inc. Wolf Berthold has fulfilled many functions, primarily in the development of recombinant therapeutic proteins and its production. Berthold has brought a number of novel and important products to market approval in the US and EU like Actilyse. He has also been involved in the construction of large-scale manufacturing plants in Germany, starting in 1985, and lately in San Diego. Berthold has helped define standards for getting important new protein therapeutics to patients.



Frankfurter Innovationszentrum
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Innovation and Entrepreneurship

The role played by the entrepreneur is not always highly appreciated in the circles of “pure” science, and yet it is the entrepreneur, too, whose success adds significant value to science. After all, it is the entrepreneur who literally makes Science literally tangible to “the people,” making the appreciation of it possible for many. Last but not least, in doing so the entrepreneur contributes significantly to the justification of public spending on research and to the high expectations, even hopes and belief in technology for a better future through science and technology. All of these aspects can be condensed into the following hypothesis:

Coupling science and innovation via entrepreneurship yields growth.

I would like to take a closer look at this statement – seemingly trivial, at first glance – and draw some conclusions regarding the interdependence of innovation and entrepreneurship. Biotechnology represents a current example of this connection.

Innovation Power as a Prerequisite for Maintaining a Competitive Edge

There is a trend that cannot be stopped to move jobs yielding only little value out of Germany. Germany simply cannot compete with the low wages in the up-and-coming industrial nations such as China, India, and Ukraine. In order to maintain and increase growth and prosperity, it is, therefore, necessary to focus on creating jobs that require high levels of qualification and jobs that produce high added value.

The readiness of individuals to dare to do something new (risk) and to realize new ideas (visions) in the form of innovative entrepreneurship constitutes the foundation and source of dynamic growth creating significant added value, highly qualified jobs and a competitive, efficient infrastructure.

Innovation and Market Economy

Innovations are based on visions. More often than not these are visions of technical simplification or great novel strategic approaches. The development of Molecular Biology with its biotechnological implementation into many new therapeutic and diagnostic possibilities in medicine is an eloquent example of this transition from vision to product.

Within our society, the potential for innovation, however, does not or only to a certain extent depend on the number of great visions and ideas it can provide. What really counts is the implementation of those ideas in a world that is ready to embrace the changes they bring. Thus rather than the elegance or beauty of the idea, it is the impact of innovation in form of the number of products and services that will actually succeed in the marketplace. In other words: in today's globalized market economy the innovation performance of a given region or country depends prima-

Science-based Entrepreneurship as Foundation of Basic Innovation



The idea that research, including basic research, is the sole responsibility of research institutions and universities and is dissociated from economic interests, neglects the fact that a more effective division of labor has emerged. Commercial companies do conduct basic research, and have to do so in order to survive. The three largest biotech enterprises worldwide – Amgen, Genentech and Biogen Idec – in my estimation spend more on basic research in selected disciplines than many German universities apply to those areas (e.g. Immunology) combined. In the United States it is also a given that academic researchers will collaborate with commercial researchers at all levels in the value creation chain of a given innovation. Here, academics may even embark on an entrepreneurial career in order to help specific ideas attain economic success.

Germany, too, has seen prominent examples of successful connections between science and industry. The German chemicals and electrical industry owes its existence and early innovation power to the fusion of scientific creativity and entrepreneurial energy: Carl Bosch (BASF founder, Nobel prize winner) and Werner

rily on the decisions of market participants. Decisions based on cost, revenue, and risk considerations that individual entrepreneurs, managers, and investors make determine the direction and the degree of innovation.

Politics also plays an important role in this. By setting a framework of beneficial regulatory policies and conditions, politics can have a decisive impact and stimulate innovation. Political means encompass many different areas, such as removing obstacles, offering innovation incentives (e.g., taxes, patent protection), promoting responsible, self-regulated research (fewer state regulatory acts) and guaranteeing the free flow of information.

Connecting different disciplines is essential for the success of innovation. The development of “innovation communities” is based on the close intraregional proximity of the players, all the diverse constituencies: bracketing the industrial sectors, and interdisciplinary networks of state agencies, i.e. federal and local authorities, market participants and social partners. They all share the common goal of forming lasting networks of “regions of excellence” that will promote innovative start-ups.

von Siemens both were brilliant inventors and scientists as well as successful and visionary entrepreneurs at the same time. Those days of success, however, are long gone. The recent past has seen the demise of quite a few large enterprises in Germany, and this was most strongly felt in Frankfurt. The Hoechst company, for over 100 years an icon of German research and industry in the fields of chemistry, pharmacology, and biology, no longer exists as a company in its own right. Especially biotechnology was not successful at Hoechst, in spite of an early and energetic beginning within the existing environment.

Unfortunately, still today many examples demonstrate the difficulties in implementing scientific discoveries in practice-oriented applications. For example, the German minister in charge of research (and innovation) stated: "... regarding nanotechnology we (Germany) hold second place worldwide – excellent results. However, those research results have not always led to focused and rapid pursuit of development of products, process innovations, or novel organizational structures."

One explanation for this phenomenon or at least part of it

can be found, I believe, in some of the central values of our (German) culture. They are deeply rooted and better suited to maintaining the status quo than to creating something new:

Cultural Aspects:

1. Structure and order are preferred
2. Predictability is preferred
3. Safety and certainty are preferred.

These are attributes of a highly developed society focused on stability, and they clash with the basics of entrepreneurship. In a culture such as this, it is hard to found and develop an enterprise.

Basics of Entrepreneurship:

1. Creativity and flexibility
2. Improvisation
3. Opportunism and quick reactions to changing situations.

The successful transformation of visions and ideas into practical applications, therefore, in addition to the creation and enhancement of entrepreneur-friendly conditions, requires a transformation on the cultural basis. Nothing short of a paradigm shift is needed, namely one from "No risk, no loss" to that of "No risk, no gain."

Incubators as Catalysts for the Successful Transformation of Innovation into Entrepreneurship

Incubators play a central role in the maturing process of a young company into an established enterprise. Not all incubators offer a combination of various services such as FIZ does. FIZ is offering a new concept with a perspective by giving help also in areas that are often alien to potential entrepreneurs, especially those with a scientific background:

1. Provision of physical resources (offices, laboratories, computers, etc.)
2. Facilitating access to funds: venture capital and other financial aid, typically provided via a combination of private and incubator-external funds
3. Centralizes office services (IT, administration, etc.)
4. Company-relevant support in the areas of accounting, legal advice, taxation as well as operational leadership and management
5. Networking: creating a work environment in which representatives from industry, research and politics can and do meet.

Incubators help to transform ideas into successful companies. Bringing together research, industry and politics by creating “innovation hot spots” leads to a win-win-win situation. Industry gains better access to promising products and technologies. Scientists have the opportunity to create practical relevance for their research and to as well as access to third-party funding to support it. And local, regional and national politicians can directly observe where political action is needed most.

Development of Innovation and Growth Clusters

Among other things, innovation and growth clusters are characterized by the geographical concentration of renowned science and research institutions on the one hand and exceptionally fast-growing small and medium-size businesses offering sophisticated products and services in the area



Photo: Ulf Kreifels

of technological novelties. These clusters develop and grow especially well around centers of multidisciplinary institutions made up of highly reputable universities and research institutions. They offer the shortest distance possible for the successful transfer of scientific discoveries and technological know-how into the market economy.

Although by no means will every single newly founded company become a success, some of those young enterprises will grow into medium-size companies and even large multinational corporations, thus resulting in a healthy mix of start-ups and established companies in relatively new growth industries with massive value creation. Examples of such development are the biotechnological centers in San Francisco and San Diego, in California, in Cambridge, both in the US and the UK and BioValley in the upper Rhine region. A similar example from the computer industry is California's Silicon Valley.

In addition to successfully combining science and industry as well as innovation and entrepreneurship, upwardly mobile economic regions are also characterized by further structural properties: an existing modern infrastructure (roads, buildings, energy, information technology), an established venture capital market, unimpeded mobility of the workforce, a high standard of living, and, last but not least, regulatory policies friendly towards entrepreneurs and research.

By providing the infrastruc-

ture and creating conditions supporting a linking of science, entrepreneurship and growth, FIZ will contribute significantly to promoting the economic and general development of the Rhine-Main region.

Summary Statements

1. One of the prerequisites for maintaining and enhancing growth and prosperity in Germany is *innovation*. It leads to the creation of highly qualified jobs and products with high value creation.
2. The decisive factor for the impact of innovation is the number of *commercially successful* novel products and services. The decisions made by individual entrepreneurs, managers and investors based on cost, revenue, and risk considerations determine the direction and the degree of innovation. It is the responsibility of politics to create favorable conditions.
3. The development of "innovation communities" should be based on the close intraregional proximity of the players and intersector and interdisciplinary networks of state agencies and authorities, market participants, and social partners. The goal is to form *lasting networks* of "centers of excellence" that will promote innovative start-ups.
4. The successful transformation of visions and ideas into practical applications also

requires a *transformation on the cultural level*. Nothing short of a paradigm shift is needed, namely one from "No risk, no loss" to that of "No risk, no gain." Such a transformation, however, can only be promoted indirectly by creating and enhancing entrepreneur-friendly conditions.

5. *Incubators such as those following the FIZ concept can play a central role* in turning ideas into successful enterprises. Bringing together research, industry and politics by creating "innovation hot spots" leads to a win-win-win situation and, therefore, to growth.
6. The signature of successful entrepreneurship is the increasing linking of science and innovation.

¹ Edelgard Buhlman, on the ARD television show "Tagesthemen", on the occasion of her party's convention in Weimar on January 6, 2004



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between industry and institutions of
higher learning, such as the Frankfurt
Pain Platform.



Frankfurter Innovationszentrum
Biotechnologie

Excellence of Three Worlds

Center for Drug Research, Development, and Safety (ZAFES)

Pharmaceutical research worldwide is in a crisis when it comes to innovations. The pipeline of new drugs that a few years ago was still a mighty river is about to become a mere trickle.

According to a report published by the US FDA in March 2004 – “Stagnation, Innovation – Challenge and Opportunity on the Critical Path to New Medical Products” – the number of IND applications has decreased from almost 100 in 1993 to not even 30 in 2003. In the past year, the bottom line was 21 truly innovative drugs approved in the US, and in Germany only 17.

Research costs, on the other hand, doubled from 1996 to 2003 to about 32 billion US Dollars worldwide. The German share for 2003 was about 3.6 billion Euro. Per approved drug, pharmaceutical companies have to allow for costs between 800 million and 1.7 billion Dollars. And every hit has to pay for a number of flops. Thus, the FDA states: “If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline, and the biomedical

revolution may not deliver on its promise of better health.” And continues: “The medical product development process is no longer able to keep pace with basic scientific innovation. Only a concerted effort to apply the new biomedical science to medical product development will succeed in modernizing the critical path.”

Think Tanks are in Demand

Additionally, Europe currently does not compare favorably with the United States in terms of the development of innovative drugs. This is not only due to the lower rate of investment increases in research and development. As the EU Commission stated in its report, “A stronger European-based pharmaceutical industry for the benefit of the patient – A call for action,” in July 2003, the United States was also more successful in coordinating public and private research. That is particularly due to the National Institutes of Health that bundle

and especially strengthen research activities. In Europe the research systems are very much fragmented, significantly hindering the development of dynamic research and innovation centers, so-called think tanks. The Commission primarily criticized the fact that researchers here will only rarely cooperate on a larger scale – neither interdisciplinary nor across the borders between science and industry.

Effective Frankfurt Networks

That is all to change now – at least in the Frankfurt-Rhine-Main region. With the help of ZAFES, the Center for Drug Research, Development, and Safety, the best knowledge from the three worlds of academia, industry and biotechnology is to be optimally utilized here. After all, Frankfurt not only offers academic research at the highest level – almost the entire value creation chain of drug development can be covered inside ZAFES – but also the international pharmaceutical industry, biotechnology and the world of finance are at home here. The region has highly qualified scientists, a scientific tradition in the areas of medicine, biology, chemistry, and information technology, a financial and service market, and, last but not least, manufacturing experience with chemical, biological and life science products. This local advantage is probably unique for Germany, possibly even for Europe. An advantage also seen by the pharmaceutical company Aventis which hopes to promote the Frankfurt's importance in the long-term by supporting ZAFES because competitive pharmaceutical research requires first-class academic networks. After all, the partners from these networks already provide one quarter of all research efforts. Thus, it is important to get the right people together early in the game in order to

efficiently implement innovation. ZAFES is a forum for doing so and thus providing a central building block for transforming the Rhine-Main region into a pharmaceutical think tank.

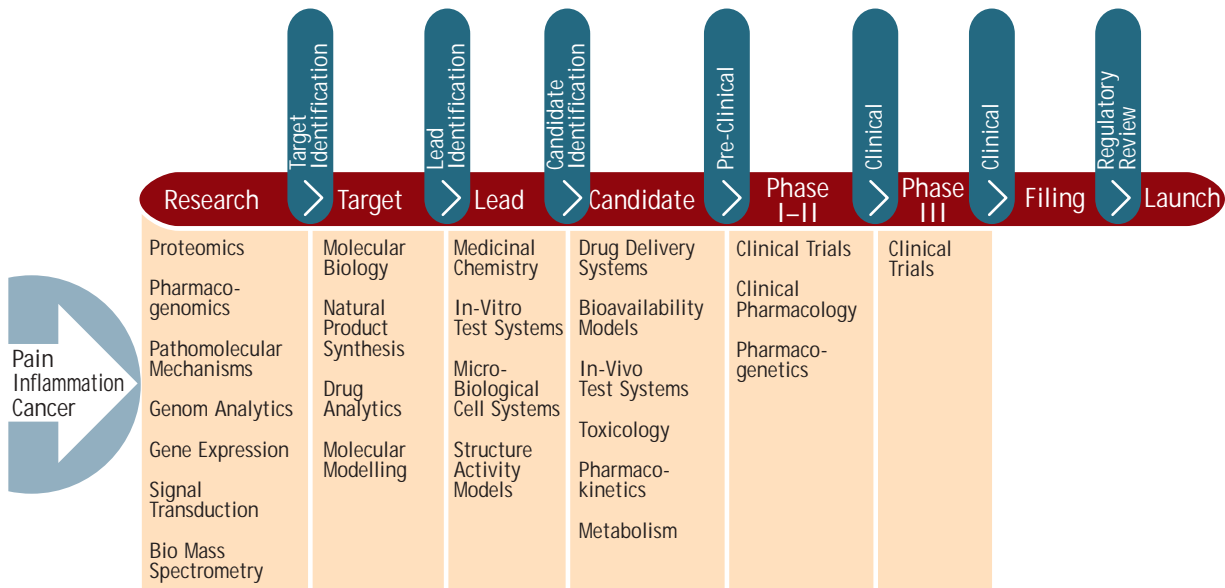
Focus on Important Indications

The scientists participating in ZAFES come from the university's departments of Chemical and Pharmaceutical Science as well as Medicine and unite their competence – initially in the research areas of pain, inflammation and cancer – with that of partners from industry and biotechnology via internal networks. Thus, they utilize both the competence of pharmaceutical and drug research at the Riedberg campus as well as that of the university hospital at the Niederrad campus in addition to that of partners in the industry. Basic research along with developmental and trial processes are thus coordinated early and efficiently. The goal is to make significant scientific contributions that will not only lead to the discovery of new drugs but also to their development into marketable medications. Therefore, entrepreneurial and crossfunctional thinking are essential at ZAFES.

The “Three-legged Frankfurt Table”

ZAFES constitutes the logical continuation of previous activities and collaborations within the university and with partners in industry. Just like a three-legged table, where one leg is represented by ZAFES and the other two by the Frankfurt Biotechnology Innovation Center (FIZ) and the Clinical Study Center Rhine/Main, the table will be stable only with all of its three legs. If one is missing, it will collapse. And the FIZ will be home not only to start-ups from the high-tech industry, young biotechnological companies and large, forward-looking collaboration projects with established enterprises. ZAFES-management will move in as well because being located in the immediate neighborhood of the scientific infrastructure of the university and other research institutions is a definite plus.

Value Chain of a Drug and ZAFES-Competence



Focus on Crossfunctional Projects

One example is the Pain Platform Frankfurt. This collaboration between Aventis and the university's pharmazentrum frankfurt conducts research into potential therapies for osteoarthritis. The new center not only facilitates the search for adequate know-how within the university but also initiates and implements concrete projects. For example, molecular biologist Prof. Rolf Marschalek of the Institute of Pharmaceutical Biology and Prof. Thomas Klingebiel, Director of the Pediatric Clinic for Hematology, Oncology, and Hemostasiology, have both

dedicated themselves to research into a life-threatening disease affecting about 600 children worldwide annually – a specific subform of acute high-risk leukemia. The goal is to develop therapeutics interfering with the pathogenic principles behind this form of leukemia. Initial biological testing systems are currently being established in preparation for pharmaceutical screening. The implementation of the screening will require further collaboration with industry which is to be initiated and coordinated by ZAFES.

A pioneering example of newly established collaborations between university and industry is Phenion. The initial step was a bilateral collaboration between the Institute for Pharmaceutical Chemistry (Dieter Steinhilber

and Henkel KGaA. Through targeted extension of the network, a company was founded collectively by Henkel KGaA and a group of further professors at Frankfurt's university, including the Director of the Clinic for Dermatology and Venerology, Prof. Roland Kaufmann. His Phenion research group investigates new therapeutic options in the areas of immunomodulation and anti-inflammatory treatment of skin diseases such as atopic dermatitis and psoriasis. Another topic is tissue engineering for the treatment of chronic skin defects.

Drug Optimization

Another team at ZAFES is pursuing the development of drug therapies for gastrointestinal inflammation processes. Here, Prof. Jennifer Dressman of the Institute of Pharmaceutical Technology, Prof. Jürgen M. Stein of the Medical Clinic II (Gastroenterology, Pneumology/Allergology) and the Röhm GmbH of Darmstadt are cooperating closely to optimize the various available drugs. Currently the initial clinical studies of the prototypes which have been developed are underway.

New ZAFES Lead Projects

In cooperation with the Berlin-based biotechnological company Medical-Enzymes new enzymatic therapies for the treatment of solid tumors are being investigated by the Director of the Medical Clinic II, Prof. Wolfgang F. Caspary and Prof. Jürgen M. Stein. The clinical trial of the first substance indicated for colon cancer started in May 2004.

Further clinical studies are in preparation, such as for the indications of breast and ovarian cancer, with the gynecological clinic of Prof. Manfred Kaufmann participating. The added value for Medical-Enzymes is the clinical research know-how as well as the broad range of ZAFES' expertise that they can draw on all along

the value creation chain up to the marketable drug – a major point in favor of the start of this and other promising ZAFES collaborations.

Center of Competence in Lipid Signaling

One of ZAFES' goals is to initiate and implement projects involving complex and crossfunctional questions that, on the one hand, could not be successfully tackled by any single institution and that, on the other hand, would result in significant therapeutic advances. Thus, a center of competence in lipid signaling is being established at ZAFES which will investigate the role of lipids and their metabolites in the human metabolism.

Lipids and their metabolites are not only essential components of the cell membrane, but also important signaling molecules participating in the regulation of elementary cellular processes such as cell growth, cell differentiation, and apoptosis. Lipid metabolism disorders play a decisive role in many diseases such as atherosclerosis, various rheumatoid and allergic diseases, cancer, and neurodegenerative disorders. Both the identification of various lipid components as mediators of cell physiological processes and insights into the regulation of the enzymes and receptors involved in them form the basis for understanding pathophysiological processes. This will

enable the development of new therapeutic strategies and – the ultimate goal – new drugs.

Here, 13 scientists from the departments of Medicine as well as Chemical and Pharmaceutical Science at Johann Wolfgang Goethe University, including professors Rudi Busse (Cardiovascular Physiology), Horst-Werner Korf (Experimental Neurobiology), Josef Pfeilschifter (General Pharmacology and Toxicology), Gerd Geisslinger (Clinical Pharmacology), Jürgen M. Stein (Gastroenterology), and Dieter Steinhilber (Pharmaceutical Chemistry) are already working in nine sub-projects to determine the molecular and cellular basis for the role of lipids in inflammatory process regulation. One of the strategic elements is the early involvement of partners, especially from the pharmaceutical industry.

Will Lipid-lowering Drugs Protect the Brain as well?

Another ZAFES project is investigating central nervous system targets of statins (cholesterol-lowering agents). Epidemiological studies have indicated a protective effect of statins in neurodegenerative diseases, such as Alzheimer's disease. Working to identify the underlying pharmacological and molecular biological mechanisms for these observations are Prof. Walter E. Müller (Pharmacological Institute for Scientists), Prof. Manfred Schubert-Zsilavecz, and Prof. Michael Karas (both at the Institute of Pharmaceutical Chemistry) in conjunction with the University of Minnesota, USA, and industrial partners Aventis and Applied Biosystems.

In order to better identify extended therapeutical uses of statins the involvement of additional ZAFES expertise in the fields of 3 Tesla MRT (Prof. Friedhelm Zanella, Institute of Neuroradiology) and clinical research (Prof. Helmuth Steinmetz, Neurological Clinic) is being envisioned.

Success through Clear Goals and Efficient Management

Twenty-seven of the university's professors are members of ZAFES, and more than 400 scientists work on the various projects and questions. Further scientific institutions such as the Paul Ehrlich Institute of Langen, the Georg Speyer House, or the Karolinska Institute of Stockholm have become associate partners of ZAFES, and the number of new suitable partnerships is growing. Their common goal: the establishment of a strong pharmaceutical think tank in Europe with a German core based in the Rhine-Main region.

This targeted networking based on matching competencies – so-called platforms – opens up completely new opportunities to drive drug development projects efficiently through the various Centers of Expertise, as demanded by the FDA, via application of new biomedical research. However, this requires an adequate environment and appropriate commitment by the researchers involved.

To achieve this, not only has the research to be top-notch, but the complexity also demands efficient management. The know-how in this area is provided by Managing Director Dr. Bernd Stowasser from the industry. As manager for Aventis, he has spent the past 8 years in execu-

tive positions in the USA and Latin America. He and his team belong to the decisive cogwheels in ZAFES's complex gear mechanism that is developing rapidly. Nominated coordinators are responsible for the crossfunctional integration of ZAFES projects and important processes. They receive organizational support to this end, for example in the areas of project management and with coordinating external networks.

ZAFES is open to all research-based companies – and perhaps some day an important drug will be approved that was made possible only by this unique constellation of networked Frankfurt know-how from the three worlds.



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Frankfurter Innovationszentrum
 Biotechnologie

Cytokines

Therapeutic Tools and Targets in Modern Medicine

Cytokines are pleiotropic, regulatory peptides that can be produced by virtually every nucleated cell in the body. The cytokine family consists of several sub-families: the interleukins, the tumor necrosis factor (TNF) family, interleukin-6 and interleukin-6-related cytokines, interferons, chemokines such as interleukin-8, transforming growth factor-beta, colony-stimulating factors, and others.

In most tissues, constitutive production of cytokines is absent or low. However, as physiologic and pathologic stimuli activate cells, the production of these autocrine, paracrine and endocrine effector molecules increases, and they, in turn, orchestrate the tissue's response to the stimulus. There is increasing evidence supporting a major role for several cytokines in various aspects of injury and repair. Cytokines are

proximal mediators of inflammation, cell death and fibrosis, but paradoxically also mediate for example the regeneration of various tissues such as the liver after injury. Recently, the practice of both blocking specific cytokines and administering these polypeptides have driven new clinical concepts and entered the field of disease management.

Among the various cytokines, one cytokine, namely the pro-inflammatory molecule TNF-alpha ($\text{TNF}\alpha$), has emerged as a key factor in various aspects of inflammatory diseases. Some of the most definitive data about its importance in various, especially chronic inflammatory disorders have come from studies neutralizing this potent pro-inflammatory cytokine i.e. by neutralizing antibodies. These new anti-TNF approaches have altered the course of clinical medicine

dealing with chronic inflammatory disorders and can be clearly added to our standard armamentarium in the treatment of many chronic inflammatory disorders such as rheumatoid arthritis, Crohn's disease, Bechterew's disease and psoriasis. Whether these innovative treatments will become standard treatment in early disease remains speculative as clinical trials in this setting are lacking. Considerable side effects, especially infectious complications, serve to remind us that new drugs have to be handled carefully and indications should be in accordance with available data from clinical trials. Alongside these diseases, efficacy of anti-cytokine drugs has been demonstrated in small clinical trials in several other inflammatory disorders of the gastrointestinal tract (ulcerative colitis, pouchitis, celiac disease, alco-



Photo: Ull Kretzels

holic hepatitis, Behcet disease) suggesting that we have entered a new exciting era in which anti-inflammatory immunotherapy might become a clinical standard in many gastrointestinal inflammatory disorders.

Whereas the neutralization of key cytokines has been an especially promising concept in recent years, the administration of various cytokines such as erythropoietin or various type I interferons (IFN) has similarly influenced medicine. IFNs were among the first cytokines to be identified and are naturally occurring substances initially described for their ability to interfere with viral replication and production. A virus-induced factor was first described by Isaacs and Lindenmann in 1957 and later called classical or type I IFN (IFN α and IFN β). The pH2-labile non-virus induced IFN was labeled "immune IFN" and later type II IFN (IFN γ). Type I IFNs

were subsequently demonstrated to exert multiple biological effects including potent immunomodulating effects. IFN α_{2a} and IFN α_{2b} are approved for the treatment of a variety of malignancies and viral diseases. IFN α is clinically useful in diseases of diverse pathogenesis and manifestations, such as chronic viral hepatitis caused by either hepatitis B or hepatitis C virus, chronic myelogenous leukemia, hairy cell leukemia, Kaposi's sarcoma, laryngeal and genital papillomas and various angiogenic diseases.

IFNs, early cytokines in the body's defense mechanisms, show surprisingly different effects on various aspects of inflammation. Whereas type II IFN has predominantly pro-inflammatory properties, type I IFNs exert many anti-inflammatory and immunoregulatory properties. Besides induction and upregulation of various anti-inflammatory cytokines by type I IFNs, one key

feature of their anti-inflammatory properties might be their potential to induce apoptosis. Induction and/or enhancement of apoptosis has been recently identified as being of critical importance in various clinically effective anti-inflammatory drugs such as infliximab or azathioprine.

IFN α was the first cytokine to be described and characterized, the first to be purified and cloned, and the first to be used clinically with beneficial effects. The mechanisms of action of IFN α are probably multiple, but the possible interactions of IFN α with the cytokine cascade and the immune system are usually not considered. Favoring Th-1 responses and suppressing Th-2 type of immune responses might give type I IFNs a profile of therapeutic agents which are warranted in diseases such as ulcerative colitis or allergic disorders. On the other hand, the potential to induce apoptosis might explain in part its efficacy



in a more Th-1-linked disease such as multiple sclerosis. These new concepts might open a new clinical field of inflammatory, non-infectious disorders where type I IFNs could play a central therapeutic role in the future.

We have entered an exciting area where modern therapeutics interfering with immune and inflammatory cascades have revolutionized medicine. This growing field of therapeutic intervention should be one of the key features and research areas investigated at our Research Campus in Frankfurt. This site's special emphasis and its strengths lie in the early clinical testing of new therapeutic principles necessary to ensure the successful development of new treatment modalities.



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Frankfurter Innovationszentrum
Biotechnologie

Aiming for Results

Biotechnological Innovations Must Yield Successful Products

“Biotech goes Business” – this often quoted slogan stands for the question that every innovation, every start-up, and every established biopharmaceutical company has to measure up to: can their ideas be translated into a promising and internationally competitive business model? Will research results yield commercially successful products and services?

Expectations are high for newly founded German biotechnology companies. In the aftermath of the start-up boom following the BioRegio initiative, business ideas today have to stand up to much more scrutiny in order to obtain the required seed money, e.g., through venture capital funding. However, there are still many who dream of founding their own company, often driven by the desire to develop a discovery made during their academic research days into an innovative application under the roof of their own businesses. True biopharmaceutical innovation, however, does not simply equal the discovery of a new gene or

the invention of a new mechanism of action of a new compound. True innovation and subsequent economic success are defined solely by an increased tangible benefit for the patient. Neither are innovative therapies created when merely a different approach for altering the course of a disease is taken without the patient benefiting from it. The decisive criterion for the success of a new company, therefore, is not only the company's edge in terms of knowledge, but the successful commercialization of proprietary technologies or the rapid introduction of the desired products. All efforts have to be directed towards that one goal.

Promoting Economically-Minded Founders

Over the past two years, venture capital investments have clearly decreased. Studies by auditors, Ernst & Young, show that after the two preceding boom years, the total amount of venture capital invested in German biotechnology was cut by more than half in 2002. In 2002, venture capital providers invested around 207 million Euro in German biotechnology start-ups (compared to about 565 million Euro in 2000 and about 525 million Euro in 2001). Although this trend is cause for concern, we should bear one aspect in mind: tying access to capital to certain requirements creates a selective process that serves a very useful purpose. In order to obtain funding these days, a young company is required to pass a maturity test proving that its business plan not only presents an exciting scientific concept but also meets all the economic de-

mands. As stated above, a great scientific invention alone is no basis for founding a company with the prospect of long-term growth and appreciation. The transformation of the invention into a solid business idea that can then be developed into marketable products and services has to be guaranteed. The successful positioning of products and/or services in international markets requires an absolute commitment to commercialization and a feeling for the market. Often scientists struggle especially with the economic and organizational sides of a business. Every potential founder, therefore, needs to reflect on the following questions: Am I willing and able to acquire this type of knowledge as well? Do I want to go it alone, or would it not be more prudent to take on board competent sup-

port, for example, in the shape of a management-minded partner? It is not at all my intention to discourage potential founders. Quite to the contrary, I wish to encourage them to not only provide scientific but also economic excellence when founding their businesses. Venture capital firms often can supply not only funding but support in that area as well.

The Role of Politics

How can society, and politics, in particular, sustainably promote innovation and its commercial exploitation? At the moment this question well deservedly takes center stage in a heated discussion, for it plays a decisive role in the future of German biotechnology. Financial subsidies alone – especially when applied in an ad-hoc fashion – are neither target-oriented nor sufficient. It does not make sense to actively promote a wave of biotechnology company foundings when the thus created companies then, while maturing, run into obstacles unnecessarily complicating the realization of their business idea. Society, similar to the founders themselves, needs to keep an eye on the goal of marketable products while organizing and promoting this new industry. Companies have to be given the opportunity of positioning their products and services in the international and domestic markets. From a national economic point of view, only then the decisive feedback loop involving taxpayers, academic research and industry – a societal value creation chain, so to speak – will be closed.

The first, publicly funded step in this chain will often be academic research, aiming at creating more knowledge, independent of economic considerations. Research at the highest level creates the growth medium for the development of all branches of modern



technology. While Germany has a good scientific basis, it certainly is not a world leader in this regard. In order to attain a top position in the future, I believe that leading research needs to be promoted much more intensely. Subsidies should be allocated based on competitive factors, and subsidized projects must be able to compete internationally. By doing that, conditions might be created that would prevent the permanent exodus of German top researchers while at the same time enabling the targeted recruitment of foreign top researchers. In addition, it is equally important to give young scientists independence and personal responsibility much sooner than it is the case now.

In order to make top research results marketable, scientists have to be encouraged to patent

their inventions. Only then is a transfer of technologies and eventually commercialization possible. Progress has been made in particular in this area over the past years.

Not every transfer of knowledge, however, needs necessarily to result in a start-up company. Although this path can be meaningful, the question needs to be asked whether it is the right path in each and every case. Does it always make sense to create new structures for the commercial exploitation of inventions, or would it not be more effective in terms of a successful implementation relying on existing companies? Founding a new business is an important way for the utilization of knowledge, but it is not the only one.

Commercial exploitation then is the industry's task. Significant

developmental efforts often are required before inventions can be turned into products of interest to the established pharmaceutical industry. These efforts are made mainly in the biotechnological industry. The long-term goal is to develop products in cooperation with the pharmaceutical industry that will conquer the international markets and create revenues. Lastly, the creation of jobs and the tax revenues from product sales complete the value creation chain.

Promoting Innovation also Means Removing Obstacles

Many business owners complain about the government's often ambiguous position on biotechnology in recent years. On the one hand, biotechnology has been identified as a key future technology and has been declared a focus of current research policies by the governing parties. The political discussion, however, is often dominated by the exploration of potential risks rather than the benefits and possibilities of the new technologies. In 1996, the BioRegio initiative sent a clear and internationally noted message: "There is a desire for biotechnology in Germany." We expect a similarly clear message from politics – today and in the years to come. One step in the right direction is the high-tech master plan intended to supply venture capital totaling 500 million Euro to young high-tech companies. More important than financial help however, are a reliable long-term legal framework and an environment which promotes innovation as basic prerequisites for the development of German biotechnology.

The EU's Biotechnology Directive must finally be Implemented

One of the most important issues in biotechnology is the implementation of the EU Directive on the legal protection of biotechnological inventions in current German law. According to this Directive it would be possible to protect inventions that are directly relevant to the functions of certain genes or sequences of genes and commercial applications derived from them. It provides more clarity regarding the patentability of biotechnological inventions, thus contributing to more legal certainty – an important prerequisite for the development of the biotechnological industry. Currently we are faced with a strange situation in which the Directive has been implemented only in a few countries



in national law, whereby patents may be valid in some countries, but not in others. As a consequence the domestic European biotechnology market is fragmented, while the American competition commands a homogenous domestic market. And although European companies have access to the U.S. market, here the same holds true as in sports – you always play better on your home turf.

Concerns have been voiced that the revised version of the Directive would compromise academic research, but these are incomprehensible. Quite the contrary, basic research as well as the competitive capacity of German biotechnology will benefit from the Directive. Patenting inventions does keep third parties from commercially exploiting them, but research will benefit from the publication of inventions in patents, gaining possibly additional impetus for further scientific development and new inventions.



Biotechnology in Germany – a Success Story to be continued

Biotechnology in Germany has developed late but well. It has benefited from various public initiatives such as BioRegio and BioChance and the genome research initiatives. The provision of seed money and the creation of regional incubators for company foundings have been and continue to be important prerequisites for the development of this industrial branch. The change in public perception of biotechnology should not be neglected either. The increasingly positive attitude, however, has to be handled with care. False hopes that are later dashed could have disastrous consequences. The current consolidation of this still infant branch of industry is a “normal” process that has occurred in the biotech industries of other countries as well. We

should not be discouraged by it; instead we should be drawing the right conclusions from these experiences. The founding of FIZ is a good and welcome step in this direction. What is especially interesting about this initiative is the fact that it is not confined to biotechnological companies but open to companies from other areas, creating opportunities for completely new synergies.



Prof. Stefan Schreiber

Prof. Stefan Schreiber is a trained Gastroenterologist and speaker of the German National Genome Research Network (NGFN). His scientific vita is characterized not only by molecular discoveries (e.g. the description of the first two disease genes in Crohn's disease) but also by clinical translation into medicine through therapeutic trials. In this capacity he has advised and steered many developments of novel biological drugs in inflammatory bowel disease. He is presently the Director of the Institute for Clinical Molecular Biology at the Christian-Albrechts-University of Kiel and also a Professor of Internal Medicine at the Department of Gastroenterology.



Frankfurter Innovationszentrum
Biotechnologie

Genome Research in Germany

The Revival of a Young Industry

About 20 years ago, regrettable political decisions prevented the advent of the genomic era in Germany for over a decade. While this had a substantial impact on academic development, it was also a driving factor in the established pharmaceutical industry's move to open research centers, mainly in North America, but also in Japan. Skilled scientists with training in modern molecular methods were in abundant supply, making these places not only competitive, but setting them apart from Germany. The globalization and consolidation of the pharmaceutical industry then led to a further reduction in the number of research sites in Germany.

In the last seven years things have changed in Germany. All it took to spark an active environment at German universities and basic research centers was modest direct funding from the German Ministry of Education and Research for a genome biology research program called the German Human Genome Project. Germany has begun to catch up with remarkable success in the academic development of genome sciences. The negative conse-

quences of genome biology's debut on the German stock exchange's special New Market index, fuelled by a mixture of greed, false hopes, and unrealistic growth perspectives among the young companies, are widely known. Nevertheless, genome biology survived this catastrophe and its development continues to advance. Through

the focused investment of several hundred million Euro, the German Ministry of Education and Research has started to transform academic genome biology into medically relevant genome research. The second phase of the National Genome Research Network (NGFN) which officially began in July 2004 has made it



Photo: Photodisc

clear that this country can meld its resources in clinical research, government-supported healthcare and genome-oriented molecular biology into remarkable success in the exploration of population diseases. This has opened new perspectives with worldwide interest returning to Germany as for some polygenic disorders, disease gene after disease gene is being discovered. In addition, the NGFN's success is not only supported by advantageous organizational structures in Germany, but also by the genetic make-up of the German population itself. It shows only little signs of genetic stratification, a phenomenon making molecular success in the genetic exploration of population diseases quite difficult in North America.

For these reasons it comes as no surprise that it is felt to now

be the time to promote commercial exploitation again. In contrast to previous events, there are only a few players on the market using small amounts of public money for the careful development of well-conceptualized start-up environments. It has now become clear that in the area of disease-oriented genome research, success in product development (i.e. genetic tests, novel treatments) is rare and – even more importantly – requires lengthy time to market. Therefore, investment has to be planned with a long-term perspective and must be accompanied by expertise. There is no more room left in this market for the raiders from the venture capital camp. The Frankfurt Biotechnology Innovation Center (Frankfurter Innovationszentrum Biotechnologie, FIZ) is a model for

successfully setting up an incubator for the second wave of commercial exploitation of genome research. Through its focus on inflammation it creates a concentrated environment that tackles a content area long neglected by many big players in the pharmaceutical industry. Nevertheless, inflammation will prove to be one of the driving principles providing answers to problems as divergent as degeneration, autoimmunity and many forms of cancer. The coming years will put these concepts to the test to prove their sustainability. If the development of the Frankfurt Center for Innovation can maintain the pace of its first two years, it will evolve into one of the major industrial think tanks for young companies in Germany and we wish it every success in the years to come.



Photo: Photodisc



Photo: Ull Kreifels



Dr. Gerd Zettlmeissl
Chief Operating Officer
at Intercell AG in
Vienna, Austria.

Before joining Intercell in 2001, Zettlmeissl led the global Industry and Quality department of Chiron Vaccines, and was the sole managing director of Chiron Behring GmbH & Co. He has a long roster of scientific publications to his name and is the holder or co-holder of numerous biotechnology patents. At Intercell he is responsible for product and business development.



Frankfurter Innovationszentrum
Biotechnologie

What Makes a Biotech Company Successful?

(Even in Times of Difficult Capital Markets)
A Personal View!

The years 2002 and 2003 have been among the most difficult ones in the short 25 years history of modern biotechnology. There were almost no IPOs during this period and private venture capital financing rounds turned out to be very difficult and long with a trend to – as compared to the past – very low valuations. Many companies even lost their right to survive during this time and very few were newly founded.

For people working in established pharmaceutical companies, which have to justify their value not only through strong

technology and development pipelines, but more importantly continuous day by day financial performance in sales and profits this development might not have been a surprise, especially after having observed the unreasonably high and – compared to “traditional” companies – not justified valuations of some biotech “dreams” in the years of the “hype” in 2000/2001.

However, nevertheless also during the difficult last two years a couple of biotech companies made their ways through successful private financing rounds and more recently reason-

ably valued IPOs or through highly priced deals with established pharma companies.

Assuming that most new biotech companies after the initial years following seed financing have established a strong scientific, technological and intellectual property basis for new products one can ask the question: What makes certain such companies more successful than others especially in times of a difficult capital market environment?



Photo: Ull Kreifels

Success Factors



Photo: digitalvision

- **Spend money** provided by venture capital or public subsidies at least as **carefully** as an established profit organisation, which has to earn its money, by managing all resources and especially head-counts with highest diligence.
- Avoid doing everything, but after having carefully analyzed the chances, risks, and opportunities **focus** the management and the organisation **on the most promising value drivers** with a strong push towards the market having always the profitability of the company in mind.
- **Establish** as early as possible **a dedicated, hard working and experienced management team** being ideally a mixture of “innovative biotech science skills” and “classical industry skills” as a further critical success factor. The “academic founders” in most cases will be able to move the company through the relatively short phase, when the basic science and technology is invented, but earlier than later would have to undergo a too long and too risky learning curve in understanding the rules and difficulties to develop and register products and to set up commercial organisations.
- **Keep the communication with your shareholders**, who finally provide the company with the resources to build success, **very active and at a level of highest honesty and respect** in “good and bad” times. Only this will create the level of trust needed for a sustained business and support.
- **Build** from the very beginning **a truly international environment in the company**. It is needless to say that pharmaceutical companies during the last five decades more and more moved from national towards a global businesses. Also small biotech companies have to prepare for this globalization and from the very beginning should bring in people with international background and look for partners and collaborators from all over the world.
- Trivially, but in practice seen much less frequently as expected, **make actual and future revenues the driving force** for all activities. This can be short term revenues by licensing technologies or early stage products to pharma costumers – by that creating also trust in the technologies and products of the company – and mid/long term revenues by choosing product candidates to be developed, which show a very balanced risk/benefit profile.

Photo: digitalvision



Photo: Uli Kreifels

It becomes obvious that most factors determining success in “traditional pharmaceutical companies” are also the ones, which finally drive the success of biotech companies.

I hope that these few basic learnings gathered during my in total 20 years working experience in traditional pharmaceutical companies (Hoechst/Behringwerke, Germany), an established biotech company (Chiron, USA), and during the last two years a typical biotech start-up company (Intercell, Austria) might be of help for some of the firms to be located at the FIZ and I would like to wish the new FIZ members all the best for a successful and brilliant future in our exciting business area.



Prof. Ulrich Hommel, Ph. D.

Prof. Ulrich Hommel oversees the Chair for Investment and Risk Management at the European Business School (EBS) in Oestrich-Winkel and is the President of EBS. He obtained his post-doctorate degree at WHU in Koblenz in 2001 and is Rudolf von Bennigsen-Foerder Foundation Professor of Finance, holds the Chair for Business Finance and Capital Markets and is the Academic Director of the Center for Entrepreneurial and Small Business Finance (ESBF). His research specialty is in the fields of risk management, corporate governance as well as the financing of start-ups and medium-sized enterprises. Hommel has published numerous books and articles in professional journals with international readerships.



Frankfurter Innovationszentrum
Biotechnologie

Biotechnology: Caught between Invention and Investment

Implications of a Value-Based Perspective for Corporate and Innovation Policy

Pharmaceutical Industry at a Crossroads

German pharmaceutical companies are used to be international leaders, both in basic and applied research. Today, however, they have fallen back in terms of market capitalization, notwithstanding top scientific achievements in some areas. This is not so much the result of severe setbacks but rather of disproportionately strong growth among foreign competitors.

The capital that went to competitors from the United States, Switzerland and France as a result of this shift and now is available to them for the research, development, and marketing of new and improved products will further enhance their competitive edge – a trend that has been confirmed by the latest events in the market for corporate control. Given these conditions German companies in the future will only have a limited ability extent to

invest in upgrading their specific competencies and to promote long-term strategies by targeted internal and external growth. Any advantages that might result from a less Anglo-Saxon style of corporate governance are thus countered.

Although the desirability of Germany as a business location from the viewpoint of domestic and international pharmaceutical companies is a result of the interactions of a range of factors, the self-enhancing process described above most likely will negatively impact the employment situation and the wage level, especially since similar developments are beginning to be seen in other areas. A clear path dependency makes today's positions relevant for economic well-being in this century and beyond.

Against this background recent calls for new national champions can be heard without taking into consideration the specific circumstances that originally were and continue to be decisive in the evolution of the German pharmaceutical industry. Primarily the current situation is, of course,

a microeconomic challenge that every enterprise has to meet in a way deemed appropriate by that enterprise.

Economic history also demonstrates that comparatively small but extraordinarily dynamic companies can, within a few decades, become corporate groups of worldwide renown. Although there is no simple solution to the problems described here, the key to revitalizing the German pharmaceutical industry obviously lies in the synthesis of scientific and business logic at the levels of entrepreneurial and innovation policy.

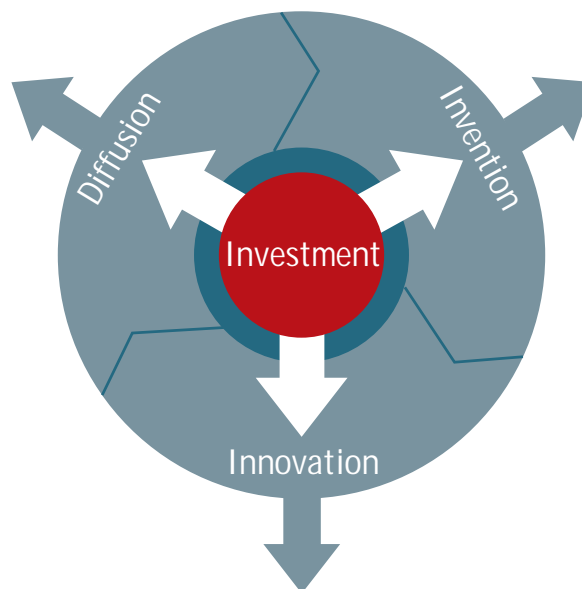
This argument will be illustrated by the area of conflict of invention and investment in which biotechnology start-ups move just like large corporate pharmaceutical groups. Innovation policy in this context is understood to be the intersection of industrial policy on the one hand and research and technology policy on the other hand. Corporate policy is understood to be the combination of strategic and financial goals, plans and measures.

Key Role of Investments

The term innovation is commonly used to refer to the point at which a novelty is actually introduced in a way that is relevant to its application. In the context discussed here, this implies the commercialization of the newly developed pharmaceutical product or platform. To be distinguished from innovation are the invention, i.e., the mental process of creating something novel, and the diffusion, i.e. the process of further spreading this novelty.

In developed national economies, in addition to these processes, that of investing also plays a central role. Supplying capital means expecting a positive return on investment at calculable risk. This expectation makes an investment fundable. Thus, successful commercialization is a prerequisite for further invention, innovation, and diffusion. A characteristic element is the occurrence of positive external effects (so-called spill-overs) which may or may not be intentional.

These definitions form the basis for the following analysis. The first step is to discuss issues and approaches to solutions in each of the four areas mentioned. In a second step suggestions for strategies and measures will be made that seem advisable from a managerial and economic point of view.



Main Issues and Starting Points

In spite of novel processes available to pharmaceutical research and development, costs at the level of invention can be expected to continue to rise. This is primarily the result of extremely low productive efficiency: Typically, only a small fraction of the initial product candidates will ever reach the market. A product is only considered truly successful when it produces revenues in excess of billion US Dollars. Enormous profit expectations are thus faced with high risks.

This situation causes a permanent threat of a lack of funds, which in turn complicates long-

term planning and forces especially small, innovative companies to target their research and development efforts at securing short- and intermediate-term funding needs. Complete business models are revised without considering specific competencies, just in order to be able to predict steady revenue flow in the near future. Principal-agent conflicts, lack of understanding of and/or interest in business matters on the part of the scientific staff as well as a focus on research projects instead of research portfolios are additional obstacles to a financially and strategically optimized allocation of available funds.

Many biotechnology companies fail to achieve productivity increases comparable to those of

pharmaceutical enterprises. Their raison d'être lies in the fact that they enable extremely risk-loving investors to invest in projects deemed unattractive by larger competitors due to their small chances of success. Eventually, the majority of projects that are born of research collaborations with academic institutions will not meet the high expectations they created.

At the level of diffusion, numerous risks emerge. On the one hand, an exactly specified period of patent protection ensures innovation incentives in the shape of monopoly dividends. On the other hand, the limited duration of such protection results in the necessity to continuously churn out new products. Therefore, quite a few portfolios in the short term depend on the acquisition of product candidates that already have reached relatively advanced stages of research and development. Such a late entry usually has a negative impact on the return on the investments made.

Another side effect of patenting that is undesirable from a company's point of view are spillovers that may enable imitators to enter competition with the originator even while patent protection is still valid. Patent risks result from the fact that often the area of applicability for a given patent cannot be conclusively determined, or that the validity of a patent may be questionable. Competitors regularly engage in lawsuits to ensure the sales of their own products, to

win payments or to damage the defendant company. In addition there are regulatory and social risks regarding the basic legal and ethic limits of patentability. Pharmaceutical companies also face liability risks. These can result in financial obligations that may even endanger the existence of the affected company.

All of these uncertainties not only impede the efficient allocation of funds, but also the fair distribution of chances and risks in collaborations, especially the adequate structuring of licensing agreements. Although collaborations play a significant role for the strategic and financial development of the entire industry, quite a few market participants still harbor false assumptions on competition. Many of them are incapable of objectively judging research achievements that do not stem from their own companies, nor can they correctly evaluate the commercial potential of these achievements.

An increase in the intensity of competition among pharmaceutical and biotechnology companies is notable on the level of innovation. This increase is apparently the very motor behind an enormous innovative pressure at all stages prior to bringing the product to market. Additionally, due to growing competition from generics manufacturers, market players succeed less and less often in making a profit from their products once patent protection has expired. In the future, those less research-driven competitors will predomi-

nantly operate out of developing countries, and due to their fundamentally different business models will rarely be affected by growing problems resulting from time- and cost-intensive regulatory approval processes.

Results from basic research are only marketable to a limited extent. The short-term pressure to succeed that burdens companies keeps them from developing forward-looking portfolios containing a larger number of uncertain, but potentially extremely profitable product candidates. Conversely, ad-hoc government funding of basic research that



Photo: Uli Kreifels

did not take into consideration commercial perspectives and risks in the past has done little for the development of a competitive biotechnological industry. From the investment perspective, many of these discrepancies can be described as a conflict of scientific and business logic. This conflict is characteristic of all research-intensive industries, but is especially apparent in the pharmaceutical industry and is becoming an urgent problem for biotechnological companies.

Strategies and Measures

Strategically, financially as well as scientifically sound risk and portfolio management in research and development is a decisive factor for the competitive capacity of biotechnological and pharmaceutical companies. Market players which are solely science-oriented will, sooner or later, always lose out among competition that is becoming more and more global. A holistic strategy in these terms demands bundling competencies from all departments and making all of them serve the common goal of creating a competitive advantage. Maximum transparency and the promotion of entrepreneurship in every form imaginable can enable even large companies to achieve this ambitious goal. Already in early stages product candidates need to be compared with respect to the associated risks and profit expectations. To the extent possible this analysis should be independent of the personal interests and the reputation of the scientists involved.

That, however, can only take place once a naïve understanding of the division of labor has been abandoned. Scientists, too, need to clearly take responsibility for the company's success. At the same time, employees with a business background have to translate available information from research and development into a financially and strategically meaningful basis for decisions.

The predominant task of innovation policy during the stage of invention is to guarantee competition in business and science education as well as in academic research. In addition, it may provide incentives for enhanced collaboration between universities and private industry, simplifying the transfer of technologies to practical applications.

A very basic requirement for scientific and economic success in the pharmaceutical industry is the professional and comprehensive management of knowledge, ensuring the diffusion of inventions within the company. Instead of a research-centered internal perspective, however, special attention needs to be paid to creating and developing collaborative networks for all



entrepreneurial functions. The consequent establishment and further development of biological and technological platforms contributes to a further increase in productivity and profitability.

In view of the complexity and almost universal applicability of economically relevant knowledge, the legal dimension of intangible assets is of central importance. Only well thought-out and long-term patent strategies will be able to ensure the company's lasting growth. As the fungibility of intellectual property increases, so does the necessity of assuming a portfolio manager's stance at the level of diffusion as well. The acquisition and sale of patents, therefore, are options that are as valuable as proprietary development. Patents can be used independently of current projects to secure future research projects or to impede competitors' research. In any case the patent portfolio needs to be structured in agreement with clearly stated financial and strategic goals. However, sufficient flexibility to allow for adaptation to a quickly changing competitive environment is also required.

The primary task of innovation

policy is to create an internationally harmonized legal framework. In combination with reliable court decisions this would significantly contribute to the fungibility of intellectual property. More generally, the material and immaterial infrastructure should be promoted, since it is the prerequisite for the development and growth of globally competitive clusters and networks.

Especially innovative biotechnology companies will benefit from a better understanding of the sales potential of the product candidates and platforms they have created. For this to happen, continuous interdepartmental feedback is required. At the same time, the business model has to correlate with the company's identifiable competencies. Targeted outsourcing as well as research- and marketing-driven M&A enable the rapid achievement of necessary scale economies and, more importantly, a company-specific profile to be brought into focus more clearly. Distinguishing oneself from the competition needs to be primarily application-related. A well thought-out brand strategy – possibly in conjunction with

early sales of proprietary generics – can additionally boost the market position of an incumbent pharmaceutical company and can insulate it to a certain degree from lower-priced competitors.

The utilization of innovative means of commercialization may be able to ensure the provision of sufficient funds for companies that have a high, research-related need for capital but whose specific competencies are outside the realm of developing product candidates that are almost ready for the market. Independent of the scientific focus of a company, spin-outs, sale/license-back transactions, and the securitization of intellectual property are useful alternatives for enlarging the financial and, therefore, the strategic scope of biotechnological and pharmaceutical companies. As competition becomes more and more international, these activities always have to be geared towards the requirements of global investors and need to be adequately communicated. Although globalization on the financial side may, of course, contribute to lowering capital costs, in biotechnological companies it serves especially to

Recommendations for Corporate and Innovation Policy

	Main Issues and Starting Points	Strategies and Measures	
		Corporate Policy	Innovation Policy
Invention	Costs explosion; low productivity; lack of planning reliability	Strategically, financially, and scientifically sound risk and portfolio management in research and development; promoting entrepreneurship and interdepartmental transparency; globalization	Competition in business and science education and academic research; incentives for enhanced collaboration of universities and private industry; facilitating technology transfer
Diffusion	Uncertain legal situation with respect to intellectual property; strong introspective focus; unproductive competitiveness	Knowledge management; collaborative networks; utilization of platforms (technology, biology, knowledge); comprehensive and flexible patent strategies	Internationally harmonized legal requirements; increasing fungibility of intellectual property through reliable court decisions; promotion of material and immaterial infrastructures for clusters and networks
Innovation	Commercial pressure to succeed; lack of marketability of basic research results; highly intense competition; time- and cost-intensive regulatory approval procedures; competition from generics	Marketability; focus in specific competencies; applications providing distinction from competitors; M&A outsourcing; dual sales strategies; branding	Ensured efficient regulatory processes; deregulation of sales channels; liberalization of the market for company control
Investments	Lack of funds; low attractiveness of basic research for private businesses; conflict between business logic and scientific logic	Utilization of innovative ways of commercialization (spin-outs, sale/license-back transactions, recording of intellectual property); risk diversification by means of collaboration; globalization in the areas of investment and funding; professional company communications	Renunciation of ad-hoc funding; capital market-oriented public-private partnerships (smart money)

make additional scientific and business know-how accessible. Globalization in the area of investments presents an attractive option for risk diversification and is primarily interesting with regard to the development of potential sales channels and the outsourcing of functions that add little value.

In order to ensure the efficient use of public funds, from a governmental point of view partnerships with privately run institutions are advantageous. In any case they are preferable to the unreserved subsidization of university-based start-ups on the one hand and tax relief and other forms of hidden or overt subsidies to large enterprises on the other hand.

Summary of Recommendations for Action

In summary, not only risks but especially chances can result from the increasing globalization of financial, product and factor markets. In order to utilize existing and emerging cooperative networks in research, development and sales to the advantage of local biotechnological and pharmaceutical companies, managerial expertise is required at all levels. Scientifically directed processes always have to be reviewed and evaluated for their economic meaningfulness.



On the part of enterprises, these insights have to be reflected in local investments, but also in stronger efforts aiming at the development and implementation of integrated research, patent, marketing, funding, and communication strategies. Correctly interpreted, innovation policy – following ordoliberal principles – will create the necessary basis for these processes by providing the required material and immaterial infrastructure. Targeted signals might, however, provide the incentive for private initiatives which alone will be able to ensure Germany's future as an attractive location for pharmaceutical and biotechnological companies operating internationally.



Dr. Florian Budde

Director in the Frankfurt Office of McKinsey & Company, Inc.

Florian Budde co-leads the European Chemical Practice of McKinsey and is a member of the leadership group of McKinsey's global Chemical Sector. He is also a core group member of the European Corporate Finance & Strategy Practice and manages the Frankfurt Office of McKinsey. In 1998 and 1999, Florian Budde spent two years in Seoul, South Korea. He has authored a number of articles about the chemical industry and the economic development in Korea after the crisis. Before joining McKinsey, he worked for IBM in the T. J. Watson Research Center in New York.



Frankfurter Innovationszentrum
Biotechnologie

The Third Wave

Biotechnology Takes on the Chemicals Industry

The pharmaceutical industry could hardly live without it anymore: biotechnology. Today, virtually every new drug benefits from biotechnological methods in research and development. In fact, more and more drugs are themselves of biological origin. This trend is set to continue in the future.

Biotechnology is gaining importance not only in the pharmaceutical industry, but also in agriculture. In the United States today already about 80 % of the soy and corn crop yield stems from plants optimized by genetic engineering. However, the benefits of biotechnology for food production are not unequivocally accepted. Especially in Europe, biotechnology is meeting with consumer skepticism.

After the red (pharmaceutical/medical) and green (agricultural) waves of biotechnology, now a third wave is spreading, namely white or industrial biotechnology. It utilizes renewable ingredients and copies nature's tried and true mechanisms of action. Thus, it preserves resources, lowers environmental impact and provides more effective and

efficient production methods than traditional processes. That way, biotechnology is paving the way for sustainable development able to unite social, ecological, and economic interests.

Industrial biotechnology is becoming more widespread on three levels: on one level, renewable ingredients are replacing the traditional fossil raw materials oil and gas. On a second level, more and more biological production processes such as fermentation and biocatalysis are being utilized instead of chemical synthesis. And on a third level, completely new products are being developed, such as biopolymers and enzymes.

Industrial biotechnology is still in its early stages. However, the trend indicates that it will become one of the key factors in the future of chemical industry.

Today biotechnologically made products already represent 5 % of worldwide sales in the chemicals industry (Fig. 1). According to a McKinsey study, this share could rise to 10 to 20 % by the year 2010 (Fig. 2).

The most intense application of biotechnology currently is

seen in the area of fine chemicals, with a market share of 15 %. A two- to fourfold increase of this share by 2010 is highly likely. The market shares of special chemicals are currently between 0 and 15 %, depending on the segment. By the end of this decade they could rise up to 50 % in individual segments, while in other areas of special chemical production, classical chemical synthesis will continue to dominate even beyond 2010. It is



Photo: PhotoDisc

Biotechnologically Produced Products already account for a 5% Market Share of Chemicals Industry Products

	Dependent on Biotechnology (Examples)	Market Share (Billions of USD)
Basic Chemicals	▪ Ethanol	15,0
	▪ Citric Acid	2,0
Amino Acids	▪ Glutamic Acid	1,5
	▪ Lysine	1,0
Vitamins	▪ Vitamin C	1,0
	▪ Vitamin B ₂	0,3
Drugs	▪ Pharmaceutical Drugs and Intermediates	7,5
Special Chemicals	▪ Enzymes	2,0
	▪ Aromas and Perfumes	1,5

5% of the chemicals industry's market is already based on biotechnology

Fig. 1

more difficult to make a prognosis for biotechnologically produced basic chemicals and polymers. In these areas, the market shares today are only 3 and 1 %, respectively. Gaining a market share of 6 to 12 %, as considered possible by experts, will likely take longer than until 2010.

According to the McKinsey study, the chemicals industry, by utilizing biotechnology, could produce an additional added value of 11 to 22 billion US Dollars by 2010.

Half of that increase would be accounted for through savings on ingredients, but also on processes. For example, vitamin B₂ is now being produced in a one-step biochemical process rather than in the traditional eight-step chemical process. This reduces costs by 40 % and also lowers the environmental impact (Fig. 3). Virtually all manufacturers of vitamin B₂ have switched to this new production process.

The other half of the predicted added value results from completely new products and processes. A whole range of cost-effective biologically based building blocks such as lactic acid and propanediol have become available. These might induce a similar rush of innovations as once ethylene, propylene, and other basic petrochemicals did.

From the biologically based building blocks many new products can be developed, e.g. in the areas of drugs, acrylic resins, food additives and high performance chemicals. Most promising among these are the biopolymers. They exhibit much more innovative dynamics than the traditional polymers that seem to have peaked in their development at the end of the 1960s. Biopolymers can be used in a variety of applications, including packaging and textile fibers. Due to their low cost and better properties they appear to be on their way

to replacing traditional polymers such as polyester.

Prognoses about the potential of biotechnology, however, are mere snapshots. As with any other emerging technology, its progress is characterized by insecurities. How quickly and comprehensively the potential of biotechnology will actually be realized also depends on the development of its environment, i.e., interaction between consumers, industry, and government.

A breakthrough will hardly be possible as long as consumers have not been convinced by the benefits of biotechnology and embrace it. Government and manufacturers should learn from the mistakes made during the introduction of green biotechnology. Manufacturers need to be prepared to invest significantly in research, production and marketing. In addition, they will need to develop a new industry culture in which both compe-

Biotechnology Share of Chemicals Market could rise to 10-20% by 2010

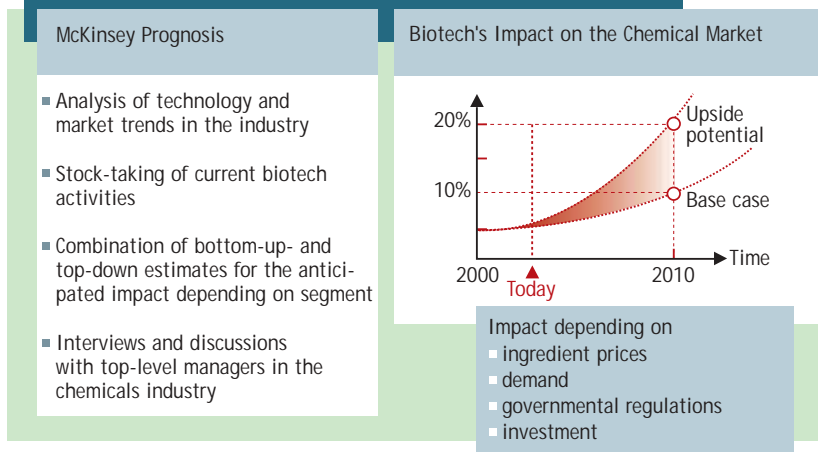


Fig. 2

tition and cooperation drive development. The government, on the other hand, has an obligation to create a favorable environment, ranging from appropriate regulatory processes to promoting innovation and providing subsidies during the start-up phase, e.g. for competitive ingredients.

The stage for a rapid expansion of biotechnology is set. In the past years the industry has overcome important hurdles. For example, there is already a wide range of enzymes, fermentation systems, and other technological platforms available. Most importantly, however, the time-to-market for technologies has drastically decreased. Enzymes now can be developed within weeks rather than years, and the process yield can be increased significantly within months, thus opening up completely new areas of application.

This innovative drive in biotechnology has awakened the interest of the large chemicals

companies. They are realizing more and more how important it is for them as companies in the industrialized countries to distinguish themselves from lower priced competitors from emerging nations by means of a technological advantage.

Thus, it is hardly surprising to find leading companies of the chemicals industry among those already utilizing biotechnology. Their sights are set on all areas from basic chemicals to special and fine chemicals and polymers. The British-Dutch Shell corporation, for example, is taking part in the production of ethanol from biomass. Following the success of Projekthaus Biokatalyse, a project on biocatalysis in which the company's scientists cooperated with others from academia and small start-ups, the German company Degussa is now starting a similar project on fermentation. According to BASF's own publications, the company is employ-

ing biocatalysis and fermentation in the production of about one third of its fine chemicals, and at DSM this is true of fully half the production. In a joint venture the American companies Cargill and Dow have built a plant to produce the biopolymer PLA at a capacity of 150,000 tons. The production is already in operation; PLA is an environmentally friendly replacement for polyester (PET) and is sold by more than 70 business partners worldwide (Fig. 4).

In addition to the giants of the chemicals industry, however, it was mostly young biotech companies that shaped this development, acting as pioneers and leading the way with their ideas. The majority of innovations by chemicals companies would not have been possible without partnerships with biotech companies and academic institutions. Start-ups such as Genencor, Codexis, and Diversa have successfully

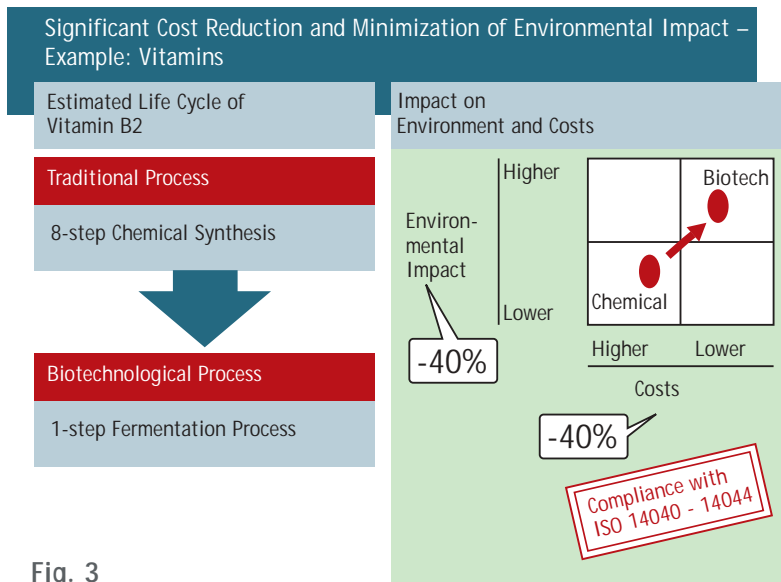


Fig. 3

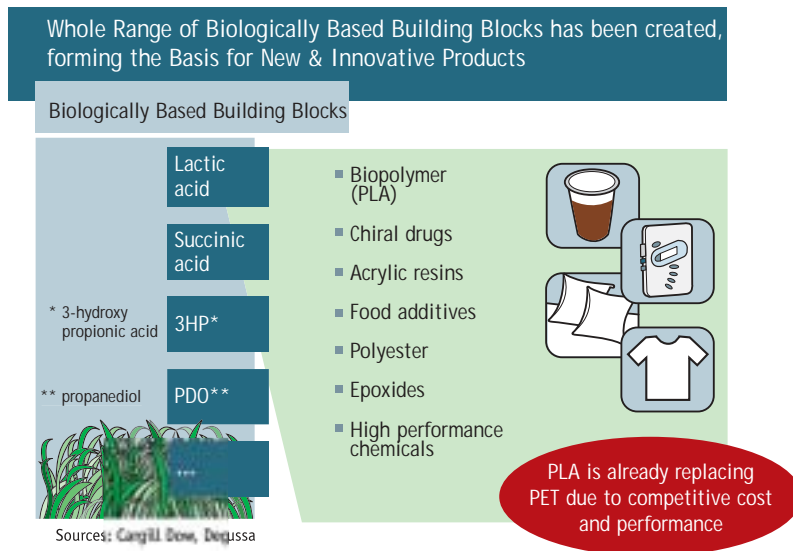


Fig. 4

positioned themselves in the market. Diversa, for example, develops biotransformation enzymes by means of targeted genetic engineering. As is the case with Diversa, biotech companies have a broad network of partnerships available. Depending on the project, these can evolve into strategic alliances or joint ventures.

Brain AG in Germany is playing a role similar to that of Diversa in the United States. The company was founded in 1993 as an independent research and development company for the life sciences industry. For years, Brain has also cooperated with Degussa AG in the optimization of enzymes. In 2000, Brain took things one step further and founded Viscum AG which is pursuing the proprietary development of a plant-based cancer therapy.

No matter whether promising approaches come from dynamic start-ups or established chemical companies – their support is also a political issue. The industry can shoulder a lot, but not everything. In the United States several governmental agencies, research institutions, and companies, therefore, have formed a cooperation in the shape of a project called “Vision 2020” to further the utilization of biotechnology over the coming two decades. The most visible progress this alliance has achieved is with the production of bio-ethanol.

A few years ago the U.S. Department of Energy set a goal of doubling the usage of bio-ethanol as fuel to about 5 billion gallons by 2010. Currently, bio-ethanol is produced worldwide mainly from cereals, corn, or sugar cane. In the future, however, biological wastes such as hay are to be used increasingly. Experts assume that further development of this technology could lower the costs of ethanol production by up to 50 % in the middle term. The U.S. Department of Energy has been subsidizing this process in the past year with about 400 million Dollars (Fig. 5).

The European Union is striving towards a similarly ambitious goal. By 2010 the share of biologically based fuels is to increase to almost 6 %.

However, unlike the U.S., the EU lacks initiatives supporting industrial biotechnology even though such support would be highly desirable. It should focus on three areas: firstly, the EU should map out a vision and a long-term strategy for the further development of biotechnology, involving the participation of all relevant stakeholders in detailing this plan. Secondly, the legislative arm needs to create a favorable framework which might include temporary subsidies for lower prices for those ingredients for which Europe currently is not competitive. Thirdly, the EU needs

to promote research in order to intensify technological development in Europe.

Failure to create this basis quickly and consequently could result in Europe's falling behind in this important technology of the future.

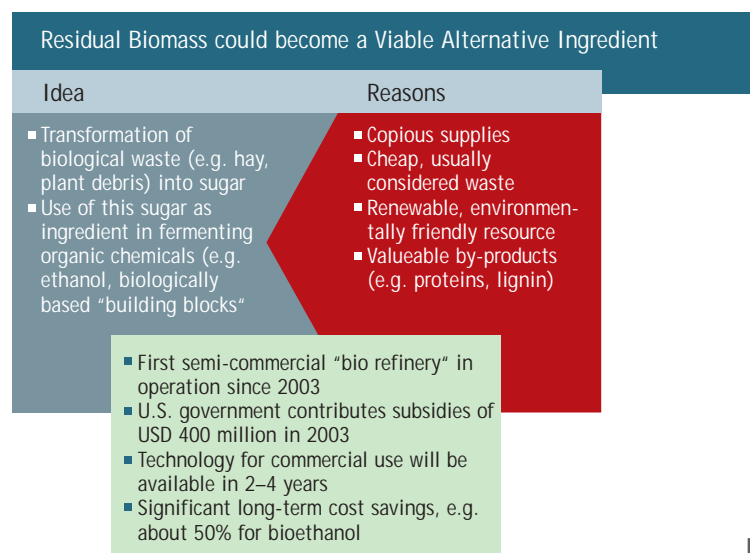


Fig. 5



Prof. Dr. Uwe Walz

Prof. Dr. Uwe Walz is a Professor of Economics at the University of Frankfurt where he holds the Chair on Industrial Organization since October 2002.

Before, he was a Professor at the University of Bochum (1995–1997) and the University of Tübingen (1997–2002). His main current research focuses on Venture Capital, Entrepreneurial Finance, and Contract Theory as well as on the Economics of Network Industries. He published widely in international journals and is director of the research program “Venture Capital and New Markets in Europe” at the Center for Financial Studies in Frankfurt and a research fellow of the Center for Economic Policy Research, London.



Frankfurter Innovationszentrum
Biotechnologie

Innovations, Venture Capital and Biotechnology

Innovations and Venture Capital

Innovations are essential to the long-term development of a highly developed economy that is poor in resources such as that of Germany. Innovations are central not only to survival in the global competition, but also required for long-term economic growth. If there is no technological progress, all other potential growth factors will eventually fade. This is true of a highly skilled work-force as well as of investments in tangible fixed assets. In the long run, investing in human resources and tangible assets makes sense only when there are new technologies to master and “better” capital assets to buy. Without new knowledge, profitable projects will be exhausted over time and the incentive to invest will disappear. These facts have been clearly demonstrated in theoretical analyses and empirical studies.

With respect to innovative activity, young companies in particular are exceptionally innovative. New companies produce

significantly more patents (with equal employment of funds) than established companies. Usually, those young companies, however, possess neither experience nor tangible assets that might serve as collateral for potential investors. This holds true for many of the new industries and especially for the fields of bio- and information technology. In the face of a lack of collateral and against a background of high uncertainty (resulting from the combination of inherent risk of R&D investments with the absence of a track record), debt suppliers (commercial banks, bond creditors) see no incentives – not even at a high interest rate – for shouldering the major uncertainty that usually accompanies young, innovative companies. Thus, traditional sources of funding such as credit lines and company loans often are not accessible to young companies. This is not so much a result of conservative behavior on the part of the banks but rather of the instrument of outside debt capital and its inherent lack of creditor participation in upside developments itself. New companies are usually limited in their financial resources,

and so the central question is where they will find the funds for their innovative activities.

In addition to funds, these companies often also lack management experience and consulting, so equity alone does not offer a solution. During the early stages of company development the organized capital markets are out of the question as well, since the high measure of uncertainty does not allow for adequate company valuations. Broadly based share ownership would also lead to a major corporate governance problem.

One possible solution has emerged in the shape of venture capitalists as specialized intermediate funding agents who ideally (!) will, in addition to funds that are presented in an equity-like manner, offer consulting services and can assume the required supervisory role. The venture capital (VC) industry has developed a number of mechanisms that take into consideration the special position of young, innovative enterprises and entrepreneurs. These mechanisms generally aim at containing the clash of interests between investors (VC companies)



and portfolio companies (young innovative companies) as much as possible. VC companies differ from other financial intermediaries not only with regard to the mechanisms applied, but also regarding the structure of company funding that is best described as a combination of bank-oriented and market-oriented funding. The goal of VC involvement is to closely work with the company and thus to form a relationship similar to that of a company's bank. However, it is understood that this involvement can and should only be of a temporary nature. The ultimate and ideal goal is to sell the company via an IPO and to thus transfer it to market-oriented funding, an idea which admittedly seems utopian during periods of poor market performance. In this case the VC company serves as a bridge between relationship-

dominated (bank-oriented) funding and the capital market as a source of funding and control mechanism.

The venture capital market in Europe and especially in Germany is a relatively new area. While the VC market in the United States is a clearly established market that plays a central role in innovation funding and that has experienced large publicity generating success with companies such as Cisco, Microsoft, Netscape, and Federal Express that have become household names since, the VC market in continental Europe did not emerge until the early 1990s. Even when adjusting for the boom years of 1999 to 2001 when many VC companies entered the market, notable growth rates can be observed. The average growth rate of portfolio sizes (gross investment) for the years 1999 to 2003 was 19 % (13.5 %). With the end of the

hype starting in 2002, however, the process of separating the wheat from the chaff by means of many market exits began, and continental Europe was left with a generation of seasoned VC managers who are now gradually approaching US standards. In spite of the high growth rates, this important source of innovation funding's share of the gross national product in continental Europe (2002: 0.3 %) and especially in Germany (2002: 0.12 %) is still significantly lower than in Great Britain (2002: 0.6 %) and in the United States. The extent to which this is due to the developmental lag of the VC market and the lack of young innovative companies shall not be discussed here.

Against the background of recent developments and the importance of the VC industry for young innovative companies it is

helpful to examine some typical tools and mechanisms more closely, especially from the viewpoint of companies seeking funding, even though these tools and mechanisms will, with different institutional conditions, vary from case to case. An important characteristic of VC funding is the gradual provision of capital, i.e. young companies obtain the required funds in several stages. Only when certain milestones have been reached, the next payment will be made. Thus, the VC company indirectly controls the project and also reserves the right to terminate it. In this way the often observed unwillingness of entrepreneurs to sell their “babies” is prevented. In addition to these implicit control rights, VC agreements often also include explicit control rights, i.e. the VC company, although a minority share holder, is given key rights to control such as veto rights for changes to the business plan, equity kickers, and changes in shareholder structure.

Since the disinvestment, i.e. the sale of the VC company's shares, is central, the agreement often contains regulations regarding the exit that are intended to solve conflicts of interest regarding the timing and mode of exit. This serves to ensure VC companies will not act from a weak position during the exit. This is necessary because VC companies often are also conceived only for a limited time, for example as funds, in order to credibly state their specialization in one phase of the company's history. All these me-

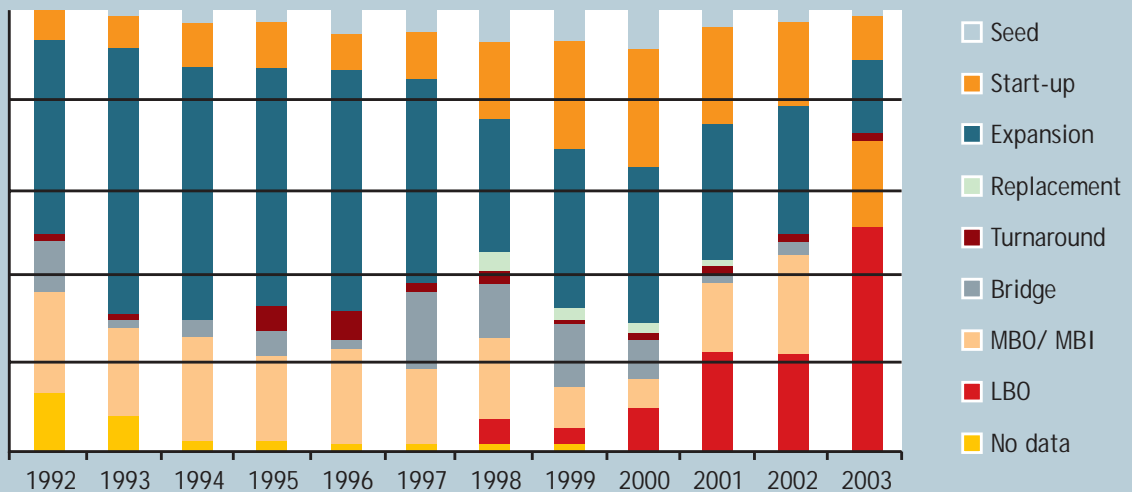
chanisms (and many more that could be listed) are part of an effort by active investors to manage the special problems that young, innovative companies face – an effort that in the end is in the best interest of all stakeholders. Without it, investing in this type of company would be burdened with too much incalculability and risk.

Venture Capital and Biotechnology

On the one hand, the biotechnology industry is predestined for funding by means of venture capital, on the other hand industry-specific problems are known to occur. In view of the high degree of uncertainty, the lack of tangible fixed assets, the often very science-oriented teams of founders and the major growth potential, cooperation with an active investor (a VC company) constitutes a useful symbiosis. This situation (in combination with the strong growth in biotechnology) is also reflected by the growing share of biotechnology companies in VC investments. In Germany, this share has continuously risen from 4.8 % of the gross investment volume in 1997 to 8.6 % in 2002 (with a temporary fall to 4.4 % in 2003). This appears to indicate not only an increased relevance of biotechnology in general, but also the importance of the collaboration between venture capital and (young) biotechnology companies.



Long-Term Development of Investments before Deductions by Phases (in %)



Source: BVK; Annual report (2003)

A decisive factor in this collaboration is the active, hands-on participation, not just as a passive supplier of funds, of the venture capitalist in the company's management, especially given that teams of founders are often strongly oriented towards the sciences.

At the same time, however, the biotechnology industry is characterized by an overall rather long and uncertain investment period (until a product reaches the market and produces positive cash flow). This results in a sometimes significant number of funding rounds, during which not only strongly increasing investments often flow into the company but also the initial owners' shares are severely diluted – a fact that, of

course, is accompanied by significant informational and control problems.

Currently, however, another important problem is becoming more prominent, especially in Germany: the withdrawal of VC investors from early phase funding. While during the second half of the 1990s an above average amount of capital went into early stage funding (seed, start-up), this process has clearly been inverted (see Figure above). Many of the large VC companies that were very active in the area of technology and early stages as late as 2000 have withdrawn from it and now focus on later funding stages. This is also reflected in the fundraising of the venture capital and private equity industries.

If this turns out to be an intermediate-term trend (as many signs indicate, not lastly the fact that this would mirror the long-term and international average), it would have consequences for the biotechnology industry and especially for start-ups and university-based fundings. The above numbers clearly indicate that in later stages funding is provided, i.e., investments are made. However, the early stage, which is essential to the long-term development of this industry in Germany (and in Hesse) continues to be problematic. Attracting somewhat more established companies to a site might be a possible partial solution, but in the intermediate and long term, successful start-ups are absolutely necessary.

So, if VC is less active in consulting and funding in early stages, what is left? For one thing, government subsidies. This should be intended to compensate for high risks and to correct the overall positive external economic effects of innovations. In Germany this is happening not lastly in the early funding stages via e. g. the BTU program of the Kreditanstalt für Wiederaufbau. However, another duty of the state is to compensate for many causes of the high risks biotech start-ups face, such as overregulation. Another source which in the United States plays a central role in seed and start-up funding and which is significantly underrepresented in Germany is that of business angels. The emergence of a significant group

of experienced and financially strong individuals who are willing to get involved in young start-ups (with entrepreneurial expertise often being the scarcer factor) is certainly an important aspect to be considered in this context. Overall it can be said – at least at this time – that areas of biotechnology that require too long an investment period do not appear to be very attractive at the time busy.

Furthering this entire process at the Frankfurt location and lowering the many hurdles by means of various activities and thus making the Frankfurt-Rhine-Main region into a vital location for the biotechnology industry are challenges for which the FIZ is most suitably equipped.



>> Success is a combination of implementing a good idea and working with the right people. >>



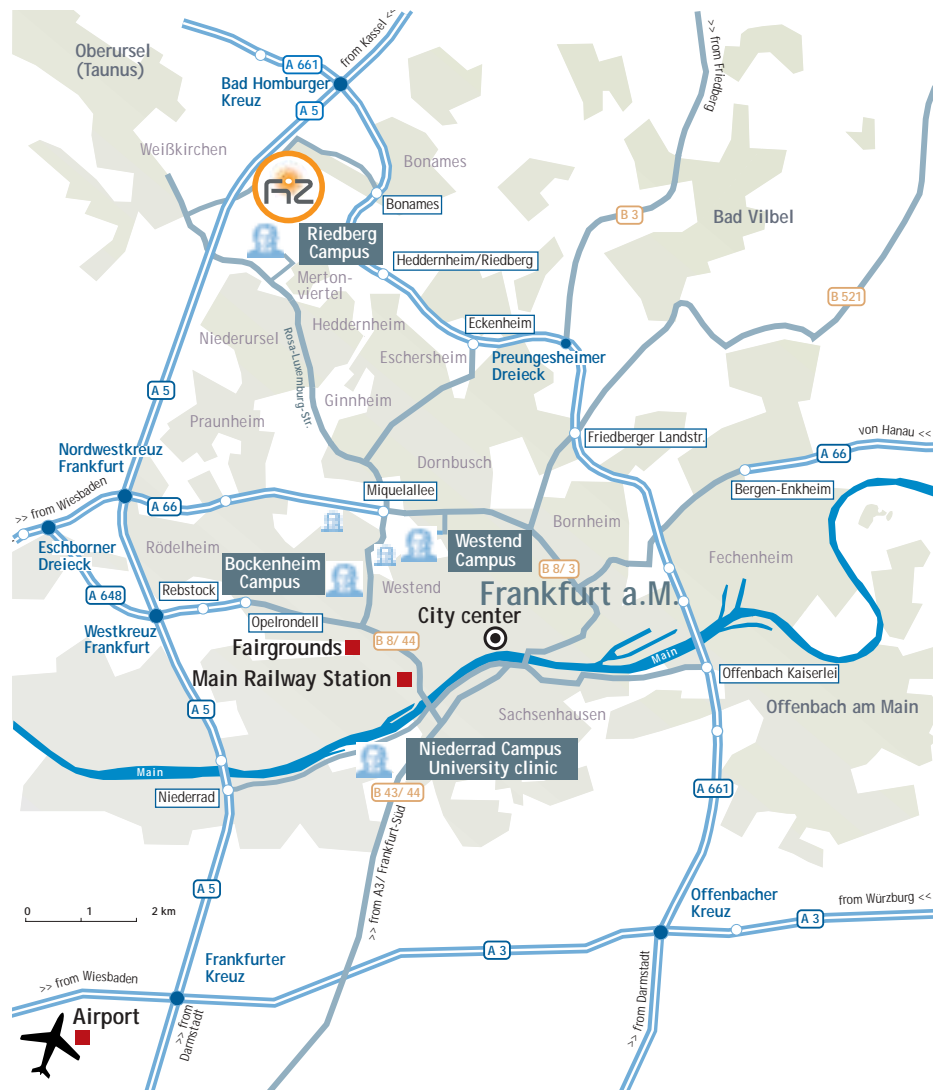
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