

Brandenburg **biotech-scene** gains *profile* and *continues to grow*

THE STRATEGIC DECISION by the government of the Federal German State of Brandenburg to target biotechnology as one of the most important motors of regional economic growth during the definition of the general long-term conditions has proven right. It is hardly surprising that, in accordance with recently published figures of BIOCUM AG, more than double the number of biotech companies is located in Brandenburg than in Saxonia and Thuringia combined. This development is based on first class research in the region, which was recently rewarded with two important successes in supra-regional call.

The new, growth-intensive field of biohybrid technologies focuses on the development of innovative biochips for the life science area. It is an encouraging sign that the production of biochips is planned for the biotechnology park at Luckenwalde and that the successful InnoRegio application, which brought in approximately 8,7 million EURO in supra-regional subsidy money, contains funds for the practical training of professional staff at the technical college.

Berlin and Brandenburg made the right decision when they concentrated on selected focus areas and asked the multi-state field-specific agency BioTOP of Berlin-Brandenburg to coordinate individual measures. Consequently, our Brandenburg activities are optimally in tune with the overall development of Berlin-Brandenburg as a biotechnology site.

Now, the challenge is to look ahead and to stimulate further growth. We are currently in the process of adding value to the most important

German site for green biotechnology in Potsdam-Golm. Construction measures for the Fraunhofer Institute of Biomedical Technology are scheduled to begin as early as next year. As a result, three Max Planck Institutes and two



Fraunhofer Institutes will be represented on the campus in addition to the institutes of the University of Potsdam. Further private companies will emerge from this scientific potential and will have the option of finding a home at the planned interdisciplinary technology park.

By founding the Economic Development Board Brandenburg, the state has combined the expertise of economic development with those of technology and innovation support. This one stop agency has become an important address for companies and investors. We are looking forward to a close cooperation with BioTOP in the area of biotechnology. Here is to wishing all the players, and particularly the members of the Network Biohybrid Technologies much success with their future work!

Dr. Wolfgang Fürniß
Minister of Economy for the State
of Brandenburg

Biohybrid Technologies

- Technological platform and market of the future
- Biosensors and biochips – development at the Department of Analytical Biochemistry at the University of Potsdam
- Biochips-applications in medicine and research

Presenting:

- Biotechnologiepark Luckenwalde
- Fraunhofer Institute for Biomedical Research
- University of Potsdam
- University of Applied Sciences Wildau

- AGOWA Gesellschaft für molekularbiologische Technologie mbH, Berlin

- Alpha-Bioverfahrenstechnik GmbH, Luckenwalde

- Applied BioSensor Technologien (ABST), Luckenwalde

- BASF Schwarzheide GmbH, Schwarzheide

- BESSY Berliner Elektronenspeicherring-Gesellschaft für Synchrotronstrahlung mbH, Berlin

- BioMed Research Gesellschaft für Bioanalytik mbH, Luckenwalde

- BioTeZ Berlin-Buch GmbH, Berlin

- biotix GmbH, Potsdam

- BST BioSensor Technologie GmbH, Berlin

- chemicell GmbH, Berlin

Biohybride Technologies – Technology platforms and *market of the future*

BIOHYBRID TECHNOLOGIES ARE an innovative and growth-intensive field of modern biotechnology that

result, which can be designed in accordance with individual requirements. Scientists and biotech companies are researching

80 % in comparison to conventional methods.

Top international research has been taking place in the



Prof. Dr. Scheller with E. Buhlmann, Ministry for Research and Technology, during the award ceremony InnoRegio.

combines the experiences of biosensor development with the possibilities of micro system technology and microelectronic chip design. The modular integration of microelectronic and biological system opens up an area of biotechnology with highly innovative products: biochips. Biochips allow for solutions in high speed throughput with multiple parameters for protein and DNA / RNA analysis. Due to the site-unrelated allocation of specific oligo-nucleotides or antibodies, a "molecular laboratory" is the

new application areas in pharmaceutical research, medical diagnostics, food analysis and gene technology.

Analysts unanimously forecast a rising tendency for the **biochip market**. They predict growth rates from 30 to 65% over a period of 4 to 6 years, and the overall market for biochips is expected to grow to an annual volume of 5 billion USD.

The processes of miniaturization, paralleling, micro-integration and mass production have the potential of implementing cost reductions of up to

areas of biosensors, bioanalysis, molecular biology and DNA analysis for years in the **Brandenburg-Berlin region**. In this regard, the Institute for Biochemistry and Biology at the University of Potsdam, the Fraunhofer Institute for Biomedical Technology as well as numerous analytical and diagnostic companies that frequently have spun off research institutes and universities deserve special mention.

The **InnoRegio competition** initiated in 1999 by the Federal German Ministry for Re-

search and Technology in the New German States came at the right time. The objective of the competition was to get players from all areas together in innovative networks and to develop and implement future-oriented profiles and products for regions in the new German states. This provided the impetus for networking the potentials existing in the region in these areas, and to make an attempt at establishing biochips as an economic factor.

Of the initial 444 applicant regions, only 50 made it into a second round, in which the task was to develop a detailed concept. A total of 23 pilot regions now have the opportunity to implement regional innovation concepts with education, research and network projects.

The **InnoRegio initiative "Biohybrid technologies in the region Potsdam-Luckenwalde"** is one of those winning regions. During the period from 2000 – 2006, a total of 8,2 million EURO will be available for creating a network and developing this technological sector

in the region. The network not only includes companies, institutions, and research facilities from the state of Brandenburg, but also biotech companies from Berlin.

The Berlin-Brandenburg region has developed into an important biotechnological site over the past years. The biotechnology park in Luckenwalde has established itself as an

essential concentration point for companies in the biotech industry. Potsdam has been able to further expand its reputation as a significant scientific site, not

only by constructing a building for natural sciences at the university, but also by adding Fraunhofer and Max Planck institutes to its Golm campus. The essential local factors for the success of the InnoRegio initiative are therefore in place.

The information and communication hub for the network is the **BioHyTec** Association for Bioanalysis and Biohybrid Technology. The association links interests and activities, supports the formation and development of cooperation and coordinates the **projects of the InnoRegio Consortium**. The network is currently in the process of im-



plementing several research and development projects in cooperation between research facilities and biotechnology companies. During the design phase of the projects, special emphasis was placed on the close cooperation between science and industry in order to develop products that are oriented toward user requirements and will enjoy high market ac-



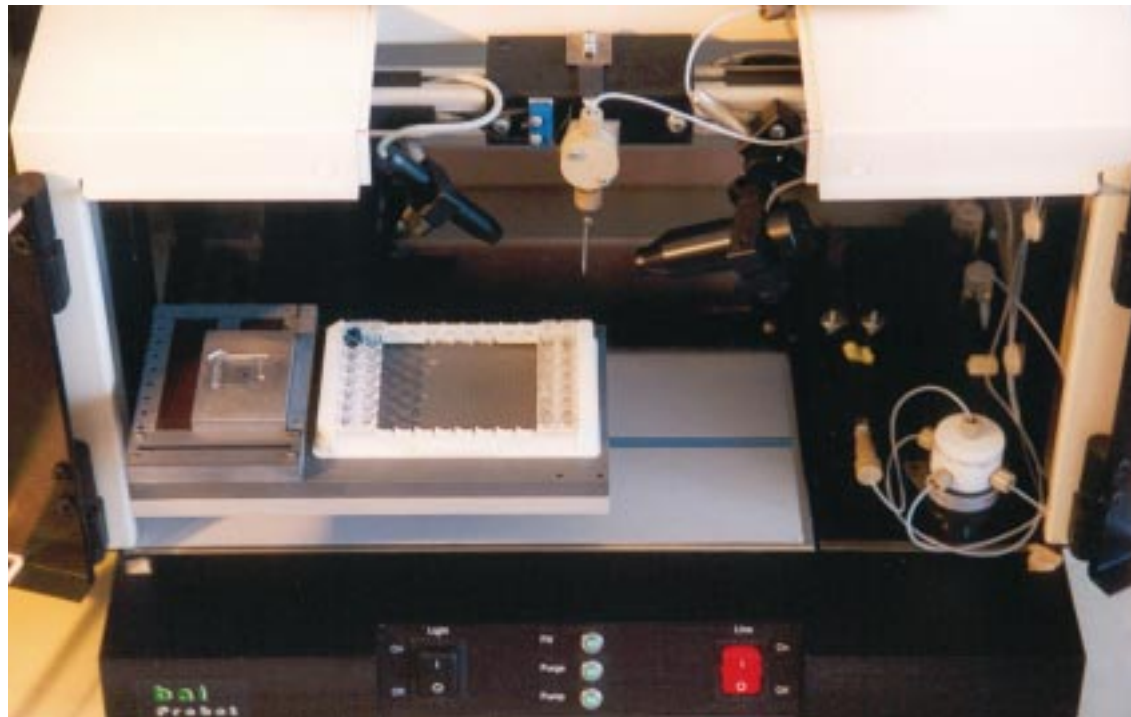
ceptance. The projects are focused on the areas of food analysis and diagnostics: Under the management of BioMed Research Gesellschaft für Bioanalytik GmbH, a project consortium of researchers and developers is working on new detection methods for mycotoxins in food. The project consortium Non-invasive Diagnostics under the management of FILT GmbH is researching the diagnosis of diseases through respiratory condensation. The company is already well known for its products in this area.

Additional research and development products are scheduled to start during the coming weeks and months. The Institut für Getreideverarbeitung GmbH (grain processing) in Bergholz-Rehbrücke is developing an antioxidant efficacy test in cosmetics, while CONGEN Biotechnologie GmbH is working on a detection system for infection diagnostics in veterinary medicine.

Both projects are intended to yield **biochips** as final products. The Fraunhofer Institute for Biomedical Technology in Bergholz-Rehbrücke, where the Biochip Competence Center has established itself as an important hub for the BioHyTec consortium in order to build a technological platform, will take over biochip development

- CONGEN Biotechnologie GmbH, Berlin
- EKF-diagnostic GmbH, Barleben
- ELBAU Elektronik Bauelemente GmbH, Berlin
- EMP Biotech GmbH, Berlin
- Erich Jaeger GmbH, Hoechberg
- FILT Lungen u. Thoraxdiagnostik GmbH, Berlin
- Kunststoffzeugnisse Helmut Schulze & Co GmbH, Luckenwalde
- IGV GmbH Institut für Getreideverarbeitung, Bergholz-Rehbrücke
- JERINI Bio Tools GmbH, Berlin
- metaGen Gesellschaft für Genomforschung mbH, Berlin
- Triple-O Microscopy GmbH, Potsdam
- WITA GmbH, Teltow

- BioTOP Berlin-Brandenburg, Berlin
- Biotechnologiepark Luckenwalde GmbH, Luckenwalde
- Deutsche Bank AG, Berlin
- Fraunhofer-Institut für Biomedizinische Technik, Bergholz-Rehbrücke
- Freie Universität Berlin, Institut für Biochemie, Berlin
- IHK Potsdam
- Koordinationszentrum für Strukturforschung, Berlin
- Kreissparkasse Teltow-Fläming, Luckenwalde
- Luckenwalder Beschäftigungs- und Aufbaugesellschaft mbH, Luckenwalde
- Max-Planck-Institut für Kolloid- und Grenzflächenforschung, Golm
- Max-Planck-Institut für Molekulare Genetik, Berlin



and production preparation. The Biochip Center, which is planned for the biotechnology park Luckenwalde, will take over the production of biochips.

As a strategic addition to the consortium projects in the area of research and development, the technical college Wildau, in cooperation with the biotechnology park Luckenwalde will



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start to offer a **new study major** in biosystems technology/ bio computing as of this winter semester. This BioHyTec project will train professionals in an internationally accredited dual study program for three years for a bachelor's degree. A master's degree requires another two years of study. The curriculum is very practical. Stu-

dents will be working directly in the companies and research facilities of the network and the region for part of the semester for gathering practical experiences. In the ideal case, they will be hired directly after completing their degree. In addition, companies will have the opportunity to influence the curriculum content to allow for need-based training.

During the coming year, the InnoRegio initiative will start additional projects, as the approved subsidy volume of 8,2 million EURO has not yet been exhausted.

As an InnoRegio initiative, BioHyTec has the task of linking players from different sectors into a network and to implement regionally integrated research, training and economic development. It is the strategic goal of the initiative to turn bio-hybrid technologies into an economic factor for the region by developing and producing biochips for the global market in

the region. In this context, BioHyTec defines itself as a network for the technological field of biohybrid technology in the biotech cluster Berlin-Brandenburg and cooperates closely with BioTOP Berlin-Brandenburg, the coordination office for biotechnology in both German states, for example, for the preparation of symposia, tradeshow and events.

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Development of biosensors and biochips

at the Department of Analytical Biochemistry of the University of Potsdam

THE SIGNIFICANCE OF analysis in our daily lives is demonstrated by current problems, such as the detection of BSE or anthrax bacteria, as well as by "prenatal implantation diagnostics." The biochemical methods used for this analysis are based on enzymes, antibodies, and nucleic acids.

The advances made in biological sciences depend to a great extent on breakthroughs in the development of analytical methods. After completing the research of the human genome, the focus is now on understanding the function of gene products and their connection through signal transduction and metabolic paths.

To understand cells as a whole, researchers need insights about the kinetics of processes and the sub-cellular distribution of all metabolic products.

The Department of Analytical Biochemistry is part of the Institute of Biochemistry and Biology at the University of Potsdam and is located in the multi-use natural sciences building of the research campus at Golm. The department is processing numerous projects involving third party funds, including EU projects and those by the research consortium BioHyTec Berlin-Brandenburg. The chairman of the department is the president of the German Association for Biochemistry and Molecular Biology (GBM).



Prof. Dr. Friedrich W. Scheller
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Research focus

The research conducted in the Department of Analytical Biochemistry is geared towards the development of analytical processes, particularly biosensors for clinical diagnosis and environmental analysis. The group has produced the first commercial European enzyme electrode, and has given decisive impulses to biosensor development in Germany.

The following methods have been established for the development of biosensors and biochips:

- Immobilization of enzymes, antibodies, and nucleic acids on transducer surfaces
- Marking of bio molecules with enzymes, redox labels and fluorescent colorants
- Configuration of biosensors

The department has particular expertise in the construction of layers over "self-assembly layers" on metallic electrodes and optical transducers.

The most important results, which were made public in over 50 publications, were achieved in the following areas:

- Sensors with coupled enzyme reactions:
 - For increasing sensitivity with substrate recycling
 - Enzyme sequences for defining new analytes
 - Anti-interference layers for eliminating interfering substances
- Detection of short-lived intermediates, such as superoxide and nitrogen oxide with redox protein in vivo and in food items.
- Implementation of heterogeneous electron transfer in



enzymes, such as glucose oxidase, cytochrome P 450, superoxide dismutase, peroxidase

- Registration of enzyme inhibitors through an affinity reaction
- Immune sensors with catalytic antibodies
- Load transfer through molecular wires

Research work is interdisciplinary, as biochemical and electro-chemical aspects are connected to one another in synergies, and requirements are dictated by the respective application areas.

Support for junior scientists

The department is integrated into the study majors of biochemistry, biology, and nutrition science at the University of Potsdam and is part of coursework in medical biotechnology at the Technical University of Berlin. In two block internships, students get hands-on experience about the modern methods of bioanalysis in the research laboratories. There, they learn to produce a glucose test strip, an enzyme electrode for malate, and a DNA chip.

They also analyze the interaction of antigens and antibodies with optical biosensors.

- Max-Planck-Institut für Molekulare Pflanzenphysiologie, Golm

- Oberstufenzentrum Teltow-Fläming, Luckenwalde

• Technische Fachhochschule
Wildau, Bioverfahrenstechnik,
Wildau

• Technische Universität Berlin,
Institut für Mikro- und Medi-
zintechnik, Berlin

• Universität Potsdam, Institut
für Biochemie und Biologie,
Potsdam

• ZAB - ZukunftsAgentur Bran-
denburg, Potsdam

Biochips – (*Microarrays*)

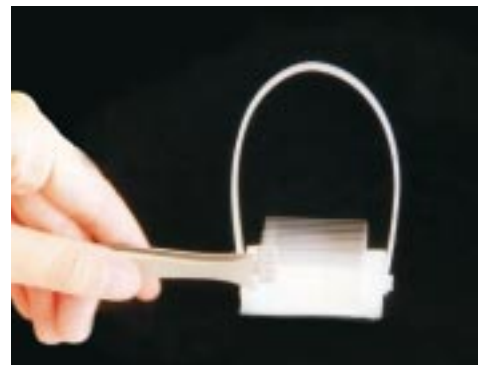
Application areas in medicine and research

BIOCHIPS OR MICROARRAYS are planar carriers in the size of object carriers or cover glasses, on which hundreds to several hundred thousands of dots with different biochemical molecules are stored.

The most frequent application of microarrays is the determination of transcription levels in cell populations (e. g., from tissue) that are as homogenous as possible. Then, the cell status and the influence of external pa-

use of our throughput scanner, the entire immunoassay is processed automatically and forms the basis for the developments of new kits or diagnostic tools.

Another example is the "molecular biology on the chip."



They can form a complementary molecule as molecular binders.

Biochips are the basis for miniaturized biochemical assays. Frequently, they are associated only with DNA chips, but in principle, all



types of biological and biochemical molecules and detection elements can be arrayed.

Even entire cells in array form can be utilized for highly parallel assays. Biochips or microarrays constitute special tools for bioanalysis, which can simultaneously determine a great number of different analytes from a single sample. The advantages over conventional methods of bioanalysis include:

- A variety of analytes is detected simultaneously in the same sample,
- The required sample quantities are minimal
- Low consumption of scarce reagents
- High miniaturization
- High sample throughput.

rameters on the expression activity are determined. Thus, the transcription activity of cancerous cells is compared on the genetic level with that of healthy cells, which allows for studying the type of derailment that takes place in cells during the development of cancer. In the case of the so-called highly condensed arrays, this process can also be carried out for the entire genome by storing representatives of all genes as probes on one microarray.

Applications of biochips with low-density arrays, i.e., arrays with a few hundred different dots, take place in a variety of bioanalytical fields. Some examples from the developments at IBMT include:

The analysis of single base deviations in genomic DNA, the so-called single nucleotide polymorphism (SNP) is a special application of the DNA chip, for which IBMT has developed a method and a device that allows for analysis in solution with recording of kinetic parameters.

A second example is the miniaturization of immunoassays, in which antibodies or antigens in spaces of 300 µm are immobilized in dots of 200 µm. Due to the

Using the method of kinetic detection, enzyme activities can be tracked in addition to binding kinetics. DNA modifying enzymes can easily be analyzed in DNA microarrays.

Our department, with experience in the area of biochip research and development, defines itself as a service provider for

- Customer-specific development of microarray assays (DNA, protein, chemical arrays)
- Chip surface modification
- Variable coupling chemistry
- Detection technology
- Processing bio computing data
- Integrated microarray concepts under one roof.

This background forms the expertise of the Biochip Competence Center of BioHyTec e.V., which represents the basis for a production center that serves as a service hub for all areas of biochip manufacturing. The Biochip Center will enable small and mid-size businesses in bioanalysis and diagnostics to get started in biochip technology by minimizing the entry risk into the new technology and providing production facilities that are not affordable for every business. ■

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University Potsdam

THE LARGEST UNIVERSITY OF BRANDENBURG, the University of Potsdam, has established life sciences as one of the focus areas of research and teaching. A full range of biosensor topics is considered in analytical biochemistry at the Institute for Biochemistry and Biology. The group is one of the three global leaders of the field when it comes to publications. The department head Frieder W. Scheller is the spokesman of both the innovation consortium "Biomolecular detection systems in biochemical analysis" and InnoRegio BioHyTec. He is an organizer of global convention on biosensors and is the



president of the German Association for Biochemistry and Molecular Biology (GBM). Patents he holds in the area of biosensors and bioanalysis are integrated into the project InnoRegio BioHyTec. ■ ■ ■

University of Applied Sciences Wildau

DURING THE PAST TEN YEARS, the Technical College Wildau has established itself as an attractive study site in the immediate vicinity of Berlin. Strongly application-related research and development as well as a lively technology

transfer guarantee training that is in tune with the latest technical and professional development and practical studies. The dual study major biosystems technology / bio computing, a training project by InnoRegio, has been accepted into the course program as of the winter semester. ■ ■ ■



Biotechnologiepark Luckenwalde

THE BIOTECHNOLOGY PARK LUCKENWALDE (BTPL), LOCATED 50 KILOMETERS

SOUTH OF BERLIN, has the appearance of a campus due to the closeness of work, research and living quarters. The laboratory facilities for rent in the Technology and Founder Center (TGZ) are completely equipped with laboratory and safety technology and feature everything from laboratory tables to autoclaves. The facilities have a central laboratory supply system.

Tenants with larger space requirements are eligible for commercial lots that are ready for construction. There currently is a total of 10 hectare of land available. This assures enough space for the expansion plans of the resident companies at BTPL, most of which are still young and small. The

management is developing customized purchasing and lease offers for this purpose.



Companies in BTPL benefit from extremely favorable conditions and subsidies (for example, small and mid-sized companies can get a 50% grant for investment cost!) Together with the management of BTPL, companies develop individual problem solutions for starting and developing companies that include aspects of business planning, financing / subsidies, HR management and GMP quality management systems.

The business focus of companies currently doing business at BTPL includes:

- Development, characterization, and production of proteins for diagnostic and therapeutic uses
- Tissue engineering
- Development and production of raw materials and reference substances for the pharmaceutical industry
- Measuring and control instruments for biotechnological processes

A biochip production center and a GMP pilot plant are in planning.

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The Fh-IBMT, AMBT and the Department of Molecular Bioanalysis & Bioelectronics

SINCE ITS BEGINNINGS IN THE YEAR 1987, THE FRAUNHOFER INSTITUTE FOR BIOMEDICAL TECHNOLOGY (Fh-IBMT) has been a partner of private enterprise by addressing issues in the fields of medical technology, ultrasound applications, medical telematics, biohybrid technologies, micro system technologies, and diagnostics. The Department of Molecular Bioanalysis and Bioelectronics in Bergholz-Rehbrücke has been involved in research and development in the area of chemical and biochemical coupling of biological functional units since 1998. In addition, it has been active in establishing nano-biotechnology, nucleic acid and biological sensors, and especially the development of biochips and lateral structuring of immobilized cells. Together with the work group "Nano Biotechnology," which is currently still located in Berlin, it forms the institute part called "Medical biotechnology" (AMBT). It is scheduled to move to a new building on the scientific campus at Golm by the end of 2004.