

# *Biotechnology in Bavaria*

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# Bavarian Top Locations





## Editorial

### Biotechnology - for a better life ...

...researching, developing and producing with this in mind are companies in the areas of science, economics and business.

High demand is the reason for these efforts. Bavarian biotechnology has further improved its profile and its significance.

This issue once again brings you exciting topics from the excellent setting of the world of biotechnology:

- Where are promising facilities for contacts and changeover from basic research to implementation effectively supported?
- Which synergies do the Bavarian research networks create and how can economic problems be supported by public capital?
- Where is the meeting point for lab technology, analysis and biotechnology?
- How can the aggressive skin cancer melanoma be effectively beaten?
- How is targeted control of the immune system for treating complex illnesses possible?
- Where are outstanding projects in biotechnological research being developed?

- What form does basic research take in the treatment of inflammatory diseases - bedside to bench and back?

Building a life that's more worth living, that's the vision of all those involved!

Walter Fürst  
Managing director

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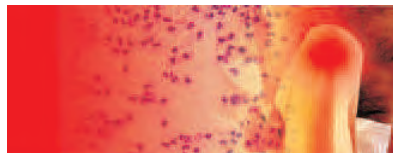
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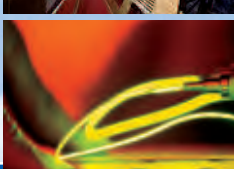
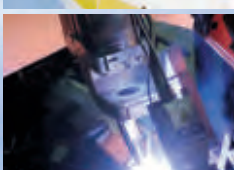
**Friedrich-Baur BioMed Center in Bayreuth – finding tomorrow's solutions for your health**

*Authors: Dipl.-Biol. Daniel Seitz, Prof. Dr. Stefan Schuster  
Friedrich-Baur BioMed Center gemeinnützige GmbH*



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Today's knowledge for tomorrow's innovations





## Success through collaboration

Success through collaboration – the guiding principle of the Bavarian biotechnology sector. The outstanding scientific community in Bavaria forms the most important foundation for constructive collaboration, crucial for a sector that exists within a global contest of the very brightest minds.

Thanks to an intelligent political course set in the ,70s and ,80s, science in Bavaria now leads Europe and, in some fields, the world - via university Life Sciences departments, Max Planck Institutes and other nonuniversity organisations like the Helmholtz Association and the Fraunhofer Society.

These developments have also seen the emergence of red biotechnology, with its biopharmaceutical research, development and manufacture, as a key focal point in Bavaria. Starting with human genome research, this has created a foundation for the establishment of Bavaria's own independent biotechnology industry. The agricultural and environmental biotechnology industries have also developed their own pre-eminent scientific communities. Industrial biotechnology links these industries and provides answers to questions of production and technical implementation, whether for the manufacture of antibodies in one of Europe's largest production facilities at Roche in Penzberg, or at smaller sites around Straubing dedicated to renewable resources and bio-fuels. Under the auspices of BioM Biotech Cluster Development GmbH, the Bavarian Biotech Cluster links these fields not only with each other but also with many other sectors. This is where links are forged between the well-developed Bavarian bio-regions of Munich Martinsried and Regensburg, and the up-and-coming regions of Nuremberg-Erlangen, Würzburg and Bayreuth. Over the last few years, each of these regions has developed its local core competencies to generate its own distinctive profile.

The last few decades in Munich have seen a focus on pharmaceutical development, and in 2010 the city's profile in 'personalised medicine' was raised even further by winning the Federal Ministry of Education and Research's "Leading-Edge Cluster Competition". Entitled "m4 - Personalised Medicine", this large funding project draws together almost €100 million from federal funds, the Free State of Bavaria and from industry. This is used to finance individual collaborations in research as well as infrastructural activities, for example the Munich tissue banks.

The Leading-Edge Cluster Competition was also a great success for the Nuremberg-Erlangen region, a centre of medical engineering excellence that knows how to make the best use of a close network of science, economy, hospitals and care facilities, as well as the innovative power of medium-sized companies.

The Regensburg region is also leading the way in the field of medical engineering, with notable achievements in interdisciplinary collaborations between medical engineering and the Regensburg BioPark biotechnology firms. Another very interesting field is the application of innovative developments from seemingly unrelated areas such as the textile and glass industries.

Würzburg has established itself as a centre of excellence in biomedical research, while Bayreuth is a strong player in the field of material science and has also increased its standing through fascinating insights into the biology of photosynthesis and its technical applications.

The Bavarian Biotech Cluster is a network of collaborations on a local, regional and international scale. Each region contributes its own unique strengths to the network and in turn benefits from the collective effort. BioM GmbH supports this process by serving as a central agency and point of contact. I am convinced that the success enjoyed by each local player has a positive knock-on effect for the whole network, and for that reason I would like to thank all partners, many of whom are represented in this brochure, for carving out this path together with such success.

This brochure gives you an up-to-date overview and its aim is to encourage you to identify new cooperation partners.

Prof. Dr. Horst Domdey  
Spokesperson for the Bavarian Biotech Cluster

# The Life Science Campus Martinsried – Perfect Location for Life Sciences

*The integration of science, economy and society is growing in importance, which is true especially in the area of biological basic research. In the long term this means for the field of biological sciences that only those sites will prosper, which can provide and effectively support the contacts and translation between basic research and application. This does not only require money, but above all short distances and the possibility of personal interaction - fast and uncomplicated. Today, the Life Science Campus Martinsried is one of the largest centers in Europe in which basic research, education, clinical research and technological innovation are combined in one campus. Located in close proximity are the faculties of Biology, Chemistry and Pharmacy and other institutions of the Ludwig Maximilians University (LMU) Munich, the Max Planck Institute of Biochemistry, the Max Planck Institute of Neurobiology and the Innovation Center for Biotechnology (IZB). The campus provides exceptional conditions for students and scientists, as well as an economic benefit to the region through the regular establishment of spin-off companies from the basic research.*

## Basic Research at the Highest Level

In 1973, the creation of the **Max Planck Institute of Biochemistry (MPIB)** was the foundation stone for the Life Science Campus Martinsried which today has a worldwide reputation. With about 850 employees from approximately 45 different nations, the MPIB is one of the largest biomedical research institutions of the Max Planck Society. In currently eight large research departments and about 25 research groups, the MPIB basic scientists work in the fields of biochemistry, cell biology, structural biology, biophysics and molecular medicine. Living cells are highly complex formations in which a multitude of molecules work together to make our organism function. Without proteins, this would be inconceivable: They coordinate



Max-Planck-Institut für Biochemie Martinsried (Photo: Max Schreder / ©MPIB) ■

the mechanisms of the cell by implementing the information contained in the genes into cellular processes and structures. Proteins give cells their shape and they are the main protagonists in all cellular processes – whether they transport substances, convey messages or carry out vital processes in their role as molecular machines.

What decides which genes are translated into proteins? How do proteins regulate highly complex cell processes and how do cells

communicate with each other? Which control mechanisms are effective in these processes and what happens when errors are made?

All these are questions which the scientists of the MPIB are seeking to answer. To elucidate the rules of cell division and specialization and to understand how cells fulfil their tasks in the body, the scientists are investigating the structure and function of the involved molecules. The size of the “study subjects” ranges in scale from the individual molecule and the cell up to the entire tissue and the organism.

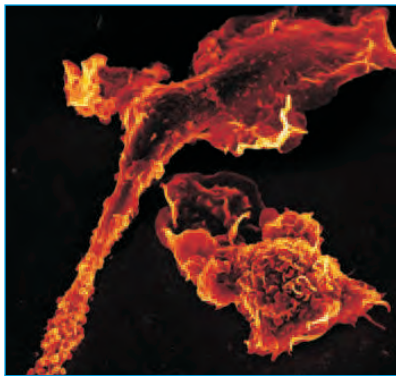
Biomedical basic research is likewise an important aspect, because disturbances of cellular signal transduction or abnormal protein structures lead to diseases such as cancer, diabetes or Alzheimer's. Deeper insights into the cellular mechanisms and structures also





help to better understand the pathogenesis of these diseases and to develop new therapy strategies.

For their analyses, the researchers use a broad spectrum of ultra-modern methods partly developed directly at the MPIB. The methodological expertise, which has increased over the years and which covers all of the research areas of the Institute, is a particular strength of the MPIB and is what makes the implementation of research projects possible at all. In particular, new methods in electron and light microscopy and mass spectrometry offer unimagined opportunities for gaining insights into cells. One Example: scientists of the institute have recently identified the messenger proteins secreted by immune cells during an immune response directing bacteria and viruses. (Science, April 2013)



Macrophages (orange) attract other immune cells to the site of inflammation by secreting messenger proteins. Copyright: Volker Brinkmann/ MPI for Infection Biology ■

Forschung und Lehre

The Max Planck Institute of Neurobiology (MPIN) is situated in the Martinsried Campus, adjacent to the Max Planck Institute of Biochemistry. MPIN stands for internationally recognized first-class basic research in the field of neurobiology. Its research focus ranges from the miniscule modifications displayed by nerve cells at the molecular level all the way to the development and interconnec-

tion of complex neuronal networks. In the course of their research, the scientists work at the cutting edge of human knowledge. The common goal of the 300 staff members working at the Institute is to extend this knowledge.

Put simply, the focus of the five MPIN research departments can be described with the following questions: How do neuronal circuits influence behavior? What happens in the brain when it learns or forgets something? How does a fly's brain process optical information? Which new methods can illuminate otherwise invisible processes? These studies are complemented by and linked with the diverse

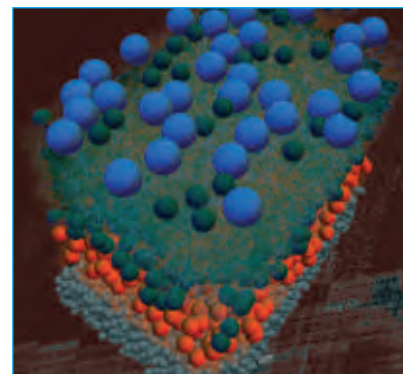


Max Planck Institute of Neurobiology in Martinsried (Photo: R. Schomer/MPIN) ■

research topics of five independent research groups at the Institute. The Institute's scientists have been exceptionally successful, for example, in developing optical methods for the investigation of neuronal activities. Contributing to this is the development of genetically coded indicators and the enhancement of microscopical techniques. Recently, the MPIN scientists were able to report a breakthrough regarding the question of how optical information is decoded in the brain. For over 50 years, a mathematical model precisely predicted the construction of the brain's elementary motion detector but the actual interconnection of the respective nerve cells remained a mystery. Now, MPIN scientists discovered the elementary motion detector in the fruit fly brain (Nature, August 2013).

A few months earlier, neurobiologists were able to show that fruit

flies use different neuronal circuits to process information about their position or movement (Nature Neuroscience, April 2013). Another group of MPIN scientists finally succeeded – after four years of work – in creating an exact diagram, showing all nerve cells and their connections in a small piece of mouse retina. To analyze these data, they were aided by some 200 students. This comparatively small insight into the brain already brought to light a new cell type as well as connections which could explain certain reactions of specific retina cells (Nature, August 2013). The results represent only a small step along the way to understand the entire connectome of a mouse's brain – the assemblage encompassing all nerve cells and their connections. MPIN scientists have developed a plan to analyze the enormous amount of data by enlisting the support of the Internet community by providing a special computer game: While playing this game, a player's decisions provide relevant information about real nerve cell connections. MPIN researchers have also achieved successes in other research fields. For example, they have developed new indicator molecules which enable the activation of auto-aggressive



Computer reconstruction of all nerve cells and their connections in a piece of mouse retina (©Kuhl & Denk) ■

immune cells in the body to be observed "live" under the microscope (Nature Methods, May 2013). This is an important step towards gaining a better understanding of



*The Life Science Campus Martinsried (Fördergesellschaft IZB mbH & Bertram aerial picture publishing house) ■*

autoimmune diseases such as Multiple Sclerosis. Scientists of the Institute were also able to show for the first time, a direct connection between chronic stress and behavioral changes resembling depression in the zebra fish (Psychiatry, June 2013). These findings could open the door to an effective search for new drugs to treat psychiatric disorders. Although applied research is not the main research goal, a number of discoveries made at the Institute are currently being tested for clinical relevance. The results generated at the Institute contribute to the development of new therapies for the treatment of a damaged nervous system, Multiple Sclerosis or Parkinson's disease. ■

*Research and teaching at the university of excellence*

Biology is the leading science of the 21st century and has central contact functions with other areas in the LMU such as medicine, physics and chemistry. Due to the rapid development in the biosciences during the last decade, it is now possible to examine the life processes in their complexity, from molecular details up to the general understanding of complex processes in their entirety. It was therefore just logical to establish the biology faculty of the **Ludwig-Maximilians-Universität München (LMU)** in a Biocenter in Martinsried. Tech-

nologically, and with regard to research the faculty of Biology has taken an early lead position so that they can maintain their hold at a national and international competitive level and are able to consolidate this position in the future.



*The Biocenter of LMU Martinsried ■*

They combine areas of science which provide for an overlapping, interdisciplinary research and a comprehensive and modern training of students. The emphasis in research ranges from the elucidation of molecular structures and performances of microorganisms (prokaryotes and eukaryotes), the evolution and function of organelles, autotrophic organisms (plants) up to the vertebrates including humans. The organismic biology concentrates on the structural and ecological variety of all organisms as well as the speciation principles. A further central position is occupied by neurobiology which integrates systemic (organismic) and theoretical formulations. The areas

with orientation toward ecological and evolutionary biology focus on the research of population genetics which is governed by theory and hypotheses, evolutionary and aquatic ecology as well as behavioral ecology. In the context of educational research, the didactics of biology refer to the different areas of biology. Finally, all Bavarian national scientific collections with biological orientation and the Botanical Garden in Munich are in close contact with the faculty.

High-ranking interdisciplinary institutions, special research areas as well as excellence institutions such as the graduate school of systemic neuroscience (GSN) or the Bernstein Center for Computational Neuroscience (BCCN\*) and also the graduate school of Life Science Munich (LSM) show that today good integration is a sustainable factor for a site. In September 2011 the construction of a Biomedical Center (BMC) unique in Europe, has been started. Here, the LMU explains, a „starting point will be created for an overall identity for teaching and research of biomedicine at the University Munich“. Importance will be attached to large-scale public areas with lots of green.

This alignment is the best prerequisite for a new generation of qualified academics and new inventions.

500 people will work there on 18,000 sqm ■

*Turning research results into business results - an essential criterion for the economy*

The Bavarian State Government recognized early on that biosciences would play a key role in the 21st Century. By founding the **Innovation and Start-Up**

\* BCCN: a “national network for computational neuroscience” supported by the Federal Ministry of Education and Research; it consolidates and integrates the capacities available in Germany in the area of experimental and theoretical neuroscience to promote new research impulses.



**Center for Biotechnology (IZB)**

in the science corridor between Martinsried and the Munich district of Großhadern, it created optimal conditions for young entrepreneurs and company start-ups from the life sciences sector, and thus the basis for a campus that today has become world famous. Here, one finds optimal building infrastructures (S1 and S2 laboratories) rentable for fair prices in a competence cluster for life sciences. For more than 18 years it has promoted the economic translation of products and services. Scientists whose research results are no longer defined as basic research, but are still not ready for the market, can immediately start their work here and rely upon extensive experience within a large network. The Martinsried campus is one of short distances – which accounts for its special stimulus.

The parent company IZB mbH has accompanied over 123 companies starting up since 1995. The opening of West II in Martinsried in 2010 meant that the IZBs in both (Planegg-Martinsried and Feising-Weihenstephan) locations grew to encompass 25,000 square meters of office and lab space. The laboratories are always completely booked

*Drug development at 4SC lab ■**Main entrance to the IZB Martinsried ■*

out, and there are many enquiries about space. This also has something to do with the outstanding infrastructure on campus: with the childcare centers “BioKids” and “BioKids2” and the café and communication meeting place “Freshmaker”, the IZB had already set high standards in 2012. In addition, the chemistry college

*CAMPUS AT HOME – IZB Residence ■*

Elhardt, which this year celebrates its 125-year anniversary, has forged new paths: the college provides hands-on practical training for technical assistants.

Again last year there were several notable financing rounds, an indication that the IZB companies have managed to remain immune from the international financial crisis for a few years to come. This could well be linked to the opportunity to obtain advice directly on site: one venture capital company works here and offers tenants its services.

And another piece of good news: the Boarding house has a name. The seven-storey futuristic looking building with 42 rooms and its

own restaurant is intended to provide accommodation for guest scientists from all over the world. The key feature of the “CAMPUS AT HOME - IZB Residence” is the Faculty Club “G2B – GATEWAY TO BIOTECH” where scientists, company executives and cooperation partners can regularly get together to exchange ideas about research results and possible joint projects in a pleasant atmosphere. In addition, CAMPUS AT HOME will have an additional gastronomic location called “SEVEN AND MORE”. This will create a new communication center for top research on the scientific campus Martinsried. The official opening is planned for October 2014. ■

For more information about the campus: [www.campusmartinsried.com](http://www.campusmartinsried.com)

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## Biotech Devices & Reagents

### Competence 4 Cells

PELOBIOTECH GmbH develops and produces cell culture media for human primary cells, stem cells and embryonic stem cells as well as supplements for tumor stem cells.

In addition to our media products, PELOBIOTECH GmbH distributes an extensive range of primary cells, stem cells and cell culture products from our exclusive partners worldwide: • Human/animal primary cells, stem cells, iPSC derived cells & media

- Diseased Cell Systems
- 3D Cell Culture Technology
- Angiogenesis Models & validated cells for Angiogenesis research
- MicroMatrix Array for the optimal cell/stem cell microenvironment (ECM and soft underground)
- Cell Culture Tools: – Hydrogels – Biomatrix Proteins &

Coating Solutions – Cell based Assays – Rec. Proteins e.g. Cytokines, Growth Factors and Chemokines (Research grade and GMP-grade) – Animal-free Cytokines – Elisa Kits – Antibodies – Dyes for Microscopy, HTS, FACS – Europium Chelates for HTS.

- Tools for DNA/RNA/Protein Purification as well as  $\mu$ -Volume Spectrophotometer

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## Biotech Therapeutics & Diagnostics

### Drug discovery and development focused on cancer and autoimmune diseases

4SC (ISIN DE0005753818) discovers and develops targeted small-molecule drugs for the treatment of diseases with a high unmet medical need in various cancer and autoimmune indications. These drugs are intended to provide patients with innovative treatment options that are more tolerable and efficacious than existing therapies, and provide a better quality of life. The company's pipeline comprises promising products in clinical development and early-stage research. 4SC's aim is to generate future growth and enhance its enterprise value by

entering into partnerships with pharmaceutical and biotech companies. The company was founded in 1997 and has been listed on the Prime Standard of the Frankfurt Stock Exchange since December 2005.

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## Industrial Biotech

### AMSilk has developed a unique process to produce biopolymers like spider silk at an industrial scale

The AMSilk®-Technology enables the production of tailor-made materials which are unrivaled by most common synthetic materials. AMSilk addresses many applications and industry sectors with new materials enabling new products with previously unachievable features.

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## Classification of amyloidoses with respect to therapy

**amYmed**

*Diagnostic Service for Amyloid Diseases in Man and Animals. The amYmed GmbH is developing immuno-reagents for distinguishing precisely the 30 or so different and mostly life-threatening diseases such as Alzheimer's disease, hereditary amyloidoses and those derived from monoclonal gammopathies, with respect to an effective therapy. The amYmed also provides a service on demand for the precise classification of the various amyloidoses, including an evaluation, for both patients and physicians. Although the different amyloidoses can be clinically similar, they represent different diseases, every one of which requires a highly precise diagnosis for appropriate treatment. The amYmed also develops comparable reagents for*

*classifying amyloidoses in animals (mammals and birds) and provides a similar diagnostic service.*

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www.amymed.net

## Tissue Engineering

## The establishment of a Bavarian Tissue Bank



*The Bayerische Gewebebank GmbH was founded in 2009 by the Medical Centre of the University Munich and the German Heart Centre Munich. The purpose of the Bavarian Tissue Bank is the processing and transmission of human tissue preparations with a production permission and license according to the tissue law. In future, it is planned to provide even further medical centers in and near Munich with tissue preparations, and not only to provide for the partners' needs. A network of extraction institutions, laboratories, tissue banks and institutions transplanting tissues is connected via the European Association of Tissue Banks – and the Bavarian Tissue Bank regards itself as a part of this association. The aim of this network is to ensure the high-qua-*

*lity, transparent and economical supply of the required tissue transplantations for patients. In the meantime, the structural requirements for the issuing of the production license have been created so that it will soon be possible to produce tissue preparations under aseptic conditions at the IZB.*

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Offices and laboratories at the Innovation- and Startup-Center Biotechnologie IZB Martinsried ■

## Biotech / Diagnostics

### Smart oral drug delivery



*Bernina Plus and HDS develop smart oral drug delivery systems for therapeutic peptides. The proprietary technology is based on artificial envelopes created by lipids.*

*In addition, these nano-particulate natural and synthetic lipids are used in coating and surface protection.*



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## Biotech Consulting & Service

### Competence in Biotechnology

*Bio<sup>M</sup> Biotech Cluster Development GmbH serves as the coordinating agency of the Munich Biotech Cluster, and is the top address for all biotechnology companies and start-ups in the region – since more than 15 years. Bio<sup>M</sup> provides support in marketing, communications, and public promotion, also maintaining an information portal at [www.bio-m.org](http://www.bio-m.org). The website offers an extensive **company database**, **news updates** and a **job exchange**. In addition to business advice and help in business development, Bio<sup>M</sup> offers a wide range of **seminars** and events to biotech entrepreneurs and their employees. In the nationwide competition "Germany's Leading-Edge Cluster" by German Ministry for Research and Education (BMBF) the "Munich Biotech Cluster m<sup>4</sup>" (coordinated by Bio<sup>M</sup>) was announced in 2010 as one of 15 winners in such different branches like automotive, software or logistics with the new focus on "**personalized medicine**" now receiving a grant of about € 40 Mio which is paralleled by a commitment of the local industry by another € 40 Mio and basic financing by the Bavarian Ministry of Economics to a total of nearly € 100 Mio for the new strategic program "m<sup>4</sup> – personalized and targeted therapies leading to drug development in a new dimension".*

*The legal unit Bio<sup>M</sup> AG functions as seed investor in innovative start-ups having a managed portfolio of about 14 companies to date.*

*On behalf of the Bavarian Ministry of Economic Affairs, Infrastructure, Transport and Technology, Bio<sup>M</sup>, with its 10 year experience in managing the*



*Munich Biotech Cluster, was additionally mandated to manage the Cluster Biotechnology Bavaria as part of the governmental "Cluster Initiative Bavaria" ([www.biotech-bavaria.de](http://www.biotech-bavaria.de)). The objective is to connect the different Biotech Regions of Bavaria within a large, statewide network. Central tasks are:*

- **Targeted scouting of research projects and Technology Transfer**
- **Network Organisation and International Representation**

*As a Bavaria-wide network organisation the Bavarian Biotech Cluster develops synergy potentials and communicates a uniform public presence as shown in the annual publication "Report Biotech in Bavaria".*

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Biotech Devices & Reagents

High Level Transfection technology



*Biontex is a research-focused genetic engineering company offering a comprehensive range of products in the field of transfection technology, including long-established reagents such as the METAFECTENE series. Our new development, the K2 Transfection System follows a completely new strategy. Transfection efficiencies are enhanced by decreasing the cells ability to detect nucleic acids.*

*A major alternative to nucleic acid transfection is the direct transport of proteins into cells – a purpose for which the new reagents in the PROTEOfectene series were specifically developed.*

*Our groundbreaking new Microfection product series enables outstanding optical properties in live cell imaging to enhance the versatility and efficiency of*

*nucleic acid and protein transfection applications. To complement these products, Biontex sells agaroses for efficient protein purification (Ni-NTA Agarose, Ni-IDA Agarose, Co-IDA Agarose, GST Agarose etc.). The product portfolio is completed by mycoplasma detection (MycosPY™) and removal (MycosRAZOR™) kits.*

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Biotech Consulting & Training

Training center for chemistry, biology and environment



*The Dr. Erwin Elhardt School of Chemistry, located in the training center for chemistry, biology and environment, is the oldest private school in Munich with more than 125 years of experience in the area of scientific technological training. State-approved chemical-technical assistants (CTAs), biotechnical assistants (BTAs) and chemical technicians are trained here.*

*Since September 2010 the vocational training of the BTAs is given in the new building of Innovation and Start-up Center for Biotechnology (IZB) in Martinsried.*

*Here, modern laboratories with state of the art equipment are available – tailor-made for this training. The practical and theoretical instruction is given in close proximity to the numerous life science companies.*

**Contact:**

**Chemieschule Dr. Erwin Elhardt**

Staatlich anerkannte Berufsfachschule

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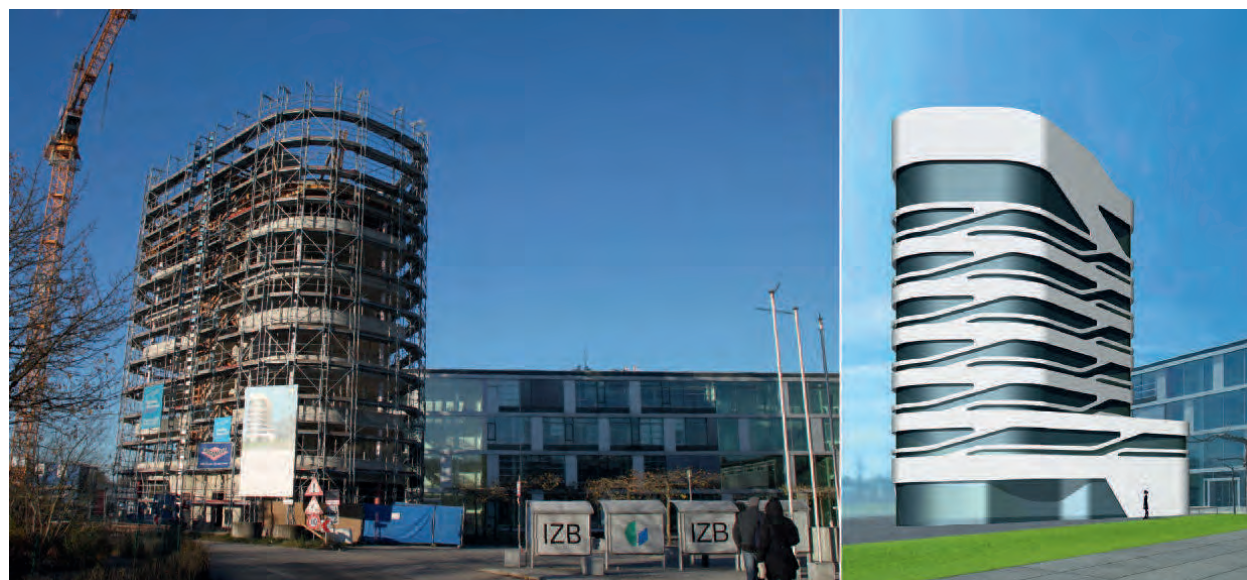
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Gemeinnütziger Schulträger:

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Ludmillastraße 30

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CAMPUS AT HOME – IZB Residence from Oktober 2014. Rooms available under [www.izb-online.de](http://www.izb-online.de) ■



## Biotech Devices & Reagents

### Authentic Chromobody® Technology

ChromoTek GmbH, founded in 2008, is a biotech company focused on the discovery and development of novel nanoprobes and cell based assays for biomedical research and early drug development. During the last years ChromoTek has developed innovative research tools including the GFP-Trap® and RFP-Trap®, two versatile pull-down reagents for biochemical analysis of fluorescent fusion proteins. In April 2011 ChromoTek successfully introduced its first cell based assay for early drug development, the U2OS Cell Cycle Chromobody®. This real-time High-Content Analysis (HCA) screening assay enables to monitor the complete cell cycle in live cells for the first time. In addition ChromoTek developed

the Fluorescent 2-Hybrid (F2H)-Assay to analyze protein-protein interactions in vivo in real time.



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## Biotech Therapeutics & Diagnostics

### Development of New Peptide Therapeutics for the Treatment of Autoimmune Diseases

conoGenetix is a privately owned biopharmaceutical company focused on the development of new peptide therapeutics for the treatment of autoimmune diseases. conoGenetix was founded in 2002 by Dr. Andreas Klostermann and Dr. Jörg Stockhaus and is located in Martinsried, Germany. The company has developed an integrated technology platform that allows for the efficient discovery of drug leads that modulate ion channel targets causatively involved in the generation of autoimmune diseases. conoGenetix runs a program targeting severe autoimmune disorders like Multiple Sclerosis (MS), Rheumatoid Arthritis (RA) and Vasculitis. Several peptides called cgtx-peptides within this program are in preclinical development. The leading indi-

cation for the cgtx-peptides will be Vasculitis – a fatal disease strongly related to Rheumatoid Arthritis. Vasculitis is a rare disease and will be a market door opener for conoGenetix.



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## Biotech Preclinical Services

### The outsourcing partner for individual and innovative analytical and formulation development of biopharmaceuticals



Coriolis PharmaService is one of the worldwide leading, independent service providers in research and development of formulations, analytics as well as established and innovative drying-technologies for biopharmaceutical drugs. Within Coriolis an interdisciplinary team of highly qualified scientists with many years of experience develops individual and innovative solutions for questions concerning therapeutic proteins, peptides and vaccines. Innovative analytical technologies, long lasting experience in formulation development, a strong scientific background and the implementation of most recent scientific advances in the field of biopharmaceutical drug development are the unique characteristics of Coriolis' services. Formulation development ranging from early screening of excipients to the final marketed liquid or lyophilized

formulation is offered. Aggregate and particle characterization by innovative analytical methods, i.e. AF4, Nano-sight® or Micro-flow imaging™ and stability/ comparability studies according to the ICH guidelines or lyophilization process development, are just some examples illustrating the outstanding services provided by Coriolis.

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Drug Discovery Service

Premium Protein and Protein Crystallography Service



CRELUX specializes in tailor made protein and protein crystallography drug discovery services. The company is privately owned and a professional and dedicated service provider for the global pharma and biotech industry.

CRELUX is a client focused provider with a portfolio of premium drug discovery services based on a top level protein expertise. In our PRIME PROTEIN programs we are advancing innovations in protein expression to promote the availability of high quality proteins. Our XPRESS portfolio of readily available crystallographic targets grants turn-around times within a few weeks. Our XPERT crystallography services from concept to high resolution complex structure are provided under tailor made agreements. Based on our unique screening technology INTRACT we

are offering compound and fragment screening. And our i2c (idea to candidate) service includes target to hit and concept to early development candidate fee-for-service projects.

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Biotech Therapeutics & Diagnostics

Therapeutics from herbal extracts for the therapy of rheumatic diseases



DoNatur GmbH develops new therapeutics from herbal extracts with traditionally confirmed therapeutic efficiency. The comprehensive analysis of the genuine extracts, the isolation and structural characterization of the active substances and the test of their pharmacological activities constitutes the main competence of the company. Over the last years DoNatur has successfully developed a new immunomodulatory acting natural substance which has been proved highly efficacious for the therapy of rheumatic diseases.

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Biotech Consulting & Service

Recognizing the bearing capacity of an idea: from the solid scientific result to the feasibility of the product



DPC Pharma Consulting was founded in 2007 by Dr. Karl Deres with offices in the IZB Martinsried Biotech Centre and in Berlin City. DPC Pharma Consulting is an advisory company offering services in the pharmaceutical/biotech industry, including interim management in the fields of business & strategic corporate development, clinical & regulatory aspects as well as R&D management. The main emphasis results from the core competence drug development in the area of chronic inflammatory diseases like auto-immune disorders and cancer. As a venture partner of the BiomedPartners, Dr. Karl Deres also supports their representation in Munich. The effectiveness of DPC Pharma Consulting lies in its ability to value and appreciate people and thereby to inspire

people: when performance is recognized, the willingness to perform increases; those who have the courage to find differences, help to make the difference.

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## Industrial Biotech

### Turning Dust into Stone

*Dust BioSolutions is a start-up company focusing on industrial applications of biocementation. Its international and multidisciplinary team has developed proprietary technologies based upon microbiologically induced calcite precipitation. A first product offers the worldwide mining industry a customized solution to control dust in a more cost-efficient and eco-friendly manner. In 2014 other applications will be refined from Dust BioSolutions product pipeline.*



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## Biotech Therapeutics & Diagnostics

### Special synthesis of oligoribonucleotides

*ELLA Biotech is an internationally active private biotech company with a focus on the synthesis of high quality special oligonucleotides for the diagnostic, chip technology and library sectors.*

*A fundamental premise for ELLA Biotech lies in a close working relationship with its customers, in order to fulfil defined synthesis standards and quality criteria, as well as to continually improve production processes.*

The company's portfolio includes (amongst others)

- high quality long-mer oligonucleotides
- special labelled oligonucleotides according to customer specifications
- dual-labelled probes for qPCR

- performance of specific oligonucleotide syntheses projects

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## Biotech Therapeutics & Diagnostics

### Stem cells from the umbilical cord – a biological life assurance

*In cooperation with the stem cell bank of the University Hospital Erlangen, eticur) currently has the capability of collecting the stem cells from the umbilical cord of newborn children in approximately 600 hospitals nationwide. These are then processed and stored in a frozen condition. During this process, all currently valid regulations for therapeutic procedures are strictly adhered to.*

*eticur) would like to inform future parents in an atmosphere of respect and integrity of the opportunities and benefits of the storage of umbilical cord blood stem cells. Furthermore, eticur) offers a safe storage and guarantees highest quality and comprehensive testing through highly qualified personnel.*

*For further information about the individual steps, from the contract up to the storage as well as the medical benefit of stem cells from the umbilical cord, we recommend visiting our internet site: [www.eticur.de](http://www.eticur.de)*

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Biotech Therapeutics & Diagnostics

Chemical proteomics and phosphoproteomics applications



*Evotec Munich is an affiliate of Evotec AG and based in Munich/Martinsried, Germany.*

*Evotec Munich is a service company specializing in chemical proteomics and quantitative phosphoproteomics methods to support the successful development of small molecule drugs.*

*Evotec Munich delivers a comprehensive analysis of a compound's mode of action in a cell. This significantly supports decision making at various stages of the drug discovery process, such as lead optimization or clinical trial candidate selection, reduces development times and predicts a drug's therapeutic outcome.*

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Biotech Therapeutics & Diagnostics

Biofluid-based Molecular Diagnostics



*Exosome Diagnostics is a leading developer of biofluid-based molecular diagnostic tests for use in personalized medicine. Exosomes are shed into all biofluids, including blood, urine, and CSF, forming a stable source of intact, disease-specific nucleic acids. The Company's proprietary exosome technology makes use of this natural stability to achieve high sensitivity for rare gene transcripts and the expression of genes responsible for cancers and other diseases. The Company is commercializing in-vitro diagnostic tests for use in companion diagnostic applications and real-time monitoring of disease. The Company maintains facilities in New York, NY, St. Paul, MN and Munich/Martinsried, Germany.*

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Biotech Therapeutics & Diagnostics

Development and marketing of biopharmaceuticals in areas of high unmet medical needs like oncology and immunology



*Neovii Biotech GmbH, formerly Fresenius Biotech GmbH, is a member of the Neopharm Group. Neovii is a global acting company, which is focused on development and marketing of biopharmaceuticals in areas of high unmet medical needs as oncology or transplantation medicines. Focal point of the activities are immunotherapeutic products based on innovative antibody technologies. The polyclonal antibody ATG-Fresenius S is established in the global transplantation medicine market since more than 25 years. In addition to the application in solid organ transplantation ATG-F is more and more adopted in the area of stem cell transplantation in cancer patients. The second product Neovii Biotech successfully developed and got approved in spring 2009 by the EMA for the European market is the trifunctional antibody Removab (Catumaxomab).*

*Neovii Biotech has operations in Germany and the US. Some research and development activities are residing in the IZB, supporting clinical development, as well as developing and validating analytical methods for manufacturing and testing of pharmaceutical antibodies. In this context protein chemistry, immunological and cell biology methods are applied.*

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## Biotech Consulting & Service

### Support in the areas of business development, marketing and sales

*FROST LIFESCIENCE offers support in the areas of business development, marketing and sales for life science and biotechnology start-up companies.*

*It is particularly important for start-up companies to enter the market at the right time, and to successfully establish their innovative technologies and products with potential customers.*

#### Services:

- Business development
- Marketing
- Sales

**FROST LIFESCIENCE**  
consulting & trade mission

*FROST LIFESCIENCE is a specialist for human primary cells and stem cells, 3D in vitro test systems (skin, angiogenesis, tumor models), cell based assays and viral gene transfer.*

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## DNA/Protein Analytics

### Ultra-fast DNA amplification and analysis with laser-heated nanoparticles

*GNA Biosolutions has developed a laser-based, optothermal method to provide the world's fastest DNA amplification and detection. The method is based on laser-heated nanoparticles within the sample solution, which also cool down immediately after irradiation.*

*As a result, the classic thermocycler can be replaced for amplification, while the detection depends on the optical characteristics of the nanoparticles instead of fluorescence measurements.*

*The product development portfolio comprises instruments and complementary assays with nanoparticles for a robust, and ultra-fast DNA detection of important microorganisms and pathogens. By*

*this means, e.g., it is possible for the first time in clinical diagnostics to detect resistant bacterial strains already during patient admission.*

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## Biotech Devices & Reagents

### Distribution of EUCOMM an EUCOMMTOOLS ES cell clones to researchers worldwide

*The EuMMCR (European Mouse Mutant Cell Repository) has been founded as the distribution unit of EUCOMM (European Conditional Mouse Mutagenesis Program). EUCOMM is the European contribution of a world wide effort to produce mouse knockout ES cell clones for all mouse genes. In EUCOMM and its successor project EUCOMMTOOLS knockout ES cell clones for more than 8000 mouse genes have been produced. When an ES cell clone is established in a mouse model via blastocyst injection, the mutation in each ES cell clone allows the conditional inactivation of the desired gene. The EuMMCR is responsible for distribution of EUCOMM and EUCOMMTOOLS ES cell*

*clones. Upon the order of an interested scientist the EuMMCR expands ES cell clones, performs a number of quality controls, and organizes the shipment for the ES cell clones to the ordering scientist.*

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Helmholtz Zentrum München  
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Industrial Biotechnology

Networking for Industrial Biotechnology



*Industrielle Biotechnologie Bayern Netzwerk GmbH (IBB Netzwerk GmbH) is an organization focusing on the promotion of real economy in the area of Industrial Biotechnology. Our objective is the transformation of valuable scientific knowledge to innovative marketable products and processes. Therefore, we expand and strengthen our network, consisting of nearly 100 members. Within this network, we combine the competences and the potentials of industry and academia to realize technology transfer nation and Europe-wide. We identify potential project partners and initiate as well as accompany research and development projects. Furthermore, we prepare relevant information for the network, the public and poli-*

*tical decision makers and increase the visibility of our network members by organizing or participating in events.*

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Biotech Devices & Reagents

Cells in focus



*ibidi develops, produces, and distributes innovative lab-ware products, instruments, and reagents for live cell analysis and cell-based assays specifically for high end microscopy. An extensive line of cell-culture biochips— $\mu$ -Slides,  $\mu$ -Dishes, and  $\mu$ -Plates—offers solutions for immunofluorescence and basic cell culture, plus complex assays, such as angiogenesis, chemotaxis, wound healing, shear stress, and flow. The instrument line includes stage top incubators, plus a unique perfusion system that provides continuous flow for the simulation of blood vessels.*

*tivity of in vitro experiments with living cells. Finally, ibidi's newest innovation, Fuse-It reagents, allow for the efficient transport of peptides and proteins directly into the cell's cytoplasm, within only a few minutes. More than 3000 publications document the extensive use of this membrane fusion technology, as well as ibidi's other successful products.*

*Recently, ibidi launched a new system for monitoring, measuring, and controlling the O<sub>2</sub> concentration in biological samples. As with the existing systems, its aim is to establish in vivo-like environments that mimic the conditions of real tissue. With this versatile system, oxygen management will improve the comparability and predic-*

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Biotech Devices & Reagents

Stabilizing and Protecting Solutions (SPS) Technology Platform to improve Stability and Quality of Proteins



*LEUKOCARE provides a proprietary formulation technology platform for stabilization and protection of proteins and biologics to partners in the fields of biopharmaceuticals, vaccines, and combination devices. LEUKOCARE's Stabilizing and Protecting Solutions (SPS) technology improve stability and quality of biologics, facilitate functionalization of various surfaces like implants, catheters or wound dressings and preserve functionality of proteins during terminal sterilization and long term storage.*

*LEUKOCARE's technologies are currently employed in 15 collaborative development projects with industrial partners.*

*The SPS technology platform is based on compositions of various excipients that are highly biocompatible and are easily adaptable to specific biomolecules and needs.*

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## Biotech Devices & Reagents

### Portable solutions for precision measurements



*The eye muscle is the fastest muscle in the human body, closing in milliseconds. One would think of it as quick as lightning. However, compared to the shortest time intervals in modern daily life it is nearly an eternity. We are facing this challenge with our patented frequency comb technology. The technology - simply put - makes it possible to measure the entire spectrum of light in the visible and near infrared, for the first time ever. Based on the technology we have developed a series of instruments over the last years that allow for finer and finer measurements. The crowning achievement of Menlo Systems is the "optical frequency synthesizer". With the portable instrument, light frequencies can be measured with a precision of*

*up to 15 digits beyond the decimal point. This allows our customers to measure time more precisely than ever – a thousand times more precisely than the Cesium atomic clock, until now regarded as the zenith of time measurement.*

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## Pharma & Chemical Industrie

### Encapsulation and Controlled-Release technology using porous nanoparticles



*NanoScape is a developer and producer of porous, nanoscale materials for the pharmaceuticals, environment (e.g. water purification membranes) and electronics (e.g. chemical gas sensors; anti-reflection-coatings) sectors. Its NanoZeolite materials are cage-like structures with very high loading capacity which, through modification of the particle size and pore diameter, functionalisation of the surface chemistry or binding of ligands, can be adapted to meet the requirements of the individual customer, allowing a wide range of pharmaceutical, biochemical, electrical and optical properties to be realised. Using such materials intelligent drug-delivery systems for active pharmaceutical ingredients (small molecules, biopharmaceuticals, vaccines)*

*and diagnostic sensors can be developed, and applications in the area of proteomics supported.*

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## Biotech Therapeutics & Diagnostics

### Risk minimization for heart attacks

*A low omega-3 index is a significant risk factor towards heart attack (acute myocardial infarction). To know ones omega-3 index can help calculate this risk. The right alimentation/ fish oil supplementation can increase the index. Omegametrix GmbH, a international reference laboratory, measures the omega-3 index in a standardised way.*



*international reference laboratory, measures the omega-3 index in a standardised way.*



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Biotech Therapeutics & Diagnostics

Creative Services for Design, synthesis and characterisation of targets



Origenis ([www.origenis.com](http://www.origenis.com)) is a privately owned biotech-company providing creative services for drug design, synthesis, and characterisation based on its unique, patented technology platform – MOREsystem®.

a priori defined biological, physico-chemical, and pharmacological profiles.

The company employs proprietary multiparametric design approaches for the directed target and indication optimised exploitation of billions of novel compounds. The unique process allows immediate realisation of designed molecules by parallel non-combinatorial synthesis, their automated MedChem optimization and biological characterisation of the products. Origenis generates and delivers rapidly patentable pre-clinical drug candidates with

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[www.origenis.de](http://www.origenis.de)

Biotech Preclinical Services

Individually Tailored Quality Management for the Life Science

• scientific • economic • regulatory valid •



PhaToCon (Pharm / Tox Concept) provides proven consulting and management services in all aspects of preclinical development and quality management.

"hands-on" mentality we have strong execution skills.

Thematic priorities and core competencies are:

Product safety and risk assessment in pharmaceutical, biopharmaceutical and medical device development carry potentially significant risks already in early R&D stages. Also, the traceability of scientific and commercial decisions in the life sciences should remain accessible for years to come. To ensure this validity and reproducibility specific industrial and regulatory quality management systems (GxP, ISO, ...) as well as guidelines (OECD, ICH, ...) are used. Our support is customized based on these standards and we deliver resources and expertise both fast and flexible. We operate from a scientific point of view and with our

- Pharmacology and Toxicology in R & D • Preclinical Development • Lab Management • Validation • Qualification
- Process optimization • Preclinical and bioanalytical methods expertise (in vitro / in vivo).

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**PhaToCon**  
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[www.phatocon.com](http://www.phatocon.com)

Bioinformatics

Software solutions for the management and analysis of chemical and biological data



quattro research GmbH develops and markets software solutions for the management and analysis of chemical and biological data in drug discovery and development.

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## Biotech Therapeutics & Diagnostics

### Novel drugs to treat diabetes, hypertension and gastric hyperacidity



*SiNatur is focused on development of novel drug products to treat diabetes, hypertension and gastric Hyperacidity. For these purposes its recently discovered drug substance SNSA is applied which is actually the first biologically active Si compound. The proprietary drug-substance SNSA of SiNatur is a*



*very potent non-toxic inhibitor of the P-type ATPases involved in several diseases. The discovery of SNSA is of deep scientific impact confirmed by*

*the lecture given by Dr. Franz Kerek (kerek@sina-tur.net) at the „12-th World congress of ATPases“ in Aarhus, Denmark (5-9 August 2008)*

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## Biotech Drug Discovery Service



### State of the art service provider for preclinical target research

*SIRION Biotech GmbH has been operating for 7 years as a specialized service provider for preclinical target research. Using proprietary viral vector (AV, LV and AAV) and RNAi technologies SIRION's customized assay cell models offer access to in depth functional gene analysis, thereby improving target identification/ validation and compound screening in a variety of industries. Their technologies have also been successfully used for primary cell immortalizations. Moreover, novel viral vectors for gene therapy and vaccine applications are under development.*

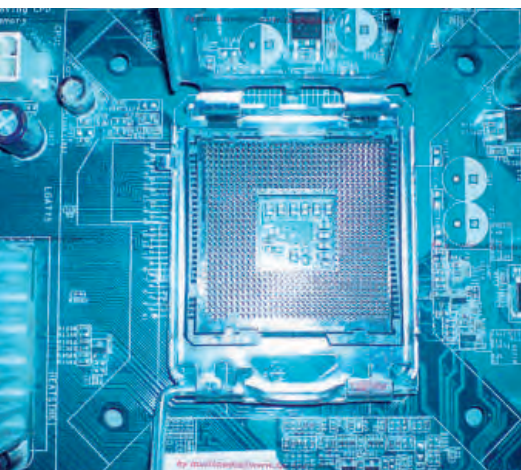
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www.cellcompetence.de

## Biotech Preclinical Services

### Digital controllers for high speed servo motors



*Smart Move designs digital controllers for high speed servo motors. Thanks to our patented technology, highest precision is possible even at fastest speeds. Researching the physics of any device in order to achieve best performance is our business, as well as the development of all necessary hardware, software and communication interfaces.*

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Medtech

## Individual system approaches and instrument development in the biological laboratory



IngenieurBüro

*Smartec IngenieurBüro is your competent partner for individual system approaches and instrument development in the biological laboratory.*

*Smartec IngenieurBüro convinces with know-how within the ranges biotechnology, analytics, genetic engineering, micro technology as well as micro fluidic. Smartec IngenieurBüro solves tasks of instrumentation for molecular and immunological process engineering.*

*Smartec IngenieurBüro supports you from the idea to all stages of the product.*

*Smartec IngenieurBüro offers complete solutions, consisting of mechanics, optics, electronics, as well as firm- and software of a hand.*

*Smartec IngenieurBüro consists of engineers and physicists which are predominantly settled in the ranges Research and Development (R&D) of bioanalytic systems.*

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Personalized Cancer Therapy

## Spheroid Microtumor Diagnostics for Individualized Cancer Therapy



*Spherotec aims at the optimization of systemic therapy in oncology using the companies proprietary Spheroid-Microtumor-Technology in two different business areas.*

*SpheroMed: In this area an innovative diagnostic test, combining Spheroid-Microtumor Technology and biomarker profiling, was developed. This test is used for identification of the individually optimal drug regimen in oncological patients before begin of systemic treatment. Thus, therapeutic agents can be chosen more specific and with less side effects for the individual patients. Testing can be performed with cytostatic drugs, antibodies and small molecules. Currently the test is under clinical validation in breast and colorectal cancer studies.*

*SpheroSelect: In this business area the patented Spheroid-Microtumor-Technology is applied for functional testing of drug candidates, new indications for established drugs and new drug combinations on behalf of Pharma and Biotech companies.*

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Biotech Therapeutics & Diagnostics

## Fc-Receptors to interfere with autoimmune diseases

*SuppreMol GmbH is leveraging the therapeutic potential of Fc receptors (FcRs) for the treatment of autoimmune diseases and allergies. Lead product of the company is a soluble FcR (SM101) that interferes with the underlying cause of the autoimmune diseases and therefore has the potential to cure the disease rather than only treating the symptoms in addition with fewer side effects as compared to the current standard therapies. The company has successfully completed a phase I study in healthy individuals with SM101 and is presently conducting two clinical phase II studies in the orphan disease Primary Immune Thrombocytopenia (ITP) and Systemic Lupus Erythematosus (SLE). Additionally SuppreMol is currently developing highly specific non-blocking antibodies against human FcγRIIB, being the sole immunosuppressive member of the Fcγ-receptor family. The non-blocking anti-FcγRIIB antibody is developed in three distinct antibody formats to allow the*



*modulation of human FcγRIIB in the treatment of a wide range of autoimmune diseases. These three mAbs are currently in preclinical development.*

*SuppreMol is a privately-owned company and started as a spin-off of the laboratory of the Nobel laureate Prof. Dr. Robert Huber of the Max Planck Institute of Biochemistry in Martinsried, Germany. The company secured in three financing rounds over 51.4 M Euros since 2006.*

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## Biotech Consulting & Service

### System house in any field of computing

*That's it as a system vendor supplies support in any field of computing.*

*Main focus are server based computing, open source*



*projects and system security as well as high availability solutions, global access, consulting and data recovery. services include project planning, implementation with ongoing support and training.*

#### Contact:

**that's it gmbh**

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that'sit

## Biotech Consulting & Service

### Your Partner tackling specific research and development process challenges

#### Who we are

*THE WORKING GROUP are seven consultants colleagues, all with many years of - complementary - professional practice from industrial work and consultancy experience who help -as member of your team- to tackle the challenges of your specific research and development process.*

#### What we do

*Active support of project teams and managers in your R&D projects as a consultant, sparring partner, coach, trainer, facilitator or project manager reaching noticeable improvements.*

#### What is your benefit

- *Strategic management of project and technology portfolio*

- *Structured ideas creation and concept evaluation for new products/services*
- *Milestone-oriented, consequent management of current R&D projects*
- *Systematic risk mitigation in intensive conceptual phases*

#### Contact:

**THE WORKING GROUP Management Consultants**

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FAX: +49 (0)911 308 44 40 00 8

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## Biotech Therapeutics & Diagnostics

### Generating new trifunctional antibody drug candidates for a better cancer immunotherapy

*TRION Research GmbH, founded in 1998, is a Biotech research company and a strategic partner of TRION Pharma GmbH focusing on the generation of novel Triomab® antibody candidates and the support of non-clinical and clinical development of Triomab® antibodies. The company offers Immunomonitoring Service, special antibody conjugation support, additional analytical service in tumor biology and further analytical support for reagent control to investigators, study sponsors and CROs.*

*The core competences of the company are:*

- *Immunomonitoring and logistical support for clinical and non-clinical studies*
  - *Determination of the patients` immune status e.g. FACS measurements, proliferation tests, cytokine multiplex assays and immune activity tests (e.g. XTT,*

*B-cell depletion assays)*

- *Determination of EpCAM+ tumor cells via cytospin preparations and immunofluorescence*
- *quantitative PCR*
- *Determination of human anti mouse antibodies (HAMA)*
- *Supply of purified antibodies (labeled and unlabeled)*
- *Development of immunological assays*

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Venture Capital VC



Venture capital for life science companies

*Vesalius focuses on the creation, financing and growth of early-stage life science companies. The Vesalius funds invest in areas with a high unmet medical need and a significant profit potential: new therapeutics, cutting-edge medical devices, innovative drug delivery technologies and diagnostic tests with a high utility level. The expertise of the team ranges from extensive operations, business development, R&D, and IP management know-how to corporate governance, M&A, and IPO experience in start-ups and mature life science companies. Furthermore, the individual team members have in-depth technical insights and competitive scouting experience in the life science sector. For*

*more information please see [www.vesaliusbiocapital.com](http://www.vesaliusbiocapital.com).*

**Contact:**

**Vesalius Biocapital**

**Christian Schneider, PhD, DVM, MBA**

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Main Entrance at the IZB Freising/Weihenstephan ■

Agro, Food, Environment



Modern aroma and flavour analytic

*Our company is a food chemistry research and development laboratory specialising in aroma and flavour analysis. aromaLAB AG researches and ana-*

*lyses the aroma composition of food on the basis of innovative processes, scientifically established methods and the most recent discoveries in the area of food chemistry. aromaLAB develops aromas for food manufacturers as well as*

*for the cosmetics, tobacco and consumer goods industries.*

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## Agro, Food, Environment

### Anerobic technologies and renewable energy systems

*ATRES is short hand for anaerobic technologies and renewable energy systems.*

*We offer consultancy and laboratory services, focused mainly on production and utilisation of biogas by means of anaerobic digestion.*

*Additionally for industrial applications we design concepts for production integrated environmental protection or process integrated protection (PIUS).*



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[www.atres-group.com](http://www.atres-group.com)

## Molecular Food Diagnostics

### Real-time PCR analytics

*GENidee is a young and innovative biotech company specialized in the development, production and sales of molecular-biological diagnostic kits for the rapid detection of food-borne pathogens and microbial contaminants in food.*

*Fast and reliable real-time PCR diagnostics is guaranteed by parallel analytics suited to the individual customer requirements.*

*GENidee offers DNA-based systems of highest quality. Using our kits directly in the production facilities enables the results of microbiological analytics to be supplied much sooner than by conventional diagnostics. The individual care of our customers and the consequent customer satisfaction is our top priority.*



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## Bioinformatics

### Development and application of innovative online measurement systems for biotechnical process state variables

*Gimbio - Society for Information Management in biotechnology - sees itself as a company offering innovative products and solutions in bioprocess technology, especially for companies in the food, brewing or biotechnology industry.*

*The guiding principle of the company is, in addition to the information gathering and processing, the development and application of innovative online measurement systems for biotechnical process state variables for the purpose of process design, modeling and simulation, with the ultimate goal of optimizing underlying bioprocesses.*



**Contact:**

**GIMBIO mbH**

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Agro, Food, Environment

## Technological properties of cereal science

The Hans-Dieter-Belitz-Institute for Cereal Grain Research conducts research projects in collaboration with industry. The projects are dealing mainly with the physical and chemical characterisation of different cereal species and the correlation of the results with technological properties. Furthermore, the effect of additives in the breadmaking process and the generation of odorants during baking are investigated. Professor Dr. Peter Schieberle is the scientific supervisor of the institute. He combines the functions of the head of the Institute for Food Chemistry of the Technical University of Munich and the director of the German Research Centre for Food Chemistry. As a result, a close contact between the two institutions is established,

giving the Hans-Dieter-Belitz-Institute the possibility to solve difficult problems in cereal science by using approaches including both, applied and basic research.

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Biotech Therapeutics & Diagnostics

## Anticalins, a unique class of target protein therapeutics

Pieris AG is an independent, clinical-staged biotechnology company advancing its proprietary Anticalin® technology to create differentiated drugs that are safer and more effective than conventional approaches. Exclusive to Pieris, Anticalins promise to address high-unmet medical needs and expand the potential of targeted therapeutics. The company currently has a diverse proprietary pipeline and has ongoing R&D collaborations with Daiichi Sankyo, the Sanofi Group, Zydus Cadila, Stelis Biopharma and Allergan. Privately held, Pieris has been funded by premier biotechnology-focused venture capital, including lead investors OrbiMed Advisors

and Global Life Science Ventures. For more information, please visit:  
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www.pieris-ag.com



Biotech Environment, Instruments

## High quality environmental monitoring and measuring

The Umwelt-Geräte-Technik GmbH (UGT GmbH) is a medium enterprise, which operates successful in the field of environmental monitoring and measuring technologies since 1992.

According to the company profile, the UGT GmbH develops, produce and distribute measurement and diagnostic tools for soil-water-air-analytics and modules for the environmental monitoring. The installation of complex soil hydrologic and meteorological measuring stations in agriculture, forest and water ecosystems is in the area of operation, as well as the installation of control stations at landfill and mining sites for remediation. To meet the requirements of a growing national and inter-

national market, the UGT GmbH establishes the branch south in Freising-Weihenstephan, close to important scientific centres.

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## DNA/Protein Analytics

### Highest quality and fast turn-around services in functional genomics



Established in 2000, vertis Biotechnologie AG is a privately held company with its core competence in the field of functional genomics. It was founded as a spin-off from the Technische Universität München-Weihenstephan. VERTIS offers highest quality and fast turn-around molecular biology services in the field of functional genomics. The company has developed an innovative technology platform which significantly accelerates the identification of candidate genes and enables the discovery of the world of naturally occurring non-coding small RNAs (sncRNA), the prototype of which is MicroRNA (miRNA). Newest results exhibited that especially the sncRNAs play a central role in the development and preservation of life.

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## Biotech Therapeutics & Diagnostics

### XL-protein: Improved biopharmaceuticals with extended plasma half-life



XL-protein is a biopharmaceutical company utilizing its proprietary 'PASylation®' technology to develop second generation biopharmaceuticals with prolonged plasma half-life. PASylation of therapeutic proteins allows less frequent and lower dosing combined with better tolerability, also opening perspectives for the life cycle management of approved biopharmaceuticals.

'PASylation' – the genetic fusion with conformationally disordered polypeptide sequences comprising the amino acids Pro, Ala, and Ser – provides a superior way to attach a solvated random chain with large hydrodynamic volume to a biologically active protein. Thus, its typically rapid clearance via

kidney filtration can be retarded by one to two orders of magnitude while the PAS moiety is biochemically inert and easily degradable.

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# BioPark Regensburg

## Successful Innovation Centre on the Danube

### Health Industry of Regensburg

- 1.4 billion Euros turnover
- 15,500 employees

### Cluster BioRegio Regensburg

- 47 companies (Life Sciences)
- 3,150 employees

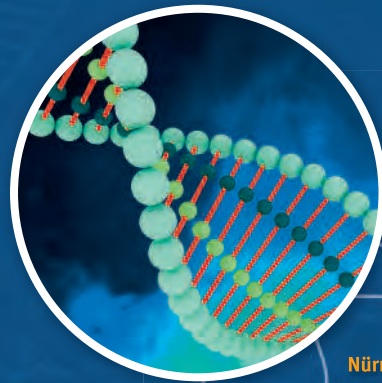
### BioPark Regensburg

- 35 tenants, 550 employees
- state-of-the-art offices & laboratories  
(18,000 m<sup>2</sup> incl. 5,400 m<sup>2</sup> S1/S2-laboratories)
- flexible leasehold concept & single office
- comprehensive range of technology & services
- excellent location factors  
(University Campus, motorway connection, childcare facility)

Get information at:

[www.bioregio-regensburg.de](http://www.bioregio-regensburg.de)

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UNESCO World Heritage  
Old Town Regensburg:  
[www.regensburg.de](http://www.regensburg.de)



Member of CLUSTER  
BIOTECHNOLOGIE  
BAYERN

**BIO**PARK  
REGENSBURG GMBH

# Regensburg – at the head of the Danube



*The BioPark Regensburg GmbH is the management and administrative headquarters of the biotechnology research cluster known as BioRegio Regensburg in Eastern Bavaria. Within the last 15 years, it has evolved into a life science cluster with interdisciplinary approaches. Currently, 48 firms with more than 3,300 employees are active in the field of life sciences in BioRegio Regensburg. As a result it has become the most important region for Biotechnology in Bavaria, second only to Munich. At the BioPark itself with its 18,000 sqms of laboratory and office space, there are currently 36 tenants active with 600 employees. Apart from companies, the BioPark accommodates university and external-university research institutes as well as patent attorneys and consultants.*

## Research at University Campus in Regensburg

With its University, the Technical University, the University Hospital and the neighboring clinics, the City of Regensburg possesses the youngest and most modern institutions in Bavaria, where 8,000 employees and 31,000 students have significantly embossed the dynamic economic location of Regensburg. The individual professorial chairs have, through various means, proven the top-class university-standard research achievements in the field of the biological sciences (the so-called life sciences). In addition to special fields of research of the German Research Association (DFG), particularly in metabolic physiology, several project assistance measures provided by the Federal Ministry of Education and Research (bmb+f) have been injected into the neurosciences and immunology for example. The José Carreras Foundation has been obtained for hematological therapies using adult stem cells. The Human Tissue & Cell Research Foundation was founded on site for the development of new methods for therapy for patients with liver

disease. The development of vaccines against the HIV virus (AIDS) was funded significantly by the Bill and Melinda Gates Foundation. In the field of infection biology the Medical Centre is a partner of the World Health Organization (WHO).

In 2008 the research network „BayImmuNet“ has commenced its activities in Regensburg. The goal is the development of new therapies and medicines for infectious diseases, tumor diseases, autoimmune and rheumatic diseases. Since 2008, the Fraunhofer Project Group for the Diagnosis and Treatment of Tumors, Metabolic Disease and Disease associated with Ageing and since 2011 the Fraunhofer Project Group for Sensor Technology Materials are located in the BioPark as external university research units. In 2011 followed the establishment of Pro-Retina, a new endowed chair for retina research and development of novel diagnostic methods for the prevention of blindness.

The East Bavarian Institute of Technology Regensburg (OTH) has started the biologization of medical engineering by creating a study course in „Biomedical

Engineering“. This program combines biological and conventional materials of the medical technology with mechanical engineering. The corresponding „Regensburg Center of Biomedical Engineering (RCBE)“ has moved into its new lab spaces at the BioPark in 2013. In 2014, the RCI (Regensburg Center for Interventional Immunology) will start up in the laboratories of the BioPark. It is supposed to link existing scientific excellence in the field of cell-based immunology and transplantation medicine in East Bavaria. The RCI is another external university institution and in the long term is intended to become established as the first institute of the Leibniz Association in Regensburg. ■

## The BioPark Regensburg

Through the foundation of the BioPark Regensburg GmbH in 1999, the City created a further catalyst for this aspiring future-focused sector. With support from the State of Bavaria, the German Government and the European Union, the BioPark was erected for 42 million € in three construction phases in 2001, 2006 and 2011 directly on the



grounds of the University. The multifunctional buildings offer in total 18,000 sqms state of the art laboratory, office and storage facilities for companies and institutes in the field of biotechnology, medical technology and associated services. In addition to use of the university infrastructure and small distances between buildings on site, Regensburg's own motorway connection facilitates direct and rapid connections to Munich, Frankfurt and Berlin.

In 2014, the BioPark Regensburg celebrates its 15 year anniversary. In this period over 300 million € have been invested in the development of the „life sciences“, of this solely 50% of it in venture capital with an impressive result for the „return of investment“: 42 companies have been founded since 1999 and the number of employees in the region has increased more than seven-fold to 3.3000.

Well-known companies like the Genent AG were founded at the BioPark as successful spin-offs of the University. The enterprise was going public in 2006 at the Frankfurt Stock Exchange and is still expanding at the Gewerbepark Regensburg. Since 2014, Genent is part of the US enterprise Thermo Fisher Scientific.

AMGEN Research GmbH is the first research center in Europe that is from one of the largest Biotech companies in the USA. In Regensburg, 10 million compounds are analysed each year to identify novel lead structures for the development of innovative drugs.

In 2008 BioPark Regensburg was awarded „Landmark“ by the Federal Initiative „Germany – Land of Ideas“. The BioPark shares its experiences in several organizations. Since 2007 the BioPark has been part of spokesman circle for the Council of German Bioregions (Ak BioRegio), since 2011 a board member of the German Association of Innovation, Technology and Business Incubation Centers (ADT) and since 2013



Areal picture of the central University campus in Regensburg ■

part of the spokesman circle of the Bavarian Centers for Founders and Technology (ARGE-TGZ). ■

### Production in the Region

A range of companies at BioRegio Regensburg have developed into international production locations for clean rooms. These include pharmaceutical companies such as Bionorica SE (Neumarkt) and Haupt Pharma Amareg GmbH (Regensburg), and also biotechnology companies such as Syntacoll GmbH (Kelheim), PAN Biotech GmbH (Aidenbach) and medical technology companies such as RKT Roding Kunststoff-Technik GmbH (Roding), Raumedic AG (Helmbrechts) and Gerresheimer Regensburg GmbH (Pfreimd). ■

### Interdisciplinary Projects

Innovation and success require constant analysis and development, and this is also true for the BioPark in Regensburg. In regular location analyses, the potential for development of BioRegio Regensburg has been analyzed. On this basis, regional interdisciplinary fields in the area are continually scanned and companies are integrated into the network. Therefore, regional companies in

the areas from the glass industry, engineering, electronic technology, textiles and nutrition were brought together with the companies from BioRegio Regensburg and the University. As a consequence, companies and clusters in the field of sensoric settled in the BioPark. One example out of this technology-spanning network is the Sensor Technology Strategic partnership with its projects in optical technologies and photodynamic (hygiene). Regensburg is also booming in the field of healthcare. With 1.4 billion € in turnover and a total of 15,500 employees, the healthcare industry has developed into an important economic sector in the city. The six Regensburg clinics currently have 8,500 employees, including 604 practicing doctors, 134 dentists and 46 pharmacists on site, offering the BioPark enough potential to force the networking within the field of health care.

Additional settlement space is already in planning: 2015, the first buildings of the R-Tech GmbH on the new Techcampus in direct neighbourhood of the BioPark will be ready for occupation. ■



### Companies of the BioRegio Regensburg (Status 2014)

For detailed company portraits, please refer to [www.bioregio-regensburg.de](http://www.bioregio-regensburg.de)

### Biotech-Companies (by OECD)

#### **2bind GmbH**

(in the BioPark, founded in 2011, 2 employee) service provider to quantify bi-molecular interactions (synthesis and modification of the substrates by microscale thermophoresis method).

#### **Active Motif Chromeon GmbH**

(founded in 2005, 5 employees) develops and produces fluorescent dyes, nanoparticles, LED compatible fluorophores and fluorescence-conjugated molecules.

#### **AlBio-Lab**

(founded in 2012, 2 employees) works on the proteome analysis by different gel electrophoresis methods, supports its customers with molecular biological DNA/RNA Analysis for Industrial Pharmaceutical biotechnology products.

#### **Amgen Research GmbH**

(in the BioPark, since 2000, 19 employees) is a subsidiary of US-based Amgen Inc., the world's largest independent biotechnology company that discovers, develops, manufactures and markets human therapeutics based on advances in cellular and molecular biology.

#### **BioGents AG**

(founded in 2002, 8 employees) develops biological attractants and repellents for pest insects. Involves the research and development of monitoring systems. Molecular biological analysis.

#### **Biometric GmbH**

(founded in 1996, 11 employees) is a laboratory for microbiological and chemical analysis - dealing with the analysis of water, hygienic control and providing microbiological analy-



*With the opening in-house of our own St. John's nursery „bamBiOni“ in BioPark III, the compatibility of having a career and a family was promoted ■*

ses of pharmaceutical products, medical devices, cosmetics and food.

#### **Curadis GmbH**

(in the BioPark since 2012, 5 employees), branch office of Curadis Erlangen. Curadis GmbH is a pharmaceutical company that focuses on research, development and commercialization of steroidal drugs for the treatment of cancer, especially breast cancer.

#### **Davids Biotechnologie GmbH**

(founded in 1996, 9 employees) production of polyclonal antibodies (in both chicken egg yolk and rabbits), development of monoclonal antibodies, production and purification of antibodies from cell cultures and bioreactors. Transient transfection of cells in cell cultures and purification of the produced proteins. Development of diagnostic methods and cell based diagnostic methods.

#### **Delphitest GmbH**

(founded in 2004, 7 employees) works on DNA diagnostics and focuses on paternity tests and other genetic analyses for private customers.

#### **Entelechon GmbH**

(founded in 1999, 16 employees) combines bioinformatics, molecular biology, DNA synthesis and protein expression into a versatile environment for projects such as the devel-

opment of diagnostic assays, directed evolution, protein engineering, or the identification and validation of cancer biomarkers.

#### **Genart/**

#### **Thermo Fisher Scientific**

(in the BioPark, founded in 1999, 250 employees) service provider for gene synthesis and downstream processes (DNA engineering and processing). Provides Synthetic Biology for customers of Pharma- and Biotech-industry. Since 2014 Genart belongs to the Thermo Fisher Scientific Inc.

#### **hepacult GmbH**

(in the BioPark, founded in 2002, 3 employees) develops and markets cell culture technology based on human liver cells and other human organs for novel drug development and new therapy for liver cell transplantation.

#### **Hyperthermics Regensburg GmbH**

(founded in 2008, 2 employees) works on commercial application of hyperthermophile microorganisms, screening and culturing of all kinds of hyperthermophiles for industrial applications.

#### **IRIS Biotech GmbH**

(founded in 2001, 14 employees) specializes in reagents for peptide synthesis, carbohydrates and pro-

ducts for life science research and supplies from grams for research organizations to multi-ton lots for productions.

#### Labor Friedle GmbH

(founded in 2003, 71 employees) Certified chemical-analytical laboratory for food ingredients, analytics of chemical residues, nutrient content analytic, examination of human biological matrices, microbiological examinations and examination of indoor air pollution.

#### Lisando GmbH

(in the BioPark, founded in 2009, 12 employees) designs and develops novel effective antibacterials to combat bacterial pathogens e.g. proteins that are designed by LISANDO in order to efficiently destroy bacteria, using an enzymatic mechanism.

#### Lophius Biosciences GmbH

(in the BioPark, founded in 2002, 21 employees) is a research based biotechnology company specialized in the development, sales & distribution of novel T cell test kits for diagnosis and concomitant treatment of infectious diseases and autoimmune disorders. (UREA-technology, Reverse T cell signalling technology (RTT)).

#### NeuroProfile GmbH

(founded in 2001, 2 employees) develops novel pharmaceuticals for diseases like Parkinson's, Alzheimer's, schizophrenia and depression by using innovative neuronal targets (disease-related genes or proteins).

#### numares GmbH

(in the BioPark, founded in 2004, 39 employees) develops and sells innovative products and applications in the fields of medicine (numares HEALTH), plant breeding (numares PLANTS) and energy (numares ENERGY) based on nuclear magnetic resonance spectroscopy (NMR), e.g. medical products for the healthcare sector and medical research.

#### Oxford BioLabs Ltd.

(in the BioPark, founded in 2009, 12 employees) is a science-based company tackling Androgenetic Alopecia (AGA). The company is developing novel therapies for the treatment of AGA, which is commonly known as male and female pattern baldness.

#### PAN Biotech GmbH

(founded in 1988, 46 employees) partner in the field of cell-culture, especially for serum-free systems, cell culture media, custom-made products and research. Application-oriented product optimisation.

#### PAN System GmbH

(founded in 2001, Subsidiary of PAN Biotech GmbH) develops, produces and markets a broad palette of innovative biotechnological systems related to cell-culture and laboratory automation, including the newest applications of bio-process technology.

#### PolyQuant GmbH

(founded in 2007, 6 employees) provides quantification of proteins, targeting drug discovery and biomarker validation. Main advantages of the technology are rapid assay development and a high accuracy.

#### PreSens GmbH

(in the BioPark, founded in 1997, 84 employees) developer and manufacturer of chemical optical sensors and systems for customers in Biotechnology, Pharmacy, Medical Devices, Food Industry and in many other scientific fields.

#### rent a scientist GmbH

(founded in 1995, 13 employees) Service provider in the field of development and optimisation of ready-for-the-market products e.g. bone cement based on Nano silver for inflectional prophylaxis.

#### Schmack Biogas GmbH

(founded in 1995, 260 employees) technology and market leader of the German biogas industry. Planning,

construction and operation of ready-to-use peripheral biogas plants. Part of the Viessmann Group since 2010.

#### Syntacoll GmbH

(founded in 1927, 70 employees) develops and manufactures innovative collagen products for medical and pharmaceutical use (implants and tissue engineering).

*Life Science Companies*  
*(Pharma, Medical Engineering, Analytics)*

#### Bionorica SE

(founded in 1933, 641 employees) develops and produces drugs from plants under GMP-conditions (phytotherapeutics) Subsidiary.

#### Bionorica Ethics GmbH

(former Delta 9 Pharma GmbH, founded in 2002) develops new active substances and drugs in the field of pain relief.

#### Cfm Oskar Tropitzsch GmbH

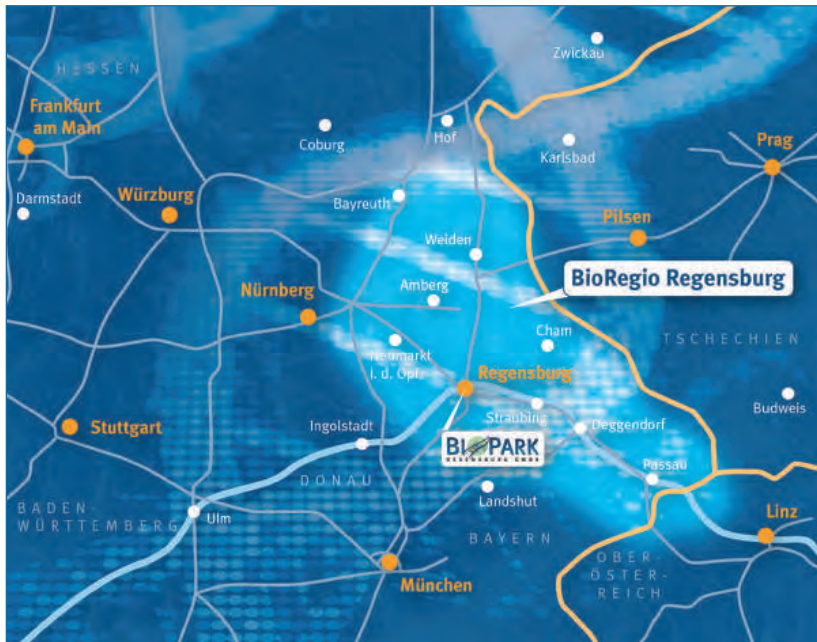
(founded in 1985, 10 employees) is specialized in rare chemicals and the contract manufacturing according to customers needs. Core areas of activity are fermentation products, phytochemicals, pharmaceutical raw materials, enzymes, venoms, metals and metal salt dilutions.

#### Degania Silicone Europe GmbH

(founded in 2002, 4 employees) is a leading silicone manufacturer of medical devices and components. The company has provided comprehensive OEM services and a complete range of finished and CE-marked products made of silicone.

#### DSM Pharma Chemicals GmbH

(since 2001, 40 employees) The company offers services in the field of chemical process development and synthesis of chemical intermediates and active substances.



Gathering area of the BioRegio Regensburg in Eastern Bavaria (part of the go-cluster initiative BMWi) ■

### Gerresheimer Regensburg GmbH

(350 employees in medical technology in Bavaria) a leading company in the business fields of tubular glass, moulded glass, life science research and plastic systems.

### Haupt Pharma Amareg GmbH

(founded in 2003, 358 employees) Focus on pharmaceutical contract manufacturing (GMP production, packaging of solid enzyme products, liquid and semi-solid medicines).

### Inotech Kunststoff GmbH

(founded in 1986, 18 employees in medical technology). Manufacturer of technical injection moulded plastic parts, e.g. for medical technology, pharmaceutical and cosmetics industries. Designs and creates prototypes for industry and research (3D-printing).

### Medical Device Partners GmbH

(founded in 2001, 2 employees) consultancy with the aim to support clients in bringing products and services successfully to the medical device market.

### Multi-Service-Monitoring

(in the BioPark, founded in 2003, 4 employees) offers services for the conduct of clinical studies in Germany, Austria, Switzerland, Czech Republic, Slovak Republic and Hungary.

### nal von minden GmbH

(founded in 2004, 100 employees) specialized in rapid tests, Elisa and homogenous enzyme immune assays in the fields of gynaecology, infectious diseases, cardiac infarct markers, detection of cancer, urology and especially drug of abuse.

### Pharma Stulln GmbH

(founded in 1984, 170 employees) produces sterile pharmaceutical products with experience of over 20 years in the manufacturing of preservative-free eye drops in single dose units. Contract manufacturing for international pharmaceutical industry.

### Raumedic AG

(founded in 2004, 565 employees) supplier for medical and pharmaceutical companies. Development and production of innovative diagnostic and acute therapeutic sys-

tems for the sectors of neurosurgery, urology, gastroenterology and traumatology.

### RKT Rodinger Kunststoff Technik GmbH

(founded in 1974, 56 employees in medical technology) develops plastic components for medical technology engineering, for example biosensors and different pharma/medical applications.

### Sensorik-Bayern GmbH

(in the BioPark, founded in 2007, 10 employees) supports the „Strategic Partnership for Sensor Technologies“ with handling of common partner projects and offers services in research and development, innovation management and business consultancy.

### Transcatheter Technologies GmbH

(in the BioPark, founded in 2005, 3 employees) develops a transcatheter aortic heart valve prosthesis.

### Interdisciplinary Companies (with Life Science Projects)

#### aquagroup AG

(founded in 2004, 22 employees) ensures a supply of germ-free drinking water right at the location of use and offers holistic hygiene concepts.

#### Delta

#### Entwicklungsgesellschaft mbH

(founded in 1994, 10 employees) works in development projects on a contracting basis for manufacturers of tables for patient positioning and technique equipment manufacturers in Germany and abroad (Medical Engineering).

### emz-Hanauer GmbH & Co. KGaA

(founded in 1948, 650 employees) develops and manufactures mechatronic systems for domestic engineering, household appliances and environmental engineering.



## eswegee Vliesstoff GmbH

(founded in 1928, 450 employees) is a global supplier of the widest range of nonwoven technologies for industrial applications as well as for the apparel industry.

## Kelheim Fibres GmbH

(founded in 1935, 500 employees) world leading producer of viscose specialty fibres for hygiene products, specialty papers, filtration, technical textiles, flock and many other applications.

## Linhardt Metallwarenfabrik GmbH & Co. KG

(founded in 1943, 1200 employees) develops and produces aluminium and plastic tubes as a partner to the cosmetics and pharmaceutical industries and as a provider of a comprehensive range of special solutions.

## MISTER Mikrosystemtechnik Regensburg

(founded in 1997, 2 employees) develops sensor technology in biosensors, diagnostics, instru-



The companies in the BioPark and the BioRegio Regensburg are well networked by the Cluster Biotechnologie Bayern in the State of Bavaria and have an international presence ■

ments for laboratory and process control. A company of the university of applied sciences.

## Pfleiderer Teisnach GmbH & Co. KG

(founded in 1881, 220 employees) develops, produces and distributes tailor-made solutions in paper for various applications, e.g. food package.

## Reinhausen Plasma GmbH

(founded in 2004, 20 employees) a highly innovative company offering plasma solutions for surface processing. It could especially play a role in wound care, sterilization and combating of hospital-acquired infections in the future.

## RG Mechatronics

(in the BioPark, founded in 2008, 1 employee in the BioPark) branch of RG Mechatronics GmbH in Seefeld, develops

medical robots (intelligent manipulators) for surgery, diagnostics and therapy.

## SCHOTT AG

Site Mitterteich (founded in 1970, former SCHOTT-Rohrglas GmbH, 1000 employees) products and services for international growth markets such as pharmaceuticals, electronics, automotive and environmental technology.

## Ullrich GmbH

(founded in 1980, 42 employees) manufactures semi-finished glass products for the industry e.g. as a primary product for lenses in xenon headlights. Service provider in special machine construction (medical technology) for the glass industry.

## Zwiesel Kristallglas AG

(founded in 1872, 630 employees) World's market leader for crystal glass in top-class international gastronomy and the hotel industry. Innovation pioneer in Tritan® technology and Biofunctional Surfaces. ■



The shared booths of Bayern Innovativ are appreciated marketing tools of BioPark tenants and BioRegio Regensburg companies ■



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# IGZ Würzburg – where knowledge becomes business

*Würzburg has huge potential to offer when it comes to the health industry, biomedicine and biotechnology as well as medicine and medical technology. The "Innovations- und Gründerzentrum" IGZ Würzburg (innovation and business incubation centre) is a major player in developing, profiling and networking the local scientific and business community.*

IGZ Würzburg is the largest business incubation centre in Lower Franconia. Opened in December 2001, it has since provided some 2,500 m<sup>2</sup> lab and 3,000 m<sup>2</sup> office space to technology-oriented entrepreneurs in their formative stages at competitive prices. All labs have high-tech equipment and can be upgraded to the higher security standard S2. It also provides conference and seminar facilities as well as consultancy services, which are currently being used by 22 companies with some 320 employees. The centre aims at safeguarding jobs, creating networks and synergies as well as promoting the region scientifically and economically. The facility is run by a separate operating company whose shareholders include the city and district of Würzburg, *Sparkasse Mainfranken* (savings bank) and the Würzburg-Schweinfurt chamber of commerce (IHK). ■

## *Würzburg – a force to be reckoned with in life sciences*

With its research centres, research groups, and postgraduate schools of medicine and life sciences, the Julius-Maximilian University ranks among the most successful universities in Germany. The Rudolf Virchow Centre for Experimental Biomedicine



*IGZ, the innovation and business incubation centre, is located in the science park on the Würzburg-Ost industrial estate (Gewerbegebiet). ■*

icine is one of the DFG-funded centres of excellence focussing on the identification of new target proteins in cancer, cardiovascular, auto-immune and inflammatory diseases, which can be the basis



*Achieved very good results in clinical phase 2: the test substance VAS203 of vasopharm GmbH from the IGZ Würzburg affects the increase in cranial pressure in craniocerebral trauma. ■*

for improved diagnosis and treatment. Completed in 2009, the dual centre of internal and operative medicine (*Doppelzentrum für Innere und Operative Medizin*) of the University Clinic Würzburg has excellent technical equipment and offers ideal conditions for patient care as well as basic and clinical research. In

2010, in the immediate vicinity opened the Comprehensive Heart Failure Centre (CHFC), an integrated research and treatment centre for cardiovascular diseases. The Comprehensive Cancer Centre (CCC) was established at University clinic Würzburg in 2011 and is recognised as a centre of excellence for oncology by German Cancer Aid (*Deutsche Krebshilfe*). The newest facility at the excellent life science site is the 2013 established interdisciplinary bank of biomaterials and data Würzburg (ibdw), one of five nationwide databases which are an important prerequisite for a better understanding of diseases and disease mechanisms. ■

## *Networking – locally and in Bavarian clusters*

At the IGZ Würzburg, a structured program is pursued above all in order to further develop the potential of life sciences in the region. Start-up companies, company relocations and existing companies are promoted and given intensive sup-



port in cooperation with the Bavarian Ministry of Economic Affairs, the Würzburg university colleges, the *netzwerk nordbayern* and the city of Würzburg economic development department. The incubation centre promotes the networking of regional companies and research institutions in the field of biotechnology and medical technology and supports their visibility through the platform BioRegion Würzburg ([www.bioregion-wuerzburg.de](http://www.bioregion-wuerzburg.de)). Furthermore, as regional partner in Lower Franconia, it ensures efficient networking with Bavarian biotechnology and medical engineering cluster initiatives and the clusters of excellence m4 in Munich and Medical Valley in Nuremberg. ■

### Support for entrepreneurs

Together with local universities and *netzwerk nordbayern*, IGZ Würzburg has developed a comprehensive program for promoting start-up activities in the region. Young scientists are offered advanced training courses with an economic and branch-specific focus. Technology scouts at colleges and research institutions in the region are screening research results for new business concepts with high economic potential at early stages. Once promising concepts and entrepre-



*The research focus of the international biotech company Patrys GmbH lies in the development of human antibodies for the treatment of cancer ■*

neurial teams are identified, start-up projects are individually and intensively supported during the whole start-up phase. IGZ Würzburg thereby provides continuous support in team-building right at the academic origins of the start-up companies. Through intensive coaching and support the IGZ tries to ensure a smooth transition for company founders between their academic and entrepreneurial careers. ■

### Start-up support bears fruit

In recent years, in close cooperation with universities and *netzwerk nordbayern*, IGZ Würzburg has done the initial work for creation of many new jobs at the incubation centre. Successful support by the IGZ and partners is reflected in the scoring of various Würzburg start-up projects in the Northern Bavaria

business plan competition: since 2007 prize-winners have come regularly from Würzburg life sciences with the teams CALPORTIN Pharmaceuticals, Xenopharm, CoBaLT, SmartmAb and Mablife. In order to promote business ideas it was possible to gain over 10 million Euros in public funding (GO-Bio, VIP, m4 award, EXIST-Forschungstransfer and EXIST-Gründerstipendium). Three start-up companies that have emerged from the pre-seed start-up programs have moved into the IGZ. Further start-up companies are expected in the coming years. ■

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#### IGZ Würzburg has a comprehensive service package for young companies:

- Hire of 3,000 m2 office space and 2,500 m2 lab space at competitive prices
- Flexible rental possible - from small units to building tracts
- High-tech equipment, labs can be upgraded to the S2 security standard
- Support in preparing and updating business plans, grant applications and initiating collaborations
- Advice on business strategies, business models, patent and brand strategies, quality management and quality assurance and corporate management questions
- Advice on financial planning and financing, support in investor talks and financing rounds as well as when negotiating with strategic, licensing and cooperation partners.

#### Other tasks include the following:

- Regional and supraregional networking
- Networking academic and industrial partners
- Collaboration in the creation and further development of a constructive climate between regional companies and institutions in Würzburg and the Mainfranken region



# Successful Through Collaborative Research

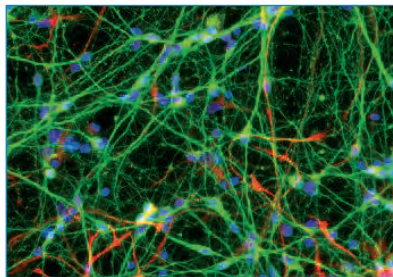
*At Bavarian Research Associations, universities team up with enterprises to jointly explore complex subject areas*

## Bavarian Research Associations

At Bavarian Research Associations, university institutions and enterprises increase their collaborative strength by working closely together. Their interdisciplinary approach serves to create synergies and boost creativity. With the support of public funding, the partners join efforts to search for solutions to scientific problems. Moreover, the Research Associations have become a breeding ground for young talents of the Bavarian economy. They offer the young generation of scientists future-oriented training opportunities and direct links to the industry. In the biotechnological sector, the research associations ForIPS, FORMOsA and ForBIMed are among these economic drivers. ■

### ForIPS

Neurological and psychiatric disorders such as Parkinson's disease pose significant therapeutic, social and health-economic challenges to society. Individuals afflicted by these diseases are often severely affected, experiencing far-reaching personal and social consequences. New and improved treatment options are needed to help these patients. The Bavarian Research Association ForIPS aims to investigate the pathomechanisms of Parkinson's disease and to develop and test new therapies. A further objective is the establishment of a



*ForIPS wants to have the induced pluripotent stem cells mature into new nerve cells (see picture). (© ForIPS) ■*

stem cell biobank. According to the spokesman of ForIPS, Dr. Jürgen Winkler, MD, Ass. Prof., Erlangen University Hospital, researchers at ForIPS focus on sporadic Parkinson's disease, the most common form of Parkinson's disease with over 85 percent of patients affected. Moreover, after Alzheimer's dementia, Parkinson's disease is the second most common neurodegenerative disease and leads to a loss of nerve cells playing an important role in the control of motoric functions. However, the molecular and cellular mechanisms responsible remain largely unknown.

### **iPS Cells - Cells Embarking on a Developmental Biological Time Travel**

Current therapy approaches can hardly stop the progression of the disease. The ForIPS researchers hope for new insights into the pathogenesis using the "Induced Pluripotent Stem Cells" technology (iPS) - one of the most

innovative biomedical developments of the recent years. With this technology, connective tissue cells of the patients can be re-programmed to the stage of pluripotency. As a result, patient-specific stem cells are generated and can be differentiated into organ-specific cells. The resulting neural cells further serve as a cellular model for the analysis of specific or individual disease causes, thus enabling the development of new treatment strategies. iPS cells are obtained from adult patients, which means that research using these cells is associated with fewer ethical issues than research projects with embryonic stem cells.

### **Deciphering Disease Processes**

In order to find new targets for therapeutic strategies it is essential to decipher the processes causing the disease. Scientists at ForIPS investigate the molecular and cellular mechanisms in the pathogenesis of sporadic Parkinson's disease in iPS-derived neural cells and search for new therapeutic approaches. In addition, researchers at ForIPS will establish a biobank for human iPS cells and will implement the iPS technology at the associated Bavarian universities. With this, an efficient platform for advanced investigation of brain diseases and other diseases may be created. ■

## FORMOsA

Many patients, especially those of older age, suffer from muscular atrophy. The pattern of the disease, as well as its treatment often poses a great challenge to medical professionals. Early detection is essential but diagnostic standards are missing and further research is needed in the field of therapy. The Bavarian Research Association FORMOsA was established with the purpose of investigating the causes of muscle atrophy as well as opportunities for its prevention. Furthermore, the project participants wish to develop new therapies and define new measurement standards for diagnostic purposes.

Muscle atrophy (sarcopenia) is a progressive loss of skeletal muscle mass and strength. The result is a



Muscle atrophy affects mostly older people, but not only (© iStockphoto) ■

limited physical performance, which leads to severe health and functional impairments. For example, the risk of falling and fracturing bones increases greatly. Some persons with this condition are still professionally active when their muscle strength begins to fade.

## A Tricky Diagnosis

Despite numerous cases, a substantial need for research in the area of disease causes as well as diagnosis and therapy exists. Until now, only few early stage risk factors are known. Trigger mechanisms can be identified for instance at the muscular, neuro-biological or hormonal level. Additionally, diet plays an important role. Currently, clinical examinations such as measuring the calf or upper arm circumference fail to reliably determine reduced muscle mass. Computed tomography and

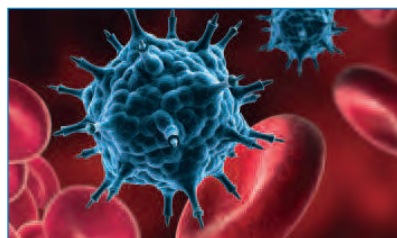
magnetic resonance imaging deliver reliable data, however, these methods are not suitable for everyday clinical practice.

## Development of a Complete Value-Added Chain

Within the framework of FORMOsA, nine scientific institutions and 18 industry partners cooperate closely to cover the entire value-added chain. This ranges from the production of biotechnological active ingredients to small and large animal models, and the development of techniques for diagnosis and treatment of muscle atrophy. The association's spokesman is Dr. Franz Jakob MD, Full Professor for Experimental and Clinical Osteology at the Orthopedic Department, University of Würzburg, Germany. ■

## ForBIMed

Despite the constant availability of new medications, improved vaccines and antibiotics, infectious diseases often spread rapidly claiming many deaths even in modern industrialised nations. There are several reasons for the persistence of infectious diseases. Many pathogens are highly adaptable, often develop multiple resistance to antibiotics or “escape the clutches“ of conventional medicines and vaccines. It is biotechnology's duty keep up to date with these dynamic challenges.



Many viruses develop resistance to certain substances, thus rendering a number of medicines ineffective (© Fotolia) ■

## Biomarkers Reveal Pathogens

The objective of ForBIMed is to discover new, pathogen and host-specific biomarkers that can serve as a basis for new diagnostics, therapeutics and vaccinations. With these, ForBIMed aims to allow for a faster

and simpler distinction between bacterial and viral infections, as well as between resistance profiles within the different groups of pathogens. In addition, the characterisation of host specific immune parameters, based on which the risk of a transplant rejection or a virus reactivation while a patient is immune suppressed is assessed, represents one of the main focal points of this project. Within ForBIMed, eleven university research groups and ten companies work together, side by side, under the leadership of Dr. Ralf Wagner, PhD, Assoc. Prof., of the University of Regensburg. ■

## Competent Support with Research Funding

The Research Associations ForBIMed and FORMOsA make use of public funds provided by the Bavarian Research Foundation, whereas ForIPS is a beneficiary of the Bavarian Ministry of Science. Bavarian universities, higher education facilities, as well as small and medium-sized companies willing to apply for public funding are offered expert advice and support prior to, during, and following the submission of the application by the Bavarian Research Alliance (BayFOR). BayFOR supports Bavarian Research Associations in the area of public relations and assists the scientists involved in operating at the European level. Like the Bavarian Research Foundation, BayFOR is partner in the Haus der Forschung (House of Research) ■

[www.hausderforschung.bayern.de/en](http://www.hausderforschung.bayern.de/en)

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# Taking Advantage of EU Research Funding

*When it comes to providing research funding, the European Union is the world leader. Between 2007 and 2013, the EU allocated around 54 billion Euros to innovative research and development projects in the 7th Research Framework Programme (FP7). For the follow-up programme Horizon 2020, the seven-year period starting in 2014, 70 billion Euros will be allocated for research and innovation funding ventures. A significant part of this sum is to be awarded for projects in the fields of biotechnology, health and life sciences. The Bavarian Research Alliance (BayFOR) helps interested scientists and entrepreneurs to make use of various funding opportunities and supports Bavarian applicants at all stages of the application process.*

## Stable Basis for Successful Research

In Horizon 2020, the new framework programme for research and innovation, the EU implements the priorities defined in the „Europe 2020“ strategy. These are reflected in the three thematic pillars of the programme: (1) increase excellence in science, (2) secure and expand Europe's industrial leadership, and (3) contribute decisively to facing the current societal challenges.

Compared to FP7, the overall budget is higher and as such shall be available for allocation within a wider range of themes. For example, unlike before the European Institute of Innovation and Technology (EIT) shall be integrated herein. In the future, the EIT will focus on the areas of higher education, research and innovation and will be responsible for the so-called knowledge and innovation communities (KICs) doing research on “Healthy Living and Active Aging“, “Raw Materials“ or “Urban Mobility“. For this purpose, the EIT will receive a budget of over 2.5 billion Euros.



Most of the funding opportunities for collaborative projects in the fields of life sciences, health and biotechnology are covered in the second and third pillar of the new programme. The third pillar (“Societal Challenges“) includes challenges such as “Health, Demographic Change and Well-Being“ and “Nutrition and Food Safety“. Funding opportunities are available for the entire innovation chain, ranging from basic research to commercialization. For this pillar alone 27 billion Euros have been set aside.

While FP7 was consistently defined as a top-down programme, with pre-defined subject areas, Horizon 2020 focuses its approach only on exploring solutions to specific societal problems. Within the framework of FP7, biotechnology was based on two major areas. A total of 8 billion Euros was allocated to health (red

biotechnology) and KBBE (Knowledge Based Bio-Economy, green and white biotechnology) to help advance promising projects and products. In recent years, the biotechnological research has gained further importance and consequently, the EU will continue to support interesting biotechnological projects with efficient funding measures. With regard to this, the second pillar of Horizon 2020 lays a focus on the “Support of Advanced Research in Biotechnology as a Future Engine of Innovation“, “Biotechnological Industrial Processes“ and “Innovative and Competitive Platform Technologies“. ■

## Great Opportunities for Small and Medium-Sized Enterprises

Already with FP7, it was the Commission's goal to increase the participation of small and medium-sized enterprises (SMEs) in funded research activities. This will be reinforced in Horizon 2020. For many calls, a certain percentage of SME participants is a prerequisite for the granting of financial support. This will benefit for example higher



education institutions which have already established reliable networks and cooperation with R&D-intensive SMEs.

In addition, new funding instruments will be provided in Horizon 2020. Around 15 billion Euros are intended for the purpose of “Securing Industrial Leadership“. As a part of this scheme, SMEs shall obtain easier access to risk financing. Another support instrument is “Innovation in SMEs“ (Eurostars). This programme is based on the “bottom-up“ principle, i.e. open to different topics and new ideas and as such, of particular interest to research-intensive SMEs or collaborative projects.

Proven public-public and public-private partnerships will be continued to be funded in Horizon 2020. These will include the Innovative Medicine Initiative (IMI) which is funded jointly by the EU and the pharmaceutical industry. It aims to strengthen the cooperation between science and the pharmaceutical industry to overcome the innovation barriers in the area of pharmaceutical development.

In implementing Horizon 2020, the EU wishes to simplify the administrative management of funded projects. For example, the calculation of indirect costs will use a flat-rate model. Thus, items such as used premises, machines, computers or laboratory instruments are reimbursed at 25 percent of the direct costs incurred by a partner. Moreover, in order to make sure that the knowledge funded by Horizon 2020 spreads faster and becomes applicable at a wider scale, research results should be made available free-of-charge on the internet according to the “open access“ principle. ■

### Providing Orientation

The great diversity of funding opportunities may present potential applicants with major obstacles. Both, finding the right funding programme and drafting a success-



ful application requires professional expertise. BayFOR offers reliable assistance to Bavarian scientists and entrepreneurs. This enterprise, sponsored by the Free State of Bavaria, offers information on funding opportunities, implements training measures and provides active support during project initiation, at the stage of setting-up international consortia and the submission of the application. Following a successful evaluation, BayFOR supports scientists and entrepreneurs in contract negotiations with the European Commission and, if required, will be in charge of project management and public relations.

BayFOR prides an excellent network at the regional, national and international level. Its liaison office in Brussels represents the interests of the Bavarian universities, promoting their visibility and acting as an intermediary with the European institutions. Moreover, BayFOR coordinates the joint activities of the Bavarian Research Associations and supports their networking activities at the European level. The scientific coordination office Bayern-Québec/Alberta/International finances bilateral research projects in the partner regions. As

a partner in the Enterprise Europe Network, BayFOR offers special consulting services tailored for SMEs which are interested in participating in EU research projects or cooperating across national borders.

As a partner in the Bavarian “House of Research“ (“Haus der Forschung“), BayFOR works closely with Bayern Innovativ, the Bavarian Centre for Innovation and Technology and the Bavarian Research Foundation. The cooperation between these four partners creates a focal point for funding and support of research and technology at the European, national and Bavarian level. ■

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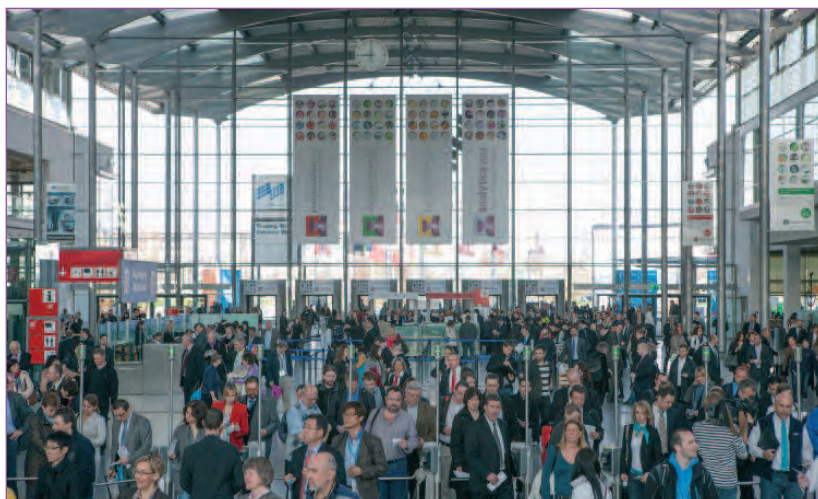
# analytica – Gathering for research and industry

*Biotechnology in Bavaria is well on its way to becoming the leading biotech location in Europe. There is plenty of investment activity, networks are being set up, and as a leading international trade fair, analytica is supporting this development.*

Every two years in the spring, the Bavarian capital becomes the linchpin of the entire analysis, laboratory-technology and biotechnology industry. Decision-makers and users—among other things from the sectors for chemistry, medicine and pharmaceuticals—gather information about the latest analysis and laboratory techniques at analytica. April 1, 2014 marks that date again: That is when more than 1,100 exhibitors from around the world will present their products and innovations. Representatives of the scientific and industrial sectors meet at the analytica Conference, which takes place at the same time as the fair. In addition, visitors can expect Best Practice presentations and lively discussions in the analytica Forums. ■

## *analytica – More than a trade fair*

Modern analysis techniques and innovative biological methods are now indispensable in most branches of industry—whether in the production of medications or quality control of drinking water. That is why analytica 2014 will revolve around food and plastics analysis as well as genetic analysis and bioanalysis. These topics will be reflected in both the trade fair



*Mandatory event for the analysis, laboratory-technology and biotechnology industry: analytica in Munich ■*

and its program of related events as well as the Live Labs. Lectures and product presentations are on the agenda three times a day. Among other things, they will deal with routine analysis applications as well as special analysis techniques. Visitors will profit from the chance to exchange ideas and information directly with manufacturers and experts, having new products explained to them, and being able to discuss specific applications. For the first time ever, a special show on occupational safety and health and safety in the workplace including experimental lectures is being held as part of the Live Labs. ■

## *analytica Conference*

From pharmaceutical analysis, bioanalysis and clinical and medical diagnostics to environmental, water and material analysis: The program of lectures at the analytica Conference covers the analysis sector in its entirety. The conference is held in conjunction with and on the first three days of the fair. For the first time ever, it is being held in the immediate vicinity of the fair, i.e. at the ICM – Internationales Congress Center München. Experts from Germany and abroad will use the conference to talk about the current state of the art and development prospects in analysis, biochemistry and





Gathering for the international scientific elite: The analytica Conference ■

latest financing trends and models. Among other things, the latest market statistics for biotechnology will be presented by Ernst & Young, and there will be a presentation on the topic of bio-economics involving Dr. Viola Bronsema, Managing Director of BIO Deutschland. In addition, start-ups will have an opportunity to make an “elevator pitch” to present their companies and their areas of activity. For the first time ever, Finance Day will be on the third day of the fair (April 3). ■

*Think tank: analytica promotes new ideas*

Both start-ups and university spin-offs give essential impetus to the scientific and commercial sectors. Future-oriented branches of industry in particular such as biotechnology and the life sciences thrive on this dynamic. analytica features a special presentation space for this branch of industry known as the InnovationArea. New technologies, products, services, research results and business ideas are presented in Hall A3. Products “Made in Germany” enjoy a unique reputation around the world. To promote the innovative strength of German start-ups, the Federal Ministry for Economic Affairs and Energy (BMWi) has been promoting

clinical diagnostics. Among other things, they will focus on food safety and the analysis of nanoparticles. The conference will also deal with classic diagnostic topics such as clinical proteomics and metallomics. The conference is organized by Forum Analytik, which is made up of Germany’s three leading scientific associations—the GDCh (German Chemical Society), the GBM (Society for Biochemistry and Molecular Biology) and the DGKL (German Society for Clinical Chemistry and Laboratory Medicine). Admission to the conference is included in the price of admission to the fair. ■

*Biotech Forum: Best practice for users*

Life scientists use refined methods to complete the puzzle of life more and more, even though they often have just a few cells or a few microliters available for their measurements. Equipment manufacturers will explain how they master these and other bioanalysis challenges in the form of Best Practice lectures and presentations in the Biotech Forum. The biotech region of Munich is considered a leading cluster for personalized medicine and targeted therapies. analytica places special importance on this future-ori-

ented topic with an additional series of lectures as part of the forum. Lectures and panel discussions on recent and future developments and methods are planned. ■

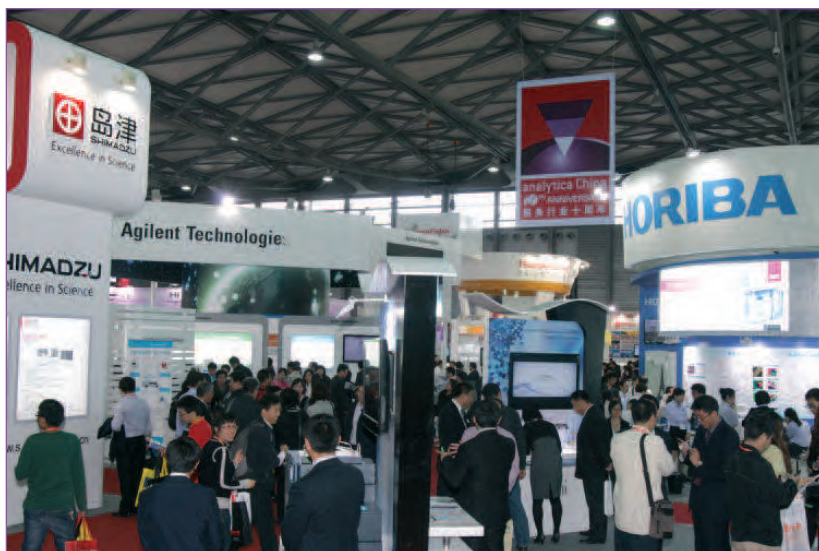
*analytica Finance Day*

Biotechnology continues to increase in significance as a key interdisciplinary technology. However, the question of reliable financing is still one of the topics that concern a number of companies. Which is one more reason to get tips from experts at analytica Finance Day. That is where start-ups and established companies in the biotechnology sector go to get valuable tips about the



The Biotech Forum features tips for life scientists ■





The analytica network brings supply and demand together ■

their participation in the fair for years. At analytica, start-ups have a chance to participate in one of two “Made in Germany” joint exhibits in Halls A3 and B2 at affordable rates and present their own technologies to an audience of international professionals. ■

#### analytica around the world

analytica hosts industry platforms in India, China and Vietnam to take growing demand for analysis techniques and biological methods in these markets into account. Biotechnology is now a

very important sector in China: Investments of more than 300 billion US dollars are planned in the scientific and technology sectors. Among other things, the focus will be on biopharmaceuticals, bio-engineering and agricultural biology. This development will be clearly noticeable at analytica China, which will feature its first large-scale biotech exhibition sector on September 24, 2014. India’s biotechnology industry is considered one of the most promising markets in the world. With annual sales volume of four billion US

dollars, it is one of the most important driving forces for the Indian economy. And in Vietnam, the potential is founded by the fact that the biotech scene did not even exist until now. The greatest demand is in the agricultural, food production and environmental sectors. As an economic metropolis, Ho Chi Minh City alone is planning to invest 70 million US dollars between now and 2015. ■



A successful export: analytica China in Shanghai ■

#### analytica: Exhibition dates at a glance

*analytica, Messe München,*  
April 1–4, 2014

*analytica China, Shanghai New International Expo Center,*  
September 24–26, 2014

*analytica Vietnam, Saigon Exhibition & Convention Center,*  
April 15–17, 2015

*analytica Anacon India, Bombay Exhibition Center,*  
Autumn 2015

#### analytica 2014: Facts and figures

**Exhibition dates:** Tuesday–Friday, April 1–4, 2014

**Venue:** Messe München, West Entrance  
Halls A1, A2, A3, B1, B2

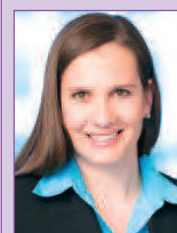
**Opening hours:** Tuesday–Thursday: 9:00–18:00  
Friday: 9:00–17:00  
[www.analytica.de](http://www.analytica.de)

**analytica Conference:** Tuesday–Thursday, April 1–3, 2014  
[www.analytica.de/conference](http://www.analytica.de/conference)

**Price of admission:** 1-day tickets start at EUR 34 (online)  
**Book tickets online at** [www.analytica.de/tickets](http://www.analytica.de/tickets)

The catalog and participating in the analytica Conference are included in the price of admission.

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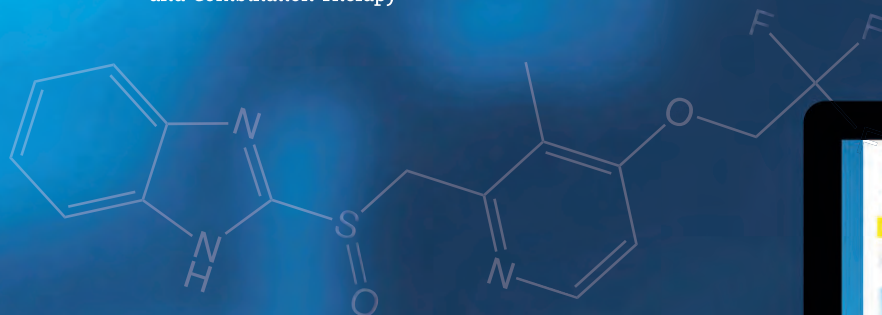
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# From Functional Genomics to Systems Biology

Since 2003, Bavaria has been promoting outstanding research in the field of biotechnology in a remarkable way. Financial funding is provided for large research networks connecting scientists of several different areas, in order to locate research focal points of biotechnology at Bavarian universities and university clinics. Working together in an interdisciplinary manner supports acceleration and increases the total research outcome. The projects of the Bavarian Genome Research Network (BayGene) have firmly established themselves at various universities since their funding period. Their achievements include nearly 400 excellent publications, numerous patents and the foundation of three companies. This clearly exemplifies the relevance of such programs for the Bavarian research environment and its international relevance. Scientific networks are a brilliant symbol of sustainable policy and BayGene has demonstrated excellent visibility among both, regional and international scientific experts. The good news is that this is a continuing positive trend. Several more attractive funding programs followed the example of the Bavarian Genome Research Network, such as BayImmuNet, a research network focused on important questions of future immunotherapy. The Free State



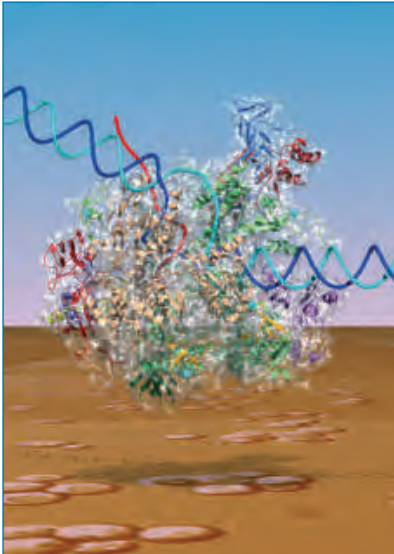
*The member of BayGene and BioSysNet are meeting frequently for joint seminars ■*

of Bavaria has now initiated another groundbreaking program within the Bavarian scientific environment, the Bavarian Research Network for Molecular Biosystems (BioSysNet), which promotes outstanding biotechnological research projects at the forefront of progress. This collaborative research project is a decisive developmental step in the funding strategy initiated with BayGene, aiming to consolidate the competitive edge of Bavarian biotechnology. BioSysNet, which has been in the Bavarian research community since 2012, together with the Gene Center, as well as a recently granted research building, are located under the umbrella of the Centre for

Molecular Biosystems Research. Both BayGene and BioSysNet maintain an active exchange of know-how with scientist across the globe. The international congress "From Functional Genomics to Systems Biology" highlights this correspondence and importance. The members of both networks invite researchers from all over the world to Bavaria in order to discuss current scientific approaches and results. The congress focuses on projects dealing with gene regulation, aiming to elucidate and understand regulatory mechanisms of gene expression and to gain novel insights into the processes and organization of living cells. The observation that a functio-







The functional mechanism of molecular machines are studied at the Gene Center. Polymerase B (Source: Prof. Patrick Cramer) ■

ning system is more than just the sum of individual factors, is the starting point of our researchers to clarify the different areas of regulation within molecular systems.

The conference takes place at the Klinikum rechts der Isar, simultaneously to the internationally renowned scientific fair analytica at the Neue Messe München. This way participants of the conference are also able to attend events related to analytica.

Consistent with the broad range of scientific contents within the BayGene and BioSysNet funded research projects, the main topics of the conference reflect a wide area of molecular and system biology research. In addition to regulatory networks of cells and their proteins, aspects of structural biology are addressed, so as to gain insight into the structure and functional mechanisms of molecular machines. Further elements of the conference include nucleic acid as well as neuronal networks. The above mentioned topics are complemented by questions arising from the translation of this basic research into personalized medicine. Particular focus is placed on approaches from system biology which deal with

clinical issues such as diagnosis and the therapy of cancer, the interaction of pathogens with host organisms and important aspects of immunological research. Hence, the participants can look forward to an exciting and diverse program, which is scheduled to start on 31 March 2014 in the large auditorium of the Klinikum rechts der Isar and ends during the afternoon of April 2. An evening reception with keynote speaker Professor Ernst Ludwig Winnacker is part of the agenda. He will give a lecture to the topic "Common experiences between scientists and artists -are there any?" Registrations are welcome via the homepages of both networks, BayGene and BioSysNet, here more detailed information on the conference can also be found.

Within the context of the conference "From Functional Genomics to Systems Biology" both networks present the results of a successful cooperation. Charles Darwin, born in 1809, has changed our perception of developmental processes with his theory of evolution. His following words could also serve as a slogan for the upcoming event which is organized as a joint effort of both research networks: „In the long history of humankind (and animal kind) those who learned to collaborate and improvise most effectively have prevailed.“

*Charles Darwin* ■

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## Symposium



# From Functional Genomics to Systems Biology

31.03. - 02.04. 2014

Klinikum rechts der Isar  
München



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# Laser as a “Pain Inductor” to measure analgesic effects of pharmaceutical compounds

Pain measurement by sole subjective rating is invalid in patients. Such measures are not suitable for detailed investigation of peripheral and central pain processing and the same holds for the efficacy evaluation of analgesics. But the human black-box should allow additional drug investigations of objectives as general efficacy principles or dose- and time-efficacy.

A major enhancement to measure pain processing and analgesia under the prerequisites “**Induce pain – to measure pain**” was established in the last two decades by introduction of Laser technology. Pain measurements need short-term temperature raises at skin level ( $>43^{\circ}$  Celsius) to overcome the thresholds of heat-sensitive nociceptors to get painful sensation. Such stimulations are only manageable in experimental conditions by Laser devices, used on normal or sensitized skin, introducing local UV or capsaicin exposure to generate somatosensory evoked potentials (SEP) from Vertex-EEG by triggering, filtering and averaging of artifact-free painful stimuli. Long-lasting impacts as slow acting cold-warm and chemical stimulations, but also short-lasting impulses, e.g. electric ones, are no suitable pain triggers and are not devoid of inherent unspecific influences – leading to negative outcomes.

Laser-SEPs can be used for following interpretations:

- Determination of sensory stimulus-intensity relationship (efficacy)

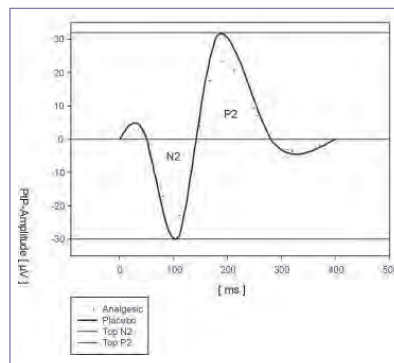


Fig. 1: N2- and P2-amplitude reduction of LEP Principle and amount of analgesic action vs. placebo ■

- Localizing type and pathways of pain-processing (peripheral and/or central preference)
- Quantification and comparison of different analgesics and combinations (dose-and time efficacy)

A similar approach and differentiation can be introduced by the additional use of different skin conditions (normal, UV and capsaicin skin). Further the main components of the Laser signal

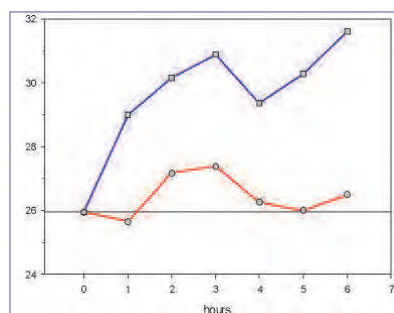


Fig. 2: LEP PtP-amplitude reduction by Pregabalin (red) vs. Placebo (blue) in irritated (sensitized), hyperalgesic (inflamed) UV-B Skin (150mg single-dose) ■

(N2- and P2-amplitude, see Fig.1) can be attributed to predominant peripheral and/or central-spinal pain processing.

Examples for compound classes investigated with the (objective) Laser model up to now are the following:

NSAIDs, opioids, cannabinoids, antihistamines, antidepressants, antiepileptics and diverse blockers, topicals.

The attenuation of Laser-induced pain on UV skin by the antiepileptic Pregabalin (red) vs. placebo (blue) is demonstrated as an example in Fig. 2.

The Laser allows answering of questions on compound efficacy in different types of analgesics with small groups of healthy subjects (e.g. 18 - 24 people) in an ethically acceptable approach without additional impacts on suffering patients in clinical pain situations. Laser studies are time- and cost-saving, can be part of proof of concepts (PoC) in drug development and of Go/No-Go decisions, thus distinctly reducing expenses of subsequent extensive patient studies. ■

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# Basic research for the treatment of inflammatory diseases – bedside to bench and back

Inflammation is a two-edged sword: On the one hand, inflammations are an essential part of the immune reaction. They help to fight infections and assist the process of wound healing. On the other hand, however, they can also damage or even destroy tissues within our body. The latter especially takes place when inflammation becomes chronic. A normal, productive inflammatory reaction starts with the elimination of the disturbing factor, e.g. a pathogen. After that, the inflammation (marked by redness and swelling among others, see box) holds up for some time, in order to heal the tissue damage caused as part of the pathogen activity and immune reaction. Only when the wound has healed does the organism return to its normal state and the inflammation subsides. This shows: Our immune system not only perceives a problem (and starts inflammation) but also recognizes when the problem is solved (and switches off inflammation). A disorder within the balance of activation and deactivation of immune reactions can lead to chronic inflammation, which often implies the damage of healthy organs. There are several possible reasons for this to happen: First of all, the immune system may not be capable of solving a problem. A well-known example for this is asbestos, which is composed of microscopically small, pointed and sharp-edged mineral fibers. Asbestos fibers, once inhaled, can be

Inflammation

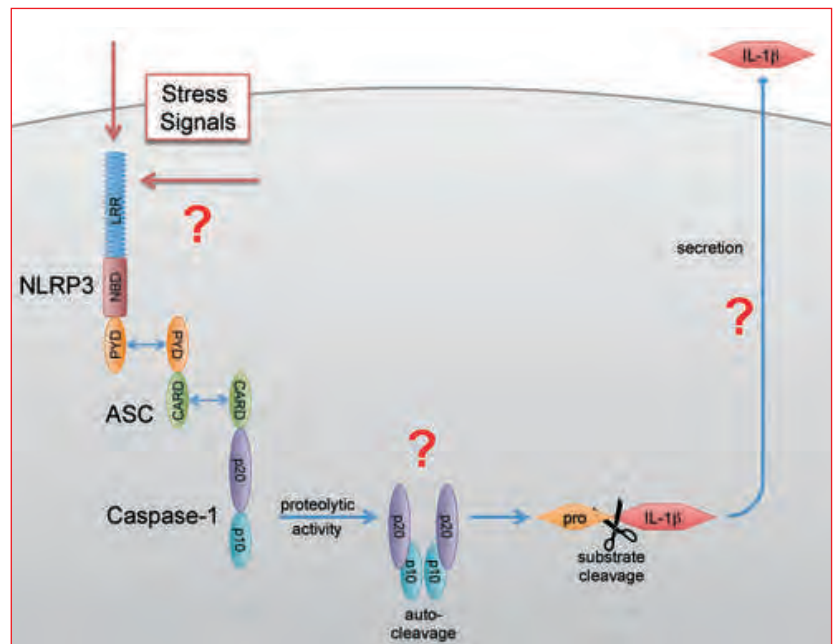


Fig. 1: The cytoplasmic sensor protein NLRP3 reacts to a combination of different cellular stress signals, which leads to the formation of a protein complex consisting of NLRP3, ASC and caspase-1. This complex, called the inflammasome, induces the activation of the protein caspase-1, which in turn cleaves the biological inactive pro-form of IL-1 $\beta$  and thereby generates the active cytokine. IL-1 $\beta$  is then secreted from the cell and induces fever and inflammatory reactions. The question marks indicate the three key questions mentioned in the article ■

neither exhaled nor degraded by our body. However, the fibers are detected as foreign objects by our immune system. Subsequently, immune cells are activated within the lung, which initiates an inflammatory reaction. Chronic inflammation and the development of scar tissue can in turn foster carcinogenesis, which is why asbestos was classified carcinogenic and the use of asbestos was prohibited. A similar situation applies for uric acid crystals, which occur in joints of patients with articular gout. Although these crystals originate within our body, they cannot be degraded. They also trigger inflamma-

tion, causing substantial pain for the patient.

A second possibility occurs when the immune system so to say overestimates a problem and induces an exaggerated immune response. A good example for this is the interaction with our intestinal flora. The bacteria which live in our intestine are essential to our health, as they help with our food intake and prevent the settling of pathogenic bacteria, among others. Thus, our immune systems should recognize and tolerate these normal bacteria. Not only does it tolerate them, it also influences the composition of the flora to our

advantage. However, the “good” bacteria are often only distinguished by minimal differences from “bad” bacteria. Therefore it may happen that the immune system mistakes good for bad and starts an inflammatory reaction against the normal flora. This in turn leads to inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis. To this end, both our individual genetic features as well as our individually distinct intestinal flora seem to contribute. It depends on the favorable or unfavorable combination of genes and flora. This is referred to as multifactorial disease pathogenesis, since not only various organs such as the immune system and the intestine itself (the epithelial barrier) but also environmental factors like the intestinal flora and lifestyle habits matter.

Lastly, the immune system may also initiate an (adverse) reaction without an external trigger, a known example of which is the category of “hereditary periodic fever syndromes (HPF)”. As the name indicates, this is a group of hereditary diseases which often affect more than one family member. Many of these diseases cause symptoms such as spontaneous skin rashes, fever and local inflammation in different organs. In some cases, such as the “familial cold autoinflammatory syndrome (FCAS)”, the outburst of symptoms is caused by cold temperatures. Both the course of this reaction and its mechanistic connection to cold temperatures were widely unknown up to a few years ago. Very often, patients had no other choice than to move to warmer regions in order to completely avoid the cold. The situation for patients only recently improved as a direct consequence of the sequencing of the human genome in 2001. It became clear that many patients with spontaneous fever and inflammatory diseases carry a mutation in the gene NLRP3 (also known as cryo-

**Inflammation** (Latin *inflammatio*) is a coordinated process which is initiated and controlled by immune cells located in all tissues of the body. The immune cells recognize pathogens or injuries and initiate the inflammatory reaction through the secretion of messenger substances (cytokines and chemokines among others). These mediators increase the permeability of blood vessels so that certain factors present in the blood can enter the tissue. Furthermore, the blood flow within the affected tissue is increased and immune cells immigrate from the blood in order to fight an infection. This leads to the typical symptoms of an inflammation, i.e. redness, swelling and increased temperature. Moreover, some messenger substances cause elevated pain sensitivity aiming at the protection of the affected organ. Proinflammatory cytokines such as IL-1 $\beta$  and TNF are essential target structures for the pharmacological treatment of inflammatory diseases.

pyrin). As a result of this new insight, these diseases are nowadays called cryopyrin-associated periodic syndrome (CAPS).

These findings brought the attention of many research groups to NLRP3 and soon it was found out that the NLRP3 encoded protein forms a complex with the proteins ASC and caspase-1 in immune

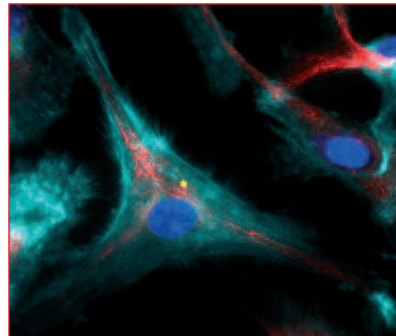


Fig.2 : Inflammasomes (yellow) form large, insoluble complexes upon activation. Dendritic cell, blue: nucleus, red and cyan: cytoskeleton ■

cells and controls the release of the messenger substance interleukin-1beta (IL-1 $\beta$ ). IL-1 $\beta$  is a highly potent pyrogen, in other words, it causes local inflammations and systemic fever reactions. Therefore, the complex consisting of NLRP3, ASC and caspase-1 is nowadays known as the inflammasome, from the Latin *inflammo* = to set on fire – to inflame, and from the Greek *soma* = body – because the complex resembles a protein body, so to say. These groundbreaking findings of basic research revealed that the symptoms of patients with NLRP3 mutations were caused by IL-1 $\beta$ . Thus, a new treatment method was soon after developed which consists of

neutralizing IL-1 $\beta$  e.g. with specific antibodies. After more than 10 years of research we now know that the inflammasome plays a role in many inflammatory diseases.

It may also be activated in the absence of mutations, for example due to the previously mentioned asbestos fibers and gout-associated uric acid crystals. The list of inflammasome related diseases nowadays includes a broad range of disorders such as arthritis, arteriosclerosis, diabetes, cancerous diseases and neurodegenerative diseases like Parkinson’s disease and multiple sclerosis. It is quite surprising that so many widely differing diseases are all associated with the same underlying cellular mechanism, namely the inflammasome. One explanation is that NLRP3 most likely acts as a sensor for cellular stress. The over production of oxygen radicals as well as cellular membrane damage and the impaired degradation of foreign substances (e.g. asbestos fibers) all contribute to the activation of NLRP3. With that said, the inflammasome constitutes a possible mechanistic explanation as to how constant tissue stress can lead to secondary diseases.

At present, the treatment of inflammasome associated diseases is based primarily on the interference with IL-1 $\beta$ , as mentioned above, by injecting patients with so-called recombinant proteins. This method has proven to be both successful and elegant; however, it is also very expensive due to the costly production of recom-

binant proteins. Moreover, some proteins have to be administered daily which is especially unpleasant for children (with children being most commonly affected by hereditary diseases). Instead of interfering with IL-1 $\beta$ , it would therefore be much more sensible to generally prevent IL-1 $\beta$  from leaving its cell of origin. In my research group located at Klinikum rechts der Isar at the Technical University of Munich, we investigate new opportunities of this kind. This project is funded by the Bavarian Research Network of Molecular Biosystems and the EU affiliated European Research Council. We mainly focus on three key questions: First, we try to understand how cellular stress is detected on a molecular level by NLRP3. Second, we want to elucidate how the inflammasome controls the release of IL-1 $\beta$  through its component caspase-1. And finally, we are interested in the general mechanism of IL-1 $\beta$  secretion. These three issues have to be thoroughly understood before we can develop a novel strategy for inhibiting IL-1 $\beta$  release.

Although many basic questions are yet to be answered, the short history of the inflammasome represents a real success story in medicine: An insight gained directly from patients (the discovery of a mutation) has led to a breakthrough in basic research (the characterization of the inflammasome), which before long has helped to develop innovative therapies for the treatment of several other diseases (e.g. gout). For other inflammatory diseases, this process is merely at the very beginning. For instance, our BioSysNet colleagues at the Dr. von Haunersches Kinderspital of the Ludwig-Maximilians-University Munich are investigating and treating children with inflammatory diseases where the cause of the symptoms is entirely uncertain. Under the direction of Prof. Dr. Christoph Klein,



*Äyä's DNA contains one tiny abnormality which makes her ill. Understanding the mechanistic relationship between the mutation and the symptoms could help improve Äyä's and potentially other patients' treatment. (Photo: Verena Müller) ■*

they search for abnormalities within the genome of these children which might be related to the diseases. One of these patients is ten-year-old Äyä. Since birth, she has been suffering from a heavy and virtually untreatable chronic inflammatory bowel disease and has already lost a large part of her colon in numerous operations. The early onset of symptoms is a clear indication for a hereditary disease or else a disease in which a single mutation is the trigger (also called a monogenetic effect). As these diseases are rare and complex, thorough interdisciplinary diagnostics, medical care and treatment are necessary, such as can be provided at the Dr. von Haunersches Kinderspital. In view of the severe disease progression, Äyä was already transferred here during her first months of life. Thanks to the technical progress in molecular genetic diagnostics, it has since been possible to fully sequence and analyze Äyä's genome or more specifically those regions responsible for protein development – a process which not long ago would have taken years and required millions. Indeed, a new genetic defect was identified within Äyä's genome. Meanwhile, mutations in the same candidate gene were detected within three

more children. Although the affected protein was already known, so far it had not been associated with chronic inflammatory diseases. Accordingly, it represents a new and promising research model. Within the context of BioSysNet, Prof. Klein's group now investigates the impact of this mutation on the function of the affected protein. We can only hope that a similar success story to that of NLRP3 and the inflammasome will emerge and that Äyä and other patients will soon have access to effective medical treatment. ■

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# Opening up laboratories with a modular concept



*The most different aspects of “flexible and modular laboratories“ are keeping the industry busy – from the laboratory planner to the manufacturer. Planners even demand “rooms without limits“ to prevent planning unreliability. At the same time, however, modular laboratories are contributing to a sustainable use of the rooms. But how can a laboratory furniture manufacturer meet these requirements? At WALDNER this had been observed under the aspects of flexibility, user friendliness, energy consumption when in operation, and life – and we found a solution: the service ceiling.*

Today it is a key requirement that the user can quickly adapt a laboratory to his needs – and this will continue to be the same also in the future. A modular and therefore also sustainable laboratory enables the customer to work therein or operate it permanently. However, certain laboratories are often only used for projects with an average duration of three years. For the laboratory furniture this means that it will be of use for the customer only as con-

vertible and flexible furniture. Therefore rooms should be best planned as being “convertible“. Such a concept, however, then has to be implemented or equipped correspondingly. This of course also applies for the technical building equipment of heating, ventilation and air conditioning (HVAC).

At WALDNER this requirement had been in the focus of development for a long time. Seven years

ago already (at ACHEMA 2006) the laboratory manufacturer launched the service ceiling into which laboratory services, gases, power supply, IT connection, lighting, air conditioning as well as ventilation systems had been integrated. Due to its adaptability it offers an efficient utilization of the laboratory under the most versatile conditions.

Thanks to the continuous development of the “service ceiling“



Modular laboratory at Luxembourg University ■



component we now have a sophisticated product with which entire floors can be opened up in a modular way. That way a laboratory corresponding to the customer's needs can be created – even if it is required for a short time only – and thus provides utmost benefit for him. The ideal condition also for rented laboratories, start-ups or science park applications. ■

## Spatial metamorphosis

New tasks more and more require an adaptation of the rooms to ever new situations. This can be quickly and easily achieved with the WALDNER service ceiling and the mobile furniture components. Exactly the equipment that is currently needed can be installed and positioned below the ceiling system either in segments or complete – without paying attention to disturbing floor installations and without long installation-related laboratory downtimes. The changes of the installations are executed through the closest connection block, for example.

The areas of a laboratory building are therefore becoming freely designable and usable as the service ceiling requires only a few fixed points. All HVAC components are provided through grids that are subject to a certain grid



Example for room supply through a service ceiling ■

size. This results in a clear separation of the laboratory furniture and the room's installations. A free design of the laboratory area is therefore accompanied by considerably reduced costs for possible room rebuilding measures. The HVAC can be adapted to e.g. ever new requirements through the service ceiling without significantly disturbing the laboratory routine.

Offices and laboratories can be installed next to each other and can be varied in their respective size – by a simple partition and sound insulation system which can be integrated into the service ceiling. ■

## Service ceiling provides solution for your project

When planning laboratory buildings the use of a service ceiling saves expensive, time-consuming coordination of the various installation trades because of clear interfaces towards the laboratory building.

Due to the supply through one point only the service ceiling, which can be distributed across any defined surface, provides all required connections to the service columns of the respective workplaces. This enables a reduction of costs as WALDNER is taking care of the coordination of the various trades' works in each room. ■



Example for flexible furniture components: sliding service column ■

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# Learning from embryogenesis for the battle against melanoma

Black skin cancer (malignant melanoma) is an aggressively growing tumor with a high and continuously rising incidence rate (the sixth most common type of tumor). A cause and effect relationship between the formation of this tumor and intensive sun radiation with frequent sun burns was been established not only through epidemiologic studies, but recently also through experimental approaches. However, it is not sensible to categorically condemn sun radiation. On the contrary, sun light is very important for the production of the essential vitamin D in our skin. Therefore, it is important to strike

a balance between maintaining the essential sustenance of our body and avoiding excessive and strong exposure to sun radiation e.g. during a summer vacation without sun protection.

Informing the public and regular medical check-ups can reduce the severe consequences of a melanoma. If a melanoma is detected at an early stage, it can be cured in most cases by total surgical removal. However, if the tumor has reached a certain penetration depth within the skin tissue, it is far more likely to spread to other parts of the body. The dissemination of tumor cells throughout the body,

the so-called metastasis, is a very early and distinct process in malignant melanoma. With as little as 1.5 mm tumor thickness the patient's risk of developing metastases is greatly increased (*fig. 1*). With a tumor thickness of more than 4 mm, the 5-year survival rate of patients drops below 50%, without even being able to detect metastases when removing the primary tumor. Again, these figures emphasize the importance of regular and thorough check-ups, as patients whose melanoma was removed at a tumor thickness of less than 1.5 mm present an identical 5-year survival rate as the "normal" population.

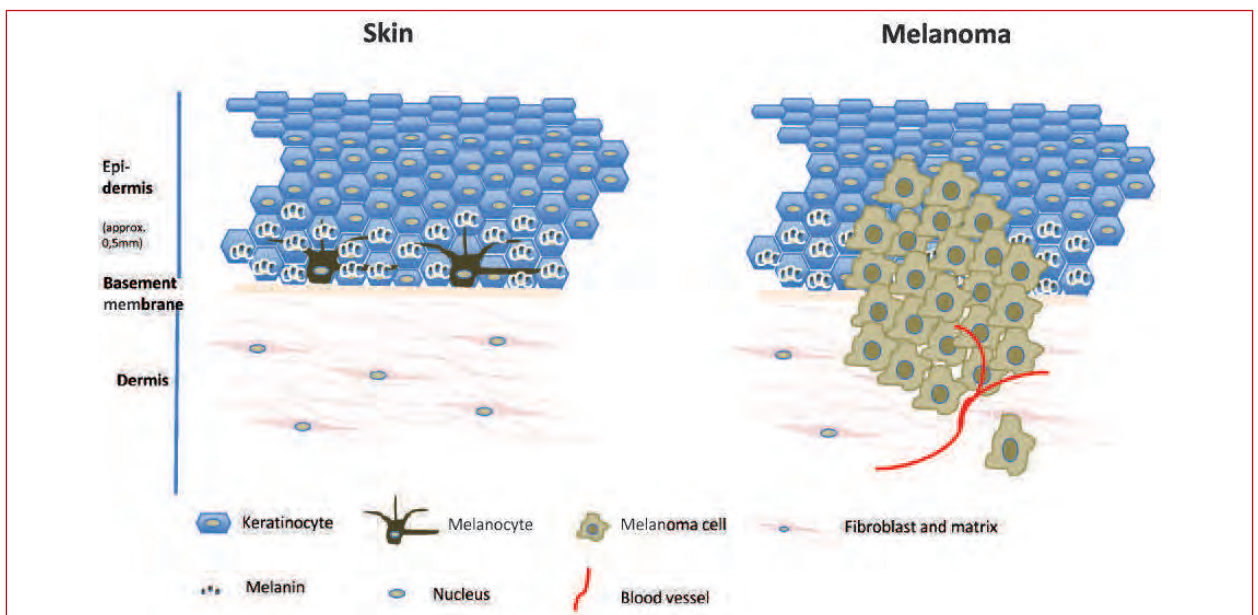
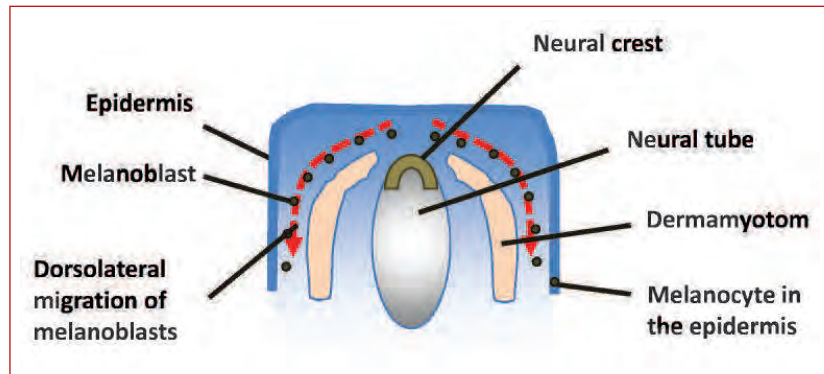


Fig. 1: Schematic illustration of the human skin

On the left side of the figure, the composition of the human skin is shown. The keratinocytes and melanocytes are located in the epidermis; the fibroblasts are located in the dermis. Fibroblasts are matrix-forming skin cells. The matrix molecules provide our skin with high stability. Epidermis and dermis are separated through a basement membrane, which prevents the migration of cells into the corresponding other compartment. On the right side, a melanoma is illustrated. The basement membrane is not able to retain the melanoma cells within the dermal compartment. They have the potential to migrate and invade, in other words they are capable of crossing these basement membrane barriers and can therefore disseminate. The "imposed" tumor supply with blood vessels is also shown ■

Especially with regard to skin tumors, which often attract attention due to their irregular pigmentation, this “protection” through medical check-ups is an easy and efficient way. As described above, in malignant melanoma it is particularly the early and strong metastatic growth which is responsible for a fatal course of the disease, if the tumor is discovered or treated too late. The penetration depth in millimeters proves this in an impressive way. Therefore, it is important for researchers to understand this aspect and to try to reveal the molecular mechanisms behind this aggressiveness. Only after gaining a thorough molecular understanding can we develop novel therapeutic options.

Melanoma cells derive from melanocytes, the pigment cells of our skin. These melanocytes lie within a certain cell layer of our uppermost layer of skin, the epidermis (*fig. 1*). Melanocytes are mainly responsible for producing the dark skin pigment, melanin. This pigment is delivered to the neighboring cells, the keratinocytes, which constitute the majority of the epidermis. In these cells, the pigment is stored around the nucleus containing our genome (DNA). This pigment barrier intercepts harmful rays of sunlight and therefore prevents damage to the DNA. When exposed to strong and continuous sun radiation, our skin or more precisely our melanocytes react with an increased production of melanin, so as to provide improved protection. This process can be observed through the tanning of our skin. If this adaptation is made impossible as a result of too strong radiation or too short time, this important protective mechanism is absent. Unlike other skin cells, melanocytes originate from the neural crest in our embryonic development (*fig. 2*). This structure is located “on the back” of the



**Fig. 2:** Migration of melanoblasts during embryogenesis  
*Schematic illustration of the migration of melanoblasts during embryonic development. The melanoblasts originate in the neural crest and spread to the dermis. They then migrate to the epidermis and differentiate to melanocytes, i.e. pigment producing cells ■*

embryo. Therefore these cells, called melanoblasts during this phase, have to spread throughout the whole body. This kind of distinct effect is very uncommon in most other cell types. Other cell types, for example epithelial cells of the intestine, are already located at the “right position” within the body at a very early embryonic stage and then only develop through controlled growth. In contrast, the progenitor cells of melanocytes, the melanoblasts, possess “tumor like” characteristics during embryogenesis. Similar to tumor cells, they are able to disseminate throughout the body and on top of that overcome barriers between different tissue types, a process which is called invasion. Nevertheless, once these cells reach their destination, they develop into normal, differentiated pigment cells, which are not more inclined to become cancerous than other cell types. We speculate that the strong potential of tumor cells to spread throughout the body is associated with their features in embryonic development. If the potentials of active migration and invasiveness are reactivated within the tumor cell, a very aggressive metastasis follows. We picture this as a kind of “program” which is deactivated in differentiated melanocytes and reactivated in tumor cells. Based on these facts, our idea postulates that only very

few molecular changes are necessary within a melanoma in order to reinitiate these characteristics in melanocytes. Within the context of BioSysNet funding, we are trying to understand these processes as a whole. We believe that with the support of this very active consortium we can follow up on our idea and find molecules which regulate this process. A molecular comparison of melanocytes, melanoblasts and melanoma cells should facilitate the identification of important regulatory molecules, which mediate a rigorous process control in healthy individuals and are lost in a cancerous disease. Ultimately it is our hope that these molecules will serve as therapeutic target molecules, which are then “attacked” in patients in order to suppress the tumor formation and metastasis. ■

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# Innate immune sensing of cytosolic DNA

## Background

A functioning immune system is vital to the defense against pathogens or removal of abnormal cells from the body. From a biotechnological point of view, a tailored use or specific control of the immune system is of paramount importance for the treatment of complex diseases. For example, our own immune stimulatory proteins such as interferons (IFN) can be used in the treatment of chronic viral diseases and cancer, while therapeutic antibodies can recruit immune effector cells to cancer cells for their elimination by specific lysis. However, the immune response can also overreact or target the body's own molecules, which can lead to autoimmune diseases and chronic inflammation such as rheumatoid arthritis, Crohn's disease or multiple sclerosis. In these cases, the targeted inhibition of immune processes could be a possible

therapeutic approach. For the coming years, a key challenge is therefore the development of therapeutic molecules that specifically activate or inhibit immune processes.

The immune system contains "innate" and "adaptive" parts. The "innate" immune system is a first line of defense against invading pathogens and activates – in addition to direct measures against the pathogens – the "adaptive" immune system. In the innate immune system PRRs (*pattern recognition receptors*) sense molecules of the invading pathogens, so called PAMPs (*pathogen associated molecular patterns*)<sup>1</sup>, which activate PRRs through conformational changes and / or by oligomerization. The activated PRRs trigger signal transduction cascades that activate the production of inflammatory cytokines and type I interferons.

The receptors of the innate immune system – in contrast to the clonally highly expanded and selected antibodies – are encoded in the germline and therefore limited in their number. How can this very limited number of PRRs detect a wide variety of pathogens (viruses, bacteria, fungi) without responding to the body's own molecules? Some of the underlying mechanisms are now well understood. On the cell membrane or in endosomal vesicles are for instance Toll-like receptors (TLRs) that recognize PAMPs such as RNA or DNA in the extracellular space or in endosomal compartments and by these means indicate the presence of viruses or bacteria. In addition, there are a number of cytosolic receptors that for example recognize cytosolic viral RNA. However, the specific recognition of cytosolic pathogenic nucleic acids is much more com-

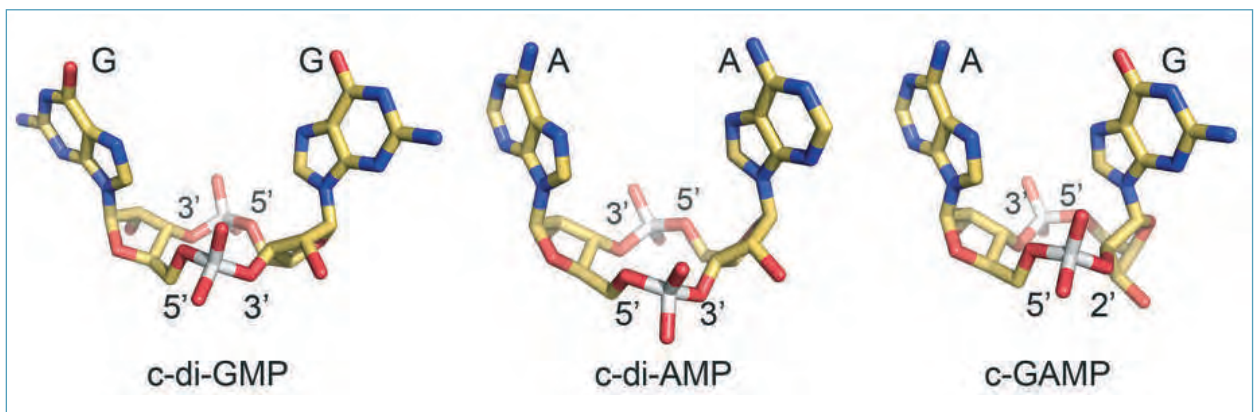


Fig. 1: Cyclic di-nucleotides:

Cyclic bis-(3',5') di-guanosine phosphate (c-di-GMP) and cyclic bis-(3',5') di-adenosine phosphate (c-di-AMP) are second messengers in prokaryotes. Cyclic (2',5'),(3',5') guanosine adenosine phosphate (c-GAMP) was recently found in mammalian cells and mediates the innate immune response to cytosolic DNA ■



plex than monitoring compartments that are normally devoid of nucleic acids, because the cytosol has a large number of different endogenous RNA molecules to which the PRRs should not respond. The specific detection of cytosolic viral RNA is mediated e.g. by RIG-I-like receptors (RLRs), which belong to the class of superfamily 2 helicases/ATPases. RIG-I and the related MDA5 recognize specific molecular features of viral RNA, such as 5' triphosphates or long double-stranded RNA regions. Formation of IFN signal requires also ATP binding or hydrolysis by RLRs and the formation of large macromolecular assemblies (signalosomes). The latter processes are still poorly understood at the molecular level and research in this direction is conducted in the Bavarian research network for molecular biosystems *BioSysNet* ([www.biosysnet.de](http://www.biosysnet.de)). ■

### The innate immune response to cytosolic DNA is mediated by STING

Cytosolic DNA is, in addition to viral RNA, a strong immune activator and stimulates the production of type I interferons. Cytosolic DNA can arise from DNA viruses, retroviruses, damaged mitochondria, intracellular bacteria or leakage of nuclear DNA fragments. Since the selective activation or inhibition of these pathways have interesting medical applications and the innate immune response to cytosolic DNA is also of great importance for basic science, the cytosolic DNA sensor was intensively sought in the past years. The research proved to be extremely difficult and tedious, however, it resulted in the discovery of a new class of second messengers in eukaryotes, cyclic dinucleotides (Fig. 1).

In 2008, the Glen Barber reported with STING (*stimulator of*

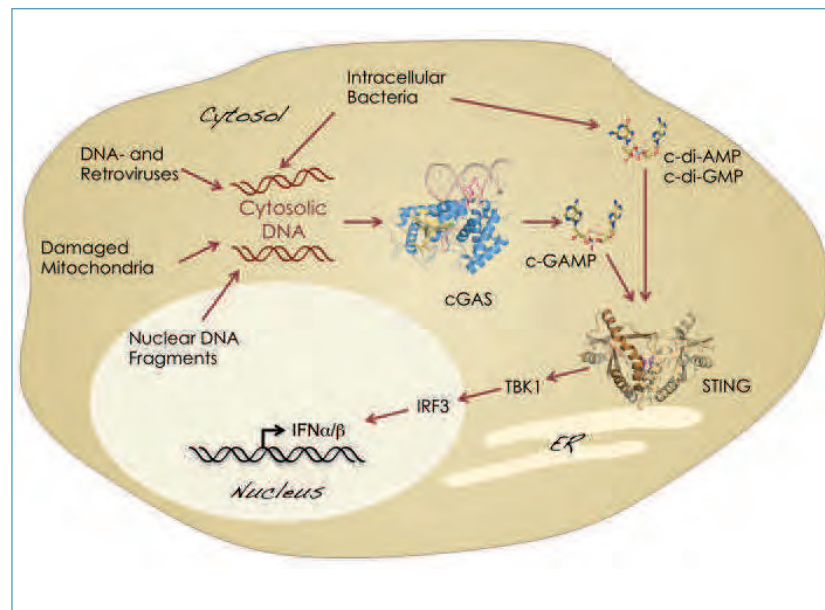


Fig. 2: Innate immune recognition of cytosolic DNA.

Cytosolic DNA is recognized by cGAS. c-GAMP, produced by cGAS, or prokaryotic c-di-AMP as well as c-di-GMP activate through STING, TBK1 and IRF3 the transcription of type I IFN genes ■

*interferon genes*) a central factor of the immune response to cytosolic DNA<sup>2</sup>. STING is a transmembrane protein, which is found predominantly in the endoplasmic reticulum (ER) but localizes to perinuclear vesicles upon by DNA stimulation. In the presence of cytosolic DNA STING activates the TANK-binding kinase 1 (TBK1), which phosphorylates the transcription factor IRF3 in a complex with STING. IRF3 then migrates into the nucleus where it activates the transcription of the IFN genes. However, STING binds DNA extremely weakly *in vitro* and it remained unclear whether STING is a direct sensor for cytosolic DNA. ■

### Cyclic dinucleotides: bacterial second messengers and immune stimulators

Indeed, STING proved to be a direct sensor for a completely different class of molecules. A few years ago, we found that a bacterial DNA sensor has a hitherto undescribed catalytic activity and produces c-di-AMP from two molecules of ATP<sup>3</sup>. In 2010, the Portnoy laboratory showed that c-

di-AMP is secreted by intracellular bacteria (*Listeria*) and stimulates the production of type I interferons<sup>4</sup>. The corresponding receptor proved to be STING<sup>5</sup>. c-di-AMP is structurally related to c-di-GMP, the prototype of cyclic dinucleotides. It consists of two nucleotide monophosphates that are circularly connected by two 3' -5' phosphodiester linkages. c-di-GMP controls motility, biofilm formation and virulence in bacteria, while c-di-AMP is involved in the response to genomic and osmotic stress as well as cell wall metabolism. While diguanylate cyclases, with few exceptions in slime molds, occur exclusively in bacteria, homologs of the diguanylate cyclases identified by us are not only found in bacteria but also in many archaea. Thus, c-di-AMP seems to be phylogenetically more widespread than c-di-GMP. In addition to c-di-GMP and c-di-AMP, c-AMP-GMP was recently described as a bacterial second messenger in *Vibria cholera* and is involved in the colonization of the host<sup>6</sup>. Thus, cyclic dinucleotides appear to be a broader and more diverse class of prokaryotic messengers. ■

### The immunoactivator STING is a sensor for cyclic dinucleotides

Shortly after it was discovered that STING is a receptor for c-di-AMP and c-di-GMP and detects bacterial second messengers in the host cytoplasm, different crystal structures helped to reveal the underlying mechanism. STING forms a dimer with a deep binding pocket for cyclic dinucleotides along the dimer axis (*Abb. 2*). After binding of a cyclic dinucleotide the pocket is closed by two surface loops. This conformational change activates STING for downstream signaling and recruits TBK1 for phosphorylation of IRF3<sup>7</sup>. The deep binding pocket and the induced fit mechanism suggests that STING is a good target protein for the development of small molecule immune regulators. In fact, the research group of Veit Hornung (Bonn) was able to show in collaboration with us that STING can be activated in cells by a low molecular weight substance (10-carboxymethyl-9-acridanone, CMA). Here, two CMA molecules replace the symmetric c-di-GMP in the murine STING binding pocket and cause a similar activating conformational change<sup>8</sup>. ■

### The cytosolic DNA immune sensor is a dinucleotide cyclase

The functional and structural characterization of STING as a direct sensor for bacterial cyclic dinucleotides raised the question how DNA activates STING. End of 2012, the Chen laboratory made a breakthrough in this regard with the identification of cGAS in mammalian cells (cyclic AMP GMP synthase)<sup>9</sup>. After stimulation with DNA, cGAS generates cyclic guanosine adenosine phosphate (c-GAMP), which then binds to and activates STING (*Fig. 2*). Subsequent

work could elucidate the structure of c-GAMP and show that it has instead two 3' -5' phosphodiester linkages, a 3' -5' phosphodiester and a 2' -5' phosphodiester linkage, an important difference to bacterial cyclic dinucleotides<sup>10,11</sup>. These results not only resolved the puzzle how STING is activated by both DNA and cyclic dinucleotides, but revealed that cyclic dinucleotides are also endogenous immune activators in humans. ■

### cGAS and OAS1 form a new family of immune sensors

How does cGAS recognize DNA? The structure of cGAS without and in complex with DNA showed that it is a member of the nucleotidyl transferase family<sup>11,12</sup>. However, cGAS has some unique structural features including a pronounced positively charged surface. B-form DNA binds to this surface with both backbone strands in a sequence independent manner, which explains how cGAS can detect a broad class of DNA ligands. Interaction with DNA leads to a conformational change in the enzyme, which results in a correct positioning of the GTP and ATP substrate molecules in the active site. cGAS catalyzes first a 2' -5' linkage between GTP and ATP followed by cyclization to c-GAMP. Interestingly, the crystal structures revealed that cGAS is related to 2'-5' oligoadenylate synthase 1 (OAS1). OAS1 generates upon binding to double stranded RNA 2'-5' linked oligoadenylates that activate the antiviral RNase L. Thus cGAS and OAS1 form a new class of evolutionarily related cytosolic nucleic acid receptors (OLRs: OAS1 - like receptors) that fight viral infections via the formation of 2'-5' linked nucleotide messenger. ■

### Outlook

The elucidation of the mechanisms of cytosolic DNA-mediated immune responses and the expanding number of different cyclic dinucleotides in prokaryotes and eukaryotes create a wealth of possibilities for intervention in the immune system and in the physiology of pathogens for therapeutic purposes. The role of bacterial cyclic dinucleotides in colonization and virulence open new ways to diminish e.g. virulence with low molecular weight antagonists and may help the immune system to overcome infections without creating resistance. In this regard, the c-di-AMP system is very interesting as target because c-di-AMP is essential in contrast to other dinucleotides. Ultimately, the newly identified molecules CGAs and STING due to the chemical structure of their substrates or ligands are promising targets for the development of small molecule activators or inhibitors for therapies around the immune system. ■

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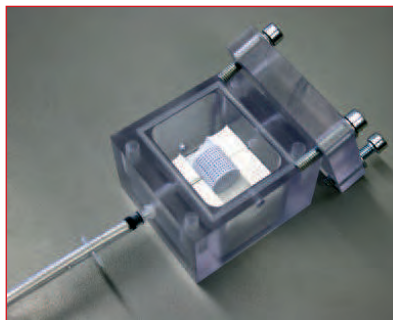
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	<p>We are conscious about both the headaches of your development staff as well as the limited scope in which you, as a project manager, have to make decisions. Use our know-how to make your project a success within the designated time and regarding the cost factor.</p> <p style="background-color: #0056b3; color: white; padding: 5px; text-align: center; font-weight: bold; font-size: 1.1em;">Project Management</p>	<p>your partner: Michael Hojnacki</p>

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# Friedrich-Baur BioMed Center in Bayreuth – finding tomorrows solutions for your health

The Friedrich-Baur BioMed Center in Bayreuth advances medical innovations to promote their transfer into clinical application and provides a biomedical research and development center for Upper Franconia at the University of Bayreuth. As a non-profit enterprise, it is part of the extensive promotion of health research by the Friedrich-Baur-Stiftung. Here, the Orthopedic Clinic and Polyclinic Großhadern (LMU) led by Prof. Jansson is an important partner. Going further, the Friedrich-Baur BioMed Center in Bayreuth collaborates with physicians and medical professionals throughout Germany. The experience of 15 years of research and development in the area of biomaterials at the former Friedrich-Baur-Institute for Biomaterials has also been integrated into the new center. We strive to realize promising approaches that emerge in the high-tech-region of Upper Franconia and transform them into new solutions for medicine and medical technology. We are supported by an academic research group at the Chair of Animal Physiology led by Prof. Schuster at the University of Bayreuth, which has been established as an interface between application and basic research. The modern analytical equipment, especially in the area of material sciences, the biological cell lab with its extensive experience in the characterization of biomaterials and the close connection to the University of Bayreuth make the FB BioMed Center a popular partner for enterprises in the region. This comprises analytical services as well as contract research,



*Sensor-integrated bioreactor with synthetic bone substitute sample, setup to monitor cell growth via pH and oxygen content ■*

which are conducted regularly. The cell lab analyzes material surfaces and three-dimensional constructs regarding their biocompatibility and their behavior towards cells and tissues. To this end, the lab has established cell and tissue cultures of cartilage and bone cells (e.g. osteoblast-osteoclast cocultures), vascularization models (CAM-assay) as well as neuron cultures. It has developed proprietary bioreactor systems with integrated biosensors, which are also being sold. ■

### *Answers from the lab – in vitro methods help animals and researchers*

In one of our projects – funded by the Swiss foundation AnimalFree-Research – we develop a standardized procedure for the selection of bone substitute materials consisting of a series of in vitro assays to determine osteoconductivity and osteoinduction, cellular resorption and vascularization. Furthermore we use neuron cell cultures to monitor the formation of neurons on biomaterials and the influence of pharmaceuticals and growth factors, applying the full range of methods in modern neuro-

biology. Our in vitro methods are optimized to allow a reliable selection of biomaterials based on tightly controlled, standardized and reproducible conditions and circumvent many limitations of animal experiments in addition to providing much more detail. Our methods thus not only substitute the common use of small animal models, which are limited in significance as to bone research, they also provide much more meaningful and faster in vitro assays in which we can preselect novel materials – a better way for both animals and humans. ■

## Friedrich-Baur BioMed Center



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