Biotechnology in Bavaria

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Health Industry of Regensburg

- 1.4 billion Euro turnover
- 15,500 employees

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Editorial

Biotechnology continues on course for success in Bavaria

The numbers and awards speak for themselves. On its 20-year anniversary (see Foreword by Dr. Horst Domdey), the network organisation Bio^{M} reported a steady and sustained upward trend of the entire biotechnology sector in Bavaria.

The scientists Prof. Karl-Peter Hopfner and Prof. Jörg Vogel were accorded special honours for funded BioSysNet projects. They each received the coveted Gottfried Wilhelm Leibniz Prize for Outstanding Work.

Interesting topics along the biotechnology value chain document the high standards of Bavarian companies in terms of research, development, and application:

- What key role do bio sciences play in the 21st century and which companies benefit and profit from optimal framework conditions?
- How can new, targeted therapeutic approaches be identified by research into disease mechanisms?
- Where can RNA biology be used against infections?
- Which protein makes organisms female and determines the basis for genetics, developmental biology, and immunity?

High hopes are attached to Bavarian biotechnology. There are many reasons to be optimistic about the future.

Managing Director

This publication is also available online at www.media-mind.info

Masthead:

Publisher:	media mind GmbH & Co. KG Hans-Bunte-Str. 5 80992 Munich/Germany Phone: +49(0)89/23 55 57-3 Telefax: +49(0)89/23 55 57-47 ISDN (MAC): +49(0)89/23 55 57-59 E-mail: mail@media-mind.info www.media-mind.info
Managing director:	Walter Fürst, Jürgen Bauernschmitt
Design + DTP:	Jürgen Bauernschmitt
Prepress:	media mind GmbH & Co. KG
Responsible editor:	Ilse Schallwegg
Published annually:	1 x annually
Printed by:	Druckerei Frischmann, Amberg

Inhaltsverzeichnis

accelerating biomedical innovation

Bio^{M} for BioEntrepreneurs

we guide you from idea to success

- Mentor Circle
- Pitch Doctor
- Boot Camp
- BioEntrepreneur Lounge
- BioAngels
- m^{4} Award

www.bio-m.org

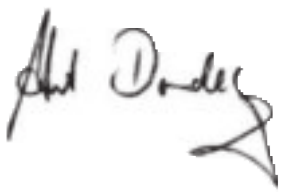
Foreword
Prof. Dr. Horst Domdey

Bio^{M}, the network organization for the biotechnology sector in Munich and Bavaria, is celebrating its 20th anniversary this year. Also the entire biotech sector in Bavaria is recognizing its anniversary – as the award in the BioRegio competition in 1996 and the following foundation of Bio^{M} presented the starting point of the location. Even though pioneers as Mikrogen (1989), MorphoSys (1992), Micromet (1993) and Medigene (1994) already existed earlier, a real founding boom started in the late 90s. Over the past 20 years, Bio^{M} has advised and accompanied more than 200 companies. Today, the sector is in a very strong position: it includes 360 companies in the biopharmaceutical field (biotechnology, pharmaceutical companies, contract research organizations, suppliers and others), thereof 225 specific biotech companies. This means that the sector shows a solid and versatile structure along the value chain in pharma industry, including production. The sector employed a total of 32,000 people in 2016. This corresponds to an increase of 4% over the previous year. The number of start-ups rose from three in the previous year to ten in 2016. The dynamic growth of the young industry is based on the excellent research facilities in Munich. More than 90% of business start-ups originate from university and non-university research institutes in the fields of biology, chemistry, medicine, pharmacology and physics. The founders were, are and will be the drivers of innovation in the sector. Bio^{M} provides a comprehensive and tailor-made offer for biotechnology start-ups from the very first steps right up to the market entry.

Bavaria offers perfect conditions particularly in red biotechnology. We are very proud that already eight drugs developed by Bavarian biotech companies (SMEs) reached market approval. With the main topic personalized medicine industrial and academic research has their fingers on the pulse of time. But we must not stop constantly developing innovative solutions. Great hopes are vested in the strong Bavarian competencies in the fields of immunotherapy, stem cell research and digital medicine, to name a few relevant topics.

I am very hopeful that Bavaria will significantly shape the “medicine of the future”.

Yours sincerely
Horst Domdey



Prof. Dr. Horst Domdey
Managing director of Bio^{M} Biotech Cluster Development GmbH and spokesman of the Bavarian Biotechnology Cluster

350 guests celebrate 20 years of Bio[M]

On April 27, 2017, Bio[M], the network organization for the biotechnology sector in Munich and Bavaria, was celebrating its 20th anniversary. 350 guests from industry, science and politics came for the ceremony event to the Max-Planck-Institute in Martinsried.

With the words: „the king is dead, long live the king“, Prof. Dr. Horst Domdey, managing director of Bio[M], opened his welcoming speech. He surprised the audience by announcing that the liquidation of the Bio[M] AG was decided the day before. But the Bio[M] AG represents only the financial arm of the corporation.

There is little interest in the instrument for start-up financing in the range from 100.000 to 200.000 Euro for newly founded companies, explained Horst Domdey. „Over the years, the High-Tech Gründerfonds and Bayern Kapital took over this function and provide sufficient capital for young companies in the Free State.“

Prof. Dr. Horst Domdey, managing director of Bio[M] (1st from left) along with congratulators. Dr. Manfred Wolter, Head of Section at the Bavarian Ministry of Economic Affairs (2nd from left) and Josef Schmid, Deputy Mayor of Munich (1st from right) gave opening speeches. Prof. Dr. Ernst-Ludwig Winnacker, Professor Emeritus, LMU München (2nd from right), gave the keynote of the evening ■

Prof. Dr. Horst Domdey, managing director of Bio[M], presented highlights of the last 20 years and current business figures of the Bavarian Biotech sector ■

The core activities of the Bio[M] GmbH will continue unchanged. Instead of financial support Bio[M] offers a comprehensive programme for founders and young companies, profound consulting in funding issues, suitable contacts and a large variety of events. „In the past two decades we created perfect conditions and a functioning network to bring our life sciences

companies in a perfect starting position", Horst Domdey said. „For our incubation programme InQLab we received the award „Clustererfolg 2017" of the nationwide programme go-cluster only last week."

Additional greetings were delivered by Head of Section Innovation, Research and Technology (StMWi) Dr. Manfred Wolter in behalf of Ilse Aigner, Bavarian State Ministry, and the Deputy Mayor of Munich, Josef Schmid. Prof. Dr. Ernst-Ludwig Winnacker gave the scientific keynote of the evening. He summarized the last twenty years of research in life sciences and expressed his delight to be part of these revolutionary times.

Subsequently a panel discussion focused on questions relating to location development and business support. In addition, Horst Domdey presented the business figures of the current Biotechnology Report. The managing director of the biotechnology network talked about his future plans for the Munich Biotech Cluster. He elucidated his vision for Munich as European Center of Excellence for healthcare of tomorrow.

Panel discussion with Dr. Viola Bronsema, managing director BioDeutschland e.V.; Dr. Helmut M. Schühsler, managing partner TVM Capital GmbH; Mathias Renz, Going Public Media AG (moderator); Dr. Peter Zobel, managing director Fördergesellschaft IZB mbH; Dr. Garwin Pichler, managing director Preomics GmbH; Dr. Simon Moroney, charmain MorphoSys AG (from left to right) ■

He furthermore introduced three current projects of Bio^{M}: InnoMuNiCH (a support network for German-Japanese cooperation concerning personalized medicine), ImmPact Bavaria (a network of Bavarian biotech companies with focus on immunotherapy) and DigiMed Bavaria (intelligent networking of patient and research data).

At the end of the evening the guests enjoyed a piece of birthday cake and had a drink together on another 20 years of Bio^{M}. ■

About Bio^{M}

Bio^{M} is the central network organization for the biotechnology sector in Munich and Bavaria and is supporting the sector in a variety of ways. The not-for-profit cluster management has built up an extensive national and international network and promotes the interaction between small and medium-sized companies in Bavaria and external companies and investors, as well as other players. Bio^{M} offers a wide range of seminars and events for the biotech industry, especially for company founders. The information portal at www.bio-m.org, offers an extensive company database, news updates and a job forum. ■

350 guests from industry, science and politics were celebrating the 20th anniversary of Bio^{M}, the network organization for the biotechnology sector in Munich and Bavaria ■

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Innovation and Start-up Center for Biotechnology (IZB)

The Bavarian State Government recognized early on that biosciences would play a key role in the 21st century. By establishing the Innovation and Start-up Center for Biotechnology (IZB) between the Martinsried and Großhadern Campuses, where 16 institutes such as the Max-Planck-Institutes of Biochemistry and Neurobiology as well as the Ludwig Maximilians University are located, it has found the best possible conditions for young biotech start-ups. In 1995, this was the cornerstone for a science center that today has reached international renown.

The two Innovation and Start-up Centers for Biotechnology, located in Planegg-Martinsried and Freising-Weihenstephan, are home to over 60 biotech companies with over 600 employees. The location Planegg-Martinsried, now spread over 23,000 m^2, is the site for start-ups focusing on medical biotechnology. Since 2002, the IZB in Freising-Weihenstephan, with a campus of 3,000 m^2, offers optimal conditions for company start-ups in the area of life sciences. Since 1995, the Innovation and Start-up Center IZB has seen more than 150 company foundations. The successful evolution of the IZB companies is reflected in some exceptional financing rounds: more than 51,6 million Euros were acquired by IZB companies through financing rounds, funding and licensing agreements in 2016.

An important criterion for the success of the IZBs is the close proximity to top research on the campus as well as the great infra-

The Faculty Club G2B is the core element of the IZB Residence CAMPUS AT HOME ■

The IZB on the Hightech-Campus Martinsried ■

structure. The Faculty Club G2B (GATEWAY TO BIOTECH), which opened in October 2014, serves as a communication center for board members and CEOs of the IZB companies, as well as professors of the Campus Martinsried, to holding briefings, discussions and events. The aim, to intensify dialogue between top researchers, is being accomplished. The Faculty Club is located on the seventh floor of the IZB Residence CAMPUS AT HOME and offers a great view of the Campus and the Alps.

The seven-storey IZB Residence building with 42 modern-designed rooms provides accommodation for visiting scientists and entrepreneurs from all over the world. The Restaurant SEVEN AND MORE, located on the ground floor of the Campus Residence, spoils you with French cuisine. The Café/Restaurant Freshmaker, located in the main building of the IZB, sets standards with its international cuisine.

Settling the Chemical School Elhardt at the IZB introduced a new way to combat the shortage of skills. It is now possible to train biological technical assistants directly on campus. The trainees, undergoing internships at IZB companies during their apprenticeship, are often able to find a job there as well – that is how such skills stay at the IZB.

Nowadays, more and more highly qualified employees want to combine a career with family. This is often frustrated by the problem of childcare. To solve this, the IZB built the childcare centers BioKids and BioKids[2]. The extraordinary concept of these establishments has been awarded the nickname, the "house of little scientists". ■

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Coriolis Pharma is a globally operating independent service provider for research and development of (bio)pharmaceutical drugs (proteins, peptides, monoclonal antibodies, RNA/DNA etc.) and vaccines.

An interdisciplinary team of highly qualified scientists with many years of experience in the development of (bio)pharmaceuticals supported by an expert scientific advisory board and state of the art analytical methods provides cutting-edge service and know-how related to the formulation development of biopharmaceuticals.

This may involve for example formulation development of (pre-)clinical material through to commercial products, lyophilization processes, stability testing, supply of pre-clinical material, and analytical services using innovative analytical technologies for higher order structural characterization, aggregation and (sub)visible particle testing, including Circular Dichroism spectroscopy (CD), analytical ultracentrifugation (AUC), Field Flow Fractionation (AF4/HF5), Micro-Flow Imaging (MFI), and Resonant Mass Measurement (RMM). Selected methods are established in full GMP compliance. ■

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Custom synthesis of Oligonucleotides

ELLA Biotech is an internationally active private biotech company with a focus on the synthesis of high quality special oligonucleotides for use in diagnostic and library sectors.
A fundamental premise for ELLA biotech lies in a close working relationship with its customers, in order to fulfill defined synthesis standards and quality criteria, as well as to continually improve production processes.

The company's portfolio includes (amongst others):

- *primers & probes for use in Diagnostic applications according to ISO 13485*
- *library oligonucleotides based on TRIMER-Technology for random mutagenesis*
- *long DNA (up to 200 bases) and RNA (up to 150 bases)*
- *large Scale Synthesis (DNA and RNA) – up to several hundred µmol final yield*
- *LightCycler®-Probes, aptamers, PTO (Phosphothioates), probes for epigenic sequencing (mC, hmC)* ■

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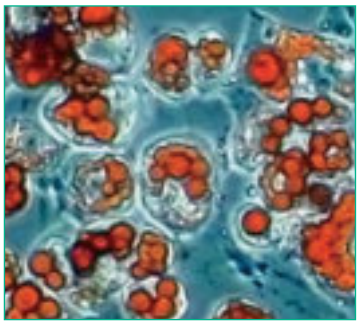
Quantitative high-end mass spectrometry for proteomic target identification and biomarker development

Evotec (München) GmbH, an affiliate of Evotec AG, has built up an excellent reputation as a research service provider for global operating pharma and biotech companies.
Through the application of



state-of-art chemical and global proteomics technologies, Evotec (München) GmbH delivers a comprehensive analysis of compounds in complex cellular systems as well as the identification of new drug targets, thus supporting its customers in the development of small molecules that are selective and with few side effects, in mode-of-action analysis of compounds, as well as in the identification and verification of molecular biomarkers. ■

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exosomedx

Exosome Diagnostics is developing and commercializing revolutionary biofluid-based diagnostics for use in personalized medicine and collaborates with pharma companies to develop sophisticated companion diagnostics (CDx).

Exosomes are messengers released by all living cells into biofluids such as blood, urine and cerebrospinal fluid and provide a stable source of cell-specific intact nucleic acids and proteins.

The company's novel exosome-based technology platform, ExoLution™, can yield comprehensive and dynamic molecular insights to transform how cancer and other serious diseases are detected, diagnosed, treated and monitored.

The European subsidiary at the IZB in Martinsried conducts product development and performs *in-vitro* liquid biopsy diagnostic tests in the ISO 15189 accredited clinical testing laboratory.

For more information, please visit www.exosomedx.com

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origenis

CNS Kinase Plattform

Origenis is a leader in small molecule drug discovery with over 17 years of experience in the field. Origenis is a privately owned company based in Martinsried, Germany.

Origenis has developed a proprietary drug discovery technology platform, MOREsystem®, to generate novel small molecules with predefined properties through a fully integrated process that combines computational design (MolMind®), chemical synthesis, biological, pharmacological, physico-chemical analysis, and patentability assessment (Cippix®).

Origenis targets kinases in the brain to fight neuroinflammation and neurodegeneration in various diseases.

Origenis CNS kinase platform delivers highly potent, selective kinase inhibitors that cross the blood brain barrier and address important disease targets in the brain. Preclinical Candidates are identified for the different targets with high potency, selectivity, bioavailability, and in vivo brain penetration.

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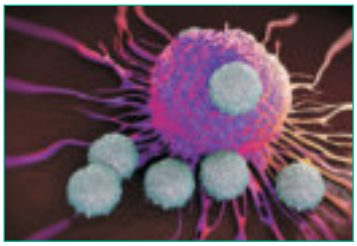
RIGONTEC

Harnessing one of the most essential pathways in the innate immune system to generate effective therapies.

Rigontec is the leader in RIG-I targeting RNA therapeutics. Utilizing our proprietary RIG-I agonist platform, we harness one of the most essential pathways in the innate immune system to pioneer a novel immuno-oncology treatment approach.



Rigontec's proprietary agonists specifically activate RIG-I, inducing both immediate and long-term anti-tumor immunity and have proven substantial local and systemic tumor regression in several relevant in vivo models.

In addition to malignant diseases, our innovative bifunctional RNA molecules can be developed for the treatment of infectious and inflammatory diseases. ■

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The BioPark in Regensburg

With the foundation of BioPark Regensburg GmbH in 1999, the City created a further catalyst for the emerging future-oriented sector. With support from the State of Bavaria, the Federal Government and the EU, the BioPark was erected for 42 million € in three construction phases (2001, 2006 and 2011) directly on the grounds of the University. The multifunctional buildings offer together on 18,000 sqm state-of-the-art laboratory, office and storage space for companies and institutes from the fields of biotechnology, pharma, medical technology, analytics/diagnostics, healthcare and associated service providers. In addition to the use of the university infrastructure and short distances on-site, its own motorway access enables a direct and rapid link to Munich, Frankfurt and Berlin. Currently there are 33 leaseholders with 561 employees active at the BioPark. In the BioRegion Regensburg there are currently 50 companies with 3,872 employees.

Successes "Made in Regensburg"

In 2014 BioPark Regensburg celebrated its 15 year anniversary. During this period 254 million €, of which 102 million € in venture capital, were invested in the development of "life sciences". The return of investment has proved remarkably successful. Since 1999 37 companies have been accompanied from their very start and the number of employees in the region has increased almost tenfold to 3800. The company Geneart AG was the first BioPark company to be listed on the Frankfurt Stock Exchange and in 2014 became part of the Thermo Fisher Cooperation. ■

Research at the University Campus Regensburg

With the University, the Institute of Technology and the Medical Centre, Regensburg possesses the youngest and most modern institutes in Bavaria. With currently around 8,000 employees and approximately 33,000 students, they definitively had a lasting effect on the momentum of this business hub on-site in recent years.

Furthermore research institutes are also situated next to companies at the BioPark. In 2001 the Competency Center for Fluorescent Bioanalytics of the University of Regensburg was established here. This was followed in 2005 by the Center for Medical Biotechnology. Since 2008 the Fraunhofer Project Group for Personalized Tumor

Successful Innovation Center on the Danube ■

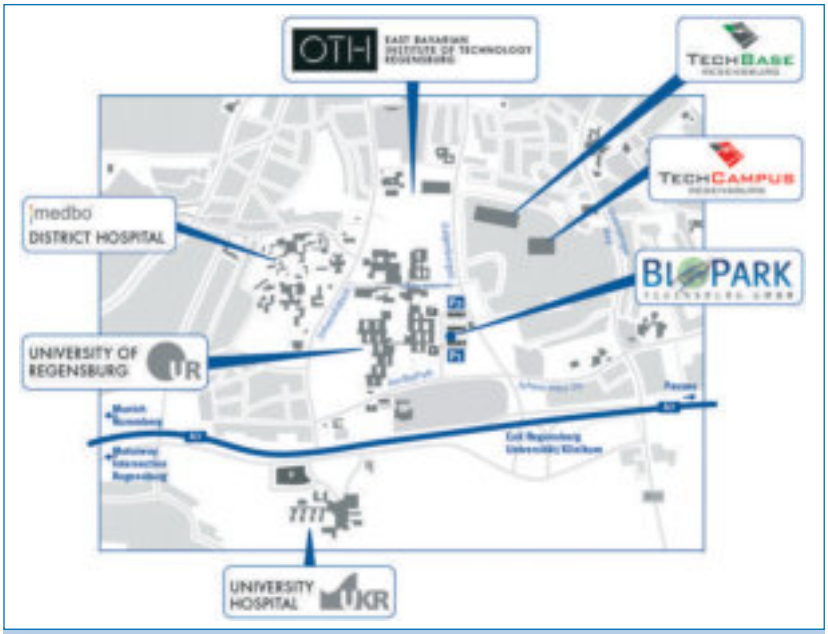
Therapy has been located here at the BioPark and since 2011 the Fraunhofer Project Group for Sensor Materials as an external university research unit. In 2013 the Regensburg Center of Biomedical Engineering (RCBE) of the East Bavarian Technical Institute (OTH) moved its laboratory premises to the BioPark. Since 2014 the Regensburg Center for Interventional Immunology (RCI) has had its premises at BioPark Regensburg. ■

Production in the Region

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

Interdisciplinary Strengths

With a location analysis and workshop events regional interdisciplinary fields were identified in the region and projects initiated with companies from the glass industry, engineering, electrotechnology, textiles and foodstuffs. Through this new cross-technology the momentum in the cluster has been able to be increased by a 13 further regional companies. A further aspect is the sensory technology cluster platform from Initiative Allianz Bayern Innovativ which is driven from Regensburg. This has gotten further networks to optic technology in medical photodynamics (OTPD) and to food safety and sterilization (LETEK) off the ground. ■



33,000 students and 8,000 employees work on the Regensburg Campus ■

New Project in Healthcare for the Region of Regensburg

In the current project the BioPark is coordinating a further expansion of its cluster activities in the field of healthcare with the integration of the six clinics on-site. Following an extensive location analysis, this was followed by workshops on the topics of cellular therapy and oncology, digitalization, an ageing society, skilled personnel and training, location marketing and business development, as well as start-ups and innovation. Currently a masterplan is being developed to capture the potential of this economic sector and outline the opportunities for the region. Regensburg is booming as a healthcare city. The entire industry currently gives 15,500 people work and has generated most recently a total turnover of 1.4 billion €. ■

BioRegio Regensburg, (updated March 2017)

Biotech Companies

2bind GmbH

(in the BioPark, founded in 2011, 8 employees) offers customers from pharma and biotech various biophysical analytical services. Besides studies of molecular interactions using the innovative MicroScale Thermophoresis (MST), we offer analyses of protein folding/stability using the nanoDSF technology.

Active Motif GmbH

(in the BioPark, founded in 2005, 2 employees) develops and produces fluorescent dyes, nanoparticles, LED compatible fluorophores and fluorescence-conjugated molecules.

Assay.Works GmbH

(in the BioPark, founded in 2016, 3 employees) Contract research organization, developing and executing tailor-made and scalable assays for bioactivity quantification in pharmaceutical, biotech and academic research.

BioEnergy GmbH

(founded 2007, 5 employees) does R&D in the field of fermentation.

BioGents AG

(founded in 2002, 18 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, 12 employees) is a laboratory for microbiological and

chemical analysis - dealing with the analysis of water, hygienic control and providing microbiological analyses of pharmaceutical products, medical devices, cosmetics and food.

ButSoEasy GmbH&Co.KG

(founded in 2014, 4 employees) offers services in the field of blood diagnostics. By a special kit it is possible to take the blood sample and to send it in the lab by yourself. The laboratory results can be accessed online.

CASCAT GmbH

(founded in 2014, 5 employees) deals with the chemo-enzymatic conversion of biomass into basic and fine chemicals.

Davids Biotechnologie GmbH

(founded in 1996, 8 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. Transiente transfection of cells in cell cultures and purification of the produced proteins. Development of diagnostic methods and cell bases diagnostic methods.

Delphitest GmbH

(founded in 2004, 4 employees) works on DNA diagnostics and focuses on paternity tests and other genetic analyses for private customers.

hepacult GmbH

(in the BioPark, founded in 2002, 1 employee) 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.

At the BioPark there are start-up companies, university institutions, firms from Germany and abroad as well as service providers ■

Iris Biotech GmbH

(founded in 2001, 17 employees) is specialized in reagents for peptide synthesis, polymeric carriers for drug delivery (PEGs) and products for life science research. Products are being supplied from grams for research to multi-ton lots for commercial productions (approx. 6500 products).

Iris Biotech Laboratories GmbH

(founded in 2013 by Iris Biotech GmbH, 4 employees) is a chemical laboratory with specific know-how in synthesizing chiral compounds, hydrophilic polymers and other fine chemicals. The majority of the work is contract research, process development and custom synthesis.

Labor Friedle GmbH

(founded in 2003, 100 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, 17 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, 20 employees) focuses on the development and marketing of innovative immune diagnostic systems to improve therapy control and personalized treatment of patients in the area of transplantation, infectious and autoimmune diseases. The company's developments are based on its expertise in cell-mediated immunity as well as on its proprietary T-activation® and Reverse T Cell Technology platforms.

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 HEALTH

(in the BioPark, founded in 2004, 65 employees) develops and markets integrated test systems for human diagnostics. The fully automated numares systems provide information about formation, extent and severity of diseases in high throughput operations. They ensure improved treatment options at high patient safety and cost-effectiveness.

Oxford BioLabs Deutschland GmbH
(in the BioPark, founded in 2009, 2 employees) is a science-based company tackling Androgenetic Alopecia (AGA), which is commonly known as male and female pattern baldness. The company is developing novel effective health and beauty therapies to help people stay young and healthy longer and to extend their quality of life.

PAN-Biotech GmbH
(founded in 1988, 56 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-Seratech GmbH
(founded in 2016, Subsidiary of PAN Biotech GmbH) develops, produces and markets biotechnological products all around the cell culture.

PolyQuant GmbH
(founded in 2007, 8 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, 87 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.

RAS AG
(founded in 2016, 20 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. Legal sucessor of rent a scientist GmbH (founded in 1995) and ras materials GmbH (founded in 2010).

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).

Thermo Fisher Scientific GENEART GmbH
(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 GeneArt belongs to the US-based Thermo Fisher Scientific Inc.

Life Science Firmen

Bionorica SE
(founded in 1933, 933 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 medicines 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, enzyms, 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, 39 employees) The company offers services in the field of chemical process development and synthesis of chemical intermediates and active substances.

FIT Production GmbH
(founded in 1995, 21 employees in medical technology) is a company of the FIT Additive Manufacturing Group and has specialized in additive engineering, serial production, mass customization and single part manufacturing in industries such as automotive and motorsports, aviation and aerospace, mechanical engineering and medical technology.

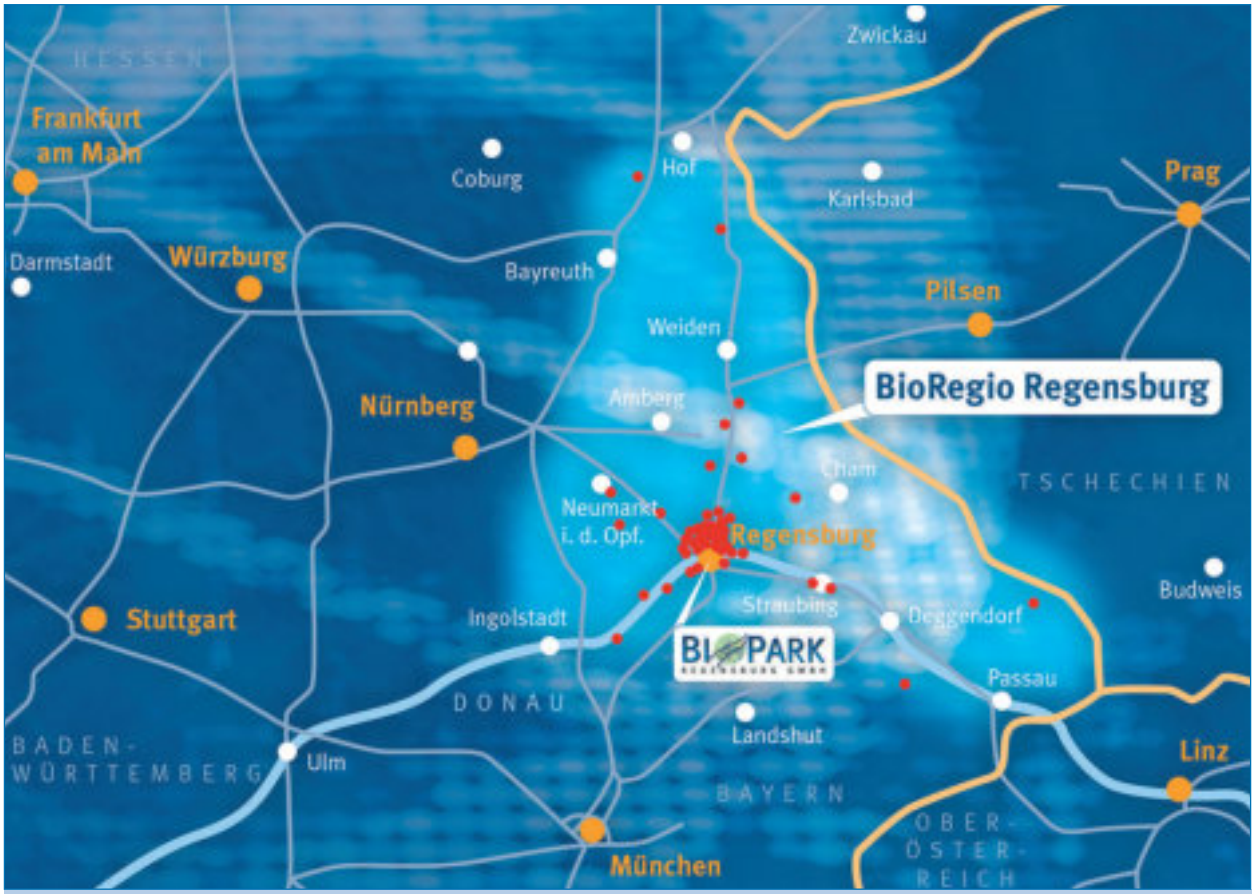
Gerresheimer Regensburg GmbH
(350 employees in medical technology in Bavaria) a leading company in the business fields of tubular glass, moulded glass, life science research and plastic systems.

Haupt Pharma Amareg GmbH
(founded in 2003, 400 employees) Focus on pharmaceutical contract manufacturing (GMP production, packaging of solid enzyme products, liquid and semi-solid medicines). Part of aenova group since 2014.

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).

Kalbitzer Innovations UG
(founded in 2011, 2 employees) develops project specific software for the application of complex analytical methods such as NMR-spectroscopy and uses of high hydrostatic pressures up to 500 MPa in biomedicine, especially in drug development and protein biotechnology.

Medical Device Partners GmbH
(founded in 2001, 2 employees) consultancy with the aim to support cli-



50 companies with 3,872 employees are active in the BioRegio Regensburg ■

ents in bringing products and services successfully to the medical device market.

Multi-Service-Monitoring

(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, 75 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, 200 employess) 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, 600 employees) supplier for medical and pharmaceutical companies. Development and production of innovative diagnostic and acute therapeutic systems 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.

TriOptoTec GmbH

(in the BioPark, founded in 2010, 2 employees) works in the area of photodynamic disinfection and decontamination.

Interdisciplinary Companies

ABB gomtec GmbH

(in the BioPark, founded in 2008, 1 employee in the BioPark) branch of ABB gomtec GmbH in Seefeld, develops medical robots (intelligent manipulators) for surgery, diagnostics and therapy.

aquagroupAG

(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 GmbH

(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 Engeneering).

emz-Hanauer GmbH & Co. KGaA

(founded in 1948, 450 employees) develops and manufactures mechatronic systems for domestic engineering, household appliences and environmental engineering.

At the BioPark 33 leasholders with 561 employees work at 18.000 sqm ■

Kelheim Fibres GmbH
(founded in 1935, 550 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, 1100 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, instruments for laboratory and process control. A company of the OTH Regensburg.

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.

relyon plasma GmbH
(founded in 2002, 20 employees) develops products for the plasma treatment for industrial and medical applications, as well as process solutions for surface cleaning and activation.

SCHOTT AG
Site Mitterteich(founded in 1970, former SCHOTT-Rohrglas GmbH, 1000 employees) products and services for international growth markets such as pharmaceutics, 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.

BIOPARK
REGENSBURG GMBH

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Wirtschaft und Medien, Energie und Technologie

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^2 lab and 3,000 m^2 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 30 companies with some 380 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). ■

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

Würzburg – a force to be reckoned with in life sciences

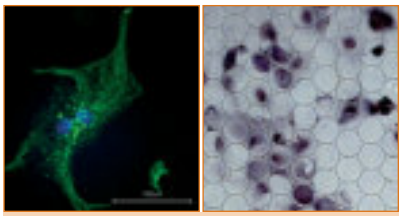
With its research centres, research groups, and postgraduate schools of medicine and life sciences, the Julius-Maximilian University ranks among the most successful universities in Germany. The Rudolf-Virchow Centre for Experimental Biomedicine is one of the DFG-funded centres of excellence focussing on the identification of new target proteins in cancer, cardiovascular, auto-immune and inflammatory diseases, which can be the basis for improved diagnosis and treatment. The dual centre of internal and operative medicine (Doppelzentrum für Innere und Operative Medizin) of the University clinic Würzburg the University Clinic Würzburg has excellent technical equipment and offers ideal conditions for patient care as well as basic and clinical research. Located in the immediate vicinity is the Comprehensive Heart Failure Centre (CHFC), an integrated research and treatment centre for cardiovascular diseases, which moved to a modern new building in 2016. The Comprehensive Cancer Centre (CCC) was established at Würzburg university hospital in 2011 and is recognised as a centre of excellence for oncology by German Cancer Aid (Deutsche Krebshilfe). The interdisciplinary bank of biomaterials and data Würzburg (ibdw), established in 2013, is one of five nationwide databases which are an important prerequisite for a better understanding of diseases and disease mechanisms. The Fraunhofer project group for the investigation of regenerative technologies for oncology was integrated in 2014 after a positive evaluation in the newly founded „Regenerative therapies for Oncology and Musculoskeletal Diseases“ translational centre, which is funded by the Free State of Bavaria. Within the scope of the Nordbayern initiative, launched in 2014, Würzburg's scientific excellence is being further expanded in the life sciences. This includes, among others, the establish-

The enrolment of patients for the clinical phase 3 was started in August 2016 based on the very good results in clinical phase 2: the test substance Ronopternin (VAS203) of vasopharm GmbH from the IGZ Würzburg affects the increase in cranial pressure in traumatic brain injury patients ■

ment of a Max Planck research group on immunology for the study of immunotherapy for cancer and other diseases, the establishment of a Helmholtz Institute for RNA-based Infection research (HIRI) as well as the „Center for Computational and Theoretical Biology“ (CCTB). ■

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 support in cooperation with the Bavarian Ministry of Economic Affairs, the Würzburg university colleges, BayStartUP GmbH 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). Furthermore, as regional partner in Lower Franconia, it ensures efficient networking with the Bavarian biotechnology cluster, the Medical Valley in Erlangen and the excellence initiative m4 in Munich. ■



Cultivation of microvascular endothelial cells (stained single cell left) by two-photon polymerization (2PP) produced ORMOCER structures (right) [1] ■

Support for entrepreneurs

Together with local universities and BayStartUP, IGZ Würzburg has developed a comprehensive program for promoting start-up activities in the region. Young scientists are offered advanced trainings 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 entrepreneurial 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. The new initiative “Gründen @Würzburg.de” (www.gruenden.wuerzburg.de) supports the networking of founders and startups in Würzburg. ■

Start-up support bears fruit

In recent years, in close cooperation with universities and BayStartUP, 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, CoBaLT, SmartmAb, Mablife, Cherry Biolabs, RealTVac, and AIM Biologicals. In order to promote business ideas, it was possible to gain over 15 million Euros in public funding (4x GO-Bio, VIP, m4 award, EXIST-Forschungstransfer and EXIST-Gründerstipendium). Four 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. ■

[1]) Source: DFG Priority Program SPP 1327 (Prof. Heike Walles, Chair Tissue Engineering and Regenerative Medicine (TERM), University Hospital Würzburg and Translational Centre Würzburg „Regenerative Therapies for cancer and musculoskeletal diseases“, Division Würzburg, the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB), and Dr. Ruth Houbertz, former Fraunhofer ISC, Würzburg, now multiphoton Optics GmbH, Head Office: IGZ Würzburg).

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*

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The Bavarian Biotechnology Scene

Bavaria is home to multiple biotech regions, in which companies in the sector are concentrated. These include the biotech region Munich/Martinsried with its Martinsried-Großhadern campus, as well as the bio-regions of Regensburg, Franconia and Straubing. So far, Bavaria is home to over 350 companies in the life sciences sector, and the infrastructure means that there is space for plenty more. ■

Facts & Figures from the Biotech Industry

- 350 companies in the field of life science are based in Bavaria
- 2.6 million students across Germany
- 350 companies based in Bavaria
- 4 elite universities with great expertise

One of the focuses of the biotechnology scene in Bavaria is on developing new therapeutics and diagnostics. In order to make it as easy as possible for new biotech companies in Bavaria to enter the market, networks such as BioMed Würzburg, BioPark Regensburg GmbH and BioM in Munich provide individual support, effective transfer of knowledge and technology, advice on financing issues and integration into the well-established network structures from the very beginning. ■

Talent and research

Many Bavarian universities, such as the LMU Munich, the Technische Universität München and the Universities of Würzburg and Regensburg, display a high level of expertise in biotechnology teaching and research and have achieved international

renown in this future technology. Biotechnology research in Bavaria does not only take place at university level, but also in a series of renowned non-university research institutions such as the Helmholtz Centre for Environmental Health and the Max Planck Institutes of Biochemistry, Neurobiology and Psychiatry. These work together closely with biotechnology companies and the universities to conduct top biotechnology research. ■

Good Reasons for Bavaria

Research & Investment – The Free State of Bavaria has invested some €80 million in life sciences in recent years. Innovative entrepreneurs and scientists are funded right from the start by the Free State of Bavaria, e.g. with start-up centres and innovation centres specifically equipped for medical technology.

Networks that work - As part of its cluster policy, the Bavarian State Government supports network-building between university research and business to the tune of €50 million.

Pure Nature - With superb mountains right at the doorstep, a magnificent low mountain range just around the corner and fairytale-like rivers and lakes nearby, surrounded by forests. Historic cities with original Bavarian charm and cosmopolitan flair at the same time. - In harmony with the environment.

International Airports – Two modern, international airports in Munich and Nuremberg are global turntables which pave an easy, safe and smooth way into Bavaria for visitors, patients and investors alike.

Bayern International – the Bavarian Bureau for International Business Relations is a key player in the promotion of Bavarian exports. With around 100 projects per year, we support Bavarian companies to explore and tap into new markets. An average of about 500 exhibitors use the joint stand for export trade each year. ■

Meet Bavarian companies at the following international trade fairs:

11.10. – 13.10.2017
BioJapan - World Business Forum
Yokohama, Japan

04.06. – 07.06.2018
BIO - Biotechnology Exhibiton
Boston, USA

Oktober 2018
BIOJAPAN - World Business Forum
Yokohama, Japan

Oktober 2018
AUSBIOTECH - Australia's Life Science Conference
Melbourne, Australien

05.11. – 07.11.2018
BIO-EUROPE - The Business Partnering Conference
Kopenhagen, Dänemark ■

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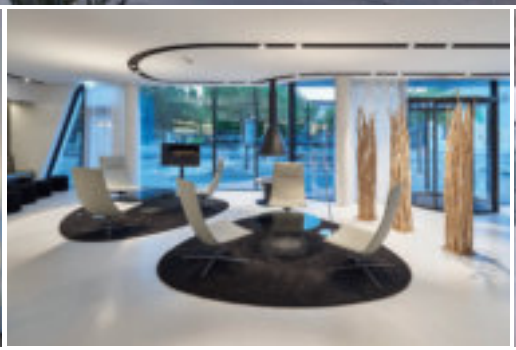

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BioSysNet: Lively Scientific Exchange

The Bavarian Research Network for Molecular Biosystems (BioSysNet) is a program of the Bavarian State Ministry of Education and Cultural Affairs, Science and the Arts. In a unique way, the program promotes outstanding projects in the field of molecular biosystems research in order to consolidate and strengthen the expertise in this area in Bavaria. This creates an ideal foundation to improve the positioning of researchers within the global landscape of competitive science and at the same time attracts international visibility for Bavarian cutting-edge research. Supporting such interconnected research projects is a hallmark of Bavarian science policy, and contributes substantially (alongside numerous important research institutions and universities) to the excellent reputation which our researchers enjoy worldwide. From a scientific point of view, our research is focused on the analysis of complex biological control systems in order to shed light on regulatory mechanisms (on a cellular and molecular level) of the genome. These funded research approaches are based on coordinated interdisciplinary collaborations in the areas of biochemistry, genetics, bioinformatics, biophysics and medicine. The project groups of BioSysNet (*Fig. 1)* are coming to the end of their five-year funding period, which has already led to an impressive track record and results, including the remarkable number of 300 high-ranking publications, as well as vastly increased international recognition. On March 15th of this year, two of the funded BioSysNet project leaders were awarded one of the most coveted scientific awards of our times, the Gottfried Wilhelm Leibniz Prize of the German Research Foundation DFG. Awarded were Prof. Karl-Peter Hopfner, Dean of the Faculty of Chemistry and Pharmacy at the Gene Center of the Ludwig-Maximilians-University Munich, and Prof. Jörg Vogel Chair of the Research Center for Infectious Diseases located at the Julius-Maximilians-University Würzburg and the Founding Director of HIRI - Helmholtz Institute for RNA-based Infection Research.

Fig. 1: *Progress through cooperation as a shared goal; the BioSysNet family at one of our member seminars. (Source: Ulrike Kaltenhauser © BioSysNet)* ■

Fig. 2: *Prof. Karl-Peter Hopfner received the Gottfried Wilhelm Leibniz Prize for his work in the field of structural and genome biology. (Source: David Aussenhofer © DFG)* ■

Prof. Karl-Peter Hopfner was recognized for his outstanding work on both structural and genome biology regarding the area of DNA repair and cellular recognition of foreign nucleic acids. *(Fig. 2)* With his research, Prof. Hopfner made groundbreaking contributions by uncovering the molecular mechanisms of multiprotein complexes, which play an important role in the recognition of damaged or viral nucleic acids. These recognition processes are key to the protection of the genome. One of the main causes for the development of cancerous diseases can essentially be found within such errors of recognition and genome repair. Based on this, Prof. Hopfner has carried out defining work regarding DNA double-strand repair. He succeeded in deciphering the mechanism of the pivotal MRN complex Mre11-Rad50-Nbs1, a sensor for DNA damages. Moreover, he focused on answering the ques-

tion how cellular sensors of the innate immune system recognize viral or bacterial DNA upon infection and was able to contribute significantly to resolving this process. These sensors need to distinguish between own and foreign RNA. Since 2007, Prof. Hopfner has held a full professorship at the Gene Center LMU Munich. He has been receiving BioSysNet funding since 2012 for one of his many projects dealing with molecular systems of innate immunity, attending to the question of how viral nucleic acids are recognized by cytosolic receptors.

Prof. Jörg Vogel is one of the worldwide leading scientists in the field of ribonucleic acid biology. He received the Leibniz Prize for his outstanding contributions to understanding the role of regulatory RNA in infection biology. *(Fig. 3)* Early on, Prof. Vogel perceived the importance of RNA biochemistry in prokaryotes. He pioneered, in this highly competitive field, the development and application of high throughput sequencing methods for RNA analysis. With these new methods, he was able to trace the impact of pathogens on the host cell. Another discovery of Prof. Vogel's gave insight into how small regulatory RNAs control protein biosynthesis, as well as RNA degradation, which contributed to the development of novel methods that are applicable to gene therapy. Together with Prof. Emmanuelle Charpentier, who was likewise awarded the Leibniz Prize in 2016, Prof. Vogel discovered the tracrRNA, i.e. transactivating RNA, a key requirement for the application of the CRISPR/Cas9 system. He unraveled general biological principals, essential to understanding pathologic microorganisms which led to novel therapeutic approaches. You can read an article of Prof. Vogel's with the title "With RNA biology against infections" on page 36-39 of this publication. His project "Small RNAs control the dynamic of gene expression" (a study on the influence of non-coding RNA molecules on the time course of gene expression changes in the model organism Salmonella) has been funded by the Bavarian Research Network for Molecular Biosystems since 2012. We are delighted to give our heartfelt congratulations to both of the distinguished scientists for this prestigious award.

Fig. 3: *Prof. Jörg Vogel received the Leibniz Prize for his work on RNA biology, with which he made groundbreaking contributions to the understanding of regulatory RNA molecules in infection biology as well as RNA functions in general.*
(Source: David Aussenhofer © DFG) ■

All other groups of BioSysNet have achieved great results as well within their funded projects. Two of the independent junior group leaders have already been offered a full professorship. Furthermore, established project leaders of other funded groups have raised international attention based on their outstanding scientific work. Through the numerous joint internal workshops, the project leaders were encouraged to discuss their results, ideas and exchange important experiences with their colleagues. Thus, virtually without effort, important collaborations were formed and cooperation between the project leaders automatically became an elementary and essential part of their scientific work. Together with the Cluster for Biotechnology in Bavaria, intergroup networking was taken to another level and thus BioSysNet junior group leaders were optimally and firmly established in the Bavarian scientific landscape. Numerous joint activities resulted in a lively and ongoing scientific discourse. We were especially happy to welcome the female managers of the Association of German Biotechnology Companies (VBU) who held their staff meeting in Munich for the second time. We would like to offer our special thanks at this point to MorphoSys AG, who organized and carried out this meeting together with BioSysNet. Not only was MorphoSys AG a great host for this event, the company also contributed with impressive presentations of its research areas as well as providing a guided tour through the laboratory facilities. *(Fig. 4)*

At the meeting of the managing directors of the Bavarian research networks, the idea was developed for a further event with a format completely new to the life sciences. Together with the task force of the Bavarian Research Networks (an institution within the Bavarian Research Alliance BayFor), we were able to host an event on "Science communication in times of social media" in the Römer Forum conference hall of the new BioSys-M building. Apart from scientists of the various research associations and networks in Bavaria, members of the High-Tech Campus Grosshadern-Martinsried were invited. Speaker Andrea Geipel (Munich Center for Technology in Society of the Technical University of Munich) and main speaker Lars Fischer (known for his "Fischblog" which was founded in 2007 and community manager of SciLogs at Spektrum der Wissenschaft) shared their theoretical and practical experiences on "Scientific blogging and commu-

Fig. 4: *Meeting of the VBU business network for female managers in the life sciences on the premises of MorphoSys AG in Planegg. (Source: Ulrike Kaltenhauser © BioSysNet)* ■

nication in social networks, YouTube, Twitter & Co" with the participants. During the subsequent panel discussion, ideas and personal experiences were exchanged and pros and cons of communication via social media were discussed with the interested audience. *(Fig. 5)*

But the most important aspect of the Bavarian Research Network for Molecular Biosystems remains the scientific achievement of the network in the field of molecular biosystems research. If you would like to gain a deeper insight into the work of our research groups funded within this program, please do not hesitate and read the article of Dr. Jan Medenbach, a junior group leader of the network based at the University of Regensburg, who in this brochure answers the question: What makes female flies female? You can find his article "A protein, which makes females" on page 44-45. Or you could go to pages 14-19, where Prof. Dr. Eckhart Wolf, a senior group leader of BioSysNet at the Gene Center LMU Munich, offers us fascinating details on the topic of "Tailor-made pigs for diabetes research and therapy". Or you could simply visit us on our homepage www.biosysnet.de.

Fig. 5: *Science communication in times of social media – an event by BayFOR and BioSysNet in the fully packed Römer Forum conference hall. (Source: Ulrike Kaltenhauser © BioSysNet)* ■

In view of the last year of the BioSysNet funding period, the members of our research network have further great intentions, plans and projects. You are all cordially invited to attend our international symposium, which will be held from 14th to 15th of March 2018 at the Biomedical Centrum (BMC) of the Ludwig-Maximilians-University Munich.
This event will simultaneously represent the framework for the final evaluation of all funded projects. We are expecting numerous participants. In addition to the BioSysNet project leaders, all members of the scientific council (the network's external committee of experts), as well as further international and renown guest speakers and partners of the network will be present. Apart from highlighting the countless new scientific findings, this event will also give room to elaborate on how successful the researchers have managed to answer the questions and issues raised in their research project. We are looking forward to inviting the biotechnological expert community to this event and are looking forward to a lively discussion and novel insights emerging from the symposium – so save the date! Being the Bavarian Network for Molecular Biosystems, we strive to create an ideal framework for scientific exchange and are happy to contribute to the exceptional research infrastructure in Bavaria. ■

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Analytica Is the Place to Meet: 10,000 Square Meters for Biotechnology

Whether bioeconomy, new drugs or safeguarding food for the whole world, biotechnology plays a key role in securing our prosperity and paving the way for a sustainable economy. Every two years, analytica in Munich provides information about new developments and trends from all areas of biotechnology. Whoever who would like to participate actively in analytica 2018 should start planning for it now. The next analytica will take place on the grounds of Messe München from April 10 to 13, 2018.

Messe München

The biotech industry is experiencing an upswing. According to Ernst & Young's annual Biotech report, the number of dedicated biotech companies rose by five per cent to 623 in Germany alone last year, while the number of employees rose by 14 per cent to 25,000 and sales grew by seven percent to 3.6 billion euros. „This positive mood was already felt at analytica 2016," Susanne Grödl stated, Exhibition Director of analytica at Messe München. „We are looking forward to the innovations that the industry will present in 2018."

analytica, the leading International Trade Fair for Analysis, Laboratory Technology and Biotechnology, has become an international meeting place for the biotech sector. It is no wonder that the industry meets specifically in Munich every two years: Bavaria and the region around the state capital have established themselves as a top location for biotechnology. With 106 biotech companies, Bavaria is the top performer in Germany, followed by the neighboring state of Baden-Württemberg with 93 companies. Germany's North has much less to offer.

The proximity of analytica to the German biotech clusters is a magnet for biotech companies from Germany and abroad. More than 280 of the 1,244 exhibitors at analytica 2016 stated that they are dealing with biotechnology, life sciences, bioanalysis or diagnostics. „Biotechnology is increasingly becoming the focal topic of analytica. With its own exhibition hall, which covers 10,000 square meters, and various supporting events, we are doing justice to increased interest in the field," Ms. Grödl emphasizes. The Biotech Forum is an integral component of analytica, in which exhibitors present best practice examples in the form of talks on all trade fair days.

Forum Biotech dedicates special topics to the trends and challenges of the industry ■

Analytics in focus

analytica covers the complete range of biotechnology. New developments for pharmaceutical research can be found at analytica as well as plant grow boxes for green biotechnology and bioreactors for white biotechnology as well as all the utensils for the biotech laboratory from microarrays to cell culture chips and all the way to thermocyclers.

However, the focus of the exhibition is still on analytical instruments. And rightly so, because advances in biotechnology-similar to other high-tech industries-rise and fall with the

further development of measurement methods. We only need to think of the immense increase in performance of sequencing devices for gene analysis and mass spectrometers for investigating complete proteomes or to the constantly improved resolution of microscopy, which now enables viewing molecular details in living cells. „analytica covers the entire range of state-of-the-art measurement techniques," Ms. Grödl emphasized, „and also shows innovations from all areas of analysis from sample preparation to liquid handling and all way to bioinformatic analysis." No other event provides such a comprehensive overview.

In the era of digital communication, trade fairs are more important than ever as real marketplaces with products that you can see first hand. As a result, analytica is far more than just an industrial exhibition of new equipment and state-of-the-art laboratory equipment. As a leading trade fair, it provides an international information platform, on which ideas are exchanged, inspiration is gathered and demands for analytics of tomorrow are discussed. After his participation in analytica 2016, Professor Dr. Markus Fischer, founder and director of the Hamburg School of Food Science, stated that „manufacturers and laboratory experts are able to discuss situational challenges and solutions on site. This format is ideal and unique."

analytica conference: bridge between science and application

analytica also bridges the gap between business and science with the analytica conference, which traditionally takes place on the first three days of the trade fair. In addition, three renowned professional organizations, the German Society of German Chemists (GDCh), the German Society of Biochemistry and Molecular Biology (GBM), and the German Society for Clinical Chemistry and Laboratory Medicine (DGKL), also invite renowned scientists from throughout the world to report about their current research. As in the previous years, approx. one-third of the talks will deal with innovations in bioanalytics, biotechnology and life sciences.

The program of the analytica conference, which includes keynote speeches and more than 20 symposiums with a total of around 120 talks, has proved its worth. Visitors surveyed at the conference in 2016 gave top ratings: 99 per cent rated the analytica conference as „excellent". The participants were especially satisfied with the relevance to the present, quality and practicality of the talks.

analytica is the international meeting place for the biotechnology ■

Financing as a perennial topic

analytica also dedicates special topic days to the trends and challenges, with which the industry is particularly concerned. For example, the perennial topic of financing biotech companies will again be on the agenda. According to the report by Ernst & Young, although international investors are again more involved in the German biotech industry, there is still a lack of capital for innovation financing. The analytica Finance Days, which has always had been a big crowd drawer in previous years, will be held for the fifth time in 2018, once again organized by GoingPublic Media AG.

As in the past two years, there also will be a theme day on personalized medicine, which will highlight the various facets of this area in talks by experts and a panel discussion. „Many exhibitors take advantage of the platform to talk to the speakers and panel participants about their own further business development," Dr. Holger Bengs stated, CEO and Managing Partner of BCNP Consulting, who will again be organizing the 2018 conference together with Going Public Media AG .

A special opportunity for SMEs

analytica provides small and medium-sized biotech companies a special opportunity to develop business relationships and tap new markets. „One of our analytica highlights was the visit of a delegation from Kazakhstan at our booth," Dr. Wolfgang Kronemeyer said, Vice President of Sales Central Europe at QIAGEN, and he emphasized that this resulted in immediate follow-up activities. With an exhibitor record of 1,244 companies from 40 countries and more than 35,000 visitors from 119 countries, analytica 2016 was more

international than ever before. In addition to E.U. countries, which accounted for a total of 56 per cent of the visitors, the top 20 countries included Turkey, India, China, Russia, Japan and the USA.

„We have developed special formats to enable start-ups and medium-sized companies to make their trade fair appearance more efficient," Ms. Grödl explained. Collaboration between Messe München and the German Federal Ministry of Economics and Labor, which has existed for several years, has resulted in the creation of joint booths called „Made in Germany". Young companies also have an opportunity there to present their products at analytica 2018 with government sponsoring.

Start your trade fair planning now

Experts recommend starting with planning a trade fair exhibit approximately one year before the event, i.e., high time for all those who want to be there in 2018. More than 530 exhibitors from over 30 countries have already signed up to participate, including international market leaders such as Agilent, Analytik Jena, Büchi, Olympus, Perkin Elmer and Waters. Large international joint booths have already committed to participate, among others, from China and Korea.

Exhibition Manager of analytica, Susanne Grödl, promises a special event for everyone, especially because analytica will celebrate its 50th anniversary next year. Ms. Grödl emphasized that team of Messe München also has above all one thing in mind in this anniversary year too: „At the world's largest industry meeting, exhibitors should be able to make the world's best business deals." The chances for this are better than ever give the positive mood in the biotech sector.

Additional information is available at www.analytica.de

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analytica covers the complete range of biotechnology ■

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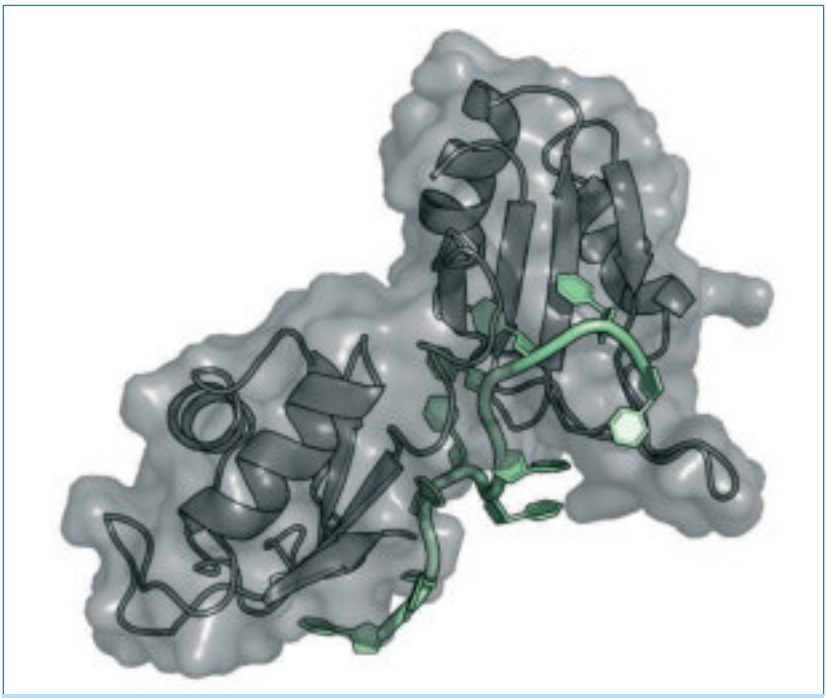
Flipping the switch between male and female development

In the common fruit fly Drosophila melanogaster, a single protein determines whether the animal develops into a male or female individual. Studying fruit fly sexual development can also teach us about human gene expression.

They are only 2.5mm in size and easy to overlook: fruit flies of the species Drosophila melanogaster. On first glance, they appear unimpressive, but they were indeed the main actors of numerous groundbreaking scientific studies and the secret stars of four Nobel prizes, teaching us the basics of genetics, development, and immunology.

Even today there is still a lot to learn from these tiny insects. More than half of their genes have counterparts in humans and the basic principles of gene regulation are shared between the two organisms. Being amenable to genetic manipulation makes them an ideal model system to study the basics of gene expression, furthering our knowledge and paving the way for medical advances.

In the laboratory, Drosophila melanogaster is reared in large numbers in plastic dishes with a layer of food at the bottom. At first glance, all animals in such a dish appear rather similar; but upon closer inspection, subtle differences can be noted. Some of the flies are smaller and darker and behave differently from the larger and more brownish ones. When two of the darker animals meet, they behave aggressively towards one another; upon meeting a larger and more brownish animal, they, however, start a friendly humming with one of their tiny wings. The small and dark animals are the males, the larger, brownish animals the females.



Structure of Sxl (grey) bound to a short RNA fragment (green) ■

But what determines the differences in appearance and behavior between the two sexes? In Drosophila melanogaster it essentially boils down to the presence or absence of a single protein named Sex-lethal (Sxl). It acts as a master-regulator that drives female development by controlling the expression of several proteins that perform key functions in diverse cellular processes. Sxl itself is produced in response to the number of X-chromosomes: male animals have a single one and do not express functional Sxl protein, whereas animals with two X-chromosomes trigger Sxl production and develop into females. Importantly, once produced, Sxl engages in an auto-regulatory feedback loop to stimulate its own production. This amplifies an initial, weak signal into a binary, all-or-nothing response

and ensures continuous expression of Sxl. This generates a ‚cellular memory' that stably flips the switch and commits to female development.

On the molecular level, Sxl is a real all-rounder: despite exhibiting a rather simple domain architecture, it controls numerous, different steps of gene expression to promote female morphology and behavior. It binds to cellular messenger RNAs (that serve as blueprints for the synthesis of proteins) and controls their processing, nuclear export and translation into proteins. For this it employs various different, regulatory mechanisms that typically result in RNP-remodeling – an exchange of proteins that interact with the mRNA. This occurs either by competition with and eviction of other regulatory factors or by recruiting additional proteins. Given its great versatility in gene regulation, Sxl is a particularly interesting protein to study. Molecular insights into its mechanism of action can help us to unravel how this seemingly simple protein can fulfill so many different tasks in gene expression.

But why is that of relevance? Politicians have questioned whether fruit fly research has to do with the public good, implying that it is mostly undertaken to satisfy a purely academic interest. This is clearly not the case! Many genetic pathways (including those that are involved in disease) are shared between flies and humans, or are similar enough to serve as models for the human counterpart. This is because regulatory mechanisms and/or pathways that prove useful are maintained by evolution. An analogy can be found in modern technology. Exemplarily, electromagnets are put to a variety of different uses. In the past, built into the Walkman, they allowed us to listen to music at the push of a button. But they can also be found in the largest machine ever built by mankind, the large hadron collider (LHC), a particle accelerator close to Geneva. In this complex physical experiment, superconducting electromagnets direct charged particles along the accelerator ring, boosting their energy along the way. Head-on collisions of the ultrafast particles allow insight into the yet unsolved mysteries of physics.

The Medenbachlab ■

Similarly, nature rarely reinvents the wheel. Regulatory principles that we learn to understand in flies are often found in humans, too. This is also true for Sxl. Despite sex determination and sexual development being markedly different between flies and mankind, Sxl-related proteins are conserved (e.g. HuR, HuB etc.). The human counterparts regulate gene expression by similar mechanisms and, importantly, interfering with their function promotes inflammation and tumor development. Hence, insights gained in the Drosophila model system also further our understanding of gene expression and regulation in humans and ultimately contribute to medical advances.

The Medenbachlab acknowledges funding by the Bavarian State Ministry for Education, Science and the Arts within the Bavarian Research Network for Molecular Biosystems (BioSysNet), the German Research Foundation (DFG, grant ME4238/1-1) and the German Federal Ministry of Education and Research (BMBF) within the framework of the e:Med research and funding concept (grant 01ZX1401D).

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Using RNA biology against infections

Most of us will know ribonucleic acid (RNA) as the molecule that reads out and transfers the genetic information stored in DNA in order to synthesize the proteins of a cell. Over the last decades, however, RNA has kept us on the edge of our seats, continuously revealing new cellular functions.

This started with the recognition that RNA can be catalytically active, similar to enzymes, enabling central functions like the splicing of messenger RNAs (mRNAs). Another milestone was the discovery of RNA interference (RNAi), exploitation of which made it possible to systematically analyze gene functions in human and other cells. Finally, CRISPR-Cas has to be mentioned here: a bacterial immune system discovered by microbiologists, which uses small RNA molecules to destroy unwanted foreign DNA. Reprogrammed CRISPR-Cas systems now permit a highly precise interference with the genome of many organisms including humans. The discovery of CRISPR-Cas showcases how RNA basic research in bacteria can revolutionize biomedicine and biotechnology. It is not for nothing that at some point, The Economist described RNA as „Biology's Big Bang".

Defects in RNA functions have been shown to play a role in a variety of human non-communicable diseases like neurodegenerative disorders or cancer. But RNA seems to be a promising molecule for the analysis of infectious diseases, too. RNA can be used to characterize pathogens and infected host cells and to capture the process of infection at a higher resolution. Furthermore, RNA can not only be used as therapeutic target molecule, but can itself be applied as a "programmable drug" to combat infections.

How come that RNA research has become so exciting recently? The reasons for this lie within several developments over the past few years, which have turned the entire field of RNA research upside down. One reason is the discovery of new classes of RNA molecules. Many of these are so-called non-coding RNAs (ncRNAs). They neither transfer genetic information nor are they directly involved in other processes of protein synthesis. Instead, ncRNAs often act as modulators of gene expression. Current research aims to decipher the underlying mechanisms and principles of these RNA switches and how they differ from those of regulatory proteins like transcription factors.

Many of these new RNA molecules could only be described in such detail because of the development of RNA high throughput sequencing ("RNA-seq"). This method functions like a high-resolution "RNA microscope", allowing us to observe gene expression in any cell or tissue. In 2010, my laboratory was the first to describe the whole transcriptome–the sum of all RNA molecules of a cell–of a medically important pathogen using RNA-seq. By applying our newly developed "Differential RNA-seq" method to *Helicobacter pylori*, a gastric bacterium that can cause stomach cancer and is carried by about 50% of all humans, we identified in one go all transcription start sites and an unexpected large number of small ncRNAs in this organism (Sharma et al. 2010). In collaboration with Emmanuelle Charpentier, we then used this method to describe tracrRNA as a core component of the CRISPR-Cas9 system in *Streptococcus* (Deltcheva et al. 2011), a discovery that helps to pave the way for the development of CRISPR-Cas9 as a revolutionary new tool for genome editing.

To date, RNA-seq has advanced to a stage where it can analyze intracellular pathogens together with their host cells at extremely high resolution. With the development of „Dual RNA-seq", which we published in 2016, we could show both, that a small ncRNA (PinT) in *Salmonella* exerts temporal control of the major virulence programs of this diarrhea-causing bacterium and how this affects defense mechanisms of the host (Westermann et al. 2016). Such understanding of small regulatory RNA molecules as modulators of bacterial virulence programs and stress responses is at the center of our research within the Bavarian Research Network BioSysNet. Besides the PinT sRNA, we were particularly interested in SgrS, a regulatory

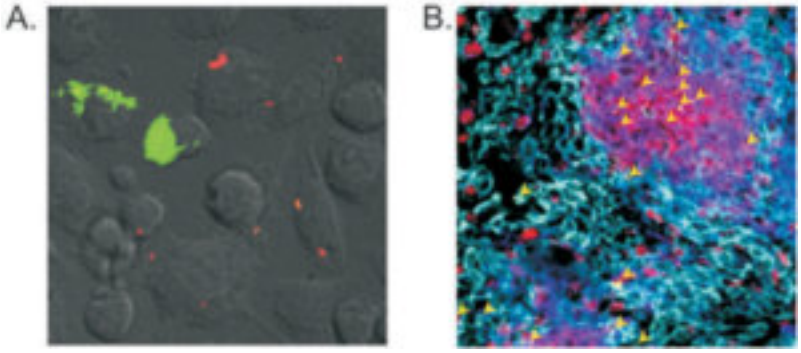

Fig. 1: *Individual Salmonella-infected cells display a high level of heterogeneity. A: Ex vivo infected macrophages with Salmonella. Within these macrophages, some Salmonella proliferate (green), whereas others do not replicate and adapt a dormancy-like state (red). This figure is property of Sophie Helaine, Imperial College London, UK.*

B: Similar cell heterogeneity is observed in Salmonella infection of animals. Shown are stainings of Salmonella-infected mouse spleen. The Salmonella bacteria (yellow arrows) occupy different niches within the tissue: some bacteria are located near to neutrophils (pink spots), whereas others co-localize with macrophages (turquoise spots). It is currently unknown which bacterial or host derived factors promote this heterogeneity. This figure is property of Dirk Bumann, Biozentrum Basel, Switzerland ■

RNA that not only coordinates the stress response to toxic sugars in many enteric bacteria (Papenfort et al. 2013) but which is also involved in the control of *Salmonella* virulence factors (Papenfort et al. 2012).

On resolving infection processes, high throughput RNA sequencing has opened up entirely new research possibilities. To date, most transcriptomic analyses of infected cells report the average of expression of genes across millions of cells; for technical reasons it was impossible to analyze individual cells by RNA-seq until recently. However, there is an emerging view that during infection processes, pathogens often develop subpopulations that display behaviors much different from that of the bulk. To assess and to analyze the consequences of this heterogeneity, my research group was among the first to use „Single-cell RNA-seq" to profile individual infected cells (Saliba et al. 2016). In this way, we revealed that the polarization of individual macrophages upon infection is tied to the growth behavior of intracellular *Salmonella*. Non-replicating bacteria were found in pro-inflammatory macrophages whose RNA signatures resembled those of non-infected, extracellularly stimulated neighboring cells. In contrast, macrophages carrying proliferating *Salmonella* resembled anti-inflammatory macrophages. We interpret this observation to mean that intracellular bacteria can actively shape their host cell environment, with non-replicating *Salmonella* evading host recognition to prevent their elimination. In summary, the analysis of individual cells using Single-cell RNA-seq offers an enormous potential for infection research; we anticipate it to be boosted further in the next few years by new microfluidic approaches. This will allow us to substantially deepen our knowledge about how pathogens find their niche in the infected host and resist antibiotic treatment.

Reflecting upon our findings over the past few years, I continue to be impressed with how extensively bacterial pathogens and their hosts make use of regulatory RNA molecules to control gene expression during infection processes. In eukaryotes, these are predominantly microRNAs, which impact the synthesis of hundreds of proteins by short base pairing with mRNA. My own research group reported that certain microRNAs in murine and human cells are important regulators of cytokine production during *Salmonella* infection (Schulte et al. 2011; Schulte et al. 2013).

These ventures into eukaryotic RNA notwithstanding, regulatory small RNA molecules in bacteria, so called sRNAs remain the major topic of my research. Just as microRNAs do in humans, these bacterial sRNAs act by short seed pairing on mRNAs and, in their sum, form complex regulatory networks to fine-tune and cross-connect bacterial gene expression post transcription. In contrast with microRNAs, however, these sRNAs not only silence mRNAs but can also activate them (Papenfort et al. 2013, Fröhlich et al. 2013). After extensive mapping efforts and the frequent use of RNA-seq, we now assume that pathogens like *Salmonella* possess about 300 different sRNAs, rivaling the number of transcription factors in these bacteria. Not all of these sRNAs are encoded by their own genes; accumulating evidence suggests that many sRNAs originate from within mRNAs to regulate other genes (Chao et al. 2016, Miyakoshi et al. 2015, Chao et al. 2017).

Trained as a biochemist, I have been particularly interested in the molecular mechanisms of these sRNAs, which we have described in dozens of publications. I have been fascinated with non-standard regulation schemes, for example, sRNAs base-pairing within mRNA coding regions (Pfeiffer et al. 2009) which substantially expands the target space for potential therapeutic applications. Moreover, we have learned much about how sRNAs manage to regulate their targets with precision. Digging into virulence control by SgrS, for example, we revealed that this RNA can distinguishes two highly similar mRNAs by a single hydrogen bond within the paired recogni-

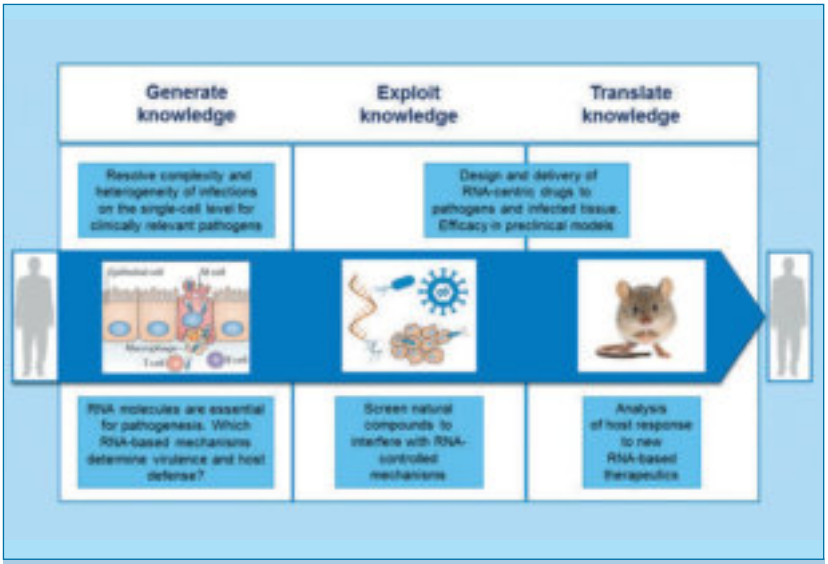

Fig. 2: *An integrative research approach to be pursued at the Helmholtz Institute for RNA-based Infection Research (HIRI)* ■

tion sequence (Papenfort et al. 2012). However, it is also evident that RNA molecules rarely act on their own but heavily depend on proteins to fulfill their function in the cell.

Many of the sRNAs that we have analyzed in *Salmonella* form molecular complexes with the Hfq protein (Chao et al. 2012, Holmqvist et al. 2016), an RNA matchmaker that is essential for virulence in many bacterial pathogens. Moreover, there had been long-standing speculations that other proteins with relevance to sRNAs exist. By developing a new approach ("Grad-seq") that combines classical biochemistry with high throughput RNA-seq and mass spectrometry, we recently discovered ProQ as a new global RNA-binding protein in bacteria (Smirnov et al. 2016, Smirnov et al. 2017).

All of this goes to show that RNA-based control mechanisms are of crucial importance in both, pathogens and their host during the course of infections. Thus, RNA molecules are ideal candidates to improve our understanding of pathogenic microorganisms, with the hope to inform new therapeutic approaches to the treatment of infections. I am therefore grateful to the Bavarian government for being given the extraordinary opportunity to take our work to the next level, by founding the Helmholtz Institute for RNA-based Infection Research (HIRI). The HIRI is an exciting joint venture between the Helmholtz Centre for Infection Research (HZI) and the University of Würzburg. Making it happen involved years of preparation, including a rigorous international assessment process. The establishment of the HIRI also acknowledges our long-standing efforts to promote early-stage researchers such as those leading young investigator groups in our Research Centre for Infectious Diseases (ZINF) which I have had the privilege to chair since 2011.

Located on the Würzburg medical campus, the HIRI will strive to pioneer an integrative concept combining scientific expertise in infection with RNA technology and knowledge. It will be the first research institution worldwide to fully focus on regulatory RNAs and their role in infection processes. Its ultimate goal is to exploit the vast potential of RNA as a diagnostic molecule, target and drug for new strategies to combat infectious diseases. Furthermore, the HIRI promises to increase the international visibility of Würzburg by bolstering the University's strength in biomedicine, particularly in RNA research and infection biology. The institute was inaugurated in a memorable ceremony at the Würzburg Residence on May 24th 2017, attended by the Bavarian State Minister of Economic Affairs and Media, Energy and Technology, Ilse Aigner.

Last but not least, I am honored to have received the 2017 Gottfried-Wilhelm-Leibniz prize, Germany's most highly renowned science award. In this way, the German Research Council (DFG) acknowledged our efforts to push the boundaries for high-resolution RNA high-throughput sequencing and to unravel the diverse roles RNA may play in bacterial infection processes. Since the award can be used for high-risk/high-gain projects, I plan to use it to develop a new generation of novel RNA-based antibiotics that target specific bacterial species. This is to say that the currently available antibiotics typically have a broad spectrum, targeting multiple members of, say, the intestinal flora. Therefore, it is difficult to investigate the individual contribution of the many hundreds of different bacteria species present in a microbiota. Notwithstanding promising first results by others, such RNA-centric programmable antibiotics are yet to overcome numerous obstacles with respect to delivery and suppression of unwanted immune reactions. To reach these aims, we will need to build bridges between basic research in microbiology and translational medicine. Würzburg offers ideal conditions for such collaborations. If we succeed at integrating these different disciplines, RNA research is likely to make yet another major contribution to our understanding and the treatment of infectious diseases. ■

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We take patients by the hand and lead them through the disease

Breast cancer is always life threatening and is one of the most common malignant diseases for women. Prof. Nadia Harbeck has made it her life's work to find the best possible therapy for her patients. She heads the Breast Center of the University of Munich (Comprehensive Cancer Center CCC LMU) at two locations in Munich (LMU Department of OB&GYN at the downtown Maistrasse campus and the Grosshadern campus). In addition, she leads the interdisciplinary Tumor Board for Breast Cancer, where individual medical histories are discussed, and she also teaches as a professor of conservative oncology at the Ludwig Maximilians University. As the only German breast cancer expert, she is a member of all international guideline groups for breast cancer. As Scientific Director of the West German Study Group (WSG), she plays a decisive role in the design and execution of clinical trials for breast cancer patients. Susanne Simon and Rainer Rutz visited and interviewed Prof. Harbeck at the Breast Center.

Translationale Forschung im Labor der Frauenklinik ■

Prof. Harbeck, your goal is to improve the everyday therapy of your patients. How do you manage this?

Prof. Harbeck: The best survival rates nowadays can only be achieved by accurate diagnosis, followed right from the start by high-quality interdisciplinary therapy concepts, taking tumor biology into consideration. This way, we can cure up to 70 or 80 percent of patients.

Who comes to your Breast Cancer Center?

Prof. Harbeck: Each year, we have an average of 700 to 800 new patients of all ages, also including pregnant women or men in about one percent of the primary diagnoses. Some are sent by their gynecologist or other cancer centers. Many search for information on the Internet and come to us directly for treatment or sometimes also to get a second opinion.

Can you briefly tell us about your professional career?

Prof. Harbeck : I have worked for 19 years at the Dept. of OB&GYN at the Technical University of Munich, last as the head of conservative oncology. Then I was director of the Breast Center of the University of Cologne for three years. In 2011, I was appointed professor and head of the Breast Center at the University of Munich (LMU). Here in Munich, I introduced parallel structures at both breast center sites as well as new therapy concepts. We also expanded our portfolio of phase II and III studies.

You are the only German expert in all international guideline groups for breast cancer and work in a leading position in one of the German breast cancer study groups. How do your patients benefit from your commitment?

Prof. Harbeck: As part of my work as Scientific Director of the West German Study Group (WSG) I am closely involved in the design of clinical trials for breast cancer patients. The aim of these trials is to develop therapy

Beratung einer Patientin mit Mammakarzinom ■

concepts that improve the chances for cure and therapy tolerability compared to current standard treatment. Our patients are very interested in participating in our clinical trials that we offer at the downtown Maistrasse campus and the Grosshadern campus. Since last year, we have also started to offer new therapy concepts such as immune therapies.

What makes the Breast Center of the University of Munich special?

Prof. Harbeck: We work with a motivated interdisciplinary team at the highest level and offer a comprehensive trial portfolio. The trend is towards individualized therapy, avoiding over- and under-treatment: here, the LMU Breast Center plays a leading role in the clinic, in research, and in teaching. In addition, the human component is enormously important. We literally take the patients by the hand and guide them through their disease.

im Dial og: To what extent do you work together with the Innovation and Start-up Center for Biotechnology?

Prof. Harbeck: We cooperate for example with Spherotec GmbH at the IZB that developed a method to find the optimal cancer drug for an individual tumor. This may have the potential of sparing unnecessary chemotherapies. Some of my colleagues have already carried out studies together with Dr. Barbara Mayer. I think that the start-up scene here in Munich is very exciting. Together with some colleagues, I have already developed an APP (CANKADO) to support therapy management and patient adherence.

Interdisziplinäres Tumorboard ■

Prof. Harbeck, you have four children. How did you manage to combine your career and family so well?

Prof. Harbeck: The beginning was not easy. There was hardly any child care and no prolonged parental allowance. After studying photography in Canada, I studied medicine in Munich. My training as a specialist took eight years instead of five. But you simply have to take different paths. For example, since I had a small baby and could not work in the clinic, I did my scientific work after the delivery and gained my academic PhD qualification (Habilitation) as the first woman at Dept. of OB&GYN at the TU Munich. Previously, women in university medicine held no leadership positions. Most committees were exclusively male. Also at the Dept. of OB&GYN at the LMU Munich, I was the first female Professor to be appointed. My family has always supported me – for this I am very grateful. I would be happy if more women were to apply for leadership positions..

What will breast cancer therapy be like in 10 years?

Prof. Harbeck: With information from molecular tests, we will offer individualized and personalized therapies and probably less surgery of the breast and axilla. Local therapy will always be part of an interdisciplinary concept but the times of "first we'll remove the tumor and then we'll worry about a therapy concept" will hopefully be long gone. ■

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Genetically tailored pigs for diabetes research and therapy

Research into disease mechanisms is important to build the basis for the development of novel, targeted therapies. The path from disease-oriented basic research towards clinical application in patients (= translational medicine) is however long and cost-intensive. Suitable animal models which allow predictions on the efficacy and safety of novel therapies are inevitable in this process. Rodent models are most widely used, but are often limited in the resemblance of human disease mechanisms and phenotypes. Therefore effects of new treatments in humans are sometimes difficult to predict on the basis of findings in rodents. Thus large animal models, which mimic anatomical and physiological parameters of humans more closely, are additionally needed. For a number of reasons the pig is a relevant and suitable translational animal model. Due to the establishment of efficient and precise techniques for genetic modification of pigs, it is possible to generate tailored pig models which mimic human disease mechanisms on a molecular and functional level. We generated several genetically engineered pig lines as models for translational diabetes research and as donors of pancreatic islets for xenotransplantation. Our projects are funded in the framework of the German Center for Diabetes Research (DZD), the Bavarian Research Network on Molecular Biosystems (BioSysNet), and the DFG-Transregional Collaborative Research Center 127 "Biology of Xenogeneic Cell, Tissue, and Organ Transplantation – from Bench to Bedside".

Introduction

The prevalence of diabetes mellitus (DM) is steadily increasing, both in juvenile and adult individuals. Currently more than 415 million people worldwide suffer from DM, and an increase to 642 million diabetic patients is expected by the year 2040 (http://www.idf.org/diabetesatlas). In addition to the steady increase of type 2 DM that is often associated with obesity, the prevalence of type 1 DM - caused by an irreversible autoimmune-mediated destruction of the insulin-producing beta cells - is increasing, particularly in children and adolescents. In 2015, the number of children suffering from type 1 DM was estimated at 542,000 worldwide (http://www.diabetesatlas.org/). Although numerous treatment options exist for the different types of DM, the disease is progressive and associated with severe alterations in multiple tissues and organs, such as diabetic nephropathy, neuropathy, retinopathy and cardiovascular complications. DM is the most prevalent cause (40%) of chronic kidney diseases, leading to terminal renal failure (http://www.die-nephrologen.de/fakten.html).

Animal models are required for studying the functions of endocrine cells in the pancreas, for investigating consequences of metabolic disturbances in different organ systems, and for efficacy and safety studies of drug candidates for diabetes therapy. In addition, animal models are important for the discovery of biomarker candidates to stratify patient collectives and to find optimal treatment strategies for subgroups of DM patients.

While classical rodent models or in vitro studies of their islets of Langerhans provide important insights into disease mechanisms, their predictive value for therapeutic effects in humans is limited (reviewed in (1; 2)). Thus additional species, including rabbits, dogs, non-human primates, and pigs, are used as additional model organisms for development of new diabetes therapies (reviewed in (3)).

For a number of reasons the pig is a highly suitable model species for translational diabetes research. Many porcine organ systems with relevance for diabetes research, including pancreas, gastrointestinal tract, and skin, are more similar to the corresponding human organs than those of many other model species (3). The human-like size and weight of pigs allows direct transfer of medical products, surgical techniques and in vivo imaging techniques to applications in human patients. Moreover, metabolic tests, such as glucose tolerance tests, can be performed with frequent blood sampling of volumes sufficient for a broad spectrum of clinical-chemical, metabolomic and other analyses. Importantly, pigs can be trained to facilitate stress-free investigations.

Currently four techniques to establish pig models for diabetes research exist: i) partial or total pancrea-

tectomy; ii) chemical destruction of the insulin producing beta cells; iii) dietary interventions (e.g. feeding a high-calorie, high-fat diet to induce obesity); and iv) genetic modifications. A broad spectrum of techniques for targeted genetic modification of pigs facilitates the generation of large animal models that mimic disease mechanisms of various types of DM on a molecular level (reviewed in (4; 5)). The combination of dietary intervention and genetic modification appears to be particularly suitable to mimic several aspects of the multifactorial type 2 DM (reviewed in (3)).

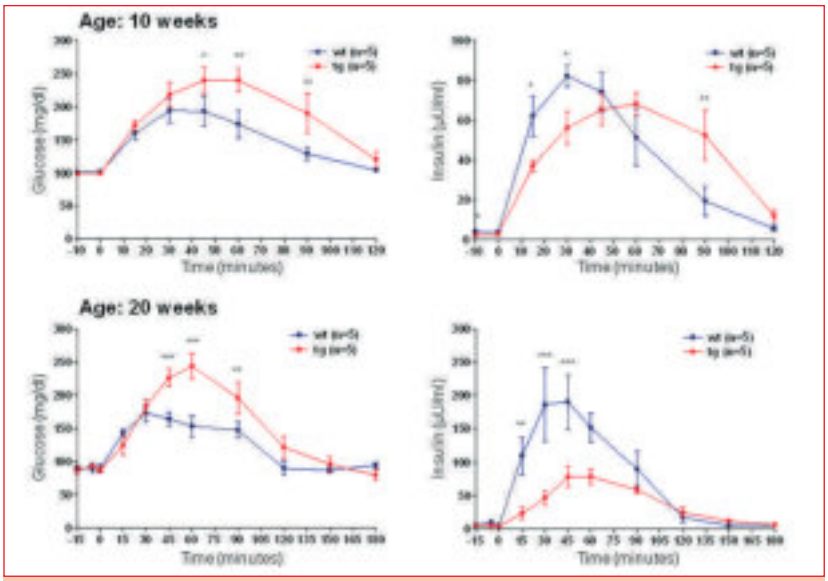


Fig. 1: *Progressive deterioration of oral glucose tolerance in prediabetic GIPR^{dn} transgenic pigs (from Renner et al., 2010)* ■

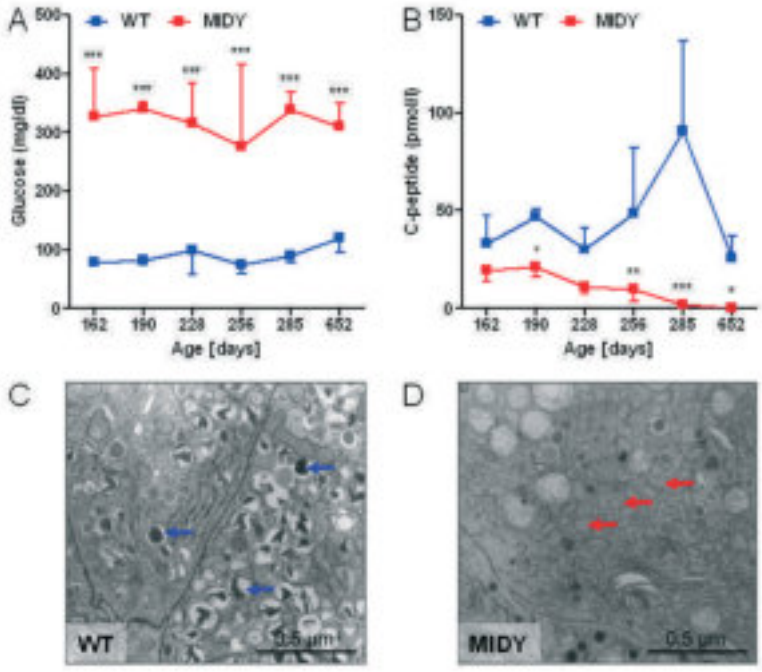
GIPR^{dn} transgenic pigs – a prediabetic large animal model

Many type 2 diabetic patients show a reduced incretin effect that is explained by a reduced function of the incretin hormone GIP (glucose-dependent insulinotropic polypeptide). The incretin hormones GIP and GLP1 (glucagon-like peptide-1) are secreted upon nutrient ingestion by specific endocrine cells in the small intestine. Among other functions, incretins bind to specific receptors of beta cells and potentiate insulin secretion. To mimic the reduced function of GIP in a large animal model, we generated transgenic pigs expressing a dominant-negative GIP-receptor (GIPR^{dn}) under the control of a rat *Ins2* promoter sequence (6). GIPR^{dn} binds GIP with similar affinity as the intact GIPR (a classical seven transmembrane domain G-protein coupled receptor), however – due to deletion of 8 amino acids and an additional amino acid exchange in the third intracellular domain of the receptor – it does not transduce the signal (1). The GIPR^{dn} transgenic pig model resembles important aspects of prediabetes, including a reduced incretin effect, impaired glucose tolerance, initially delayed and in later stages quantitatively reduced insulin secretion *(Fig. 1)*, and a progressive reduction of beta cell mass. The reproducible and progressive phenotype of this model was used in a targeted metabolomics approach to identify biomarker candidates that change in their plasma concentration with progression of the phenotype in the prediabetic period. In particular, metabolomic signatures of amino acids and lipids were identified that showed a high correlation with beta cell mass. (7). Moreover, the GIPR^{dn} transgenic pig model was used to characterize effects of the GLP1 receptor agonist liraglutide, which is clinically approved for treatment of adult type 2 diabetics, in juvenile organisms (8).

INS^{C94Y} transgenic pigs: a clinically diabetic large animal model

The expression of mutant insulin may – depending on the type of mutation and the expression level – lead to permanent neonatal DM (now termed mutant insulin gene induced diabetes of youth – MIDY) (9). In humans more than 50 different mutations of the *INS* gene are known. We generated transgenic pigs that express mutant insulin C94Y (9). A corresponding mutation was also found in MIDY patients. The C94Y mutation in our pig model disrupts one of the two disulfide bonds between the A and B chain of the insulin molecule, resulting in misfolded insulin, accumulation of proinsulin in the endoplasmic reticulum (ER), and chronic ER stress that cannot be solved by intrinsic repair mechanisms, the so-called unfolded protein response (UPR). This finally results in beta cell apoptosis. MIDY piglets get diabetic within the first week after birth. Since beta cell mass is unaltered at this stage, a deficit in insulin secretion seems to be the primary cause. With increasing age a loss of beta cell mass is observed. At age 4.5 months the beta cell mass of MIDY pigs is 70% reduced compared to wild-type littermates, and the beta cells show morphological hallmarks of ER stress *(Fig. 2)*. We thus developed an insulin substitution therapy that restored normoglycemia and almost normal growth.

MIDY pigs are an interesting model for a broad range of applications, such as the preclinical testing of novel treatments or diagnostics (e.g. new insulin formulations, continuous glucose monitoring systems, insulin pumps, artificial pancreas), or the evaluation of early stages of diabetic complications in the kidneys, eyes, or microvasculature. Already at age 5 months reduced capillarisation and pericyte investment was observed in myocardium of MIDY pigs compared to age-matched controls. After experimental induction of an ischemic lesion, the myocardium



Fi. 2: *Consequences of expression of mutant insulin C94Y in MIDY pigs. (A) Permanently elevated fasting blood glucose levels. (B) Decreasing plasma C-peptide concentrations indicating perturbed insulin secretion and a decrease in beta cell mass. (C, D) Ultrastructural changes of beta cells from MIDY pigs (age: 4.5 months), which are indicative of ER stress. Beta cells of wild-type (WT) pigs (C) show multiple insulin granules (blue arrows). In beta cells from MIDY pigs, the number of insulin granules is markedly reduced and characteristic dilations of the endoplasmic reticulum are visible (D; red arrows; from Renner et al., 2013)* ■

responded with increased fibrosis. Local gene therapy with thymosin B4 markedly improved capillarisation and pericyte investment in wild-type pigs, but only to a lesser extent in MIDY pigs (10). These findings are clinically relevant since reduced capillarisation and pericyte investment is also observed in myocardium from diabetic patients.

The Munich MIDY pig Biobank – a unique resource for studying systemic consequences of diabetes mellitus

To study the consequences of insulin insufficiency and chromic hyperglycemia in a multi-organ, multi-omics approach, we established a comprehensive biobank from four 2-year-old MIDY pigs and five age-matched controls ((11); see report in (12)). In this context, the first standardized protocol for systematic sampling and processing of a broad spectrum of organs and tissues from porcine biomedical models was established (13). Die Munich MIDY pig Biobank harbors more than 20,000 redundant samples of different body fluids and of ~50 different organs and tissues. Tissue samples were preserved to facilitate holistic molecular profiling studies (e.g. of transcriptome, proteome, lipidome, metabolome), transcript and protein localization studies as well as qualitative and quantitative pathohistological investigations. The retina of MIDY pigs showed interesting diabetes-associated alterations with similarities to diabetic retinopathy in human patients (14).

In vitro studies of pancreatic islets to understand maturation and function of beta cells

Functional studies of the endocrine cells in the islets of Langerhans are a prerequisite for better understanding the various forms of DM. Since the access to human islets from healthy or diabetic subjects is limited, islets from rodent models are often used for in vitro studies, revealing important knowledge on beta cell function. Several therapeutic concepts for DM are based on the idea to activate the regeneration of beta cells or the transdifferentiation of pancreatic progenitor cells or other endocrine cell types into beta cells. Due to structural (e.g. distribution of the various endocrine cell types) and molecular differences (e.g. transcription factors of endocrine cells) between rodent and human islets of Langerhans, findings in rodent islets may not adequately resemble the situation in human islets. Alternatively, porcine islets of Langerhans can be used as a model. Islets of adult pigs are structurally similar to human islets, but their isolation is difficult and expensive. In contrast, the isolation of neonatal islet-like cell clusters (NICCs) from piglets is less difficult, but NICCs are immature and require maturation in vitro. To facilitate monitoring of this process in living cells, we generated transgenic pigs expressing enhanced green fluorescent protein (eGFP) under the control of the porcine *INS* promoter (15). The use of this model facilitates in vitro and in vivo maturation studies of NICCs *(Fig. 3)* and molecular analyses of FACS-sorted beta cells.

Genetically modified pigs as donors for xenotransplantation of pancreatic islets

Type 1 diabetic patients in a very labile metabolic condition are difficult to treat with insulin and may suffer from frequent episodes of severe unaware hypoglycemia. While islet allotransplantation would be the treatment of choice, human donor organs are limited. As a source for xenogeneic replacement of beta cells, either islets from adult donor pigs or NICCs may be used. Adult pig islets are difficult to isolate, and the donor pigs must be maintained under designated pathogen-free conditions for a long time. The isolation of NICCs is less problematic, but they are immature upon isolation and require time in vitro or in vivo to mature and become fully

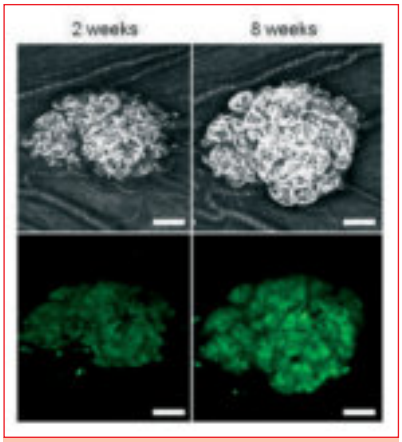


Fig. 3: *Neonatal islet-like cell clusters (NICCs) from INS-eGFP transgenic pigs can be used to study cell proliferation and maturation of NICCs in vitro and in vivo (from Kemter et al., 2017)* ■

functional. By using NICCs from *INS*-eGFP transgenic pigs this maturation process can be monitored in vitro (see above) and – after transplantation - in vivo (15).

Rejection of xenografted porcine islets can be prevented by micro- or macroencapsulation (reviewed in (16)), or by genetic modification of the islet donor pigs. The genetic modifications required depend on the transplantation site. Intraportal infusion of islets into the liver is so far the preferred application route, but intraperitoneal, subcutaneous, and intramuscular islet delivery as well as transplantation into the bone marrow has been tested.

An important hurdle to clinical xenotransplantation of porcine islets is their T-cell mediated rejection. This can be overcome by preventing the co-stimulation of T cells. Activation of T cells involves the interaction of a T-cell receptor with a peptide-loaded MHC (major histocompatibility complex) molecule on an antigen-presenting cell (APC). In addition, a second signal that is induced by the interaction of co-stimulatory molecules on T cells and APCs is required. A prominent pair of co-stimulatory molecules is CD28 on T cells and CD80/CD86 on APCs *(Fig. 4)*. Their interaction can be blocked by soluble molecules, such as CTLA4-Ig or LEA29Y, a variant with higher affinity for CD80/CD86, thus inhibiting T-cell activation. While these co-stimulation blocking agents are usually applied systemically, genetic engineering of the donor pigs facilitates their local expression in the xenograft, potentially preventing its T-cell mediated rejection without systemically blocking T-cell activation. To test this hypothesis for islet xenotransplantation, we generated transgenic pigs expressing LEA29Y under the control of the porcine *INS* promoter specifically in the pancreatic beta cells (17). After transplantation into diabetic immunodeficient mice, LEA29Y transgenic and wild-type (WT) pig islets were able to restore glucose homeostasis. Subsequent application of human immune cells resulted in rejection of the WT pig islets, whereas the LEA29Y transgenic islets were protected *(Fig. 4)*. Interestingly only very low concentrations of LEA29Y were detected in the circulation of the islet-grafted mice, supporting the concept of local suppression of T-cell mediated xenograft rejection (17). A recent study demonstrated that LEA29Y transgenic pig islets can control glucose homeostasis of beta cell deficient mice with a humanized immune system for many months (18).

New Research Center for the generation, characterization and implementation of genetically tailored pig models for medical research

With funding from the Bavarian State Ministry for Education and Culture, Science and Arts we were able to establish the Center for Innovative Medical Models (CiMM) *(Abb. 5)*, a state-of-the-art facility for the generation and maintenance of porcine biomedical models. CiMM was opened in December 2016 by importing pregnant sows from a certified farm that is free of pathogens. Their offspring are currently being used as recipients for importing our genetically modified pig lines via embryo transfer. This concept prevents transmission of any pathogens and ensures very high hygienic standards in the new facility. CiMM includes also facilities for surgery and treatment trials; it is thus ideally suited to perform translational research projects in collaboration with medical groups. This is not limited to the areas of diabetes research and xenotransplantation, but includes research on monogenic diseases such as cystic fibrosis or Duchenne muscular dystrophy for which we have already established genetically tailored pig models (19; 20). To integrate our activities in a European context, we have established the EU COST Action BM1308 „Sharing Advances on Large Animal Models – SALAAM“ with 24 participating countries (see http://www.salaam.genzentrum.lmu.de/). In addition, we have a close collaboration with the Meiji University International Institute for Bio-Resource Research (MUIIBR) in Japan, which has also generated a number of interesting pig models. Via collaboration with CiMM, these models can be made available to scientists in the area of Munich and beyond.

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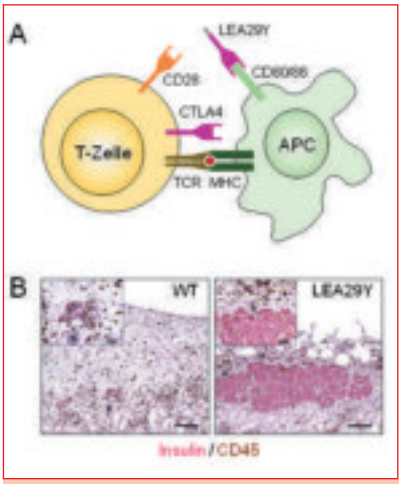

Fig. 4: *Protection of xenografted porcine pancreatic islets against T-cell mediated rejection by local expression of LEA29Y. (A) Principle of co-stimulation blockade of T cells. Activation of T cells requires interaction between the T-cell receptor and a peptide-loaded major histocompatibility complex (MHC) on an antigen-presenting cell (APC). In addition a second signal such as the interaction between CD28 und CD80/CD86 is required. The interaction of CTLA4 and CD80/CD86 blocks T-cell activation. The latter can also be achieved by the soluble molecule CTLA4-Ig or its affinity-optimized version LEA29Y. (B) Transplantation of neonatal islet-like cell clusters (NICCs) from wild-type (WT) or INS-LEA29Y transgenic pigs (LEA29Y) into immune deficient diabetic mice results in an insulin-positive cell mass that is able to normalize their blood glucose level. If the mice are subsequently reconstituted with human peripheral blood mononuclear cells (PBMCs), the WT islets are rejected while the LEA29Y transgenic islets are protected (from Klymiuk et al., 2012). CD45 labels infiltrating T cells* ■

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Fig. 5: *New Research Center for the generation and characterization of genetically tailored pig models for medical research* ■

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From 3D-printed Scaffolds to in vitro tissue culture – modern medical technology in Upper Franconia at the Friedrich-Baur BioMed Center in Bayreuth

The Friedrich-Baur BioMed Center in Bayreuth is a non-profit organization that promotes the development and realization of medical innovations in of Upper Franconia, giving the region a medical center for research and development. The Orthopedic Clinic and Polyclinic Großhadern of the LMU, headed by Prof. Jansson, is an important clinical partner. The FB BioMed Center has active contacts with further medics and medical professionals all over Germany and the world. ■

A step into the future – the next generation Rapid Prototyping

3D printing has always been a focus of our development. Competence in Rapid Prototyping reaches back as far as 2003 with the participation in Bavarian pioneer projects, meanwhile we work on refinement and integration into clinical routine. Highly precise models of complicated bone deformations are created from imaging data and printed with a material that feels and can be worked on just like real bone. They help solve intricate cases of infant skull defects, where ingenious operational methods are planned. They make it possible to exchange interesting cases between international experts in medical seminars. Dispense plotting technique is expanded to process a wide range of materials, crossing the borders of traditional 3D printing. In powder bed printing, we use proprietary resorbable ceramic powder-mixtures to print custom-made bone substitute material – sturdy implants with individual geometry and optimized pores and surfaces for secure biological integration. The implants can bear screws at any chosen position and even be reshaped during operation by the surgeon.

Our 3D-printed bone models are used for operational planning, technique improvements and training workshops, as they are uniquely precise and can be worked on like real bone ■

Based on the longstanding experience with processing 3D data and printing with various rapid prototyping techniques, the Friedrich-Baur BioMed Center gGmbH is now working on expanding classical printing techniques to stretch the limits – integrating robotics, modifying the building platform, using different extrusion methods… This enables us to develop new solutions for additive manufacturing. Here, we are always looking for interested partners to open new horizons. ■

Material development and biological research in one institute

The FB BioMed Center has an innovative concept: engineering sciences, with material and process development, are integrated with a cell lab in a hybrid construct. In the biological labs, we do more than just testing materials for their biocompatibility. Tissue culture systems, which include tumor cultures in three dimensional polysaccharide carriers, combine with high-tech bioreactors and biosensors constructed in our institute to form the base for substance evaluation, physiological effects and novel biomaterials. A special project is the standardized in vitro characterization of bone implants including induced osteoblasts, osteoclasts (resorption) in co-culture and vascularization assays as a complete substitute for animal testing, sponsored by the swiss foundation AnimalFreeResearch. The Invitro-BoneSpec system gives you a cost-effective, precise and reproducible investigation set for the suitability of novel bone implant or substitute materials. ■

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Nanomedicine – The SEON-Concept

Nanotechnology promises a broad spectrum of applications for medical imaging and molecular diagnosis, as well as improved and targeted treatments for patients. However, the implementation of nanotechnology-based methods for the treatment of cancer or other diseases requires an interdisciplinary approach combining the expertise of health professionals, biologists, pharmacists, chemists, engineers and physicists.

Superparamagnetic iron oxide nanoparticles (SPIONs) deserve a close attention, as they can be utilized both for diagnostic imaging and for therapeutic approaches as drug carriers. Currently, SPIONs are used for magnetic cell separation in vitro and as contrast agents for MRI and for a new imaging modality called "Magnetic Particle Imaging" (MPI), which is at present under development. But above this, SPIONs offer the unique possibility of combining drug delivery and diagnostic imaging, serving as so-called "theranostics". From the drug delivery point of view, SPIONs are of high interest for the individual treatment of solid tumors, because they can be used for magnetic accumulation of drugs in the tumor region. Additionally, they can be used for local hyperthermia via alternating magnetic fields and after treatment their local distribution can be monitored by MRI.

A promising drug delivery approach utilizing SPIONs is Magnetic Drug Targeting (MDT), which enables the targeted local accumulation of chemotherapeutics for the locoregional treatment of cancer. Using this new treatment concept, the Section of Experimental Oncology and Nanomedicine (SEON) already showed very promising preclinical results in an animal tumor model *(Fig. 1)*.

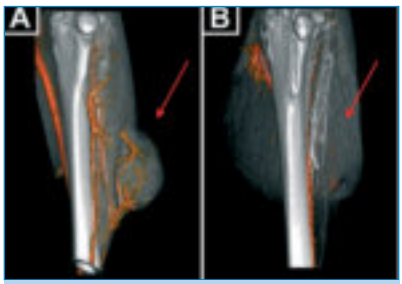

Fig. 1: *Tumor remissions were achieved in 30 % of the treated animals within 7 to 11 weeks after a single application of 5% to 10% of a usual single systemic dose of chemotherapy. A) VX2-tumor at the hind limb of a rabbit before the treatment. B) Hind limb of the same rabbit 11 weeks after the treatment – the tumor shows a complete remission. Image: SEON* ■

The declared aim of SEON is to translate the effective therapeutic treatment by MDT into a clinically used therapy. To achieve this goal, a multitude of different requirements have to be fulfilled. Among those, a highly reproducible and standardized production process of the nanoparticles is one of the prerequisites. Additionally, standardized physicochemical characterization, nanotoxicological evaluation as well as ex vivo and in vitro models, which simulate in vivo conditions, are crucial. By these tests, the necessary parameters (e.g. magnetic field strength and gradient, nanoparticle concentration and drug dose etc.) are identified to enable successful preclinical animal studies. The results of these studies are the basic requirement before starting the GMP-compliant production of the drug-loaded nanoparticles and their approval by the responsible authorities.

Additionally, the cooperation with physicists and engineers is crucial for the successful implementation of a suitable technical application environment in a clinical setting and for the noninvasive evaluation of the particle distribution in the tumor region after the treatment.

The Section of Experimental Oncology and Nanomedicine, which is located at the University Hospital Erlangen, Germany, addresses these fields of research with a special focus on targeted drug delivery by using magnetic nanoparticles and external magnetic fields. The aim of this work is to improve the treatment of solid tumors and metastases by reducing the side effects of cancer therapy. This therapy holds the promise of improved outcomes in cancer patients and an improved quality of life during and after the treatment. ■

Further information can be found at: *http://www.hno-klinik.uk-erlangen.de/seon-nanomedizin/*

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