m⁴ – Personalized Medicine and Targeted Therapies

A NEW DIMENSION IN DRUG DEVELOPMENT

Leading-Edge Cluster Munich

ABSTRACTS

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In 2010, the initiative „m⁴—Personalized Medicine and Targeted Therapies“ was among the winners of the Leading-Edge Cluster Competition (Spitzencluster-Wettbewerb) launched by the German Federal Ministry of Education and Research (BMBF) to boost Germany’s innovative strengths.

Over a period of 5 years, the Leading-Edge Cluster will receive funding of up to EURO 40 million, matched by similar amounts of capital from business or private investors and additionally more than EURO 10 million from the Bavarian Ministry of Economic Affairs, Infrastructure, Transport and Technology.

With its joint strategy „m⁴—Personalized Medicine and Targeted Therapies“ the biotechnology and pharmaceutical companies, the clinics and research institutions of the greater Munich area have aligned with the cluster management organisation BioM Biotech Cluster Development GmbH to focus on and overcome the central challenges of today’s drug development: Insufficient drug safety and efficacy, a lack of efficiency in the process of drug development due to long development cycles, extensive costs and high attrition rates.

This booklet provides an insight into the exciting research projects of m⁴. More than 30 cooperation projects with about 100 partners from the Munich conurbation will be performed, including an especially large number of projects in which small and medium-sized biotech companies are cooperating with research institutes in the region. We classified these different R&D-projects in several thematic areas which nevertheless show smooth transitions: “Personalized Medicine
Leading-Edge Cluster Munich

$m^4$ — Personalized Medicine and Targeted Therapies

(“Personalized Medicine (PM)”, “Targeted Therapies (T)”, “Production Process (P)” and “Preclinical Models (PK)”). All of these projects have direct connections to the second pillar of our joint strategy: five structural projects starting from basic research and going right to market approval will improve the infrastructure for Personalized Medicine and will help make value creation in drug development faster and more efficient.

By connecting the four mayor players (Science, Hospitals, Biotech and Pharma Industry, Clustermanagement) the Munich Biotech Cluster is ready for the next step in evolution:

- to extend Munich’s leading position as biotechnology location in Germany and Europe
- to comprehensively implement the concept of Personalized Medicine along the value added chain of drug development
- and to become an internationally recognized center and model region for Personalized Medicine

We warmly welcome new partners to advance this vision further!
Leading-Edge Cluster Munich

m⁴ — Personalized Medicine and Targeted Therapies
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SP1
m⁴ Trial Service Center

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The m⁴ Trial Service Center will be a central point of consulting and support for all research and development partners in the Munich Biotech Cluster to plan and coordinate clinical studies. In cooperation with local facilities, the main focus of the center will be proof of concept and piloting phase I studies in the areas of personalized medicine and targeted therapy as the linkage between clinical development as well as biomarker research and validation. The final aim is to translate successful pilot projects into ongoing cost-effective units.

Build a sustainable Central Service Organization
A one stop shop in the cluster, which will offer support and advice of early phase clinical trials.
- Improve and enhance a systematic patient recruitment

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m⁴ — Personalized Medicine and Targeted Therapies

- over all clinical centers in Munich
- Provide a clinical research knowledge management system
- Support of drug development process between preclinical and clinical trials
- Link clinical development and biomarker research
- Enhance the identification and validation of biomarkers
- Acquisition of biological material from clinical studies
- Installation of a web-based knowledge management system

Support the process of Translational Medicine

Compilation of concepts for
- An Early clinical development center
- Advice and mediation to technology platforms
- Service for protocol development and study design, evaluation of study concepts
- Improved recruitment by providing the linkage to clinical study networks
- Consulting services and infrastructure (including transfer from animal model to human patient, identification of biomarkers, focus on Personalized Medicine)
SP2
m⁴ Biobank Alliance

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High-quality biological samples with appendant clinical data are not only a prerequisite for the identification and validation of biomarkers, but also a highly valuable resource for the whole process of preclinical development. m⁴ Biobank Alliance will embrace and expand Munich’s excellent resources of tissue and serum samples annotated with relevant patient’s data and provide a standardized, market-oriented access. m⁴ Biobank Alliance will expand Munich’s competence profile for biomarker research, develop Munich’s profile as a recognized centre for biobanking, and build a sustainable infrastructure for sample collection and utilization in biomedical research. m⁴ Biobank Alliance will

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develop standardized protocols for an optimized process for sample handling as well as a testing strategy for sample quality, including state of the art characterization of biological samples (based on signal pathways, -omics). A uniform web-interface will make databases and relevant information accessible across several institutions (Tumorregister, EKG Studiendatenbank, KORA-Biobanken). A market analysis will evaluate the requirements concerning indication and quality of biological samples. Unified ethical and legal frameworks will be developed, covering the whole process from informing the patient to the utilization of the sample. Based on existing sample collections, biobanking expertise of all university clinics as well as other institutions in Munich will be combined for the collection of tumor tissues with corresponding normal tissue, tissues for inflammatory and metabolic diseases, and non-tissues (urine, stool, sputum, blood). The Biobank service will be available for researchers in companies as well as universities and other institutions. The idea would be to generate a self supporting but non-profit organization, which realizes not only an integrative marketing effort but i.e. an effective concept for benefit and access sharing.
SP3

\textbf{m}^4 \text{ Data Integration System}

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\textit{m}^4 \text{ Data Integration System} will be the IT cornerstone for an integrative network of the cluster and will link cluster management, structural projects (\textit{m}^4 \text{ Trial Service Center} and \textit{m}^4 \text{ Biobank Alliance}), and research projects. The external and internal information platform will support networking of researchers, physicians and companies along the value added chain. The project will establish an innovative integrated data management system and will be expandable by using a open source framework and generic solutions.
The m⁴ Data Integration System will develop and implement a data integration solution for heterogeneous, distributed systems that will allow structured acquisition of data and extensive annotation of samples. IT-based screening will facilitate patient recruitment for clinical trials.

A safety concept will be developed and implemented, including administration of user rights, security of data and processes, anonymization and protection of data privacy. The m⁴ Data Integration System web portal will offer an integration solution to access information from different databases via a service-oriented interface, displaying information tailored to target audience.
SP4
m⁴ Scouting & Incubation

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m⁴ Scouting & Incubation aims to optimize the process of
innovation in terms of technology transfer, financing, coop-
eration and exchange of knowledge. The programme will
exploit the innovative and commercial potential of acade-
imic research in Munich and give impulses for application-
oriented research in the target markets of m⁴. m⁴ Scouting
& Incubation is to increase the number and quality of spin-
offs and to continuously fill the development pipeline of the
m⁴ Cluster with new innovative projects. For the identified
projects, an early collaboration with m⁴ Biobank Alliance

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and m⁴ Clinical Trial Service Center is planned.

Specialised m⁴ Scouts will allow for the active search for innovative R&D projects at Munich Universities and research institutions. They will perform a market-oriented analysis, offer information and help to apply for the m⁴ Award. The m⁴ Science Club constitutes a large pool of experienced academic emeriti and former industry managers offering mentoring and coaching for selected research projects.

The m⁴ Award is a new regional pre-seed funding programme for highly innovative research projects in the target markets of m⁴. The projects will be evaluated by a panel of experts from biotech/pharma industry and venture capital regarding their innovativeness, feasibility and market opportunity. The winners will be awarded with funding, consulting and the benefits of m⁴ Incubation. The latter includes up to 2 years of funding, as well as consulting and an individual and professional project management. After the incubation period, the projects should have reached proof-of-concept and preferably have spin-off potential.
SP5
m⁴ eAcademy

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The m⁴ eAcademy will add two specialized master programmes with focus on the value added chain of personalized medicine to the excellent training programmes offered at Munich’s universities.

The goals are to offer a specific, comprehensive training in drug development and to educate optimally trained staff members for the location. To this end, a conceptual design of the curricula will be set up and an eLearning platform will be developed. The options for commercialization and implementation at universities or a commercial provider will be evaluated.

The m⁴ eAcademy will offer 2 new master programmes in

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English designed for 3 semesters. The curricula can be attended full time as well as part-time or individual modules only.

**Executive MBA Life Sciences Management**
The programme addresses young professionals with a background in Economic Science or Life Science and mediates knowledge for managers in the biotech and pharma section.

**Master of Science Translational Medicine**
Addresses graduates from Medicine or Life Sciences and prepares them for positions in research and development specialized on drug development.

The m⁴ eAcademy follows a blended learning concept with eLearning as a standardized preparation for classroom teaching units (8 days per semester). Possible extensions of the eLearning platform are an ePortfolio and a m⁴ specific job market.
PM1

Network of Excellence for Neuroendocrine Tumors Munich (NeoExNET™)

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Neuroendocrine Tumors of the gastrointestinal tract (GEP-NET) and of the pituitary represent a heterogeneous group of tumors. The resulting diversity of patient cohorts, thus, poses a particular challenge for clinical trials. To overcome this limitation within the proposed project we aim at the establishment of a Network of Excellence for Neuroendocrine Tumors which will allow assessment of therapeutic targets ranging from pre-clinical in vitro and in vivo testing as well as clinical phase I-IV trials. As common molecular pathways dysregulated in the course of tumorigenesis of this tumor entity allow therapeutic targeting by a number of pipeline compounds from the Novartis Oncology Group a

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strategic alliance between the involved academic centers and Novartis has been established. The proposed platform will concentrate leading centers in the field and provide a unique opportunity to further strengthen the international competitive position and visibility for this rare group of diseases.

The Neuroendocrine Tumor Center (NeoExNET\textsuperscript{M}) comprises a Clinical Study Platform, a Preclinical Study Platform and Central facilities which are situated at the University Clinic Munich (Campus Großhadern and Innenstadt) and in the Max Planck Institute for Psychiatry. This structure is complemented on all levels with the specific expertise of the Novartis Oncology Group. Project decisions within NeoExNET\textsuperscript{M} are taken by a Network Governing Board which consists of one member from each participating institute and a Novartis representative and will meet on a regular basis. Overall, NeoExNET\textsuperscript{M} as a structure will allow recruitment of a sufficient number of patients with heterogeneous disorders of the neuroendocrine system whilst applying standardized diagnostic criteria and procedures for the collection of biological material and employing an array of technological approaches in the participating laboratories.
PM2

Individualisation of cancer therapy combining biomarker profiling and functional drug screening in the Spheroid Microtumor Model

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Most tumor types in an advanced stage only show a minor response to standard chemotherapy. So, the 5-year survival rates are less than 50%. These unsatisfactory results cannot be significantly improved using targeted therapy based on one single biomarker.

Therefore the aim of the project is the personalisation of cancer therapy using a comprehensive biomarker profile combined with the functional test of a variety of drugs in mono- and combination therapy in the Spheroid Microtumor model. Based on the individual tumor characteristics,
the most efficient drugs with the lowest side effects are selected for each cancer patient. The technology platform will be validated in colorectal and gastric cancer as well as ovarian, cervical and breast cancer.

Procedure
1) Design of a protein chemical and genetic biomarker profile for different tumor types focussed on drugable molecules and therapy resistance markers.
2) Therapy selection using the Spheroid Microtumor technology: Identification of the most effective drugs for the individual tumor sample across different cancer types.
3) Correlation of the biomarker profile and the results obtained in the functional drug screening tests with clinical response to therapy and survival rates.
4) Determination of the therapeutic score for the individual cancer patient.

Partners wanted
1) Pharma/Biotech companies offering promising drugs
2) Clinical trials with a need for diagnostic tests to stratify individual cancer patients
PM4
Immunomonitoring in context of “investigator-initiated trials” with the Triomab® antibodies FBTA05 and catumaxomab

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Broad immunomonitoring programs along investigator-initiated trials (IIT) with patients suffering from peritoneal carcinomatosis or malignant B cell diseases will give novel insights into the induction of anti-tumor responses elicited by two bispecific trifunctional Triomab® antibodies anti-EpCAM x anti-CD3 catumaxomab (Removab®) or anti-CD20 x anti-CD3 FBTA05 (Lymphomun™), respectively.

For the first time, the possible induction of long-lasting tu-
more-specific immune responses due to cancer therapy with Triomab® antibodies will be analyzed along clinical studies. In addition, the elimination of CD133+ EpCAM+ putative cancer stem cells will be monitored during immunotherapeutic interventions with catumaxomab (IIT PC02 “multicenter, open-label phase II study to evaluate the efficacy of a 2-cycle immunotherapy with trifunctional bispecific antibody catumaxomab in addition to systemic chemotherapy in patients with peritoneal carcinomatosis from gastric or colorectal adenocarcinoma”).

Moreover, as it is further known from preclinical studies and some case observations secondary humoral and cell-mediated immunity induced by FBTA05-mediated immunization events will be comprehensively studied along the IIT trial STP-LYM-01 (“phase I/II dose-escalation study of the investigational trifunctional bispecific anti-CD20 x anti-CD3 antibody FBTA05 and donor lymphocyte infusion in patients with CD20-positive low- and high-grade B cell lymphoma after allogeneic stem cell transplantation”).
PM5
Development of innovative stem cell-based therapeutics for the treatment of malignant and non-malignant diseases

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Apceth GmbH & Co. KG

Novel therapy approaches based on mesenchymal stem cells (MSCs) hold great promise for the treatment of malignant and non-malignant diseases, where no adequate treatment options are available today.

Ongoing preclinical and clinical studies pave the way for successful application of the stem-cell based therapeutics particularly in the field of regenerative and anti-inflammatory medicine and cancer therapy. Due to acute and broad medical needs stem cell research is one of the most dynamic areas of life sciences today. It is expected that by the year 2013 the global market share for stem cell
therapies will amount to 32 billion $ with a predicted annual growth rate of 15%.

Apceth GmbH & Co. KG is a biotech company with expertise in development and production of the cell-therapeutics based on native and modified human MSCs. With its know-how, S2/GMP-facilities and Cleanrooms B/A Apceth stands on the interface of preclinical development, GMP-production and clinical trials. After obtaining the Manufacturing License for cell-based therapeutics, Apceth is about to start Clinical Trials Phase I/II for the treatment of Peripheral Arterial Disease with the cell therapeutics based on autologous unmodified human MSCs.

Within the “m^4-Cluster Initiative” comprehensive in vitro and in vivo preclinical and proof-of-concept studies of the novel therapies based on autologous genetically modified MSCs for the treatment of solid tumors will be conducted. These studies will be accompanied by identification and application of the tumor-specific biomarkers and will support development of a highly personalized cancer therapy and the oncoming clinical trials.
PM6
Determination of Immune- and Tumor-Parameters in Tumor Patients

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Cure of cancer is dependent on the individual response of tumors to therapy such as surgery, ionizing irradiation, chemo- and molecular therapies. Protection against tumor relapse and the development of distant metastases is regulated by the genetic variability of tumors, the tumor micromilieu and the immune status of a patient.

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Since standard morphological and immunohistochemical analyses for tumor staging are time-consuming, cost-intensive and display only a snap-shot of the disease there is a high medical need to develop new strategies for a more accurate definition of the aggressiveness of a tumor disease. The new method also should allow a close-meshed monitoring of the response to a therapeutic concept by a fast and reliable test system. The serum of a patient can be easily obtained and provides an ideal source for repeated analysis.

However, at present, a single tumor marker has not yet been defined in the serum which is able to predict the aggressiveness of a tumor and the outcome of a therapy. With the expertise of the consortium in different tumor-related markers, which contribute to tumor immunogenicity, we aim to study a panel of different parameters with antibodies for a better characterization of an individual tumor disease and for the prediction of the clinical outcome. The biotech companies involved in the project will adapt these methods, optimize the antibodies directed against the markers into kits and support the commercialization of the newly developed marker set.
PM7
Non-invasive Monitoring of Molecular Therapies in Oncology: Imaging Biomarkers of Therapy Response Bench-to-Bedside

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Introduction: With increasing importance of angiogenesis inhibitors in clinical therapies development of non-invasive and reproducible surrogate parameters of therapy response to angiogenesis inhibition is undergoing intense investigation. Traditional radiologic response evaluation such as tumor size dependent RECIST criteria have shown to be less valid to assess drug efficacy, as pharmaceutical properties are not primarily cytotoxic. Therefore, other surrogate response markers have to be introduced to quantify the more subtle early effects of novel anti-angiogenic agents. Multiple preclinical studies have highlighted the potential of dynamic contrast-enhanced (DCE-) imaging using magnetic
resonance (MRI) and computed tomography (CT) to generate functional parameters of microcirculation thought to reflect tumor response to anti-angiogenic treatment. Pivotal variables are the contrast media and the kinetic model applied for standardized analysis of signal intensity data.

**Material and Methods:** DCE-MRI/CT using experimental and clinically approved contrast media will be applied to generate functional parameters of tumor microcirculation via kinetic analyses with established and innovative kinetic models. Effects of different classes of anti-angiogenic agents on human cancer xenografts in rats will be investigated with DCE-MRI/CT and validated by immunohistochemistry and PET. **Aims:** Identification, validation and standardization of non-invasive biomarkers of therapy response to anti-angiogenic therapy using DCE-MRI/CT in an experimental setting with subsequent translation into clinical practice. Evaluation of novel classes of MRI/CT contrast media, developed for human use, focusing on a potential reduction of radiation exposure (CT) and augmented sensitivity. Identified imaging biomarkers will be translated into a clinical setting in patients to develop an integrated software platform for standardized analysis and calculation of parameters.
PM8
Development and evaluation of new CT- and MRI-
Techniques for evaluation of pharmaceutical treatment response

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Very early detection of treatment response will provide great influence on further medical treatment but may also include economic aspects. Until now therapy response is determined by measurements of morphological changes. New developments in CT (spectral CT) as well as in MRI (functional and/or molecular imaging) will provide additional functional parameters (e.g. blood flow, perfusion, cell death, etc.) for estimation of treatment response. In this project, we will develop and evaluate new CT, MRI, and optical imaging methods which will allow for an estimation of

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therapy response at very early stage of medical treatment. Our research plan is divided into 5 sub-projects: 1. Development of new CT methods for detection of new contrast materials. 2. Improvement of MRI-diffusion imaging for general and whole body applications. 3. Improvement of cell labeling techniques for optical imaging and MRI under therapy. 4. Evaluation of inflammatory processes using optical imaging including evaluation of different fluoroscopic contrast agents with respect to granulation tissue and overlay with x-ray imaging. 5. Development of magnetic virus targeting for tumor therapy.

The research will be conducted in collaboration of Technical University Munich with Helmholtz Zentrum Munich and Philips Healthcare. The department of radiology will lead the clinical and preclinical research and evaluation of new monitoring methods. Philips provides state-of-the-art MRI and CT technology and support from their research laboratories. In conclusion, our research will focus on development of new CT- and MRI-techniques for early evaluation of treatment response. Thus it will lead to better individual patient care and improved cost effectiveness.
PM 9
Evaluation of a new concept of radiodiagnostic and radiotherapy by using a small cyclic peptide with a threefold specificity for tumor cells

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itm has the worldwide exclusive rights from the Burnham Institute (UCSB) for a small peptide (CRGDKGPDC) called iRGD. The peptide has been identified and isolated from a phage display library by its affinity to tumor xenografts in mice from prostate, pancreas and breast cancer cells. The mechanism of action is threefold:

- binding to highly vascularised endothelial cells surrounding the tumor by the RGD sequence.
- cleavage by a specific protease localised on the tumor cell
- integration of the CendR peptide (CRGDK) into the tumor cell by activating the Neuropilin I receptor

Large particles like nanoworms (80 x 30 nm) coupled to

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Cys1 have been shown to integrate into tumor cells. First results with biopsies from fresh tumor material have shown that the same mechanism also works in humans.

itm together with its partner from Dept. of Nuclear Medicine will develop the iRGD peptide in the preclinical studies until clinical phase I. This will include the development of radionuclides and process developments for the radioactive labelling of the DOTA-iRGD peptide according to GMP guidelines and all the preclinical testing in animals.

The iRGD molecule coupled with the chelator DOTA can be used for diagnosis (labelled with Ga-68) as well as for therapy (labelled with Lu-177). So the iRGD molecule is the ideal candidate for individualised medicine.

We will expect that tumor specific radiodiagnostic and radiotherapy can gain a new momentum in the treatment of different tumors. As iRGD is integrating into tumor cells this opens up the possibility for therapy with beta- and alpha-emitting nuclides, which has been shown to overcome resistance against chemo- and radiotherapy in certain tumor types.
PM10
Development of microfluidic synthesis apparatus and methods for 18-fluoride labeled PET tracers in radiopharmacy research and personalized medicine

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Positron emission tomography (PET) is an in vivo imaging technology for medical and research applications. The diagnostic information of PET systems is determined by the selected radiotracer. Further improvements can be achieved by utilizing customized tracers which target the specific biologic processes of concern. Various receptors are over-expressed in particular disease types and radiolabeled macromolecules binding to these receptors can be used for scintigraphic visualization with PET. However, complex molecules are often difficult to label via conventional approaches. A method recently reported
by our group employs a direct 18F–19F isotopic exchange using [19F]di-tert-butylphenyl fluoroisilane as a highly efficient silicon-based fluoride acceptor called SiFA. Based on this knowledge, an optimized SiFA radiolabeling method will be developed and transferred to a microfluidic synthesis platform. Microfluidic technologies have been selected for their potential to increase reaction efficiencies due to a very high surface to volume ratio, as well as fast and precise temperature control. Additional advantages are more efficient usage of cost-intensive hot-cell space, low consumption of scarce reagents as well as a highly controlled, flexible, reproducible and reliable radiotracer synthesis due to process automation, and low-cost, interchangeable, disposable and quality-assured microfluidic key components.

The access to a more diverse spectrum of radiopharmaceuticals in combination with an efficient and reliable microfluidic production and research platform will extend the application area of positron emission tomography (PET). Economic, personalized radiotracer production focused on patient specific disease patterns enables exploration of alternative PET diagnostics and treatment in oncology and neurology. 1) Schirrmacher et al.: 18F-Labeling of Peptides by means of an Organosilicon-Based Fluoride Acceptor, Angew. Chem. 2006, 45, pp. 6047-6050.
PM12
Innovative Pathogenesis for Rhythm Disturbances & Risk Stratification in Cardiac Safety Assessments

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The disturbances in cardiac rhythm contribute substantially to the cardiovascular mortality and morbidity. Heart rhythm disturbances can occur in drug safety assessment, i.e. in clinical trials, with a serious life-threatening risk. The Drug-induced arrhythmia increases the risk stratification in cardiac clinical trials, so that it anticipates the development of new therapy strategies.

In this project, the genetic pathogenesis of the cardiac rhythm disturbances (individual susceptibility) will be investigated.

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By employing a special genome-wide association study (GWAS), the genetic contributions to the heart rhythm disturbances will be examined, so that new disease genes and their corresponding pathogenesis can be identified. Furthermore, the new detected disease genes and certain morphology-based surrogate ECG biomarkers will be compared and correlated in order to optimize and enhanced the risk stratification in cardiac clinical trials and drug safety assessments.
PM13
Development of prognostic, diagnostic, and therapeutic approaches in personalized medicine by integral network analysis

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A main goal of personalized medicine is to understand genetic diversion of individuals in order to predict disease outcome and effective therapies. In most cases, such biomarkers are derived by statistical analysis. This approach, however, suffers from the large number of genetic differences between patients and the noise level in biological samples. Therefore we want to develop an approach that aims at understanding the latent disfunction caused by the disease from regulatory networks. The goal behind this approach is to derive biomarker-sets which detect the significant functional modification which cause the disease and not just correlate with it.

To carry out these analyses we will integrate clinical data

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with genomic and transcriptomic data generated by Next Generation Sequencing (NGS). Based on these datasets a workflow will be generated that creates regulatory networks for each disease group. Thereby multiple lines of evidence will be taken into account including metabolic and proteomic data like gene regulatory interactions, literature, expert-curated annotations, and canonical pathways. In a second step, the networks will be examined for significant regulatory subgroups of genes/gene-products to derive biomarker-sets. Accounting for essential regulatory mechanisms the goal is to identify a more robust biomarker with respect to biological noise than statistical ones.

Thus, the sensitivity and specificity of diagnosis and/or prognosis should be improved compared to a single biomarker. The results of this analysis will be transferred back into the m4-data integration system for experimental evaluation and clinical trial by the m4-trial center. Successfully verified biomarker-sets can be used as a genetic test and will improve the diagnostic and/or prognostic predictions within the disease group.
PM 14
Reversible Streptamer reagents for clinical cell therapy

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The therapeutic potential of minimally manipulated cells opens up new avenues for the development of individualized therapies. For this purpose, a mild isolation procedure of defined cell populations is necessary under conditions approvable by regulatory authorities. The Streptamer technology is an attractive new option to purify cells for therapeutic applications.

The basic principle is based on the reversible labeling of cells with a positive selection marker. Subsequent targeted disruption of the multimeric complexes under very mild conditions enables the complete dissociation of the Streptamer reagents from the target cell population. The com-

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Complete removal of all reagents enables the Streptamer isolation procedure to circumvent potential side effects in clinical applications and provide cells with uncompromised biological function.

This project will focus on the development of new reversible selection reagents (MHC/Fab-Streptamers) to improve clinical cell isolation to offer optimal solutions for innovative personalized cell therapy. Streptamer-selected cells will be evaluated in preclinical mouse models to show ‘proof of principle’. Especially adoptive cell transfers will be used to analyze critical parameters (phenotype, cell numbers) of the cell product. As the Streptamer technology focuses on selection of therapeutically relevant cells, existing (approved, GMP-grade) magnetic isolation techniques are applied and adapted to the Streptamer isolation platform. The development of novel serial positive magnetic isolation techniques (by combining different reversible Fab/MHC-Streptamers) is of special interest. Ultimate goal is to optimize all procedures to reach highest purities and to transfer lab-scale protocols to GMP conform isolation procedures.
PM15
“Blood Donor BioBank“ - an innovative platform for the identification of early diagnostic markers

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Biobanks represent powerful tools for the identification of prognostic and diagnostic markers. The Bavarian Red Cross Bloodbank maintains a collection of 4.5 Mio blood samples obtained and stored under standardized conditions in a fully automated and access controlled storage facility. A large pool of regular and highly compliant blood donors allows for the conduction of large scale prospective studies. Pre-diagnostic plasma samples obtained in regular time intervals before diagnosis of severe diseases represent unique, valuable resources for the identification of early diagnostic markers.

Since its launch in 2006, nearly 70,000 donors have given their informed consent to participate in the “Blood Donor
BioBank”. All ethical and technical issues, such as data protection or sample storage and retrieval, were solved meeting highest standards, so that the “Blood Donor BioBank” is operating effectively since then.

The aim of the current project is a redesign and structural expansion of the “Blood Donor BioBank”. Samples will be selected according to medical indication and stored in a separate, additional storage system. In addition, an extensive socio-demographic and medical characterization will be carried out for selected samples. Healthy donors will be followed up in order to identify further “Blood Donor BioBank” participants and people at risk. A network among physicians, disease centers, health care officials and the m⁴ bio-bank alliance partners shall be established in order to achieve maximum impact and acceptance of the “Blood Donor BioBank”. We aim for economic independence and long-term sustainability by contracting industrial and academic research organizations.
PM16
Efficacy prediction of targeted cancer drugs

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The development of mechanism-based targeted drugs such as monoclonal antibodies represents a paradigm shift in the therapy of many diseases and most notably in cancer. Despite showing less side effects than conventional chemotherapies, targeted drugs are often active only in a subset of patients. Thus, biomarkers that allow classification of responder and non-responder are clearly needed. However, the identification of reliable biomarkers by conventional technologies such as genomic based platforms is far from routine. Therefore, KINAXO and Roche want to evaluate whether protein based phosphorylation signatures might serve as biomarkers as they directly link cellular malfunctions to individual cancer modes. In contrast to conventional diagnos-
tic methods such as antibody based approaches, mass spectrometry based phosphoproteomics allows identification and quantification of thousands of protein phosphorylations by combining sophisticated enrichment strategies with high-end mass spectrometric and bioinformatic analyses. Quantitative phosphoproteomics thus facilitates a systems-wide analysis of cellular signal transduction events, which is indispensable for the understanding of cancer relevant signaling processes.

Recently, innovative technologies such as isotopic labeling with amino acids in cell culture (SILAC), which allows quantitative mass spectrometry, were adapted to the analysis of tissue samples. In the discovery phase, the so called “Super-SILAC” approach is applied for example to analyze xenografts derived from mice that show response or resistance, respectively, when treated with targeted drugs under development. The identified differences in the respective phosphorylation patterns from the discovery phase will then serve as candidates for predictive phospho-signatures. In parallel, mass spectrometric based approaches will be established to analyze phosphorylation signatures from patient samples. The signatures identified in the model systems will then be used in a subsequent clinical validation phase to evaluate their predictive value.
PM17
smart™ - knowledge management infrastructure for m^4

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One aim of the cluster initiative m^4 is to build a systematic and sustainable knowledge base for personalized medicine and targeted therapies. The smart™ infrastructure provided by Biomax can help to build such a knowledge base. Smart™ is a highly flexible environment, which supports fast integration of heterogeneous data providing a semantically correct representation for reporting and data mining. Data coming from different sources, e.g., public databases or experimental results from different project groups, can be combined into a growing interconnected knowledge network. A web portal component allows users to easily browse and query the data network, and also to report results in standardized formats.

The open and flexible structure of the smart™ environment

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can help to build close associations between lead and cooperation projects. For different user groups, specialized data portals can be configured allowing access to defined sub-sets of the knowledge network.
smartm consists of four modules:
smart-km: knowledge management framework based on semantic networks
smart-portal: easy to access web portal solution for publishing to different user communities
smart-doc: an environment to generate standardized reports and abstracts applying semantic technologies
smart-SK: search optimization, topic suggestions and data mining through social knowledge network monitoring
All smart modules combined provide for a faster, better and more flexible way to answer questions related to personalized medicine and therapy.

Access to the smartm infrastructure is available through the following links:
https://ssl.biomax.de/m4/
https://ssl.biomax.de/m4/bioxm/jnlp
Users can get access on request by contacting andreas.fritz@biomax.com
T2
COR-1 in heart failure – a cyclic peptide which neutralizes anti-ß1 receptor-antibodies.
A novel approach in personalized medicine.

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Background: A novel concept for the treatment of heart failure is the neutralization of antibodies against the ß1-adrenergic receptor (Anti-ß1AR-Ab). COR-1 is an innovative drug which was tailored to treat the subgroup of patients in which these antibodies occur, and which can be identified by a specific companion bio-assay. It therefore represents a novel approach in personalized medicine.

In a rat model of autoimmune cardiomyopathy, COR-1 (given iv once monthly) neutralized Anti-ß1AR-Ab and prevented and/or treated Anti-ß1AR-Ab-induced myocardial damage, and completely reverted LV dysfunction over 3 – 6 months.
A first clinical phase I trial designed as a randomized, single blind, placebo-controlled study in 50 human volunteers showed that COR-1 in five dose groups (10 – 240 mg) was well tolerated, no drug-related side effects occurred. Pharmacokinetics revealed a favourable profile with an almost complete serum clearance within 60 minutes after administration. Pharmacodynamic investigation showed dose-dependent efficacy with almost complete scavenging of pathological anti-β1 receptor antibodies ex vivo at the two highest doses. No anti-COR-1 auto-antibodies occurred.

Aim of the currently planned study is to investigate the antibody-neutralizing cyclic peptide COR-1 in human patients with heart failure. The response to therapy should be significantly higher than with existing therapeutic concepts which are hampered by a large amount of non-responding patients, who do not profit from the respective therapies, but rather suffer from their side-effects.
T3
Preclinical and clinical development of a PI3 Kinase Inhibitor for the treatment of tumours

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The phosphatidylinositol 3-kinase (PI3K) pathway is a critical signal transduction pathway that regulates multiple cellular functions. Aberrant activation of this pathway has been identified in a wide range of cancers. The aim of this project is the development of a cancer therapy which selectively treats patients with genetic alterations in the PI3K signalling cascade.

So far, preclinical studies have shown that PI3K pathway inhibitors may have single-agent activity in a few types of genetically defined cancers, for example cancers with PI3KCA mutations or PTEN-deficient cancers. Data also suggest that
cancers with KRAS mutations as present in many colon cancers may be fairly resistant to PI3K inhibition.

Within the scope of this project the PI3K inhibitor WX-037 will be developed pre-clinically as monotherapy followed by clinical phase I studies in patients. Additionally it is planned to evaluate combination therapy with the MEK inhibitor WX-554 in pre-clinical and clinical setting. To this end, the ultimate goal will be to combine targeted therapies to achieve tumour regressions.

The project will be integrated into the cluster at various links, in particular interacting with the Biobank-Alliance, the Clinical Trial Service Center and ‘Verbund Molekulare Bildgebung’ (Molecular Imaging) to develop a patient tailored therapeutic approach within the cluster.
T4
MOR202, a novel targeted therapy for the treatment of multiple myeloma

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We developed a monoclonal antibody as innovative treatment for patients suffering from multiple myeloma (MM), a hematological cancer caused by the proliferation of malignant plasma cells. Despite recent advances in therapy, and more widespread use of transplant regimens, the majority of MM patients develop resistance to treatment, with median survival rates of less than 30 months for relapsed disease. There is a high unmet medical need for innovative forms of treatment to improve disease response rates and overall survival, with less toxicity.

Due to their high specificity, monoclonal antibodies repre-
sent a promising strategy for improving therapeutic efficacy. MorphoSys has developed a highly specific, human recombinant monoclonal antibody (MOR202) against CD38, a membrane protein which is highly expressed on malignant plasma cells and is thus a promising target for MM therapy. MOR202 is a tumor targeting, monoclonal antibody intended to recruit and activate specialized killer cells which can destroy the tumor cells. The antibody has demonstrated efficacy in a number of preclinical myeloma models, supporting entry into early phase clinical testing for safety and preliminary efficacy in a phase I/IIa clinical trial in patients with relapsed/refractory myeloma.

The project will be performed in collaboration between MorphoSys and the Klinikum rechts der Isar. Other clinical study centers in Germany and Austria will also be included. We will assess biomarkers to identify, for example, potential correlations with clinical response, which could guide further clinical investigation and may support selecting patients who would benefit from therapy.

In summary, based upon its target specificity and preclinical data, MOR202 is a promising novel candidate for myeloma therapy.
T5

Fc-Receptors as Targets for the Therapy of Autoimmune Diseases

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SuppreMol GmbH is a privately held biotechnology company that pioneers a novel approach for the treatment of autoimmune diseases which could lead to the cure of these disorders instead of merely treating their symptoms. The therapeutic approach is based on a unique expertise in the field of Fcγ receptors (FcγRs) which play a central role in the human immune system during the fight of infections, but also in autoimmune diseases.

The investigated drug SM101 is a recombinant, soluble human FcγRIIb protein. It competes with membrane bound FcγRs on immune cells for the interaction with immune
complexes (IC) and thereby prevents the binding of these IC to the cells. As a result, the feedback loop of autoantibody production, IC formation, and re-stimulation of immune cells is interrupted and additional inflammation, organ damage and immunological activation will be prevented. SM101 has been validated in relevant mouse models such as Collagen-induced Arthritis (RA), Experimental Autoimmune Encephalomyelitis (MS), and NZBW-F1 (SLE) and has shown strong efficacy in terms of decrease in inflammation and autoimmune reaction.

In the present subproject, it is the goal to develop SM101 for the treatment of Systemic Lupus Erythematosus (SLE) to demonstrate “Proof-of-Concept” in a multicentric Phase IIa study. SLE is a systemic autoimmune disease mainly affecting women in the child bearing age. During the disease flares are observed in which IC-mediated complications occur that can affect different organs. Focus of the development are SLE subcategories that primarily effect the kidneys (lupus nephritis) and the lung (lupus pulmonitis).
Heart failure represents a major public health problem affecting approx. 2% of the adult population in developed countries. Despite progress achieved by current medical and device treatment, the overall survival rate of patients diagnosed with heart failure remains poor and the development of novel treatment options is urgently needed. Ischemic and hypertensive heart disease are the most frequent causes of myocardial dysfunction. Both lead to prominent interstitial fibrosis, which is increasingly recognized as an important pathogenetic factor contributing to pathological cardiac hypertrophy, impaired contractility and malignant arrhythmias. Therapeutic strategies that directly aim to prevent the for-
mation of interstitial fibrosis are currently missing. Recently, we have described a microRNA-based mechanism that controls the survival of cardiac fibroblasts through regulation of the ERK-MAPkinase pathway. We found microRNA-21 (miR-21) to be highly upregulated in the failing myocardium where it de-repressed ERK-MAPkinase signalling through inhibition of the MAPkinase-inhibitor Sprouty-1. Therapeutic interference with a synthetic inhibitor directed against miR-21 (antagomir-21) effectively prevented the formation of interstitial fibrosis and cardiac hypertrophy in a mouse model of cardiac disease (left ventricular pressure overload). The current project aims to develop this novel anti-fibrotic therapeutic strategy towards application in a large animal model. In TP6, we will further characterize our established model of myocardial infarction-induced heart failure in the pig and develop a pressure overload-induced model of cardiac dysfunction. Together with QualiMed GmbH, we will apply antagomir-21 with a retroinfusion device regionally to the myocardium via coronary veins and test for efficacy of tissue uptake, knockdown of miR-21 expression and modification of miR-21 target genes in the myocardium. We will then conduct a therapeutic trial in both animal models and determine its effects on myocardial fibrosis, hypertrophy and cardiac function.
Tailored inhibitors against essential bacterial virulence factors

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The emergence of antibiotic resistance and cross-resistance is challenging medical care as well as pharmaceutical industry. However, the medical need is hardly met by the development of novel antibiotic substances, of which only few have been approved in the recent years.

The aim of this project is to develop novel small molecule inhibitors against important bacterial targets as highly selective antiinfective agents. This approach aims to reduce side effects as well as cross resistance.

The inhibitors are directed against bacterial proteins which are essential for establishment of the infection. The project will start with Helicobacter pylori g-
glutamyltranspeptidase as the first target and employ innovative technologies for small molecule drug discovery. New and powerful methods in computational and synthetic chemistry will be used for hit generation, hit-to-lead optimization, and ultimately aim for the development of a preclinical candidate.

In parallel, new targets will be identified and addressed to continuously expand the development pipeline. These will consecutively be transferred to the following steps in the drug discovery value chain.
T10

Development of TLR antagonist therapeutics for TLR-mediated autoimmune diseases

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Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoreactive B-cells producing autoantibodies to certain cellular macromolecules. Increased expression of type I interferon (IFN) occurs in immune cells (plasmacytoid dendritic cells, pDC) of lupus patients, is associated with disease severity, and may contribute to disease development linking pDC activation to SLE pathogenesis. Inappropriate or excessive activation of TLR7 and 9 by self RNA or DNA sequences is involved in the observed activation of the pDC IFN-alpha pathway in SLE pa-
Leading-Edge Cluster Munich
\(m^4\) — Personalized Medicine and Targeted Therapies

Suppressive synthetic oligonucleotides block DNA-mediated TLR9 and RNA-mediated TLR7/8 stimulation, and can presumably prevent autoimmunity. Investigating improved TLR7/8/9 antagonists and appropriate formulations will result in candidates for therapeutic development.

Our work will focus on the identification of improved antagonists specific for TLR7 or TLR9. Selected candidates will be tested for their in vivo efficacy in a lupus animal model (MRL\(^{lpr/lpr}\)) by assessing severity of disease. Disease markers, such as serum cytokine and autoantibody levels, will be determined by ELISA. Furthermore, severity of glomerulonephritis as morphological hallmark of SLE will be evaluated by histology, immunohistology and renal function. In addition, conjugates of phosphorothioate modified 2-deoxy-ribose 20mer's, inhibitors for TLR3/7/9, but difficult to deliver in vivo, will be designed, and tested for their in vivo activity. Additional improved in vivo delivery systems will be evaluated, either by combinations of LL37 and Hsp90 with inhibitory oligonucleotides or by oral delivery formulations which will be tested for their efficacy in MRL\(^{lpr/lpr}\) mice.
T12
Establishment of siRNA as new therapeutic platform suitable for personalized healthcare – Dynamic polymer systems to facilitate safe and efficient cytoplasmic delivery of siRNAs

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siRNA presents a novel class of therapeutics for multiple indications, especially also previously “undruggable” targets or individual patient groups with distinct gene mutations. For medical application, siRNA delivery vehicles for the specific and safe transport of siRNA to the target site are limiting. A modular approach bringing together chemically modified engineered siRNA, precise biodegradable polymers, and targeting ligands will form the basis of a platform to design ideal siRNA delivery vehicles for multiple indications.

Precise polymers are generated as libraries of monodisperse
carriers that are screened for optimum siRNA delivery in established in vitro and pharmacological in vivo model systems, specifically for tumor treatment.

Effective siRNA complexes will be subjected to optimization of formulation and stability studies, including cryoconservation and lyophilization, as a step towards clinical development. Efficient siRNA carrier formulations will be tested in pharmacological in vivo tumor models for their therapeutic effects against cancer.

The pharmaceutical development will be carried out by Roche Kulmbach GmbH, the Bavarian site and world-wide “Center of Excellence for RNAi Therapeutics” of Roche.
T14
Targeting of Biotherapeutics to the Lungs for Treatment of Chronic Lung Diseases

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The overall objective is the development of innovative, competitive biotherapeutics (e.g. proteins, antibodies) for improved treatment options for chronic lung diseases. In this project the preclinical basis for the development of inhalable biotherapeutics is created. A new application method (COALA-MOUSE-SYSTEM) will be developed by the Activaero GmbH, which is highly effective and hence ideal for new types of drugs (T14a). The Helmholtz Zentrum München will develop a biomonitoring method for determination of the biologically active dose of drugs delivered to the lungs (T14b). These new methods will be utilized to characterize the efficacy of a novel inhalable biotherapeutics.

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The project is structured according to the following work plan:
1. Development of a computational model to calculate the deposition of drug aerosols in the lungs
2. Evaluation of the clinical applicability of candidates for new biotherapeutics from an economic and clinical perspective
3. Development of the COAALA-MOUSE-SYSTEM for efficient and regionally targeted delivery of the biotherapeutics to the lungs of mice
4. Selection of a potentially new biotherapeutics and a matching REPORTER-MOUSE-DISEASE-MODEL for biomonitoring of the biologically active dose delivered to the lungs of mice
5. Characterization and validation of the COAALA-MOUSE-SYSTEM, the biomonitoring method of biologically active pulmonary dose and the computational model for pulmonary drug delivery
6. Preclinical investigation of the selected novel biotherapeutics for treatment of a chronic lung disease (proof-of-concept study)
7. Rating of the selected biotherapeutics on the basis of the study results in terms of efficacy and economic aspects
T15
PASylation®: Superior biopharmaceuticals with extended plasma half-life

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Many of the biopharmaceuticals currently used successfully in human therapy, e.g. erythropoetin, hormones, antibody fragments or peptides, are of relatively small molecular size and, thus, suffer from rapid kidney filtration. This leads to disappointingly short circulation times and considerably restricts their therapeutic benefit. Hence, in most cases repeated injections at short intervals and high dosage are required in order to achieve the desired therapeutic effect.

PASylation®, the genetic fusion with conformationally disordered polypeptide sequences comprising the amino acids Pro, Ala, and Ser, overcomes these problems and provides a
superior way to attach a solvated random chain with large hydrodynamic volume to a biologically active protein. Thus, the typically rapid renal clearance can be retarded by a factor 10 to 100. In contrast to established strategies to extend plasma half-life such as chemical conjugation with polyethylene glycol (PEG), the biological PAS moiety is fully biodegradable, biochemically inert, and does not require in vitro coupling.

Within the collaboration project, the innovative PASylation technology will be applied to different classes of biopharmaceuticals. A PASylated peptide hormone and a clinically relevant antibody fragment will be designed and produced in E. coli, followed by biochemical and biophysical characterization. The effects of the PAS moiety on pharmacokinetics will be examined in different organisms. Finally, an in vivo proof-of-concept for two PASylated proteins is anticipated.

This project will provide a basis for the development of superior biopharmaceuticals that permit less frequent and lower dosing together with better tolerability, thus making treatment cheaper and supporting patient compliance and safety.
T16
Recombinant spider silk films as new delivery device for biopharmaceuticals

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Thin films based on spider silk proteins produced using recombinant techniques represent a promising biomaterial. The combination of these protein films with low molecular weight pharmaceuticals and/or biopharmaceuticals is envisioned to be a useful depot for controlled drug release in the body.

During the research project, a reproducible production process for spider silk films concerning thickness, surface topology and chemical stability will be established. Critical factors are the underlying protein formulation and the environmental conditions during film casting. A detailed analysis
of the mechanical properties of spider silk films as well as information about biodegradation and compatibility are a prerequisite for their application in medical products. Polymers used in this field generally have to display a high mechanical stability, suitable biodegradation properties – not too fast and not too slow – and biocompatibility.

The loading of the film matrix with pharmaceuticals can be performed using several different methods. Starting from solution, the agent can be either mixed with the silk protein before casting the film. This results in a homogeneous distribution of the drug all over the silk film. A second approach starts with the already produced protein film which is subsequently loaded with the pharmaceutical on the surface. Embedding a layer of the pharmaceutical between two spider silk films displays the third available method tested in the research project. The success of the loading is controlled by investigating the release and degradation rates of the pharmaceutical from the spider silk film using *in vitro* and *in vivo* assays.
T17

Structure-based characterization of therapeutic antibodies

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During the past years, the development of monoclonal antibodies has been a major driving force in the discovery of new therapeutics against a plethora of severe human diseases including inflammatory diseases and several forms of cancer. The basis of an antibody’s efficacy is its ability to bind a specific target molecule with high affinity and selectivity, thereby altering e.g. cellular signaling, triggering apoptosis or recruiting the immune system to destroy cancer cells.

The efficacy and mode of action of a therapeutic antibody is based on the interaction with its target, defined by a specific epitope. Structural data, clarifying this interaction dur-
ing the early stages of antibody discovery is of great importance. It allows for selection of potential candidates according to their specific binding site, thereby accelerating the process of lead candidate selection or generation of improved follow-up compounds by directed molecular evolution. X-ray crystallography is the state-of-the-art technology to elucidate the three-dimensional structure of protein samples. However, currently this technology is only rarely used in antibody lead candidate selection, due to the complex process of crystallization and structure solution together with low sample throughput.

During this project both partners will collaborate to establish a technology platform for efficient elucidation of antibody-antigen-complex structures. MorphoSys will provide relevant antigen and antibody molecules, Proteros will provide advanced x-ray technology and structure solution know-how. Furthermore, known challenges in crystallizing whole IgG molecules and establishing production platforms for complex antigen molecules will be addressed, allowing for a faster and more efficient engineering of therapeutic antibodies.
P2
Transgenic Livestock Platform for Production of Recombinant Antibodies for Therapeutic Applications

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The main objective of our project is the development of single chain antibodies as a therapeutic drug against metastasizing forms of prostate carcinoma. Proliferation and activity of T cells will be stimulated by binding CD28 receptors. We will start with the construction of expressions cassettes for recombinant antibody fragments against PSMA (prostate specific membrane antigen) for transfection of tissue culture systems. In parallel we will generate recombinant bispecific antibodies in transgenic rabbits and characterize, test, and evaluate these antibody fragments.

For improving the amount of scFv antibodies we will breed transgenic lines carrying different constructs. To quantify
the concentration of collected plasma samples and purified antibodies new SRM (Selected Reaction Monitoring) assays will be developed and evaluated. These assays will also allow to evaluate ELISA protocols and to improve purification processes. The final goal of this part of the project is to establish a GMP production and purification of single chain PSMA antibodies.

Antibody fragments produced in transgenic rabbits will be tested by binding studies with human tumour and T-cells and by killing assays. Cross reactivity with different tissue and organ samples will be studied. Cytokine and histamine release of human PBMCs will be evaluated and toxicology studies will be performed. Purified scFv antibodies will also be tested in vivo in an established mouse model for human prostate carcinoma. After finishing the preclinical studies our purified antibodies should be ready for FIM studies.
P3
Qualification and Operation of the Sterile Facility in the Department of Pharmacy, LMU Munich

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The manufacturing of dosage forms (e.g. lyophilisates or parenteral solutions) is an essential although often disregarded step in the development of biopharmaceuticals, especially in the context of personalized medicine.

At the department of Pharmacy a sterile facility has been installed that meets the latest technical standard and current legal requirements.
Due to limited staff capacity it was not possible to perform the necessary validation steps and to compile the relevant documentation required for an application for a manufacturing license.
With the help of the start-up funding from the cluster initia-
tive Munich it will be possible to complete the last missing tasks.

Once the requirements are met, the sterile facility will be a flexible and cost-effective tool for the manufacture of sterile dosage forms for the cluster initiative:
The equipment can be used flexibly and the manufacture is usually possible at short notice.
The sterile facility offers the capacity for the production of batch sizes of approximately 2 - 10 liters. The filling of the preparation is feasible in vials and ampoules (1 - 100 ml). The equipment offers the possibility of filling only some few containers or loads of several thousand containers.

The sterile facility will:
- be a central service unit for the m⁴ Clinical Trial Center.
- be a critical interface between the development of new biopharmaceuticals in the lab and their first application in humans in the clinic.
- make it easier for the partners within the cluster initiative, especially research groups and small and medium-sized enterprises to enter the clinical phase of their projects.
PK1
Platform „Advanced Preclinical Animal Models“

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Suitable animal models for the evaluation of efficacy and safety of new drugs or therapeutic concepts are critical for their translation into clinical application. Although rodent models are widely used, they do not always reflect the clinical situation. Thus, animal models mimicking human anatomy and physiology more closely are urgently required. In this respect the pig is an excellent candidate. As monogastric omnivores pigs share many anatomical and physiological characteristics with humans. The excellent reproductive performance of the pig is ideal for a model organism. The first pig whole genome sequence and many other genomic resources will be available in the near future. Importantly, efficient and precise techniques for the genetic modification

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of pigs (reviewed in Aigner et al., J Mol Med 88, 653-664, 2010) are established in our consortium, facilitating the generation of tailored disease models. Models for important disease areas, such as diabetes (Renner et al., Diabetes 59, 1228-1238, 2010), cancer, osteoporosis, and cystic fibrosis are already established or in the process of being generated.

In addition, immunosuppressed and/or immunodeficient pig models will be generated by genetic engineering to facilitate the evaluation of biodistribution and therapeutic effects of human stem cells in large animal models. According to the recommendations of the International Society for Stem Cell Research this is an essential step in the clinical translation of stem cell therapies. Efficient techniques for targeted modifications of the pig genome facilitate the generation of tailored large animal models reflecting human disease mechanisms at the molecular level. These advanced preclinical animal models should provide an ideal link between the widely used rodent models and the human patient. Thus, an improved prediction of efficacy and safety of new therapies can be expected. In addition, large animal models may be useful in the discovery of biomarkers for companion diagnostics. Both should catalyze the process of drug development.
Bio\textsuperscript{M} Biotech Cluster Development GmbH

Bio\textsuperscript{M} serves as the management agency of the Biotech Cluster Munich for more than 12 years. Bio\textsuperscript{M} is the first contact point for all biotechnology companies and startups in the region.

Bio\textsuperscript{M} provides support in marketing, communications, and public promotion, also maintaining an information portal at [www.bio-m.org](http://www.bio-m.org).

The web site offers an extensive company-database, news updates and a job forum. In addition to business advice, Bio\textsuperscript{M} offers a wide range of seminars and events to biotech entrepreneurs and their employees.

Through our extensive network we can also assist Munich companies in finding the right contacts and partners critical to a successful business development. For example, Bio\textsuperscript{M} is local partner of the EBD-Event “BIO-Europe” 2010, the biggest partnering event for Biotech and Pharma in Europe.

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m^4 — Personalized Medicine and Targeted Therapies

On behalf of the Bavarian State Ministry of Economic Affairs, Infrastructure, Transport and Technology, BioM was mandated to manage the Bavarian Biotechnology Cluster as part of the governmental “Cluster Initiative Bavaria” (www.biotech-bavaria.de).

The Munich Biotech Cluster is a constantly growing hotbed of innovation. The Greater Munich Area counts over 20,000 persons employed by more than 350 companies in the life science sector (Biotech, Pharma, CRO, Suppliers). In addition excellence in science at the universities, Max-Planck-Institutes and the Helmholtz Zentrum München with about 10,000 scientists puts Munich to the top regions all over Europe.

Since 2010, BioM manages the m^4 program being funded by the Leading-Edge Cluster Competition part of the national “Hightech-Strategy”. Management in this respect includes project monitoring, controlling, evaluation and revaluation.

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