munich biotech CLUSTER

m⁴ Personalized Medicine in Munich

www.m4.de

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Content

Editorial

Dear Reader,

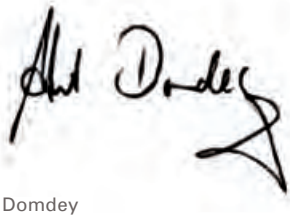
Since its beginnings in the late 1980s, the biotechnology sector in the Greater Munich area has always had a lively history. Within the first 5 years, 30 companies were founded, of which *MorphoSys*, *Medigene* and *Micromet* are the most famous. In 1996, a second wave of companies were founded, following the region's success in the federal government's BioRegio Competition, leading also to the establishment of *Bio^{M} Biotech Cluster Development* GmbH. Since then, *Bio^{M}* has been serving as a cluster management agency and has supported the region in the transformation process towards a leading European biotech cluster.

For the strategic development of the region, the cluster management is constantly in discussions with the key players in Bavaria, the biotech companies as well as academic research institutions and – a quite recent and valuable completion – the university hospitals. All of them share the idea and vision that personalized medicine is the key strategy for better patient care and for effective drug development, suitable to sharpen Munich's profile in the global competition and to meet the needs of tomorrow's healthcare system.

The idea benefited enormously when, in 2010, the Munich initiative m^4 – *Personalized Medicine and Targeted Therapies* was successful in the nation-wide *Leading-Edge Cluster Competition* and attracted funding and investments of a total of € 100 million, including project funding for companies as well as academic partners and improvements of the local framework conditions for the development of personalized medicine. All these activities aim to develop Munich into an *International Centre of Excellence for Personalized Medicine* by the year 2020.

In this booklet, you will find all projects of the m^4 programme, a snapshot of personalized medicine in Munich. Many more highly interesting projects in personalized medicine as well as a growing number of companies with expertise in the field are active in the Greater Munich area. For further information (e.g. up-to-date news, a company data base, a job market and an events calendar), please visit the website of the Munich Biotech Cluster m^4:
www.m4.de

Best regards,



Horst Domdey
CEO, Bio^{M} Biotech Cluster Development GmbH
Speaker of the Leading-Edge Cluster m^4
Martinsried, June 2012

Personalized Medicine

In recent years, discussions between the biotechnology industry, local researchers and clinicians in Munich have led to an initiative for personalized medicine, aiming for improved patient care and accelerated drug development. These three partners – brought together by the cluster management agency *Bio^{M}* – formed the nucleus for the long-term vision of personalized medicine in the drug development sector of the Greater Munich area, and thus for the Leading-Edge Cluster initiative *m⁴ – Personalized Medicine and Targeted Therapies*.

m⁴ represents the four key players that potentiate their strengths by collaboration: the biotech industry, the academic research institutes, the hospitals and the cluster management.

This brochure gives an overview of the more than 40 ongoing projects funded within Munich's Leading-Edge Cluster programme, focusing on targeted therapies in cancer, heart failure or immunological diseases, on biomarkers in high medical need indications like multiple sclerosis and on disease-independent biomarker panels – just to mention a few topics of the projects described starting from page 14.

The strategic aims of m⁴ are:

- Advancing cooperations between biotech companies and academic research, especially for biomarker development
- Accelerating the translational process from research to patient care by connecting research and hospitals more closely
- Strengthening platform technologies for drug and biomarker development
- Improving framework conditions for personalized medicine through infrastructure projects, for example by a combined biobanking initiative
- Enhancing competencies along the two value added chains of therapeutics and diagnostics

With the momentum of this programme, Munich is developing into one of the main drivers in this field in Europe and is setting the groundwork for growing into a *Center of Excellence for Personalized Medicine*.

The Leading-Edge Cluster Competition

The Leading-Edge Cluster Competition was launched in 2007 by the German Federal Ministry of Education and Research (BMBF) to support the strategic development of high-performance clusters. It aims to strengthen Germany's position as a top location for innovation, capable of facing international competition as well as securing and creating growth and jobs in the process. The competition is open to clusters formed by business and science in all sectors. The initiative *m⁴ – Personalized Medicine and Targeted Therapies* placed the Munich Biotech Cluster among the winners of the second round of the Leading-Edge Cluster Competition in 2010. Funding of around € 40 million granted by the BMBF is matched by industry partners who will contribute more than the equivalent amount from their own resources. The Bavarian Government is providing € 2 million to support the development of the cluster management and a further € 8.5 million for a Bavaria-wide pre-seed funding programme for personalized medicine (see page 33, m⁴ Award). The management of the Leading-Edge Cluster m⁴ was commissioned to the not-for-profit organisation *Bio^{M} Biotech Cluster Development GmbH*.

Healthcare Today and Tomorrow

Today, Germany maintains one of the best-developed healthcare systems, but the ageing society is also increasing economic and scientific challenges, as a higher life expectancy is connected with a higher risk of illness.

Major breakthroughs in research and development in the therapeutics industry have been made in the last decade, but there are still many diseases without a satisfactory cure – often those with a lower number of people being affected. These so-called *orphan diseases* still represent an unmet medical need. For common diseases, there are often several drugs available, but blockbuster drugs for very widespread diseases like hypertension, heart failure or cancer only show low efficacy: some patients respond well to the therapy but others do not. And even worse, severe side effects may afflict some patient groups. In these cases, the physician has to try different therapy options until a suitable treatment is found.

Diseases – even with the same symptoms – differ because patients are different. Every person has a different genetic predisposition that can lead to a an increased susceptibility for a certain medical condition. Genetic variations and different pathomechanisms compromise therapy response. Life style and epigenetic factors affect the metabolism, which is important, among others, for the uptake and release of a drug. Even the individual support by family and friends as well as the personal attitude can be variables at the crossroad of being healthy or getting ill. In combination, all these factors decide whether a drug is effective or not in the individual patient.

It is not possible and not affordable – at least not in the near future – to develop a tailored drug for every individual patient. However, there is undoubtedly a need to improve patient care, to better select the right drug for the right patient, to avoid treatments that are not effective and to minimize the risks of severe side effects. Personalized medicine aims to answer these challenges by *stratification* – by dividing patients into subgroups according to certain physiological or genetic parameters, which subsequently allows a more specific treatment.

Drugs against	Effectiveness in %
Hypertension (ACE inhibitors)	10 - 30
Heart Failure (beta blocker)	15 - 25
Depression	20 - 50
Asthma (beta-2-agonists)	40 - 70

The effectiveness of medical drugs is limited, e.g. only a fraction of patients responds to certain standard therapies and subsequently has to be treated with an alternative. For efficient health care, stratification of patients into subgroups, which are treated according to their specific diagnosis, is required. Source: The Personalized Medicine Coalition, 2006.

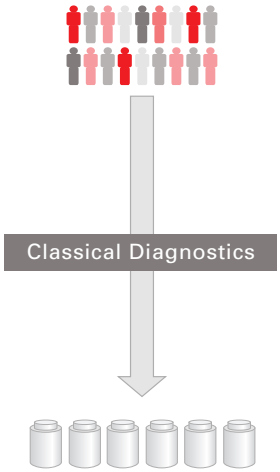
Biomarkers - the Key for Stratification

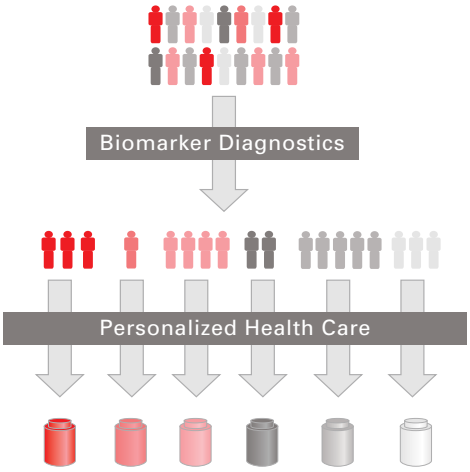
A therapeutic biomarker can be every measurable capable to aid therapy decision by:

- Predicting effectiveness
- Predicting drug tolerance
- Assisting dose finding
- Monitoring therapy response

Biomarker tests (companion diagnostics) provide information on molecular markers, e.g. a combination of genetic information, protein levels and immunological components. In addition to the clinical data of the patient, this serves as a guideline for estimating the success of a therapeutic strategy before, during and after drug treatment. Prognostic biomarkers serve to estimate disease progression.

Further biomarkers are needed for patient stratification for targeted therapies, that are one aspect of personalized medicine. Targeted therapies directly address the molecular cause of a disease, rather than interfere with general





Personalized medicine strives to provide more effective and safer therapies by providing tailored treatments for subgroups of patients.

cell processes like cell division, as it is done in common chemotherapies. For example, a tumour may be caused by a mutation in a certain signalling pathway controlling cell proliferation, which can constitute the biomarker for this specific type of cancer. A specific inhibitor of this pathway, that may even selectively address the mutation, can subsequently constitute an anti-tumour agent. Thus, for targeted therapies, the biomarker is the drug target molecule itself.

To date, the use of biomarkers as a companion diagnostic is still not routine. But once it becomes widely understood that companion diagnostics, which constitute only 2-3 % of the overall health care costs, can positively influence about 70-80 % of this total expenditures, efforts will intensify to establish more biomarker tests in routine clinical applications. Once this first step is made, the next step will be to develop diagnostics for preventive care, allowing medical intervention before a disease even appears.

m⁴ – Personalized Medicine and Targeted Therapies

Addressing the development of targeted therapies and orphan diseases, the high number of innovative small and medium-sized biotech enterprises in the Munich biotech region, with its close proximity to academia and both university hospitals, has the ideal prerequisites to strengthen the efforts towards personalized medicine in Germany. Driven by the Leading-Edge Cluster Competition, researchers in the biotech companies, at the universities, and the hospitals closed ranks to develop more specific therapies and biomarkers. Due to their very close cooperation, it is possible to transfer current research into clinical development much faster. Through the strong involvement of the biotech industry, the further development of new drugs will be realised. Current local developments are, for example, a targeted therapy for heart insufficiency which relates to a specific high-risk group of patients (company *Corimmun*, see page 20) as well as an innovative targeted therapy for the treatment of multiple myeloma being developed by *MorphoSys* (see page 16) - just to mention two of the many innovative approaches within the Munich Biotech Cluster m⁴ (see page 14). The four m⁴ partners – biotech industry, academic research, hospitals and the cluster management are shortly portrayed on the following pages (see page 8).

What's in a Name?

Is it personalized medicine, individualised medicine or stratifying medicine? Each of these terms has its pros and cons: "personalized medicine" is an internationally established catch phrase but from a philosophical point of view the term "person" should be reserved for addressing a human being as a whole, with psychological and social aspects, and is used incorrectly when referring solely to biological factors. This is one reason why (at least in Germany), the wording "individualised medicine" has its advocates. "Individualised" indeed stresses the biological aspects but it might also raise false expectations of drugs tailor-made for each single patient. "Stratifying medicine" seems factually correct, but cumbersome and for non-experts incomprehensible. Therefore it is rarely used and there is no ideal wording.

Additionally, one should remember that the term "personalized medicine" is rather new, but the embracement of genomics and molecular biology does not re-invent medicine. It simply uses and combines all diagnostic methods available to deliberate about therapy options. In this respect, personalized medicine shows no major difference to the medicine practiced ever since the beginning of health care. Maybe therefore, in some years, it will neither be called personalized, nor individualised, nor stratified medicine, but just "medicine".

Interview Science and Society

Prof. Domdey, how would you define personalized medicine?

Personalized medicine strives to improve patient care by identifying individual factors that allow for a prediction of disease progression and therapy outcome. This concept of integrated, patient-oriented care adjusts the whole decision-making process to the individual needs of a patient by combining and analysing all available data: patient history, clinical records and molecular information. It is true that the inclusion of previously not that easily available genetic information was the starting point of a personalized medicine concept, but it is a common misconception that personalized medicine solely means genetic determinism. It is the meaningful combination and integration of data that will lead to the development of more specific drugs and test systems, which will in turn lead to better patient care.

Many people show a reluctance towards genetic testing. How would you answer to the fear of the "transparent patient"?

I am confident that this worry can be put at ease as soon as the patients realise the actual benefit for their health. Of course, a trustful patient-practitioner relationship is needed to share sensitive genetic information – but this is true for all kinds of patient data. It is crucial that the patient does not perceive genetic testing as a verdict or destiny, but as an empowering tool that permits informed decisions. Therefore, we need excellently trained practitioners and informed patients.

Would you recommend whole-genome sequencing for everybody?

I think these techniques should be used with a sense of proportion and purpose, rather than economic interest. There are cases where targeted sequencing provides the one missing piece of information for a clear diagnosis or choice of treatment. On the other hand, a calculated assessment of a person's risk of developing a certain disease at one time or another does not provide any help for most people. Personalized medicine will unleash its full potential only when diagnostic data can be translated into an effective, preventive health service.

Interview with Prof. Dr. Horst Domdey, CEO of Bio^{M} Biotech Cluster Development GmbH and speaker of the Leading-Edge Cluster m^{4}.

To date, there is quite a hype about personalized medicine. Why are you confident there is more to it than pharma's next marketing gag?

I do not feel that personalized medicine is mainly driven by the pharmaceutical industry. It was rather started by practitioners who were wondering why some patients benefited from a therapy whereas others did not, and by researchers who unravelled signalling pathways and thought of drugs specifically addressing target molecules. Today, personalized medicine is already clinical routine in some indications. For example, the treatment of acute myeloid leukaemia is not feasible anymore without the prior diagnosis of the specific disease subtype. In other medical fields, personalized medicine is still in its early stages, but as soon as its benefits are proven, patients and practitioners demanding the best possible treatment will be the driving force for a wider implementation of personalized medicine concepts.

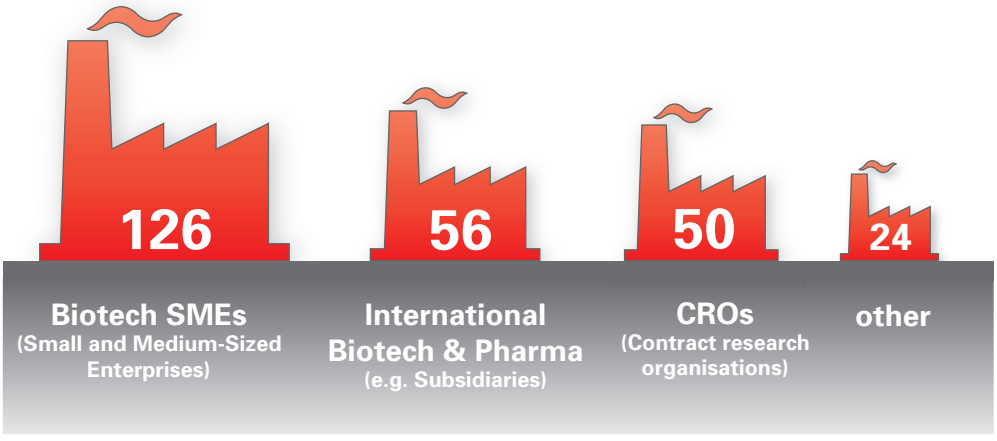
Munich Biotech Cluster m⁴

The Biotech Industry in Munich

The remarkable academic research background in Munich has been the basis for numerous innovative spin-off companies since the early 1990s. This has led to the development of a dynamic and well-connected biotech cluster of international recognition. Today, 256 companies are working in the biotech sector in the Munich region – half of them small and medium-sized enterprises (SMEs) followed by subsidiaries of international biotechnology and pharmaceutical companies as well as (clinical) contract research organisations (CROs). Among the international pharmaceutical companies, *Roche Diagnostics*, a pioneer in personalized medicine, has to be mentioned as one of the triggers or trendsetters for the Munich biotech development. Their site in Penzberg (south of Munich) is the largest research & development and production plant of *Roche* in Europe with more than 4800 employees.

The core competence of the regional biotech sector is the development of novel, innovative drugs and diagnostics. A big part of this is the research and the development of orphan drugs, which are therapeutics for niche indications that address significant unmet medical needs. The core of companies with drug development projects is embedded in a regional network of companies providing state-of-the-art technology platforms, consumables, reagents and equipment, as well as strong and versatile service providers.

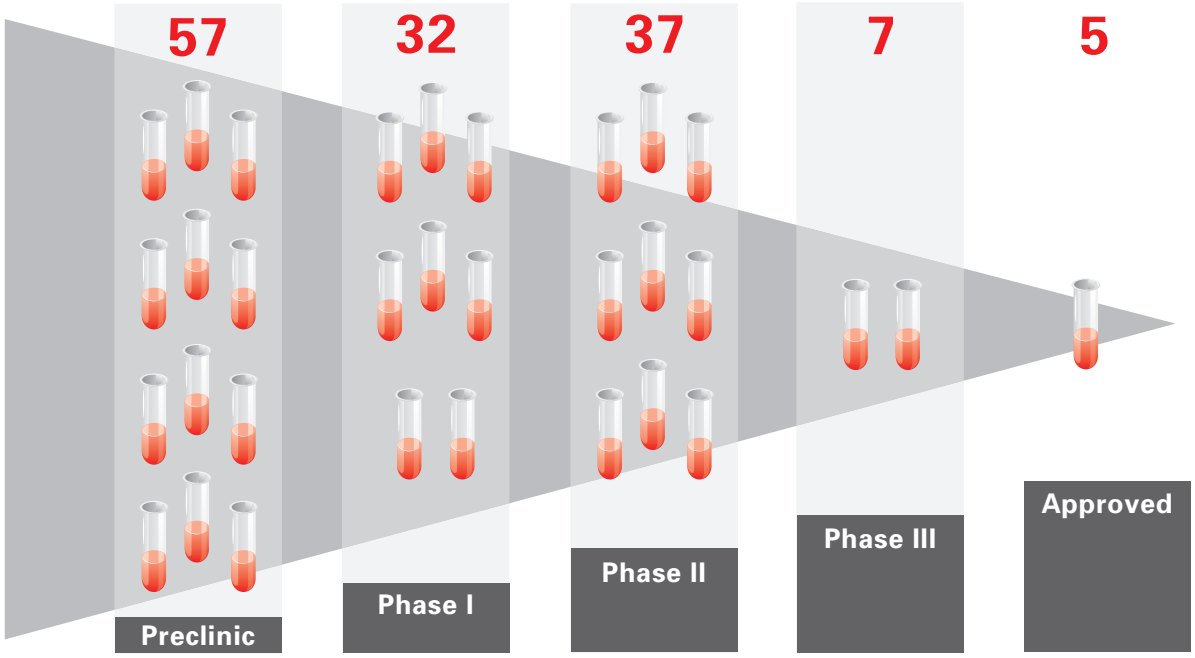
Munich-based *Medigene* was the first biotech company in Germany to receive approval for a drug by the FDA (US Food and Drug Administration) in 2003. In 2009, *TRION Pharma* together with *Fresenius Biotech* got the very first "Munich Antibody" approved by the EMA (European Medicines Agency), removab, which is a trifunctionally active antibody interacting with three different targets on tumour cells and cells of the immune system. Today, 5 out of the 9 SME-developed biotechnology drugs that are approved in Germany are "made in Munich".



Number of biotech companies in the Greater Munich area. Source: Bio^{M}, 2011.

Taken together, Munich's innovative SMEs working on therapeutics are accumulating a currently well-filled pipeline of drug candidates comparable to a big pharmaceutical company. Cancer therapeutics, especially for leukaemia, pulmonary cancer and solid tumours, account for almost half of the pipeline candidates (45 %). About 8 % of the drug development projects target inflammatory as well as autoimmune disease, for example rheumatoid arthritis. A smaller fraction deals with cardiovascular diseases, infections, neurological diseases and other conditions. The wide spectrum of indications is also reflected by the projects included in the m⁴ programme, as described starting from page 14. Most of the biotech SMEs focus on targeted therapies and cooperate with diagnostics companies more and more frequently to develop companion diagnostics.

Indications of drug development programmes in Munich's small and medium-sized biotech enterprises in percent. Missing 31 % other or undisclosed. Source: Bio^{M}, 2011.



Number of clinical studies for drug candidates of Munich's small and medium-sized biotech enterprises. Source: Bio^{M}, 2011.

Cluster Management by Bio^{M}

Since 1996, Munich's biotech sector has been supported by *Bio^{M} Biotech Cluster Development GmbH*, a not-for-profit service company located on the life science campus Martinsried in the Southwest of Munich. *Bio^{M}* is sponsored by the Bavarian State Ministry of Economic Affairs, Infrastructure, Transport and Technology and the German Federal Ministry of Education and Research and has been commissioned with several tasks and projects which aim to foster Bavaria's biotechnology sector.

Bio^{M} offers several services, in particular for small and medium-sized biotech enterprises:

- Network of Bavarian and international biotech locations
- Start-up consulting
- Financing & funding opportunities
- Business development
- Scouting & technology transfer
- Coaching & training
- Internationalisation strategies
- Public relations & marketing
- Trade fairs & events
- Databases (companies, job opportunities and more)

Please visit:
www.bio-m.org and www.m4.de

Academic Research in Munich

One of the main sources of Munich's biotech industry is formed by the excellent basic research in all fields of life sciences carried out at the two internationally renowned universities as well as in various other academic research institutions like the *Max Planck Institutes* and the *Helmholtz Zentrum München.*

Basic research perpetually brings forward new and innovative therapy concepts. New-found understanding of biological pathways in medical conditions, for example, has often inspired new approaches for targeted therapies. Munich is characterised by a remarkably close connection between academic research and the industrial application of scientific results, providing ideal conditions for progress of the personalized medicine approach to drug development.

The **Ludwig - Maximilians - Universität** (LMU) is one of the largest universities in Germany and comprises humanities as well as natural sciences with the departments biology, chemistry and pharmacy, medicine and physics. A central research facility of the LMU is the *Gene Center* dedicated to interdisciplinary research in the field of molecular biology and biochemistry, focusing on the regulation of gene expression and systems biology. This institution was established on the

Campus Martinsried/Großhadern. Front, from left to right: Biozentrum of the Ludwig-Maximilians-Universität (LMU), Innovation and Start-up Center for Biotechnology (IZB), Max Planck Institute of Biochemistry. Back, from left to right: Department of Pharmacy and Chemistry (LMU), Gene Center, and university hospital Klinikum der Universität München (LMU). Source: IZB.

Innovation and Start-up Center IZB Martinsried. Source: IZB.

campus Martinsried/Großhadern in the Southwest of Munich in 1984 and became a crystallisation nucleus for the emerging biotech sector. Nearby, the *Innovation and Start-up Center for Biotechnology IZB Martinsried* was opened in 1995 and today, after several extensions, it hosts about 60 biotech start-up companies. One of its former tenants is *Micromet*, which was founded as a spin-off from the LMU in 1993. The specialist for trifunctional anti-cancer antibodies was recently acquired by *Amgen* in the so far largest biotech deal in Germany. In direct vicinity, the *BioMedical Center* is being built, which will interlink biomedical basic and clinical research, bringing together the currently dispersed scientists in one location to facilitate and boost interdisciplinary ideas and projects.

The **Technische Universität München** (TUM) focuses on application-oriented research in engineering and natural sciences. The technical campus in the North of Munich in Garching hosts among others the departments of chemistry and physics as well as a number of start-up companies. The same combination of research and industry is set in Freising-Weihenstephan, where the TUM maintains the *Center of Life and Food Science* in close proximity to the life science incubator *IZB Freising*. Research on this life science campus is focused on basic biosciences like microbiology of pathogens, genetics or protein sciences as well as the life cycle of food and renewable raw materials – on the site where beer brewing was reinvented around 1040 AD in central Europe.

In Munich, three institutes of the **Max Planck Society** address life science topics: the Max *Planck Institute of Biochemistry*, the *Max Planck Institute of Neurobiology* and the *Max Planck Institute of Psychiatry*. Providing world class protein research since 1973, the *Max Planck Institute of Biochemistry* was the initial point of today's high tech campus Martinsried/Großhadern. One of its most famous spin-offs is *U3 Pharma*, which today is an affiliate of *Daiichi Sankyo* and constitutes their Munich-based European cancer research center. The pipeline focuses on targeted therapies that address genetic mutations in the patient's receptor molecules to provide a personalized treatment.

The **Helmholtz Zentrum München** – *German Research Center for Environmental Health* is located at the northern city boundary. The center's scientific institutes and independent research departments are dealing with key topics of human health like diabetes, respiratory diseases or neurodegenerative disorders. The overall research objective is to transfer newly gained knowledge into medical applications.

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Technische Universität München

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Technische Universität München, Campus Garching. Source: Faculty of Informatics, TUM.

Hospitals in Munich

With its two university hospitals, Munich is a world-renowned location for high tech medicine.

The **Klinikum der Universität München** of *Ludwig-Maximilians-Universität* is one of the largest hospitals in Europe with about 2,300 beds. Its largest facility is the Klinikum Großhadern, further hospitals are located in the city center. The university hospital of *Technische Universität München* is called **Klinikum rechts der Isar** and provides about 1,100 beds.

Both university hospitals provide patient care in a wide range of specialised clinics. Cooperation projects between the hospitals help to further improve patient care for rare medical conditions, e.g. neuroendocrine tumours (see page 24). The high case numbers make Munich an interesting location for clinical studies, also for rare diseases.

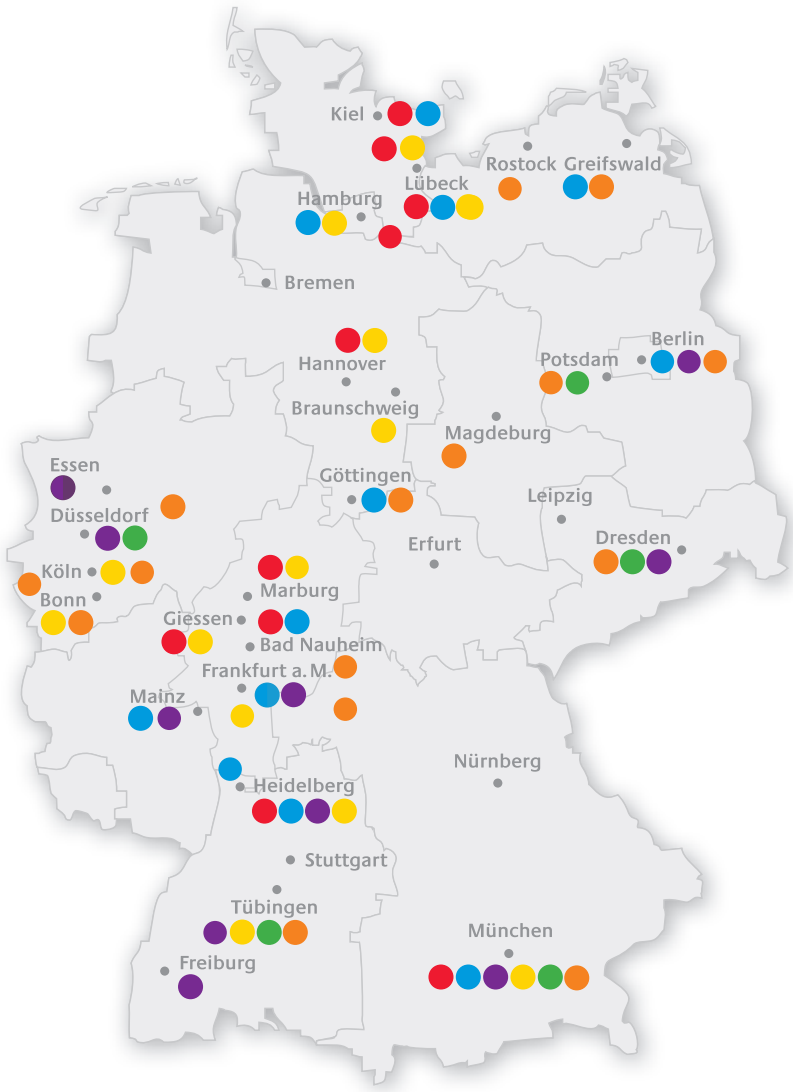
Excellent preclinical and clinical research in all fields of medicine is carried out in the hospitals and in various research facilities, e.g. the autonomous *Munich Heart Center* and the newly established *Munich Cancer Center*. Additionally, a new central institute for a translational oncology research *(TranIsaTUM)* is being established. It will host interdisciplinary teams with the ambition to accelerate the transfer of scientific results into patient care.

Both university hospitals transfer innovative developments and scientific results not only into better patient care, but also into state-of-the-art teaching of medical students. Besides the university hospitals, there are more than 65 further public or private clinics in the region.

The university hospitals cooperate intensively with academic institutions in medical research, for example in the **German Centers for Health Research**, a nation-wide call by the German Federal Government. Starting in 2009 with

University hospital Klinikum der Universität München (LMU), Klinikum Großhadern. Source: Rainer Herrmann.

University hospital Klinikum rechts der Isar (TUM). Source: Klinikum rechts der Isar der TU München.



German Center for Lung Research (DZL)
German Center for Cardiovascular Research (DZHK)
German Consortium for Translational Cancer Research (DZK)
German Center for Research into Infectious Diseases
German Center for Diabetes Research (DZD)
German Center for Neurodegenerative Diseases (DZNE)

German Centers for Health Research. Source: BMBF/BIOCOM.

an overall budget of € 700 million, six virtual centers connecting partner institutions all over Germany have been established. The aim is to pool cutting-edge research in a number of particularly important common indications: cancer, cardiovascular diseases, metabolic diseases, infectious diseases, lung diseases and neurodegenerative diseases. The focus on translational research will transfer scientific results into regular medical care faster and more effectively. Munich is the only location in Germany that is represented in all six centers, impressively demonstrating its broad competence in biomedical and health sciences and in all main indications.

Projects

All projects funded by the Leading-Edge Cluster m⁴ are united by the goal to foster personalized medicine in Munich. There are currently 35 m⁴ research and development projects ongoing, mainly cooperations between biotech companies and academic research groups. They combine their knowledge to address different problems in the value added chain of personalized medicine: they include drug development projects in preclinical or clinical development, proof of concept studies of new therapeutic or diagnostic approaches, as well as platform technology developments. Additionally, five m⁴ structural projects are being established to improve the local frame work conditions for personalized medicine at the location. The m⁴ Biobank Alliance brings together the key players from the region and addresses the need of high quality biosamples for biomarker research. It establishes common standards and a central access point for industry research projects (see page 28). As companion diagnostics and biomarker validation add new challenges to clinical trials, the m⁴ Trial Service Center is being set up as a central point of information for clinical development focusing on innovative and adaptive study designs including biomarker development (see page 27). Further programmes support technology transfer (m⁴ Scouting & Incubation, page 32), specifically train high-level staff (m⁴ eAcademy, see page 31), and manage data flow (m⁴ Data Integration System, see page 30) to further develop the sustainable development of personalized medicine in Munich.

m⁴ Research and Development Projects

Oncology

The concept of personalized medicine originated in tailored cancer therapies. Today, most of the approved drugs with obligatory or recommended companion diagnostics are anti-tumour agents with other indications slowly picking up. Even though many cancer drugs are on the market, there is still a medical need as tumours can originate and develop very differently and therefore need different treatments taking into account multiple parameters from the molecular basis up to the patient´s life situation. Correspondingly, various projects funded by the Leading-Edge Cluster *m⁴ – Personalized Medicine* deal with diagnosis and therapy of cancer with the goal of better patient treatment.

Therapeutic Antibodies

MorphoSys is one of the world's leading biotech companies with a proprietary technology platform called the HuCAL-antibody library. Together with its partners from the pharmaceutical industry (*Novartis, Roche, Pfizer*, among others), *MorphoSys* has developed a therapeutic pipeline with more than 70 antibody-based drug candidates, e.g. against cancer, rheumatoid arthritis, and Alzheimer's disease. To date, 21 antibody development programmes are in diverse stages of clinical trials. One of them is the m⁴ project, which is advancing the clinical development (phase I/IIa) of MOR202, a targeted therapy against the haematological cancer **multiple myeloma** (see page 16). Besides MOR202, there are two further company-owned antibody programmes in clinical development: an anti-GM-CSF antibody in the indications rheumatoid arthritis as well as multiple sclerosis and an anti-CD-19 antibody in the leukaemias CLL and SLL.

TRION Research in cooperation with *TRION Pharma* is dedicated to antibody therapeutics against cancer and utilises a unique class of **trifunctional antibodies** with the ability to activate the patient's immune defence. Solitary cancer cells which have outlived chemotherapy or radiation therapy and could cause a later relapse are detected by the antibodies and exposed to the immune system for destruction. In 2009, the trifunctional antibody Catumaxomab, the world's first drug of this class and the first therapeutic antibody that was developed from idea to market in Munich was launched onto the European market. The m⁴ project is investigating long-term vaccination-like effects of a treatment with trifunctional antibodies by **immune monitoring** in two investigator-initiated trials: the agent catumaxomab in the indication peritoneal carcinomatosis originating from gastric or colorectal cancer in a phase II trial, and the candidate drug FBTA05 in a phase I/II trial in the indication malignant B-cell lymphoma. It was shown that the antibody catumaxomab directed against the target antigen EpCAM stimulates a comprehensive immune response against the tumour. Thus, this induction of vaccination-like effects could imply that a long-term treatment would not be necessary, for the relief of patients as well as healthcare providers.

Small Molecules

On the border between small molecules and therapeutic antibodies resides the anticalin technology of *Pieris*. Anticalins are engineered lipocalins, which are endogenous low-molecular weight human proteins capable of specifically binding and releasing small molecules. They share a common β-barrel scaffold and have highly variable binding regions, which are modified to obtain ant calins with high affinity and selectivity for diverse target molecules. The company's proprietary PRS-110 compound targets c-Met, a cellular receptor that plays a key role in cancer cell growth and metastasis. The goal of this m⁴ project is to characterise and prepare a drug candidate for early clinical development and in parallel delineate a biomarker strategy and diagnostic methodology for patient selection.

Similarly, a small molecule agent developed by *WILEX* specifically targets a critical signal transduction pathway. *WILEX* is a biopharmaceutical company focusing on diagnostic and therapeutic products for the specific detection and targeted treatment of various types of cancer. They have several antibodies and small molecules in the pipeline, e.g. against clear cell renal cancer as well as breast and pancreas cancer. The anti-cancer drug candidate WX-037 inhibits the phosphatidylinositol 3-kinase (PI3K) pathway, which is mutated in most types of cancer and therefore of high therapeutic interest. Within the scope of the m⁴ project, the small molecule WX-037 will be developed as a mono-therapy and also in combination with the MEK inhibitor WX-554 against solid tumours and various cancers in preclinical studies followed by clinical phase I trials.

The development of targeted drugs often starts with the computer-based (*in silico*) design of small molecules capable of addressing a selected cellular target. The company *4SC* employs a proprietary technology for this *in silico* design of chemical compounds, supporting its research projects from hit identification to characterisation of drug candidates. The company-owned pipeline comprises several molecules already in clinical testing, e.g. against inflammatory bowel disease and liver cancers. Within the m⁴ project, for the first time a preclinical development programme combined with a parallel biomarker strategy is performed for a Toll-like receptor agonist, which is known to induce a **tumour-specific immune response** and hereby exert a therapeutic effect.

Highlight Project

MOR202, a Novel Targeted Therapy for the Treatment of Multiple Myeloma

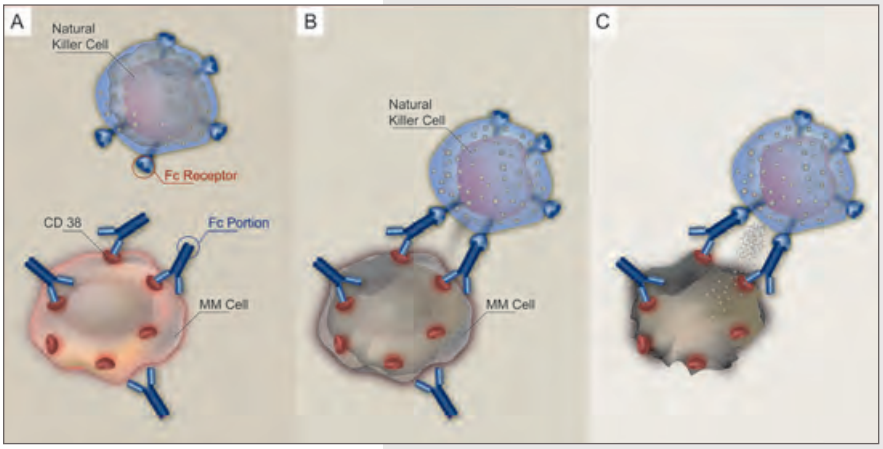
T. Dechow[1], C. Peschel[1], J. Amersdorffer[2], S. Leclair[2], S. Steidl[2], J. Endell[2], L. Rojkjaer[2], U. Moebius[2]

[1] III. Medizinische Klinik, Klinikum rechts der Isar der Technischen Universität München

[2] **MorphoSys AG**, Martinsried

This m[4] project is dedicated to preclinical and clinical studies including biomarker development for an innovative treatment of patients suffering from multiple myeloma (MM). This haematological cancer is caused by the malignant proliferation of plasma cells, the antibody-producing cells in the bone marrow. Typical attributes for MM are an abnormal production of an antibody (also called M-protein) as well as an interference with the production of normal blood cells. Furthermore, bone lysis is observed, leading to symptoms such as bone fractures and bone pain. The bone lysis is associated with hypercalcemia. Both the hypercalcemia and the high level of M-protein promote renal dysfunction. One to four people per 100,000 each year develop MM which constitutes 1 % of all cancers. Despite recent advances in therapy, the majority of MM patients relapse or develop resistance to treatment. The median survival rate is less than 30 months for relapsed or refractory patients. There is a high unmet medical need for innovative forms of treatment which improve therapy response rates and overall survival while lacking the severe side effects of current chemotherapy agents.

In general, due to a high specificity of monoclonal antibodies for their targets, they are able to provide a good efficacy and safety profile. *MorphoSys* has developed a highly specific, fully human recombinant monoclonal antibody (MOR202) against CD38, a membrane protein which is highly expressed on malignant plasma cells.



MOR202-mediated killing of an multiple myeloma (MM) cancer cell. The MOR202 antibodies bind to the CD38 target. B and C: Immune cells like natural killer (NK) cells recognise the bound antibodies, get activated and induce targeted killing of the MM cells. Source: MorphoSys AG.

MOR202 is intended to recruit and activate specialised killer cells of the immune system (NK cells). Once activated these NK cells can destroy the tumour cells (see illustration). Using this mechanism MOR202 has demonstrated efficacy *in vitro* and *in vivo* in a number of preclinical models. In an orthotopic xenograft murine model of MM, MOR202 reduced the M-protein as well as the tumour mediated bone lysis. Synergistic effects on M-protein and bone lysis were observed when MOR202 was co-administered with either bortezomib (a proteasome inhibitor) or lenalidomide (an immunomodulatory agent). These findings support further investigation of MOR202 combination regimens in clinical trials.

MOR202 is currently being tested in a phase I/II clinical trial in relapsed/refractory myeloma patients. The m[4] project is performed in collaboration between *MorphoSys* and the *Klinikum rechts der Isar (Technische Universität München)* and also includes other clinical study centers in Germany and Austria. In the trial, biomarkers specific for the antibody´s mode of action are also being assessed. This exploratory approach aims to identify correlations of markers with clinical trends. If successful, such biomarkers might be applied for patient stratification in order to preselect patients who might best benefit from MOR202 therapy.

m⁴ Research and Development Projects

Oncology Biomarkers

The development of mechanism-based targeted drugs led to a paradigm shift in the therapy of many diseases, most notably in cancer. Despite showing fewer side effects than conventional chemo-therapeutics, targeted drugs are often active only in a subset of patients. Thus, biomarkers that allow a discrimination of responders and non-responders are urgently required. *Evotec Munich* (formerly *KINAXO*) and *Roche Diagnostics* collaborate to evaluate how well **protein-based phosphorylation signatures** might serve as biomarkers, as they directly link cellular malfunction to individual cancers. The project has developed new mass spectrometry methods and has identified new biomarkers for pharmacodynamics and response prediction in a mouse xenograft model and currently aims to validate the biomarkers in clinical trials.

In contrast, **genetic biomarkers** are the focus of the cooperation between *Exosome Diagnostics* and Prof. Carola Berking (Department for Dermatology and Allergology, university hospital *Klinikum der Universität München*): The aim is to develop a minimally invasive diagnostic assay to characterise **malignant melanoma**, a cancer with highly increasing incidence, high risk of metastasis and high mortality. Somatic mutations in the RAF-, RAS- and other cancer related genes, are important in malignant melanoma as well as in most other cancers. In this project, tumour-specific mutations will be detected using Next Generation Sequencing technology and RNA extracted from exosomes from blood or urine from cancer patients. Exosomes are microvesicles which are secreted into body fluids (e.g. blood, urine, cerebrospinal fluid) and show a stable mRNA-content even in biobanked samples. *Exosome Diagnostics* intends to offer the diagnostic assays as a service out of the company's laboratories in Martinsried, e.g. to aid therapy decisions as well as the early detection in the case of a relapse.

The consortium of Prof. Dr. Gabriele Multhoff (Department of Radiation Oncology, university hospital *Klinikum rechts der Isar*), PD Dr. Udo Gaipl (Department of Radiation Oncology, *university hospital Erlangen*), Prof. Dr. Franz Rödel (Department of Radiotherapy and Oncology, *Johann-Wolfgang Goethe-Universität*, Frankfurt), and *Life Technologies* (Regensburg) pursues the innovative strategy of integrating comprehensive biomarkers into clinical trials. Four marker proteins (AnnexinA5, HMGB1, Hsp70, Survivin) in the serum of cancer patients are quantified to allow a precise **prediction of individual responses** and monitoring of the outcome of anti-tumour therapies, particularly radiotherapy, and to unveil induction of anti tumour immunity at an early stage.

Biomarkers and the development of a therapeutics score for various types of cancers are also the focus of a joint m⁴ project of *Spherotec* and the surgical and gynaecological departments of the university hospital *Klinikum der Universität München* (Prof. Karl-Walter Jauch, Dr. Nina Ditsch) as well as the gynaecological department of the university hospital *Klinikum rechts der Isar* (Prof. Viktor Magdolen). The project rests on two pillars: the biopathological profiling of tumour samples from different entities and the advancement of the **spheroid microtumour technology**. For the spheroid microtumour model, cancer cells of patients are cultivated in heterotypical 3-D cell clusters which more accurately reflect the *in vivo* situation than former 2-D models. Therefore, the spheroid model is expected to give a reliable prediction of the tumour's response to *in vivo* administration of different anti-tumour agents. Taken together, the score and the spheroid-testing will allow for a patient-specific **therapy response prediction** and aid therapeutic decisions. Furthermore, the platform is interesting for drug discovery and preclinical testing, as employed by the m⁴ partner *Trion Pharma* (see page 15).

m⁴ Research and Development Projects

The m⁴ project of Dr. Michael Quante (Medical Department, T*echnische Universität München*) and Prof. Dr. Karl-Friedrich Becker (Department of Pathology, *Technische Universität München*) aims to establish new **biomarkers for prognosis and early detection** of esophageal adenocarcinoma. As the cancer has a very poor prognosis with a median survival of less than one year, it is crucial to develop preventive strategies. The main risk factor for esophageal adenocarcinoma is Barrett's esophagus, an inflammation-dependent replacement of squamous epithelium by metaplastic columnar epithelium in the distal esophagus, which was recently reconstructed in a mouse model. The project will investigate distinct biomarkers of malignant degeneration found in the mouse model as well as new biomarkers from patient samples in a prospective clinical study. As an alternative to formalin fixation, the project will utilise and validate a new fixation system (PAXgene) developed by the project partner *PreAnalytix / QIAGEN* (Hilden).

Cell Therapy

The company *apceth* is one of the leading European pioneers in **cell and gene therapeutics** in the field of pharmaceutical development, production and clinical implementation. As the sole company in Bavaria, *apceth* holds a manufacturing license for the GMP production of clinical-grade somatic cell therapeutics. In early 2011, *apceth* started a clinical trial phase I/II for the treatment of advanced limb ischemia. As a partner in the m⁴ programme, *apceth* contributes its unique expertise in the innovative and fast developing *Advanced Therapy Medicinal Products (ATMP)* field to the cluster network. The m⁴ project of *apceth* is focused on the preclinical development of a gene therapy product based on genetically modified mesenchymal stem cells for the personalized therapy of advanced or metastatic cancer. In 2013, this gene therapy ATMP will enter clinical development in the treatment of advanced **pancreatic cancer**. Within this project, the company is establishing and utilising preclinical mouse models and large animal porcine models, the latter in cooperation with the m⁴ partners Prof. Angelika Schnieke (Department of Lifestock Biotechnology, *Technische Universität München*), Prof. Eckhard Wolf (Gene Center, *Ludwig-Maximilians-Universität München*) and *MWM Biomodels* (see page 23). This preclinical strategy is combined with the development of a specific panel of predictive biomarkers to enable optimal patient stratification and highly personalized cancer treatment.

Cardiovascular Diseases

As in oncology, stratification of patients in other widespread diseases will help to improve patient care, for example for cardiovascular diseases. *Corimmun* is developing a candidate targeted drug tailored to a specific high risk group of **heart failure** patients (see page 20). For risk stratification, the clinical trial phase II utilises an innovative ECG-monitoring system which was developed in the m⁴ cluster: The m⁴ project of Prof. Stefan Kääb (Department for Cardiovascular Surgery, university hospital *Klinikum der Universität München*) aims to optimise and enhance risk stratification for drug-induced arrhythmias in clinical trials, since drug induced arrhythmias can be caused by any class of drug and have the potential to influence the drug-safety assessment and thus the outcome of the trial. Novel ECG-biomarkers as well as novel genomic biomarkers found by genome-wide-association studies are employed to give a risk evaluation of cardiac rhythm disturbances.

Heart failure is also the focus of a joint project between both university hospitals in Munich, led by Prof. Stefan Engelhardt (Department of Pharmacology and Toxicology, *Technische Universität München*) and Prof. Christian Kupatt (*Klinikum der Universität München*). They are investigating a **functional nucleic acid as a therapeutic**: Antagomir-21 is a microRNA which has been shown to prevent fibrosis and heart failure in a mouse model and is currently being tested in a large animal model. Since porcine models are particularly suitable for cardiovascular studies due to their physiological similarity to humans, a porcine model of fibrosis in ischemic cardiomyopathy is being established in cooperation with the m⁴ project "preclinical models" (see page 23). For retroinfusion of the therapeutic agent through the coronary veins into the cardiac muscle, an apparatus has been developed by *QualiMed* (Winsen) in this project.

Autoimmune Diseases

SuppreMol is developing targeted therapies which address distinct receptors of the immune system. In the human immune system, the so-called Fcγ receptors play a central role in defence against infections and in autoimmune responses. *SuppreMol's* lead candidate SM101 is a soluble form of a Fcγ receptor which is able to bind auto-antibody/auto-antigen complexes and thereby suppresses the activation of immune cells. Currently, SM101 is being tested in clinical trials in phase I/II for the orphan disease primary immune thrombocytopenia and, within the m⁴ project, for **systemic lupus erythematosus**. The drug development is accompanied by biomarker development in cooperation with *Protagen* (Dortmund). For this, signatures of auto-antibodies are being analysed, which can be used for the identification of patients showing a promising response towards the therapy. In a second m⁴ project, *SuppreMol*, together with Prof. Matthias Mack from the *Universität Regensburg*, is developing cytokine IL-3 as a biomarker in rheumatoid arthritis. This biomarker shall enable an early diagnosis and therapy of **rheumatoid arthritis** to prevent permanent joint damaging effects. In parallel, an anti-IL-3-antibody will be developed for therapeutic intervention.

Auto-antibodies as biomarkers are also employed in the cooperation project of Prof. Bernhard Hemmer (Clinic for Neurology, university hospital *Klinikum rechts der Isar*) and *Roche* (Grenzach). The m⁴ project studies the potential of the recently identified auto-antibody KIR4.1 as a biomarker in **multiple sclerosis**, an inflammatory demyelinating disease of the central nervous system with a presumed autoimmune pathogenesis. Therapy of this heterogeneous disease at present lacks a diagnostic tool to allow prediction of progression risk and consideration of therapy options or monitoring with therapy. Without these biomarkers, a timely and tailored therapy is hardly possible, which can lead to a belated start of therapy or severe side effects. The aim is to determine KIR4.1 auto-antibody levels in serum of large patient groups to estimate the suitability of this biomarker for patient stratification with respect to prognosis and treatment response.

In a variety of cellular functions, for example in immune processes including those in autoimmune reactions, ion channels are involved. These ubiquitous transmembrane proteins selectively control the passage of ions across the plasma membrane. *conoGenetix biosciences* offers a unique screening platform for the isolation of **ion channel active peptides**. The focus of the m⁴ project of *conoGenetix* are peptides with established efficacy against autoimmune diseases, which will be further investigated to accelerate their translation from preclinical to clinical testing.

Highlight Project

COR-1 in Heart Failure

Corimmun GmbH, Martinsried

Medizinische Klinik I, Klinikum der Universität München, Ludwig-Maximilians-Universität

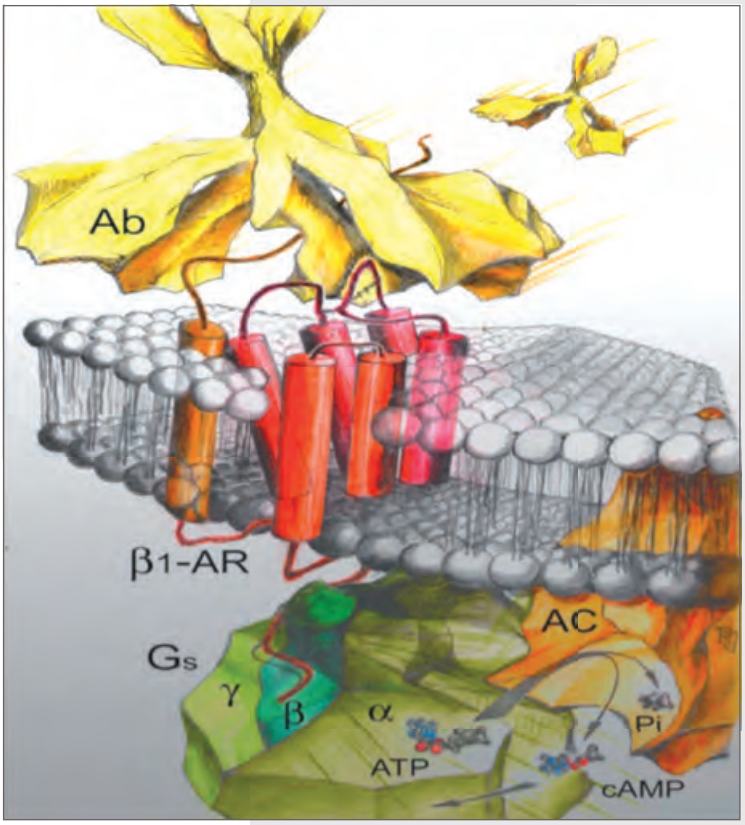
Kardiologische Klinik der Universität Regensburg

Kardiologische Klinik der Universität Tübingen

Deutsches Zentrum für Herzinsuffizienz, Würzburg

This m[4] project demonstrates how personalized medicine is evolving from its classical indication, oncology, to conquer new territory. The Munich-based biotech company *Corimmun* and several clinical partners are furthering the clinical development of a therapeutic against chronic heart failure and started a clinical study phase II with the candidate drug COR-1 in September 2011.

Chronic heart insufficiency (e.g. dilatative cardiomyopathy) is characterised by a weakened and enlarged heart muscle and is a frequent cause for intensive drug administration or even heart transplantation, given a donor organ is available. Until now, the therapy of this widespread medical condition is unsatisfactory, because even with the best available treatment still 50 % of patients die within 5 years from the first diagnosis. High mortality rates particularly affect a specific high risk group: about half of the patients have a markedly worse prognosis than the other half. These patients develop antibodies against the beta-1-adrenergenic receptor. The auto-antibodies lead to a chronic overstimulation of the receptor, followed by impairment of the heart muscle and a reduced heart function. The candidate drug COR-1 is a cyclic peptide capable of scavanging and neutralising the auto-antibodies.



Specific auto-antibodies against the beta-1-adrenergenic receptor attack the heart muscle, leading to a low-grade, but constitutive stimulation of signaling pathways in its cells and therefore chronically damaging the heart. Source: Trends Cardiovasc Med 2006;16:20-24.

Functional auto-antibodies also occur in other forms of chronic heart failure and constitute a to date not addressed pathomechanism. If a patient develops the specific anti-beta-1-AR-antibodies, this can be assessed by a rapid laboratory test (companion diagnostic assay), which has also been developed by *Corimmun*.

In the recent patient study, pre-selected patients of the high risk group are treated with the targeted therapeutic. The precedent phase I study showed good tolerance and no adverse effects. This is in stark contrast to the currently approved medical drugs for the condition (e.g. beta blockers, ACE inhibitors, AT1 antagonists or digitalis glycosides), which show a high rate of adverse effects and therefore often reduce the patients' quality of life. Due to the pre-selection of patients, the therapy response rate is expected to be markedly improved, compared to the current undifferentiated medication with insufficient success rates caused by high numbers of non-responders. A high effectiveness of the novel therapy would allow a reduced size of the clinical studies: inclusion of fewer patients would be sufficient to demonstrate statistical relevant effectiveness. In this way, the additional effort for a stratification strategy would be offset by savings in the clinical development.

m⁴ Research and Development Projects

Bacterial Infections

In a globalised world, multi-resistant pathogens like the hospital bug *MRSA* are a health threat of increasing concern, strongly emphasising the medical need for new anti-infectives, which ideally target individual bacterial pathogens in order to avoid the emergence and spreading of resistances. The m⁴ project of *Priaxon* and Prof. Markus Gerhard (Department of Medicinal Microbiology, Immunology and Hygiene, *Technische Universität München*) aims at identifying new lead structures that selectively address pathogen-specific bacterial targets essential for infection. The rational design of these **small molecules** is based on *Priaxon's* unique dual technology platform comprising chemical informatics and innovative synthesis chemistry.

In his second m⁴ project, Prof. Markus Gerhard (Department of Medical Microbiology, Immunology and Hygiene, *Technische Universität München*) is collaborating with the diagnostics company *Mikrogen*. Infection with the human pathogen *Helicobacter pylori* is the number one **risk factor for stomach cancer** and therefore is of high medical and economic relevance. This m⁴ project aims to validate a highly immunogenic serine protease as a reliable biomarker for *H. pylori* infection and to develop a prognostic seromarker for carcinoma. In the second part of the project, Prof. Gerhard together with the crystallography expert *Proteros biostructures,* is attempting to identify new lead candidates for drugs addressing this essential protein.

Neurological and Psychiatric Disorders

Understanding the mechanisms that lead to severe mental disorders is one of the big challenges in today's healthcare system, reinforced by the ageing society. *Origenis* runs its own patented drug discovery platform and is focusing on anti-inflammatory drugs and treatments for conditions of the central nervous system. Current research has established the overactivation of the neurotoxic kinase LRRK2 as a trigger for **Parkinson's disease**. This m⁴ project aims to develop LRRK2-specific ligands suitable for the *in vivo* visualisation of neurodegenerative disorders via MRT and PET. These ligands will reveal the spatio-temporal allocation of LRRK2 and help to understand the disease mechanisms, as well as provide a tool for patient stratification and even anti-Parkinson therapies.

For **schizophrenia**, sequencing studies have revealed that copy number variants have a functional relevance in a subgroup of patients. The m⁴ project of Prof. Hans-Werner Mewes (Department of Genome-oriented Bioinformatics, *Technische Universität München*) and Prof. Dan Rusjescu (Genetic Research Center, *Ludwig-Maximilians-Universität München*) in cooperation with *Eurofins Medigenomix* employs Next Generation Sequencing to improve the knowledge about genetic variations in schizophrenia patients as a first step towards drug development.

Technology Platforms

The therapeutic potential of minimally manipulated cells opens up new avenues for the development of individualised therapies. For this purpose, a mild isolation procedure of defined cell populations is being developed in the m⁴ project of Prof. Dirk Busch (Department of Medicinal Microbiology, Immunology and Hygiene, *Technische Universität München*) in cooperation with *Stage Cell Therapeutics*. With the Streptamer technology, cells are reversibly labeled with a positive selection marker allowing a subsequent complete removal of all reagents as well as consecutive isolation steps with multiple parameters. The project focuses on the development of new reversible selection reagents (MHC/Fab-Streptamers) to improve **clinical cell isolation** under conditions approvable by regulatory authorities.

priaxon

MIKROGEN DIAGNOSTIK

proteros

origenis

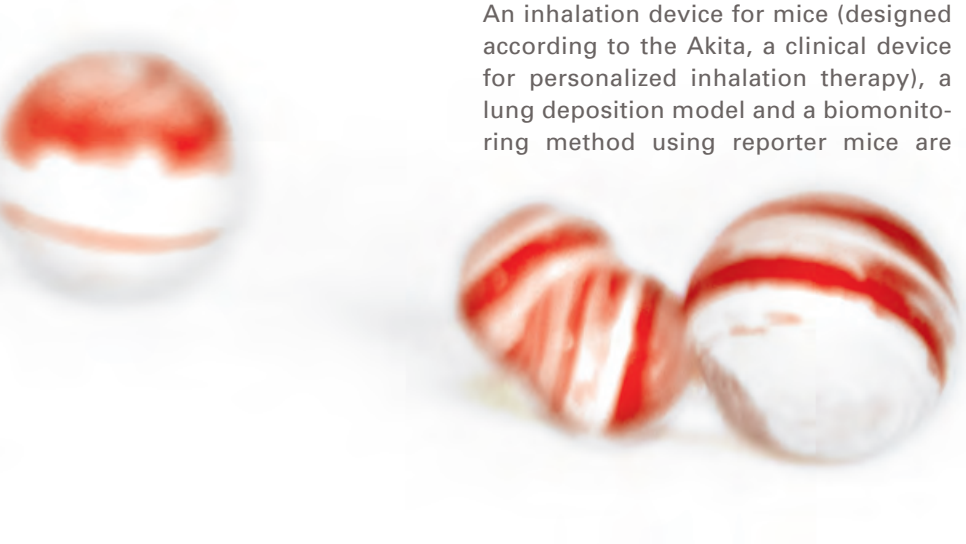
eurofins

STAGE cell therapeutics

m⁴ Research and Development Projects

Recent progress in systems biology has dramatically increased the understanding of pathomechanisms and thus the definition of potential drug targets, often specifically addressed by therapeutic antibodies. For the rational design and engineering of antibodies, a detailed structural knowledge of the antigen-antibody-interaction surface is needed. Therefore, the antibody expert *MorphoSys* (also refer to highlight project page 16) and the expert for X-ray crystallography *Proteros biostructures* have joined forces to establish a technology platform for the efficient **structural analysis of antibody-antigen-complexes**. Besides the characterisation of Fab-antigen complexes, the project deals with the known challenges of crystallisation of full-length IgG molecules. The ultimate goal of the project is to establish an integrated production and crystallisation platform for antibody-antigen-complexes, to allow a more rapid and efficient selection and development of therapeutic antibodies (see page 14).

There is an urgent need for inhaled (bio-)therapeutics against chronic lung diseases. **Preclinical systems to test new inhalative therapeutics** constitute a bottleneck in drug development. The joint project of *Activaero*, the *Comprehensive Pneumology Center* and the *Helmholtz Zentrum München* (Prof. Otmar Schmid) aims to establish a predictive, preclinical method for determining effective drug delivery of biotherapeutics and small molecules against chronic lung disease in mouse models. An inhalation device for mice (designed according to the Akita, a clinical device for personalized inhalation therapy), a lung deposition model and a biomonitoring method using reporter mice are established. In a proof-of-concept study with mice, the effectiveness of this method is being investigated by applying proteasome inhibitors for treatment of lung carcinoma and lung fibrosis. This will allow an evaluation of the new methodologies and the investigation of the efficacy of a new substance type (proteasome inhibitors) for inhalation therapy of chronic lung disease.



Molecular Imaging

Newly developed imaging technologies allow for an early assessment of therapy efficacy, which is relevant medically as well as economically. Early detection of non-responders, for example, can accelerate a necessary adjustment of a therapy and prevent unsuccessful treatment. The prediction of a therapeutic response only by morphological parameters like tumour size is no longer sufficient, as these are not *ad hoc* changing parameters. In two m⁴ projects magnetic resonance tomography (MRT), computed tomography (CT), and optical imaging (OI) are used to further extend the **functional imaging** approach with parameters such as blood flow, perfusion, diffusion, cell death, product kinetics etc. This development of multiparametric analyses enables clinicians and researchers (such as drug development companies) to determine the success or non-response of a therapy at a very early stage.

The m⁴ projects of Prof. Konstantin Nikolaou (Department for Clinical Radiology, university hospital *Klinikum der Universität München*) in cooperation with *Siemens Healthcare* (Erlangen) and the project of Prof. Ernst Rummeny (Department of Radiology, university hospital *Klinikum rechts der Isar*) in cooperation with *Philips Healthcare* (Hamburg), have both established functional imaging techniques in animal models which will now be translated into clinical routine.

Positron emission imaging (PET) and related therapy requires radioactively labelled substances - **radio tracers** - which have a very short half-life and therefore do not allow prolonged transportation or storage times before use. Additionally,

only very low quantities are needed, especially for individualised health care using radiotracers that are coupled to specific target structures. To solve these problems, a **microfluidic marker kit** is under development by *GE Healthcare* together with Prof. Peter Bartenstein (Department for Nuclear Medicine, *Ludwig-Maximilians-Universität München*). This kit aims to make it practical and economically viable, to produce single patient doses of radiopharmaceuticals for daily treatment routine.

The company *ITM* is focusing on the production and marketing of radioisotopes which can be used for therapeutic and imaging applications. Within the m⁴ project, an iRGD peptide is being used for a targeted localisation of radioisotopes to vascularised tumours. The application can be used as an imaging tool via positron emission tomography (PET) or as a targeted therapy to destroy the tumour by **peptide-receptor radioisotope therapy**, depending on the selected coupled radioisotope. As the same target molecule will be used for diagnosis as well as for therapy, iRGD is an excellent example in the area of personalized medicine. Compared to a radiation therapy from the outside, this approach strives to be more effective but milder and could be more easily tailored to different tumours.

Preclinical Models

Rodent models are widely used to test the efficacy, toxicology and pharmacokinetics of therapeutic agents. However rodent data is often not representative of the human situation due to the considerable physiological differences and evolutionary distance. There is growing evidence that minipig and pig models often resemble humans more closely in disease characteristics and pigs are increasingly being employed in therapeutic development. Prof. Eckhard Wolf *(Gene Center, Ludwig-Maximilians-Universität München)* and Prof. Angelika Schnieke (Department of Livestock Biotechnology, *Technische Universität München*) have long standing experience in large animal models and are now establishing new **porcine models for diabetes, cystic fibrosis and various cancers** in cooperation with *Minitüb*, a specialist in reproduction technology. All models are in the process of validation and characterisation. For the first time it has also been possible to generate an inducible gene expression system for the pig. Another very new field is a cooperation with *apceth*, where genetic manipulation of porcine mesenchymal stem cells has been established to facilitate anti-tumour therapy (see page 18).

Innovative Therapeutics and Materials

Therapeutic nucleic acids as a new class of therapeutics are in the focus of two m⁴ projects. In a cooperation of Prof. Wagner with *Roche Kulmbach* a substance library of optimised nucleic acids (miRNA, siRNA) has been generated, and their efficacy shown *in vivo*. A complementary approach is used by *Intana Biosciences*: here the modifications are set on the effector proteins of the Argonaut family (Ago) and not on the siRNA itself. A functional binding assay based on FCS/FCCS technology has been established, giving proof of concept for higher selectivity and affinity of RNAi and Ago-proteins.

A new technological biopolymer, **spider silk**, with outstanding properties like high tensile strength and biocompatibility is being tested within the m⁴ project of *AMSilk*. Spider silk films are characterized and investigated for their suitability in the biomedical world e.g. as a platform technology for drug delivery in targeted therapies that benefit from the non-toxic production conditions. In cooperation with Prof. Gerhard Winter (Department for Pharmacy, *Ludwig-Maximilians-Universität*), homogeneous films with high mechanical stability have been developed and are now being tested in combination with different active pharmaceutical ingredients for binding and in release studies.

m⁴ Research and Development Projects

Infrastructure

With its "Blood Donor BIOBANK", the *Bavarian Red Cross Blood Donor Service* (BSD) offers a unique and innovative resource for biomarker research: the world's first **blood donor based biobank**. With the m⁴ funding, it was possible to initiate this unique collection of biological material together with associated medical data, opening up new possibilities for the development of targeted diagnostics and therapies. Overall, the BSD maintains a unique collection of over 4 million plasma samples, making it one of the largest sample collections worldwide. The clinical data are validated by the donor's physicians for diseases like cancer, Crohn's disease, multiple sclerosis, diabetes or cardiovascular diseases, among many others. In addition to the retrospective analysis of serial, pre-diagnostic plasma samples, the well-established infrastructure of the BSD and the large pool of regular blood donors offer the unique possibility of conducting large scale prospective studies or screening campaigns. First studies have already been successfully conducted to screen for the risk of developing colon cancer or diabetes or to gather lifestyle data. Close cooperation with the m⁴ Biobank Alliance (see page 28) will provide the research institutes and industry with standardised processes and a reliable supply of high quality biosamples.

The **Network for Neuroendocrine Tumours Munich** (Prof. Günter Stalla, *Max Planck Institute of Psychiatry*; Prof. Felix Beuschlein, Prof. Christoph Auernhammer, university hospital *Klinikum der Universität München*; *Novartis Pharma*; Prof. Klaus Kuhn, *Technische Universität München*) has established a platform for preclinical and clinical data of very rare neuroendocrine tumours of the gastro-entero-pancreatic system and tumours of the pituitary gland, which is unique in Germany. The partners from the different hospitals share a common biobanking system and utilise standardised, partly even personalized tumour models for testing therapeutic substances under development (provided by the partner *Novartis*). Investigator-initiated trials in these special indications are made possible by a common IT system with combined patient cohorts and an optimised recruiting system implemented by the m⁴ Data Integration System (see page 30).

As data evaluation is considered the main bottleneck of personalized medicine, two bioinformatics projects are developing new platforms for data analysis. By the analysis of molecular data (-omics technologies), *Genomatix Software* reconstitutes **regulatory networks** that are capable of defining new biomarker candidates and sets of candidates that can then be used for clinical validation.

The smart[m] **knowledge management** platform established by *Biomax Informatics* provides a platform for knowledge management of project data, clinical data and collaboration networks which is used by the m⁴ community (for example the Institute for Pathology of the university hospital *Klinikum Rechts der Isa*r and the m⁴ Trial Service Center).

Production of test samples/investigational products following the standards of good manufacturing practice (GMP) is an important link between the development of new products and their testing in animal and clinical studies. Compounds in small quantities for first experiments and studies, but already in high quality according to GMP standards, are needed for drug development. Therefore a **GMP facility** for small quantities and special products is being set up at the Department for Pharmaceutical Chemistry of *Ludwig-Maximilians-Universität* (Prof. Gerhard Winter). The GMP manufacturing license from the Bavarian state and the production start in the core facility is expected in 2013.

The proportion of therapeutic antibodies among all newly approved drugs is steadily increasing, which at the same time enhances the need for optimised production processes. *Agrobiogen* is aiming to optimise and improve the production of antibodies via a platform using transgene rabbits, specifically for the production of **bispecific single chain antibodies**.

Most biopharmaceuticals currently in use for human therapy, e.g. interferons, hormones, antibody fragments or peptides, have a relatively small molecular size and thus are subjected to rapid kidney filtration. This problem leads to disappointingly short circulation times and hampers therapeutic benefit. **PASylation**, the genetic fusion of the molecules with conformationally disordered polypeptide sequences composed of the amino acids Pro, Ala, and Ser, provides an advantageous solution by attaching a solvated random chain with a large hydrodynamic volume to a biologically active protein. Thus, the typically rapid clearance via kidney filtration can be retarded by a factor 10 to 100, allowing less frequent and lower dosing to achieve the desired therapeutic effect. Compared with PEGylation, which leads to similar biophysical properties, PASylation provides several advantages, in particular biodegradability and one-step biotechnological production as a fusion protein, avoiding chemical coupling and processing steps. During this collaborative m⁴ project between *XL-protein* and the *Technische Universität München* (Prof. Arne Skerra) four PASylated biological drug candidates (Fab fragments, hGH, Exendin-4) will be constructed and characterised *in vitro* and *in vivo* in order to validate PASylation for the generation of novel biologics with promising applications in personalized medicine.

m⁴ Structural Projects

For an excellent progression of research & development activities in the field of personalized and translational medicine, a functional infrastructure along the value added chains of therapeutics and biomarker development is essential.

Therefore, interdisciplinary m⁴ teams are working together in five strategic projects to generate an infrastructure for the m⁴ cluster sustaining future support in the following fields:

1) Faster and innovative clinical development: Service and support of the translational phase into early clinical development including innovative study design by the **m⁴ Trial Service Center**

2) High quality biosamples: Centralised access to the regional biobanks providing high quality biosamples in combination with clinical data
- the **m⁴ Biobank Alliance**

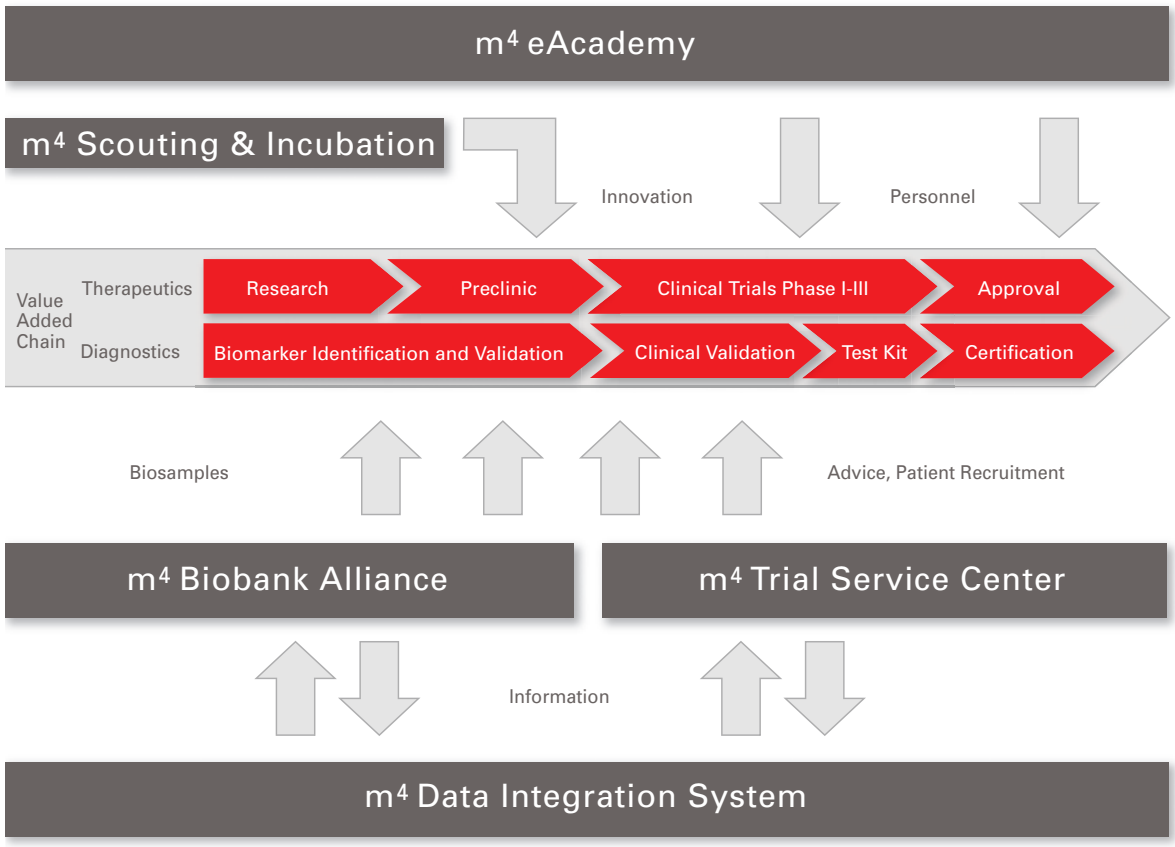
3) Data integration and -analysis: Integration and management of research and clinical data – a combination of the two worlds by the **m⁴ Data Integration System**

4) Qualified staff: Optimised education and advanced trainings for scientists and managers in the field of pharmaceutical development
- the **m⁴ eAcademy**

5) Optimised technology transfer: Identification and support of innovative projects – accelerating the time span from idea to product by the **m⁴ Scouting & Incubation** programme

The overall aim is to optimise the drug development process, for better medicines for the patient and an overall reduction of development times.

The m⁴ structural projects support the value added chain of personalized medicine.



m⁴ Trial Service Center

Central Service for (Pre-) Clinical Development

The m⁴ Trial Service Center will be the central service and consulting unit for translational research facilitating the process *from bench to bedside and back.* The services are available to partners from industry as well as research organisations or cooperation projects of both groups. The main goal is to accelerate the process from preclinical to clinical development by providing intensive guidance during the set-up and handling of early clinical studies. This is handled either by experts of the center itself or by establishing contact with experts in special areas service providers from the m⁴ network.

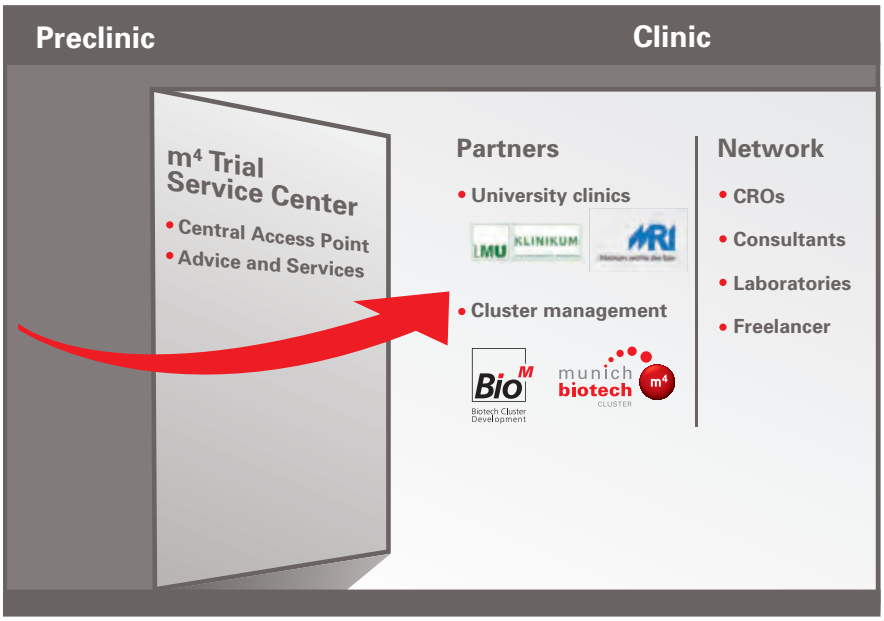
The Initiators:

a strong partnership between the two university hospitals

University hospital *Klinikum rechts der Isar*: Prof. Dr. Christian Peschel, Director Haematology and Oncology

Ludwig-Maximillians-Universität: Prof. Dr. Ulrich Mansmann, Director of the Institute for Medical Informatics, Biometrics and Epidemiology (IBE)

The development of personalized medicine drugs requires innovative and adaptive clinical trial concepts and validation studies for biomarkers. However, expert advice is already invaluable and necessary during the preclinical development phase. Thus, new and sophisticated study designs as well as continuous consulting from preclinical to clinical studies are the main focus of the m⁴ Trial Service Center, building up a so far quite unique expertise in this field in Germany. First pilot studies are already taken care of supporting the planning and set-up of the protocols for *first in man* and *proof of concept* studies for partners in the cluster. For carrying out the clinical trials, there is a close collaboration with the study centers of the two university hospitals in Munich as well as with local contract research organisations (CROs). With a broad network of experts in different molecular and clinical fields as well as service providers (CROs, academic researchers, study personnel), the m⁴ Trial Service Center can provide to the partners much-needed know-how as well as different technologies required for the translational process of the partners' projects. On the administrative side, the m⁴ Trial Service Center strives to set-up a general contract template drawn by both university hospitals and industry partners. This is intended to faciliate and fasten contract conclusion for clinical trials. Further aims are to optimise the process and possibilities of patient recruitment together with the m⁴ Data Integration System and to promote and support the set-up of an oncological phase I unit in cooperation with the German consortium for Translational Cancer Research. Being involved in biomarker validation studies with biosamples, data mining processes, study consulting and liaising with experts, the m⁴ Trial Service Center takes an integrative role within the m⁴ network of industry partners, further m⁴ structural projects, the German Centers for Health Research and the hospitals (see page 12).



The m⁴ Trial Service Center serves as a central service point for clinical studies with a focus on personalized medicine.

m⁴ Biobank Alliance

Technische Universität München

Klinikum rechts der Isar

LMU Ludwig-Maximilians-Universität München

LMU Klinikum

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

Central Access to Human Biosamples –

optimisation of research on personalized medicine and biomarker development

For academia and industry, access to high quality patient biosamples is the key and at the same time the bottleneck to identifying and verifying biomarkers successfully. With growing numbers of activities in biomarker research and companion diagnostics development, the demand for high quality biosamples is increasing steadily. Furthermore, due to continuously improving technologies and deeper understanding of cellular processes, the quality requirements of biosamples are increasing, too.

In the m⁴ Biobank Alliance, already existing biobank initiatives in the Munich region joined their experience and competences to provide a one-stop access point to the resources at different institutions, but under shared highest quality standards.

The m⁴ Biobank Alliance will be established as a sustainable biobank governance and a not-for-profit biobank services organisation to provide access to human biosamples out of one hand, to facilitate the possibilities for industry and academia to use high quality biosamples for biomarker research and development. Besides high quality standards the compliance with highest ethical and legal standards, as well as common and standardised processes for biosample collection according to established standard operating procedures (SOPs) will be assured. These are the prerequisites for a market-oriented quality management and a competitive organisation.

The Initiators:

expertise in collection and use of human biosamples

Technische Universität München:
Prof. Heinz Höfler, Prof. Helmut Friess,
PD Dr. Klaus-Peter Janssen

Ludwig-Maximilians-Universität:
Prof. Thomas Kirchner,
Prof. Karl-Walter Jauch,
PD Dr. Wolfgang Thasler

Helmholtz Zentrum München:
Prof. Heinz-Erich Wichmann

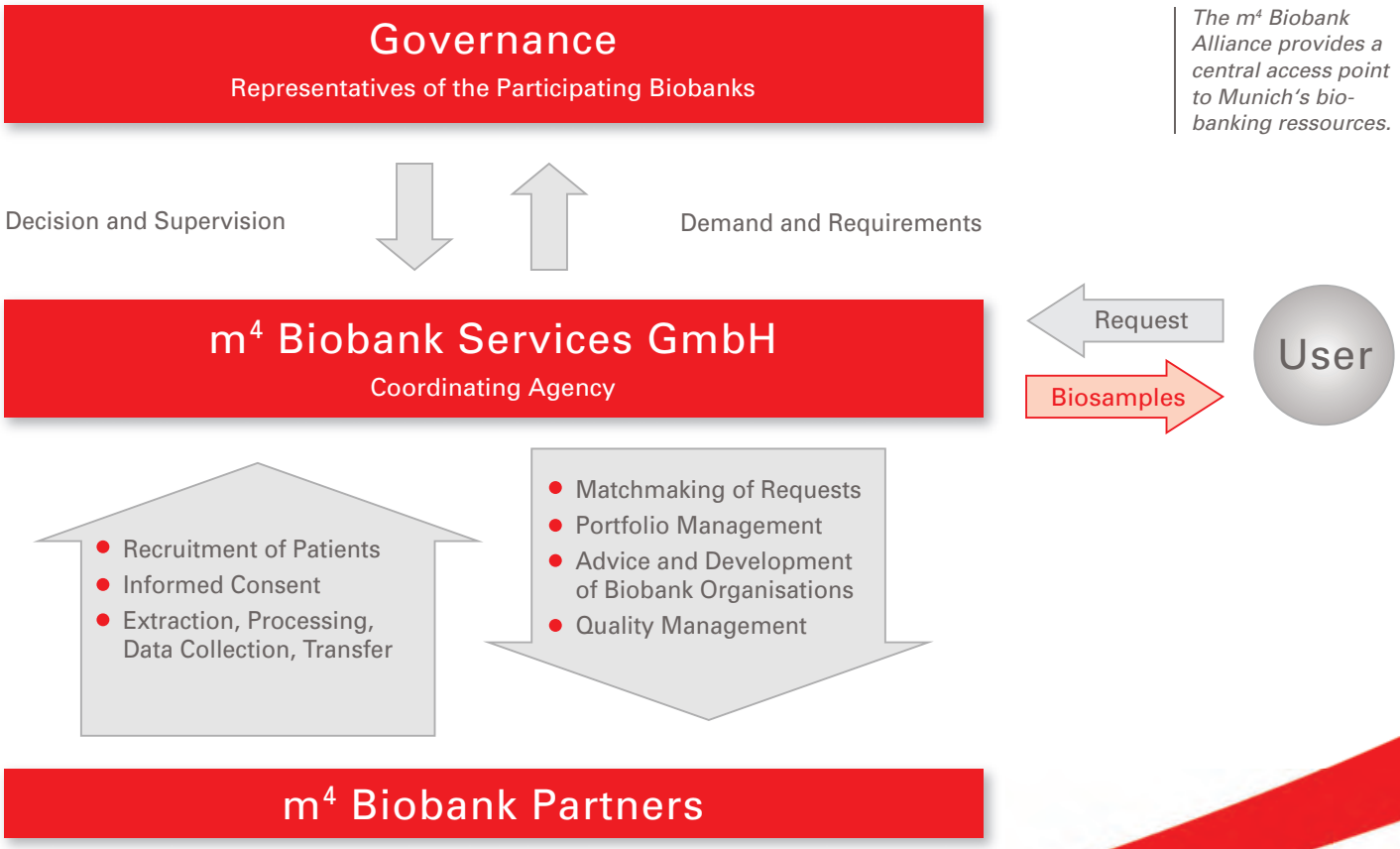
m⁴ Biobank Service GmbH –
a sustainable and competitive business model

The m⁴ Biobank Service GmbH needs to fulfil the high demands from the patients´ side, as well as from academia and industry in competition with other international providers to contribute to the progress of personalized medicine and biomarker development:

The set goals are compliance with the ethical and legal framework (informed consent, ethics committee vote, data protection), transparency and trust of patients and customers, compliance to common quality standards, provision of clinical data, short delivery times and custom made service offers.

The foundations for all these requirements have been set, the processes will now be established and optimised during pilot projects with industry partners. The final organisation structure is expected to be up and running mid 2013. A governance structure for decision and supervision processes will be established in parallel to the m⁴ Biobank Service GmbH handling the administrative part.

The main advantage for industry partners will be the central access point, where biosamples and data will be bundled. All biosamples will be of the same high quality, so contributions of different biobank partner institutes may be used in one study. Special inquiries (e.g. fresh or frozen material) will be addressed on demand. The advantages for the institutes will be common cross-university standards for quality and ethics of biosamples, lower administrative load and support for their own biobanking efforts and related research.



The m⁴ Biobank Alliance provides a central access point to Munich's biobanking ressources.

m⁴ Data Integration System

Technische Universität München

Klinikum rechts der Isar

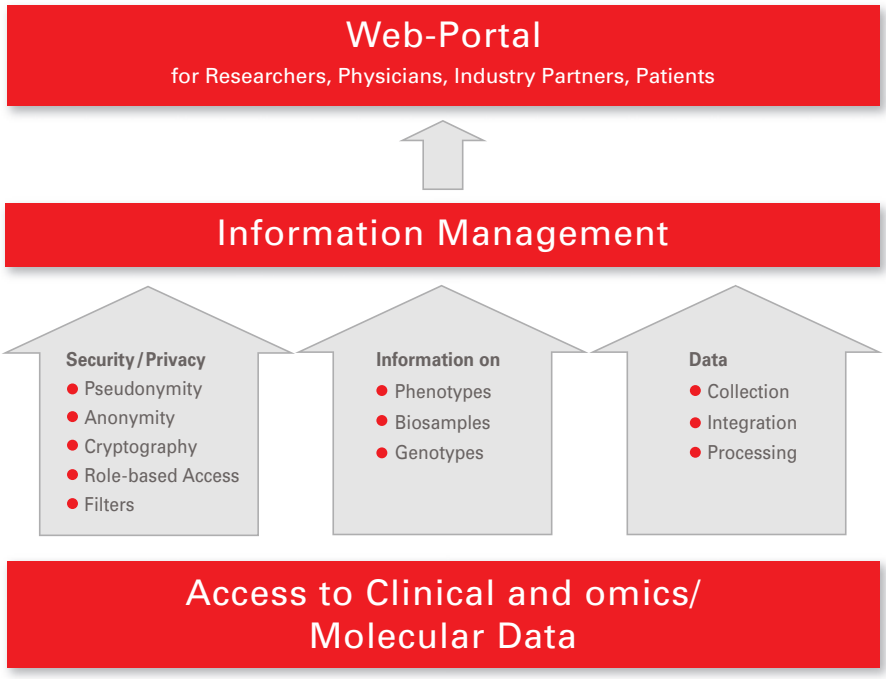
LMU Ludwig-Maximilians-Universität München

LMU Klinikum

HelmholtzZentrum münchen
Deutsches Forschungszentrum für Gesundheit und Umwelt

The new IT Backbone of the Cluster

Progress in personalized medicine is coming along with a significant depth of data and information that has to be managed and interpreted. The first step is data collection and integration from research and clinics, and also from different universities, medical centers and institutes. For this purpose, an innovative architecture has been designed which has resulted in IT systems linking the different institutions in the cluster and making an integrative and standardised data processing possible. The concepts have been developed in alignment with the ethics committees and the data protection officers of both university medical centers, and they are compliant with the TMF standards (*Technologie- und Methodenplattform für die vernetzte medizinische Forschung e.V.*).



The m⁴ Data Integration System provides the IT backbone for the m⁴ cluster.

The establishing of a complete information chain to combine information, knowledge and resources as well as to manage the processes is essential for the whole cluster: from the patient and the clinicians to the researchers and, finally, to the industry.

The Initiators:

key institutes in information- and data-processing in the region

University hospital *Klinikum rechts der Isar:* Prof. Dr. Klaus Kuhn, Director of the Institute for Medical Statistics and Epidemiology (IMSE)

Ludwig-Maximilians-Universität: Prof. Dr. Ulrich Mansmann, Director of the Institute for Medical Informatics, Biometrics and Epidemiology (IBE)

A Key to Innovative Concepts in Translational Medicine

This new infrastructure will connect different institutes as well as researchers and clinicians and will optimise the use of clinical data for improving translational research. The concepts of the m⁴ Data Integration System are closely related to those of the structural projects m⁴ Trial Service Center and m⁴ Biobank Alliance.

A major focus of the project lies on ethical and data-protection issues. Informed consent, privacy, and security are of critical importance for the collection and use of patient data, which in turn are essential for the circle *from bench to bedside and back*. Anonymisation, pseudonymisation, and the use of cryptography are key elements of the architecture, as well as role-based access and usage-dependent filters.

m⁴ eAcademy

Blended Learning:

Executive Master of Business Administration Life Sciences and Master of Science Translational Medicine

Excellently trained professionals are the prerequisite for a successful implementation of personalized and translational medicine along the value chain. The m⁴ eAcademy is developing two innovative curricula to complement the existing education programmes and to qualify the employees of the regional and international life science industry as well as possible for tomorrow´s challenges. The courses will further strengthen the excellent competence profile of Munich as a center of academic education.

Extra-occupational Qualification Concept

The m⁴ eAcademy has a strong focus on direct practical relevance, based on eLearning with minimal time of attendance. The different modules are developed and executed by the *Ludwig-Maximilians-Universität* together with external partners from industry to assure a concept with high practical relevance. Lectures, case studies, as well as discussions, group work and individual work integrating current topics from life science industry will be part of the courses. The teaching materials will be permanently updated by interviews and seminar recordings. The concept is based on eLearning tools and answering to a current demand for high-level, specialist education with minimal time of attendance nevertheless providing extensive coaching of the scholars. The international courses in English will start in the winter semester 2013/14. Duration of both courses will be four semesters.

The Initiators:

interdisciplinary teams with technical and educational know-how

Ludwig-Maximilians-Universität:

Prof. Dietmar Harhoff,
INNO-tec – Institute for Innovation Research, Technology Management and Entrepreneurship

Prof. Dr. Ulrich Mansmann,
Institute for Medical Informatics, Biometrics and Epidemiology

Arnim Rubner, Research and Technology Transfer, Spin-offs, Virtual University

Prof. Martin Fischer, Institute for Teaching and Educational Research in Health Sciences

The m⁴ eAcademy establishes two specialised master courses with a modular set-up.

m⁴ Scouting and Incubation

Partner:

Biotech Cluster Development

Technische Universität München

LMU Ludwig-Maximilians-Universität München

ascenion

Max-Planck-Innovation

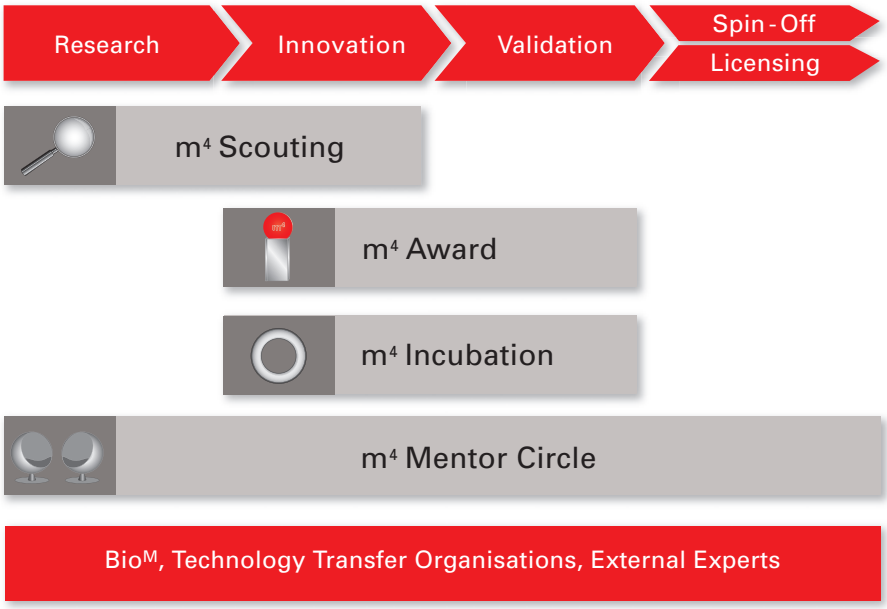
Bayerische Patentallianz
we manage innovations

Identification and Support of Research Projects

with high innovative potential
in personalized medicine

For the m⁴ cluster, sustained competitiveness in the field of personalized medicine will strongly depend on innovation-based strengths including the ability to develop new products and to apply new technologies. Universities and public research organisations, in particular, considerably contribute to this process. Therefore, the overall goal of the project is the optimisation of the technology transfer process by fostering innovation and start-up activities for therapeutic and diagnostic development projects in the field of pesonalized medicine. Promising academic projects will be identified, supported and actively coached to convert scientific breakthroughs and technological achievements into industrial and commercial successes.

The programme provides financial support through a pre-seed fund complemented by active coaching and project management to develop ideas into marketable assets. These efforts should distinctly increase the number and quality of spin-offs and strengthen technology transfer into the existing biotech industry.



m⁴ Scouting & Incubation includes several complementary approaches to support the technology transfer process.

The Initiators:

joint project of the cluster's technology transfer organisations

- *BioM Biotech Cluster Development GmbH*
- *TUM ForTe – Office for Research and Innovation, Technische Universität München*
- *LMU Entrepreneurship Center (KFT), Ludwig-Maximilians-Universität*
- *Ascenion*
- *Max-Planck Innovation*
- *Bayerische Patentallianz*
- In close cooperation with the *Bavarian Ministry of Economics, Infrastructure, Transportation and Technology.*

To explore the academic potential within the field of personalized medicine and to accelerate the commercialisation of promising products and technologies, the following activities have been developed:

- **m⁴ Scouting:** dedicated m⁴ technology scouts located at the two Munich universities to identify and support projects with potential commercial value, especially in personalized medicine
- **m⁴ Award:** a new pre-seed fund supporting innovative projects with high spin-off potential
- **m⁴ Incubation:** active coaching by professional advisors, individually tailored project management solutions and support from external experts
- **m⁴ Mentor Circle:** mentoring programme for scientists interested in commercialisation of research findings or founding of spin-offs, by experienced mentors from academia and industry

m⁴ Award

The m⁴ Award is a regional pre-seed funding programme launched by the Bavarian Ministry of Economic Affairs, Infrastructure, Transport and Technology and supported by the Federal Ministry of Education and Research. It addresses research groups in Bavaria that are developing innovative therapies and technologies within the field of personalized medicine. Funding is intended for projects in the pre start-up phase that hold a high commercialisation potential.

The goal of the m⁴ Award is to assist teams of scientists in their efforts to reach proof of concept with their innovative product ideas. Along with project funding, the prize provides fundamental coaching with project management, special experts and mentors for developing start-up and application concepts. The aim is to make the projects eligible for follow-up financing and ideally to lead to the formation of a company. The sought outcome will be an increase of the number of top-quality spin-offs addressing the future market of personalized medicine in Bavaria.

Five Awardees in 2011

In 2011, five awardees out of 80 applicants from all over Bavaria were selected for their excellent innovations. Their projects address the development of therapeutics for different indications, as well as a technology platform. With a better understanding of pathomechanisms and molecular signalling pathways, basic research unveils ever new targets for medical drugs. The m⁴ awardees Dr. Felix Hausch (*Max Planck Institute of Psychiatry*, Munich) and Prof. Dr. Oliver Ritter (university hospital Würzburg) employ new target molecules to develop therapies against depression and heart failure, respectively. Two other winning teams develop innovative cancer therapies to activate the body's own immune defence: Prof. Dr. Karl-Peter Hopfner (*Gene Center* of the *Ludwig-Maximilians-Universität*) works on personalized, tri-functional antibodies against special forms of leukaemia and Prof. Dr. Dolores Schendel (*Helmholtz Zentrum München*) is establishing a cell therapeutic: individualised vaccination against prostate carcinoma. The fifth awarded project aims to fight neurodegenerative disorders such as Alzheimer's and Parkinson's disease: the team of Dr. Joel Schick and Dr. Markus Conrad (*Helmholtz Zentrum München*) is developing a technology platform to screen new agents for their neuro-protective effectiveness.

The winners of the m⁴ Award 2011. Source: Bio^M, 2011.

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