Bavarian Research Cooperations

Tremendous advances in stem cell and genome research

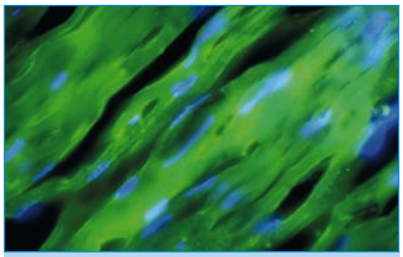
For the scientists led by Professor Wolf Mutschler at the Department of Surgery and Outpatient Clinic of the LMU Munich, the beginning of 2012 marks the end of an era: for almost three and a half years, they have been developing new forms of treatment for degenerative diseases of the musculoskeletal system (e.g. osteoporosis, disc degeneration and the degeneration of tendons) as part of the ForZebRA Research Cooperation. ForZebRA is funded by the Bavarian Research Foundation and is one of currently 14 Research Cooperations in Bavaria that bring together experts from various scientific disciplines. Four Cooperations are currently active in the biotechnology sector: three are researching medical subjects, while FORPLANTA (see page 42) focuses on green genetic engineering. ■

ForZebRA: hope for people with degenerative diseases

Conventional therapies used to treat degenerative diseases are based on damage limitation - whereas the goal of ForZebRA was to eliminate that damage. Regenerative medicine has set itself the goal of cell-based renewal and repair of damaged tissue instead of limiting itself to drug-based and/or surgical improvement of the function of existing tissue.

From fundamental research …

To research the molecular causes of degenerative diseases, investments first had to be made in fundamental research and models developed in parallel in which therapeutic strategies could be verified under suitable biomechanical conditions. The spectrum therefore ranged from the scrutiny of stem cell biology to large animal models.



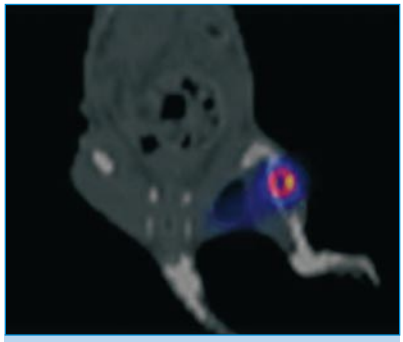
Subproject 1: Cell biology and genomics ■

In subproject 1, led by Professor Franz Jakob from Würzburg, a platform for "cell biology and genomics" was created that focused on gene expression in mesenchymal stem cells (precursor cells of connective tissue) and in stem cells during the course of their differentiation. The researchers paid particular attention in the process to the differences in the gene expression patterns in younger and older people. The results represent significant advances in the understanding of stem cell biology. The team was able, for example, to characterise the first therapeutic target molecules that appear to be suitable for initiating countermeasures against aging and degeneration.

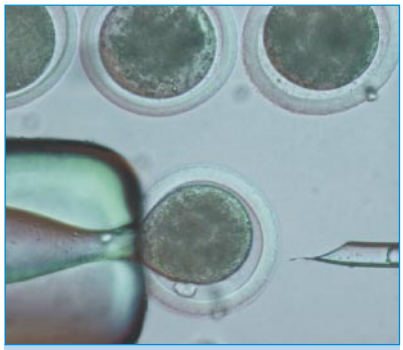
… to regenerative therapy

The findings from the first platform were factored into a second: "cell application and cell tracking". The researchers led by Professor Peter Bartenstein and Professor Matthias Schieker, both from the LMU, were able to develop molecular and also functional imaging methods that allow the therapeutic strategies tried out in pre-clinical animal testing to be pursued with regard to the cells involved, the vitality of the newly-formed tissue and ultimately its function.

The third platform, "large animal models", is particularly important for musculoskeletal diseases since only it is able to simulate suitable biomechanical conditions of the type found in humans. During the course of ForZebRA, the researchers on this subproject led by Professor



Subproject 2: Cell application and cell tracking ■



Subproject 3: Large animal models ■

Eckard Wolf (LMU) and Professor Angelika Schnieke (TUM) developed the principles for cloning pigs that have an immune deficiency and which are therefore suitable for trialling human cell-based constructs without triggering rejection reactions. This will mean that a highly attractive large animal model will be available in future for the validation of innovative therapy options in the field of regenerative medicine. ■

www.forzebra.de

ForNeuroCell II: new treatment methods for Parkinson's and other diseases

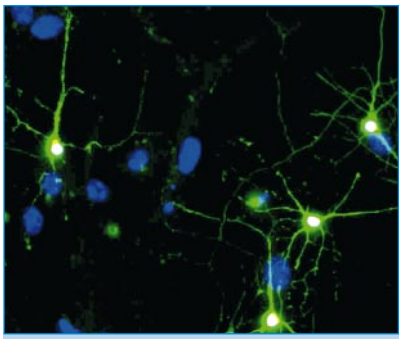
The central domain of research of the ForNeuroCell II Research Cooperation, funded by the Bavarian State Ministry of Sciences, Research and the Arts, is the regulation of adult neural stem cells and their potential for regenerative cell replacement therapy. Great hopes are being pinned on the therapeutic use of stem cells for diseases of the nervous system, such as Parkinson's, Alzheimer's or even paraplegia.

Specifically programming stem cells

The specific programming of an individual's stem cells represents one strategy for the replacement of lost nerve cells. In a modified approach, the team led by Dr. Benedikt Berninger and Professor Magdalena Götz from the Helmholtz Centre in Munich/Institute for Physiological Genomics at the LMU successfully reprogrammed post-natal glial cells ("support cells" in the brain) of mice into specific, synapse-forming subtypes of nerve cells. This conversion of astroglial cells into specific neurons could offer a valuable alternative to the transplantation of nerve cells which can be obtained from embryonic or neural stem cells.

Fluoxetine stimulates neurogenesis

A further area of focus lies in the pre-clinical testing of substances capable of mobilising endogenous, i.e. the body's own, stem cells. A study by the working group led by Professor Jürgen Winkler, Department of Molecular Neurology in Erlangen, used an animal-based Parkinson's disease model to investigate the influence of



Nerve cells from glial cells: Immunostaining reveals several neurons (GFP green) that have formed from the insertion of neurogenin 2 from astroglial cells obtained from the postnatal cerebral cortex ■

Fluoxetine on the new formation of nerve cells in the hippocampus (adult neurogenesis). Adult neurogenesis plays an important role in learning and memory formation, as well as in emotional processes such as anxiety and depression. Findings from various studies indicate that there is a probable link between reduced adult neurogenesis and the development of anxiety and depression. Depressive symptoms are also seen in 40-70 % of patients with Parkinson's disease before the development of motor symptoms. The study now shows that, in this animal model, in which adult neurogenesis is markedly impaired, the long-term oral administration of Fluoxetine can increase the new formation of nerve cells by a third and that this effect is mediated by the neurotrophins BDNF and GDNF. This study could lead to new pathways in the treatment of the neuro-psychiatric symptoms of patients with Parkinson's disease.

New technology for the non-invasive monitoring of differentiation

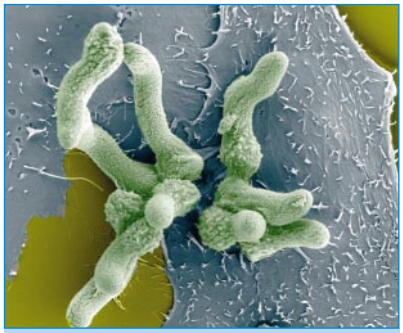
Electrical activity or membrane depolarisation plays an important role in the neural differentiation of stem cells and in the maturity, integration and function of neural cells. Channel rhodopsin-2 (CHR-2) is a protein which, following activation by light, forms an ion-permeable channel. By integrating CHR-2 into the cell membrane of neural cells, light stimulation causes the cell to depolarise. Dr. Albrecht Stroh and his colleagues have succeeded for the first time in expressing this optogenetic protein in embryonic stem cells and thereby optically stimulating stem cells and neurons differentiated from stem cells. Thanks to an automated microscopy system, researchers are therefore able to demonstrate the direct causal role of depolarisation in the neuronal differentiation of stem cells. The possible uses range from the non-invasive monitoring of the differentiation of stem cells to cell tracking and the detection of their functional integration in a neuronal network *in vivo*. ■

www.bayfor.org/forneurocell2

FORPROTECT: Diagnosis and treatment of infectious diseases and cancer

In contrast to ForZebRA and ForNeuroCell II, FORPROTECT focuses on medical microbiology. FORPROTECT is funded by the Bavarian Research Foundation and focuses its re-

search on the development of new approaches to the diagnosis and treatment of infectious diseases and cancer. In FORPROTECT, scientists from the LMU Munich, the Universities of Würzburg and Regensburg and partners from industry all work together. After the first two funding phases, the experts were already able to demonstrate clear results in the diagnosis of infections.



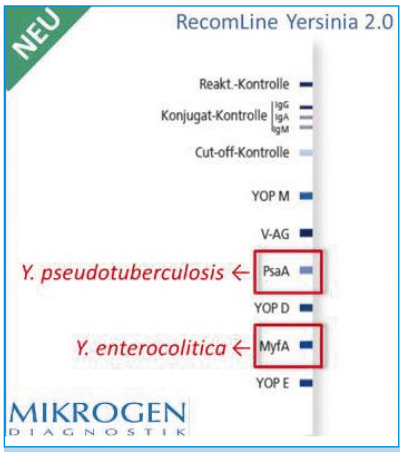
Electron microscopy image of Aspergillus-infected human epithelial cells ■

A new test for differentiating strains of Yersinia

Researchers at the Max von Pettenkofer Institute in Munich have been able to identify two new antigens for the serological diagnosis of Yersinia infections that can lead to intestinal diseases (enteropathogenic Yersinia). The subsequent evaluation of these antigens was carried out by industry partner Mikrogen GmbH in Neuried, a company specialising in diagnostic tools for infectious diseases that leads the way on the national and international stage. The tests are now complete, and the improved test entitled *recom*Line Yersinia 2.0 IgG, IgA [IgM] now allows differentiation between the two strains of Yersinia *Yersinia enterocolitica* and *Yersinia pseudotuberculosis*.

Improved treatment thanks to new uses for mass spectrometers

The introduction of "matrix-assisted laser desorption/ionisation – time of flight" mass spectrometry (MALDI-TOF MS) to identify bacteria is one of the most



RecomLine Yersinia 2.0 IgG, IgA [IgM] from Mikrogen GmbH. The new PsaA and MyfA antigens allow serological differentiation between Y. pseudotuberculosis *and* Y. enterolitica *infections* ■

important advances in the field of microbiological diagnostics in recent years. The team at the Max von Pettenkofer Institute is working with the leading manufacturer of these devices, Bruker Daltonik, to research possible uses in the field of antibiotic sensitivity testing of multi-resistant pathogens. The aim is to significantly shorten the analysis period while at the same time ensuring high levels of precision, which would lead to faster and more specific treatments for life-threatening infections. The scientists are also working on more sophisticated methods for diagnosing fungi and the use of mass spectrometry methods for epidemiological problems such as the mapping of infection chains and sources of outbreaks. ■

www.bayfor.org/forprotect

Collaborative research – a model for success

Alongside interdisciplinarity, collaboration between universities and industry also helps to expand the borders of scientific disciplines and yield new findings. Many groundbreaking results in biotechnology would not have been possible without this collaboration. Bavaria therefore provides considerable support for collaborative research.

The main sponsors in Bavaria are the Bavarian Research Foundation and government ministries, the most active being the State Ministry of Sciences, Research and the Arts. The Bavarian Research Alliance (BayFOR) is a reliable partner to the Bavarian Research Cooperations. It takes care of the coordination of joint activities, networks the Cooperations and their members at European level and provides support for their PR activities. ■

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