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Students Study Programme Experimental Medicine: S. Fischer, M. Stützle, F. Stiefel
Additional Members of Thesis Advisory Committees: G. Grillari (Vienna), M. Fändrich (Ulm), T. Noll (Bielefeld)

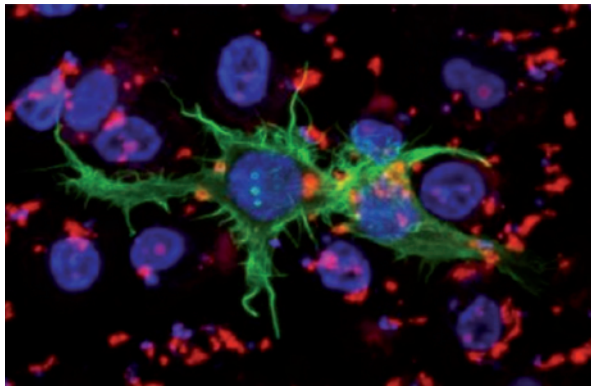
Institute of Applied Biotechnology

Pharmaceutical and Industrial Biotechnology

Head: Kerstin Otte

Research and development at our laboratories are focused on the production processes for products of pharmaceutical and industrial biotechnology. The production process includes cell line establishment, fermentation of eukaryotic and prokaryotic cells, protein purification and protein analytics. The focus of our various research projects ranges from upstream and cell line development for biopharmaceutical production to crystallization of biopharmaceutical proteins and protein aggregation in the production process. Industrial biotechnology deals with synthetic multienzyme systems for multiple step reactions.

Biopharmaceuticals are medicines mainly produced by animal cells. Among conventional cell and process engineering to improve productivity, the potential of microRNAs is still unexplored. MicroRNAs are short single-stranded and evolutionary conserved RNA molecules that play a central role in many cellular processes. They influence gene expression by interaction with mRNAs and are able to modify cellular pathways. Two PhD projects focus on the use of microRNAs in the production process for biopharmaceuticals. The PhD project of Fabian Stiefel aims at identifying microRNAs, which are relevant



Confocal laser scanning micrographs illustrating the cellular localization of fluorescent labeled small double-stranded RNA (red) in CHO DG44 suspension cells transiently transfected with a cationic polymer. A Lifeact-GFP encoding plasmid was co-transfected to indicate the actin cytoskeleton (green). Cell nuclei were counterstained with DAPI (blue). Images were obtained at 63x magnification.

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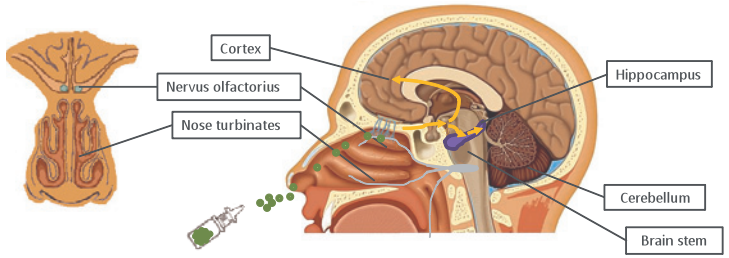
for the production process in production cell lines, and at investigating their potential for process control. Simon Fischer focuses in his PhD project on the modification of microRNAs in CHO cells for the optimization of the production process for biopharmaceutials. A large scale microRNA screen will identify a number of targets to improve production in order to avoid translational burden of the cell (Fig. 1).

The development and testing of the intranasal application of CNS active antibody formats is the PhD project of Martina Stützle (Fig. 2). Therapeutic antibodies are important for many indication areas. Antibodies are usually not able to pass the blood-brain barrier although small peptides can be delivered by intranasal application. In this project, different antibody formats are developed and delivered by means of aerosols, and are tested for potency, safety and quality.

The PhD project of Fabian Bickel aims at understanding mAb aggregation mechanisms and the systematic development of additives to avoid aggregation. Certain substances like osmolytes are known to protect organisms against different kinds of stress such as temperature, pH shifts, high salt concentrations or high pressure. Based on the properties of these compounds, new molecules will be developed with the aid of chemometrics.



Intranasal application of a CNS-active antibody aerosol

Selected Publications:

- *Park SH, Das BB, Casagrande F, Tian Y, Nothnagel HJ, Chu M, Kiefer H, Maier K, De Angelis AA, Marassi FM, Opella SJ (2012): Structure of the chemokine receptor CXCR1 in phospholipid bilayers. Nature 2012 Nov 29;491(7426):779-83. doi: 10.1038/nature11580. Epub*
- *Boubeva R, Reichert C, Handrick R, Müller C, Hannemann J and Borchard G (2012): New Expression Method and Characterization of Recombinant Human Granulocyte Colony Stimulating Factor in a Stable Protein Formulation. CHIMIA. Vol. 66, (5): 281-285.*
- *Carius L, Hädicke O, Grammel H (2012): Stepwise reduction of the culture redox potential allows the analysis of microaerobic metabolism and photosynthetic membrane synthesis in Rhodospirillum rubrum. Biotechnol Bioeng. doi: 10.1002/bit.24734.*
- *Thaisuchat H, Baumann M, Pontiller J, Hesse F, Ernst W (2011): Identification of a novel temperature sensitive promoter in CHO cells. BMC Biotechnol. 11(1):51. doi: 10.1186/1472-6750-11-51.*
- *Zang Y, Kammerer B, Eisenkolb M, Lohr K, Kiefer H (2011): Towards protein crystallization as a process step in downstream processing of therapeutic antibodies: screening and optimization at microbatch scale. PLoS One. 6(9):e25282. Epub 2011 Sep 22.*
- *Schindowski K, von Bohlen, Halbach O, Strelau J, Ridder DA, Herrmann O, Schober A, Schwaninger M, Unsicker K (2011): Regulation of GDF-15, a distant TGF-β superfamily member, in a mouse model of cerebral ischemia. Cell Tissue Res. 343(2):399-409.*