Vacancies for Master students / Diploma thesis in iPSC-based research

Research group INSPIRE:

Our research group (INSPIRE – *in vitro* sepsis research) is based at the University Hospital Jena / Center for Sepsis Control & Care in Jena Lobeda. Our work is very interdisciplinary involving scientists from medicine, chemistry, biology, and microbiology as well as physics and material science. Main foci are the development, characterization and functional validation of micro-physiological cell culture systems (Organ-on-Chip systems) emulating human organ functions *in vitro*. These systems are deployed for biomedical research to elucidate molecular mechanisms in inflammatory and infectious diseases as well as they function as test and screening tools for drug candidate selection and nanoparticle studies. With these micro-physiological systems we want to streamline translational research and help to transfer results from basic research to clinical applications faster and more reliable. Currently, we are looking for master students / diploma students to establish micro-physiological cell culture systems based on induced pluripotent stem cells (iPSCs).

Preferred start date: October 1st /November 1st in 2018
Duration: 1 year (minimum)

Requirements:

- Bachelor degree / prediploma in Biology, Biochemistry, Biotechnology, Molecular Medicine , Life Science or similar studies
- basic experiences in cell culture techniques, preferably several weeks hands-on practice (students with skills in iPSC or stem cell culture will be given preference!)
- first experiences in biochemical assays, immunocytochemistry, flow cytometry, microscopy
- language skills: English
- accurate, well-documented and well-organized work flow
- ability to work in a team
- self-initiative and motivation

Note:

Students who are interested and qualify for the projects will have to run a test phase of two weeks in our labs as these are two ambitious projects

Contact:

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Project 1

Establishment of a human iPSC-based micro-physiological liver model

The human liver is the largest organ of the body (around 1.5 kg in a 70 kg human) and has a multitude of functions, including metabolism of carbohydrates, proteins and lipids but also clearance of toxins and pathogens. Approximately 70%–80% percent of all liver cells are parenchymal cells known as hepatocytes. Non-parenchymal cells (NPC) account for about 40% of total liver cells and include hepatic stellate cells, Kupffer cells (KC) and liver sinusoidal endothelial cells (LSEC) that shield hepatocytes from the bloodstream and blood-borne pathogens. *Ex vivo* it has been shown that NPCs are central modulators of hepatocyte biology and a prerequisite of a proper hepatocellular function *in vitro.* Previously, we have established a fully functional micro-physiological organ model of the human liver *in vitro* comprising all relevant cell types that has been successfully used for functional analysis of inflammatory events during sepsis as well as nanoparticle studies. So far this model is based on several cell lines. Hepatoma-derived cell lines are easy to use, have simple logistics and are cost-effective in maintenance. However, those benefits are often outweighed by a number of other limitations. Most cell lines are derived from carcinoma and are therefore primed in a disease-like state. Further, cell lines have a limited biological relevance compared to primary cell types, due to defects in signaling pathways and cellular dedifferentiation or transformation of cell lines by viruses. Consequently, cell lines are less suitable for disease modelling and pharmaceutical screening purposes.
We are now exploiting different strategies to further improve our model by integrating primary cell material as well as induced pluripotent stem cell (iPSC)-derived parenchymal and non-parenchymal cells to overcome cell line-derived limitations. Human iPSCs can be passaged over a long time in culture and have the potential to differentiate into virtually all cell types of the human body.

Aim of this project is to establish a iPSC-based three-dimensional human micro-physiological cell culture model of the liver within a biochip. Therefore iPSCs will be differentiated into hepatocytes and non-parenchymal cells and characterized for individual cellular markers in immunohistological, immunocytochemical and flow cytometry analysis. This will include CYP enzyme expression, glycogen storage, albumin and urea secretion for hepatocytes; vascular marker expression and vascular plexus formation for endothelial cells as well as vitamin A storage for hepatic stellate cells. Eventually, strategies to assemble all cell types into a three-dimensional human micro-physiological cell culture model of the liver within a biochip will be tested and validated.

Project 2

Establishment of a human iPSC-derived myeloid precursor cell culture and functional characterization thereof derived macrophages

In the human body, all blood cells are derived from two lineages of precursor cells in the bone marrow: lymphoid progenitor cells and myeloid progenitor cells. Among others, myeloid progenitor cells give rise to monocytes that can infiltrate tissue and differentiate into macrophages. Tissue-resident macrophage populations are the key component of the innate immune system and play a pivotal role in host defense against pathogens. Further they have been shown to support tissue integrity and homeostasis. Kupffer cells represent the largest population with 80 – 90 % of all tissue-resident macrophages. They are located in the sinusoids of the liver where they primarily function as a large scavenger cell population that phagocytizes cell and microbial debris and even gut-derived microbial microorganism that reach the liver through the bloodstream. In this context, tissue-resident macrophages are important to emulate fully functional human micro-physiological organ models *in vitro*. However, donor availability and donor-dependent variations as well as different HLA types of cell lines and donor-derived macrophages are of concern for data reproducibility. Thus micro-physiological models based on cells from one donor would help to overcome several limitations. Human iPSCs have the potential to differentiate into virtually all cell types of the human body and have the potential to overcome these limitations.

Aim of this project is to establish a multistep protocol for differentiating human induced pluripotent stem cells into functional macrophages. The project will involve the set-up of a continuous and stable myeloid precursor cell culture to constantly derive progenitor cells for several months that can be further differentiated into functional macrophages within days. Macrophage differentiation and purity of the culture will be characterized by flow cytometry and immunocytochemistry. Subsequently, macrophages will be challenged by bacterial lipopolysaccharide stimulation and bacterial BioParticle application to functionally validate their cytokine profiling capacity and phagocytosis capacity. Eventually, iPSC-derived macrophages will be integrated into a human micro-physiological organ model of the liver.