Forschungsprojekt mit humanen embryonalen Stammzellen /
Projet de recherche utilisant des cellules souches embryonnaires humaines

R-FP-S-1-0002-0000

Referenznummer / numéro de référence	R-FP-S-1-0002-0000
Projekttitel / titre du projet	*Differenzierung von humanen embryonalen Stammzellen zu verschiedenen somatischen Zelllinen*
Projektstand / état du projet	abgeschlossen
Projektleiter_in / direction du projet	Martin Graf
Institut, Firma / institut, société	Stem Cell Platform F. Hoffmann – La Roche AG Grenzacherstrasse 124 CH-4070 Basel
Projektbeginn / début du projet	Oktober 2010
Voraussichtliche Dauer / durée probable	120 Monate
Ziele des Projekts / but du projet	Das Ziel der geplanten Forschung ist die Entwicklung von Differenzierungsprotokollen zur Etablierung verschiedener somatischen Zelllinien ausgehend von humanen embryonalen Stammzellen (hES), wie z.B. Endothelzellen, Kardiomyozyten, Hepatozyten und Adipozyten. Diese Zelllinen sollen in der Präklinischen Forschung zur in vitro Charakterisierung von Substanzen dienen, deren physiologischen Wirkmechanismen und nicht-physiologischen Nebenwirkungen untersucht werden sollen. Diese Arbeiten werden in Zusammenarbeit mit dem Massachussets General Hospital (MGH) und der Universität Harvard in Cambridge/Boston, USA, durchgeführt. Die hier verwendeten humanen embryonalen Stammzellen sollen dazu dienen, zuverlässige und effektive Differenzierungsprotokolle auszuarbeiten, um sie dann auf induzierte pluripotente Stammzellen (hiPS) anzuwenden.

Verwendete hES Zelllinien / Lignées de cellules utilisées	
CSES2	BAG-hES-IMP-0049
Hues1	BAG-hES-IMP-0035
Hues3	BAG-hES-IMP-0036
SA001	BAG-hES-IMP-0031
H1 (WA01)	BAG-hES-IMP-0001
H9 (WA09)	BAG-hES-IMP-0016
SA167	BAG-hES-IMP-0030
H7 (WA07)	BAG-hES-IMP-0034
Hues9	BAG-hES-IMP-0039

Projektergebnis / résultat du projet

The development of disease related cellular models that mimic in vivo physiological processes is challenging and needs novel technologies. So far, many functional assays use cell culture models derived from primary tissue or artificially immortalized cell types. Such models have been widely used due to their expandability, and ease of handling and cultivation. However, such models are often not from human origin, and/or may carry karyotype abnormalities. These anomalies often result in phenotypic changes and question the disease relevance of such models. Primary cell cultures offer an alternative to recombinant cell lines; however, their use in !arge drug screening campaigns is restricted due to difficulties to generate !arge quantities of primary cells. In addition, donor variability makes it difficult to generate robust and reproducible results in compliance with drug development regulations.
The utilization of pluripotent stem cells by the pharmaceutical industry for the development of cellular assays for drug discovery has during the last years moved towards center stage. The isolation of human pluripotent stem cells from the inner cell mass of a blastocyst (known as human embryonic stem cells; hESC) provided the opportunity to expand this cell source indefinitely. In addition, their pluripotent nature, suggests that they could be used to derive many, if not all, differentiated cell types of the human body. Considering this, various efforts have been tried to implement pluripotent stem cell-based technologies for drug screening. This includes efforts trying to identify conditions that induce pluripotent stem cell differentiation toward specific cell types. The ability to cultivate pluripotent & progenitor cells, expand and bank these cells using defined culture media conditions is an important feature for the use of cells in drug discovery.
One general challenge in the establishment of disease relevant assays with the help of stem cells is the time required. We experienced more than one time that it took too lang - once a robust assay was established the project was already discontinued. A strategy that could help here, is the establishment of differentiation protocols for cell types that are relevant in multiple diseases prior to any drug project. However, this requires a strong strategic input from the different disease areas, a lot of operational freedom and lang range perspective as well as a drug project independent budget.
Over the last -years we have gained strong expertise in the differentiation of pluripotent stem cells towards multiple cell types that have been utilized for multiple drug discovery projects. Even after the discovery of induced pluripotent stem cells hiPSC, it was crucial to use hESCs as it was not yet clear if hiPSCs resemble a similar pluripotent state as hESC. One essential point was the adoption of existing hESC based differentiation protocols to hiPSC lines. Same differentiation protocols did work more efficiently with hESCs than with hiPSCs and the scientific community was uncertain about the caveats of the newly developing hiPSC technology.