Break-out session on Animal and Cellular Models and Pathophysiology

Animal Models - Peter Fickert

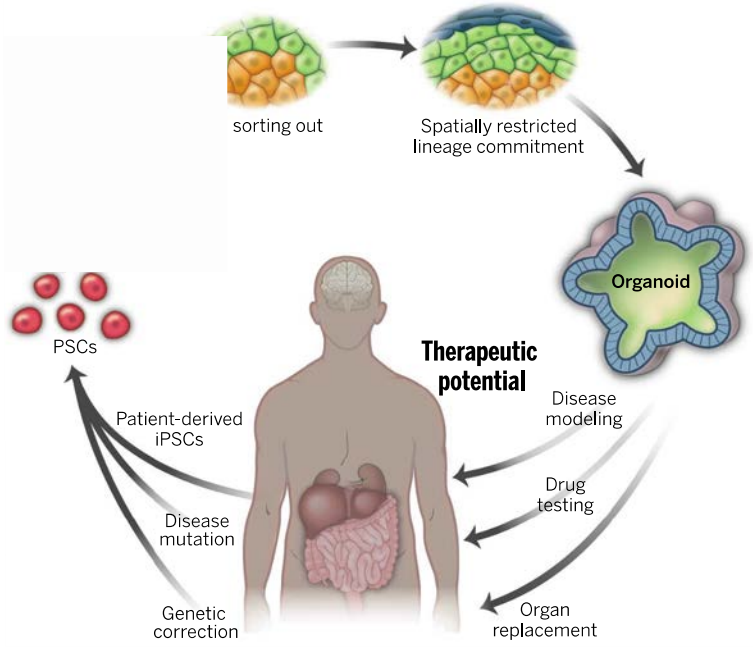
Cellular Models - Romina Fiorotto
- Carol Soroka

Pathophysiology - Carlo Spirli

CCA - Jesus Banales

Modeling human biliary diseases

- Lack of experimental models reproducing human biliary diseases.
- Primary human cholangiocytes are difficult to isolate, de-differentiate after a few passages, and in very short supply, as they need liver transplant samples.
- Stem cell technology:



Induced pluripotent stem cells (iPSCs)

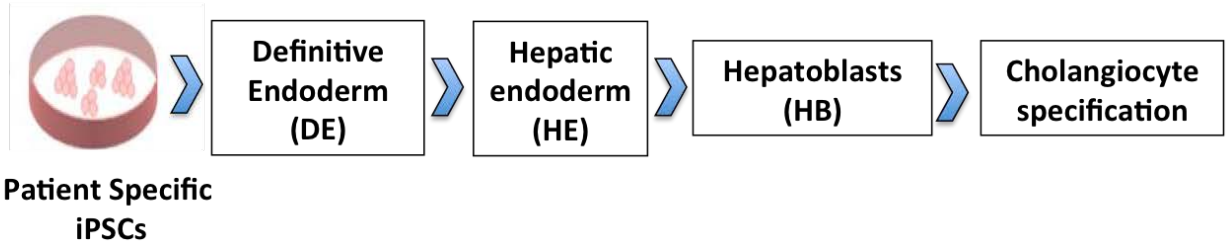
- derived from biopsy samples (i.e skin, blood)
- differentiate into the somatic cell of interest
- high replicative potential
- patient-specific cells

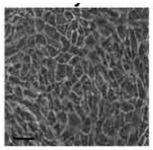
Biliary organoids

- well differentiated
- long-term genetic stability in culture

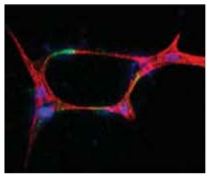
Lancaster et al., Science 2014

Current protocol for differentiation of cholangiocytes from human iPSCs

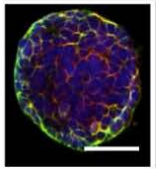




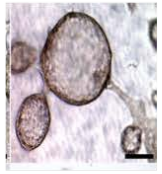
Dianat N et al. Hepatology, 2014



De Assuncao et al.Lab Invest, 2015



Sampaziotis F et al. Nature Biotech. 2015



Ogawa M et al. Nature Biotech. 2015

Future TASKS

- ✧ Development of a polarized monolayer
- ✧ Establishment of a 3D tubule structure
- ✧ Sub-culture of iPSC-derived cholangiocytes after differentiation

What are the advantages of organoid technology for the study of PSC?

- Directly isolated from livers of patients with PSC, requiring no reprogramming; 7 days to viable organoids to freeze down
- Biobank of organoids from patients can be maintained, thus eliminating the need for fresh tissue for each study.
- Organoids can be used in high throughput analysis of gene and protein expression in various diseases.
- Organoids will permit personalized medicine, where we can directly correlate phenotype and genotype with patient history and prognosis.
- Organoids can be used in pharmacotherapeutic studies.

Generation of Cellular Models Relevant for Human PSC

- Human BEC from liver explants/biopsies

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- iPSC-derived PSC cholangiocytes
- PSC biliary organoids
- Biobanking

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Discussion

Collaborations:

- Tissue acquisition
- Gene/protein expression
- Innate Immunity
- Pharmacotherapeutics

Comparison of the different models for common changes in innate immunity

- Activation of innate immune pathways in response to DAMPs and PAMPs
- Gene expression profiling of immune pathways
- Response to drugs