Human Stem Cells Models for Drug Discovery

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Martin Graf, Veronica Costa, Christoph Patsch, Sannah Zoffmann, Mark Burcin
Roche Innovation Center Basel
Disease Relevant Cellular Models

1. **Patient**
   - **Screening**
   - **iPSCs**
   - **Somatic cell types**
   - **Genome editing**
   - **Disease in a dish**
   - **Drug**
Disease Relevant Cellular Models

Patient → Drug → Screening → Disease in a dish → Somatic cell types → iPSCs

Our cellular models:
- Neurons
- Adipocytes
- Cardiomyocytes
- Endothelial Cells
- RPEs
- Hepatocytes
hiPSC platform for autism and neurodevelopmental disorders

Mechanistic understanding and drug screening

In collaboration with:

- Tuberous sclerosis (TSC2 LoF)
- Phelan-McDermid syndrome (SHANK3 LoF)
- Angelman syndrome (UBE3A LoF)
- Neurexin mutations
- 15q11 duplication

Genome edited hESCs

- TSC2+/- and TSC2-/-
- SHANK3+/- and SHANK3-/-
Challenges with Stem Cell Models in Drug Discovery

IMI StemBANCC
Challenges - Stem Cell Models in Drug Discovery

- **Phenotypic screens are long and complicated**
  - → Long cell maintenance/maturation in 384 well plates
  - → Medium change 2-3 / week
  - → Edge effects
  - → Variations add up over time and with every manipulation
  - → danger of bacterial contaminations
Example 1 – how do the cells look after 6 weeks

hiPSCs → NSC → 1 week → 2 weeks → 3 weeks → 4 weeks → 5 weeks → 6 weeks → Neuronal culture

Images Opera: 28 fields per well (mosaic view)

Immunostain & fixation
Imaging on Opera
Seeding density and differentiation
Cell Density Effects Differentiation Capacity

5000 cells per well plated in 384 well PE Cellcarrier plates (45'000/cm²)

Neurons: HuCD/dendrites: MAP2/Nuclei: Hoechst

Courtesy of Sannah Zoffmann
Seeding density and differentiation

Cell Density Effects Cell Identity

1800 cells per well plated in 384 well PE Cellcarrier plates (16’000/cm²)

Neurons: HuCD/dendrites: MAP2/Nuclei: Hoechst

Courtesy of Sannah Zoffmann
Seeding density and differentiation
Effect on Morphology of Seeding Density

Relatively narrow density window where healthy neurons are formed and the culture is suitable for HCS

Courtesy of Sannah Zoffmann
Trick 1 – Start with more than one cell density

- hiPSCs
- NSC
- Neuronal culture

1 week → 2 weeks → 3 weeks → 4 weeks → 5 weeks → 6 weeks → Neuronal culture
**Trick 2:**
Shorten cell maintenance/maturation time

- Cell maintenance/maturation time in 384 well plates as short as possible (as long as necessary)
  - Maturation in flasks
  - Freeze down huge batch of pre-differentiated cells
Reducing well to well variability
Re-plating of predifferentiated cells as late as possible

Continous

Replated

Courtesy of Christoph Patsch
Summary of Tricks

- Shorten cell maintenance time in 384 well plates
- Plate more than one cell density → use most suited one
- Super-humid incubators (>>95% humidity)
- Use incubator only for one experiment at a time
- Medium change with 384 well pipettor’s
- Automated data evaluation in HCS → enables for normalization
Challenges with Stem Cell Models in Drug Discovery

IMI StemBANCC
IMI StemBANCC* at a Glance

- Innovative Medicine Initiative (IMI) project
- Consortium of 11 Pharma and 23 Academic/SME
- Duration: 5 years
- Budget: 55 mio Euro (26 mio IMI funding)
- >150 scientist involved
- Coordinator: Martin Graf, F. Hoffmann-La Roche Ltd
- Managing Entity: Zameel Cader, University of Oxford
- www.stembancc.org

*STEM cells for Biological Assays of Novel drugs and predictive toxicology
The StemBANCC Project

500 Patients

Identify phenotypes, Study the disease in vitro, Develop assays . . .
Patient Populations

- Parkinson’s Disease
- Alzheimer’s Disease
- Neuropathy
- Bipolar Disorders
- Autism Spectrum Disorders
- Schizophrenia
- Migraine
- Diabetes
- Adverse Drug Responders

This project has received support from the IMI Joint Undertaking (GA n° 115439); financial contributions from FP7/2007-2013 and EFPIA in kind contributions.
StemBANCC – Key Objectives

- Recruit 500 Patients including clinical datasets
- Produce & bank high quality iPS
- Develop differentiation protocols
- Study the “disease in a dish” → identify phenotypes
- Develop in vitro models
- Dissemination - Sustainability
Value for the StemBANCC Participants

- **Access** to high diversity of **patient iPS & control lines**
- **Access** to **Genome Edited lines** (patient mutations and isogenic controls)
- **Access** to huge number of **SOPs** (cultivation & differentiation & assays)
- **Access** to **Know-How** – very important in such a highly dynamic field
- **Access** to hands on **trainings**
- **Access** to a huge **network** – academic and pharma
Access to Cell Lines

- StemBANCC is transferring its patient iPS to EBiSC:
- EBiSC: European Bank for induced pluripotent StemCells
- [www.ebisc.org](http://www.ebisc.org)
Acknowledgment - StemBANCC - Partners

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• Prof. Nils HOPPE

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Doing now what patients need next