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Der Einsatz von induzierten pluripotenten Stammzellen in der Pharmaforschung

- Use of induced pluripotent stem cells in pharmaceutical research -

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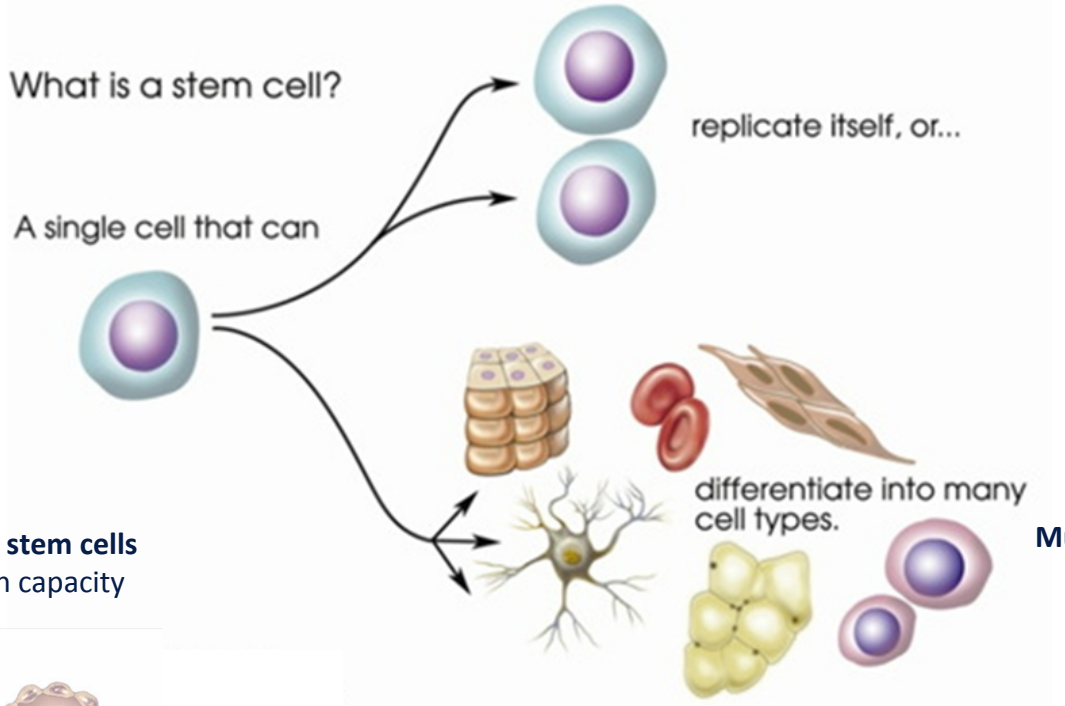
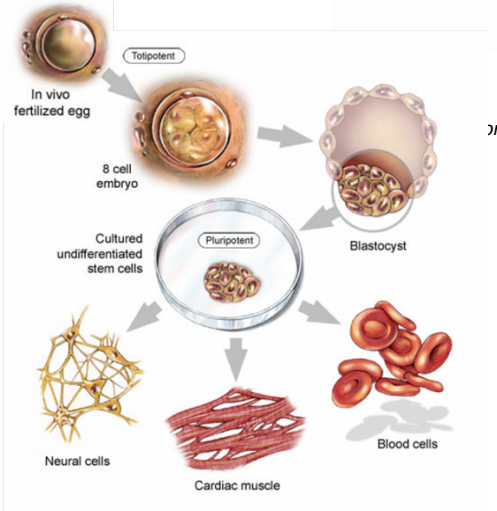
Stem cell types



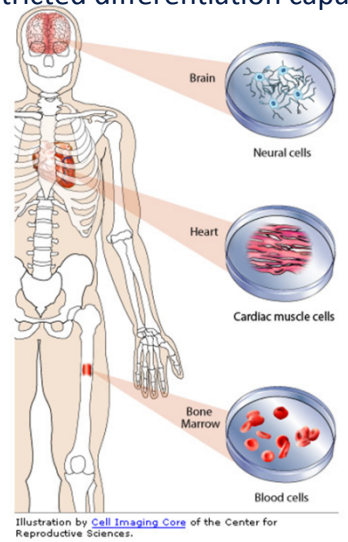
...n.org/blog/stem-cell-research-the-basics-types-of-research-medical-status-and-ethical-drawbacks/

Pluripotent ´embryonic´ stem cells
trilineage differentiation capacity



http://topworldofhealth.blogspot.com/2011/10/stem-cells-learn-about-types-and.html

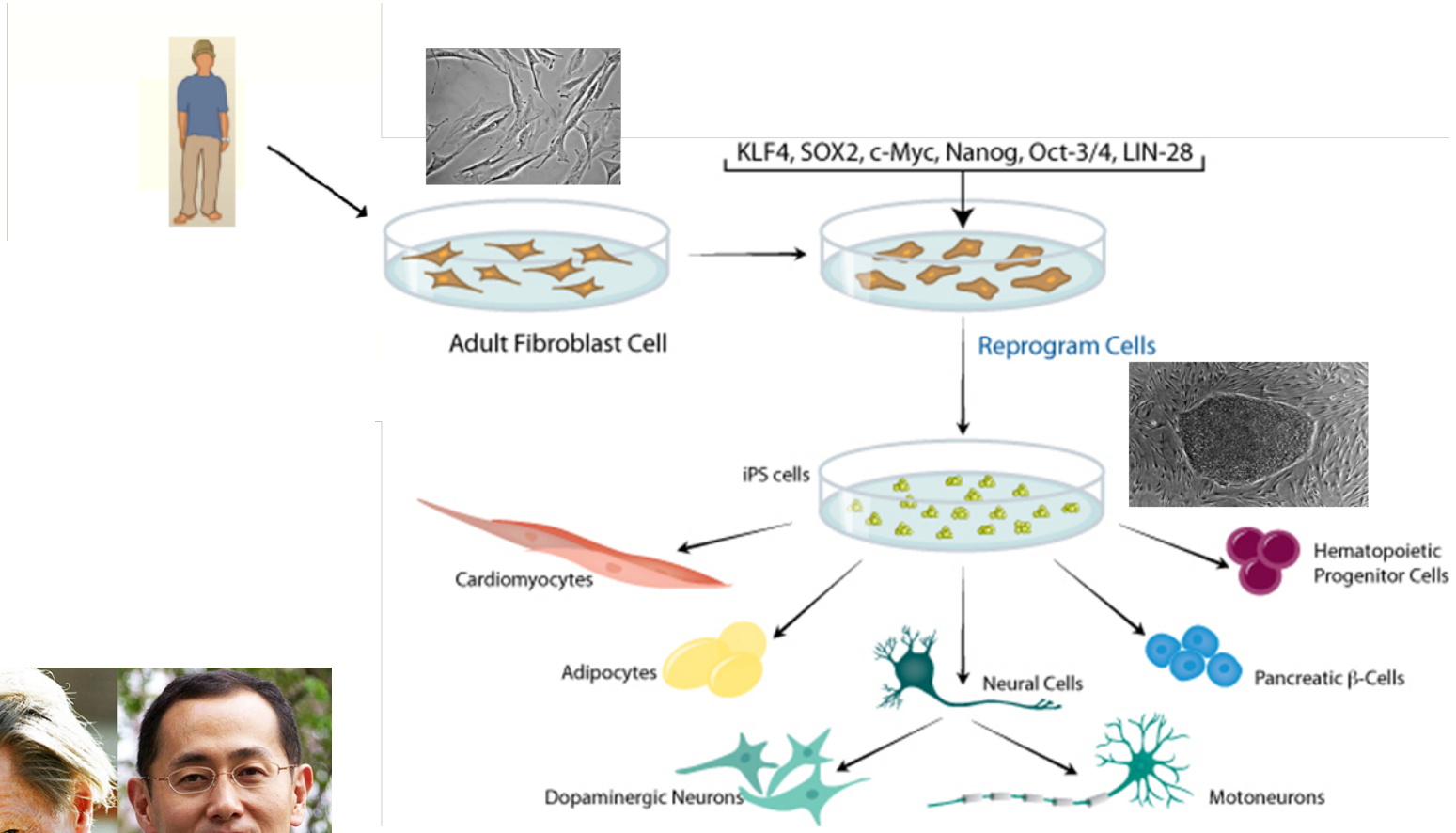
Multipotent ´ fetal or adult´ stem cells
restricted differentiation capacity

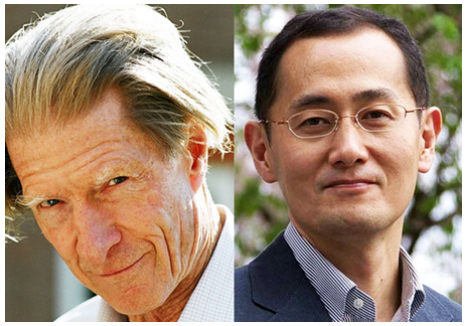


http://www.biologyjunction.com/stemcell_article.htm

Generation of human induced pluripotent stem cells

Reprogramming of cellular fate from adult stage to embryonic stem cell stage





Sir John Gurdon and Shinya Yamanaka
Nobel Prize in Physiology or Medicine 2012

Takahashi and Yamanaka, 2006

Human iPSCs as new source of cells for biomedical research

- **hiPSCs are uniquely useful stem cells**

- Derived from adult tissue via non-invasive methods

- Can be expanded indefinitely

- Fully pluripotent, i.e. can be differentiated into any cell type

- Amenable to gene engineering

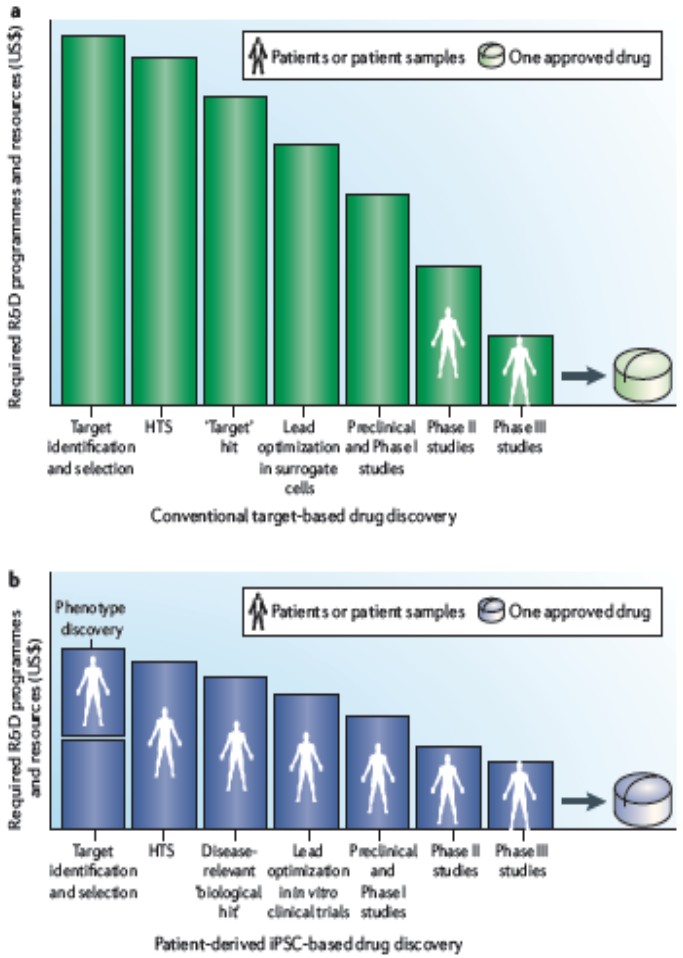
- **Distinct advantages over embryonic stem cells**

- Can be created via streamlined & non-invasive meth

- Eliminates ethical issues regarding tissue source

- Enables diversity of genotype and phenotype

- Enables study of human patient-specific material



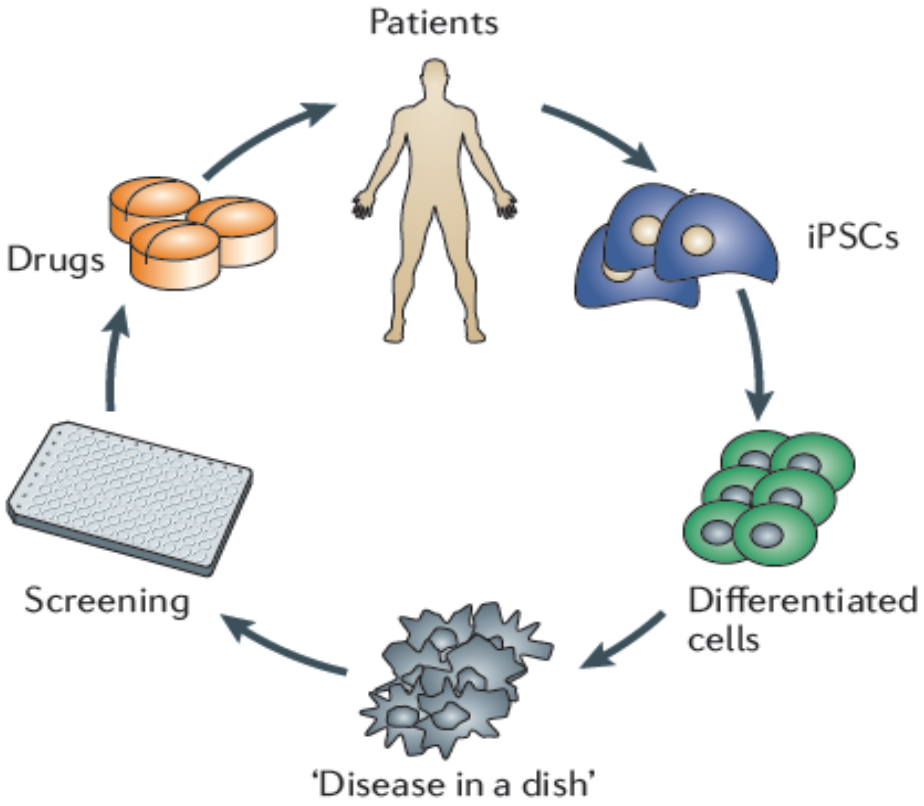
Grskovic M, Nat Rev Drug Disc 2011

The potential use of induced pluripotent stem cells in drug discovery and development is huge

Opportunity to 'revitalize' drug discovery

- **'Disease-in-a-dish': Investigation of disease biology at the molecular and cellular level.** This research is expected to result in a better understanding of underlying disease mechanisms and concomitant identification of **relevant targets** for therapeutic intervention or use as **biomarkers**.
- **Industry-scale screening for identification of lead molecules in conjunction with phenotypic 'read-outs'.** In this context it is worth mentioning that phenotypic screening has contributed to the majority of 'first-in-class' drugs approved by the FDA between 1999 and 2008, as demonstrated by a very recent analysis (Swinney et al., 2011).
- **Drug repositioning.** Assays employing patient-derived hiPS cell types will allow testing the efficacy of drugs for novel diseases.
- **Safety studies for identified lead molecules.** Such studies will for instance be carried out with patient-derived myocytes and hepatocytes to address cardio- and hepatotoxicity.
- **Efficacy studies for diseases for which no animal models exist.** Mimicking patient responses in hiPS-derived model systems will enable to investigate responses to drug treatment for diseases for which no animal models are available.
- **Personalized medicine.** Such patient-derived model systems will allow the development of personalized medicines by early identification of patients most likely to respond to a specific drug treatment.
- **Cell and gene therapy.**

Use of hiPSCs in drug discovery

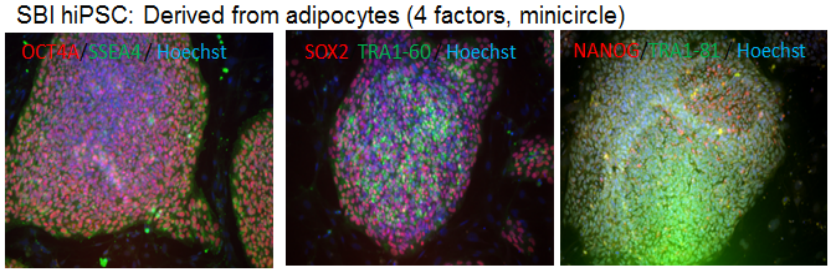


Adapted based on: Grskovic et al. Nature Reviews, Dec 2011

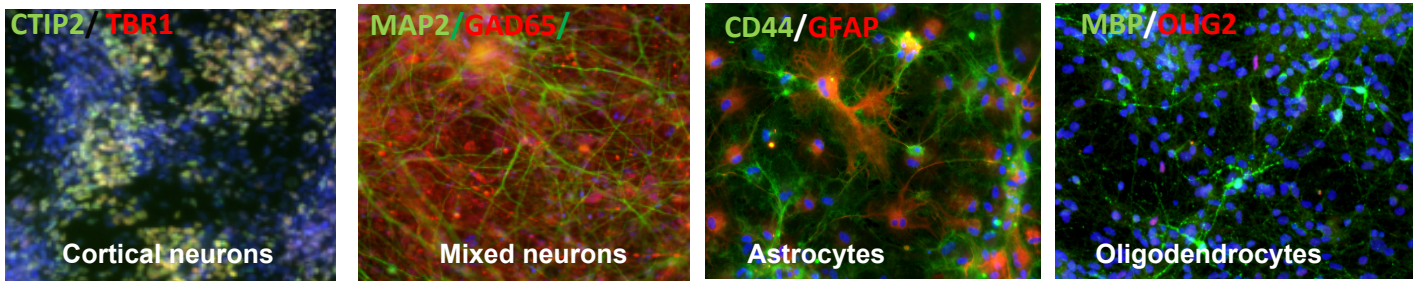
AbbVie's hiPSC neuroscience platform - I

- Part of human preclinical drug discovery

1. **hiPSC biobank (GEOS registration); input from in-house and commercial sources and StemBANCC**
2. Procedure for **culture and quality control of hiPSC lines** in place and applied to in-house lines
   - pluripotency markers by immunofluorescence and qPCR
   - genetic stability by karyotyping (G-banding and CytoSNP analysis)



3. **In-house differentiation protocols and characterization** of hiPSC lines to specialized cells established
   - cortical glutamatergic neurons
   - astrocytes
   - mixed GABA-ergic, glutamatergic neurons
   - Oligodendrocytes



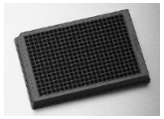
AbbVie's hiPSC neuroscience platform - II

4. **Standardized semi-automated procedures** in place for use of hiPSC-derived neurons in drug discovery assays

Neural induction from hiPSC

Batch expansion of neural stem cells

Cell seeding



Bi-weekly medium change

Phenotypic or target-based assays

DIV0 DIV12 DIV30-40 DIV80-100

STEMBANCC

…is a large-scale, academic-industry partnership in the area of adult stem cell research. It brings a consortium of 35 partners together who share their experience and collaborate in 12 work packages.

The goal of STEMBANCC is to generate and characterise high quality human induced pluripotent stem (iPS) cell lines to study a range of chronic diseases (e.g. diabetes and neurodegeneration) and test for drug efficacy & safety in vitro

Committed EFPIA in-kind contribution: € 21 million
IMI-JU funding: € 26.0 million
5 year project: Nov 1, 2012 - Oct 31, 2017

The Need to be Addressed:

Preclinical tests in many cases do not reflect what happens in 'real life' when the drug is administered in patients

In vitro tests can help reducing animal use, but many of these early tests rely heavily on animal cells, and when human cells are used, they have often been extensively modified to survive in culture and so no longer behave naturally

Urgent need of a well-characterized and renewable supply of cells that more accurately mimic what happens in humans.

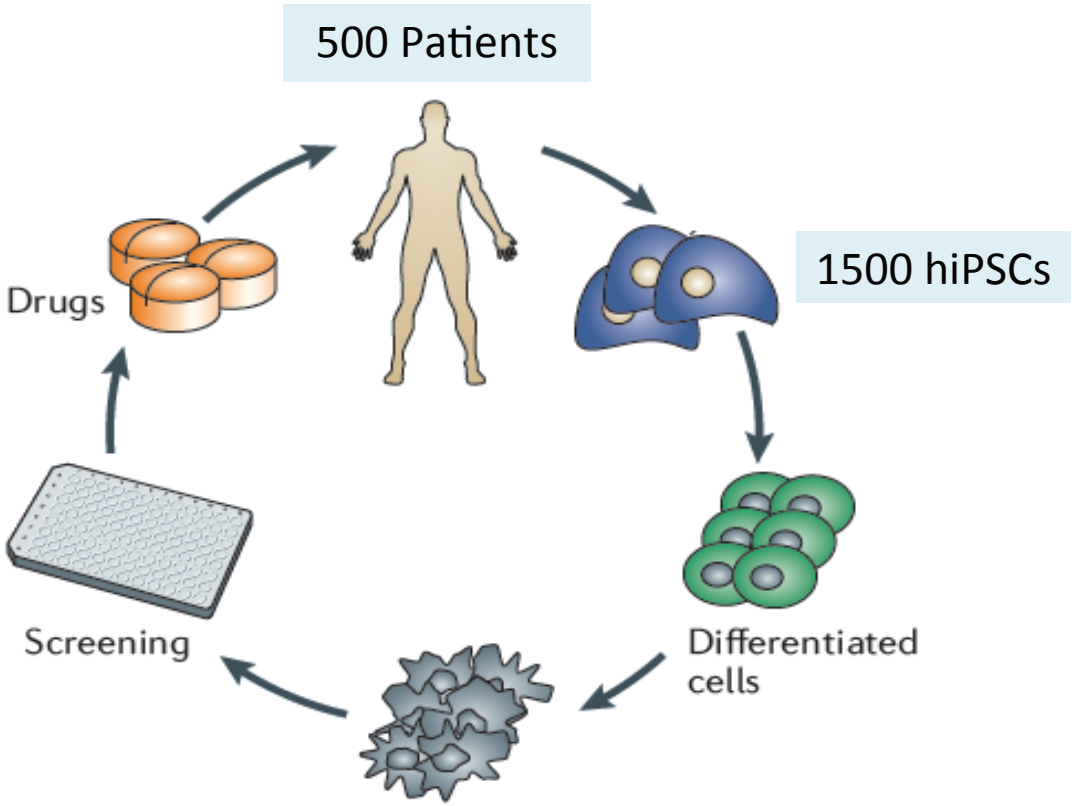
The Promise from STEMBANCC:

Test systems using more relevant, differentiated human cells which will help to better predict clinical outcomes & reduce animal use

The Role of AbbVie:

AbbVie is leading WP8, focusing on patient-derived iPS cell generation in the area of neurological disease, and as a key member of WP 10 also contributes to the generation of iPS models in drug safety

The ambitious *StemBANCC* goals



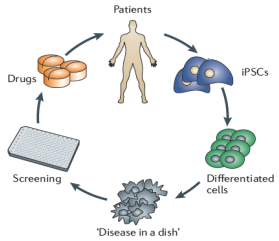
Disease areas

- Diabetes
- PNS
- CNS

Toxicology

Adapted based on: Grskovic et al. Nature Reviews, Dec 2011

‘Revitalization of drug discovery‘



- Ultimately, differentiated human iPS cell line-based models will help to improve and speed up the drug development process, ensure that patients benefit from more effective and safer drugs, and at the same time reduce the extent of animal experimentation

Acknowledgements

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