Creation of disease model systems to understand and correct genetic diseases through gene or other therapy using iPS cells derived from somatic cells: *the iPS study*
Addendum A: "Informatie voor proefpersonen en bijbehorend toestemmingsformulier voor de vervaardiging en het gebruik van geïnduceerde Pluripotente Stamcellen (iPS cellen) voor patiënten met een cardiovasculaire aandoening."

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Primary Objective: to derive iPSCs from patients with a variety of diseases caused by genetic mutations or genetic predisposition to disease or of unknown origin. The cells will be propagated and differentiated into a variety of somatic cell types...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Cardiac and vascular disorders congenital
Study type	Observational non invasive

Summary

ID

NL-OMON45114

Source
ToetsingOnline

Brief title
The iPS study

Condition

- Cardiac and vascular disorders congenital
- Congenital eye disorders (excl glaucoma)
- Congenital and peripartum neurological conditions

Synonym
genetic disease, heritable disorder

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,NWO/ZonMW,EU H2020

Intervention

Keyword: drug screening, genetic correction, genetic disease, in vitro disease model, iPS cell

Outcome measures

Primary outcome

Main study parameters/endpoints:

- Ability to generate iPSCs and differentiated derivative cells from patients*

somatic cells

- Ability to investigate the phenotype associated with the disease-specific

cells

- Ability to (genetically) repair the underlying cause of the disease

- Ability to generate lineage reporter hiPSC lines

- Ability to ameliorate disease phenotype using small molecules, drugs or

si/shRNA

Secondary outcome

- Ability to screen for new compounds/ development of new drugs.

Study description

Background summary

Embryonic stem cells (ESC) are self-renewing and pluripotent, which means they can grow indefinitely in culture and can be differentiated into every cell type of the human body. However, they are derived from blastocyst stage human embryos, in the Netherlands surplus to requirements for in vitro fertilization as governed by the EmbryoWet 2002. No genetically defective human embryonic stem cells have yet been derived under the EmbryoWet in the Netherlands. The EmbryoWet states that should there be alternatives to destruction of human embryos for deriving pluripotent cells then these sources should be used by preference. A new development in basic stem cell research has recently suggested that there may now be a candidate alternative. These are induced pluripotent stem (iPS) cells [1, 2]. iPSC can be derived from adult somatic cells by overexpression of specific transcription factors with the help of a variety of integrating and non integrating vectors. POU domain class 5 transcription factor1 (OCT4), SRY- box containing gene 2 (SOX2), proto * oncogene c*MYC and Kruppel * like factor 4 (KLF4) were the four factors initially described needed but there are now multiple variant cocktails which all seem to lead to iPSCs from both mouse and human that closely resemble mouse and human ESCs respectively. In addition hiPSCs have been generated from a variety of somatic cell sources. Whilst not yet suitable for transplantation and cell therapy purposes because of teratoma risk and multiple other reasons, hiPSCs are very interesting for deriving pluripotent stem cells carrying specific genetic mutations or other disease phenotypes of presently unknown origin. If derived from somatic tissue from patients this would i) obviate the need for using IVF embryos *rejected* following pre-implantation genetic diagnosis ii) broaden the range of diseases from which it is possible to derive pluripotent cells in the Netherlands (PGD is not allowed for all genetic diseases at present) and iii) does not require CCMO approval since iPSCs do not fall under the EmbryoWet. Most importantly however, it would enable the generation of many different diseased cell types from patients. In the case of cardiac diseases, for example, it would be possible to use a tissue biopsy from a patient to derive iPS cells and differentiate them into cardiomyocytes in order to investigate at the cellular level what effects the genetic mutation has on heart cells, without the need for a heart biopsy. Likewise for other cell types that are difficult to access through biopsies (eg brain, liver,

muscle etc) or for diseases that are very rare and for which the cells cannot be cultured for an indefinite period human iPSC will be an excellent source of tissue for disease research [3].

While mutant mouse models exist for some of these diseases, they often exhibit different phenotypes than humans because physiology differs so significantly in humans and mice. Just as examples: mouse heart beats at 500-600 times per minute whilst humans only at 60 times per minute; some mutations causing muscular dystrophy in humans do not have orthologous regions of the same gene in mice. In addition, disease genes may only cause a disease phenotype in a human genetic background Therefore models which use human cells are in most cases superior to understand the disease pathogenesis and devise therapeutic interventions. The use of human stem cells promotes compliance with the 3Rs for animal experiments (reduce, refine, replace).

Study objective

Primary Objective: to derive iPSCs from patients with a variety of diseases caused by genetic mutations or genetic predisposition to disease or of unknown origin. The cells will be propagated and differentiated into a variety of somatic cell types using in vitro differentiation protocols and compared with control iPS cell derivatives. Control iPSC lines have already been generated using annonymized waste tissue from the Dept of Dermatology and have been differentiated into various cell types including cardiomyocytes, vascular endothelial cells, blood cells, neurons, and smooth muscle cells. Control lines have also been marked transgenically with lineage reporters. They are shared with external researchers according to LUMC guidelines for collaboration using donated annoymized tissue.

Secondary objectives: (i) to identify the most suitable tissue source for each reprogramming method used and (ii) to establish a genotype related phenotype, which will allow study of the mechanisms underlying the disease pathogenesis, and analysis of therapeutic interventions by genetic or drug mediated repair of the defect (iii) to develop therapies for disease phenotypes captured by the patient hiPSC (iv) to couple phenotype with related clinical manifestations of disease, drug responses and whole genome sequencing. This may be in collaboration with external researchers.

Study design

Acquisition of donor material
Donor material will be collected from various tissue sources and annonymized by key-coding. Skin will be obtained by 4 mm punch biopsies; for isolation of blood cells maximally 80 ml of peripheral blood will be collected. Fat tissue, oral mucosa and heart muscle tissue can only be obtained in the context of necessary surgical procedures. For children only non-invasive procedures

(urine, milk teeth) or minimally invasive procedures (peripheral blood with a maximum volume of 40 ml, keratinocytes from hair) apply. Other tissues can only be obtained in the context of necessary surgical procedures. Where possible non-invasive collection of somatic tissues will apply for all patients and controls. Cord blood will serve as an additional source for reprogramming if available; derivative iPSC are suitable for studying disease in neonates. Fibroblasts, keratinocytes, cardiac progenitor cells (CPCs), endothelial blood outgrowth cells, erythroblasts or other blood cell progenitor, renal epithelial cells or mesenchymal stromal cells will be isolated according to the tissue source, expanded and frozen stocks will be prepared. Which tissue source is chosen for reprogramming depends on what is most conveniently available as part of routine patient treatment. Secondary use (studies on cell types not related to the primary disease of the patient, beyond the duration of the project, implementing emerging and established research methods) is part of the consent procedure.

Generation of iPSC
For the generation of iPS cells the transcription factors, OCT4, SOX2, KLF4 and occasionally cMyc will be overexpressed with the help of integrating or non-integrating DNA or RNA agents. As part of the basic characterization iPSCs will be induced to differentiate into derivatives of all three primary germ layers to confirm pluripotency. After generation of the tissue-specific cell types from the iPSCs, the differentiated cells will be characterized using appropriate molecular, biochemical and functional assays, aimed to precisely delineate the signature of the affected cells in the context of the disease. This will take place in the iPSC core facility. Suitable candidate cellular pathways will then be targeted by genetic and pharmacologic methods in either the undifferentiated cells or in the differentiated derivatives of interest aiming to repair the cellular defect. This will take place in the department responsible for the investigator initiated research after transfer of the iPSCs under key-code.
We intend to generate multiple (3-5) iPS cell lines from each patient, as already carried out for healthy control individuals. Multiple lines are needed since it is unclear how much variability there will be in differentiation potential and phenotype. This forms the baseline for determining how many patients with different diseases will be included. At present, data is being published in excellent peer reviewed journals with 2-3 patient iPS cell lines with similar functional mutations. This will likely be sufficient for each particular disease in first instance. The present capacity of the LUMC iPSC core facility is approximately 60 new lines per year, which corresponds to approximately the same number of patients.

Storage of data and material
hiPSC lines generated by the LUMC iPSC core facility (and somatic cells if requested) will be given to the principal investigator who originally requested the generation iPSCs by the LUMC iPSC core facility.

Frozen backup stocks of somatic cells and hiPSCs will be kept in dedicated liquid nitrogen tanks of the Department of Anatomy and Embryology (S-05-11, liquid nitrogen tank 11, T37P2-262S05). All lines derived from LUMC patients are property of the LUMC and will only be distributed to third parties in agreement with the principal investigator using a standard LUMC Material Transfer Agreement (copy attached).

Key-coded (annonymized) patient-specific information will be stored in the database of the LUMC iPSC core facility, which is only accessible to the staff of the facility. For LUMC patients, the code will be kept in the accredited central database of the LUMC in which all patient information is stored. The database is behind the LUMC firewall and is not accessible from outside the hospital network. For all other (non-LUMC) patients, their physicians/hospitals will be responsible for key-coding. Somatic cells and hiPSCs will only be used and accessible by researchers after removal of all information allowing patient identification and coding. This conforms with the Personal Data Protection Act (Wbp) of the Netherlands.

Study burden and risks

Insights into the mechanism of human disease facilitate the development of new treatment modalities that either reduce the rate of development of even reverse disease symptoms. hiPSC lines can be created from every individual that captures both normal and disease genotypes. The collection of tissues or body fluids to collect somatic cells is minimally or non-invasive. The benefits for gaining insights into disease and creating new treatments outweigh the risk of collecting the tissues and cells.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Patients suffering from diseases of genetic or non-genetic origin, including but not limited to cardiovascular, neural and blood disorders. Related or unrelated healthy individuals will serve as controls.
In principle patients of all ages are eligible, as some forms of hereditary disease already affect patients at young age and may potentially even be fatal at that age.

Exclusion criteria

Patients tested as HIV or hepatitis positive.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-01-2016
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO

Date:	02-07-2014
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Approved WMO

Date:	24-07-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	27-08-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO

Date:	10-09-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	27-10-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	05-10-2016
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	25-08-2017
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL45478.058.13