Experimental CFTR correctors for the treatment of Cystic fibrosis.

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Ethical review	Approved WMO
Status	Pending
Health condition type	Respiratory disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON46144

Source
ToetsingOnline

Brief title
ERARE-INSTINCT

Condition

- Respiratory disorders congenital

Synonym
Cystic Fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC Rotterdam
Source(s) of monetary or material Support: EU ERARE INSTINCT (ZONMW)

Intervention

Keyword: CFTR, CFTR correctors, Cystic Fibrosis, induced pluripotent stem cell

Outcome measures

Primary outcome

The cell material will be used in selection and testing of CFTR correctors and potentiators in established and novel assays in vitro. The primary objective is Identification and testing in advanced cellular model systems in vitro of novel CFTR directed compounds (correctors and potentiators) for the treatment of patients with rare trafficking mutations.

Secondary outcome

Further development of organotypic human and personalized (*organ on a chip*) cell culture systems in which compounds can be tested, to improve the efficacy of pre-clinical research in CF and other chronic lung disease.

Study description

Background summary

Rationale: Effective drugs for the treatment of Cystic Fibrosis (CF) patients with trafficking mutations are not yet available, and associated lung and liver pathologies remain untreatable. Novel compounds have to be identified, and tailored in combination to specific CFTR mutations, to different tissues, or even to the individual patient.
Immortalized cell lines overexpressing mutant CFTR are typically used to screen candidate molecules but have proven to be poor predictors of clinical efficacy. The complexity of CFTR maturation and turnover requires the use of cellular models that closely recapitulate the specific properties of the clinically most affected organs. Importantly, current screening efforts based on primary airway cells or intestinal organoids cannot specifically target single rare CFTR mutations, or mimic multiple cell types.
To address these unmet needs we generate induced pluripotent stem cells (iPSCs) from patients homozygous or compound heterozygous for the common F508del and

rare trafficking mutations. The iPSCs will be genetically corrected to provide adequate isogenic controls and to express CFTR from one allele only with the mutation of interest. Reporters will be introduced to facilitate high throughput screening. Identified compounds will be functionally validated and the mechanism of action will be elucidated in iPSC-derived and primary organotypic culture. This approach allows testing compound combinations in personalized surrogate models of CF lung and liver disease, up to the pre-clinical stage in particular targeting rare CFTR trafficking mutations.

Study objective

The objective of the present application is to obtain cell material in the form of blood, from two patients homozygous for the trafficking mutation N1303K rare mutations for which no effective treatment is available, to generate induced pluripotent stem cells (iPSCs) and primary cells for functional assays.

Study design

Collected cell materials from the two selected CF patients will be used to generate induced pluripotent stem cells (iPS), to identify (by high throughput screening) and validate (in organotypic cell culture models) novel CFTR targeted therapeutics.

Study burden and risks

Only CF patients with known mutations of interest (rare CFTR trafficking mutations) and well described pathology are eligible, in this case two patients with a N1303K CFTR trafficking mutation aged 11 and 24 years. These studies will contribute to the development of an effective treatment for patients carrying these mutations, for which an effective treatment does not exist.

Blood samples are drawn using standard procedures during routine examination of the patients, so that no additional puncture is necessary. The procedure is widely used in clinical practice and usually well tolerated, involving limited discomfort and negligible risk. For this study a 20 ml blood additional sample will be drawn.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

In order to be eligible to participate in this study, the subjects must meet all of the following criteria:
- Diagnosed with CF, confirmed with 2 known CFTR mutations of interest
- Authorised by informed consent

Exclusion criteria

A subject who meets any of the following criteria will be excluded from participation in this study: Absence of any of the previous inclusion criteria.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	07-05-2017
Enrollment:	2
Type:	Anticipated

Ethics review

Approved WMO

Date:	15-06-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL61623.078.17