# DEfective HUman SAlivary gland stem cells: the cause of Primary Sjögren*s syndrome?
# -DEHUSAPS study-

Published: 21-03-2016
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To assess whether salivary gland stem cell (SGCS) defects are key to salivary gland pathogenesis in pSS.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Autoimmune disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON43500

**Source**
ToetsingOnline

**Brief title**
DEHUSAPS study

### Condition

- Autoimmune disorders

**Synonym**
Sjögren's disease, Sjögren's syndrome

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Groningen
**Source(s) of monetary or material Support:** Reumafonds

## Intervention

**Keyword:** Regeneration, Salivary gland, Sjögren's syndrome, Stem cells

## Outcome measures

### Primary outcome

To define pSS SGSC defects using self-renewal and organoid formation techniques

on pSS-derived SGSCs.

### Secondary outcome

Through comparison to healthy SGSCs, transcriptome and proteome screens will

unveil key pSS SGSC defects. Relating potential pSS modulators to patient

biopsy banks, and chemically and/or genetically interfering with their activity

will validate our findings.

# Study description

### Background summary

Salivary glands (SGs) of patients with primary Sjögren*s Syndrome (pSS) harbor lymphocytic infiltrations, and demonstrate gradual and permanent deterioration in saliva production. Although extensively studied, no definitive cause of pSS pathology has been reported. However, available evidence indicates that the glandular epithelium plays an important role in the process. These cells are targeted by the autoinflammation processes and also demonstrate immunological functions. Possibly, intrinsic defects of the gland-specific parenchyma contributes significantly to pSS development. This project will address this issue.

### Study objective

To assess whether salivary gland stem cell (SGCS) defects are key to salivary gland pathogenesis in pSS.

### Study design

1) Establish the differentiation/proliferation/apoptosis tendencies of salivary

gland stem cells in pSS. This will be achieved using parotid gland biopsies from patients grouped in 4 categories: 1) *healthy control patients* (=n=20); 2) non-pSS sicca patients (n=20); 3) incomplete pSS patients, i.e. patients that do not full fill all the criteria for pSS (yet; n=20), and 4) pSS patients (n=20). Parotid biopsies will be obtained during the diagnostic work-up for pSS (patients may qualify as non-pSS sicca, incomplete pSS or pSS). Parotid biopsies from *healthy* subjects will be obtained from patients subjective to an elective neck dissection as part the treatment for head and neck cancer (parotid salivary gland not affected by the underlying disease).
2) Elucidate mediators of SGSC defects in pSS using transcriptome and proteome screens. Total RNA will be extracted from both salisphere cultures (SGSCs), and organoids (mini SGs) from patients and RNA sequencing (RNASeq) performed comparatively between each category.
3) Validate putative mediators of pSS using pSS tissue and saliva samples. We will validate mediators/processes initially by returning to our stocks of saliva and samples from patient categories 1-4 and examining activity of identified pathways/mediators.
4) Interfere with pSS disease by genetically/chemically disrupting putative pSS-mediator signals. Proof of principle that these molecules/processes are salient to pSS will be obtained by chemical and/or genetic manipulation of their expression/activity. Genetic manipulation will be achieved using CRISPR-Cas9 gene editing technology. Function-blocking antibodies or chemical inhibitors will be used to modulate activity of proteins implicated in pSS. Concurrent monitoring of the SGSC and organoid culture dynamics following these manipulations will allow us to determine if we can *rescue* the phenotype of SGSCs and organoids from pSS biopsies.
5) Establish the immunological (response) capabilities of the organoids derived from SCGCs.
In order to establish a full in vitro model for pSS as an autoimmune disease, we will explore the immune modulating capabilities of pSS SGSCs.

**Study burden and risks**

This is a minimal risk study. The saliva collection is a non-invasive procedure and the biopsy, as is the saliva collection, will be part of the subject*s routine clinical care for diagnostic purposes. The parotid gland tissue needed for the experiments will be collected simultaneously with the diagnostic biopsy via the same surgical approach. It is presumed that taking this extra amount of tissue, similar to the amount of tissue needed for the diagnostic work-up, will not increase the morbidity of the diagnostic procedure as our intervention studies with biologicals (rituximab, abatacept) has learned us that taking repeated biopsies from the same parotid gland is not accompanied by increased morbidity of the surgical procedure.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

• Presents with classic dry mouth symptoms presumed to be pSS.
• Willing to have exam of oral cavity.
• Scheduled for parotid biopsy for routine diagnosis and care.
• Scheduled for saliva collection for routine diagnosis and care (not in controls).

## Exclusion criteria

• History of radiation therapy to the head or neck.
• Another auto-immune disease, sarcoidosis, hepatitis C, IgG4 disease, HIV (all exclusion criteria for classifying a subject as pSS).

# Study design

## Design

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

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-04-2016 |
| Enrollment: | 80 |
| Type: | Actual |

# Ethics review

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|---|---|
| Approved WMO Date: | 21-03-2016 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |
| Approved WMO Date: | 29-10-2018 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Groningen (Groningen) |

# 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 | NL56147.042.15 |

# Study results

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|---|---|
| Date completed: | 23-03-2019 |
| Actual enrolment: | 93 |