# Skin B cells in the progression from cutaneous lupus to systemic lupus

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

## Summary

### ID

NL-OMON56119

**Source**
ToetsingOnline

**Brief title**
CLE to SLE

### Condition

- Autoimmune disorders
- Epidermal and dermal conditions

**Synonym**
Cutaneous lupus, skin lupus

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Foreum foundation

## Intervention

**Keyword:** B cells, Cutaneous lupus erythematosus, Systemic lupus erythematosus

## Outcome measures

### Primary outcome

Objective 1: Characterization of autoreactive B cells in CLE and SLE

• Frequency and phenotype of autoreactive B cells in skin and circulation

• Specificities of antibodies from cutaneous B cell supernatant in ELISA

Objective 2: Determine the mechanisms for B cell tolerance breakthrough and

plasma cell differentiation in the skin of CLE and SLE patients

• Transcriptome of B cells in skin (scRNAseq)

• B cell receptor repertoire of cutaneous B cells

• Immune cell landscape of B cells in skin (imaging mass cytometry).

### Secondary outcome

NA

# Study description

### Background summary

In this study we aim to identify the immunological mechanisms underlying the break of tolerance checkpoints in Systemic Lupus Erythematosus (SLE). Autoimmune diseases are characterized by dysfunction of the immune system in which an immune response is mounted against ones* own tissue causing disease. Many autoimmune diseases are autoantibody-mediated, meaning that antibodies cause tissue inflammation and damage.1 Antibodies are produced by plasma cells, the terminal differentiation stage of B cells. Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease in which autoantibodies cause systemic inflammation and damage.
In healthy individuals, production of autoantibodies is prevented in a process

called immune tolerance. Tolerance in B cells consists of several checkpoints throughout B cell development. A tolerance checkpoint is defined as the stage in B cell development where a block in maturation occurs. Though the tolerance checkpoints in early B cell development have been quite well-characterized, the checkpoints after B cell activation are not yet defined and understood, though they are crucial in prevention of autoimmune diseases.
Although developments in recent years have led to identification of B cell activation pathways with increased activity in SLE, how and where tolerance is broken in SLE is not well understood, due to a lack of access to an early or pre-disease state.
In this study, we propose to take a novel approach by determining the transition of cutaneous lupus erythematosus (CLE) to systemic disease (SLE). CLE is a skin disorder that can occur as isolated disease limited to the skin. However, depending on the subtype of CLE, up to 40% of CLE patients progress to SLE, and thus can be used as a unique approach to study the development of systemic autoimmunity.
We hypothesize that the skin is an initial site where B cell checkpoints are broken, but still locally confined in CLE. Maturation of the immune response in the skin can ultimately lead to systemic disease (SLE).

**Study objective**

In this proposal, we therefore aim to characterize in detail the cutaneous B cell response in patients with isolated CLE (CLE only) and patients with systemic and cutaneous disease (SLE/CLE).
Primary Objectives:
1. Characterize autoreactive B cells in CLE and SLE
2. Identify mechanisms for B cell tolerance breakthrough and plasma cell differentiation in transition of CLE to SLE

**Study design**

This is an interventional, cross-sectional, single center study in which biomaterial (sera, plasma, PBMCs, skin biopsies) will be collected from the patients at a single timepoint.

In this study biopsies and a blood sample will be obtained combined with a routine visit to our clinic. Isolated immune cells will be analysed using spectral flow cytometry, in vitro cultures, and single cell RNA sequencing to construct a comprehensive overview of molecular alterations of B cells from SLE and CLE patients.

Peripheral blood will be drawn from 25 patients with isolated CLE and 25 patients with combined CLE/SLE.
Four skin biopsies will be collected of these patients: (2 x 4 mm) unaffected skin and (2 x 4 mm) affected skin for both groups (25 in each group).

**Study burden and risks**

Two four mm skin biopsies will be obtained from lesional skin and non-lesional skin at a routine visit to the clinic. There are no high risks to be expected with this approach. There is only a (very low) risk (<5%) of a wound infection after biopsy. No direct benefit from participation is expected for this study.

# 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

1. Age >= 18 years.
2. Diagnosis of CLE is made by dermatologist based on clinical features and histopathological examination.

3. In case of a SLE, this diagnosis is made by a rheumatologist based on 2019 ACR/EULAR classification criteria for SLE.
4. Patients who have read, understood, and signed an informed consent document related to this specific study.

### Exclusion criteria

- Patients with any other dermatological of systemic disorder which would interfere with the results, at the discretion of the investigator.
- Patients using topical corticosteroids and topical calcineurin inhibitors at biopsy site within one week prior to enrolment.
- Patients who are or have been treated with specific B cell depleting/modifying therapies (Rituximab, Belimumab, Cyclophosphamide)in 12 months prior to inclusion.

## Study design

### Design

**Study type:** Observational invasive

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Basic science |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-12-2023 |
| Enrollment: | 50 |
| Type: | Anticipated |

## Ethics review

Approved WMO

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| Date: | 17-11-2023 |
| Application type: | First submission |

| | |
|---|---|
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# 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 | NL84801.058.23 |