

# DRUG TREATMENT OF ME/CFS: WHAT HAVE WE LEARNT SINCE 2007?

Olav Mella

Cancer Clinic, Haukeland University Hospital

Bergen, Norway

## CONFLICT OF INTEREST

Haukeland University, through its commercialization company Vestlandets Innovasjonsselskap AS, holds a pending patent application related to plasma cell-targeting treatments for ME/CFS.

WO2021038097A1: Method for the treatment of chronic fatigue syndrome using an inhibitory or cytotoxic agent against plasma cells.

Olav Mella is listed as an inventor for this application.

## HOW WAS OUR INTEREST WAKENED?

Since 2004 we saw several patients who **had ME/CFS** and later got cancer. Some of these **sponaneously described** major ME-symptom **improvement after** start og cancer **drug treatment**, mostly with cyclophosphamide with or without rituximab

These observations **aroused our interest**, as we knew there was no known effective treatment

So we were **biased to believe** that drugs could help ME patients – if we found out **which drugs** and **how to use** them

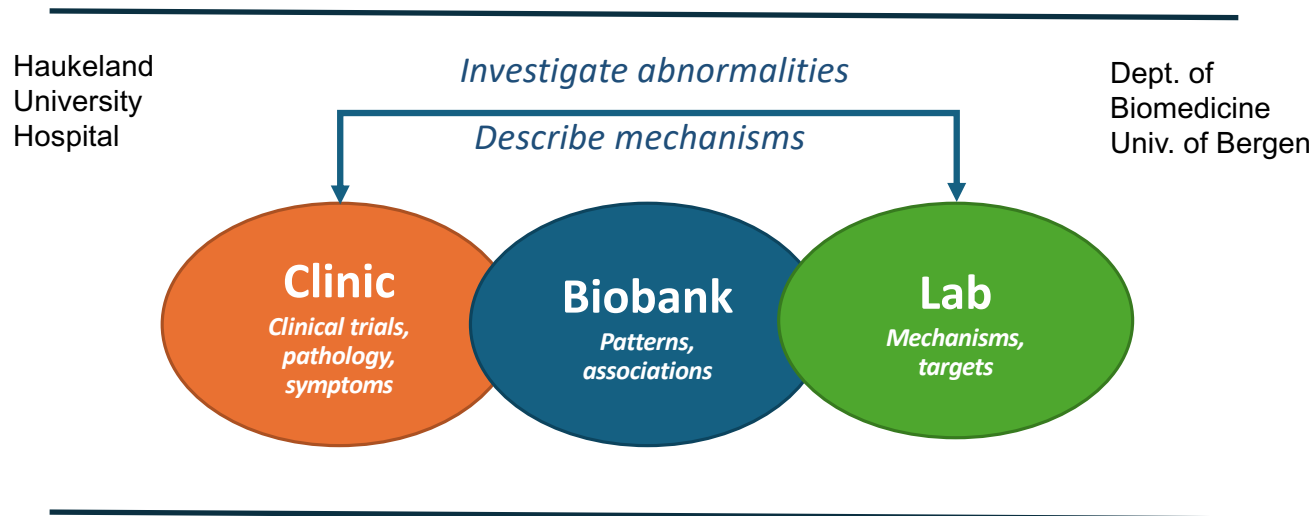
We started to believe that ME has it's **origin in the immune system**. Therefore we concentrated on **immune manipulation**

## STARTED WITH SMALL INTERVENTIONAL DRUG TRIALS WITH THE INTENTION OF DOING TRANSLATIONAL STUDIES BASED ON THE PATIENT MATERIAL

- No medical **specialty** within the hospital **had** the **responsibility** for the ME patients
- Little funding, limited manpower resources, some hostility within the hospital. Had experience in clinical trials, but none in ME (like the rest of the world)
- Believed **our observations with ME patients, who** got cancer and improved **despite** the cancer treatment that we had expected they would get worse from, **could be important**
- So we **started drug trials** and **allied up** with partners at University of Bergen and others, especially for spin-off studies

The Bergen research group combines work on clinical trials in ME/CFS with translational laboratory work using samples from patients included in the trials

We aim to increase understanding of the disease mechanisms, and to develop rational treatment.



## WE STARTED WITH RITUXIMAB (LEAST TOXIC)

**Rituximab:** a therapeutic monoclonal antibody that specifically targets  
**CD20+ B-lymphocytes**

A case series (**BMC Neurol 2009**)

A small randomized and placebo-controlled phase II trial (**Plos One 2011**)

An open-label phase II trial with rituximab maintenance treatment  
(**Plos One 2015**)

Rituximab was **well tolerated**. Seemed to result in **good responses** in a **subgroup** of the patients, pending **maintenance** doses

## CYCLOPHOSPHAMIDE TRIAL: A MORE BROADLY ACTING CYTOTOXIC AND IMMUNE MODULATING DRUG

- **Schedule chosen** based on experience from treatment of established autoimmune diseases
- **40** patients with **moderate to severe** ME/CFS disease (not mild, not very severe). **6 intravenous infusions** cyclophosphamide at **4-week** intervals
- Short term subjective **toxicity was tougher** than expected (but little hematotoxicity). Possible long-term toxicity: early menopause, infertility
- **55%** of the patients judged to be **responders**, sustained response in most

# A NATIONAL MULTICENTRE, RANDOMIZED, DOUBLE-BLIND AND PLACEBO CONTROLLED PHASE III STUDY USING RITUXIMAB INDUCTION AND MAINTENANCE IN ME/CFS

**Purpose** of the RituxME study: To **verify or refute** if **B-cell depletion** using rituximab is **associated with clinical benefit** in ME/CFS patients

**151** patients were randomized and **commenced treatment** (CCC, 18-65 yrs, duration 2-15 yrs)

**Induction:** **Rituximab** (or **placebo**) 2 infusions 2 weeks apart. 500 mg/m<sup>2</sup>, max 1000 mg IV

**Maintenance:** **Rituximab** (or placebo) 500mg at 3,6, 9 and 12 months

**Observation/symptom recording** til 24 months

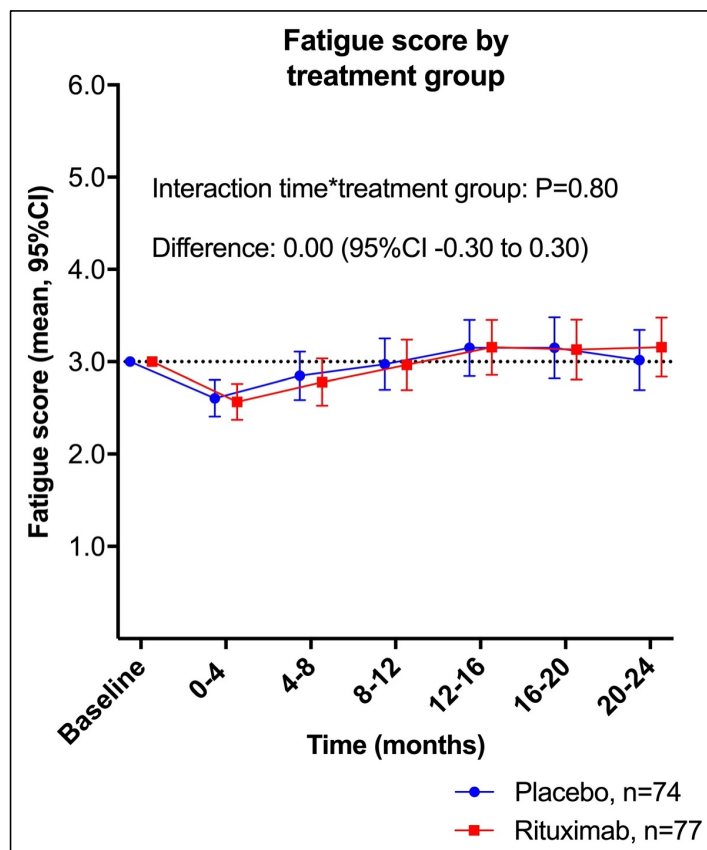
**Substudies:** assessed at baseline and 18 months.

- Endothelial function

- Cardiopulmonary exercise tests for two following days

- Gastrointestinal function

# THE RITUXME STUDY TURNED OUT NEGATIVE



No differences between rituximab and placebo, in subgroups:

by severity, by disease duration, by gender, with or without infection upfront

**Annals of Internal Medicine** ORIGINAL RESEARCH

**B-Lymphocyte Depletion in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome** April 2019

A Randomized, Double-Blind, Placebo-Controlled Trial

Øystein Fluge, MD, PhD; Ingrid G. Rekeland, MD; Katarina Lien, MD; Hanne Thürmer, MD, PhD; Petter C. Borchgrevink, MD, PhD; Christoph Schäfer, MD; Kari Sørland, RN; Jörg Aßmus, PhD; Irini Ktoridou-Valen, MD; Ingrid Herder, MD; Merethe E. Gotaas, MD; Øivind Kvammen, MD; Katarzyna A. Baranowska, MD, PhD; Louis M.L.J. Bohnen, MD; Sissel S. Martinsen, RN; Ann E. Lonar, RN; Ann-Elise H. Solvang, RN; Arne E.S. Gya, RN; Ove Bruland, PhD; Kristin Risa, MSc; Kine Alme, MSc; Olav Dahl, MD, PhD; and Olav Mella, MD, PhD

## WHY WAS THE RITUXME STUDY NEGATIVE?

Many possible reasons: Endpoints, especially lack of **objective endpoints**, too **low doses** of rituximab as **maintenance**, **placebo** mechanisms in both arms – or rituximab does **not work sufficiently** in this setting

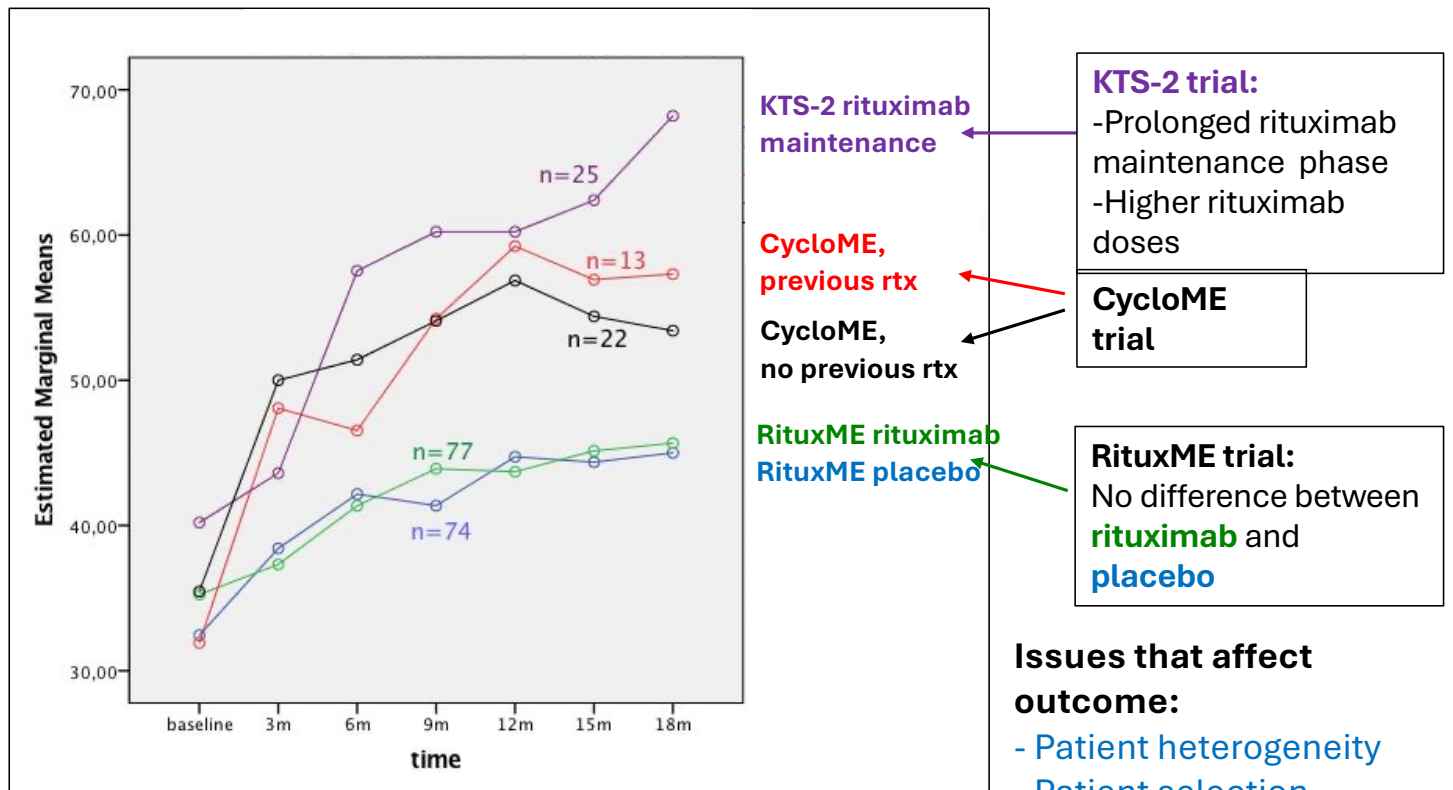
In patients with ME according to CCC, not preselected by some unknown measure, rituximab **should not be used outside of clinical trials**

Nevertheless, we know that a **subgroup does respond**, both in our hands and with other investigators. This subgroup is **not big enough to be disclosed** in a placebo-controlled trial.

Looking back: what **did we learn** from our studies with **rituximab** involved?

Most patients with clinical response had **recurrence after some months**, often to a function level higher than pretreatment

# SF-36 PHYSICAL FUNCTION IN OUR CLINICAL TRIALS



**KTS-2 trial:**  
 -Prolonged rituximab maintenance phase  
 -Higher rituximab doses

**CycloME trial**

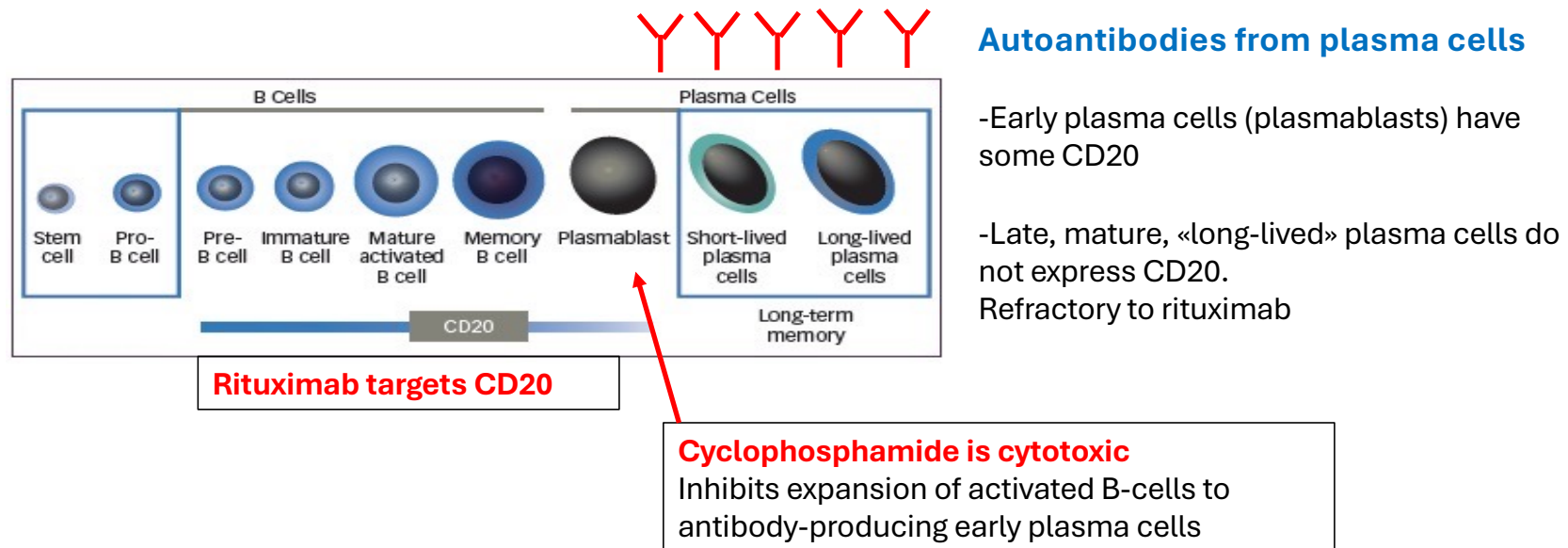
**RituxME trial:**  
 No difference between rituximab and placebo

**SF-36 Physical Function**  
 Scale 0-100  
 Normal population:  
 mean 84 (95%CI 72-97)

- Issues that affect outcome:**
- Patient heterogeneity
  - Patient selection
  - Patient expectations
  - Placebo mechanisms
  - Natural symptom variation

# HOW DOES RITUXIMAB WORK IN ME/OUR TRIALS?

We have and still believe, that a **variant of autoimmunity** and **autoantibodies** are involved in ME. In established autoimmune disease, **long lived plasma cells (LLPC)** have been recognized as a resistance mechanism (due to **lack of membrane CD20**)



## WHAT HAPPENED WITH RITUXIMAB AND CYCLOPHOSPHAMIDE?

Rituximab **eliminated AB and AAB production by CD20 pos plasma cells** and plasmablasts. Protracted B-cell depletion (KTS-2 trial) with high doses of rtx, probably some lack of **recruitment of LLPC**

Cyclophosphamide probably mainly acts by **inhibiting** the course of activated **B-cells to AB-producing plasmablasts** (in addition to a **general effect** on all **proliferating cells** in the immune system and other tissues)

Does drug treatment help in the long run? **6 year results** of the CycloME study and RituxME study (Rekeland et al., PLoS One 2024):

Cyclo treated **17.6%** had SF36 **PF >90**, **44.1%** SF36 **PF>70** **Resetting** of immune system?

## WHAT ARE LLPC AND CAN THEY BE REACHED BY DRUGS?

LLPC are the plasma cells that **produce antibodies (AB)** after common **vaccinations**

They are not many, but can **produce continuous amounts** of highly specific AB (2000 molecules per second), spreading them eventually **in the blood stream**

LLPC reside **in privileged sites** in the bone marrow and gut walls and can **live for decades** (but also need renewal)

What if clones of LLPC by some mechanism start **producing a defect or faulty** AAB, or if the signal to **stop** making a normal **(functional) AAB** after an infection is not given – can that **result in ongoing symptoms** usually seen during the peak of an infection (without the inflammation)?

**LLPC** can be **targeted** by drugs (next talk prof. Fluge)

# ACKNOWLEDGMENTS IN DRUG TREATMENT OF ME

When patients respond, they **improve** (not necessarily to the same extent) **in all symptoms**. Indicates that **a central mechanism** in the pathophysiology of the disease is **touched**

Responses to immune modulating treatment: points at the **immune system** as the important target that can be the **solution giving major improvements**

The various drug treatments show different kinetics: **Ritux** response at **4-9 mths** after start, **Cycloph.** more variable (more acute side effects) **2-8 mths**, **plasma cell targeting** at ..... Probably can be explained by **how the different drugs work**, although the ultimate effects are the same

Both the clinical symptoms of ME and the observations when patients respond indicate that **major signaling dysfunctions**, probably through **functional AAB** are involved (affect circulatory system, nervous system, GI, GU, respiratory system etc.)

Immune drugs **work at a different level** than where the symptoms **are created** – our individual **immune adaptive systems** may govern any **response**. An **intervensjon** in the immune system will **affect the fine-tuned balance** and compensatory alterations may result