

May. 13<sup>th</sup>. 2025@Berlin



# Rituximab trial in JAPAN

Wakiro SATO, MD. PhD.  
Section of research and development strategy  
Translational Medical Center  
National Center of Neurology and Psychiatry (NCNP)  
Tokyo, JAPAN

International ME/CFS Conference 2025

COI

*Wakiro Sato*

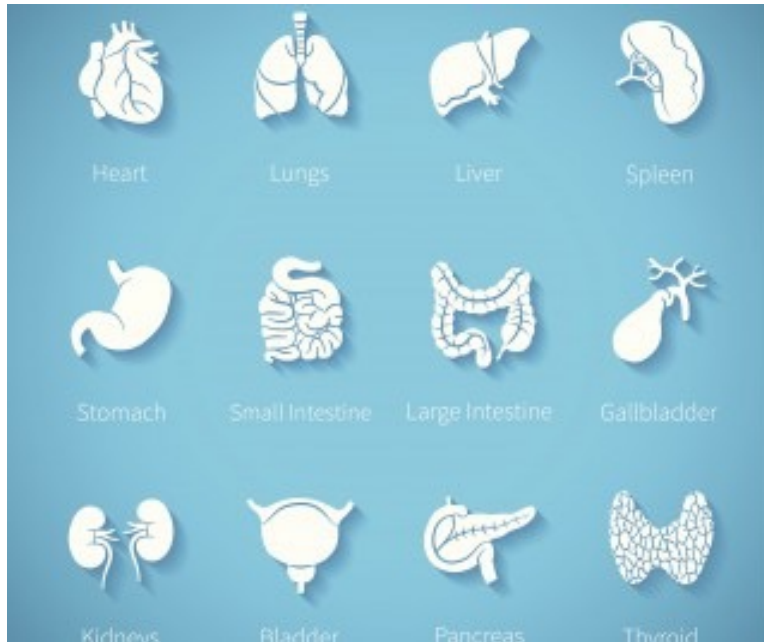
*Translational Medical Center*

*National Center of Neurology and Psychiatry (NCNP)*

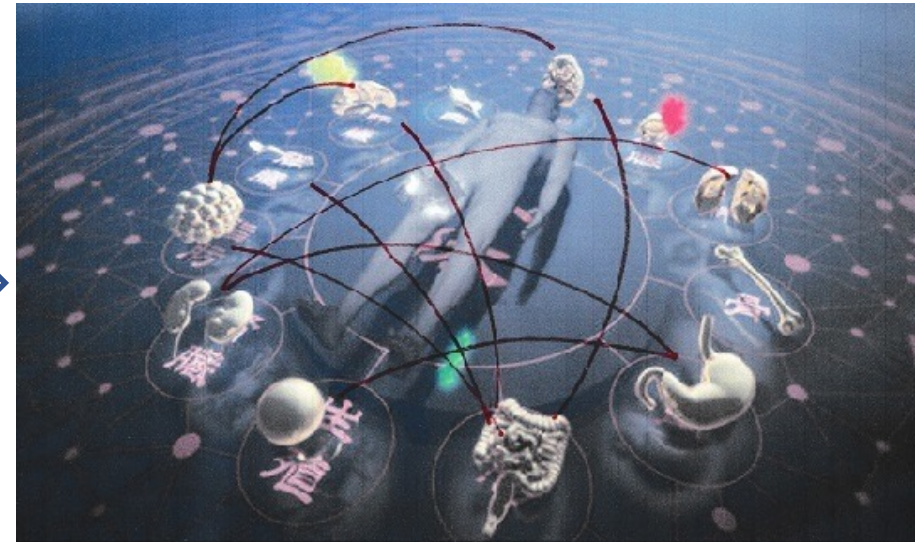
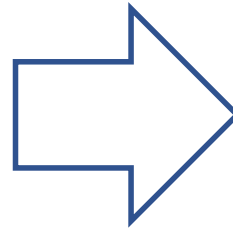
research funded by Zenyaku Kogyo Co., Ltd.

# Paradigm shift in Medicine

from NHK special 'Jintai'



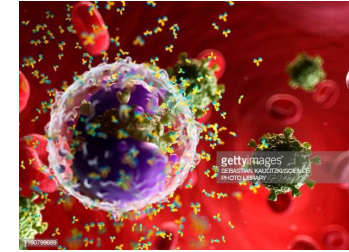
Organ-specific medicine



Understanding the network of body

- *Neuroimmunology: pay attention to the "in between" of the nervous system and the immune system.*
- *Both systems respond to BOTH external AND internal information.*

# B cell/autoantibody in ME/CFS



## <Autoantibodies>

- Autoantibodies (various anti-GPCRs-Abs) (Loebel M et al. 2016; Tanaka S et al. 2003)
- **Link between autoantibodies and brain MRI** (network analysis, free water-corrected DTI) (Fujii H, et al. 2020, Kimura et al. 2023)

## <B cell abnormalities>

- Deviated functional B cell subsets (Bradley, 2013; Ramos, 2015; Brenu E, 2015; Mensah, 2016)
- Differentiation defect in B cell development (Nguyen, C. B. et al. 2017)
- Clonal expansion (Milivojevic, M., et al. PloS one, 15(7), 2020)
- **Skewing of B cell receptor repertoire** (Sato W et al. 2021)

## <Treatment target>

- Responders of B cell depletion therapy (Fluge, O. 2009, 2011, 2015)
- Responders of immunoabsorption therapy (Tölle, M. et al. 2020 et al. )

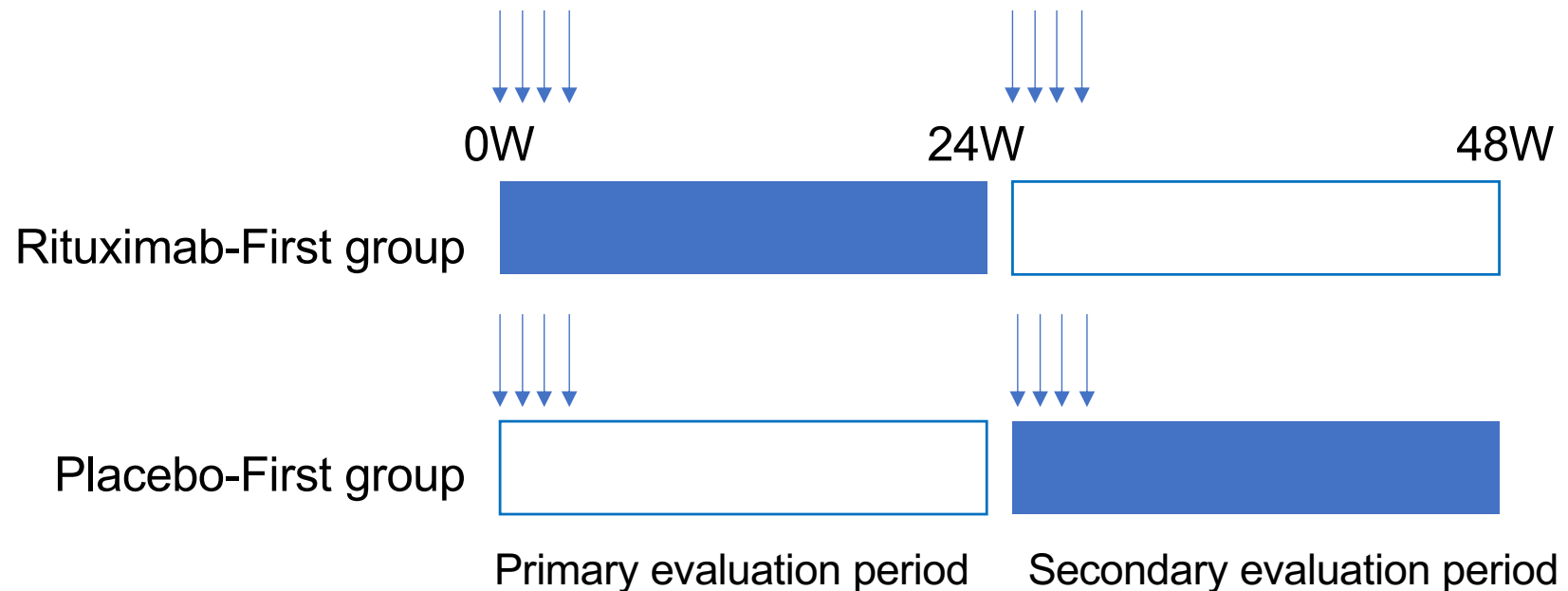


# TITLE

**An *exploratory*, placebo-controlled, double-blind,  
phase II study  
to evaluate the efficacy and safety of rituximab  
in ME/CFS**

*⌘ What indicators are associated with treatment efficacy?*

- a physician-initiated, single-center
- number of the subjects (N=30)
- randomized into Rit-first group and Placebo-first group
- rituximab dose (375 mg/m<sup>2</sup>/week iv. x 4 times)



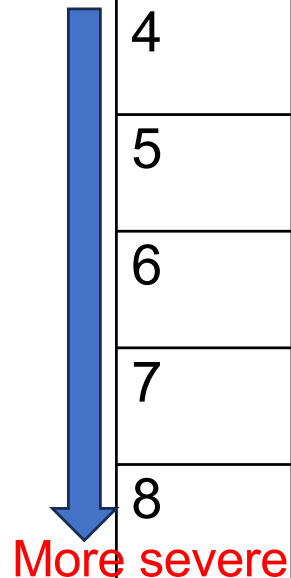
# Selection of the patients

- Typical case but not restrictive...
- Well-characterized...(recruited from our clinic)

# Selection Criteria

- **18-65 years of age**
- **Meeting Canadian consensus criteria**
- **Performance Status (PS) of 4 or higher.** Matsuda Y, et al. (2009) *Psychiat Clin Neuros* 63(3):365-373.

Score	Condition
0	No complaints; able to carry on normal activity without fatigue
1	Able to carry on normal activity, but sometimes feel fatigued
2	Able to carry on normal activity or to do active work with effort; requires occasional rest
3	Several days a month, unable to carry on normal activity or to do active work; requires rest at home without work
4	Several days a week, unable to carry on normal activity or to do active work; requires rest at home without work
5	Unable to carry on normal activity or to do active work at all, although able to do light tasks; requires rest at home without work for several days a week
6	Requires rest at home without work for over one-half of a week; able to do light tasks in good health
7	Unable to carry on normal activity or to do light tasks at all; able to care for self without assistance
8	Remains in bed for more than one-half of each day; able to care for self to some extent, but requires frequent assistance
9	Unable to care for self; must remain in bed with day-long assistance



## Exclusion criteria (excerpts)

(7) Patients **with coexisting or pre-existing severe\* immune system disorders** (excluding autoimmune diseases such as thyroiditis and type 1 diabetes)

(8) Patients who have received systemic **immunosuppressive treatment** (e.g. immunoglobulin therapy, azathioprine, cyclosporine, mycophenolate mofetil) within a year, monoclonal antibodies or other drugs acting on the immune system (e.g. anti-CD20 antibody products including rituximab) or any comorbidity requiring treatment with immunosuppressive agents (except for treatment with small doses of steroids of 5 mg/day or less)

(9) Patients who have **started alternative medicine** (e.g. acupuncture, moxibustion, repeated sauna therapy (WAON)) within 12 weeks prior to the start of investigational drug treatment

(10) Patients with **severe\* endogenous (primary) depression**

## Prohibited concomitant medicines/therapies

- (1) No new so-called **alternative medicine**, such as acupuncture, moxibustion or Japanese warming therapy, is to be initiated during the clinical trial period.
- (2) Concomitant use of systemic **immunosuppressive treatment** (e.g. cyclosporine) listed in the Exclusion Criteria is prohibited during the clinical trial period.
- (3) Monoclonal antibodies and other **drugs acting on the immune system** are not administered during the course of the clinical trial. (4) Steroid treatment at small doses of prednisolone equivalent of 5 mg/day or less is excluded, except in the case of treatment for adverse events. In the case of treatment for adverse events, any dose may be administered.
- (4) **Immunoglobulin therapy** is not initiated during the study period.
- (5) No marketed drugs (including biosimilars) containing the same ingredients as the study drug used in the trial, and no other study drugs other than the study drug and control drug specified in the protocol, will be administered during the clinical trial period.

# Endpoints

- Primary
- Secondary
  - Clinical evaluation
  - Biomarker (exploratory)
  - Others (safety etc.)

# Primary Endpoint

the proportion of patients with an improvement of Performance Status (PS)  $\geq 1$  at 24 weeks.

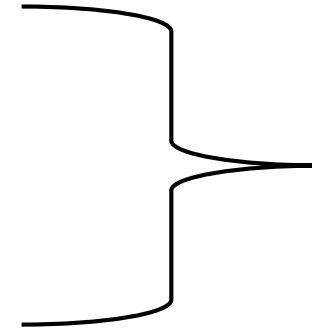
ADL improvement

Adjustment factors:

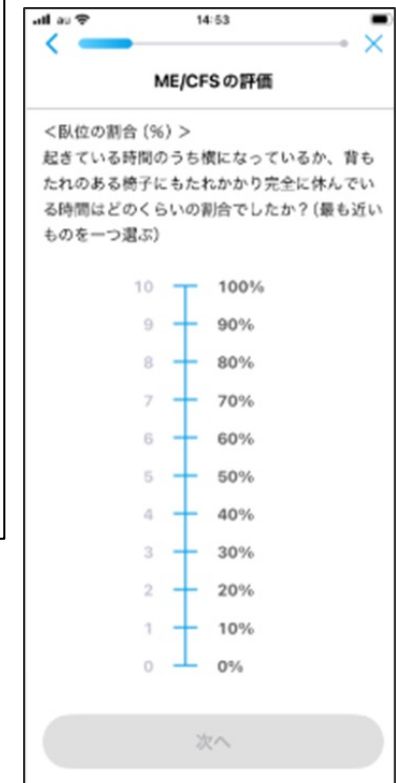
- PS score (milder=4-6 or severer=7-9)
- prior infectious-episode onset (pos or neg)
- Anti- $\beta 2$ -adr-R-Abs (pos or neg)

# Secondary endpoints (Clinical)

1. **Supine** position (% of awaking time)
2. Activities with **sitting** position (% of awaking time)
3. Activities with **upright** position (hrs)
4. Fatigue level at rest (supine position)
5. Post Exertional Malaise Record
6. Modified Borg scale
7. **Fatigue Score** (Primary endpoint on the trial in Norway)
8. Other symptom scores (SF-36, COMPASSS-31, Pain-analog scale, The Pittsburgh Sleep Quality Index (PSQI) )
10. Hand grips (kg)



Daily Input  
by smartphone  
(ePRO)



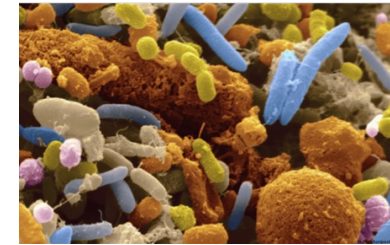
## ※ 7. Fatigue Score (Primary endpoint in the trial in Norway)

(continued)

Weeks from intervention	0	2	4	6	8	10
Date						
<b>FATIGUE</b>						
Fatigue	3					
Post-exertional exhaustion	3					
Need for rest	3					
Lack of daily functioning	3					
<b>PAIN</b>						

# Secondary Endpoints (Biomarkers)

*What indicators are associated with treatment efficacy?*



- Gut microbiome
- Brain imaging (MRI, SPECT)
- **Immune biomarkers**
- Metabolomics

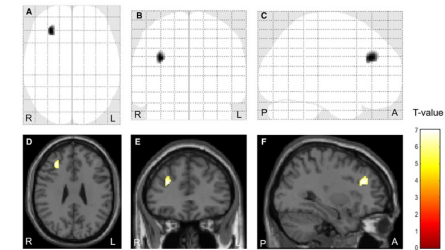
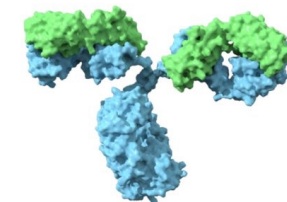
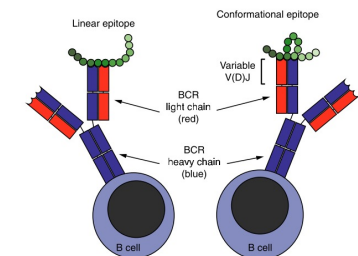
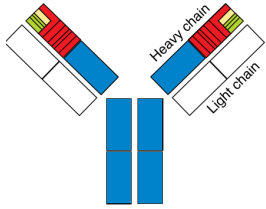


Fig 1. The results of the voxel-based correlation analysis between biomarkers: cortisol and autoantibody titer against  $\beta 1$  adrenergic receptor. There is a significant positive correlation in the right dorsolateral prefrontal cortex.

## Immune biomarkers

- Anti- $\beta 1/\beta 2$ -Adr-R-Abs, Anti-M3/M4-acy-R-Abs (CellTrend GmbH)
- Comprehensive Immune cell subset (flowcytometry)
- IGHV 3-30/IGHV 3-30-3 frequency (qPCR)



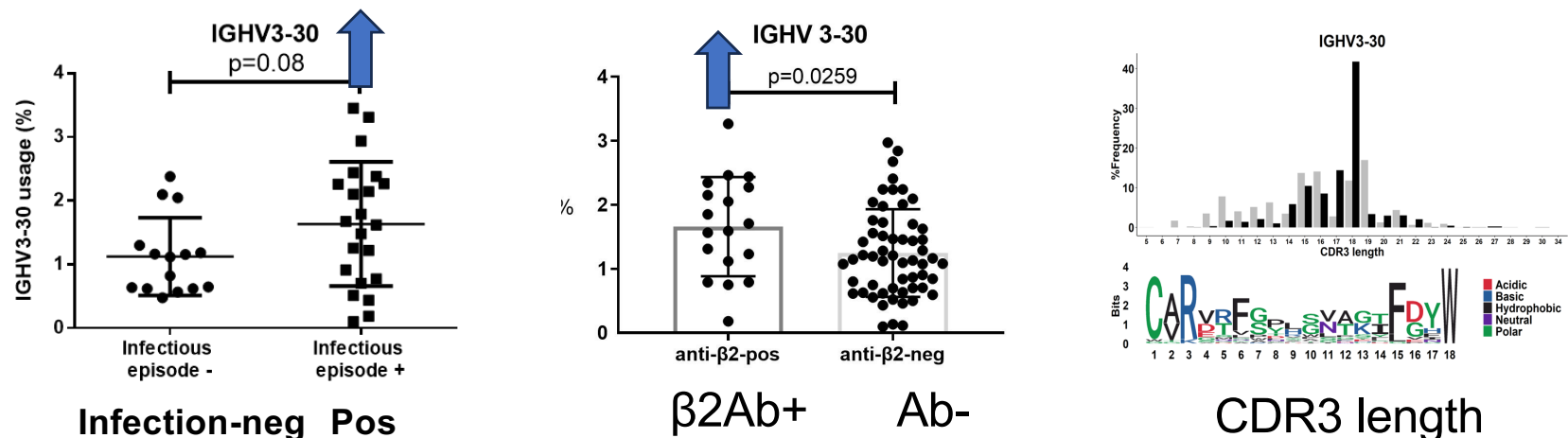


# B cells with IGHV 3-30/IGHV 3-30-3

## Comprehensive B cell receptor (BCR) repertoire analysis

- 1) more frequent in **obvious infectious episode-onset** patients
- 2) more frequent in patients with **short disease duration**
- 3) correlate to IFN response gene expressions in plasmablasts (**Ab-secreting B cells**)
- 4) more frequent in **anti-adrenergic  $\beta 1/\beta 2R$ -Ab-positive** patients
- 5) Specific length peaks by CDR3 length analysis -> **evidence of clonal selection**
- 6) A **proteomics study also** suggested association of IGHV3-23/30 with ME/CFS

(Milivojevic, M. et al. PloS one 15, e0236148.2020 )



(Sato, Wakiro, et al. Brain, Behavior, and Immunity 95 (2021): 245-255.)

# Secondary Endpoints

Standard practice in Rituximab trial

- Safety profiles
- Pharmacokinetics
- Anti-drug antibody (ADA)
- B cell/ T cell frequency

# Acknowledgement

## National Center of Neurology and Psychiatry (NCNP)

- Department of Immunology, Institute of Neuroscience
- Department of Neurology, NCNP hospital
- Department of Radiology, NCNP hospital
- Department of Clinical Data Science, Clinical Research and Education Promotion Division, NCNP hospital
- Department of Clinical Research Support, NCNP hospital
- Translational Medical Center, NCNP

**Zenyaku Kogyo Co., Ltd.**

**SUSMED, Inc**

**CMIC HOLDINGS Co., LTD.**

**RIKEN**

**CellTrend GmbH**



Prof. T. Yamamura



Dr. T. Okamoto