Press Release

September 21,2022

MiCAN Technologies Inc.

Our research on antibody-dependent enhancement of infection using cMylc cells has been published in "Scientific Reports".

MiCAN Technologies, Inc. (Headquarters: Kyoto, Japan; President: Kazuo Miyazaki) has conducted a joint research project using immortalized myeloid lineage cells 【cMylc (coronavirus optimized myeloid lineage) cells】generated from iPS cells for research on novel coronavirus (SARS-CoV-2) with the Research Institute for Microbial Diseases, Osaka University. The study on antibody-dependent enhancement of infection (ADE) using cMylc cells, anti-SARS-CoV-2 therapeutic antibodies and sera after mRNA-vaccination has been published in the British online scientific journal Scientific Reports on September 16, 2022 (Japan Standard Time).

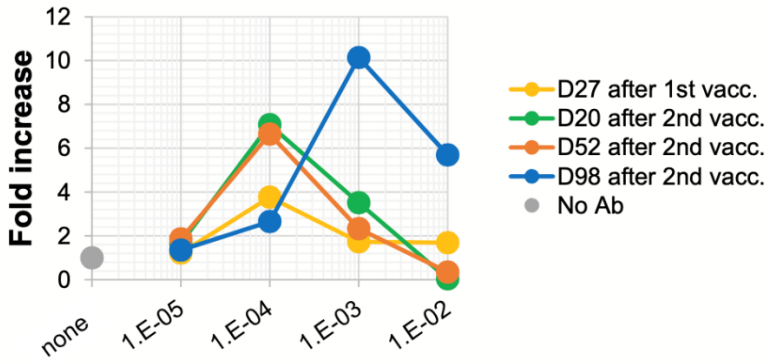
<Outline>

MiCAN Technologies, Inc. has generated immortalized myeloid cells (cMylc cells) for SARS-CoV-2 research from human iPS cells, and is conducting collaborative research using cMylc cells with the Research Institute for Microbial Diseases, Osaka University. Last year, we reported the results of our research on ADE and inflammatory cytokine production using cMylc cells and post-recovery blood samples from patients severely infected with SARS-CoV-2 in the same journal (Sci Rep. 2021 Dec 9;11(1):23713. doi: 10.1038/s41598-021-03273-0).

In this issue, we reported in the same journal the results of our studies on potential ADE in anti-SARS-CoV-2 therapeutic antibodies and sera from mRNA-vaccinated volunteers using cMylc cells.

Although the preventive and therapeutic effects of anti-SARS-CoV-2 therapeutic antibodies are clear, little attention has been paid to the influence of the remaining and dwindling therapeutic antibodies in vivo. Here, we demonstrate that certain antibodies approved as therapeutic anti-SARS-CoV-2 neutralizing antibodies may cause ADEs at a narrow range of antibody concentrations. In addition, sera from mRNA vaccinators initially showed neutralizing activity, but some sera were found to show ADE activity over time. These results indicate the possibility that adverse effects may occur in addition to the therapeutic and preventive effects of therapeutic antibodies and vaccines.

<Reference: Partial introduction of the contents of the paper, from Fig 3 A>



Serum samples from mRNA-vaccinated volunteers (HC2 in the paper) were diluted and added to a mixture of cMylc cells (denoted K-ML2(AT) clone35 in the paper) and SARS-CoV-2 (original strain), and the ADE responses were evaluated. Blood samples were collected four times in total from 27 days after the first vaccination (yellow) to 98 days after the second vaccination (blue), and the obtained sera were used for evaluation. The horizontal axis in the figure above shows the concentration of added serum (1.E-2 on the right side of the figure above indicates the point where the serum was diluted 100-fold and 1.E-3 indicates the point where the serum was diluted 1,000-fold and evaluated), and the vertical axis shows the fold increase (viral increase), which is illustrated as the specific activity compared with the viral increase in the serum-free state (gray point) as 1. For example, the green line in the above figure is the result of evaluating serum 20 days after the second vaccination. Serum samples were diluted 100 to 100,000 times and evaluated. Horizontal axis of the green line: At the point of 1.E-2 (100-fold dilution), where the serum concentration is high, the vertical axis Fold increase approaches 0, indicating that the virus is neutralized by the addition of serum. On the other hand, at 1.E-4 (10,000-fold dilution), the vertical axis exceeds 1, indicating the possibility of enhanced infection. In addition, no neutralizing activity was observed in the serum (blue) at day 98 after the second vaccination, and only ADE activity was detected.

<Future work>

The phenomenon discovered in this study was evaluated in a limited number of samples and after the first and second vaccinations, and has yet to be correlated with clinical symptoms. MiCAN Technologies will further analyze the samples and develop a kit to predict susceptibility to coronavirus infection and severity of illness, thereby contributing to global health.

<Published Journals>

Scientific Reports
Sci Rep **12**, 15612 (2022), https://doi.org/10.1038/s41598-022-19993-w

<Title of paper>

Reevaluation of antibody-dependent enhancement of infection in anti-SARS-CoV-2 therapeutic antibodies and mRNA-vaccine antisera using FcR- and ACE2-positive cells

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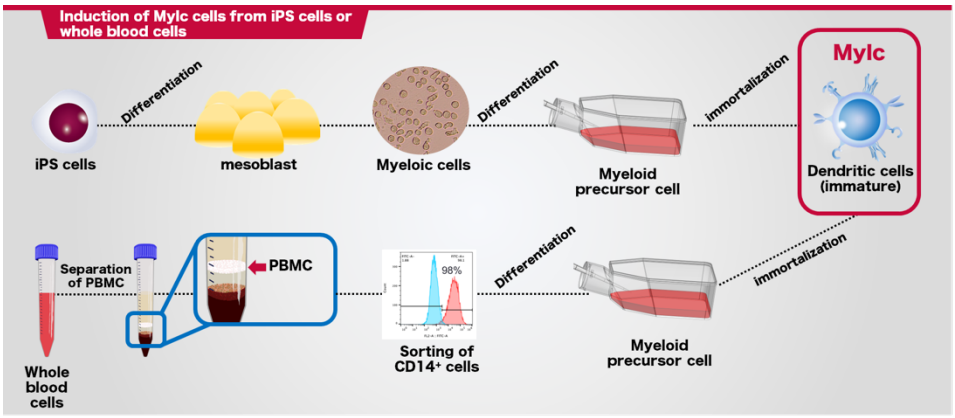
■Terminology

※1 Mylc™ cell

Mylc™ cells are research cells introduced by MEDINET from Kumamoto University and other institutions and launched in December 2019, which can be induced to differentiate into blood cells from iPS cells, human peripheral blood mononuclear cells, etc., to provide a stable

and large supply of myeloid cells for research on viral infections and immune diseases.
（Myeloid cells can be produced from various types of iPS cells (Mylc™ cells are shown in the red box in the figure below). Three Mylc cell lines (K-ML, D05, PhF) were used in the paper.)



※2 Myeloid cells
Refers to granulocytes (neutrophils, eosinophils, and basophils), dendritic cells, and macrophages among blood cells.

※3 cMylc cells
These are Mylc cells derived from iPS cells developed by our company and processed (expressing ACE2 and TMPRSS2) for novel coronavirus research. In the paper, cMylc cells are referred to as K-ML2(AT) clone 35. These cells are for university research. Please contact us for cMylc cells for commercial companies.

※4 Previous reports using cMylc cells
We published the results of our research with the Research Institute for Microbial Diseases, Osaka University, in Scientific Reports last year. For details, please refer to "The potential of COVID-19 patients' sera to cause antibody-dependent enhancement of infection and IL-6 production," Sci Rep. 2021 Dec. 9;11(1):23713. doi: 10.1038/s41598-021-03273-0.