SACI Office of Society Academia Collaboration for Innovation
KYOTO UNIVERSITY

Drug discovery for Charcot-Marie-Tooth Disease Using Patient-Derived iPS Cell Lines

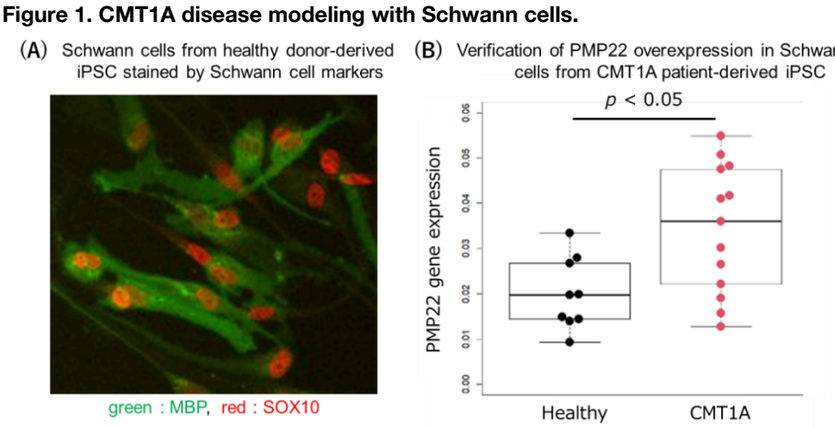
Background

Charcot-Marie-Tooth disease (CMT) is one of the most common rare diseases affecting approximately 1 in 2,500 - 5,000 people, or 3 million people in total worldwide. It is characterized by progressive peripheral neuropathy. The disease appears in two main forms: demyelination of the myelin sheath, which is formed by Schwann cells wrapping around the axon, or degeneration of the axon itself. There are various types of CMT caused by mutations in different genes. CMT1A, caused by a duplication of the *PMP22* gene, is the most common demyelinating type, affecting ~50% of individuals with CMT. CMT2A, caused by mutations in the *mitofusin-2* (*MFN2*) gene, is the most common axonal defect type. Gene therapies and small molecules are under development for different CMT types, however, there are currently no available treatments or cures for CMT patients. SCAD is a spin-off from Kyoto University that specializes in the development of disease models using patient-derived iPS cell lines for CMT1A and 2A, conducting drug discovery research to clarify pathology and explore therapeutic drugs, as well as pursuing cell therapy for neuropathies using pluripotent stem cells.

Technical Summary

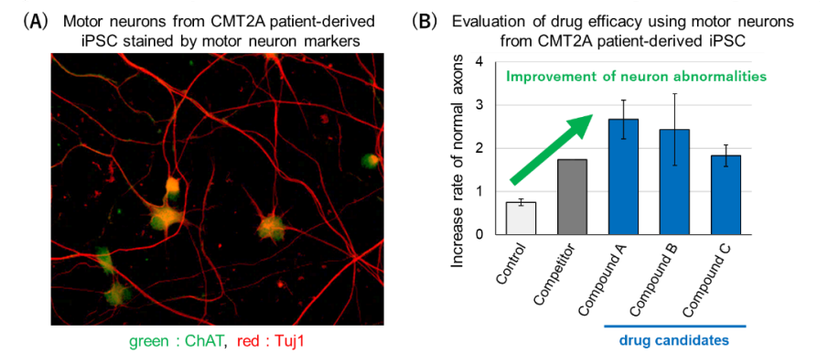
For CMT1A, SCAD has developed a protocol to produce high-quality Schwann cells from human iPS cells. They first examined Schwann cells from normal iPS cells (Fig.1A). Subsequently, they derived two iPS cell lines from CMT1A patients and managed to produce Schwann-like cells. Examination of animal models of CMT1A indicate impaired Schwann cell differentiation (Fredrich et al., *Nature Medicine*, 2014), which may explain the difficulty faced by SCAD in producing mature Schwann cells from the patient-derived iPSCs. This observation suggests that impaired Schwann cell differentiation is an important phenotype of the disease and could be a target for therapy development. SCAD confirmed that Schwann-like cells generated from patient-derived iPS cells had increased expression of *PMP22*, recapitulating the disease mechanism (Fig.1B).

Figure 1. CMT1A disease modeling with Schwann cells.



For CMT2A, SCAD has developed a protocol to produce high-quality motor neurons from patient-derived iPS cells. They established three iPSC lines and utilized the derived neurons for drug screening (Fig.2A). Through this process, they successfully identified several drug candidates which demonstrated efficacy in improving axonal and mitochondrial defects in the cells (Fig.2B), as well as showing efficacy in CMT2A model mice.

Figure 2. CMT2A patient-derived iPSCs for disease modeling and drug development.



SCAD is currently seeking collaborators and/or strategic business partners to investigate the pathophysiology of CMT and conduct drug discovery research using patient-derived iPS cell lines. Additionally, SCAD is endeavoring to develop cell therapy for CMT1A using Schwann cells produced from pluripotent stem cell lines.

Technology Readiness Level

3

Drug screening has been validated in patient-derived iPS cells and in a mouse model of CMT2A

Potential Applications

- CMT1A and 2A disease modeling
- CMT1A and 2A drug screening

Possible Collaboration Mode(s)

- R&D collaboration
- Licensing

Patent No

Patent pending (for CMT2A)

Inventor(s)

Norio Nakatsuji, Ph.D., Emeritus Prof. Kyoto Univ.
Takayuki Kiboku
Haruka Sato

SOCIETY ACADEMIA COLLABORATION FOR INNOVATION (SACI)
Kyoto University Division

215, 2/F, International Science Innovation Building
Kyoto University, Yoshida-honmachi, Sakyo-ku, Kyoto
606-8501 JAPAN

Email: gtcunit@mail2.adm.kyoto-u.ac.jp
Phone: +81-75-753-5692