Tetraploid Cardiomyocytes
-Application to the Cardiotoxicity Evaluation-

Background

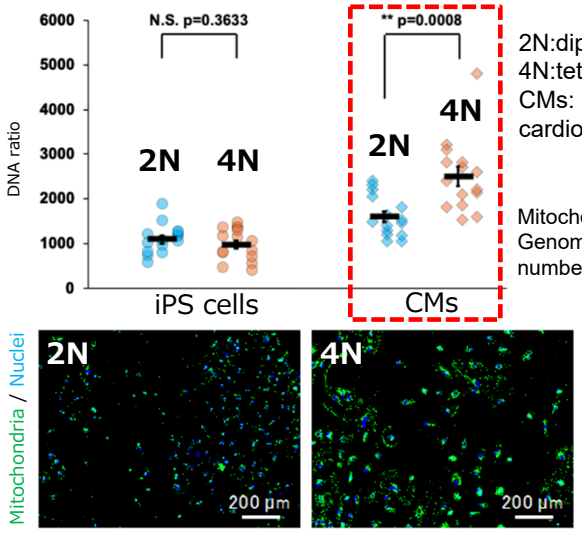
- Human heart is primarily composed of tetraploid(4N) cardiomyocytes. Generating human 4N cardiomyocytes through the differentiation of diploid(2N) iPS cells is difficult.
- Human iPS cells derived 2N cardiomyocytes are currently utilized for cardiotoxicity evaluation of pharmaceuticals related to "arrhythmia". On the other hand, the evaluation methods for "contractile force" have not yet been established.

Summary

- We developed human 4N iPS cells by fusing human 2N iPS cells, and subsequently, they were successfully **differentiated into 4N cardiomyocytes**.
- The developed 4N cardiomyocytes showed characteristics including: **(1) have more mitochondria, (2) stronger contractile force, (3) faster contraction speed, and (4) more resistant to cardiotoxicity**. These cells could be **useful for evaluating the cardiotoxicity of pharmaceuticals**.

Experimental Data

(1) Have more mitochondria

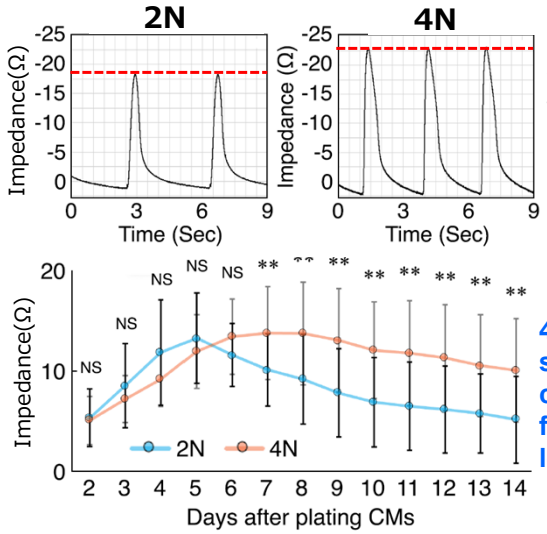


2N:diploid
4N:tetraploid
CMs: cardiomyocytes

Mitochondria DNA / Genomic DNA copy number

Mitotracker staining

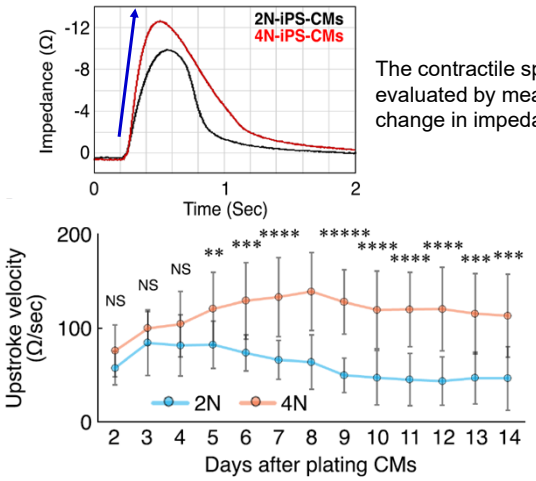
(2) Stronger contractile force



The contractile force was evaluated using impedance.

4N CMs kept stronger contractile force over a long period.

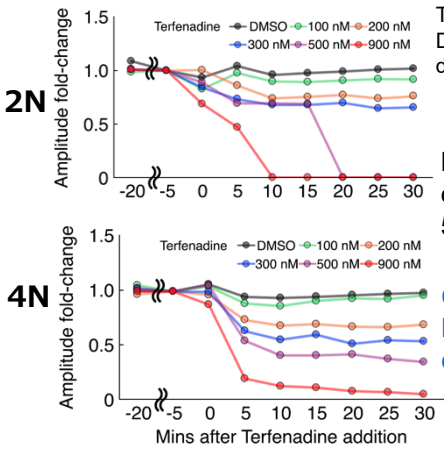
(3) Faster contraction speed



The contractile speed was evaluated by measuring the change in impedance.

4N CMs kept faster contractile speed over a long period.

(4) More resistant to cardiotoxicity



Terfenadine:
Developed as an anti-allergy drug, but blocks K+ channels

Beating stopped completely over 500 nM in 2N.

On the other hand, beating maintained even at 900 nm in 4N

Patent

PCT/JP2024/080141 "PLURIPOTENT STEM CELL HAVING DOUBLED CHROMOSOME"

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