Cardiovascular Physiology lab

Organ-on-a-chip team

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Reproduce human organ function

Experimental animals are often used to study disease mechanisms and drug effects. However, human physiology and animal physiology are different, and drugs act differently on animals than they do on humans.

We solve these problems with biomedical engineering approach: **microfluidic organ-on-a-chips using human cells**. This state-of-the-art technology enables more accurate assessment of drug effects without sacrificing animals.

We are seeking colleagues who will change the history of medical science together.

Basic principle of our research

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By controlling the mechanical and biological environments of cultured cells, we reproduce the functions of organs such as the heart, brain, and lungs.

Just as blood flow maintains the function of blood vessels and hypertension causes heart failure, the mechanical environment plays important roles in the manifestation of cell function and pathology.

By skillfully combining mechanical and biological factors, we reproduce functions of organs such as a heart with a more realistic contractile force and a kidney with a substance transport, that has never been possible before.

Top: Culture of cardiac tissue with periodic mechanical stretch stimulation. Bottom: Programmable controller for mechanical stretch stimulation.

Highlight

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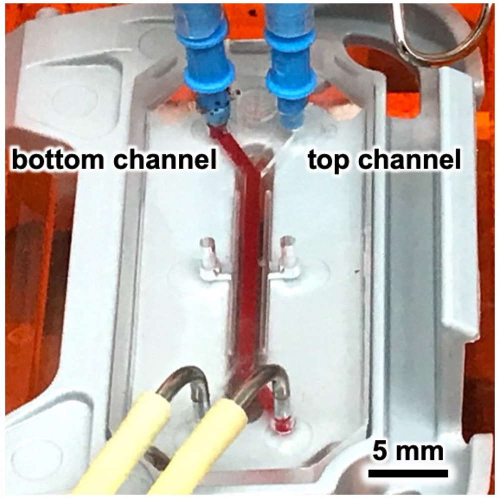
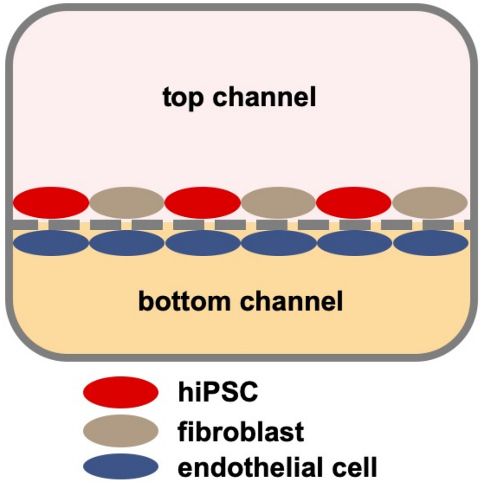
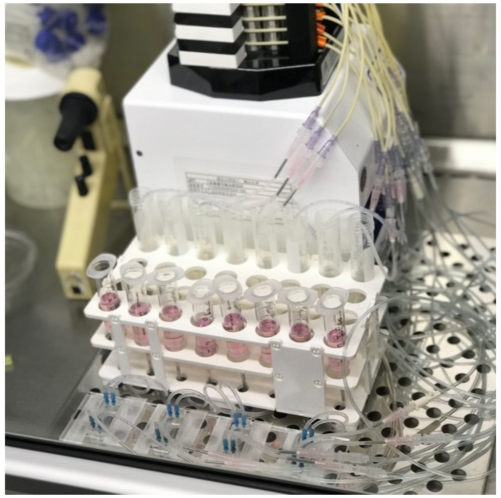
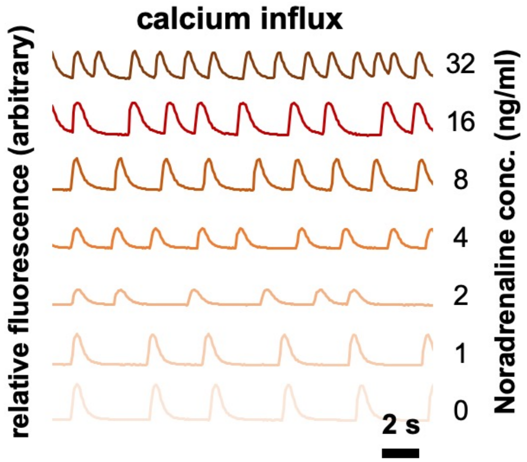
Human heart-on-a-chip

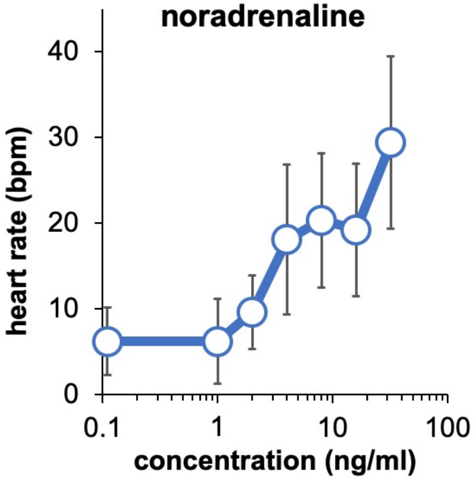
We developed a human heart-on-a-chip model that was confirmed by the functional response to noradrenaline and the histological evidence of sarcomere structure and vasculature, with a capability of live imaging.

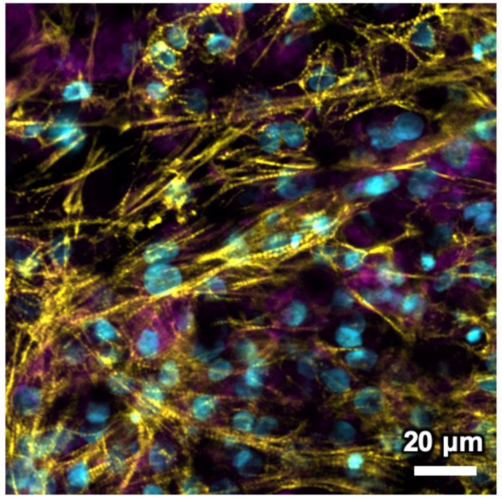












Our technologies

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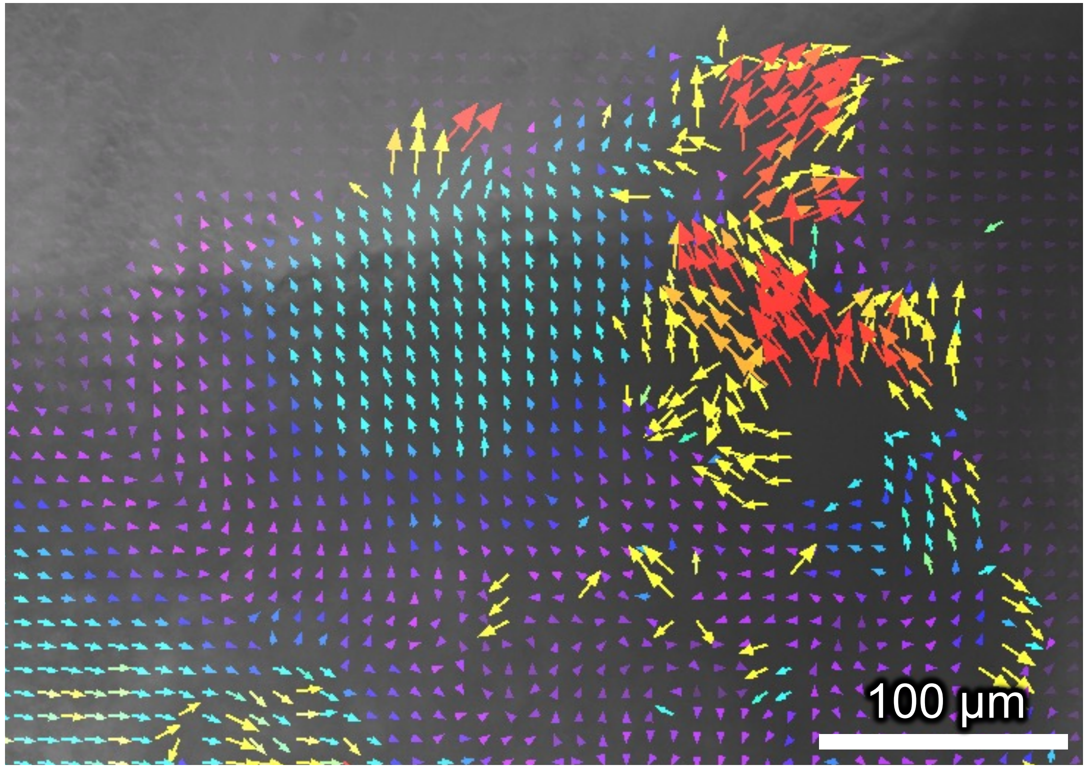
From stem cell biology, gene editing, microfluidics, finite element analysis to computer programming, our research is supported by a wide range of technologies. For example, we use vector field analysis for the video-based contractility analysis of iPS cardiomyocytes (shown below) by programming with the image analysis software ImageJ. Hardware control with LabView programming, or supercomputing with shell scripts are used, as needed.

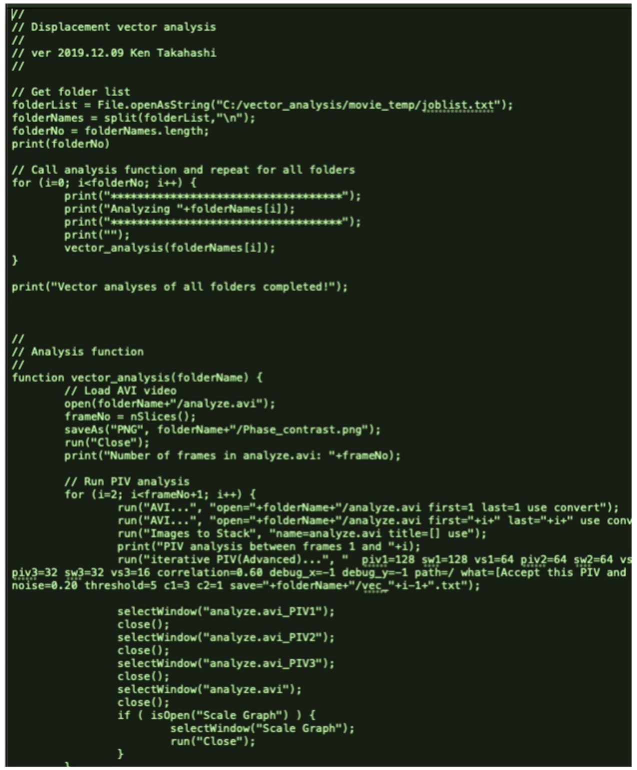


NOTE: Displacement vectors D(x,y) are calculated for every 16×16 pixels between the reference frame (the first frame) and all subsequent frames (frames 1 vs. 2, 1 vs. 3, 1 vs. 4, etc.). The result is calculated for every frame and saved as "vec_x.txt" (*x* is a frame number). A vector of maximum displacement, M(x, y), is defined for every (x, y) pair as follows:

$$M(x,y) = D_k(x,y)$$

where *k* represents the frame number at which $|D_k(x,y)| = \max[|D_2(x,y)|, |D_3(x,y)|, \ldots, |D_n(x,y)|]$ and *n* denotes the last frame. The result is saved as "Max_vector.txt". |M(x, y)| represents the maximum displacement caused by cardiomyocyte contraction at the analysis point (x, y). Contractility value *C* in arbitrary units is calculated as follows:

$$C = \sum_{xy} |M(x,y)|$$



```
//
// Displacement vector analysis
//
// ver 2019.12.09 Ken Takahashi
//

// Get folder list
folderList = File.openAsString("C:/vector_analysis/movie_temp/joblist.txt");
folderNames = split(folderList,"\n");
folderNo = folderNames.length;
print(folderNo)

// Call analysis function and repeat for all folders
for (i=0; i<folderNo; i++) {
        print("**********************************");
        print("Analyzing "+folderNames[i]);
        print("**********************************");
        print("");
        vector_analysis(folderNames[i]);
}

print("Vector analyses of all folders completed!");



//
// Analysis function
//
function vector_analysis(folderName) {
        // Load AVI video
        open(folderName+"/analyze.avi");
        frameNo = nSlices();
        saveAs("PNG", folderName+"/Phase_contrast.png");
        run("Close");
        print("Number of frames in analyze.avi: "+frameNo);

        // Run PIV analysis
        for (i=2; i<frameNo+1; i++) {
                run("AVI...", "open="+folderName+"/analyze.avi first=1 last=1 use convert");
                run("AVI...", "open="+folderName+"/analyze.avi first="+i+" last="+i+" use conv
                run("Images to Stack", "name=analyze.avi title=[] use");
                print("PIV analysis between frames 1 and "+i);
                run("iterative PIV(Advanced)...", "  piv1=128 sw1=128 vs1=64 piv2=64 sw2=64 vs
piv3=32 sw3=32 vs3=16 correlation=0.60 debug_x=-1 debug_y=-1 path=/ what=[Accept this PIV and
noise=0.20 threshold=5 c1=3 c2=1 save="+folderName+"/vec_"+i-1+".txt");

                selectWindow("analyze.avi_PIV1");
                close();
                selectWindow("analyze.avi_PIV2");
                close();
                selectWindow("analyze.avi_PIV3");
                close();
                selectWindow("analyze.avi");
                close();
                if ( isOpen("Scale Graph") ) {
                        selectWindow("Scale Graph");
                        run("Close");
                }
```

Contractility analysis of iPS cardiomyocytes. Left: vector field map of contractility. Middle: mathematical background of the analysis. Right: ImageJ macro codes for analysis.

Equipments

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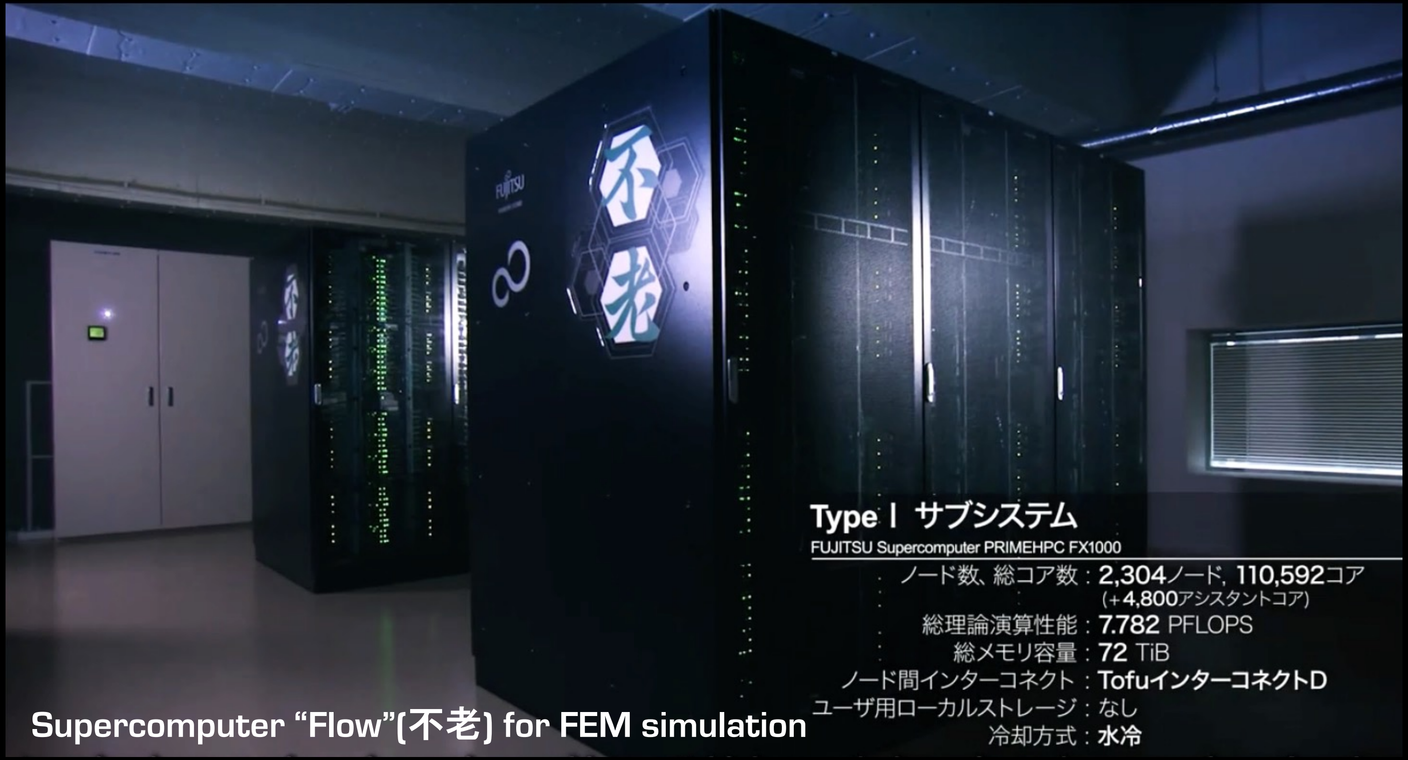
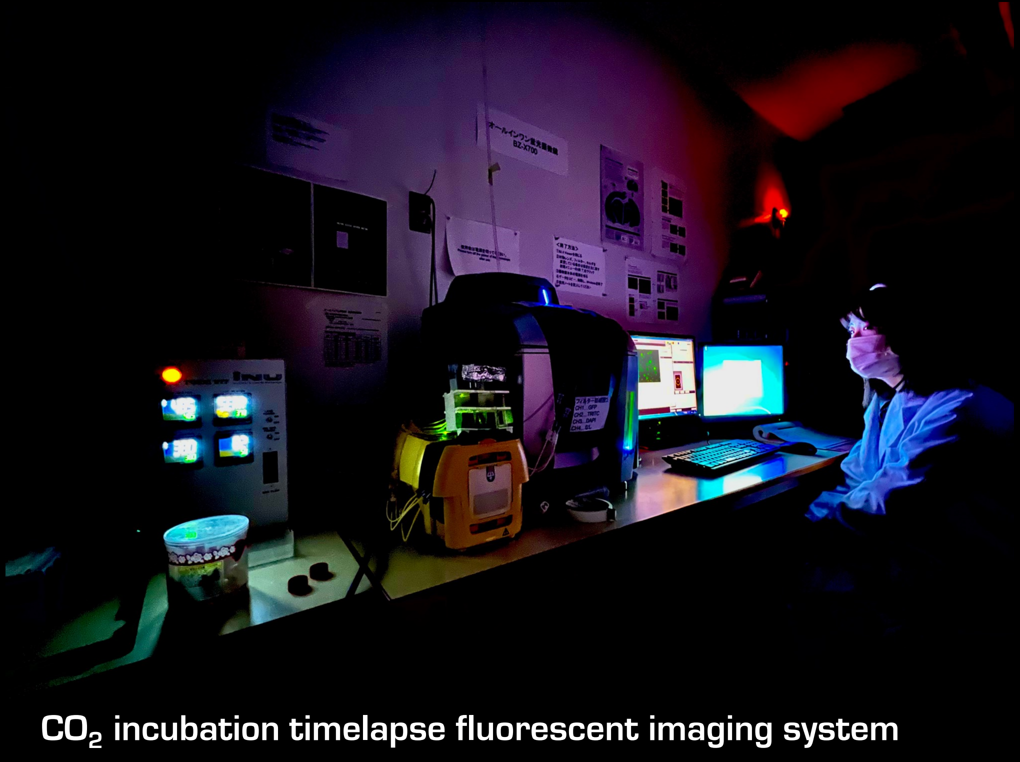
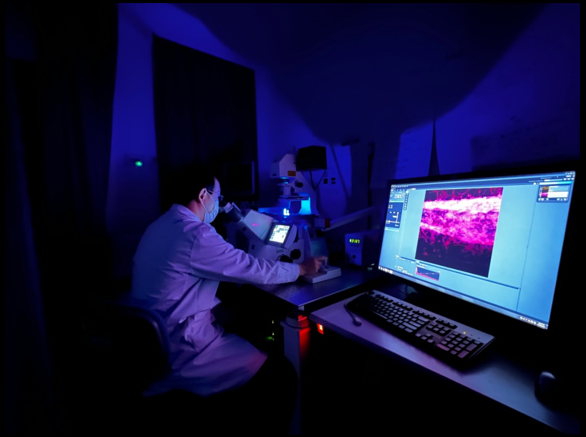
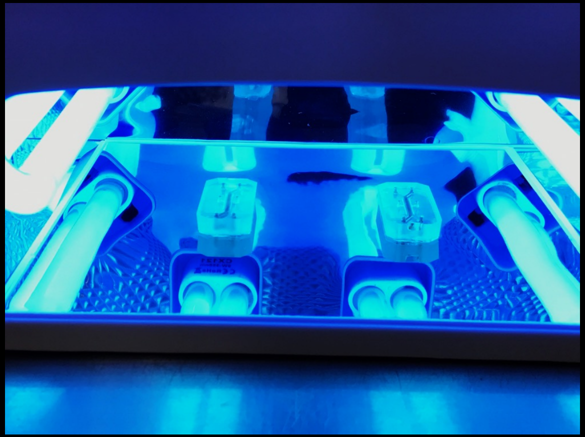


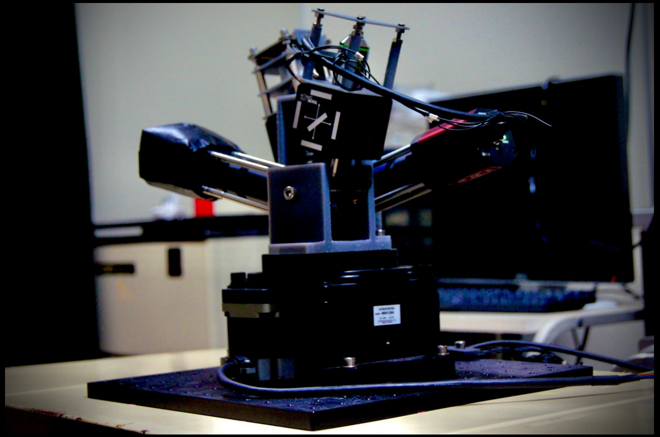
Supercomputer “Flow”(不老) for FEM simulation



CO_2 incubation timelapse fluorescent imaging system







Key technologies/concepts

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- Organ-on-a-chip
- Microfluidics
- Mechanical stress (pressure, shear stress, flow rate, stretch)
- Finite element analysis
- Supercomputer
- 3D printing
- Extracellular matrix
- Induced pluripotent stem (iPS) cells
- Cellular differentiation
- Live microscopic observation
- Gene editing (CRISPR/Cas9)
- Molecular biology
- Reconstruction of organ function (e.g. heart contraction, nutrient reabsorption in kidney, etc.)
- Disease modeling (e.g. heart failure, myocardial infarction, lung fibrosis, cancer, etc.)
- Exosomes
- Personalized medicine
- Drug screening

Our works

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- Takahashi K, Liu Y, Wang M, Liang Y, Naruse K. Live imaging of nitric oxide release in vascular endothelial cells in response to mechanical stimuli on an organ chip. ***Eur Heart J*** 43(Suppl. 2): ehac544.3027, 2022. doi: 10.1093/eurheartj/ehac544.3027
- Liu Y, Wang M, Liang Y, Naruse K, Takahashi K. Development of a human heart-on-a-chip model using induced pluripotent stem cells. fibroblasts and endothelial cells, ***Eur Heart J*** 42(Suppl. 1): ehab724.3190, 2021. doi: 10.1093/eurheartj/ehab724.3190
- Liang Y, Wang M, Liu Y, Wang C, Takahashi K, Naruse K. Meta-Analysis-Assisted Detection of Gravity-Sensitive Genes in Human Vascular Endothelial Cells. ***Front Cell Dev Biol*** 9: 689662, 2021. doi: 10.3389/fcell.2021.689662
- Liu Y, Liang Y, Wang M, Wang C, Wei H, Naruse K, Takahashi K. Model of Ischemic Heart Disease and Video-Based Comparison of Cardiomyocyte Contraction Using hiPSC-Derived Cardiomyocytes. ***J Vis Exp*** 159, 2020. doi: 10.3791/61104
- Matsuda Y, Takahashi K, Kamioka H, Naruse K. Human gingival fibroblast feeder cells promote maturation of induced pluripotent stem cells into cardiomyocytes. ***Biochem Biophys Res Commun*** 503(3): 1798-1804, 2018. doi: 10.1016/j.bbrc.2018.07.116

More works

Team members

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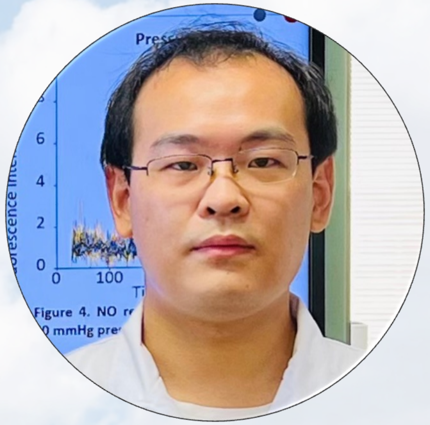
Research Associate Professor

Mengxue Wang
PhD student



Yun Liu, MD
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Qiang Li
Master's student

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Master's student
(MEXT scholarship student)

Hisayasu Kamada
Undergraduate student
(Department of Medicine)

Xiaoxia Han
Exchange student

Keiji Naruse, MD, Ph.D.
Professor