BIOGRAPHICAL SKETCH

NAME: Patrick C.H. Hsieh

INSTITUTE: Institute of Biomedical Sciences (IBMS), Academia Sinica

CURRENT POSITION: Distinguished Research Fellow and Division Chief

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	DURATION MM/YY-MM/YY	FIELD OF STUDY
Kaohsiung Medical College, Taiwan	M.D.	09/85-06/92	Medicine
Tong-In Military Hospital, Taiwan		09/92-06/94	Military Doctor, Medicine
Chang-Gang Hospital, Kaohsiung		07/94-06/96	Resident, General Surgery
National Taiwan University Hospital		07/96-06/98	Resident, CV Surgery
National Taiwan University Hospital		07/98-06/99	Chief Resident, CV Surgery
University of Washington, Seattle	Ph.D.	09/99-12/03	Bioengineering
Harvard Medical School, Boston	PDF	02/04-07/06	Cardiovascular Medicine

EMPLOYMENT

INSTITUTION AND LOCATION	POSITION TITLE	DURATION MM/YY-MM/YY	FIELD OF STUDY
National Cheng Kung University, Tainan, Taiwan	Assistant Professor	08/06-07/10	Clinical Medicine, Surgery, BME
National Cheng Kung University, Tainan, Taiwan	Associate Professor	08/10-07/13	Clinical Medicine, Surgery, BME
National Cheng Kung University, Tainan, Taiwan	Professor	08/13-01/14	Clinical Medicine, Surgery, BME
NCKU Hospital, Tainan, Taiwan	Attending Surgeon	09/06-01/14	Cardiovascular Surgery
IBMS, Academia Sinica, Taipei, Taiwan	Joint Assistant Research Fellow	07/09-06/12	Cardiovascular
IBMS, Academia Sinica, Taipei, Taiwan	Joint Associate Research Fellow	07/12-01/14	Cardiovascular
IBMS, Academia Sinica, Taipei, Taiwan	Associate Research Fellow	02/14-10/15	Cardiovascular
IBMS, Academia Sinica, Taipei, Taiwan	Research Fellow	11/15-10/19	Cardiovascular
IBMS, Academia Sinica, Taipei, Taiwan	Distinguished Research Fellow	11/19-present	Cardiovascular
IBMS, Academia Sinica, Taipei, Taiwan	Division Chief	09/17-present	Cardiovascular
Institutional Review Board (IRB) Committee, Academia Sinica	Chair	10/22-present	IRB of Medical Ethics
National Taiwan University, Taipei, Taiwan	Professor	02/16-present	Medical Genomics & Proteomics
NTU Hospital, Taipei, Taiwan	Attending Surgeon	04/16-08/19	Cardiovascular Surgery
University Of Washington, Seattle, WA, USA	Affiliate Professor	08/11-present	Bioengineering
University Of Wisconsin-Madison, Madison, WI, USA	Visiting Professor	08/17-present	Medicine, Stem Cells & Regenerative Medicine

I. PERSONAL STATEMENT

A brief self-introduction of research path/career, 200–300 words.

Although the field of cardiac stem cell therapy has significantly advanced over the past years, the premise of regenerating or replacing diseased human myocardium with functional tissue remains unsatisfied. As a physician-scientist and a bioengineer, my research group aims to promote heart regeneration and rejuvenation through engineering the intramyocardial microenvironment for endogenous reparative cells to be reactivated, reprogramed and repopulate the diseased myocardium. Using genetic fate-mapping approaches in mice, we and others have demonstrated potential for endogenous repair and regeneration by the heart itself following injury. We carry out transgenic mice to identify the molecular and cellular mechanism regulating this potential, and develop novel strategies aiming to create a favorable microenvironment to augment this nature power for spontaneous heart regeneration. Our team has employed an approach bringing investigators from a broad variety of backgrounds, including stem cell genetics and biochemistry, biophysics and biomechanics, materials science and controlled drug/gene delivery, synthetic and biochemical engineering, and clinical medicine. This combination has allowed us to work together and interact in a way traditionally not available at an individual lab.

II. HONORS

Include up to five of your most significant professional distinctions and services.

2021 Distinguished Alumnus Award, Kaohsiung Medical University, Taiwan
2017 TECO Award, TECO Technology Foundation, Taiwan
2015 Outstanding Research Award, Ministry of Science and Technology, Taiwan
2014 Chair in Biotechnology, Taiwan Bio-Development Foundation (TBF)
2012 Outstanding Research Award, National Science Council, Taiwan

III. CONTRIBUTIONS TO SCIENCE

Briefly describe up to five of your most significant contributions in your career to science.

1. **Adult cardiomyocyte regeneration and rejuvenation by intra- and extra-cardiac cells** Evidence has shown that the mammalian myocardium has regeneration potential, but regeneration may occur at a rate inadequate to repair the extensive myocardial injury typical of human diseases. However, the molecular and cellular mechanisms controlling heart regeneration remain largely unknown. Using adult cardiomyocyte fate-mapping, we have demonstrated that endogenous stem/progenitor cells contribute to adult mammalian cardiomyocyte replacement following injury but do not contribute significantly to cardiomyocyte renewal during normal aging. We further demonstrated that cardiomyocytes are replenished by endogenous cells at the peri-infarct border zone within 7 days after infarction, which is mediated by COX-2-driven inflammation and can be enhanced by PGE2 treatment. Furthermore, by combining genetic fate mapping and parabiosis model, we provide direct evidence showing that circulating hematopoietic cells acquire cardiac cell fate in the infarcted area by means of cell fusion and transdifferentiation.
    a. Wu JM, Hsueh YC, Ch'ang HJ, Luo CY, Wu LW, Nakauchi H, Hsieh PC*. "Circulating cells contribute to cardiomyocyte regeneration after injury." *Circ Res*. 2015;116:633-41.
    b. Hsueh YC, Wu JM, Yu CK, Wu KK, Hsieh PC*. "Prostaglandin E_2 promotes post-infarction cardiomyocyte replenishment by endogenous stem cells." *EMBO Mol Med*. 2014;6:496-503.

c. Lin YD, Luo CY, Hu YN, Yeh ML, Hsueh YC, Chang MY, Tsai DC, Wang JN, Tang MJ, Wei EI, Springer ML, Hsieh PC*. "Instructive nanofiber scaffolds with VEGF create a microenvironment for arteriogenesis and cardiac repair." *Sci Transl Med*. 2012;4:146ra109.

d. Hsieh PC, Segers VF, Davis ME, MacGillivray C, Gannon J, Molkentin JD, Robbins J, Lee RT*. "Evidence from a genetic fate-mapping study that stem cells refresh adult mammalian cardiomyocytes after injury." *Nat Med*. 2007;13:970-4.

2. **Use of pluripotent stem cells-derived cardiac cells for research and development** Pluripotent stem cell-derived cardiomyocytes have great potential for use in research and medicine, but limitations in their maturity currently constrain their usefulness. We found that coculturing murine and human embryonic stem cell-derived cardiomyocytes with endothelial cells improves their maturity by upregulation of microRNAs 125b, 199a, 221, and 222, which all target on and downregulate ErbB4 for promoting cardiomyocyte maturation. We also work on basic biology of pluripotent stem cells including iPSCs, and have established the Taiwan Human iPSC Consortium, providing a centralized core facility and resource center for promoting iPSC research and applications in Taiwan. We have generated and fully characterized a total of 432 human iPSC lines, among which 110 lines are deposited at the Taiwan iPSC Biobank, open to the public for research use.

a. Huang CY, Nicholson MW, Wang JY, Ting CY, Tsai MH, Cheng YC, Liu CL, Chan DZH, Lee YC, Hsu CC, Hsu YH, Yang CF, Chang CM, Ruan SC, Lin PJ, Lin JH, Chen LL, Hsieh ML, Cheng YY, Hsu WT, Chen CH, Hsu YH, Wu YT, Hacker TA, Wu JC, Kamp TJ, Hsieh PC*. "Population-based high-throughput toxicity screen of human iPSC-derived cardiomyocytes and neurons." *Cell Rep*. 2022;39:110643

b. Hsu W, Huang C, Yen CY, Cheng A, Hsieh PC*. "The HER2 inhibitor lapatinib potentiates doxorubicin-induced cardiotoxicity through iNOS signaling." *Theranostics*. 2018;8:3176-3188.

c. Chen CY, Lee DS, Yan YT, Shen CN, Hwang SM, Lee ST, Hsieh PC*. "Bcl3 bridges LIF-STAT3 to Oct4 signaling in the maintenance of naïve pluripotency." *Stem Cells*. 2015;33:3468-80.

d. Lee DS, Chen JH, Lundy DJ, Liu CH, Hwang SM, Pabon L, Shieh RC, Chen CC, Wu SN, Yan YT, Lee ST, Chiang PM, Chien S, Murry CE, Hsieh PC*. "Defined microRNAs induce aspects of maturation in mouse and human embryonic-stem-cell-derived cardiomyocytes." *Cell Rep*. 2015;12:1960-7.

3. **Cell reprogramming and gut microbiome-derived metabolites for heart regeneration** In mammals, the response to heart injury shows some similarities to newts and zebrafish with borderzone myocytes remodeling by disassembly of myofilaments, changes in metabolism, and general de-differentiation; however, little proliferation and repair occurs in the adult mammalian heart. We demonstrate that forced expression of the Yamanaka OSKM factors in transgenic mouse cardiomyocytes initiates an early stage of induced pluripotent stem cell reprogramming marked by a metabolic shift in the cardiomyocytes with induction of proliferation. This early reprogrammed state and borderzone remodeling myocytes shares a shift in metabolism with ketogenic substrates playing an increased role and our preliminary data demonstrate the rate limiting enzyme for ketone body production, 3-hydroxy-3-metylglutaryl-CoA synthase 2 (HMGS2), upregulated. We postulate that by optimizing this metabolic shift in the injured heart we can promote active cardiomyocyte proliferation and regeneration of heart tissue.

a. Cheng YY, Gregorich Z, Prajnamitra RP, Lundy DJ, Ma TY, Huang YH, Lee YC, Ruan SC,

Lin JH, Lin PJ, Kuo CW, Chen P, Yan YT, Tian R, Kamp TJ, Hsieh PC*. "Metabolic changes associated with cardiomyocyte dedifferentiation enable adult mammalian cardiac regeneration." *Circulation* 2022; 146:1950-1967.

b. Tang TW, Chen HC, Chen CY, Yen CY, Lin CJ, Prajnamitra RP, Chen LL, Ruan SC, Lin JH, Lin PJ, Lu HH, Kuo CW, Chang CM, Hall AD, Vivas EI, Shui JW, Chen P, Hacker TA, Rey FE, Kamp TJ, Hsieh PC*. "Loss of gut microbiota alters immune system composition and cripples post-infarction cardiac repair." *Circulation* 2019;139:647-659.

c. Cheng YY, Yan YT, Lundy DJ, Lo AH, Wang YP, Ruan SC, Lin PJ, Hsieh PC*. "Reprogramming-derived gene cocktail increases cardiomyocyte proliferation for heart regeneration". *EMBO Mol Med*. 2017;9:251-264.

4. **Tissue engineering and nanotechnologies for cardiovascular repair and drug delivery**
Cardiovascular tissue engineering aims to repair, replace, and regenerate damaged tissues by delivery of cell therapy. However, few evidence has been shown for long-term engraftment of transplanted cells. We propose that, ultimately, successful tissue repair and regeneration will require precision control of the intramyocardial microenvironment through designed biomaterials and nanotechnologies, which provide beneficial adhesion, growth, or migration signals for cell therapy, and may regulate sustained local release of factors following cell, gene or protein delivery.

a. Huang SS, Lee KJ, Chen HC, Prajnamitra RP, Hsu CH, Jian CB, Yu XE, Chueh DY, Kuo CW, Chiang TC, Choong OK, Huang SC, Beh CY, Chen LL, Lai JJ, Chen P, Kamp TJ, Tien YW, Lee HM, Hsieh PC*. "Immune cell shuttle for precise delivery of nanotherapeutics for heart disease and cancer." *Sci Adv.* 2021;7:eabf2400

b. Wu JP, Cheng B, Roffler SR*, Lundy DJ, Yen CY, Chen P, Lai JJ, Pun SH, Stayton PS, Hsieh PC*. "Reloadable multidrug capturing delivery system for targeted ischemic disease treatment." *Sci Transl Med*. 2016;8:365ra160.

c. Tang AC, Chang MY, Tang ZC, Li HJ, Hwang GL, Hsieh PC*. "Treatment of acute thromboembolism in mice using heparin-conjugated carbon nanocapsules." *ACS Nano*. 2012;6:6099-107.

5. **Translational and preclinical development in cardiac regenerative medicine**
We have shown that functional biomaterials may impact a broad spectrum of potential for clinical application. To translate these results, we have used human stem cell therapy and pig models of myocardial infarction to explore the therapeutic approaches. We show approaches that combining different hydrogels and cell therapy significantly improved both systolic and diastolic cardiac functions after infarction, some of which are currently undergoing clinical trials.

a. Chang MY, Huang TT, Chen CH, Cheng B, Hwang SM, Hsieh PC*. "Injection of human cord blood cells with hyaluronan improves postinfarction cardiac repair in pigs." *Stem Cells Transl Med*. 2016;5:56-66.

b. Chen HJ, Chen CH, Chang MY, Tsai DC, Baum EZ, Hariri R, Herzberg U, Hsieh PC*. "Human placenta-derived adherent cells improve cardiac performance in mice with chronic heart failure." *Stem Cells Transl Med*. 2015;4:269-75.

c. Lin YD, Yeh ML, Yang YJ, Tsai DC, Chu TY, Shih YY, Chang MY, Liu YW, Tang AC, Chen TY, Luo CY, Chang KC, Chen JH, Wu HL, Hung TK, Hsieh PC*. "Intramyocardial peptide nanofiber injection improves postinfarction ventricular remodeling and efficacy of bone marrow cell therapy in pigs." *Circulation*. 2010;122:S132-41.

IV. SELECTED PUBLICATIONS OVER THE LAST FIVE YEARS

ORCID ID: 0000-0002-8910-3596

1. Cheng YY, Gregorich Z, Prajnamitra RP, Lundy DJ, Ma TY, Huang YH, Lee YC, Ruan SC, Lin JH, Lin PJ, Kuo CW, Chen P, Yan YT, Tian R, Kamp TJ, Hsieh PC*. "Metabolic changes associated with cardiomyocyte dedifferentiation enable adult mammalian cardiac regeneration." *Circulation* 2022;146:1950-1967.
2. Chen SL, Lundy DJ, Ruan SC, Chen HC, Chao YK, Cheng YY, Prajnamitra RP, Liao CC, Lin CY, Lai JJ, Hsieh PC*. "The gut microbiota regulates acute foreign body reaction and tissue repair after biomaterial implantation." *Biomaterials* 2022;289:121807.
3. Huang CY, Nicholson MW, Wang JY, Ting CY, Tsai MH, Cheng YC, Liu CL, Chan DZH, Lee YC, Hsu CC, Hsu YH, Yang CF, Chang CM, Ruan SC, Lin PJ, Lin JH, Chen LL, Hsieh ML, Cheng YY, Hsu WT, Chen CH, Hsu YH, Wu YT, Hacker TA, Wu JC, Kamp TJ, Hsieh PC*. "Population-based high-throughput toxicity screen of human iPSC-derived cardiomyocytes and neurons". *Cell Rep.* 2022;39:110643.
4. Huang SS, Lee KJ, Chen HC, Prajnamitra RP, Hsu CH, Jian CB, Yu XE, Chueh DY, Kuo CW, Chiang TC, Choong OK, Huang SC, Beh CY, Chen LL, Lai JJ, Chen P, Kamp TJ, Tien YW, Lee HM, Hsieh PC*. "Immune cell shuttle for precise delivery of nanotherapeutics for heart disease and cancer." *Sci Adv.* 2021;7:eabf2400.
5. Prajnamitra RP, Chen HC, Hsieh PC*. "Swaying leukocyte traffic from the bone marrow." *Nat Biomed Eng.* 2020;4:1026-1027.
6. Lee JJ, Cheng SJ, Huang CY, Chen CY, Feng L, Hwang DY, Kamp TJ, Chen HC*, Hsieh PC*. "Primary cardiac manifestation of autosomal dominant polycystic kidney disease revealed by patient induced pluripotent stem cell-derived cardiomyocytes." *EBioMedicine* 2019;40:675-684.
7. Lundy DJ, Lee KJ, Peng IC, Hsu CH, Lin JH, Chen KH, Tien YW, Hsieh PC*. "Inducing a transient increase in blood brain barrier permeability for improved liposomal drug therapy of glioblastoma multiforme." *ACS Nano.* 2019;13:97-113.
8. Tang TW, Chen HC, Chen CY, Yen CY, Lin CJ, Prajnamitra RP, Chen LL, Ruan SC, Lin JH, Lin PJ, Lu HH, Kuo CW, Chang CM, Hall AD, Vivas EI, Shui JW, Chen P, Hacker TA, Rey FE, Kamp TJ, Hsieh PC*. "Loss of gut microbiota alters immune system composition and cripples post-infarction cardiac repair." *Circulation* 2019;139:647-659.
9. Hsu WT, Huang CY, Yen CY, Cheng AL, Hsieh PC*. "The HER2 inhibitor lapatinib potentiates doxorubicin-induced cardiotoxicity through iNOS signaling". *Theranostics* 2018;8:3176-3188.
10. Hsieh PC*, Kamp TJ*. "To be young at heart". *Cell Stem Cell* 2018;22:475-476.