

Reproductive Science Laboratory

Lab Introduction

- 1. Establishment of decidual cell conditional knockout or overexpressing mouse model-Elucidate the role of various genes expressed by decidual cells in pregnancy complications:** The pathogenesis of pregnancy complications, including preeclampsia, miscarriage and intrauterine growth restriction, is initiated early in pregnancy. The absence of early presentation is a major obstacle in studying pathogenesis, diagnosis, prevention, and treatment of these complications. Our previous data suggested that decidual cells play a pivotal role in the pathogenesis of pregnancy complications. Since decidual cells are the major cell type in the decidua, studying the role of specific gene expressed by decidual cells in the pathogenesis of pregnancy complication is important in understanding the mechanisms of the development of adverse pregnancy outcomes. Thus, this project will conditionally knockout or overexpress specific gene in the decidual cells in various mouse models to study the function of each gene.
- 2. The effects of adipose-derived stem cells on the pathogenesis of endometriosis:** Since its discovery in 2001, adipose-derived stem cells (ADSCs) have been recognized as multipotent stem cells. ADSCs were also shown to serve as immune regulators by releasing growth factors and cytokines. Compared to bone marrow, adipose tissues contains 100-500 folds more stem cells. Thus, an increasing number of studies have been conducted using ADSCs for the treatment of various diseases. Endometriosis is a common gynecological disorder that usually induces chronic pelvic pain and infertility. The current therapies for endometriosis are associated with a high recurrence rate. Thus, this project will evaluate the inhibitory effects and their mechanisms of ADSCs on the development of endometriosis. The effects of ADSCs on the endometrial receptivity will also be examined.
- 3. The effects of Guizhi Fuling Wan on fetal programming and pregnancy by affecting fetal-maternal interface:** Our preliminary data demonstrated that Guizhi Fuling Wan (GFW) not only prevents spontaneous abortion but also improves the growth of fetal-placental units. The improvement of postnatal physical and neurobehavioral development by prenatal GFW treatment was also observed in the offspring born with intrauterine growth restriction (IUGR). In addition, placental expression of neutral amino acid transporters is up-regulated in mouse treated with GFW. We will employ a three-tiered approach using *in situ* (clinical specimens), *in vitro* (primary cell cultures) and *in vivo* (mouse) models to investigate the mechanisms responsible for GFW-induced postnatal developmental improvement in the offspring born with IUGR.
- 4. Establishment of outcome measure for adenomyosis using clinical and imagery information by deep computer learning:** Adenomyosis causes dysmenorrhea, pelvic pain, menorrhagia, and subfertility. Currently, the grading of adenomyotic lesions is mainly based on the pathological examination of the surgical specimens. The interpretation of the imaging results is usually subjective and dependent upon the experience and shrewdness of the examiners. A robust evaluation in determining the therapeutic options and in assessing the conditions of patients receiving medical

treatments is lacking. A considerable number of patients are misdiagnosed due to the image similarities between adenomyosis and other disorders, such as uterine leiomyoma. Thus, an objective and standardized quantitative grading system in describing the severity of this disease will provide a better communication and guidance among clinicians and pathologists. This project plans to establish a standardized modality for the detection and quantification of the lesions by artificial intelligence (AI) using deep computer learning.

- 5. Epigenetic control of macrophage polarization under the influence of first trimester decidual cells treated with pro-inflammatory stimuli:** Our preliminary data showed that macrophages polarize toward M1 subtype in the decidua from patients with spontaneous abortion. Protein arginine methyltransferase 5 (PRMT5) recruitment at the promoter of interferon regulatory factor-7 (IRF-7) and the expression of PRMT5 and IRF-7 in macrophages are increased by M1 stimuli. IRF-7 expression in macrophages is also enhanced by conditioned media from IL-1 β - or TNF- α -treated first trimester decidual cells. This project will investigate the mechanisms of histone modification through which macrophages polarize under the influence of first trimester decidual cells.
- 6. The role of mitochondrial dysfunction in the pathogenesis of adenomyosis:** The pathogenesis of adenomyosis is associated with TGF- β 1-induced epithelial-mesenchymal transition (EMT) and ultimately fibrosis. Since the cross-talk between dysfunctional mitochondria-derived reactive oxygen species (ROS) and TGF- β 1 signaling pathways has been demonstrated. This proposal will test the association between mitochondrial dysfunction and adenomyosis formation via TGF- β 1 signaling pathway using *in vitro* and *in vivo* models.
- 7. The effects of Guizhi Fuling Wan on implantation:** Embryo implantation is crucial for successful pregnancy. A successful implantation strongly depends on the embryo quality and the physiological state of the uterine endometrium. This study plans to test whether GFW can enhance the trophoblast invasion and endometrial receptivity.
- 8. The effects of Guizhi Fuling Wan on endometrial receptivity:** In traditional Chinese medicine, endometriosis and infertility are manifested by stagnation of vital energy (qi) and blood stasis. Adequate implantation and placentation is required for successful pregnancy. Disorders of the endometrium and endometriosis result in significant reduction of endometrial receptivity and ultimate infertility. The centuries-long use of GFW to treat such diverse ailments as blood stagnation and stagnation of vital energy (qi) attest to its unprecedented safety record. The central theme of this project is discovery of novel mechanisms and therapeutic application of GFW in improving pregnancy outcomes.
- 9. Therapeutic effects of YIV906 on ovarian cancer therapy:** Huangqin soup is a Chinese herbal formula formulated by Zhang Zhongjing about 1,800 years ago in the late East Han Dynasty to treat gastrointestinal diseases, such as dysentery. Huangqin soup-derived YIV906 was found to alleviate such side effects of gastrointestinal tract as diarrhea, nausea, and vomiting caused by chemotherapy. Clinical trials conducted in the United States and Taiwan in recent years are mainly focused on colorectal, hepatic, and prostatic cancers. In addition to its expected effects on reducing side effects, YIV906 was also found to enhance the efficacy of chemotherapy. However, the research for ovarian cancers is lacking. As one of three major gynecological cancers, ovarian cancer ultimately tends to have no effective drugs available for its chemotherapy. This proposal aims to investigate the effects

of YIV906 on ovarian cancer chemotherapy.

Principal Investigator:

Professor Se-Te Joseph Huang, M.D., Ph.D.

Contact Information:

Rm. 10612-2, Incubation and Research Bldg.

No. 6, Yida Rd., Yanchao District, Kaohsiung 82445, Taiwan, ROC

TEL: +886-7-615-1100 ext. 5022 (Office), 5924 (Lab)

Email: ed108566@edah.org.tw

Email: jhuang3@health.usf.edu

Email: huang3@isu.edu.tw

Educations:

2000 **Ph.D.** Department of Cell and Molecular Physiology at the University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

1984 **M.D.** National Yang-Ming University, Taipei, Taiwan, ROC

Clinical and Academic Experiences:

<u>Duration</u>	<u>Department</u>	<u>Position</u>
2019 - present	School of Medicine, College of Medicine, I-Shou University, Taiwan, ROC	Professor
2020 - present	Department of Obstetrics and Gynecology, Morsani College of Medicine, University of South Florida, Tampa, FL, USA	Professor
2016 - 2020	Department of Obstetrics and Gynecology, College of Medicine, University of South Florida, Tampa, FL, USA	Associate Professor
2015 - present	Department of Obstetrics and Gynecology, E-Da Hospital, Taiwan, ROC	Attending physician
2015 - present	Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan, ROC	Visiting Associate Investigator
2013 - present	Mackay Memorial Hospital, Taipei, Taiwan, ROC	Consultant
2012 - present	School of Medicine, Shanghai Jiao Tong University, Shanghai, PRC	Visiting Professor
2015 - 2018	College of Medicine, I-Shou University, Taiwan, ROC	Associate Professor
2012-2015	Department of Obstetrics and Gynecology, College of Medicine, The Ohio State University, Columbus, OH, USA	Associate Professor

2009-2012	Department of Obstetrics, Gynecology and Reproductive Sciences, School of Medicine, Yale University, New Haven, CT, USA	Assistant Professor
2004-2009	Department of Obstetrics, Gynecology and Reproductive Sciences, School of Medicine, Yale University, New Haven, CT, USA	Associate Research Scientist
2000-2003	Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics at the Stanford University Medical Center, under the instruction Linda C. Giudice, M.D., Ph.D., Stanford, CA, USA	Postdoctoral Fellow
1991-1993	Department of OB/GYN, Taiwan Provincial Feng-Yuan Hospital, Taichung, Taiwan, ROC	Attending Doctor
1990-1991	Department of OB/GYN, Taiwan Provincial Feng-Yuan Hospital, Taichung, Taiwan, ROC	Chief Resident
1987-1990	Department of OB/GYN, Taiwan Provincial Feng-Yuan Hospital, Taichung, Taiwan, ROC	Resident
1986-1987	Department of OB/GYN, Taipei Municipal Jen-Ai Hospital, Taipei, Taiwan, ROC	Resident
1984-1986	Military Surgeon of the Air Force of the Republic of China (Taiwan), Ping-Tung Air Force Hospital and Ma-Kung Air Force Base Hospital	Lieutenant
1982-1984	Taipei Veterans General Hospital, Taipei, Taiwan, ROC	Intern

Team Members:

Collaborating Investigators:

Chi-Chang Chang, M.D., Ph.D. Department of Obstetrics and Gynecology

Yu Chang, M.D., Ph.D. Department of Obstetrics and Gynecology

Chih-Chen Chen, M.D., Department of Obstetrics and Gynecology

Chi-Wai Ruan, M.D., Department of Obstetrics and Gynecology

Yun-Hsiang Hung, M.D., Department of Obstetrics and Gynecology

Nari Kay, M.D., Department of Obstetrics and Gynecology

Chi-Feng Fu, M.D., Department of Obstetrics and Gynecology

Yu-Ta Chou, M.D., Department of Obstetrics and Gynecology

Yu-Chieh Fang, M.D., Department of Obstetrics and Gynecology

Chun-Nan Chen, M.D., Department of Obstetrics and Gynecology

Team Members

Chun-Yen Huang, Ph.D.

Ya-Chun Yu, M.S.

Wen-Ying Chiu, M.S.

Techniques & Equipment

A. Cell & tissue culture:

Inverted phase contrast microscope

Vacuum suction pump

Magnetic cell sorting (MACS) system

B. Molecular biology:

Devices for protein electrophoresis

Devices for nucleic acid (including power supply and horizontal electrophoretic tank)

C. General purpose equipment:

Low temperature centrifuge

Microcentrifuge

Digital dry bath

Thermostatic water bath

Magnetic stirrer

Vortex, orbital and rocking shakers

Balance

pH meter

Oven

D. Sample storage devices:

Liquid nitrogen tank (165 L)

E. Frequently used techniques:

Cell and tissue primary isolation and culture

Cell-based assays

PCR

qPCR

Western blotting

Flow cytometry

ELISA

Paraffin block sectioning

Immunohistochemistry

Immunofluorescent staining

Microarray

Next generation sequencing

Animal disease models: Intrauterine growth restriction/spontaneous abortion, dendritic cell/macrophage depletion, endometriosis, adenomyosis, decidual cell conditional knockout

Research Projects

Project titles	PI	Source	Duration
Establishment of decidual cell C-C motif ligand 2 conditional knockout mouse model-Elucidate the role of Ccl2 in decidual cells in pregnancy complications (MOST 109-2314-B-650-009-MY3)	Se-Te Joseph Huang	MOST, Executive Yuan, ROC	08/01/2020- 07/31/2023
YIV906 additive effect when add in Paclitaxel and Carboplatin on ovarian cancer chemotherapy	Chi-Feng Fu	EDMRP	02/01/2022- 01/31/2023
The effect of each individual herb of Guizhi Fuling Wan on inhibiting endometriosis development	Nari Kay	EDMRP	02/01/2022- 01/31/2023
Eosinophils play a role in the pathogenesis of adenomyosis mediated by TGF- β 1	Chih-Chen Chen	EDMRP	02/01/2022- 01/31/2023
Development of an AI model in evaluating the quality of cultured gestational tissue-derived stem cells using computer vision	Se-Te Joseph Huang	EDMRP	01/01/2022- 12/31/2022
The effects of Guizhi Fuling Wan on endometrial receptivity	Se-Te Joseph Huang	EDMRP	01/01/2021- 12/31/2021
YIV906 on ovarian cancer chemotherapy in mouse model	Chi-Feng Fu	EDMRP	01/01/2021- 12/31/2021
The role of mitochondria in the pathogenesis of adenomyosis	Nari Kay	EDMRP	01/01/2021- 12/31/2021
The effect of attenuated TGF- β 1 on endometrial receptivity	Chun-Yen Huang	EDMRP	01/01/2021- 12/31/2021
Establishment of outcome measure for adenomyosis using clinical and imagery information by deep computer learning	Se-Te Joseph Huang	EDMRP	08/01/2020- 01/31/2022
Therapeutic effects of PHY906 on ovarian cancer chemotherapy	Chi-Feng Fu	EDMRP	01/01/2020- 12/31/2020

The role of mitochondrial dysfunction in the pathogenesis of adenomyosis	Nari Kay	EDMRP	01/01/2020-12/31/2020
The effects of Guizhi Fuling Wan on implantation	Chi-Wai Ruan	EDMRP	01/01/2020-12/31/2020
The crucial component(s) of Guizhi Fuling Wan in inhibiting endometriosis development	Yu-Ta Chou	EDMRP	01/01/2020-12/31/2020
The crucial component(s) of Guizhi Fuling Wan in fetal-placental development	Yu-Chieh Fang	EDMRP	01/01/2020-12/31/2020
Attenuated TGF- β 1 improves pregnancy outcome in mice with induced adenomyosis by restoring uterine receptivity	Chun-Yen Huang	EDMRP	01/01/2020-12/31/2020
Regulation of decidual antigen-presenting cell polarization in spontaneous abortion (MOST 108-2314-B-650-004)	Se-Te Joseph Huang	MOST, Executive Yuan, ROC	08/01/2019-07/31/2020
The clinical presentation of the tongue diagnosis in early spontaneous pregnancy loss and preterm labor	Yun-Hsiang Hung	EDMRP	03/01/2019-02/29/2020
The role of fibroblast-tomyofibroblast in the pathogenesis of adenomyosis	Nari Kay	EDMRP	03/01/2019-02/29/2020
Establishment of loxP-Ccl2 knockout mouse and its application in investigating the pathogenesis of pregnancy complications	Chun-Yen Huang	EDMRP	03/01/2019-02/29/2020
The effects of Guizhi Fuling Wan on fetal programming (MOST 107-2320-B-650-001)	Se-Te Joseph Huang	MOST, Executive Yuan, ROC	08/01/2018-11/30/2019
The effect of Guizhi Fuling Wan (GFW) on intrauterine growth restriction	Se-Te Joseph Huang	EDMRP	04/01/2018-03/31/2019
Study on TGF- β 1 in the pathogenesis of adenomyosis	Nari Kay	EDMRP	04/01/2018-03/31/2019
The successful pregnancy rate in the mice with adenomyosis	Chun-Yen Huang	EDMRP	04/01/2018-03/31/2019
Cellular and molecular mediators of Zika virus replication in decidua and mechanisms of Zika virus transmission from maternal decidua to the placental/fetal unit	Charles J Lockwood	Florida State Government	07/01/2017-06/30/2018
Effects of Chinese herbal formula on fetal programming	Se-Te Joseph Huang	Women's Health Collaborative	07/01/2017-06/30/2018

		Seed Grant USF Foundation Fund	
Establishment of conditional knockout mouse and its application in investigating the pathogenesis of pregnancy complications	Se-Te Joseph Huang	EDMRP	04/01/2017-03/31/2018
Early prediction of preeclampsia by a multi-parametric model	Chun-Yen Huang	EDMRP	04/01/2017-03/31/2018
Regulation of decidual antigen-presenting cell polarization in spontaneous abortion	Chi-Feng Fu	EDMRP	04/01/2017-03/31/2018
The effects of a traditional Chinese herbal formula, Guizhi Fuling Wan, on the development and maintenance of endometriosis	Chih-Chen Chen	EDMRP	04/01/2017-03/31/2018
The effects of kisspeptin on the treatment of PCOS-induced infertility	Se-Te Joseph Huang	EDMRP	04/01/2018-03/31/2017

Selected Publications (2016~2022): (* Correspondent)

1. Hung YH, Huang CY, Yu YC, Kuo CY, S. **Huang SJ***. Breast Cancer with Trastuzumab Treatment in Mid-Gestation Complicated with Placental Defects and Fetal Growth Restriction-A Case Report. *E-Da Med J* (In press)
2. Chan HY, Liu HW, Chen CN, **Huang SJ***. Interstitial pregnancy, a rare ectopic pregnancy: A case report. *E-Da Med J* (in press)
3. Tey SJ, **Huang SJ**, Chen CC. Ovarian dysgerminoma with torsion: A case report. *E-Da Med J* (in press)
4. Chen CC, Huang CY, Shiu LY, Yu YC, Lai JC, Chang CC, Fu CF, **Huang SJ***. Combinatory effects of current regimens and Guizhi Fuling Wan on the development of endometriosis. *Taiwanese J Obstet Gynecol*, 2022, 60(1):70-74.
5. Tey SJ, **Huang SJ**, Chen CC. Ovarian dysgerminoma with torsion: A case report. *E-Da Med J* (in press)
6. Kay N, Huang CY, Yu YC, Ruan CW, Chang CC, Tsai IM, **Huang SJ***. TGF- β 1 neutralization improves pregnancy outcomes by restoring endometrial receptivity in mice with adenomyosis. *Reproductive Science*, 2021, 28(3): 877-887.
7. Kuo CY, Chiu V, Hsieh PC, Huang CY, **Huang SJ**, Tzeng IS, Tsai FM, Chen ML, Liu CT, Chen Y R. Chrysophanol attenuates hepatitis B virus X protein-induced hepatic stellate cell fibrosis by regulating endoplasmic reticulum stress and ferroptosis. *Journal of Pharmacological Sciences*, 2020, 144(3): 172-182.
8. Kay N, Huang CY, Shiu LY, Yu YC, Chang Y, Suen JL, Tsai IM, **Huang SJ***. The effects of anti-TGF- β 1 on epithelial-mesenchymal transition in the pathogenesis of adenomyosis. *Reproductive Science*, 2020, 27(9): 1698-1706.
9. **Huang SJ***, Chen CP, Buchwalder L, Yu YC, Piao L, Huang CY, Schatz F, Lockwood CJ. Regulation of CX3CL1 Expression in Human First Trimester Decidual Cells: Implications for Preeclampsia *Reprod Sci* 2019, 26(9):1256-65.

10. Chang Y , Kay N , Huang MR , **SJ Huang**,* Tsai EM. Laparoendoscopic single-site supracervical hysterectomy with manual morcellation: a retrospective study. *J Minim Invasive Gynecol* 2018, 25(6):1094-1100.
11. Wu XQ, Ding H, Nie MF, Piao L, Zhang HW, **Huang SJ***. Risk factors and underlying mechanisms for postmenstrual spotting associated with cesarean scar defect: A retrospective study. *J Reprod Med* 2018, 63(1-2):6-12
12. Li HM, Sung FC, Li SC, Huang YK, Chang Y, Chang CC, **Huang SJ**, Lin CL, Kao CH. The effect of antibiotic prophylaxis for acute pelvic inflammatory disease after hysterosalpingography: a retrospective cohort study. *Curr Med Res Opin* 2018, 14:1-6.
13. Vannuccini S, Tosti C, Carmona F, **Huang SJ**, Chapron C, Guo SW, Petraglia F. Pathogenesis of adenomyosis: an update on molecular mechanisms. *Reprod BioMed Online* 2017, 592-601.
14. Chen MF, **Huang SJ**, Huang CC, Liu PS, Lin KI, Liu CW, Hsieh WC, Shiu LY, Chen CH. Saikosaponin A Induces Apoptosis through Mitochondria-Dependent Pathway in Hepatic Stellate Cells. *Am J Chin Med* 2017, 45(2):351-368.
15. Yen CF, **Huang SJ**, Lee CL, Wang HS, Liao SK. Molecular characteristics of the endometrium in uterine adenomyosis and its biochemical microenvironment. *Reprod Sci* 2017, 24(8):1176-1186
16. Yen CF, Liao SK, **Huang SJ**, Tabak S, Arcuri F, Lee CL, Arici A, Petraglia F, Wang HS, Kayisli UA. Decreased endometrial expression of leukemia inhibitory factor receptor disrupts the stat3 signaling in adenomyosis during the implantation window. *Reprod Sci* 2016, 24(8):1176-1186.
17. Chen MF, **Huang SJ**, Huang CC, Liu PS, Lin KI, Liu CW, Hsieh WC, Shiu LY and Chen CH. Saikosaponin d induces cell death through caspase-3-dependent, caspase-3-independent and mitochondrial pathways in mammalian hepatic stellate cells. *BMC Cancer* 2016, 16:532-43.
18. Li M, Piao L, Chen CP, Wu XQ, Yeh CC, Masch R, Chang CC, **Huang SJ***. Modulation of decidual macrophage polarization by M-CSF derived from first trimester decidual cells-implication in preeclampsia. *Am J Pathol* 2016, 186(5):1285-1266.