

Reproductive Science Laboratory

Lab Introduction

1. **Therapeutic effects of YIV906 on ovarian cancer therapy:** Huangqin soup is a Chinese herbal formula from 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 side effects of the gastrointestinal tract such 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, research on 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.
2. **Establishment of an 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 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 better communication and guidance among clinicians and pathologists. This project plans to establish a standardized modality for detecting and quantifying lesions by artificial intelligence (AI) using deep computer learning.
3. **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 genes expressed by decidual cells in the pathogenesis of pregnancy complications is important in understanding the mechanisms of the development of adverse pregnancy outcomes. Thus, this project will conditionally knockout or overexpress specific genes in the decidual cells in various mouse models to study the function of each gene.
4. **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 the 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.

5. **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 are required for a successful pregnancy. Disorders of the endometrium and endometriosis result in a 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) attests to its unprecedented safety record. The central theme of this project is the discovery of novel mechanisms and therapeutic applications of GFW in improving pregnancy outcomes.
6. **The role of TGF- β 1 and 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 the TGF- β 1 signaling pathway using *in vitro* and *in vivo* models.
7. **The effects of adipose-derived stem cells (ADSCs) and umbilical cord-derived stem cells (UCSCs) on the pathogenesis of endometriosis:** Endometriosis is an inflammatory disease in women happens in 10% of reproductive age and causes 60% of women with pelvic pain and 30% to 50% of infertility. An inflammatory environment is found in the peritoneal environment, ectopic tissues, and eutopic endometrium of women with endometriosis. Although both surgical and medical treatments are effective for treating complications associated with endometriosis, the recurrent rate is estimated to be more than 20% 2 years and 40-50% 5 years after treatment(s). Thus, the development of new therapeutic strategies is required to improve the efficacy of treatment for endometriosis. Mesenchymal stem cell-derived conditioned medium (MSC-CM) is suggested to be involved in many pathophysiological processes, such as wound healing, immunoregulation, and regeneration. MSC-CM contains adipokines, cytokines, and growth factors and displays the ability to suppress inflammation by down-regulating pro-inflammatory and up-regulating anti-inflammatory elements. Our aim is to test ASCD, UCSCs, and their conditioned medium to inhibit the development of endometriosis via their anti-inflammatory effect and improve endometrial receptivity.
8. **The effects of ADSCs and UCSCs on the reversal of fibrosis and improvement of endometrial receptivity in adenomyotic mice:** Adenomyosis is characterized by the presence of endometrial glands and stroma within the myometrium. Patients with adenomyosis usually suffer from subfertility, pelvic pain, hypermenorrhea, dyspareunia, and dysmenorrhea. Like endometriosis, it is estrogen-dependent and progesterone-resistant. Although numerous studies have focused on the pathogenesis of endometriosis, the current understanding of the mechanisms associated with the pathogenesis of adenomyosis is limited. MSCs represent stem cells isolated from mesenchyme of various tissues, including adipose tissue and gestational tissues, including umbilical cord, amniotic

fluid, and placenta. MSCs can either inhibit or augment inflammatory responses in a microenvironment-dependent manner. Our aim is to test ADSCs, UCSCs, and their conditioned medium to reverse the epithelial–mesenchymal transition and inhibit fibrotic development in adenomyosis.

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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>
2023 - present	E-Da Dachang Hospital Attending Physician, Kaohsiung, Taiwan, ROC	Vice Superintendent of Medical Affairs
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
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
2016 - 2020	Department of Obstetrics and Gynecology, College of Medicine, University of South Florida, Tampa, FL, USA	Associate 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:

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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
Inverted phase fluorescent microscope
CO₂ incubator
Laminar flow
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
ELISA reader
PCR machine
Oven

D. Sample storage devices:

Liquid nitrogen tank (36 L & 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
A therapeutic effect of secretome from adipose-derived stem cells conditioned medium in treating adenomyosis	Se-Te Joseph Huang	EDMRP	01/01/2024-12/31/2024
Parameter setting for high-intensity focused ultrasound in treating uterine myomas with the assistance of artificial intelligence	Chi-Chang Chang	EDMRP	01/01/2024-12/31/2024
Reversal of fibrosis and improved endometrial receptivity in the adenomyosis mice by a xenograft of mesenchymal stem cells	Yun-Hsiang Hung	EDMRP	01/01/2024-12/31/2024
Reversal of fibrosis and improvement of endometrial receptivity in the adenomyotic mice by umbilical cord-derived mesenchymal stem cells	Chih-Chen Chen	EDMRP	01/01/2024-12/31/2024
Gestrinone improves pregnancy outcome via enhancement of endometrial receptivity in mice with endometriosis	Chun-Nan Chen	EDMRP	01/01/2024-12/31/2024
The role of HIF-1 α in mediating mitochondrial dysfunction-activated TGF- β 1 production in adenomyosis	Nari Kay	NSTC, Executive Yuan, ROC	08/01/2023-07/31/2024
Gestational tissue-derived stem cells for cell therapy: characterization and functional studies	Se-Te Joseph Huang	EDMRP	01/01/2023-12/31/2023

The effect of gestational tissue-derived stem cells on the healing of fetal membranes	Yun-Hsiang Hung	EDMRP	01/01/2023-12/31/2023
The role of HIF-1 α in mediating mitochondrial dysfunction-activated TGF- β 1 production in adenomyosis	Nari Kay	EDMRP	01/01/2023-12/31/2023
The effects of conditioned media derived from gestational tissue-derived stem cells on inflammatory diseases	Chih-Chen Chen	EDMRP	01/01/2023-12/31/2023
Cell study of progesterone (Dienogest) for ovarian cancer treatment	Chi-Feng Fu	EDMRP	01/01/2023-12/31/2023
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	NSTC, 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
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

Selected Publications (2016~2024): (* Correspondent)

1. Fang YC, Yu YC, Huang CY, **Huang SJ***. The improvement of endothelial function by Guizhi Fuling Wan via its effects on IL-1 β -treated first trimester decidual cells and subsequent interaction with macrophages. E-Da Med J, (Accepted)
2. 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)
3. Chan HY, Liu HW, Chen CN, **Huang SJ***. Interstitial pregnancy, a rare ectopic pregnancy: A case report. E-Da Med J (in press)

4. **Huang SJ***, Huang CY, Huang YH, Cheng JH, Yu YC, Lai JC, Hung YP, Chang CC, Shiu LY. A novel therapeutic approach for endometriosis using adipose-derived stem cell-derived conditioned medium-A new hope for endometriotic patients in improving fertility. *Frontier Endocrinol* 2023 14:1158527.
5. Tey SJ, **Huang SJ**, Chen CC. Ovarian dysgerminoma with torsion: A case report. *E-Da Med J* 2022 9(4):20–4.
6. 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.
7. Tey SJ, **Huang SJ**, Chen CC. Ovarian dysgerminoma with torsion: A case report. *E-Da Med J* (in press)
8. 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.
9. 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.
10. 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.
11. **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.
12. 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.
13. 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
14. 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.
15. 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.
16. 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.
17. 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
18. 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.
19. 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.
20. 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.