



Name: Hsu, Hsien-Yeh (許先業)

教授， 國立陽明大學 醫學生物技術暨檢驗學系

Email: hsienyeh@gmail.com

EDUCATION AND POSITIONS HELD:

Education:

Taiwan University (Taiwan)	Bachelor	1971~1975	Agriculture Chemistry
Cornell University (USA)	Master	1976~1978	Biology & Life Science
Cornell University (USA)	Ph.D.	1980~1984	Biology & Life Science

Professional:

National Yang-Ming University			
Department of Biotechnology and Laboratory Science in Medicine	Professor	2002~present	
Institute of Biophotonics Engineering	Adjunct Professor	2006~present	
National Yang-Ming University			
Department of Biotechnology and Laboratory Science in Medicine	Associate professor	1997~2002	
Cornell University Medical College, NY, USA			
Department of Medicine	Assistant Professor	1994~1997	
Cornell University Medical College, NY, USA			
Department of Pathology	Research Associate	1991~1994	

Massachusetts Institute of Technology, MA, USA

Department of Biology

Postdoctoral Associate

1990~1991

Genzyme Inc./Gene-Trak Systems, MA, USA

Research and Development

Project Leader, Staff Scientist

1987~1990

Penicillin Assays Inc., MA, USA

Research and Development

Senior Research Scientist

1984~1987

HONORS:

Oversea Studentship to Cornell University, Minister of Education, Taiwan, 1976

NIH Research Award, Cornell University Medical School (Weill Medical College of Cornell University), USA, 1993

Academia Sinica Research Award for Junior Research Investigators, 2003

International Society of Atherosclerosis; Investigator Award, 2003

RESEARCH INTERESTS:

Investigation of the role of Extract of *Ganoderma lucidum* (Reishi, or Ling-Zhi, a medical fungus) polysaccharides (EORP), in T cells and in functions of regulatory T cells

Our previous studies indicated Extract of *Ganoderma lucidum* polysaccharides (EORP) exerts immuno-modulatory functions. The regulatory T cells (Tregs) play a bi-functional regulation between Th1 and Th2, which potentially prevent autoimmune disorders including asthma (氣喘), systemic lupus erythematosus (SLE, 紅斑性狼瘡), rheumatoid arthritis (RA, 類風濕症關節炎), psoriasis vulgaris (乾癬). In addition, Tregs may exert anti- and anti-inflammatory. Our preliminary results indicated EORP induces naïve CD4⁺T cells into CD4⁺CD25⁺FOXP3⁺ regulatory T cells, which could inhibit effector T cells *in vitro*. Hence, we plan to investigate (1) Whether EORP is able to stimulate Tregs, (2) does and how EORP-mediated Tregs involve in immunological responses. Currently, using inflammatory bowel disease of mice model or other autoimmunity animal models, we will further investigate the mechanism for the role of Tregs involved in EORP alleviation of “autoimmune-like” diseases.

靈芝與 T 細胞及調節性 T 細胞: 靈芝在先前研究已經知道具有免疫調節的功效，而再免疫系統中扮演免疫調節的其中一個角色就是調節性 T 細胞，此類型之 T 細胞可以調節 Th1 及 Th2 細胞之免疫平衡，避免自體免疫的發生，除此之外，調節性 T 細胞也同時具有抗過敏和抗發炎的功效，因此我們想知道靈芝是否透過活化調節性 T 細胞進而達到免疫調節的功效，在我們的研究中發現，靈芝可以誘導 Naïve CD4⁺T 細胞轉變為 CD4⁺CD25⁺FOXP3⁺調節性 T 細胞，且此誘導出之調節性 T 細胞在體外實驗發現具有抑制效用型(effector) T 細胞之功用，同時，我們選用(Inflammatory bowel diseases, IBD) or other autoimmunity diseases 的動

物模式中也發現靈芝可以減輕其病症，其可能的機制可能與調節性 T 細胞具有相關性。

The development of Extract of *Ganoderma lucidum* (Reishi, or Ling-Zhi) polysaccharides (EORP) to an anti-cancer drug

Lung cancer as one of the most common cancers in Taiwan as well as in the world represents a major public health problem (it is also listed as the number 1 cancer occurrence). Currently, only parts of the drugs are useful to a sub-group of patients in lung cancer, the need to develop an effective and drug in cure of lung cancer. At present, one of our projects is focused on the inhibitory effects of extract of *Ganoderma lucidum* (Reishi) polysaccharides (EORP) on lung cancer. The accumulated documents indicated that human immune system plays important roles in the development of lung cancer. In the collaboration with Academia Sinica and biotechnological industry, we plan to apply the functions of EORP-regulated immunity to investigate the function of human immune system in the prevention of lung cancer. In essence, we will use lung cancer cells including non-small lung cancer cells (NSLCC) bearing mice to examine the mechanism for EORP inhibition NSLCC *in vitro* and *in vivo*.

靈芝與肺癌的關係: 在世界上由於肺癌已在癌症死亡率的排名是第一名，癌症又高居國人十大死因之首，而現今的藥物只對部分人有所效果，所以非常需要新藥開發。目前我們實驗室主要研究於靈芝多醣體對於肺癌生長的抑制效果(與中央研究院基因體中心，生醫技術產學合作與臨床配合)，在先前的許多文獻也發現免疫功能在肺癌患者中的重要性，同時由於靈芝多醣體對於免疫系統調節有非常重要的角色及影響。因此，我們以小鼠模式研究靈芝多醣體對於小鼠體內實際抑制肺癌的效果，並探討免疫系統扮演的角色與機制，在我們先前的研究已經對於靈芝多醣體對於免疫系統扮演的角色有部分的認識，而靈芝多醣體在體內主要是扮演免疫調節的角色，可能是具有雙向調節免疫系統，在不同的情況下，可能是促進或是抑制免疫系統，我們未來將同時結合標靶藥物探討其是否有加乘的抑制效果。

***Cordyceps sinensis* (*Hirsutella sinensis*) mediate signalings in the regulation of cytokines expression**

Cordyceps sinensis is considered as one of effective immune regulatory Chinese traditional medicines. Importantly, *Hirsutella sinensis* (HS), a true anamorph of Chinese caterpillar fungus was isolated from *Cordyceps sinensis*. Using the fermented HS mycelia as experimental source, we examined the effects of HS on molecular, cellular and immunological aspects of immune related cells including monocytes/macrophages and mice. In essence, we focus on pro- and anti-inflammatory related cytokines expression (e.g., IL-1, IL-1Ra, IL-10, etc.) from immune cells and mice animal model. In addition, we we'll dissect the essential (key) components, e.g., polysaccharides, protein from HS, we will further investigate the immuno-modulator functions. *Hirsutella sinensis*-mediated signal transduction in regulation of cytokines expression would aid our understanding of *Cordyceps*-mediated human immunological activities.

冬蟲夏草自古以來即廣為流傳是一種神奇的免疫聖藥，生長在青康藏高原之上，我們實驗室與中央研究院團隊、生醫技術產學合作，以發酵的方式取得冬蟲夏草菌正宗絲體，萃取出有效成分，來研究冬蟲夏草何以為一種功能如此神奇的中草藥。我們以分子及細胞生物學、免疫細胞學做為研究平台，探討冬蟲夏草是否可以活化免疫細胞，增強免疫力。在現在的研究方向主要是著重在冬蟲夏草與抗發炎的相關性，我們以單核球白血球的幾種細胞激素(IL-1、IL-1Ra、IL-10)做為指標來探討，並配合小鼠實驗來確認在活體中冬蟲夏草的功用。未來我們更將延伸到其他相關免疫細胞，希望可以找到冬蟲夏草中與免疫相關確切的多醣或

蛋白分子。

Application of molecular/cellular biology and biophotonic methods to investigate the role of lipid raft/micro-domain in receptor-mediated signalling and immune responses

In our recent studies, we utilized instruments of biophotonic to investigate the roles of lipid rafts in Reishi-mediated pro-inflammatory cytokine (proIL-1, IL-1) and anti-inflammatory cytokine (IL-1Ra) production within macrophages. In our previous study, we found the specific signaling cascades regulated by external stimulation within macrophages are lipid raft involved. Hence we will focus on the mechanism Reishi polysaccharides activate lipid rafts and then regulate signaling cascades to enhance macrophages function. What we want to clarify is the role of Reishi polysaccharides-mediated macrophages in immune system, and we also combine various methods, which include biochemistry, molecular cell biology, and collaborated with biophotonic experts to investigate the processing of Reishi polysaccharides-mediated lipid rafts conformations, and the flow path these lipid rafts transfer polysaccharides entering macrophages to enhance immune function. Our purpose is to understand the molecules compositions of lipid rafts which Reishi polysaccharides-induced within macrophages, and the single molecules movement (e.g. Reishi polysaccharides, TLR2, 4, etc.) by biophotonic methods to clarify the relationships between Reishi polysaccharides and macrophages.

在我們的研究計畫中，我們以巨噬細胞做為研究平台，配合利用生醫光電設備、工具方法來探討靈芝调控巨噬細胞產生：第一介白素的前驅物(prointerleukin-1)及第一白介素(interleukin-1)，在此機制中脂質筏所扮演的角色。我們已知道，細胞接受外界的刺激後所引起細胞內部產生的訊息调控需要透過脂質筏的幫助，有關靈芝多醣體如何透過脂質筏來活化巨噬細胞的訊息傳導是我們現今研究的重點。我們所關心的是靈芝多醣體在增強免疫力功效中，巨噬細胞所扮演的角色，並且希望配合以多種生化、分生技術與生醫光電工程領域的結合，來了解脂質筏如何把靈芝多醣體送進巨噬細胞中並且使巨噬細胞增加免疫功能，最終的目的我們希望可以透徹的了解複雜的脂質筏中所含的內容分子，以及希望以光學的方式在活體細胞中看到單一分子(如靈芝多醣體)的移動，以釐清靈芝多醣體與巨噬細胞的關係。

SELECTED PUBLICATIONS:

Feng-Ling Yang, Kuo-Feng Hua, Yu-Liang Yang, Wei Zou, Yen-Po Chen, Shu-Mei Liang, **Hsien-Yeh Hsu***, and Shih-Hsiung Wu*. TLR-independent induction of human monocyte IL-1 by phosphoglycolipids from thermophilic bacteria. *Glycoconjugate Journal*, 2008 July 25(5): 427-439, (*Corresponding author: Hsien-Yeh Hsu)

Hsien-Yeh Hsu*, Li-Chieh Chu, Kuo-Feng Hua and Louis Kuo-Ping Chao. Heme oxygenase-1 mediates the anti-inflammatory effect of Curcumin within LPS-stimulated human monocytes. *Journal of Cellular Physiology*, 215: 603–612, 2008, (*Corresponding author: Hsien-Yeh Hsu)

Hsien-Yeh Hsu*, Kuo-Feng Hua, Wei-Chi Wu, Jason Hsu, Shih-Ting Weng, Tsai-Leng Lin, Chun-Yi Liu, Ruey-Shyang Hseu, and Ching-Tsan Huang, Reishi Immuno-modulation Protein Induces Interleukin-2 Expression via Protein Kinase-Dependent Signaling Pathways within human T

- Cells. *Journal of Cellular Physiology*, 215: 15-26, 2008, (*Corresponding author: Hsien-Yeh Hsu)
- Ming-Tzo Wei, Kuo-Feng Hua, Jowey Hsu, Artashes Karmenyan, Kai-Yu Tseng, Chi-Huey Wong, **Hsien-Yeh Hsu***, and Arthur Chiou*. The interaction of lipopolysaccharide with membrane receptors on macrophages pretreated with extract of Reishi polysaccharides measured by optical tweezers. *OPTICS EXPRESS*, 15: 11020-11032, 20 August 2007, (*Corresponding author: Hsien-Yeh Hsu)
- Kuo-Feng Hua, **Hsien-Yeh Hsu***, Louis Kuoping Chao, Shui-Tein Chen, Wen-Bin Yang, Jason Hsu, and Chi-Huey Wong. *Ganoderma lucidum* Polysaccharides Enhance CD14 Endocytosis of LPS and Promote TLR4 Signal Transduction of Cytokine Expression. *Journal of Cellular Physiology*, 212: 537–550, 2007, (*Corresponding author: Hsien-Yeh Hsu)
- Chien Chou*, **Hsien-Yeh Hsu***, Hsieh-Ting Wu, Arthur Chiou, Chih-Jen Yu, Kai-Yu Tseng, Zheng-Yuan Lee and Tsu-Shin Chan. Fiber-optic biosensor for detection of C-reactive protein and monitor of protein binding kinetics. *Journal of Biomedical Optics*, 122, 024025 March/April 2007, (*Hsien-Yeh Hsu and Chien Chou are equally contributed, and are co-corresponding authors)
- Hsien-Yeh Hsu***, Hua-Lin Wu, Sai-Koong Tan, Vivian Pei-Hsin Li, Wei-Ting Wang, Jason Hsu, and Ching-Hsun Cheng. Geldanamycin Interferes with Heat Shock Protein 90 in Lipopolysaccharide-transduced Signaling of Interleukin-1 Expression and Apoptosis within Macrophages. *Molecular Pharmacology*, 2007, 71: 344-356. (*Corresponding author: Hsien-Yeh Hsu)
- Hsien-Yeh Hsu**,[@] Kuo-Feng Hua,[@] Yu-Chang Su, Li-Chih Chu, Huan-Wen Chih, Chi-Huey Wong, Su-Sing Yang, and Louis Kuoping Chao. Alkali-soluble polysaccharides of *Rhizoclonium riparium* alga induces IL-1 gene expression via protein kinase signaling pathways. *Journal of Agricultural and Food Chemistry*, 54, 3558-3565, 2006. ([@]First author, contributed equally to work)
- W. P. Hu, **H.-Y. Hsu***, A. Chiou, G. L. Chang, K. Y. Tseng, S.-J. Chen. Immunodetection of native and modified C-reactive protein using surface plasmon resonance biosensing. *Biosensors & Bioelectronics*, 21: 1631-1637, 2006 (*Corresponding author: Hsien-Yeh Hsu)
- Hsien-Yeh Hsu***, Kuo-Feng Hua, Chun-Cheng Lin, Chun-Hung Lin, Jason Hsu, and Chi-Huey Wong. Extract of Reishi Polysaccharides Induces Cytokine Expression via Toll-like Receptor 4-modulated Protein Kinase Signaling Pathways. *Journal of Immunology* 173: 5989-5999, 2004