



林錫賢 Hsi-Hsien Lin

教授 Professor

電話：03-2118800 ext 3321

傳真：03-2118469

信箱：hhlin@mail.cgu.edu.tw

個人網頁：<https://sites.google.com/site/hhlinlab/>

學經歷

Education:

- 1992/8 – 1997/12 博士，美國田納西大學 橡樹嶺生物醫學研究所
Ph.D., Oak Ridge Graduate School of Biomedical Sciences, University of Tennessee – Knoxville, TN, U.S.A.
- 1987/8 – 1989/6 碩士，國立台灣大學醫學院 生物化學研究所
M.S., Institute of Biochemistry, College of Medicine, National Taiwan University,
Taipei, Taiwan
- 1983/8 – 1987/6 學士，國立成功大學 生物系
B.S., Department of Biology, National Cheng Kung University, Tainan, Taiwan

Research Experience:

- 2011/8 – present **Professor/Laboratory Head**, Laboratory of Molecular Immunology, Department of Microbiology and Immunology, Chang Gung University, Taiwan.
- 2007/8 – 2011/7 **Associate Professor/Laboratory Head**, Laboratory of Molecular Immunology, Department of Microbiology and Immunology, Chang Gung University, Taiwan.
- 2004/12 – 2007/7 **Assistant Professor/Laboratory Head**, Laboratory of Molecular Immunology, Department of Microbiology and Immunology, Chang Gung University, Taiwan.
- 2000/7 – 2004/11 **Group leader/Senior Research Fellow**, Sir William Dunn School of Pathology, the University of Oxford, UK.
Functional study of the EGF-TM7 receptors.
- 1998/7 – 2000/7 **Research Fellow**, Sir William Dunn School of Pathology, the University of Oxford, UK.
Functional study of the EGF-TM7 receptors.
- 1997/12 – 1998/6 **Postdoctoral Research Scientist**, Oak Ridge National Laboratory, TN, U.S.A.
Gene expression profiling using genosensor (DNA chip) technology.
- 1992/8 – 1997/12 **Graduate Research Assistant**, University of Tennessee – Knoxville, TN, U.S.A.
Studied the functions of novel genes identified by differential display in c-myc mutant mice
- 1989/7 – 1992/7 **Research Assistant**, Department of Medical Research, Veterans General Hospital – Taipei, Taiwan.
Molecular cloning and sequence analysis of a common precursor for a putative hemorrhagic protein and rhodostomin.
Studied the effect of snake venom platelet inhibitor (Rhodostomin) on cell attachment.
- 1987/6 – 1989/6 **Graduate Research Student**, Institute of Biochemistry, College of Medicine, National Taiwan University, Taipei, Taiwan.
Growth and characterization of a newly established human pituitary tumor cell line.

1986/6 – 1987/6 **Undergraduate Research Student**, Department of Biology, National Cheng Kung University,
Tainan, Taiwan.

Studied the mechanism of δ -aminolevulinic acid synthetase.

研究方向

The research of my laboratory focuses principally on the functions and regulation of adhesion GPCRs. Specific interest includes:

1. The identification and characterization of, and the structural-functional study of the EGF-TM7 receptors, including EMR2, CD97 and F4/80.
2. The signaling pathways of EMR2 and CD97 receptors.
3. The role of adhesion-GPCRs in osteoclast differentiation and function.
4. Molecular and functional characterization of BFPP-associated GPR56 mutations.
5. The identification of the cellular ligand(s) of GPR56.
6. The role of GPR56 in tumor biology.
7. The expression and functional characterization of GPR56 in immune system.

We are well experienced in various biological assays of macrophage and neutrophil functions as well as tumor biology. Most modern technologies in molecular biology, cell biology, immunology, proteomics and biochemistry are well established in the laboratory.

本實驗室研究方向專注於黏合型 G 蛋白質耦合受體功能與調控，目前有幾個研究方向：

- 1、類上皮生長因子七次穿膜受體其特性的研究以及有關於他們特殊結構的探討，當中包含下列幾個分子：EMR2、CD97 與 F4/80
- 2、EMR2、CD97 受體的訊息傳導的研究
- 3、研究黏合型 G 蛋白質耦合受體在蝕骨細胞分化與功能所扮演的角色
- 4、探討人類腦部前額疾病 BFPP 的致病基因 GPR56 的功能與結構的特性
- 5、尋找 GPR56 在細胞上的受質
- 6、GPR56 在腫瘤生物學中所扮演的角色
- 7、探討 GPR56 在免疫細胞表現與功能所扮演的角色

本實驗室專精於免疫細胞，如巨噬細胞、嗜中性粒細胞的功能以及腫瘤生物方面的各種生物分析方式，同時也建立了分子生物學、細胞生物學、免疫學、蛋白質體學、生物化學方面的技術。

著作(2011-present)

***: corresponding author; &: co-first author**

- 2011
1. C.-C. Hsiao, H.-Y. Chen, G.-W. Chang and H.-H. Lin* 2011 GPS autoproteolysis is required for CD97 to up-regulate the expression of N-cadherin that promotes homotypic cell-cell aggregation. *FEBS Letters* 585(2):313-318. (SCI, IF=3.623) (corresponding author)
 2. J. Q. Davies&, H.-H. Lin&*, M. Stacey&, S. Yona, G.-W. Chang, S. Gordon, J. Hamann, L. Campo, C. Han, A. L. Harris and S. B. Fox 2011 The leukocyte adhesion GPCR EMR2 is aberrantly expressed in human breast carcinomas and is associated with patient survival. *Oncology Reports* 25(3):619-27. (SCI, IF=2.662) (co-first author, corresponding author)
 3. N.-Y. Chiang, C.-C. Hsiao, Y.-S. Huang, H.-Y. Chen, I.-J. Hsieh, G.-W. Chang, H.-H. Lin* 2011 Disease-associated GPR56 mutations cause bilateral frontoparietal polymicrogyria via multiple mechanisms. *J. Biol. Chem.* 286(16): 14215-14225. (SCI, IF=4.125) (corresponding author) [Article featured on *Global Medical Discovery* (www.globalmedicaldiscovery.com)]

4. S. Gordon*, J. Hamann, H.-H. Lin, M. Stacey 2011 Celebrating 30 years: F4/80 and the related adhesion-GPCRs. *Eur. J. Immunol.* 41: 2472-2476 (SCI, IF=4.227) (invited review) (cover page)
5. Y.-M. Peng, Martijn D.B. van de Garde, K.-F. Cheng, P.A. Baars, R.A.W. van Lier, C.R. Mackay, H.-H. Lin*, and J. Hamann* 2011 Specific expression of GPR56 by human cytotoxic lymphocytes. *J. Leukoc. Biol.* 90: 735-740. (SCI, IF=4.018) (co-PI, co-corresponding author). [Article featured on www.MDLinx.com]
6. T.-Y. Chen, T.-L. Hwang, C.-Y. Lin, T.-N. Lin, H.-Y. Lai, W.-P. Tsai, H.-H. Lin* 2011 EMR2 receptor ligation modulates cytokine secretion profiles and cell survival of LPS-treated neutrophil. *Chang Gung Medical Journal* 34(5): 468-477. (corresponding author) (100 年度長庚醫誌優秀論文獎貳獎)
7. H.-H. Lin and S. Gordon 2012 Chapter 1: Macrophage phenotype in tumours. In T. Lawrence and T. Hagemann (eds.) *Tumour-Associated Macrophages*. page 3-16, Springer Science+Business Media, LLC (Invited book chapter).
8. H.-H. Lin* 2012 Adhesion family of G protein-coupled receptors and cancer. *Chang Gung Medical Journal* 35(1): 15-27. (invited review) (corresponding author).
9. Y.-S. Huang, N.-Y. Chiang, C.-H. Hu, C.-C. Hsiao, K.-F. Cheng, W.-P. Tsai, Simon Yona, Martin Stacey, Siamon Gordon, G.-W. Chang* and H.-H. Lin* 2012 Activation of myeloid cell-specific adhesion class G protein-coupled receptor EMR2 via ligation-induced translocation and interaction of receptor subunits in lipid raft microdomains. *Mol. Cell. Biol.* 32(8): 1408-1420 (SCI, IF=4.398) (co-first and co-corresponding author)
10. H.-H. Lin* and M.-L. Kuo 2012 News and Perspectives: The 2011 Nobel Prize in Physiology or Medicine. *Chang Gung Medical Journal* 35(2): 93-95. (invited review) (co-first and co-corresponding author)
11. J. Hamann and H.-H. Lin 2012 "EGF-TM7 receptors", In Gordon, S. (ed.), *Macrophage Heterogeneity and Function*, The Biomedical & Life Sciences Collection, Henry Stewart Talks Ltd, London (online at <http://hstalks.com/?t=BL1473268-Lin>)
12. D. Araç, G. Aust, D. Calebiro, F. B. Engel, C. Formstone, A. Goffinet, J. Hamann, R. J. Kittel, I. Liebscher, H.-H. Lin, K. R. Monk, A. Petrenko, X. Piao, S. Prömel, H. B. Schiöth, T. W. Schwartz, M. Stacey, Y. A. Ushkaryov, M. Wobus, U. Wolfrum, L. Xu, and T. Langenhan 2012 Dissecting signaling and functions of adhesion G protein-coupled receptors. *Ann. N. Y. Acad. Sci.* 1276: 1-25. (SCI, IF=4.706)
13. H.-H. Lin* 2013 Chapter 8, Autoproteolytic cleavage of adhesion-GPCRs at the GPCR proteolysis site: molecular mechanism, structure and functional significance. In Leon V. Berhardt (ed.) *GPCRs: Molecular Pharmacology, Drug Targeting and Signaling Regulation*. *Advances in Medicine and Biology* 60: 199-210. Nova Science Publishers, Inc. (invited book chapter)
14. W.-Y. Tseng, Y.-S. Huang, N.-Y. Chiang, Y.-P. Chou, Y.-J. Jan Wu, S.-F. Luo, C.-F. Kuo, K.-M. Lin, H.-H. Lin* 2013 Increased soluble CD4 in serum of rheumatoid arthritis patients is generated by matrix metalloproteinase (MMP)-like proteinases. *PLoS ONE* 8(5): e63963. (SCI, IF=2.806) (corresponding author)
15. H.-H. Lin* 2013 G protein-coupled receptors and their (bio)chemical significance win 2012 Nobel Prize in Chemistry. *Biomedical Journal* 36(3): 118-124. (corresponding author)
16. C.-C. Hsiao, W.-C. Wang, W.-L. Kuo, H.-Y. Chen, T.-C. Chen, J. Hamann, H.-H. Lin* 2014 CD97 inhibits cell migration in human fibrosarcoma cells by modulating TIMP-2/MT1-MMP/MMP-2 activity. *FEBS Journal* 281(21):4878-91. (doi:10.1111/febs.13027)(SCI, IF=3.902) (corresponding author)
17. I. Liebscher, B. Ackley, D. Araç, D. M. Ariestanti, G. Aust, Byoung-il Bae, B. R. Bista, J. P. Bridges, J. G. Duman, F. B. Engel, S. Giera, A. M. Goffinet, R. A. Hall, J. Hamann, N. Hartmann, Hsi-Hsien Lin, Mingyao Liu, Rong Luo, A. Mogha, K. R. Monk, M. C. Peeters, S. Prömel, S. Ressler, H. B. Schiöth, S. M. Sigoillot, H. Song, W. S. Talbot, G. G. Tall, J. P. White, U. Wolfrum, Lei Xu, and Xianhua Piao 2014 New functions and signaling mechanisms for the class of Adhesion G protein-coupled receptors. *Ann. N. Y. Acad. Sci.* 1333: 43-64. (SCI,

2012

2013

2014

IF=4.706)

- 2015
18. J. Hamann, G. Aust, D. Araç, F. B. Engel, C. Formstone, R. Fredriksson, B. L. Harty, C. Kirchhoff, B. Knapp, A. Krishnan, I. Liebscher, **H.-H. Lin**, D. C. Martinelli, K. R. Monk, M. C. Peeters, X. Piao, S. Prömel, T. Schöneberg, T. W. Schwartz, K. Singer, M. Stacey, Y. A. Ushkaryov, M. Vallon, U. Wolfrum, M. W. Wright, L. Xu, T. Langenhan, H. B. Schiöth 2015 International Union of Basic and Clinical Pharmacology. XCIV. Adhesion G Protein-Coupled Receptors. *Pharmacological Reviews* 67(2):338-367. (SCI, IF=17.893)
 19. T.-Y. Yang, N.-Y. Chiang, W.-Y. Tseng, H.-L. Pan, Y.-M. Peng, J.-J. Shen, K.-A. Wu, M.-L. Kuo, G.-W. Chang, **H.-H. Lin*** 2015 Expression and immunoaffinity purification of recombinant soluble human GPR56 protein for the analysis of GPR56 receptor shedding by ELISA. *Protein Expression and Purification* 109:85-92 (SCI, IF=1.351) (corresponding author)
 20. C.-C. Hsiao[&], K. Keysselt[&], H.-Y. Chen, D. Sittig, J. Hamann, **H.-H. Lin***, G. Aust* 2015 The Adhesion-GPCR CD97/ADGRE5 inhibits apoptosis. *The International Journal of Biochemistry & Cell Biology* 65:197-208 (SCI, IF=3.505) (co-corresponding author)
 21. **H.-H. Lin*** 2015 Tumor-associated adhesion-class G protein-coupled receptors. *Adaptive Medicine* 7(4): 175-185. (invited review) (corresponding author)
- 2016
22. N.-Y. Chiang, G.-W. Chang, Y.-S. Huang, Y.-M. Peng, C.-C. Hsiao, M.-L. Kuo, **H.-H. Lin*** 2016 Heparin interacts with adhesion-GPCR GPR56/ADGRG1, reduces receptor shedding, and promotes cell adhesion and motility. *J. Cell Sci.* 129:2156-2169 (SCI, IF=4.431) (corresponding author)
 23. Cheng-Jang Wu, Chun-Hao Lu, Li-Chen Chen, Duc T. Nguyen, Yi-Shu Huang, **Hsi-Hsien Lin**, Chun-Yen Lin, Ming-Ling Kuo 2016 CD4 down regulation and raft dissociation by the non-depleting YTS177 antibody hinder murine T helper cell activities *Biochemical and Biophysical Research Communications* (accepted) (SCI, IF=2.466).
 24. G.-W. Chang[&], C.-C. Hsiao[&], Y.-M. Peng, F.A. Vieira Braga, N.A.M. Kragten, E.B.M. Remmerswaal, M.D.B. van de Garde, R. Straussberg, G. M. König, E. Kostenis, V. Knäuper, L. Meyaard, René A.W. van Lier, K.P. van Gisbergen, **H.-H. Lin***, J. Hamann* 2016 The adhesion G protein-coupled receptor GPR56/ADGRG1 is an inhibitory receptor on human NK cells. *Cell Reports* 15:1757-1770 (SCI, IF=8.282) (co-corresponding author)(This article was recommended in F1000Prime as being of special significance in its field by F1000 Faculty Member Jacques Zimmer)
<http://f1000.com/prime/726360335?subscriptioncode=6eddd323-c280-496f-bca2-5659f844a6c6>
 25. **H.-H. Lin***, M. Stacey* 2016 G protein-coupled receptors in myeloid cells. *Microbiology Spectrum* Aug. 2016, 4(4) doi:10.1128/microbiolspec. MCHD-0028-2016 (co-corresponding author)
 26. Matthias Nieberler, Robert J. Kittel, Alexander G. Petrenko, **Hsi-Hsien Lin***, Tobias Langenhan* 2016 Control of Adhesion GPCR function through proteolytic processing. (invited chapter) *Handbook of Experimental Pharmacology* 234:83-109 (co-corresponding author)
 27. Jörg Hamann*, Cheng-Chih Hsiao, Kodi Ravichandran, and **Hsi-Hsien Lin*** 2016 Adhesion GPCRs as modulators of immune cell function. (invited chapter) *Handbook of Experimental Pharmacology* 234: 329-350 (co-corresponding author)
 28. Chien-Hao Huang, Wen-Juei Jeng, Yu-Pin Ho, Wei Teng, Yi-Chung Hsieh, Wei-Ting Chen, Yi-Cheng Chen, **Hsi-Hsien Lin**, I-Shyan Sheen, and Chun-Yen Lin 2016 Increased EMR2 expression on neutrophils correlates with disease severity and predicts overall mortality in cirrhotic patients. *Sci. Rep.* 6, 38250; doi: 10.1038/srep38250 (SCI, IF=4.259)
- 2017
29. Nien-Yi Chiang[&], Yen-Ming Peng[&], Horng-Heng Juang, Tse-Ching Chen, Hsiao-Lin Pan, Gin-Wen Chang, **Hsi-Hsien Lin[#]** 2017 GPR56/ADGRG1 activation promotes melanoma cell migration via NTF dissociation and

- CTF-mediated $G\alpha_{12/13}$ /RhoA signaling. *J. Inv. Dermatol.* 137:727-736 (corresponding author) (SCI, IF=6.287)
30. Kuan-Yu I, Yi-Shu Huang, Ching-Hsun Hu, Wen-Yi Tseng, Chia-Hsin Cheng, Martin Stacey, Siamon Gordon, Gin-Wen Chang, **Hsi-Hsien Lin*** 2017 Activation of EMR2/ADGRE2 induces macrophage differentiation and inflammatory responses via $G\alpha_{16}$ /Akt/MAPK/NF- κ B signaling pathways. *Frontiers in Immunology* April 3; 8:373 (corresponding author) (SCI, IF=6.429)
 31. Wen-Yi Tseng, I-Shu Huang, **Hsi-Hsien Lin**, Shue-Fen Luo, Kay McNamee, Felix Clanchy, Richard Williams 2017 TNFR1 and TNFR2 signalling and its clinical implications. *Cytokine* (SCI, IF=3.488) (published online 26 October 2016) (<http://dx.doi.org/10.1016/j.cyto.2016.08.027>)
 32. Wen-Yi Tseng, Yeong-Jian Jan Wu, Tai-Yun Yang, Nien-Yi Chiang, Wen-Pin Tsai, Siamon Gordon, Gin-Wen Chang, Chang-Fu Kuo, Shue-Fen Luo*, **Hsi-Hsien Lin*** 2017 High levels of soluble GPR56/ADGRG1 are associated with positive rheumatoid factor and elevated tumor necrosis factor in patients with rheumatoid arthritis. *Journal of Microbiology, Immunology and Infection* (accepted) (co-corresponding author) (SCI, IF=2.973)
 33. **Hsi-Hsien Lin***, Cheng-Chih Hsiao, Caroline Pabst, Josée Hébert, Torsten Schöneberg and Jörg Hamann* 2017 Adhesion GPCRs in regulating immune responses and inflammation. *Advances in Immunology* (co-corresponding author) (2015 SCI, IF=7.064)
 34. Kuo-An Wu[#], Chih-Ching Wu[#], Chi-De Chen, Chi-Ming Chu, Li-Jane Shih, Yu-Ching Liu, Chia-Jung Yu, **Hsi-Hsien Lin***, Chia-Yu Yang* 2017 Proteome profiling reveals novel biomarkers to identify parapneumonic effusions. *Sci. Rep.* (SCI, IF=4.259) (co-corresponding author)