CV
22 Sep 2023

林倩伶　Chien-Ling Lin, Ph.D.

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Assistant Research Fellow
Institute of Molecular Biology
Academia Sinica, Taipei, Taiwan

EDUCATION

University of Massachusetts Medical School, Worcester, MA, USA 2005-2012
Doctor of Philosophy, Program in Molecular Medicine

University College London, London, United Kingdom 2002-2003
Master of Science, Neuroscience

National Taiwan University, Taipei, Taiwan 1998-2002
Bachelor of Science, Zoology

SCIENTIFIC POSITIONS

Assistant Research Fellow 2017-
Institute of Molecular Biology, Academia Sinica, Taiwan

Jointly Appointed Assistant Professor 2019-
Genome & Systems Biology Degree Program, National Taiwan University, Taiwan

Postdoctoral Research Associate 2012-2016
Brown University, USA

Research Associate 2003-2005
Institute of Biomedical Sciences, Academia Sinica, Taiwan

HONORS & AWARDS

Y. Z. Hsu Science and Technology Paper Award（有庠科技論文獎） 2023
Far Eastern Y. Z. Hsu Foundation, Taiwan

Outstanding Young Scholar Research Grant 2023-2026
National Science and Technology Council, Taiwan

The Young Scholars' Creativity Award（傑出人才基金會年輕學者創新獎） 2020
The Foundation for the Advancement of Outstanding Scholarship, Taiwan

Outstanding Young Scholar Research Grant 2020-2022
Ministry of Science and Technology, Taiwan

Career Development Award, National Health Research Institutes, Taiwan 2020-2023

MOST Talented Scholar Fellowship（科技部延攬特殊優秀人才補助） 2017-2020
Ministry of Science and Technology, Taiwan

Initial Employment Academic Research Grants（中研院新聘學術獎） 2017-2019
Academia Sinica, Taiwan

Oral Presentation Award, Boston Taiwanese Biotechnology Symposium, USA 2016

BioMed Postdoc Travel Award, Brown University, USA 2015

Oral Presentation Award, Boston Taiwanese Biotechnology Symposium, USA 2015

Oral Presentation Award, Boston Taiwanese Biotechnology Symposium, USA 2014

Studying Abroad Scholarship, Ministry of Education, Taiwan 2009

Honorable Award of Poster Exhibit 2007
The 22nd Joint Annual Conference of Biomedical Sciences, Taiwan

Dean's Award for Outstanding Achievement in the Core Curriculum 2006
University of Massachusetts Medical School, USA

Overseas Research Students Awards, Universities UK, United Kingdom 2003

College Student Research Scholarship, National Science Council, Taiwan 2001

Presidential Award, National Taiwan University, Taiwan 1999

PUBLICATIONS

a. research articles

1. Hung-Lun Chiang*, Yi-Ting Chen*, Jia-Ying Su*, Hsin-Nan Lin, Chen-Hsin Albert Yu, Yu-Jen Hung, Yun-Lin Wang, Yen-Tsung Huang and **Chien-Ling Lin**. 2022. Mechanism and modeling of human disease-associated near-exon intronic variants that perturb RNA splicing. ***Nature Structural & Molecular Biology*** 29:1043-1055. (*contributed equally)
2. Hsiao-Jung Kao, Hung-Lun Chiang, Hsiao-Huei Chen, Pi-Chuang Fan, Yi-Fang Tu, Yen-Yin Chou, Wuh-Liang Hwu, **Chien-Ling Lin**, Pui-Yan Kwok and Ni-Chung Lee. 2020. De novo mutation and skewed X-inactivation in girl with BCAP31-related syndrome. ***Human Mutation*** 41:1775-1782.
3. Allison J Taggart*, **Chien-Ling Lin***, Barsha Shrestha, Claire Heintzelman, Seong Won Kim and William G Fairbrother. 2017. Large-scale analysis of branchpoint usage across species and cell lines. ***Genome Research*** 27:639-649. (*contributed equally)
4. Yen-Tsung Huang, Su Chu, Eric B Loucks, **Chien-Ling Lin**, Charles B Eaton, Stephen L Buka and Karl T Kelsey. 2016. Epigenome-wide profiling of DNA methylation in paired samples of adipose tissue and blood. ***Epigenetics*** 11:227-236.
5. **Chien-Ling Lin***, Allison J Taggart*, Kian Huat Lim*, Kamil J Cygan, Luciana Ferraris, Robbert Creton, Yen-Tsung Huang, and William G Fairbrother. 2016. RNA structure replaces the need for U2AF2 in splicing. ***Genome Research*** 26:12-23. (*contributed equally)
6. Yen-Tsung Huang, Thomas Hsu, Karl T. Kelsey and **Chien-Ling Lin**. 2015. Integrative analysis of micro-RNA, gene expression, and survival of glioblastoma multiforme. ***Genet Epidemiol.*** 39:134-143.
7. Moris Nechama, **Chien-Ling Lin** and Joel D. Richter. 2013. An unusual two-step control of CPEB destruction by Pin1. ***Mol Cell Biol.*** 33: 48-58. Correction: 2017. 37: pii:e00220-17.

8. **Chien-Ling Lin**, Yen-Tsung Huang and Joel D. Richter. 2012. Transient CPEB dimerization and translational control. ***RNA*** 18: 1050-1061.
9. **Chien-Ling Lin**, Veronica Evans, Shihao Shen, Yi Xing and Joel D. Richter. 2010. The nuclear experience of CPEB: implications for RNA processing and translational control. ***RNA*** 16: 338-348.
10. Andrew C. Lin, Chin Lik Tan, **Chien-Ling Lin**, Laure Strochlic, Yi-Shuian Huang, Joel D. Richter and Christine E. Holt. 2009. Cytoplasmic polyadenylation and cytoplasmic polyadenylation element-dependent mRNA regulation are involved in *Xenopus* retinal axon development. ***Neural Development*** 4: 8.
11. Shiaw-Wei Tyan, Ming-Chi Tsai, **Chien-Ling Lin**, Yun-Li Ma and Eminy H. Y. Lee. 2008. Serum- and glucocorticoid-inducible kinase 1 enhances zif268 expression through the mediation of SRF and CREB1 associated with spatial memory formation. ***Journal of Neurochemistry*** 105: 820-832.
12. Yi-Shuian Huang*, Ming-Chung Kan*, **Chien-Ling Lin** and Joel D. Richter. 2006. CPEB3 and CPEB4 in neurons: analysis of RNA-binding specificity and translational control of AMPA receptor GluR2 mRNA. ***EMBO Journal*** 25: 4865-4876. (*contributed equally)

b. review articles

1. Rachel Soemedi, Kamil J. Cygan, Christy Rhine, David T. Glidden, Allison J. Taggart, **Chien-Ling Lin**, Alger M. Fredericks, William G. Fairbrother. 2017. The Effects of Structure on pre-mRNA Processing and Stability. ***Methods*** 125:36-44.
2. **Chien-Ling Lin**, Allison J Taggart, William G Fairbrother. 2016. RNA Structure in Splicing: an Evolutionary Perspective. ***RNA Biol.*** 13:766-771.

INVITED ORAL PRESENTATIONS

1. **Mechanism and Prediction of Splicing Errors Caused by Disease-Relevant Mutations.** *2023 Biomedical Research Symposium of National Health Research Institutes, Miaoli, Taiwan.* Aug 2023.
2. **SpliceAPP: Predict Splicing Errors of Human Mutations.** *The 29th Federation of Asian and Oceanian Biochemists and Molecular Biologists Conference & the 2022 Chinese Society of Biochemistry and Molecular Biology Conference. Virtual*. Oct 2022.
3. **SpliceAPP: Predict Splicing Errors of Human Mutations.** *East Area Joint Conference of Biotechnology and Biomedicine, Hualien, Taiwan.* Sep 2022.
4. **Systematic Characterization of Branchsite Mutations Perturbing RNA Splicing.** *Young Scientists' Forum, Philippine Society of Biochemistry and Molecular Biology. Virtual.* Dec 2020.
5. **Systematic Characterization of Branchsite Mutations Perturbing RNA Splicing.** *Department of Biological Science and Technology, National Chiao-Tung University. Hsinchu, Taiwan.* Nov 2020.
6. **Large-Scale Analysis of Branchpoint in Normal and Disease Status.** *AS-Malaysian Universities Academic Symposium. Academia Sinica, Taipei, Taiwan.* June 2019.

7. **Large-Scale Analysis of Branchpoint in Normal and Disease Status.** *Institute of Biomedical Informatics. National Yang Ming Universit*y, Taipei, Taiwan. Dec 2018.
8. **Large-Scale Analysis of Branchpoint in Normal and Disease Status.** *International Symposium Evolutionary Genomics and Bioinformatics. Taiwan Society of Evolution and Computational Biology, Taipei, Taiwan.* Oct 2018.
9. **Large-Scale Analysis of Branchpoint Usage.** *RPAS-NTU Retreat. RNA Program in Academia Sinica. New Taipei City, Taiwan*. Dec 2017.
10. **Genome-Wide Study of RNA processing.** *Student Retreat. Graduate Institute of Life Sciences, Academia Sinica and National Health Research Institutes. New Taipei City, Taiwan.* Aug 2017.
11. **Genome-Wide Study of the Splice Site Recognition in Pre-mRNA Splicing.** *Institute of Cellular and System Medicine, National Health Research Institute. Miaoli, Taiwan.* Feb 2017.
12. **Genome-Wide Study of the Splice Site Recognition in Pre-mRNA Splicing.** *Institute of Molecular and Genomic Medicine, National Health Research Institute. Miaoli, Taiwan.* Feb 2017.
13. **Tangled in Pre-mRNA Splicing: Secondary Structure and Branch Site Selection of Splicing.** *Institute of Biochemistry and Molecular Biology, National Yang-Ming University. Taipei Taiwan.* Feb 2017.
14. **Tangled in Pre-mRNA Splicing: Secondary Structure and Branch Site Selection of Splicing.** *Institute of Molecular Biology, Academia Sinica. Taipei, Taiwan.* Jan 2017.
15. **Genome-Wide Study of the Splice Site Recognition in Pre-mRNA Splicing.** *Graduate Institute of Medical Genomics and Proteomics, National Taiwan University Medical School. Taipei, Taiwan*. Jan 2017.
16. **Genome-Wide Study of the Splice Site Recognition in Pre-mRNA Splicing.** *Genomic Research Center, Academia Sinica. Taipei, Taiwan*. Jan 2017.
17. **Tangled in Pre-mRNA Splicing: Secondary and Lariat Structure in Splicing.** *Institute of Molecular and Cellular Biology, National Taiwan University. Taipei, Taiwan.* Dec 2016.
18. **The Second Life of Intron.** *Boston Taiwanese Biotechnology Symposium. Cambridge, Massachusetts.* July 2016.
19. **Profiling lariats in vivo reveals novel splicing mechanisms.** *Cold Spring Harbor Laboratory meeting on Eukaryotic mRNA Processing. Cold Spring Harbor, New York.* August 2015.
20. **Genome-wide Lariat profiling reveals the Structure and Function of Branched Intermediates of Splicing.** *Boston Taiwanese Biotechnology Symposium. Cambridge, Massachusetts.* June 2015.
21. **An ancient class of structured intron demonstrates a widespread role for dinucleotide repeats in vertebrate gene expression.** *Boston Taiwanese Biotechnology Symposium. Cambridge, Massachusetts.* June 2014.
22. **Profiling intermediates of gene expression in vivo: a novel application of NGS.** *Illumina Rhode Island Sequencing Seminar. Providence, Rhode Island.* June 2014.

SCIENTIFIC REVIEW

- Awards committee of the RNA society for solicitation and evaluation of the awards provided by the RNA society (2022-2025)
- Consulting reviewer for research grant proposals submitted to Ministry of Science and Technology, Taiwan (2019, 2020, 2023)
- Consulting reviewer for Career Development Program of National Taiwan University (2018)
- Consulting reviewer for manuscripts submitted to: *Nature Cancer* (2023), *Cell Reports* (2023), *Gene* (2023), *Nature Structural & Molecular Biology* (2023), *Molecular Cell* (2023), *International Journal of Molecular Science* (2023), *Scientific Report* (2018).
- Scientific poster judge for: The 28th Annual RNA Society International Conference (2023), Graduate School of Molecular and Cellular Biology at National Taiwan University (2018, 2022, 2023), Genome and Systems Biology Degree Program of National Taiwan University and Academia Sinica (2018), RNA Program of Academia Sinica (2017)

Funding over the past five years

Title	Period	Agency	Budget (unit 1,000 NTD)
IMB intramural funding	2017/09–2023/12	IMB	2023: 3,100 2022: 3,100 2021: 3,100 2020: 3,450 2019: 3,450
Investigation of how 5’ UTR alternative splicing fine-tunes gene expression upon neuron differentiation	2023/01-2023/12	IMB Synergistic Pilot Program	650
Decode the Developmental Regulation of Neuronal RNA Splicing and the Splice-Site Mutations in Depression	2022/01–2022/12	IMB Synergistic Pilot Program	620
In Vivo Tagging of Molecular Components Underlying Learning-Induced Novel Synapse Formation	2021/01–2021/12	IMB Synergistic Pilot Program	650
Pervasive Tissue-Specific 5'UTR Exon Skipping Enriches Diversity of Gene Expression	2023/08-2026/07	National Science and Technology Council	2022: 2,550 2021: 2,550 2020: 2,550
Massively Parallel Functional	2020/08-2023/07	Ministry of Science	2022: 1,771

Analysis of Human Disease-Relevant Mutations in mRNA UTRs		and Technology	2021: 1,708 2020: 2,120
Systematic Detection and Functional Restoration of Splicing Mutations of Tuberous Sclerosis Complex	2020/01-2023/12	National Health Research Institute	2023: 1,637 2022: 1,637 2021: 1,674 2020: 1,970
Viral susceptibility induced by insufficient RNA turnover	2018/08-2020/07	Ministry of Science and Technology	2019: 1,350 2018: 1,350

TEACHING EXPERIENCE

Special Topics in Model Organismic Genomics 2019-2023
National Taiwan University Medical School
– RNA-seq and beyond
TIGP Bio Seminar 2021 Fall
Taiwan International Graduate Program_Bioinformatics
Topics and Seminars in Genome and Systems Biology (GenSys5005) 2021 Fall
Genome and Systems Biology Degree Program of National Taiwan University and Academia Sinica
Molecular and Cell Biology 2018-2023
Taiwan International Graduate Program_Molecular and Cell Biology
-- From DNA to RNA
Student Seminar (organizer) 2022-2023
Taiwan International Graduate Program_Molecular and Cell Biology

DEPARTMENT/UNIVERSITY SERVICE

Admission Committee 2019-
Taiwan International Graduate Program_Molecular and Cell Biology, Academia Sinica (2020-)
Graduate School of Department of Life Sciences, National Central University (2020)
Translational Medicine Ph.D. Degree Program, National Yang-Ming University (2020)
Genome and Systems Biology Degree Program, National Taiwan University and Academia Sinica (2019)

Education Program Committee 2018-
Taiwan International Graduate Program_Bioinformatics, Academia Sinica

Bioinformatics Core Committee 2018-
Computer Facility Committee 2018-

Education Committee – Summer Intern Program (Chair 2020) 2018-
Education Committee – Student Affair 2018-
Recreational Activity Committee 2023-
Institute of Molecular Biology, Academia Sinica

CONTRIBUTIONS TO SCIENCE

Gene expression is largely driven by transcription regulation. However, the post-transcriptional regulation fine-tunes the gene expression pattern in almost all biological processes, and therefore needs to be very precisely controlled. My research focus has been on the post-transcriptional regulation at the RNA level, including pre-mRNA splicing, mRNA translational regulation and mRNA stability. The biological and pathological processes I have tackled include early embryonic development and chronic lymphocytic leukemia and glioblastoma survival.

1. Maternal mRNA translational control in early developmental stages

mRNA translational regulation determines the timing and quantity of protein produced. In oocytes, a key RNA-binding protein that silences or activates the translation is cytoplasmic polyadenylation element binding protein 1 (CPEB1). Through its own phosphorylation, it can switch the translation status of its binding mRNAs. Therefore, I have focused on the modification and turnover of CPEB1 protein, and found its dimerization and destruction is critical for tuning the mRNA expression for the oocyte and early embryonic development. Moreover, I found that the nuclear-cytoplasmic shuttling of CPEB1 is critical to convey tight translational control. The study unveiled the mechanism of maternal RNA translational regulation that drives the early embryonic development.

a. Lin CL, Huang YT, Richter JD. Transient CPEB dimerization and translational control. *RNA.* 2012;18(5):1050-61.4.
b. Nechama M, Lin CL, Richter JD. An unusual two-step control of CPEB destruction by Pin1. *Mol Cell Biol.* 2013;33(1):48-58.
c. Lin CL, Evans V, Shen S, Xing Y, Richter JD. The nuclear experience of CPEB: implications for RNA processing and translational control. *RNA*. 2010;16(2):338-48.

2. Modeling sequence determinants of the splicing outcome

Pre-mRNA splicing is a remarkable post-transcriptional regulatory step to remove introns and to ligate exons. Branch site recognition is the first step of splicing reaction and predetermines the splice site. However, little is known about the branch site, because its information is lost with the excised intron right after the splicing reaction. Therefore, I systematically characterized the key element branch site for the splicing site recognition. By analyzing the branch site motifs, I found that base pairing of branch site and U2 small RNA was imperfect and sometimes with frameshift, which explains the degenerative branch site motif in mammals. In addition, as opposed to the generally accepted “A” branchpoint, we found that the “C” branchpoint is predominantly present in small introns. The “C” branchpoint introns are more stable, are transported to the cytoplasm, potentially with significant biological functions (in preparation). My findings demonstrated that branch site recognition determines the splicing outcome in the normal and the disease context.

In spite of the degeneracy of the splicing signal, I was able to establish a predictive model to predict splicing errors of human splicing mutations using high-throughput splicing assays and statistical learning. The model out-competes all available predictive models, including SpliceAI developed by Illumina®. The model is not only highly accurate, but also outputs explanatory splicing determinants. For 3'ss, exon structure as well as splice site competition explains the 3'ss choice, whereas the 5'ss choice largely depends on basepairing with the spliceosome snRNA. We applied the prediction on human health data and successfully identified splicing mutations that associated with aberrant health indices and disease risks. In sum, we provide the most powerful tool to detect splicing errors for precision diagnosis.

a. Taggart AJ*, Lin CL*, Shrestha B, Heintzelman C, Kim S, Fairbrother WG. Large-scale analysis of branchpoint usage across species and cell lines. *Genome Res.* 2017;27(4):639-49.
b. Chiang HL*, Chen YT*, Su JY* et al. Mechanism and modeling of human disease-associated near-exon intronic variants that perturb RNA splicing. *Nat Struct Mol Biol.* 2022;29:1043-1055.

3. RNA structure-mediated pre-mRNA splicing

RNA structures regulate the actual spacing among sequence elements and may provide binding platforms for RNA-binding proteins. RNA secondary structure has been reported to be a regulation target of pre-mRNA splicing. However, no genome-wide structural determinants for splicing has been reported prior to our study. Through comparative genomics, we identified an evolutionarily conserved long complementary runs of AC and GT repeats co-occurring at two ends of zebrafish introns. In human, similar stable intronic secondary structure is produced by complementary GGG and CCC repeats at 5' and 3' end of the introns, respectively. In addition, intronic structure is positively associated with the density of the single nucleotide polymorphisms of the neighboring exons, suggesting that the secondary structure could rescue the loss of splicing element in the exons. Furthermore, disruption of structures can lead to splicing defects and disease outcomes. These observations support that secondary structure has a critical biological function for RNA processing and the loss of its accuracy is pathogenic.

a. Lin CL*, Taggart AJ*, Lim KH* et al. RNA structure replaces the need for U2AF2 in splicing. *Genome Res.* 2016;26(1):12-23.
b. Lin CL, Taggart AJ, Fairbrother WG. RNA structure in splicing: An evolutionary perspective. *RNA Biol.* 2016;13(9):766-71.
c. Soemedi R, Cygan KJ, Rhine CL, Glidden DT, Taggart AJ, Lin CL et al. The effects of structure on pre-mRNA processing and stability. *Methods.* 2017;125:36-44.