BIOGRAPHICAL SKETCH

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NAME: Cheng-Ming Chiang

eRA COMMONS USER NAME (credential, e.g., agency login): cheng_ming_chiang

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
National Taiwan University (Taiwan, R.O.C.)	B.S.	1980-1984	Chemistry & Biology
University of Rochester (Rochester, NY)	Ph.D.	1987-1991	Biochemistry & Virology
University of Rochester (Rochester, NY)	Postdoc	1991-1992	Biochemistry & Virology
Rockefeller University (New York, NY)	Postdoc	1992-1995	Biochemistry & Mol. Biol.

A. Personal Statement

I am currently a Professor of Biochemistry and Pharmacology in the Simmons Comprehensive Cancer Center at the University of Texas Southwestern Medical Center. My research interests focus primarily on eukaryotic transcription, gene regulation, chromatin dynamics, epigenetics, post-translational modification, and molecular virology with biochemical, molecular biological, genetics, genomics, proteomics, and chemical biology approaches to address the fundamental mechanisms of human papillomavirus (HPV) gene regulation and genome replication. Using *in vitro*-reconstituted HPV chromatin transcription systems that faithfully recapitulate nucleosome phasing *in vivo* and biochemical fractionation of nuclear protein complexes, we identified human bromodomain-containing protein 4 (BRD4) as the long-sought cellular cofactor critical for HPV-encoded E2 repressor function in inhibiting HPV E6 and E7 oncogene expression (*Genes Dev*. 20: 2383-2396, 2006). Since then, we have continued to analyze the molecular action of BRD4 in HPV transcription and DNA replication, as well as virus-independent BRD4 involvement in various biological systems during normal developmental processes, cell fate decision and lineage commitment, and perturbed physiological and pathological conditions including keratinocyte differentiation, heart dysfunction, and cancer initiation and progression. Our finding that phosphorylation of BRD4 plays a key role in chromatin targeting and functional coregulation with DNA-binding proteins and chromatin regulators (*Mol. Cell* 49: 843-857, 2013) led to subsequent uncovering of phospho-BRD4 as a biomarker for triple-negative breast cancer progression (*Nature* 529: 413-417, 2016; *Cancers* 13: 1246, 2021), cognition in brain learning and memory (*Sci. Adv.* 7: eabf4376, 2021), drug addiction, and formation of phase-separated nuclear condensates modulating enhancer-driven compartmentalization to dictate chromatin dynamics. Our recent elucidation of opposing functions of BRD4 protein isoforms in breast cancer using cell-based systems, xenograft and knock-in transgenic mouse models, and genome-wide transcriptome profiling, DNA-binding, and chromatin association further highlights the importance of biological control by BRD4 protein isoforms, interactome switches, network rewiring, enhancer landscaping, and post-translational modification (*Mol. Cell* 78: 1114-1132, 2020). My goal in this application is to define the role of BRD4 long (L) and short (S) isoforms and two newly identified phospho-BRD4-targeting compounds (**14** and **90**) in breast cancer brain metastasis. With decades-long research in various scientific disciplines and review panel experiences, I have the confidence to lead the project and complete the experiments within the proposed timeframe.

Ongoing Research Projects:

NIH 1RO1CA251698-01 Chiang (PI) 06/01/20 – 05/31/25
"Opposing Functions of BRD4 Isoforms in Breast Cancer"
The goals of this proposal are: 1) To define the biological role of BRD4-L and BRD4-S in different breast cancer cells and mouse models; 2) To elucidate the mechanistic action of BRD4 isoforms and their coregulators in breast cancer subtypes; and 3) To identify gene targets and pathways uniquely and commonly regulated by BRD4 isoforms.

Role: PI

Completed:

Texas CPRIT Grant # RP190077 Chiang (PI) 03/01/19 – 08/31/22
"Molecular Action of Phospho-BRD4-Targeting Compounds in Breast Cancer"
The goals of this proposal are: 1) To define the action of phospho-BRD4-targeting compounds in cultured breast cancer cells; and 2) To evaluate the anticancer potency of phospho-BRD4-targeting compounds in mouse models and patient-derived xenografts (PDXs).
Role: PI

Texas CPRIT Grant # RP180349 Chiang (PI) 03/01/18 – 08/31/21
"Therapeutics Targeting Cancer-Associated HPV Replication"
The goals of this proposal are: 1) To refine hit compounds inhibiting HPV replication via analog analysis and chemical modification; 2) To identify compound targets by cellular, biochemical, molecular, and structural approaches; and 3) To evaluate biological effects of compound inhibition using epithelial cell differentiation systems.
Role: PI

Citations:

1. Lewis, M., S.-Y. Wu, and C.-M. Chiang. 2022. Conditional human BRD4 knock-in transgenic mouse genotyping and protein isoform detection. ***Bio-protocol*** 12: e4374. PMID: 35530522
2. Tang, P., J. Zhang, J. Liu, C.-M. Chiang*, and L. Ouyang*. 2021. Targeting bromodomain-containing protein 4 for drug discovery: from current progress to technological development. ***J. Med. Chem.*** 64: 2419-2435. (**Chiang and Ouyang, co-corresponding authors*) PMID: 33616410
3. Wu, S.-Y., C.F. Lee, H.T. Lai, C.T. Yu, J.E. Lee, H. Zuo, S.Y. Tsai, M.J. Tsai, K. Ge, Y. Wan, and C.-M. Chiang. 2020. Opposing functions of BRD4 isoforms in breast cancer. ***Molecular Cell*** 78: 1114-1132. PMID: 32446320
4. Iftner, T., J. Haedicke-Jarboui, S.-Y. Wu, and C.-M. Chiang. 2017. Involvement of Brd4 in different steps of the papillomavirus life cycle. ***Virus Res.*** 231: 76-82. PMID: 27965149

B. Positions, Scientific Appointments, and Honors

Positions:

7/2007-present	Professor, Simmons Comprehensive Cancer Center, Department of Pharmacology and Department of Biochemistry, University of Texas Southwestern Medical Center at Dallas
8/2000-6/2007	Associate Professor, Department of Biochemistry, Case Western Reserve University, Ohio
8/1995-8/2000	Assistant Professor, Department of Biochemistry, University of Illinois at Urbana-Champaign

Scientific Appointments:

NIH Virtual intramural site visit review of NCI's Experimental Immunology Branch (September 13-15, 2023)

Pew Biomedical Scholars National Advisory Committee (May 19, 2021 - present)

Faculty of 1000 (Faculty Opinions), Control of Gene Expression, Faculty Member (January 19, 2004 - present)

NIH 2023/05 ZCA1 PCRB-9 (M1) S "R13 NIH Support for Scientific Conferences (PA-21-151)" Special Emphasis Panel (March 7, 2023)

Journal of Biological Chemistry, Editorial Board Member (3 terms) – 2003-2008, 2010-2015, 2017-2022

DoD CDMRP Breast Cancer Research Program Cell Biology-6 Peer Review Panel (Nov 30-Dec 1, 2021)

DoD CDMRP Breast Cancer Research Program Cell Biology-9 Peer Review Panel (December 3-4, 2020)

NIH 2020/05 HIV-Associated Malignancy Research Special Emphasis Panel (March 26-27, 2020)

NIH 2020/01 ZDE1 GZ (13) R NIDCR RFA-20-001 "Oral Health in People Living with HIV and Additional Non-Communicable Diseases" Special Emphasis Panel (November 14, 2019)

External Advisory Committee (EAC) Member, Louisiana State University Health Sciences Center at Shreveport, Center for Molecular and Tumor Virology (July 2014 - 2019)

NIH ZCA1 RPRB-L (J1) P NCI Program Project III (PO1) Special Emphasis Panel (October 17-18, 2017)

NIH ZCA1 RTRB-R (M2) R NCI Collaborative Consortia for the Study of HIV-Associated Cancers (U54) Special Emphasis Panel (April 5-6, 2017)

NIH ZCA1 RPRB-N (J1) P NCI Program Project Review III (PO1) Review Committee (October 13-14, 2016)

NIH NIDCR Award for Sustaining Outstanding Achievement in Research (SOAR) R35 SEP (June 8, 2016)

NIH ZCA1 SRB-L (M1) 1 NCI RO3 & R21 Omnibus SEP-6 Special Emphasis Panel (March 7-8, 2016)

NIH ZCA1 SRB-L (J1) S NCI RO3 & R21 Omnibus SEP-6 Special Emphasis Panel (Oct 8-9, 2015)

NIH ZRG1 IDM-V (55) R Detection of Pathogen Induced Cancer Special Emphasis Panel (Oct 28, 2014)

NIH AIDS-associated Opportunistic Infections and Cancer (AOIC) Study Section (July 11, 2014)

Taiwan National Health Research Institutes Scientific Review Committee 3 Study Section (July 5-8, 2014)

NIH ZCA1 RPRB-O (M2) S NCI Cooperative Agreement (U54) Special Emphasis Panel (May 8-9, 2014)

NIH AIDS-associated Opportunistic Infections and Cancer (AOIC) Study Section (November 21, 2013)

NIH ZDE1 RK(18)1 Epigenomics of Virus-Associated Oral Diseases Special Emp. Panel (June 18-19, 2013)

NIH ZCA1 RTRB-Z(M1)R Omnibus R03/R21 – Therapeutics Special Emphasis Panel (Feb. 27-28, 2013)

International Human Frontier Science Program, Research Grant Review Committee (2009-2013)

NIH Virology - B (VIRB) Study Section, Regular Member (July 1, 2007 - June 30, 2011)

International Human Frontier Science Program, Research Grant Letter of Intent Selection Committee (2010)

ACS Genetic Mechanisms in Cancer (GMC) Study Section, Atlanta, Regular Member (2007-2010)

NIH ZRG1 OBT-H(02)S Oncology 1 – Basic and Translational Special Emphasis Panel (October 13, 2009)

American Association for the Advancement of Science (AAAS), Grant Review Panel for the King Abdulaziz City for Science and Technology (KACST) in Saudi Arabia (March 24, 2009)

Honors:

Yushan Scholar awarded by the Ministry of Education, Taiwan, 2019

Recipient of 2019 F1000 Faculty (now Faculty Opinions) Member of the Year Award for Cell Biology

Recipient of 2018 F1000 Faculty (now Faculty Opinions) Member of the Year Award for Cell Biology

Recipient of 2017 F1000 Faculty (now Faculty Opinions) Member of the Year Award for Cell Biology

Mt. Sinai Health Care Foundation Scholar, 2000-2004

The Pew Scholar in the Biomedical Sciences, 1996-2000

The Helen Hay Whitney Foundation Postdoctoral Fellow, 1993-1995

The Aaron Diamond Foundation Postdoctoral Fellow, 1993-1995

The Wallace O. Fenn Award, University of Rochester, 1991 (best Ph.D. thesis within the Medical Center)

The Walter Bloor Award, University of Rochester, 1991 (best Ph.D. thesis within the Biochemistry Dept.)

C. Contributions to Science

1. Development of FLAG Epitope Tagging Technology for Protein Complex Purification

Purification of recombinant proteins and multisubunit protein complexes has been a challenge for most investigators worldwide. In the early 1990s, I pioneered FLAG epitope tagging for covalent linkage to a protein-coding sequence and developed an effective peptide elution method for purifying FLAG-tagged recombinant human general transcription factors, including TBP, TFIIB, TFIIEα, and TFIIEβ, from bacteria (Ref. 1a). The success of this methodology prompted me to generate stable human HeLa cell lines constitutively expressing FLAG-tagged human TBP for purification of naturally assembled protein complexes, such as TFIID and TFIIIB, from human cells (Ref. 1b). In addition to constitutive expression of a FLAG-tagged subunit of a large protein complex, my lab also developed an inducible expression system based on the availability of tetracycline to bypass cytotoxicity caused by constitutive expression of a potentially toxic protein, thus allowing purification of FLAG-tagged human TFIIH and RNA polymerase II with differential phosphorylation states at its largest subunit RPB1 (Ref. 1c). Since many recombinant proteins become insoluble when overexpressed in bacteria or lacking an interacting partner, my lab further developed a FLAG tag- and hexahistidine-based coexpression system for purification of dimeric human transcription factors, such as the c-Jun/c-Fos AP-1 complex, from insoluble bacterial inclusion bodies (Ref. 1d). Our decades-long efforts in the development of FLAG tag technology have

made it possible for purification of large protein complexes from any cell line and organism and have greatly facilitated proteomic analysis of interaction networks commonly used in the scientific community these days.

1a. Chiang, C.-M. and R.G. Roeder. 1993. Expression and purification of general transcription factors by FLAG epitope-tagging and peptide elution. ***Peptide Res.*** 6: 62-64. PMID: 7683509

1b. Chiang, C.-M., H. Ge, Z. Wang, A. Hoffmann, and R.G. Roeder. 1993. Unique TATA-binding protein-containing complexes and cofactors involved in transcription by RNA polymerases II and III. ***EMBO J.*** 12: 2749-2762. PMID: 7687540 PMCID: PMC413525

1c. Kershnar, E., S.-Y. Wu, and C.-M. Chiang. 1998. Immunoaffinity purification and functional characterization of human transcription factor IIH and RNA polymerase II from clonal cell lines that conditionally express epitope-tagged subunits of the multiprotein complexes. ***J. Biol. Chem.*** 273: 34444-34453. PMID: 9852112

1d. Wang, W.-M., A-Y. Lee, and C.-M. Chiang. 2008. One-step affinity tag purification of full-length recombinant human AP-1 complexes from bacterial inclusion bodies using a polycistronic expression system. ***Protein Expr. Purif.*** 59: 144-152. PMID: 18329890 PMCID: PMC2354920

2. In Vitro Reconstitution of the General Transcription Machinery

Our ability to purify essentially any protein and complex from prokaryotes and eukaryotes contributes not only to the cloning of cDNAs encoding components of the general transcription machinery, such as the TBP-associated factors (TAFs) in human TFIID (Ref. 2a), but also allows *in vitro* reconstitution of the entire transcription event with only recombinant general transcription factors (GTFs) and highly purified FLAG-tagged multiprotein complexes, making it possible for functional dissection of every GTF, including TAFs, during the recruitment process of basal and activator-dependent transcription (Ref. 2b). Other than defining the roles of TAFs in TFIID and the general transcription positive cofactor 4 (PC4), we further purified different forms of human Mediator complexes and elucidated the functional redundancy and unique properties of these three human general transcription cofactors (i.e., TFIID, Mediator, and PC4; Ref. 2c). A comprehensive review of the human general transcription machinery and general cofactors written by my former graduate student (Mary Thomas) and myself in 2006 has been a highly cited publication in the transcription field (Ref. 2d).

2a. Chiang, C.-M. and R.G. Roeder. 1995. Cloning of an intrinsic human TFIID subunit that interacts with multiple transcriptional activators. ***Science*** 267: 531-536. PMID: 7824954

2b. Wu, S.-Y., E. Kershnar, and C.-M. Chiang. 1998. TAF_{II}-independent activation mediated by human TBP in the presence of the positive cofactor PC4. ***EMBO J.*** 17: 4478-4490. PMID: 9687514 PMCID: PMC1170779

2c. Wu, S.-Y., T. Zhou, and C.-M. Chiang. 2003. Human Mediator enhances activator-facilitated recruitment of RNA polymerase II and promoter recognition by TATA-binding protein (TBP) independently of TBP-associated factors. ***Mol. Cell. Biol.*** 23: 6229-6242. PMID: 12917344 PMCID: PMC180944

2d. Thomas, M.C. and C.-M. Chiang. 2006. The general transcription machinery and general cofactors. ***Critical Reviews in Biochemistry and Molecular Biology*** 41: 105-178. PMID: 16858867

3. Mechanistic Studies of HPV Chromatin-Dependent Transcription and Gene Regulation

My training in the molecular study of human papillomaviruses (HPVs), particularly the pioneering discovery of HPV-encoded E1 and E2 proteins in viral DNA replication (Ref. 3a), and my expertise in biochemical analysis of human transcription factors allow me to make unique contributions to HPV biology, especially in the area of transcriptional regulation. We identified the mechanism by which HPV E2 protein inhibits transcription preinitiation complex assembly (Ref. 3b) and, most importantly, developed the first *in vitro*-assembled HPV minichromosome that faithfully recapitulates *in vivo* nucleosome phasing, leading to the discovery of bromodomain-containing protein 4 (BRD4) as the cellular factor critical for E2-mediated inhibition of HPV transcription (Ref. 3c). Recently, we have illustrated the mechanistic action of BRD4 phosphorylation in viral and cellular gene transcription, as well as in controlling E2-driven HPV *origin* replication, and further developed phospho-BRD4-binding peptoids that are more selective than bromodomain and extra-terminal domain (BET) inhibitors in defining the function of BRD4 phosphorylation in gene regulation and chromatin dynamics (Ref. 3d).

3a. Chiang, C.-M., M. Ustav, A. Stenlund, T.F. Ho, T.R. Broker, and L.T. Chow. 1992. Viral E1 and E2 proteins support replication of homologous and heterologous papillomaviral origins. ***Proc. Natl. Acad. Sci. USA*** 89: 5799-5803. PMID: 1321423 PMCID: PMC402105

3b. Hou, S.Y., S.-Y. Wu, T. Zhou, M.C. Thomas, and C.-M. Chiang. 2000. Alleviation of human papillomavirus E2-mediated transcriptional repression via formation of a TATA binding protein (or TFIID)-TFIIB-RNA polymerase II-TFIIF preinitiation complex. ***Mol. Cell. Biol.*** 20: 113-125. PMID: 10594014 PMCID: PMC85067

3c. Wu, S.-Y., A.Y. Lee, S.Y. Hou, J.K. Kemper, H. Erdjument-Bromage, P. Tempst, and C.-M. Chiang. 2006. Brd4 links chromatin targeting to HPV transcriptional silencing. ***Genes Dev.*** 20: 2383-2396. PMID: 16921027 PMCID: PMC1560413

3d. Wu, S.-Y., D.S. Nin, A-Y. Lee, S. Simanski, T. Kodadek, and C.-M. Chiang. 2016. BRD4 phosphorylation regulates HPV E2-mediated viral transcription, origin replication, and cellular *MMP-9* expression. ***Cell Reports*** 16: 1733-1748. PMID: 27477287 PMCID: PMC4981545

4. Covalent Modification-Regulated p53 Function in Normal and Cancer Cells

To elucidate the tumor suppressor function of p53 that is inactivated by HPV-encoded E6 oncoprotein, we discovered an epigenetic mechanism by which E6 suppresses p53-dependent target gene transcription through inhibiting p300 histone acetyltransferase-mediated acetylation of p53 and nucleosomal histones, which occurs independently of the E6-induced p53 degradation pathway that is well recognized in both ubiquitin and HPV fields (Ref. 4a). Via the use of *in vitro*-reconstituted enzymatic assays developed in my lab with only recombinant human proteins, we defined unambiguously the biochemical pathways in which sumoylation and acetylation regulate p53 transcription and chromatin-binding activity (Ref. 4b). This helps resolve many unanswered questions regarding the functional role of sumoylation and acetylation in regulating the transcription and tumor suppressor function of p53 in normal and cancer cells (Ref. 4c). Other types of post-translational modifications, such as phosphorylation and methylation, also play important roles in regulating p53 function through cell cycle progression and in maintaining genomic stability (Ref. 4d).

4a. Thomas, M.C. and C.-M. Chiang. 2005. E6 oncoprotein represses p53-dependent gene activation via inhibition of protein acetylation independently of inducing p53 degradation. ***Molecular Cell*** 17: 251-264. PMID: 15664194
4b. Wu, S.-Y. and C.-M. Chiang. 2009. Crosstalk between acetylation and sumoylation in regulating p53-dependent chromatin transcription and DNA binding. ***EMBO J.*** 28: 1246-1259. PMID: 19339993 PMCID: PMC2683057
4c. Wu, S.-Y. and C.-M. Chiang. 2009. p53 sumoylation: mechanistic insights from reconstitution studies. ***Epigenetics*** 4: 445-451. PMID: 19838051 PMCID: PMC4749140
4d. Chiang, C.-M. 2012. p53-Aurora A mitotic feedback loop regulates cell cycle progression and genomic stability. ***Cell Cycle*** 11: 3719-3720. PMID: 22982999 PMCID: PMC3495809

5. Elucidation of BRD4 Function in Gene-Specific Targeting and Cancer Therapeutics

Our finding of BRD4 as a crucial regulator inhibiting E2-mediated HPV transcription prompted our interest in understanding the molecular action of BRD4 as a universal epigenetic reader protein in regulating pathway-specific gene transcription. A mini-review written by Dr. Shwu-Yuan Wu and myself in 2007 that proposes a model for BRD4 involvement in gene targeting and factor recruitment, while establishing an indisputable role of BRD4 and its related BET family proteins (BRD2 and BRD3) in transcriptional regulation, has been highly cited by most investigators working on the BET family proteins (Ref. 5a). Our demonstration of BRD4 in enhancing DNA-binding proteins, such as HPV E2, binding stably to their chromatin target sites illustrates the importance of BRD4 in recruiting gene-specific targeting factors (Ref. 5b). With an unbiased screen of over 100 purified candidate proteins for their potential interaction with BRD4, we discovered direct BRD4 association with G9a histone methyltransferase, ACF chromatin remodeler, and many DNA-binding transcription factors, including p53, YY1, c-Jun, c-Myc/Max complex, C/EBPα, and C/EBPβ (Ref. 5c). Intriguingly, we identified two evolutionarily conserved domains in BRD4 whose selective contacts with bromodomains are regulated by CK2-mediated phosphorylation that triggers BRD4 binding to acetylated chromatin as well as recruitment of DNA-binding proteins such as p53, providing a molecular mechanism accounting for the gene-specific targeting activity of BRD4 (Ref. 5c). In addition to post-translational modification, the switching between BRD4 protein isoforms also plays an important role in cell fate decision and cancer progression (Ref. 5d).

5a. Wu, S.-Y. and C.-M. Chiang. 2007. The double bromodomain-containing chromatin adaptor Brd4 and transcriptional regulation. ***J. Biol. Chem.*** 282: 13141-13145. PMID: 17329240
5b. Lee, A-Y. and C.-M. Chiang. 2009. Chromatin adaptor Brd4 modulates E2 transcription activity and protein stability. ***J. Biol. Chem.*** 284: 2778-2786. PMID: 19038968 PMCID: PMC2631962
5c. Wu, S.-Y., A-Y. Lee, H.-T. Lai, H. Zhang, and C.-M. Chiang. 2013. Phospho switch triggers Brd4 chromatin binding and activator recruitment for gene-specific targeting. ***Molecular Cell*** 49: 843-857. PMID: 23317504 PMCID: PMC3595396
5d. Wu, S.-Y., C.F. Lee, H.T. Lai, C.T. Yu, J.E. Lee, H. Zuo, S.Y. Tsai, M.J. Tsai, K. Ge, Y. Wan, and C.-M. Chiang. 2020. Opposing functions of BRD4 isoforms in breast cancer. ***Molecular Cell*** 78: 1114-1132. PMID: 32446320

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