BIOGRAPHICAL SKETCH

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NAME: Chang, Ching-Wen

eRA COMMONS USER NAME (credential, e.g., agency login): CHC435

POSITION TITLE: Supervisor Research Assistant Member in Infectious Diseases

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
Da-Yen University, Taiwan	B.A.	06/1999	Food Engineering
National Chung-Hsing University, Taiwan	M.Sc	07/2001	Biochemistry
National Taiwan University, Taiwan	Ph.D.	07/2011	Biochemical Science
McGill University	Fellow	06/2016	Stem Cell Biology
University of California San Diego	Postdoc	08/2018	Placental Biology
Michigan State University	Postdoc	08/2020	Stem Cell Biology
UMass Chan Medical School	Instructor	08/20/2022	Infectious Diseases

A. Personal Statement

For the past four years, I have dedicated my efforts to the development of novel cellular tools to support antiviral discovery and disease research. To date, I have established several human cell-based infection models and assays that enable the rapid assessment of compound efficacy, facilitating early "GO/NO GO" decisions in antiviral drug development. To promote broader access to these tools, I have deposited them in the non-profit public repository, ATCC. Additionally, I regularly share my expertise with external laboratories, as I believe the true value of our tools lies in the research, they enable rather than solely in individual publications.

I am also deeply committed to educating the next generation of scientists and have actively mentored students and postdoctoral fellows throughout my academic career. Several of my mentees have successfully progressed to top graduate programs or continued their research at UMass Chan Medical School. As a junior faculty member at the Hackensack Meridian Health Center for Discovery and Innovation, I have channeled my passion for tool development into creating innovative cellular systems for antiviral drug discovery. Although this represents a shift from my previous research focus, we have already produced five manuscripts—three published, one under revision, and a fourth slated for submission next month as well as filed one patent application in October, 2024.

My background includes studying human disease models during my graduate studies, characterizing the biochemical activities of factors in the cAMP pathway, researching stem cell development and mechanisms during my postdoctoral training, and developing novel siRNA tools and cell models for the rapid advancement of pan-viral therapeutics as an instructor. This diverse experience uniquely positions me to pursue an interdisciplinary research agenda aimed at accelerating scientific progress through innovative technologies, while simultaneously applying these tools to develop novel therapeutics.

Ongoing and recently completed projects relevant to this proposal:

Metropolitan AntiViral Drug Accelerator (MAVDA, U19AI171401) 05/31/2022-05/31/2025
Project leaders: David Perlin, Ph.D.; Charles Rice, Ph.D.
Institute: Hackensack University Medical Center; The Rockefeller University
Role: Virology Core coordinator

Ferring COVID-19 Investigational Grants in Reproductive Medicine (completed) 07/01/2021-07/01/2022
Role: PI

Citations
Meyer C, Garcia A, Miller M, Huggins D, Myers R, Hoffmann HH, Ashbrook A, Jannath S, Liverton N, Kargman S, Zimmerman M, Nelson A, Sharma V, Cangialosi J, Penalva-Lopez S, Ramos-Espiritu L, Menezes MR, Larson C, Nitsche J, Alwaseem H, Molina H, Steinbacher S, Glickman JF, Perlin D, Rice C, Meinke P, Dolgov E, Alvarez N, **Chang CW**, Oswal N, Jimenez IG, Rasheed R, Goldgirsh K, Davis J, Ganichkin O, Tuschl T. Small-molecule inhibition of SARS-CoV-2 NSP14 RNA cap methyltransferase. Nature. Accepted on Oct 31, 2024.

Hariharan VN*, Shin M*, **Chang CW***, O'Reilly D, Biscans A, Yamada K, Guo Z, Somasundaran M, Tang Q, Monopoli K, Krishnamurthy PM, Devi G, McHugh N, Cooper DA, Echeverria D, Cruz J, Chan IL, Liu P, Lim SY, McConnell J, Singh SP, Hildebrand S, Sousa J, Davis SM, Kennedy Z, Ferguson C, Godinho BMDC, Thillier Y, Caiazzi J, Ly S, Muhuri M, Kelly K, Humphries F, Cousineau A, Parsi KM, Li Q, Wang Y, Maehr R, Gao G, Korkin D, McDougall WM, Finberg RW, Fitzgerald KA, Wang JP, Watts JK, Khvorova A. Divalent siRNAs are bioavailable in the lung and efficiently block SARS-CoV-2 infection. Proc Natl Acad Sci U S A. 2023 Mar 14;120(11):e2219523120 (*co-first author)

Chang CW, Parsi KM, Somasundaran M, Vanderleeden E, Liu P, Cruz J, Cousineau A, Finberg RW, Kurt-Jones EA. A Newly Engineered A549 Cell Line Expressing ACE2 and TMPRSS2 Is Highly Permissive to SARS-CoV-2, Including the Delta and Omicron Variants. Viruses. 2022 Jun 23;14(7):1369.

Chang CW, Wakeland AK, Parast MM. Trophoblast lineage specification, differentiation and their regulation by oxygen tension. J Endocrinol. 2018 Jan;236(1):R43-R56.

B. Positions, Scientific Appointments, and Honors

2022-	Faculty Member in Infectious Diseases, Center for Discovery and Innovation (CDI)
2022-	Guest Investigator, Infectious Disease, Rockefeller University
2022-	Associate Research Scientist, Aaron Diamond AIDS Research Center, Columbia University
2022-	MAVDA Virology Core Coordinator (CDI, Rockefeller University, Columbia University)
2020-2022	Instructor, Department of Medicine, UMass Chan Medical School
2018-2020	Staff Scientist, Animal Sciences, Michigan State University
2016-2018	Postdoctoral Fellow, Pathology, UCSD
2013-2016	Postdoctoral Fellow, Medicine, McGill University
2015-2016	Desjardins Studentship Award in Child Health Research, Canada
2011-2013	Postdoctoral trainee, Institute of Biological Chemistry, Academia Sinica, Taiwan
2011-2013	Academia Sinica Postdoctoral Fellowship Award, Taiwan

C. Contributions to Science
1. Discovery of fully chemically stabilized siRNAs that target regions of the SARS-CoV-2 genome conserved in all variants of concern. The continuous evolution of SARS-CoV-2 variants complicates efforts to combat the ongoing pandemic, underscoring the need for a dynamic platform for the rapid development of pan-viral variant therapeutics. Oligonucleotide therapeutics are enhancing the treatment of numerous diseases with unprecedented potency, duration of effect, and safety. Through the systematic screening of hundreds of oligonucleotide sequences, we identified fully chemically stabilized siRNAs and ASOs that target regions of the SARS-CoV-2 genome conserved in all variants of concern, including delta and omicron. We successively evaluated candidates in cellular assays, followed by viral inhibition in cell culture, with eventual testing of leads for in vivo antiviral activity in the lung (#Hariharan, #Shin, and #Chang et al. PNAS. 2023). In recently published work, we also report the generation of a suitable human cell line for SARS-CoV-2 studies by transducing human ACE2 and TMPRSS2 into A549 cells. We show that subclones highly expressing ACE2 and TMPRSS2 are susceptible to infection with SARS-CoV-2, including omicron variants. These subclones express more ACE2 and TMPRSS2 transcripts than existing commercial A549 cells engineered to express ACE2 and TMPRSS2. Additionally, the antiviral drugs EIDD-1931, remdesivir, nirmatrelvir, and nelfinavir strongly inhibit SARS-CoV-2 variants in our infection model (*#Chang and #Parsi et al. Viruses. 2022).

a. Hariharan VN, Shin M, **Chang CW**, O'Reilly D, Biscans A, Yamada K, Guo Z, Somasundaran M, Tang Q, Monopoli K, Krishnamurthy PM, Devi G, McHugh N, Cooper DA, Echeverria D, Cruz J, Chan IL, Liu P, Lim SY, McConnell J, Singh SP, Hildebrand S, Sousa J, Davis SM, Kennedy Z, Ferguson C, Godinho BMDC, Thillier Y, Caiazzi J, Ly S, Muhuri M, Kelly K, Humphries F, Cousineau A, Parsi KM, Li Q, Wang Y, Maehr R, Gao G, Korkin D, McDougall WM, Finberg RW, Fitzgerald KA, Wang JP, Watts JK, Khvorova A. Divalent siRNAs are bioavailable in the lung and efficiently block SARS-CoV-2 infection. Proc Natl Acad Sci U S A. 2023 Mar 14;120(11):e2219523120
b. **Chang CW**, Parsi KM, Somasundaran M, Vanderleeden E, Liu P, Cruz J, Cousineau A, Finberg RW, Kurt-Jones EA. A Newly Engineered A549 Cell Line Expressing ACE2 and TMPRSS2 Is Highly Permissive to SARS-CoV-2, Including the Delta and Omicron Variants. Viruses. 2022 Jun 23;14(7):1369.

2. Human trophoblast stem cell differentiation and regulation. Proper formation and function of the placenta is required for normal fetal growth and development in utero. Early development of the human placenta occurs under low oxygen conditions. One major mechanism by which oxygen regulates cellular function is through the hypoxia-inducible factor (HIF), a transcription factor complex stabilized under low oxygen tension. HIF is known to play a role in trophoblast differentiation in rodents; however, its role in human trophoblast differentiation has been poorly understood. I and former colleagues at University of California, San Diego (UCSD), investigated this important medical issue. Using RNA profiling of sorted populations of primary first-trimester trophoblasts, I and colleagues evaluated the first stage of extravillous trophoblast (EVT) differentiation. We discovered that oxygen regulates EVT differentiation through HIF-dependent modulation of various cell adhesion and morphology-related pathways.

a. **Chang CW**, Wakeland AK, Parast MM. Trophoblast lineage specification, differentiation and their regulation by oxygen tension. J Endocrinol. 2018 Jan;236(1):R43-R56.
b. Wakeland AK, Soncin F, Moretto-Zita M, **Chang CW**, Horii M, Pizzo D, Nelson KK, Laurent LC, Parast MM. Hypoxia Directs Human Extravillous Trophoblast Differentiation in a Hypoxia-Inducible Factor-Dependent Manner. Am J Pathol. 2017 Apr;187(4):767-780.

3. The molecular mechanisms involved in the regulation of GCM1 activity in human placenta. I started my reproductive biology research in Taiwan. I and former colleagues discovered and characterized many molecules that are involved in trophoblast cell fusion into the multinucleated syncytiotrophoblast layer, an important phase of human placental development (Chang et al. 2011, Molecular and Cellular Biology). In significant research endeavor, I studied the activity mechanisms of human placental villi development. I implemented engineered GCM1 genes into cellular genomes in order to study GCM1 functioning. I identified methods for improving the cell-based approaches to the identification of GCM1-associated proteins. I studied the isolated protein complex using a combination of LTQ-Orbitrap mass spectrometry and the tandem affinity purification approach. We discovered several novel GCM1-associated molecules vital to the process of placental villi development. We showed that the receptor exchange protein directly activated by cAMP (EPAC) upregulates GCM1 DNA-binding activity with downstream effectors. We further investigated EPAC-triggered signaling cascade through a series of kinase inhibitors screening with a GCM1-specific luciferase assay to identify the EPAC pathway's major downstream effector as CaMKI. We showed that Ser47 in GCM1 is a significant CaMKI phosphorylation site using mass spectrometry. Moreover, we developed a highly unique polyclonal anti-phosphor-Ser47 GCM1 antibody. We showed that this site is a requirement in the SENP1-mediated desumoylation and SENP1(SUMO specific peptidase1) interaction, which is necessary for the GCM1 DNA binding-activity incited by the removal of small ubiquitin-like modifier (SUMO) modification (Chang et al. 2013, Molecular Human Reproduction). My research enhances the capabilities of GCM1 activity regulation, which is a key priority in the fight against pregnancy-related diseases

a. **Chang CW**, Cheong ML, Chang GD, Tsai MS, Chen H. Involvement of Epac1/Rap1/CaMKI/HDAC5 signaling cascade in the regulation of placental cell fusion. Mol Hum Reprod. 2013 Nov;19(11):745-55.
b. **Chang CW**, Chang GD, Chen H. A novel cyclic AMP/Epac1/CaMKI signaling cascade promotes GCM1 desumoylation and placental cell fusion. Mol Cell Biol. 2011 Sep;31(18):3820-31.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/chingwen.chang.1/bibliography/public/