BIOGRAPHICAL SKETCH

.

NAME: CHIA-WEI CHENG

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	START DATE	END DATE	FIELD OF STUDY
National Taiwan University (NTU) Taipei, Taiwan	B.S-M.S	06/2002	06/2008	Biological Sciences
University of Southern California (USC) Los Angeles, CA	Ph.D.	08/2009	08/2014	Biological Sciences, Gerontology
Massachusetts Institute of Technology (MIT) Koch Institute for Integrative Cancer	Postdoctoral Fellow	04/2015	present	Stem Cell Biology Cancer biology

A. Personal Statement

Sharing the ambitions of pioneers in dietary research and stem cell biology, I have been studying how organismal diet regulates adult stem cell fates and its applications in regenerative medicine. I conducted my Ph.D. research in Dr. Valter Longo's laboratory at USC Davis School of Gerontology, where I studied insulin/ IGF-1 (IIS) nutrient sensing signaling in the context of therapeutic fasting and tissue regeneration. During my Ph.D. years, I discovered that fasting or the mimetic diet through dampening IGF-1 signaling promotes the hematopoietic regeneration and reverses chemo-induced and age-related immunosuppression (Cheng et al., 2014, *Cell Stem Cell*) and stimulates the pancreatic beta-cell regeneration in both type 1 and type 2 diabetes models (*Cheng et al., 2016, Cell*). My postdoctoral studies at MIT Koch Institue continue this line of research and further benefit from my mentor Dr. Omer H. Yilmaz's expertise in intestinal stem cell (ISC) biology, and my senior co-mentor Dr. David M. Sabatini's expertise in nutrient-sensing signaling and cell metabolism. We have recently identified a Fatty acid β-oxidation (FAO)-dependent metabolic shift that is essential for the pro-regenerative effects of fasting in ISCs of young and aged mice (Mihaylova and Cheng et al., 2018, *Cell Stem Cell*). This finding forms the scientific premise of my current research highlighting the intriguing signaling role and therapeutic potential of ketone bodies, the downstream metabolites of FAO, in regulating stem cell functions in the aged intestine. With Dr. Yilmaz's support, I have generated several transgenic mouse models targeting the gene encoding the key ketogenic enzyme HMGCS2 (3-Hydroxy-3-Methylglutaryl-CoA Synthase 2). Currently, in collaboration with Dr. Aviv Regev, I am keen to study ketogenic control of intestinal stem cell functions and lineage decisions at at single-cell resolution. I will also establish subject-derived human organoid cultures, the miniature organ-like structures that self-organize in 3D culture, for drug screening targeting the ketone body signaling.

B. Positions and Honors

Positions and Employment

2008-2009 MOE-elite scholar in the Laboratory of Dr. David Chan California Institute of Technology (Caltech) and Dr. Valter D. Longo University of Southern California (USC).
2009-2014 PhD student in the Laboratory of Dr. Valter D. Longo, USC.
2015-present Postdoctoral researcher in the Laboratory of Dr. Ömer H. Yilmaz, Koch Institute at Massachusetts Institute of Technology (MIT).

Licensure and Certifications

2008- Present Animal Care and Use (USC, CA and MIT, MA)

2010- Present X-ray Irradiator operation, USC, CA
2015- Present Human Subjects Protection (HS) / Good Clinical Practice (GCP) / HIPAA
2017 R: Basics, Plots, and RNA-seq Differential Expression Analysis (Harvard Chan Bioinformatics Center)

Other Experience and Professional Memberships

2012 - Present Member, International Society of Stem Cell Research (ISSCR)
2017 - Present Member, National Academy of Inventors (NAI)
2017 - Present Member, American Association for Cancer Research (AACR)

Honors

2008-2011 Ministry of Education Elite scholarship, Taiwan
2010 USC-IEB Interdisciplinary Research Merit Award, CA
2012-2013 Women in Science and Engineering (WiSE) awards
2015 Heinz Osterburg Prize for doctoral research (USC:Gerontology)
2016-2017 Ludwig postdoctoral fellowship for cancer research (MIT: Koch Institue)
2017-2020 Helen Hay Whitney Foundation (HHWF) postdoctoral fellowship

Issued Patents

1. Methods And Formulations Promoting Tissue/Organ Regeneration, Longevity And Healthspan Valter D. Longo, **Chia-Wei Cheng**, Sebastian Brandhorst, Min Wei. (US20140112909 A1)
2. Fasting condition as dietary treatment of diabetes Valter D. Longo, **Chia-Wei Cheng** (US20150004280 A1)

C. Contribution to Science

i. Fasting and fasting mimetics promoting adult stem cell functions and tissue regeneration

During my Ph.D. years in Dr. Valter Longo's laboratory, I have been studying how fasting regulates adult stem cell function and how it influences tissue regeneration and organismal aging. I have also acquired expertise in the experimental techniques of these fields. My thesis reports two major discoveries in stem cell biology: (1) prolong fasting protects hematopoietic cells from chemotoxicity and promote hematopoietic stem cells (HSCs) self-renewal to reverse immunosuppression, through dampening a nutrient-sensing pathway (i.e. IGF-I/PKA) and (2) cycles of fasting mimetic diet, as well as transient PKA and mTOR inhibitions, reactivate prenatal-development gene expression (i.e. *Sox17* and *Ngn3*) in adult pancreas, leading to β-cell regeneration and reversed diabetic phenotypes. My postdoctoral works continue this line of research while focusing on fasting metabolism in intestinal stem cells (ISCs). I have identified Fatty acid β-oxidation (FAO) as the critical metabolic switch mediating the beneficial effects of fasting on ISCs and *Hmgcs2*, the gene encoding rate-limiting enzyme of ketone body production, as a downstream effector of FAO-mediated stemness. Currently, I am investigating the signaling role of the stem-cell derived ketone bodies in regulating ISC self-renewal and lineage decisions in homeostasis and response of fasting.

1. **Cheng CW**, Biton M, Haber A, Rickelt S, Butty V, Whary MT, Levine SS, Mino-Kenudson M, Deshpande V, Hynes RO, Fox JG, Regev A and Yilmaz ÖH. Endogenous ketones instruct intestinal stem cell fate through Notch signaling. ***(in revision).***
2. Mihaylova MM*, **Cheng CW***, Cao AQ, Tripathi S, Mana MD, Bauer-Rowe KE, Abu-Remaileh M, Clavain L, Erdemir A, Lewis C, Freinkman E, Huang Y, Bell G, Deshpande V, Carmeliet P, Katajisto P, Sabatini DM and Yilmaz ÖH. (***co-first author**) Fasting-Activated Fatty Acid Oxidation Enhances Intestinal Stem Cell Function. (2018). ***Cell Stem Cell.*** PMID:29727683
3. **Cheng CW**, Villani V, Buono R, Wei M, Kumar S, Yilmaz OH, Cohen P, Sneddon J, Perin L, and Longo V. Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes. (2017). ***Cell.*** PMID:28235195
4. Brandhorst S, Choi I, Wei M, **Cheng CW**, et al. Periodic diet that mimics fasting multi-system regeneration, enhanced cognitive performance and healthspan. (2015) ***Cell metabolism***. PMID:26094889
5. **Cheng CW**, Gregor B. Adams, Laura Perin, Min Wei, Xiaoying Zhou, Ben S. Lam, Stefano Da Sacco, Mario Mirisola, David Quinn, Tanya Dorff, John J. Kopchick and Valter D. Longo. Prolonged fasting reduces IGF-1/PKA to promote hematopoietic-stem-cell-based regeneration and reverse immunosuppression. (2014). ***Cell Stem Cell***. PMID: 24905167

ii. Mechanisms underlying the effects of dietary interventions on chemotoxicity and tumor progression

The vulnerability of cancer cells to nutrient deprivation and their metabolic dependency/inflexibility are emerging hallmarks of cancer. My research indicates that dietary restrictions including fasting, fasting-mimicking diets (FMDs) and low-protein diets lead to wide alterations in growth factors and in metabolite levels, generating environments that impede the tumor progression and sensitize the tumors to chemotherapy-induced DNA damages or T-cell mediated anti-cancer immunity. On the other hand, these dietary interventions enhance stress resistance and stimulate the regeneration of normal tissue. Targeting the nutrient-sensing signaling pathways underlying the differential sensitization and stress-resistance effects, therefore, represents a potential strategy to increase treatment efficacy, to prevent resistance acquisition and to reduce side effects of cancer therapies.

1. **Cheng CW** and Yilmaz ÖH. FAOund the Link: Phospholipid Remodeling and Intestinal Stem Cell Growth and Tumorigenesis. (2018). ***Cell Stem Cell***. PMID:29395049
2. **Cheng CW** and Yilmaz ÖH. Starving leukemia to induce differentiation. (2017). ***Nature Medicine***. PMID:28060803
3. Dorff TB, Groshen S, Garcia A, Shah M, Tsao-Wei D, Pham H, **Cheng CW**, Brandhorst S, Cohen P, Wei M, Longo V, Quinn DI. Safety and feasibility of fasting in combination with platinum-based chemotherapy. (2016). ***BMC Cancer.*** PMID:27282289
4. Di Biase S, Lee C, Brandhorst S, Manes B, Buono R, **Cheng CW**, Cacciottolo M, Martin-Montalvo A, de Cabo R, Wei M, Morgan TE, Longo VD. Fasting-Mimicking Diet Reduces HO-1 to Promote T Cell-Mediated Tumor Cytotoxicity. (2016). ***Cancer Cell***. PMID:27411588.
5. Levinea ME, Suareza JA, Brandhorsta S, Balasubramaniana P, **Cheng CW**, Madia F, Fontana L, Mirisola MG, Wan J, Passarino G, Kennedy BK, Cohen P, Crimmins EM and Longo VD. Low protein intake is associated with a major reduction in IGF-I, cancer, and overall mortality in middle aged but not elderly subjects. (2014). ***Cell Metabolism***. PMID: 24606898

iii. Roles of growth hormone (GH)/insulin like growth factor 1(IGF-1) signaling in human aging and diseases

In several mouse models, mutations that are associated with decreased GH/IGF-1 signaling or decreased insulin signaling have been associated with an enhanced lifespan. To understand the relevance of reduced insulin and IGF-1 signaling in human longevity and health, we surveyed Ecuadorian individuals who carry mutations in the growth hormone receptor (GHR) gene that lead to severe GHR and IGF-1 (insulin-like growth factor-1) deficiencies (GHRDs). We found that the GHRD subjects exhibited a significantly low incidence of cancer and no diabetes. Using serum from GHR-deficient human subjects, we demonstrates that GH/IGF-1 deficiency causes reduced expression of RAS, PKA (protein kinase A), and TOR (target of rapamycin) and up-regulation of SOD2 (superoxide dismutase 2) in human cells, analog to changes that promote cellular protection and life-span extension in model organisms or caused by dietary interventions. These results provide evidence for the role of evolutionarily conserved pathways in the control of aging and disease burden in humans.

1. Wei M, Brandhorst S, Shelehchi M, Mirzaei H, **Cheng CW**, Budniak J, Groshen S, Mack WJ, Guen E, Di Biase S, Cohen P, Morgan TE, Dorff T, Hong K, Michalsen A, Laviano A, Longo VD. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. (2017). ***Science Translational Medicine***. PMID:28202779
2. **Cheng CW** and Yilmaz ÖH. IGFBP3 and T1D: Systemic Factors in Colonic Stem Cell Function and Diabetic Enteropathy. (2015). ***Cell Stem Cell***. PMID:26431180.
3. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, **Cheng CW**, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P, Longo VD. Growth Hormone Receptor Deficiency Is Associated with a Major Reduction in Pro-Aging Signaling, Cancer, and Diabetes in Humans. (2011). ***Science Translational Medicine***. PMID: 21325617

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1PqJza-jkur5j/bibliography/54667245/public/?sort=date&direction=ascending.

D. Research Support

Ludwig postdoctoral fellowship for cancer research 01/01/2016-01/01/2017

"Impact of aging on intestinal stem cell metabolism and tumorigenesis"

Helen Hay Whitney Foundation (HHWF) postdoctoral fellowship 04/01/2017-04/01/2020

"Single Cell Circuitry of Diet-mediated Intestinal Tumorigenesis"