BIOGRAPHICAL SKETCH

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NAME: Wang, Weidong

eRA COMMONS USER NAME (agency login): Wangokc

POSITION TITLE: Assistant Member, Oklahoma Medical Research Foundation

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Shanghai Medical University, Shanghai	MB	07/1988	Medicine
Fudan University Medical Center, Shanghai	MS	07/2000	Basic Medicine
Columbia University, New York, NY	PHD	02/2006	Genetics & Development
The Scripps Research Institute, San Diego, CA	Postdoctoral Fellow	10/2008	Chemical Biology & Regenerative Medicine
Genomics Institute of Novartis Research Foundation, San Diego, CA	Postdoctoral Fellow	06/2009	Chemical Biology & Regenerative Medicine

A. Personal Statement

I have been working on beta cell biology using chemical biology approaches since 2006 after I obtained my Ph.D. in genetics and development from Columbia University. I am interested in pancreatic beta cell regeneration and survival, which could provide a means for a cure for diabetes, a disease caused by severe beta cell loss. One of my major goals was to use chemical and functional genomics approaches combined with high-throughput screening (HTS) technology to identify small molecules or biologics that promote beta cell proliferation, survival, and differentiation. This research has led to 2 publications (PNAS and JACS) as well as two patent applications, one of which has been exclusively licensed by Novartis Pharmaceuticals Corp. for further drug development. Prior to joining Oklahoma Medical Research Foundation (OMRF), I worked in a biotech company iPierian, a leading company in the application of induced pluripotent stem cell (iPSC) technology for disease modeling and drug discovery, as a senior scientist to further apply my expertise in both stem cell/ regenerative biology and HTS technology for the discovery of new therapeutics. At iPierian, I have worked on developing protocols to efficiently differentiate human iPSCs to pancreatic beta cells. We have successfully achieved the efficient reprogramming and human iPSCs and their differentiation to beta cell precursors. Two patents have been filed based on my work at iPierian.

Since joining OMRF as an Assistant Member in early 2011, I have continued to work on pancreatic beta cell differentiation and beta cell survival, in combination with HTS technology. We have initiated several high throughput screens to successfully identify chemicals that protect beta cells against ER stress, that modulate ER stress, and that protect beta cells against chronic high glucose. We have characterized some hit compounds and identified that several compounds were able to significantly lower blood glucose levels and concomitantly increase beta cell mass and number in diabetic animal models. So far, we have a paper published in ACS Chemical Biology. We also have two manuscripts currently in revision for publication in JMC and BMC, respectively, and 3 manuscripts ready for submission in June, with all of them focusing on chemical synthesis and SAR studies. 3 patents have been filed since I joined OMRF, 2 of which are for the identification of small molecules for beta cell protection and modulation of ER stress.

Taken together, I have multiple years of extensive experience in beta cell biology, high throughput screening, assay development, medicinal chemistry and drug discovery and development. These experiences position me well for the undertaking of the proposed research in this application.

1. Wang W, Walker JR, Wang X, Tremblay MS, Lee JW, Wu X, Schultz PG. Identification of small-molecule inducers of pancreatic beta-cell expansion. Proc Natl Acad Sci U S A. 2009 Feb 3;106(5):1427-32. PubMed PMID: 19164755; PubMed Central PMCID: PMC2635822.
2. Shen W, Tremblay MS, Deshmukh VA, Wang W, Filippi CM, Harb G, Zhang YQ, Kamireddy A, Baaten JE, Jin Q, Wu T, Swoboda JG, Cho CY, Li J, Laffitte BA, McNamara P, Glynne R, Wu X, Herman AE, Schultz PG. Small-molecule inducer of β cell proliferation identified by high-throughput screening. J Am Chem Soc. 2013 Feb 6;135(5):1669-72. PubMed PMID: 23330637.
3. Tran K, Li Y, Duan H, Arora D, Lim HY, Wang W. Identification of small molecules that protect pancreatic β cells against endoplasmic reticulum stress-induced cell death. ACS Chem Biol. 2014 Dec 19;9(12):2796-806. PubMed PMID: 25279668; PubMed Central PMCID: PMC4273981.

B. Positions and Honors

Positions and Employment

1989 - 1992	Resident in Medicine, The 2nd Affiliated Hospital, Nanjing Medical University, Nanjing
1993 - 1996	Fellow in Cardiology, The 2nd Affiliated Hospital, Nanjing Medical University, Nanjing
1997 - 2000	Graduate Research Assistant, Fudan University Medical Center, Shanghai
2001 - 2006	Graduate Research Assistant, Laboratory of Dr. Gary Struhl, Columbia University, New York, NY
2006 - 2008	Postdoctoral Associate, Laboratory of Dr. Peter Schultz, The Scripps Research Institute, San Diego, CA
2008 - 2009	Postdoctoral Associate, Laboratory of Dr. Peter Schultz, Genomics Institute of the Novartis Research Foundation, San Diego, CA
2009 - 2011	Senior Scientist, iPSC-based Drug Discovery Program, iPierian, Inc., South San Francisco, CA
2011 -	Assistant Member, Immunobiology & Cancer Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK

Other Experience and Professional Memberships

2009 -	Member, International Society for Stem Cell Research (ISSCR)
2009 - 2010	Member, Society for Biomolecular Sciences (SBS)
2010 -	Member, Society for Laboratory Automation and Screening (SLAS)
2011 -	Member, American Diabetes Association (ADA)

Honors

1999	Orient Scholarship, Ministry of Education, China
2000	Dean's Fellowship, Columbia University, New York
2001	Dean's Fellowship, Columbia University, New York
2002	Dean's Fellowship, Columbia University, New York

C. Contribution to Science

1. During my Ph.D. study, I worked on the mechanism of Notch signaling pathway activation, specifically on how the transmembrane Delta/Serrate/Lag2 (DSL) ligands on the "signal-sending" cells activates Notch receptor on the "signal-receiving" cells. Notch is a single-pass transmembrane protein that is cleaved in response to ligand, allowing the cytosolic domain – a transcriptional activator – to gain access to the nucleus and regulate target genes. The key step in signaling is ligand-induced cleavage and shedding of the ectodomain of Notch: this precipitates intramembrane cleavage of Notch by γ-Secretase, and untethers the cytosolic domain from the plasma membrane. The major, outstanding problem in the field of DSL/Notch signaling is how ligand binding induces the ectodomain cleavage that activates the receptor. Despite decades of research, this fundamental question remained unanswered by the time of Ph.D. study. I discovered two fundamental requirements for Notch activation: (i) that DSL ligands must be endocytosed by "signal-sending" cells to induce cleavage and activation of Notch on the surface of "signal-receiving" cells, and (ii) that ligand can only activate Notch if it is internalized by the adapter protein Epsin and not by

other endocytic pathways. These discoveries have provided new insight on Notch activation and serve as the foundation for the current model that Epsin-dependent endocytosis is essential because it allows ligands, as they are being internalized into the sending cell, to "pull" on the ectodomain of Notch on the receiving cell with sufficient force to unfold a Negative Regulatory Region (NRR) exposing it to proteolytic cleavage. The ability of cells to convert mechanical force into biological signals is fundamental to their ability to sense their environment and communicate with each other.

a. Wang W, Struhl G. Drosophila Epsin mediates a select endocytic pathway that DSL ligands must enter to activate Notch. Development. 2004 Nov;131(21):5367-80. PubMed PMID: 15469974.
b. Wang W, Struhl G. Distinct roles for Mind bomb, Neuralized and Epsin in mediating DSL endocytosis and signaling in Drosophila. Development. 2005 Jun;132(12):2883-94. PubMed PMID: 15930117.

2. Pancreatic β-cell loss is a key element in the pathogenesis of both type 1 and type 2 diabetes. Once regarded as post-mitotic, β-cells in the adult pancreas can replenish at a basal level and expand significantly to meet metabolic demands during pregnancy and obesity, primarily via replication of preexisting β-cells. These observations suggest the possibility of expanding primary β-cells ex vivo for transplantation and even of directly regenerating the endogenous β-cell mass in the pancreas of diabetic patients by pharmacological means. A major goal of my postdoctoral research is to develop therapeutics that increases the replication of functional β-ells. To achieve this, I initiated a novel unbiased cell-based high throughput screening (HTS) for compounds that enhance the proliferation of β-cells. This is the first of such a screen for identification of small molecule inducers of β-cell replication. This type of screen requires large quantity of β-cells. However, large number of primary β-cells is difficult to obtain, and their quality varies from batch to batch. In addition, traditionally immortalized β-cells grow at the maximum pace and it will be difficult to observe the proliferative effect of any compounds using these cells. To overcome this technical obstacle, I established an assay for HTS using β-cells which are reversibly immortalized by introducing SV40 T antigen (TAg) oncoprotein under the control of Tet-On system such that cells proliferate when TAg is induced in the presence of tetracycline (Tet), but undergo growth arrest and behave as functional β-cells upon withdrawal of Tet, thus providing a means of generating huge quantities of homogeneous β-cells required for large-scale screens. Using this approach, I identified ~80 potent compounds that are able to induce β-cell replication. This research has led to 2 publications (PNAS and JACS) and two patent applications, one of which has been exclusively licensed by Novartis Pharmaceuticals Corp. for further drug development.

Patent/Invention:

1. Wang, W. and Schultz, P.G. "Compounds that induce pancreatic beta-cell expansion" U.S. Application Serial No. 12/617,630, filed on Nov. 12, 2009.

2. Wang, W., Shen, W., Tremblay, M., and Schultz, P.G.. "Compounds that induce cell cycle re-entry in rodent and human beta cells" U.S. Application Serial No. 61/548, filed on Oct. 19, 2011

a. Wang W, Walker JR, Wang X, Tremblay MS, Lee JW, Wu X, Schultz PG. Identification of small-molecule inducers of pancreatic beta-cell expansion. Proc Natl Acad Sci U S A. 2009 Feb 3;106(5):1427-32. PubMed PMID: 19164755; PubMed Central PMCID: PMC2635822.
b. Shen W, Tremblay MS, Deshmukh VA, Wang W, Filippi CM, Harb G, Zhang YQ, Kamireddy A, Baaten JE, Jin Q, Wu T, Swoboda JG, Cho CY, Li J, Laffitte BA, McNamara P, Glynne R, Wu X, Herman AE, Schultz PG. Small-molecule inducer of β cell proliferation identified by high-throughput screening. J Am Chem Soc. 2013 Feb 6;135(5):1669-72. PubMed PMID: 23330637.

3. Pancreatic β cell dysfunction and death are key elements in the pathogenesis of both type 1 and 2 diabetes and increasing evidence indicates that endoplasmic reticulum (ER) stress is a major underlying cause of this decline. Thus, compounds that prevent ER stress-induced β cell death hold promise as potential therapeutic agents for diabetes. However, no small molecules had been reported to be β cell-protective against ER stress. In fact, no high throughput screen for such compounds has been reported. We are the first to initiate such a screen to successfully identify compounds that protect β cells against ER stress-induced dysfunction and death. Several tested compounds significantly lower the hyperglycemia in

diabetic animals. These compounds could serve as leads for further drug development for treatment of diabetes.

Patent/Invention:

1. Wang, W. "Nitrofuran Derivatives that Induce Apoptosis in Breast Cancer Cells by Activating Protein Expression" U.S. Patent Application Serial No.: 62/158,924 Filing Date: May 8, 2015

2. Wang, W. "Triazole Derivatives for Protecting β Cells Against Endoplasmic Reticulum Stress" U.S. Patent Application Serial No.: 62/160,363 Filing Date: May 12, 2015

a. Tran K, Li Y, Duan H, Arora D, Lim HY, Wang W. Identification of small molecules that protect pancreatic β cells against endoplasmic reticulum stress-induced cell death. ACS Chem Biol. 2014 Dec 19;9(12):2796-806. PubMed PMID: 25279668; PubMed Central PMCID: PMC4273981.

4. iPSCs can be generated from differentiated somatic cells such as fibroblasts by the introduction of four transcription factors. iPSC technology offers unprecedented potential for cell-based regenerative medicine, disease modeling, and drug discovery. However, several obstacles must be addressed before the full potential of this technology can be realized. First, iPSC derivation with current protocols is highly inefficient. Second, random genomic integration of viral vectors may not only pose serious clinical concern but also interfere with the differentiation process of iPSCs. Small molecules could potentially replace the reprogramming factor(s) or enhance reprogramming efficiency. As a senior scientist in a biotech company iPierian, I established a novel screening assay, the first of such a screen, for human fibroblast cell reprogramming. Using this assay system, I identified several compounds that enhance the reprogramming efficiency. STGFb inhibitors have since been incorporated in many iPSC-reprogramming protocols. Part of this work has led to two patent applications.

Patent/Invention:

1. Grskovic, M., Dimos, J., Strulovici, B., Bakhtiarova, A. and Wang, W. “TGF-β pathway inhibitors for enhancement of cellular reprogramming of human cells” International Application No. PCT/US10/26451, filed on Mar. 5, 2010.

2. Wang, W. and Grskovic, M. “Methods for enhancing the efficiency of cellular reprogramming” U.S. Application Serial No. 61/240,144, filed on Sept. 4. 2009.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/myncbi/weidong.wang.1/bibliography/43698956/public/?sort=date&direction=ascending

D. Research Support

Ongoing Research Support

2013/03/01-2018/02/28
1P20 GM103636-01A1 , NIH/NIGMS
Thompson, Linda F. (PI)
Expanding Excellence in Developmental Biology in Oklahoma
Project 5: “Derivation of pancreatic beta cells from human induced pluripotent stem cells” The major goals of this project are 1: Define the roles of the Notch and Wnt pathways in the process of human β-cell differentiation. 2: Genetically identify and define distinct populations of hiPSC-derived pancreatic lineages at molecular and cellular levels. 3: Define the proliferative and differentiation potentials of hiPSC-derived β-cell progenitors.
Role: Co-Investigator

2013/09/01-2016/08/31

AR132-042, Oklahoma Center for the Advancement of Science and Technology
Wang, Weidong (PI)
Developing a New Version of TALEN Gene-editing Technology for Gene Therapy and Biomedical Research
The goal of this grant is to develop a new version of TALEN with efficient nuclear translocation and genome editing capacity.
Role: PI

2013/09/01-2015/08/31
AR132-043, Oklahoma Center for the Advancement of Science and Technology
Wang, Weidong (PI)
Discovering Small Molecules that Protect Beta Cells Against ER Stress-induced Death for Treatment of Diabetes
Aim 1: Identify chemicals that protect beta cells from ER stress-induced cell death in a cell-based HTS. Aim 2: Validate the cytoprotective activities of hit compounds and map the ER stress-mediated UPR pathways modulated by confirmed hits using a battery of secondary assays.
Role: PI

2012/07/01-2015/06/30
HR12-156, Oklahoma Center for the Advancement of Science and Technology
Wang, Weidong (PI)
Pancreatic Beta Cell Differentiation from Human IPS Cells
The major goal of this project is to establish differentiation protocols to efficiently generate functional beta cells from human iPS cells, facilitated by creating fluorescent reporter iPSC lines. Maturity and function of the differentiated beta cells or their precursors will be investigated in vivo after their transplantation into mice.
Role: PI

Completed Research Support

2014/01/01-2014/12/31
4340-04-06-0, Oklahoma Center for Adult Stem Cell Research
Wang, Weidong (PI)
Understanding diabetes pathogenesis using patient-specific human iPS cells
Role: PI

2012/07/01-2013/06/30
4340-04-05-0, Oklahoma Center for Adult Stem Cell Research
Wang, Weidong (PI)
Generation of TALEN-based knock- in fluorescent reporter human iPS cells for dissecting b-cell differentiation”
Role: PI

2011/11/01-2012/07/31
5P30 RR031152-02, NIH
James, Judith (PI)
Science in a Culture of Mentoring (COBRE Phase III)
Pilot Project: Generating disease-specific thymic epithelial progenitors from human T1D patient-derived iPSCs
Role: Co-Investigator