CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
R1219

Project Title:
Recruitment of First-Time, Tenure-Track Faculty Members

Award Mechanism:
Recruitment of First-Time, Tenure-Track Faculty Members

Principal Investigator:
Wang, Pei

Entity:
The University of Texas Health Science Center at San Antonio

Lay Summary:

Dr. Pei Wang received her Ph.D from Department of Cellular and Molecular Biology at Baylor College of Medicine in 2004. Then she joined Dr. Seung Kim's laboratory in Department of Developmental Biology at Stanford University School of Medicine and Howard Hughes Medical Institute for her postdoctoral training.

During her graduate studies, Dr. Wang investigated the poorly understood normal developmental functions of Alzheimer's Disease genes, presenilin 1 and 2 and amyloid precursor protein (APP). Using mouse genetics and embryonic stem cells, she discovered presenilins as a determinant of renal vesicle patterning in the developing mouse kidney through the Notch signaling pathway. Next, she investigated how APP family proteins are involved in neural-muscular junction formation. The double mutant mice of APP and APP like protein 2 (APLP2) exhibit aberrant apposition of presynaptic marker proteins with postsynaptic acetylcholine receptors and excessive nerve terminal sprouting. The number of synaptic vesicles at presynaptic terminals is dramatically reduced. These structural abnormalities are accompanied by defective neurotransmitter release and a high incidence of synaptic failure. She identified APP/APLP2 as key regulators of structure and function of developing neuromuscular synapses.

After she finished her groundbreaking graduate work, she moved to Stanford University and joined Dr. Seung Kim's laboratory. She was struck by the power of human embryonic stem cells (hESC) which in principle could generate all the cell types in the body. She dedicated her efforts to develop methods to study pancreas development and diseases using hESCs. She generated new genetically-modified embryonic stem cell lines (both human and mouse), and 'knock-in' mice to study formation of endoderm, one of the germ layer which gives rise to internal organs including pancreas and liver. Investigating the development of inaccessible human tissues like embryonic endoderm with embryonic stem cell (ESC) has been hindered by a lack of methods for marking and isolating specific cells, as well as tracing fates of their progeny toward differentiated lineages. She used homologous recombination in hESCs to generate a hESC reporter line with an enhanced green fluorescent protein (eGFP) transgene inserted into a locus encoding a postulated marker of human endoderm, SOX17. This cell line permitted purification of SOX17+ hESC progeny by fluorescence activated cell sorting (FACS) and unveiled specific cell surface protein combinations that allowed FACS-based isolation of primitive gut tube endodermal cells produced from unmodified hESCs and from induced pluripotent stem cells (iPSC). FACS-isolated SOX17+ endodermal cells differentiated to progeny expressing markers of

liver, pancreas, and intestinal epithelium, providing unprecedented evidence that human gastrointestinal lineages derive from SOX17+ cells. Her research approach using prospective isolation, lineage tracing, and developmental studies of hESCs has revealed fundamental aspects of human endodermal biology.

At University of Texas Health Science Center at San Antonio, Dr. Wang will use her expertise in mouse and human ES cell gene targeting and genetics, pancreas development, histological assessment, signal transduction, and disease pathogenesis to study Pancreatic ductal adenocarcinoma (PDAC), one of the most aggressive and deadly human malignancies. She will build a set of novel genome editing tools that allow us to inactivate multiple signaling pathways in a controlled temporal and sequential manner. The immediate goals are: 1) to understand the basis for tumor heterogeneity, 2) to establish methods for drug screening using genetically engineered human ductal cells, 3) to identify tumor initiating cells, and 4) to characterize the molecular properties of TICs. The long-term goals are to identify markers and methods for early diagnosis of PDAC and to inform the development of effective therapeutic strategies.