CALIFORNIA STATE SCIENCE FAIR
2017 PROJECT SUMMARY

Name(s)

Brian Xia

Project Number

S0527

Project Title

Molecular Basis for Developing Single Molecule Based Anti-Aging Therapies to Prevent Aging Related Diseases in Humans

Abstract

Objectives/Goals

Aging-delaying interventions often prevent multiple aging-related diseases (ARDs). My recent studies have characterized EZH2-mediated H3K27me3 as the first evolutionarily conserved epigenetic mechanism underlying transgenerational inheritance of early-life nutritional programming of longevity, supporting translational studies in humans [1,2], and identified a longevity-extending EZH2-selective inhibitor (EPZ-6438) to prevent heart disease, type 2 diabetes and aging-related memory loss in aged flies, providing the first-ever proof-of-concept of single molecule-based long-lasting epigenetic therapies for simultaneous prevention of multiple ARDs (unpublished results). Excitingly, dietary restriction has very recently been extended to human participants for safe and effective alleviation of cardiovascular disease, diabetes and cancers simultaneously [3]. My current study was to identify the shared nutrition-mediated molecular and epigenetic mechanisms among aging and ARDs, and further validate EPZ-6438 as a promising nutrition-responsive broad-spectrum therapy for human diseases.

Methods/Materials

Integrative methods were employed for public data mining, bioinformatic analyses, RNA-seq with human H9 ESCs (embryonic stem cells) and disease characterization with aged flies after treatment of EPZ-6438.

Results

My results have (i) revealed the Sirt1-EZH2-p53 pathway as a shared mechanism among aging and ARDs, and 12 related druggable targets, providing the molecular basis for developing novel anti-aging therapies to simultaneously prevent multiple ARDs, (ii) identified 868 EPZ-6438-impacted genes enriched in multiple pathways and various biological processes involved with cardiovascular diseases, diabetes, dementia and cancers, validating the drug as a promising multi-disease therapy in humans, (iii) further identified Klf4 and Sox21, suggesting a possible mechanistic connection between EPZ-6438-mediated H3K27me3 inhibition and Nobel Prize-winning Yamanaka factors to delay aging and ARDs [4].

Conclusions/Discussion

My research has thus validated the emerging concept of delaying aging through epigenetic reprogramming, and demonstrated that single molecule-based, nutrition-responsive, multi-disease therapies may be developed and delivered to delay aging and various ARDs in humans, opening up novel avenues for aging research and drug development.

Summary Statement

My work has revealed the molecular basis for developing novel anti-aging therapies by identifying a shared EZH2-mediated mechanism among aging and human diseases, and validated an EZH2-selective inhibitor as a promising therapy in humans.

Help Received

Drs. Ed Gerstin, Steve de Belle, Wendong Huang & Dustin Schones for supporting & mentoring me; Drs. Yanhong Shi & Qiuhao Qu for culturing H9 ESCs; Dr. Juan Du for supervising me on RNA-seq; Dr. Shouzhen Xia, Ms. Gihei Kim & Mr. Michael Lee for teaching me various lab procedures.