CALIFORNIA STATE SCIENCE FAIR
2016 PROJECT SUMMARY

Name(s)

Brian S. Xia

Project Number

36400

Project Title

Single Molecule Based Transgenerational Therapies to Extend Healthspan and Prevent Multiple Aging Related Diseases

Abstract

Objectives/Goals

The objective of this study was to examine whether E(z)/EZH2-dependent H3K27me3 may be one epigenetic mechanism underlying transgenerational programming of longevity, and EZH2 inhibitors (e.g., EPZ-6438) may extend longevity by preventing multiple aging-related diseases (ARDs) in a transgenerational manner.

Methods/Materials

Antibodies and EPZ-6438 are commercially available. The dietary manipulations were developed through publicly available nutritional data and literature research. Integrative methods were employed for longevity analysis, western blotting, disease and behavioral characterization after various post-eclosion treatments.

Results

My results have 1) revealed E(z)-dependent H3K27me3 as the first such epigenetic mechanism, 2) identified EPZ-6438 to extend longevity and prevent multiple ARDs, and 3) provided the first-ever proof-of-concept for transgenerational epigenetic therapy with individual molecules for simultaneous prevention of multiple ARDs.

Conclusions/Discussion

Longevity-improving epigenetic therapies may prove to be revolutionary, in combination with personalized medicine (i.e., therapy decisions tailored to individual patients based on genetic risk information and molecular characterization) and DOHaD (Developmental Originals of Health and Disease) approach. First, therapeutic interventions delivered at an early developmentally-appropriate time may be very effective to prevent the onset of ARDs in adults and even cross generations, especially considering that current disease-risk-reduction interventions have been primarily targeted to adults while are not necessarily effective. Second, the single compounds which extend longevity by delaying multiple ARDs could prevent many diseases simultaneously and thus greatly extend healthspan of life. Third, one important trend for drug discovery is the ongoing shift from single-target-oriented molecules to network- or biological system-active compounds and to 'epi-drugs'. Finally, my results also provided a new avenue to combat genetic diseases. E(z) regulates a large number of genes through the PRC2-mediated repression mechanism, and thus its inhibitor may achieve network-active purpose on their own. Such knowledge can also be combined with personalized medicine and DOHaD approach to promote appropriate risk reduction interventions in early life, and motivate healthier choices and meaningful behavior changes in adults.

Summary Statement

This project has demonstrated the efficacy of early-life administration of a single-molecule therapy in extending healthspan and preventing multiple aging-related diseases in a long-lasting cross-generational manner.

Help Received

My mentor provided laboratory space, reagents, and equipment; and guidance in experimental design and data analysis. I independently performed literature research, formulated a novel idea, collected data, and drew conclusions.