



Using the fruitfly, *Drosophila melanogaster* to Understand the Genetic Basis of Aging



Dr. Jeff Leips¹, Dr. Michelle Starz-Gaiano¹, Dr. Peter Abadir, MD²

¹Dept of Biological Sciences, University of Maryland Baltimore County, Baltimore MD 21250

²Johns Hopkins Bayview Medical Center, Baltimore, MD 21224

Introduction

- All organisms deteriorate with age
- Aging **decreases the quality of life** of the elderly
- In human populations, **individuals differ** in rates of physiological decline with age
- Individual differences** in aging is partially attributable to **genetic differences** among individuals
- The actual **genes that are responsible for these differences** among individuals are largely unknown and so limiting our ability to design treatments

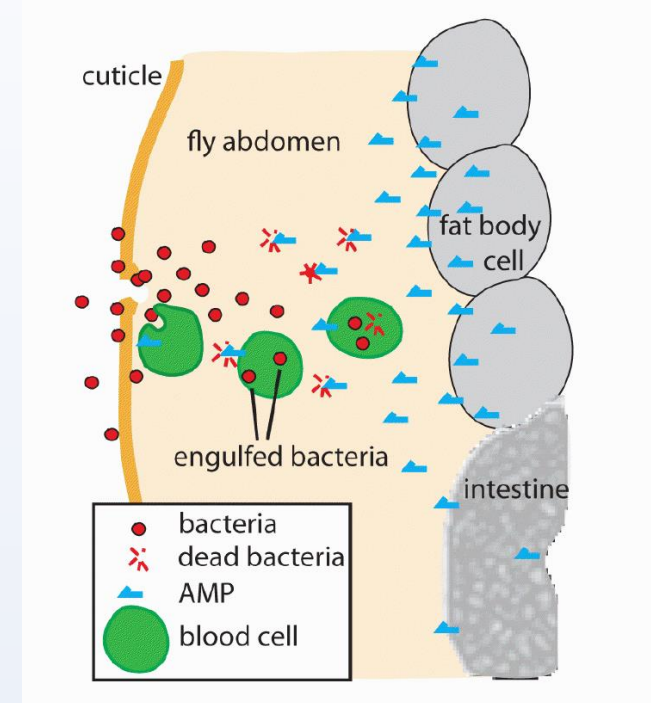
Why Use Drosophila?

- Flies show **similar age-related declines to that of humans**
 - decline in **physical strength** with age
 - decline in **walking speed** and **endurance** with age
 - decline in **ability to fight infection** with age
- Many** fully sequenced genomes,
 - > **60% of fly genes shared with humans**
- Efficient and Economical Model Organism:**
 - **Short life span** (~50 days) allows measurement of genetic influences on age-related decline across entire life span
 - **Inexpensive** to observe and maintain **large populations** (maximizes statistical power to detect genetic effects)
- Genomic mapping techniques** to identify genes contributing to variation in aging **well developed**
 - 1000's of genetic resources allow **experimental manipulation genes** to **validate** genetic effects on aging
- Ideal organism for **training the next generation of scientists**



Drosophila as a model to understand the genetics of age-related decline in immune function

- Age-related decline in immunity places a substantial burden on the healthcare system: **infection-related hospital admission is among the most costly and the most common in the elderly¹**

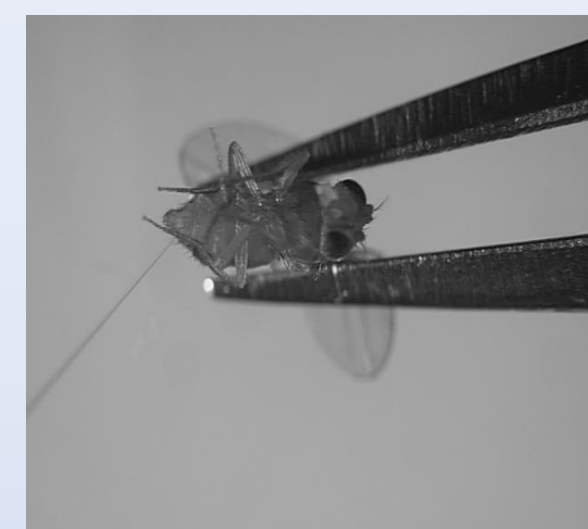


Innate immune response

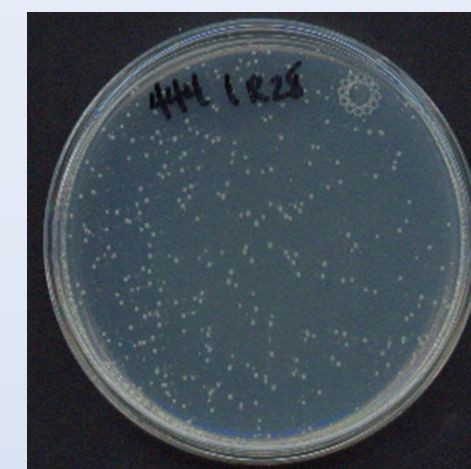
- Two main components
 - Phagocytosis
 - Production of Antimicrobial Proteins
- Conservation of Genes/Signaling Pathways in flies and humans

Measuring the Immune Response: Infection Assay

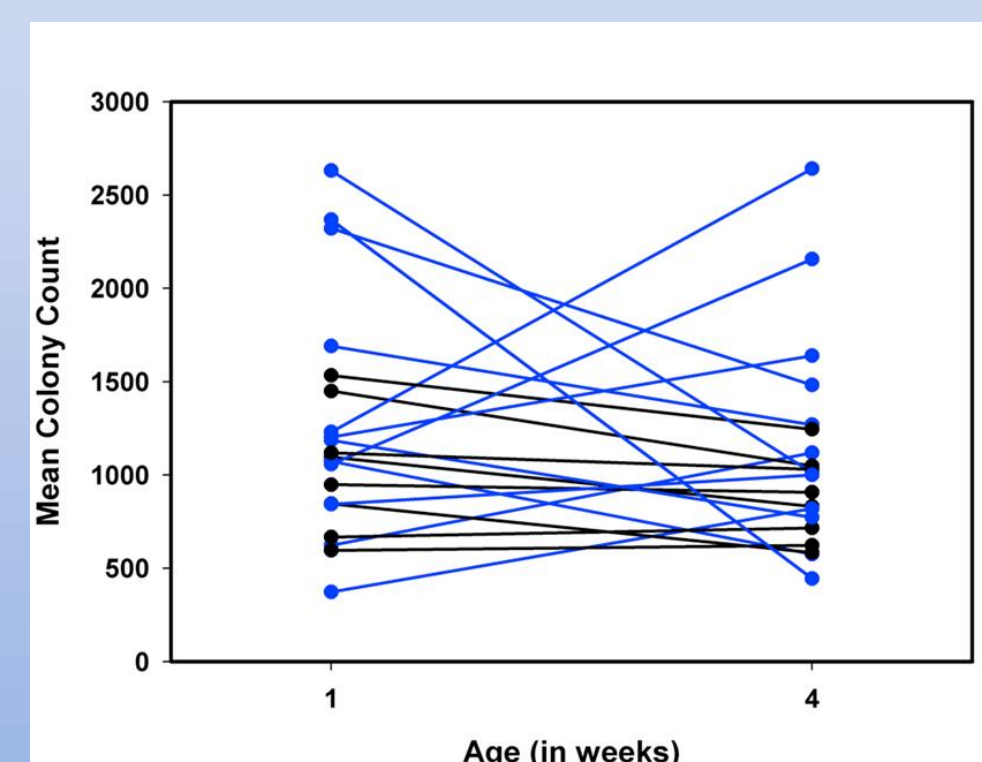
Microinject Bacteria



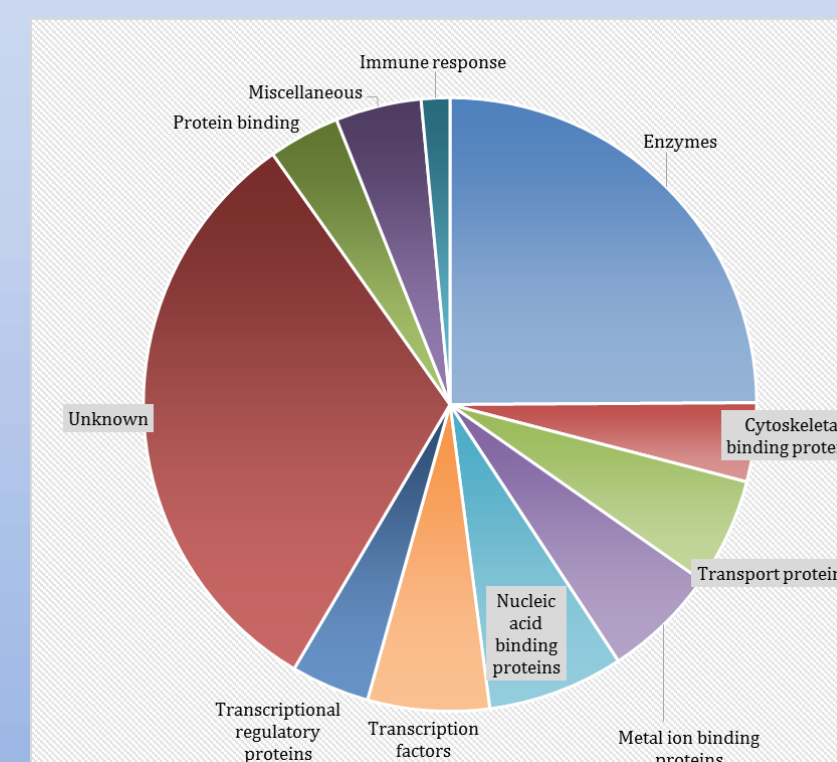
Measure Infection Level 24 hours after infection



Effect of aging on the ability to clear infection differs among genotypes

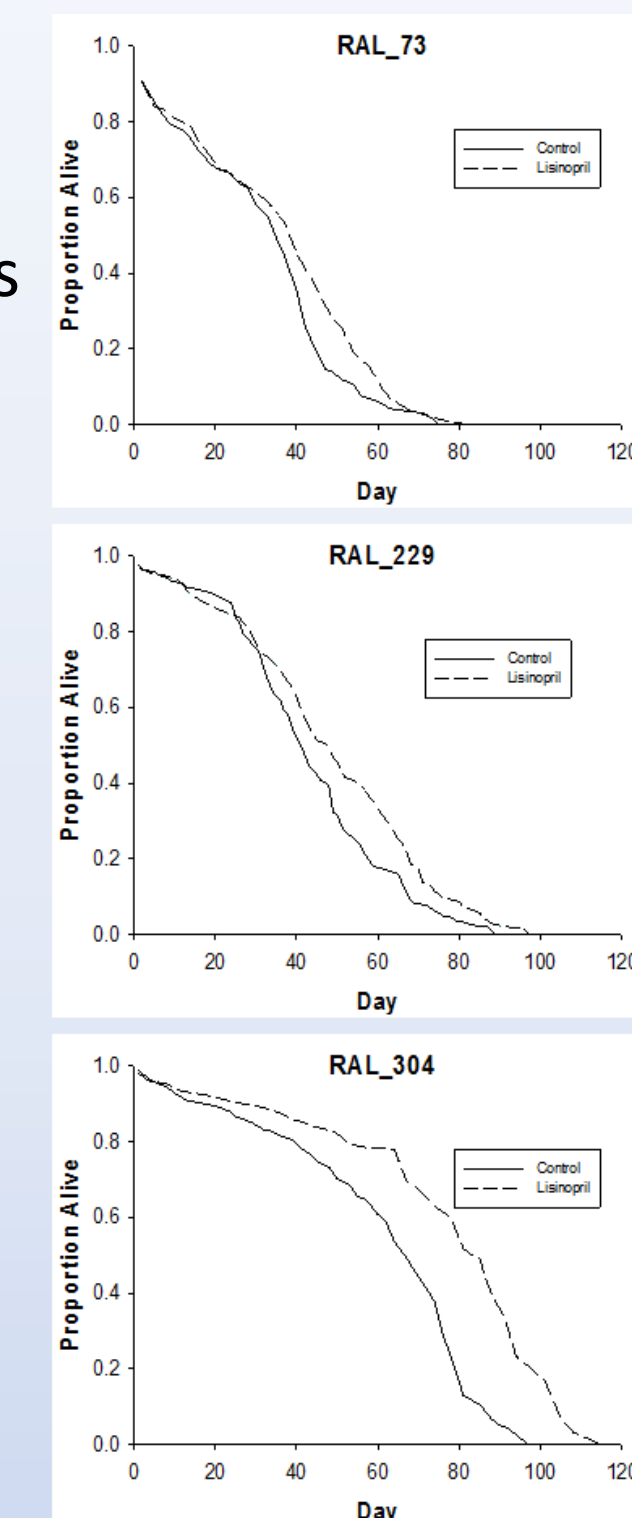


Genome wide expression experiment identified ~ 250 genes that contribute to individual variation in age-specific ability to fight infection,

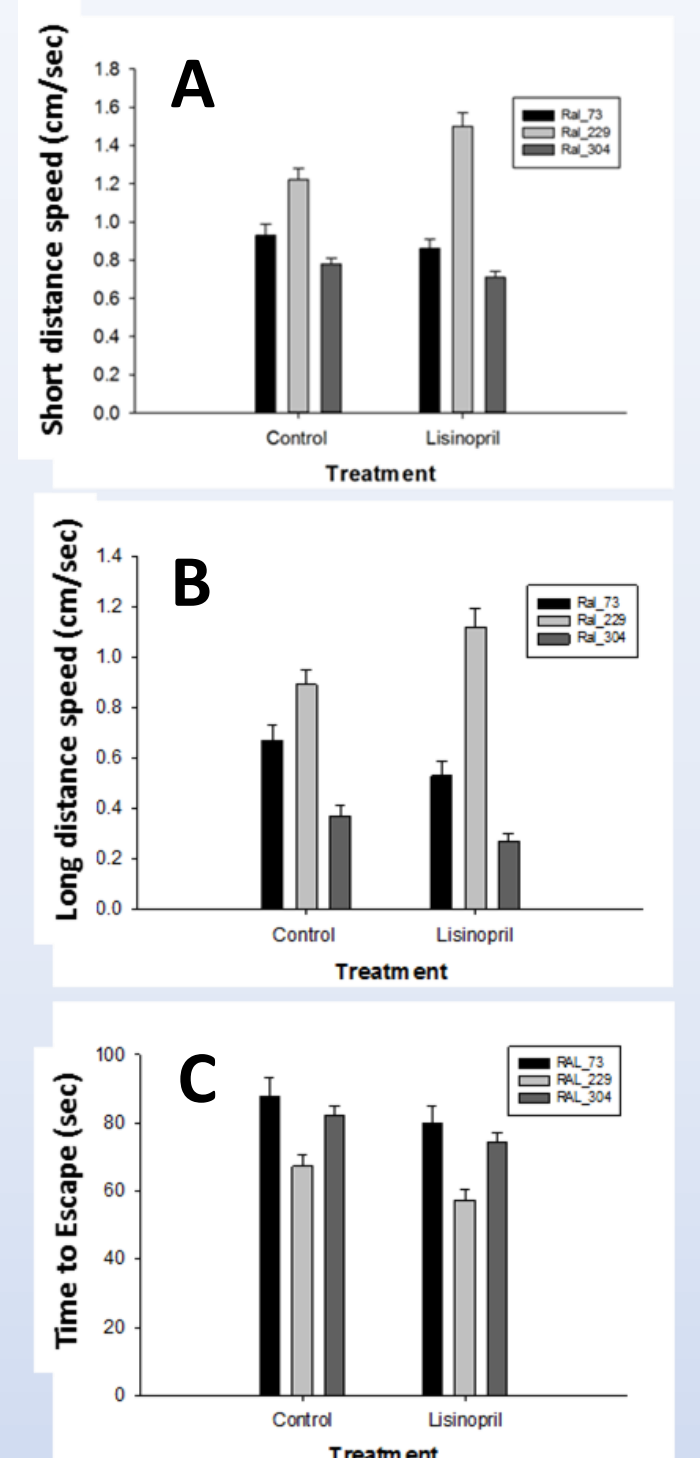


Using Drosophila to understand individual variation in response to drug treatment

- Individual differences in response to drug treatment is often related to genetic differences among individuals³
- We are examining the genetic basis of the response to Lisinopril (a commonly prescribed drug to treat age-related changes in blood pressure - drug not effective for all patients.
- Effects of Lisinopril treatment in flies generally mimics effects in humans
- Genotypes differ in their response to drug treatment
- Mapping efforts underway to identify genes that contribute to individual differences in drug response.



Lisinopril treatment extends life span in genotype specific manner A: RAL_73, B: RAL_229, C: RAL_304



The effect of Lisinopril on A) Short distance climbing speed, B) Long distance climbing speed depended on genotype. C) Lisinopril improved strength in all lines.

References

- High, KP 2004. Infection as a cause of age-related morbidity and mortality. Ageing Research Review, 2004. 3: p. 1-14.
- Felix, T.M., Hughes, K.A., Stone, E.A., Drnevich, J.M., Leips, J. 2012. Age-specific variation in immune response in *Drosophila melanogaster* has a genetic basis. Genetics 191:989-1002
- Cavallari LH. 2012. Tailoring drug therapy based on genotype. J Pharm Pract. 25:413-416.

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