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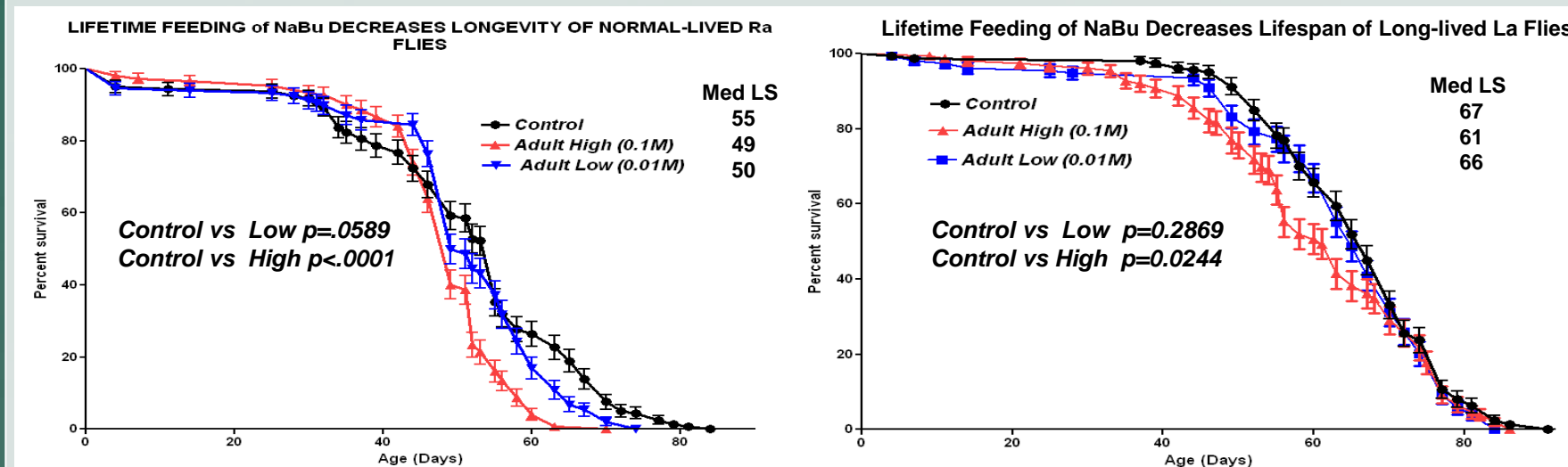
## ABSTRACT

There is a major interest in identifying drugs that extend longevity in model organisms, particularly those acting in a stage-specific manner. The histone deacetylase inhibitor (HDACi), 5-methyl butyrate, was shown to extend *Drosophila* longevity only when administered for part of the life cycle (Kang and Benzer, 1999). We have confirmed and extended that finding. We find that sodium butyrate (NaBu) is toxic to *Drosophila* when administered continuously over its entire larval and/or adult lifespan. We tested the effects of NaBu during each of the three adult phases (e.g. the health, transition, and senescent spans) on two different strains: the normal-lived Ra strain, and the long-lived La strain. The Ra strain showed no significant longevity effect when NaBu was fed during the health span (days 1-21) but showed a maximal dose-dependent increase in median and mean lifespan of 12.5% and 11.2%, respectively, after low dose NaBu treatment during the transition and senescent spans (days 22-63). However, NaBu treatment significantly reduced the longevity of the long-lived La animals when administered during any phase of the life span, suggesting that the La animals are dependent in part on a longevity-determinant mechanism involving histone deacetylation. Our data show that drugs affecting HDACs are both stage- and genotype-specific, which implies that drug targets change as gene expression patterns change during the lifespan.

## INTRODUCTION

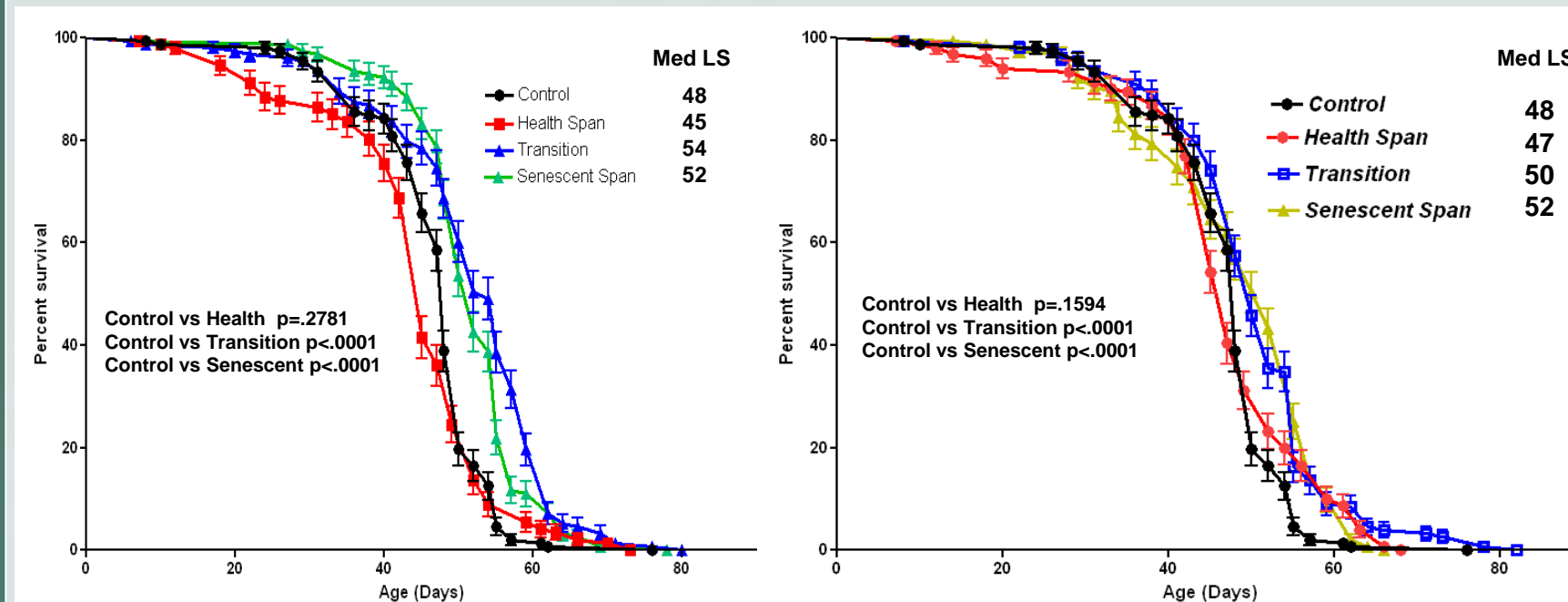
Given stage-specific patterns of gene expression, then genotropic compounds may well have stage-specific effects which would be difficult to discern from whole-life treatments if deleterious effects in the health span, for example, preceded beneficial effects in the senescent span. By this reasoning, one might expect that beneficial compounds with an anti-aging effect specific for the transition- and senescent spans may not be rare. The practical implication is the possibility that compounds with beneficial stage-specific effects may have potential as the progenitors of possible human anti-aging drugs. Even though aging *per se* is not presently recognized as a medical condition requiring treatment, these data nonetheless lend empirical support to the idea that future drugs should be able to mimic the effects of gene regulatory mechanisms causing significant increases in longevity of model organisms (Kenyon, 2010).

### 1. Lifetime NaBu Adult Feeding Decreased Longevity in Both Normal-lived (Ra) & Long-lived (La) Strains



The Ra strain are especially sensitive to NaBu, showing significant decreases in longevity at both dosages. The long-lived La animals are only affected by the high dose.

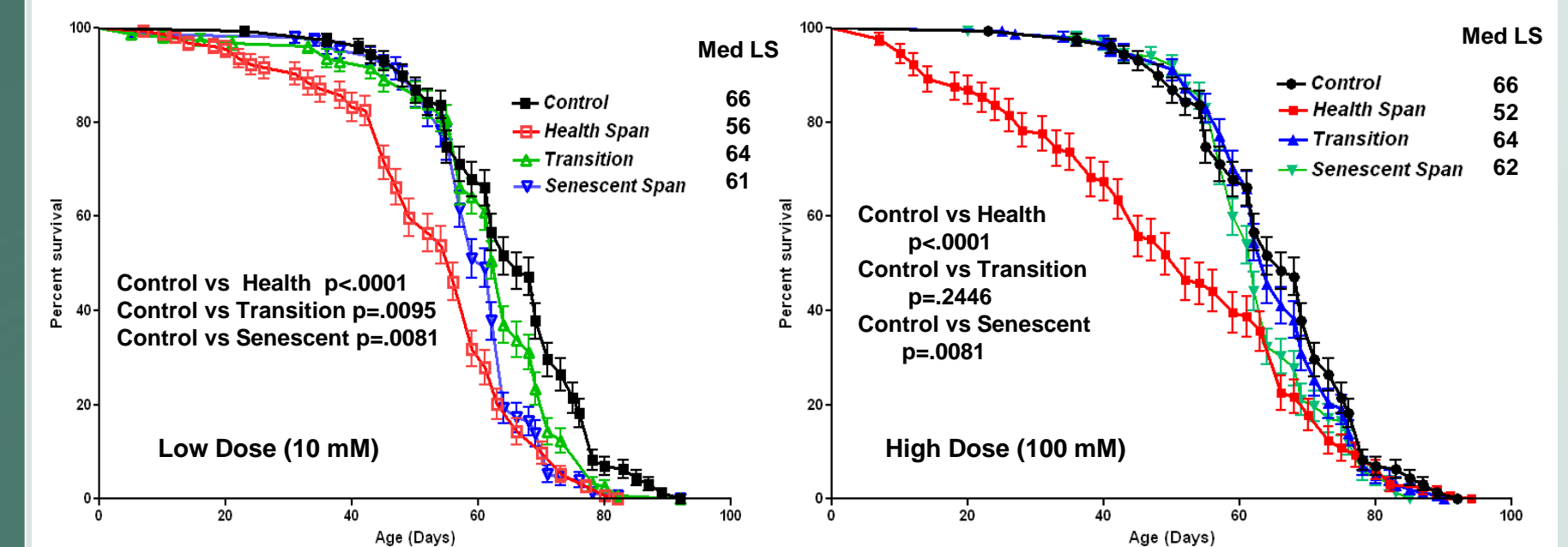
### 2. NaBu Has Beneficial Stage-Specific Effects on Ra Longevity But Only At Low Dose (10mM)



In the Ra normal-lived animals, the health span is insensitive to NaBu feeding at either dose. However, NaBu feeding during the transition and/or senescent span increases the median and maximum longevity of the animals.

## RESULTS

### 3. NaBu Has A Significant Negative Effect on Longevity of the Long-lived La Strain If Administered At Either The Health Span or the Senescent Span



The La long-lived animals only show decreased longevity following NaBu treatment, regardless of the dosage or the life stages involved. This suggests that the La animals depend on HDACi-dependent processes. NaBu acts as a harmful drug for long-lived organisms, but acts as a beneficial late-acting pro-longevity drug for normal-lived organisms.

## CONCLUSIONS

THESE OBSERVATIONS SUGGEST THAT La ANIMALS RELY ON A NaBu-DEPENDENT PROCESS DURING THEIR HEALTH & SENESCENT SPANS.

THE Ra ANIMALS LIKELY RELY ON AN ENDOGENOUS HDACi-DEPENDENT ACTIVITY DURING THEIR HEALTH SPAN BUT NOT DURING THEIR TRANSITION NOR SENESCENT SPANS.. THUS SELECTION FOR LONGEVITY LIKELY RESULTED IN AN ACTIVATION OF HDACi-DEPENDENT GENE EXPRESSION PATTERNS IN LATE LIFE.

THE LATE-LIFE APPLICATION OF NaBu AT THE LOW DOSE ACTS AS A PRO-LONGEVITY DRUG WHICH INCREASES MEDIAN LS BY ~12%

IN A COMPANION POSTER WE DESCRIBE THE CHARACTERIZATION OF AN EARLY ACTING PRO-LONGEVITY DRUG. THE OBVIOUS DOUBLE-DRUG EXPERIMENT IS NOW IN PROGRESS.