Selective Histone Deacetylase Inhibitors as Therapeutics for Huntington's Disease

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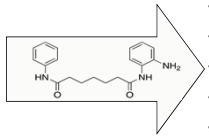
Introduction

The Life Sciences Summer Institute (LSSI) connects high school students to San Diego's Life Sciences Industry since. Students complete a one-week pre-internship "boot camp" training followed by 7-weeks of paid research work experience.

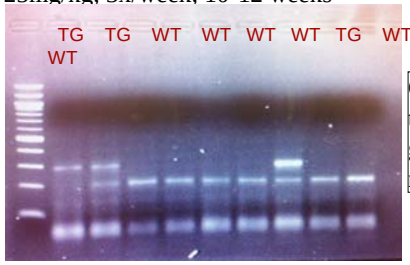
This summer influenced my future career choice by increasing my understanding and appreciation for both research and the under-appreciated creativity in science.

Methods



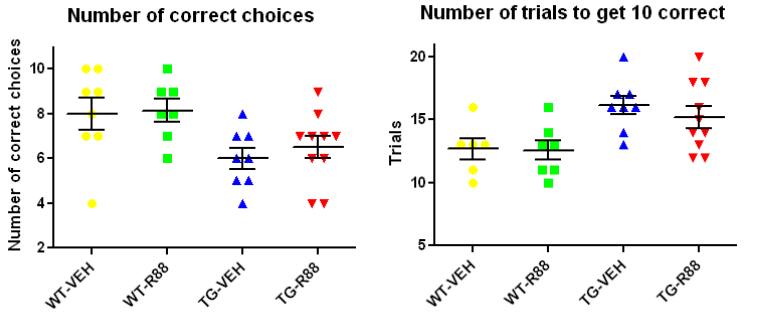
- Body weight
- Rotarod
- Open Field Activity
- Clasping
- Tremors
- Truncal Dystonia

- In-vivo mouse studies
- Groups of Huntington's disease (N171-82Q) transgenic (TG) mice and Wildtype (WT) littermate control mice
- Treatment with R88 or vehicle: subcutaneous injection; 25mg/kg; 3x/week; 10-12 weeks

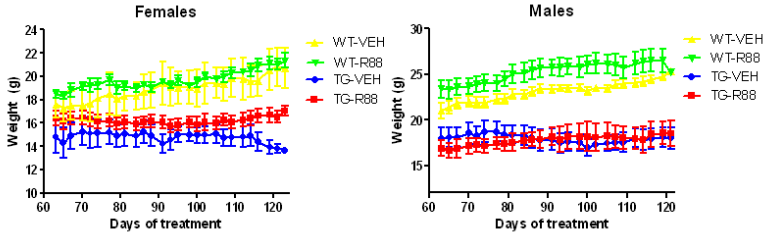


Genotyping was through PCR and gel electrophoresis methods.

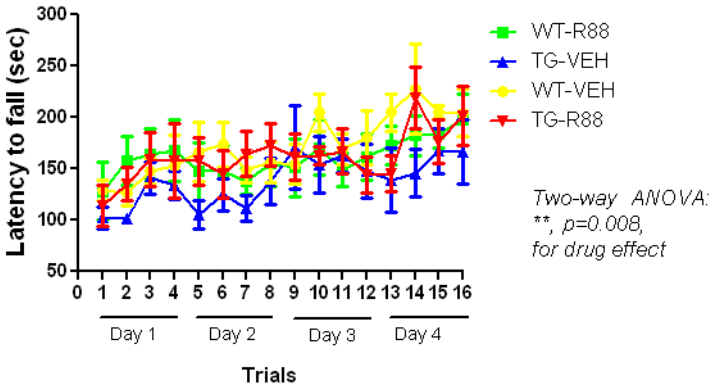
Results



T-Maze Data: Mice were first habituated to a food reward of Froot-Loops, then habituated to the T-Maze, then trained in a forced alternation trial to test spatial navigation and working memory.



Bodyweight Data: Mice were weighed 3 times per week.



Rotarod Data: Measure of balance, coordination, physical condition, and motor-planning. Important in clinical trials due to concern about potential impairment in motor behavior.

Conclusion

- **Goal:** Identify improved compounds for therapeutic application for Huntington's Disease.
- Using a novel Histone Deacetylase (HDAC) 1 and 3 targeting inhibitors at different dose regimens in various HD model systems
- In cooperation with Repligen Corporation (Waltham, MA), who will support the advancement of a lead compound into human clinical trials for HD.
- R88 Results
- Slight improvement in body weight for females
- Slight improvement in cognitive behavior (T-Maze)
- Significant improvement in motor skills (Rotarod)
- Truncal dystonia, clasping, and open field activity were not used in data analysis due to time constraints.
- Continued Testing: additional compounds will be tested in hopes of finding a better clinical candidate
- **Lab Goal:** Utilize genome-wide approaches to investigate the molecular bases of Huntington's disease
- Achieve a better understanding of gene regulation and its dysfunction in neurodegenerative disorders in order to provide a basis for new therapeutic approaches and disease prevention

Acknowledgements

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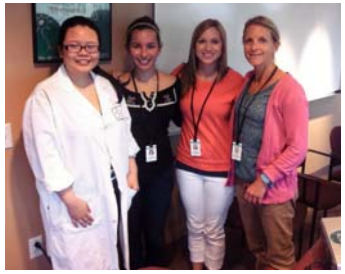

Citations

- Haiqun Jia, Ryan J. Kast, Joan S. Steffan, and Elizabeth A. Thomas, **Selective histone deacetylase (HDAC) inhibition imparts beneficial effects in Huntington's disease mice: implications for the ubiquitin–proteasomal and autophagy systems**, Hum. Mol. Genet. (2012) 21 (24): 5280-5293 first published online September 10, 2012doi:10.1093/hmg/dds379
- Graphs: Dr. Beth Thomas, PhD.