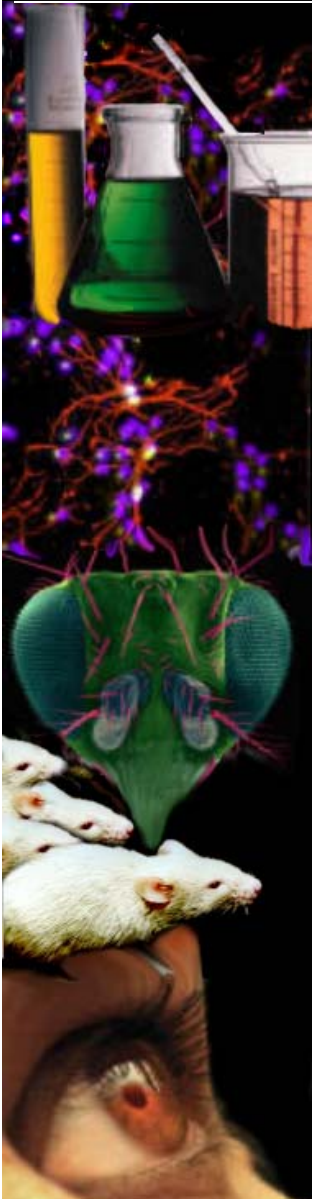


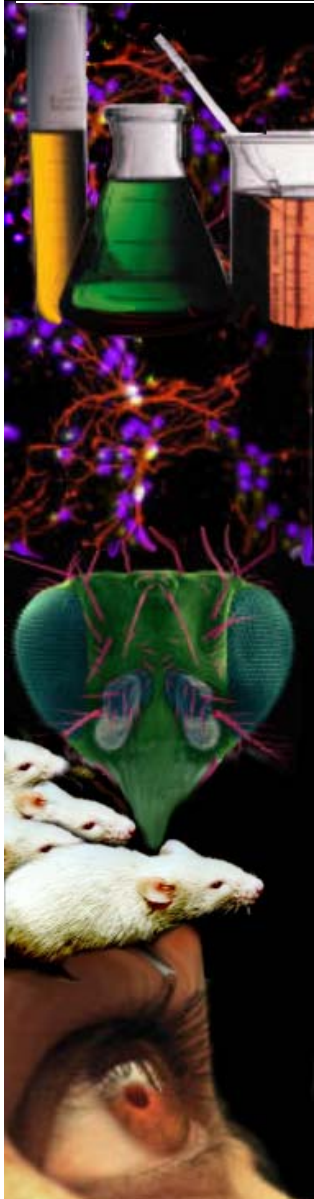
Models for Neurological Disorders



Huntington Disease

HD

Huntington Disease



R6/2 is the first developed and most widely used transgenic model for HD

Carries exon-1 of mutant human huntingtin gene ~120 CAG repeats

Observed phenotype ~ 6 weeks of age

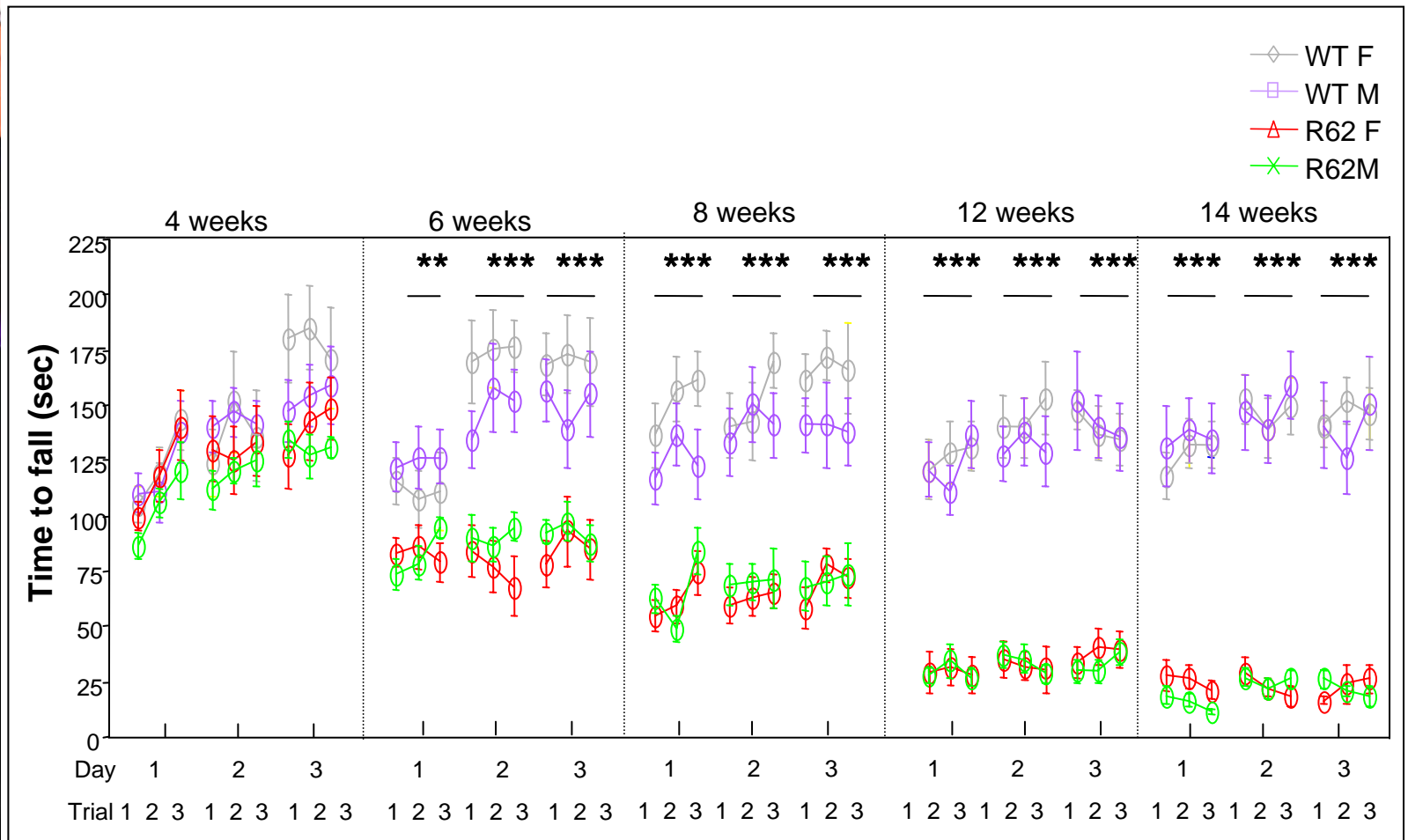
Phenotype includes: changes in body weight, declines in open field activity and rotarod performance and cognitive deficits

Neuropathology includes neuronal intranuclear inclusions and cellular dysfunction

Median premature death at ~ 16 weeks

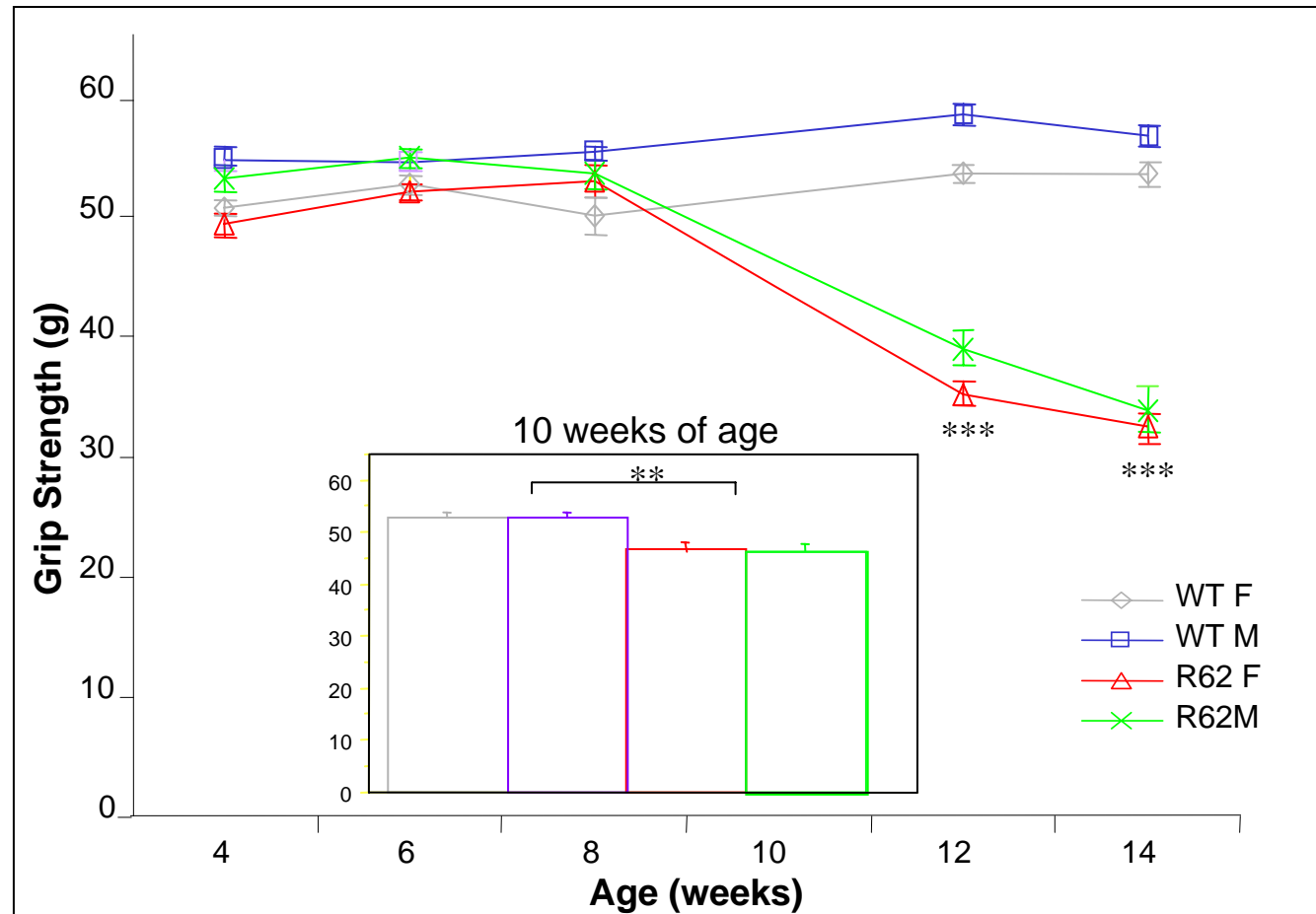
Rotarod

Impaired Rotarod Performance in R6/2 Mice



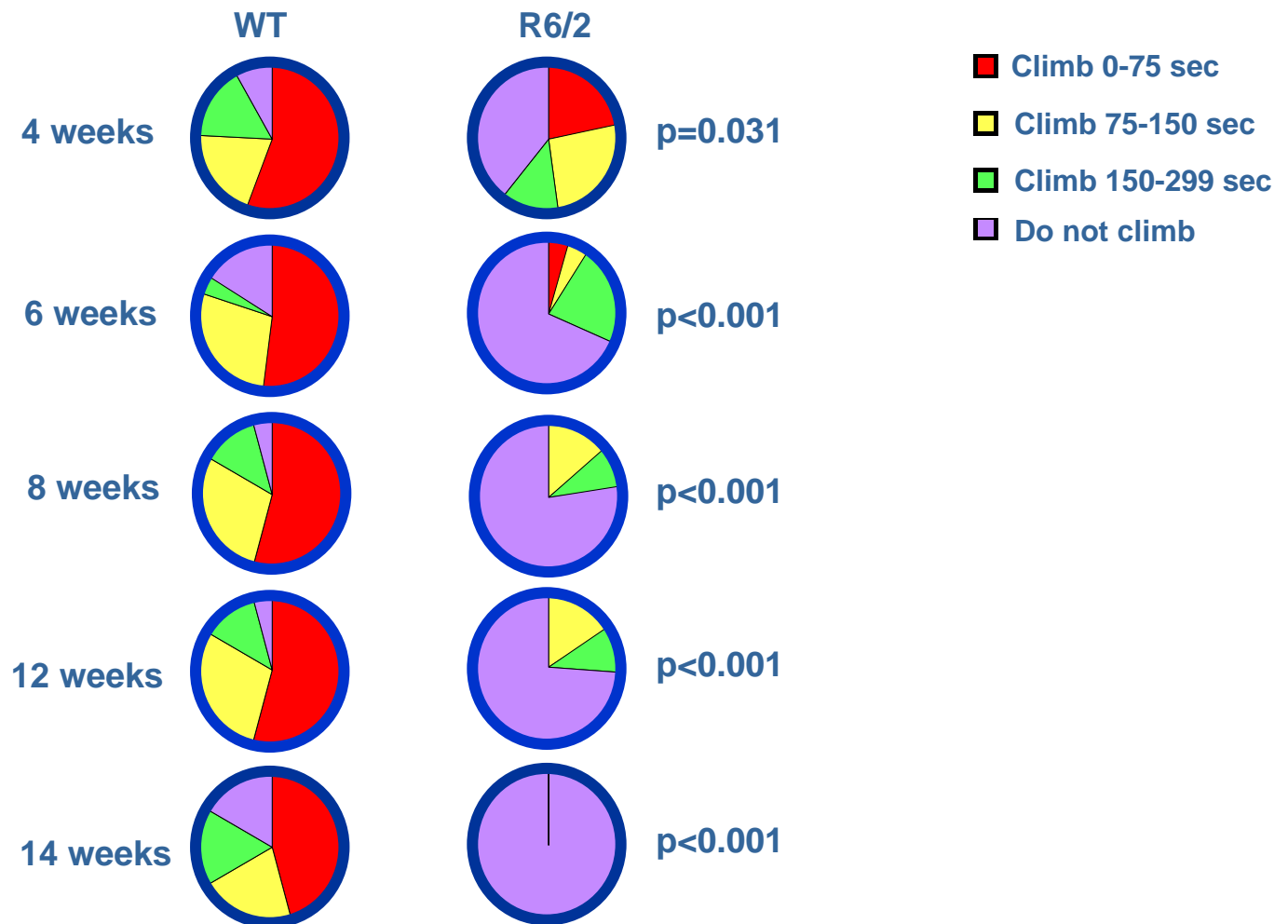
Grip Strength

Reduced grip strength starting at 10 weeks



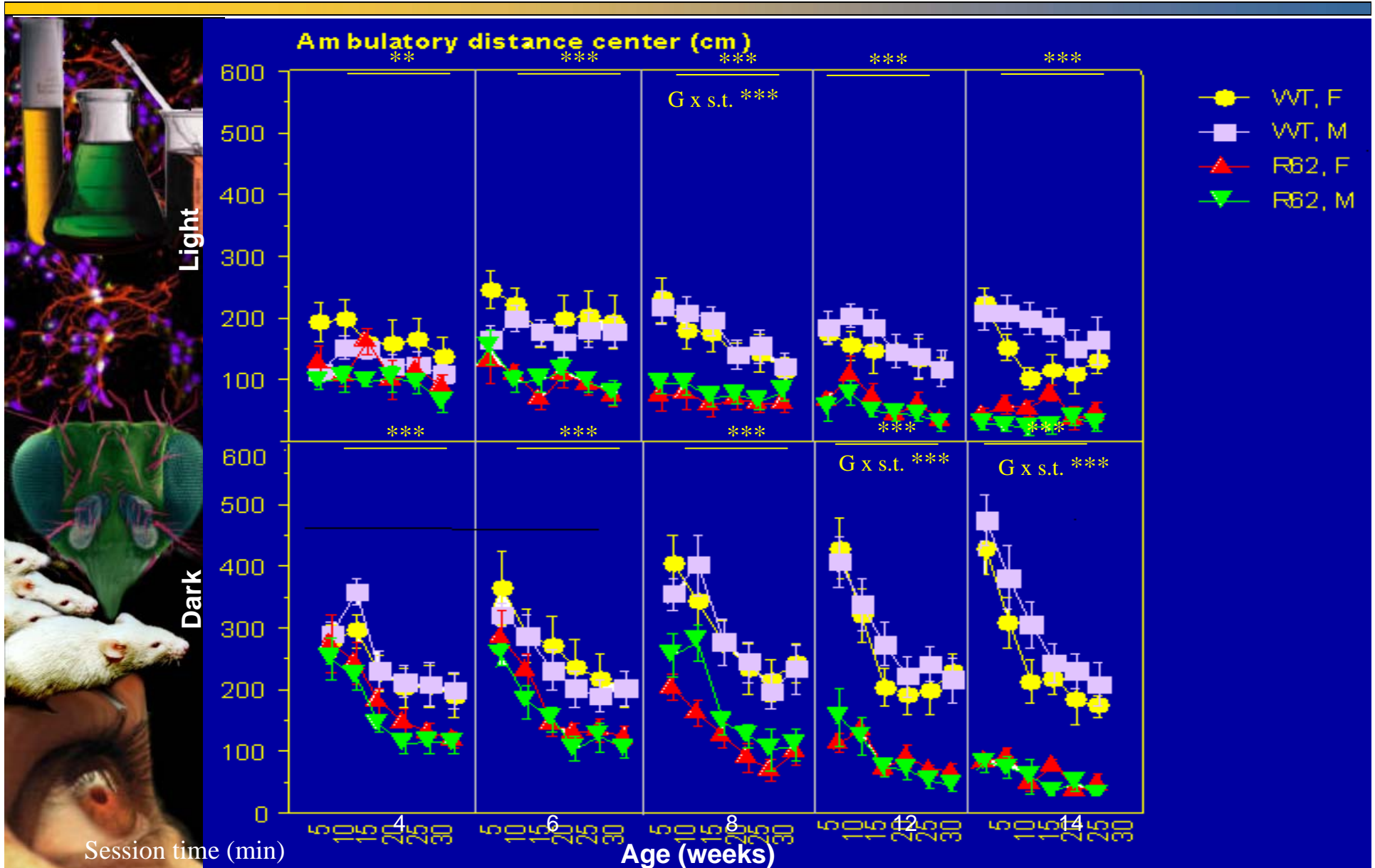
Rearing - Climbing

R6/2 mice climb less with age



Open Field

Locomotion in the center with R6/2 mice



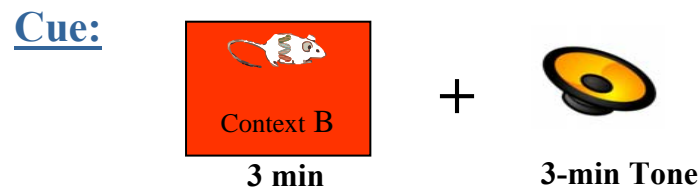
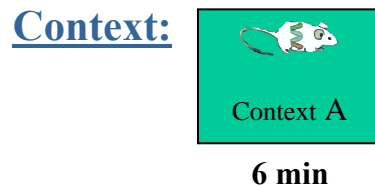
Cognitive deficits in R62 mice

Mice who receive an aversive stimulus paired to a tone in a context will freeze upon re-presentation of the context (Contextual Fear Conditioning) or the tone (Cued Fear Conditioning).

Training:



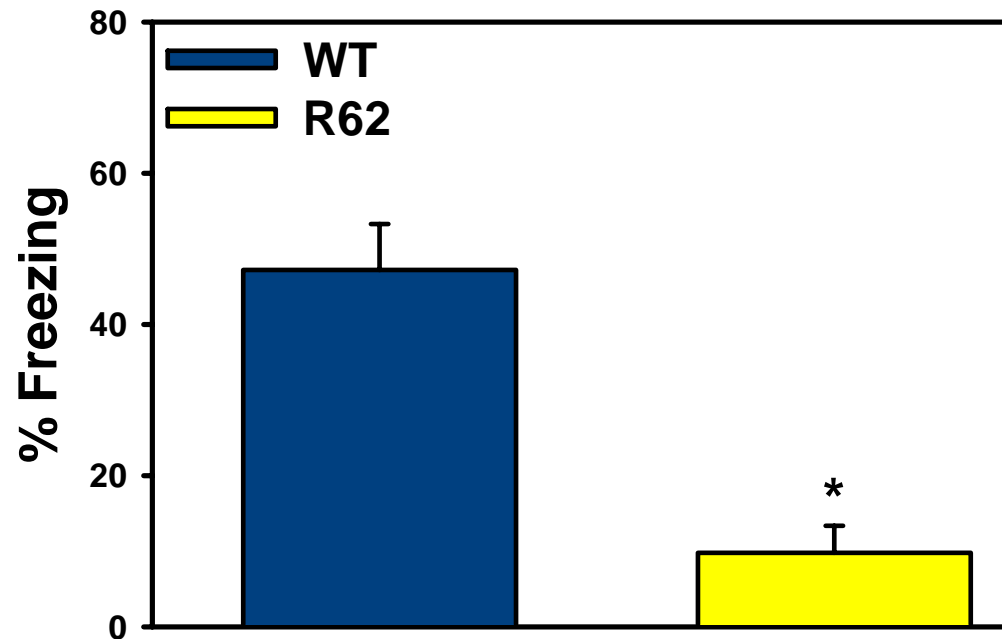
Testing (after 24 hrs):



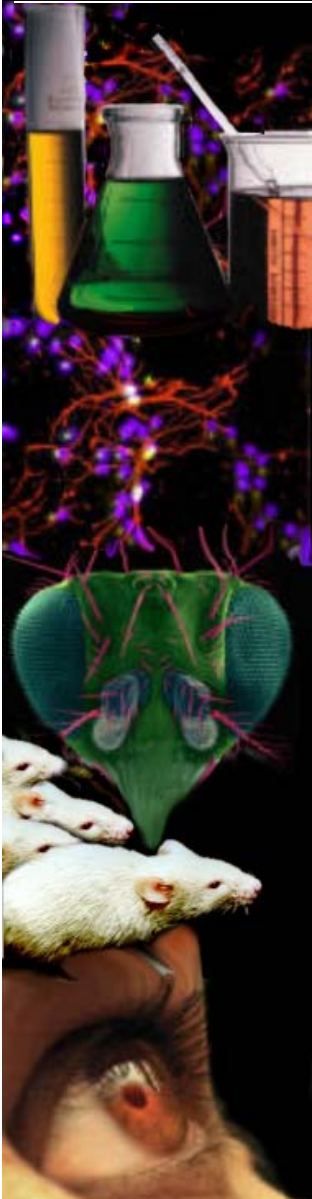
Cognitive deficits in R62 mice

➤ Contextual Fear Conditioning

- R62 mice display less freezing compared to WT mice 24 hrs after training.



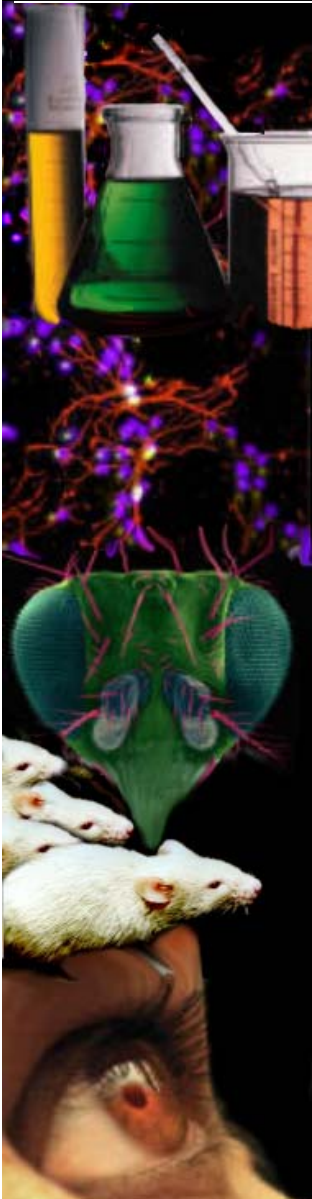
9 weeks of age



Cognitive deficits in R62 mice

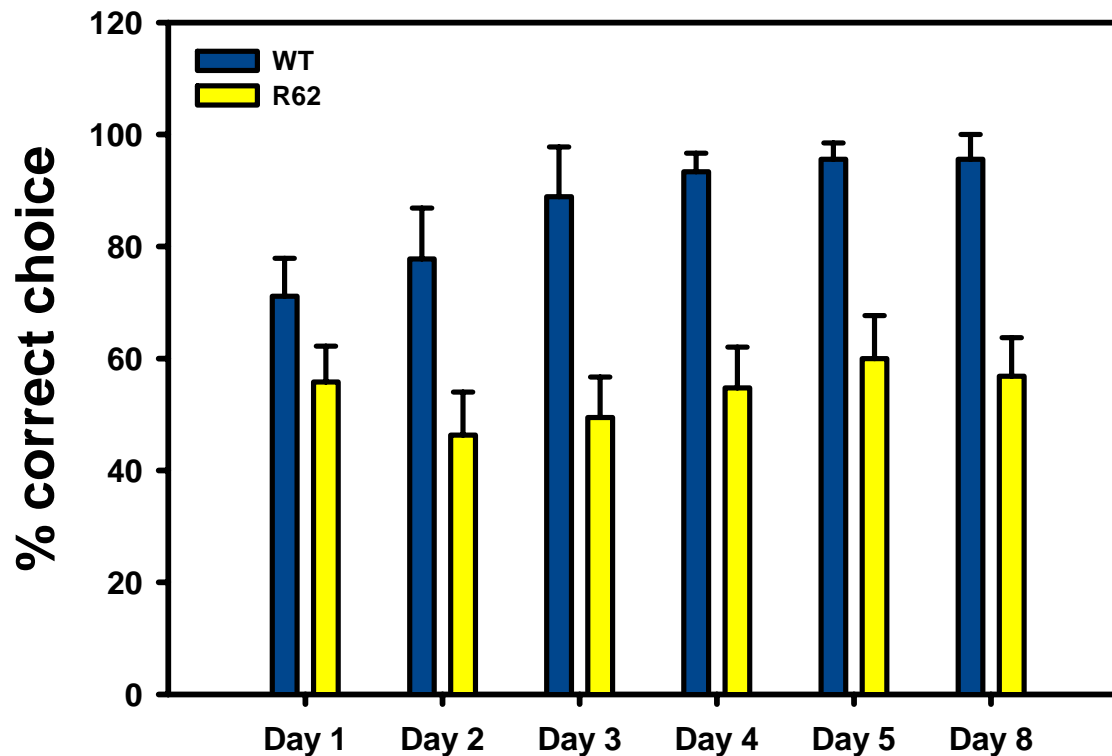
2 Choice Swim Tank Test

- The swim tank is a simple learning protocol where mice learn to escape an aversive water environment by climbing onto a platform.
- The location of the platform is signaled by a light at one end of the aquarium, so mice need only to learn to go away from or toward the light.
- Mice are placed in the center of a water-filled aquarium and the choice of direction towards the platform is recorded.



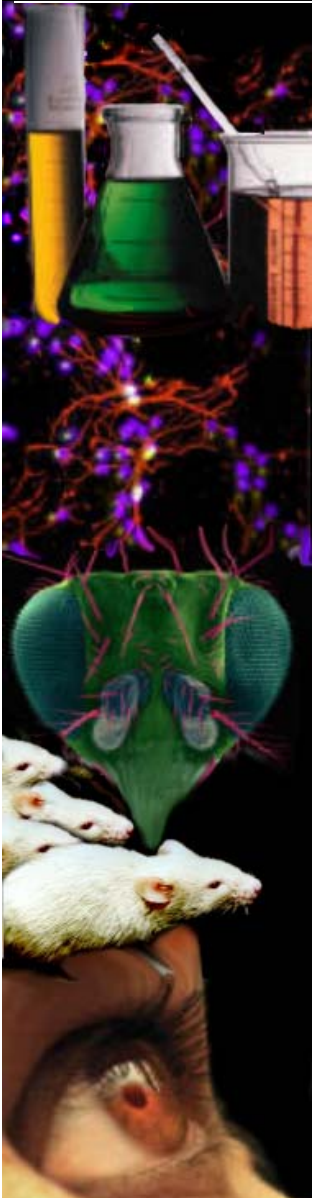
Cognitive deficits in R62 mice

- ➔ R62 mice show acquisition deficits in the 2 choice swim tank test
- ➔ Mice were given 5 trials each day to locate a hidden platform.

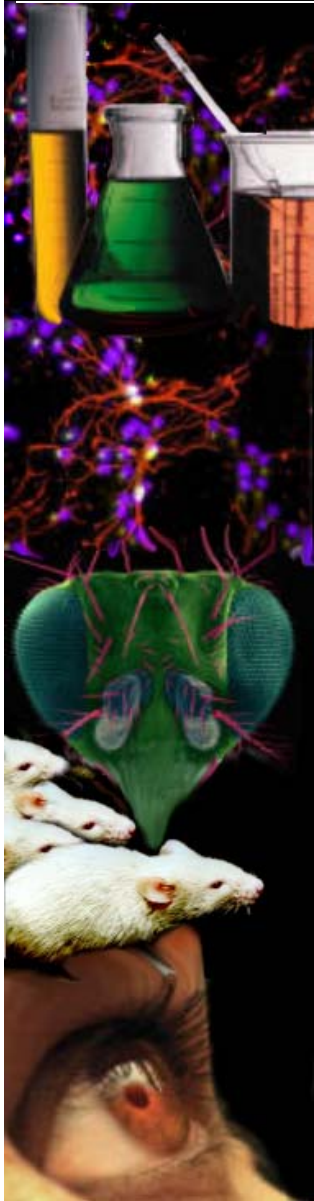


7-8 weeks of age

Confidential



Cognitive deficits in R62 mice

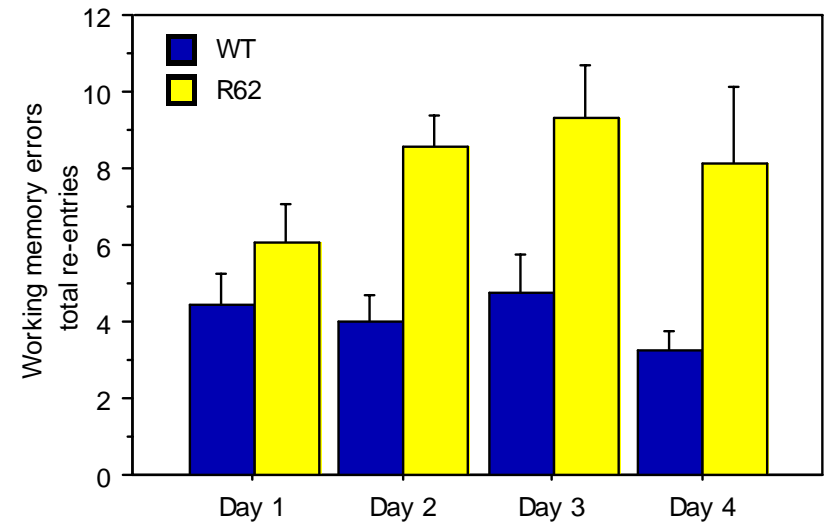
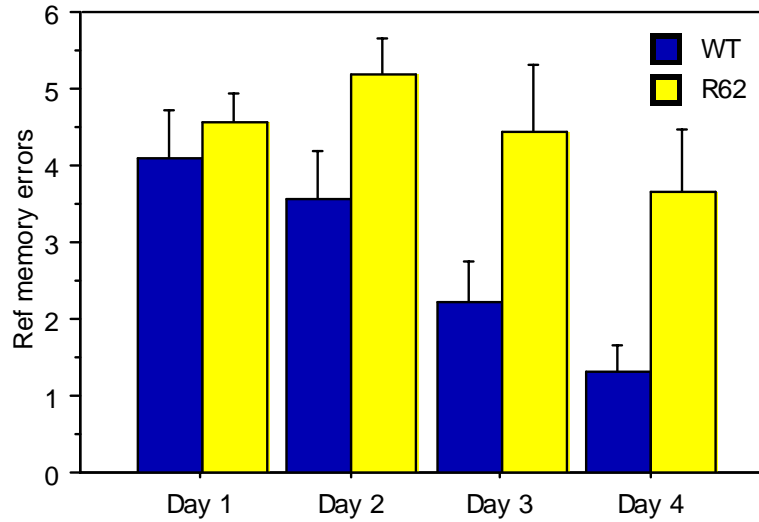
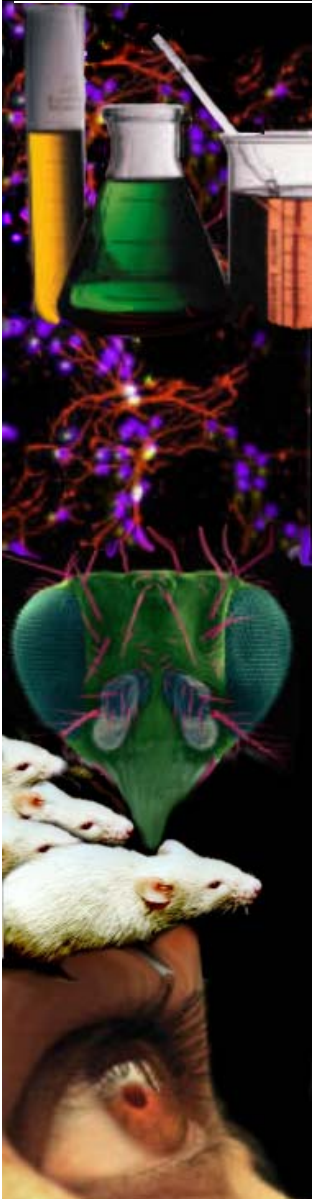


- ▶ **Holeboard measures a mouse's ability to remember the location of 4 baited holes in a 16 hole chamber. This is used to assess both reference memory and spatial working memory performances.**
- ▶ **Reference memory errors are defined as re-entries into non-**



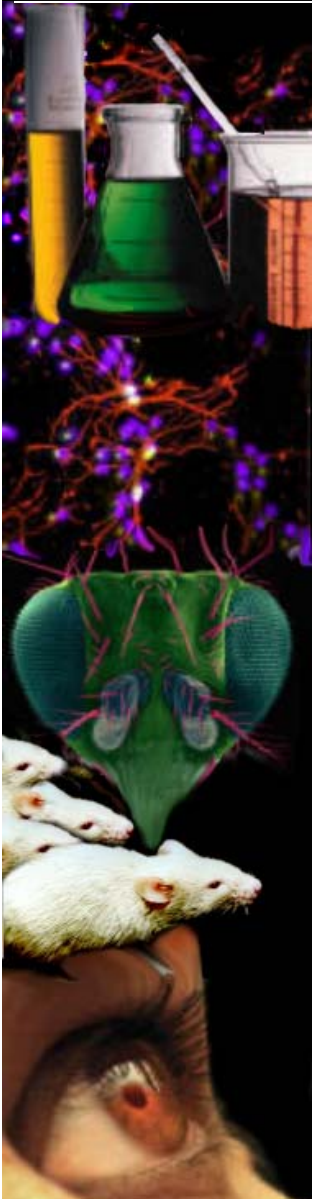
PsychoGenics

Reference memory errors and working memory errors are higher in R62 mice compared to WT mice



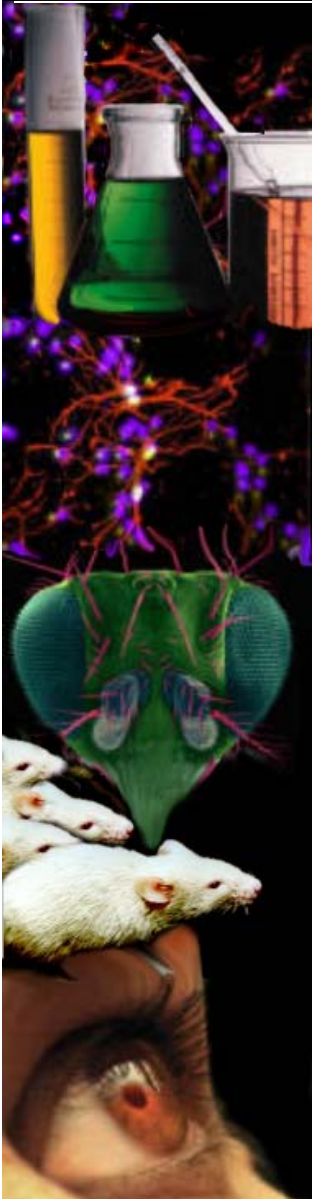
6 weeks of age

Confidential



Amyotrophic Lateral Sclerosis - ALS

SOD1 transgenic mouse



SOD1 is the most commonly used transgenic model for ALS

Contains a mutant allele human SOD1 (G93A) substitution

Observed phenotype ~ 12 weeks of age

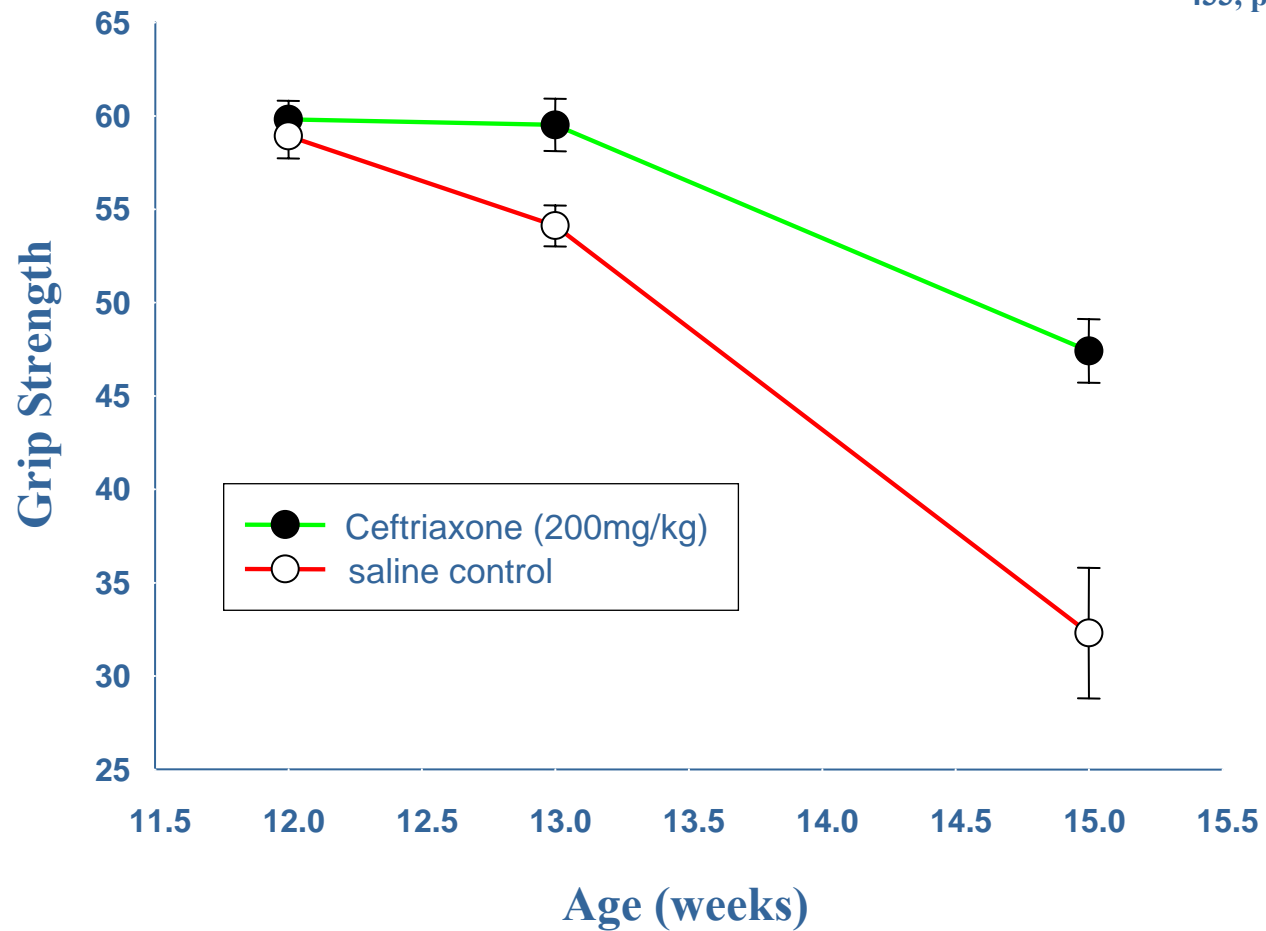
Phenotype includes: changes in body weight, declines in grip strength and general motor activity

Median premature death at ~ 18 weeks

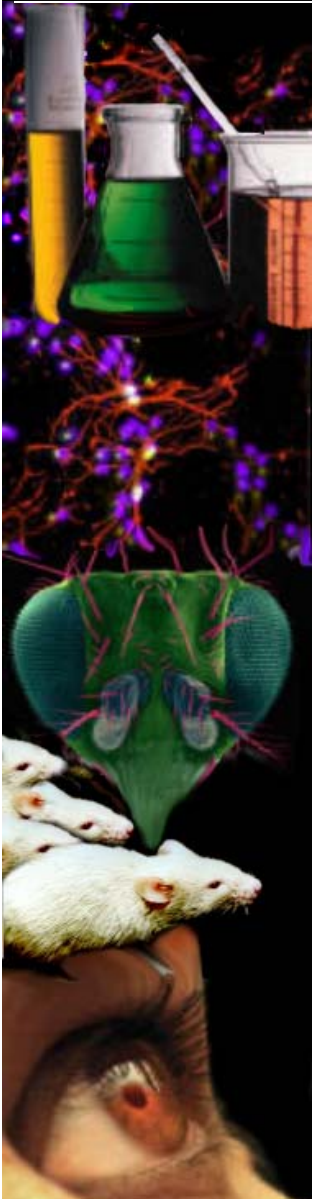
Grip Strength

Ceftriaxone Treatment in SOD1 Mice

(Nature, Jan 2005, vol. 433, pg 473-477)



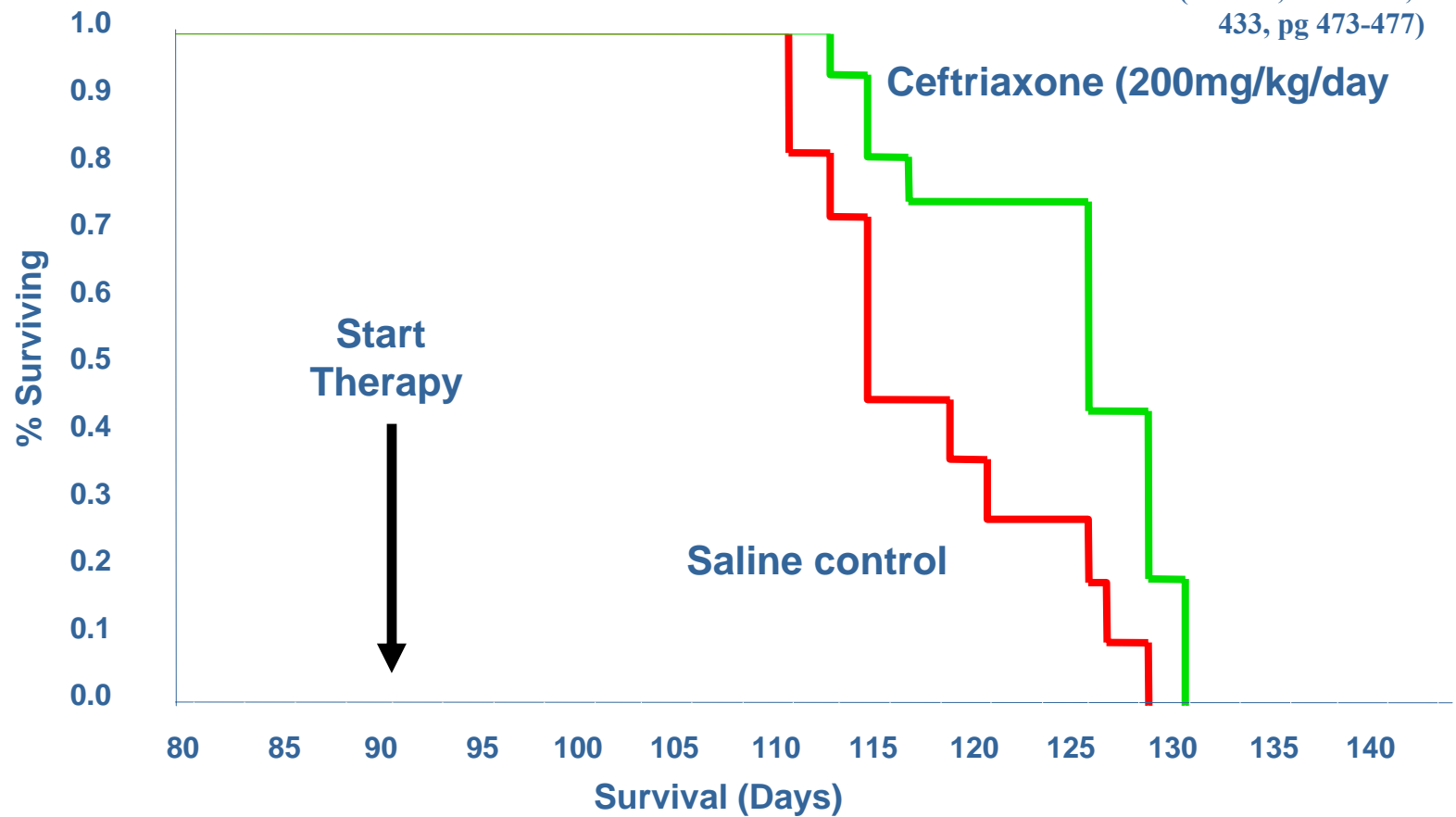
Confidential

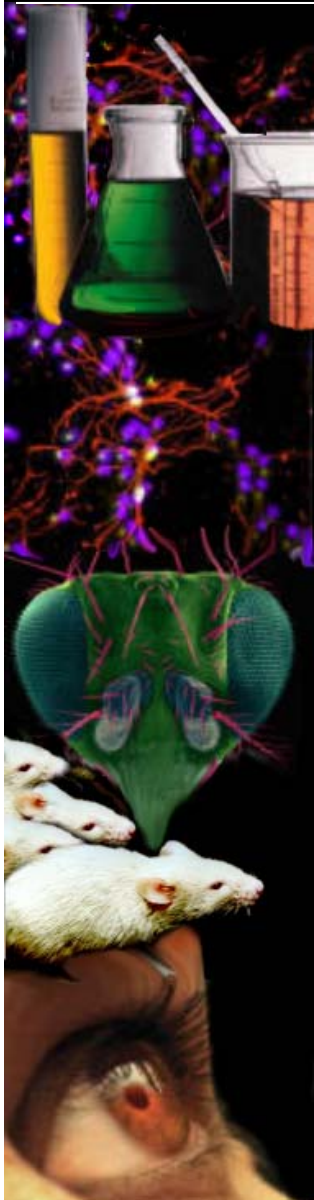


Survival

Ceftriaxone Treatment in SOD1 Mice

(Nature, Jan 2005, vol. 433, pg 473-477)

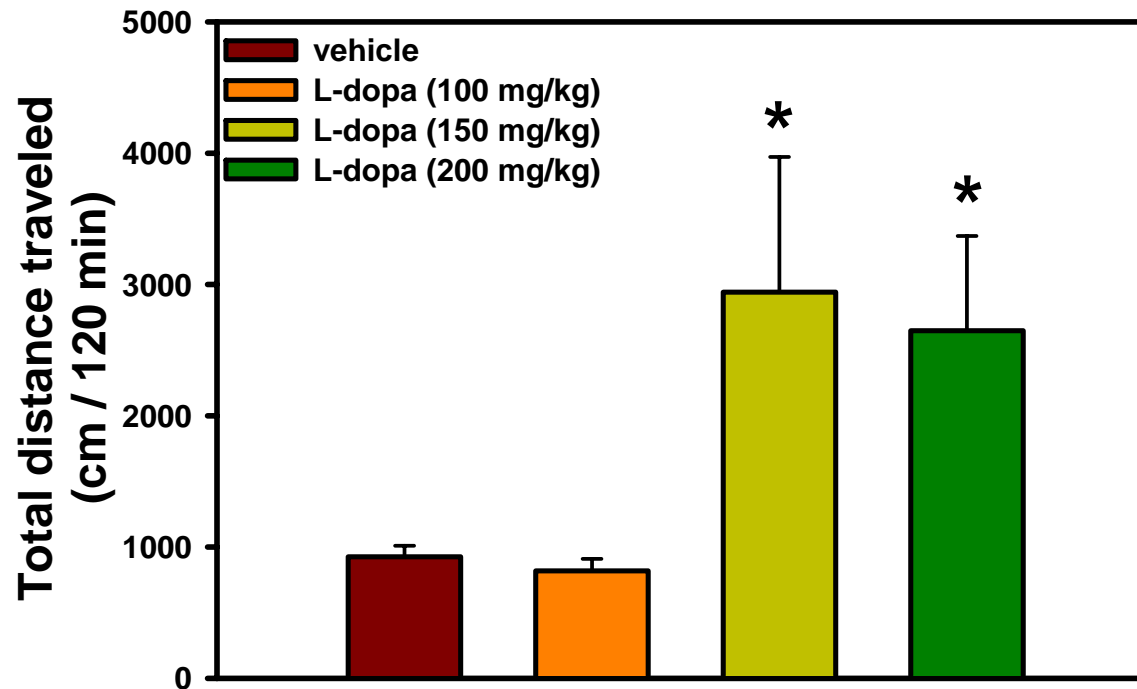
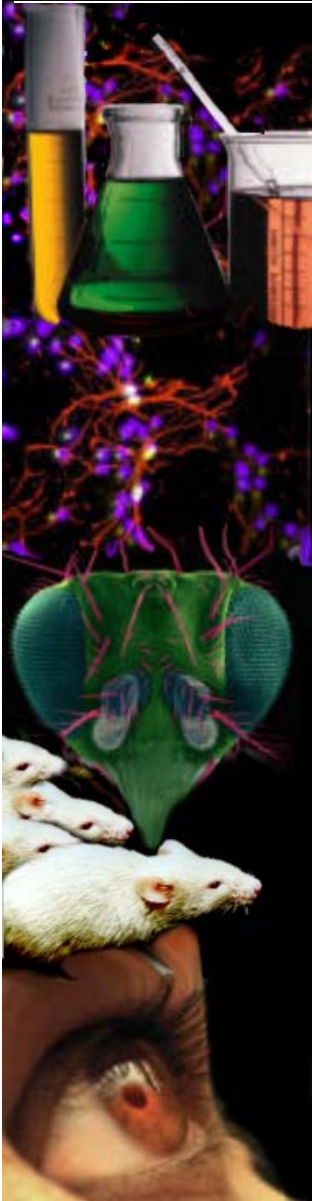


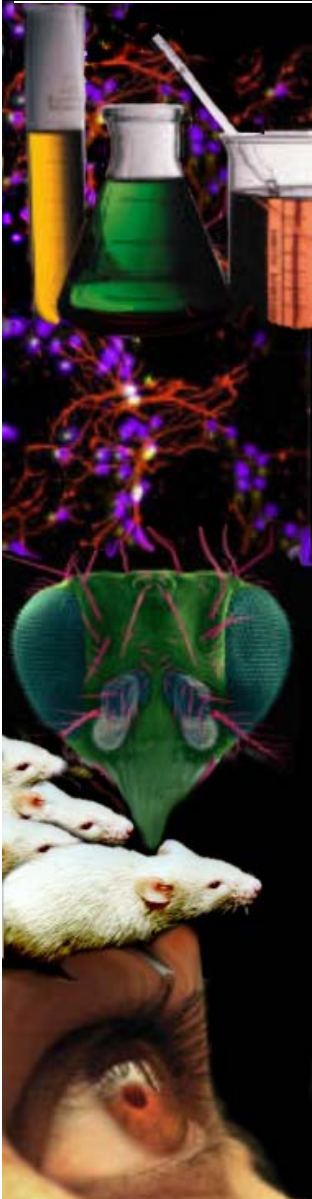


Parkinson Disease

PD

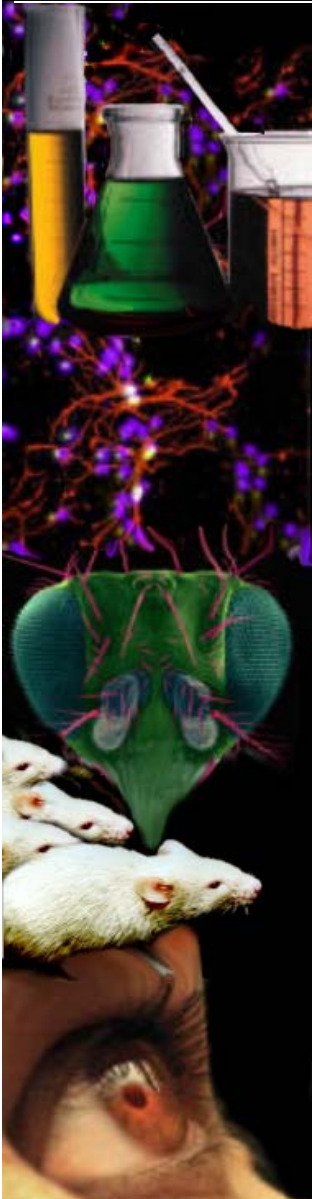
Reserpine-induced hypoactivity





Spinal Muscular Atrophy

SMA



There are three forms of human SMA with varying severities.

The SMN2 $\Delta 7$ transgenic model provides a descriptive phenotype for testing compounds

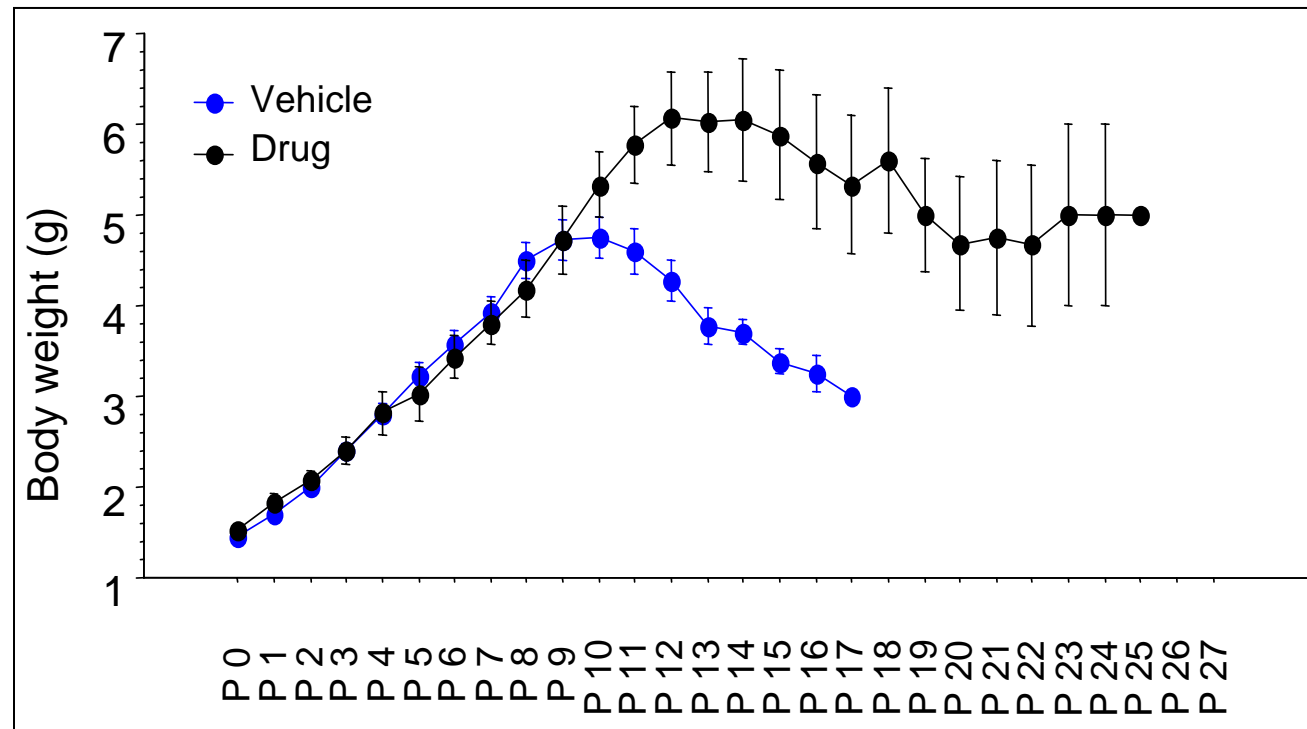
Phenotype includes: changes in body weight, declines in motor function

Median premature death at ~ 15 days

Developed a multi-functional battery of tests to rapidly screen compounds using the SMN2 $\Delta 7$ model

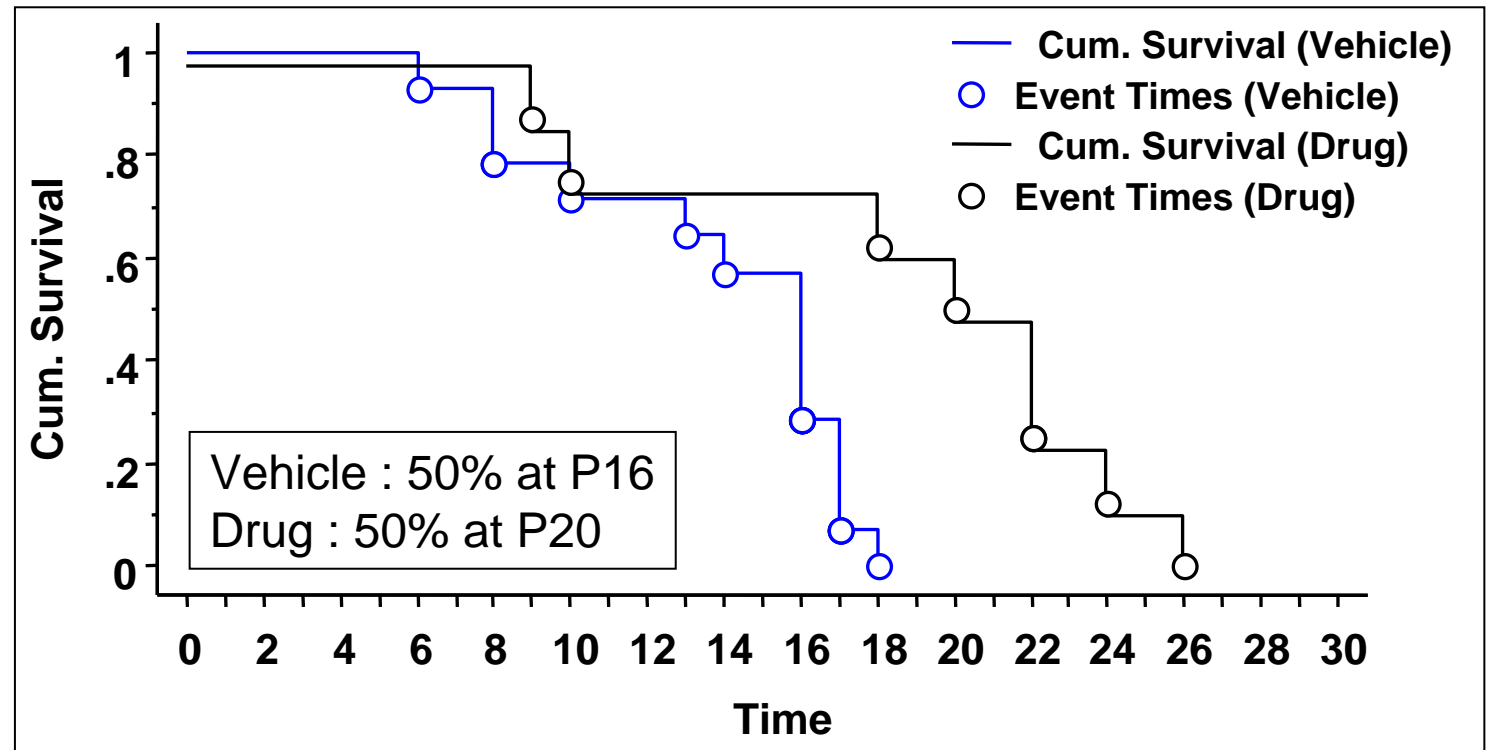
Body Weight

Drug candidate prevents the decline in body weight normally observed at ~P8

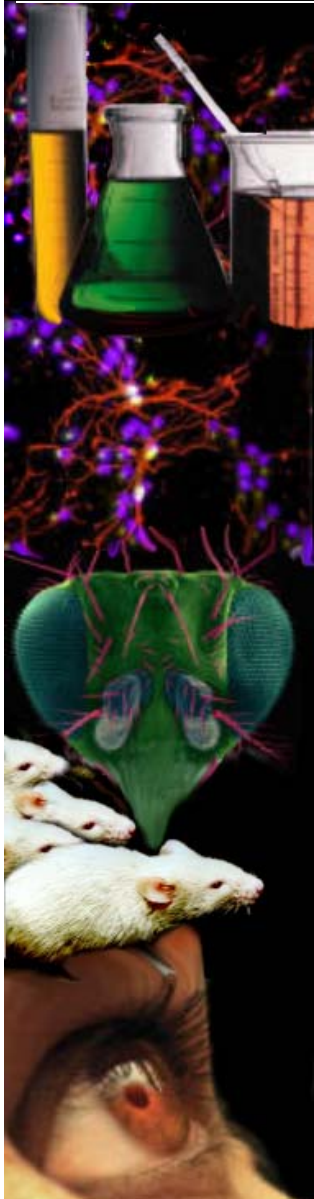


Survival

Drug candidate increases time of survival



Tube Test: Hind Limb Strength



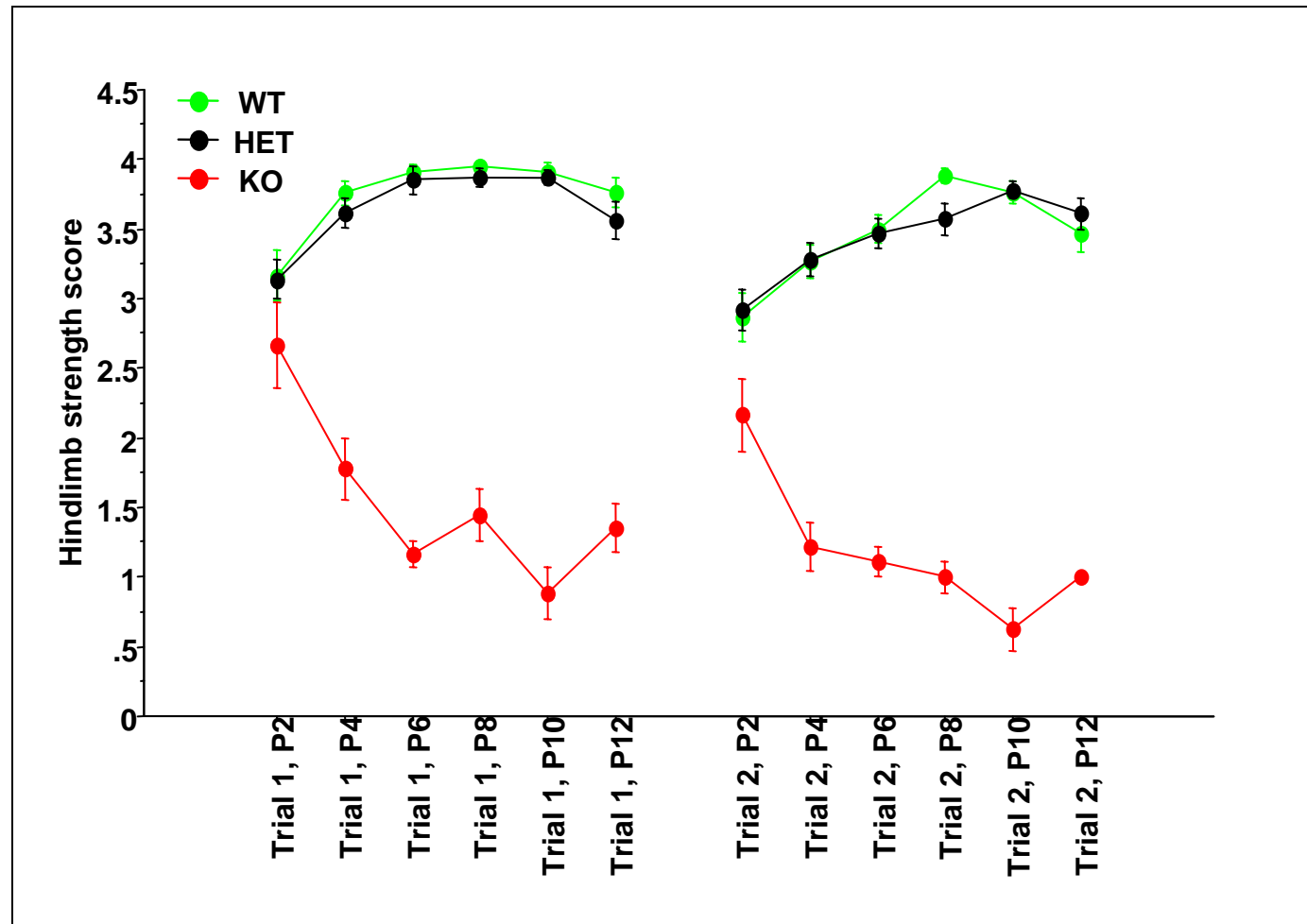
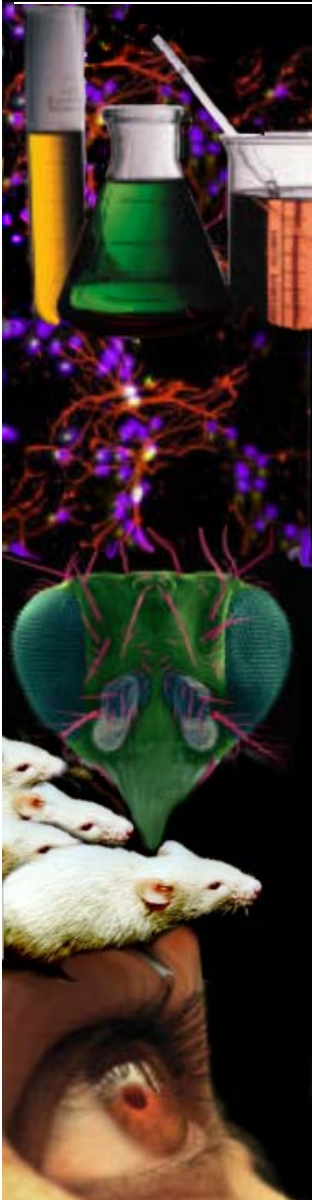
The tube test is a novel test developed at PsychoGenics designed to test neonates (P 2 – 12) hind-limb strength (HLS) and general body tone.

The test is performed in 2 consecutive trials

Parameters measured:

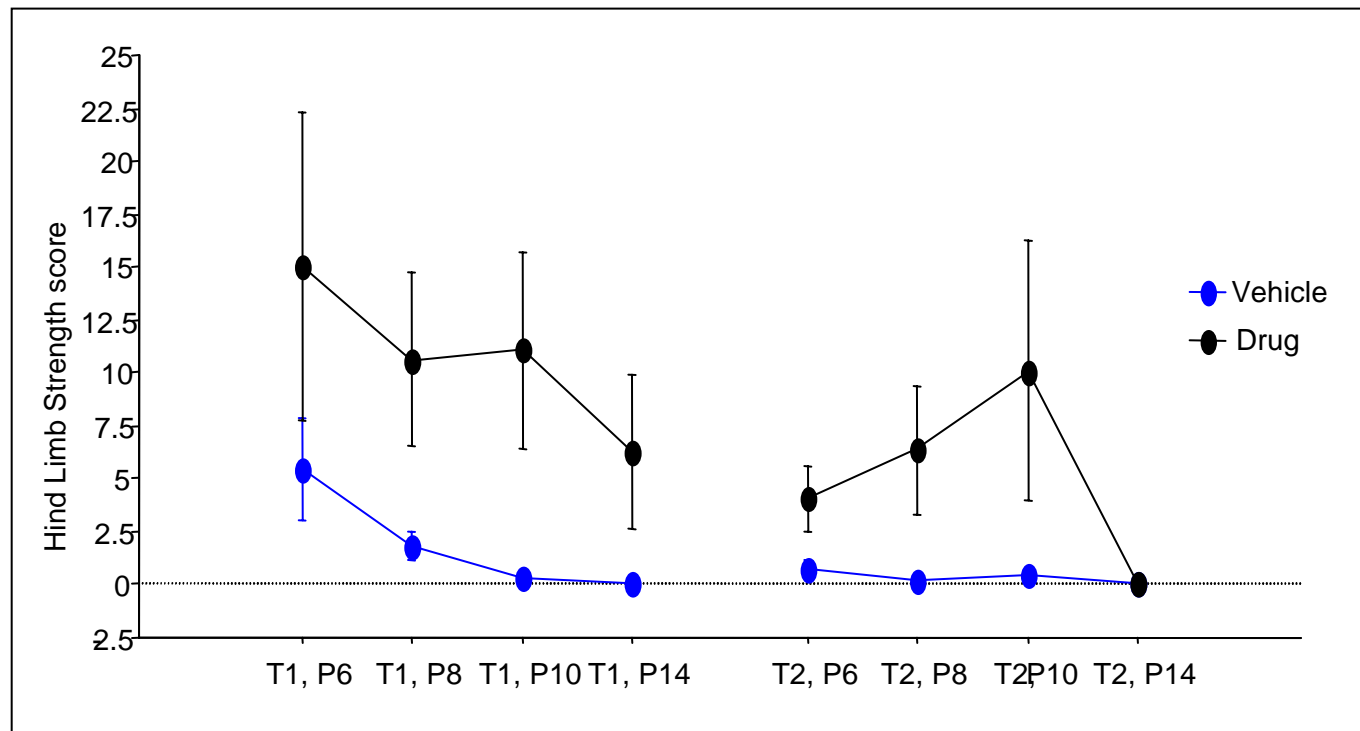
- 1) Time spent hanging (sec)
- 2) Number of pulls
- 3) HLS score (0 – 4)

Tube Test: Hind Limb Strength Score

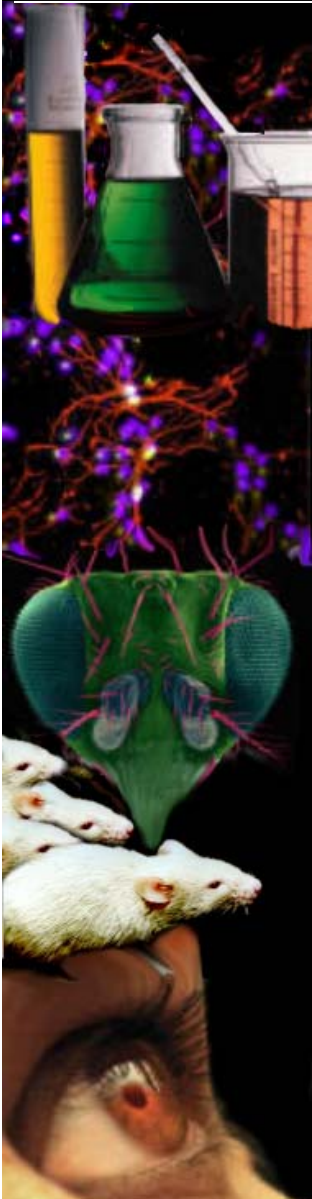


Tube Test: Hind Limb Strength

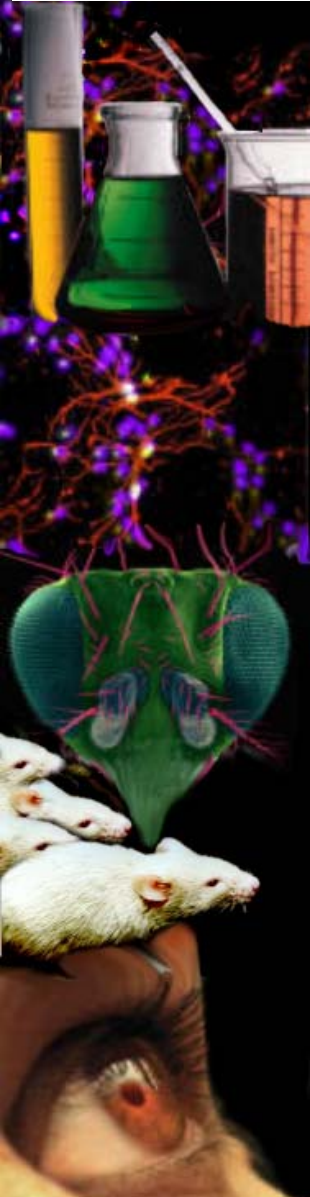
Drug candidate increases motor strength as measured by hind limb strength



Phenotyping



Phenotyping



- **Phenotyping can involve:**
 - **Comprehensive list of behavior tests that encompass a wide range behaviors**
 - **An abridged list of tests on generalized areas of behavior**
 - **Specific tests in the area(s) of interest eg. psychosis and/or cognition**

Phenotyping

The following is a list of standardized behavior tests used for phenotyping.

We require two groups of mice to accommodate tests that cannot be run on the same animal.

Group A

- Paw Print
- Grip Strength
- Visual Cliff
- Rotarod
- Elevated Plus Maze
- Open Field
- Holeboard
- PTZ

Group B

- Stress Induced Hyperthermia
- Metabolic Cages
- Pre-pulse Inhibition of Startle
- Forced Swim
- Tail Flick
- Amphetamine
- Formalin

