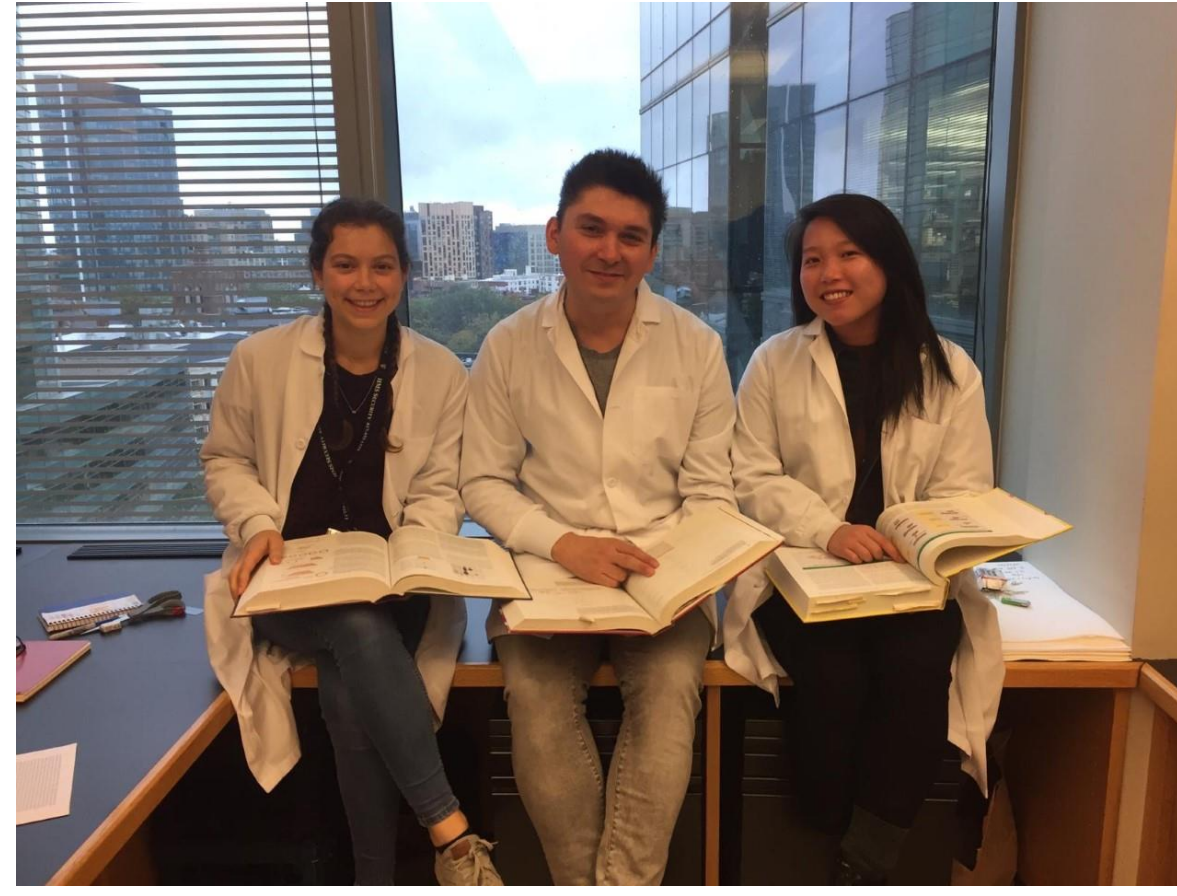


## Maria Moran

Harvard Medical School  
Department of Genetics  
Yankner Laboratory  
Supervisor: Dr. Liviu Aron  
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### BACKGROUND

REST is a basic leucine zipper transcription factor that acts as a scaffold and recruits chromatin-modifying enzymes to coordinate epigenetic changes.

It is implicated in many diseases including:

- Huntington's
- Parkinson's
- Alzheimer's
- Epilepsy
- Memory
- Neuropathic pain
- Deafness
- Cancer

Alzheimer's disease is a neurodegenerative disease.

Pathology:

- Amyloid beta plaques
- Hyperphosphorylated tau tangles
- Brain inflammation
- Brain atrophy

Prevalence: 10 % of adults over 65 years old  
Cost: \$549 billion per year in the US alone

Ageing causes deterioration of function and increases the risk of many diseases including:

- Neurodegenerative diseases
- Cardiovascular disease
- Type 2 diabetes
- Cancer
- Osteoporosis
- Hypertension

### MY EXPERIENCE

I found the team at the Yankner lab friendly, welcoming, and willing to help and teach me. I learnt a lot and became a lot more confident. I loved moving abroad, there was so much to explore in the city and surrounding areas. It was also easy to take trips further away such as NYC and Puerto Rico.

### AIMS

We identified several REST activators which we hypothesised would alleviate the symptoms of ageing, Alzheimer's, and inflammation.

Our aims were to investigate the effects of these REST activators on brain function, health span, and lifespan and to describe the cellular and molecular mechanisms that underly these effects.

### METHODS

I learnt and used many techniques over the course of my placement including:

- Mouse colony maintenance
- Genotyping
- PCR and qPCR
- Sample preparation
- Protein concentration assay
- Western blotting
- Protein carbonylation assay
- Lipid peroxidation assay
- LA-ICP-mass spectrometry
- Cell culture treatment
- Behavioural testing

I worked with our mouse models. We had several different strains including REST knockouts, AD models, and inflammation models.

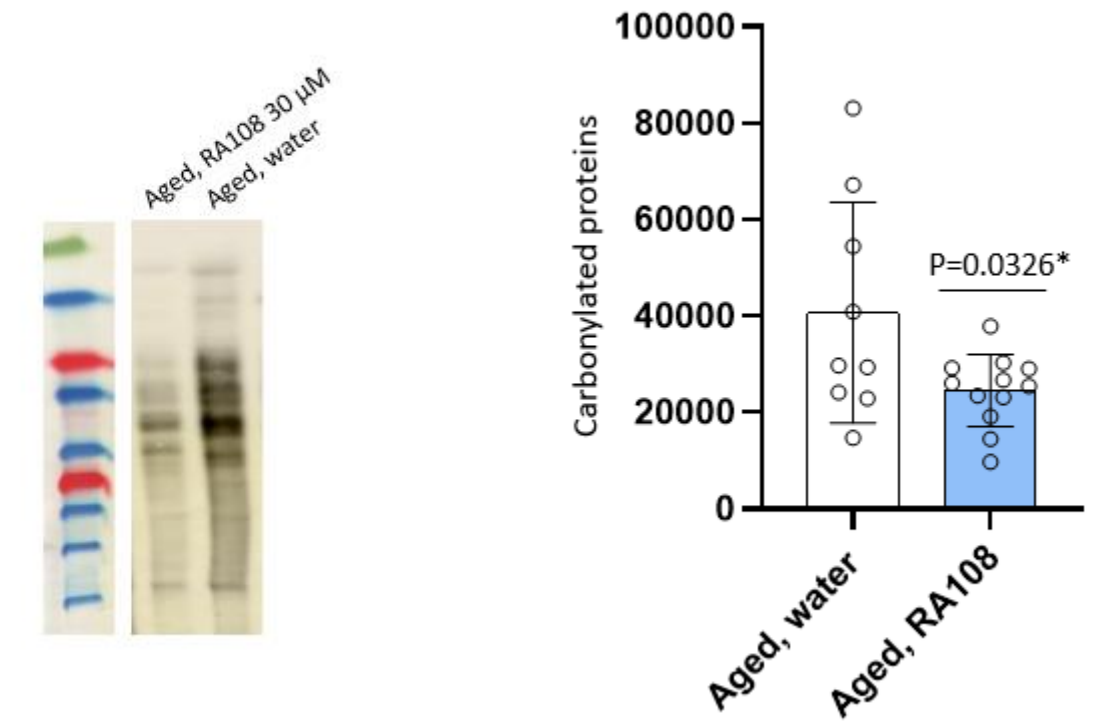
I had to check the mice every day, looking for dead and ill mice, including dermatitis, tumours, eye diseases, and poor body condition.

I had to genotype new litters and perform behaviour tests on treated mice.

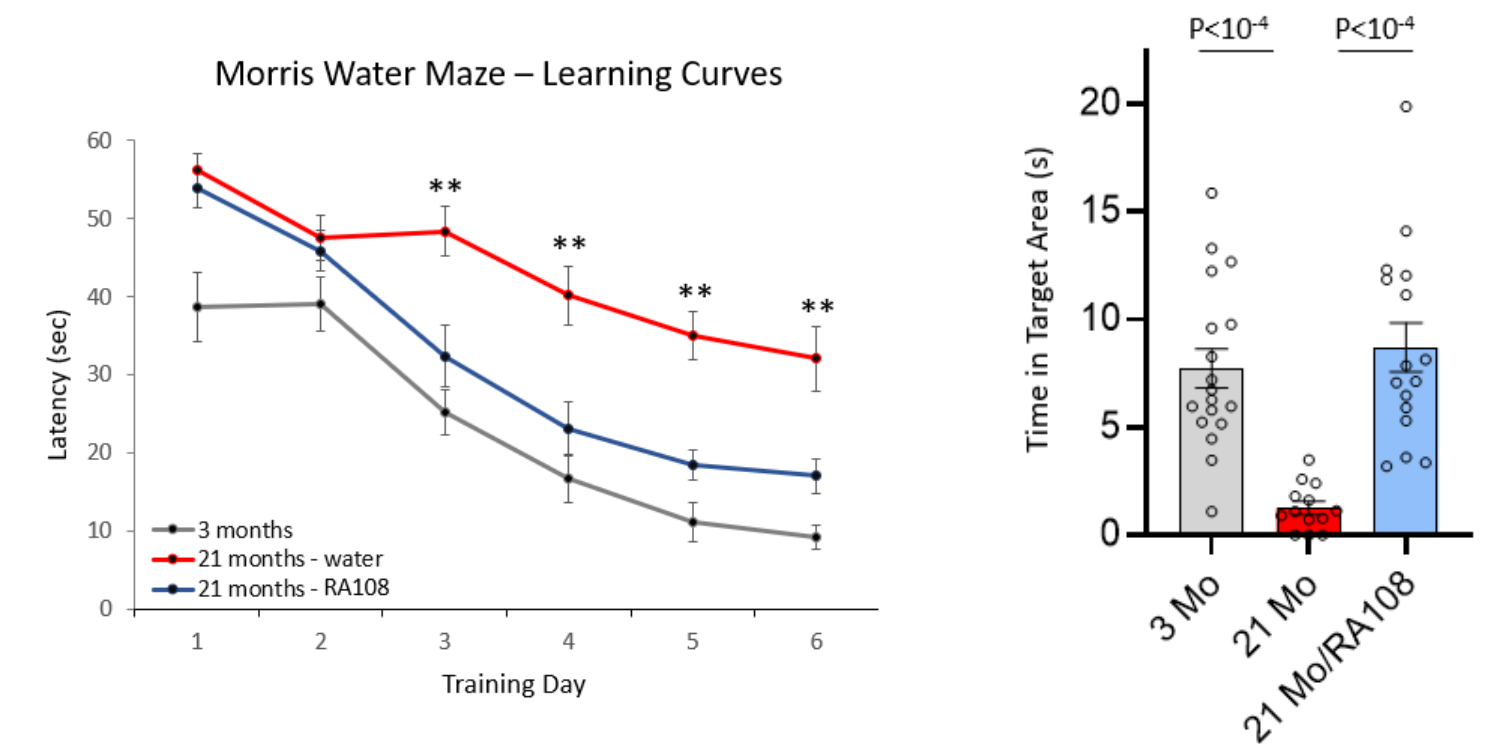
I also worked in the lab, primarily doing Western blots and PCR. I carried out other assays, worked with cell cultures, and learnt about staining.

### RESULTS

Below are a couple of examples of the results obtained from this research, demonstrating the positive impacts of our drugs on ageing and Alzheimer's.



In aged mice, the REST activator RA108 significantly decreased protein carbonylation, an indicator of oxidative damage. Oxidative damage increases with age and disrupts cell function. This suggests that **REST activation may protect against oxidative damage during ageing.**



Aged mice treated with RA108 improved learning (left) and memory (right) in the Morris water maze. The effects are consistent with a rejuvenation of brain function. This suggests that **REST activation protects against age-related cognitive decline.**

Other results from our experiments show that REST knockout impairs cognitive function while REST activation upregulates proteins in the autophagy and unfolded protein response pathways. These play a critical role in preventing accumulation of misfolded proteins, such as amyloid beta and tau.

### CONCLUSIONS AND FUTURE WORK

Our REST activators alleviate pathology and cognitive decline in both Alzheimer's disease mouse models, and mouse models of ageing. They also improve aspects of ageing and may promote successful ageing.

REST activators may be tested in other models of Alzheimer's disease and ageing. They may also be tested in human clinical trials. Taken together, our results indicate that REST activation represents a novel neuroprotective strategy during ageing.

