Rewiring Memory: How Biology and Technology Are Transforming the Aging Brain

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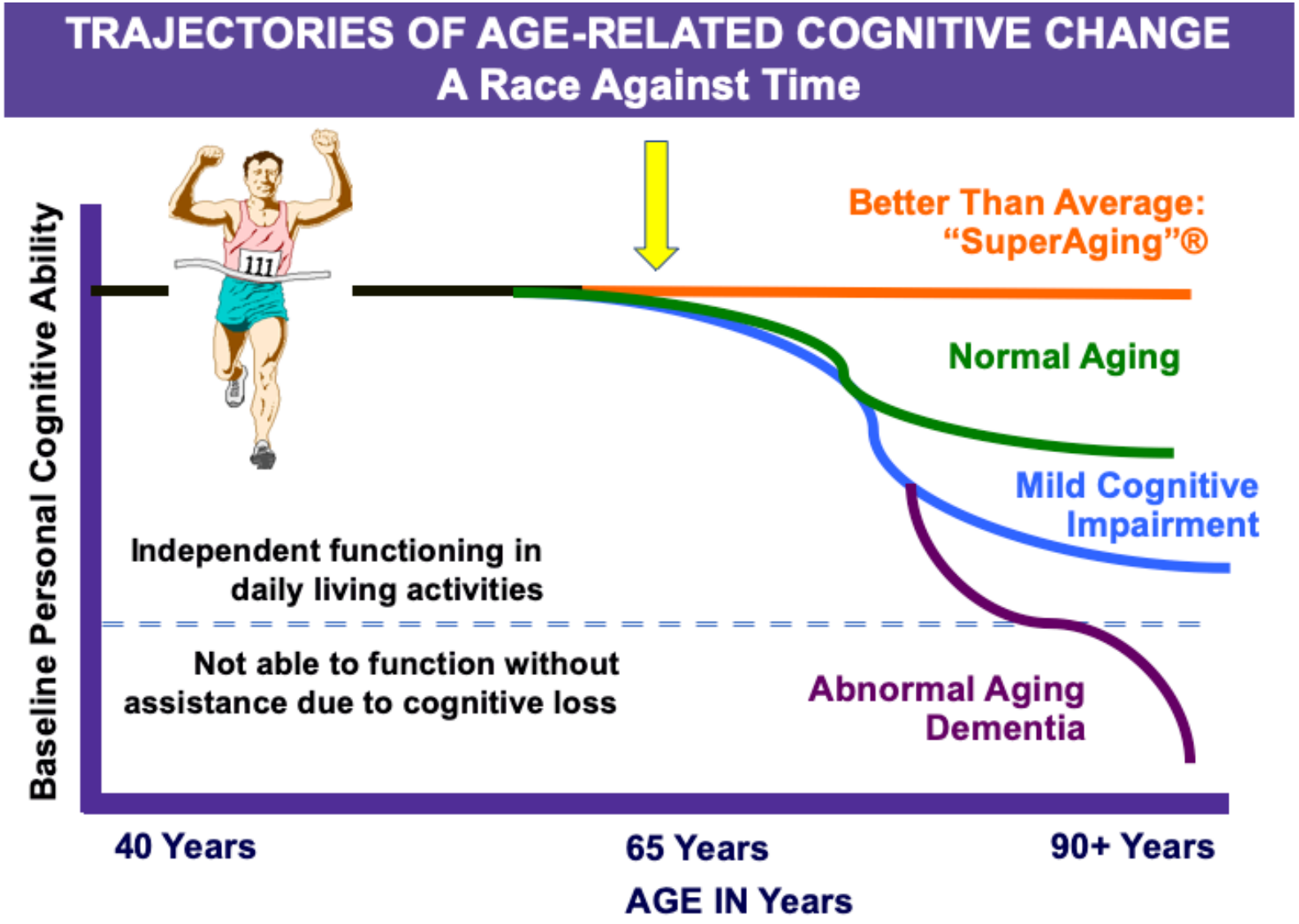
Why study the neurobiology of memory?

1. 140 million Americans suffer from neurological, neurodegenerative and psychiatric disorders
2. Many of these disorders are associated with impaired or altered memory
3. 1 in 9 adults over 45 suffer from memory loss
4. 1 in 3 adults over 70 suffer from memory loss

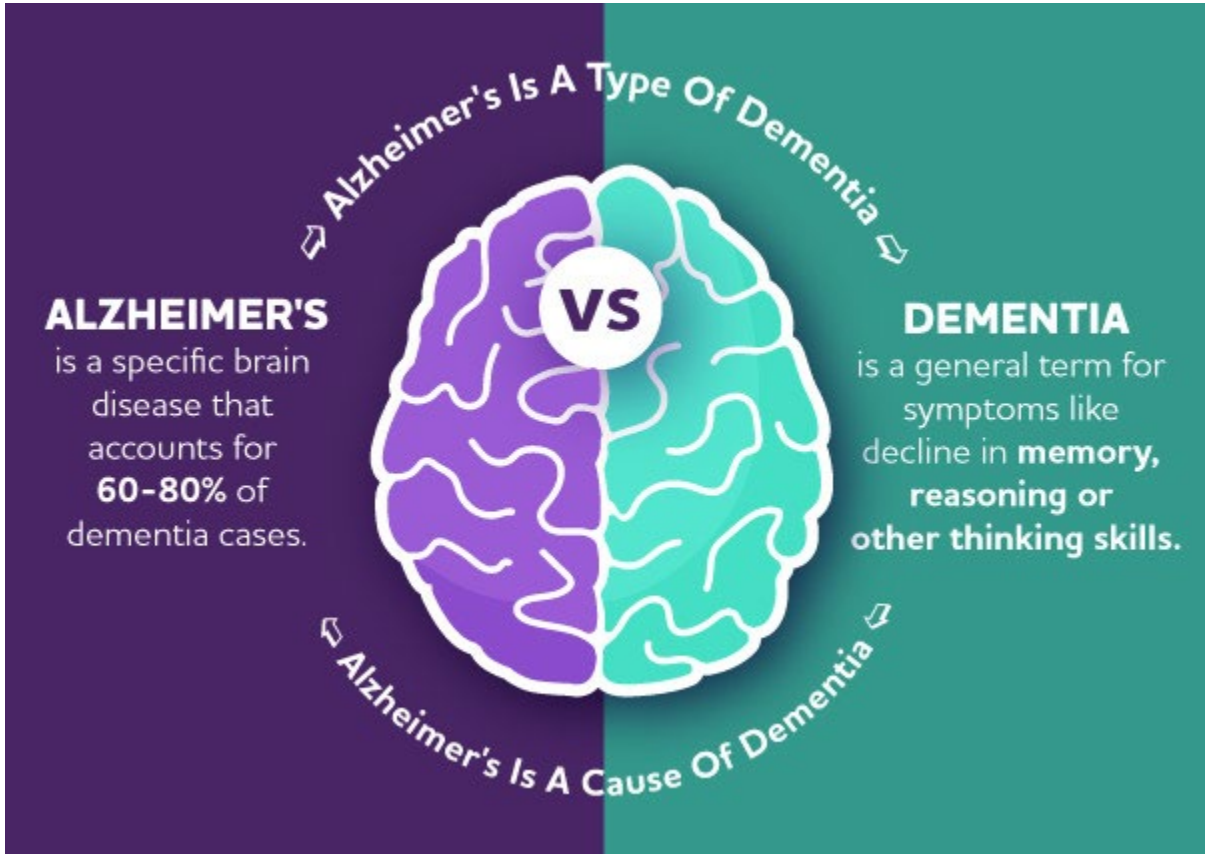
- **Understand the basic mechanisms of memory formation and how they are altered in disease states, which could lead to novel therapeutic strategies to reverse these impairments**

Age-related memory loss



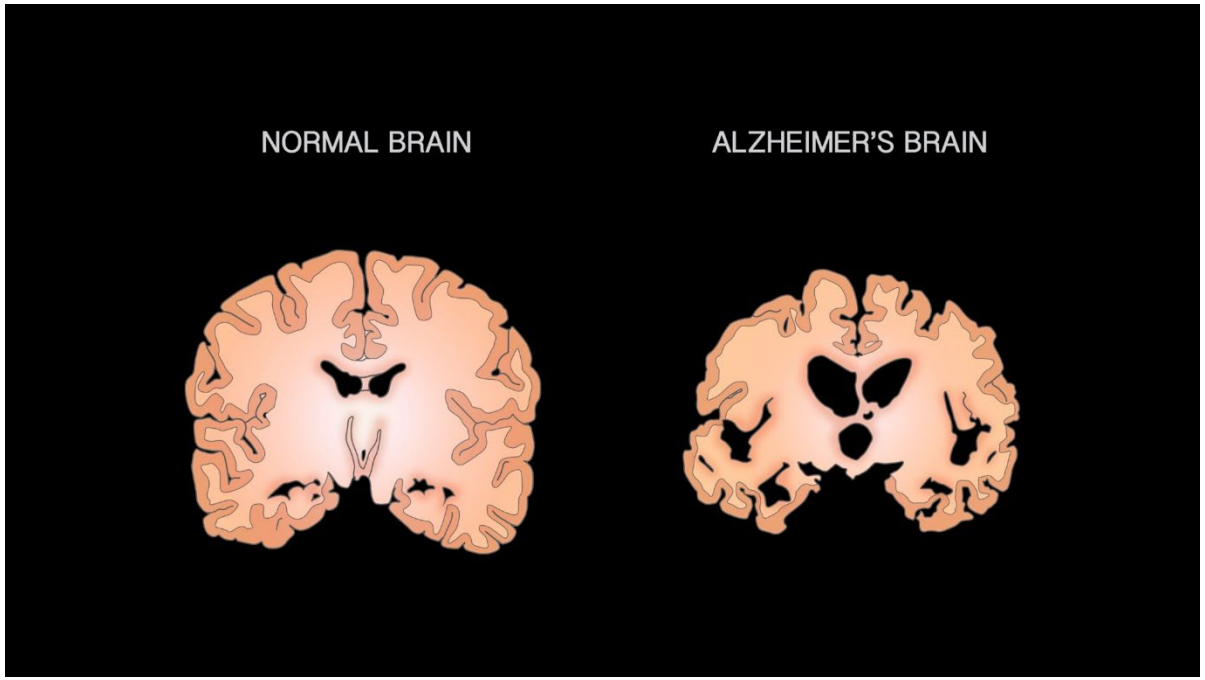
Age-related memory loss

- Almost 40% of people over 65 experience memory loss
- In 2025, 7.2 million Americans had Alzheimer's disease, affecting 1 in 9 people (11%) over age 65
- In the U.S., the economic impact was $781 billion in 2025



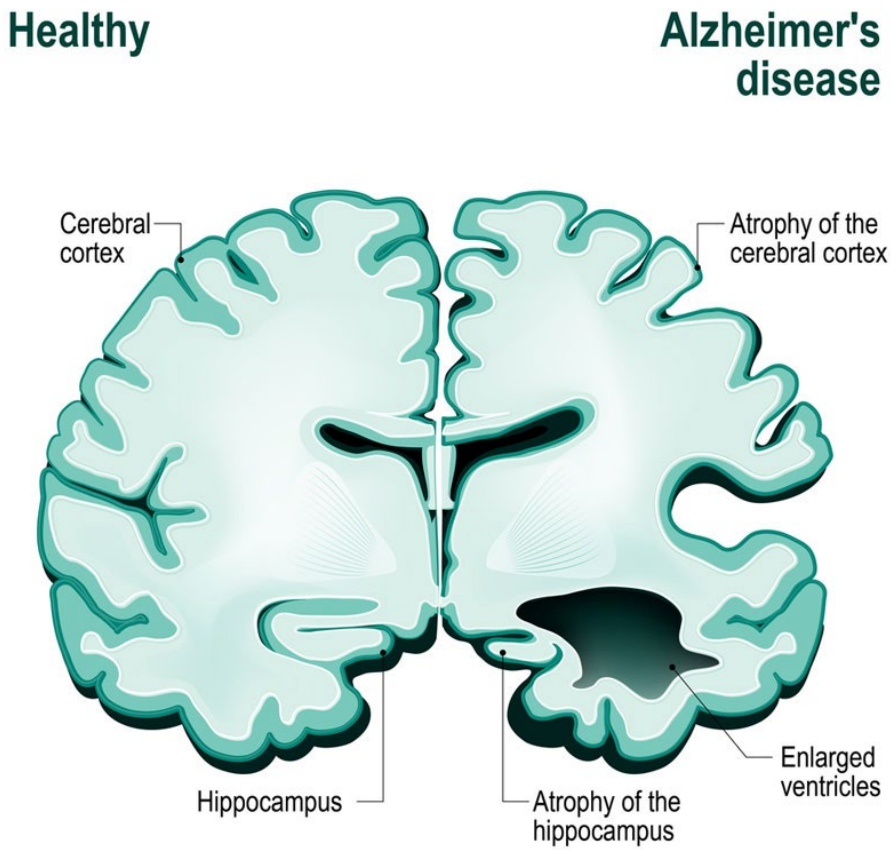
Age-related memory loss

- Alzheimer's disease is often diagnosed late in disease progression
- Mild cognitive impairment is a significant risk factor for developing Alzheimer's disease
- **If we can identify those mechanisms which lead to age-related memory loss, we can intervene *before* Alzheimer's disease progresses to more advanced stages**



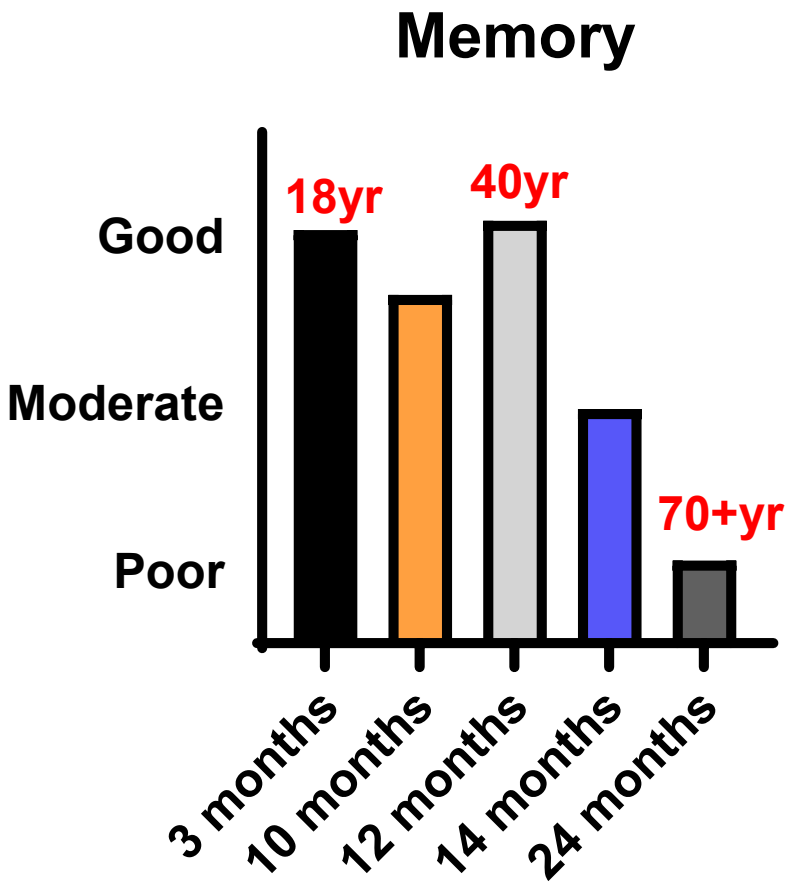
The hippocampus

- Critical for forming and storing new memories
- Has various changes in functioning with age
- Among the first impacted in Alzheimer's disease
- **What changes in the hippocampus with age and how does this make us susceptible to Alzheimer's disease?**



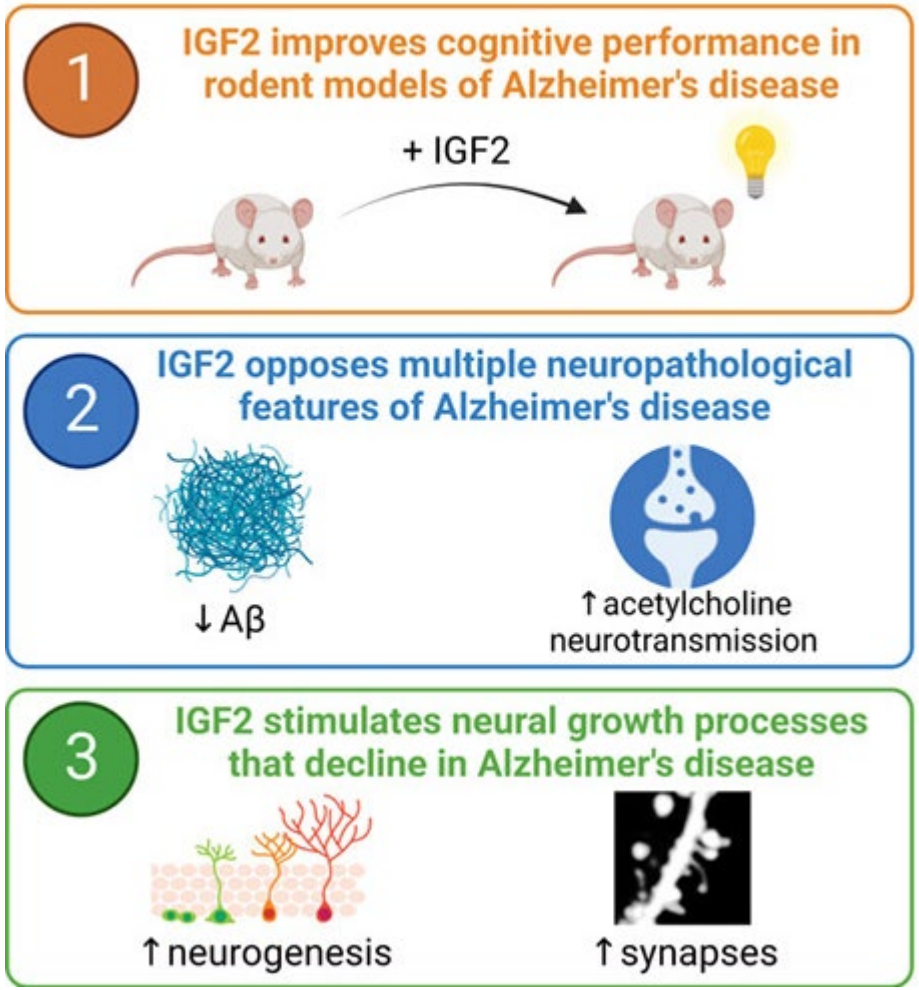
Rat model of age-related memory decline

- Exhibit complex behaviors, including empathy, social play and anxiety-liked behaviors
- Share 98% of their DNA with humans
- Show memory loss with age like humans

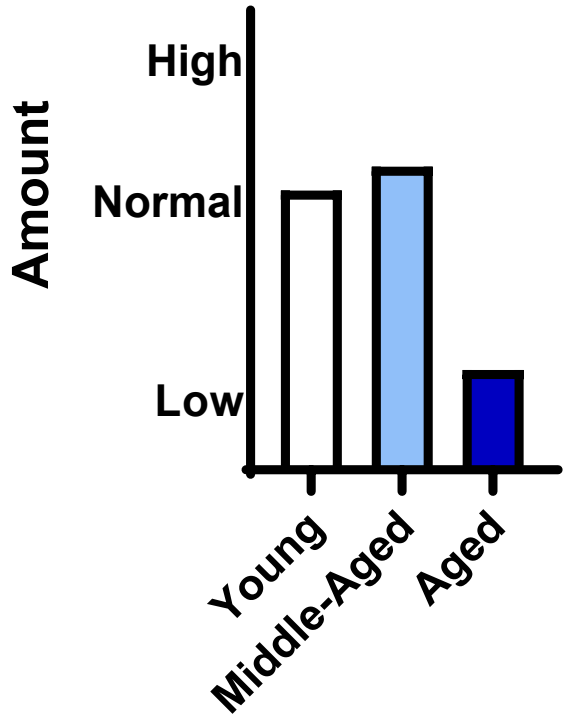


What changes in the hippocampus as we age?

IGF2

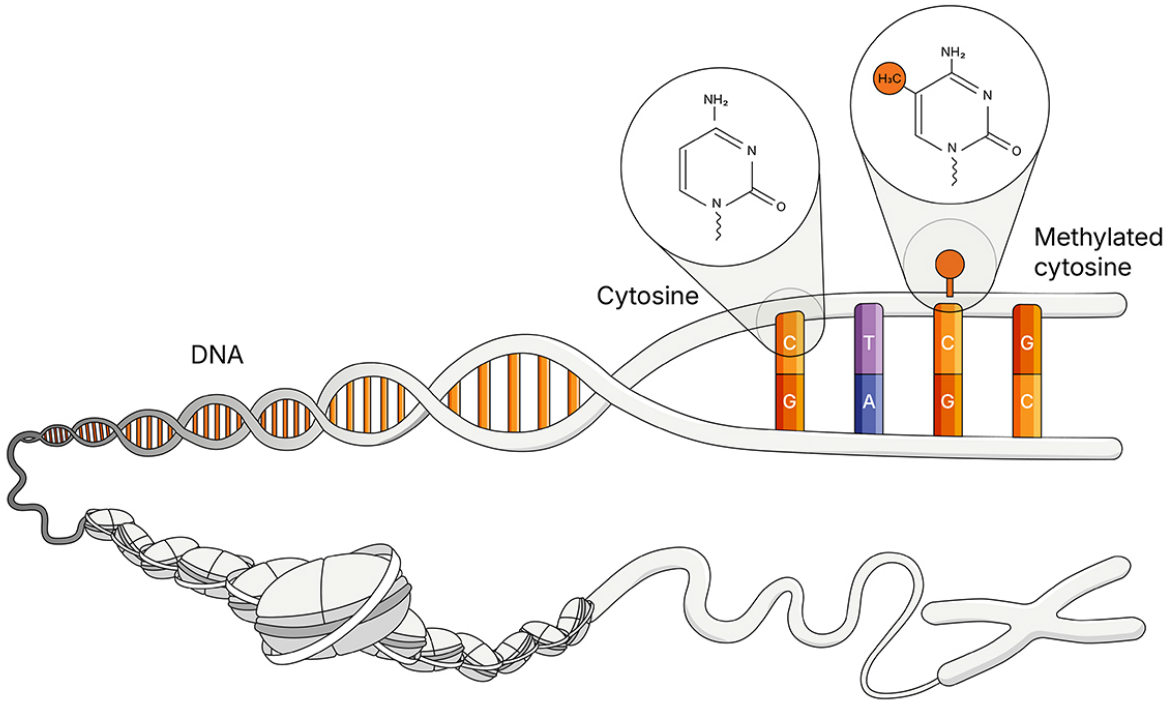


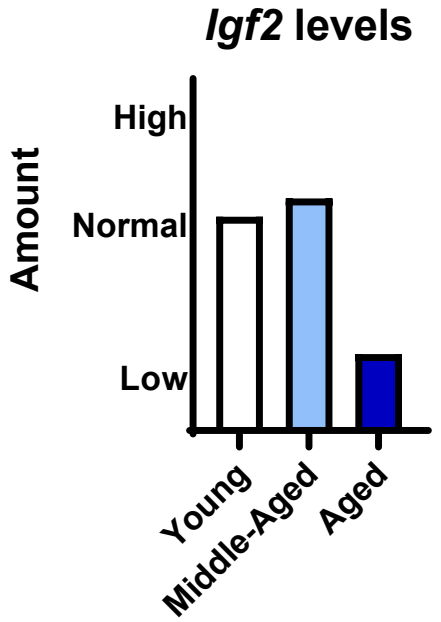
Igf2 levels

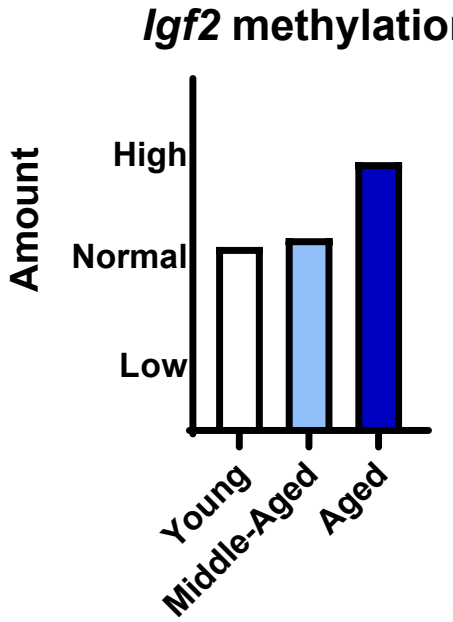


Why is *Igf2* expression declining in the hippocampus as we get older?

What changes in the hippocampus as we age?



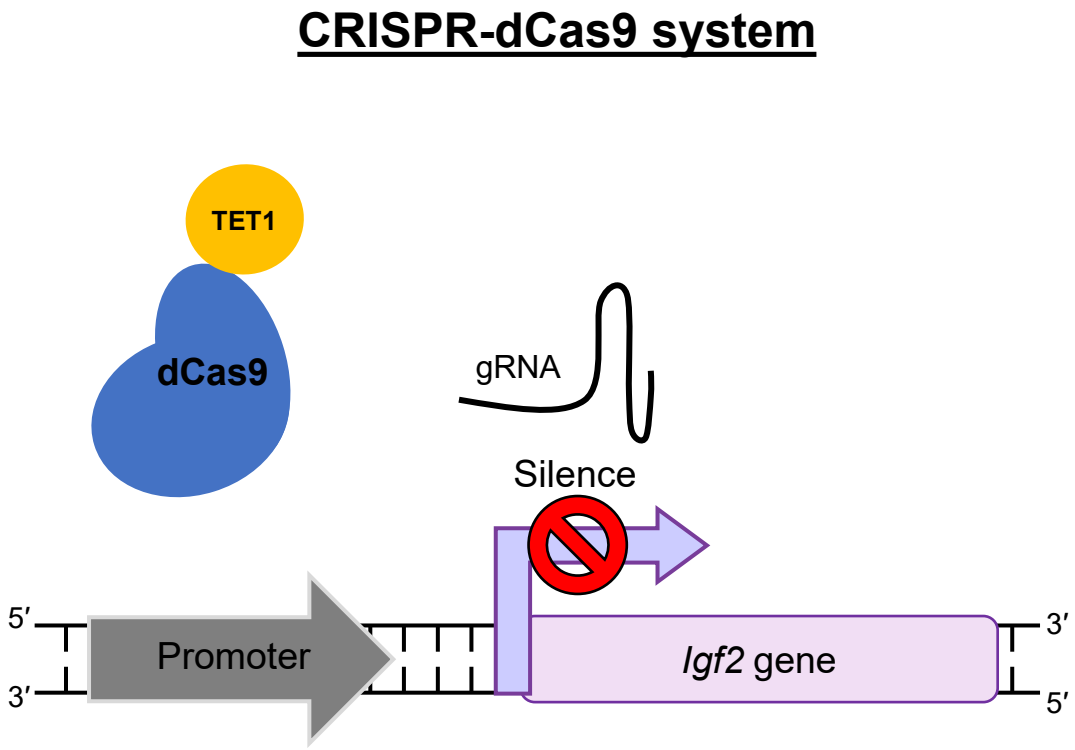


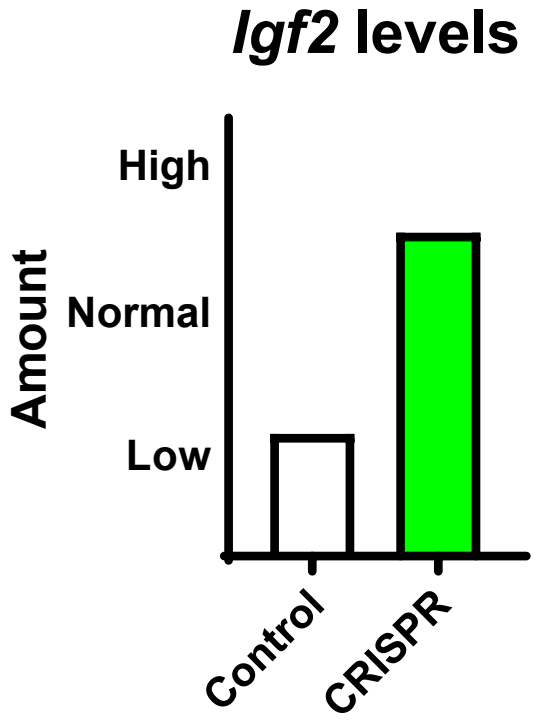


CRISPR/Cas9

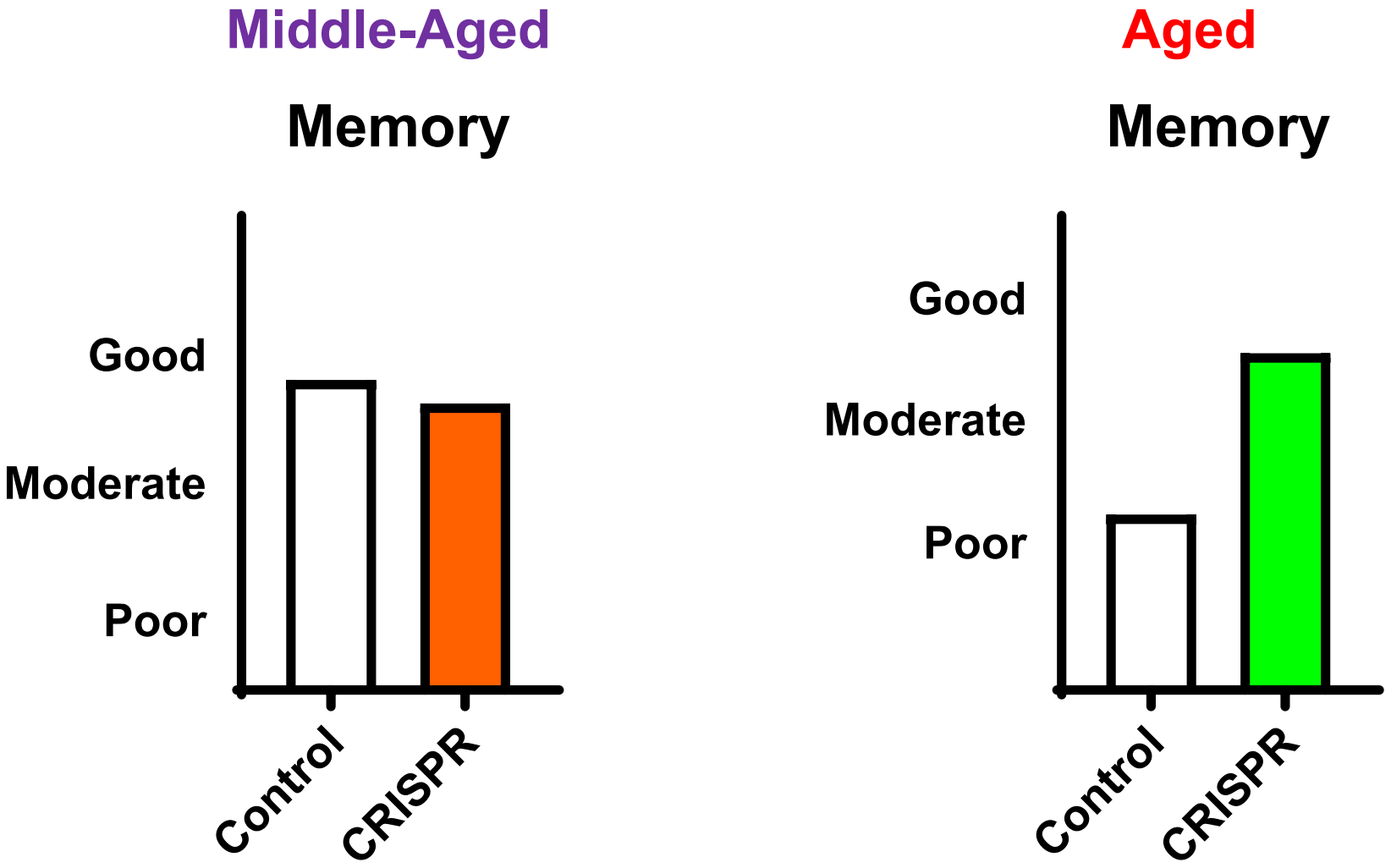
- Widely known gene editing tool that resulted in a Nobel Prize
- Has been used in research, agriculture and medicine
- Uses go far beyond what is general described to the public

Correcting methylation changes in the aging brain





Correcting methylation changes in the aging brain



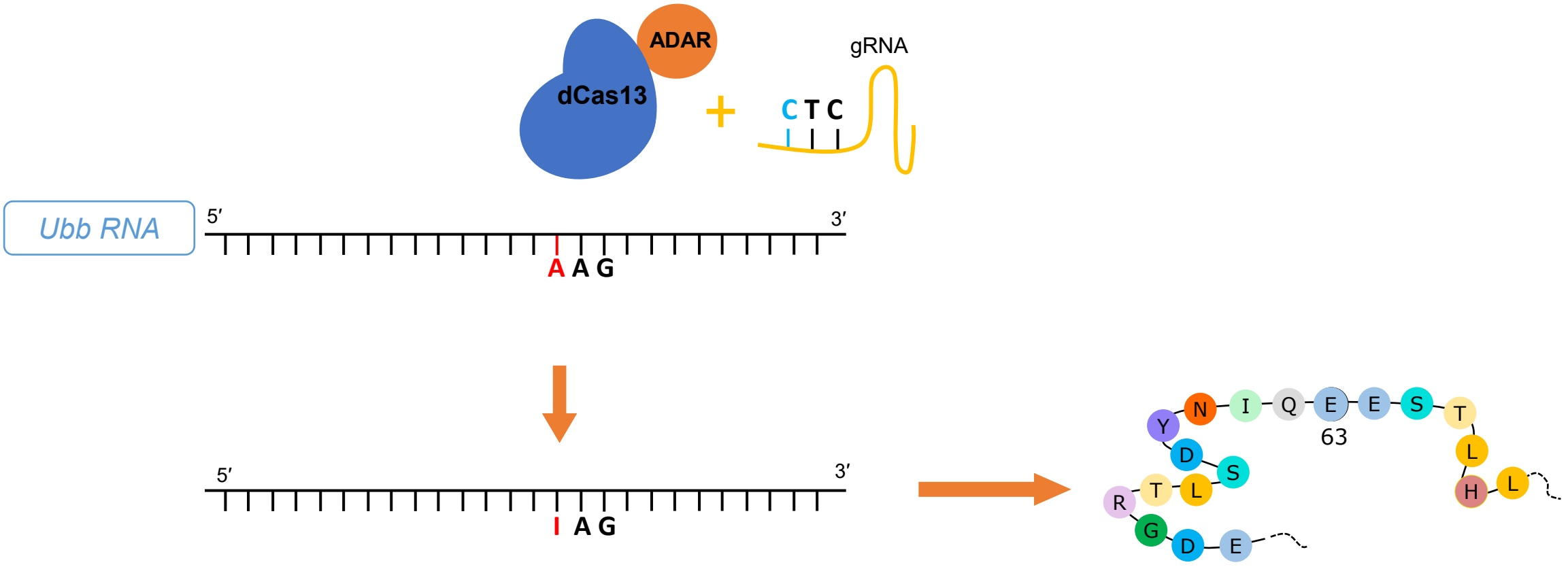
Summary

	Young Adult	Middle-Aged	Aged	Aged w/CRISPR
Memory	**Normal**	**Normal**	**Decreased**	**Normal**
***Igf2* levels**	**Normal**	**Normal**	**Decreased**	**Normal**
***Igf2* methylation**	**Normal**	**Normal**	**Increased**	**Normal**

What changes in the hippocampus as we age?

- Ubiquitin is present in essentially all species
- Widely implicated in disease, from cancer to Alzheimer's disease
- One form, K63 ubiquitin, has been shown to be bad for memory when increased in the hippocampus
- With age, K63 ubiquitin increases in the hippocampus

Manipulating K63 ubiquitin with CRISPR-dCas13



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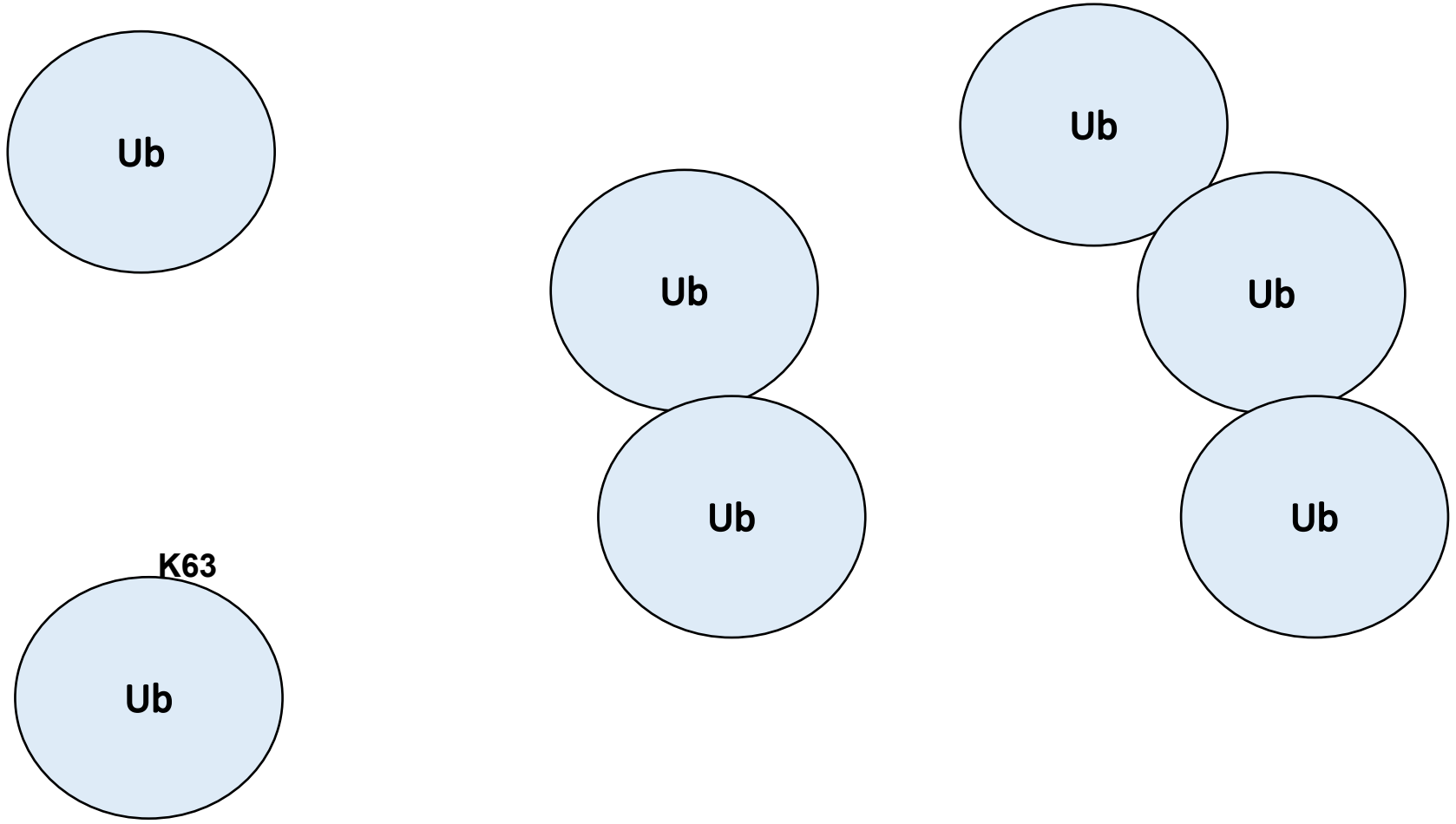
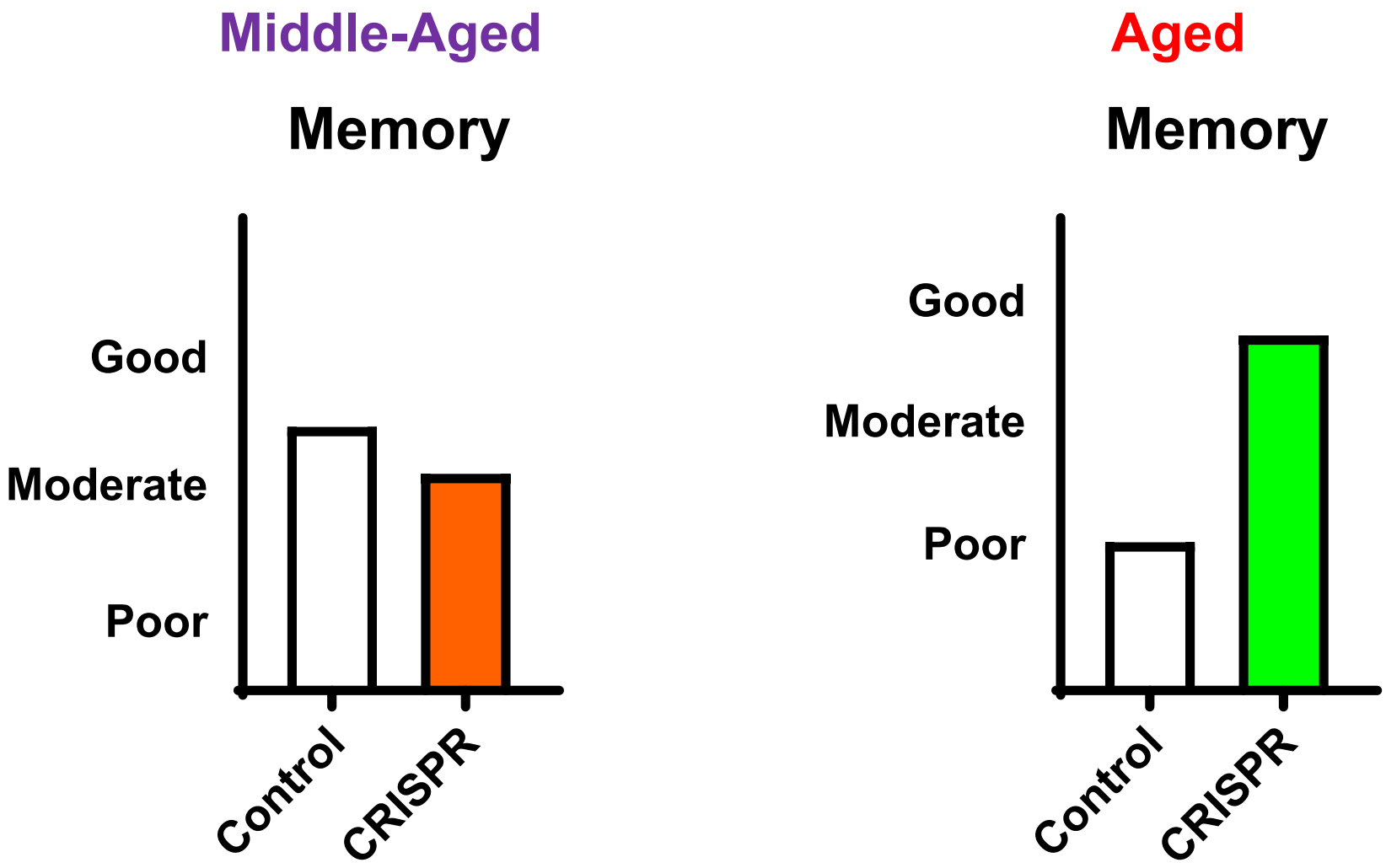


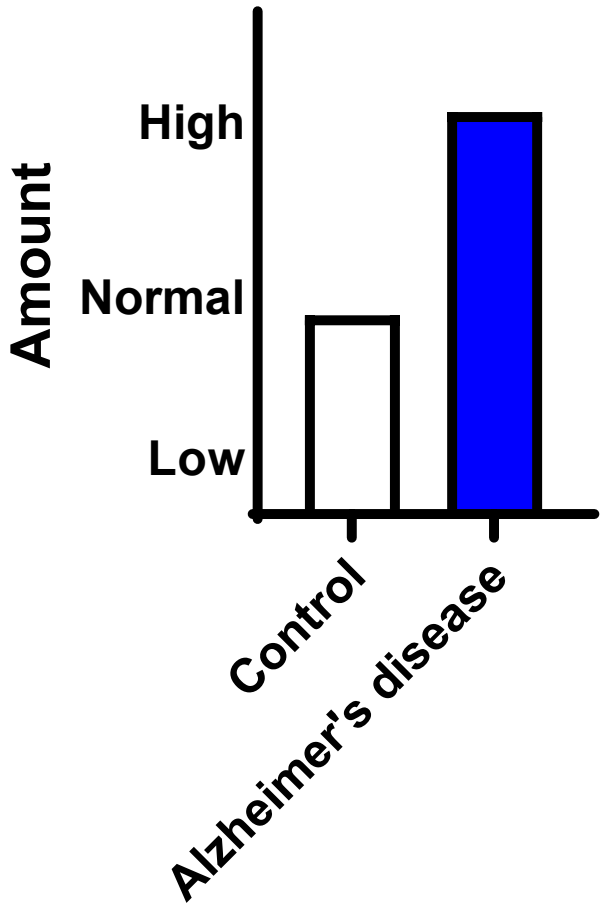
Correcting K63 ubiquitin changes in the aging brain



K63 ubiquitin – obesity and Alzheimer's disease

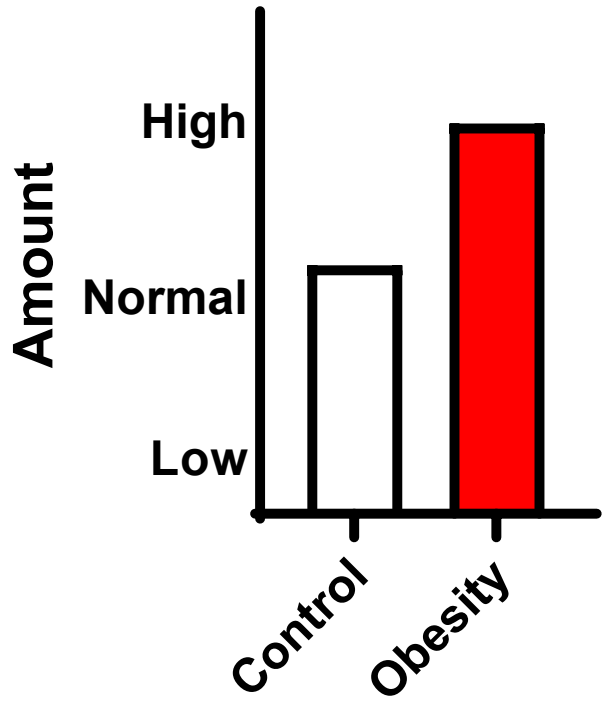
Alzheimer's disease

K63 ubiquitin levels



Obesity

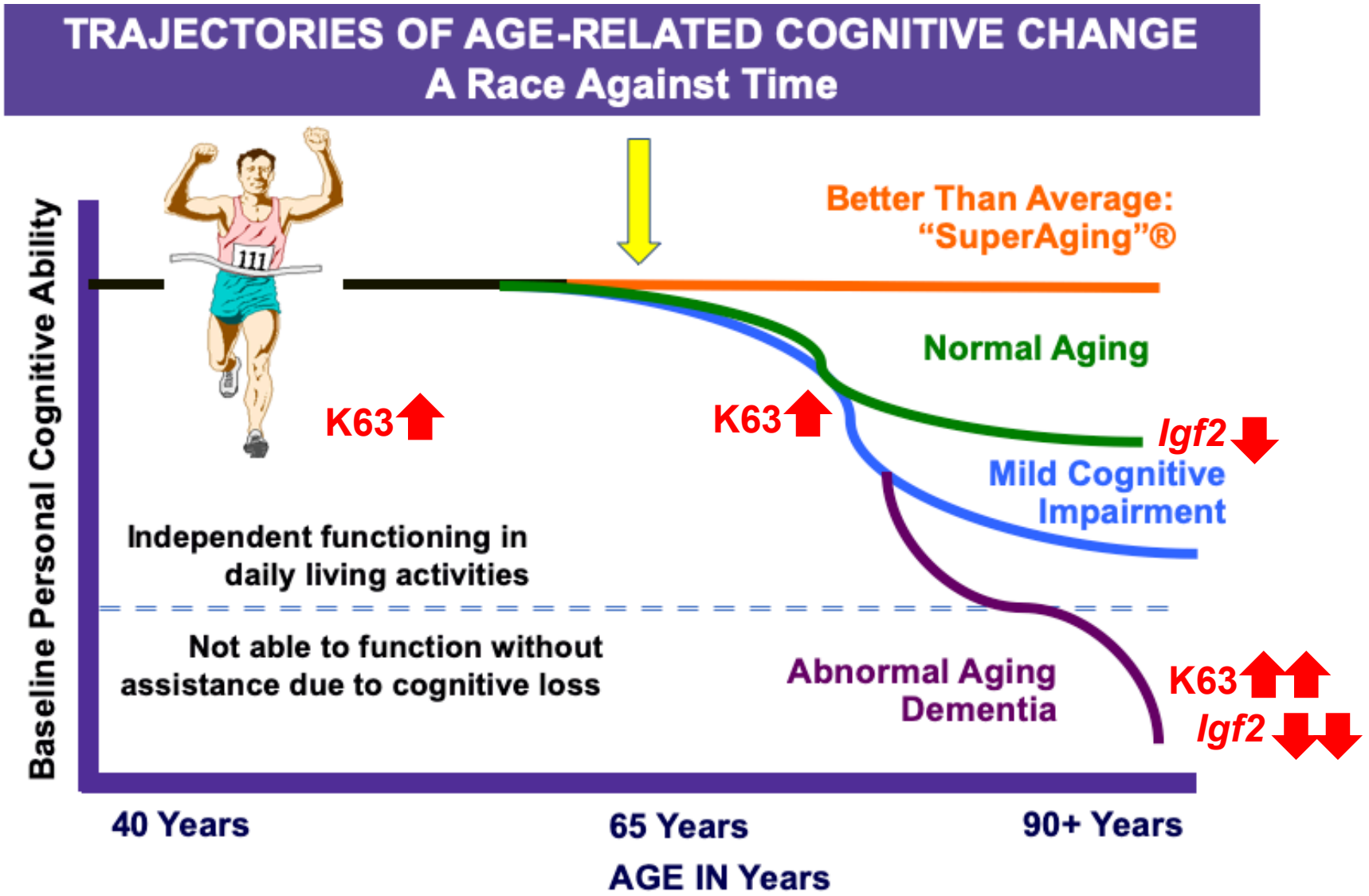
K63 ubiquitin levels



Summary

	Young Adult	Middle-Aged	Aged	Aged w/CRISPR
Memory	**Normal**	**Normal**	**Decreased**	**Normal**
K63 ubiquitin levels	**Normal**	**Increased**	**Increased**	**Normal**
***Igf2* expression**	**Normal**	**Normal**	**Decreased**	**Normal**
***Igf2* methylation**	**Normal**	**Normal**	**Increased**	**Normal**
H2B ubiquitin	**Normal**	**Normal**	**Decreased**	**Normal**

Putting back into context



Where do we go from here?

1. Answering the 5 W's
   - The **WHAT** (Igf2 and K63 ubiquitin) are known
   - The **WHERE** (hippocampus) is known
   1. Identifying **WHEN** these changes occur with age is critical
   2. Determine **WHY** these mechanisms change with age
   3. Determine **HOW** these mechanisms contribute to age-related memory loss and Alzheimer's disease

2. From bench-to-beside: How can this information be translated into the clinic?

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