GENE EXPRESSION CHANGES TRIGGERED BY AMYLOID BETA TOXICITY

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OVERVIEW

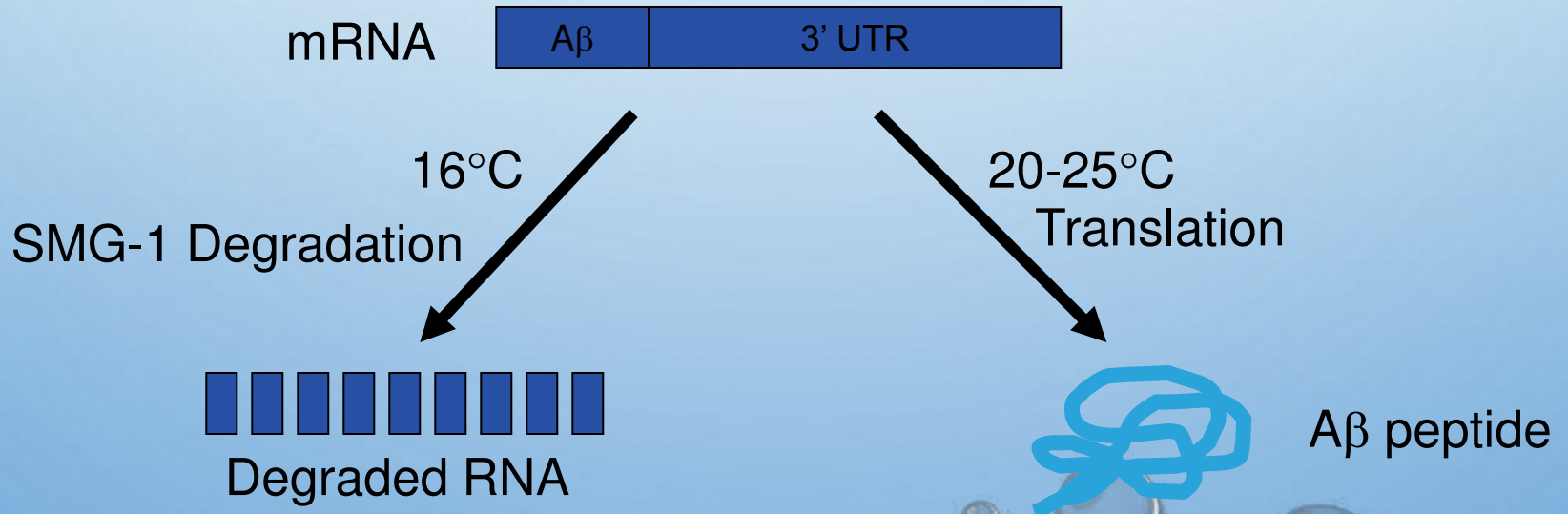
- Model organism
- Gene expression alterations induced by Aβ
- Aβ-specific gene alterations
- Membrane damage
- Proteasome modulators

WHY STUDY GLOBAL GENE EXPRESSION IN NEMATODES?

- Ease of genetic manipulations
- Short lifespan
- Common pathways and orthologues
- Inducible expression system

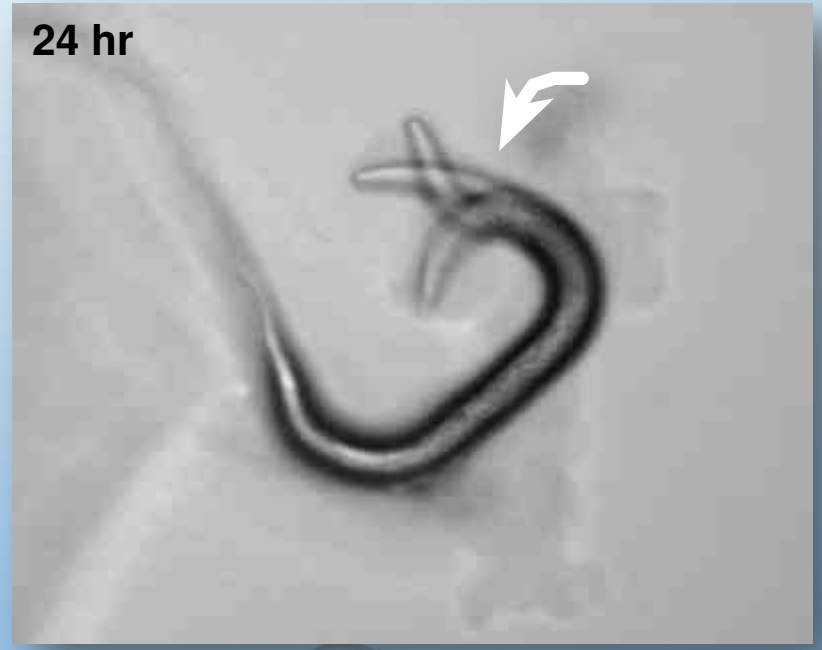
TEMPERATURE-INDUCIBLE Aβ EXPRESSION

- SMG-1 is an mRNA surveillance protein.
- Temperature inducibility is enabled by a *smg-1*^{ts} mutation.



HUMAN Aβ IS TOXIC IN WORMS

- $A\beta_{1\text{-}42}$ expression in body-wall muscle causes irreversible paralysis phenotype



MICROARRAY STUDIES

Strains:

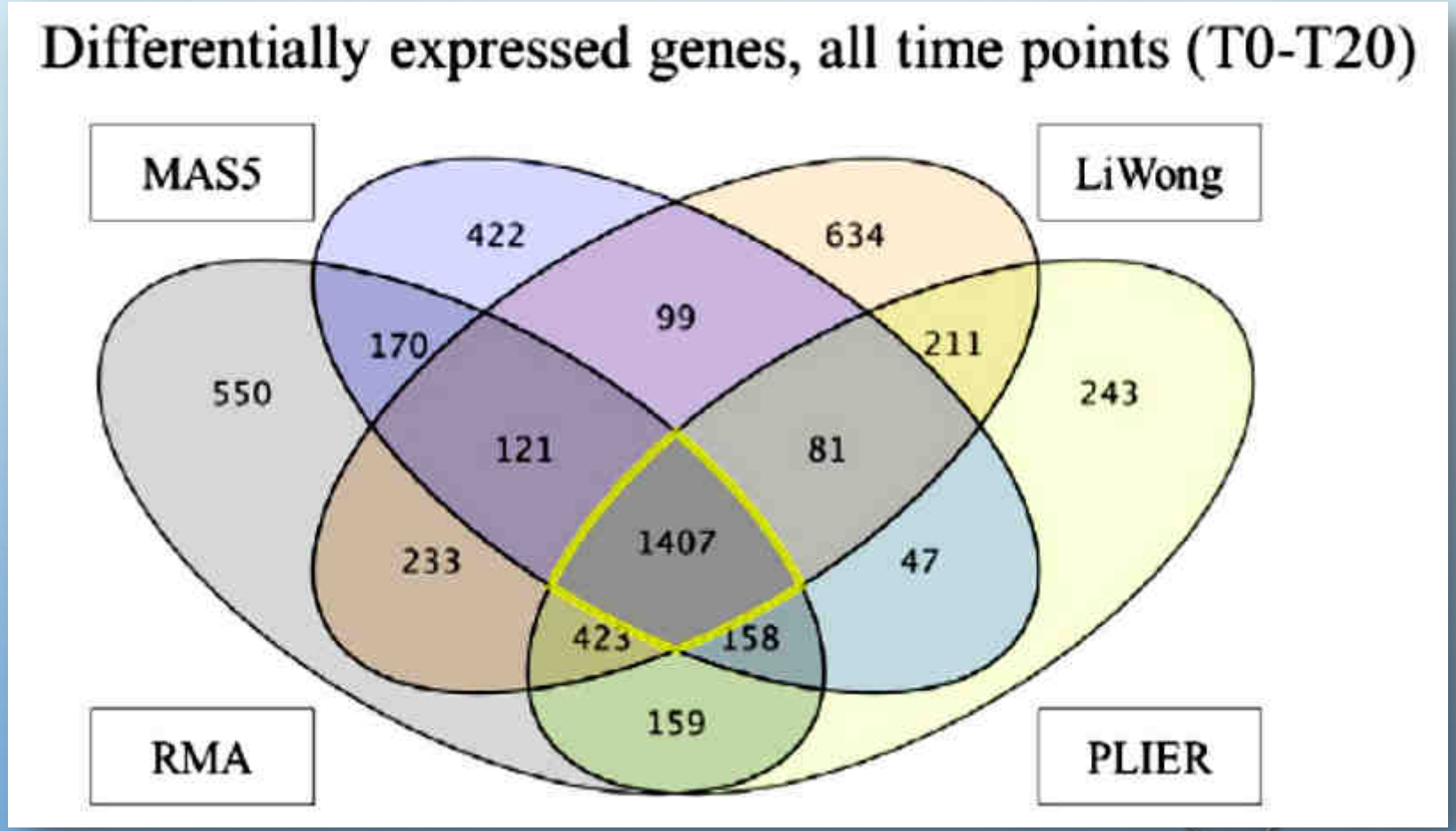
- $A\beta_{1\text{-}42}$-expressing animals (CL4176)
- GFP::degron-expressing animals (CL2337)
- Soluble GFP-expressing animals (CL2179)

MICROARRAY STUDIES

Experimental Design:

- Synchronous animals were grown at 16 ℃ for 36 hours.
- Transgenes were induced at 25 ℃
- Worms were harvested at T0, T4, T8, T12, T16, and T20

DIFFERENTIALLY EXPRESSED GENES IN Aβ ANIMALS



DIFFERENTIALLY EXPRESSED GENES IN Aβ ANIMALS

Differential gene expression in Aβ and GFP_{deg} animals

Time point	All Aβ	Aβ-specific	General misfolded protein response
Entire time course	1315 (1407)	957 (1009)	364 (398)
Up at T8	108 (117)	47 (50)	61 (67)
Down at T8	43 (46)	35 (38)	8 (8)
Up at T16	221 (233)	78 (81)	144 (152)
Down at T16	51 (54)	25 (27)	26 (27)
Up T8–T16	30 (32)	18 (18)	12 (14)
Down T8–T16	12 (12)	11 (11)	1 (1)

FUNCTIONAL ANALYSIS OF DIFFERENTIALLY EXPRESSED GENES

- **Aβ-specific genes:**
- Aging
- Insulin signaling
- Mitochondrial unfolded protein response
- Proteasome degradation pathways
- Membrane damage response

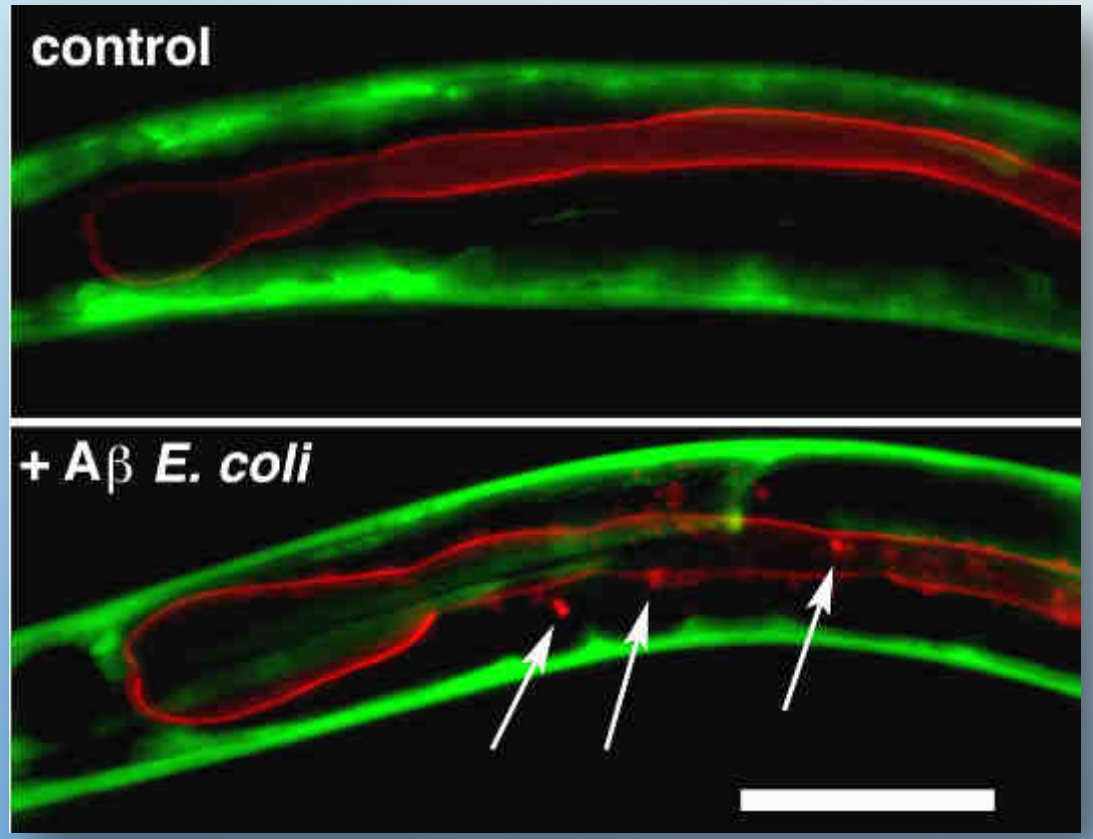
FUNCTIONAL ANALYSIS OF DIFFERENTIALLY EXPRESSED GENES

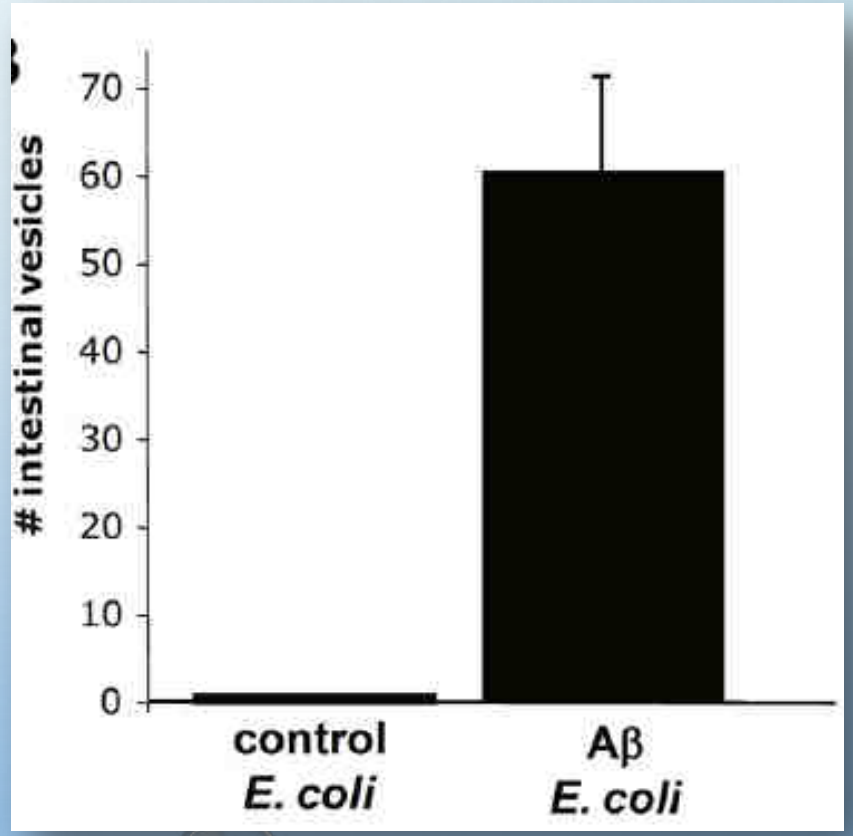
- **Common genes:**
- Stress response genes
- Immune response

Aβ TOXICITY AND MEMBRANE DAMAGE

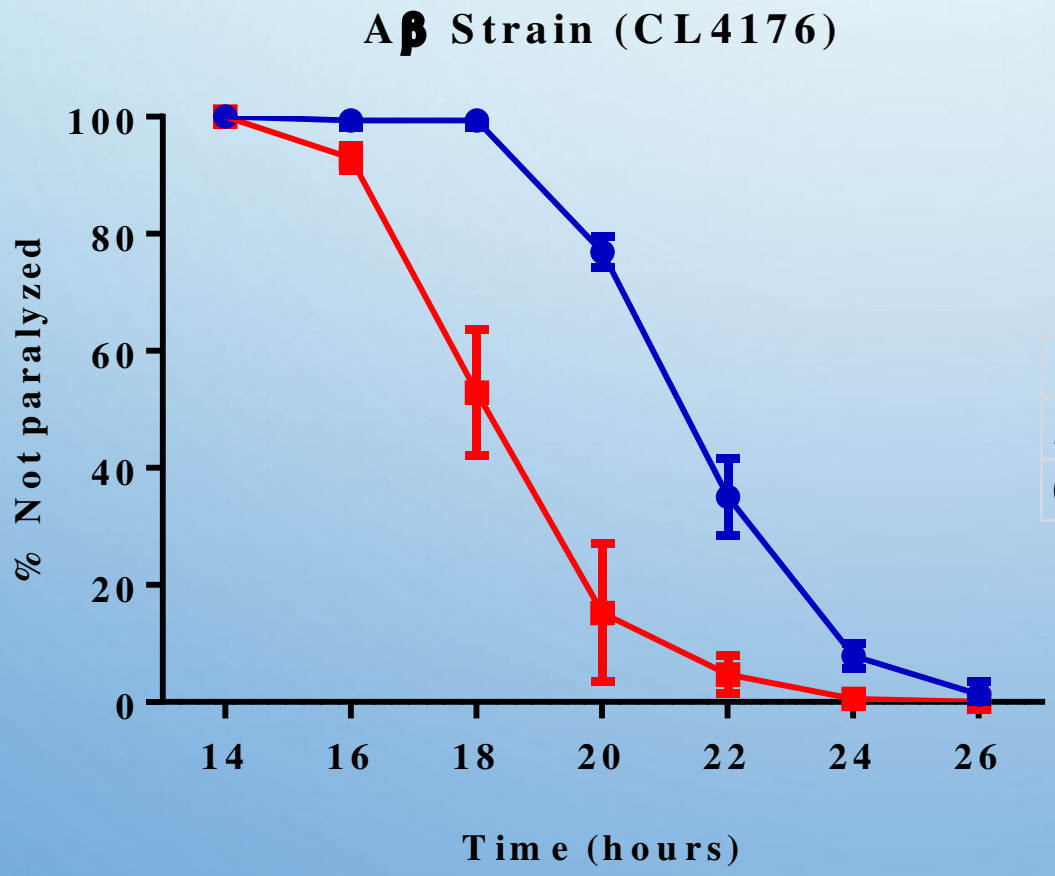
- Previous studies suggested Aβ may form membrane pores
- Overlap between Aβ and Cry5B genes
- Questions:
  - Intestinal expression of Aβ?
  - KGB-1 and Aβ toxicity?

INDUCTION OF MEMBRANE DAMAGE RESPONSE



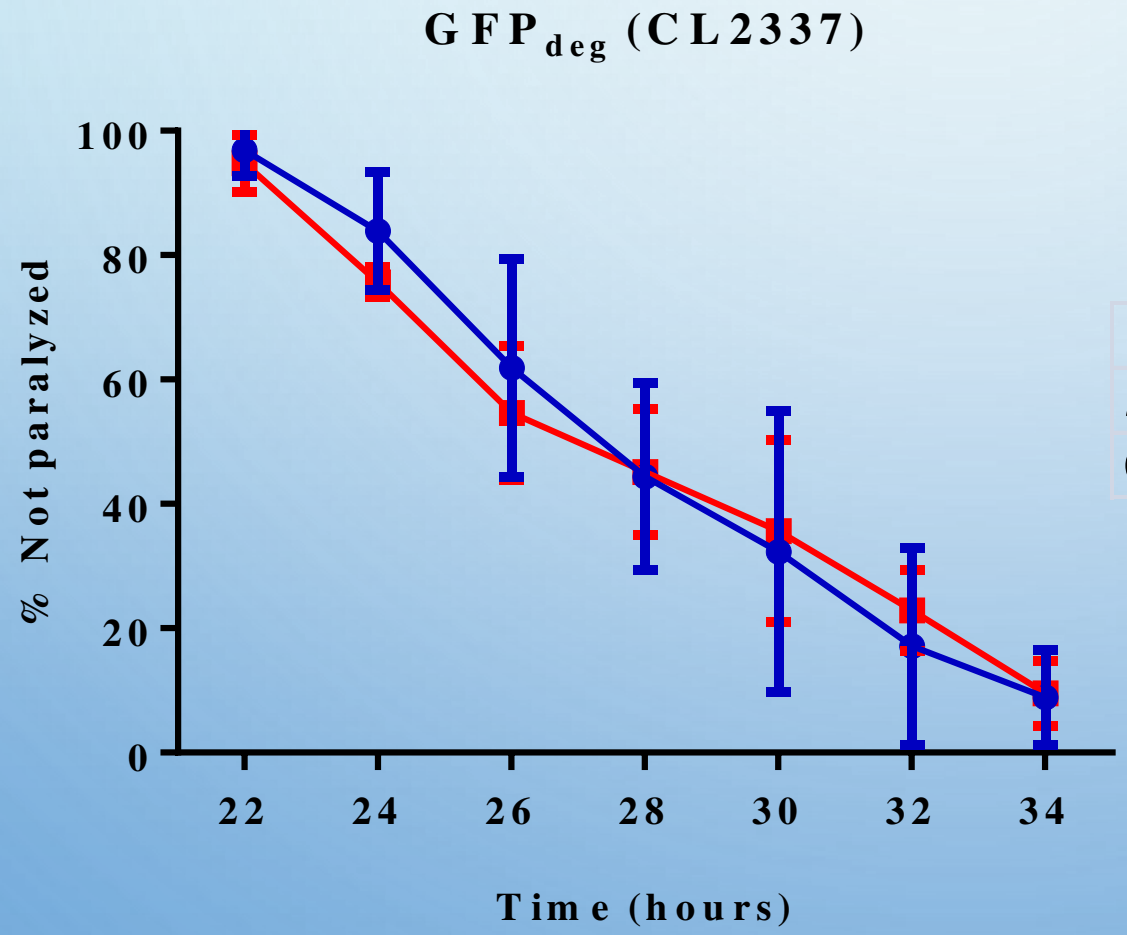


kgb-1 RNAi knock down in Aβ animals



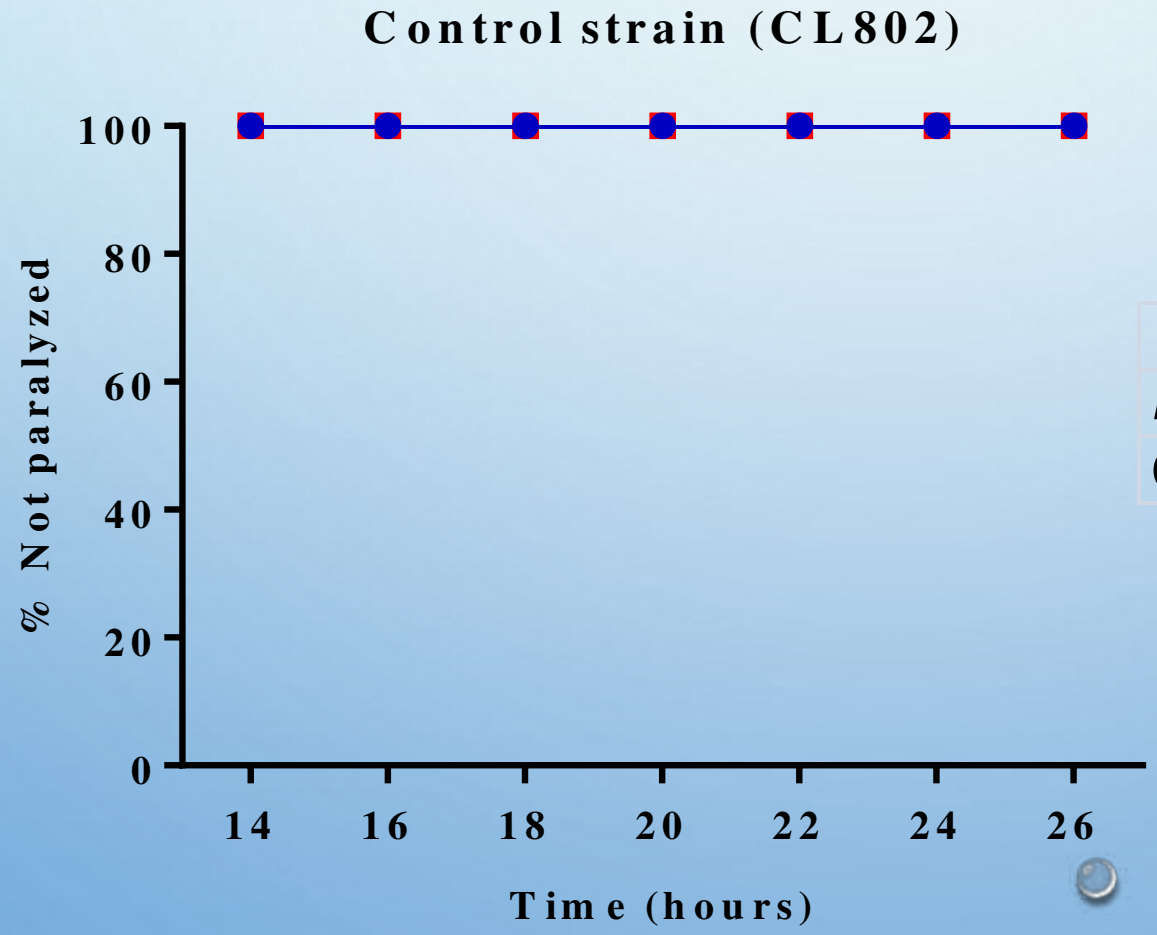
	n1	n2	n3	P value
kgb-1 RNAi	63	51	70	0.0001
Control RNAi	40	53	50	

kgb-1 RNAi knock down in GFP_{deg} animals



	n1	n2	n3	P value
kgb-1 RNAi	46	59	67	0.8967
Control RNAi	62	58	102	

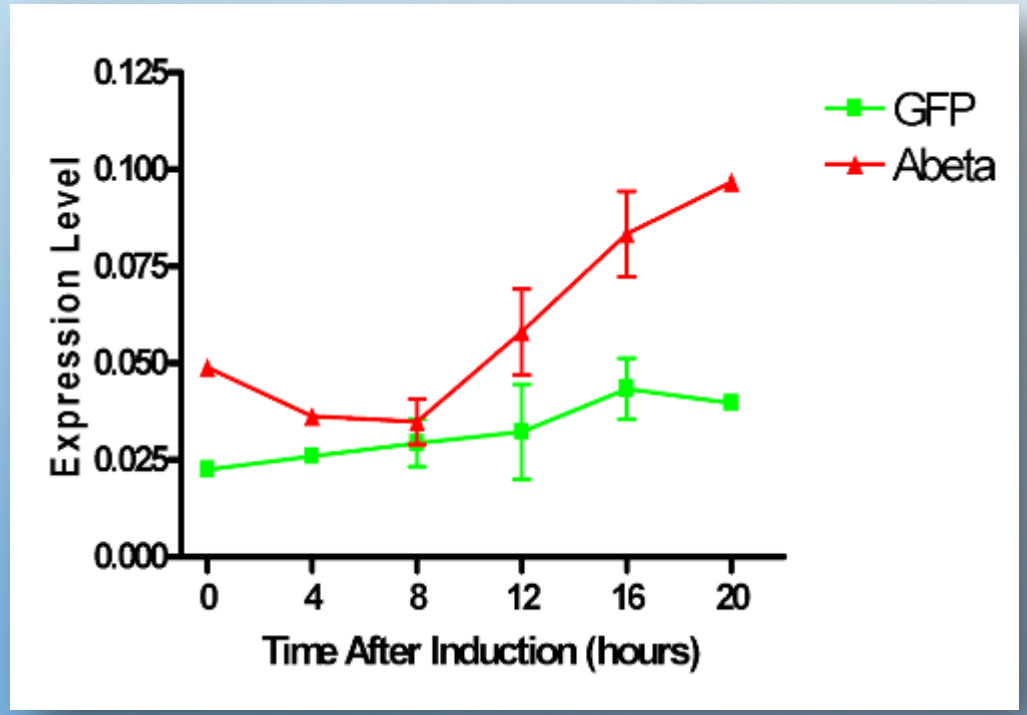
kgb-1 RNAi knock down in isogenic control animals



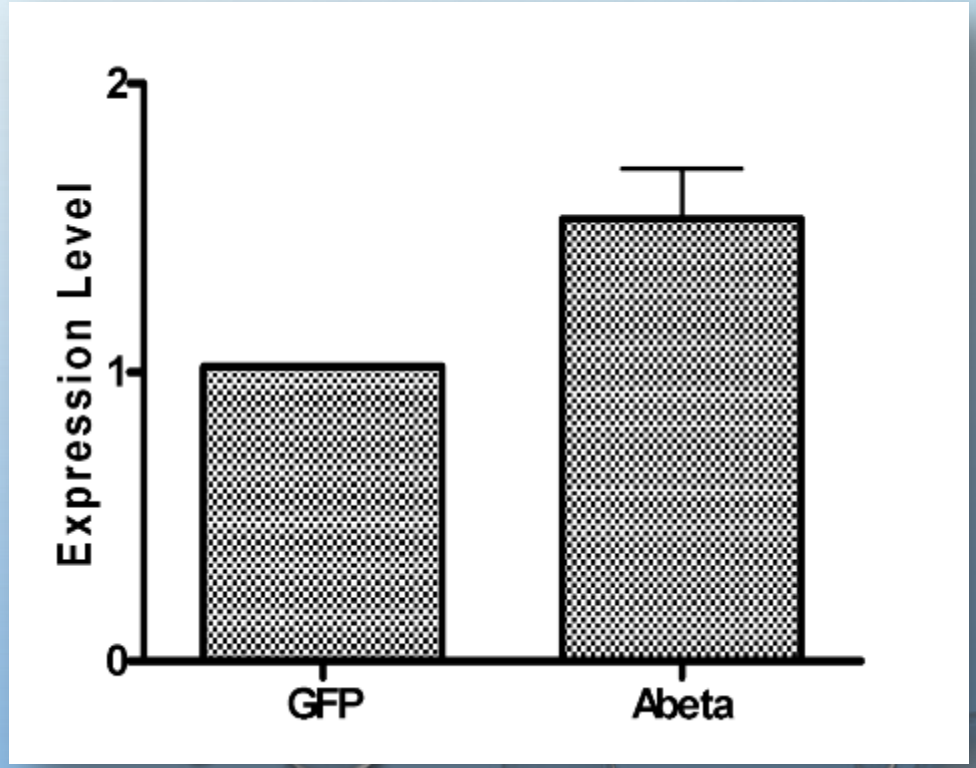
	n1	n2	n3
kgb-1 RNAi	62	44	28
Control RNAi	65	47	41

$A\beta_{1\text{-}42}$ INDUCES *aip-1* EXPRESSION

aip-1 expression by Microarrays

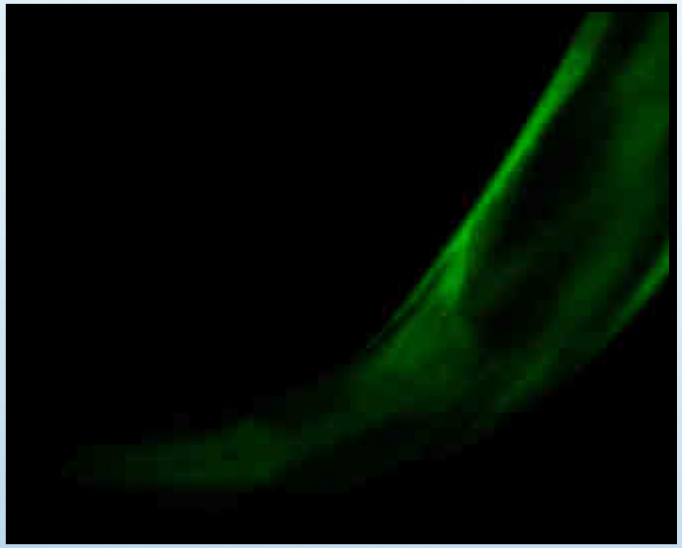


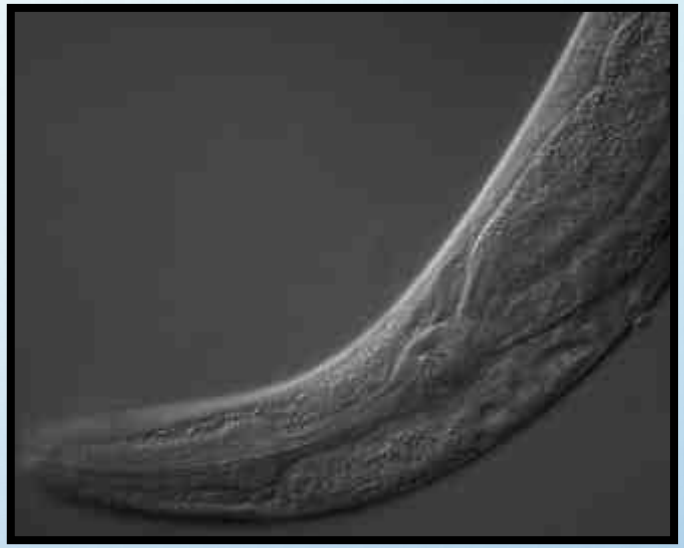
aip-1 expression by RT-PCR



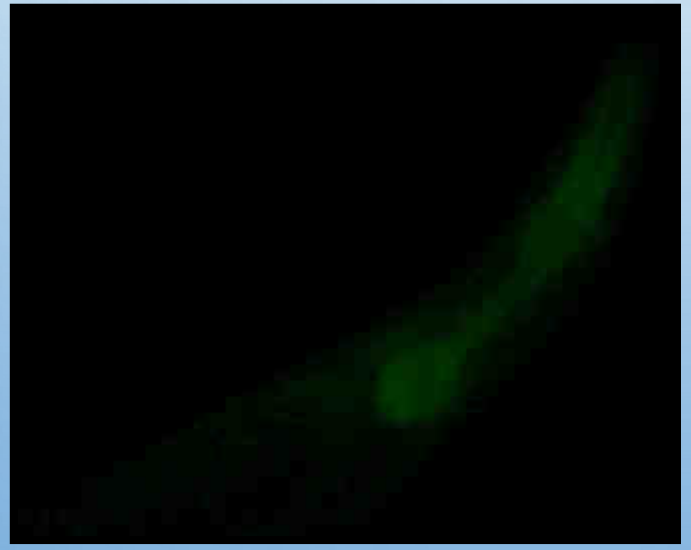
TRANSCRIPTIONAL REPORTER: *aip-1*/GFP

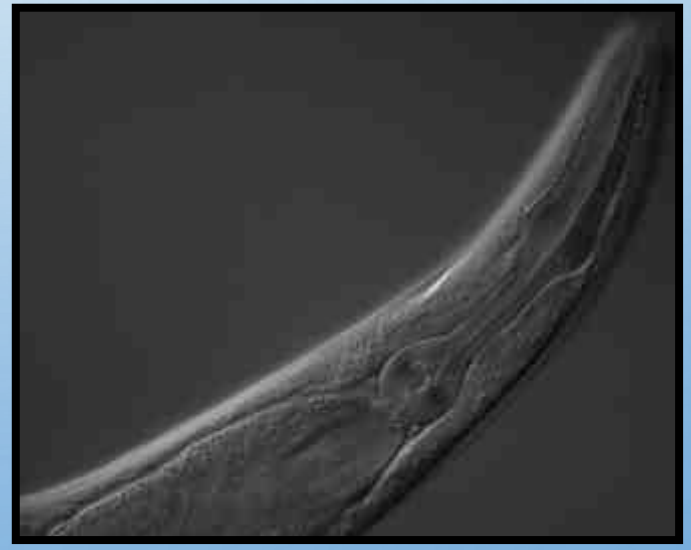
25°C
Aβ induced





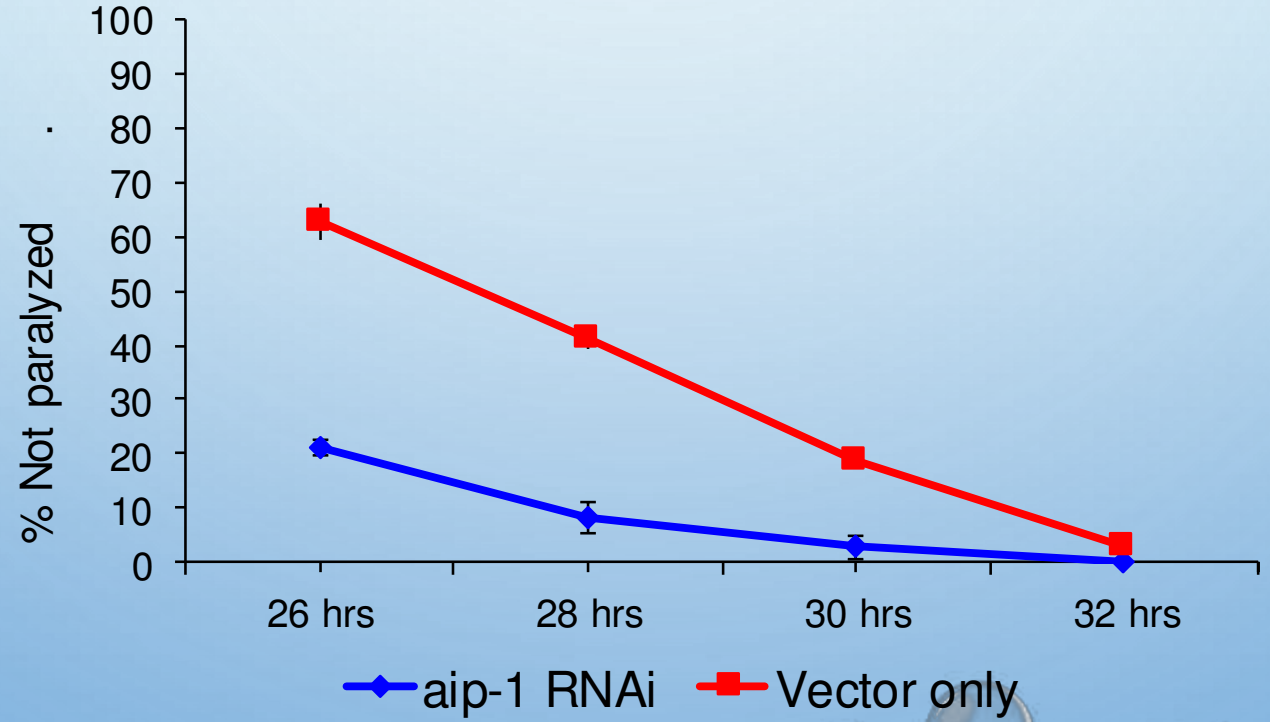
16°C
No Aβ induction





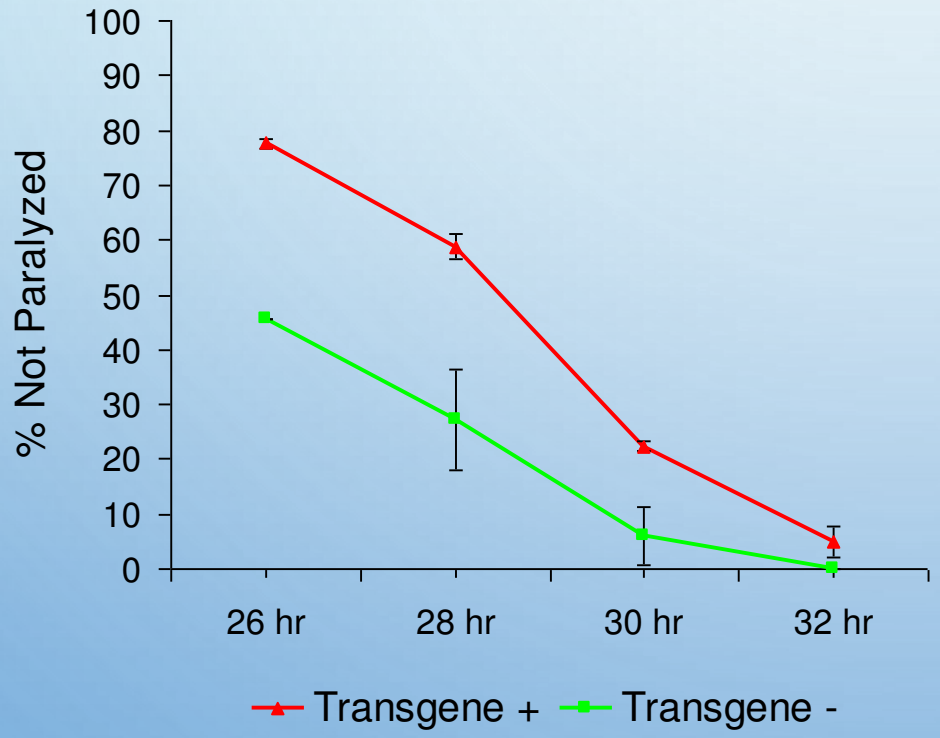
KNOCKING DOWN OF *aip-1* ENHANCES Aβ TOXICITY

myo-3/$A\beta_{1-42}$

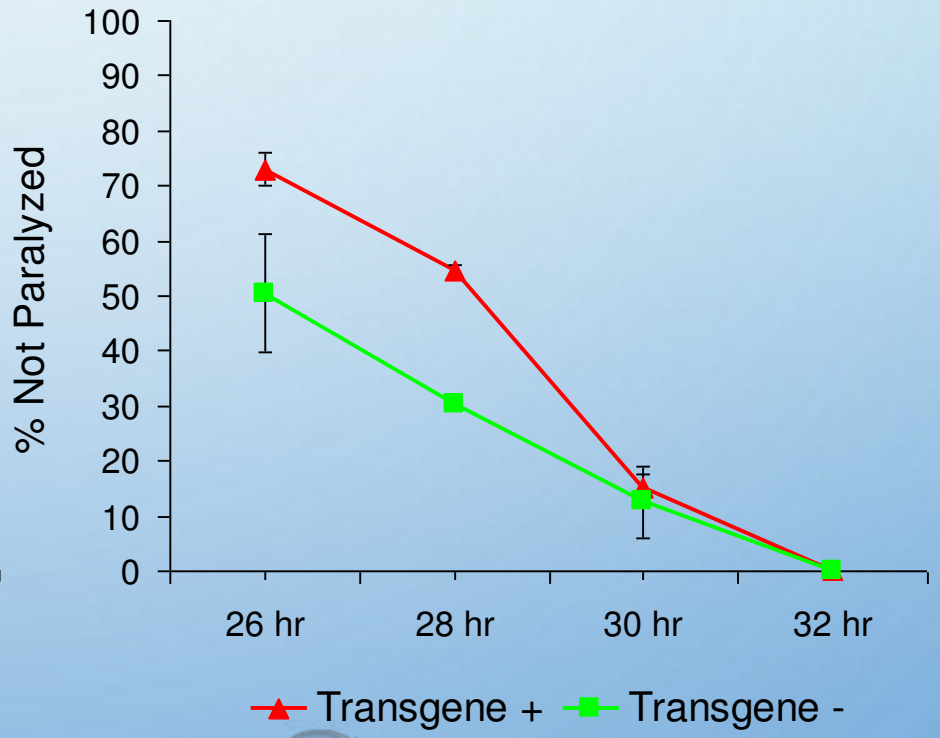


aip-1 OVER-EXPRESSION DELAYS ALLEVIATES Aβ TOXICITY

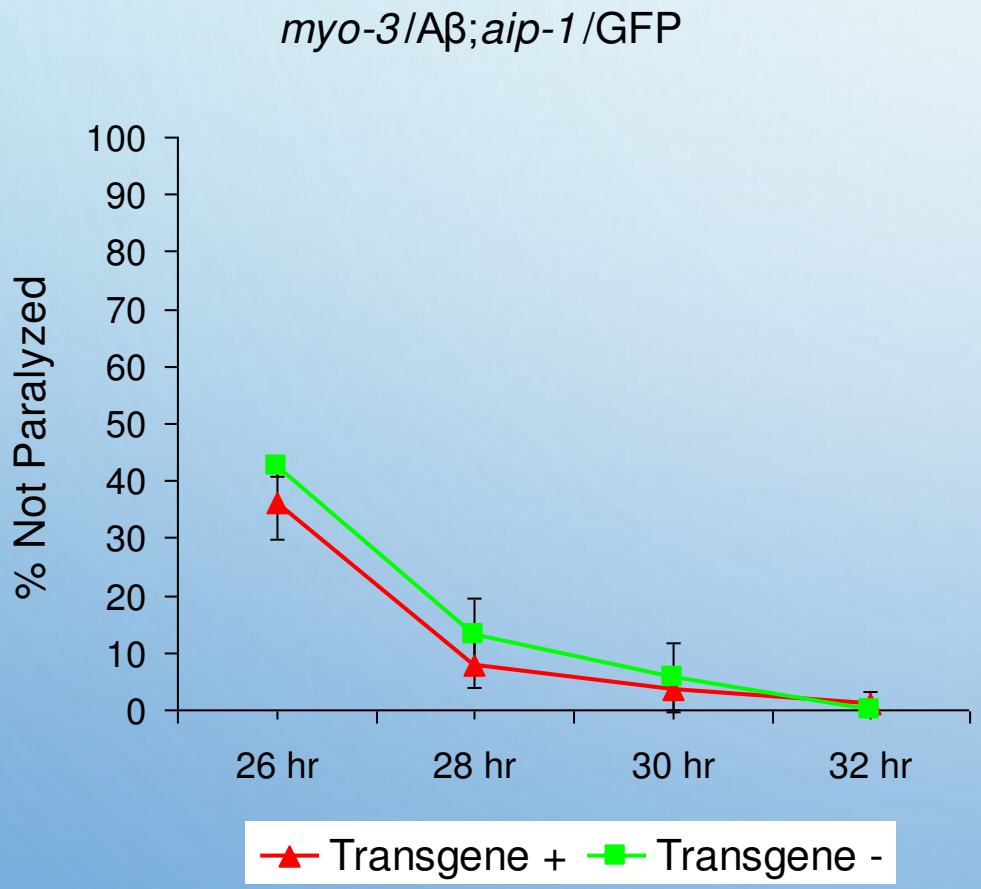
myo-3/aip-1

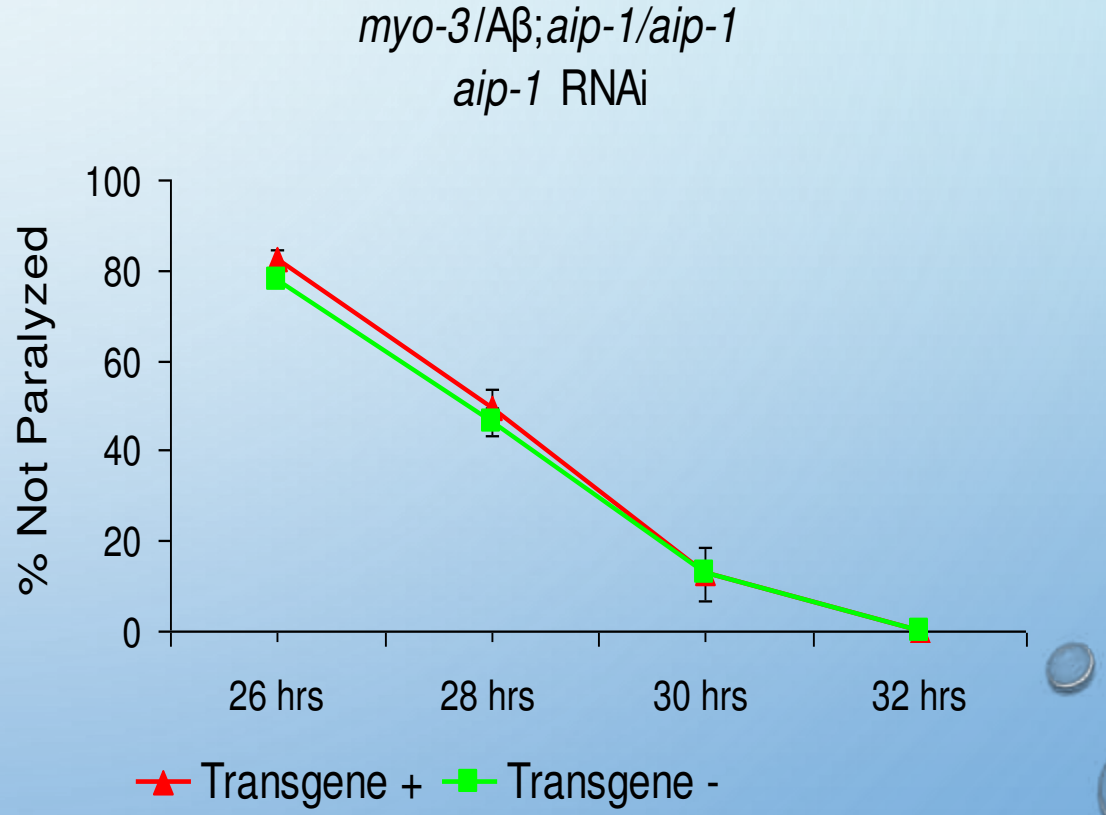


aip-1/aip-1

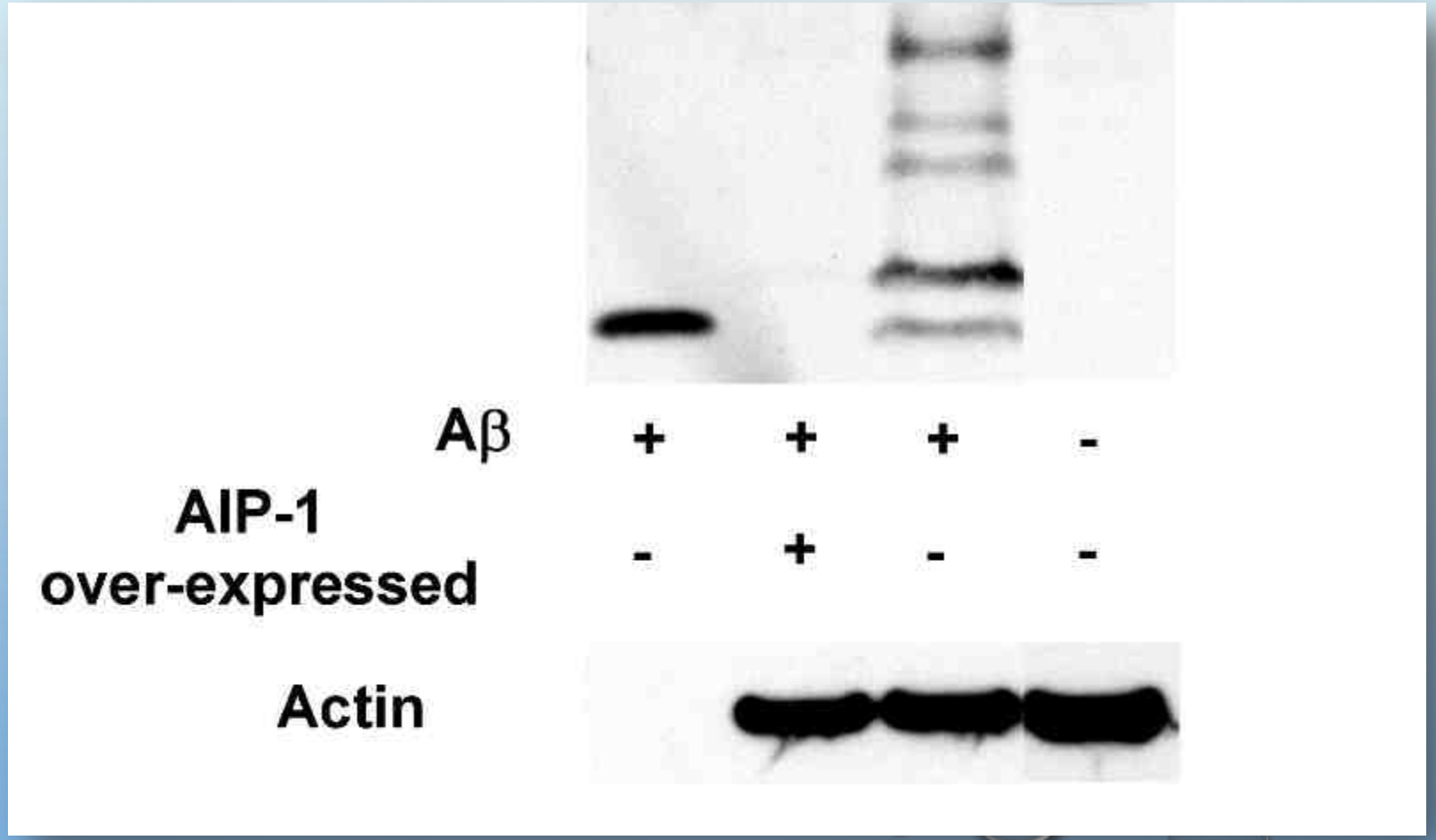


A COUPLE OF CONTROLS



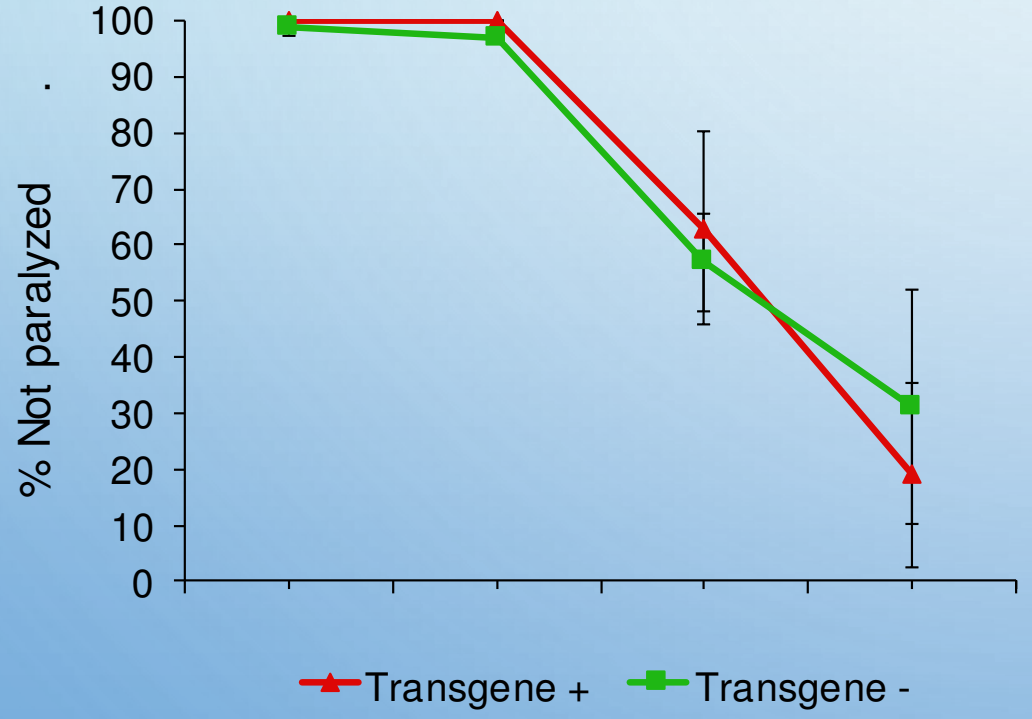


AIP-1 DECREASES ACCUMULATION OF Aβ

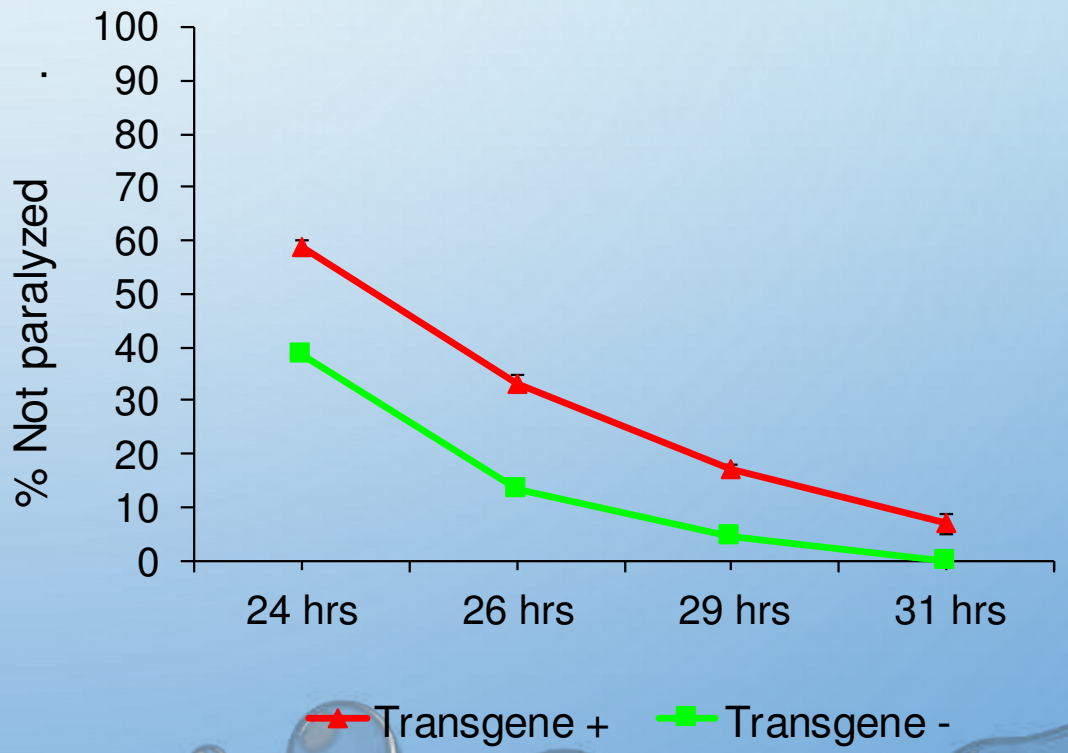


A HUMAN HOMOLOGUE IS PROTECTIVE IN WORMS

myo-3/AIRAP



myo-3/AIRAPL



SUMMARY

- Aβ-specific genes include ones involved in aging, insulin signaling, mitochondrial unfolded protein response, membrane damage repair, and proteasome function.
- Aβ toxicity appears to be mediated, at least in part, by membrane damage.
- AIRAPL, but not AIRAP, is protective against Aβ toxicity.

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