

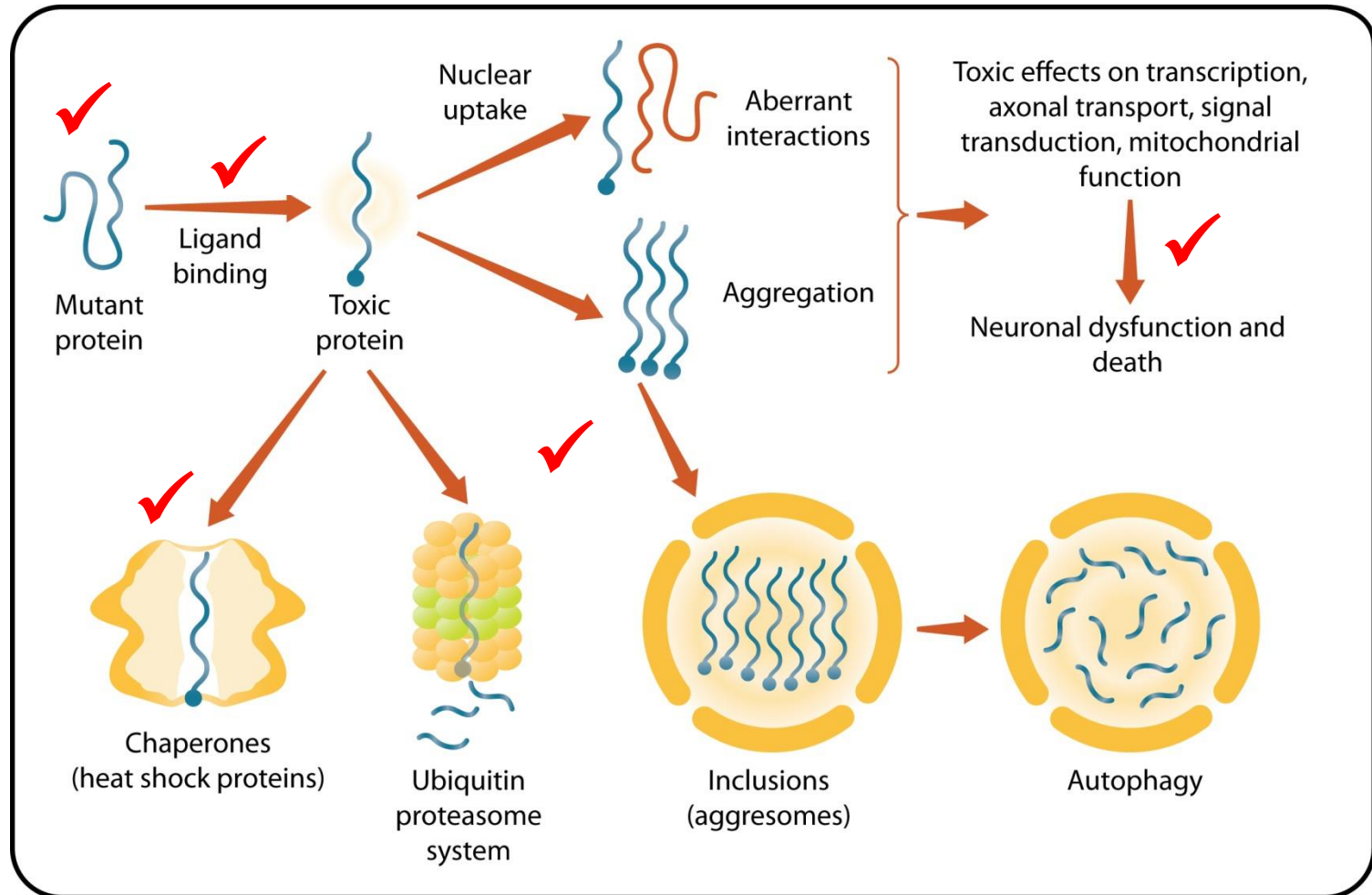
# Therapeutics development for Kennedy's disease

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# SBMA: therapeutic targets



✓ = efficacy in mice

# Therapeutic approaches that work in mice

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- Reducing androgen levels: leuprorelin, dutasteride
- Enhancing heat shock proteins to protect against the mutant protein: 17-AAG
- Neuroprotection and enhanced mitochondrial function: naratriptan, pioglitazone

# Therapeutic approaches that work in mice

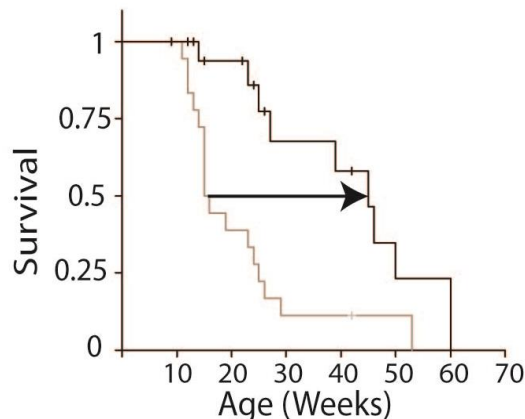
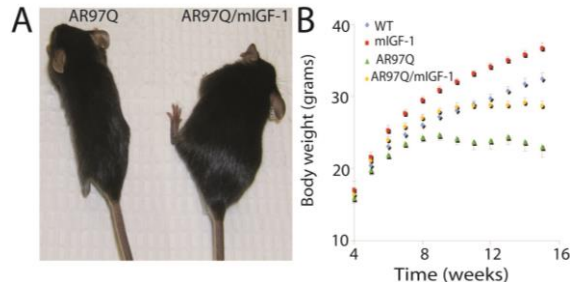
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- Changing phosphorylation of the disease gene product to make it less toxic: IGF-1
- Selective AR modulation: ASC-JM17
- Decreasing mutant protein expression: micro-RNA and antisense oligonucleotides (ASOs)

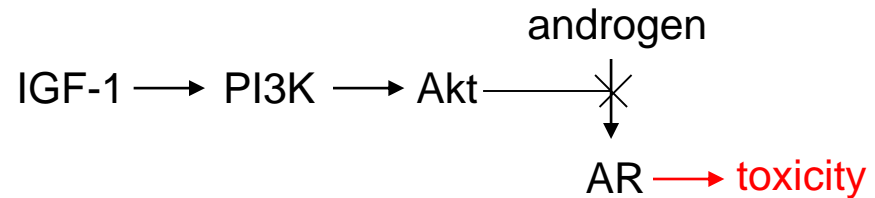
# Overexpression of IGF-1 in muscle attenuates disease in a mouse model of spinal and bulbar muscular atrophy

Palazzolo I, Stack C, Kong L, Musaro A, Adachi H, Katsuno M, Sobue G, Taylor JP, Sumner C, Fischbeck K, Pennuto M

Neuron. 2009



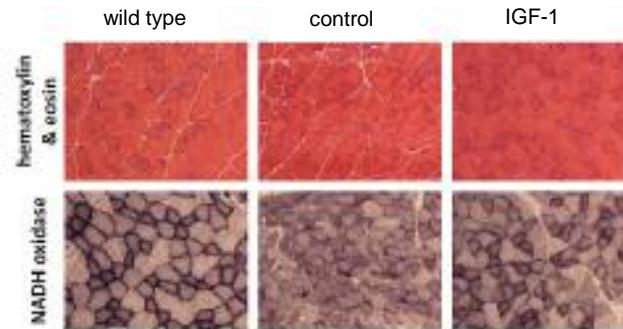
- Phosphorylation of mutant AR by Akt blocks its toxicity.
- Akt activation by IGF-1 mitigates AR toxicity in cell culture and in transgenic mice.



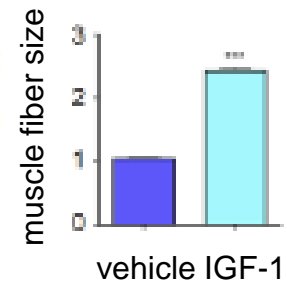
# IGF-1 treatment for SBMA

- IGF-1 overexpression blocks AR toxicity through Akt-mediated phosphorylation.

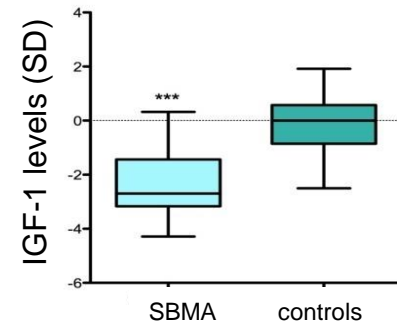
- IGF-1 treatment improves muscle pathology and behavior in SBMA mice:



(Rinaldi et al, 2012)



- SBMA patients have low serum IGF-1, allowing room for therapeutic benefit:



# Proof of concept trial for SBMA

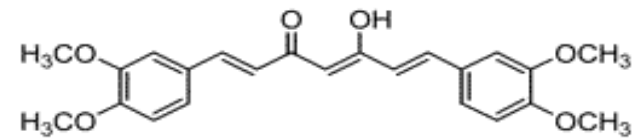
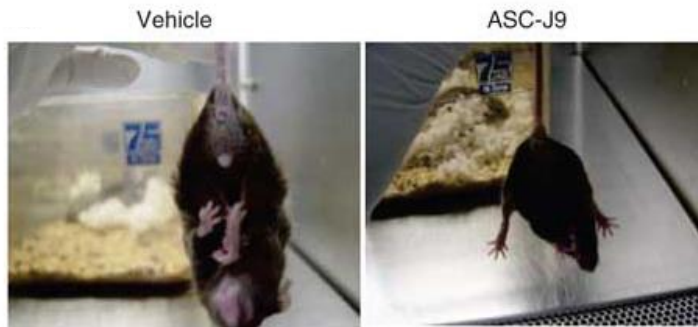
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- Rationale for IGF-1 pathway: BVS857
- Safety risks: hypoglycemia
- Biological measures: muscle volume by MRI, muscle histology & biochemistry
- Efficacy measures: muscle strength & function
- 2 part study:
  - A. Dose escalation, safety
  - B. 12 week controlled efficacy trial

# ASC-J9 ameliorates spinal and bulbar muscular atrophy phenotype via degradation of androgen receptor.

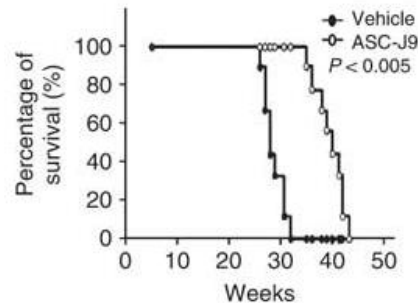
Yang Z, Chang YJ, Yu IC, Yeh S, Wu CC, Miyamoto H, Merry DE, Sobue G, Chen LM, Chang SS, Chang C

Nature Med. 2007



ASC-J9

Vehicle ASC-J9

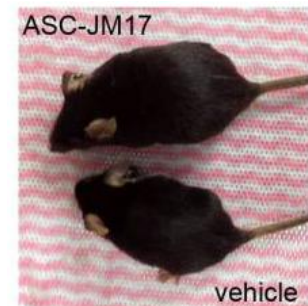
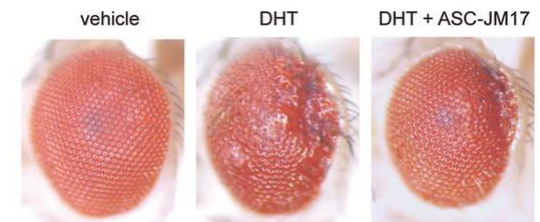
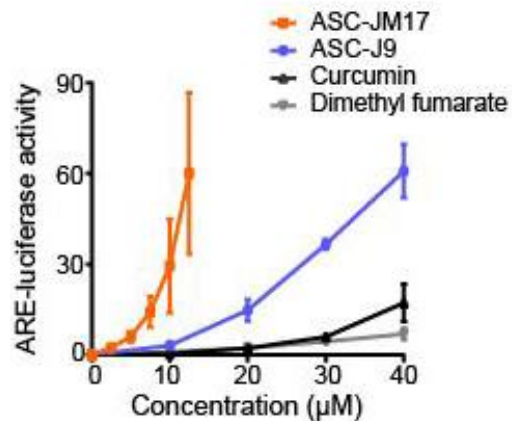
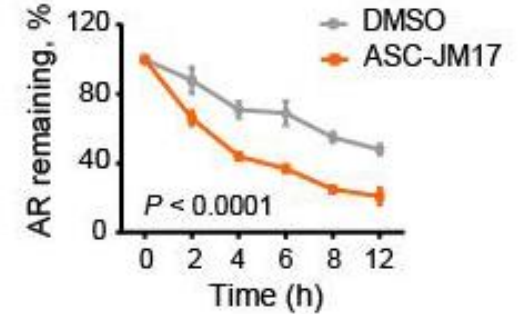
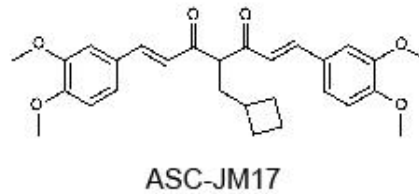


- NIH study confirms beneficial effect of ASC-J9 and orally bioavailable derivative ASC-JM17.



# AR modulator ASC-JM17

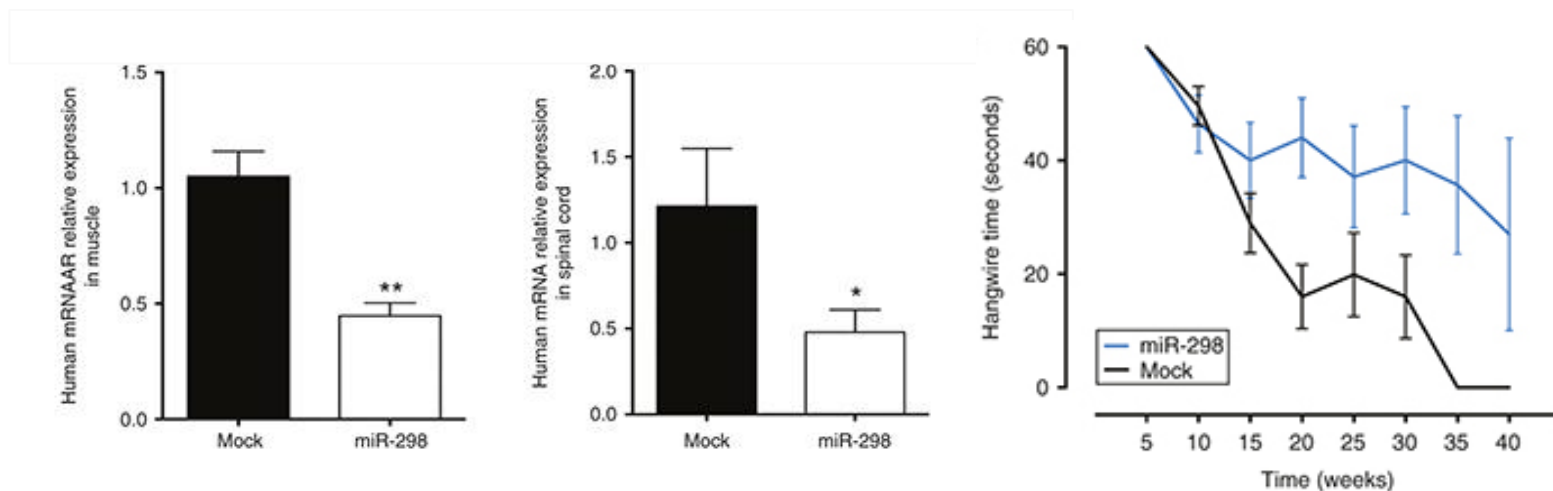
ASC-JM17 accelerates mutant androgen receptor degradation, activates cellular protective responses through Nrf1/Nrf2, and rescues the phenotype in transgenic flies & mice.



(Bott et al, 2016)

# miRNA-mediated suppression of mutant AR

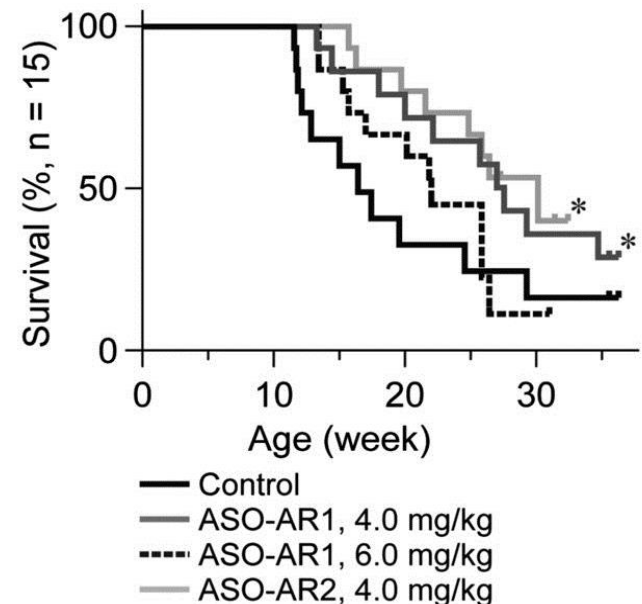
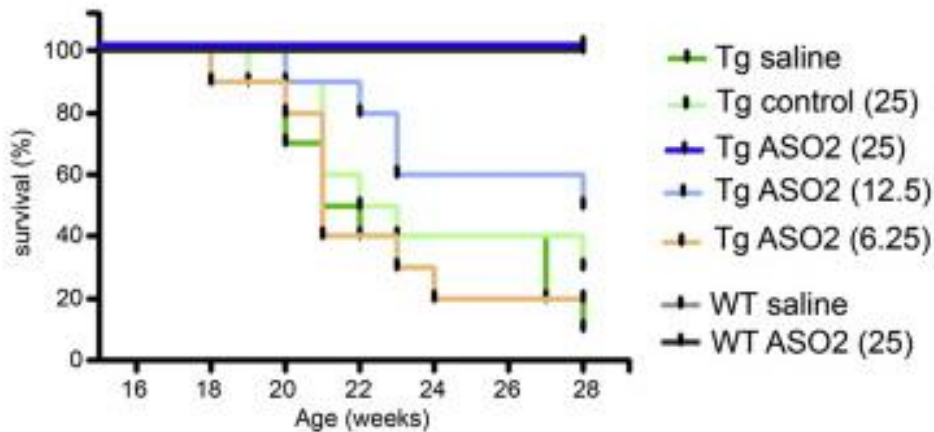
AAV9-mediated IV delivery of miR-298 targeting AR 3'UTR results in good distribution to muscle & spinal cord, reduction in mutant AR mRNA & protein levels, and mitigation of disease manifestations in SBMA mice:



(Pourshafie et al, 2016)

# ASO-mediated suppression of mutant AR

ASO targeting AR reduces mutant mRNA and protein levels and mitigates disease manifestations with peripheral or central administration in mice:



(Lieberman et al, 2014; Sahashi et al, 2015)

# SBMA clinical plans

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- Further clinical studies with drugs targeting IGF-1 pathway (e.g., mecasecmin, human growth hormone)
- Proof of concept clinical trial of ASC-JM17
- Proof of concept clinical trial with antisense oligonucleotide targeting AR, based on promising preclinical results (Lieberman et al, 2014; Sahashi et al, 2015 )

Nothing we do, however virtuous, can  
be accomplished alone ...

Reinhold Niebuhr

