NU Tech
Technology Partnership of Nagoya University, Inc.

(A69)

Noble therapeutics targeting a neuromuscular disease, Spinal and bulbar muscular atrophy

Background:

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is a neuromuscular disorder characterized by muscle weakness and atrophy. SBMA is caused by the expansion of the polyglutamine tract in the androgen receptor (AR) gene. Leuprorelin acetate potentially improves neurological symptoms in SBMA patients, although the effect of this drug is limited by its adverse reaction.

Technology Overviews:

Researchers in Nagoya University have successfully identified the therapeutics of SBMA targeting the spatiotemporal dysregulation of signaling pathways in SBMA. By using Bio-rad Bio-plex assays, the expression levels of phosphorylated proteins were measured in the spinal cord and skeletal muscle specimen of a mouse model of SBMA (AR-97Q mice) at three stages. As a result, the level of phosphorylated Src was markedly up-regulated both in the spinal cords and skeletal muscles before the onset of neurological symptoms. In spinal cord, the activation of Src sustained until the advanced stage of the disease. Src pathway was also up-regulated in neuronal and muscle cell models of SBMA. Furthermore, the intraperitoneal administration of a Src kinase inhibitor (SKI) improved the phenotypes and lifespan of AR-97Q mice. Therefore, SKIs are candidate therapeutics for SBMA.

Fitures:

Figure 1. Method.

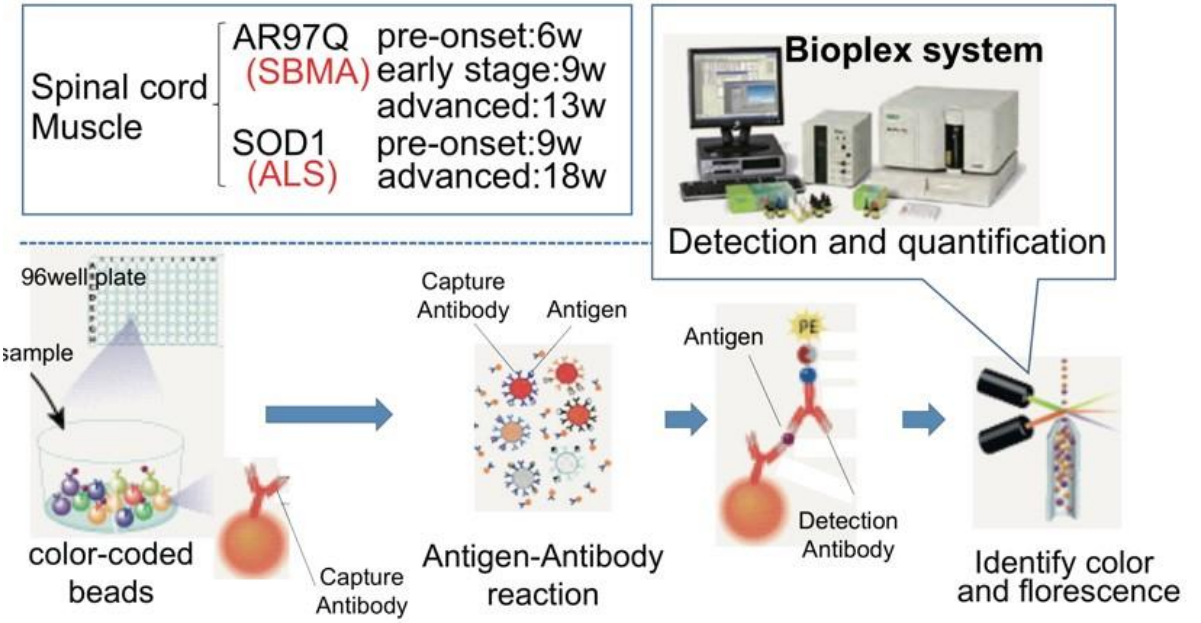

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Figure 2. Abnormally phosphorylated proteins in AR-97Q mice.

A

	AR-97Q					
	spinal cord			muscle		
	6w	9w	13w	6w	9w	13w
Src	*1.18	*1.12	*1.23	1.39	3.54	0.44
Stat3	*1.26	1.03	0.92	*1.96	1.09	1.27
p38MAPK	*1.23	0.84	1.16	8.76	1.63	1.03
c-Jun	*1.24	0.88	*1.20	1.58	1.81	*5.21
IGF-1R	*1.21	*1.19	0.93	0.96	*2.78	1.06
IRS-1	1.19	0.48	1.23	*3.94	8.19	2.11
Akt	*1.80	*0.71	0.93	*2.23	*4.06	1.50
IkBa	*1.58	*1.37	1.14	0.81	*1.28	12.7
p70s6k	1.19	0.94	1.19	*1.96	2.02	*2.50
Erk1/2	1.17	1.22	*0.83	1.21	0.83	0.61
Smad2	*1.08	*0.87	1.04	1.74	1.62	1.68
GSK	1.03	0.98	1.01	*1.14	*1.45	*1.44
c-Abl	1.11	0.98	1.04	1.14	1.02	*1.65
JNK	1.04	*1.23	1.06	0.63	*4.21	*2.53
VEGFR	1.10	0.98	*1.30	1.35	*1.68	*1.49
mTOR	0.97	0.82	1.16	1.14	*1.79	*3.23
HSP27	1.04	1.00	1.13	0.94	*3.23	1.43

0.50-0.85 ≦0.50 1.15-2.00 ≧2.00

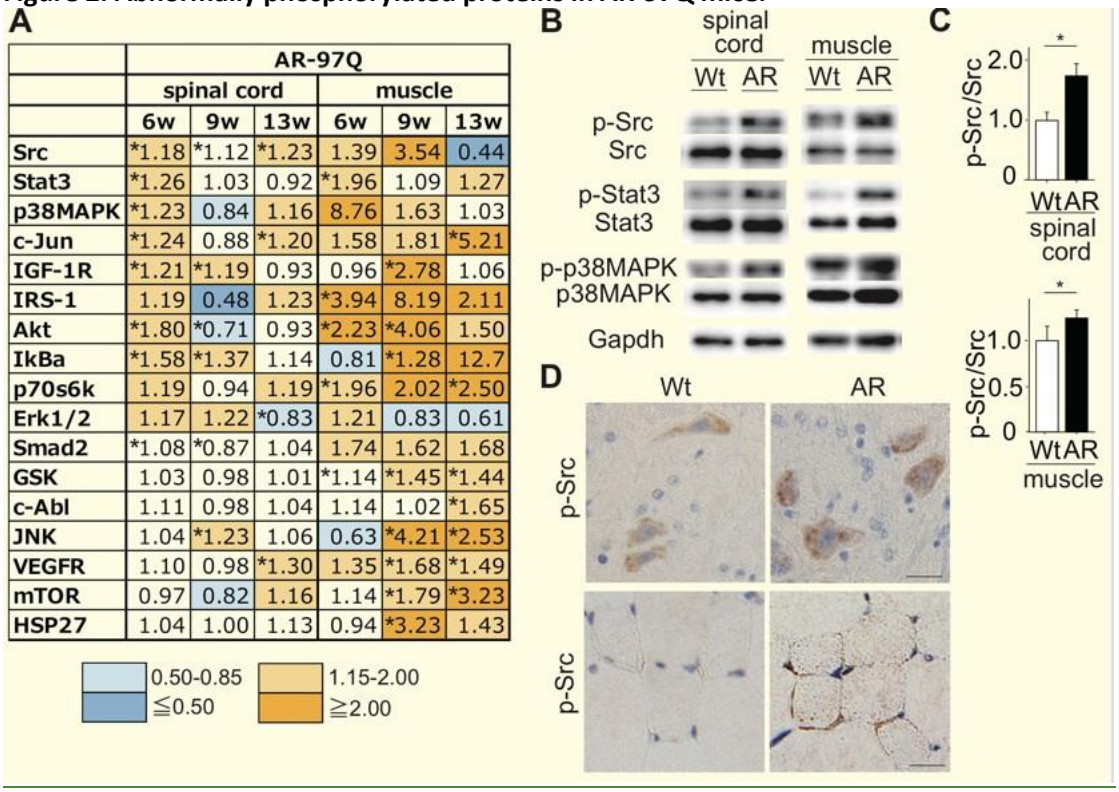

Figure 3. Phosphorylation levels of Src, Stat3 and p38MAPK in cellular models of SBMA.

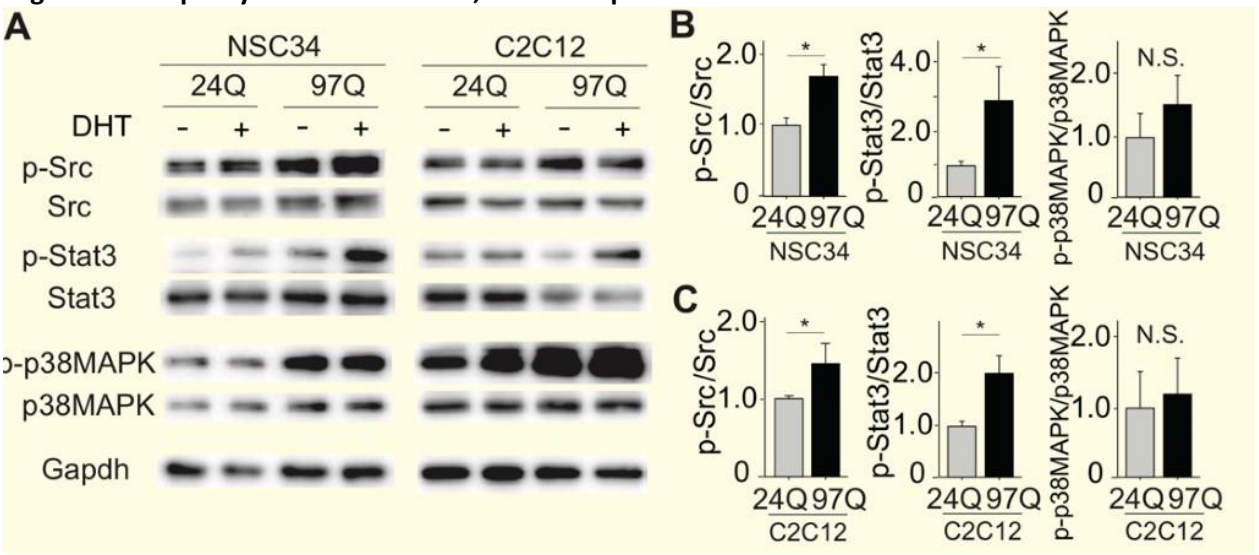

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Figure 4. Src kinase inhibitor (SKI:A419259) improves the viability of cellular models of SBMA (n=3).

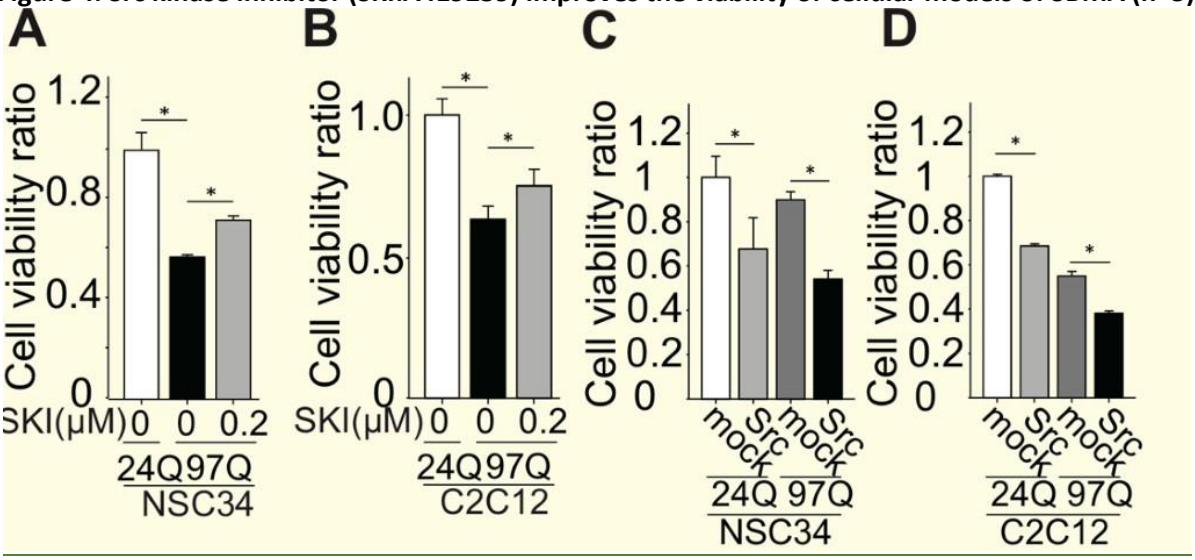

Figure 5. A419259 improves neuromuscular phenotypes of the mouse model of SBMA.

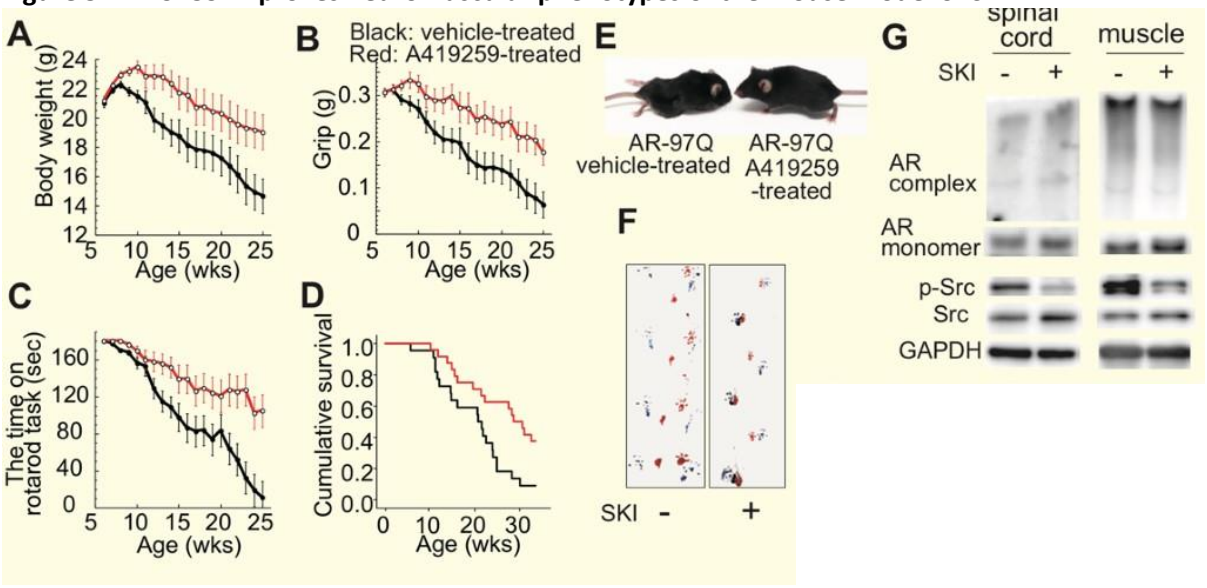

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Figure 6. Downstream targets of Src in mouse and cellular models of SBMA.

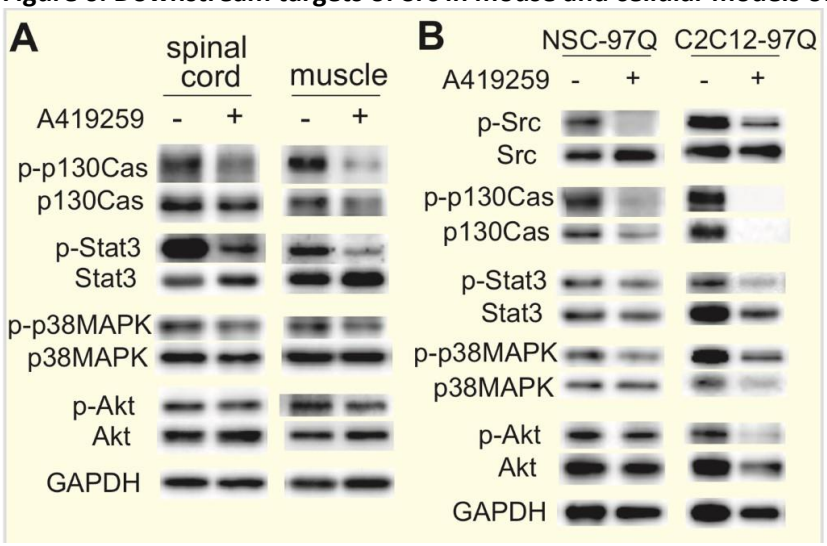
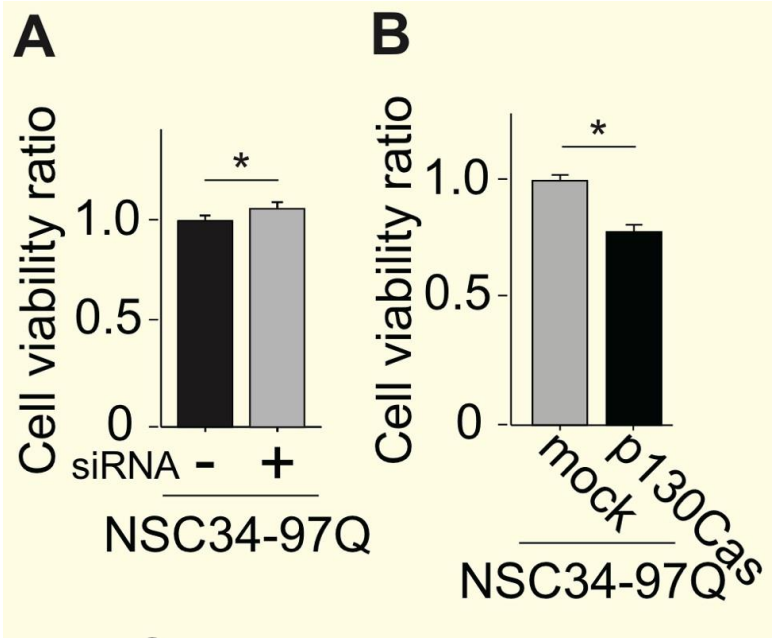


Figure 7. Phosphorylation of p130 exerts toxicity in the cellular model of SBMA.



Further Details:

(Poster Presentation) Madoka Iida *et al.*, Development of therapeutics targeting the spatiotemporal dysregulation of signaling pathways in spinal and bulbar muscular atrophy. 59th Annual Meeting of the Japanese Society of Neurology. May 2018.

Seeking: Licensing

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