



Androgen Receptor and skeletal muscle health: One step closer to understanding SBMA

Ambra Speciale, DPhil student
Rinaldi Lab

Kennedy Disease Patient Day – 10 July 2022
London



UNIVERSITY OF
OXFORD

The lab



The study

Acta Neuropathologica (2022) 143:713–731
<https://doi.org/10.1007/s00401-022-02428-1>

ORIGINAL PAPER



AR cooperates with SMAD4 to maintain skeletal muscle homeostasis

Mitra Forouhan¹ · Wooi Fang Lim¹ · Laura C. Zanetti-Domingues² · Christopher J. Tynan² · Thomas C. Roberts¹ · Bilal Malik³ · Raquel Manzano⁴ · Alfina A. Speciale¹ · Ruth Ellerington¹ · Antonio Garcia-Guerra¹ · Pietro Fratta³ · Gianni Sorarú^{5,6} · Linda Greensmith³ · Maria Pennuto^{6,7} · Matthew J. A. Wood^{1,8} · Carlo Rinaldi^{1,8} 

Received: 15 November 2021 / Revised: 10 April 2022 / Accepted: 27 April 2022 / Published online: 6 May 2022
© The Author(s) 2022

Spinal and Bulbar Muscular Atrophy (SBMA)

Genetic disease caused by a defect in the X chromosome



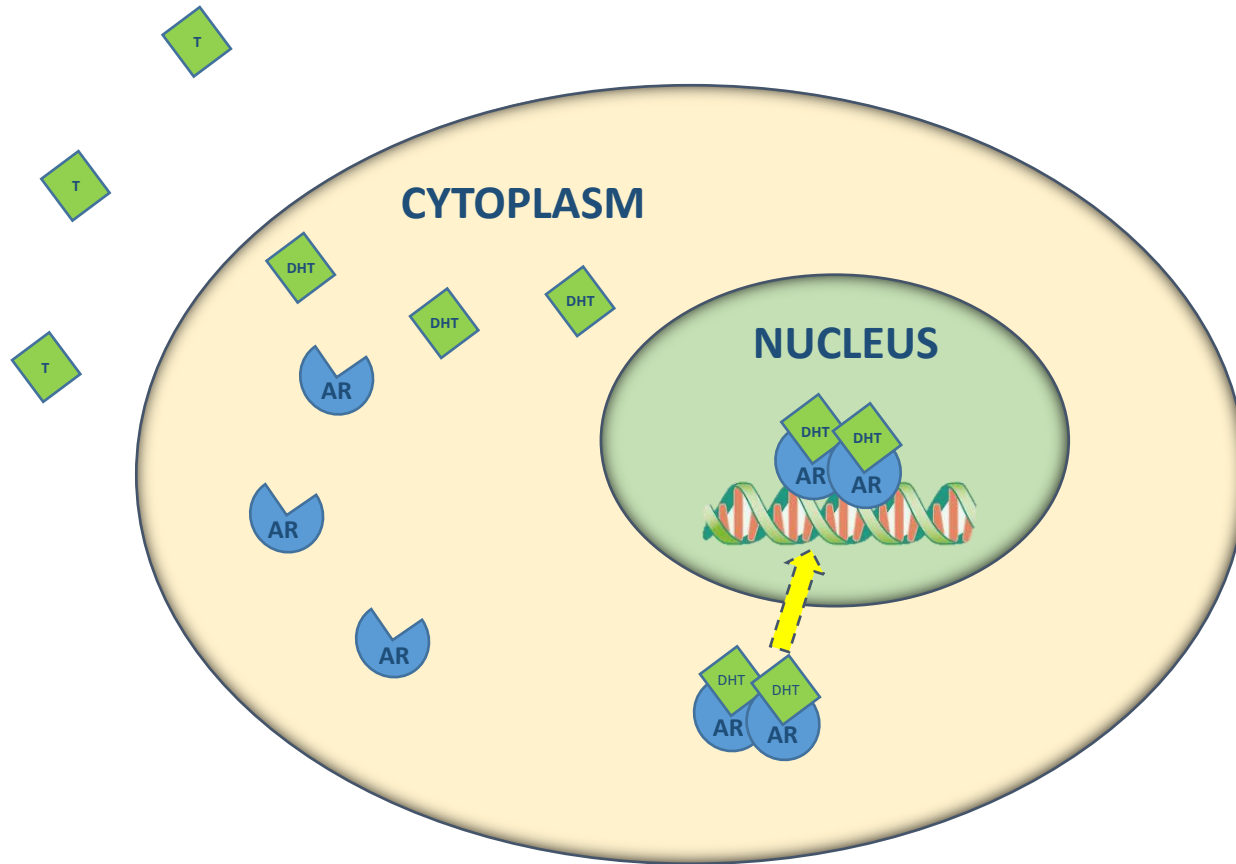
Altered Androgen Receptor protein
(polyQ AR)

Loss of nerve cells in the spinal cord
and brainstem (motor neurons)

Primary muscle pathology

Progressive muscle weakness,
muscle twitches, difficulty in
swallowing and gynecomastia

Androgen Receptor



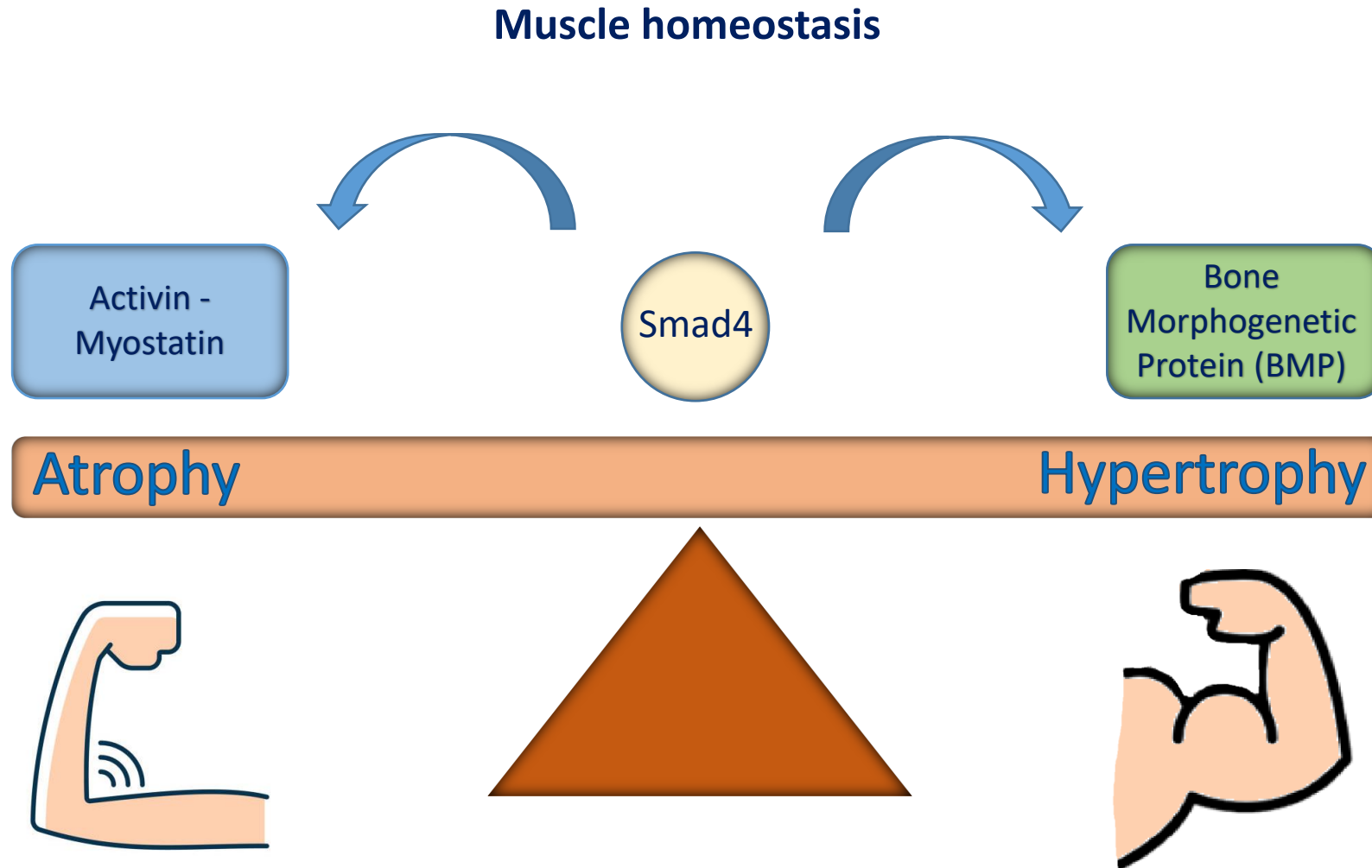
Reproductive function

Motor neuron
homeostasis

Preservation and
increase of muscle mass

How?

Main players of muscle health

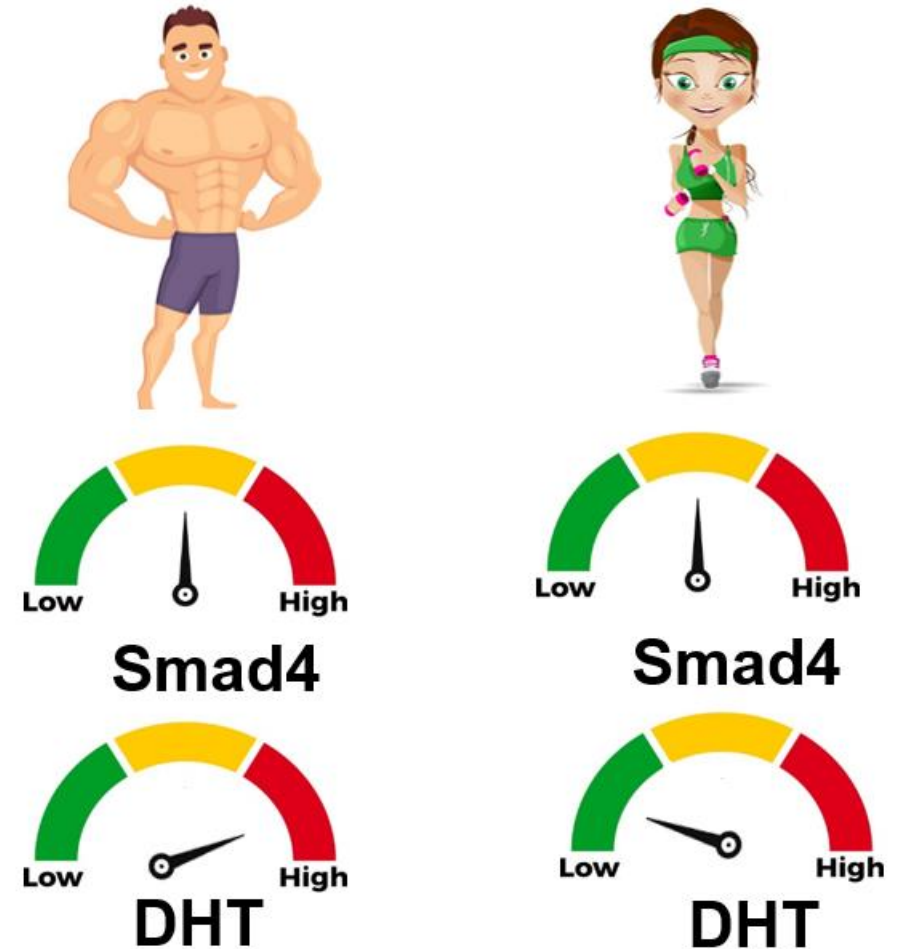
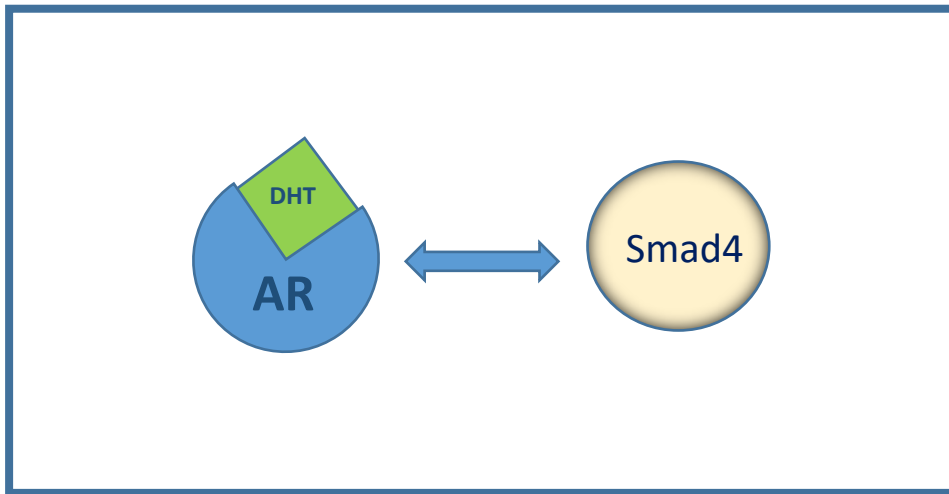


Where and how is Androgen Receptor involved in this balance?



Where and how is Androgen Receptor involved in this balance?

Androgen Receptor **interacts** with Smad4

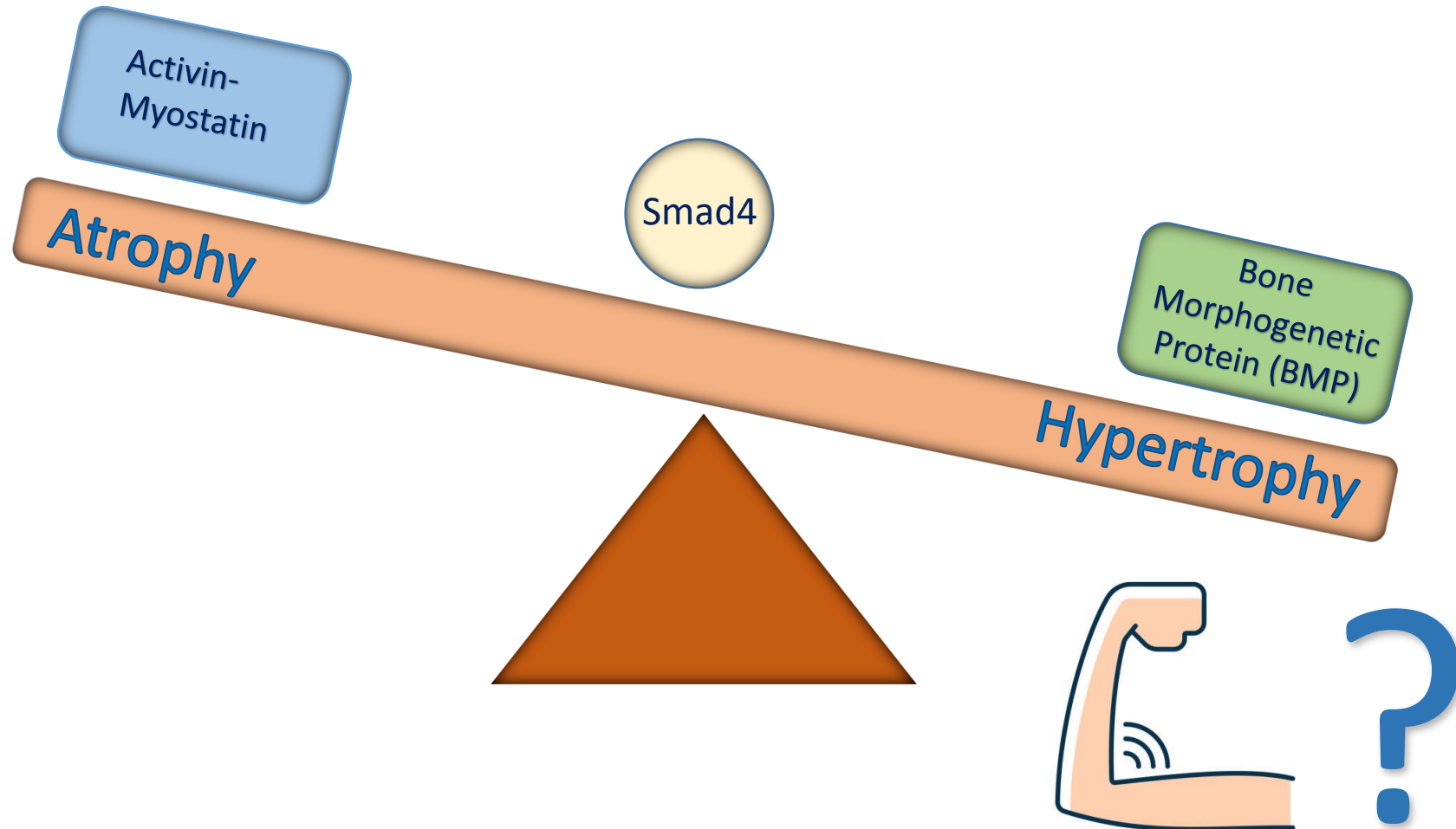




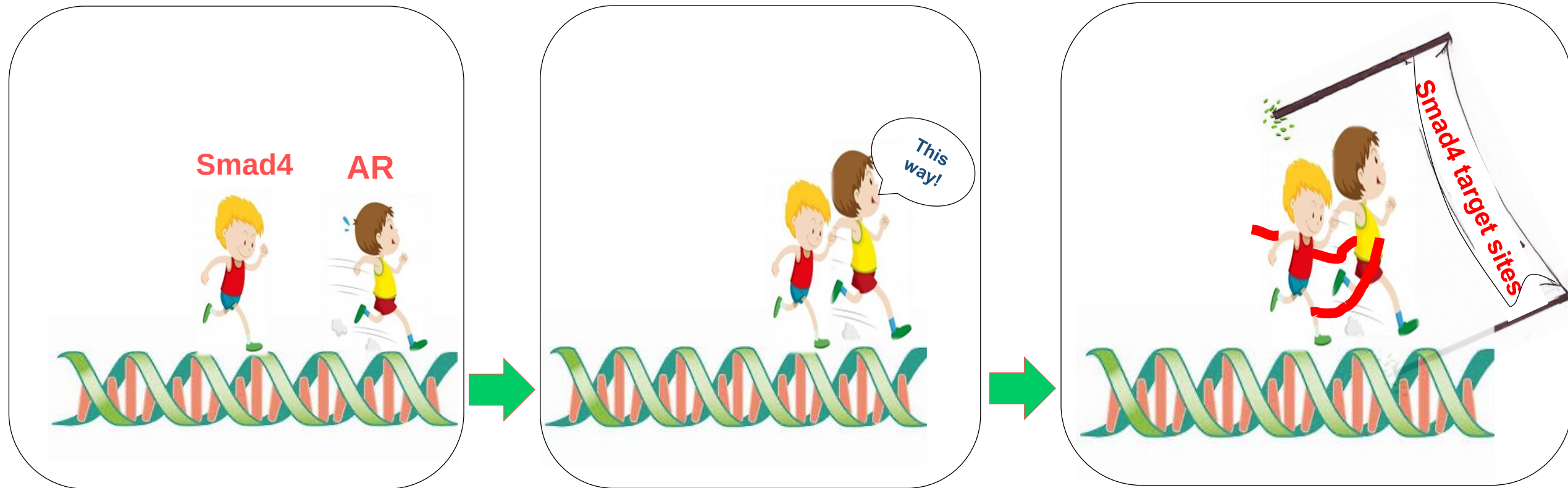
What happens to muscle homeostasis in SBMA?



What happens to muscle homeostasis in SBMA?

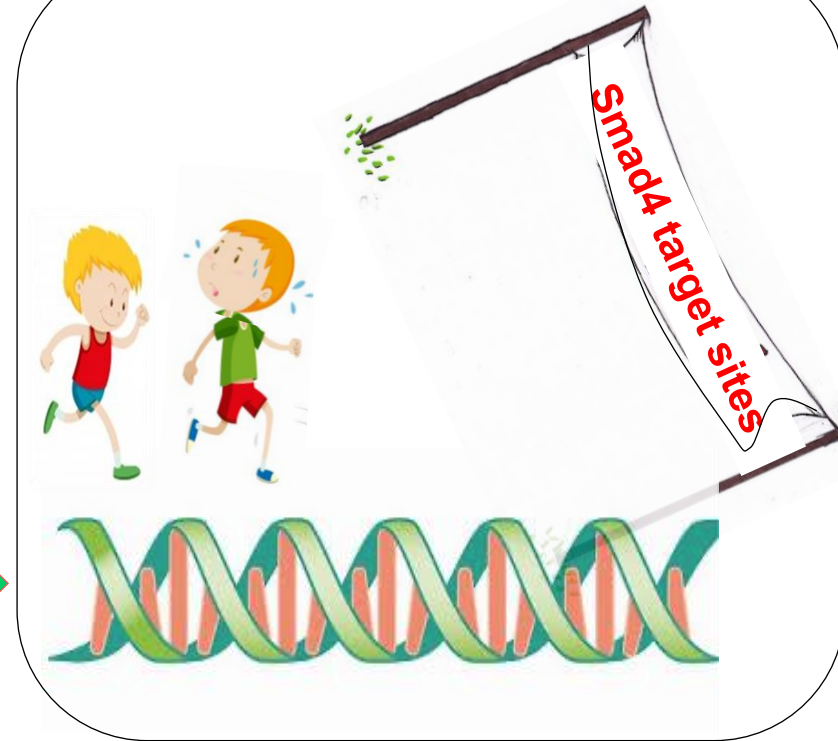
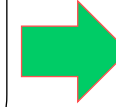
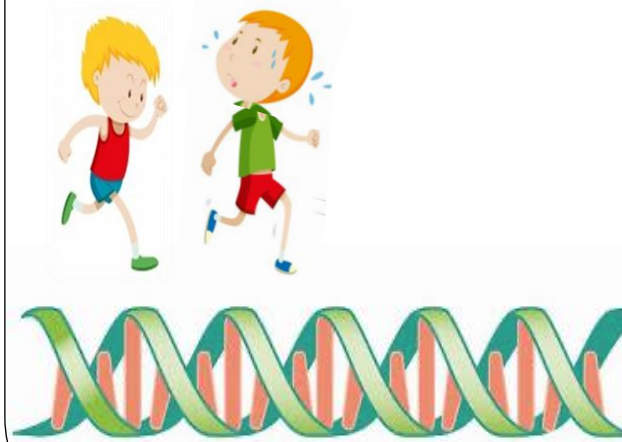
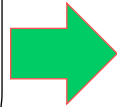
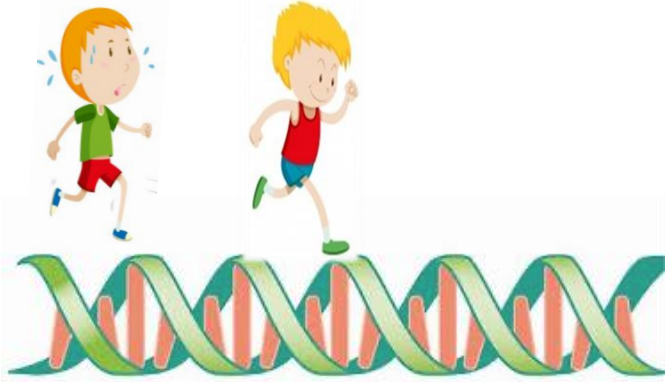


Androgen Receptor cooperates with Smad4



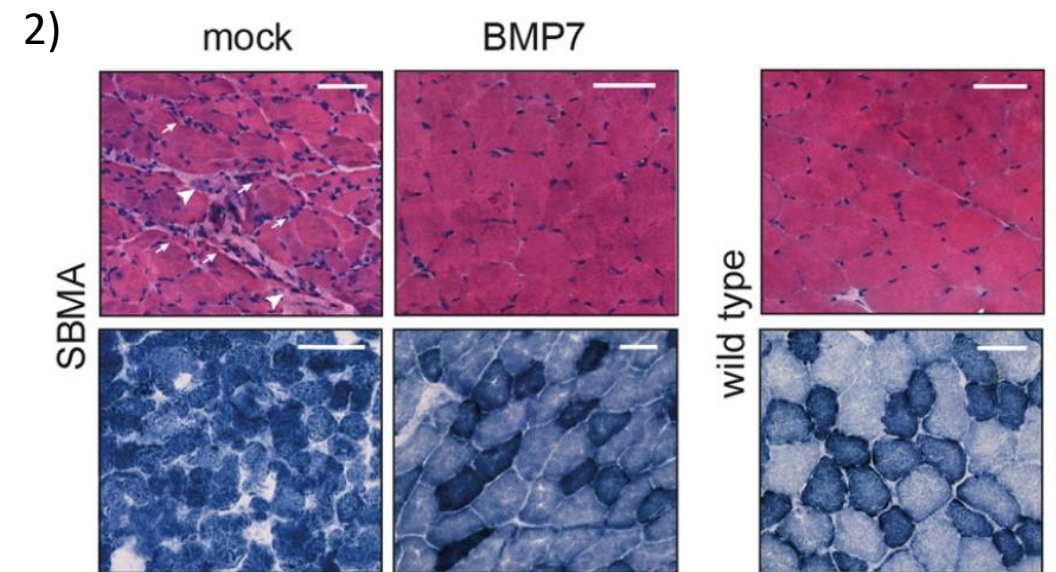
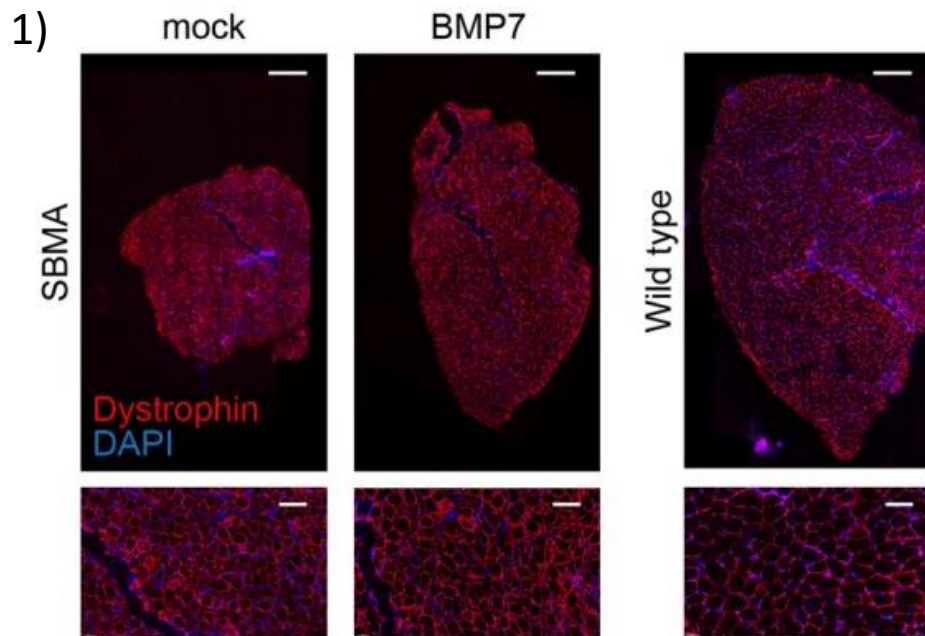
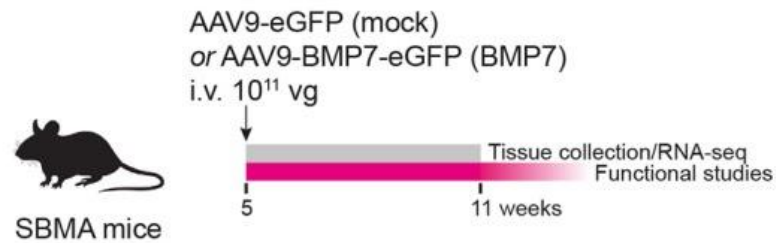
Androgen Receptor cooperates with Smad4

PolyQ AR Smad4



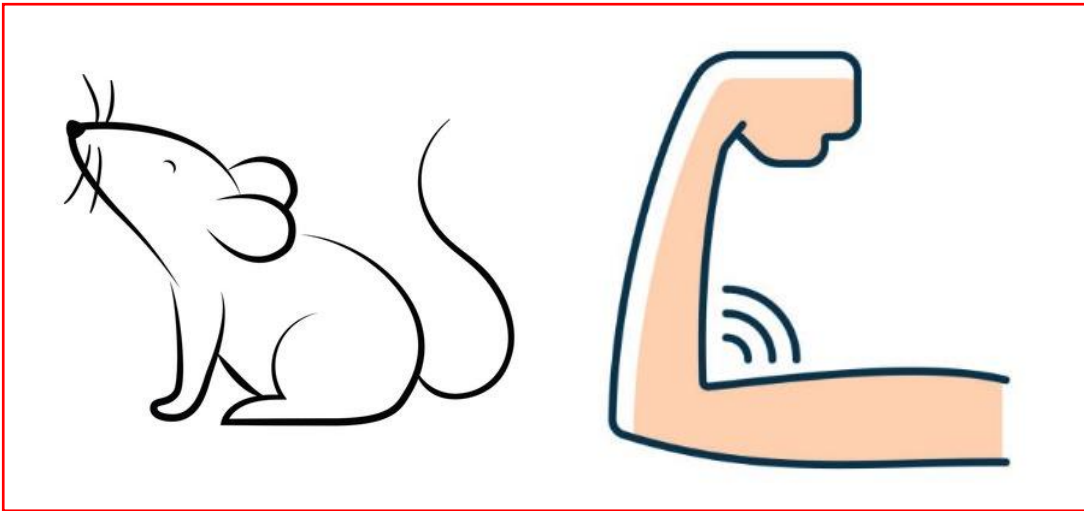
Mitra Forouhan, PhD

BMP treatment improves muscle health in vivo

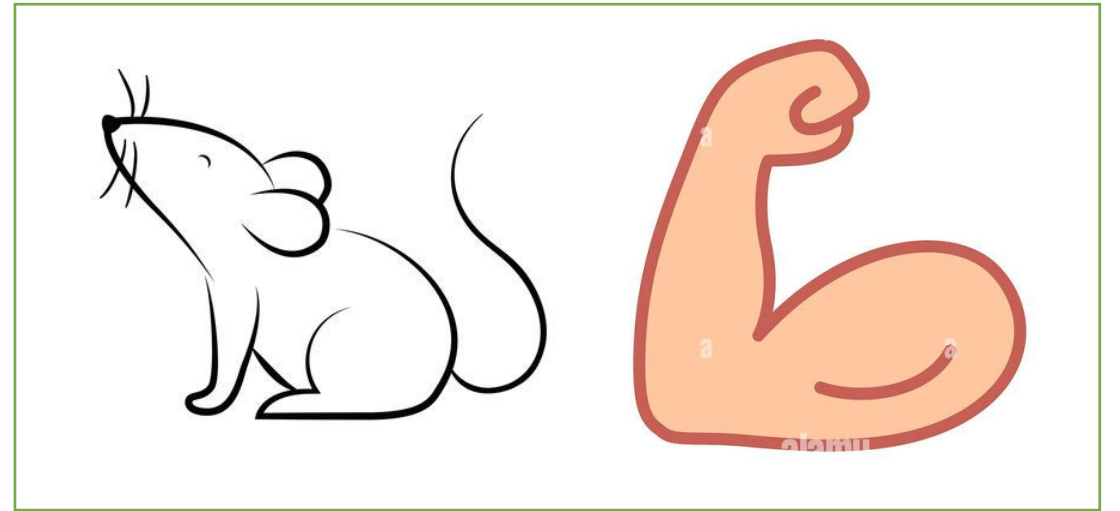


BMP treatment improves muscle health in vivo

SBMA MOUSE



BMP-TREATED SBMA MOUSE



How can we get to clinic?

BMP therapy in patients not advisable because of possible side effects

Development of treatments to modulate the cooperation between AR and Smad4

Take-home messages

Androgen Receptor is one of the main players of muscle homeostasis

The interaction of mutant Androgen Receptor with Smad4 is not efficient to activate the hypertrophy programme in SBMA

The development of treatments to modulate the cooperation between AR and Smad4 could counteract muscle atrophy in SBMA

Thank you



Mitra Forouhan, PhD
Rinaldi Lab
Wood Lab

