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UNIVERSITY OF OXFORD

DEPARTMENT OF PAEDIATRICS

Institute of Developmental & Regenerative Medicine

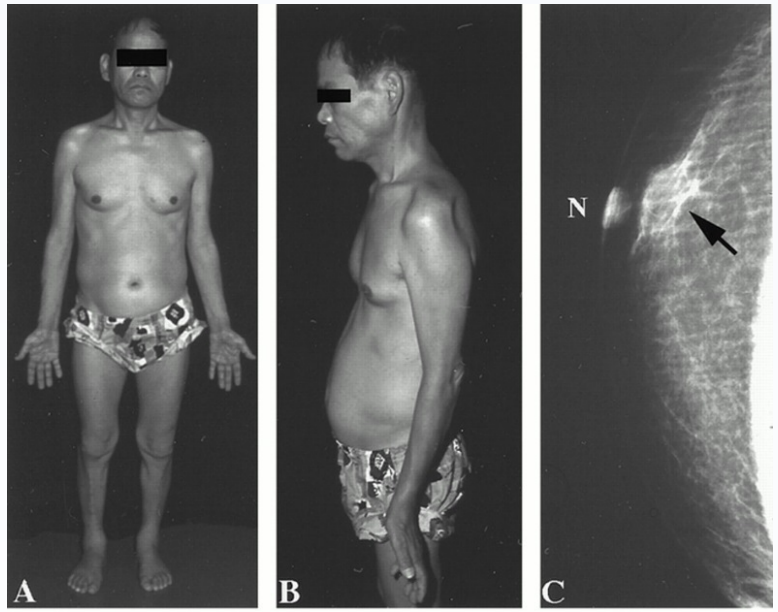
# KD UK PATIENT DAY 2022

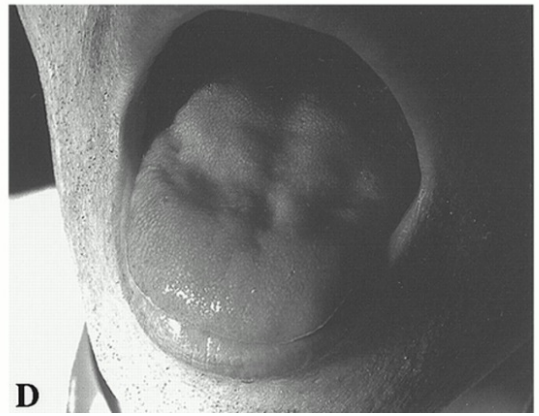
# New Gene Therapy Strategy for SBMA

Catheryn Lim, PhD

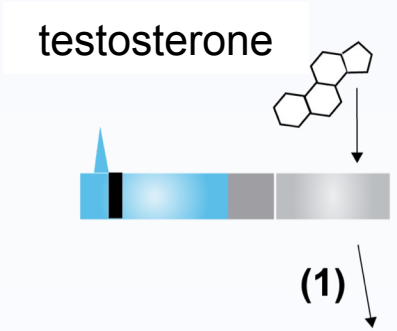
# Spinal and bulbar muscular atrophy / Kennedy's Disease

- Genetic defect on X chromosome
- Mutation in androgen receptor gene – faulty androgen receptor protein that is both less functional and toxic to nerve cells and muscle cells.
- Loss of motor neurons and primary muscle atrophy.
- Partial androgen insensitivity syndromes.

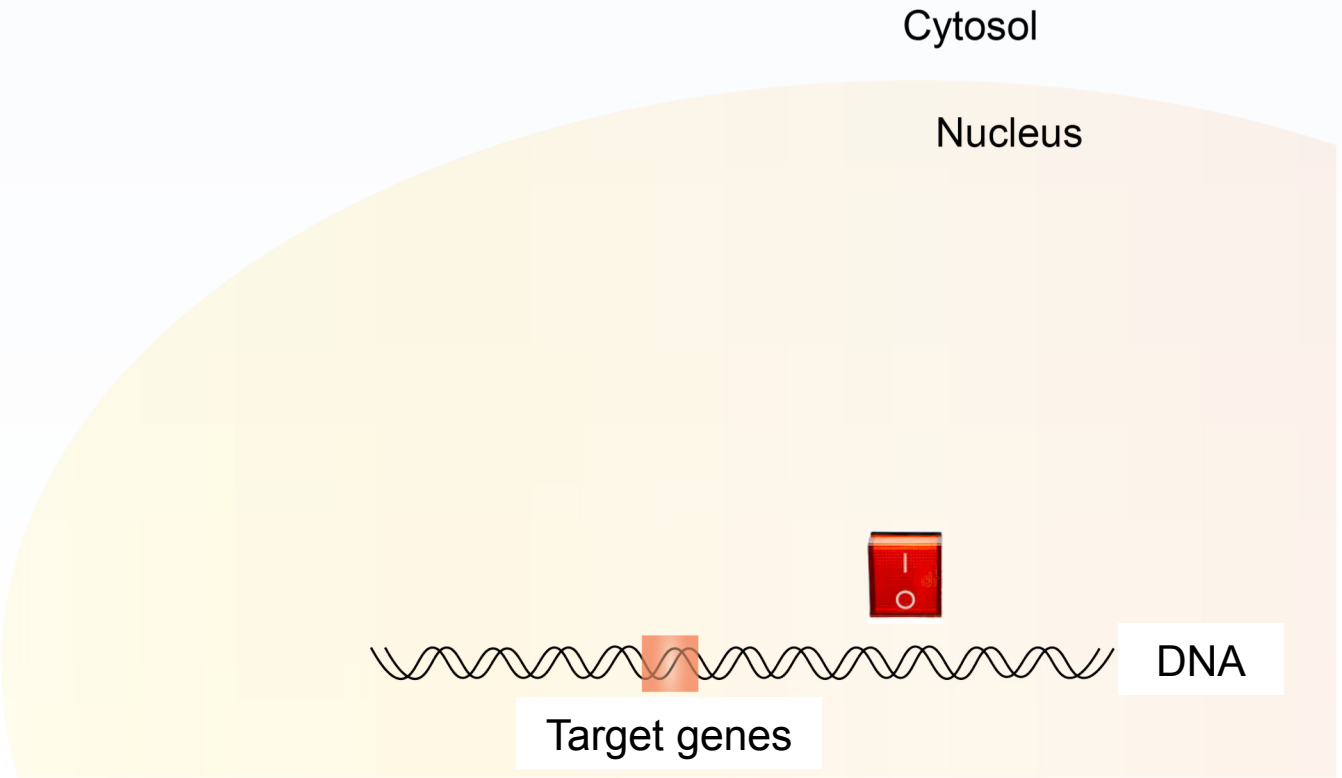


# Androgen receptor protein (AR) as a molecular switch




AR = Molecular switch



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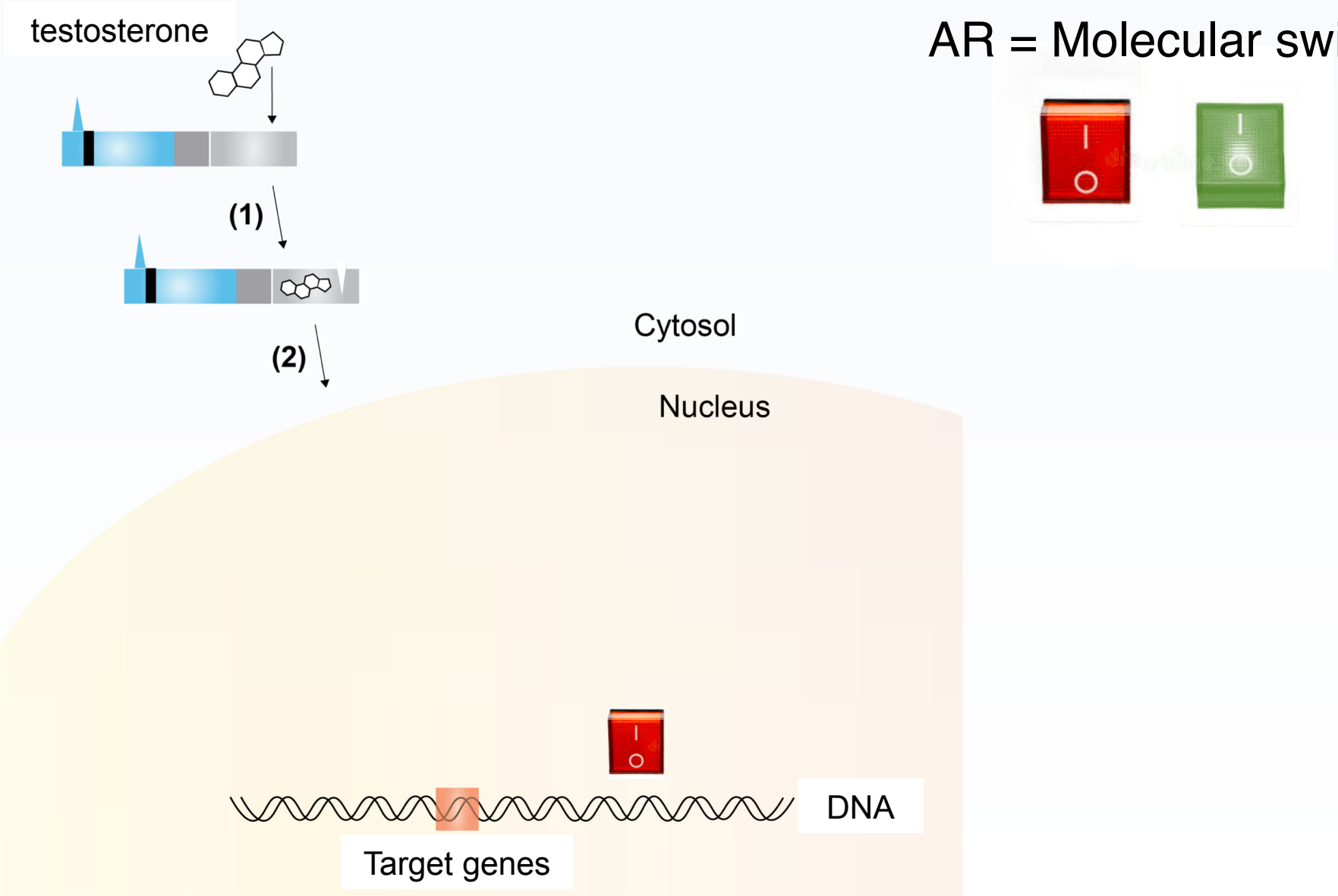


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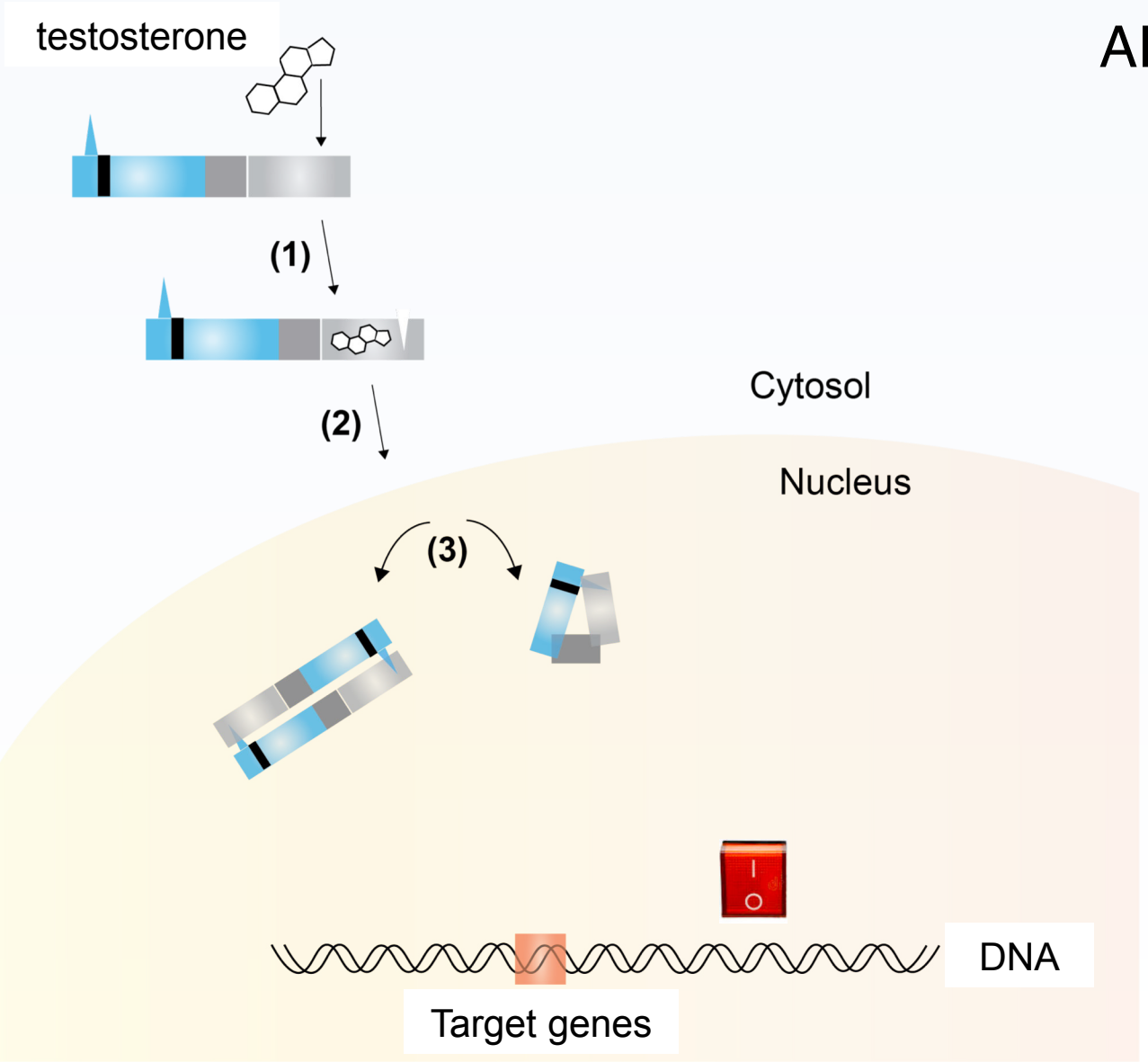


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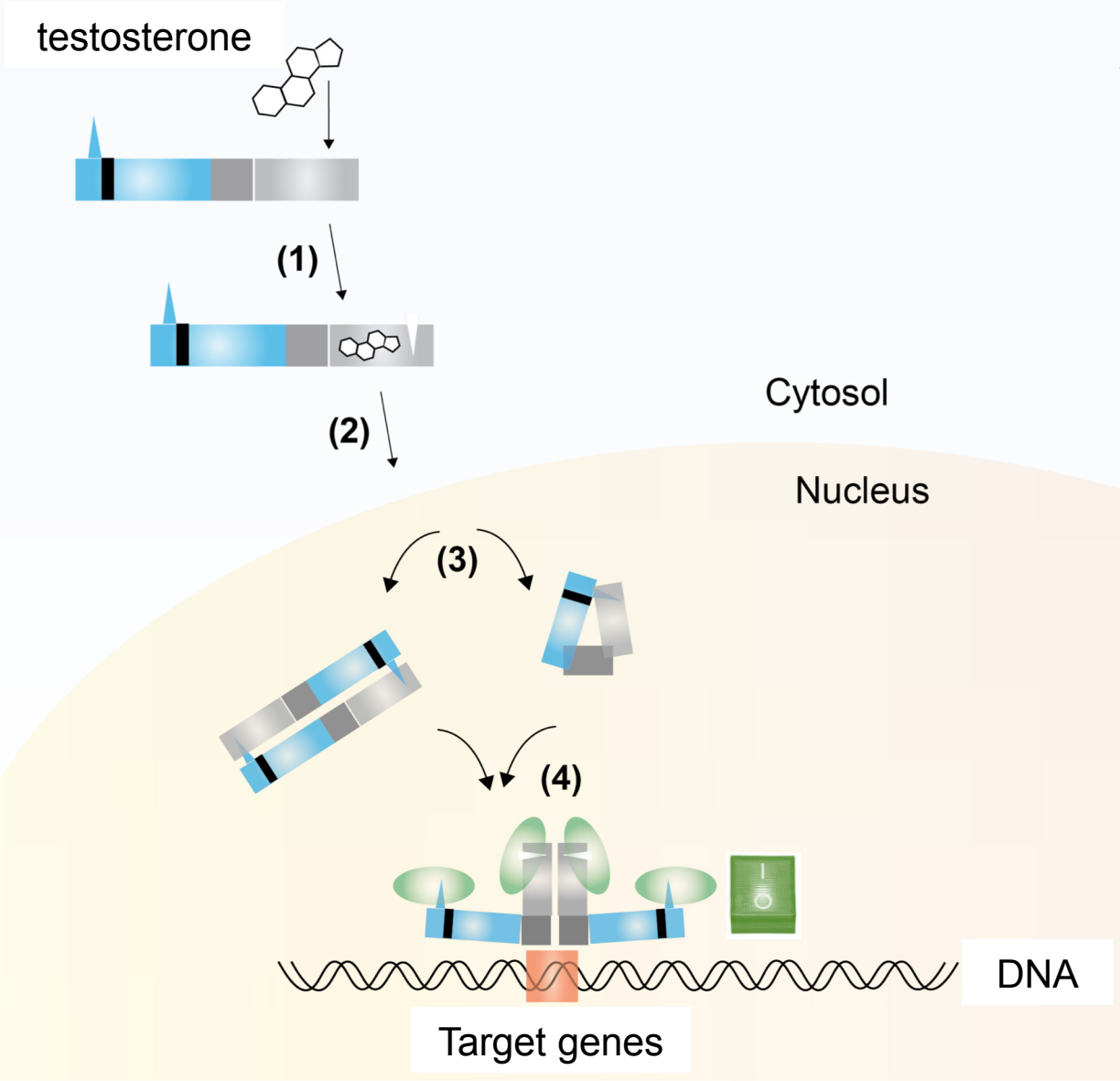


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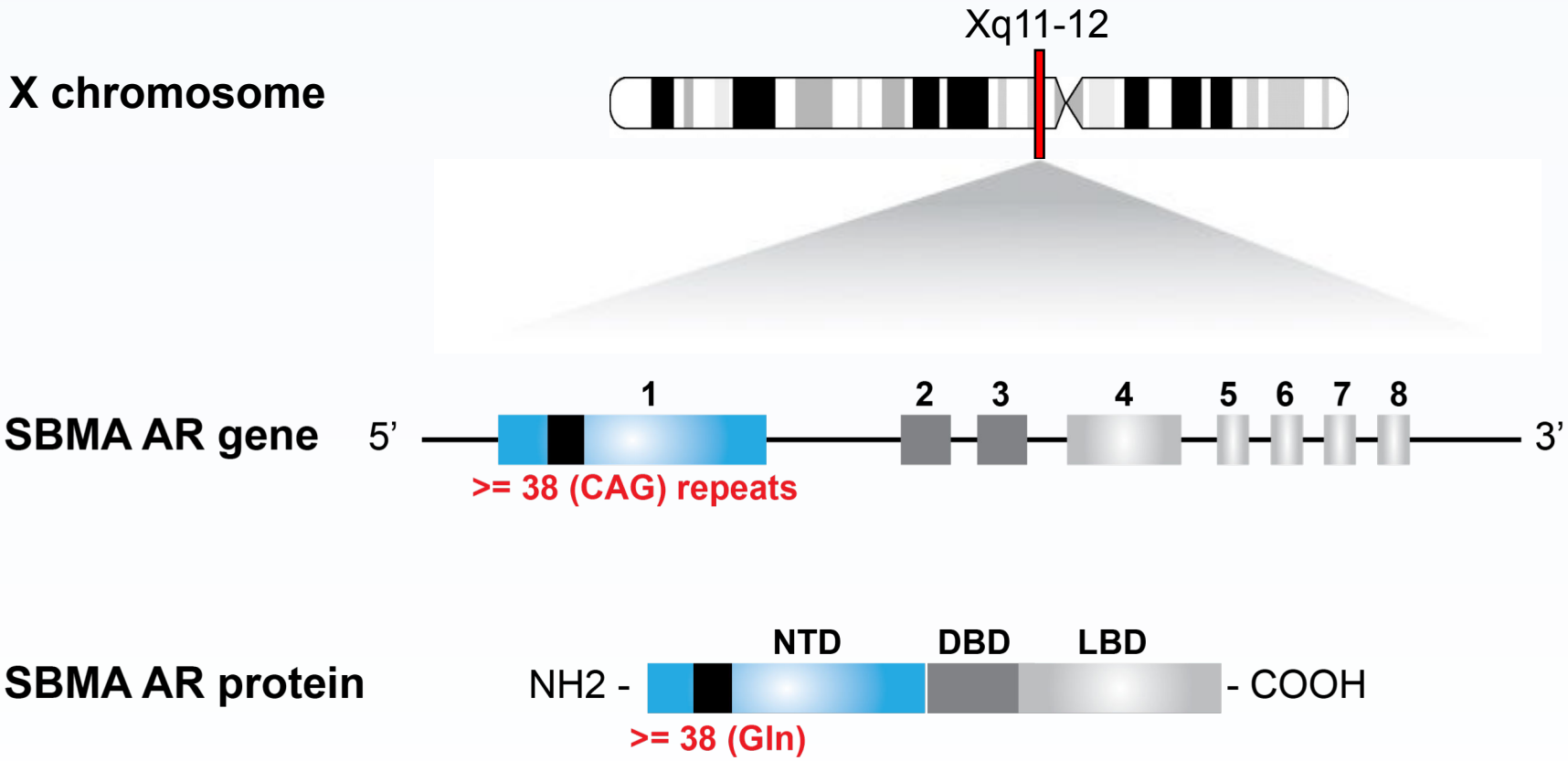
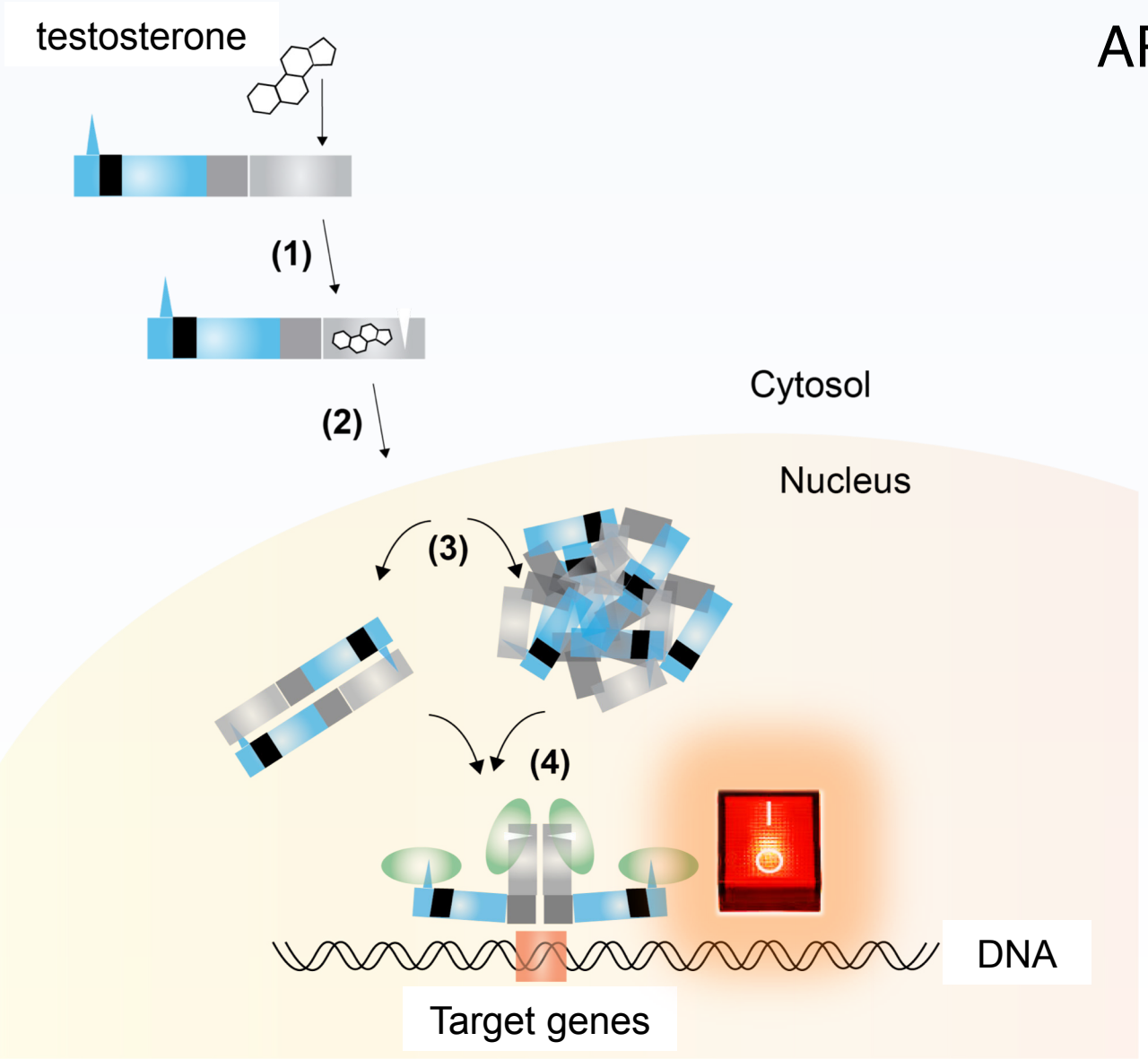
# CAG repeat expansion in androgen receptor gene



# Androgen receptor in SBMA



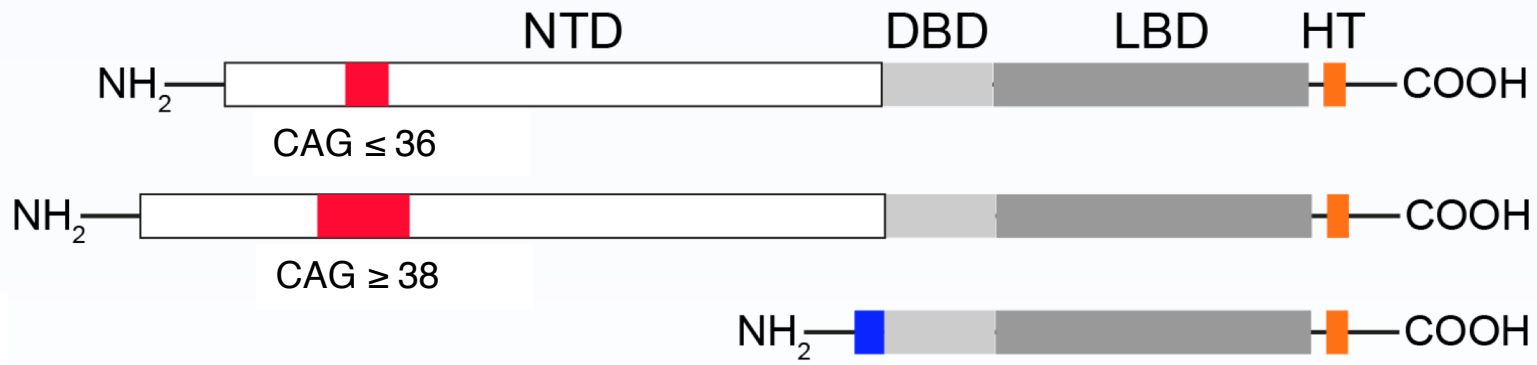

AR = Molecular switch

# A shorter version of androgen receptor (AR 2)

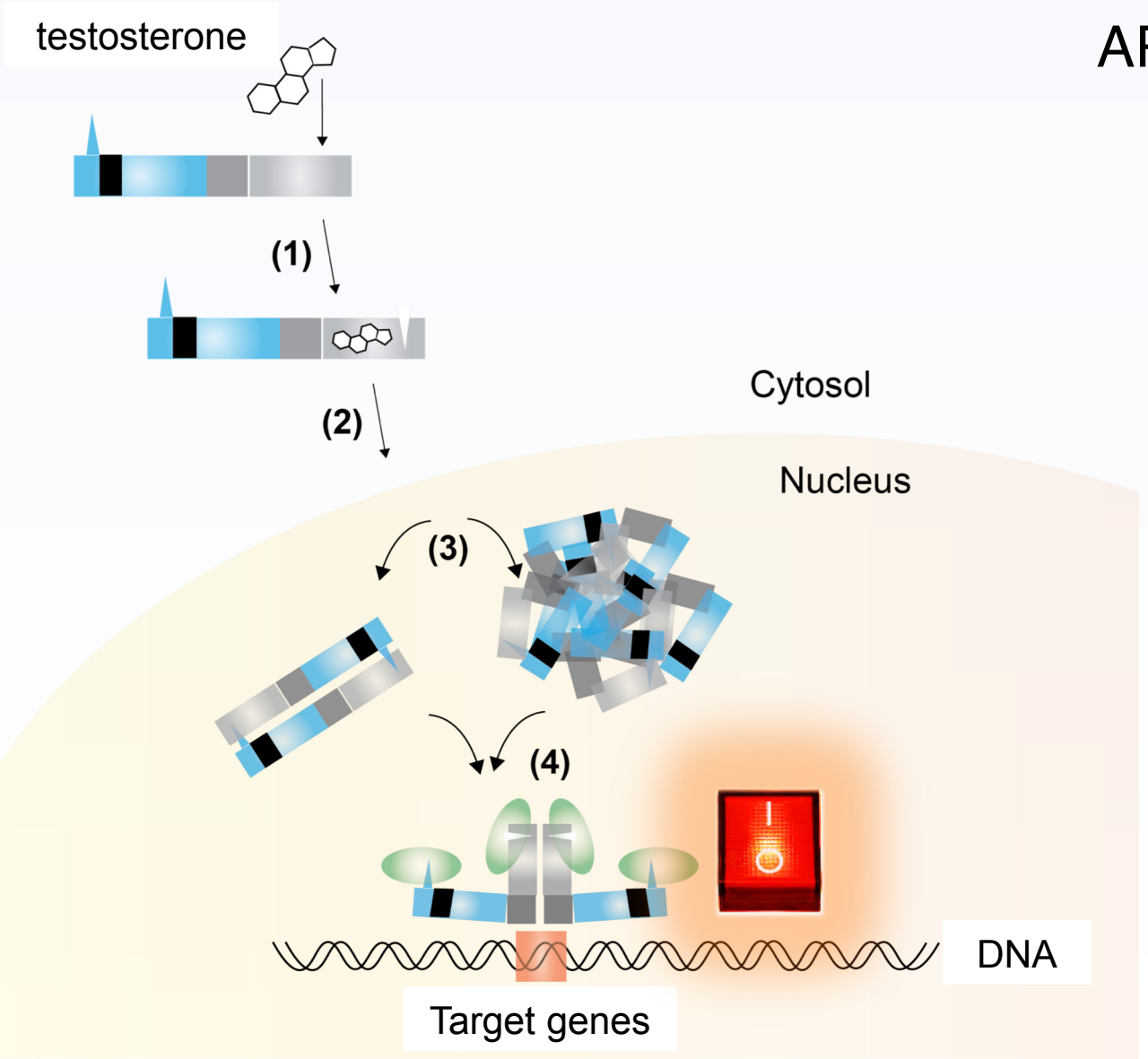
Normal androgen receptor

SBMA androgen receptor

Androgen receptor isoform 2

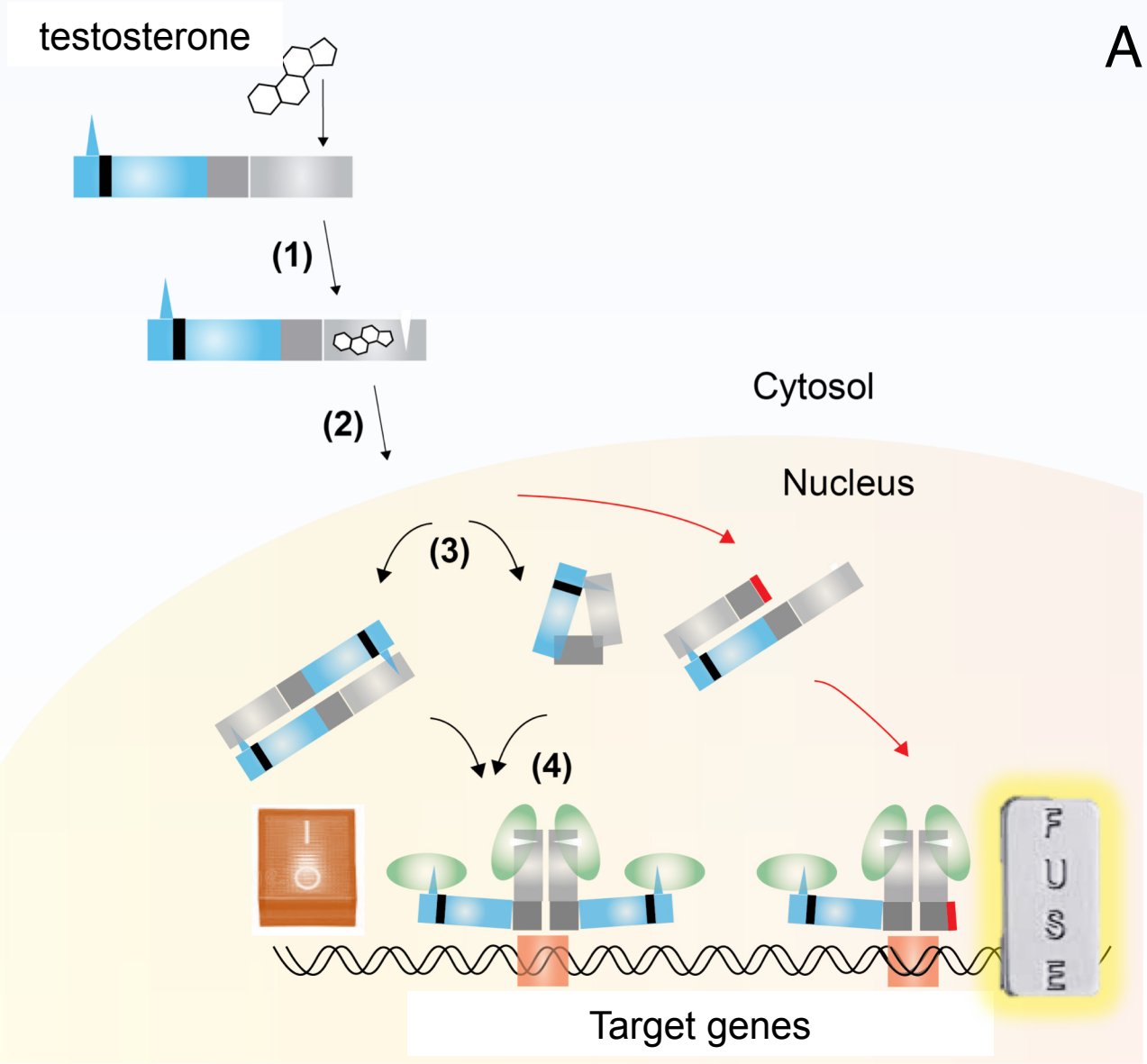


# Androgen receptor in SBMA



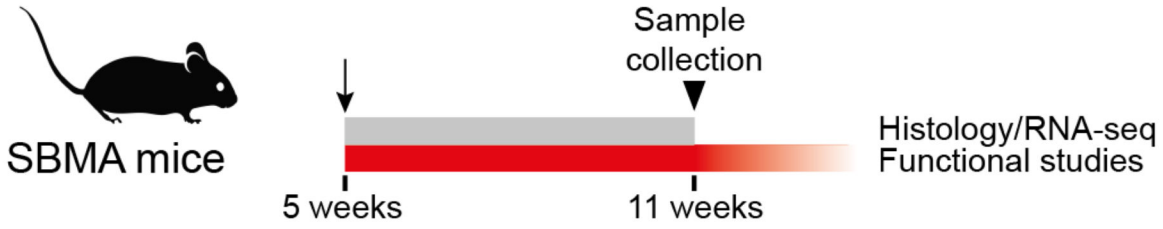

AR = Molecular switch

# AR2 reduces the activity of SBMA AR

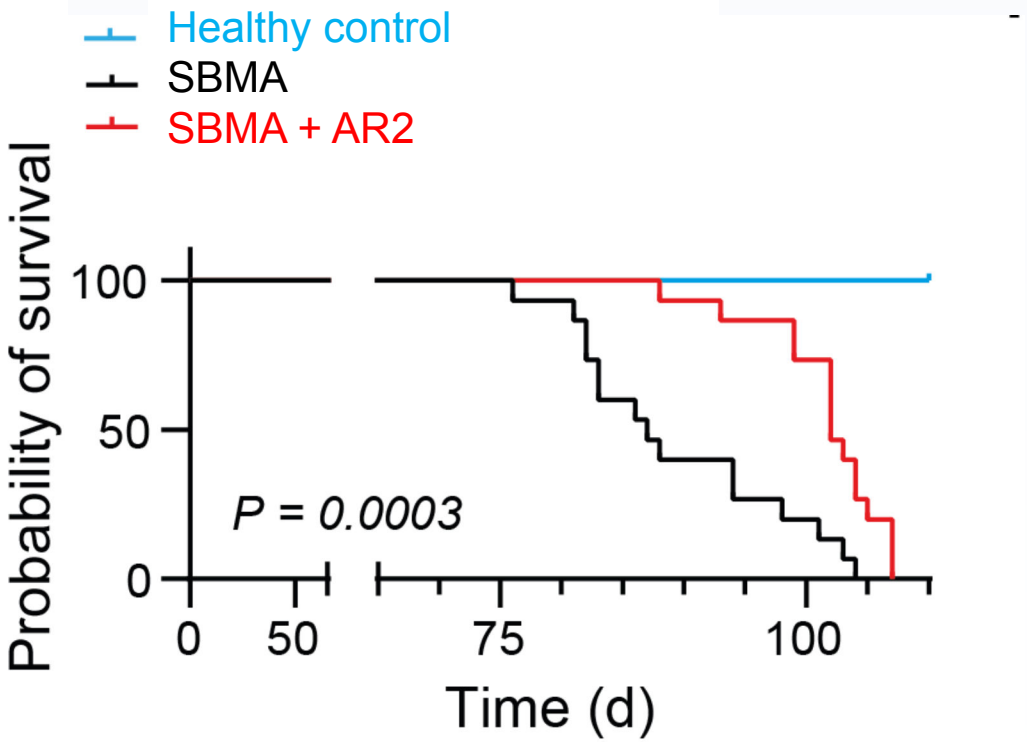



AR = Molecular switch

# Delivery of a copy of AR2 gene reverses SBMA disease phenotype in SBMA mouse model

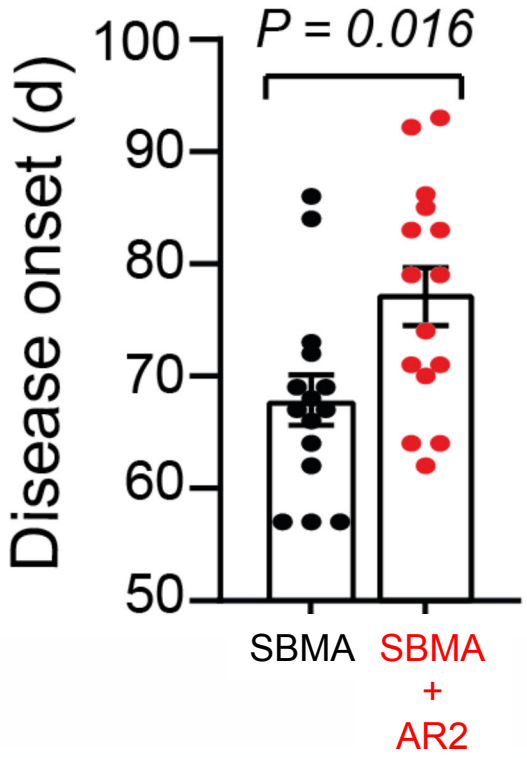



**Improved survival**



# Delivery of a copy of AR2 gene reverses SBMA disease phenotype in SBMA mouse model

## Delayed disease onset

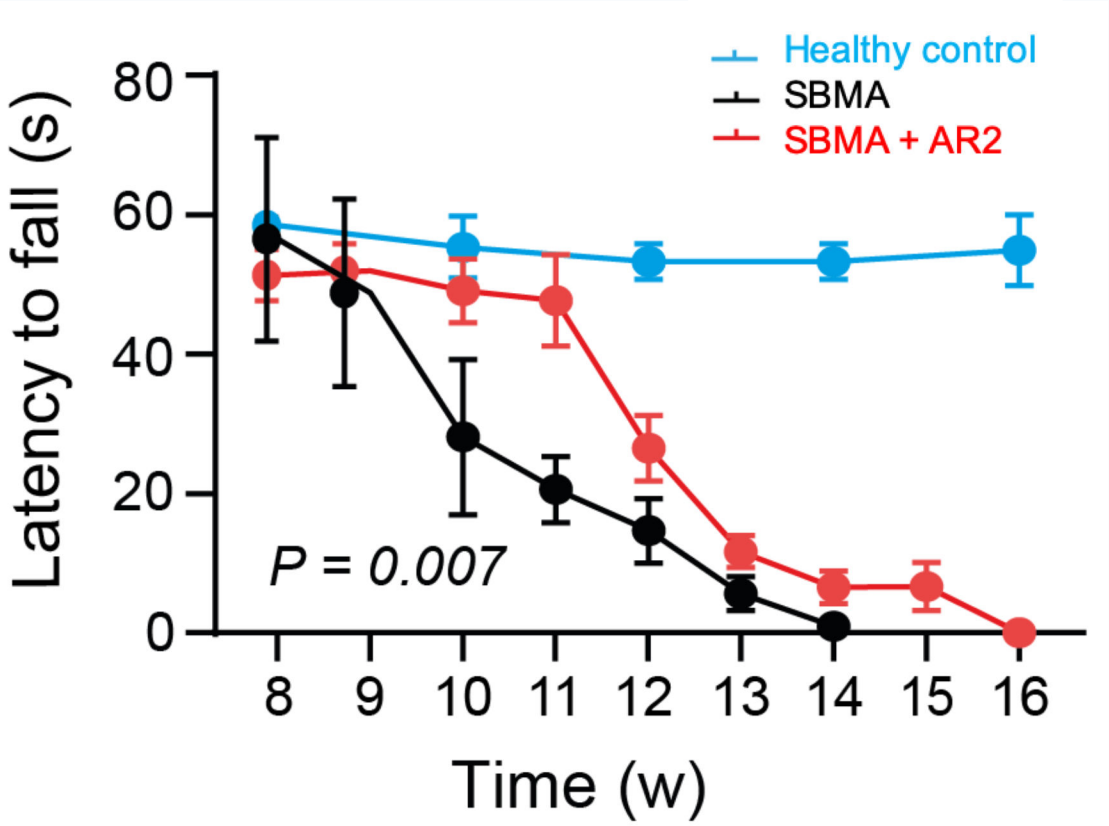


# Delivery of a copy of AR2 gene reverses SBMA disease phenotype in SBMA mouse model

Delayed disease onset




Improved motor function



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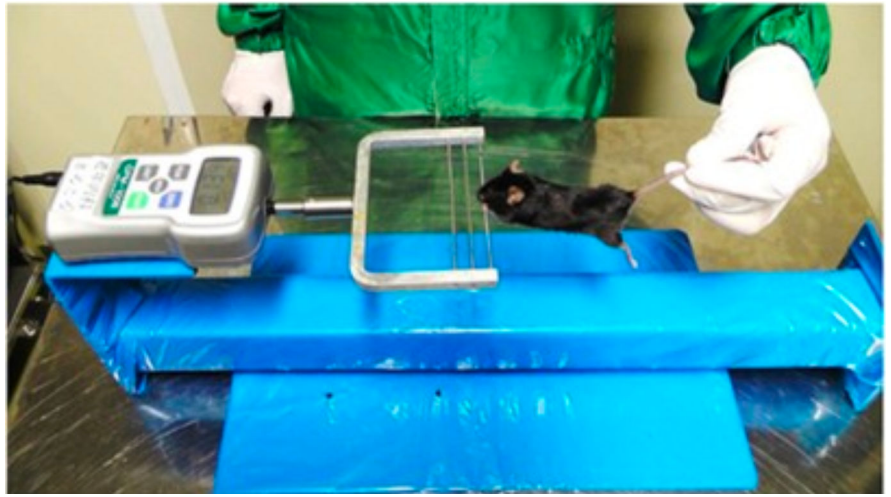
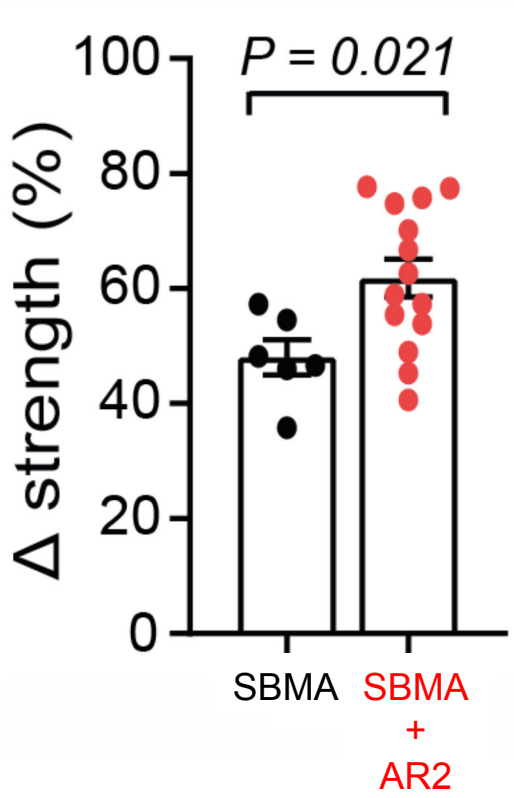
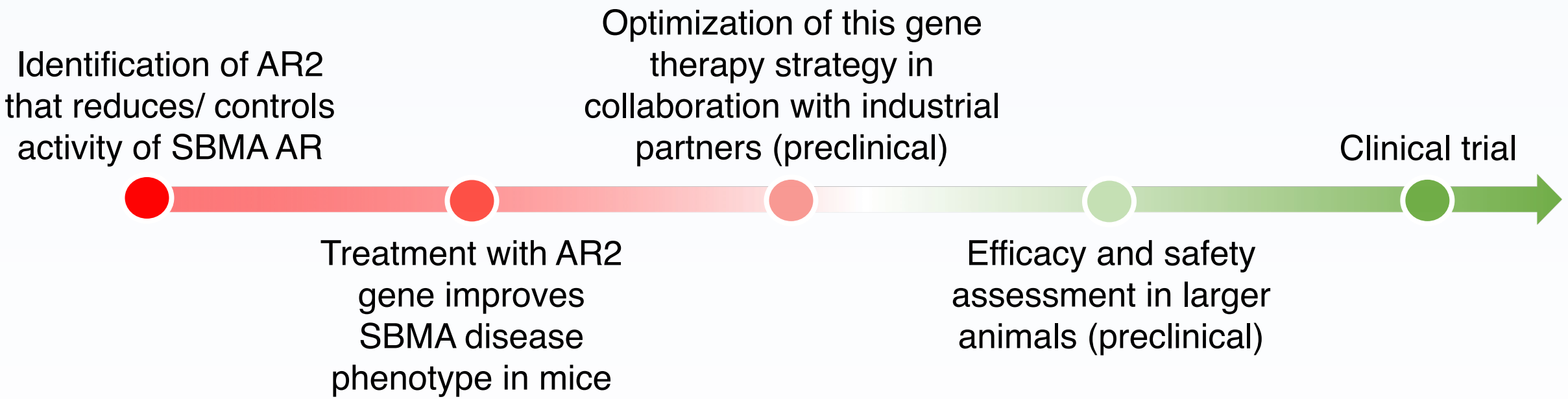




# Conclusion and future



# Acknowledgement

SCIENCE ADVANCES | RESEARCH ARTICLE

DISEASES AND DISORDERS

## Gene therapy with AR isoform 2 rescues spinal and bulbar muscular atrophy phenotype by modulating AR transcriptional activity

Wooi F. Lim[1], Mitra Forouhan[1], Thomas C. Roberts[1], Jesse Dabney[2], Ruth Ellerington[1], Alfina A. Speciale[1], Raquel Manzano[2], Maria Lieto[2], Gavinda Sangha[2], Subhashis Banerjee[2], Mariana Conceição, Lara Cravo[1], Annabelle Biscans[3], Loïc Roux[2], Naemeh Pourshafie[4], Christopher Grunseich[4], Stephanie Duguez[5], Anastasia Khvorova[3], Maria Pennuto[6,7], Constanza J. Cortes[8], Albert R. La Spada[9], Kenneth H. Fischbeck[4], Matthew J.A. Wood[1,10†], Carlo Rinaldi[1,10*†]



Rinaldi's team

Kennedy's Disease ASSOCIATION

MDA® Muscular Dystrophy Association