FSHD Therapeutic Approaches: RNAi (Pt 1)

RNAi (RNA interference) is a natural biological mechanism evolved to maintain an organism's genome integrity.

RNAi is a form of post-transcriptional gene silencing (PTGS), the gene being targeted is still "ON" but the target RNA is rapidly and specifically degraded so the gene product (protein) is never made.

Therapeutic RNAi approaches in FSHD target the DUX4 mRNA for degradation.

PTGS, termed "co-suppression" or "quelling" at the time, was first studied in plants in the 1980s. Attempts to generate transgenic plants with increased gene expression from a transgene resulted in in a surprising decrease in expression from both the endogenous gene and the transgene.

Transformation of petunias with chalcone synthase gene or *CHS* (a precursor for plant pigment) from a transgene results in less pigmentation due to the decreased expression of the endogenous *CHS* gene.

van der Krol *et al.* (1990) *Plant Cell* 2:291-99.

The RNAi system at play, however, was not uncovered until 1998 using a different system, the nematode *C. elegans*, by Andrew Fire and Craig Mello who were awarded the 2006 Nobel Prize in Medicine and Physiology

No one understood at the time, but here is what was going on: