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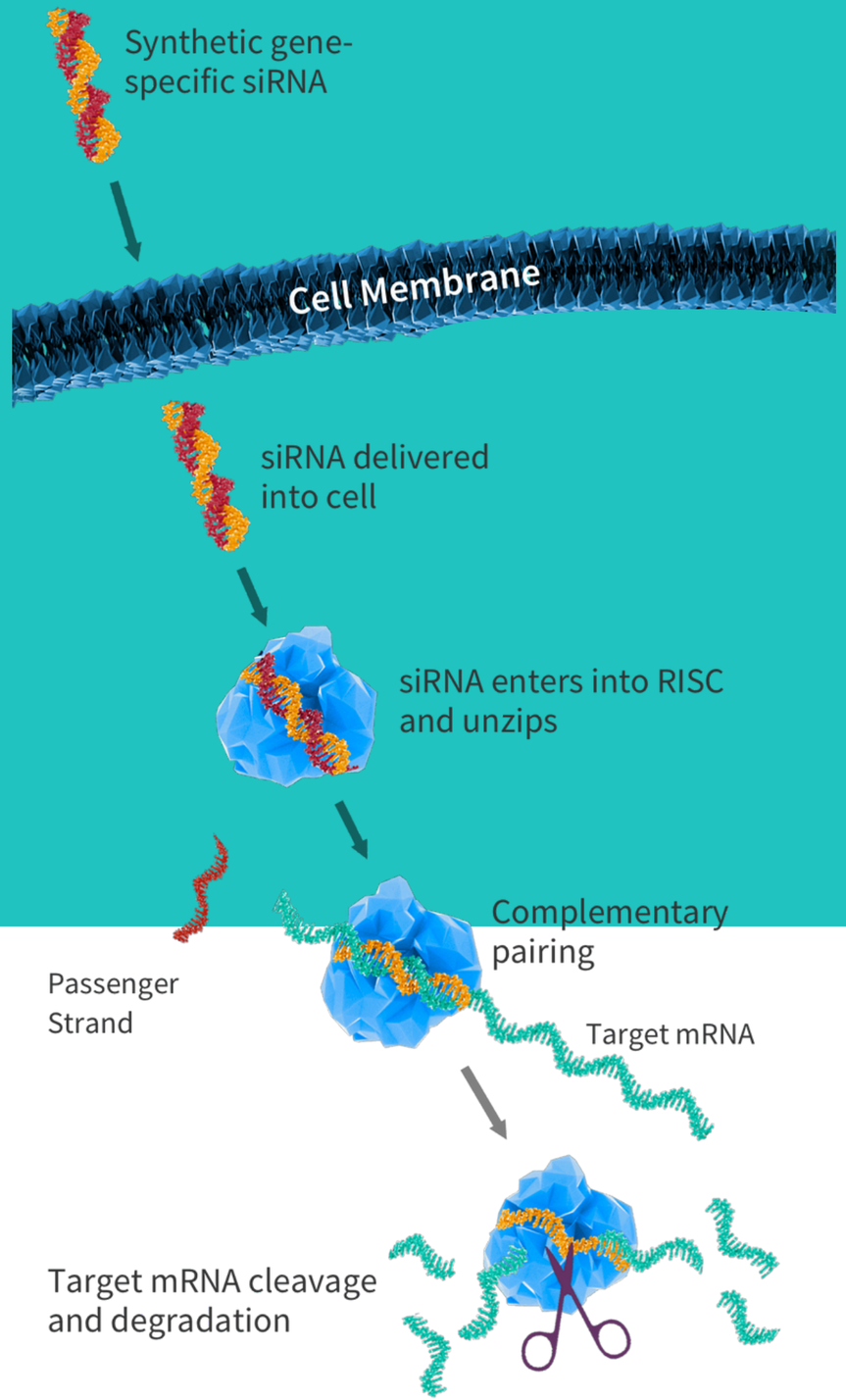
RNA interference (RNAi)

RNAi in *C. elegans*: A powerful tool for gene function and therapeutic discovery

Be Inspired

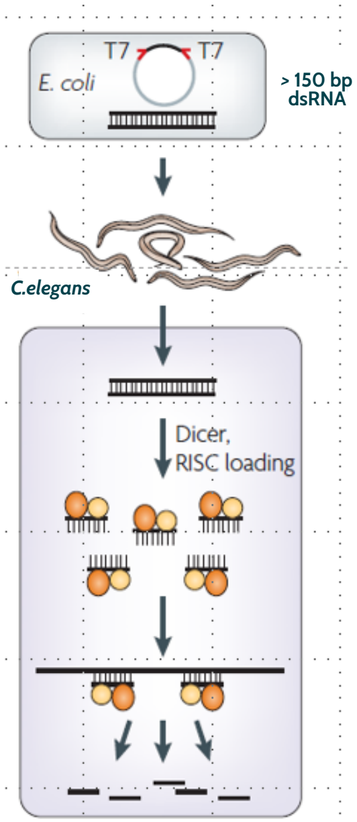


RNAi: An ancient mechanism conserved from *C.elegans* to humans

Tool in worms

RNAi libraries:
Collection of bacteria engineered to produce dsRNA corresponding to a specific *C.elegans* gene

Feeding *C.elegans* bacteria expressing dsRNA



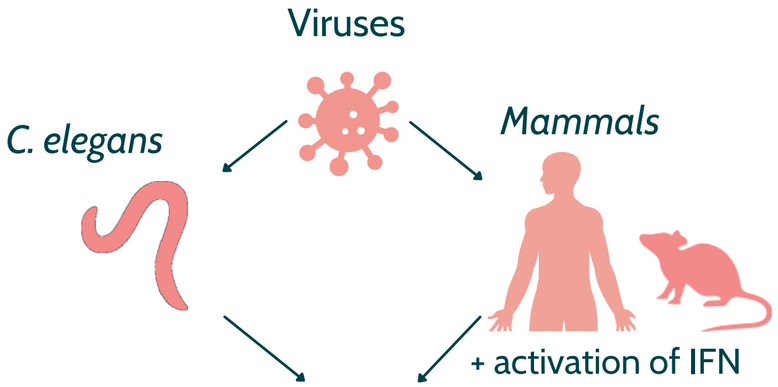
Mechanistic process

Processing the dsRNA (Dicer) and target silencing (RISC)

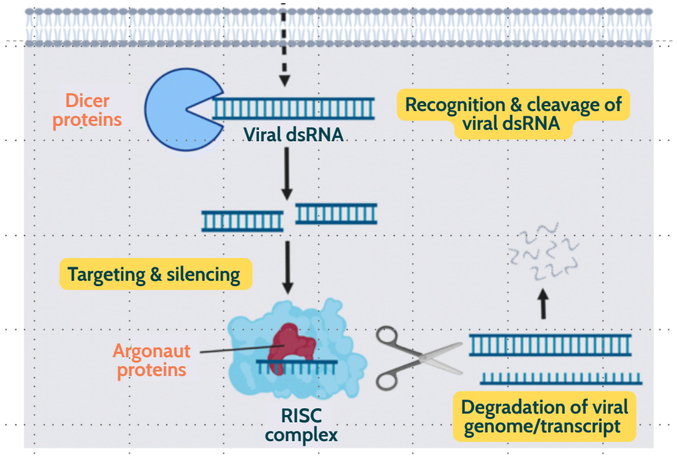
Amplification and systemic spread

Local RNAi trigger → whole body knockdown

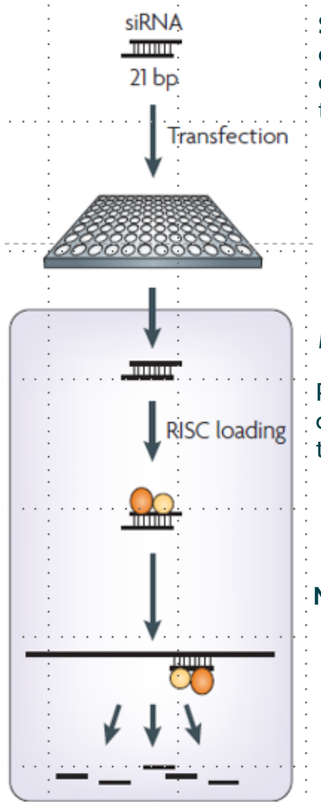
Conserved mechanism



Antiviral defense



Tool in human cells



Synthetic siRNAs:
chemically synthesized duplexes directly transfected into cells

Mechanistic process

Processing the dsRNA/siRNA (Dicer) and target silencing (RISC)

No systemic spread

From *C. elegans* to RNAi therapeutics: A discovery that launched a field

1998
Fire and Mello unveil RNAi mechanistics
Nature

2001
Elbashir et al. demonstrate siRNA-induced RNAi in human cells,
Nature

2003
Evaluation for therapeutic purposes: siRNA-effector based therapy in mice

2006
Fire and Melio win Nobel Prize in Physiology or Medicine

2008
First clinical trials with RNAi therapeutic candidates

2018
FDA approval of first RNAi therapeutic for clinical use

onpattro
(patisiran) lipid complex injection 10 mg/5 mL

TTR in *C. elegans*: Modeling pathology and the therapeutic effect of the first RNAi drug for amyloidosis (Onpattro®)

TTR aggregation:

→ Impaired function of various tissues/organs

→ Cell-nonautonomous proteotoxic pathways (similar finding in AD, PD, Huntington's disease)

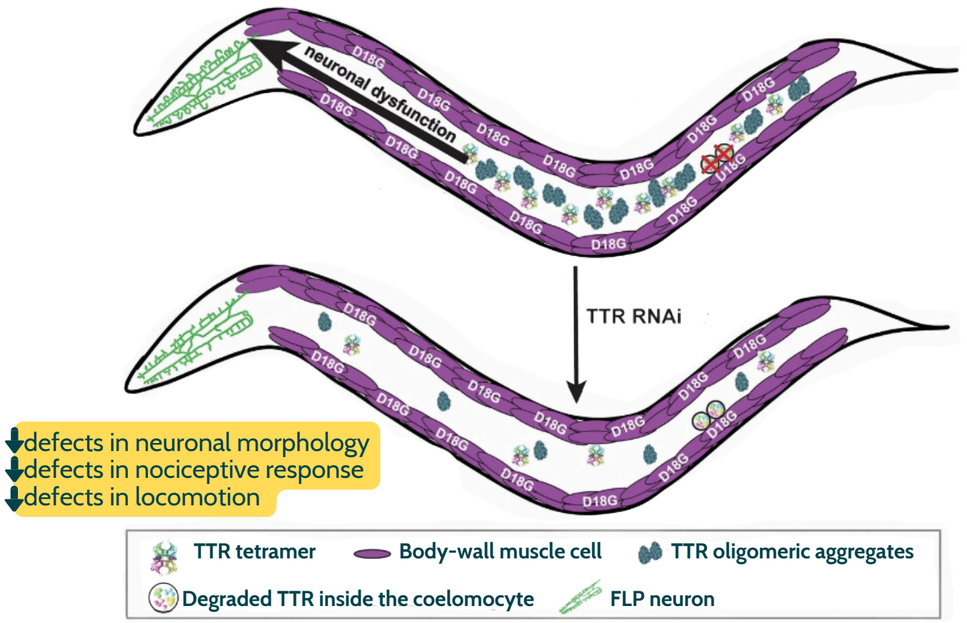
→ **TTR amyloid diseases** (Over 115 different TTR mutations associated with human diseases)

Models of human TTR proteotoxicity:

✗ **Transgenic mice:**
- failed to recapitulate cell-nonautonomous disease phenotypes

✓ ***C. elegans*:**
- TTR secretion and aggregation in a cell-nonautonomous way
- Demonstrate disease-relevant pathology

C. elegans: a platform to decode protein aggregation in neurodegeneration



Findings in *C. elegans* predict mammalian outcomes

C. elegans model expressing human TTR reproduces pathology, and RNAi knockdown of TTR rescues defects. This is conceptually consistent with the therapeutic rationale behind Onpattro® (patisiran).

First FDA-approved RNAi therapeutic for clinical use

Onpattro® (patisiran)

Madhivanan et al., *PNAS* 2018

From RNAi in *C. elegans* nervous system to drug repurposing for Alzheimer's disease (AD)

The current therapeutic approaches for Alzheimer's disease (AD) are symptomatic treatments for cognitive and behavioral progressions → need for new therapeutic approaches or drug repurposing strategies

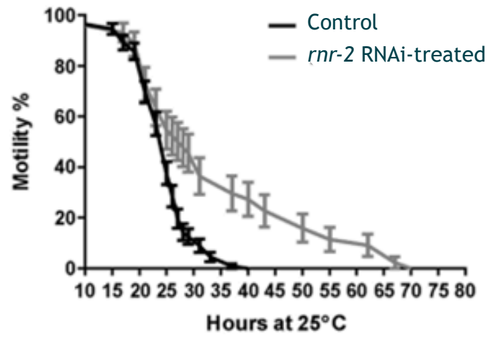
C. elegans AD transgenic model

GMC101 strain

Overexpressing human $A\beta_{1-42}$ that leads to an irreversible paralysis

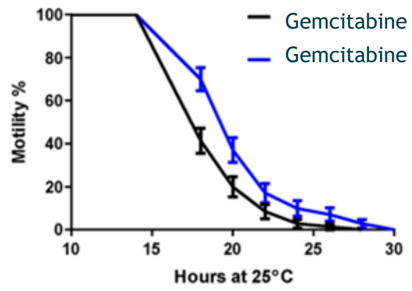
↓

RNAi treatment against *rnr2* (*RRM2B* homologue)



Improvement of the symptoms of the AD model
Brokate-Llanos et al., *Oxford Academic Journal,* 2024

Gemcitabine was known to inhibit RRM2B function
Pereira et al., *Computational Chemistry Journal*, 2004



Potential drug repurposing: gemcitabine (RRM2B inhibitor)

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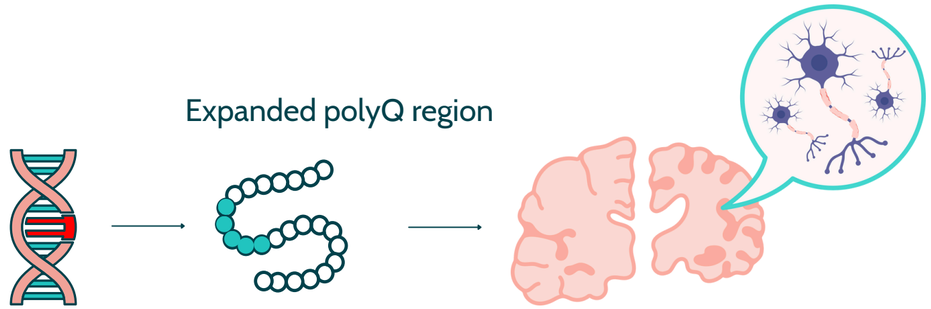
From RNAi in *C. elegans* nervous system to therapeutic approaches

Huntington´s disease (HD)



C. elegans HD transgenic model

Heterologous expression of expanded polyQ

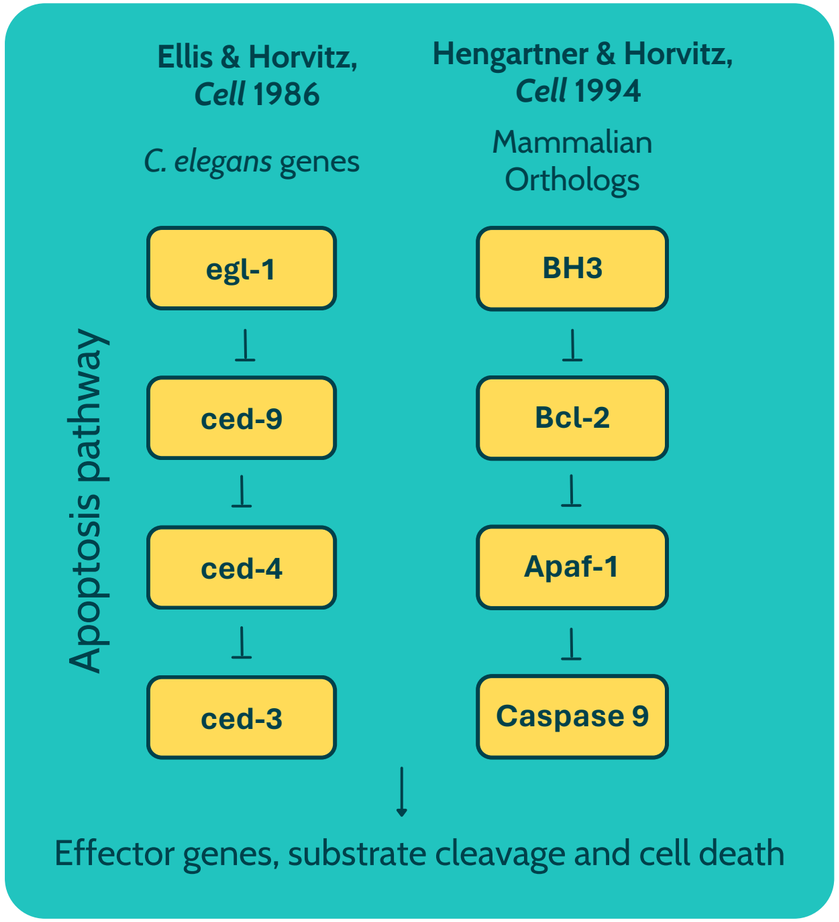
↓ Genome-wide RNAi screen

Identify pathways of polyQ toxicity (e.g., proteostasis, protein clearance, chaperones), which underpin the rationale for reducing mutant HTT expression.
Nollen et al., *PNAS*, 2004

Therapeutic approach: small molecules

C. elegans HD models provided essential mechanistic insight into polyQ toxicity and led to FDA-approved molecules (repurposed) that modify disease phenotypes (Cordeiro et al., *Science Direct* 2025)

C. elegans apoptosis genes revealed the role of Bcl-2, now targeted in life-saving leukemia therapies (Venclexta®)



Fire et al., *Nature* 1998

- *C.elegans* RNAi confirmed conservation of apoptosis genes (ced-9= Bcl-2), providing the mechanistic rationale for targeting Bcl-2 in oncology.

Example: Venclexta® (Bcl-2 inhibitor)
Souers et al.,*Nat Med* 2013*:* a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets.

FDA-approved in 2016 for CLL, later expanded to AML.

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C. elegans RNAi identified the target for an FDA-approved veterinary drug emodepside (Profender®, veterinary use)

emodepside / Profender® was discovered & developed via phenotypic anthelmintic screening (Bayer).

Regulatory approvals:

- EU 2005 (EPAR)
- US FDA/CVM 2007 (NADA 141-275).

Target discovery uncovered in *C. elegans*

Guest M. et al., *Int J Parasitol* 2007
Phenotypic discovery in *C. elegans*

↓

Welz C. et al., PLoS Pathogens 2011
RNAi + rescue confirms SLO-1 as a target

- Slo-1 encodes the large-conductance calcium-activated potassium (BK) channel.
- It is highly expressed in the nervous system and body-wall muscles

C. elegans + RNAi is a powerful combination for rapid, cost-effective, whole gene discovery and validation

How to use the RNAi tool in *C. elegans*?

- Disease modeling → demonstration of disease-relevant pathologies → advancement of therapeutic approaches.
- Identify known molecules that rescue phenotypes → drug repurposing.
- Knockdown libraries (86% of *C. elegans* genes) → target discovery → *in vivo* screening engine for human disease genes.
- Simple model → translatable insights into human pathways (50% of the human disease genes have clear orthologues in *C.elegans*) → Novel targets.

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