Roundworm study paves way for better RNA-based drugs to treat human disease

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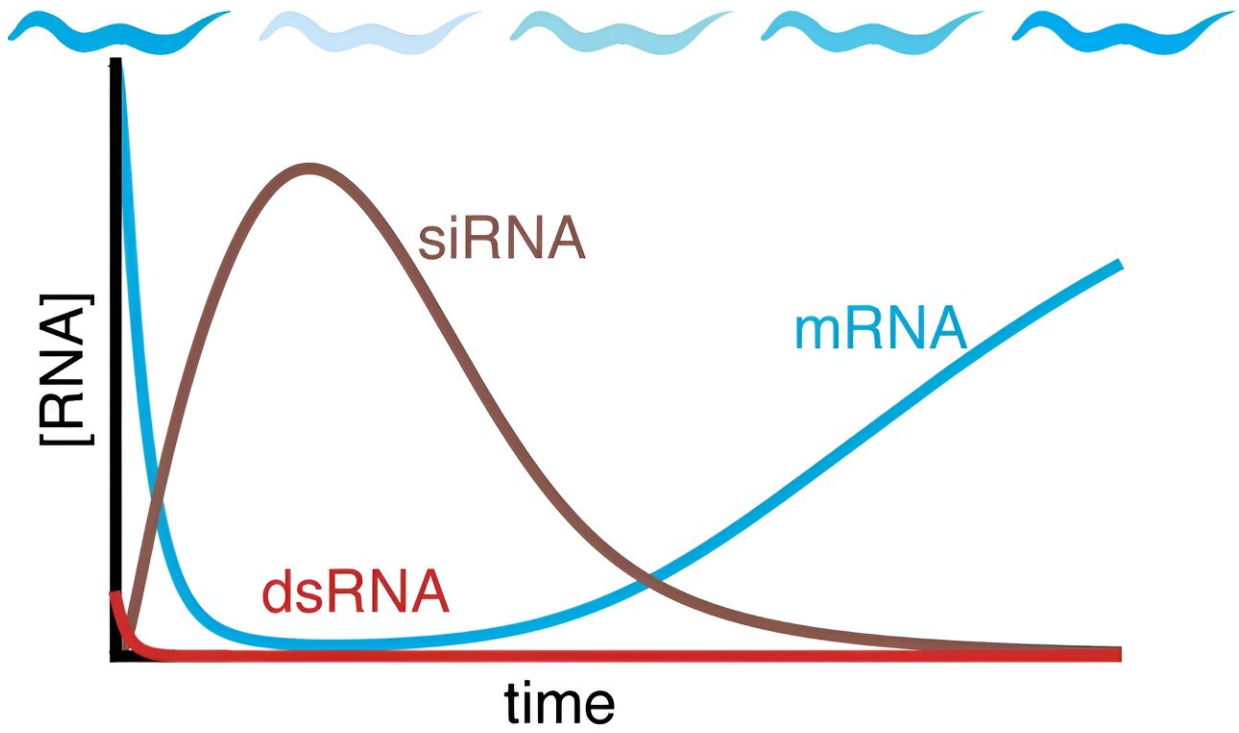


Gene silencing by dsRNA (red) can lose potency despite the production of more silencing RNAs (siRNA, brown) within worms, resulting in the recovery of gene expression (blue) over time. Image courtesy of Antony Jose. Credit: Antony Jose

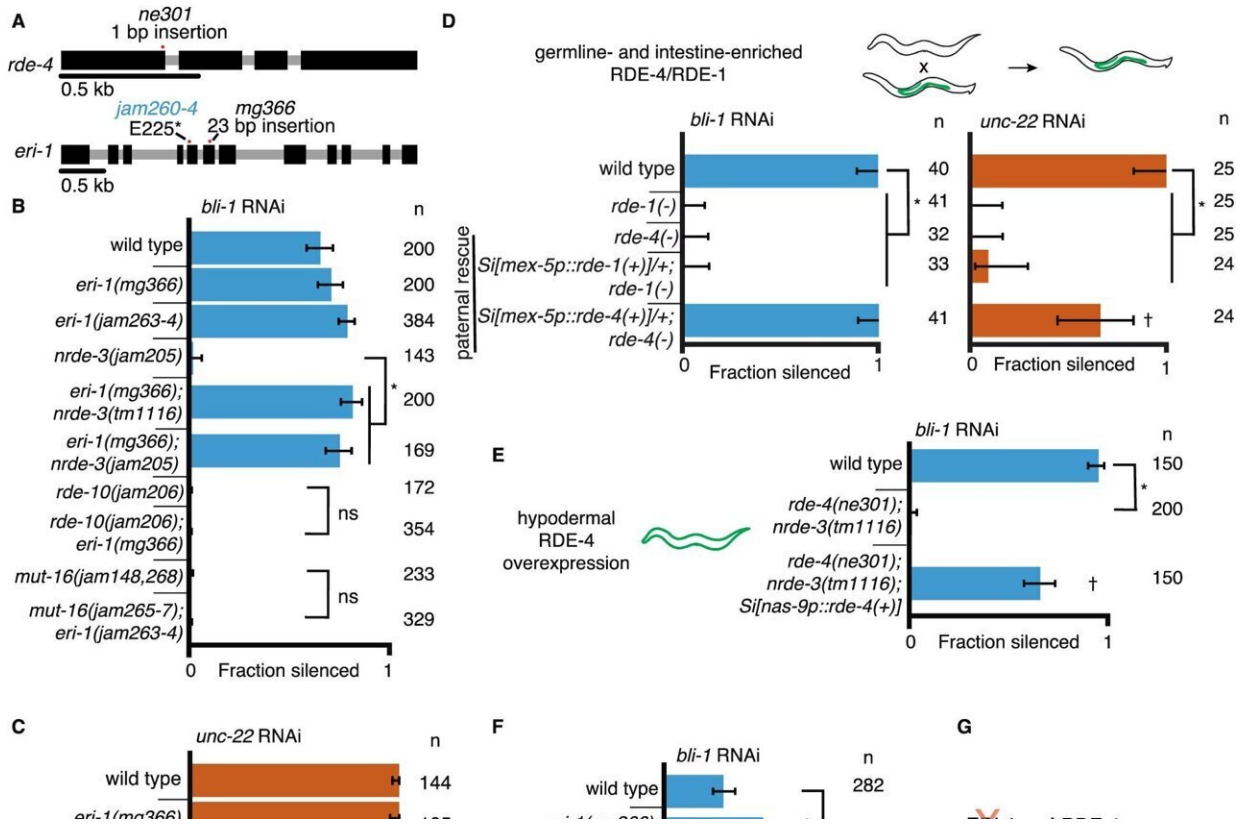
RNA interference (RNAi) therapeutics have garnered significant attention in clinical research due to their potential for treating various diseases, including genetic disorders, viral infections and cancer. These

therapeutics can target and silence disease-causing genes with high precision, minimizing off-target effects and improving treatment outcomes.

As the number of RNAi-based treatment studies expands, questions about how long RNAi benefits can last and if it's possible to fine-tune RNAi need to be answered. University of Maryland scientists used microscopic roundworms as a model to investigate the mechanisms behind RNAi and how they can be optimized for medical use in humans. The team published its findings in the journal *eLife* on August 20, 2024.

"In recent years, RNA interference has really made an impact on the scientific world because it can be used to develop drugs that selectively silence disease-causing genes. We're already seeing it in action in sectors like agriculture and some RNAi therapies are already approved for human use," said the study's senior author Antony Jose, an associate professor of cell biology and molecular genetics at UMD. "RNAi is very promising, but there are still many fundamental questions about how to make RNAi more effective."

In the study, Jose and his team used quantitative modeling, simulations and experiments with the roundworms to dig deeper into the process. The researchers found that the effects of gene silencing could wear off over time, but they were surprised to learn that the effects eventually disappeared even in non-dividing cells (cells that don't reproduce and duplicate).



Gene-specific requirements for NRDE-3 can be bypassed in two ways. Credit: *eLife* (2024). DOI: 10.7554/eLife.97487.3

"It makes some sense to expect that constantly dividing cells could eventually dilute an RNAi-based drug," Jose explained. "But the real head-scratcher is how the drug's efficacy is lost even in cells that don't divide. Surprisingly, this applies even in worms, where RNAs are amplified—essentially making more of the drug.

"Our work reveals that there must be some mechanism that degrades the effects of RNAi over time—and researchers have to take that mechanism into consideration when developing dosing schedules for RNAi drugs so that they can maintain effectiveness as long as they're needed."

These findings highlight the need to consider drug resistance when developing RNAi-based treatments, according to Jose. Just as bacteria can become resistant to antibiotics, we may also become resistant to silencing over time.

"If we don't consider factors such as the longevity of our RNA interventions, then we will forever be creating treatments that will eventually stop working," Jose noted. "Instead, we have to consider resistance at the very beginning of drug development and think harder about what genes to target so that the drug remains as effective for as long as needed."

The study also offered new insights into how different regulatory proteins within the worms' cells worked together to control gene silencing. Jose's team highlighted three important regulatory proteins that influenced gene silencing and found that they provided multiple interconnected paths for the control of certain targeted genes. For the researchers, getting a better understanding of these networks of interactions could lead to breakthroughs in fine-tuning RNAi therapies for maximum impact on human patients.

"Losing certain proteins can make it harder to silence some genes but not others," Jose said. "Knowing how these proteins work together to affect genes can make a difference when designing drugs tailored to an individual."

Looking ahead, Jose's team plans to investigate the RNAi degradation process more closely and identify the key features that make some genes more susceptible to silencing than others. They hope that their research is paving the way for improvements to this emerging yet promising class of therapeutics.

"Our ultimate aim is to catalyze progress toward more potent, durable

and tailored gene-silencing therapeutics for a wide range of diseases," Jose said.

More information: Target-specific requirements for RNA interference can arise through restricted RNA amplification despite the lack of specialized pathways, *eLife* (2024). DOI: 10.7554/eLife.97487.3, elifesciences.org/reviewed-preprints/97487v1

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