

# Milasen

**M**ilasen is a one-of-a-kind drug created to treat a unique mutation in Mila Makovec's *CLN7* gene — a mutation she inherited from her mother.

*CLN7* (also known as *MFSD8*) is one of more than a dozen genes known to be associated with Batten disease. The *CLN7* protein's exact function is yet to be proven, but it is thought to shuttle materials in and out of lysosomes, cellular structures that process the cell's waste products. When the protein is mutated, lysosomes can't "take out the trash," and the cell eventually becomes overwhelmed and dies. When this occurs in the brain and eye, the result is declining cognitive and motor functions, seizures and blindness. This is unfortunately what was happening in Mila.

## Mila's one-of-a-kind mutation: a retrotransposon disrupting splicing

Batten disease is recessive, requiring two *CLN7* mutations. While the mutation Mila inherited from her father was easily found by standard clinical testing, the mutation she shares with her mother couldn't be found until Timothy Yu, MD, PhD, and his colleagues in the Division of Genetics and Genomics at Boston Children's Hospital looked at her entire genome — and that of her parents and brother — and examined the raw data.

Yu and colleagues realized that both Mila's and her mother's *CLN7* genes are hosting an uninvited guest: a retrotransposon. Sometimes called jumping genes, transposons are genetic sequences that can "hop" into DNA at various locations. In Mila's case, the insertion was found in *CLN7*, within a non-protein-coding genetic sequence known as an intron.

Transposons are ubiquitous in our genomes, and are even thought to play a role in evolution, helping us quickly acquire new traits. The human genome is thought to host more than 2,500 of Mila's particular type of retrotransposon alone. The vast majority of these have no impact on health. But in Mila's case, the inserted retrotransposon prevents proper assembly of the *CLN7* protein.

Cells use DNA as a blueprint to make RNA by splicing together the essential bits of code. The cell machinery then reads the RNA to build the protein. In Mila's case, two specific RNA sequences, which we'll call A and B, are spliced together to create the final template for the *CLN7* protein. But Yu and colleagues found that the retrotransposon in Mila's maternal *CLN7* gene is positioned in the middle of the cut site between A and B. This creates what is known as an "exon trap," disrupting the splicing process. A isn't correctly joined to B, and the instructions required to build the *CLN7* protein are prematurely terminated. The truncated *CLN7* protein can't do its job, leading to lysosome dysfunction.

## Milasen: A customized drug

Mila's maternal mutation, though complex, turns out to have a clever fix: a customized piece of code that hides the misplaced signal from the splicing machinery of Mila's cells, restoring normal splicing. Yu's team, which developed it, named it milasen.



Yu and colleagues generated an oligonucleotide — a short chain of artificially created RNA. It consists of 22 nucleotides that exactly mirror and bind to the misplaced genetic code. The "oligo" acts as a molecular band-aid, essentially masking the exon trap in Mila's RNA, allowing the cellular splicing machinery to avoid it. This enables the cell to produce a normal *CLN7* protein.

In laboratory studies of Mila's cells, normal splicing of the *CLN7* gene was restored after administering the drug. Yu's collaborators at Northwestern University further showed that lysosomal activity was restored, and the damaging protein build-up in the cells was halted.

## About splice switching oligonucleotides

Though one of a kind, milasen is part of an emerging class of drugs known as splice switching oligonucleotides, which include the recently approved Spinraza® and Exondys 51® (for spinal muscular atrophy and Duchenne muscular dystrophy, respectively).

Oligo-based drugs have many advantages. Their toxicity is remarkably low, and they can be administered intrathecally (through the spinal canal), allowing for widespread penetration through the brain and spinal cord via the cerebrospinal fluid. When oligos reach neurons, they are taken up readily; no packaging or transporting elements are needed to get them into the cell. Finally, oligos are relatively easy to customize with different RNA or DNA sequences.

## A new paradigm for treating genetic conditions

The creation of milasen in such a short time frame — less than a year — is a ground-breaking precedent that could revolutionize how genetic conditions are treated. Yu believes that now that the process is established, oligos could be made for other genetic disorders, starting with those involving splicing errors, simply by plugging in the necessary sequence. And the drug development process — from diagnosis to synthesis and treatment, in close collaboration with the FDA and industry advisors — could potentially be applied in many other rare or one-of-a-kind conditions.

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