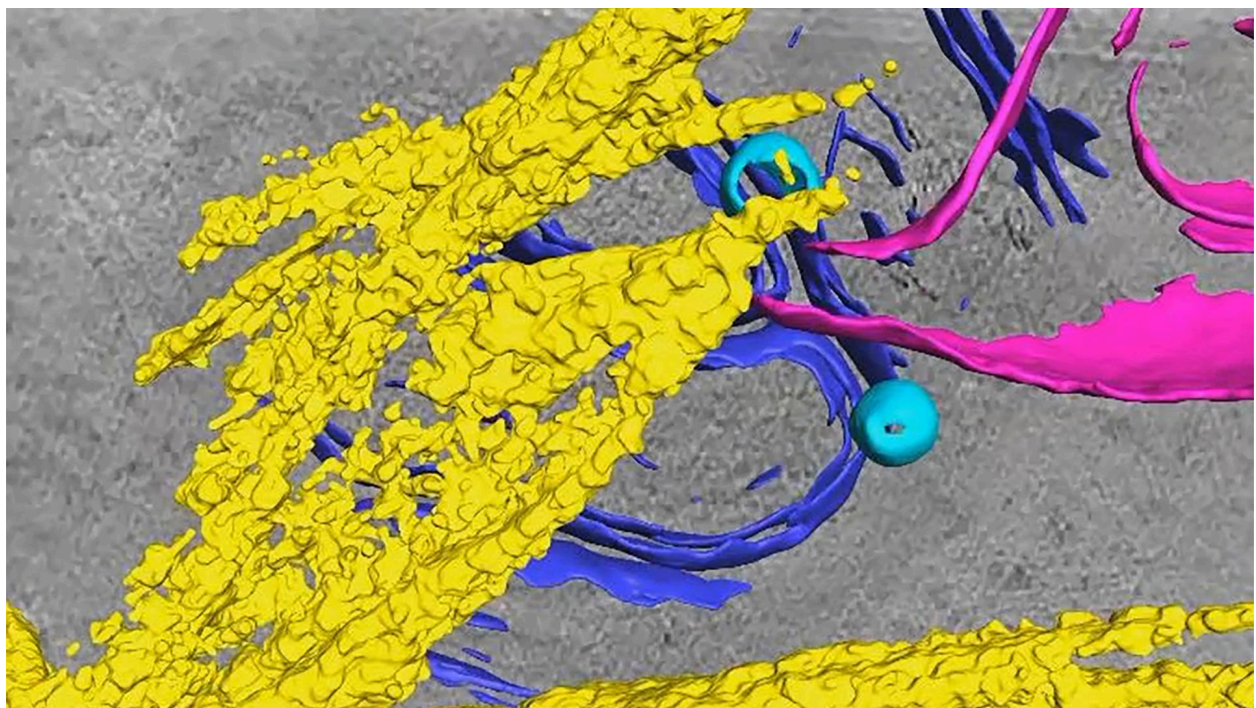


COLUMBIA | Zuckerman Institute

MORTIMER B. ZUCKERMAN MIND BRAIN BEHAVIOR INSTITUTE

Protein Fibers, a Hallmark of Alzheimer's, Spotted Making Deliveries to Sperm

The discovery might one day lead to a potentially safer way to bring gene-editing CRISPR tech into cells



Fibrils (yellow) inside a sperm cell (William Mallen / Fitzpatrick lab / Columbia's Zuckerman Institute).

FOR EMBARGOED RELEASE: Monday, October 26, 11 a.m. ET

NEW YORK, NY — Unexpectedly, a kind of protein that is usually linked with diseases in the brain may play a vital role in semen, helping shepherd genetic material into sperm cells, scientists at Columbia's Zuckerman Institute [report](#) today in the research journal *Molecular Cell*.

These findings raise the possibility that these proteins, known as amyloids, may one day help improve gene-editing technologies such as CRISPR.

“This is wild biology,” said senior author on the paper [Anthony Fitzpatrick](#), PhD, a principal investigator at Columbia’s Zuckerman Institute. “Amyloids are most often thought of as a hallmark of Alzheimer’s, Parkinson’s and other neurodegenerative diseases in the brain, but they also have functional roles throughout the body, and keep turning up in unexpected places.”

This unusual project had an even more unusual starting point: the virus HIV. Previous research had found that amyloid fibrils present in semen could help HIV enter cells in the reproductive tract, explained [William Mallen](#), PhD, the study’s lead author, who conducted this research while he was a doctoral student in the Fitzpatrick lab.

Dr. Fitzpatrick, an expert on amyloids in brain research, wondered if those fibrils could also help materials naturally in the body enter sperm: specifically, the genetic molecule RNA, which helps turn instructions encoded in DNA into protein molecules. Scientists knew that seminal fluid contains lots of small RNAs, thought to play a major role in what genes are active in developing embryos. But how this RNA gets chaperoned from seminal fluid into sperm to influence the embryo — that was a mystery.

The potential link the researchers made between amyloids and RNA was how HIV uses RNA as its genetic material, as is true with roughly half of all known viruses. Since amyloids could help HIV enter cells, maybe it could do so with RNA in general.

Amyloids seemed promising escorts for RNA, in part because these amyloids are positively charged, while RNA is negatively charged, and for molecules, like magnets, opposites attract. Using fluorescent labels on both kinds of molecules, Dr. Mallen found that they do bind together, and speculated that the amyloids have a protective function. While RNA is quite fragile, amyloids are exceptionally durable, so packaging RNA in an amyloid scaffold could help the genetic molecules survive harsh conditions.

The researchers next analyzed sperm using cryo-electron tomography (cryo-ET), which fires beams of electrons at frozen specimens to create 3D images of the samples. Cryo-ET can achieve near-atomic-level resolution, the most powerful form of microscopy used in biology today. Using amyloid proteins labeled with flecks of gold, the scientists confirmed these molecules could in fact enter sperm, and not just, say, embed onto their surfaces.

“Seeing those amyloid fibers inside sperm cells was just so extraordinary to me,” said Dr. Mallen, who is now in medical school at the University of Vermont. “There were hints of this happening earlier in our other experiments, but actually seeing this totally blew us away.”

In addition, the researchers used a fluorescent protein to assess the rate at which RNA entered the sperm and found that amyloids could greatly enhance that. Once RNA that was bound to amyloid made its way into cells, a protein known as clusterin could help separate RNA from amyloid.

"It's a seminal discovery," Dr. Fitzpatrick said. All in all, he said they were a testament to Dr. Mallen, "a fearless graduate student willing to pursue real swing-for-the-fences type of science." Dr. Mallen noted that at the Fitzpatrick lab, "everything is 'go big or go home.'"

While the researchers do not yet know what the amyloid-shuttled RNA does once inside the sperm, previous research found that RNA in semen can switch genes on or off in offspring. These epigenetic modifications can be shaped by a parent's experiences and be inherited from generation to generation.

"There are metabolic disorders such as insulin resistance that recent papers have shown can be passed down the paternal line in mice, and it's thought RNA is how," Dr. Mallen said. "By learning how disorders based on epigenetics work, we can come closer to how to possibly treat or prevent them."

The researchers also suggest that amyloids might one day serve as tools to deliver RNA into cells. For instance, the gene-editing technology known as CRISPR, which uses RNA, has triggered a revolution in genetics for how it can help scientists modify genes in a cheap, fast and easy way, with hundreds of clinical trials currently testing how CRISPR might find use in gene therapies.

In experiments, amyloid fibrils could not only bring small RNAs into sperm, but RNA molecules large enough to encode a green fluorescent protein. Embryos fertilized using this sperm could generate at least 10 times more of this protein than sperm exposed to this RNA without the amyloids. These findings suggest that scientists could one day use amyloids to, say, shuttle therapeutic genes into cells and embryos.

The researchers noted that CRISPR often currently relies on modified viruses as a delivery mechanism, which can trigger immune reactions.

"Since the amyloid fibrils we looked at are human-based, hopefully the immune system won't react in the same way they do to the repurposed viruses often used in gene therapy," Dr. Mallen said.

###

The [paper](#), "Amyloid-mediated RNA uptake by sperm for embryonic delivery," was published in *Molecular Cell* on October 26, 2026.

The full list of authors includes William S. Mallen, Nataliya Zabello, Susan Brenner-Morton, Simone Sidoli, Feng-Xia Liang, Joseph Sall, Jason Yin, Priyanka Mathews, Mengmeng Zhu, Guoan Zhang, Carolyn L. Lee, Ya-Cheng Liao, and Anthony W.P. Fitzpatrick.

This work was funded by the Hevolution Foundation, the ERC-CFAR Center for AIDS research, the Einstein-Mount Sinai Diabetes center, the NIH Office of the Director (S10OD030286), the Vagelos Precision Medicine Fund, and the NYU Langone Health Microscopy Laboratory (RRID: SCR_017934), which is partially funded by NYU Cancer Center Support Grant NCI P30CA016087.

The authors report no conflicts of interest.