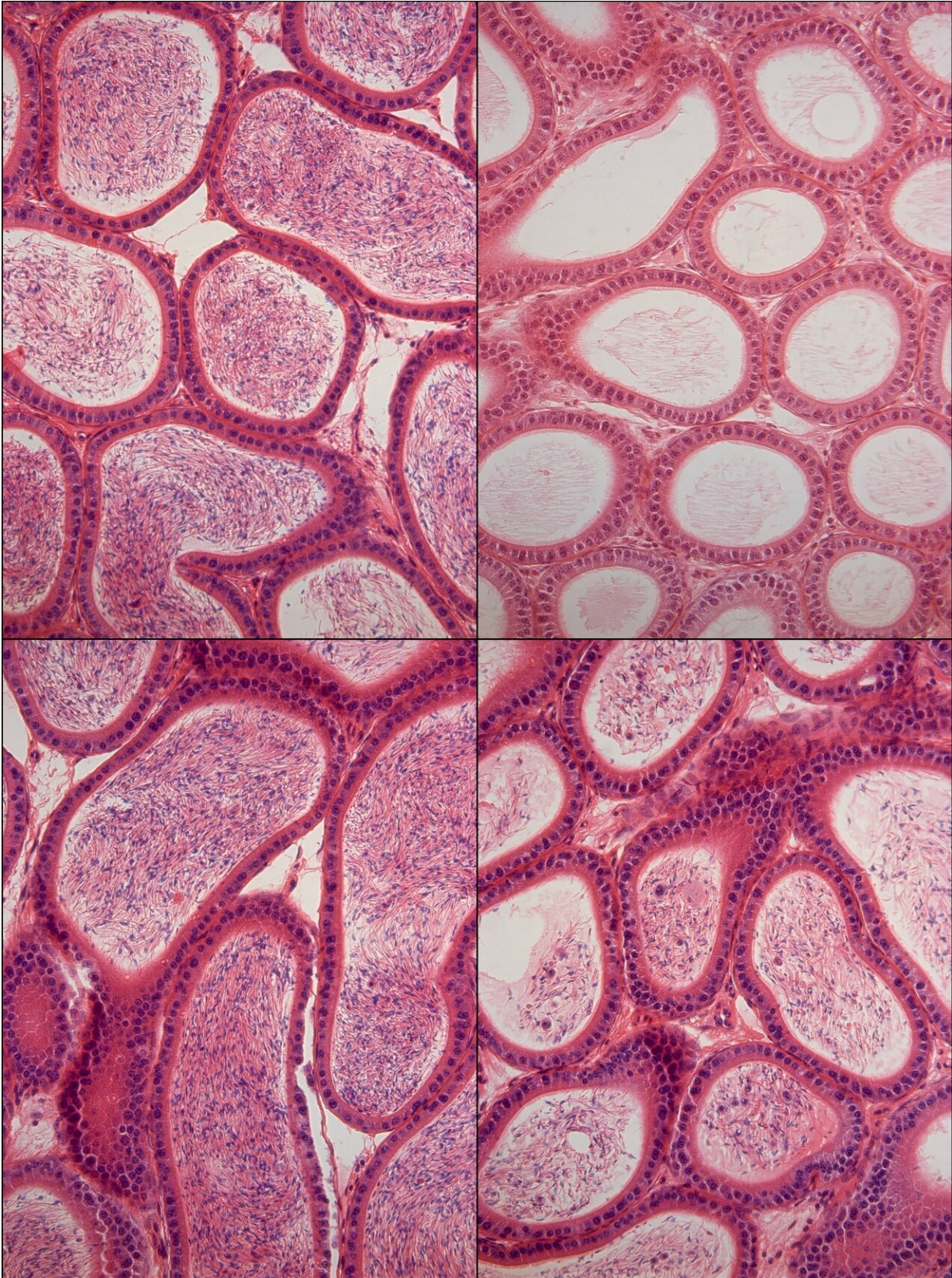


Scientists discover new target for reversible, non-hormonal male birth control

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Sperm, pictured inside each round cell, were not generated while mice took the HDAC inhibitor drug (top right), but after 60 days off the drug, spermatogenesis was recovered (bottom right). The left column shows sperm at the same time points in a mouse that did not receive the drug. Credit: Salk Institute

Surveys show most men in the United States are interested in using male contraceptives, yet their options remain limited to unreliable condoms or invasive vasectomies. Recent attempts to develop drugs that block sperm production, maturation, or fertilization have had limited success, providing incomplete protection or severe side effects.

New approaches to male contraception are needed, but because sperm development is so complex, researchers have struggled to identify parts of the process that can be safely and effectively tinkered with.

Now, scientists at the Salk Institute have found a new method of interrupting sperm production, which is both non-hormonal and reversible. The study, published in *Proceedings of the National Academy of Sciences*, implicates a new protein complex in regulating [gene expression](#) during sperm production.

The researchers demonstrate that treating [male mice](#) with an existing class of drugs, called HDAC (histone deacetylase) inhibitors, can interrupt the function of this protein complex and block fertility without affecting libido.

"Most experimental male birth control drugs use a hammer approach to blocking sperm production, but ours is much more subtle," says senior author Ronald Evans, professor, director of the Gene Expression Laboratory, and March of Dimes Chair in Molecular and Developmental Biology at Salk. "This makes it a promising therapeutic approach, which

we hope to see in development for human clinical trials soon."

The human body produces several million new sperm per day. To do this, sperm [stem cells](#) in the testes continuously make more of themselves until a signal tells them it's time to turn into sperm—a process called spermatogenesis. This signal comes in the form of [retinoic acid](#), a product of vitamin A. Pulses of retinoic acid bind to retinoic acid receptors in the cells, and when the system is aligned just right, this initiates a complex genetic program that turns the stem cells into mature sperm.

Salk scientists found that for this to work, retinoic acid receptors must bind with a protein called SMRT (silencing mediator of retinoid and thyroid hormone receptors). SMRT then recruits HDACs, and this complex of proteins goes on to synchronize the expression of genes that produce sperm.

Previous groups have tried to stop sperm production by directly blocking retinoic acid or its receptor. But retinoic acid is important to multiple organ systems, so interrupting it throughout the body can lead to various side effects—a reason many previous studies and trials have failed to produce a viable drug. Evans and his colleagues instead asked whether they could modulate one of the molecules downstream of retinoic acid to produce a more targeted effect.

The researchers first looked at a line of genetically engineered mice that had previously been developed in the lab, in which the SMRT protein was mutated and could no longer bind to [retinoic acid receptors](#). Without this SMRT-retinoic acid receptor interaction, the mice were not able to produce mature sperm. However, they displayed normal testosterone levels and mounting behavior, indicating that their desire to mate was not affected.

To see whether they could replicate these genetic results with pharmacological intervention, the researchers treated normal mice with MS-275, an oral HDAC inhibitor with FDA breakthrough status. By blocking the activity of the SMRT-retinoic acid receptor-HDAC complex, the drug successfully stopped sperm production without producing obvious side effects.

Another remarkable thing also happened once the treatment was stopped: Within 60 days of going off the pill, the animals' fertility was completely restored, and all subsequent offspring were developmentally healthy.

The authors say their strategy of inhibiting molecules downstream of retinoic acid is key to achieving this reversibility.

Think of retinoic acid and the sperm-producing genes as two dancers in a waltz. Their rhythm and steps need to be coordinated with each other for the dance to work. But if you throw something in that makes the genes miss a step, the two are suddenly out of sync and the dance falls apart. In this case, the HDAC inhibitor causes the genes' misstep, halting the dance of sperm production.

However, if the dancer can find its footing and get back in step with its partner, the waltz can resume. In the same way, the authors say that removing the HDAC inhibitor allows the sperm-producing genes to get back in sync with the pulses of retinoic acid, turning sperm production back on as desired.

"It's all about timing," says co-author Michael Downes, a senior staff scientist in Evans' lab. "When we add the drug, the stem cells fall out of sync with the pulses of retinoic acid, and sperm production is halted, but as soon as we take the drug away, the stem cells can reestablish their coordination with retinoic acid and [sperm production](#) will start up

again."

The authors say the drug doesn't damage the sperm stem cells or their genomic integrity. While the drug was present, the sperm stem cells simply continued regenerating as stem cells, and when the drug was later removed, the cells could regain their ability to differentiate into mature sperm.

"We weren't necessarily looking to develop [male contraceptives](#) when we discovered SMRT and generated this mouse line, but when we saw that their fertility was interrupted, we were able to follow the science and discover a potential therapeutic," says first author Suk-Hyun Hong, a staff researcher in Evans' lab. "It's a great example of how Salk's foundational biological research can lead to major translational impact."

More information: Targeting nuclear receptor corepressors for reversible male contraception, *Proceedings of the National Academy of Sciences* (2024). [DOI: 10.1073/pnas.2320129121](https://doi.org/10.1073/pnas.2320129121).
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Provided by Salk Institute

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