Cancer-Fighting Compound Might Double as Reversible Male Contraceptive

A protein-blocking compound has been found to impair sperm production in mice without the use of hormones

By Roxanne Khamsi

The discovery of a hormone-free way to immobilize sperm in mice could lead to the development of oral contraceptives for men. (This image actually shows Eucalyptus macrocarpa stamens under high magnification, which somewhat resemble sperm cells swimming en masse.) Image: flickr/Squil

The serendipitous finding that a potential cancer-fighting compound temporarily halts sperm production in mice has seeded new hopes for a reversible male contraceptive pill. At a time when the only non-hormonal contraceptive choices for men consist of condoms and vasectomies, the finding, published today in the journal *Cell*, has stirred the interest of pharmaceutical companies, although it's quite far from entering clinical trials.

Several new contraceptives that rely on steroid hormones are in the works to reduce sperm production in men. However, most products developed to date seem to carry undesirable side effects, such as acne and perturbations of cholesterol levels. So, scientists have sought to halt sperm production with compounds that do not alter hormones, targeting everything from calcium ion channels on the tails of sperm to the production of retinoic acid, a metabolite of Vitamin A that has a role in their development. A team led by Dolores Mruk at the Population Council's Center for Biomedical Research in New York has even reported in *Nature Medicine* on the discovery of a chemical compound known as Adjudin that can stop sperm-forming cells from adhering to the Sertoli cells that nurture them.

The new findings announced today also describe a non-hormonal drug for stopping sperm—but contraception was the furthest thing from the minds of James Bradner and his colleagues at the Dana-Farber Cancer Institute who initially developed the experimental compound.

As we reported last year, Bradner's team had investigated a small molecule called JQ1 for its ability to thwart cancer by acting on a protein named BRD4. They showed success in mice with multiple myeloma, and other groups soon reported similar findings in animal models of leukemia and lymphoma. Bradner has been downright evangelical about the drug ever since, shipping it to more than 250 labs worldwide, according to a profile of Bradner published last week in *Nature*.

As part of their homework in understanding the specificity of JQ1, Bradner's group found that it also targeted a similar protein, called BRDT, which comes from a completely different chromosome than BRD4. In a quick survey of the scientific literature, Bradner noticed a study that linked mutations in BRDT to fertility problems in men, so he reached out to reproductive biologist Marty Matzuk of the Baylor College of Medicine in Houston to study its contraceptive effects in mice.

"This project for us started very much as a side project," says Bradner. "We planned together to do a critical first experiment to explore the effects of JQ1 on sperm count and motility. We went right *in vivo*. And we were shocked at how well the drug worked."

In one experiment involving about a dozen male mice, the half that had received BRDT daily for three weeks had a sperm count of just over 1 million stored in a part of their epididymis, an order of magnitude lower than their control counterparts, which had 10 million sperm in that same section. The drug also hampered sperm motility and shrank the animals' testes—a sign, says Bradner, that it was working (though it is not a desirable side effect in humans).

Further tests demonstrated that a high-dose regimen of the drug for several months prevented the male mice from siring pups, though the fertility of the mice rebounded after the drug was removed. "The pups are totally normal," Bradner says, noting that they performed well on behavioral tests and had normal fertility.

Birth defects remain a "key concern" should the drug move forward toward human trials one day, according to William Bremner, an endocrinologist at the University of Washington in Seattle who was not involved in the current study. But he says that there is good reason to continue studying JQ1 as a potential male contraceptive. "There is reasonable similarity of mice and humans [regarding] spermatogenesis and the blood-testes barrier. Not complete, but close, so mice are reasonable predictors of a human effect."

But given that people typically use contraceptives for years on end, Mruk would like to see longer studies of the drug to really assess its safety profile. "Short-term side effects can be identified rather quickly," she says, "but long term side-effects can take decades to fish out."

Bradner agrees that many follow-up experiments remain to be done. For one, he notes, "it's unanswered what the role of BRDT is in spermatogenesis", although it appears to have a key role in the transcription of genes. Bradner has reached out two drug companies, Britain's GlaxoSmithKline and Tensha Therapeutics of Cambridge, Massachusetts, both of which have worked on inhibitors for the class of proteins to which BRDT belongs. "Both companies expressed some interest," he says.

The story does not end there for JQ1—just last week researchers from the Boston University School of Medicine found evidence suggesting that it might activate latent HIV in immune cells, and could therefore potentially be useful in eradicating the virus from the body.