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Novel drug regenerates erectile nerves damaged by prostate surgery

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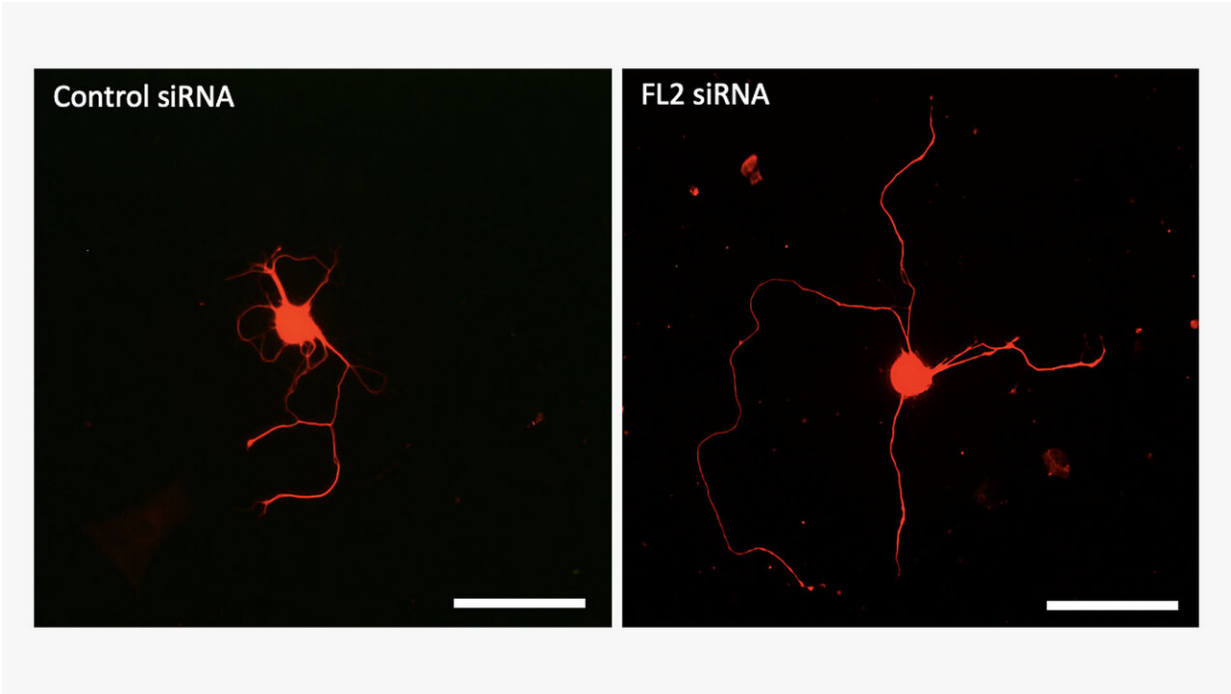

These images show neurons cultured in petri dishes and treated with either control (inactive) siRNA (left) or the siRNA drug itself (FL2 siRNA) (right). Neurons treated with the drug regenerate their axons (the thin fibers extending from the neurons' central bodies) at a significantly faster rate than control-treated neurons. Scale bar = 0.10 mm. Credit: Lisa Baker, Ph.D./ Albert Einstein College of Medicine

Researchers at Albert Einstein College of Medicine have developed a

topical drug that regenerates and restores the function of erectile nerves damaged by radical prostatectomy, the most common treatment for localized prostate cancer. The drug was tested in rats, and the findings were published online today in *JCI Insight*.

"Erectile dysfunction (ED) after radical prostatectomy has a major impact on the lives of many patients and their partners," said study co-leader David J. Sharp, Ph.D., professor of physiology & biophysics and of ophthalmology and visual sciences and professor in the Dominick P. Purpura Department of Neuroscience at Einstein. "Since rats are reliable animal models in urologic research, our drug offers real hope of normal sexual function for the tens of thousands of men who undergo this surgery each year."

Radical prostatectomy—surgery to remove the prostate gland—is considered the definitive treatment for localized prostate cancer. "Despite the advent of so-called nerve-sparing procedures, the surgery can damage the cavernous nerves, which control erectile function by regulating blood flow to the penis," said study co-leader Kelvin P. Davies, Ph.D., professor of urology and of physiology & biophysics at Einstein. He notes that about 60% of patients report having ED 18 months after surgery, and fewer than 30% have erections firm enough for intercourse after five years. Viagra and similar ED treatments are rarely effective in these patients, he said.

A decade ago, Dr. Sharp and colleagues discovered that the enzyme fidgetin-like 2 (FL2) puts the brakes on skin cells as they migrate towards wounds to heal them. To speed wound healing, the researchers developed an "anti-FL2" drug: small interfering RNA molecules (siRNAs) that inhibit the gene that codes for FL2. Packaged in gel nanoparticles and sprayed on mice, the siRNAs not only healed wounds twice as fast as untreated wounds but also regenerated damaged tissue. A February 2021 study in rats found that the siRNAs also aided the healing

of corneal alkaline burns.

Dr. Sharp, Dr. Davies, and their teams realized that injured nerves might be especially amenable to this gene-silencing drug: For unknown reasons, the FL2 gene becomes over-active after injury to nerve cells, causing the cells to produce copious amounts of FL2 enzyme.

The Einstein team evaluated the drug using rat models of peripheral nerve injury in which the cavernous nerves were either crushed or severed, mimicking the nerve damage associated with radical prostatectomy. The siRNA gel was applied to the nerves immediately after injury.

When treatment was applied following a nerve crush injury, siRNA treatment enhanced nerve regeneration (regrowth) and restored nerve function as shown by cavernosometry, a test in which blood pressure within the penile shaft is measured after cavernous nerves are electrically stimulated. At three and four weeks post-therapy, the treated animals had significantly better erectile function compared to controls. After a month, the blood pressure response of the treated animals was comparable to that of normal animals.

Remarkably, even after nerves were severed, the drug treatment induced nerve regeneration and partial recovery of erectile function. Regenerated nerves were observed in 7 out of 8 treated animals, but not in any of the control animals (severed nerves treated with nonfunctioning siRNAs). The siRNA drug was able to heal gaps of several millimeters between the severed nerve ends—a result previously achieved only by nerve grafting, according to Dr. Sharp. "Functionally, the result from siRNA treatment was equivalent to or better than nerve grafting," he added.

The researchers also found that penile shafts of treated animals had higher levels of the enzyme nitric oxide synthase compared to controls.

The enzyme produces the nitric oxide needed to trigger the sequence of events leading to erections. "This is important because drugs like Viagra don't work if there's no nitric oxide to kick things off," said Dr. Sharp. "But if we can restore even some of the nitric oxide in these nerves, Viagra and other ED drugs may then be able to exert their effects."

Dr. Sharp's team is currently studying whether the siRNAs can promote nerve regeneration after spinal cord injuries.

The study is titled "Fidgetin-like 2 negatively regulates axonal growth and can be targeted to promote functional nerve regeneration."

Provided by Albert Einstein College of Medicine

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