Podcast Interview: Polina Lishko

PNAS: Welcome to Science Sessions. I'm Leigh Cooper. Although women have a number of options for contraceptives such as the pill, the vaginal ring, or the patch, these forms of birth control are not without side effects. As for men's options, they are largely limited to condoms or vasectomies. Polina Lishko of the University of California, Berkeley wants to devise a unisex contraceptive with few side effects. I spoke to Lishko at the World Conference of Science Journalists in San Francisco last October, where she presented work on what she calls "molecular condoms" for sperm cells, including a paper published in PNAS last May. Lishko begins with an introduction to the sperm cell.

Lishko: Sperm cells are quite diverse among species. They have different morphology. Some of the molecular mechanisms which drives their ability to find and fertilize an egg is also differ among species. Humans are the smallest sperm cell except for the sperm cell of blue whale which is even smaller. And the largest sperm cell would be of fruit fly, *Drosophila*, which is almost the size of the fly itself.

PNAS: Lishko focused on sperm cells as a target for contraceptives because of their unique morphology. By specifically targeting a sperm cell, she could avoid affecting cells throughout the rest of the human body, unlike today's hormone-based contraceptives. The steroid hormones in hormone-based contraceptives can cross the plasma membranes of cells throughout the body, alter cell physiology, and accumulate in fat deposits.

Lishko: An ideal contraceptive would be some compound which would be able to clear from the blood circulation as fast as possible and would be targeting its target during a short time. An ideally it won't be able to go inside the cell and produce a long-term side effects, or long-term changes in the physiology of the cell.

PNAS: Lishko focused on an ion channel called CatSper, which is found in sperm cells. CatSper is a calcium channel implicated in sperm motility. When the calcium concentration in the sperm tail rises, the tail changes its swimming pattern. It switches from a swishing fish tail motion to sharp cracks like a bullwhip. This shift allows the sperm to drill through the protective sheath around the egg to fulfill fertilization. Without the whipping motion, the sperm cannot penetrate the egg.

Lishko: CatSper is only expressed on sperm cell plasma membrane, never else in the body. Not in a single other type of cell. It is a unique sperm specific channel. And targeting CatSper is a good strategy, because it has been also shown on mice and humans that deletion of this channel result in male infertility without any other side

effects. Sperm cell without CatSper channel, they will just happily swim around, but they won't be able to fertilize a single egg.

PNAS: Lishko also wanted to understand what cues from the egg activated the CatSper channel.

Lishko: It's turn out in primates, this cue is progesterone. It is a steroid hormone, which is produced by the ovulated egg. And not by the egg itself, but by the cells which surround the egg. Because the egg doesn't leave ovaries alone. It is still surrounded by the small cells, which are remnant of the ovary. These cells actually produce progesterone. So they form a progesterone gradient, which sperm cells are able to sense. It is how they find the egg. But the moment sperm cell enters this layer of those cells and approaches the egg, the high concentration of progesterone in the vicinity triggers CatSper channel to opening.

PNAS: Lishko says that researchers know that some steroid hormones can interfere with fertilization. For example, stress hormones and the male hormone testosterone can result in infertility.

Lishko: We tested what those hormones can do. Whether they would mess up with the same pathway which progesterone triggers, and it's turn out that actually they do. So testosterone and much more potently cortisol, the stress hormone, are able to compete with progesterone and prevent sperm cell from going into this powerful drilling motion. It also explains, for example, why this CatSper channel is not activated in the male reproductive track.

PNAS: Humans have used contraceptives for thousands of years, often relying on medicinal herbs. Lishko and her team tested a number of the active compounds found in plants traditionally used as contraceptives and medicines. They focused on two compounds. The first, pristimerin, comes from plants used for antifertility by native tribes in South America and in China. The other compound was lupeol, which is found in olives and mangoes.

Lishko: Both those compounds seems to be working very well by preventing human sperm cell from going into this powerful drilling motion, which makes them very interesting candidate for future contraceptives. And they able to compete progesterone in much stronger way than testosterone. And actually they're stronger even than cortisol.

PNAS: Lishko and colleagues have patented their "molecular condoms" and are working to start a company to develop contraceptive products. Lishko says that the next step

would be nonhuman primate trials, a stepping stone to clinical trials. Their first goal would be to create an emergency contraceptive, as in principle emergency contraceptives might be easier to get approved than long-term contraceptives.

Lishko: Because emergency contraceptive is supposed to be given one time, it's a one-time exposure. Once emergency contractive is approved, we would definitely go into long-term studies. Our timeline, emergency contraceptives first, followed by long-term female, and eventually male or unisex, contraceptive. If you can give people a choice, whether it be male or female contraceptive, we would be able to lift enormous burden from women who are currently primarily responsible for contraception.

PNAS: Thank you for listening. You can find more Science Sessions podcasts at PNAS.org.