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> ONE MONTH, ONE PROTEIN <

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asking life to be patient

Vivienne Baillie Gerritsen

Watercolour by Amélie Frison (Switzerland)

Courtesy of the artist

One thousand, every heartbeat. That is the rate at which sperm multiply in a healthy human male individual the moment puberty kicks off. It is a lot. And each sperm is potentially fertile. Ejaculation is therefore a very serious affair, and pushes one lonely egg into dangerous terrain if pregnancy is not desired. This is where contraceptives come in. Contraceptives for men – other than condoms and vasectomy – remain a tricky affair for a number of reasons. One being the sheer amount of sperm a contraceptive has to consider. Finding a solution at the level of the egg seems – naturally – less of a hassle than looking for something able to deal with millions of sperm at a time. Which is no doubt one of the reasons – though by far not the sole reason – that the popular pill came crashing into our society in the 1960s. Fifty years later, there is hope that a male contraceptive has been found. It all has to do with a protein known as Bromodomain testis-specific protein and a small inhibitor molecule known as JQ1.

Contraception – male or female – is nothing new. In fact, it has been around ever since it became clear that what men put into women was capable of making a baby. The Ancient Greeks would have been the first to put two and two together. From then on, all sorts of potions were devised to counter fertilisation. In the Ebers Papyrus, an Egyptian medical papyrus dating back to 1550 BC, women are told how to make a paste out of dates, acacia and honey, which they can then spread onto wool and use as a pessary. All sorts of herbs were also used: the contraceptive property of hemp seeds (*Cannabis sativa*) and rue (*Ruta graveolens*) were described in early medical writings in 40AD for instance. And many more followed, in many different societies.

The use of condoms, interestingly, may well have stemmed more from a way to prevent sexually transmitted diseases than to avoid pregnancy. Though some historians and archaeologists argue that loincloths were used in Ancient civilisations, it is only in the 16th century that there is an unquestionable description of condoms used to prevent the spread of syphilis. These consisted of dry linen sheaths that had been soaked in a

chemical solution and were attached to the end of the penis by way of a ribbon.

None of these methods though have ever proved to be 100% birth proof. It was only with the advent of the pill in the very early 1960s that an effective and simple method seemed to have been found – though it does mean tampering with a woman's menstrual cycle. Besides vasectomy, which can only really be performed on men who do not wish to conceive at all any more, there has been no marketable male contraceptive. Most fairly recent trials have involved meddling with the male hormone testosterone, which work reasonably well, but have never made it to the chemist's counter. So the Bromodomain testis-specific (BRDT) protein and JQ1 come as a refreshing prospect in the world of birth control. Indeed, the BRDT-JQ1 system does not interfere with any of the male hormone pathways. Instead, it acts at the very beginning of spermatogenesis and interferes with sperm development.

BRDT belongs to the large human bromodomain family. As its name suggests, its sequence presents a certain number of bromodomains. Typically, the domain is represented by a bundle of four alpha helices that forms a binding pocket which is able to recognise acetylated lysine residues such as those on the ends of histones. Acetyl-lysine recognition by BRDT is a prerequisite to the protein binding to histone H4 for instance. When this happens, the DNA/histone arrangement is remodelled, and genes involved in spermatogenesis are set off. Now if BRDT were unable to carry out its function, then sperm would not develop.

Scientists discovered that a potent thienodiazepine inhibitor known as JQ1 was able to do just this: JQ1 slips into BRDT's acetyl-lysine binding pocket thus making it impossible for BRDT to link to H4. As a result, the genes needed for sperm cells to mature are not triggered off and spermatogenesis is impeded. When JQ1 was injected into mice, the sperm number and motility were very much reduced, and there seemed to be no effect whatsoever on the male hormone pathways. JQ1 seems to act upon BRDT only. Even better, when JQ1 therapy is withdrawn, males recover all their reproductive capacities.

Though mice and men are worlds apart, the good news is that the bromodomains of their BRDT proteins are almost identical. Consequently, scientists believe that there is a great chance that JQ1 should work as an effective contraceptive in men too. It is not the first time that scientists have announced ground-breaking news in this field. But it is the first time that they have found a contraceptive that does not involve male hormones. However, it will still take a few years to find out if there are any long-term side effects, such as developmental malformations in progeny, besides finding a way of taking the contraceptive orally rather than by injection. Contraception has been on the minds of humans for a long time, for many good reasons. An undesired pregnancy entails an awful lot – both in Western societies but also in third world countries. If scientists can develop contraceptives that are not only affordable but also acceptable in societies other than our own, it can only be a giant leap for civilisation.

Cross-references to UniProt

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