


# Prolistem<sup>®</sup>

AZOOSPERMIA TO HAPPINESS

 +1 845 233 6550

 [Info@Prolistem.com](mailto:Info@Prolistem.com)

 [www.Prolistem.com](http://www.Prolistem.com)

# ABOUT PROLISTEM®

Prolistem is the culmination of a lot of hard work, research, and thinking. Our main goal in all our research is to find solutions that can help other people.

Thirty years ago, men with azoospermia had no options for having children. In the 1990s, a new surgery was developed to extract viable sperm directly from the testicles. This, along with advancements in technology and equipment, led to the improvement of the TESE procedure into MicroTESE, providing new hope for more couples with azoospermia.

Spermatogenesis is a highly researched subject. The more we learn and understand about this complex process, the more new ideas and solutions are developed. We can think of it like a puzzle – the more pieces we discover, the clearer the picture becomes.

Previous research on Spermatogonial Stem Cells, we developed a unique technique to isolate and culture them in-vitro, producing sperm in a lab dish.

Our two main goals were to learn more about stem cell behavior and develop new methods to create sperm in the lab for men with azoospermia.

This incredible research was conducted in collaboration with the Institute of Reproductive- and Regenerative Biology, Centre of Reproductive Medicine and Andrology, Münster. Prof. Stefan Schlatt and Dr. Jan-Bernd Stukenborg were instrumental in this breakthrough, and we have published several articles about this topic.

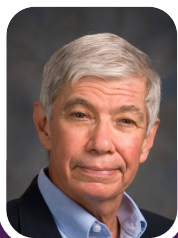
During our research, we made a fascinating discovery. We explored the effects of various substances like cytokines, growth factors, and hormones on Spermatogonial Stem Cell growth and development. Surprisingly, we found that testosterone had the opposite effect – it inhibited Spermatogonial Stem Cell growth.

Building on this knowledge, our research at MD Anderson Cancer Center, University of Texas, revealed that testosterone suppression renews Spermatogonial Stem Cells ability to proliferate and differentiate. However, without testosterone, sperm production remains absent.

Incredible people, incredible research – our team at MD Anderson Cancer Center, with Prof. Marvin Meistrich and Prof. Gunapala Shetty, played a crucial role.



Dr. Mahmoud Abuelhija



Prof. Marvin Meistrich



Dr. Gunapala Shetty

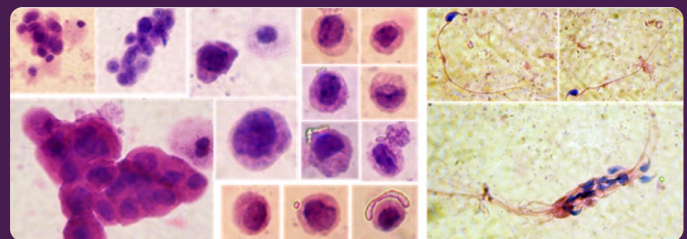


Dr. Jan-Bernd Stukenborg



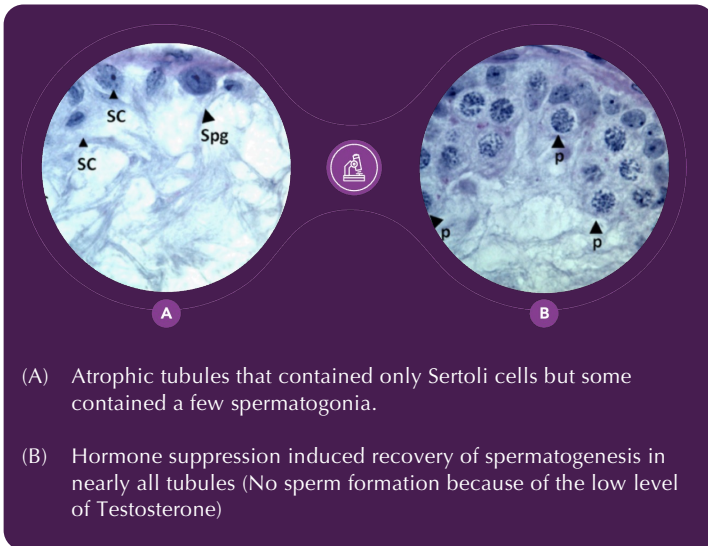
Prof. Stefan Schlatt

## SPERM in LAB DISH



- Mahmoud Abu Elhija. Differentiation of murine male germ cells to spermatozoa in a soft agar culture system. *I Asian J Androl* 2012; 14(2):285-93. doi:10.1-38/aja.2011.112. Epub 2011 Nov 7.
- Jan-Bernd Stukenborg, Joachim Wistuba, C Marc Luetjens, Mahmoud Abu Elhija. Coculture of spermatogonia with somatic cells in a novel three-dimensional soft-agar-culture-system. *J Androl*. May-Jun 2008; 29(3):312-29. doi: 10.2164/jandrol.107002857. Epub 2007 Nov 28.
- Jan-Bernd Stukenborg, Stefan Schlatt, Manuela Simoni, Ching-Hei Yeung, Mahmoud Abu Elhija. New horizons for in vitro spermatogenesis? An update on novel three-dimensional culture systems and tools for meiotic and post-meiotic differentiation of testicular germ cells. *Mol Hum Reprod*. 2009 Sep; 15(9):521-9. doi: 10.1093/molehr/gap052. Epub 2009 Jun 27.

# ABOUT PROLISTEM®



Connecting all the dots from our and other research led to the birth of Prolistem.

In 2012, our company MedHija LLC was founded. By 2017, we secured a patent and successfully created Prolistem, specifically designed for Non-Obstructive Azoospermia.

Our vision is to become the gold standard of azoospermia treatment worldwide. And we won't stop here – we'll continue our research journey to find more solutions that can help others.

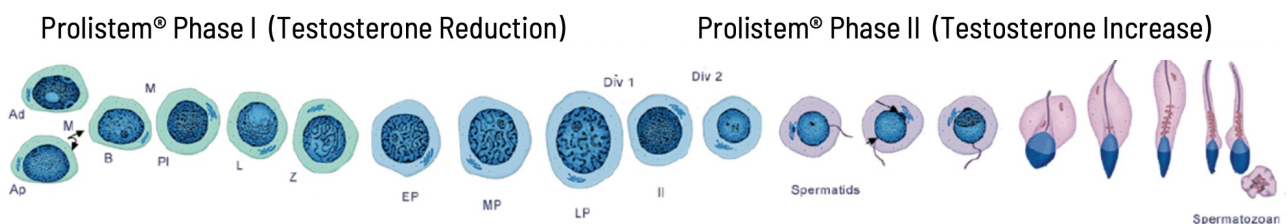
## PROLISTEM® TREATMENT

Prolistem® is a comprehensive and targeted solution for men struggling with non-obstructive azoospermia. Through a two phase treatment process, Prolistem® increases the chances of reproductive success for men with this condition.

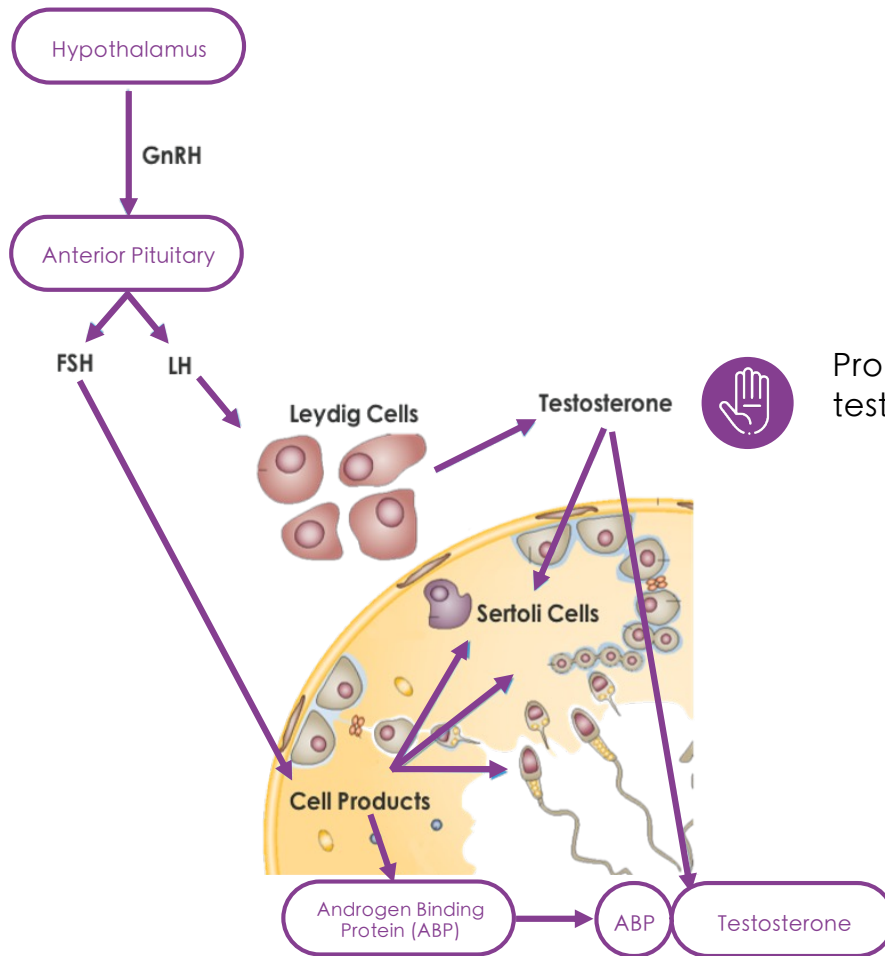
Similar to rebooting a smartphone to fix functional issues, Prolistem® facilitates the "Spermatogenesis Restarting Process" to restore sperm production by temporarily lowering testosterone levels.

Phase one of the Prolistem® treatment (three bottles over three months) decrease testosterone levels to create an optimal environment for sperm production and promote differentiation into the next stages of sperm production

Phase two of the Prolistem® treatment (three bottles over three months) designed to enhance sperm count, motility, and quality. During this phase, testosterone levels are restored to normal to facilitate healthy sperm production.



# Hormonal Cascade in Male Reproductive Regulation



Prolistem® temporarily reduce testosterone levels by PHASE I

GnRH is released by the hypothalamus in the brain. It stimulates the anterior pituitary gland to release two key hormones: LH (Luteinizing Hormone) and FSH (Follicle-Stimulating Hormone).

LH stimulates the Leydig cells in the testes to produce and release testosterone. Testosterone is the primary male sex hormone and plays a crucial role in the development and maintenance of male reproductive tissues and secondary sexual characteristics.

FSH acts on the Sertoli cells within the testes. Sertoli cells release androgen-binding protein (ABP) under the influence of FSH. ABP helps bind and transport testosterone within the seminiferous tubules, the site of sperm production.

This localized increase in testosterone concentration supports sperm production.

# HOW DOES PROLISTEM® WORK?

Recent research suggests a potential solution with testosterone reduction, though the exact mechanism is not fully understood. Our studies, along with others, indicate that in azoospermia, healthy stem cells face barriers to development in the testis due to environmental factors.

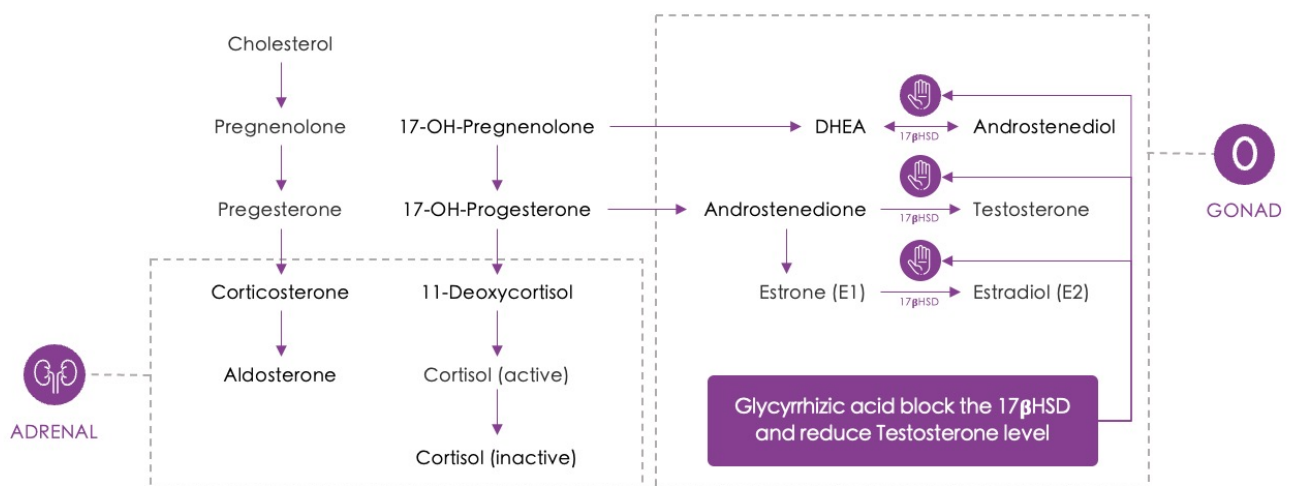
Crucial to the orchestration of spermatogenesis are Sertoli cells, which create a specialized niche within the testicular environment. These cells employ both classical and non-classical signaling pathways, featuring an intricate network of signaling molecules, receptors, and intracellular cascades.

Under normal conditions, there exists significant cross-talk between classical and non-classical pathways, with testosterone emerging as a key player in coordinating these signals.

Testosterone influences the expression of genes pivotal to various signaling cascades, contributing to the overall regulation of spermatogenesis. Additionally, testosterone integration across both pathways creates a microenvironment conducive to optimal sperm production.

Prolistem® using unique components such as glycyrrhizic acid, omega-3 fatty acids and lignans which undergoes in-vivo hydrolysis to glycyrrhetic acid. This acid functions by blocking  $17\beta$ -hydroxysteroid dehydrogenase ( $17\beta$ HSD), an enzyme responsible for converting androstenedione to testosterone.

The extraction process and concentration of this acid are proprietary information held by the company, as it serves as a key secret ingredient in Prolistem.



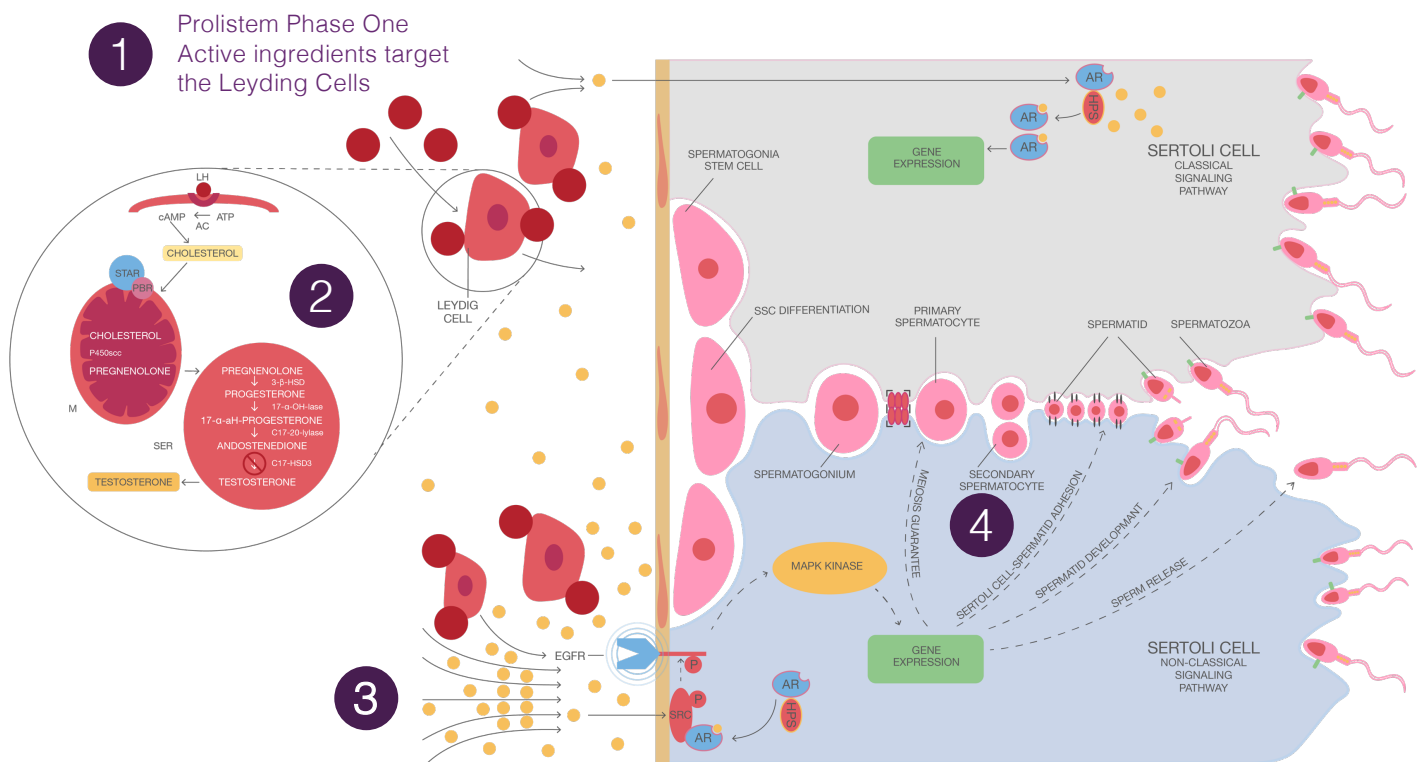
# PROLISTEM® PHASE ONE

Our investigations, combined with insights from other studies, suggest that testosterone reduction, serves as a catalyst for increased activity in non-classical pathways, including the MAPK and PI3K/Akt pathways.

These pathways, known for their roles in cellular signaling and survival, become more pronounced in the context of lowered testosterone levels.

Notably, the Notch signaling pathway, involved in cell fate determination and differentiation, emerges as a potential player in adapting to the altered testosterone environment. This suggests a multifaceted interplay of signaling pathways in response to testosterone reduction, further emphasizing the complexity of the mechanisms at play.

As we delve deeper into the intricate world of spermatogenesis and its regulation, the role of testosterone reduction, especially facilitated by Prolistem, emerges as a promising avenue for restoring sperm production in azoospermia cases. The dynamic interplay between classical and non-classical signaling pathways, orchestrated by Sertoli cells, highlights the need for continued exploration to unlock the full potential of this therapeutic approach.



1 Prolistem Phase One active ingredients target the Leydig Cells

2 Block the testosterone production in the Leydig Cells

3 Testosterone reduction increased activity in non-classical pathways

4 Activate kinases that help maintain spermatogenesis (the non-classical way)

# PROLISTEM® PHASE TWO

Prolistem® Stage Three (Phase Two) is the only treatment on the market that is designed based on real research and knowledge and has been approved to be effective for men's sperm health (Oligospermia)

Prolistem® goes beyond sperm health – it targets the entire sperm production process inside the testis. The active ingredients focus on supporting germ cells, Leydig cells, and Sertoli cells for comprehensive reproductive well-being.

## Group 1 – The Retinoic Acid Effect

Retinoic Acid (Vitamin A) acts on both Sertoli cells and germ cells and pushes undifferentiated spermatogonia into the differentiation pathway and, eventually, meiotic prophase.

## Group 2 – Sperm Health

Vitamin D, E, B12, Zinc, Thiamin, Icarin, Punicalagins, Ellagic acid, Anthocyanins, Ginsenosides, Polysaccharides, Triterpenoids, Macamides, Glucosinolates, Alkaloids, Protodiosci, Steroidal saponins. The active ingredients have demonstrated the ability to enhance sperm viability and morphology, while also fostering the concentration of antioxidants, catalase, and peroxidase. These factors play a crucial role in supporting spermatogenesis.

## Group 3 – Testosterone Booster

The active ingredients have demonstrated the capability to enhance testosterone production from Leydig cells through both direct and indirect pathways. Vitamin D, Icarin, Punicalagins, Ellagic acid, Anthocyanins, L-dopa (levodopa), Various alkaloids, Ginsenosides, Polysaccharides, Triterpenoids.

## Group 4 – DNA Damage

Folic acid, polyphenols, resveratrol, anthocyanins, quercetin, terpenes, phenolic compounds, quercetin, punicalagins, ellagic acid, anthocyanins reduced DNA fragmentation in normal human spermatozoa

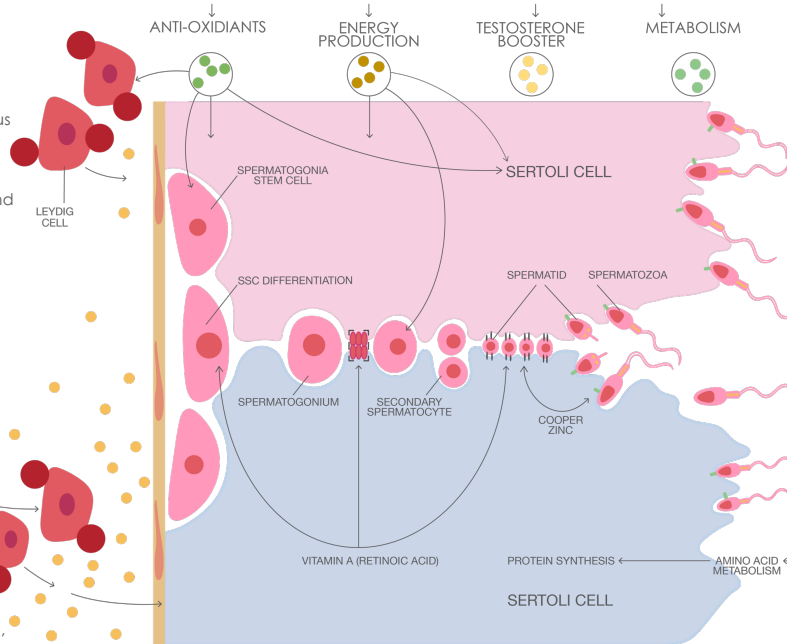
### ANTIOXIDANTS

- Vitamin C, E
- Polyphenols, Resveratrol, Anthocyanins, Quercetin
- Punicalagins, Ellagic acid, Anthocyanins
- L-dopa (levodopa), Various alkaloids
- Terpenes, Phenolic compounds
- Terpenoids (ginkgolides and bilobalides)
- Ginsenosides, Polysaccharides, Triterpenoids
- Riboflavin
- Thiamin

### TESTOSTERONE BOOSTER

- Vitamin D
- Icarin
- Punicalagins, Ellagic acid, Anthocyanins
- L-dopa (levodopa), Various alkaloids
- Ginsenosides, Polysaccharides, Triterpenoids

### PROLISTEM PHASE TWO ACTIVE INGREDIENTS



### SPERM CONCENTRATION

- Vitamin C, E
- Thiamin
- Icarin
- Macamides, Glucosinolates, Alkaloids
- Protodiosci, Steroidal saponins

### SPERM VIABILITY

- Vitamin B12
- L-Arginine

### SPERM MOTILITY

- Vitamin D, E, B12
- Zinc
- Punicalagins, Ellagic acid, Anthocyanins
- Ginsenosides, Polysaccharides, Triterpenoids
- Macamides, Glucosinolates, Alkaloids
- Protodiosci, Steroidal saponins



Scan the code for more details on active ingredients.

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# CHART FOR DECIDING ON PROLISTEM® TREATMENT

