

# Improving human male reproductive health and fertility with increasing age—an interview with Prof. Marco G. Alves

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## Abstract

The article is an interview with Prof. Marco G. Alves, Department of Medical Sciences, Institute of Biomedicine (iBiMED), University of Aveiro, Campus de Santiago Agra do Crasto, Aveiro, Portugal, conducted by Zijian Tian of the Department of Urology, The Second Hospital of Tianjin Medical University, Tianjin, China, on behalf of *Aging Pathobiology and Therapeutics*.



Marco G. Alves, PhD

Marco G. Alves holds a PhD in Biochemistry, specializing in bioenergetics, from the University of Coimbra, Portugal. He has been actively working in the fields of andrology, male reproductive health, and metabolism. Currently, he is a Principal Investigator at the Institute of Biomedicine, University of Aveiro, where he leads the Sertoli Cell and Gamete Biology lab. Prof. Marco G. Alves has published over 200 peer-reviewed papers, including works in *Nature Aging*, *Nature Reviews Urology*, *Human Reproduction Update*, and *Trends in Endocrinology & Metabolism*. He serves on the editorial boards of 15 peer-reviewed journals and is the inventor of two patents. Passionate about teaching and sharing his knowledge globally, he has delivered over 60 lectures around the world in recent years. (<https://www.researchgate.net/profile/Marco-Alves-11>)

**Zijian Tian:** Can you introduce us to the main area of research that you and your team have been doing lately? What is the biggest difficulty you are currently facing in your research?

**Marco G. Alves:** The Sertoli Cell and Gamete Biology Lab is dedicated to investigating the fundamental processes that govern gamete production and functionality. We ultimately aim to provide a scientific foundation for improving human reproductive health and fertility. To achieve this, we conduct studies using both normal and pathological human tissues, which allows us to gain insights into reproductive health and fertility. In addition to human tissue studies, we employ cell-based and rodent animal models. These models enable us to bridge the gap between basic research and clinical applications, enhancing our understanding of reproductive processes. Moreover, since in recent years there has been a growing body of evidence suggesting that environmental toxins and endocrine disruptors have a significant impact on human reproductive health, our lab has expanded its research focus to investigate how these agents influence fertility. More recently, our recent research has concentrated on examining the impact of metabolic diseases on spermatogenesis and testicular metabolism. We are particularly interested in understanding the potential transgenerational effects of metabolic cues in male parents to the offspring. By studying these metabolic signatures, we aim to uncover the underlying mechanisms that may influence reproductive health across generations. Senescence has emerged as a major factor related to metabolic dysfunction. Thus, we aim to study the impact of male progenitor age in testis, sperm and offspring. Overall, the Sertoli Cell has a multifaceted research approach to allow advance in the field of reproductive biology and contribute to the development of novel strategies for improving reproductive health and addressing fertility issues.

**Zijian Tian:** Why did you choose Endocrinology, Metabo-

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lism and Male Reproduction as your main research area? What attracts you most about this field?

**Marco G. Alves:** After completing my PhD in biochemistry with a specialization in bioenergetics, I decided to move to a new university and explore a different area of research. During that period, I identified a gap in the study of the relevance of metabolic processes in reproduction, particularly regarding the male partner. I realized there was an opportunity to make a meaningful impact by establishing a new line of research focused on this overlooked aspect of reproductive health. However, the challenges were considerable. Many colleagues discouraged me, noting that research funding predominantly supports studies on female fertility, with males often considered merely as sperm donors. But I found that basic research on male fertility was quite limited, leaving space for innovation and discovery.

Given my background in bioenergetics and the understanding that spermatogenesis is a metabolically regulated process, I identified this as a promising starting point. Hormones, known to regulate reproductive processes, also play crucial roles as metabolic regulators. However, there were gaps in knowledge regarding the interplay between hormones and testicular metabolism. Recognizing the trend of delayed parenthood and the common belief that men can father children at any age, we began investigating how aging affects male reproductive health, not only for the individual but also for his offspring.

**Zijian Tian:** Unlike women, male fertility does not usually have an endpoint. However, testicular senescence occurs with the aging process. What methods can we use to uncover the dysregulated pathways of testicular senescence?

**Marco G. Alves:** It is true that biologically, men can father children at any age. However, the consequences of delayed parenthood are not fully understood. Additionally, the molecular mechanisms by which aging alters testicular physiology and function remain largely unknown. To uncover the dysregulated pathways caused by testicular senescence, several advanced methods and approaches can be employed. These methods span various fields of molecular biology, omics (proteomics, metabolomics, transcriptomics, epigenomics), and bioinformatics. It is crucial to complement these techniques with imaging techniques and functional assays to consolidate the findings. Despite some significant descriptive observations, the functional impact of aging on the testis is still largely unexplored. The challenge lies in linking detected biomarkers to specific functional alterations. A comprehensive approach involving multi-omics analyses and advanced imaging, combined with functional assays, is essential to map out the complex interplay between aging and testicular function. That way we can gain a deeper understanding of the underlying mechanisms.

**Zijian Tian:** As we know, disease models play a critical role in research investigations. What models (animal or cellular) do you typically use to study testicular senescence?

**Marco G. Alves:** Studying testicular senescence in humans is particularly challenging. To unravel the mechanisms involved, we employ a strategy that combines cell and

animal-based models with validation using human samples whenever possible. We use rodent models of different ages to identify age-related changes and their functional relevance to the male reproductive system. These models provide insights into testicular aging and allow us to study the molecular and cellular mechanisms in a controlled environment. We have access to human Sertoli cells isolated from testicular biopsies of men with anejaculation due to obstructive azoospermia or varicocele in the non-biopsied testis. This enables us to perform in vitro experiments with human Sertoli cells from men of different ages or under specific treatments. Additionally, we study human sperm samples to investigate age-related changes in sperm physiology and seminal fluid. Seminal fluid, often overlooked, holds potential as an indicator of male reproductive function. By analyzing changes in seminal fluid composition and sperm quality, we aim to uncover biomarkers and mechanisms of testicular aging. Overall we can say that our approach integrates findings from animal and cell-based models with human data, enabling us to validate and refine our understanding of testicular senescence. This multifaceted strategy allows us to advance our knowledge of male reproductive aging and identify potential targets for intervention.

**Zijian Tian:** Reproductive research necessarily involves medical ethics. How do you see the impact of ethical issues on reproductive research? Do these issues impede the development of reproductive medicine?

**Marco G. Alves:** Medical ethics is a pillar of integrity in research, and we cannot ignore its principles. However, the current level of complexity in ethical discussion has become a barrier to groundbreaking research and innovation. All good scientists support the role of ethical committees, scrutiny, regulation, and adherence to guidelines. The problem lies in the extensive bureaucracy that requires scientists to spend excessive time navigating ethical approval processes instead of focusing on their research. Ethical committees should function not only as regulators but also as facilitators of excellence and impactful research. While the regulatory aspect is well-managed, the facilitative role often falls short. In the field of reproductive medicine, discussions tend to focus more on restrictions than on exploring alternative methods to achieve research goals. When no alternatives exist, it is essential to find ways to support and enable the research to proceed ethically. Medical ethics should be implemented alongside a supportive structure that helps scientists address and overcome ethical concerns. This approach would ensure that ethical standards are maintained while also promoting innovation and scientific progress.

**Zijian Tian:** What are the next research priorities for your research team? Will there be research related to clinical translation?

**Marco G. Alves:** Male reproductive health is often not prioritized by most journals, and research in this field frequently faces discouragement. Publishing outside specialized journals is particularly challenging. One prevalent misconception is that men can father children at any age

without complications. However, it is well-documented that the likelihood of problems during pregnancy and in the child increases with the father's age. Another misconception is that for fertility treatment, one spermatozoon is sufficient, and men produce thousands. Our work focuses not only on how aging and metabolic cues affect male reproductive health but also on the health of the offspring. Recently, we published a paper analyzing the metabolomics of human seminal fluid, identifying an aging-related increase in amino acid content. While these findings are promising, their full relevance remains under debate. From a cellular perspective, new data suggest that Sertoli cell lysosomes may impact the aging-related decline in testosterone production by Leydig cells. We are particularly interested in understanding how these mechanisms can be pharmacologically altered. This line of research holds potential for developing targeted treatments to mitigate the effects of aging on male reproductive health and improve outcomes for both fathers and their offspring.

**Zijian Tian:** As a young researcher and a clinical doctor, I have found it difficult to do both jobs well. Do you have any suggestions on how to balance research and clinical work?

**Marco G. Alves:** I often say that research must be driven by passion. No one does research to get rich; it is the passion for discovery and knowledge that fuels us. The challenge, however, lies in balancing teaching, clinical work, and research. The key to achieving this balance is meticulous planning. Careful experimental design is essential to ensure that time is used efficiently. I meticulously plan each experiment to avoid wasting time and resources. Delegation is also critical. While I review each piece of raw data, my years of experience have taught me how to effectively delegate tasks within my team. Trust in your team is paramount. Having a reliable and competent team allows you to delegate with confidence, ensuring that the work progresses smoothly even when you are engaged in other duties as clinical or teaching activities. Aligning clinical and teaching work with research interests is another strategy to enhance productivity. When your activities overlap, it creates a natural synergy. Collaboration and brainstorming are vital components of success. The more you collaborate and engage with your partners, the more productive you become. Collaboration should not be confined to your institution; use global connectivity to find and work with the right people. Whether it is for improving experimental design, generating ideas, or improve and co-authoring papers. Good scientists are generally generous and willing to assist.

Mentorship also plays an essential role in creating an efficient scientific environment. Foster a culture of mentorship with your students and seek mentorship from colleagues. This reciprocal relationship promotes growth and efficiency. Setting clear goals and regularly assessing outcomes are crucial. If the current path leads to excessive stress or burnout, reevaluate your approach. Research should be a source of creativity and pleasure, enhancing your mental and physical health. While challenging, bal-

ancing these aspects of your career is achievable with the right strategies and mindset.

**Zijian Tian:** Where do you see the next 5 years in male reproduction?

**Marco G. Alves:** There have been significant biotechnological advancements in the field of male reproductive health. For instance, machines now exist that can measure reactive oxygen species in seminal fluid and determine parameters associated with sperm quality. However, while these technologies focus on the endpoint of male fertility—sperm—there remains a substantial need for a deeper understanding of the basic mechanisms that mediate male reproduction. More basic research is essential to elucidate the processes that control testis physiology. There is also increasing interest in understanding how the health of the male partner contributes to offspring health. This field of research is gradually gaining attention and is likely to gain momentum in the coming decade. The epigenetic contributions of the father to the offspring are proving to be far more relevant than initially thought, presenting a vast area for further exploration and improvement. Another emerging hot topic is the impact of lifestyle on male reproductive health. Beyond merely describing effects, the goal is to identify definitive biomarkers that can lead to more effective treatments for male infertility and mitigate the impacts of harmful behaviors. The potential for breakthroughs in this area is substantial, offering hope for better diagnostic tools and therapeutic strategies soon.

**Zijian Tian:** What would be your best advice for young doctors and researchers to learn and develop?

**Marco G. Alves:** It is important to embrace the challenges that come with balancing clinical, research, and teaching duties. Few professions undergo as much scrutiny as ours, with evaluations from institutions, funding agencies, and peer reviewers for publications. This rigorous process is unavoidable, but it is crucial to find joy in your discoveries and take pleasure in your work. Happiness in what you do gives purpose and meaning to the journey. Building a network across institutions with colleagues you enjoy working with is pivotal, as you will spend a significant amount of time collaborating with them. Cultivating these relationships can make your professional life more fulfilling and productive. Generosity and humility are also pivotal. Strive to be remembered not just for your achievements but for your kindness and positive impact on others. Not everyone will win a Nobel Prize, secure a tenure track position, or receive international recognition, and that is perfectly fine. The true measure of success is finding happiness in your chosen path and making a meaningful contribution, regardless of external accolades. Your greatest discovery will be the joy and satisfaction you derive from your work and the positive difference you make in the lives of others.

**Zijian Tian:** Thank you for your time.