International Network for Young Researchers in Male Fertility

Autumn edition - 2016

INYRMF Newsletter

In this issue:

Main responsible for this issue:

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Greetings

Dear INYRMF member,

"Autumn is a second spring when every leaf is a flower". With these words we welcome you to the new Autumn newsletter!
In this edition, we announce the 10th INYRMF meeting and report on the special session of our network organized at the 9th European Congress of Andrology. In addition, we highlight the fate of paternal mitochondria upon fertilization and the role of RHOX10 in the establishment of mouse spermatogonial stem cells. Further on, you can read an interview with our network's father, Frank Tüttelmann, and learn more about the first artificial inseminations.
Enjoy your reading!

The INYRMF board

INYRMF Bulletin

Great news! We are happy to inform you that the 10th (!) INYRMF meeting will take place on **September 11th-13th, 2017** in **Brussels, Belgium**. We are reaching the first decade of young researchers meetings! Is there a better spot than Brussels, the cradle of ICSI with its famous 'Manneken Pis', for this special event?

Through our long-established collaboration with the European Academy of Andrology (EAA), INYRMF hosted a session at the 9th European Congress of Andrology. Professor Rafael Oliva, from the University of Barcelona, gave an inspiring talk on the recent advances in sperm proteomics. Furthermore, three younger researchers shared their research projects at our session.

EAA offered travel grants to 4 INYRMF members participating at the congress. The winners were: Elena Casamonti, Estelle Lecluze, Sara Marchiani and Thierry Almont. Congratulations to all of them!

And last but not the least, three new members have joined our board! Welcome Isabelle, Pablo and Tiina!

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Press Highlights

Paternal mitochondria are activated for "self-eating" upon fertilization

This year the Nobel Assembly at Karolinska Institutet awarded Yoshinori Ohsumi the Nobel Prize in Physiology or Medicine for "his discoveries of mechanisms for autophagy". Excitingly, autophagy, a fundamental process for degrading and recycling cellular components, is a key player in the elimination of paternal mitochondria in early embryonic development. The basic autophagic process is quite simple: it involves encapsulation of cellular components by double membrane vesicles called autophagosomes and their fusion with lysosomes containing enzymes capable of degrading their contents.

With only a few exceptions, and despite the fact that paternal mitochondria enter oocytes during fertilization, animal mitochondria are exclusively maternally inherited. The mechanisms behind this *mitochondrial Eve paradigm* have been studied by many researchers, but some pieces of the puzzle are still missing. Zhou and colleagues just found one of these pieces by identifying the enzyme that mediates sperm mitochondrial breakdown after fertilization. The results were published in *Science* last July.

While scrutinizing fertilization in the worm *Caenorhabditis elegans* by electron microscopy and tomography, the authors observed that sperm mitochondrial inner membranes were disrupted soon after fertilization. Their detailed observations have actually suggested that paternal mitochondria are partly destroyed by a self-originated break event before autophagosome assembly and degradation. With the aim of identifying mitochondrial factors potentially involved in this process, Zhou and co-workers screened 217 mitochondrial genes by RNA interference. This led to the identification of CPS-6 (a mitochondrial endonuclease G) that is required for the rapid removal of paternal mitochondrial genome (mtDNA) in the early embryo. Further observations suggested that sperm mitochondria are depolarized and damaged soon after entering the oocyte and that CPS-6 translocates from the mitochondrial inner membrane space to the matrix, where it catalyzes mtDNA degradation. This mitochondrial damage potentially activates the maternal autophagy and proteasome machineries, culminating in clearance of paternal mitochondria (mitophagy). Loss of paternal CPS-6 delays paternal mitochondrial elimination, which in turn results in increased embryonic lethality. Interestingly, this implies that the elimination of sperm mitochondria is actually needed for normal development.

Curiosity spot!

The word autophagy originates from the Greek words *auto* (self) and *phagein* (to eat).

Reference

Zhou Q, Li H, Li H, Nakagawa A, Lin JL, Lee ES, Harry BL, Skeen-Gaar RR, Suehiro Y, William D, Mitani S, Yuan HS, Kang BH, Xue D. (2016). **Mitochondrial endonuclease G mediates breakdown of paternal mitochondria upon fertilization.** *Science*; 353(6297):394-9.

RHOX10 effectuates spermatogonial stem cell establishment

A vast amount of research has focused on spermatogonial stem cells (SSCs). As a result, our understanding of their role in supporting spermatogenesis has flourished over the past decades. Prospermatogonia (ProSG), also known as gonocytes, are the cells giving rise to SSCs. Specifically, multiplying (M) ProSG are derived from primordial germ cells (PGCs), which, in turn, give rise to transitional (T1) ProSG. After a mitotically silent but otherwise intracellularly active period, where they re-establish DNA methylation marks erased in PGCs and M PRoSG, T1 ProSG resume mitosis and become secondary transitional (T2) ProSG. T2 ProSG have the special ability to migrate from the centre of the seminiferous tubule to its periphery housing the SSC niche. However, the specific transcription factors that drive this conserved migratory step were still unknown.

Song *et al*. 2016 identified RHOX10 as at least one of these factors. Their discovery started with the generation of mutant mice designed to conditionally delete the entire 33-gene X-linked homeobox gene cluster. Histology of the seminiferous tubules of the knockout mice showed missing or immature germ cell layers coupled with a progressive spermatogenic decline, a phenotype characteristic of mice defective in either the generation or maintenance of SSCs. Next, they showed that germ-cell-specific ablation of *Rhox* genes expression, but not loss of somatic-cell-expressed *Rhox* genes, resulted in reproductive defects indistinguishable from those in global *Rhox* knockout mice. This still did not pinpoint which gene in the *Rhox* cluster was responsible for the putative SSC defect in the *Rhox* knockout mice. By selectively depleting spermatogonia using irradiation and ruling out which *Rhox* genes were not spermatogonia-specific, they regarded *Rhox10* as the best candidate. To test their candidate, Song *et al.* created a *Rhox10* knockout model. The critical role of RHOX10 in spermatogenesis was confirmed since loss of *Rhox10* resulted in a comparable phenotype to loss of the entire *Rhox* cluster.

Subsequently, they studied the underlying mechanism of the RHOX10 transcription factor. Based on a battery of markers and techniques, including single-cell RNA sequencing, the authors postulated that the Rhox10 factor drives the initial establishment of SSCs by promoting the differentiation of mitotically inactive T1-ProSG into mitotically active T2-ProSG and driving the migration of T2-ProSG into the SSC niche.

Interestingly, during the process, unique gene signatures of T1 and T2 ProSG were defined, which might help further elucidate the processes involved in normal and abnormal (testicular tumours) differentiation of ProSG to SSC. Simultaneously, their findings have the potential to lead to diagnostic and treatment approaches for male infertility.

Curiosity spot!

Homeobox genes are master regulatory genes: by mutating these genes in flies, researchers were able to put a leg where an antenna should sprout out!

Reference

Song H-W, Bettegowda A, Lake BB, et al. (2016). **The homeobox transcription factor RHOX10 drives mouse spermatogonial stem cell establishment.** *Cell Reports*;17(1):149-164.

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Tête-à-tête with Frank Tüttelmann

Frank Tüttelmann (Prof. Dr. med.) is a senior physician and group leader at the Institute of Human Genetics of the University of Münster, Germany. He is a well-known researcher in Human Genetics in Andrology and has published dozens of papers in the field. His work has been awarded with several national and international prizes. In 2006, Frank was part of the group that founded the INYRMF and was the first president of the INYRMF. Thus, he will always be considered as **our network´s father**. Between 2006 and 2013, and together with other INYRMF board members, he was responsible for the growing of INYRMF and for the establishment of most of the activities that are still on today.

When and why did you decide to work in Male Fertility?

Maybe surprisingly, but also maybe not so uncommon, I did not really decide to work in this field. When I finished my studies, I was looking for a position as an MD at a university hospital, because I explicitly wanted to do research. Yet, at that time, such positions were very rare for MDs (which has completely changed today), but by luck or fortune, I had the chance to have an interview with Ebo Nieschlag at the Institute of Reproductive Medicine, Münster (now Centre of Reproductive Medicine and Andrology) and started to work there. I then quickly adopted Andrology as "my" field and specifically genetics, which was largely inspired by Manuela Simoni and Jörg Gromoll. As I never left this road from then on, you see that for me it enormously depended on the great characters and surroundings - and I never regretted sticking with this very specific field.

You were one of the "Young Testis Club" (now INYRMF) founders and your name will always be associated with it. What was the main motivation for its foundation? Can you briefly tell us the story of the beginning of our network?

The inspiration came from a similar network that was already established in Germany for "Young Active Researcher in Endocrinology" (YARE, also still around). Again, Jörg Gromoll played an important role, because he came up with the idea that something comparable could be useful for young researchers in Andrology too. Thus, Jan Stukenborg, myself and some others from Münster before the European Testis Workshop (ETW) in 2006 in Bad Aibling contacted well-established researchers in the fields to propose some of their young scientists to join our efforts. We were able to recruit some people before and some more during the ETW and came up with a board of more than 10 young researchers in the field of Male Infertility distributed over Europe. I am quoting from the mission statement that is still a very valid summary of our ideas why we founded the network: "YTC (now INYRMF) should encourage the formation of global networks among young researchers. Exchange of technologies, protocols, data, etc. should help especially young researchers to perform better research. Moreover, networks may lead to international collaboration and the opportunity to apply for large grants." We already in Bad Aibling distributed some tasks like setting up a homepage and contacting more potential members. We also planned to have the still present bi-annually stand-alone meetings and one-day-meetings adjacent to the ETW. As basically all of this has been pursued now over 10 years, these seem to have been good ideas!

How would you define your experience as INYRMF President? Which difficulties did you have to face and what were your main rewards?

The experience with INYRMF and specifically the people "on board" was always educational and also great fun - we e.g. had some very memorable board meetings! This does not mean that we did not face obstacles, e.g. recruiting funding for our meetings, but because we all functioned so well together, it always worked out. In the beginning, a lot of my time went into getting in contact with the Andrology societies (EAA, ISA) and asking (convincing!) them for affiliation, space during their congresses for an INYRMF session, and, last not least, money. These are now well-established connections and setups that are beneficial for all sides. As in many other situations, probably the largest difficulties are surrounding the funding for the meetings. We wanted to keep costs low to allow participation for everyone, but this of course means collecting quite substantial amounts of funding. As mentioned, the EAA and ISA have been very supportive, but other sources have become more and more difficult.

For me and others involved in organizing INYRMF, this work was indeed rewarding not only on the personal level but also by becoming well-connected and well-known at an early stage in the career, i.e. even before my research had some notable breakthroughs, the "important people" in Andrology already knew me because of my activities in INYRMF.

You have recently made the transition from "young-to-senior" researcher. Could you share with us how did you do this path? And do you have any advices for young researchers wanting to reach the same goal?

This directly follows from my last remarks: being known is a not to neglect "currency" already or especially as a young researcher! Of course the ultimate goal is to achieve this by performing great science, but this is largely unplannable. Thus, I do advise anyone to also take part in extracurricular activities like the INYRMF board and other scientific societies.

Many young researchers still need to be convinced to join country-specific or international societies in their fields, but I really think that taking an active part in these is important and will also be beneficial.

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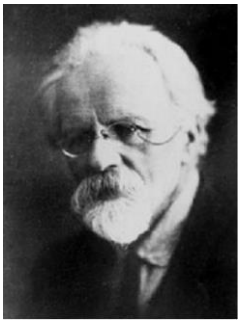
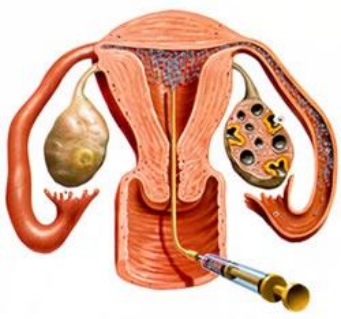
The history of ART: Artificial insemination





(Left) In 1922, the Russian scientist Ilya Ivanovich Ivanov developed the methods of artificial insemination as we know them today (source: ref 1). (Right) The procedure of artificial insemination in human (source: www.attainfertility.com)

Artificial insemination (AI) is the deliberate introduction of sperm into a female's uterus or cervix to achieve *in vivo* fertilization without sexual intercourse. It is a fertility treatment for humans mostly adapted from the work on cattle dairy.

The early steps towards the development of AI actually took place four centuries ago with the first microscopic description of sperm by Antonie van Leeuwenhoek in 1678 (see also the INYRMF winter newsletter of 2015). More than 100 years later, in 1784, the first documented successful insemination was done by Lazzaro Spallanzani in a dog, which whelped three pups 62 days later.

The first application of AI in human was performed in London in the 1770s by John Hunter. He injected semen collected in a warmed syringe into the vagina. In the mid 1800s, James Marion Sims reported the first pregnancy achieved after AI (though many failed attempts as he believed ovulation occurred during menstruation).

It were the pioneering efforts of Ilya Ivanovich (picture) that established AI as a practical procedure very similar to the procedures used today. He designed devices, such as semen extenders, and studied AI extensively in animals, especially cattle. His findings were included in an important paper published in 1922 in the Journal of Agricultural Science.

In the 1930s, the first cooperative dairy AI organizations was introduced in Denmark and the US. It was clear that the application of AI could generate enormous economic benefits through control of diseases, the genetic improvement of milk production by working type traits, and the reduction of lethal genes. Not long after, in the US and other Western countries, the number of AI cooperatives increased rapidly with, nowadays, more than 90% of dairy cows being artificially inseminated.

After the introduction and availability of donor sperm in addition to the better knowledge on sperm washing procedures (mostly due to the introduction of *in vitro* fertilisation (IVF)), AI has become a booming business as fertility treatment in humans as well. However, albeit its success, AI is still subject of critical socio-cultural and ethical debates in many countries worldwide.

References:

1) Ombelet W. and Robays JV (2010). **History of human artificial insemination**. *F, V & V in ObGyn*; Monopgrah:1-5.
2) 2) Foote RH (2002) **The history of artificial insemination: Selected notes and notables**. *American Society of Animal Science:* 1-10.

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Highlighted websites

Science Impact regularly launches travel grants. They support the attendance to any life-science related scientific meeting. Check it out!

http://scienceimpact.co/

Scientific colloquia: mark your calendar!

International Congress of Andrology 2017

Copenhagen (Denmark), 6th-9th May 2017

http://www.ica2017.dk/

Abstract submission deadline 15th January 2017

North American Testis Workshop - "From Testis Differentiation to Sperm Production" and 42nd American Society of Andrology annual conference - "New Concepts and Perspectives in Male Reproduction Health"

Miami (Florida, USA), 19th-22nd April and 22nd-25th April 2017

http://andrologysociety.org/meetings/asa-annual-meeting/future-meetings/general-meeting-information.aspx

Abstract submission deadline 17th January 2017

International Conference on Reproductive Biology and Comparative Endocrinology

Hyderabad (India), 9th-11th February 2017

http://www.icrbce2017.org/

Miniposter submission deadline 31st December 2016

Frontiers in Reproduction (FIR) course
Molecular and Cellular Concepts and Applications

Massachusetts (US), 29th April - 11th June 2017

http://www.mbl.edu/fir/apply/

Application deadline 11th January 2017

Jobs Ads & Funding Prospects

15 PhD positions

Multidisciplinary research training program to uncover cellular control of immuno-metabolism and prostate cancer progression
European Marie Skłodowska-Curie Innovative Training Network (ITN) "Tribbles Research and Innovation Network" (TRAIN)

Deadline: Open until positions are fulfilled

http://train-itn.eu/

PhD position

MRC WIMM Prize PhD Studentship (Oxford, United Kingdom)
PhD position in the labs of Prof Anne Goriely and Prof Andrew Wilkie to study *Selfish Selection in the Human Testis*

Deadline: 6th January 2017

http://www.imm.ox.ac.uk/wimm-prize-phd-studentships-2017

2 Postdoctoral positions

Postdoctoral fellows in Molecular Oncology (Bellinzona, Switzerland)
Prof. Alimonti lab, Institute of Oncology Research (IOR)

Deadline: 31st January 2017

http://ior.iosi.ch/site/?p=1037

PhD position

Development of Antibody-Based Imaging and Therapeutic Agents Directed Against Cancer Testis Antigens (ONCQ; Oxford, United Kigdom)
PhD position in the lab of Prof Katherine Vallis

Deadline: 6th January 2017

http://www.oncology.ox.ac.uk/project/6-development-antibody-based-imaging-and-therapeutic-agents-directed-against-cancer-testis

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British Andrology Society

American Society of Andrology

DGA Deutsche Gesellschaft für Andrologie e.V.