Network for Young Researchers in Andrology
International Network for Young Researchers in Male Fertility

Spring edition - 2017

NYRA Newsletter

In this issue:

Main responsible for this issue:
Pablo Hurtado Gonzalez
Dorte Egeberg Palme
Jennifer Muth

Greetings

Dear NYRA member,

Spring is finally here and we hope this newsletter is interesting enough to have a break from the flowers and the sun.
In this issue we have gathered new exciting press highlights about long non-coding RNAs in mouse sperm and the first sperm quality results in man conceived by intracytoplasmic sperm injection (ICSI). Furthermore, we bring you personal insights from a medical doctor working both with "hard-core" science and patients. And finally, you will also find an interesting historical tale about ICSI, and a lot of important dates to mark in your calendar. Enjoy your reading!

Cheers,
The NYRA board

NYRA Bulletin

We are happy to announce that the registration for our 10th meeting is now open. This year the meeting will take place September 11th to 13th in Brussels, the cradle of ICSI. We have invited Prof. Herman Tournaye (University Hospital Brussels, Belgium), and Prof. Ewa Raipert-De Meyts (University Hospital Copenhagen, Denmark) to update us on the future of men in reproduction and on testicular dysgenesis syndrome. And to broaden our perspectives, Prof. Stefan Schlatt (University of Muenster, Germany) will give an overview about the available *in vivo* and *in vitro* models to study testicular function.
Furthermore, to maximize interaction between young researchers, at least 10 abstracts will be selected for an oral presentation during this 3-day meeting. For more information about the program, the registration and abstract submission deadlines, please see our website: www.youngresearch.eu

Network for Young Researchers in Andrology
International Network for Young Researchers in Male Fertility

Spring edition - 2017

NYRA Newsletter

Press Highlights

Systematic identification and characterization of long non-coding RNAs in mouse mature sperm

Sperm cells have generally been considered to be transcriptionally and translationally inert due to the high sperm chromatin condensation. Early studies suggested that the few RNAs detected in the paternal gamete were left overs with no biological function, or contaminants from surrounding cells. However, a rapidly growing number of papers have proven this wrong. Recently both tsRNAs and miRNAs in sperm cells have shown to play a role in paternal heredity of diet-induced obesity and metabolic disorders. And now in a recent *PLOS one* article, the group of Xuhui Zeng, at the Nanchang University in Nanchang, China, have systematically described long non-coding RNAs (lncRNAs) present in mouse mature sperm.

In the present study, Zhang and colleagues collected and purified sperm from 8-week old mice vas deferens and caudal epididymides, and extracted total RNA. The RNA was fragmented to about 140-160 nt and converted into a DNA library through end repair, adaptor ligation, reverse transcription circularization, and PCR amplification. The library was sequenced by a strand-specific transcriptome deep sequencing approach. Lastly the high-quality clean reads were aligned to reference sequences using the SOAPaligner/SOAP2 software, and gene expression levels were calculated using the FPKM method (fragments per kilobase transriptome / million mapped reads). Based on the ”Cis and Trans” RNA-RNA interaction principle targeted coding genes of differently expressed lncRNAs were found. GO analysis (http://www.geneontology.org) and the KEGG database (Kyoto Encyclopedia of Genes and Genomes) were applied to illustrate the function of the differentially expressed lncRNA via the function or implicated signalling pathway of the targeted genes. In the end the expression of few lncRNAs were verified by RT-PCR, FISH-staining and qPCR.

With this approach, Zhang and colleagues identified 20,907 known lncRNA transcripts from 18,422 known annotated lncRNA genes and predicted 4,088 novel lncRNA transcripts in mature mouse sperm. Furthermore, they found that the number and average expression level of lncRNAs were higher than those of mRNAs in mature sperm. Comparison of the found lncRNA library to libraries of heart, hippocampus, liver, lung, spleen, and thymus revealed that 6,983 (3,575 annotated lncRNA and 3,408 predicated novel lncRNA) were exclusively expressed in testis and sperm. In addition, by comparing to earlier identified lncRNA and mRNA expression levels in round spermatids, Zhang and colleagues identified 4,040 upregulated lncRNAs and 4,261 downregulated lncRNAs, and 1,280 upregulated mRNAs and 3,619 downregulated mRNAs, which furthers the idea that lncRNAs have potential functions in mature sperm. However, the exact regulatory effects of lncRNAs on spermatogenesis and sperm function remains elusive and is indeed a topic worthy for deeper investigation.

Zhang X, Gao F, Zhang P, Wang Y, Zeng X (2017). **Systematic identification and characterization of long non-coding RNAs in mouse mature sperm.** *PLoS ONE* 12 (3): e0173402.

Did you know?

LncRNAs are defined as non-protein coding RNAs longer than 200 bp. They are regulatory molecules that modulate a wide variety of functions and are involved in pathophysiologic processes and human diseases.

Network for Young Researchers in Andrology
International Network for Young Researchers in Male Fertility

Spring edition - 2017

NYRA Newsletter

Reproductive health status of young adult ICSI offspring: the first results

ICSI is routinely used in couples with difficulties in conceiving due to severe male factor infertility. However, there are reasonable concerns that male offspring may inherit the deficient spermatogenesis from their fathers. Previously, normal pubertal development, intact Sertoli and Leydig cell function as well as comparable levels of inhibin B and testosterone have been described in pubertal ICSI boys when compared to spontaneously conceived peers. In contrast, information on the gonadal function and sperm quality of ICSI offspring in adulthood remained inconclusive.

As the worldwide oldest ICSI offspring have recently reached young adulthood, the first results on the health status of these men were published by a research group from Brussels. Belva and colleagues conducted a study between March 2013 and April 2016 at the Universitair Ziekenhuis Brussel (UZ Brussel), which is part of a larger follow-up project focusing on reproductive parameters of young adults between 18 and 22 years that were conceived after ICSI. In particular, they investigated the semen quality and reproductive hormone levels (FSH, LH, inhibin B and testosterone) and compared them to men that were born after spontaneous conception.

Young ICSI adults showed significantly lower sperm concentration, total sperm count and total motile sperm count in comparison to controls. Overall, the risk of having sperm concentration and total sperm counts below the World Health Organization (WHO) reference values (15 million/ml and 39 million, respectively) is increased in ICSI offspring compared to controls. In addition, Belva *et al.* wanted to investigate whether poor sperm quality in the fathers were predictive for the sperm quality of their sons. By correlating the semen parameters of ICSI men with those of their fathers at the start of their ICSI treatment 20 years ago, they did not find a clear correlation between the semen parameters of the ICSI men and their fathers, e.g. only 40% of the fathers with total sperm count < 39 million had sons with total sperm count < 39 million.

Regarding the hormone values, no statistically differences were observed between mean levels of FSH, LH, testosterone and inhibin B of ICSI adults in comparison to the control group. However, it was demonstrated that young adult men born after ICSI are more likely to have inhibin B levels below the 10th percentile and FSH levels above the 90th percentile. Further, inhibin B and FSH were shown to consistently correlate with semen characteristics including sperm concentration and total sperm count, which corroborates the previous findings.

The studies were mainly limited by their small study population (54 ICSI men) and the specific background of the participants (male factor infertility). Nowadays, the indications for ICSI have been extended, *e.g.* ICSI is also being performed with non-ejaculated sperm. Thus, a generalization of the results cannot be made to all offspring born after ICSI.

In summary, Belva and colleagues present the first results on semen quality and reproductive hormones in a small group of ICSI men, indicating reduced sperm quantity and quality as well as conspicuous hormone parameters in young adults born after ICSI for male infertility in their fathers. Larger studies are required to confirm these findings.

References:

1) Belva F, Bonduelle M, Roelants M, Michielsen D, Van Steirteghem A, Verheyen G, Tournaye (2016). **Semen quality of young adult ICSI offspring: the first results.** *Hum Reprod* 31(12):2811-2820.

2) Belva F, Roelants M, De Schepper J, Van Steirteghem A, Tournaye H, Bonduelle M (2017). **Reproductive hormones of ICSI-conceived young adult men: the first results.** *Hum Reprod* 32(2):439-446.

Network for Young Researchers in Andrology
International Network for Young Researchers in Male Fertility

Spring edition - 2017

NYRA Newsletter

Tête-à-tête with Rod Mitchell

Rod is a Group Leader within the MRC Centre for Reproductive Health at the University of Edinburgh. He is also a Consultant Paediatric Endocrinologist at The Royal Hospital for Sick Children in Edinburgh.

His research interests are focused on the role of the germ-stem cell niche on germ cell development in the fetal and early postnatal testis.

To know more, follow him on twitter!: https://twitter.com/RodTMitchell

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

I am not sure I did! It wasn't really planned. My PhD was in fetal germ cell development which gave me an insight into germ cells and fertility. I was also interested in the effects of in-utero environmental and pharmaceutical exposures on male reproductive health. Also, given my background in Paediatric Endocrinology I had developed a clinical and research interest in fertility preservation for prepubertal boys with cancer. This combination made a career in male fertility unavoidable!

Can you name the greatest success(es) in your career?

Switching from full-time Clinician to Clinician Scientist and establishing a research group was a challenge and I hope would be considered a success! I think establishing the first UK clinical and research service for fertility preservation in prepubertal boys is also a success as this may offer our male cancer patients some optimism for the future.

Can you name a moment of failure (and which lesson did you learn with it)?

I could name several, although I guess that if you learnt from it then it wasn't a failure! I have had all the usual setbacks, the paper that didn't get into the journal you hoped for, the grant that you were proud of that didn't get funded, the experiment that didn't live up to its promise. But the 'ups and downs' are part and parcel of a career in science and the thing you learn is to try and handle this better.

Which advice(s) would you give to young researchers in Male Fertility?

I would advise you to put yourself out there, be enthusiastic, always try and seek out new opportunities even when they are not obvious or easy. Have a plan but be prepared to change it if something new and exciting comes up. Most importantly - When you experience 'failure'...keep the faith. When you experience 'success'...ENJOY IT!

What do you think about the collaborative work between clinicans and basic researchers in Andrology? What works well and what could be improved from your point of view?

Collaboration between clinicians and scientists is crucial particularly for a clinically relevant subject such as Andrology. Combining expertise from both sides and meeting in the middle is the key and I would say generally this works well. Interpreting laboratory findings in terms of human and clinical relevance is certainly an area that we could improve.

Network for Young Researchers in Andrology
International Network for Young Researchers in Male Fertility

Spring edition - 2017

NYRA Newsletter

The history of ART: *Intracytoplasmic Sperm Injection*

By 1990, around 90,000 babies were born thanks to IVF. However, many doctors and couples had already realized that a large number of cases showed reduced treatment efficiency, usually related with male infertility. When the semen showed low level of sperm (<500,000 sperm) and these sperm had visible differences in morphology and motility, oocytes were not fertilized in the same proportion as the ones from other couples. This meant fewer formation of embryos and hence, more difficulties in achieving the final goal of pregnancy.

It was not until the end of the 80s that the first groups started to experiment with different techniques to overcome these difficulties. One of the first techniques developed was partial zona dissection (PZD), where the oocyte zona pellucida was carefully disrupted in order to create a small opening, allowing the sperm to access the plasma membrane of the oocyte directly. PZD resulted in a number of successful pregnancies during the period of study. However, this technique was quickly discarded as a result of a high inconsistency.

Other laboratories tried a more successful method called subzonal insemination (SUZI). In this technique, a small number of motile sperm were microinjected inside the perivitelline space. Although more consistent than PZD, SUZI still produced a small number of fertilized oocytes, around 15-20%.

After the development of these techniques, it was then the turn for intracytoplasmic sperm injection (ICSI), where a single motile sperm is injected directly into an egg. Different groups started this challenging research. Some of them were able to fertilize eggs, although these had problems to undergo a normal development. But in 1992 the first group announced a successful birth of a child conceived by ICSI. This goal was achieved by Gianpiero Palermo at the Center for Reproductive Medicine, UZ Brussel and Free University of Brussels.

Since then, the technique has been widely and successfully used for egg fertilization. To date, hundreds of thousands of babies have been born worldwide thanks to this technique, showing an exponential growth curve. As a result of the high fertilization success rates seen in ICSI, this technique is now more commonly used than traditional IVF techniques. However, this has attracted a degree of concern due to the lack of sperm selection present in ICSI in comparison with IVF.

References:

1) Devroey P and Van Steirteghem A (2004). **A review of ten years experience of ICSI**. *Hum Reprod Update* 10 (1): 19-28.
2) https://en.wikipedia.org/wiki/intracytoplasmic_sperm_injection
3) http://www.hfea.gov.uk/ivf-figures-2006.html
Svalander P *et al*. (1994) **Subzonal insemination (SUZI) or in vitro fertilization (IVF) in microdroplets for the treatment of male-factor infertility**. *J Assist Reprod Genet* 11 (3):149-55.

NYRA Newsletter

Scientific colloquia: mark your calendar!

33rd Annual Meeting of ESHRE Geneva (Switzerland), 2nd-5th July 2017 ***https://www.eshre2017.eu/***	**Registration OPEN**
Annual meeting of the Canadian Fertility and Andrology Society Vancouver (Canada), 14th-16th September 2017 ***https://cfas.ca/events/vancouver-2017/***	**Registration OPEN**
GRC in germinal stem cell biology Hong Kong, 18th-23rd June 2017 **http://www.grc.org/programs.aspx?id=15863**	**Registration/ Abstract deadline 21st May 2017**
4th world congress in reproductive biology (WCRB2017) Okinawa (Japan), 27th-29th September 2017 **http://www.wcrb2017.jp/date.html**	**Registration OPEN**
5th World Congress of the International Society for Fertility Preservation Vienna (Austria), 16th-18th November 2017 ***http://www.isfp2017.cme-congresses.com/***	**Abstract submission deadline 1st October 2017**

Network for Young Researchers in Andrology
International Network for Young Researchers in Male Fertility

Spring edition - 2017

NYRA Newsletter

Jobs Ads & Funding Prospects

PhD positions

Edinburgh medical school, University of Edinburgh, Scotland, United Kingdom

Human masculinisation disorders: investigation of mechanistic origins using an animal model

Deadline**: 1st of June 2017**

http://www.ed.ac.uk/biomedical-sciences/postgraduate-studying/phd-research-programmes/university-of-edinburgh-career-development-phd

PhD positions

CELLS IN MOTION Cluster of Excellence Graduate School

International Max Planck Research School Molecular Biomedicine and Cells in Motion Graduate School

Joint PhD program of the University of Münster and the Max Planck Institute for Molecular Biomedicine

16 PhD Positions in Münster (Germany): Imaging Cellular Processes and Disease

The joint graduate program of the **Excellence Cluster Cells in Motion** (CiM) and the **International Max Planck Research School – Molecular Biomedicine** (IMPRS-MBM) offers positions to pursue PhD projects in the areas of **biology, chemistry, physics, mathematics or computer science**. We are looking for young scientists with a vivid interest in **interdisciplinary** projects to **image cell dynamics** from the **subcellular to the patient level**. PhD projects range from the analysis of basic cellular processes to clinical translation, from the application of novel biophysical approaches and the generation of mathematical models to the development of new imaging-related techniques and compounds.

For online application and further information go to

www.cim-imprs.de

Highlighted website

Are you looking for a travel grant for your next conference? Check out this website! You can apply to get funding for the next NYRA meeting in Brussels.

More info here: http://www.tebu-bio.com/cms/1081/Get_your_400EUR_tebu_bio_Travel_Grant.html

facebook **Follow us!!** LinkedIn **http://www.youngresearch.eu/**

Collaborating societies

E·A·A · British Andrology Society · American Society of Andrology · DGA Deutsche Gesellschaft für Andrologie e.V.