International Network for Young Researchers in Male Fertility

Summer edition - 2016

INYRMF Newsletter

In this issue:

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Greetings

Dear INYRMF member,

Welcome to our Summer newsletter 2016!
In this sun-filled edition, we offer several pleasant readings to be perfectly enjoyed while drinking a glass of freshly brewed ice tea!
To begin with, we are proud to describe the great success achieved during the last satellite INYRMF meeting held in Rennes, France. Following, we provide an overview on the latest discoveries about the structure beyond sperm-egg interaction and the role of the Nuclear Factor-Y B (NF-YB) in spermatogonial stem cell self-renewal and proliferation in freshwater flatworms. Lastly, enjoy the interview with Dr Rajpert-De Meyts and our Memoirs dedicated to the the discoverer of the homonymous cells, Franz von Leydig.
With Science, Sea and Sun, might your Summer be much Fun!

The INYRMF board

INYRMF Bulletin

Our 9th meeting is well over – we hope that you enjoyed it as much as we did. It took place in Rennes, France (9th-10th June, 2016) and was mainly organized by Dr Pierre Calvel and Thomas Darde. The meeting was a great success and we wish to thank all participants for contributing to that. The scientific quality of the young researchers' talks and discussions was really appreciated! If you want to know more about this meeting, you will find a report on our webpage. A unique feature of this meeting was the celebration of the 10th anniversary of our network with a special program combining presentations from experts in our field with talks given by young promising scientists. We also proposed open debates during where the participants had the opportunity to discuss "Ethics in Biology of Reproduction" and "Past, present and future perspectives for reproductive biology and male fertility" in depth with the invited experts. As a special tribute, three PhD students were granted free registration to the ETW. Furthermore, Anna-Lena Hempfling, PhD fellow at the University of Giessen, was awarded a prize sponsored by the International Society of Andrology for the best oral presentation during our meeting. Again, a very special thanks to Pierre Calvel and Thomas Darde, for organizing such a great event! Next year our meeting will take place in Brussels. Hopefully we will see you there ☺

Anna-Lena Hempfling (left) was awarded for the best oral presentation. Here together with INYRMF president Alexandra Amaral (right).

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Press Highlights

When sperm meets egg: the structure behind.

Human fertilization is enabled by the interaction between two proteins: IZUMO1, which is produced by sperm, and JUNO, its receptor on eggs. However, the details of this interaction have been elusive so far. Last June, two papers in *Nature* have shed some light on this issue by presenting the structures of IZUMO1, JUNO and the two proteins in complex, determined by X-ray crystallography at atomic-level resolution. IZUMO1 was first identified in 2005 by its binding to an antibody that blocked sperm–egg fusion. The protein remains concealed at the intracellular level in the inner acrosomal membrane until the acrosome reaction occurs, when the inner membrane becomes part of the cell surface. JUNO was identified almost a decade later as a membrane-anchored protein that is required for female fertility, sperm–egg membrane fusion, and egg binding by IZUMO1. However, structures of the extracellular domain of IZUMO1, human JUNO and the JUNO–IZUMO1 complex remained unknown until now.

Aydin *et al*.[1] and Ohto *et al*.[2] have solved the structures of these two proteins. Both groups found that the extracellular region of IZUMO1 has two domains — a four-helix bundle at the protein's amino terminus and an immunoglobulin-like domain at the carboxy terminus. The two domains are connected by a hinge region consisting of a β-hairpin structure with loops at either end that are anchored to the two folded domains by disulfide bonds. The researchers show that IZUMO1 and JUNO form a high-affinity complex: in fact, a surface of JUNO distant from the pocket binds the outside of the hinge and makes contacts with both IZUMO1 domains. Ohto and colleagues crystallized structures of free and JUNO-bound IZUMO1 in the same elongated conformation. By contrast, Aydin *et al.* report that IZUMO1 alone adopts a boomerang-shaped conformation, in which the hinge is almost 40° more closed than that of JUNO-bound IZUMO1.

The authors validated the approximate shape using a technique known as small-angle X-ray scattering, providing low-resolution structural information about the protein in solution and thereby avoiding potential conformational biases that can arise in X-ray crystallography owing to crystal packing. These data indicate that the boomerang-shaped conformation is probably the predominant conformation of IZUMO1 in solution. Moreover, although JUNO binds to the outer hinge surface, the region most strongly stabilized by this binding seems to be inside the hinge. This suggests that the hinge can adopt different positions in IZUMO1 alone, but that JUNO fixes the conformation of IZUMO1 by simultaneously binding to both domains. Ohto and colleagues introduced genetic mutations into mouse Izumo1 that strongly reduced the affinity of the Izumo1–Juno interaction. Expression of wild-type mouse Izumo1 in monkey kidney cells (which do not normally express Izumo1) enabled these cells to bind efficiently to mouse eggs that lacked the zona pellucida, whereas cells that expressed the mutant protein could not. These results clearly confirm the interface identified in these structures and its importance in mediating sperm–egg interaction.

Curiosity spot!

IZUMO1 was named after a Japanese marriage shrine.
JUNO was named after the Roman goddess of love and marriage.
So Romantic!

References:

1) Aydin,H.,Sultana,A.,Li,S.,Thavalingam,A.&Lee,J.E. (2016). **Molecular architecture of the human sperm IZUMO1 and egg JUNO fertilization complex**. *Natur*e Jun 15;534(7608):562-565.

2) Ohto U, Ishida H, Krayukhina E2 Uchiyama S, Inoue N, Shimizu T. (2016). **Structure of IZUMO1-JUNO reveals sperm-oocyte recognition during mammalian fertilization**. *Nature* Jun 15;534(7608):566-569.

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Blood-flukes contain genes required for sperm production.

Gametes are the source and carrier of genetic information, essential for the propagation of all sexually reproducing organisms. Male gametes are derived from a progenitor stem cell population called spermatogonial stem cells (SSCs). SSCs give rise to male gametes through the coordination of two essential processes: self-renewal to produce more SSCs, and differentiation to produce mature sperm. Disruption of this equilibrium can lead to excessive proliferation of SSCs, causing tumorigenesis, or can result in aberrant differentiation, leading to infertility. Spermatogenesis is a highly prolific process, relying on SSCs for continual production of progeny. Intuitively, the maintenance of the fine balance between SSCs self-renewal and differentiation is of fundamental importance. Moreover, understanding the mechanisms of SSCs maintenance is crucial for the treatment of several physiological and disease conditions.

To better understand how SSCs maintain this balance, Iyer and collegues[1] studied a planarian (*Schmidtea mediterranea*) male germ cell-specific transcription factor, Nuclear Factor-Y B (NF-YB), which is required for the maintenance of early planarian male germ cells. They demonstrated that NF-YB plays a role in the self-renewal and proliferation of planarian SSCs, but not in their specification or differentiation. Using RNA interference (RNAi), researchers lowered the expression of the gene and showed that it is necessary for SSC proliferation: for instance, *NF-YB(RNAi)* resulted in progressive loss of male germ cells in *S. mediterranea* starting from the stem cell population. They repeated the experiment in the planarian's parasitic cousin, *Schistosoma mansoni*, commonly known as blood-fluke, which is a causative agent of schistosomiasis, one of the major neglected tropical disease.

In the first instance, they found that the function of NF-YB in regulating male germ cell proliferation is conserved in schistosomes. Upon schistosome NF-YB suppression, they observed the same effect as in the planarian, i.e. a loss of proliferating cells in the parasite testes. The authors provide several explanations to this observation. SSCs may be undergoing apoptosis but the signal may be too weak or transient to be detected, or they may use a non-apoptotic mechanism of cell death. It is also possible that the early germ cells could be entering the differentiation pathway aberrantly, resulting in apoptosis of the differentiating cells.

According to the authors, the relevance of their data lies beyond the fact that the reproductive output of *S. mansoni* is the primary cause of the morbidity associated with schistosomiasis. They believe that their findings can help elucidate the complex relationship between self-renewal and differentiation of SSCs in mammals, also with beneficial implications for understanding and controlling schistosomiasis.

Curiosity spot!

Unlike other trematodes, schistosomes are **dioecious**, with distinct sexual dimorphism between male and female.

References: Iyer H, Collins JJ , Newmark PA. (2016). **NF-YB Regulates Spermatogonial Stem Cell Self-Renewal and Proliferation in the Planarian Schmidtea mediterranea.** *PLOS Genetics* Jun Jun 15;12(6):e1006109.

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Tête-à-tête with experts: Ewa Rajpert-De Meyts

Ewa Rajpert-De Meyts, MD, PhD, DMSc, is a senior scientist and research director at the Department of Growth & Reproduction of the main research hospital (Rigshospitalet) of Copenhagen University, in Denmark. Her background is in medicine (she graduated from Silesian Medical University, Poland, where she also trained as paediatrician) but most of her career has been spent in research. She first trained in basic endocrinology, with focus on glucocorticoid receptors (the topic of her PhD), at the International Institute of the Cellular & Molecular Pathology (ICP, currently de Duve Institute) in Brussels, Belgium. She subsequently spent more than 3 years training in molecular biology of gamma-glutamyl transpeptidases in the Division of Medical Genetics, Children's Hospital & University of Southern California, Los Angeles, USA. Finally, she relocated to Denmark and since 1991 has been studying developmental aspects of human reproduction, germ cell pathobiology and testicular cancer.

Ewa contributed to more than 250 scientific publications. She was the main organizer of several international meetings, including a series of Copenhagen Workshops on Germ Cell Cancer, and the 18th European Testis Workshop held in 2014 in Elsinore (Helsingør), in Denmark. Lastly, she served as the last Editor-in-Chief of *International Journal of Andrology,* and since 2012 as co-Chief-Editor of *Andrology*, the merger of *IJA* with its American counterpart, *Journal of Andrology*.

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

My path to this field was a bit accidental, as I looked for a new field of study after relocating from California to Denmark, where I followed my Belgian husband. I knew though that my new field had to be related to endocrinology and development, because of my previous background, but did not think about male fertility at the beginning. I was lucky that my CV attracted the attention of my mentor, Professor Niels E. Skakkebæk at the Copenhagen University Hospital, a world-famous scientist, who suggested that I take on germ cell cancer. I have not looked back since and still feel fascinated by this unusual cancer. Its uniqueness is linked to its origin from germ cells – arguably the most interesting cells in the body – and to the developmental pathogenesis of this cancer. As most of the INYRMF members probably know, men with impaired fertility, especially linked to disruption of testicular development have a highly increased risk of germ cell cancer. That way I got interested in germ cell function in general, as well as in genetic disorders linked to male infertility.

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

In the real world only few scientists experience a carrier-changing great success, such as a ground-breaking discovery. Most often the success is measured by smaller achievements, usually obtained in a team work with likewise thinking and driven individuals. I was lucky to work in a couple of such teams, especially in my own department, but also during collaborative projects with other groups. I contributed to defining the origin of the most common testicular cancer from fetal germ cells that failed to develop properly. I also helped to dissect

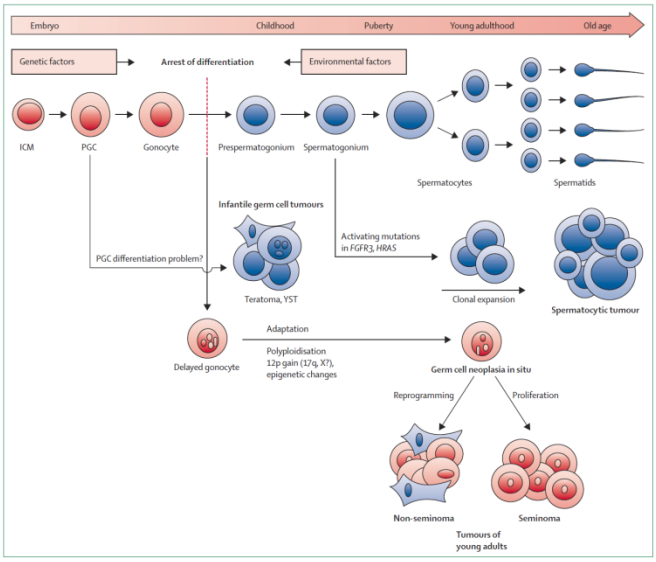
other mechanisms leading to germ cell malignancy. I consider these small discoveries leading to the understanding of the germ cell cancer pathogenesis as my greatest achievement. I have to mention also here that I consider a personal success if a young researcher, whom I train advances to the next step of career in science, especially young women, whose road to scientific independence is still a bit more difficult than that of men.

Can you name a moment of failure and explain which lesson you learned from it?

Moments of failure are quite frequent in a scientist's life – you will all experience failed experiments, wrong interpretation of data, as well as rejected grant applications and manuscripts. Each failure is a lesson – just pause to think about what happened and try to find a logical explanation for what went wrong. Then repeat the experiment, find a new interpretation, resubmit the paper ….

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

My answer to this question follows the previous one. If you choose a career in science you need a hefty dose of perseverance and enthusiasm, to deal with small failures and to enjoy every successful experiment and each discovery, no matter how small. These small daily discoveries and the feeling of creating something new will keep you going. You also need to be curious and always think about the next step, but not before confirming in another way what you have found so far. At the early stage of your career, try to learn as much as you can from your mentors and older colleagues. Do not be afraid to ask questions and remember to check the literature – very often someone 'has been there and done that', including your senior colleagues in the lab, saving you some unnecessary efforts. But do not always follow your mentor's advice, if you feel that your idea is better – go for it. You also need a collaborative spirit – do not try to compete with your colleagues in the lab – work together and you will get the results faster. It is also sweeter to share the joy of achieving something together with your colleagues. Finally, every young scientist ought to change topics of research and labs at least a couple of times, preferably including travel abroad – just as I did. That will not only teach you how to deal with different cultures and approaches, but also broaden your horizons immensely, so you will think more out of the box while looking how to solve challenges.



During her scientific life, Ewa Rajpert-De Meyts contributed to the understanding of the pathogenesis of testicular cancers originating from fetal germ cells that fail to develop properly.
Figure from Rajpert-De Meyts E, McGlynn KA, Okamoto K, Jewett MA & Bokemeyer C (2016). **Testicular germ cell tumours**. *Lancet* Apr 23;387(10029): 1762-74.

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Memoirs: Franz von Leydig – pioneer of comparative histology

Franz von Leydig (source: ref 1)

At the age of 13 Franz von Leydig became the proud owner of a microscope and 36 years later he had published extensively morphological descriptions of anything that could "crawl or walk" of his surroundings, including the interstitial cell in the testis.

In 1821, Franz von Leydig was born in Rothenburg ob der Tauber (on the Tauber river), Germany. His father was a public official but also known as a keen gardener and beekeeper and it is probably from here Leydig's interest for botany and zoology was founded. Leydig's academic career began in 1840 with the completion of *Biennium Philosophicum*, a 2 year long period of general studies for students in Bavaria at the Philosophical Faculty in Würzburg and in Münich. Hereafter he started his studies in medicine in 1842 at the University of Würzburg. During his medical studies he became a teaching assistant at lessons on microscopic anatomy and the access to microscopes surely facilitated Leydig's own histological studies. In 1847 he received his medical doctorate degree with the dissertation entitled: "Yolk cleavage in the animal world and its significance".

Leydig stayed in Würzburg for several years and paved his way to a professorship. It was during these years that Leydig described the histology of male reproductive organs, including some cells lying in clusters between the seminiferous tubules, in a variety of species, i.e. primates, bats, marsupials, rodents, pigs and horses etc. Leydig, however, had no idea of the endocrine nature of these cells – now known as Leydig cells.

In 1857 Leydig became a professor of Zoology and Comparative Anatomy at the University of Tübingen and here he published his most important work, the book "Lehrbuch der Histologie des Menschen und der Tiere" (Handbook of the histology of man and animal). This book includes an introduction to the history of histology together with vast morphological descriptions of vertebrates and invertebrates, including a description of the Leydig's organ found in fish and larvae. Some attributed him with the title of "The father of comparative histology" for this work.

Leydig retired in 1887 from his position at the University of Bonn. However until his death in 1908, Leydig kept his curiosity for the field. He kept on visiting his former colleagues at University of Würzburg to learn the new histological techniques of tissue cutting and staining, e.g. the use of a microtome. But he also published more than 40 scientific articles and his book of reminiscence (*Horae Zoologicae*) during these years.

References: 1) Schneider MR, **Franz von Leydig (1821–1908), pioneer of comparative histology (2012)**. Journal of Medical Biography 20: 79–83
2) *Contemporary Endocrinology: The Leydig Cell in Health and Disease*. Edited by: A.H. Payne and M.P. Hardy . 2007 Humana Press Inc., Totowa, New Jersey

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Highlighted websites

http://www.howstuffworks.com

HowStuffWorks got its start in 1998 at a college professor's kitchen table. From there, it quickly grew into an award-winning source of easy-to-understand answers and explanations of how the world actually works.

Scientific colloquia: mark your calendar!

Mammalian Reproduction Gordon Research Conference
Waterville Valley, (USA,NH), 21st – 26th August, 2016
https://www.grc.org/programs.aspx?id=16762

Online Registration Is now OPEN

The 20th World Meeting on Sexual Medicine, Global Chinese Andrology and Sexual Medicine Congress
Beijing (China), 22nd – 25th September 2016
http://www.wmsm.org

Online Registration Is now OPEN

9th *European Congress of Androloy*
Rotterdam (The Netherlands), 17th – 23rd September 2016
http://www.ecacongress2016.com
Please indicate at registration that you are a member of INYRMF

Online Registration Is now OPEN

American Society of Reproductive Medicine Scientific Congress and Expo
Salt Lake City (USA), 15-19 October 2016
www.asrmcongress.org

Early bird rates until 1th of September 2016

Jobs Ads & Funding Prospects

Post-doctoral Fellowships

Research Associate - Baumann Lab (Kansas City, KS, USA)

Two postdoctoral positions are available in the lab of Peter Baumann to study the evolution and molecular mechanism of parthenogenesis in vertebrates.

Project 1: Cellular and molecular basis of parthenogenesis

Project 2: Hybridization, Ploidy and Regulation of Gene Expression

Deadline: 10th September, 2016

http://www.nature.com/naturejobs/science/jobs/580451-postdoctoral-position-in-gametogenesis

PhD position

MRC Centre for Reproductive Health (CRH), Edinburgh, UK

3-year PhD programme in reproductive health

Deadline: none.

http://www.ed.ac.uk/studying/postgraduate/degrees

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