University Hospital of Münster . Centre of Reproductive Medicine and Andrology . Dept. of Clinical and Surgical Andrology . 48129 Münster

Centre of Reproductive Medicine and Andrology

Department of Clinical and Surgical Andrology

Professor Sabine Kliesch, M. D.
Chief Physician

Postal address:
Albert-Schweitzer-Campus 1, Building D11,
D-48129 Münster

Street address:
Domagkstraße 11, D-48149 Münster

T +49 251 83-56096 / 56097
F +49 251 83-56093
Operator: T +49 251 83-0

sabine.kliesch@ukmuenster.de
www.ukmuenster.de

Münster,

Report of the Centre of Reproductive Medicine and Andrology (CeRA) of the University Hospital of Münster and the University of Münster, Germany, as an EAA Training Centre, reporting period 2014 – 2017

Date of report:
January 25, 2018

Centre of Reproductive Medicine and Andrology and Institute of Reproductive and Regenerative Biology:
Director: Prof. Dr. rer. nat. Stefan Schlatt since July 1, 2008

Department of Clinical and Surgical Andrology:
Chair: Prof. Dr. med. Sabine Kliesch since June 1, 2008
Director of the EAA Training Centre

Address of Centre:

Albert-Schweitzer-Campus 1, Gebäude D11 (Domagkstr. 11)
48149 Münster
Germany

Contact Details of the Heads of the Clinical and Basic Research Units:

Professor Kliesch
phone: +49/2 51/83-5 60 97
fax: +49/2 51/83-5 60 93
e-mail: sabine.kliesch@ukmuenster.de / andrologie@ukmuenster.de
URL: https://www.ukm.de/index.php?id=repro_uebersicht

Professor Schlatt
phone: +49/2 51/83-5 60 99
fax: +49/2 51/83-5 48 00
e-mail: stefan.schlatt@ukmuenster.de
URL: https://www.medizin.uni-muenster.de/cera/

The Centre of Reproductive Medicine and Andrology was initially recognized as an EAA Training Centre in 1994 and subsequently re-evaluated in 2001, 2010 (site visit) and 2014. The Centre consists of two main institutions, the Institute of Reproductive and Regenerative Biology (IRRB) and the Department of Clinical and Surgical Andrology. The recognition for Specialized Surgical Treatment was granted by the University Hospital Münster in 2016. The Department of Clinical and Surgical Andrology is responsible for patient care, medical training of clinical andrologists, andrological teaching of medical students as well as clinical research. In addition to the andrological, endocrinological and urological work-up of andrological patients, the CeRA is responsible for the andrological and embryological aspects of the IVF laboratory. The Fertility Centre of the University Hospital functions as a collaboration of the Department of Gynecology and Obstetrics of the University Hospital and our Centre. This report covers the period from June 2014 until now. Since 1986, the Centre has been and continues to be a WHO Collaborating Centre for Research in Male Reproduction.

The last annual report was submitted and renewal of WHO – CeRA relationship was granted in 2017. Since 1999, the Centre runs a Quality Management Program and was constantly accredited (ISO 9000-2) by TÜV Rheinland for the fields of Andrology, Endocrinology, Reproductive Medicine and Urology. Last renewal occurred in February 2017.

Present staff

The staff of the Centre underwent major changes in the past three years.

Prof. Dr. rer. nat. Timo Strünker was awarded the position of Full University Professor in Molecular Reproductive Physiology. Professor Strünker is a basic researcher and PhD in Biochemistry (University of Cologne). He obtained postdoctoral training at the Helmholtz Research Center Jülich, Jülich, Germany and in pharmaceutical industry (Grünenthal). He acted as independent research group leader of the "Sperm Physiology" group at the Max Planck Research Center Caesar in Bonn, Germany before he accepted the position at the University of Münster and started his new research group in summer 2015.

Prof. rer. nat. Jörg Gromoll, Prof. Dr. med. Michael Zitzmann, Dr. rer. nat. Jochen Wistuba, Dr. med. Claudia Krallmann, Dr. med. Jann-Frederik Cremers (since March 2017), PD Dr. rer. nat. Verena Nordhoff (since 2017) and PD Dr. med. Julia Rohayem (since Jan 2018) have permanent positions. Professor Gromoll, Dr. Wistuba and PD Dr. Nordhoff are part of the IRRB, Professor Zitzmann, Dr. Krallmann, Dr. Cremers and PD Dr. Rohayem belong to the Clinical Department. Dr. Cremers joined the CeRA in 2016, other new physicians are the urologists Alexander Sahi (2016), Dr. Johannes Golsong (2017), Dr. Bettina Scheffer (2017). 8 research assistants, 9 medical doctors, 7 post-graduates, 13 technical assistants and 10 (patients´) secretarial staff as well as 2 animal caretakers comprise the rest of the Centre and are distributed within the two institutions as detailed in Table 1. Altogether, 20 positions are funded by the University, 23 are funded by the University Hospital, and the others are funded as specified in Table 1.

Professor Kliesch was Secretary of the Board of the German Society of Andrology (DGA) from 2007 – 2013 and of the German Society of Urology (DGU) from 2008 – 2015, responsible for public relations of the Society. She still is Head of the Working Group Andrology and the Patient Academy of the DGU. Since 2010 she has been a member of the advisory board for men's health of the Federal Centre for Health Education (Bundeszentrale für gesundheitliche Aufklärung, BZgA). Moreover, she acts and has recently been re-elected as Head of the Quality Control Program of the German State Medical Board (Bundesärztekammer, BÄK) for Semen Analysis and member of the German State Medical Board Quality Control Program for Laboratory Diagnostics. She is elected member of the German Society of Cancer Diseases (DKG, Deutsche Krebsgesellschaft) and represents the Working Group for Urologic Cancer. She is the Spokeswoman of the Interdisciplinary German Testicular Cancer Study Group of the DKG. Since 2017 she has been the responsible coordinator for the German Society of Urology to build up the first evidence-based Guideline on Germ Cell Tumors of the AWMF and DKG program (S3 Guideline). Since 2011 she is Guidelines Office panel member and co-author of the Guideline on Male Hypogonadism of the European Association of Urology. She is part of the interdisciplinary organizing and writing committee of the Guideline on Fertility Protection in Oncological Diseases that was accomplished in 2017 and will be published online in 2018 by the AWMF as a consensus guideline (S2k). She is the Director of the WHO Collaboration Center Münster and Director of the EAA Training Centre Münster.

Professor Schlatt has acted as Secretary of the International Society of Andrology (ISA) from April 2009 – 2017. He is member of the Board of the German Society of Andrology (DGA). He has been spokesman of the male subgroup of the ESHRE Task Force on fertility preservation and coordinator of the Special Interest Group Andrology (SIGA) of ESHRE. Since 2012, he has been Chairman of the KFR (Clinical Research Group for Reproductive Medicine e.V.), supporting research activities of the CeRA. He has recently been elected into the permanent commission on animal ethics of the Senate of the Deutsche Forschungsgemeinschaft. He is also a member of the scientific board of the German Primate Centre, Göttingen.

Professor Gromoll was President of the German Society of Endocrinology (DGE) from 2012 – 2014.

Professor Zitzmann is a member of the Board of the International Society for Men's Health and since 2014 Member of the Board of the German Society of Andrology. He has been assigned by the EAA to lead the writing of guidelines on Klinefelter's syndrome. He is also part of the writing group "EAA Guidelines for Diagnosis and Treatment of Male Hypogonadism". Since 2012, Prof Zitzmann has been an accredited specialist for sexual medicine (Fellow of the European Council of Sexual Medicine). In July 2017, Professor Zitzmann was elected member of the Royal Society of Medicine.

PD Dr. Nordhoff is head of the Working Group of Reproductive Biologists of the DVR e.V. (Dachverband Reproduktionsmedizin, Umbrella Organization for Reproductive Medicine). She is the leading embryologist of our institution and responsible for the IVF laboratory.

PD Dr. Rohayem is actively involved in the German Society of Paediatric Endocrinology and Diabetes and responsible for the Working Group "Puberty and Gonads". Dr. Rohayem is responsible to build up and coordinate the outpatient clinic for andrology in adolescence that started in November 2015.

Professor Nieschlag is an active Emeritus Professor at the CeRA. He has been acting as Chairman of the Quality Control Program of the German Society of Andrology (QuaDeGA) since 2009. About 700 laboratories are participating in this scheme, 10% from abroad. The program is supported by the CeRA infrastructure and performed with expertise from CeRA staff.

All senior CeRA scientists and clinicians are members of Editorial Boards and function as Associate Editors for leading journals in the field of andrology, endocrinology, urology and reproductive medicine/biology.

Collaboration with other institutions

Intense collaborations with several institutions and research networks of the University of Münster exist and provide support for interdisciplinary research projects. Most intense collaborations are established between CeRA and the Institute of Human Genetics. Both institutions have been successful in applying for a DFG Clinical Research Unit 326 entitled “Male germ cells: from genes to function”. In addition, the Clinical Research Unit is based on local partnership with the Institute for Cell Biology of the ZMBE Münster (Professor Raz), the Children’s Hospital (Professor Omran) and the Institute of Medical Informatics (Professor Dugas). The Max-Planck-Institute for Molecular Biomedicine (Professor Schöler) in Münster and the Institute of Human Genetics of the University Duisburg-Essen (Professor Horsthemke) are involved as external partners. Details of the scientific projects of the CRU are presented below.

Apart from the Clinical Research Unit, local research collaborations continue or began with the Institutes of Microbiology, Radiology, Urology, Clinical Chemistry, Medical Psychology, the Clinic for Psychosomatic Diseases, the Eye Clinic, the Institute for Genetics of Heart Diseases and the Institute of Physiology.

Profs. Schlatt, Strünker and Gromoll are involved in projects and activities of the Interdisciplinary Center for Clinical Research (IZKF Münster) and the Excellence Cluster “Cells in Motion”. Professor Schlatt is Spokesman of the Commission of the Universitate rectorate for the use of animals in experimental research. As part of our research and clinical activities in regard to testicular cancer, several collaborations are established with the German and the European Cancer Collaborative Study Groups by Professor Kliesch. The long lasting close collaboration with Professor Bergmann, Veterinary Anatomy, and Professor Meinhardt, Anatomy of the University of Gießen, has been intensified as well as the well-established co-operations with the Department of Urology and Andrology of the University of Gießen and the Center for Reproductive Medicine and Andrology of the University of Halle (Director: Prof. Dr. med. H.M. Behre), both active EAA Training Centres. Young scientists from Germany and abroad regularly visit the CeRA for training, including EAA stipends:

In January and February 2016, **Mohamed Wael Ragab** joined our institution for two months as EAA stipend. Within this short period, he started a research project on benign testicular tumour that is still ongoing. Moreover, he analyzed a sub-cohort of Klinefelter patients with a manuscript under revision (Ragab, M., Zitzmann, M., Nieschlag, E., Kliesch, S., Rohayem, J. A history of undescended testes in men with Klinefelter syndrome does not reduce the chances for successful microsurgical testicular sperm extraction. Submitted 2017), presented the data at national and international congresses and finalized a book chapter on varicocele (Ragab, M.W., Kliesch, S. Varicocele. In: Simoni, M., Huhtaniemi, I. (eds.) Endocrinology: Endocrinology of the Testis and Male Reproduction. Springer International Publishing AG, Cham, Switzerland, 2017, 1115-1144).

An active Alexander von Humboldt Foundation partnership with the University of Manipal, India, provided funds for several exchange visits and the organization of German-Indian workshops in 2014 and 2016 in Manipal and 2017 in Münster. Fellowships from foreign countries but also the German Academic Exchange Service (DAAD) and the German Association of Urology (East-West Exchange Programme) provide funds for PhD fellowships. Currently, two PhD students (Heloisa Lopes Lavorato from Brazil, Raul da Costa from Venezuela) are supported by international PhD fellowships. Continued DAAD funding is also provided for academic exchange projects with the University of Coimbra, Portugal to Professor Schlatt/Dr. Amaral and the Monash University, Clayton, Australia to Profs. Strünker and O'Bryan.

International collaborations are specifically intense in the Marie Curie International Training Program
(Growsperm, http://www.growsperm.eu). This program has grown out of longstanding relationships between its members. Two PhD students (Swati Sharma from India, Mina Mincheva from Bulgaria) are being trained since 2015 and will defend their dissertations in January 2018. Academic members of the Growsperm consortium are research teams at AMC in Amsterdam, NL, Free University Brussels, Belgium, the Department of Woman and Child Health at Karolinska University, Sweden, the MRC Human Reproductive Science Unit, Edinburgh, UK, and the Universities of Sapienza, Rome, Italy, and Helsinki, Finland. The number of collaborating institutions has been extended even further with the recruitment of Professor Strünker. He is collaborating

with various national and international partners, including the Max Planck Research Center Caesar (Professor Kaupp, Professor Wachten). The Rigshospitalet in Copenhagen (Professor Skakkebaek), and Washington University at St. Louis (Professor Lingle), to name only a few.

Management of andrological patients

The Department of Clinical and Surgical Andrology is active in the diagnosis and treatment of infertile patients, hypogonadal males, patients with endocrine disorders and those with sexual dysfunction. Oncological patients are provided with care regarding their reproductive health concerns including fertility preservation. In case of germ cell tumours, our Department is accredited as a second-opinion centre of the DKG. Most of the patients present with severe problems, as the Department of Clinical and Surgical Andrology is acknowledged as a secondary and tertiary referral centre. The number of consultations and diagnostic and routine laboratory tests are listed in Tables 2 and 3 and increased steadily since 2008.

The outpatient clinic has two different premises since October 2012, with an outpatient clinic located downtown (Von-Vincke-Straße 14) in addition to the main building located at the University Campus (Domagkstraße 11), both under the responsibility of Professor Kliesch. The diagnostic and therapeutic work-flows are identical for the patients seen in both locations.

Diagnostic and laboratory tests:

Ultrasonography of the scrotal content as well as transrectal sonography of the prostate and seminal vesicles is performed routinely as a complement to the physical investigations. Ultrasonography and duplex sonography of the penile structures is performed in patients with erectile dysfunction or ejaculation disorders, including duplex sonography in pharmacologically stimulated patients with erectile dysfunction. Abdominal sonography of the retroperitoneum is offered as well as sonography of the thyroid gland and the peripheral arteries.

Semen analysis is performed according to the new WHO guidelines 2010 with an established internal and external quality control program and may be supported by a computer-assisted sperm motility analysis (CASA: Hamilton-Thorne). With more than 4,000 semen samples

analyzed per year (Table 3), the andrology laboratory serves as a WHO reference laboratory providing information and guidance on techniques and instruments employed in the analysis of semen. As such, procedures are conducted as per the WHO guidelines and the veracity of the results assessed by internal and external quality control programs. The laboratory participates in the British (UKNEQAS), the European (ESHRE) as well as the German (QuaDeGA) scheme, where it also serves as the instigating centre. The accuracy and precision of seminal plasma biochemistry assays are gauged by participation in the Karolinska Institute programme. Bacterial culture of semen is performed in collaboration with the Institute of Microbiology. DNA integrity testing can be offered in selected patients if indicated.

For **endocrinological** diagnosis, in 2017 about 40,000 hormone determinations per year are performed using a fully automatic hormone analyser for patient care as well as for research purposes (Table 3). All hormone assays are subject to quality control according to the stringent criteria of national and international regulating agencies. The development of new techniques for measuring well-known hormones as well as the introduction of methods for new hormones are one of the Centre's core activities. Inhibin B, AMH and DHT as well as 25-hydroxy-vitamin D3 have now been added to the list of laboratory tests measured.

Testicular histology: Testicular biopsies are examined for diagnostic and treatment purposes in cases of azoospermia, for detection of germ cell neoplasia in situ and testicular cancer, and for sperm retrieval. Annually, more than 2,100 PAS and 980 PLAP stainings are performed in our histology lab by trained technicians. For semi-quantitative analysis, the score system according to Bergmann & Kliesch is used.

Genetic diagnostics: Like in the last years we continued to screen infertile men with sperm counts <1 million for microdeletions in the **AZF** region. For this we are applying a multiplex PCR recommended by the EAA guidelines and we are successfully participating on an annual basis in the EMQN External Assessment Quality Schemes for AZF. In addition, we are determining the **CAG** repeat number in the androgen receptor in patients with signs of androgen resistance, being known to be a modulator of androgen action. The unique setting at the

CeRA not only allows to perform routine diagnostics (such as AZF deletions and CAG repeat analysis), but also paves the way for DNA-based association studies, screens for mutation analysis of candidate genes as well as the development of new genetic markers for male infertility. Very recently we added **epigenetics** to our DNA diagnostics. We now are studying whether aberrant methylation could contribute to impaired spermatogenesis. We have set up a normal range of methylation profiles to study infertile patients in much more depth. Apart from this, **FSH receptor and promotor polymorphism** are within the focus of our very recent and successful work to study genetic causes of male infertility. Moreover, in cooperation with the Institute of Human Genetics an **azoospermia panel** was introduced into the routine diagnosis in infertile men.

Bone density and body composition measurements: Since January 2014 bone density can be measured by DXA scan, indicated especially in male hypogonadal patients who are at risk for osteopenia. In addition, in patients with metabolic syndrome, body composition can be measured as well. Especially for future studies in hypogonadal patients, this instrument will give access to important and new data.

Specialized outpatient services are offered for:

Male infertility

Systematic work-up of infertile males and – in cooperation with the gynaecological partners – the infertile couple leads to specialization on severe cases of infertility with a high proportion of 12% being azoospermic. Moreover, patients with infertility and hypogonadism are medically treated according to best available evidence. In conjunction with the CRU, we aim to better characterize the “idiopathic” infertile patient and identify subtle (epi-)genetic alterations. Surgical treatment options, mostly microsurgical approaches, are offered if indicated with 200 patients yearly treated with micro TESE, another 50 males undergoing microsurgical fertilization procedures.

Fertility Clinic (ART)

In collaboration with the Women’s Hospital, childless couples are cared for in the fertility outpatient clinic. Our department concentrates on the male partner and the IVF laboratory. We conduct a joint program for assisted reproductive techniques including intrauterine

insemination, in-vitro fertilization and intracytoplasmic sperm injection. The Fertility Clinic was reorganized with the aim to increase patient numbers treated under the responsibility of PD Dr. med. A. Schüring specialized in Gynaecological Endocrinology and Reproductive Medicine. By now, a constant staff of 3 gynaecologists for counselling and treating the female patients is present in the Fertility Clinic. Weekly interdisciplinary conferences are part of the routine work-up of the couple. As a result of the structural changes initiated in 2012, the patient numbers treated by IVF and ICSI could be doubled and resulted in more than 400 cycles at the end of 2017. In addition to a second new intracytoplasmic sperm injection (ICSI) microscope (Nicon Ti-5 microscope equipped with two Eppendorf micromanipulators which operate electronically with a memory function and are thereby faster during an ICSI), new technologies like a laser and polarization filter (PolarAIDETM Octax) which detects the birefringence of dense objects in the oocyte are implemented during routine lab work flow. The new laser is useful in selecting sperm for ICSI particularly in azoospermic men, where sperm are retrieved by testicular sperm extraction (TESE). Being an andrological centre, severe andrological cases with only few and immotile sperm in semen or testicular samples are frequent. Up to 25-30% of our patients receive ICSI treatment with testicular spermatozoa. By using the laser microscopy, the distinction of viability of spermatozoa is possible. As a consequence live sperm can be selected and used for injection. When the number of sperms is smaller than the number of oocytes, the polarization feature helps select the best oocyte for these sperm. The utilization of these two new features has enhanced our fertilization rates for TESE-ICSI and by improving the selection of pronuclei increased our pregnancy rates. In addition, we implemented new techniques in the IVF laboratory setting: Vitrification of oocytes is offered since the end of 2013 and Ca ionophore-assisted ART was implemented in January 2014. Weekly interdisciplinary conferences ensure the best treatment for the couple.

Apart from the close interaction with the Fertility Clinic of our Department, we in addition cooperate with a Private Practice for Reproductive Medicine in Münster (Dr. med. A. Mempel/Mrs. S. Stratmann). We see all males of the infertile couples treated there. Diagnostic procedures and therapeutic options for the male are

performed in our Department. Weekly interdisciplinary conferences ensure the best treatment for the couple.

Endocrine disorders/hypogonadism

The endocrinology outpatient clinic deals with diagnosis and treatment of primary and secondary hypogonadism, including Klinefelter's syndrome, delayed pubertal development and the ageing male as well as patients with gynecomastia. All relevant clinical and hormonal tests are provided. All modern hormone replacement schemes (oral, transdermal and injectable testosterone preparations) are available as well as stimulatory treatment protocols in males with secondary hypogonadal patients and infertility. The panel of hormones analyzed has recently been expanded by dihydrotestosterone (radioimmunoassay), inhibin B, AMH and 25-hydroxy-vitamin D3 (ELISA).

Sexual dysfunction: erectile and ejaculation disorders

Patients with ejaculatory or erectile dysfunction are seen in the outpatient clinic in increasing numbers. This part of the clinic deals with erectile dysfunction, Peyronie's disease, penile curvatures and ejaculation disorders. Diagnostics include duplex sonography of the penile vessels and pharmacostimulatory tests. The treatment options available cover the whole spectrum of medical and pharmacological intracavernous treatment, reconstruction of the penile curvature and implantation of penile prostheses. Especially in patients with Peyronie's disease, surgery comprises plaque incision and grafting techniques as well as penile implants. In 2017, the technology of low-intensity shock wave therapy (Li-ESWT) in patients with mild to moderate erectile dysfunction and/or Peyronie's disease was introduced in the therapeutic setting.

Oncological andrology

This part of our clinic provides the infrastructure and expertise for patients seeking cryopreservation of their semen (or spermatozoa of the testis if azoospermia is diagnosed) prior to undergoing oncological treatment. Most patients have testicular cancer, leukaemia or lymphoma at the time of diagnosis. We see an increasing number of patients seeking help concerning persistent azoospermia after recovery from the oncological disease. We have also established collaboration

with the Oncological Department of the Children's Hospital to provide options to pubertal boys with oncological diseases and their need for fertility preservation. Most patients are referred to us by the Department of Paediatrics, the Department of Oncology and the Department of Urology. In 2012, we founded the Network "Androprotect" with the intention to establish a network of paediatric oncologists, urologists and andrologists that offers male patients with childhood cancer and male patients with prepubertal gonadal insufficiency the option to preserve gonadal stem cells. Meanwhile, cooperation with the universities of Frankfurt, Hamburg and Erlangen could be established.

Surgical andrology (urological andrology)

Since June 2008, we are able to offer all andrological surgical procedures to patients in our Department. These treatment options include all microsurgical procedures such as **microsurgical testicular and epididymal sperm extraction** techniques, **microsurgical varicocele ligation, microsurgical vasovasostomy and vasotubulostomy** for fertilization and **diagnostic testicular biopsies** (to detect GCNIS). Concerning the severest group of infertile males, the azoospermic patients, we extended our activities regarding TESE-ICSI and MESA-ICSI cycles in the last 10 years. The German IVF Registry shows a frequency of 3-5 % of these procedures in all ICSI cycles. In our Centre, the proportion of treatment with TESE or MESA sperm was as high as 29% of patients in 2017. Since June 1, 2008, responsibility for these surgical procedures was transferred from Urology to our Department. The **microsurgical testicular sperm extraction** technique is implemented as a standard procedure for non-obstructive azoospermia since 2008 with about 200 micro TESE patients per year.

Patients with erectile disorder refractory to medical treatment can be treated by the implantation of **penile prostheses**. In case of penile curvatures, mainly in combination with **Peyronie's disease**, the surgical correction of penile curvature can be offered either with simple Nesbit procedures or preferably with plaque incision and grafting procedures with or without combination with penile implants. Hypogonadal patients or cancer patients whose treatment results in anorchia can be provided with **testicular prostheses**.

Testicular cancer patients diagnosed at our Department can receive surgical treatment in our clinic. Further treatment involving chemotherapy or radiotherapy is undertaken in close collaboration with the Department of Urology and the Department of Radiotherapy. The surgical procedures are done by Professor Kliesch and Dr. Cremers as her Deputy together with two to three urologists in training at our Department. Since 2008, patient numbers treated have been increasing steadily (2008 : 70 pts., 2009: 160 pts., 2013: 253 pats., **2017: 372 pats.**).

Adolescents' Andrology

In 2015, we started to set up a specialized outpatient service for adolescents with andrological problems. Within 14 months more than 300 new patients with rare and severe diseases were admitted and our collaboration with paediatric colleagues was intensified. This project is part of the permanent clinical and research position of Julia Rohayem, MD, paediatric endocrinologist and andrologist. This project will overcome the lack of care of endocrinologically and andrologically ill adolescent patients and aims to improve the standards of care in the field of reproductive health in adolescence.

Clinical database Androbase

Due to Professor Nieschlag's activities and the commitment of Professor Frank Tüttelmann, former co-worker of the Centre and now scientist in the Institute of Human Genetics of the University, respectively, a well adopted database for andrological patients was established. Named *Androbase*©, this software allows the digital documentation of all patient- and proband-related entries, all laboratory results and all clinical findings/diagnoses. Furthermore, this software also allows to do continuous development and to build up an enormously valuable database providing the basis for systematic analysis of andrological patients and andrological diseases. After an official evaluation of the University IT Department, Androbase has become the official and fully supported database for the CeRA and the Institute of Human Genetics (GeneSys©). Within the last 3 years all prerequisites were established to switch from patient records to a fully digital patient record system. Since the end of 2014, we rely on a merely electronic patient data system with Androbase.

Medical education and clinical training program in andrology

MDs receive training in all clinical activities: fertility clinic, endocrinology, erectile dysfunction, oncological andrology including cryopreservation, surgical andrology and, in collaboration with the Women's Hospital, assisted reproduction. New MDs are first assigned to a senior assistant and are gradually permitted more responsibility in the clinical care of patients. All patients/couples are presented to the Clinical Director or the Senior Registrar and all cases are discussed in the weekly clinical rounds (3 hours every Wednesday). MDs perform and/or interpret diagnostic procedures themselves (i.e. endocrine function tests, semen analysis, imaging procedures) and pass through the clinical laboratories to train in semen analysis and hormone assays for several weeks. Those remaining longer than one year (on average, MDs stay for 3 to 5 years) receive training in ultrasonography, including transrectal and duplex sonography and histological evaluation of testis samples. All MDs participate in weekly rounds with the gynaecologists. They are also involved in clinical trials and hence receive training in conducting trials subject to the strict rules of the European and USA regulatory agencies. MDs also engage in laboratory work which may be clinical and for basic research. In their individual research projects and by participating in the regular Progress Reports of all collaborators (every Friday), they learn how to conduct research. Interaction of the Centre members involved in this interdisciplinary research occurs at weekly meetings where recent results and the direction of current projects are discussed. New research topics, techniques and highlights from meetings attended are discussed in the weekly Journal Club. To compile grants, individual counselling is offered and extended scientific meetings (XXL Meeting) on a monthly basis have been implemented in 2013. The weekly and monthly research meetings and the Journal Club are presented in English promoting the use of scientific language for all scientific co-workers. From the German authorities, Professor Kliesch is licensed to conduct full training in andrology and the 12-month urology training. Professor Zitzmann is licensed for training in internal medicine for twelve months and endocrinology for another twelve months. Since 2014 another 2 andrologists (W. Moussa 2016, K. Czeloth 2014) have passed the EAA exam and 6 the German exam at the State Medical Board (G. Spiliopoulos 2015, W. Moussa 2016, J.-F. Cremers 2016, A. Soave

2016, E. Vorona 2017, A. Sahi 2017). Moreover, two colleagues were trained in Urology for 12 months each in our Department.
Medical students regularly visit our Centre for shorter or longer teaching periods. Since 2009, the Centre has been engaged in the curricular teaching program of the Medical Faculty during the regular semester. For this purpose, we have compiled a case for an e-learning module concerning a male infertile patient. This e-learning program was first introduced in 2009 and has been well accepted and well evaluated by the medical students of the fifth clinical semester. Since 2010, another two electronic cases have been developed. We cover the field of male hypogonadism, erectile dysfunction and male infertility by these electronic patients. Moreover, the scientific co-workers of both our institutions take part in regular teaching lessons. Once per year a three-day Summer School in Reproductive Biology and Medicine is offered to advanced biology and medical students. This Summer Academy is restricted to a maximum of 40 participants and will be presented for the 28th time in 2018. Since 2010 it is included in the curriculum of the Medical Faculty.
The Centre maintains a very well equipped library maintaining all relevant journals in the field of reproductive medicine and biology, reproductive endocrinology and andrology. Furthermore an impressive list of monographs and text books is available. The library is equipped with electronic access to the Central and Medical Libraries and the internet and also provides modern IT equipment for PPT presentations. Since the library holds space for up to 50 people, it presents a perfect and heavily frequented place for all scientific meetings and educational events with up to 50 participants. The library is also the forum for regular seminars on topics in reproductive medicine/biology. Seminars are offered either on Wednesday to our own staff but also to members of the medical and other faculties at the University of Münster. Apart from seminars with invited speakers, the Centre organized a seminar series entitled “Six to Six”. This series is specifically dedicated to translational topics and is usually presented by a basic researcher and a clinician focusing on a topic from different points of view.
Apart from the medical teaching and the teaching of the residents in urology and andrology, the Centre offers regular training courses (10 to 12 per year) for semen analysis for medical doctors and technical assistants. Up to now, 130 courses took place with 1625 participants.

During a one-day course, the participants are trained in the practical performance of semen analysis and the evaluation of its results and learn the essentials of the internal and external quality control.

Research activities

The CeRA is engaged in a wide-ranging research programme, resulting in an impressive list of publications. Some of the most relevant topics studied are explained in the following chapter:

DFG Research Group of Germ Cell Potential (2008 – 2016) (Coordinator: Prof. Dr. rer. nat. J. Gromoll)

The Research Unit aimed to explore and exploit the potential of germ cells. It combined stem cell research and reproductive medicine. Using modern cellular and molecular techniques (stem cell culture, 2D and 3D microscopy, methylation analysis, expression profiling and proteomics), it investigated the development and decline of the germ cell potential during in vivo and in vitro gametogenesis. A major focus was on the genetic and epigenetic determinants of the germ cell potential. The 11 projects took advantage of the particular strengths of well-established animal models and clinical studies. The Research Unit was composed of basic and clinical scientists who work in gynaecology, andrology, veterinary medicine, genetics and developmental biology. The RU 'Germ Cell Potential' was officially terminated at the end of 2016. The publication record of the RU has been excellent and was the basis for the application of a new CRU, which was granted in July 2017.

DFG Clinical Research Unit 'Male Germ Cells: From Genes to Function' (2017 – 2020)
Spokesman: Prof. Dr. rer. nat. J. Gromoll
Research Coordinator: Prof. Dr. med. Frank Tüttelmann

Male infertility is a genetically and clinically highly heterogeneous disease. Thus, unravelling the underlying causes and the pathophysiology is challenging and requires an integrated approach. This Clinical Research Unit (CRU) investigates human male germ cell function from complete germ cell loss to sperm dysfunction at the genetic, epigenetic, and molecular level. We joined clinical and basic research institutions that primarily study male germ cell function with institutions that primarily focus on stem cells, paediatrics, and powerful animal models. Thus, this CRU consists of the three layers basic science, a network of research projects, and clinical research.

These are interconnected by the 'DNA', i.e. the concerted research on the epi-/genetics of male germ cells and the professorship of 'Reproductive Genetics'. The seven research and one core projects are tightly interlinked and address a unifying hypothesis: A wide spectrum of leading pathologies with the common denominator of male infertility share common epi-/genetic causes. The CRU will overcome the classical concept of male infertility as an isolated disease and create an integrated view allowing both forward (gene to patient) and reverse (patient to gene) approaches to identify novel epi-/genetic factors and associated phenotypes that impact germ cell function. This will significantly improve the diagnostic yield in infertile male patients and, ultimately, improve patient care.

Central to the CRU is a tenure track professorship for Reproductive Genetics, which was awarded to Professor Frank Tüttelmann.

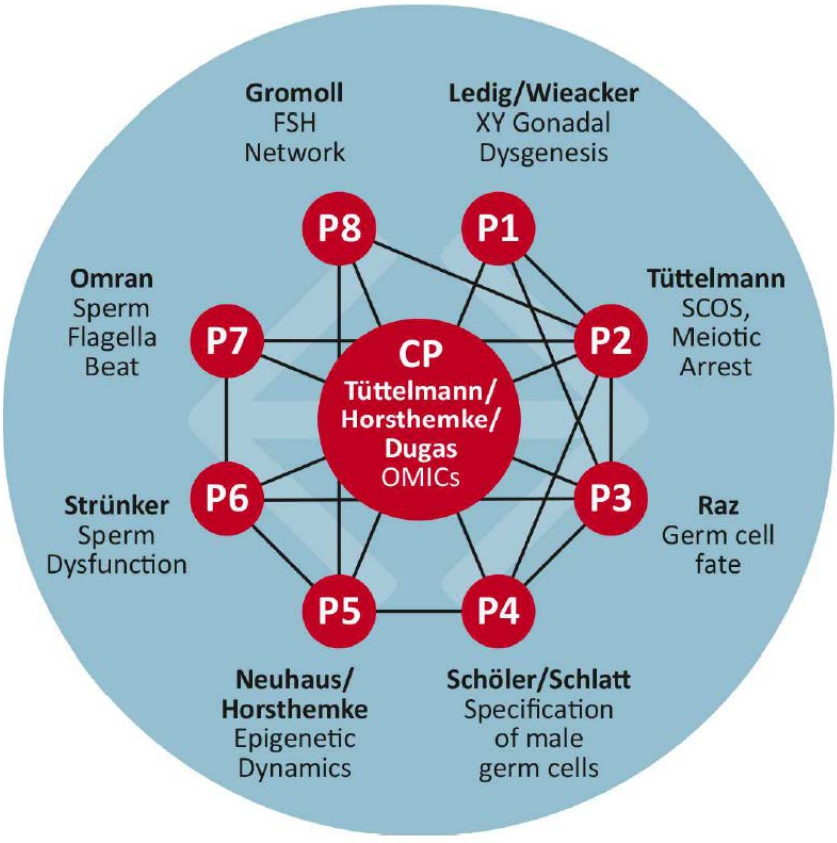

Fig. 1. Scheme of the CRU 'Male Germ Cells' displaying the different projects and their PIs and the links in between.

In vitro *spermatogenesis*

To transfer male germ line differentiation into a culture dish has been approached by reproductive scientists for almost a century (reviewed in Reuter et al 2012) but still remains experimental. The topic has faced increasing importance as the need for methods providing in vitro matured spermatozoa is forced by an increasing number of in particular young patients suffering from malignant diseases which can fortunately be cured nowadays and become long-term survivors. However, the therapies used still provoke long-term infertility as a severe side effect of treatment, and no sufficient method is available to preserve fertility in those boys which cannot provide a semen sample for cryopreservation before surgery. As conventional cell cultures do not provide the spatial arrangements which testicular cells encounter in their natural environment, we developed three-dimensional cell culture approaches to reconstitute tubulogenesis and spermatogenic differentiation in matrices as well as artificial scaffolds using murine models; providing a microenvironment that resembles the three-dimensional (3D) *in situ* organization of the seminiferous epithelium better. We demonstrated previously that male mouse germ cells in 3D matrices soft agar culture system; methylcellulose culture system are able to form morphologically mature elongated spermatids. In a more recent approach granted by the Medical Faculty, we used collagenous sponges as artificial scaffold and were successful in colonization of these by isolated testicular cells which formed clusters resembling features of early tubulogenesis (Reuter et al, 2014, in press), but although undifferentiated spermatogonia could be maintained in this system for several weeks, no spermatogenic progress was observed yet, very likely due to different culture media needed from a yet unidentified stage onwards. Nevertheless these approaches will contribute important basic data along the route to develop strategies for fertility preservation by culture of the male germ line. We recently transferred the method to primate testicular cells from marmosets and could confirm the observations made in rodents (unpublished data). These studies are now continued systematically in order to translate the methodology into human spermatogenesis. Innovative studies exploring the effects of nanostructures of cell culture surfaces and the co-culture with pluripotent stem cells were applied to understand the process of testicular morphogenesis. A collaboration with physicists at the CENTECH nanotechnology centre provided access to cutting edge

technology. The reassembly of cord-like structures in vitro could facilitate the construction of cell culture systems to promote spermatogenesis. We have recently published our data on cord formation using rat primary Sertoli cells (Pan et al., 2013). We are convinced that these data provide the foundation of novel concepts for creating testicular cultures to promote spermatogenic activation.

Pluripotent stem cells in the primate testis

Unipotent spermatogonia are derived from potentially pluripotent primordial germ cells. Primate testes contain two types of spermatogonia: a) reserve stem cells and b) self-renewing progenitors. While rodents generate about 4,000 sperm per initial stem cell division, in man an initial progenitor division creates only 16 sperm, leading to very different kinetics in spermatogenesis in rodents and primates. So far, no systematic studies have explored the ontogenetic differentiation of male germ line stem cells in primates, and it is not known whether truly pluripotent stem cells remain in the testes even in adulthood. The adult primate testis contains two types of undifferentiated spermatogonia: the Adark-spermatogonia, reserve stem cells, and the Apale-spermatogonia, self-renewing progenitor cells. Histological criteria have been used for decades to distinguish the spermatogonial subpopulations, but so far no conclusive data have been generated on the biological roles of each of these subpopulations, and definitive biomolecular markers for each subpopulation are not yet known. In this ongoing study we address whether pluripotent spermatogonial precursors in the cynomolgus monkey (Macaca fascicularis) are gradually eliminated from the developing testis by (potentially reversible) differentiation into unipotent spermatogonia. We also examine whether the distinct spermatogonial subpopulations in the adult testis of a non-human primate, the rhesus monkey (Macaca mulatta), express distinct biomolecular marker combinations, and we have recently extended our study, now also including adult human testicular tissue. We use a panel of markers which allows us to histologically detect spermatogonia at various stages of differentiation in the adult monkey's testis. Using the expression of Oct3/4, Ap-2γ, VASA, GFRα1, Nanog, PGP 9.5, Tra -1-81, and Tra-1-60, we identify sub-populations of spermatogonia, aiming to determine the total number of pluripotent cells in a non-human primate's testis. These studies will provide insight into the mechanisms behind differentiation

of pluripotent germ line cells into unipotent testicular stem cells in primates. Our data may enable us to select a target population in foetal, neonatal and adult primate testes for the isolation and derivation of pluripotent stem cells. Recently we have explored morphogenesis of seminiferous tubules in xenografts and collagenous matrices. We have shown that soluble factors and surface modalities which can be engineered by nanostructure technologies influence the aggregation and tubule formation of testicular somatic cells. It is our goal to prepare *in vitro* conditions for generation of sperm from stem cells *ex vivo*.

Stem cell characterization and physiology in humans

Enrichment of human and marmoset spermatogonia as prerequisite for in-depth transcriptional and epigenetic analyses

While some studies reported that human spermatogonial stem cells (SSC) can be maintained *in vitro* and show characteristics of pluripotency, the germ cell origin and the differentiation potential of these cells was subsequently called into question. In previous studies we have established an integral approach for the unequivocal detection of human as well as marmoset spermatogonia *in vitro* (Kossack et al. 2013; Langenstroth et al. 2014). We succeeded in conclusively showing that an integral approach comprising the 1. detailed characterization of the starting material, 2. use of unambiguous markers for the characterization of cultures and 3. use of biopsies lacking the germ cell population as negative control are prerequisites for the establishment of spermatogonial cultures. Using this approach we have unveiled the epigenetic properties of spermatogonia in the adult marmoset testis and have demonstrated that the androgenetic pattern remains stable *in vitro* (Langenstroth-Röwer et al. 2017). Moreover, isolation of individual human spermatogonia employing micromanipulation and subsequent single cell expression analyses has been performed to unravel the transcriptional fingerprint of human spermatogonia. Unexpectedly though, heterogeneous transcription profiles have been detected, indicating the existence of a heterogeneous spermatogonial stem cell pool (Neuhaus et al. 2017). Whereas previous studies focused on the molecular properties of spermatogonia in samples with qualitatively normal spermatogenesis, the focus of future studies will

be to unveil the aberrant transcriptional pathways or epigenetic patterns that are associated with male infertility.

The role of the CXCL12-CXCR4 system in the homing process of adult testicular stem cells

It has been shown using mice as animal model that an induced stem cell loss leads to an up-regulation of the chemokine Cxcl12 in several organs. This induced gradient of Cxcl12 facilitates the recruitment of Cxcr4-positive adult stem cells and thereby aids tissue regeneration. Whereas other groups focused on mice as animal model, we employed non-human primate (NHP) models, which share important properties regarding the spermatogonial stem cell system with the human. Irradiation of testicular tissues of NHPs with 0, 1 and 4 Gy and subsequent grafting into recipient mice supported germ cell differentiation in the untreated tissues (0 Gy group). In treated tissues, a dose-dependent reduction of spermatogonia was observed though in the 1 Gy and the 4 Gy treatment group. Intriguingly, expression of CXCL12 in Sertoli cells was increased in tissues treated with 1 Gy, showing recolonization of spermatogonia, compared to 4 Gy tissues which were largely devoid of spermatogonia (Tröndle et al. 2017). Future studies will elucidate if an up-regulation of CXCL12 is directly associated with recolonization of spermatogonia following germ cell loss or if 4 Gy treatment results in an impairment of Sertoli cell function, which may limit the chances of spermatogonial recovery.

Sperm physiology

The working group formerly led by Con Mallidis, PhD, has focused on investigating the causes, identifying the manifestations and developing methods of circumventing sperm nuclear DNA damage. Specifically we have studied different instigators of oxidative stress, be they physiological (i.e. diabetes, infection) or induced (i.e. UV irradiation, Fenton reaction), chronicling their effects and characterizing their actions. We have developed a novel means of assessing individual sperm allowing us to non-invasively and non-destructively appraise the chemical and molecular integrity of each cell. The technique, Raman microspectroscopy, also opens the possibility of developing a means of assessing, selecting and providing nDNA intact sperm for use in ART. In a parallel study, the clinical applicability of the technique has been assessed, characterizing tissue and cells from germ cell tumours in an

effort to identify markers that will allow for more accurate and timely therapeutic options. In the past three years, these studies have resulted in the publication of 10 original research articles, 3 reviews, 2 book chapters, 2 technical notes and garnered 4 favourable commentaries.

Molecular Reproductive Physiology

This new group led by Professor Strünker utilizes sperm as a model to elucidate the basic principles underlying sensory signal transduction. Swimming up the oviduct resembles a relay race during which sperm might be instructed by long- and short-range cues to navigate by chemotaxis, rheotaxis, thermotaxis, or a combination thereof. The signalling pathways and molecules that govern sensory signalling in sperm are similar to those in sensory neurons that detect for example mechanical force, odours, or light. By the kinetic stopped- and quenched-flow technique and patch-clamp recordings, combined with fluorescent ion- and voltage-sensitive indicators, the Strünker group studies sensory signal transduction in human, mouse, and sea urchin sperm. In particular, the group is interested in the ion channels, receptors, and cellular messengers that allow sperm to register chemical cues released by the egg as well as oviductal flow velocities and temperature gradients. Moreover, by high-speed microscopy, the control of the swimming behaviour by chemical cues and gradients of flow velocities is studied. A major aim is to decipher by a function-to-gene approach the role of ion channels in sperm from patients seeking for assisted reproduction, and to shed light on the mechanisms underlying sperm dysfunction and male infertility. We hope that in the next couple of years, insights provided by this research will facilitate evidence-based selection of Assisted Reproductive Technology (ART) treatment. In the past 2.5 years, the work of Professor Strünker at the CeRA resulted in 5 original research articles and one review.

Fertility Preservation

Male fertility preservation is one of the most urgent needs in the field of Andrology. Fortunately, increasingly successful therapies nowadays result in much improved survival rates of childhood cancer patients. However, a typical side effect of such therapies is the long-term to permanent damage of the germ line. Other than adults, prepubertal boys have no chance to store semen, i.e. the only way to preserve their fertility is to store testicular tissue and to develop methods of ex situ

maturation into gametes for ART. All methods so far are still experimental and research is needed to keep the promise made to these boys when undergoing cure and tissue retrieval.
Thus, we focus on various approaches to understand what is needed to provide such techniques in the future and to develop techniques and methods in order to encounter this medical dilemma of treating a life threatening disease by harming fertility. During the last years we conducted various studies with regard to the topic, utilizing both human tissue from transgender patients as well as animal models: Using xenografting experiments, we analysed radiation effects on prepubertal monkey testes elucidating so far undescribed alterations on the somatic cell function, i.e. the spermatogonial stem cell niche (Westernströer et al. 2014, 2015, Tröndle et al. 2017), features of primate SSCs were addressed in vitro as well as in vivo (Langenstroth et al 2014, Schneider et al. 2015), and finally we tested various in vitro approaches to examine the potential of murine and human testicular cells to self-assemble in conventional and three-dimensional cell cultures (Reuter at al. 2014, Mincheva et al. submitted). All of these studies aim at the overall goal to provide techniques for gamete maturation ex situ in the future.

Pathophysiology of sex-chromosomal imbalance in the male

Klinefelter men exhibit a karyotype of 47,XXY linked to pronounced phenotypical changes affecting endocrinological regulation and reproductive function accompanied by cognitive defects but also resulting in increased mortality and morbidity (reviewed in Wistuba et al. 2017 a,b). Recently, we found additional evidence for a cardiovascular risk profile and disturbed testicular vasculature (Zitzmann et al. 2015, Tüttelmann et al. 2014, Damm et al. 2016). Although addressed in many studies since its discovery, the knowledge and understanding of molecular and genetic mechanisms underlying the syndrome are still limited, mainly due to the lacking experimental access that requires reliable animal models. We therefore established and utilized a Klinefelter mouse model closely resembling features of the human KS as germ cell loss, Leydig cell hyperplasia, normal inactivation of the second X-chromosome, hypergonadotropic hypogonadism, and cognitive deficits (Wistuba et al 2017a).
In a project granted by the DFG, we could make use of these animals over the last years to analyze in detail the postnatal developmental

course of the germ cell loss and found that spermatogonial stem cell marker expression is fading very early in life, we observed changes in the Sertoli cell number and physiology, and we could provide evidence that the testicular vascularization is disturbed and might be involved into both the germ cell loss as well as the endocrine phenotype (Werler et al. 2014). Similarly, we could also establish a link between findings from the mouse model concerning genes escaping from X inactivation which we were able to determine to be expressed in a tissue- and gene-specific manner in the mice with findings from the Münster EXAKT project in which these escapee genes were shown to play also an important role in the human patients (Zitzmann et al. 2015). As a substantial part of the pathophysiology of the syndrome is clearly of genetic origin, we broadened our analyses by implementing other models of sexchromosomal trisomies in close collaboration with Professor Arnold, UCLA. Those animals are currently analyzed in order to clarify the specific consequences of X-linked gene expression to phenotype variants.
Furthermore, in a local collaboration with the experimental ophtamologists, we were able to detect a clear eye phenotype in KS men (Brand et al. 2017), a feature of KS which was overlooked so far. Interestingly this phenotype is not present in the mouse model, providing us with the chance to figure out the specific pathways affects by comparative analyses.

Assisted reproductive technology

The DFG granted in 2015 a new collaborative application of the Max Planck Institute in Münster and the CeRA as continuation of our first grant “Towards an educated use of assisted reproductive technology: evaluation of the impact of culture media on mouse development based on standard assays and novel non-invasive microfluidic tools” (Verena Nordhoff, CeRA/Michele Boiani, MPI). In this 2015 grant, we aim to better understand the interplay of intrinsic factors (i.e. genetic predisposition or ‘nature’) and extrinsic factors (i.e. environment or ‘nurture’) in the genesis of the viable, less viable and non-viable embryonic states. We want to understand how the differences in embryo viability are wired in molecular terms: whether they hinge on the more or less permissive state of the zygote that precedes the start of in-vitro culture, or whether they are acquired during *in-vitro* culture,

or both. To tackle this problem, a 2-cell embryo bisection assay was established.
We first analyzed whether the bisected two cells are both equal (nature). And to our great astonishment, they are not equal in terms of expression data (Casser et al. Scientific reports 2017). This questions the concept of totipotency of the two-cell stage.
Furthermore we found that the culture of bisected cells in different human culture media (nurture) has a great impact on cell numbers at the blastocyst stage (Casser et al. ESHRE 2017, Price for best basic research poster). Further studies are ongoing and will help us to elucidate the impact of nature and nurture.

Epi-genetic diagnosis and research on male infertility

Very recently we implemented the routine screening for the FSHB haplotype in all patients at the CeRA. Together with the FSH receptor single nucleotide polymorphism we have now a genetic setup in which we could identify a subgroup of patients which would benefit from an FSH treatment, allowing for the first time a pharmacological approach to cure male infertility. We have developed a sensitive method based on the laser-capture microdissection of routinely fixed testicular biopsies that enables the analysis of the DNA methylation levels of several genes in cell-specific samples. Using this strategy, we are studying the DNA methylation levels of several genes in individual cell types derived from testicular biopsies ranging from complete spermatogenesis to meiotic arrest. In addition, by using micromanipulation, we are able to obtain samples containing a maximum of 10 spermatozoa. The measurement of DNA methylation levels in these small sperm samples is less affected by intra-individual variability and a large screening of epigenetic heterogeneity in sperm samples in currently ongoing.

Clinical studies on male infertility, male hypogonadism and hormonal male contraception

Male contraception has always been a key target in the research of our Centre. A hormonal approach to reach this goal has been targeted by our researchers in collaboration with other centres. In 2009, the worldwide largest efficacy trial on hormonal male contraception under the auspices of the WHO and CONRAD was initiated using testosterone undecanoate and norethisterone in injectable forms.

Münster participates as a leading centre with more than 50 couples and is the central laboratory for this multi-national trial. The first manuscript on the trial was published in 2016.
In 2009, we started with a controlled observational trial on the effects of testicular cancer and its treatment on the occurrence of hypogonadism and the metabolic syndrome. This project is ready for publication by now.
In 2010, a clinical research award of the Medical Faculty was given to the researchers of the Centre in collaboration with the Human Genetics Department to investigate the epigenetic effects of the supernumerary X-chromosome in Klinefelter men in relation to parental origin, gene activation, the CAG repeat polymorphism, cardiovascular risk and inflammation as well as fertility. The study is finished and the manuscript presently under review. The project was named the **Münster EXAKT project**: epigenetics and clinical applications in Klinefelter syndrome. The study is finished and the manuscript was published in 2015.
In addition, the clinical results of microsurgical TESE procedures in Klinefelter patients since 2008 were analyzed and parameters were identified to predict TESE outcome, especially in respect to age. Age and markers of Leydig cell function, but not of Sertoli cell function could be identified to predict the success of sperm retrieval in a cohort of 135 adolescents and adults with Klinefelter's syndrome.
In 2011, a clinical prospective multicentre trial started to investigate the induction of puberty and fertility with hCG/rFSH in boys with hypogonadotropic hypogonadism. The aim of the study is to elucidate the best induction treatment in respect to the psychological and physical health of boys and adolescents. The recruitment of the study is finished and treatment phase was accomplished at the end of 2015, showing best effects in young adolescents treated with gonadotropins and published 2016. In addition, with the help of a medical thesis, the best differential diagnosis between constitutional delay of puberty and true hypogonadotropic hypogonadism was re-evaluated in a cohort of 50 young adolescents. Serum inhibin B, less so INSL 3, and AMH levels were identified to be helpful in discriminating between constitutional delay of growth and puberty (CDGP) and hypogonadotropic hypogonadism (HH) in boys with delayed puberty.
In 2012/2013, a clinical prospective controlled international multicentre trial investigating the efficacy and tolerability of a new oral

testosterone preparation was performed. Patient enrolment and treatment is finished and evaluation is ongoing.
Our Centre participated in worldwide register study on the treatment of male hypogonadism in 1,438 men. Several trials concerning testosterone and its action and modulation by CAG polymorphisms were performed concerning spatial abilities and psychological issues and published.
Recently, we set up a study to elucidate the reproductive capacity in ageing men (**Fertility in Ageing Men, FAMe**) with healthy probands 18 to 80 years old to have a baseline cohort for further in-depth analysis of the process of ageing in the male. This study was awarded with the best oral presentation at the Congress of the German Society of Urology 2017 (Dr. J.-F. Cremers) and supported by a research grant of the German Society of Andrology (DGA) in 2016 (Dr. J.-F. Cremers).

Research funding

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Publications

Since the last EAA report in 2014, more than 140 peer-reviewed articles have been published and more than 25 book chapters have been written and can be found in the attached list.

Professor Sabine Kliesch, MD Professor Stefan Schlatt, PhD