EAA Andrology Training Centre

Centre Report





Centre identification School of Medicine University of Zagreb/University Hospital "Zagreb" Šalata 3, HR-10000 Zagreb/Kišpatićeva 12, HR-10000 Zagreb, Croatia Phone/Fax.: +385 1 45 90 251 e-mail: davor.jezek@mef.hr Director of the Centre: Prof. Dr Davor Ježek

**CENTRE REPORT** 

#### **History of Centre**

Although the EAA training centre in Zagreb (Croatia) was certified in 2016, reproductive medicine started to develop almost 60 years ago under the auspices of the School of Medicine University of Zagreb and University Hospital "Zagreb". At the beginning of 1953, the outpatient clinic for the treatment of sterility was established at the Clinic for Gynaecology and Obstetrics. It was the first organised activity to investigate and treat infertility in Croatia and the wider region. With the development of the medical profession and staff, a new department aroused: Department of Gynaecological Endocrinology and Sterility (1962) followed by the Centre for Gynaecological Endocrinology and Fertility (1977). Finally, in 1988 (up to the present time) the Centre was transformed into the Department of Human Reproduction. From the very beginning, the Department has a well-established andrology laboratory subjected to internal and external quality control. Six years later, the Department became a reference centre of the Ministry of Health and Social Welfare of the Republic of Croatia. The EEA training centre Zagreb and Department of Human Reproduction are strictly collaborating and are involved in a series of important activities, some of them listed in a chronological order: children and adolescent andrology and gynaecology (1967-1970); research and treatment of amenorrhea and intersexualism with the determination of the karyotype; new interpretations of the Morris syndrome, menopause praecox and gonadal dysgenesis (1962-1970); complex corrective surgery of abnormal sexual organs including hypo- and epispadias, vaginal aplasia, uterus duplex (1974); establishment of the Family Planning Centre (1978); foundation of the Centre for IVF and other methods of assisted fertilization (1982); beginnings of in vitro fertilization (IVF) (1982) with the first baby born with IVF (1983) (7th centre in the world); foundation of the outpatient clinic for sexually transmitted diseases (STD) (1986); embryo cryopreservation (1992); first application of intracytoplasmic microinjection of spermatozoa - ICSI (1994); introducing biopsy of the testis/ testicular sperm extraction / TESE / and TESE/ICSI procedure (1996); vitrification of embryos (2005) and oocytes (2009); application of oncofertility

procedures (2011); establishing of the first Testicular tissue biobank at the level of Republic of Croatia (2013). Today, all forms of research, diagnosis and treatment of male infertility are being applied in the EAA Training Centre Zagreb. In 2017, advanced methods of diagnosing DNA damage in spermatozoa have been introduced. The treatment of infertility is additionally accomplished by identifying ovarian reserve, risk of ovulation stimulation, and possible factors that reduce fertility and success of IVF. Modern approaches to andropause, contraception, gynaecological endocrinology, paediatric and adolescent andrology and gynaecology, as well as perimenopausal medicine, have been introduced. Overall, 15 clinical departments/clinics of the University Hospital "Zagreb" are included in the health care of the infertile couple. Leading role play Clinics for Urology and Gynaecology and Obstetrics. EAA The current director of the EAA Training Centre Zagreb is Prof. Dr Davor Ježek (EAA academician) and the clinical responsible is Prof. Dr Željko Kaštelan, the Head of Clinic of Urology. Zagreb, October 29, 2024

### **Organization of Centre**

EAA "Zagreb" is part of the University of Zagreb School of Medicine and University Hospital Zagreb (KBC "Zagreb"). KBC "Zagreb" functions as an umbrella health institution in the Republic of Croatia and is recognised by the Ministry of Health as a hospital of the highest category. For decades, the hospital has had a strong tradition of providing health services in the field of reproductive medicine and andrology. Given the complex nature of diagnostic, therapeutic and diagnostic-therapeutic procedures in the field of reproductive medicine, as many as fifteen clinics and clinical institutes of KBC "Zagreb" form a kind of intertwined network that functions within the EAA training centre in Zagreb.

These are the following clinics and clinical institutes:

Urology Clinic

Clinic for Women's Diseases and Obstetrics

Clinic for Internal Medicine

Clinic for Dermatovenerology

#### Book I

Pediatric Clinic Clinic of Neurology Oncology Clinic Clinic for Cardiovascular Diseases Psychological Medicine Clinic Clinic for Anesthesiology, Resuscitation and Intensive Care Clinical Department of Transfusion Medicine and Transplantation Biology Clinical Department of Pathology and Cytology Clinical Department for Laboratory Diagnostics Clinical Department of Clinical and Molecular Microbiology Clinical Department of Diagnostic and Interventional Radiology.

The key role in the EAA training centre Zagreb plays the Clinic for Urology. The Clinic is the largest urological institution in the Republic of Croatia and takes care of urological patients from all parts of the country. In addition to caring for urological patients, the Clinic is a place where specialist and subspecialist training in the field of urology and andrology is performed. Under the auspices of the Clinic, in addition to several reference centres of the Ministry of Health, there is also the EAA Center. In operational Theatre 2 (URO2), the Clinic of Urology has the necessary equipment to perform an open testicular biopsy that is part of the procedure of medically assisted fertilisation. In cooperation with the Department for Transfusion Medicine and Transplantation Biology (Testis biobank) and the Clinic for Women's Diseases and Obstetrics, a complex diagnostic-therapeutic procedure TESE / ICSI is performed. Besides, penile and urethroplasty techniques and treatment of erectile dysfunction have been developed within the Clinic. At the uro-oncology department, patients are provided with a full range of diagnostic and therapeutic procedures to treat various types of urological diseases (stones, BPH, etc.), with special emphasis on treating patients with malignant urological tumours. The most complex oncology patients who need an individual and multidisciplinary approach are treated here. The operative program covers tumours of all urological organs: kidney, ureter, bladder, prostate, testis and penis. Procedures performed in such patients reflect modern guidelines in urological surgery and include radical tumour nephrectomy (removal of the kidney

with the tumour), partial nephrectomy (removal of the tumour while preserving part of the kidney), radical nephroureterectomy (removal of the kidney and prostate), radical cystectomy (removal of the bladder) with all forms of urine drainage, radical orchidectomy (removal of testicles with a tumour), and surgical procedures for penile tumours. The Prostate Center is a functional unit of the Urology Clinic, opened on December 19, 2016. Its main function is to simplify the process and shorten the time required for diagnostic processing and treatment of prostate disease. In 2019, the Clinic obtained robotic surgery equipment for advanced urology and abdominal operations. For many years, the Clinic of Urology of the University Hospital Center Zagreb is the largest centre for kidney transplantation in the Republic of Croatia, and after our country joined Eurotransplant in 2007 and achieved top results in transplant medicine, it became a central place for education in the field of kidney transplantation. The Clinic of Urology is particularly developing transurethral techniques of minimally invasive procedures. Transurethral endoscopic technique is used in the treatment of benign prostatic hyperplasia, bladder cancer, urolithiasis, etc. With excellent collaboration with endocrinologists, nephrologists and oncologists, patients are provided with a wide range of laparoscopic surgeries. More than 100 laparoscopic procedures are performed annually at the Clinic. Examples of such procedures are laparoscopic adrenalectomy, laparoscopic retroperitoneal lymphadenectomy (determination of disease stage or after chemotherapy as part of the treatment of patients with the testicular tumour), laparoscopic and retroperitoneal nephrectomy, radical nephrectomy and other interventions.

Please, refer to ORGANIZATIONAL CHART

### **Educational activities**

EEA Training Centre Zagreb participates in the graduate education of students of medicine in 2 study programmes: Medical Studies in Croatian language (annual intake: 300 students) and Medical Studies in English (annual intake: 50 students). During the courses entitled "Urology" and "Gynaecology and Obstetrics", essential principles of treatment of infertile male/couple are presented. The Centre also

Book I

participates in postgraduate education of endocrinologists, urologists and gynaecologists (annual intake: 15-20 postgraduate students per postgraduate programme). EAA Training Centre Zagreb is contributing to PhD studies via courses entitled "Biomedicine and Health" where new scientific advances in the area of andrology are presented. The Centre is especially active in sub-specialisation in andrology (in Croatia it is a part of the specialization in urology). Under the auspices of EAA, the Centre organized already three editions of the andrology school entitled "Testis Histology and Pathology for Clinical Andrologists and Embryologists" (in years 2017, 2019 and 2022) and five Andrology Symposia (in years 2017, 2018, 2019, 2022 and 2023). The aforementioned andrology school was pursued together with EAA Training Centre in Copenhagen.

### **Research activities**

# Center of Excellence of the Medical Faculty of the University of Zagreb for Reproductive and Regenerative Medicine

In 2014, EAA Training Centre was awarded the status of Centre of Excellence for Reproductive and Regenerative Medicine by European Commission. The Centre has two research units (for reproductive and regenerative medicine). In the year 2017, the Centre of Excellence was awarded a grant from EU (grant no. K.K. 01.1.1.01.0008, 5 mils. EURO) to pursue with the project entitled "The reproductive and regenerative medicine: the investigation of new platforms and potentials" (2017-2027).

### The research unit "Biomedical research of reproduction and development"

The research unit "Biomedical Research of Reproduction and Development" of the Center of Excellence of the Medical Faculty of the University of Zagreb was created in response to the health needs of modern Croatian society. It is generally known that in the EU (including the Republic of Croatia) 15% of couples have fertility problems. The recent demographic data point to the fact that there is a very worrying annual deficit of 15,000 newborns in Croatia. For example, only the school year 2012/2013. 130 classes of "first-graders" were enrolled less than a year earlier. It is estimated that 80,000 couples in Croatia are infertile, and only 12,000 couples are treated. There is also a very dangerous trend of delayed childbirth: as many as 31% of Croatian women give birth to their first child at the age of 31-35. years of age, and only 14% of couples decide to have a third child. Epidemiological data in the last 15 years also indicate a worrying increase in infertility in our country of 5%. There is also a higher incidence of testicular neoplasms, the most common tumour of young men aged 15-28 years and congenital anomalies. All these above-mentioned problems of the younger Croatian population were the motive for gathering a multidisciplinary group of scientists from the basic, clinical and public health fields of reproductive medicine. The research unit, in addition to its headquarters at the Medical Faculty of the University of Zagreb, gathers a wide range of the following institutions and professional societies: University Hospital "Zagreb", Clinic for Children's Diseases in Zagreb, University Hospital "Sisters of Mercy", Clinical Hospital "Holy Spirit ", IMI (Institute for Medical Research and Occupational Medicine), the Croatian Society of Clinical Genetics and the Croatian Society of Human Genetics. The project tasks of the Research Unit (modelled on the FP7 and Horizon 2020 projects) can be roughly divided into basic and translational research and public health actions and training of young researchers. Of course, these studies are intertwined and interconnected and include the following tasks:

1. Investigations of epigenetic markers during the reproduction and development of mammals

- 2. Epigenetic studies of congenital anomalies
- 3. Epigenetics and germ cell tumours
- 4. Biomarkers of abnormal pregnancy
- 5. FSHR gene polymorphism
- 6. Human testis and sperm

As can be seen, the focus of the research is on epigenetics. Epigenetic research will include the study of gene expression regulation at the level of DNA methylation -

reversible genetic changes that are both hereditary and can be modified by lifestyle. Such regulation is necessary for the normal development of gametes, embryonic stem cells, embryos and placenta, so deviation from this can lead to infertility, abnormal placenta development and congenital anomalies. Epigenetic changes play an important role in the initiation and development of tumours and other human diseases. Specific epigenetic markers detected in various disorders may serve as biomarkers with prognostic values. Epigenetic therapy is already available today. Besides, the Centre conducts studies on animal models and different human populations using genetic and non-genetic methods and provides a link between basic research on reproduction and development of mammals (conducted on animal models in vivo and in 9 Centre Report vitro) and clinical research on male infertility, placental dysfunction, congenital anomalies and genetic disorders. This will enable two-way translation, basic research towards problems in medical practice and vice versa. Of particular importance is the study of the environmental impact on the mother and newborn through a multidisciplinary approach involving genetic, epigenetic, immunological, genotoxicological and endocrine biomarkers, which will be analysed and interpreted by complex multiparametric analyses. Translational research includes the improvement of some forms of clinical practice of reproductive medicine. Efforts will be made to introduce the method of freezing and cultivating spermatogonia as a kind of stem cells which, if modified and autotransplant, can restore spermatogenesis in an infertile man. Particularly important translational research will focus on oncofertility. It is planned to introduce a tissue bank of immature gonads of girls and boys with malignant diseases as well as mature ovaries to store gametes for future autotransplantation before chemo and radiotherapy. Public health and other actions intended to be taken include the printing of educational leaflets describing the selfexamination of the testicles.

In 2024, the Centre of Excellence applied for a new EU project worth 1.5 mil. EURO. The project application got positive reviews and, currently, the Centre is waiting for the definitive decision of the Ministry of Science, Education and Youth.

### A project of Croatian research fund: EPI-SEM

In 2017, Croatian agency for research awarded the EAA Training Centre Zagreb with the project entitled "Epigenetic biomarkers in blood and ejaculate in patients with seminoma" (budget: 128.684 EURO). Testicular germ cell (TGCT) tumours are the most common tumours of the younger male population in the world. Our epidemiological study from 2011 showed the highest trend of increasing incidence rate in the world and high mortality in the Croatian population. "Model-based" research on risk trends and demographic trends from 2014 highlights the Croatian population as one of the three most vulnerable in Europe and predicts that in Croatia by 2025, one in 100 men will be diagnosed with TGCT per year. Seminoma is the most common type of TGCT, with a trend of further increase. Both (micro) environmental and (epi) genetic factors are thought to lead to its development. Today, epimutations of DNA methylation stand out as tumour biomarkers due to their high frequency and pronounced chemical and biological stability, which gives them an advantage in the development of non-invasive diagnostics. It is precisely the research of biomarkers from body fluids that is strongly encouraged today as this concept is considered one of the foundations of personalized medicine. The proposed prospective study hypothesises that biomarkers of seminoma at the level of free DNA methylation can be identified in blood plasma and ejaculate. In parallel with the anamnestic and clinical treatment, a comprehensive study of DNA methylation will be performed on samples of patients before and after therapy and the results will be compared with samples of healthy men. Comparison of free DNA and tumour DNA methylation results, as well as variations in gene copy number, will clarify the proportion of tumour DNA in body fluids, eliminate background free DNA noise from healthy tissue, and show the impact of genomic aberrations on informative free DNA methylation analysis. Comparison of these results with protein expression of the examined genes in seminomas in samples of the same patients will clarify the relationship between the methods of modern molecular pathology and the proposed new approaches in the development of personalized medicine. Scientific contribution in the field of development of epigenetic biomarkers in body fluids of oncology patients is expected.

#### A project of Croatian research fund: EPI-PRO

In 2018, Croatian agency for research awarded the EAA Training Centre Zagreb with the project entitled "Epigenetic markers of prostatic carcinoma" (budget 276.315 EURO). Epigenetic disorders can be identified extremely early in the development of human disease and represent a dynamic area of research for potential biomarkers. Awareness of the competitiveness of epigenetic research is slowly developing in Croatian science, which is recording a decline in prostate cancer (RP) research. However, RP is the second most common cancer and the third leading cause of death in men from cancer in the Republic of Croatia, the incidence of which is growing steadily, as well as mortality. It is thought that epigenetic biomarkers (EB) would allow for earlier diagnosis and a higher survival rate. Methylation of DNA and microRNA (miRNA) stand out as EB, and several EB prostate cancers have been identified in tumour tissue research. This research is based on the latest concept in the development of EB in the 11 Centre Report framework of male reproductive health -EB research in the causes of liquid biopsies, i.e. in ejaculate and blood. RP-associated genes and miRNAs were selected for molecular analysis in accordance with the latest findings in the literature. In the semen and blood of patients with RP, non-cellular DNA methylation profiles (cfDNA) will be determined by pyrosequencing, and miRNA expression by qPCR or ddPCR. Epigenetic and expression profiling will also be performed on tumour samples of the same patients. In addition to research activities, the project intends to raise awareness of the benefits of introducing epigenetic issues in established research groups, educate future young researchers and contribute to the development of non-invasive diagnostics of RP. Therefore, a new multidisciplinary Group for the Research of Epigenetic Biomarkers (epiMark) was established within this project.

### **Clinical activities**

Clinical activities & techniques are as follows:

- Semen analysis
- Comprehensive endocrinological analysis
- Outpatient clinic ( andrology + endocrinology)
- Outpatient clinic for sexually transmitted diseases (STD)
- Outpatient clinic for infertility couple

- Outpatient clinic for psychological counselling of infertile couple, gender dysphoria, erectile dysfunction etc.

- Management of erectile dysfunction

- Ultrasound of the testis, prostate, accessory glands, retroperitoneal lymph nodes etc.,

CT and NMR facilities

- Genetics of male infertility (karyogram, Y chromosome microdeletions (including extended analysis), CFTR

- Comprehensive microbiology analysis

-cTESE, m-TESE

- Histology of testicular biopsies
- IVF facility applying advanced ART including programmed and snap freezing
- Management of varicocele
- Prostate centre (BHP, US, biopsies, laparoscopic and robotic surgery)
- Management of testicular neoplasms (uro-oncology team)
- Penoplasty and penile prosthesis
- Vasectomy & vasectomy reversal

### Name and address of Centre

European Academy of Andrology Training Centre ZAGREB School of Medicine University of Zagreb/University Hospital "Zagreb" Šalata 3, HR-10000 Zagreb/Kišpatićeva 12, HR-10000 Zagreb, Croatia, EU Phone/Fax.: +385 1 45 90 251

Type of CentreUniversityXUniversity HospitalXPrivate Centre	
Other (please	
specify]	
1. Director	Prof. Davor Ježek, M.D., Ph.D.
Academician X Regular Meml	ber EAA Certified Clin. Andrologist
2a. Clinical responsible	Prof. Željko Kaštelan, M.D., Ph.D.
Academician Regular Meml	ber EAA Certified Clin. Andrologist
2b. Clinical responsible	Dinko Hauptman, M.D., Ph.D. , urology/andrology specialist
Academician Regular Meml	ber X EAA Certified Clin. Andrologist
2c. Clinical responsible	Zoran Zimak, M.D., urology/andrology specialist
Academician Regular Meml	ber EAA Certified Clin. Andrologist

13

# 3. Present Staff (Senior Scientists)

1)	Name Degree Speciality	Prof. Ana Katušić Bojanac, Ph.D. biologist Genetics
Academician [	Regular Memb	er X EAA Certified Clin. Andrologist
2)	Name Degree Speciality	Prof. Nino Sinčić, M.D., Ph.D. Medical doctor Genetics
Academician [	Regular Memb	er EAA Certified Clin. Andrologist

Insert any additiona	staff below	(if requ	ired)
----------------------	-------------	----------	-------

MD/Biologists/ 1)	Chemists Name Degree	Zoran Zimak
	Speciality	Urology/Andrology
	Full time/part time	Full time
Academician	n Regular Men	nber EAA Certified Clin. Andrologist
2)	Name	Nikola Knežević
	Degree	Prof., M.D., Ph.D.
	Speciality	Urology
	Full time/part time	Full time
Academician	n Regular Men	ber EAA Certified Clin. Andrologist
3)	Name	Tvrtko Hudolin
	Degree	Prof., M.D., Ph.D.
	Speciality	Urology
	Full time/part time	Full time
Academician	n Regular Men	ber EAA Certified Clin. Andrologist
4)	Name	Nina Gelo
	Degree	Biologist, Ph.D.
	Speciality	Clinical embryology (ESHRE certified)
	Full time/part time	Full time
Academician	n Regular Men	iber EAA Certified Clin. Andrologist
5)	Name	Dinka Pavičić Baldani
	Degree	Prof., M.D., Ph.D.,
	Speciality	Gynaecology and Obstetrics, human reproduction
	Full time/part time	(ESHRE Board Member) Full time
Academician	n Regular Men	ber EAA Certified Clin. Andrologist
6)	Name	Lana Škrgatić
,	Degree	Prof., M.D., Ph.D.
	Speciality	Gynaecology and Obstetrics, human reproduction
	Full time/part time	Full time
Academician	n Regular Men	nber EAA Certified Clin. Andrologist

Name Marina Šprem Goldštajn 7) Prof., M.D., Ph.D. Degree Speciality Gynaecology and Obstetrics, human reproduction Full time Full time/part time Academician Regular Member EAA Certified Clin. Andrologist Maja Banović 8) Name Assoc. Prof., M.D., Ph.D. Degree Gynaecology and Obstetrics, human Speciality reproduction Full time/part time Full time Academician Regular Member EAA Certified Clin. Andrologist 9) Name Marija Vilaj Degree Biologist Speciality Molecular biology Full time/part time Full time Academician Regular Member EAA Certified Clin. Andrologist 10) Name Monika Trupinić Biologist Degree Speciality Molecular biology Full time/part time Full time Academician Regular Member EAA Certified Clin. Andrologist 11) Name Tina Dušek Prof., M.D., Assoc. Prof. Degree Speciality Endocrinololgy Full time/part time Full time Regular Member EAA Certified Clin. Andrologist Academician 12) Name Saša Kralik Degree Biochemist, Ph.D. Clinical Biochemistry Speciality Full time/part time Full time

16

# Insert any additional staff below (if required)

# Specialists

1) Name	
2) Name	
3) Name	
4) Name	
5) Name	
PhD Students	
1) Name	Ana Planinić, M.D.
2) Name	
3) Name	
Nurses	
1) Name	
2) Name	
3) Name	
Laboratory Technicians	
1) Name	Suzana Tutić Lazić
2) Name	Tomislav Popović
3) Name	
Administrative Personnel	
1) Name	Tara Dmitrović
2) Name	Barbara Kalenić
3) Name	

# 4. Clinical Activity

A. Outpatients: Consultations per year in the last 3 years

	2021	2022	2023
New patients	1171	1146	1213
Follow-up patients	528	563	593
Type of patients in the last years (%)	2021	2022	2023
	07	00	00

(70)			
Infertility	27	22	33
Erectile dysfunction	5	3	6
Hypogonadotropic Hypogonadism	0.21	0.23	0.24
Klinefelter	1.4	1.3	1.8
Gynaecomastia	1.5	1.0	1.5
Varicocele	11	14	12
Cryptorchidism	3	0	4
Male sex accessory gland infections	14	12	13.5
Testicular tumours	4.7	3.6	4.2
Disorders of gender identity	0.022	0.018	0.025
Other			

B. Ultrasound (testis, penile, prostate) \*

	2021	2022	2023
Total	945	933	1019
Controls	423	419	458

\* performed at the Department of Radiology

C. Andrological surgery procedures

	2021	2022	2023
Testicular biopsies	47	48	35
Varicocele ligation	30	29	32
Prostate biopsies	481	496	537
BPH	185	177	196
Prostate cancer	279	294	328
Vasectomy			1
Vaso-vasostomy			0
Other			

5. A. Andrology laboratory activity

	2021	2022	2023
Semen analyses	543	522	578
Sperm antibodies	0	0	0
Seminal markers	543	522	578
5. B. Andrology laboratory activity			
Sperm banking donors	Yes		No X
Sperm banking cancer patients	Yes	X	No
If yes:			
	2021	2022	2023
Number of samples	37	36	48
<b>5. C.</b> Histopathologial evaluation of bio	opsies	Yes X	No
5. D. Reproductive Hormones Assays		Yes X	No
If yes please specify type of assays and Reproductive Hormones Assays (FSH, LH, testosterone, SHBG, prolacti	l number of san n) 536	ples in the last yea	r
<b>5. E.</b> Y chromosome microdeletions ac EAA/EMQN guidelines	cording to	Yes X	No
<i>If yes</i> number of tests in the past year			48
Participation to the EAA quality control scheme?		Yes	K No
<i>If no,</i> specify if available in another lab of the same hospital		Yes	No
Blood karyotyping		Yes X	No
<i>If no,</i> specify if available in another lab of the same hospital		Yes	No
Other genetic tests (please specify) FISH sperm YES Pre-implantation genetic diagnosis No Amniotic fluid karyotyping YES	)		

#### 20 6. Collaborations with other Clinical Units of the University/Hospital **IVF Unit** Yes X No If yes please specify: Children, Endocrinology, IVF, Urology, Genetics, Pathology **Urology** Clinic Yes Х No **Endocrine Clinic** No Yes Х Genetics Lab/Unit Yes Х No Paediatric Unit Yes Х No **Central Hospital Laboratory** No Yes Х **Private Centres** Х Yes No *If yes* please specify: testicular biopsies 7. Clinical teaching activity Duration of training (years): 5 Number A: Trainees in the last five years 85 B: Trainees who passed EAA-ESAU\exam for Clinical Andrologist in 0 the last 5 yrs C: Trainees working in the centre preparing to pass the EAA-ESAU 2 examination D: PhD Students 11 E: Medical Students 350/annualy F: Other students (MSc) 0 8. Formal Andrology teaching program Yes Х No *If yes:* specify duration (years/months): Months 6 Years Hours of formal teaching **Professional training** (weeks/months) per year **Medical Students** 40 2 weeks 24 months PhD Students 120 Post Graduate students 360 12 months Trainees 360 24 months Other degrees (please specify)

#### 9. Research Activity (maximum 1 page)

Please shortly describe the main research topics of the center and list the most relevant papers in peer review journals (with IF) related to these activities. *The full list of publications (years 2015 - 2020) are presented at the end of this report.* 

The research unit "Biomedical Research of Reproduction and Development" of the Centre of Excellence of the Medical Faculty of the University of Zagreb was created in response to the health needs of modern Croatian society. The research unit, in addition to its headquarters at the Medical Faculty of the University of Zagreb, gathers a wide range of the following institutions and professional societies: University Hospital "Zagreb", Clinic for Children's Diseases in Zagreb, University Hospital "Sisters of Mercy", Clinical Hospital "Holy Spirit ", IMI (Institute for Medical Research and Occupational Medicine), the Croatian Society of Clinical Genetics and the Croatian Society of Human Genetics. The project tasks of the Research Unit (modelled on the FP7 and Horizon 2020 projects) can be roughly divided into basic and translational research and public health actions and training of young researchers. Of course, these studies are intertwined and interconnected and include the following tasks:

1. Investigations of epigenetic markers during the reproduction and development of mammals

- 2. Epigenetic studies of congenital anomalies
- 3. Epigenetics and germ cell tumours
- 4. Biomarkers of abnormal pregnancy
- 5. FSHR gene polymorphism
- 6. Human testis and sperm

As can be seen, the focus of the research is on epigenetics. Epigenetic research will include the study of gene expression regulation at the level of DNA methylation reversible genetic changes that are both hereditary and can be modified by lifestyle. Such regulation is necessary for the normal development of gametes, embryonic stem cells, embryos and placenta, so deviation from this can lead to infertility, abnormal placenta development and congenital anomalies. Epigenetic changes play an important role in the initiation and development of tumours and other human diseases. Specific epigenetic markers detected in various disorders may serve as biomarkers with prognostic values. Epigenetic therapy is already available today. Besides, the

Centre conducts studies on animal models and different human populations using genetic and non-genetic methods and provides a link between basic research on reproduction and development of mammals (conducted on animal models in vivo and in vitro) and clinical research on male infertility, placental dysfunction, congenital anomalies and genetic disorders. This will enable two-way translation, basic research towards problems in medical practice and vice versa. Of particular importance is the study of the environmental impact on the mother and newborn through a multidisciplinary epigenetic, approach involving genetic, immunological, genotoxicological and endocrine biomarkers, which will be analysed and interpreted by complex multiparametric analyses. Translational research includes the improvement of some forms of clinical practice of reproductive medicine. Efforts will be made to introduce the method of freezing and cultivating spermatogonia as a kind of stem cells which, if modified and autotransplant, can restore spermatogenesis in an infertile man. Particularly important translational research will focus on oncofertility. It is planned to introduce a tissue bank of immature gonads of girls and boys with malignant diseases as well as mature ovaries to store gametes for future autotransplantation before chemo and radiotherapy. Public health and other actions intended to be taken include the printing of educational leaflets describing the selfexamination of the testicles.

In 2024, the Centre of Excellence applied for a new EU project worth 1.5 mil. EURO. The project application got positive reviews and, currently, the Centre is waiting for the definitive decision of the Ministry of Science, Education and Youth.

#### **10. Research Funding**

Please specify the amount of available funds in the last 3 years and their source (Government, European Union, University, Local Government, Pharmaceutical Industries, Banks, Foundations....)

Year	2021
Total amount (€)	2.5 mil. EURO
Funding	European union (KK.01.1.1.01.0008.)
Source(s)	

**Year** 2023

Book I

Total amount (€)	10.000 EURO
Funding	University of Zagreb
Source(s)	
Year	2023
Total amount (€)	20.000,000 EURO
Funding	University of Zagreb
Source(s)	

### **ORGANIZATION CHARTS**

# Organization charts legend: Department / Unit Structure

#### Organization charts legend: Department / Unit Structure

Unit Name	EAA Training Centre Za University Hospital Zaj	agreb Director EAA Centre: Prof. Dr. Davor Ježek
Head	Head: Prof. Dr. Željko k	Caštelan
Staff member 1 Staff member 2 Staff member 3 Staff member 4	Dr. Dinko Haputman Dr. Zoran Zimak Marija Vilaj Suzana Tutić	Clinic for Urology
Outpatient Clinics Embryology Ovarian stimulation Ultrasound Occute retrieval	Dr. Mihajlo Strelec. D	r. Marina Šprem
Embryo transfer	Dr. Lana Škrgatić. Dr.	Avicic Baldani, Clinic for Gynaecology and Obstetrics
FNA / TESE Diagnosis of infertility Counseling of infertile couple	Nina Pleše Gelo, Gabr	ijela Kirinec
Cryopreservation of sperm Ethics in Andrology	Clinical services	Clinic for Internal Medicine Clinic for Dermatovenerology Pediatric Clinic
		Clinic of Neurology
		Click for Carling and Pierra
		Clinic for Cardiovascular Diseases
		Clinic for Anesthesiology Resuscitation and
	Andrology Symposia	Intensive Care
Contribution to EAA training	Testis Histology School	and Transplant Biology Clinical Department of Pathology and
		Clinical Institute for Laboratory Diagnostics
		Clinical Department of Clinical and
		Molecular Microbiology
		Clinical Department of Diagnostic and Interventional Radiology

# **CENTRE PHOTOS**







### FULL LIST OF PUBLICATIONS (with IF) of staff members from the last 5 years

Planinic A, Maric T, Himelreich Peric M, Jezek D, Katusic Bojanac A. Dynamics of HSD17B3 expression in human fetal testis: implications for the role of Sertoli cells in fetal testosterone biosynthesis. Front Cell Dev Biol. 2024 Jul 30;12:1429292. doi: 10.3389/fcell.2024.1429292. PMID: 39139451; PMCID: PMC11319120. (IF = 4.6, Q1)

Klarić ML, Marić T, Žunić L, Trgovec-Greif L, Rokić F, Fiolić A, Šorgić AM, Ježek D, Vugrek O, Jakovčević A, Barbalić M, Belužić R, Katušić Bojanac A. FANCM Gene Variants in a Male Diagnosed with Sertoli Cell-Only Syndrome and Diffuse Astrocytoma. Genes (Basel). 2024 May 28;15(6):707. doi: 10.3390/genes15060707. PMID: 38927643; PMCID: PMC11202954. . (IF = 3.5, Q2)

Hasan H, Peng W, Wijayarathna R, Wahle E, Fietz D, Bhushan S, Pleuger C, Planinić A, Günther S, Loveland KL, Pilatz A, Ježek D, Schuppe HC, Meinhardt A, Hedger MP, Fijak M. Monocytes expressing activin A and CCR2 exacerbate chronic testicular inflammation by promoting immune cell infiltration. Hum Reprod. 2024 May 22:deae107. doi: 10.1093/humrep/deae107. Epub ahead of print. PMID: 38775335. (IF = 6.0, Q1)

de la Iglesia A, Egeberg DL, Marcu D, Richer G, Houston BJ, Ammar O, Saritas G, Delgouffe E, Jezek D, Krausz C, Rajpert-De Meyts E, Behre HM. Leading at the vanguard of andrology: The Network for Young Researchers in Andrology joins forces with the European Academy of Andrology. Andrology. 2024 May;12(4):781-784. doi: 10.1111/andr.13633. Epub 2024 Mar 20. PMID: 38506242. (IF = 3.2, Q1)

Krasic J, Skara Abramovic L, Himelreich Peric M, Vanjorek V, Gangur M, Zovko D, Malnar M, Masic S, Demirovic A, Juric B, Ulamec M, Coric M, Jezek D, Kulis T, Sincic N. Testicular Germ Cell Tumor Tissue Biomarker Analysis: A Comparison of Human Protein Atlas and Individual Testicular Germ Cell Tumor Component Immunohistochemistry. Cells. 2023 Jul 13;12(14):1841. doi: 10.3390/cells12141841. PMID: 37508506; PMCID: PMC10378501. (IF = 5.1, Q1)

Cannarella R, Jezek D, Condorelli RA, Calogero AE. Editorial: Male idiopathic infertility: Novel possible targets, volume II. Front Endocrinol (Lausanne). 2023 Mar 6;14:1172878. doi: 10.3389/fendo.2023.1172878. PMID: 36950697; PMCID: PMC10026698. (IF = 3.9, Q1)

Raos D, Oršolić D, Mašić S, Tomić M, Krasić J, Tomašković I, Gabaj NN, Gelo N, Kaštelan Ž, Kuliš T, Bojanac AK, Barešić A, Ulamec M, Ježek D, Sincic N. cfDNA methylation in liquid biopsies as potential testicular seminoma biomarker. Epigenomics. 2022 Dec;14(23):1493-1507. doi: 10.2217/epi-2022-0331. Epub 2023 Feb 1. PMID: 36722130. (IF = 2.27, Q2)

Nagirnaja L, Lopes AM, Charng WL, Miller B, Stakaitis R, Golubickaite I, Stendahl A, Luan T, Friedrich C, Mahyari E, Fadial E, Kasak L, Vigh-Conrad K, Oud MS, Xavier MJ, Cheers SR, James ER, Guo J, Jenkins TG, Riera-Escamilla A, Barros A, Carvalho F, Fernandes S, Gonçalves J, Gurnett CA, Jørgensen N, Jezek D, Jungheim ES, Kliesch S, McLachlan RI, Omurtag KR, Pilatz A, Sandlow JI, Smith J, Eisenberg ML, Hotaling JM, Jarvi KA, Punab M, Rajpert-De Meyts E, Carrell DT, Krausz C, Laan M, O'Bryan MK, Schlegel PN, Tüttelmann F, Veltman JA, Almstrup K, Aston KI, Conrad DF. Diverse monogenic subforms of human spermatogenic failure. Nat Commun. 2022 Dec 26;13(1):7953. doi: 10.1038/s41467-022-35661-z. PMID: 36572685; PMCID: PMC9792524. (IF = 14.7, Q1)

Bašković M, Zaninović L, Sansović I, Meašić AM, Katušić Bojanac A, Ježek D. Trends in the treatment of undescended testes: a pediatric tertiary care center experience from Croatia. World J Pediatr Surg. 2022 Oct 31;5(4):e000461. doi: 10.1136/wjps-2022-000461. PMID: 36474738; PMCID: PMC9716856. (IF = 0.8, Q4)

Peng W, Kepsch A, Kracht TO, Hasan H, Wijayarathna R, Wahle E, Pleuger C, Bhushan S, Günther S, Kauerhof AC, Planinić A, Fietz D, Schuppe HC, Wygrecka M, Loveland KL, Ježek D, Meinhardt A, Hedger MP, Fijak M. Activin A and CCR2 regulate macrophage function in testicular fibrosis caused by experimental autoimmune orchitis. Cell Mol Life Sci. 2022 Nov 24;79(12):602. doi: 10.1007/s00018-022-04632-4. PMID: 36434305; PMCID: PMC9700630. (IF = 6.2, Q1)

Cannarella R, Bertelli M, Condorelli RA, Vilaj M, La Vignera S, Jezek D, Calogero AE. Analysis of 29 Targeted Genes for Non-Obstructive Azoospermia: The Relationship between Genetic Testing and Testicular Histology. World J Mens Health. 2023 Apr;41(2):422-433. doi: 10.5534/wjmh.220009. Epub 2022 Jul 14. PMID: 36047072; PMCID: PMC10042652. (IF = 4.0, Q1)

Himelreich Perić M, Takahashi M, Ježek D, Cunha GR. Early development of the human embryonic testis. Differentiation. 2023 Jan-Feb;129:4-16. doi: 10.1016/j.diff.2022.07.001. Epub 2022 Jul 16. PMID: 35961887. (IF = 2.2. Q3)

Planinić A, Marić T, Bojanac AK, Ježek D. Reinke crystals: Hallmarks of adult Leydig cells in humans. Andrology. 2022 Sep;10(6):1107-1120. doi: 10.1111/andr.13201. Epub 2022 Jun 15. PMID: 35661438. (IF = 3.2, Q1)

Krasic J, Skara L, Bojanac AK, Ulamec M, Jezek D, Kulis T, Sincic N. The utility of cfDNA in TGCT patient management: a systematic review. Ther Adv Med Oncol. 2022 May 25;14:17588359221090365. doi: 10.1177/17588359221090365. Erratum in: Ther Adv Med Oncol. 2022 Jun 14;14:17588359221108536. doi: 10.1177/17588359221108536. PMID: 35656387; PMCID: PMC9152191. (IF = 4.3, Q2)

Book I

Himelreich-Perić M, Katušić-Bojanac A, Hohšteter M, Sinčić N, Mužić-Radović V, Ježek D. Mast Cells in the Mammalian Testis and Epididymis-Animal Models and Detection Methods. Int J Mol Sci. 2022 Feb 25;23(5):2547. doi: 10.3390/ijms23052547. PMID: 35269690; PMCID: PMC8909951. (IF=4.9, Q2)

Bašković M, Krsnik D, Himelreich Perić M, Katušić Bojanac A, Sinčić N, Sonicki Z, Ježek D. Astaxanthin Relieves Testicular Ischemia-Reperfusion Injury-Immunohistochemical and Biochemical Analyses. J Clin Med. 2022 Feb 26;11(5):1284. doi: 10.3390/jcm11051284. PMID: 35268375; PMCID: PMC8911179. (IF=3.0, Q1)

Bašković M, Knežević N, Ježek D. Scrotal cooling as a protective method in tissue preservation after testicular torsion. Cent European J Urol. 2021;74(4):601-602. doi: 10.5173/ceju.2021.0244. Epub 2021 Nov 6. PMID: 35083083; PMCID: PMC8771140. (IF=1.4, Q3)

Raos D, Abramović I, Tomić M, Vrtarić A, Kuliš T, Ćorić M, Ulamec M, Katušić Bojanac A, Ježek D, Sinčić N. CNV Hotspots in Testicular Seminoma Tissue and Seminal Plasma. Cancers (Basel). 2021 Dec 31;14(1):189. doi: 10.3390/cancers14010189. PMID: 35008352; PMCID: PMC8750740. (IF=4.5, Q1)

Cannarella R, Condorelli RA, Jezek D, Calogero AE. Editorial: Male Idiopathic Infertility: Novel Possible Targets, Volume I. Front Endocrinol (Lausanne). 2021 Nov 17;12:797228. doi: 10.3389/fendo.2021.797228. PMID: 34867832; PMCID: PMC8635955. (IF=3.9, Q1)

Hauptman D, Perić MH, Marić T, Bojanac AK, Sinčić N, Zimak Z, Kaštelan Ž, Ježek D. Leydig Cells in Patients with Non-Obstructive Azoospermia: Do They Really Proliferate? Life (Basel). 2021 Nov 19;11(11):1266. doi: 10.3390/life11111266. PMID: 34833142; PMCID: PMC8624241. (IF=3.2, Q1)

Mokos M, Planinić A, Bilić K, Katušić Bojanac A, Sinčić N, Bulić Jakuš F, Ježek D. Stereological properties of seminiferous tubules in infertile men with chromosomal and genetic abnormalities. Minerva Endocrinol (Torino). 2022 Mar;47(1):11-22. doi: 10.23736/S2724-6507.21.03589-2. Epub 2021 Jul 30. PMID: 34328293. (IF=2.5, Q3)

Bašković M, Bojanac AK, Sinčić N, Perić MH, Krsnik D, Ježek D. The effect of astaxanthin on testicular torsion-detorsion injury in rats - Detailed morphometric evaluation of histological sections. J Pediatr Urol. 2021 Aug;17(4):439.e1-439.e12. doi: 10.1016/j.jpurol.2021.03.020. Epub 2021 Mar 27. PMID: 33839034. (IF=2, Q2)

Caltabiano R, Condorelli D, Panza S, Boitani C, Musso N, Ježek D, Memeo L, Colarossi L, Rago V, Mularoni V, Spadola S, Castiglione R, Santoro M, Aquila S, D'Agata R. Glucagon-like peptide-1 receptor is expressed in human and rodent testis.

Andrology. 2020 Nov;8(6):1935-1945. doi: 10.1111/andr.12871. Epub 2020 Aug 11. PMID: 33460247. (IF=3.2, Q1)

Raos D, Krasic J, Masic S, Abramovic I, Coric M, Kruslin B, Katusic Bojanac A, Bulic-Jakus F, Jezek D, Ulamec M, Sincic N. In Search of TGCT Biomarkers: A Comprehensive In Silico and Histopathological Analysis. Dis Markers. 2020 Nov 6;2020:8841880. doi: 10.1155/2020/8841880. PMID: 33224314; PMCID: PMC7666710.

Raos D, Ulamec M, Katusic Bojanac A, Bulic-Jakus F, Jezek D, Sincic N. Epigenetically inactivated RASSF1A as a tumor biomarker. Bosn J Basic Med Sci. 2021 Aug 1;21(4):386-397. doi: 10.17305/bjbms.2020.5219. PMID: 33175673; PMCID: PMC8292865. (IF=3.1, Q2)

Abramovic I, Ulamec M, Katusic Bojanac A, Bulic-Jakus F, Jezek D, Sincic N. miRNA in prostate cancer: challenges toward translation. Epigenomics. 2020 Mar;12(6):543-558. doi: 10.2217/epi-2019-0275. Epub 2020 Apr 8. PMID: 32267174. (IF=3.0, Q2)

Kordić M, Tomić D, Soldo D, Hauptman D, Ježek D. Reinke's crystals in perivascular and peritubular Leydig cells of men with non-obstructive and obstructive azoospermia: a retrospective case control study. Croat Med J. 2019 Apr 30;60(2):158-165. doi: 10.3325/cmj.2019.60.158. PMID: 31044589; PMCID: PMC6509619. (IF= 1.5, Q2)