CENTER FOR MEN'S HEALTH, LOS ANGELES BIOMEDICAL RESEARCH INSTITUTE AT HABOR-UCLA MEDICAL CENTER, TORRANCE, CALIFORNIA, USA

Full name and address of the Center
Center for Men's Health,
Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center,
Division of Endocrinology, Department of Medicine,
Harbor-UCLA Medical Center,
1124 W. Carson Street,
Torrance,
CA 90502, USA.

Full name and address of the Director
Professor Ronald S. Swerdloff,
Professor of Medicine,
David Geffen School of Medicine at UCLA,
Chief, Division of Endocrinology,
Associate Chair, Department of Medicine,
Harbor-UCLA Medical Center
1000 W. Carson Street,
Torrance,
CA 90509, USA
Telephone: 1-310-222-1867
Fax: 1-310-533-0627
E-mail: swerdloff@labiomed.org

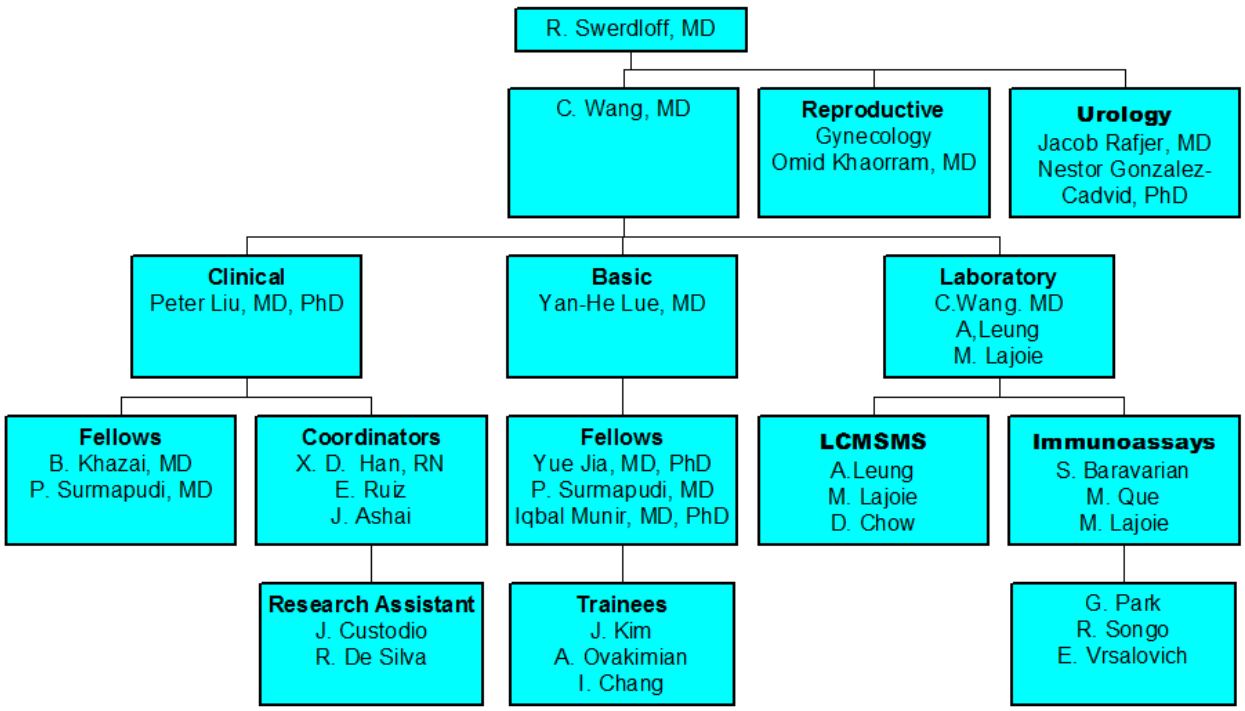
History of the Center
The Center of Men's Health (Harbor-UCLA Male Reproductive Research Center) was established in 1973 under the current director Professor Ronald Swerdloff. It is located the Los Angeles Biomedical Research Institute (LA BioMed) on the campus of the Harbor-UCLA Medical Center. All faculty of the center are faculty of the David Geffen School of Medicine at UCLA. Harbor-UCLA Medical Center, a public hospital serving the indigent population of the South Bay of Los Angeles County, includes the hospital and clinics (both operated by the Los Angeles County Department of Health Services) along with research facilities under the auspices of the Los Angeles Biomedical Research Institute (LA BioMed). Covered under the Center umbrella is a WHO Collaborating Center for Research in Human Reproduction and a NIH (National Institute of Health) Contraceptive Clinical Trial Network Center in the Male area. The training of Andrology in the United States is not clearly defined and generally takes place in the Division of Urology or the Division of Endocrinology. Andrology unlike Obstetrics and Gynecology is not a recognized sub-specialty and there is no formal program of training or accreditation by the American Society of Andrology or any other accreditation committee. In recent years the American Society of Andrology introduced a Challenge Test which provides scores but is not an accreditation test. The Center of Men's Health under the direction of Dr. Swerdloff specializes in the training of both basic and clinical andrologists. The Endocrinology and Metabolism training program funded by an NIH training grant continuously for 35 years provides both research and clinical training.

Present Staff and Organization of the Center
The present staff and organization of the center are depicted in Figure 1.

Collaboration
Collaborating clinicians, investigators and faculty within the institution includes: Obstetrics and Gynecology (Professor Anita Nelson and Professor Omid Khorram); Radiology-Ultrasonography (Dr. Robert Sinow); Oncology and Women's health (Professor Rowan Chlebowski); Rehabilitation Medicine (Professor Richard Casaburi); Cardiology (Professor Matthew Budoff); Urology and Urology Research (Professors Jacob Rajfer and Nestor Gonzales-Cadavid); Pediatric Andrology (Associate Professor Catherine Mao and Professor Paul W.N Lee). Our collaborations with other institutions within Los Angeles include UCLA-Westwood Campus with Pediatric Endocrinology (Professor Pinchas Cohen and Associate Professor Kuk-wha Lee), Division of Rheumatology (Professor Ram Singh) and Mass Spectrometry Core (Professor Julian Whitelegge); Neurosurgery at John Wayne Cancer Institute (Professor Daniel Kelly); and Endocrinology (Professor Fouad Kandeel, City of Hope Medical Center). Collaborators outside of Los Angeles include: Professor William Bremner and his colleagues in Seattle (Male Contraception); Professors Peter Snyder (Philadelphia), Shalendar Bhasin (Boston), Alvin Matsumoto (Seattle) and Glenn Cunningham (Houston) (The Testosterone Trial); Population Council (Professor Regine Sitruk-Ware and Dr. Narendar Kumar). International collaborators include: Reproductive Biology Laboratory at Nanjing Medical University (Professors Sha, Zhou and Cui) and the Jiangsu Family Planning Research Institute (Professor Xin-Hai Wang), China; Professor Yi-Xun Liu, Institute of Zoology, Chinese Academy of Science, Beijing, China; Professor David Handelsman and Associate Professor Peter Liu, University of Sydney; Dr. Krista Erkkila, University of Helsinki; and Dr. Jason Lerch, Mouse imaging Centre, Toronto Centre for Phenogenomics.

Management of Patients with Andrological Problems

Fig.1 Organization Chart of the Center of Men's Health



The patients andrological problems are seen at the Medical Center's Endocrine, Pituitary, Diabetes, Pediatric Endocrinology, Urology and Reproductive Endocrinology Clinics. The clinic statistics are given in Table 1. Patients with hypogonadism are generally seen and investigated in the Endocrine clinic where approximately 5% of patients have male hypogonadism, infertility and transsexualism. Most of the patients in our Diabetic Clinic have Type 2 diabetes and about 20 % of these have male hypogonadism or erectile dysfunction. Patients with hypogonadism associated with pituitary and hypothalamic problems are investigated and treated in the Pituitary Clinic where about 25 to 35% of the patients have male hypogonadotrophic hypogonadism due to pituitary tumors. The Medical Center will support the use of gonadotropins for induction of spermatogenesis with special medication request and justification for a limited number of patients. The hormone analyses for these patients are performed by the Medical Center's Clinical Chemistry Department and most of the specialized tests are sent out to Reference Laboratories. Patients with

ambiguous genitalia, cryptorchidism, and micropenis, delayed or precocious puberty are referred to the Pediatric Endocrine Clinic running on the same days as the adult clinics. In the urology clinic (Chief of Urology, Dr. Rajfer) about 7 to 10 % of the subjects present with erectile and sexual dysfunction, hypogonadism, and male infertility. In addition Dr. Rajfer performs testicular microdissection and sperm extraction from testis for approximately 40 to 50 patients per year with male infertility. The infertile couple is usually initially investigated in the Reproductive Endocrinology Clinic (Chief of Reproductive Endocrinology, Dr. Khorram). Because infertility treatment is not covered by insurance and the government sponsored MediCare and Medical programs in California, patients seen in our public medical clinics have no additional resource and little access to infertility diagnosis and treatment. The Medical Center supports ovulation induction by clomiphene and a very limited ovulation induction with gonadotropins by special request. Thus the wide range of male infertility, genetics of male infertility and ART investigations and treatment are not available through the Medical Center and performed through the private clinics of Drs. Swerdloff, Rajfer and Khorram (see Table 1). The Center's Andrology Laboratory supports semen analyses and preparation of samples for IUI for

these private clinics. IVF and ICSI and testicular extraction or epididymal aspiration of sperm is not performed on campus but in associated ART clinics (Dr. Khorram and Rajfer).

Table 1. Number of Clinic Visits and Procedures, last three years

		2009	2010	2011	Pro-jected 2012
Endo-crine	Total	2312 **(139)**	2069 **(132)**	2008 **(123)**	2103 **(120)**
	New	**218** **(11)**	206 **(8)**	199 **(14)**	220 **(12)**
Diabetes	Total	2734 **(456)**	2545 **(397)**	2946 **(425)**	3045 **(512)**
	New	187 **(28)**	197 **(32)**	235 **(36)**	245 **(30)**
Pituitary	Total	543 **(84)**	527 **(87)**	503 **(92)**	514 **(89)**
	New	102 **(19)**	96 **(18)**	98 **(21)**	104 **(22)**
Urology	Total	**(1285)**	**(1279)**	**(1262)**	**(1298)**
	New	**(87)**	**(93)**	**(86)**	**(90)**
Repro-ductive Endo	Total*	1243	1329	1385	1420
	New*	402	425	418	437
Pediatric Endo		639 **(53)**	732 **(62)**	642 **(58)**	763 **(72)**
Dr. Swerd-loff	Androl ogical	114 **(64)**	126 **(57)**	123 **(59)**	116 **(60)**
Dr. Rajfer	TESE	**(29)**	**(29)**	**(31)**	**(32)**
Dr. Khor-ram	Infer-tility	480 **(134)**	510 **(162)**	550 **(152)**	568 **(176)**
	IVF	120	135	140	152
	ICSI	60	65	70	73
	IUI	25	35	40	43

Number in parenthesis and in bold are patients with andrological problems (hypogonadism, sexual dysfunction, infertility, other andrological issues)
*Approximately 15% have infertility

Endocrine Metabolic Research and Andrology Laboratory

The Endocrine and Metabolic and Andrology Laboratory is directed by Dr. Wang and licensed by the State of California and CLIA and operates under Good Laboratory Practice. Hormone assays performed include testosterone, free testosterone, DHT, estradiol, and adrenal androgens by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS); FSH, LH, SHBG, levonorgestrel, inhibin β, by fluoro-immunoassays (FIAs), immunoradiometric assays or ELISA. The laboratory is equipped with tow Liquid Chromatography Tandem Mass Spectrometers. The laboratory participates in external quality control programs run by the College of American Pathologists. In addition, the laboratory also participates in the Center of Disease Control Steroid Hormone Standardization Program since its inception. The laboratory also runs rat and mouse FSH FIAs and LH FIAs and the heterologous inhibin assay for rat inhibin. All assays have been extensively validated with standardized quality control procedures according to guidelines set by regulatory agencies. The laboratories also house the clinical research data management unit with a consultant. All samples are bar-coded before or upon arrival in the laboratory and the state of the sample, the location of the samples is then logged into an electronic ledger system. The laboratory to follow HIPAA guidelines with regards to confidentiality of the patient's protected health information.

The Andrology Core Laboratory is equipped with two Olympus BH-2 microscopes both for light and fluorescence microscopy and a Hamilton-Thorne Research computer assisted sperm analysis (CASA) system. Tests regularly performed are routine semen analysis and occasionally for sperm preparation for intra-uterine insemination. Advanced sperm function tests include acrosome reaction, sperm motility characteristics by CASA, and zona free hamster egg penetration test are for research purposes. The laboratory is responsible for the semen analyses primarily for diagnostic workup for the infertile men and functions as the core laboratory clinical study protocols and basic science research projects. Our laboratory has participated in many multi-center clinical trials and currently serves as the central laboratory for external quality control and morphology examination for one reproductive toxicology study. The laboratory is licensed by the State of California and CLIA for the human semen analysis and participates in the External Quality Control program of the College of American Pathologists. Table 2 shows the number of assays and semen analyses we have performed for the last three years.

Table 2. Number of Laboratory Tests done by the Endocrine Research and Andrology Laboratory for the Past Three Years

	Yr 2009	Yr 2010	Yr 2011	Projected Yr 2012
T	2707	1802	4047	5870
Free T	97	402	581	1260

	Yr 2009	Yr 2010	Yr 2011	Projected Yr 2012
FSH	190	484	1726	2014
LH	179	459	1714	2010
SHBG	159	0	2602	2142
DHT	2555	1703	1161	2488
E2	1199	686	631	1620
Semen Analyses	256	538	275	175

Clinical Training Program

The clinical andrology training program is directed by Professors Swerdloff and Dr. Christina Wang and the faculty that include the newly recruited Professor Peter Liu, and Research Professor Yan-He Lue. All MD fellows are expected to attend the Core Curriculum. The topics relevant to Andrology include: Hormone action, hormone receptors and signaling pathways; hormone assays and problems; sexual differentiation and ambiguous genitalia; normal, delayed and precocious puberty; hypopituitarism and gonadotropin secreting tumors; male infertility diagnosis, investigation and treatment; male hypogonadism including male aging; androgen and androgen therapy; male and female sexual dysfunction, transsexualism; and osteoporosis. The clinical trainees attend clinics at least two sessions per week. Those M.D. fellows who are specifically interested in reproductive medicine are encouraged to participate in a supplementary male (Drs. Swerdloff - male infertility and hypogonadism; Rajfer's-erectile dysfunction and male infertility; Kandeel's-male sexual dysfunction) and female reproductive clinics (Dr. Khorram's Reproductive Endocrinology and Infertility Clinics).

In addition, Drs. Swerdloff, Rajfer and Wang meet with the trainees for Andrology Tutorials where the trainee are required to read relevant up-to date literature on topics and discussed in tutorial sessions (6 sessions of 1.5h exposure). The clinical trainees are required to spend time in Endocrine Research and Andrology laboratory to learn the basics of hormone assays and semen analyses. Those trainees involved in clinical research on male contraception, androgen biology, metabolism, and pharmacology, and reproductive toxicology meet weekly for at least 1 ½ hours with Drs. Swerdloff, and Wang, project research coordinators, project technical staff, Dr. Peter Christenson (Biostatistician), and volunteer coordinators to discuss progress, problems, statistical analysis and ongoing strategy. All MD trainees are required to take the mandatory training in he Protection of Human Research Subjects, HIPAA and Good Clinical Practice required by the Institution. The trainees supported by the NIH training grant are required to enroll in the UCLA Training Program in Translational Research leading to a Certificate or Master in Clinical Research.

MD/PhD fellows doing basic research participate in the 1 ½ hour per week Reproductive Laboratory Research Meeting, each fellow presents their ongoing work to a group of about 10 fellows, research associates, students and investigators. Each fellow has an opportunity to speak once every 6-8 weeks and shares in all discussions.

Research fellows meet frequently and regularly with their research mentor and in smaller multidisciplinary focus groups. Since 2009, all incoming research fellows have a primary mentor and a secondary mentor in another discipline e.g. a clinical investigator mentor and a laboratory based investigator. In addition, trainees doing basic research attend Saturday morning weekly strategy and program development sessions. All fellows are expected to attend the Basic Science Seminar Series (covering broad molecular biology and physiology topics) and the Biostatistics Course. In addition, the trainees are encouraged to attend the UCLA Clinical and Translational Science Institute (CTSI) sponsored research training courses including Biomedical Research and Experimental Techniques, Responsible Conduct of Research, Introduction to the Principles and Practice of Clinical Research which run throughout the year. MD Fellows are required to attend the weekly Endocrine Clinical Conference (didactic lectures) and the weekly Endocrine Grand Rounds (case presentations and discussions, journal club by trainees and faculty).

The MD trainees are usually accepted for no less than 2 (Clinical Track- requirement for Endocrinology certification in Internal Medicine), and often 3 years (Academic Track) and each will work under the close supervision of one or more of the primary mentors. The Ph.D. trainees will spend full-time in research activities; M.D. trainees in the academic track spend year 1 in clinical training and attending research training curriculum. In year 2 to 3, they will spend at least 75 % or more of their time in research.

Research Activities

1. Clinical Research

The Male Reproductive group at Harbor-UCLA includes both basic and clinical scientists from diverse scientific backgrounds studying the mechanism responsible for the control of spermatogenesis, androgen metabolism and therapy, male reproductive toxicology, iNOS and stem cell replacement in erectile

dysfunction amongst others. Our trainees participate as sub-investigators in these studies.

a. Male Contraceptive studies: The center led by Drs. Swerdloff and Wang has conducted many research studies on the development of a male hormonal contraception including earlier studies on testosterone ester, GnRH agonists and antagonists, and most recently on long acting implants of levonorgestrel with various preparations of testosterone. The center is one of the two NICHD, NIH Contraceptive Clinical Trial Network Center in the Male. These centers have a bi-directional communication with the NICHD where clinical studies are designed together and the centers are ready to complete phase 1 to 3 studies when new promising lead for male contraception has completed pre-clinical and toxicology studies. The first protocol approved will examine the suppression of spermatogenesis by transdermal application of testosterone and Nestorone 9 a new potent progestin) gels on suppression of gonadotropins to determine the dose of Nestorone required to suppress both LH and FSH. Once this study was completed a proof of concept study was designed to compare the effectives of testosterone gel alone or with Nestorone gel in suppressing sperm production. This study that enrolled 99 subjects in Los Angeles and the other Contraceptive Clinical Trial Network Center at the University of Washington showed that transdermal application of the combination of testosterone and Nestorone was effective in suppressing spermatogenesis. The study report manuscript has been submitted for review. Currently the center submitted an Investigational New Drug application to the US-FDA for a phase 1 study of a new androgen, Dimethandrolone which is orally active and binds to the androgen and progesterone receptor. The study just started at our study as well as the University of Washington.

b. Late Onset Hypogonadism: Dr. Swerdloff is a member of the steering committee that developed the National Institute of Aging (NIA) testsosterone interventional treatment study (T Trial). This study which started recruitment 2010 has completed enrollment for half of the required 800 participants in 12 centers in the United States. The primary aim of the study is to test whether testosterone treatment of elderly men whose serum testosterone levels are unequivocally low - and who have symptoms and objectively measured abnormalities in one of four areas that could be due to low testosterone (physical, sexual, cognitive function, or vitality) –will result in more favorable changes in those abnormalities than placebo treatment. The four are coordinated but have different eligibility criteria, end points and power analyses for the required subject. In addition there are sub-studies to examine the effect of testosterone on anemia, bone health and cardiovascular disease risks by CT angiography. Adverse events are monitored including detailed assessment of cardiovascular adverse events. The recruitment is anticipated to end in 2014.

c. Hormone Replacement Studies in Hypogonadal Men: Drs. Swerdloff and Wang have performed Phase I, II, and III studies on various formulations of testosterone and 5 alpha dihydrotestosterone (DHT) as replacement for hypogonadism in young, middle-aged, and older men. Our center was the lead center in early studies of transdermal testosterone gel. Since then our center studied the pharmacokinetics and pharmacodynamics of buccal, long acting injectable and higher concentration testosterone lotion in hypogonadal men and served as lead authors for the publications on these delivery studies. Currently the center is involved a phase 3 study of a new formulation oral testosterone undecanoate in hypogonadal men based on phase 2 studies performed at our center.

d. Male Reproductive Toxicology Studies: Drs. Swerdloff and Wang have performed human reproductive toxicology studies for a number of pharmaceutical companies on compounds that are in phase 2 or 3 clinical trials but needed additional data to assure regulatory agencies of reproductive safety. Examples include studies on 5 alpha reductase inhibitors, phosphodiesterase inhibitors IV and V, gabapentin, endothelin receptor blockers, botulinium toxin and others. Our semen and hormone laboratories have served as the central or coordinating centers for a number of these trials.

e. Klinefelter Syndrome: Dr. Swerdloff and the center is collaborating with Ram Singh, MD to study the reported higher incidence of autoimmune disease such as systemic lupus erythematosis and the associated with the extra X chromosome.

f. Semen characteristics and reproductive health and relationship to possible environmental toxicants: Our center participated in a NIEHS and EPA supported study to characterize regional differences in sperm quantity (in partners of pregnant women) and to relate those differences to differences in exposure to putative environmental toxins. Our study showed geographical differences in semen parameters in different parts of the United Sates and relationship of these parameters to putative endocrine disruptors. Dr. Swan, a collaborator, continued follow-up studies in children born to mothers who participated in the study examine their behavior in relationship to the levels of the endocrine disruptors.

2. Basic Research

a. Regulation of Spermatogenesis: We have utilized mice (normal and mutant), rat, and monkey models and then extend our studies to men to characterize the regulatory pathways that lead to regressed states of spermatogenesis associated with experimental male contraceptives and exogenous testicular stress such as transient testicular hyperthermia. We have delineated that the hormonal deprivation resulted in accelerated apoptosis in the hormone sensitive middle stages of spermatogenesis whereas heat affected the early and late stages. The pachytene spermatocytes and round spermatids at the middle stages are most vulnerable to hormone deprivation. In contrast, pachytene spermatocytes and early spermatids at stages I-IV at stages XII-XIV are most susceptible to heat treatment. The apoptosis occurred through mitochondria-dependent intrinsic pathway signaling.

In the human study, we found that Insulin Growth Factor Binding Protein-3 (IGFBP-3) was significantly up-regulated during apoptosis of germ cells induced by testicular hormonal deprivation. Subsequent studies showed that IGFBP-3 induced and its binding partner humanin protected against germ cell death. Furthermore, studies in our laboratory showed that IGFBP-3 interacts with BAX, a pro-apoptotic protein that is critical in the mitochondrial pathway of germ cell death in the apoptotic pathway. The laboratory is now focused on the investigation of the pro-survival peptides in protecting germ cell death induced by testicular stresses including cancer chemotherapeutic agents. We are investigating the interaction with its putative trimeric membrane receptor and the mechanisms of action of humanin in protecting male germ cell as well as the somatic cells.

b. Mouse Model of Klinefelter syndrome. We have used a breeding scheme where XXY mice are generated by utilizing a four-generation breeding scheme that involves the use of a structurally rearranged Y chromosome, Y*, yielding approximately 50% of the live born male offspring in the fourth generation with a XXY karyotype. Adult XXY mice have small testes, decreased serum T levels, and elevated serum FSH levels. The testes of adult XXY mice contained small seminiferous tubules with intraepithelial vacuolization and absence of germ cells whereas Leydig cells appeared to be more abundant than their XY littermates. We have studied osteopenia, learning dysfunction, germ cell loss, and testosterone deficiency in 41 XXY mice. In the neurobehavioral studies, we have demonstrated that learning ability was delayed in XXY compared to XY mice but improved with practice and testosterone replacement, Changes in gender preference behavior was noted in XXY. In collaboration with the mouse imaging center in Toronto, Canada, our preliminary mouse brain MIR data from 10 adult XXY and 10 littermate XY mice suggests change in the bed nucleus of the stria terminalis (BNST) and in the hypothalamus in XXY brain as compared with XY brain. This may indicate that the neurobehavioral changes in XXY individual may result from the anatomic alterations in brain structure. In the studies of testes, we have characterized the germ cell loss by apoptosis and germ cell migration as the mice progress from day 1 to 10 days of age and subsequently into adulthood. The preliminary data suggests that the early differentiation of gonocytes may be a cause of the germ cell loss in their early life of XXY individual. Adult XXY mice have low testicular venous and peripheral blood levels of testosterone (with elevated LH and FSH levels) yet have normal to elevated intra-testicular testosterone levels. In-vitro production of testosterone in isolated Leydig cells and in the whole testis showed increased production of testosterone in the XXY mice compared to XY mice. This suggests testosterone is sequestered in the testes. Germ cell transplants from XY mice to XXY mice shows seeding of the GFP labeled XY donor germ cells into 41XXY immature and adult recipients with progression to spermatocyte or spermatid germ cells. While overexpression of non-X inactivated genes is believed to be a likely molecular basis for the disorder, the reasons for phenotypic heterogeneity are only partially understood and the relative roles of tissue specific genes versus T deficiency needs further study.

c. Stem cell in the testis: Autologous transplantation of reprogrammed stem cell may provide a new approach for treatment of acquired or congenital testicular failure. We have demonstrated that transplanted adult bone marrow cells, in a favorable testicular environment, differentiate into somatic cell and germ cell lineages in mice. Our preliminary data demonstrating that Very Small Embryonic Like Stem Cells (VSELs) were able to colonize in recipient seminiferous tubules of c-Kit mutant (genetically depletion of germ cells) and busulfan treated (chemotherapeutic agent induced depletion of germ cells) mice at 6 month after transplantation. However, we were not able to show donor VSELs differentiate into sperm in recipient testes. Recently, we have established mouse testis organ culture system in our laboratory. The preliminary data showed that XY gonocytes from 3dpp testes cultured for 4 weeks were able to differentiate into late spermatocytes in this testicular organ culture system. The study is ongoing to define the culture condition to induce gonocytes differentiation into haploid germ cells in vitro. This culture system will allow us to establish method to induce reprogrammed adult stem cells transdifferentiation into germ cells in vitro and study the underlying molecular mechanisms.

d. Penile Diseases and Erectile Dysfunction (ED) – The group of Drs. Rajfer and Gonzales-Cadavid studied the role of iNOS in an animal model of Erectile Dysfunction. Their group has shown recently that corporal veno-occlusion dysfunction occurred in aging rats making this model suitable for the mechanism causing and possible novel treatment of ED in man. Their group is focusing on understanding fibrosis as a mechanism of Peyronie's Disease. They injected Transforming Growth Factor (TGF)-β1into the tunica albuginea of mice used this as an animal models of Peyronie's disease and myofibroblasts cultures as an in vitro model of plaques. The profibrotic factors including TGF-β1, plasminogen activator inhibitor 1, reactive oxygen species are induced by trauma to the tunica albuginea, leading to myofibroblast accumulation and excessive deposition of collagen. There is alos increased in inducible nitric oxide synthase, leading to increased nitric oxide and cGMP levels that act as an endogenous antifibrotic mechanism. Long-term continuous administration of phosphodiesterase type 5 inhibitors counteracts the development of a Peyronie's Disease-like fibrotic plaque in a rat model.

Research Funding

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Publications

The following are selected publications from the center from 2009 to 2102 April.

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Site Visit Schedule

EAA Site Visit April 26th , 2012

Site Visitors: Professors Jorma Toppari (Turku, Finland0 and Csilla Krausz (Florence, Italy)

Time	Agenda	Responsible Person
800-830	Breakfast and Introductions	Prof. R. Swerdloff/ C. Wang
830-900	Overview of andrology and training activities	Prof. R. Swerdloff
900-930	Andrology training and research in urology	Prof. J. Rajfer
930- 1000	Andrology training and research in reproductive medicine	Prof. O. Khorram
1000-1015	Andrology laboratory training	Prof. C. Wang
1015-1030	Questions and discussion	
1030-1100	Break	
1100-1115	Overview of clinical research projects	Prof. R. Swerdloff
1115- 1130	Cardiovascular trial of the T Trial	Dr. B. Khazai (Trainee)
1130-1145	Phase I study of Dimethandrolone	Dr. P. Surampudi (Trainee)

1145-1215	Questions and Discussion	
1215 -1315	Lunch Break	
1314-1345	Visit to clinical and research facilities	
1345-1400	Overview of Basic Research	Prof. C. Wang
1400-1430	XXY mice model for Klinefelter's syndrome	Prof. Y. Lue
1430-1445	Humanin and the Testis-Introduction	Prof. C. Wang
1445-1515	Humanin action and its trimeric receptors	Drs. Y. Jia and P. Surampudi (Trainee)
	Humanin a cytoprotector	A. Aikoui (Trainee)
1515-1545	Questions and Discussion	
1545- 1630	Internal Discussion of the Review Board and Drafting of the Report (to be continued on the next morning)	Prof. Toppari and Krausz
1630 -1800	Lectures by Site Visitors "Y chromosome deletions and male Infertility" "Endocrine disruptors and testicular function'	Prof, Csilla Krausz Prof. Jorma Toppari