Methods:

In addition to discussing some of the controversies that exist, we will also examine the use of in vitro systems for the study of diseases such as Parkinson's and Rett syndrome. The recent demonstration of in vitro reprogramming using transduction of 4 transcription factors by Yamanaka and colleagues can be used to develop guidelines for vasectomy, addressing many of the controversies using published studies. Vasectomy reversal, although somewhat uncommon, provides couples with a cost-effective method for having children after previous vasectomy. Outcomes are dependent upon several factors which should be addressed on an individual basis.

Results:

We have used this technology to generate isogenic pairs of cells that differ exclusively at a disease causing mutation. The talk will describe the use or isogenic pairs of mutant and control iPSCs to establish in vitro models for the study of diseases such as Parkinson’s and Rett syndrome.

Conclusion:

Vasectomy is a highly efficacious, minimally invasive form of permanent contraception. Evidence-based literature has been used to develop guidelines for vasectomy, addressing many of the controversies using published studies. Vasectomy reversal, although somewhat uncommon, provides couples with a cost-effective method for having children after previous vasectomy. Outcomes are dependent upon several factors which should be addressed on an individual basis.

Methods:

The recent AUA Guidelines were developed using an evidence-based approach. A systematic review of the literature using the MEDLINE and POPLINE databases with search dates January 1949-August 2011 was conducted to identify peer-reviewed relevant publications. The search identified almost 2,000 titles and abstracts. Application of inclusion/exclusion criteria yielded an evidence base of 275 articles. Only a small subset of these articles is referenced in this summary. A complete list of references and a full explanation of AUA guideline methodology can be found in the unabridged text of Vasectomy: AUA Guideline (2012), which is available online at http://www.auanet.org/content/media/vasectomy.pdf. Although there is not a similar document for vasectomy reversal, a group of experts are currently in the process of assembling a literature search to develop similar Best Practice guidelines.
SPEAKER ABSTRACTS

vitro gonocyte differentiation were several related to the ubiquitin proteasome system. Indeed, active proteosomal degradation was required for differentiation. Next, we examined the mechanisms involved in vitro retinoic acid-induced gonocyte differentiation, and identified two signaling pathways crosstalk with the retinoic acid pathway, src and JAK/STAT. We previously reported that gonocyte proliferation also involves signaling crosstalk between PDGF and estradiol, mediated by Erk1/2 activation. Thus, gonocyte functions appear to require the coordinated activation and interaction of several signaling pathways. These findings suggest that more than one signal transduction pathways are necessary to maintain a tight control of germ cell function within the very dynamic environment of the developing testes, which is flooded by factors regulating somatic cell proliferation and/or differentiation. Funding provided by NSERC, CIHR, CSR and RQR grants and awards.

SUNDAY, APRIL 6, 2014
9:15 a.m. – 10:45 a.m.

SYMPOSIUM I – Stem Cells in the Male Reproductive Tract
REGULATION OF SPERMATOGONIAL STEM CELLS IN THE ADULT TESTIS
William W. Wright, PhD
Division of Reproductive Biology, Department of Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Spermatogonial stem cells (SSCs), a subset of the undifferentiated A single (A<sub>s</sub>) spermatogonia, are the foundation of spermatogenesis. SSCs give rise to non-stem A<sub>pr</sub> spermatogonia, which along with the A paired (A<sub>p</sub>) and the A aligned (A<sub>a</sub>) spermatogonia, constitute the transit-amplifying progenitor spermatogonia. It is know that the Sertoli cell product, glial cell line-derived neurotrophic factor (GDNF), is essential for maintaining numbers of these cells, but it is unknown whether the specific cells that this growth factor affects are A<sub>s</sub>, A<sub>pr</sub> and/or A<sub>a</sub> spermatogonia, or whether SSCs and progenitor spermatogonia are equally responsive to changes in GDNF signaling. To examine these issues we used a chemical-genetic approach to inhibit GDNF signaling in the adult, and identified cells by their expression of GFRα1 and their connection to one or more cells. Results showed that inhibition of GDNF signaling for two days suppressed replication of A<sub>s</sub>, A<sub>pr</sub> and A<sub>a</sub> spermatogonia. Furthermore, their replication was stimulated when GDNF was added to cultured seminiferous tubules for two days. We next asked whether in vivo GDNF suppressed a late step in spermatogonial differentiation, expression of Kit. Results show that in vivo inhibition of GDNF signaling for three or seven days progressively increased the percentages of A<sub>s</sub>, A<sub>pr</sub> and A<sub>a</sub> spermatogonia expressing this marker of differentiation. Finally, we report that SSCs are lost more slowly than progenitor spermatogonia when GDNF signaling is inhibited. This suggests that SSCs are less responsive to changes in GDNF signaling than are progenitor spermatogonia.
acquire a new mutation over a man’s life would increase explaining the paternal age effect. We studied the above RAMP mutations in the testes of unaffected men using a testis dissection and mutation detection approach. We rejected the hot spot hypothesis for each disease mutation. Instead our data were consistent with normal SSC rarely undergoing any one of these RAMP mutations but, when they do, they acquire a proliferative advantage over the non-mutated SSC. This advantage increases the frequency of sperm carrying the mutated allele and the risk that a father will have an affected child as he ages. It is surprising that some mutations that have a selective advantage in the testis might reduce the fitness of those individuals who inherit it.

I will discuss the evidence to support these assertions. I will also suggest plausible molecular mechanisms that might explain the selective advantage of the mutated spermatogonial stem cells based on what is known about mouse and human spermatogenesis.

SUNDAY, APRIL 6, 2014
4:45 p.m. – 5:30 p.m.

LECTURE II
NOVEL SPERMATOGENIC PATHWAYS AND MALE CONTRACEPTION
Martin M. Matzuk, MD, PhD, Denise Archambault, PhD, Julio Castaneda, PhD, Zhifeng Yu, PhD, Mary Titus, Ryan Matzuk, Julio Agno, Ramiro Ramirez-Solis, PhD, James Bradner, MD and Masahito Ikawa, PhD
Baylor College of Medicine, The Wellcome Trust Sanger Institute, Dana Farber Cancer Institute and Harvard Medical School, and Osaka University

Objectives: Over the last two decades, our research program has focused on the identification and functional analysis of genes and pathways involved in mammalian reproduction. In the process, we have identified novel genes involved in germ cell intercellular bridge formation (e.g., TEX14) and the piRNA pathway (e.g., GASZ). Infertility in male mice lacking a specific gene would indicate that the gene product would be a novel target for contraception in men. Our goals are to identify and characterize germ-cell specific genes required for fertility and determine if these proteins are druggable targets for contraception.

Methods: We have taken a discovery-based approach to uncover male fertility required genes and small molecules that target these essential proteins for a reversible contraceptive effect.

Results: We have already published papers on some of the novel testis-specific gene products, and in 2012, we showed that JQ1 can target BRDT for a reversible contraceptive effect in mice.

Conclusions: Our discovery-based approach has opened up new avenues of research in our laboratory and the fields of infertility and contraception. We believe that germline-specific proteins are excellent targets for reversible contraception in men.

Funding for our research has been provided by the Eunice Kennedy Shriver National Institute of Child Health and Human Development.

MONDAY, APRIL 7, 2014
8:00 a.m. – 9:00 a.m.

WOMEN IN ANDROLOGY LECTURE
HORMONE SIGNALING AND REPROGRAMMING IN HUMAN PROSTATE STEM CELLS
Gail S. Prins, PhD
Department of Urology, University of Illinois at Chicago

Early-life exposures to estrogens reprograms the rat prostate gland structure and epigenome leading to differentiation defects and increased susceptibility to cancerous lesions with aging (1). We hypothesize that developmental estrogenization of the prostate occurs, in part, through stem and progenitor cell reprogramming that permits long-term memory of this exposure throughout life. To address whether this occurs in humans, we developed in vitro and in vivo models utilizing cells from organ donors as well as human embryonic stem cells (hESC). Stem and progenitor cells were isolated from primary prostate epithelial cells (PrEC) of young, disease-free donors using FACS and 3-D prostate-associating (PS) culture. Studies confirmed both cell populations as ERα + and ERβ + and showed that estradiol-17β (E2) significantly increased their proliferation. The estrogenic endocrine disruptor, bisphenol A (BPA), likewise increased stem-progenitor cell self-renewal and stem-related gene expression. Further, findings identify reprogrammed genes and snRNAs in prostate progenitor cells with E2 and low-dose BPA exposure suggesting epigenetic reprogramming. While E2 initiated genomic ERE signaling, both E2 and BPA activated membrane ERs with rapid induction of p-Akt and p-Erk. Additional studies identified distinct roles for ERs with ERα driving stem cell self-renewal and ERβ promoting stem cell entry into a differentiation pathway.

An in vivo model to assess carcinogenicity was developed using human PS cells mixed with rat UGM and grown as renal grafts in nude mice, forming normal human prostate epithelium at one month. Exposure to E2 + T for 2 – 4 months led to PIN or PCa at low incidence (13%). Developmental BPA exposure was modeled by daily feeding of hosts for two weeks after grafting (0.39-1.35 ng free-BPA/ml serum). Upon E2 + T for 2 – 4 months, the PIN/PCa incidence increased (P<0.01) to 33-36%. Similar modeling utilizing hESC reveals that BPA can augment prostate stem-cell self-renewal and is sufficient drive prostate pathology in the mature human prostate epithelium. Together these findings indicate that early stage progenitor and stem cells in the human prostate are direct E2 and BPA targets and that developmental BPA exposure reprograms the human prostate epithelium leading to elevated PCA susceptibility.

A decision by healthcare providers to give testosterone replacement therapy to an older male patient should rely on careful consideration of the potential benefits and risks of such therapy. Each patient, however, offers at least a subtly different clinical presentation, so weighing the relative benefits and risks for a specific patient is not always straightforward. The clinical evidence to support testosterone replacement for older men are relatively limited. During this symposium, several brief clinical cases will be presented to highlight some typical clinical situations. Each case will be followed by a review of the current literature as it pertains to the treatment issues being considered. Cases scenarios will include management of a hypogonadal man with cardiovascular disease, who has both fatigue and decline in physical function. We will also discuss treatment considerations for a hypogonadal man with erectile dysfunction who also has a history of radical prostatectomy for prostate cancer.

The manipulation of gonadotropin action in genetically modified mice has provided us with novel information about qualitative and quantitative aspects of the hormonal control of spermatogenesis. We tested in the hypogonadal luteinizing hormone receptor knockout (LuRKO) mouse the concept of the hormonal male contraception, i.e. that a single dose of testosterone (T) supplementation can suppress gonadotropins and testicular T production while simultaneously maintaining extragonadal sexual and anabolic androgen actions. It was found that the dose-responses of all extragonadal and intragonadal actions of T were practically identical. Hence, a single dose of T that would produce suppression of gonadotropin and testicular T production without simultaneously turning on spermatogenesis could not be defined. This explains why the hormonal male contraception with T has insufficient efficacy. In another study we crossed the LuRKO mice with a transgenic mouse expressing a constitutively activated mutant of follicle-stimulating hormone receptor (FSHR-CAM). While the LuRKO mice are azoospermic, the FSHR-CAM mutant males have no apparent phenotype. Interestingly, the LuRKO/FSHR-CAM double mutants had normal spermatogenesis. This was initially interpreted to be due to stimulation of Leydig cell T production by Sertoli cell-derived paracrine factors stimulated by enhanced FSHR function. However, spermatogenesis persisted in the double mutant mice when they were treated with antiandrogen (flutamide). This indicated that missing androgen stimulation of spermatogenesis can be compensated for by enhanced FSH action. Hence, it appears that T and FSH have additive and complementary effects on spermatogenesis. It was shown earlier that FSH/FSHR knockout male mice have largely normal spermatogenesis. Here we demonstrate that enhanced FSH stimulation can compensate for the absence of androgens in the maintenance of spermatogenesis.

Mammalian sperm become fertilization competent in the female tract in a process known as capacitation. This process is correlated with functional changes in sperm parameters such as the activation of sperm motility known as hyperactivation and the preparation to undergo a physiologically induced acrosome reaction. Taking into consideration the highly differentiated and compartmentalized nature of sperm, it can be postulated that the molecular basis of capacitation should account for independent changes occurring in different sperm compartments such as the flagellum (e.g. hyperactivation) and the head (e.g. preparation for the acrosome reaction). At the molecular level, capacitation is associated with the activation of a PKA-dependent phosphorylation cascade and with hyperpolarization of their membrane potential. It has been shown in multiple species that activation of PKA is needed for hyperactivation and to prepare the sperm for the acrosome reaction. Capacitation is also associated with the increase in intracellular Ca\(^{2+}\) concentrations. Work from our laboratory indicates that there is a crosstalk between the cAMP and the Ca\(^{2+}\) pathway. On one hand Ca\(^{2+}\) regulates cAMP synthesis and also its degradation. On the other hand, cAMP and PKA are upstream of the increase in Ca\(^{2+}\) needed for hyperactivation and for the sperm to acquire fertilizing capacity.

The age of paternity is increasing and there is growing societal concern regarding the potential consequences of this increase to progeny. Several epidemiological studies have established clear links between paternal age and an increased incidence of conditions such as autism, diabetes, cardiovascular anomalies, and schizophrenia in the next generation. Using animal studies, we have found that increasing paternal age affects progeny outcome, sperm quality, and the response to oxidative stress. We found significantly altered expression of genes involved in DNA damage/repair, the response to oxidative stress, and cell adhesion in isolated pachytene spermatocytes, but not in round spermatids, from young and aged rats. Further analysis of pachytene spermatocytes demonstrated that genes involved in the base excision repair (BER) and nucleotide excision repair (NER) pathways were specifically altered during aging. These studies established that aging is associated with differential reg-
SPEARER ABSTRACTS

ulation of DNA repair pathways. Furthermore, in aged males there was an increase in 8-oxo-2’-deoxyguanosine (8-oxodG) immunoreactivity in the testes and in the number of spermatozoa positive for 8-oxodG; thus, downregulation of the BER pathway led to oxidative-stress re-
in the testes and in the number of spermatozoa positive for 8-oxodG; an increase in 8-oxo-2´-deoxyguanosine (8-oxodG) immunoreactivity
ulation of DNA repair pathways. Furthermore, in aged males there was
from aged rats led us to hypothesize that spermatogonial stem cells
may be affected. Using CD9+ enriched GFP-marked spermatogonial
cells from young and aged rats and transplanting them into the testes
of busulfan-treated nude mice, we found that both colony numbers and
size were affected by age. The transcriptomes of FACS-isolated sper-
matogonial cells were analyzed to evaluate molecular changes occur-
ing in these cells with age. In the aged CD9+ enriched cells, an altered
gene expression was found for transcripts involved in mitosis and in
DNA damage response. These molecular alterations in the spermatogon-
ial enriched population of cells from the testes of aged rats imply that
stem/progenitor spermatogonia are contributors to the germ cell origin
of reproductible aging.
These studies were funded by the Canadian Institutes for Health Re-
search.

MONDAY, APRIL 7, 2014
3:30 p.m. – 4:15 p.m.

LECTURE III
THE STRESS HORMONE CORTICOTROPIN-RELEASING FACTOR ACTS IN THE BRAIN AND THE TESTES TO REGU-
LATE TESTOSTERONE SECRETION
Catherine Rivier, PhD
The Salk Institute for Biological Studies, La Jolla, CA

Objectives: Testosterone (T) secretion is usually considered hor-
monally regulated by hypothalamic gonadotropin-releasing hormone
(GnRH), the ensuing secretion of LH and the feedback provided by testicular steroids. However, dissociated LH and T release is observed
under a variety of stressors. This led us to propose the existence of a
multisynaptic neural pathway between the brain and the testes, in-
dependent of the pituitary that inhibits T secretion. Evidence for this
pathway was further indicated by the ability of intracerebroventricu-
larly (icv) administered corticotropin-releasing factor (CRF) or mono-
amines, to block the T response to hCG.

Methods: We injected the retrograde tracer pseudorabies virus (PRV)
into the testes, lesioned specific sites of the proposed circuit and identi-
fied the brain regions of the proposed pathway by double labeling with
PRV, CRF and/or and tyrosine hydroxylase (TH).

Results: PRV staining was found in the spinal cord, the locus coeruleus (LC) and the paraventricular nucleus (PVN) of the hypothalamus.
Co-labelling of CRF and PRV was found in the PVN, and co-labelling of
PRV and TH in the PVN, the LC and the ventral norepinephrine
pathway of the brain stem. Spinal cord transection at T7-T8 prevent-
ed brain staining, and restored hCG-induced T release in rats injected
with CRF or monoamines icv. The inhibition of these icv treatments is
not due to sympathetically-mediated vasoconstriction of, or decreased
blood flow to the testis, and is mimicked by their microinfusion into
the PVN. CRF, isoproterenol or alcohol also decreased testicular levels
of the steroidogenic acute regulatory protein and the peripheral-type
benzodiazepine receptor.

Conclusions: We propose that in the male rat, Leydig cell function de-
pends on both a fast, pituitary-independent neural pathway, as well as
a slower hormonal pathway represented by the classical hypothalam-
ic GnRH/pituitary LH connection. CRF and catecholamines may act
as neurotransmitters in the brain-testicular circuit. Alcohol and other
stressors may inhibit male reproductive functions not only through their
known effects on hypothalamic GnRH and/or pituitary LH, but also
through the proposed neural circuit.
Funding provided by by NIH grant AA 12810.

MONDAY, APRIL 7, 2014
4:15 p.m. – 5:00 p.m.

LECTURE IV
PHARMACOLOGICAL REGULATION OF STEROID BIOSYN-
THESIS: FROM TESTIS TO BRAIN
Vassilios Papadopoulos, PhD
The Research Institute of the McGill University Health Centre and the
Department of Medicine, McGill University, Montreal, Quebec, Can-
da

Gonadal and adrenal steroidogenesis are increased by pituitary hor-
mones which accelerate the delivery of the substrate cholesterol from
intracellular stores to mitochondrial CYP11A1. Placenta and brain
make steroids in a hormone-independent manner, in the case of placa-
enta to satisfy fetal-maternal requirements, and in the case of brain to
form small amounts locally needed to control neuronal function. Con-
sidering the role of steroids as mediators of development, reproduction,
body homeostasis, adaptation and behavior, it is obvious that changes
in the rate of steroid formation could result in pathological states. In
the testis, reduced serum testosterone (T) is common among subfertile
and infertile young men. Reduced T is also common in aging men and is
often associated with mood changes, fatigue, depression, decreased
lean body mass, metabolic syndrome, and reduced sexual function. Al-
though T-replacement therapy has been the treatment of choice in both
young and aging men, the undesired side-effects associated with flood-
ng the body with large amounts of T drove the search for the develop-
ment of repair therapies designed to restore the ability of the testis itself
to make T. In contrast, in the case of excessive steroid production as-
associated with Leydig cell tumors, inhibitors of steroid formation might
be used to control the rate of excessive steroid synthesis. In the brain,
steroids have both long-term and rapid effects, acting as local regula-
tors of neural development and excitability. Changes in neurosteroid
levels are linked to the development of neuropsychiatric and neurologi-
cal disorders such as depression, anxiety and neurodegeneration. Local
administration of neurosteroids is unfeasible, and treatment of patients
with large amounts of neuroactive steroids is unsafe. Thus, there is a
clear need for developing repair therapies that restore the brain’s ability
to make neurosteroids. Progress in the development of compounds that
target proteins involved in cholesterol transport into mitochondria in
the testis and brain, and in this way help to control steroid biosynthesis
in these organs, will be discussed.
SPEAKER ABSTRACTS

TUESDAY, APRIL 8, 2014
8:00 a.m. – 9:15 a.m.

SYMPOSIUM IV – PSA and Prostate Cancer Debate: Is PSA Screening A Rational Approach?

PSA AND PROSTATE CANCER SCREENING DEBATE

William J. Catalona, MD
Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

The US Preventive Services Task Force (USPSTF) and American Urological Association (AUA) guidelines take steps in the wrong direction for patient-centered care and, if implemented, would deprive many men of the opportunity to pursue shared decision-making about life-saving PSA testing. A more forward-looking approach is needed.

These guidelines are based on incomplete data and inaccurate estimates of the benefits and harms of PSA testing. Guidelines panels rely on evidence from randomized clinical trials (RCTs) and statistical modeling studies, but the available RCTs provide little reliable evidence, and some are profoundly flawed. Many medical organizations have reviewed the same body of evidence and formulated vastly divergent guidelines, ranging from the USPSTF recommending against PSA testing for any man, to the European Association of Urology recommending a baseline PSA test beginning at age 40-45, with follow-up testing for all men with a life expectancy of ≥10 years, always with shared decision making between the man and his doctor.

The RCTs were conducted over a limited time period and do not reveal true information about absolute benefits of screening over a lifetime. The use of RCT data to estimate benefits and harms of PSA testing underestimates benefits and exaggerates harms. In assessing benefits, the USPSTF and AUA panels focused solely on prostate cancer death without considering avoiding suffering from metastases that might not have resulted in a cancer death. An analogy would be a study of the benefits of wearing seatbelts in cars. Is the benefit only the deaths prevented, or should it also include the catastrophic injuries prevented that did not result in death? Avoiding metastases significantly shifts the balance of harms and benefits, as men diagnosed with metastases ultimately require more treatments and have more side effects.

In assessing the harms of testing, the panels cast a net over a variety of side effects of PSA testing, biopsy, and treatment that range from minor to serious. The possible harms of a simple blood test should not be linked with those of biopsy and treatment, and few of these side effects reach the extreme of a prostate cancer death.

The AUA guidelines do not recommend screening men <55 years old with an average risk of prostate cancer. The primary objective of baseline testing in men in their 40s is to assess the risk for subsequent life-threatening prostate cancer. Men in their 40s in the top 10% of PSA levels for their age group account for almost half of all prostate cancer deaths up to 30 years later, and those with levels above 1 ng/mL warrant more careful monitoring. A high baseline PSA in a man in his 40s is a stronger risk factor than African heritage or a positive family history. It is impossible to fully assess whether a man is at high risk without measuring a baseline PSA in early middle age.

The AUA did not recommend testing men <55 years is that the RCTs have not adequately tested PSA screening in this age group. The available evidence suggests it is beneficial. Starting testing at age 55 is too late. There is no reason to believe that if PSA testing works in men 55 to 69 years old, it would not also work in men 45-55 years old. Although the AUA guidance document explains that the panel does not recommend against PSA testing for men 40-55 years old, the actual guidelines statement uses the language, “we do not recommend.” Rather, it should read, “there is insufficient evidence to recommend for or against early detection in men younger than 55.”

The AUA panel’s suggestion for longer testing intervals needs to be reconciled with the realization that less frequent testing limits the ability to detect aggressive cancers that have the shortest preclinical phases and that, with less frequent testing, there remains the undesirable effect of detecting all of the low-risk cancers (length-time bias), possibly doing more harm than good.

The AUA also does not recommend routine testing in men >69 years old, despite the fact that 50% of prostate cancer deaths occur in men diagnosed after age 75. Age 70 is too young to stop testing in healthy men who have a 10-15 year life expectancy. Therefore, testing in men over 70 should be performed on an individual basis with shared decision-making. In the absence shared decision making, men are more than twice as likely not to undergo testing.

There has been a 75% reduction in metastatic disease at the time of prostate cancer diagnosis and more than a 45% decrease in the age-adjusted prostate cancer mortality rate in the U.S. during the PSA era, largely attributable to PSA testing. Similar trends have been observed in other countries where PSA testing is widely practiced. Restricting PSA testing too much would significantly compromise these benefits.

TUESDAY, APRIL 8, 2014
8:00 a.m. – 9:15 a.m.

SYMPOSIUM IV – PSA and Prostate Cancer Debate: Is PSA Screening A Rational Approach?

CHOOSING WISELY ABOUT PSA TESTING: WHY SAYING “NO” IS A GOOD HEALTH-CARE CHOICE

Timothy Wilt, MD, MPH

Questions remain whether PSA screening and subsequent early treatment for screen detected prostate cancer provides lifetime benefits that exceed harms. Yet, PSA screening for prostate cancer is common. However, current data indicate that this balance is not favorable, especially as currently practiced in the U.S. through at least 15 years and results in large health care costs. Implementation of high value prostate cancer care requires a change in practice through science-based educational and policy initiatives. A review of the goals of cancer screening strategies, best evidence regarding the main benefits and harms of prostate cancer screening, current prostate cancer screening recommendations as well as the principals and ethics of high-value care will be presented. I will provide suggestions on guiding clinicians in implementation of high-value prostate cancer care and helping their patients to choose wisely about PSA testing.
A targeted approach to PSA based screening that involves shared decision making for the average risk asymptomatic man between ages 55-69 years. This led the panel to recommend against routine screening for other age groups at average risk. Overall 40 percent reduction in prostate cancer mortality that occurred over the last two decades. This would be consistent with the decline in prostate cancer mortality reported in randomized prostate cancer screening trials in which there was minimal contamination of controls and low prescreening rates. However, an approach to screening that assumes that benefits will be shared equally among all ages and risk groups (non targeted), and results in treatment of most individuals after diagnosis regardless of cancer aggressiveness, resulted in over treatment rates that are estimated to be 30 percent or more. Thus, a more targeted screening approach is necessary to reduce the harms associated with screening (false positive tests, over diagnosis, over treatment), the panel recommended against annual screening for those who choose to be screened.

Conclusions: A panel under the auspices of the AUA recommended a targeted approach to PSA based screening that involves shared decision making for the average risk asymptomatic man between ages 55-69 years.
Objectives:

Brown University

RISK ASSESSMENT TO ENVIRONMENTAL TOXICANTS: IMPLICATIONS FOR RESPONSE OF HUMAN FETAL TESIS XENOTRANSPLANTS

Thomas Knudsen, PhD
US EPA/ORD/NCTT, Research Triangle Park, NC

Addressing safety aspects of drugs and environmental chemicals relies extensively on animal testing; however, the quantity of chemicals needing assessment and challenges of species extrapolation require alternative approaches to traditional animal studies. Newer in vitro and in silico approaches focus on predictive modeling of adverse outcome pathways (AOPs) using computational and high-throughput screening (HTS) data for thousands of chemicals and hundreds of HTS assays in EPA's ToxCast inventory. Virtual Tissue Models (VTMs) built for developmental processes simulate multiscale disruptions in the system and provide a quantitative spatio-temporal prediction of how chemicals might impact embryo-fetal development. Virtual embryo models integrate empirical data with embryological information to simulate dynamic biological tissue architectures relevant to specific AOPs. This approach is being used to evaluate chemical effects on development, such as disruption of blood vessel formation (angiodyplasia), palatal fusion (cleft palate), limb outgrowth (ectrodactyly) and urethral fusion (hypospadias) among other systems. Simulations of endocrine and vascular pathways can be parameterized in this way, using in vitro data for chemical prioritization and early lifestyle exposure considerations. This work was funded by the US EPA under its Chemical Safety for Sustainability Research Program but does not reflect US EPA policy.

Results:

Adult male athymic nude mice were castrated, and human fetal testis fragments (gestational week 16-22) were xenografted into the renal subcapsular space. Hosts were treated with human chorionic gonadotropin for 4 weeks to stimulate testosterone production. During weeks 3 and 4, hosts were exposed to DBP (500 mg/kg/d po) or abiraterone acetate (75 mg/kg/d po), a potent irreversible CYP17A1 inhibitor.

Methods:

Adult male athymic nude mice were castrated, and human fetal testis fragments (gestational week 16-22) were xenografted into the renal subcapsular space. Hosts were treated with human chorionic gonadotropin for 4 weeks to stimulate testosterone production. During weeks 3 and 4, hosts were exposed to DBP (500 mg/kg/d po) or abiraterone acetate (75 mg/kg/d po), a potent irreversible CYP17A1 inhibitor.

Results:

Abiraterone acetate significantly reduced host testosterone and the weights of androgen-sensitive host organs, while DBP had no effect on androgenic endpoints. DBP produced a near-significant increase in multinucleated germ cells in the xenografts, an indication of an effect upon seminiferous cords.

Conclusions:

We have developed an assay, similar to the Hershberg assay, that evaluates human fetal testis for anti-androgenic effects of environmental toxicant exposure. Abiraterone acetate dramatically reduced steroidogenesis in human fetal testis xenografts. Similar to the mouse, but unlike the rat, 500 mg/kg/d DBP had no effect on human fetal testis testosterone production. These results provide novel, human-relevant mechanistic insight into the effects of phthalates on the developing male reproductive tract.

Funding:

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