Topics for WS – where are S&G most important?

- **Sex difference, Relevant for translation:**
  - Lipid levels
  - Contractility
  - Myocardial hypertrophy and failure
  - Genome analysis
  - Cell death and regeneration
  - Sex differences in vascular function
  - Smoking toxicity: Inflammation
  - Sex hormones
  - Developmental origin of health and disease
- **Not mentioned:**
  - Stem cell function depends on sex –
- **Drug development**
- **Methodology: Cells and animals do have sex**
High density lipoprotein (HDL)-based drug therapy for women with diabetes to promote regression of increased cardiovascular disease (CVD)

- High rates of diabetes are of particular concern because of the enhanced elevation in CVD risk documented in women with diabetes compared to men with diabetes
- Relation between diabetes and lipid levels (see below)
- Oxidation of HDL, different HDL function in women and men (?)

Therapeutic approach in women?

Raising HDL levels in mice improves glucose tolerance

Lehti, M, & Hofmann, SM; Circulation, 2013 Nov 26;128(22):2364-71
QUESTION: Do male-female differences in cardiac contractile function originate at the cellular level?
Sex affect contractility at the cellular level

Sex and sex hormones affect calcium (and contractility) at the cellular level

E2 regulates gene expression differently in male and female hearts

Gene expression profile after E2 administration in human heart

E2 upregulates Mylip in men only

G Kararigas et al, JACC, Febr 2012
E2 downregulates a contractile protein in men only

MLC, regulator of contraction
Estrogen decreases contraction in male, not in female cardiac myocytes

Relevance: old men frequently have high estrogen levels

G Kararigas, JACC, 2012
Abdominal Aortic Aneurysms

- Permanent dilation of the abdominal aorta
- Increase of >50% of normal diameter
- Common occurrence in aged populations
- Major cause of mortality in the elderly
- Usually associated with atherosclerotic based diseases

Lisa Cassis, Lexington
Castration of male mice remolds progressing AAAs to have thicker walls
Testosterone promotes AAA formation in males, and can also increase AAA formation in females (adults or neonates),

Testosterone influences the progression of established AAAs, as castration halts progressive dilation of established AAAs and increases wall size.
Sex hormones

Pleiotropic effects of estrogens: beneficial vs harmful

- Reproduction / sexual characters
- Oral contraception
- Climacteric symptoms (1960)

In women

- Testosterone → aromatase
- Estradiol (E2) → Estrogen Receptor Alpha

In both women and men

- Breast and uterus proliferation → cancer
- SERMs (Tamoxifen)

Cardio-vascular and metabolic homeostasis
- Prevention of CAD when early initiation
- Prevention of diabetes type II

JF Arnal, Toulouse, FR
Sex differences exist in whole Genome analysis – and are mainly overlooked!

Sex differences in disease risk from reported genome-wide association study findings

Linda Y. Liu · Marc A. Schaub · Marina Sirotan · Atul J. Butte

Human Genetics 2012
Smoking toxicity

Iliara Campesi:

CS is more common among men (21.5%) than women (17.3%) but women seem to be at significantly greater risk of developing a smoking related disease than men.

In young adults, sex-gender modulates the effects of regular smoking on global DNA methylation, endothelial functions, monocytes-derived macrophages function and transsulfuration pathway.

CS affects inflammatory response, endothelial function, transsulfuration and global DNA methylation more in women than in men.
Tobacco smoke affects expression of peroxisome proliferator-activated receptor-γ in monocyte/macrophages of patients with coronary heart disease

BJP 158: 1276-1284 (2009)

A Amoruso¹, G Guinella¹, E Rondano¹, C Bardelli², LG Fresu¹, V Ferrero², F Ribichini², C Vassanelli² and S Brunelleschi¹,³
Cell death and degeneration,

W Malorni, Rome, IT

- The prevention of cell death (in cardiovascular or neurodegenerative diseases) or its induction (in cancer) represent key therapeutic targets.
- We demonstrated a gender disparity in the susceptibility to cell death and different mechanisms have been demonstrated.

- The major need in the field of cell sex studies is the availability of valuable models.
- For some diseases (e.g. autoimmune, hematological) peripheral blood cells can be used.
- For others, the culture system is critical. In particular, for cancer and neurodegenerative diseases the question is still open.
Sex differences in liver gene expression:

Gregor Majdič
Developmental Origins of Health & Disease

Sexual Dimorphism in Developmental Programming (M>F)

In humans

- Dutch famine offspring obesity and dyslipidaemia (Roseboom et al, 2006)
- Low birthweight and hypertension in young adults males (Flanagan et al, 2000)
- Relationship between childhood and maternal fat mass (Gale et al, JCEM, 2007)
- Birthweight and basal metabolic rate in adulthood (Sandboge et al, 2011)
- Birthweight and vascular compliance (Broyd et al, J Hypertens, 2005)

In animals

- BP in offspring of fat fed rats (Khan et al, 2003)
- BP offspring of undernourished rats (Kwong et al, 2000; Ozaki et al, 2001)
- Insulin resistance, BP, fat mass in offspring of obese dams (Nivoit et al, 2009; Samuelsson et al, 2008)
- BP in offspring of dexamethasone treated sheep (Dodic et al, 2002)
- Behaviour in offspring of fat fed monkeys (Sullivan et al, 2010)
Sexual dimorphism: Origins and Mechanisms over the life course

state of the art

Genetic factors Sex-biased genes

Y genes Palindrome Sink
X Dosage Escapees Sink
Imprinted genes
Mito chondria

Inter dependence

Microbiome
Genetic Epigenetic Hormones
Aging

Trans generational effects

Spatio temporal fluctuations plasticity

XY para logues
Chromatin marks ≠ classes
Non CpG meth...

Hor -mones Organizational

Environ mental influences
Hor -mones Activa tional

Epigenetic combinatorial complexity, dynamics liability

Develop mental program ming
Ontogeny mosaic
Tissue specificity
Rhythms circadian cyclic seasonal

C.Junien

Variations = cues to ≠ disease mechanisms
Developmental Origins of Health & Disease

1. Developmental plasticity -> functional capital
2. Long term effects
3. Transmission to subsequent generations
4. Sexual dimorphism

the 4 pillars of DOHaD

C. Junien
Developmental Origins of Health & Disease

Impact of the Environment

(K.Kublickiene & C.Junien)
Methodological aspects

Males still dominate animal studies

Gender gap. The percentage of women in the total population presenting with a disease (purple; see ref. 1) outstrips the percentage of females in rat and mouse models of that disease (green; data from Web of Science). Only studies with ‘female’ or ‘male’ as keywords were captured, so the chart underestimates male bias relative to a survey of individual articles by field.

Cardiovascular physiology is usually studied in young male mice - hardly ever females.

Mortality in myocardial infarction in the mouse model

Usually, therapies are developed in males, protective pathways in females are not analyzed. Some of the drugs effective in males are not effective in females.
Drug development

Improvement in total group and in males, not in females

All!

Therapy

N=373

$p=0.0076$ without 24h

Survival in % after MI

Males!

Therapy

$p=0.0149$

Survival in % after MI

Females

Therapy

$p=0.4223$

Percent survival after MI

Unsöld B, CVR 2014
The problem: how can we study S&G out of the natural context?
Whom to invite to WS, where and when

- Active researchers (50%)
- Journal editors
- Funding organization representatives

- Berlin

- December 2014 – February 2015

www.charite.de/gender
Suggested references from discussants

References

- Pollitzer, Nature 2013
- Ritz, The FASEB J, Jan 2014

David Page is a geneticist, the director of the Whitehead Institute. He is the best messenger for the study of sex differences in disease. His arguments are perfect. David Page [https://www.youtube.com/watch?v=nQcgD5DpVlQ](https://www.youtube.com/watch?v=nQcgD5DpVlQ)