Methods & Techniques for Integrating the Biological Variable Sex in Preclinical Research
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Session IV: Cultivating a Culture of ‘Sex Matters’ across Multiple Disciplines

- **Purpose:**
  - To discuss when sex matters and when the biological variable of "sex" should be considered in science
  - To determine where gender fits into the research realm
  - To determine if there is a research space for single sex studies and if such studies will result in no harm
To discuss when sex matters & when the biological variable of “sex” should be considered in science

- Sex should always be considered in scientific research

- American Physiological Society: “…researchers who define themselves as physiologists consider “sex” as a critical variable to be included in the design of their experiments, selection of experimental material, interpretation of their results, and in their critique of the literature”… “sex is cornerstone for translation of basic physiological principles to human health and to individualized, evidence-based medicine.” (Miller et al. 2014)

- Sex chromosomes in every cell – non-gonadal functions: innate immunity, androgen sensitivity, mitochondrial function, etc.

- Sex steroids produced by gonads & programmed by chromosomes dictate genomic & non-genomic processes that affect cell processes
To discuss when sex matters & when the biological variable of “sex” should be considered in science

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- Example: Estradiol modulates CV function (heart, vasculature, kidneys, brain); various brain regions express estrogen receptors (ERα, ERβ) that regulate BP & sympathetic outflow – must understand mechanisms to develop SERMs to treat neurogenic HTN (Hay et al. 2014).

- Example: Clinical & epidemiological studies indicate that women with Type 1 DM are more at risk for CVD and have significantly poorer outcomes after clinical CV events than men; how sex contributes to underlying mechanism is unclear (Manigrasso 2012).
To determine where gender fits into the research realm

- “Gender”: cultural construct and refers to behaviors that might be directed by specific stimuli (audio, visual, olfactory, etc.) or by psychosocial expectations that result from assigned or perceived sex. Thus, gender can influence biological outcomes (Miller 2012)

- Humans may self-report their sex according to gender

- Some studies are designed to examine psychosocial (gender) influences on physiological outcomes

- Based on experimental design, investigator must decide how gender fits into particular research paradigm
To determine if there is a research space for single sex studies & if such studies will result in no harm

- Reproductive function: single sex studies
  - Pregnancy: Contributing factors to pre-eclampsia (Wang et al. 2009)
  - Pregnancy: Remodeling of uterine vasculature (Osol & Mandala 2009)
  - Erectile dysfunction (Lasker et al. 2013)

- Non-reproductive function: male & female or single sex?
  - BP control/HTN: sex differences in many facets (Sandberg & Ji 2012)
  - CV, respiratory, musculoskeletal, immunological, GI, neurological
  - Some (albeit few) questions/hypotheses may require one sex
References Cited


When approaching a new research question, what methodology can be used to determine whether or not sex should be considered? Are there circumstances when you can justify studying a single sex?
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- Virginia M. Miller, PhD, Mayo Clinic

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- Working across disease states, what role does sex play? How do we think about sex with regard to disease co-morbidities?