Plenary 1: When sex matters for human and non-human species: the role of basic biology

How to be sure what sex your cells are: Cell DB with sex description

Hee Young Paik, DSc, ¹  Suk Kyeong Lee, PhD² , Mina Park, PhD³
Center for Gendered Innovations in Science and Technology Research (GISTeR), KOFWST, Korea

¹ Professor Emeritus, ³ Instructor, Seoul National Univ., Korea
² College of Medicine, Catholic Univ. of Korea

June 18, 2018
FDA recommended manufacturers to reduce dose for women to ½ of regular dose

In clinical studies, after 8 hours of regular dose, women were 5 times more likely, compared to men, not to be awake
Drug Development Process

Discovery Stage
- Identify Target
- Identify Compounds
- Establish Activity
- Select Clinical Candidates
- Test Safety

Development Stage
- Human Clinical Trial Phase I
- Human Clinical Trial Phase II
- Human Clinical Trial Phase III
- Human Clinical Trial Phase IV

Preclinical phase
- Submit Application for Clinical Trial (IND/CTX/CTA)

Clinical phase

Post-Marketing
- Submit Registration for Regulatory Approval (NDA/BLA/MAA)
Important to know the sex of research subjects!

- In humans and whole *animals*: relatively easy to identify sex
• How about sex of cells?
Does Sex of cells matter?  YES!!

• “Sex Cell Matters”

  • Biological mechanisms and pathways found from studies using cultured cells are often the basis for the development of new diagnostic and therapeutic interventions in human medicine.

  • Only half of the population have the same sex as the cells on which the diagnostic test or treatment was developed.
• Sex influences in **stem cells & primary cells**
  
  • **Stem cells:**
    
      
      Sex influences regeneration ability of muscle-derived stem cells
  
  • **Primary Cells:**

---

**Innate Gender-based Proclivity in Response to Cytotoxicity and Programmed Cell Death Pathway**

Redox state and gender differences in vascular smooth muscle cells

Walter Malornis, Elisabetta Straface, Paola Matarrese, Barbara Ascione, Rita Coimy

**Myelin Basic Protein-primed T Cells of Female but Not Male Mice Induce Nitric-oxide Synthase and Proinflammatory IMPLICATIONS**

Subhajit Das, From the Section of Neurology, Northeastern Ohio Universities College of Medicine, Kent, Ohio

**ASSOCIATION FOR ACADEMIC SURGERY**

The Role of Estrogen Receptor α and β in Regulating Vascular Smooth Muscle Cell Proliferation Is Based on Sex

Melissa E. Hoey, Qun Jiang, Division of Plastic Surgery, University of Michigan, Ann Arbor, Michigan

**Intrinsic sex-specific differences in microvascular endothelial cell phosphodiesterases**

Jianjie Wang

1 Department of Biomedical and Physiology, and 2Neuropharmacology, University of North Carolina, Chapel Hill, North Carolina

**Sex-specific activation of cell death signalling pathways in cerebellar granule neurons exposed to oxygen glucose deprivation followed by reoxygenation**

Annette M. Gage, Mary Ann Wilbourn, Michael V. Johnston, and Min Ahmad Hossain

1 Department of Neuroscience, Boston Children’s Hospital, Harvard Medical School, Boston, Massachusetts

---
• In most of preclinical studies, cell lines are used.
• Sex of cells used are rarely reported!
  • Taylor et al. *Biology of Sex differences*, 2011
    • Looked into the sex of cells in the papers published by 10 major journals
    • 50~100% of papers did not report sex of cells.
    • None of the 101 studies reviewed used cells from only female animals
    • Randomly Selected 100 articles from papers published in *AJP-Cell Physiology* in 2013
    • Distribution of papers by sex of cells used
      • Male 20%
      • Female 5%
      • Unspecified 75%
Why sex of cell lines omitted in published articles?

• Sex of cells
  ▪ May be **regarded irrelevant** because cells derived from male and female organisms display the similar general characteristics - organelles and functions.
  ▪ May be **considered unnecessary** since others did not report sex of the cells in general.
  ▪ May **not be known** to the investigators.
Insufficient sex description of cells supplied by commercial vendors

Mi-Na Park,¹ Ji Hyun Park,² Hee Young Paik,¹ and Suk Kyeong Lee³
# Sex of Cell lines and Hybridomas

## Human Cell Lines and Hybridomas

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Undefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT CC</td>
<td>588</td>
<td>538</td>
<td>285</td>
</tr>
<tr>
<td>EC ACC</td>
<td>1562</td>
<td>1781</td>
<td>345</td>
</tr>
<tr>
<td>JCR B</td>
<td>209</td>
<td>191</td>
<td>262</td>
</tr>
<tr>
<td>Total</td>
<td>2359</td>
<td>2510</td>
<td>892</td>
</tr>
</tbody>
</table>

## Mouse Cell Lines

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Undefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT CC</td>
<td>6652</td>
<td>1302</td>
<td></td>
</tr>
<tr>
<td>EC ACC</td>
<td>53</td>
<td>137</td>
<td></td>
</tr>
<tr>
<td>JCR B</td>
<td>8</td>
<td>156</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7971</td>
<td>1595</td>
<td></td>
</tr>
</tbody>
</table>

## Rat Cell Lines

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Undefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT CC</td>
<td>27</td>
<td>11</td>
<td>192</td>
</tr>
<tr>
<td>EC ACC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCR B</td>
<td>12</td>
<td>20</td>
<td>95</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>31</td>
<td>328</td>
</tr>
</tbody>
</table>

## Other Animal Cell lines

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Undefined</th>
</tr>
</thead>
<tbody>
<tr>
<td>AT CC</td>
<td>29</td>
<td>63</td>
<td>68</td>
</tr>
<tr>
<td>EC ACC</td>
<td>1</td>
<td></td>
<td>27</td>
</tr>
<tr>
<td>JCR B</td>
<td>24</td>
<td>12</td>
<td>66</td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>76</td>
<td>161</td>
</tr>
</tbody>
</table>
Problems

• Sex description is **not provided** for most of the animal cell lines sold by major global cell vendors.

• Vendors do not provide **sex-based search engines**

  → difficult for researchers to design experiments using a well-balanced sex distribution of cells, which is now required by granting agencies of many countries

• What can we do???
Gendered Innovations Activities in Korea: Major Roles of WISET, KOFWST, and now GISTeR

Introduction: Oct. 2013
Expansion of Studies: 2014 ~2015
GS 6 – Asia Pacific: 2014 ~2015
Major Activities of GISTeR

- Proposal for legal basis
- Research funding policy
- Guideline development and dissemination for researchers and journals
- Curriculum development for higher education

Policy Research Team

Development of GI Policy and Guidelines

- Amendment of Framework Act on Science and Technology (Moved by Hon. Rep. S.M. Lee)
- Policy recommendations to NRF (Research Fund)
- Guidelines for researchers and experts
- Policy recommendation to KOFST (Journals)
- Graduate course in Gender-based Medicine
18 case studies in four areas
(2 are international cooperative studies)
GISTeR aims to develop research cases in various fields where sex and gender analysis can be introduced and to spread the Gendered Innovations based on these cases.

GENDERED INNOVATIONS DB SEARCH

- Literature DB
- Env. chemical DB
- Cell DB with sex description
- Gender and Diet-disease studies
- Blog big data and gender

http://gister.re.kr/#!/main
Establishing Cell DB with sex description

Sources:

- American Type Culture Collection (http://www.atcc.org)
- ECACC (https://www.pheculturecollections.org.uk)
- Korean Cell Line Bank (http://cellbank.snu.ac.kr)
- JCRB Cell Bank (http://cellbank.nibiohn.go.jp)
Information entered for each cell

<table>
<thead>
<tr>
<th>Species</th>
<th></th>
<th>Tissue of origin</th>
<th></th>
<th>Cell type</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Rat</td>
<td>Lung</td>
<td>Colon</td>
<td>Epithelial</td>
<td>Fibroblast</td>
</tr>
<tr>
<td>Mouse</td>
<td>Others</td>
<td>Cecum</td>
<td>Pancreas</td>
<td>lymphocyte</td>
<td>B-Lymphoblast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tongue</td>
<td>Skin</td>
<td>T-lymphoblast</td>
<td>Monocyte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mammary gland</td>
<td>Liver</td>
<td>Melanoma</td>
<td>Neuronal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Kidney</td>
<td>Stomach</td>
<td>Glial</td>
<td>Keratinocyte</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervices</td>
<td>Testis</td>
<td>Embryonic</td>
<td>Hybridoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
<td>Leukemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Melanoma</td>
<td>Brain</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bone</td>
<td>Ovarian</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder</td>
<td>Head and Neck</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex/Gender</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed (Male&amp;Female)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Category</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Coll line</td>
<td>Hybridoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary cell</td>
<td>Stem cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic disease</td>
<td>Others</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vendor</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ATCC</td>
<td>ECACC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JCRB</td>
<td>KCLB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Total No. of Cells: 6,247
Search Example 1:

Human Colon Cancer Cell Line
Human colon cancer cell lines: 134
### GP5d

<table>
<thead>
<tr>
<th>Species</th>
<th>Human Caucasian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex &amp; Gender</td>
<td>Unknown</td>
</tr>
<tr>
<td>Age</td>
<td>Unknown</td>
</tr>
<tr>
<td>Category</td>
<td>Cell line</td>
</tr>
<tr>
<td>Disease</td>
<td>Cancer</td>
</tr>
<tr>
<td>Tissue of origin</td>
<td>colon</td>
</tr>
<tr>
<td>Cell type</td>
<td>epithelial</td>
</tr>
<tr>
<td>Culture properties</td>
<td>Adherent</td>
</tr>
<tr>
<td>Vendor</td>
<td>ECACC</td>
</tr>
</tbody>
</table>

**List**
Human colon cancer cell lines, **Male:** 51
Human colon cancer cell lines, Female: 49

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Sex/Gender</th>
<th>Tissue of origin</th>
<th>Disease</th>
<th>Category</th>
<th>More Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCA-46</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
<tr>
<td>HCA-2</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
<tr>
<td>HCA-7</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
<tr>
<td>HT29/219</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
<tr>
<td>WiDr</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
<tr>
<td>LS180</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
<tr>
<td>LS174T</td>
<td>Female</td>
<td>Colon</td>
<td>Cancer</td>
<td>Cell line</td>
<td></td>
</tr>
</tbody>
</table>
Human colon cancer cell lines, 
Unknown: 34
<table>
<thead>
<tr>
<th>Cell type</th>
<th>Vendor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epithelial</td>
<td>ATCC</td>
</tr>
<tr>
<td></td>
<td>JCRB</td>
</tr>
<tr>
<td>Fibroblast</td>
<td>ECACC</td>
</tr>
<tr>
<td></td>
<td>KCLB</td>
</tr>
<tr>
<td>lymphocyte</td>
<td>GCAAC</td>
</tr>
<tr>
<td>B-Lymphoblast</td>
<td>GCAAC</td>
</tr>
<tr>
<td>T-Lymphoblast</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Monocyte</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Melanoma</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Neuronal</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Glial</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Keratinocyte</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Embryonic</td>
<td>GCAAC</td>
</tr>
<tr>
<td>Hybridoma</td>
<td>GCAAC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data</th>
<th>More Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>SW 403</td>
<td></td>
</tr>
<tr>
<td>SW 1417</td>
<td></td>
</tr>
<tr>
<td>SW 948</td>
<td></td>
</tr>
<tr>
<td>HT29</td>
<td></td>
</tr>
</tbody>
</table>
Human colon cancer cell lines, **Female**, **Epithelial**: 41
<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Vendor</th>
<th>More Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>C70</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SW 48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT29/219</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS174T</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Human colon cancer cell lines, Female, Epithelial, ECACC: 18
Search Example 2:

Mouse Lung Cancer Cell Line
Mouse Lung cancer cell lines: 18
Mouse Lung cancer cell lines, Male: 0
Mouse Lung cancer cell lines, Female: 5

<table>
<thead>
<tr>
<th>Species</th>
<th>Sex/Gender</th>
<th>Category</th>
<th>Disease</th>
<th>Tissue of origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Female</td>
<td>Cell line</td>
<td>Cancer</td>
<td>Lung</td>
</tr>
<tr>
<td>AB1</td>
<td></td>
<td>Mouse BALB/c</td>
<td>Female</td>
<td>lung</td>
</tr>
<tr>
<td>AB12</td>
<td></td>
<td>Mouse BALB/c</td>
<td>Female</td>
<td>lung</td>
</tr>
<tr>
<td>AB22</td>
<td></td>
<td>Mouse CBA</td>
<td>Female</td>
<td>lung</td>
</tr>
<tr>
<td>AC29</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
</tr>
<tr>
<td>AE17</td>
<td></td>
<td></td>
<td></td>
<td>Lung</td>
</tr>
</tbody>
</table>
Mouse Lung cancer cell lines, Unknown: 13
Mouse Lung cancer cell lines, Female, ECACC:5
Cell DB Search

mouse, cell line, lung, cancer, female, ecacc

Search results 5:

- **AC29**
  - Mouse CBA | Female | lung | Cancer

- **AB1**
  - Mouse BALB/c | Female | lung | Cancer

- **AB12**
  - Mouse BALB/c | Female | lung | Cancer

- **AB22**
  - Mouse C57BL/6J | Female | lung | Cancer

- **AE17**
  - Mouse C57BL/6J | Female | lung | Cancer
Values of GISTeR Cell DB

• **Total 6,247 cells** sold by major global vendors - ATCC, ECACC, JCRB, KCLB - are registered (as of 2018.6.7): Human : 3,812 / Mouse : 1,367 / Rat : 411 / Others : 657

• Easy and quick search by clicking menu lists or entering information desired (Cell name, Species, Sex, Category, Disease, Tissue of origin, Cell type, Vendor)

• Unique - no other known cell DBs providing similar service world wide

• It is a new DB, please send us your suggestions and ideas!
  - on website (http://gister.re.kr) or by e-mail (gister@kofwst.org)