It is time to integrate sex as a variable in preclinical and clinical studies

Heisook Lee1,2, Youngmi Kim Pak3, Eui-Ju Yeo4, Yong Sung Kim5, Hee Young Paik1,6 and Suk Kyeong Lee7

Clinical studies have historically been largely composed of male subjects, even though physiology and disease pathology between men and women may differ beyond just their reproductive organs1. As a result, drug side effects that may affect women preferentially—or more drastically—have often not been discovered until after marketing approval2. Importantly, the situation continues to improve as females become better represented in clinical trials.

The use of animals and/or cells to investigate disease pathophysiology or the therapeutic potential of experimental drugs optimizes clinical trial design. Clinical trials have often failed to confirm the expected benefits of new drugs that show favorable benefic/trisk profiles in preclinical studies. These failures may be due to the fact that preclinical studies are often conducted on only male animals, while clinical trials include both men and women. Thus, better monitoring for potential differences in the efficacy and side effects of a drug based on the sex of subjects during preclinical studies may maximize the success rate of clinical drug development.

Few animal experiments use both sexes, and subgroup analyses (by sex) are not reported even if experiments do include both sexes3. Additionally, few scientists consider that the sex of cells can impact experimental results (e.g., cell proliferation, differentiation, response to stimulus, and apoptosis)4.

Recently, funding agencies including the European Commission (EC), Canadian Institutes of Health Research (CIHR), and the US National Institutes of Health (NIH) have taken steps to integrate sex and gender into the whole research process (i.e., study design and preclinical/clinical study reports)5. In 2016, Sex and Gender Equity in Research (SAGER) guidelines were published for an equitable approach to gender medicine5. Accordingly, influential scientific journals are revising their editorial policies requiring clear reporting of the sex/gender of research subjects (including cells, animal models, and humans) and to analyze data by sex7.

Experimental & Molecular Medicine would also benefit from revised guidelines reflecting these changes. The guidelines may include the following: (1) Correct usage of the terms “sex” and “gender”. Sex is related to reproductive organs, hormones, and chromosomal complement. Sex is used for both humans and animals and refers to the whole organism or related materials (e.g., cells or tissue). Gender is generally used only for humans and refers to socio-culturally constructed roles, norms, identities, and power relations that shape “feminine” and “masculine” behaviors8. (2) Clear reporting on sex/gender of research subjects. (3) An effort to balance the male to female ratio in animal experiments; if that is not possible, discuss the limitation of the study or provide scientific rationale for using only one sex of animals.

The need to integrate sex and gender as biological variables in basic, preclinical, and clinical studies should no longer be overlooked in unbiased and reproducible research. Researchers often refer to previously published papers when setting up research hypotheses, designing experiments, and interpreting results. As more papers that consider sex as a biological variable are published, more researchers will consider sex differences in their studies and accelerate these changes.

Author details
1Center for Gendered Innovations in Science and Technology Research (GISTeR), Korea Federation of Women’s Science and Technology Associations (KOFWST), 22 Teheran-ro 7-gil, Gangnam-gu, Seoul, Republic of Korea
2Department of Mathematics, Ewha Womans University, Seoul, Republic of Korea
3Department of Physiology, Kyung Hee University College of Medicine, Seoul, Republic of Korea.

© The Author(s) 2018

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.
Conflict of interest
The authors declare that they have no conflict of interest.

Publisher's note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 16 April 2018 Accepted: 20 April 2018
Published online: 23 July 2018

References
1. Gochfeld, M. Sex differences in human and animal toxicology. Toxicol. Pathol. 45, 172–189 (2017).
2. GAO-01-286R. (available at https://www.gao.gov/new.items/d01286r.pdf).
3. Zakinaez, Y., Cosgrove, K. P., Potenza, M. N. & Mazure, C. M. Balance of the sexes: addressing sex differences in preclinical research. Yale J. Biol. Med. 89, 255–259 (2016).
4. Klein, S. L. Immune cells have sex and so should journal articles. Endocrinology 153, 2544–2550 (2012).
5. Duchesne, A., Tannenbaum, C. & Einstein, G. Funding agency mechanisms to increase sex and gender analysis. Lancet 389, 699 (2017).
6. De Castro, P., Heidar, S. & Babor, T. F. Sex And Gender Equity in Research (SAGER): reporting guidelines as a framework of innovation for an equitable approach to gender medicine. Commentary. Ann. Ist. Super. Sanita 52, 154–157 (2016).
7. Enserink, M. Sloppy reporting on animal studies proves hard to change. Science 357, 1337–1338 (2017).
8. Miller, V. M. In pursuit of scientific excellence: sex matters. Am. J. Physiol. Gastrointest. Liver Physiol. 302, G907–G908 (2012).