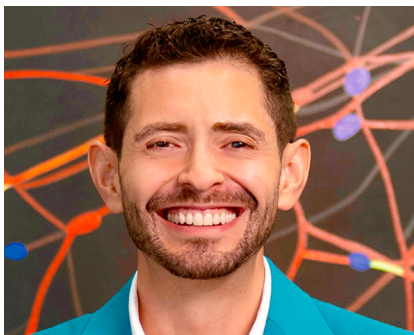


## Voices

# The future of sex and gender in research

Our understanding of sex and gender evolves. We asked scientists about their work and the future of sex and gender research. They discuss, among other things, interdisciplinary collaboration, moving beyond binary conceptualizations, accounting for intersecting factors, reproductive strategies, expanding research on sex-related differences, and sex's dynamic nature.

**Brian A. Aguado**

Shu Chien-Gene Lay Department of Bioengineering, University of California, San Diego  
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## Sex as a bioengineering variable

For decades, we have acknowledged the impact of sex and gender on health and disease in biomedical and clinical research, but they remain understudied. Sex and gender are not the same, yet both variables inform each other and can exert disparate effects on health and disease. Our male-biased approach to research typically assumes that small molecules or implanted devices would function similarly irrespective of sex or gender. Male-focused research has led to innumerable gender disparities in healthcare, with women more likely to be misdiagnosed or treated with suboptimal therapeutic regimens, resulting in worse health outcomes for women.

I seek to dismantle the male-biased approach to bioengineering research. My laboratory uses biomaterials and tissue engineering tools to understand how sex chromosomes regulate sex differences in cardiovascular diseases independently of hormone regulation. We rely on hydrogels as cell culture tools to understand sex chromosome regulation of cellular phenotypes, as opposed to conventional tissue culture plastic tools that do not accurately recapitulate the *in vivo* environment or capture sex-specific phenotypes. Our research serves as a call to action for other bioengineering laboratories to consider sex and gender in their research so that we can collectively resolve sex-based disparities in our understanding of disease and push toward equitable health outcomes irrespective of sex or gender.

**Daniel L. Jeffries**

Institute of Ecology and Evolution, University of Bern

## Sex in nature

A multitude of reproductive strategies are found in nature. Many plants self-fertilize, many insects switch between clonality and sexual reproduction, some fish can change sex, and some organisms forgo sexual reproduction altogether. Importantly, the strategy a species uses shapes almost every facet of its biology, including its behavior, physiology, genome, and its potential for adaptation. Knowledge of reproductive strategies is therefore extremely valuable, not only for understanding the natural world but also for efficient agricultural practices, for conservation, or for predicting the response of species to environmental change.

Biologists have long studied which situations and evolutionary forces created this diversity of reproductive strategies, yet many questions remain: How many times has sex/ asexuality evolved? Why and how do species switch between reproductive modes? What are the developmental, ecological, and genomic constraints/consequences of transitions between reproductive strategies? How do these things relate to the emergence of new species? And how does reproductive strategy influence a species' ability to adapt and respond to changing environments, and especially to climate change? Answering these, and many more questions, is challenging and requires knowledge of reproductive strategies across a vast number of species. To that end, we have recently launched the [Tree of Sex \(v2.0\)](#) to catalog all existing information relevant to reproductive systems in nature. We encourage researchers to consider how the reproductive strategy of their study species may be important and welcome all who would like to join us in studying this fascinating aspect of biology.



**Rebecca Jordan-Young**  
Barnard College

### The future of research on sex and gender requires interdisciplinary collaboration

Advancing the science of gender and sex requires robust interdisciplinary collaboration, particularly with gender and sexuality scholars outside of biological disciplines. The “elephant in the room” in discussions of interdisciplinary collaboration is the uneven institutional power and epistemic authority among disciplines whereby biosciences are afforded primacy over other disciplines. This mirrors the prevailing research approach that suggests a neat distinction between “sex” (as biology) and “gender” (as social), often paired with the premise that *sex is both distinct from and prior to gender*. Yet strong evidence indicates that gendered mechanisms effect biological sex-based differences. Sex-linked biology develops in an iterative relationship with complex environments, which for humans always includes social and historical processes and situations. These range from individuals’ culturally shaped yet idiosyncratic rearing and socialization experiences; to community-level economic, material, and psychological resources; to higher-level processes and structures that shape life opportunities—all of which are differentially distributed according to assigned sex and/or perceived gender. Understanding the structures and processes relevant to these gendered mechanisms is neither simple nor intuitive; scholars across all social sciences and humanities fields have developed theories, methods, and fields of evidence that are indispensable to a mature science of gender and sex. Genuinely robust collaborations will entail the articulation of research questions at the outset from a position informed by decades of insight into gender and sex that are currently cordoned off into disciplinary silos. Failing to do so amounts to willful ignorance and will impede scientific progress.



**Sabra L. Klein**  
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### Sex differences in immunity

Sex chromosome complement, gonadal tissue, and concentrations of sex steroids all contribute to biological differences between males and females. Differences in sex development (DSDs), including sex chromosome DSDs, and incongruence between sex assigned at birth and gender identity occur. Biological differences between sexes impact the immune system. Males and females do not have different responses to allergens, vaccine antigens, tumors, viruses, bacteria, parasites, fungi, or self-antigens; the kinetics and magnitude of their immune responses differ, with females often having greater responses than males. Greater immunity in females can be beneficial, e.g., when faced with microbial insults or tumors, but can be detrimental when responding to self- or innocuous antigens or transplanted tissues. Females are more likely than males to suffer from autoimmune diseases, allergies, and tissue transplant rejection. Based on publication numbers, sex differences in immunity are most often studied in the context of autoimmunity. Future research needs to place greater emphasis on other aspects of sex differences in immunity. I was once asked why sex differences in immunity matter and if these differences would impact survival rates. During the COVID-19 pandemic, males were twice as likely as females to be hospitalized, admitted into the intensive care unit, and die, with the pandemic significantly increasing the gender gap in life expectancy. Yes, sex differences matter.

**Elle Lett**

Health Systems and Population Health and Center for Antiracism and Community Health, University of Washington School of Public Health  
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### A time for creativity without binary constraints

Science's rigid commitment to binary sex and gender quashes creativity and limits progress. Before we mapped the genome, Western society had stereotyped gender roles. Once we began to understand the relationship between genetics and embryogenesis, we retrofitted them to characteristics we had previously defined as masculine and feminine.

The scientific status quo looks at sex or gender differences like a two-party system. It reduces the integration of heritable genetic variants and imprinting, *in utero* exposures, hormone profiles, gene-environment interactions, and nurtured development into a two-level categorical trait. How is this precise?

What if, instead, we imagined a world where society's baggage didn't encumber scientific conceptualization? What if we were free to "explore" without pre-specified destinations? We would view the rich tapestry of biological and social elements that create a person's sex and gender much differently; people with differences in sex development wouldn't be pathologized but would be seen as honoring the diversity of which human biology is capable. We would acknowledge and study "gender" as it is—a multifactorial construct composed of the social, biological, and environmental interactions of many human traits with continuous distributions. We would approach sex and gender with the same precision that we do other areas. We'd focus on the aspects of these constructs most relevant to our research questions. There are scientists already doing this, and many of them are openly transgender. This makes sense—scientists failed by the societal commitment to the gender binary often live, think, and study outside of it.

**Nina Stachenfeld**

The John B. Pierce Laboratory  
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### Gender equity requires inclusiveness

The NIH Office of Research on Women's Health defines "sex" as a multi-dimensional biological construct and "gender" as a multi-dimensional social and structural construct. Assessing both in human research is critical, yet the distinctions between the two are imperfect. Over the last six years, I have led two committees at Yale University that focus on gender equity as their primary goal and served on a committee focused on child and family care for the last three (a key issue in gender equity). One of our committees' biggest challenges is to include more races, genders, and ethnicities. This is not a new challenge, as feminist groups and movements have faced this inclusivity and outreach challenge for decades.

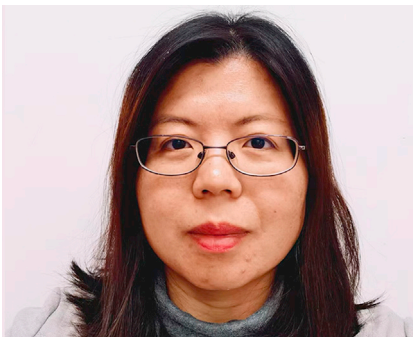
It is also critical that we investigate how sex, gender, genetic differences, race, and other social determinants of health intersect when exploring scientific questions. Research demonstrates the impact of gender by showing us the many ways in which social experience impacts health. Further, gender-affirming hormone therapy affords transgender and gender diverse (TGD) individuals the opportunity to align their secondary sex characteristics with their gender identity, but it can also be associated with cardiovascular risk, mild hypertension, and dyslipidemia. These risks make it necessary to identify prevention targets that will not interfere with gender transition and maintenance. Critically, long-term research involving TGD people is desperately needed. These examples are the beginning; we need to hear from all voices as we work to improve gender equity and perform our research, teaching, and patient care.



**Jessica Tollkuhn**  
Cold Spring Harbor Laboratory

### Brain sex is a state defined by hormones

Most sex differences in physiology and behavior are a consequence of signaling by so-called sex hormones such as estrogen. The nuclear receptors for these hormones are transcription factors, which are recruited to DNA when bound by their respective hormonal ligand. Although there is a rich history of research on the molecular mechanisms of hormone-mediated transcription in cell lines, there remains minimal knowledge of the genomic targets of sex hormones in the diverse tissues that express their receptors. My group studies the actions of sex hormone receptors in the brain by working directly within the sparse neuronal populations that express a given receptor. We found that estrogen receptor alpha ( $ER\alpha$ ) acts with exquisite specificity by invoking genes unique to each neuronal cell type to generate a diverse repertoire of sex-differential gene expression programs in both females and males. Our data from neonates and adults show that sex differences in neural gene expression reflect the acute hormonal milieu—in essence, mammalian brain sex is a flexible state defined by fluctuating sex hormones rather than immutable sex chromosomes. Our work provides a paradigm for the broader investigation of *in vivo* hormone receptor biology throughout the body as well as a novel perspective for considering the dynamic nature of sex within and between individuals.



**Xiaohong Xu**  
Institute of Neuroscience, Chinese Academy of Sciences

### The development of sex differences

Our journey to becoming sexually active adults unfolds slowly postnatally. This process involves the gradual development of sex-specific traits influenced by hormonal changes, interactions with other developmental processes, and the environment. Beyond reproductive characteristics, sex differences often represent variations between two overlapping curves that are marginally shifted in population means. However, misconceptions arise due to the perception that these sex differences are binary, perhaps stemming from the sex determination process.

Recognizing the protracted and multifaceted developmental trajectory through which sex differences emerge emphasizes the necessity to view sex not merely as a binary determinant but as a modulating force within the spectrum of individual variation. Sex differences are individual variations manifested along the axis of the sex. Existing studies focus on the resulting sex differences in adulthood; however, the scarcity of research examining the nuanced unfolding of sex differences during postnatal development highlights a crucial area for future exploration. Comprehensive time-sequential investigations can elucidate how sex-based traits interact within critical developmental periods such as puberty to shed light on the functions of the observed adult sex differences.

Understanding the fundamental framework of postnatal development enables us to grasp how sex-based traits influence and fine-tune characteristics to enhance fitness in sexually reproducing animals. This comprehension may also elucidate sex-related susceptibilities and vulnerabilities to diseases.

### DECLARATION OF INTERESTS

The authors declare no competing interests.