Modulation of Immunity by Steroid Hormones and Implications for Transgender Health

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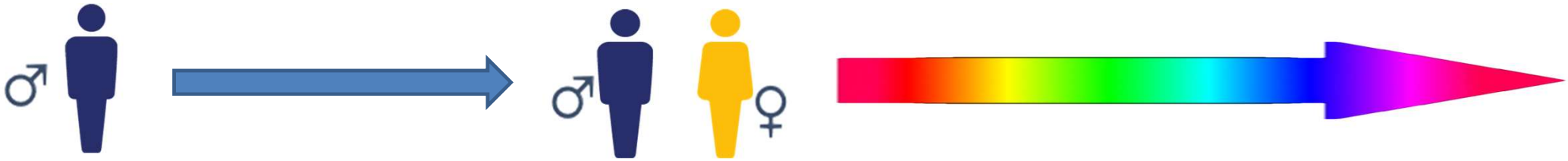
EPATH 4-6 SEPTEMBER 2025 HAMBURG, GERMANY

Outline

- Consequences of sex steroid hormones and genes encoded by X and Y chromosomes for immunity
- Impact of gender affirming hormone therapy on immune function
- Implications for transgender health

Slow integration of sex and gender in immunological research



for centuries, immunology research focused on cisgender males

Review

SeXX matters in immunity

J.G. Markle[1] and E.N. Fish[2,3]

[1] St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, 10065, USA
[2] Toronto General Research Institute, University Health Network, Toronto, Canada
[3] Department of Immunology, University of Toronto, Toronto, Canada

Sex bias in trials and treatment

Gender inequalities in biomedical research are undermining patient care. In pieces, **Alison M. Kim**, **Candace M. Tingen** and **Teresa K. Woodruff** call on jour and researchers to give women parity with men, in studies and in the clinic.

Immune Cells Have Sex and So Should Jou Articles

2012

Sabra L. Klein

The W. Harry Feinstone Department of Molecular Microbiology and Immunology, Biochemistry and Molecular Biology, Johns Hopkins Bloomberg School of Public H Maryland 21205

Klein (201

nature

NIH to balan and anim

Janine A. Clayton and Francis S. Collins research funded by the US National Institu

The New York Times | http://nyti.ms

HEALTH | NYT NOW

Labs Are Told to Start Including a Neglected Variable: Females

By RONI CARYN RABIN MAY 14, 2014

nature COMMUNICATIONS

EDITORIAL

https://doi.org/10.1038/s41467-022-30398-1 OPEN

2022

Raising the bar on sex and gender rep research

Sex, Gender and Diversity

Importance to Research Projects

DFG

Bonn, 23 April 2020

Von Anna-Lena Scholz

Menü ZEIT CAMPUS

GESCHLECHTERFORSCHUNG

DER UNSCHARFE BLICK

WR

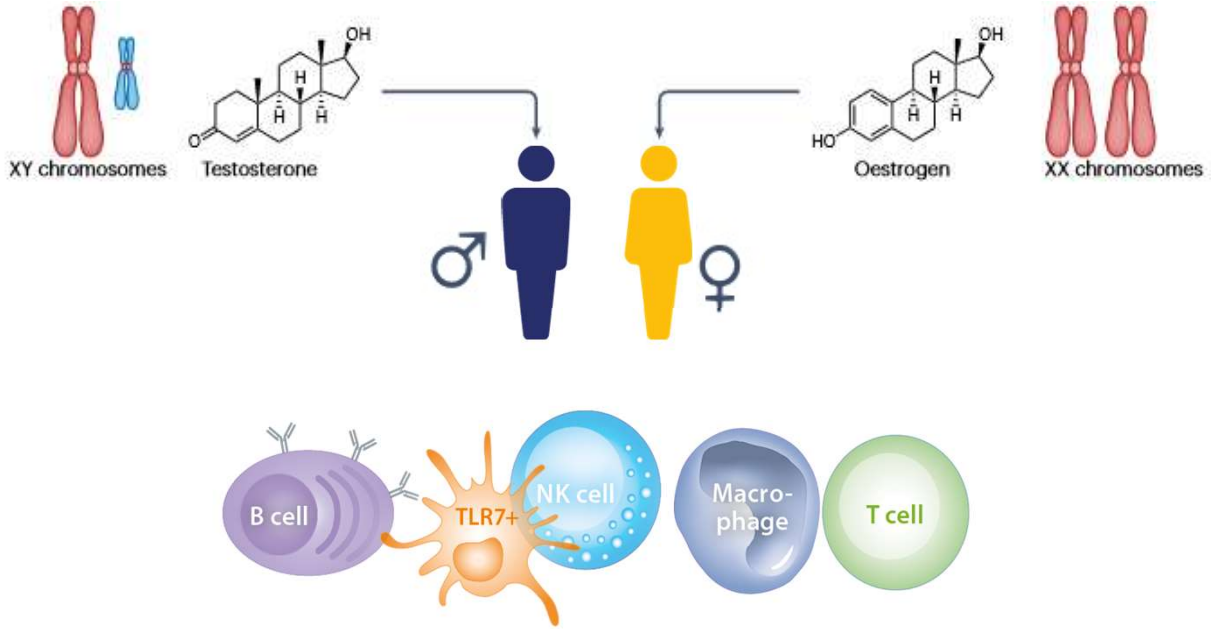
2023

DER WISSENSCHAFTSRAT BERÄT DIE BUNDESREGIERUNG UND DIE REGIERUNGEN DER LÄNDER IN FRAGEN DER INHALTLICHEN UND STRUKTURELLEN ENTWICKLUNG DER HOCHSCHULEN, DER WISSENSCHAFT UND DER FORSCHUNG.

HINTERGRUNDINFORMATION Köln 10 07 2023

Geschlechterforschung in Deutschland

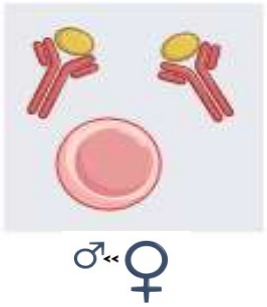
Impact of variations in genes encoded by X/Y chromosomes and in sex steroid hormones on immunity

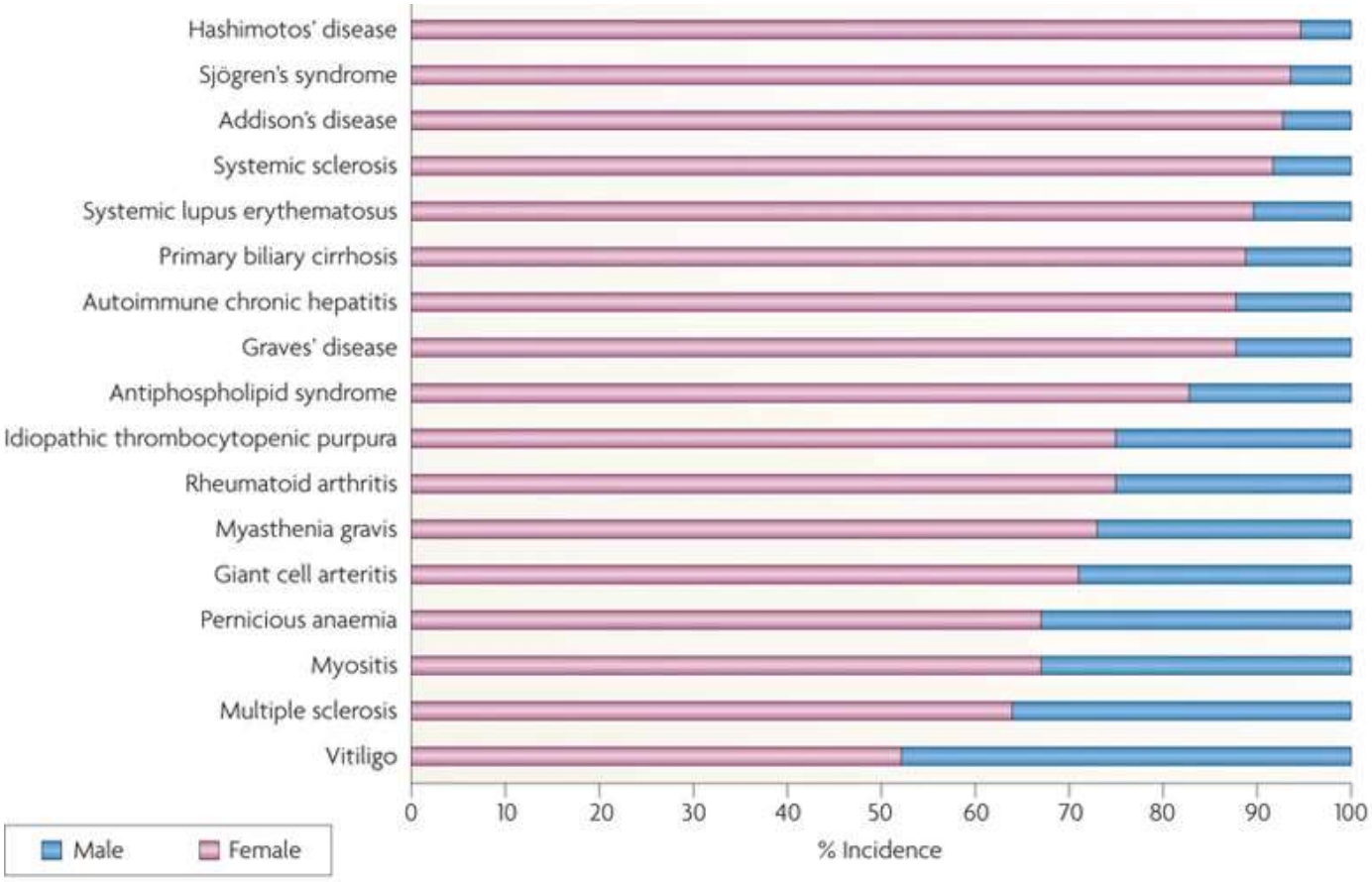


adapted from Forsyth et al. | Nat. Rev. Immunol. 2024

People assigned female at birth are more frequently affected by autoimmune diseases

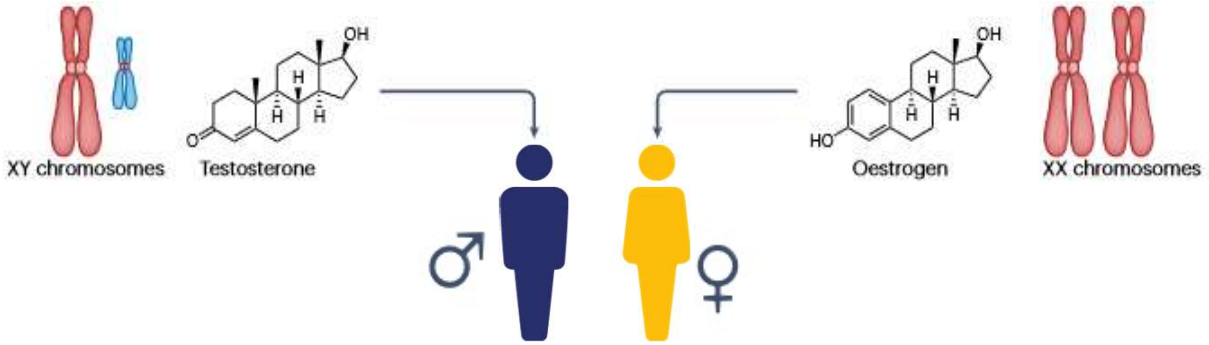
Autoimmunity



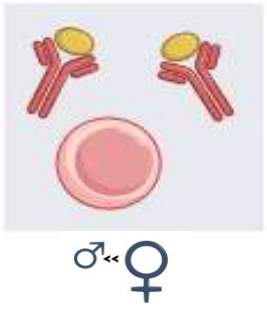


Libert et al. | Nat. Rev. Immunol. 2010

Variations in genes encoded by X/Y chromosomes and in sex steroid hormones impact infectious diseases and vaccinations

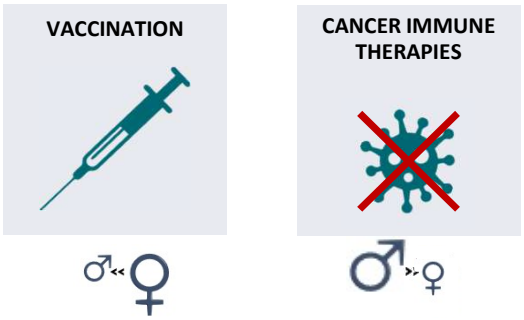


Autoimmunity



Infectious diseases

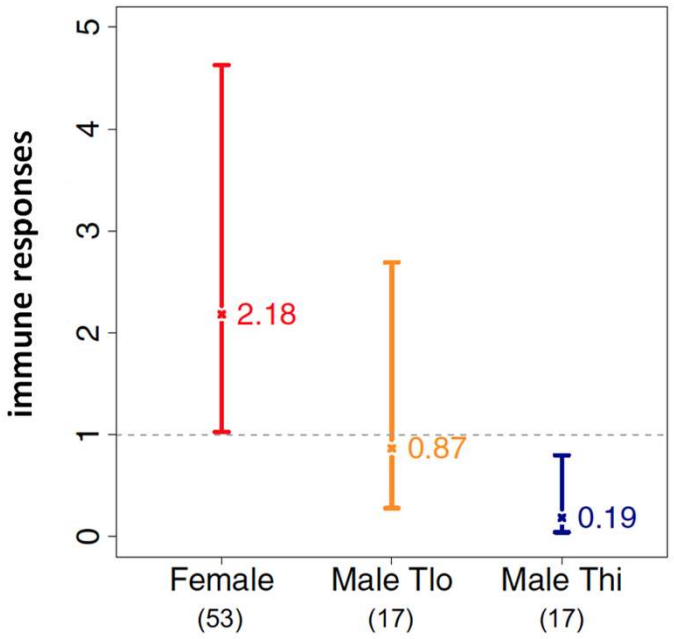
Immune interventions



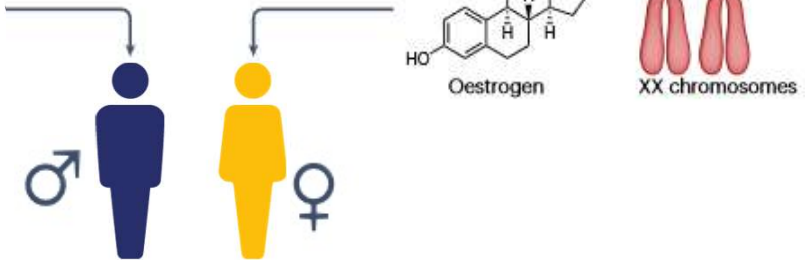
adapted from Forsyth et al. | Nat. Rev. Immunol. 2024

Higher testosterone levels at time of vaccination are associated with lower vaccine-induced immune responses

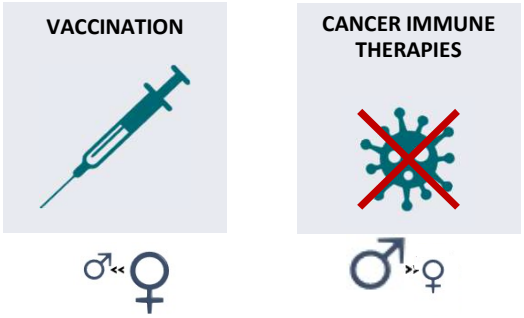
Influenza Vaccination



Furman et al. | PNAS. 2014



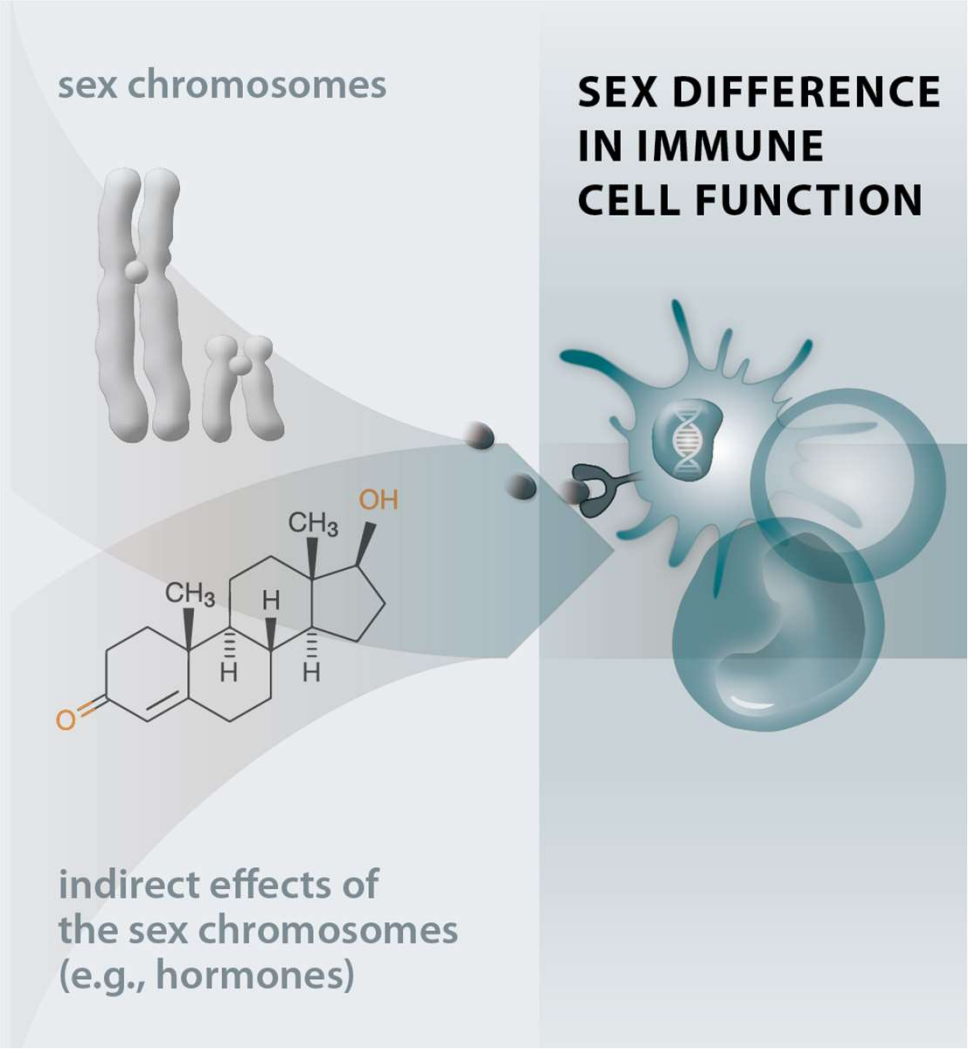
Immune interventions



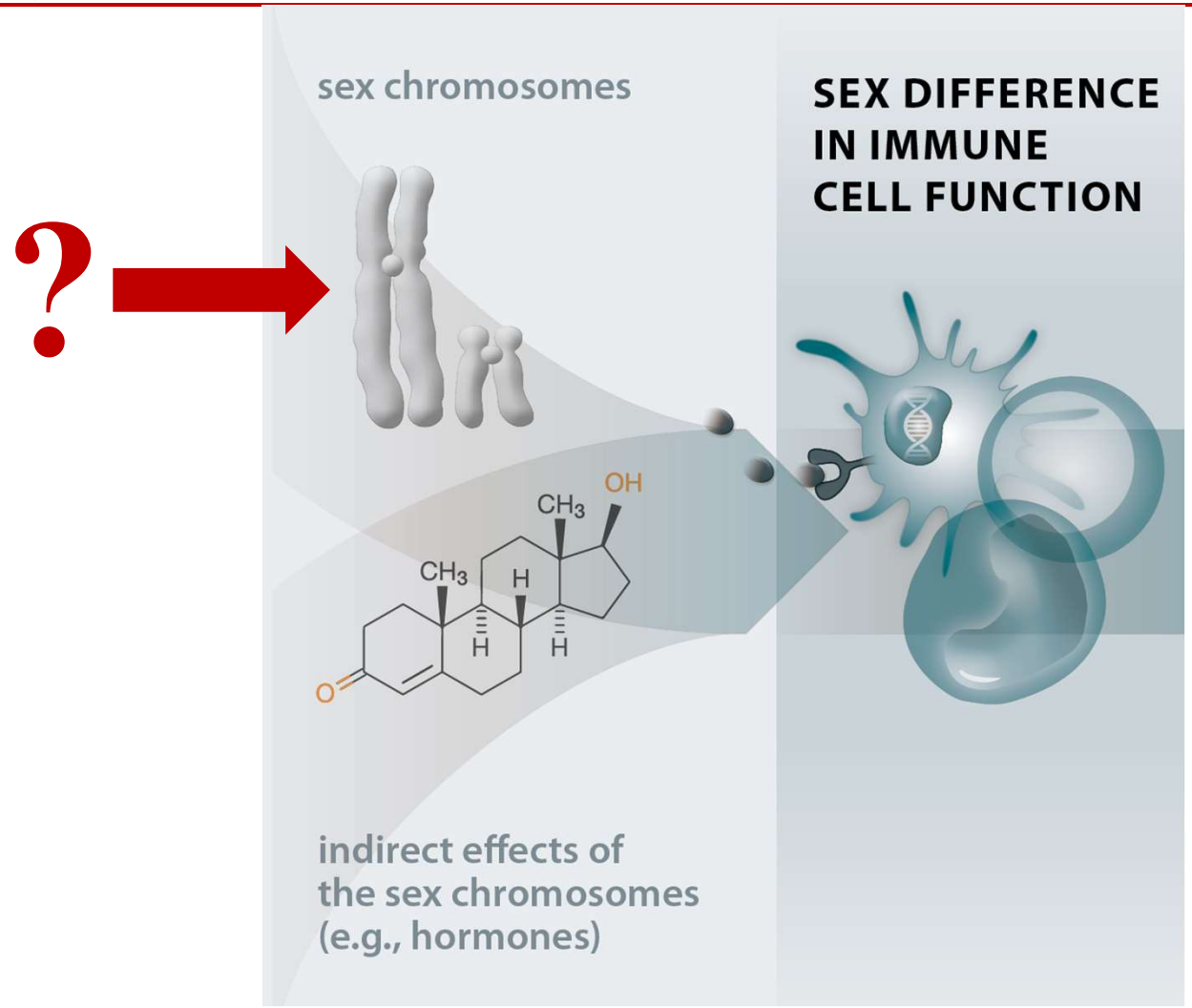
How do variations in expression of genes encoded by X/Y chromosomes and in steroid hormones impact immune function?

RU 5068

DFG



Impact of variations in expression of genes encoded by X and Y chromosomes on immune function



a Receptors & associated proteins

AR	Androgen receptor
AGTR2	Angiotensin receptor 2
CSF2RA	Colony-stimulating factor 2 receptor α (granulocyte-macrophage)
GPCR	G-protein coupled receptors 23, 50, 101, 112, 119, 174 and CX-chemokine receptor 3
CYSLTR1	Cysteinyl leukotriene receptor 1
IL-1RAP1	Interleukin-1 (IL-1) receptor accessory protein-like 1
IL-1RAP2	IL-1 receptor accessory protein-like 2
IL-2RG	IL-2 receptor γ-chain
IL-3RA	IL-3 receptor α-chain
IL-9R	IL-9 receptor
IL-13RA1	IL-13 receptor α1-chain
IL-13RA2	IL-13 receptor α2-chain
IRAK	IL-1 receptor-associated kinase
NGFRAP1	Nerve-growth-factor receptor associated protein 1
TLR7	Toll-like receptor 7
TLR8	Toll-like receptor 8

b Immune-response related proteins

XSCID	X-linked severe combined immunodeficiency
ELK1	Involved in B-cell development
EPAG	Early lymphoid activation protein
GATA1	GATA-binding protein 1
GTD	Gonadotropin deficiency
IDDMX	X-linked susceptibility to insulin-dependent diabetes
IGBP1	CD79A, immunoglobulin binding protein 1
IGSF1	Immunoglobulin superfamily member 1
ITGB1BP2	Integrin-β_1-binding protein 2
CD99	Also known as MIC2; associated with T-cell function
MTCP1	Mature T-cell proliferation 1
PFC	Properdin P factor, complement
TIMP1	Tissue inhibitor of metalloproteinase 1
CD40L	CD40 ligand
Z39IG	An immunoglobulin superfamily protein

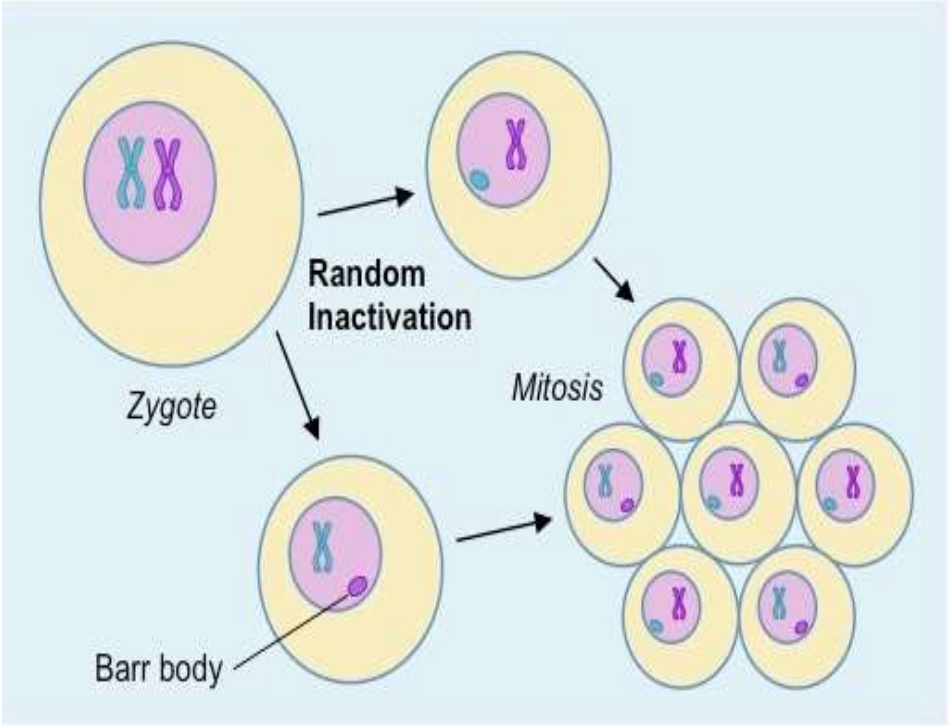
c Transcriptional & translational control effectors

RHOGAP	RAS homologue (RHO) GTPase activating proteins 4, 6
CDC42GEF	Cell-division cycle 42 guanine-nucleotide-exchange factors 6, 9
ETK	Also known as BMX
BTK	Bruton agammaglobulinaemia tyrosine kinase
CDX4	Caudal homeobox transcription factor 4
TRAP170	A co-factor for SP1 transcription factor activation
DUSP	Dual specificity phosphatases 9, 21
EEF	Eukaryotic translation elongation factors 1α13, β4
EIF	Eukaryotic translation initiation factor 1A*, 2a
FOXP3	Forkhead box P3 (associated with the development and function of regulatory T cells)
GAB3	Growth-factor-receptor-bound protein 2-associated binding protein 3
HDAC	Histone deacetylases 6, 8
IKKγ	IκB kinase; also known as NEMO
MAPKKK15	Mitogen-activated protein kinase kinase kinase 15
NFκBRF	Nuclear factor-κB (NF-κB) repressing factor
NRK	NF-κB-inducing kinase-related kinase
NXF	Nuclear RNA export factors 2, 3, 4, 5
PAK3	p21 (also known as CDKN1A)-activated kinase 3
PPP	Protein phosphatases 1, 2*, 6
PRKCI	Protein kinase C*i*
S6K	Ribosomal protein S6 kinase
SWI/SNF	SWI/SNF-related, matrix associated, actin-dependent regulator of chromatin
STK9	Serine/threonine kinase 9
TAF1	TATA-box-binding protein-associated factor 1, TFIID subunit
UBE1	Ubiquitin-activating enzyme E1
UBE2A	Ubiquitin-conjugating enzyme E2A
USP	Ubiquitin-specific proteases 9*, 11, 26, 27, 511
WASP	Wiskott–Aldrich syndrome protein

Genes on X chromosome

Fish, Nat Rev Imm 2008

Inactivation of second X chromosome (Barr Body)



Summary of the Process of X-Inactivation

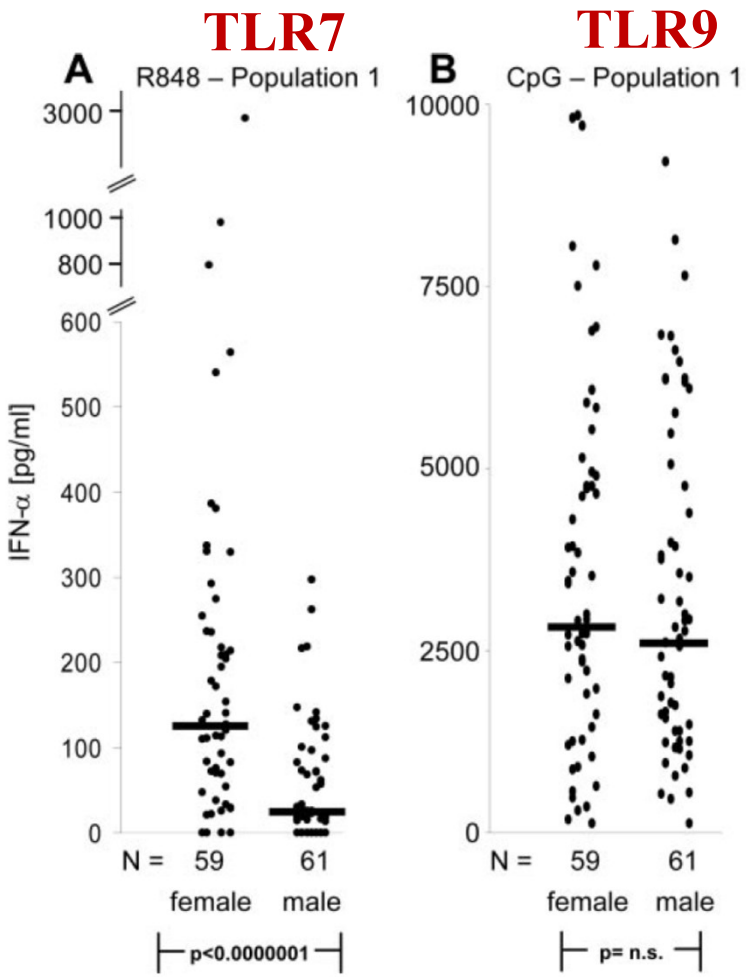
Barr Body in a Human Nucleus

TLR7 escapes X chromosomal inactivation (XCI)

Souyris et al., Sci Immunol 2018

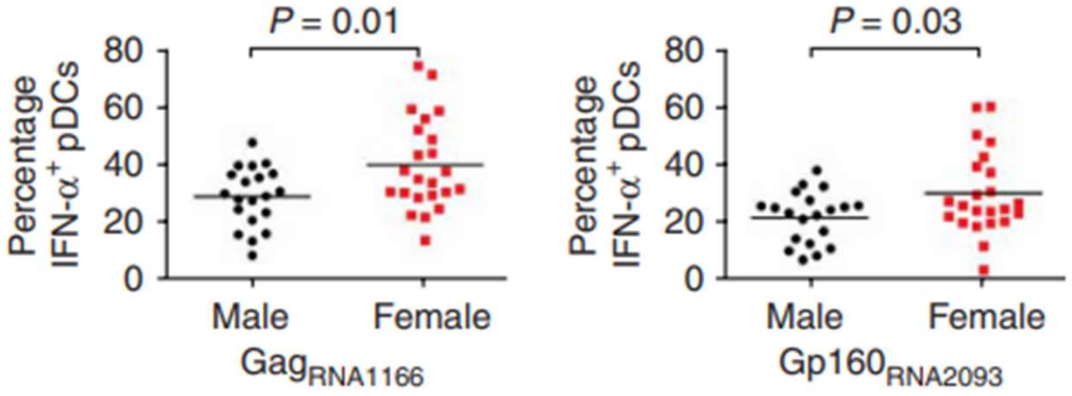
Stronger TLR7-induced IFNα responses in cisgender females

- **TLR7 senses viral RNAs and induces IFNα production by immune cells**
- **IFNα has strong antiviral activity**

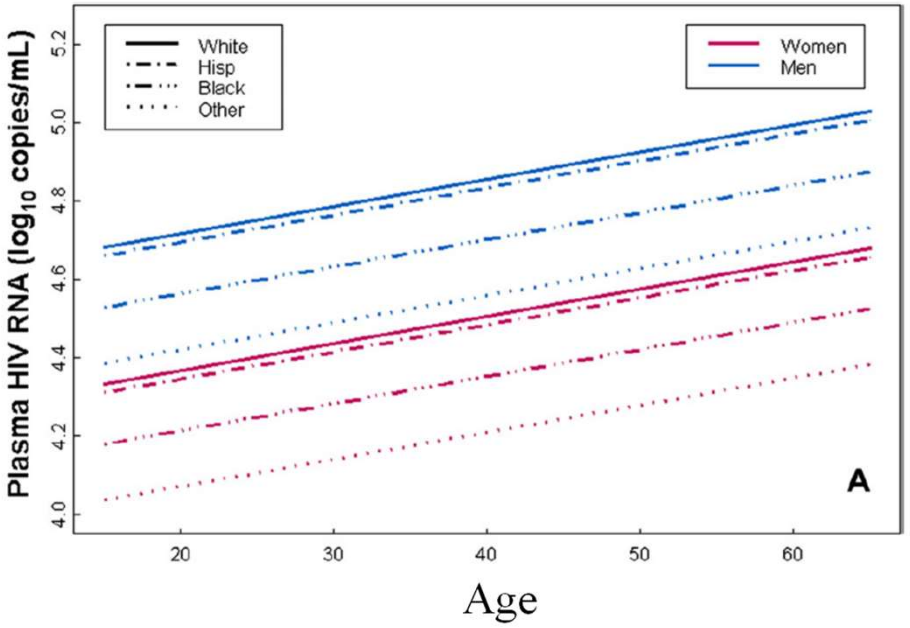


Berghöfer et al. JI 2006

Stronger TLR7-induced IFNα responses to HIV-1 and better control of viremia in cisgender females

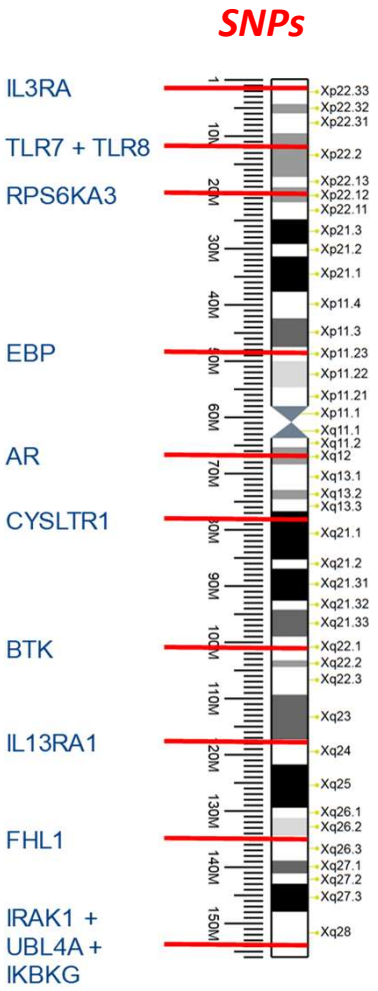


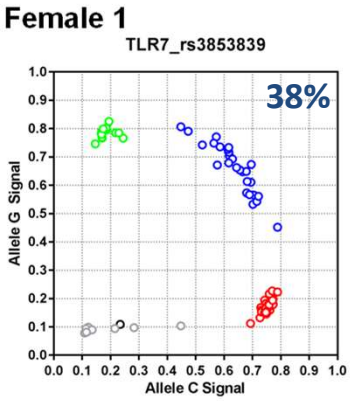
Meier et al. Nat Med 2006

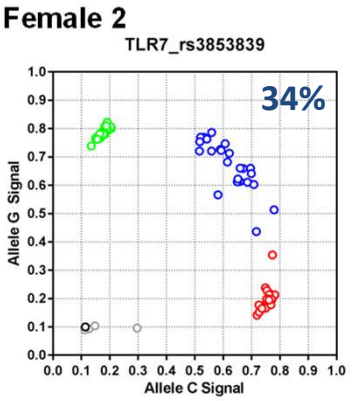


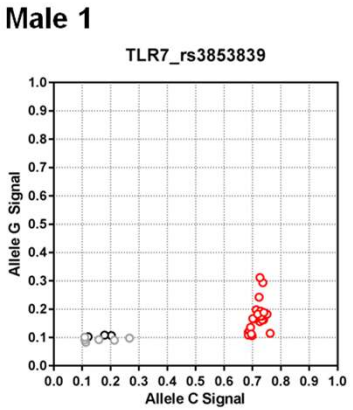
Meditz et al. JID 2011

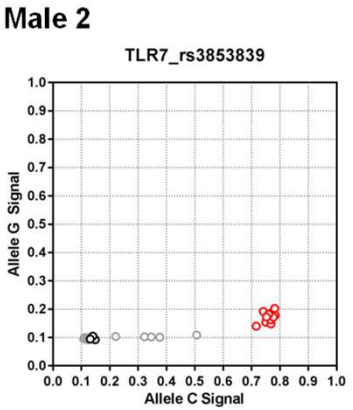
Escape from XCI for many genes on the X chromosome





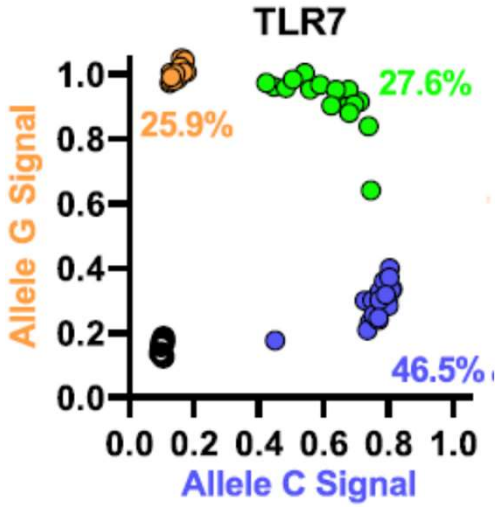


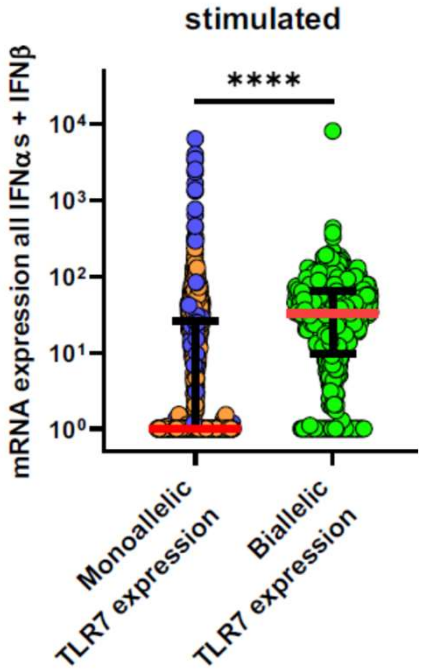




Hagen et al. Cell Rep 2020

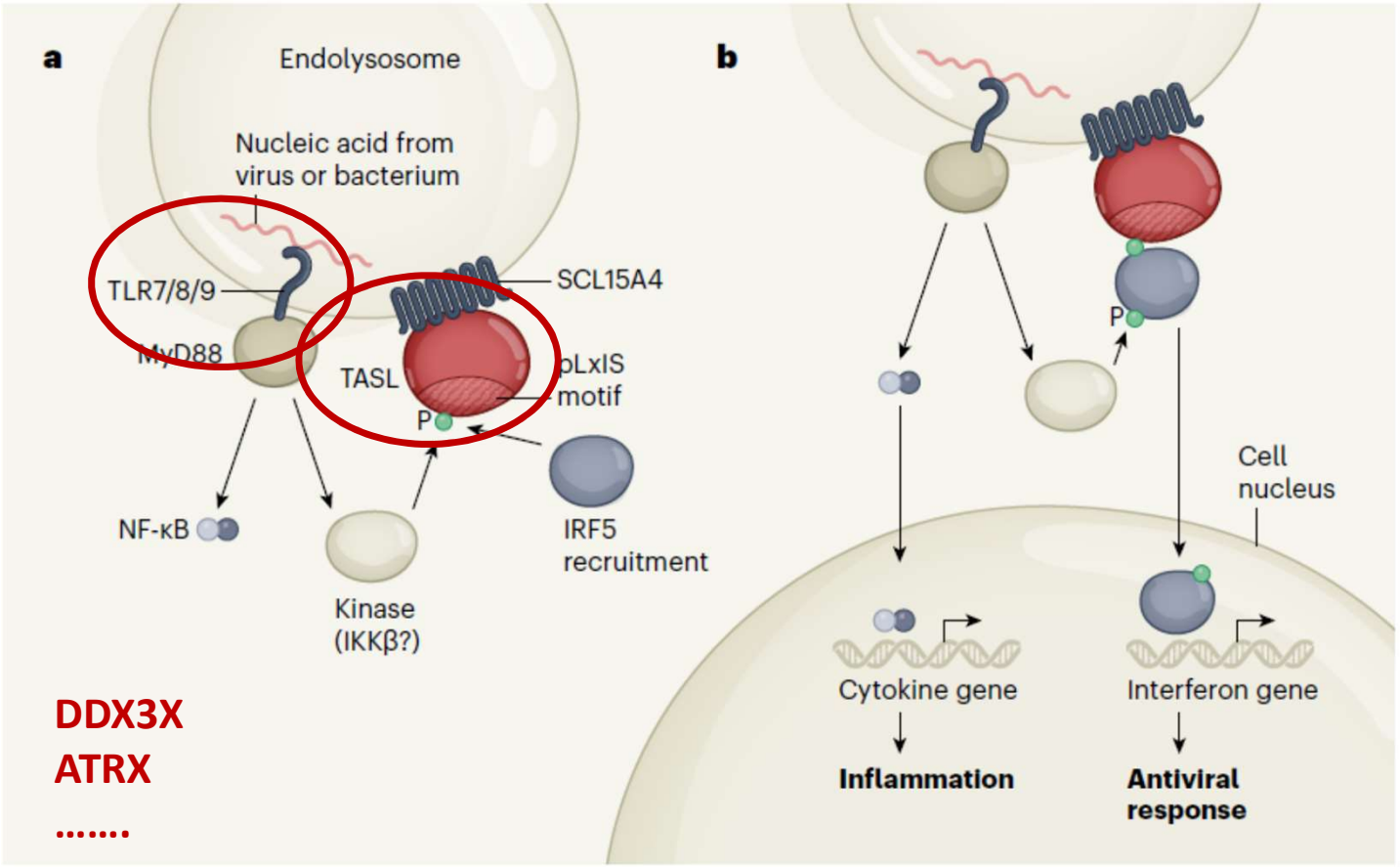
pDCs with *biallelic expression* of TLR7 produce more IFNα after TLR7 stimulation





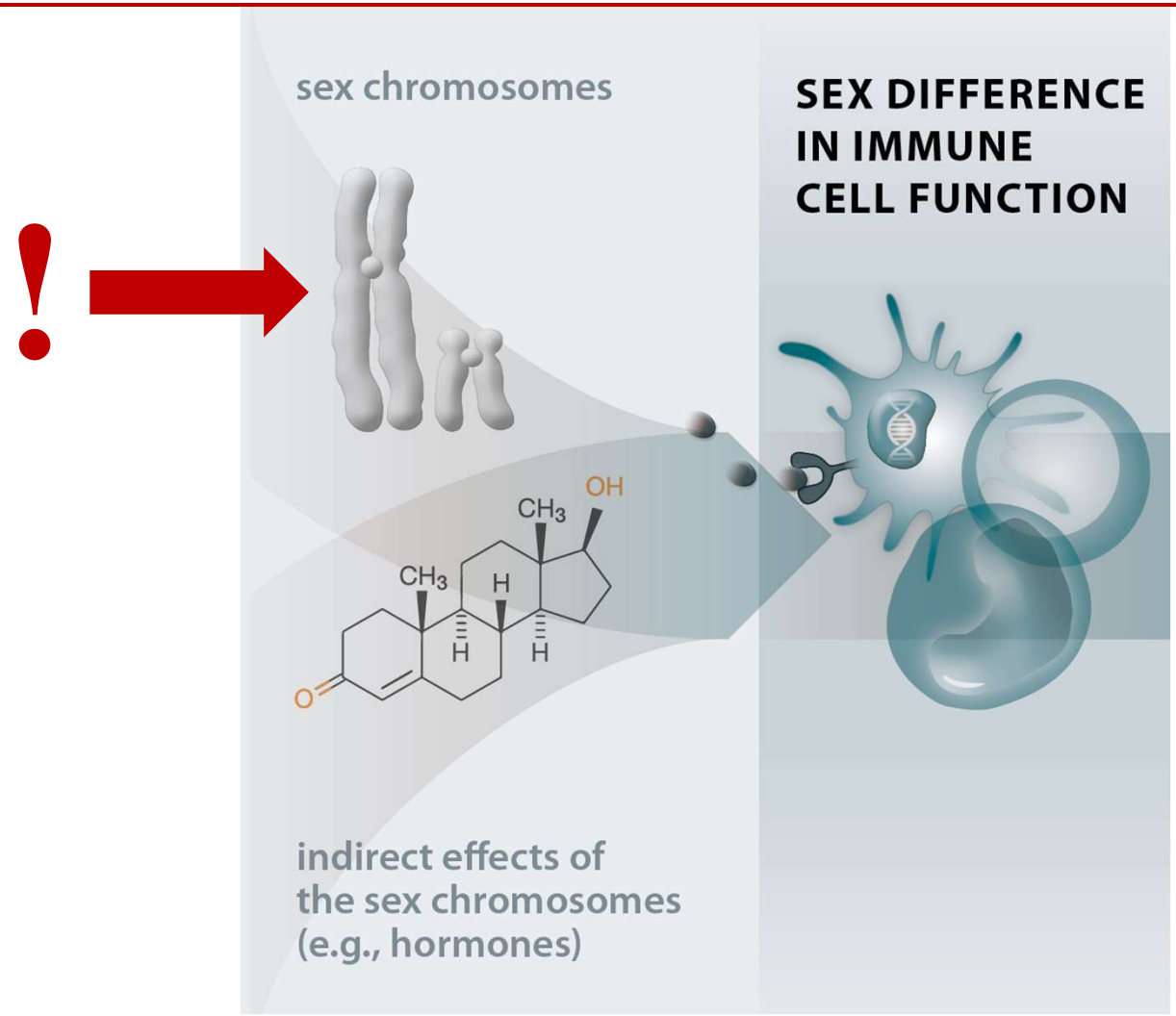
Hagen et al. Cell Rep 2020

Several genes in the TLR7/IFN-I pathway are located on the X chromosome and can escape XCI

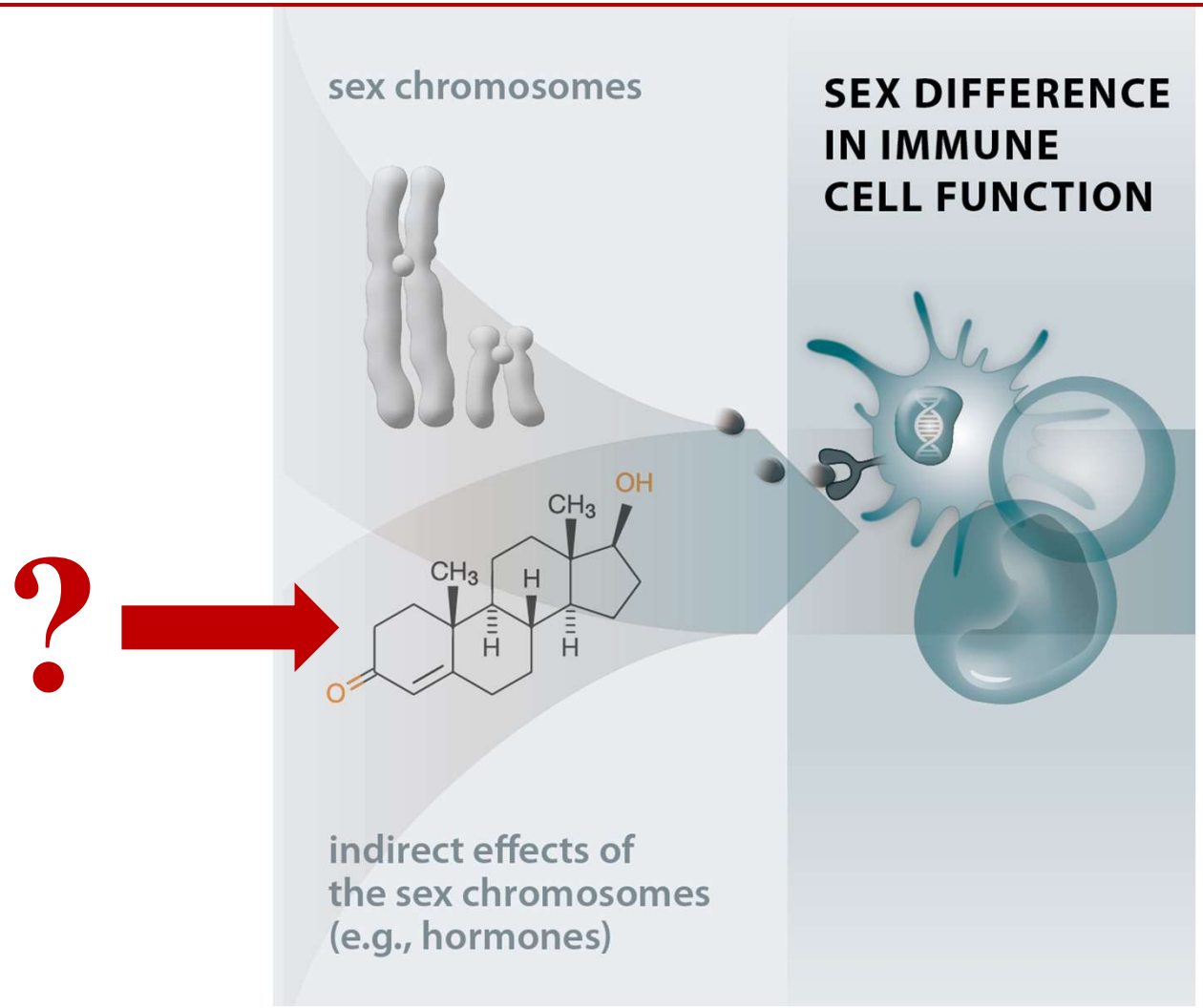


Heinz et al. Nature 2020
Schmacke & Hornung, Nature 2020

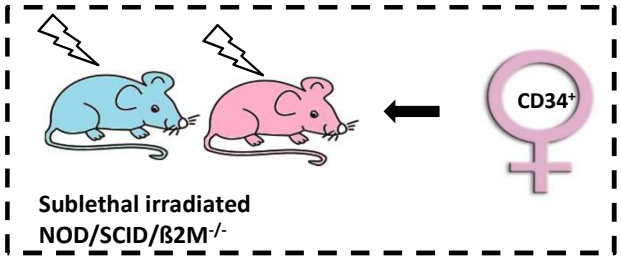
Impact of variations in expression of genes encoded by X and Y chromosomes on immune function

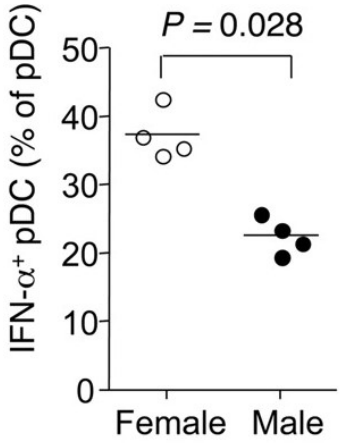


Impact of variations in steroid hormone levels on immune function

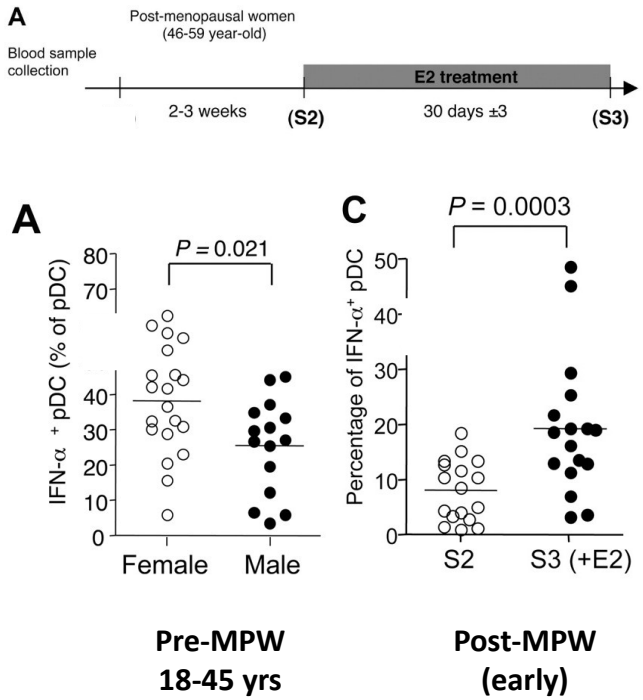


Estrogen regulates TLR7 responses of pDCs





TLR-7 mediated pDC response is shaped by sex of the host rather than cell-intrinsic X-linked genetic factors.



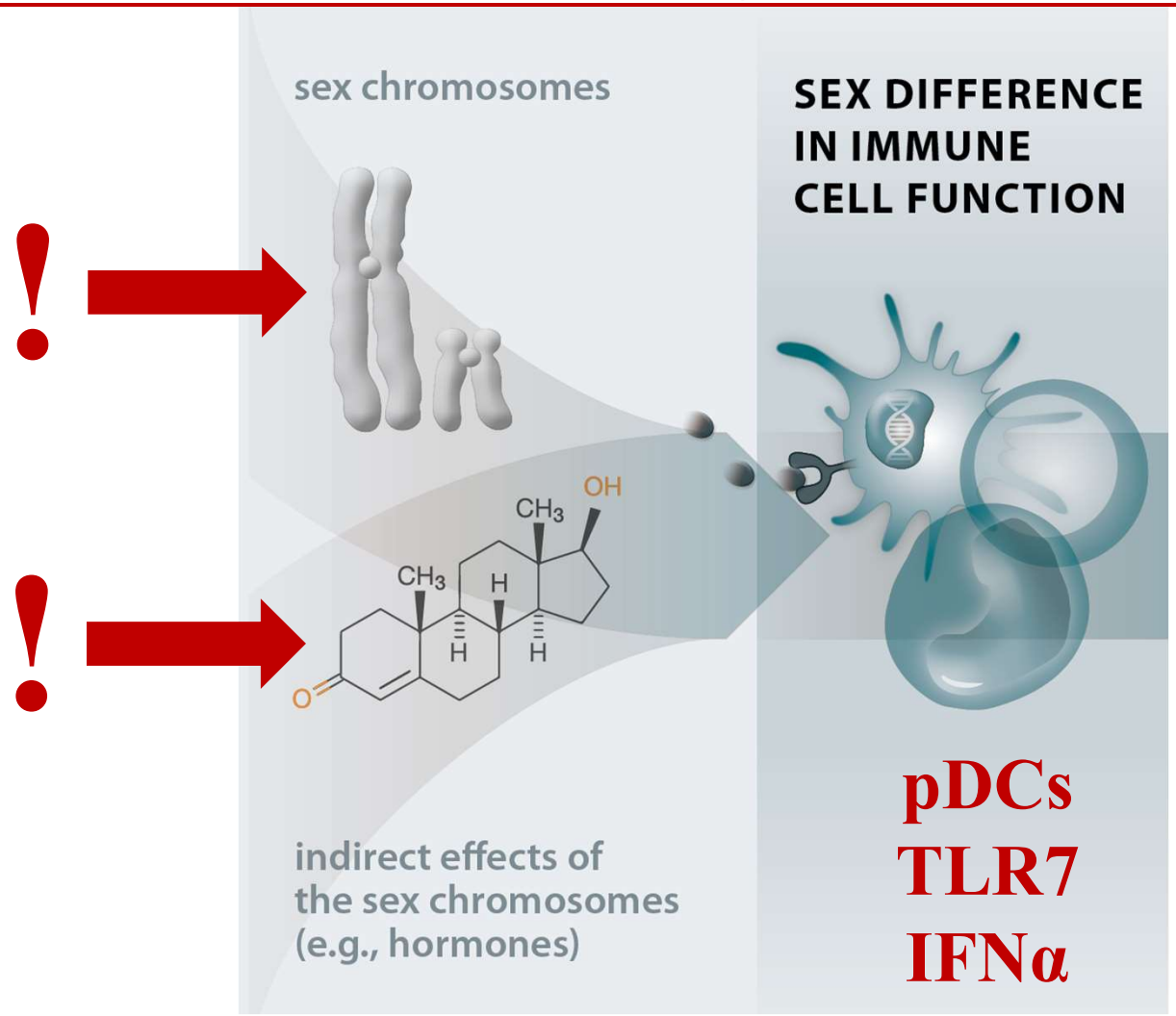
Pre-MPW 18-45 yrs

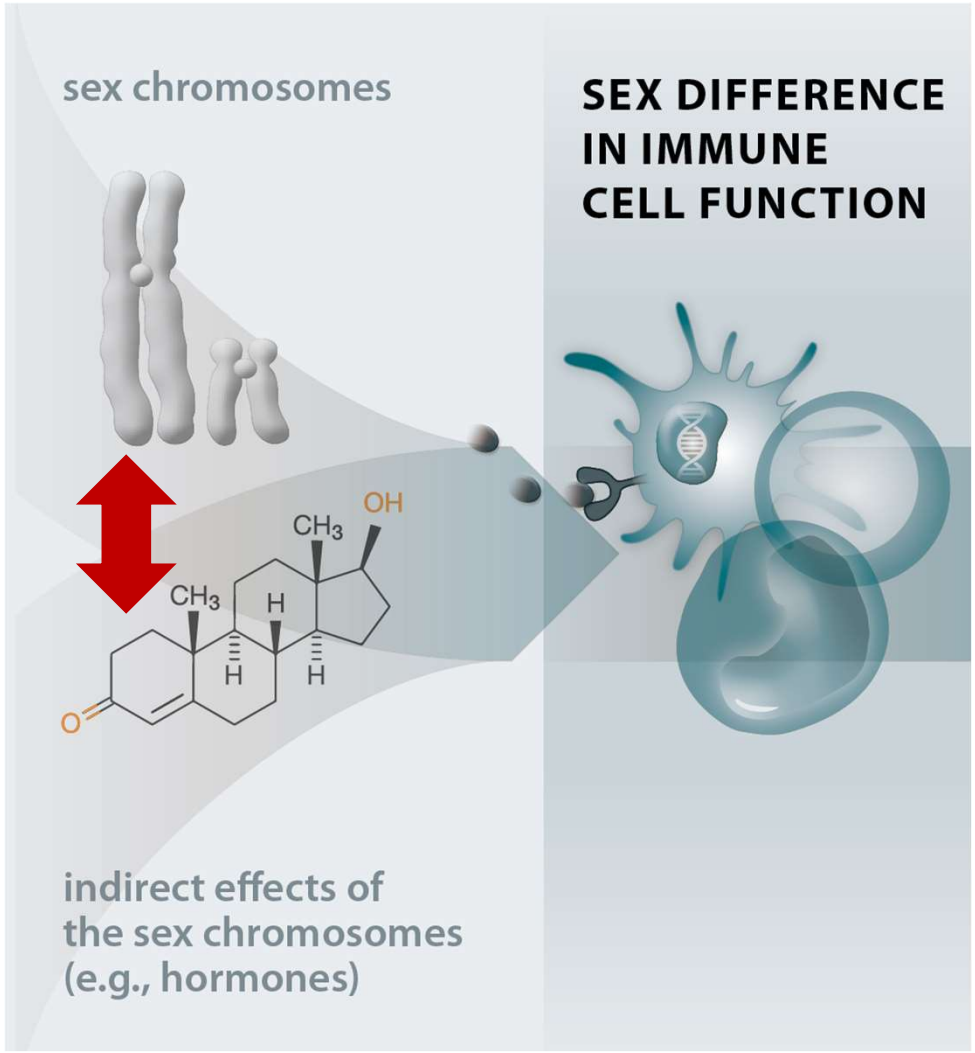
Post-MPW (early)

- **Oestradiol deprivation results in decreased IFNa production by pDC.**
- **Oestradiol treatment upregulate TLR-responsivness in pDC.**

Seillet, C et al (2012) *Blood*

Variations in expression of genes encoded by X and Y chromosomes and in steroid hormone levels can impact immune function




sex chromosomes
SEX DIFFERENCE IN IMMUNE CELL FUNCTION
OH
CH3
CH3
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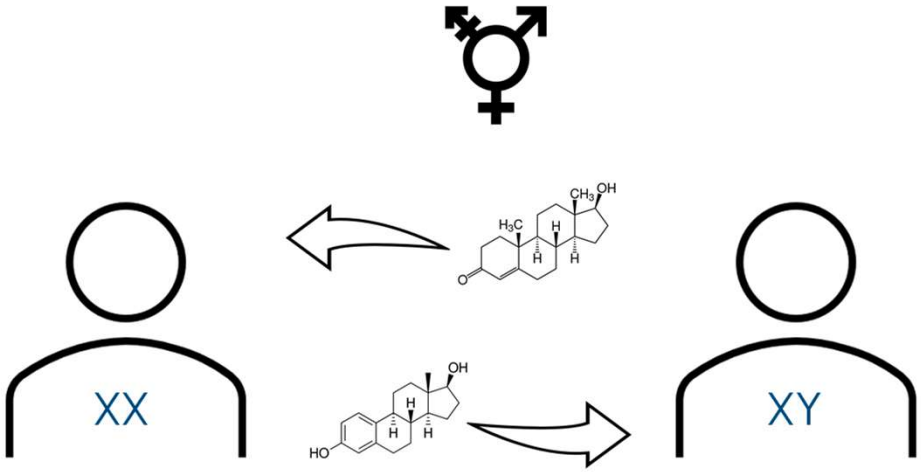
indirect effects of the sex chromosomes (e.g., hormones)

Outline

- Consequences of sex steroid hormones and genes encoded by X and Y chromosomes for immunity

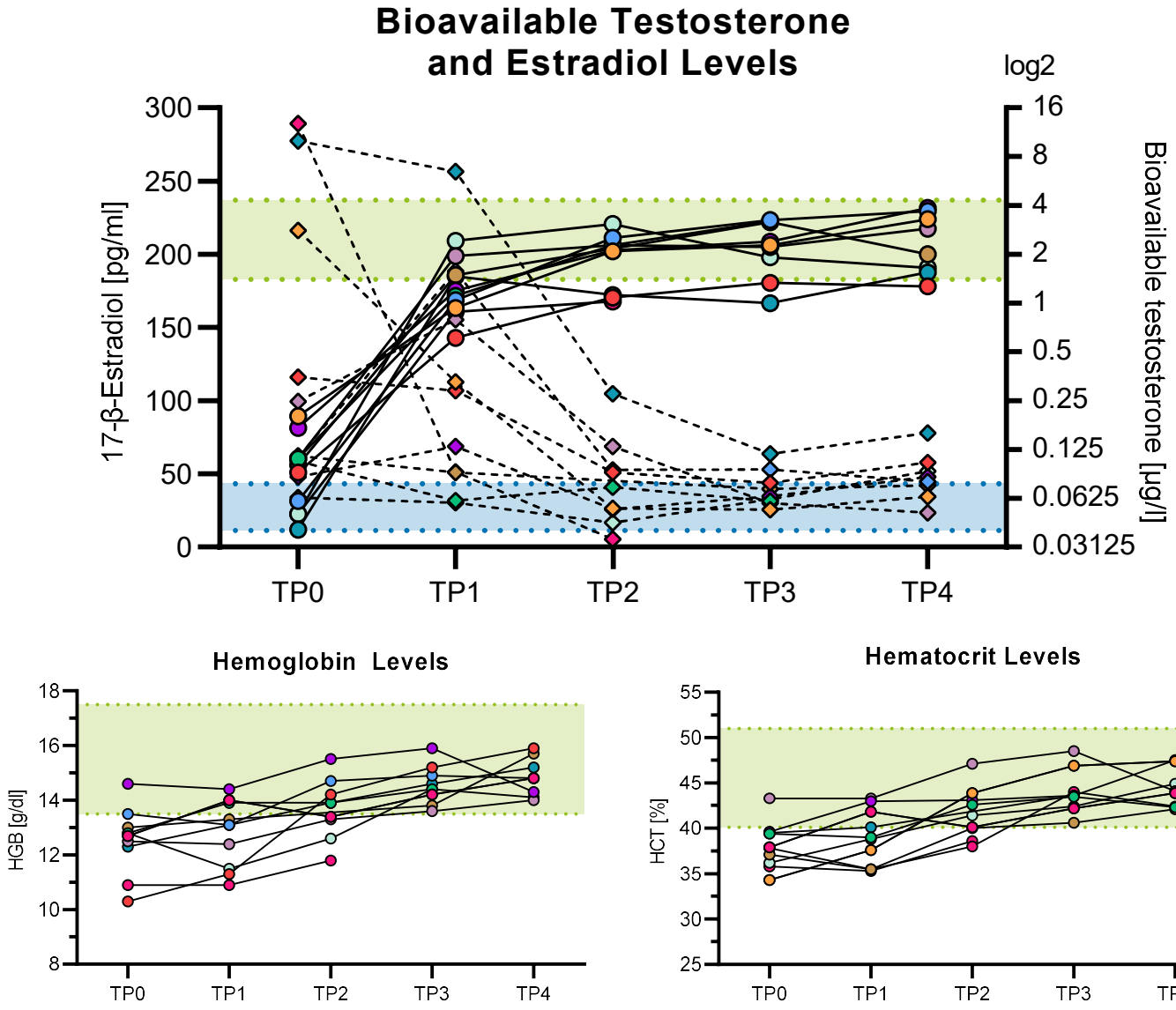
- **Impact of gender affirming hormone therapy on immune function**



Hamburg Transgender Cohort

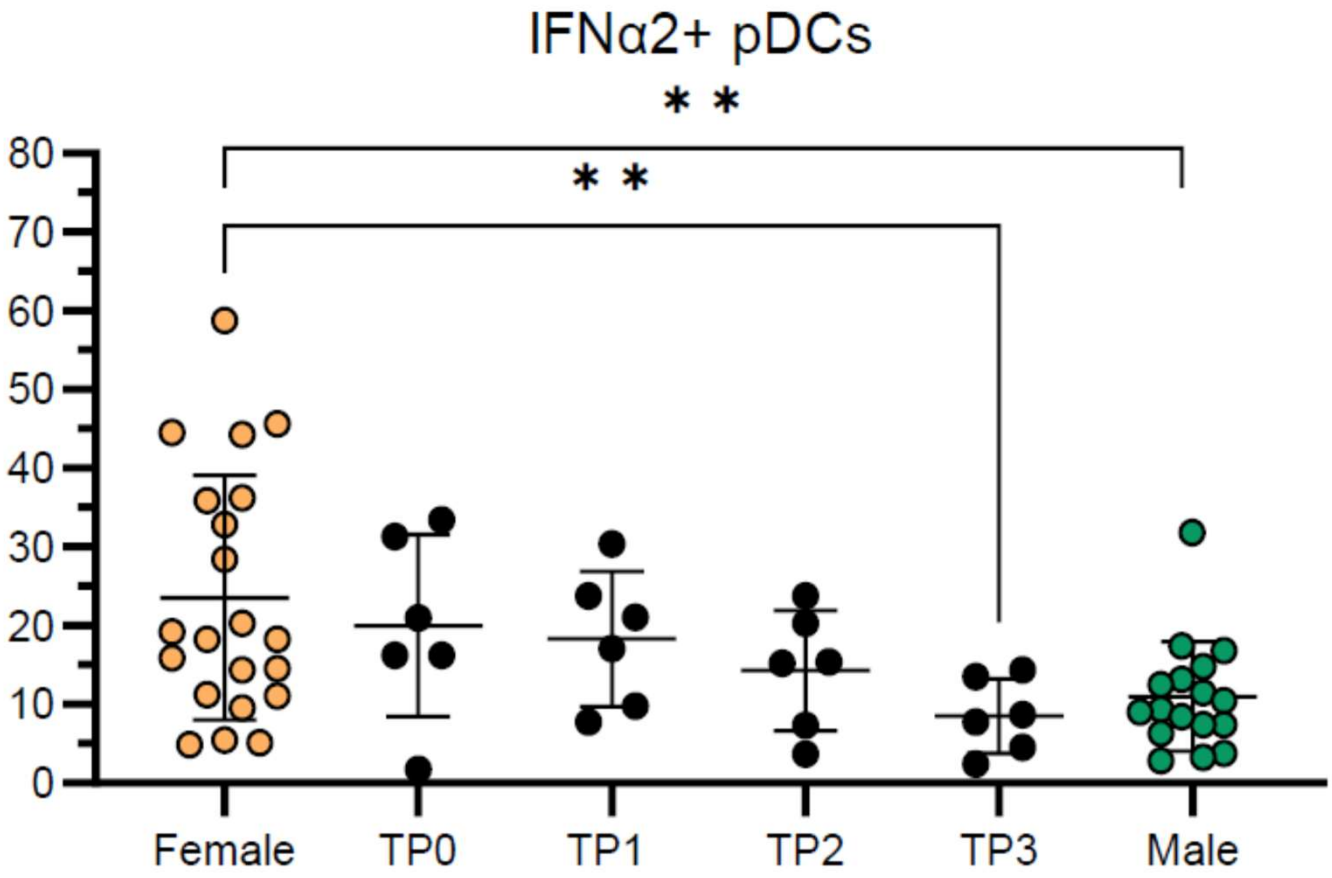
samples from transgender individuals receiving **gender-affirming hormonal treatment**

→ isolated assessment of the role of **sex hormones** (allosomal status is unchanged)

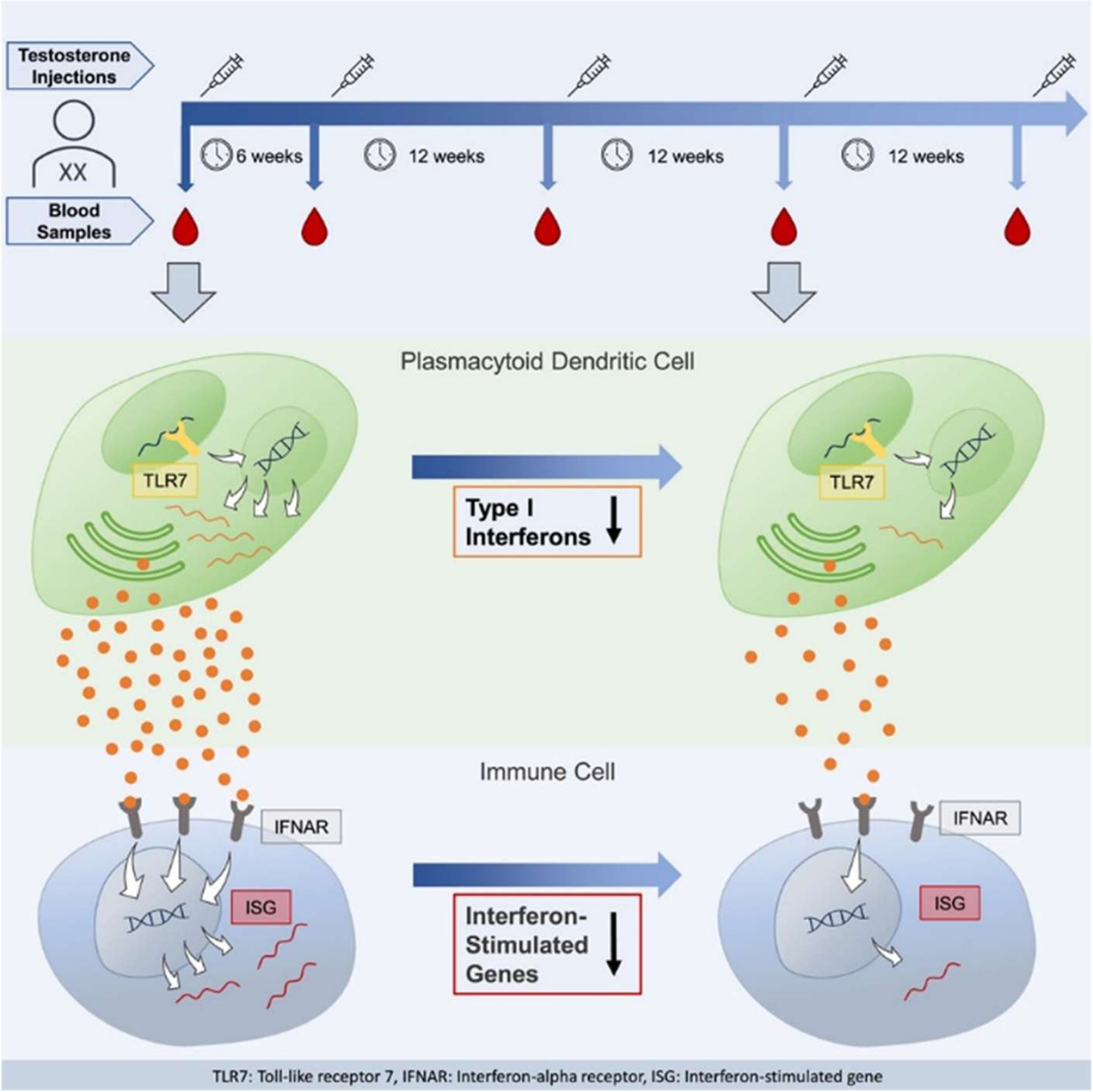


Grünhagel et al, iScience 2023

Decline in TLR7-induced IFNα responses during testosterone treatment in trans men



Grünhagel et al, iScience 2023



Decline in Type I IFN responses under testosterone treatment in trans men

Grünhagel et al, iScience 2023

Article

Immune system adaptation during gender-affirming testosterone treatment

https://doi.org/10.1038/s41586-024-07789-z

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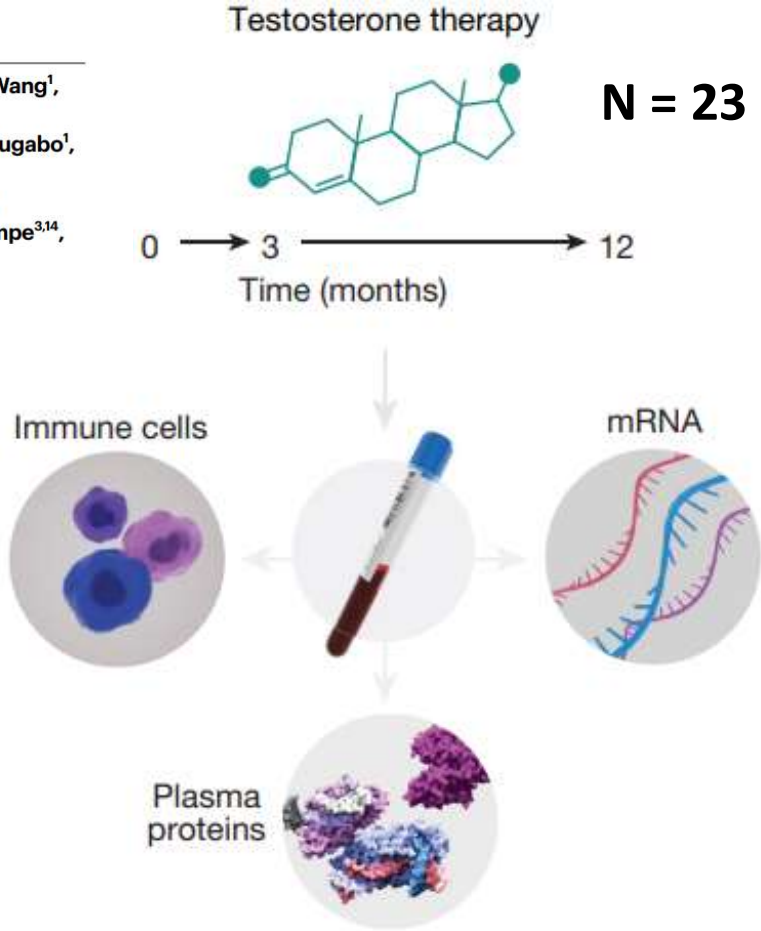

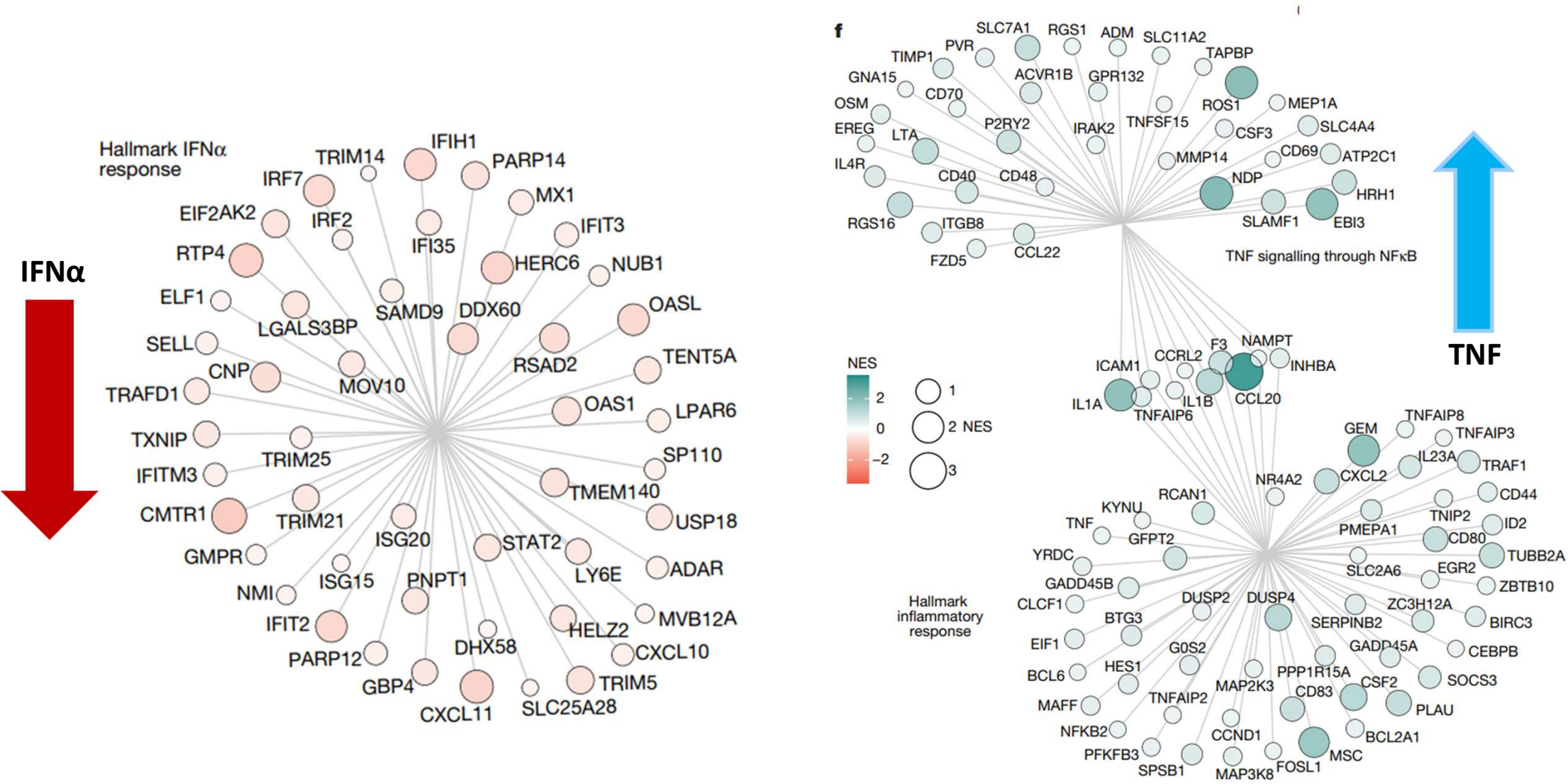

Lakshmikanth et al., Nature 2024

Rockefeller University Press
J. Exp. Med. 2025 Vol. 222 No. 4 e20241253

BRIEF DEFINITIVE REPORT

Estrogen influences class-switched memory B cell frequency only in humans with two X chromosomes

Hannah Peckham[1,2,3], Anna Radziszewska[1,2], Justyna Sikora[7], Nina M. de Gruijter[1,2], Restuadi Restuadi[1,3], Melissa Kartawinata[1,3], Lucia Martin-Gutierrez[1,2], George A. Robinson[1,2], Claire T. Deakin[1,3,5,6], Lucy R. Wedderburn[1,3,5], Elizabeth C. Jury[1,2], Gary Butler[3,4], Emma S. Chambers[7], Elizabeth C. Rosser[1,2*], and Coziana Ciurtin[1,2,4*]

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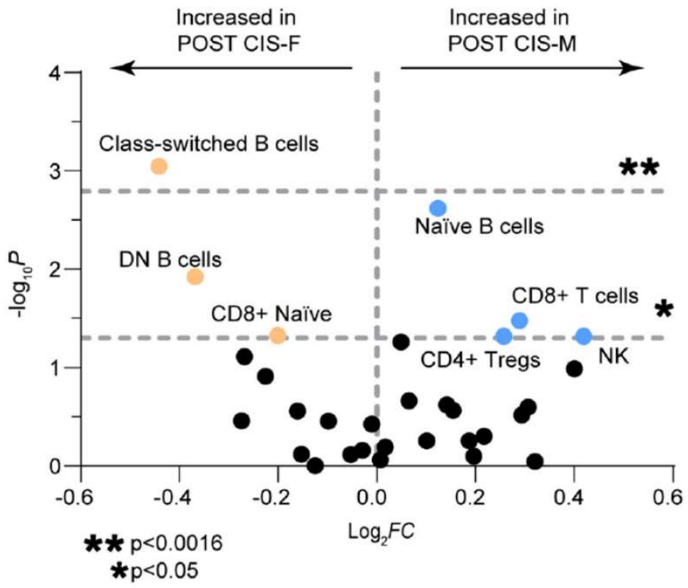
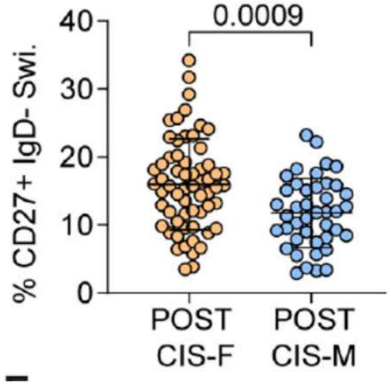
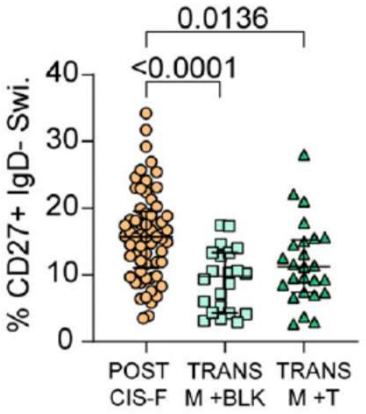
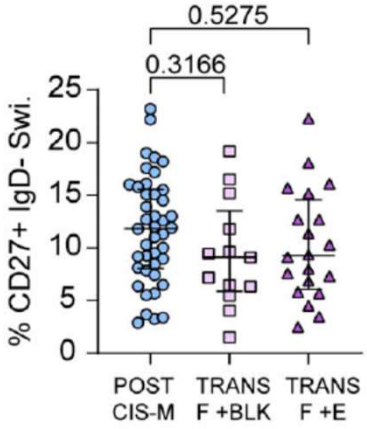
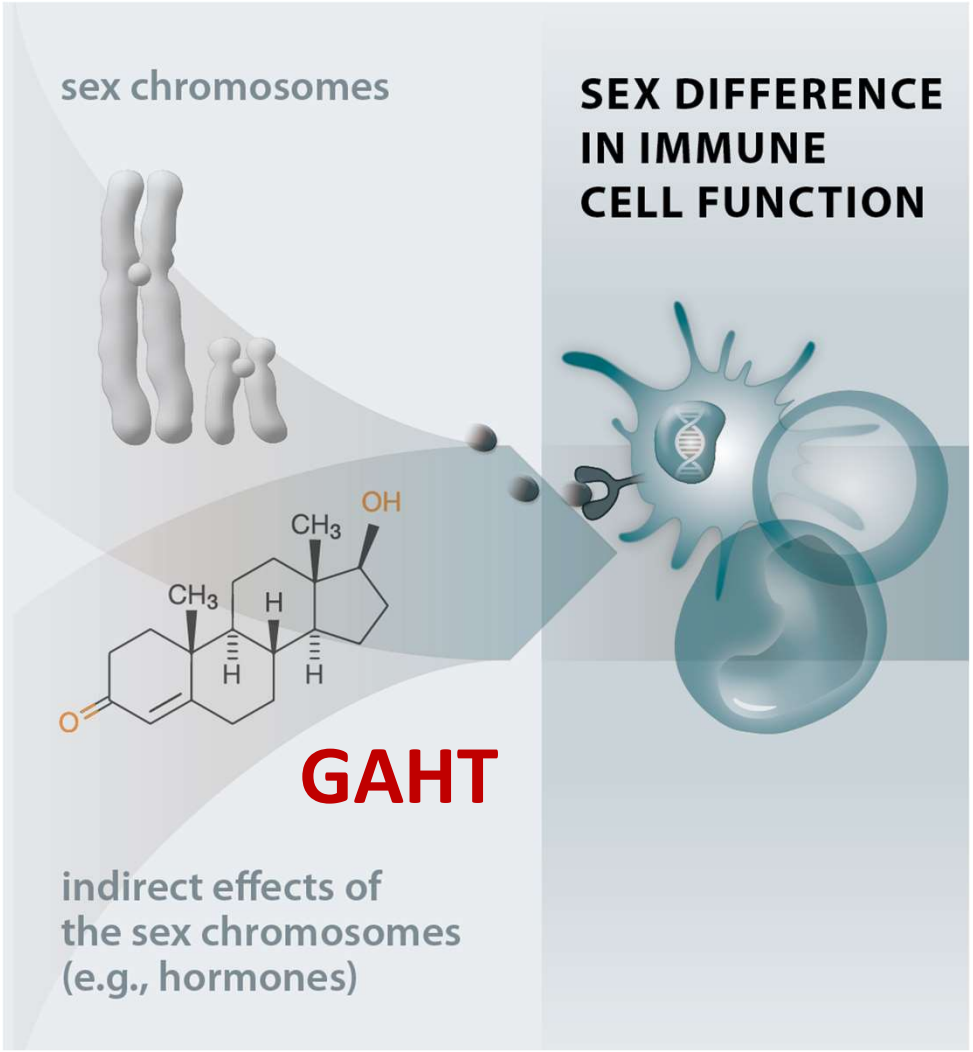










- Reduction of Type I IFN responses by pDCs in TM
- Reduction of effector CD4+ T cell activity in TM
- Reduction of B cell activity in TM

- Increase in TNF responses of monocytes in TM
- Increase in Treg activity in TM

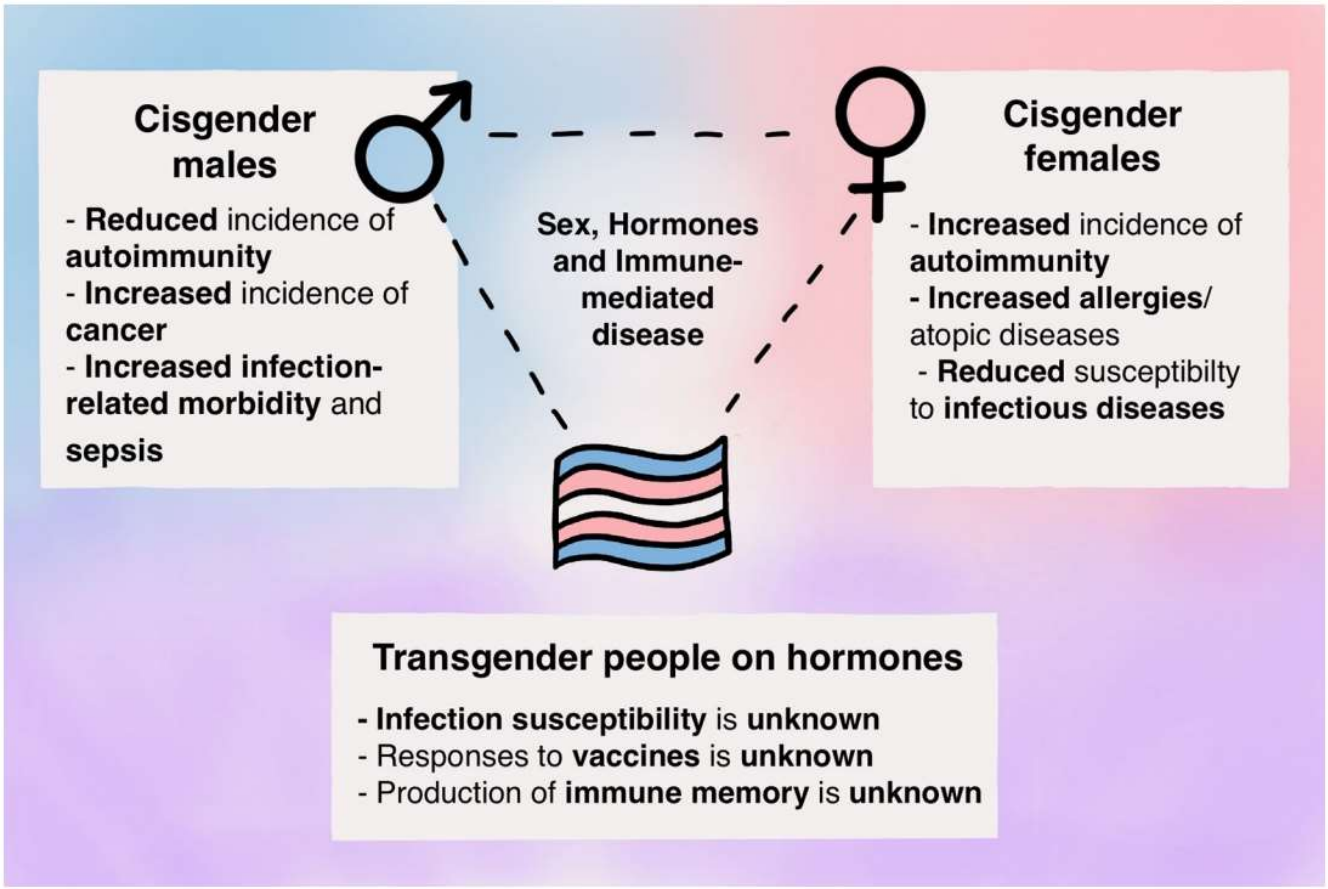
- Reduction of Treg activity in TW

Changes in immune function during GAHT are immune cell-type specific

Outline

- Consequences of sex steroid hormones and genes encoded by X and Y chromosomes for immunity
- Impact of gender affirming hormone therapy on immune function
- **Implications for transgender health**

Implications of GAHT for transgender health – limited data



White et al., Ther Adv Endocrinol Metab 2022

ORIGINAL ARTICLE

Higher Rates of Certain Autoimmune Diseases in Transgender and Gender Diverse Youth

Santhi N. Logel,[1,*,†] Johsias Maru,[2] Jax Whitehead,[3] Cassandra Brady,[4] Abby Walch,[2] Michael Lasarev,[5] Jennifer L. Rehm,[1] and Kate Millington[6,‡]

Transgender Health
Volume 9, Number 3, 2024

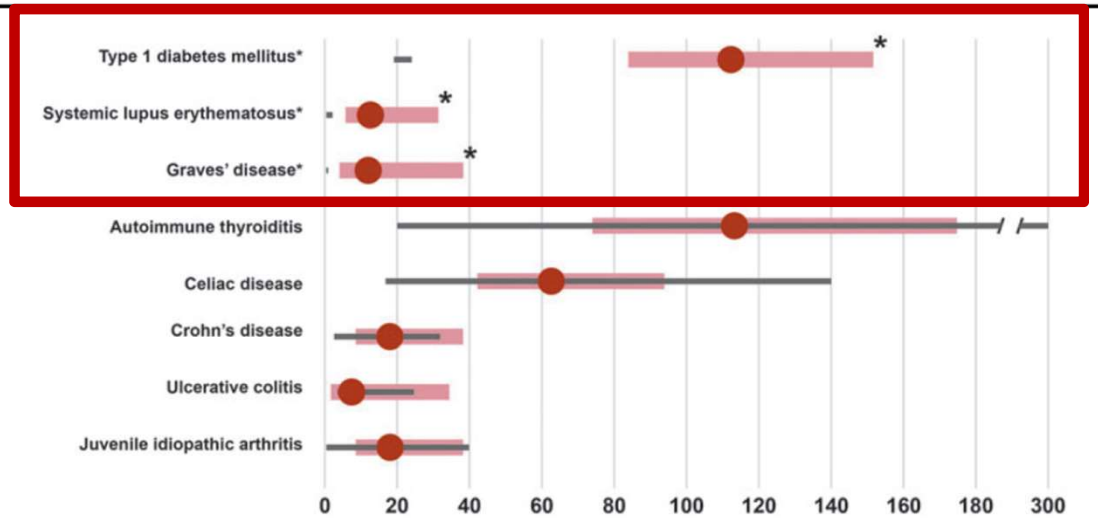
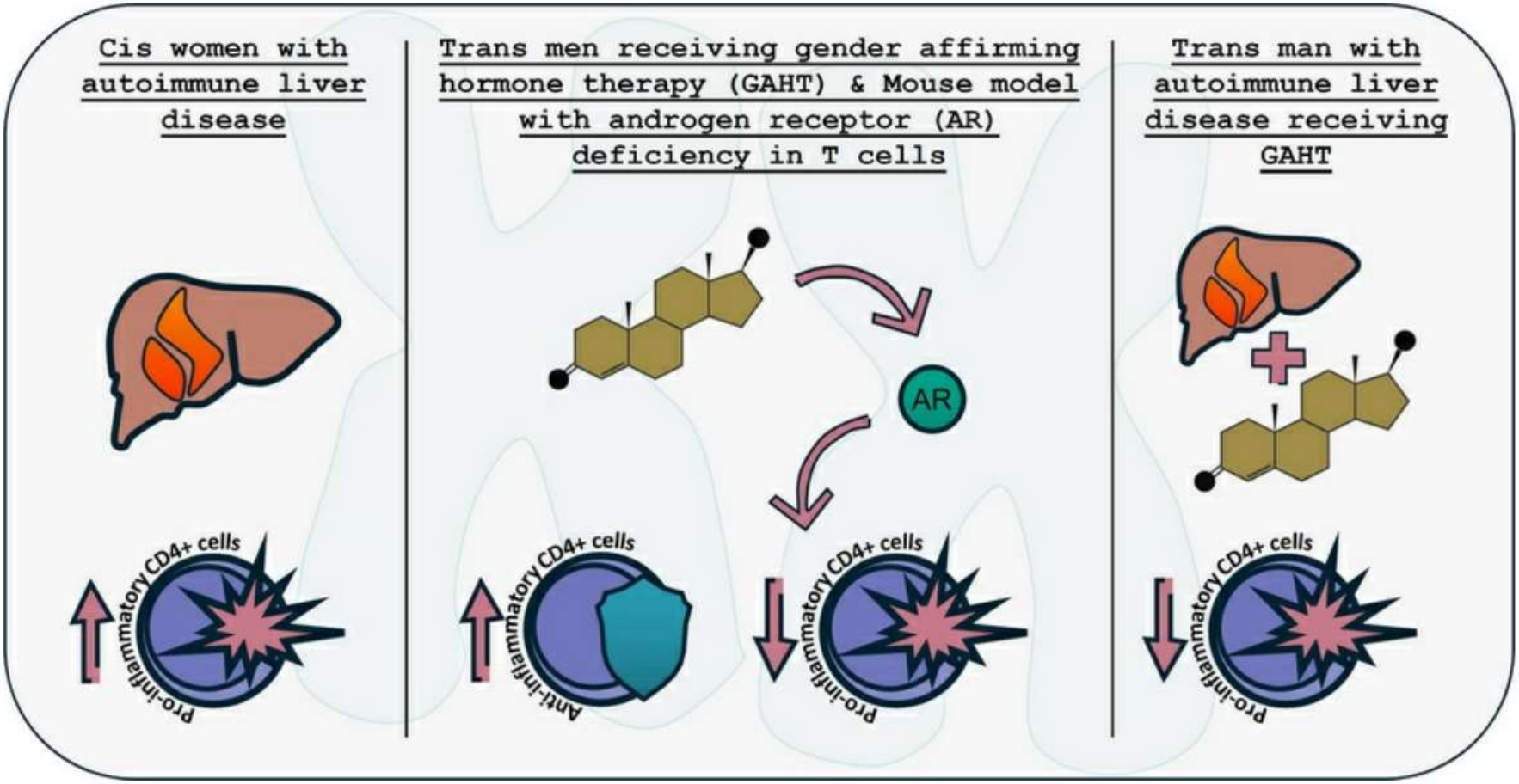


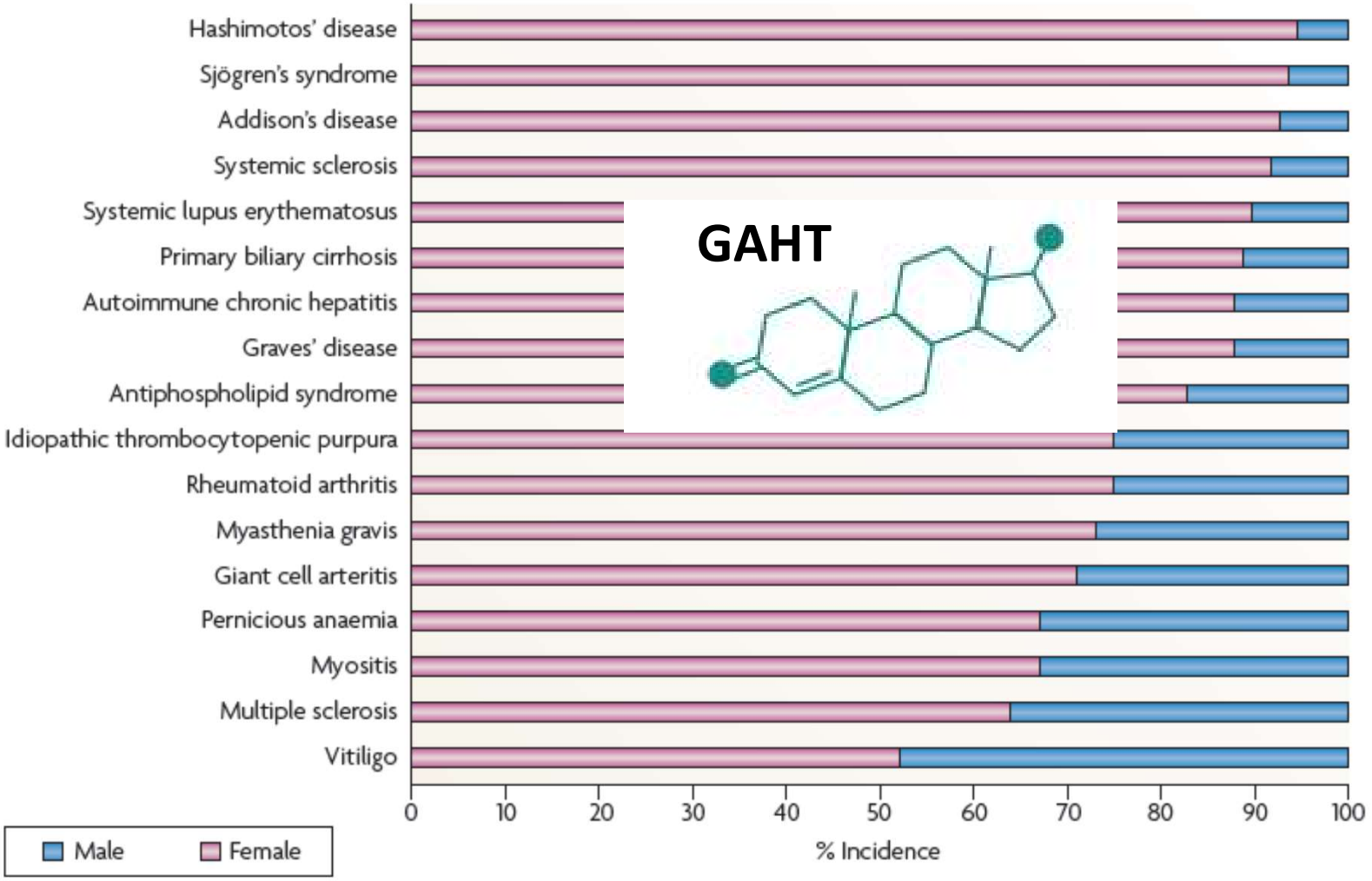
FIG. 1. Autoimmune disease prevalence rates per 10,000 in the general and TGD populations for individuals < 26 years old. Prevalence rates in the general population (gray) are reported as a range. Prevalence rates in the TGD population are reported as rates (solid red circles) with 95% confidence intervals indicated by the red bars. The asterisk indicates autoimmune diseases, in which the prevalence rates were higher in TGD youth compared to the general population (second generation *p*-value = 0.000). TGD, transgender/gender diverse.

Reduction of pathogenic CD4+ T cells inflammation during GAHT resulted in clinical improvement of AIH in a transman



Henze et al, JCI insights 2025

Impact of GAHT on autoimmune diseases

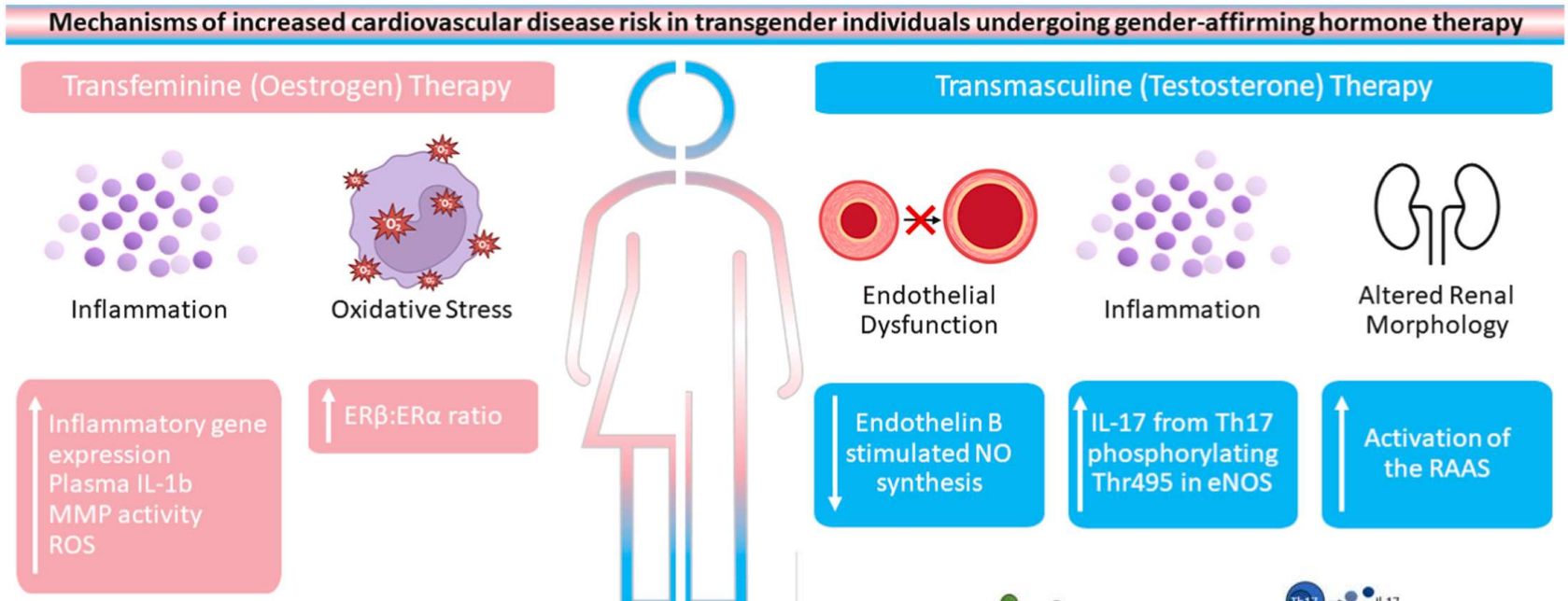


TW ↑

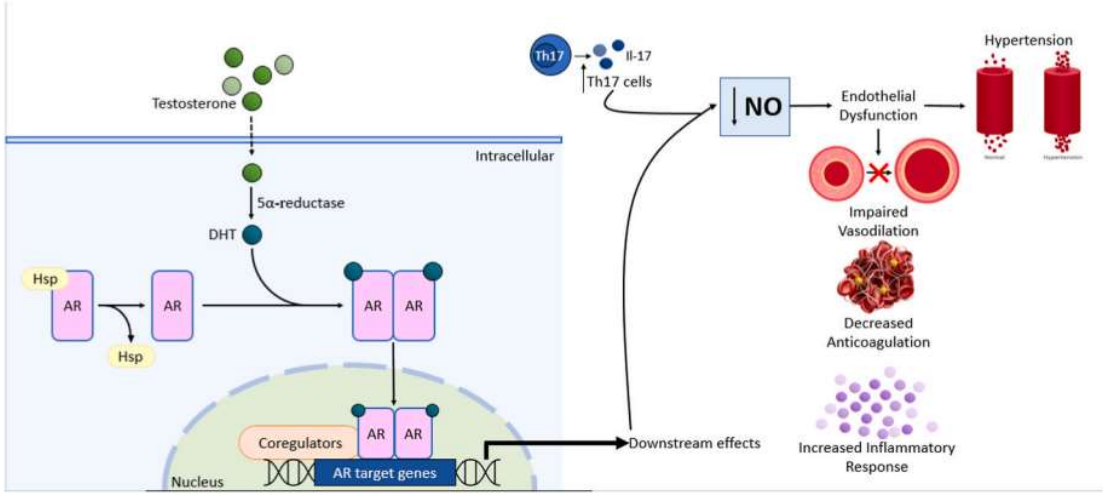
TM ↓

Libert et al. | Nat. Rev. Immunol. 2010

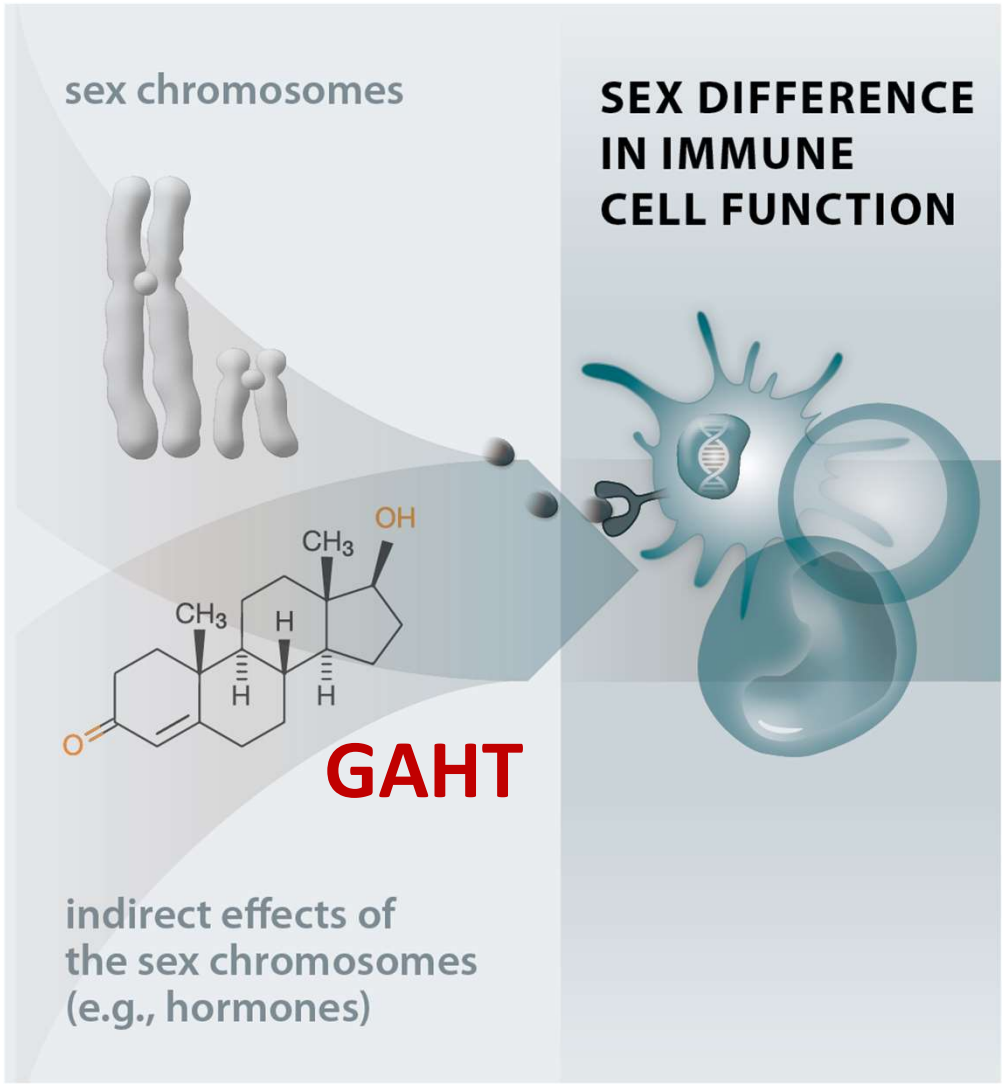
Impact of GAHT on cardiovascular risk



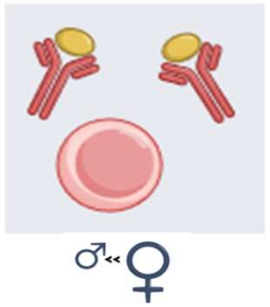
Murthy et al., Atherosclerosis 2023



Conclusions



Autoimmunity



♂ << ♀

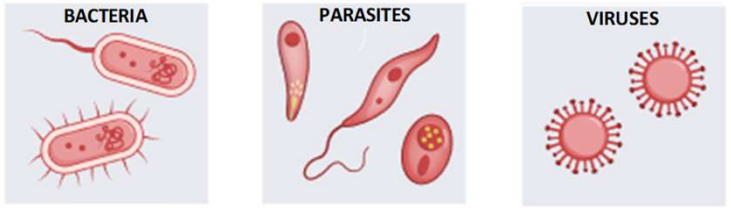
TW > TM

Cardiovascular

♂ >> ♀

TM ≥ TW

Infectious diseases



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Christoph Schramm

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Chistoph Dorn, amedes experts
Blood donors

Research Unit 5068
Sex differences in immunity

DFG Deutsche Forschungsgemeinschaft

Hamburg | Ministry of Science, Research, Equalities and Districts

Leibniz Association