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Exploring genetic and immune underpinnings of the sexual dimorphism in tumor response to immune checkpoints inhibitors: A narrative review

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ABSTRACT

Introduction: In spite of the undisputed relevance of sex as critical biologic variable of the immune landscape, still limited is our understanding of the basic mechanisms implicated in sex-biased immune response thereby conditioning the therapeutic outcome in cancer patients. This hindrance delays the actual attempts to decipher the heterogeneity of cancer and its immune surveillance, further digressing the achievement of predictive biomarkers in the current immunotherapy-driven scenario. *Body*: The present review concisely reports on genetic, chromosomal, hormonal, and immune features underlying sex-differences in the response to immune checkpoint inhibitors (ICIs). In addition to outline the need of robust data on ICI pharmaco-kinetics/dynamics, our survey might provide new insights on sex determinants of ICI efficacy and suggests uncovered pathways that warrant prospective investigations.
Conclusion: According to a sharable view, we propose to widely include sex among the co-variates when assessing the clinical response to ICI in cancer patients.

1. Introduction

In the last decade, immune checkpoint inhibitors (ICIs) have prompted a paradigm shift in the treatment of several solid and hematologic malignancies, including non-small cell lung cancer (NSCLC) (Ribas and Wolchok, 2018), malignant melanoma and genitourinary cancers (Lin et al., 2022; Lalani et al., 2022). At present, ICIs are approved for the first and more-line treatment in advanced NSCLC (Pasello et al., 2020), with the notable exception of consolidation durvalumab, which is employed in unresectable locally-advanced NSCLC after radical chemoradiation (CRT) (Gray et al., 2020). Nonetheless, the profound and long-lasting benefit derived from ICIs in metastatic setting (Gadgeel et al., 2020; Paz-Ares et al., 2020) is still achieved in a limited fraction of patients, thus making imperative the identification of prognostic and predictive biomarkers able to guide patient selection (Tray et al., 2018).

The central role of tumor immune microenvironment (TIME) has been repeatedly demonstrated (Altorki et al., 2019; Binnewies et al., 2018; Mazzaschi et al., 2018), mainly involving the assessment of PD-L1 status, that is currently the only approved ICI-biomarker, tumor infiltrating lymphocytes (TILs) density and phenotype, and activating (i.e. interferon-γ) or inhibitory (i.e. CD38, transforming growth factor-β) signalling pathways. Moreover, as cancer immunoediting and immune response also engage the peripheral circulation, the contribution of circulating immune cells, cytokines, growth factors and chemokines has been intensively investigated (Buder-Bakhaya and Hassel, 2018; Nixon et al., 2019; G. Mazzaschi et al., 2020).

Genomic and RNA-based studies exploring predictors of ICIs responsiveness have designated tumor mutational burden (TMB) and neoantigen signature as potential biomarkers in NSCLC patients (Rizvi et al., 2015; Fumet et al., 2020; Anagnostou et al., 2017). Other currently explored relevant factors are embodied by human leukocyte antigens (HLAs) (McGranahan et al., 2017) and distinct somatic mutations (i.e., serine/threonine kinase 11, *STK11*) (Skoulidis et al., 2018). Recently, a 18-gene pan-tumor signature (Tumor Inflammation Signature, TIS) associated with high response to PD-1 inhibitors, was proposed (Danaher et al., 2018).

Multiple clinical aspects, including age, performance status (ECOG PS), number and sites of metastatic involvement, concomitant interfering drugs (i.e. corticosteroids, proton pump inhibitors, antibiotics) or the occurrence of immune-related adverse events (irAEs) have shown to significantly affect the response to ICIs (Brueckl et al., 2020; L. Huang et al., 2020; Buti et al., 2021).

How sex impacts on the actual immunotherapy scenario and on the

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urgent need of predictive biomarkers of ICI efficacy remains largely uncovered. Thus, the aim of the present review is to provide a concise survey on sex related genetic and immune features implicated in the response to ICIs.

2. Current knowledge on sex and response to immune checkpoint inhibitors

Sex differences in cancer biology are well documented and may be responsible for a greater risk of cancer development and mortality in man, reaching up to twice that of women in specific tumor subtypes (Cook et al., 2009, 2011). It is a long-standing notion that sex, meaning the biological differences between men and women, and gender, implying behavioural differences derived from being male or female, represent variables potentially affecting immune responses to both foreign and self-antigens (Roved et al., 2017). However, whether sex difference (Márquez et al. 2020; Roved et al., 2017) is a relevant determinant of clinical outcome in cancer patients treated with immunotherapy remains unclear.

ICIs are humanized or human monoclonal antibodies whose therapeutic task is essentially addressed to the reinvigoration/rejuvenation of the immune mediated anti-tumor cytotoxic response (Huang et al., 2017). This is achieved mainly by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) or true receptor blockade resulting in cleavage of either the ligand (i.e. PD-L1) or the receptor (i.e. PD-1) at cancer-immune synapse (Ribas and Wolchok, 2018). On one side, targeted drug-receptor affinity as different IgG class of therapeutic antibodies (mostly IgG1 while IgG4 for anti PD-1) are undoubtedly crucial to trigger the immune response and represent important variables potentially conditioned by sex. On the other side, the different immune background in male and female might critically trains the quantitative and functional state of relevant effector and suppressor cells both at tumor sites and in the circulation. The fine molecular mechanisms by which sex-related genetic, hormonal, and environmental cues act on each of these steps responsible for ICI efficacy are currently not elucidated.

2.1. Sex differences in ICI pharmacokinetics and pharmacodynamics

Before addressing the question whether a distinct outcome occurs in male and female cancer patients following ICIs, a necessary pre-requisite is to provide a succinct description of sex-associated pharmacokinetics (PK) and pharmacodynamics (PD) of this class of therapeutic agents.

PK and PD studies focused on ICI and data on relationships between exposure and response are still inconsistent. Patient- (i.e. age, sex, ethnicity, body mass index, liver and renal function, ECOG PS) and tumor-associated (i.e. tumor burden, immunogenicity) factors are known to affect drug clearance, however their effect on ICI PK has been estimated to reach at most 30% (Desnoyer et al., 2020). Intriguingly, sex does not uniformly impact on ICI clearance as male sex is associated with faster clearance of the anti-CTLA4 tremelimumab and the anti-PD-1 nivolumab, while that of the anti-PD-L1 durvalumab decreases in female patients (Desnoyer et al., 2020). Observations on differential PKs of other analogous (Centanni et al., 2019) or recently introduced (Melhem et al., 2022) ICI agents according to sex are inconclusive. Overall, PD and PK studies strongly suggest to incorporate sex among the clinical covariates to assess ICI efficacy in cancer patients (Bajaj et al., 2019).

2.2. Sex differences in the response to ICI: clinical evidence

Based on large-scale meta-analyses and systematic reviews (Conforti et al., 2018; Wallis et al., 2019; Grassadonia et al., 2018; Pala et al., 2022), an intense and open debate on whether cancer immunotherapy efficacy is different between male and female patients is still ongoing. In a meta-analysis of randomized clinical trials including 11,351 ICI-treated patients (67% men and 33% women, with a predominance of melanoma [32%] and non-small cell lung cancer [31%]), Conforti et al. reported that the magnitude of ICI response was sex-dependent, as male patients achieved greater benefit than females (Conforti et al., 2018). Conversely, a more recent meta-analysis of all available ICI-based clinical trials across several cancer types (13,721 patients, 67.9% men and 32.1% women) did not document any significant difference in overall survival (OS) when comparing the effectiveness of these treatments between the sexes (Wallis et al., 2019). Moreover, performing subgroup analyses, including disease site, line of therapy, class of immunotherapy, and study methodology, no meaningful sex-associated differences in clinical outcome were observed (Wallis et al., 2019). An additional metanalysis of phase III randomized clinical trials showed better results from immunotherapy in man for all advanced cancers with the exception of melanoma (Grassadonia et al., 2018). Accordingly, by a machine learning algorithm on a multiscale analysis on more than 1000 patients with different tumor types, male sex resulted a positive predictor among the 12 biomarkers enclosing a score for the response to immunotherapy (Litchfield et al., 2021). These contrasting findings are based on subgroup hazard ratios (HR) of published clinical trials lacking the analysis of individual patients, and/or the differential distribution of age, smoking habits and clinicopathological characteristics, such as PD-L1 expression and TMB, thus further clouding the significance of the obtained results. In an attempt to shed new light on sex-related difference in ICI efficacy according to well-known biomarkers, a post hoc analysis of prospective individual patient data from five clinical trials (OAK, POPLAR, IMvigor210, KEYNOTE-001, and CheckMate-012), and a meta-analysis of nine randomized controlled trials (RCTs) have been also conducted stratifying patients according to PD-L1 status (Li et al., 2020). The authors documented that survival benefits from ICI in male and female were greatly influenced by PD-L1 expression, especially in NSCLC, thus recommending to jointly consider sex and PD-L1 in the clinical decision-making in the setting of ICI treated cancer. Concerning tumor mutational status, it has been reported that several solid neoplasms in women display a lower TMB (Xiao et al., 2016) which is associated to a lower response rate to immunotherapy in melanoma (Van Allen et al., 2015). Nonetheless, more recent receiver operating characteristic-based analyses to define high *vs* low TMB on three datasets of NSCLC patients showed a better performance in predicting a greater benefit from ICI in female tumors with high TMB (Wang et al., 2019).

2.3. Sex differences in immune related adverse events

An additional important aspect with biological and clinical implications arisen from the advent of immunotherapy is represented by the occurrence of irAEs. Not surprisingly, therapeutic inhibition of CTLA-4 or PD-1/PD-L1 checkpoints, the natural machinery instrumented to survey non-self antigens, may result in autoimmune manifestations (Shankar et al., 2020). Although irAEs have been repeatedly reported to positively impact on ICI response in NSCLC (Shankar et al., 2020; Hussaini et al., 2021; Grangeon et al., 2019), the biological basis of this phenomenon requires to be deeply investigated. Even more limited is the documentation on whether female patients, carrying a natural propensity for autoimmunity, are more (Kitagataya et al., 2020) or less (Triggianese et al., 2020) prone to develop irAEs. A recent analysis on a large cohort ($n = 23,296$) of cancer patients disclosed a 49% increased risk of AEs in female receiving immunotherapy compared with males (Unger et al., 2022), reinforcing the notion of sex-driven pharmaco-kinetics, -dynamics and -genomics differences with relevant implication on clinical outcome.

3. Sexual dimorphism in immune response

Genetic, behavioural, environmental and hormonal factors are implicated in sexual dimorphism of the immune system (Naqvi et al., 2019). Estrogen and androgen responsive elements are present in promoter regions of a consistent number of immune related genes (Hannah et al., 2008), as sex hormones receptors are expressed by a variety of

immune cells (Mantalaris et al., 2001; Arruvito et al., 2008; Dosiou et al., 2008). The understanding of such sex related diversities may benefit from the advanced knowledge achieved on the role of microbiome in shaping the immune response. The microbiome has been implicated in the development of inflammatory, autoimmune and neoplastic (Huang et al., 2018) diseases in humans (Yatsunenko et al., 2012; Haro et al., 2016; de la Cuesta-Zuluaga et al., 2019) and mice (Sheng et al., 2021; Markle et al., 2013). Due to the ability of microbes to process and/or synthetize estrogen and androgen metabolites (Taneja, 2018), gut microbiota regulates immune functions in a sex-specific manner. The gender dimorphic microbiome is under intense biological and clinical scrutiny, leading the scientific community to coin the term 'micro-genderome' (Vemuri et al., 2019; Flak et al., 2013).

Evidence of a sexual dimorphism in the modulation of cholesterol homeostasis, mainly exerted by proprotein convertase subtilisin kexin-like 9 (PCSK9) (Ghosh et al., 2015), reinforces the notion of a sex/gender-dependency of immune metabolic pathways, ultimately conditioning tumor immune landscape (Ma et al., 2019) and response to ICIs.

3.1. Genetic basis of sex differences in immunity

Sexual dimorphism of the human immune system is detectable as early as within the first 6 months after birth, as genetic-transcriptional analysis of the thymus have documented that sex hormones and XX and XY genomic backgrounds condition autoimmune regulator (AIRE) interactors (Moreira-Filho et al., 2018). AIRE is a transcription factor expressed by thymic (Anderson et al., 2002) and extrathymic (Poliani et al., 2010) cells, including stromal (Bergström et al., 2019) and circulating (Suzuki et al., 2008) elements, displaying features shared with dendritic cells (DCs) and therefore critically implicated in central tolerance. Intriguingly, animal models (Zhu et al., 2013) and human studies (Nguyen et al., 2020; Kalra et al., 2018) have pointed to a regulatory role of AIRE in cancer immune surveillance. However, this contention cannot be widely applied to a variety of neoplastic diseases since conflicting results have been reported (Klamp et al., 2006). Keeping on the immunotherapy scenario, unveiling the distinctive clinical significance of AIRE expression in cancer and/or immune cells in female and male patients, represents an area of prospective studies with potential therapeutic spill-over.

Importantly, sex-associated dichotomic immune response can be elicited because immune relevant genes, as *interleukin 2 RG* (*IL2RG*), *IL-13RA2* and *TLR7-8*, coding for cytokine receptors, or androgen receptor (*AR*) and *forkhead box P3* (*FOXP3*) for transcription factors (Kawai and Akira, 2006; Kleina et al., 2015; Lubahn et al., 1988; Su et al., 2009; Souyris et al., 2019; Zhao et al., 2020), are X-linked. Of note, sex biased expression patterns are generated by the escape from X chromosome inactivation (XCI) in nearly 1/4 (23%) of X-linked genes (Tukiainen et al., 2017). In addition to their largely documented role in female proneness to develop autoimmune diseases (i.e. lupus erythematosus), numerous XCI-escaped genes have also been implicated in tumor-suppressing functions (Clocchiatti et al., 2016; Dunford et al., 2017). As an example, the protection of females from bladder cancer has been associated with the biallelic expression of *KDMA6*, a sex-biasing tumor suppressor gene that escaped XCI in females (Dunford et al., 2017; Kaneko and Xue, 2018; Ntziachristos et al., 2014). Although not peer reviewed, a very recent study identified *KDM6A* as the most differentially regulated gene escaping XCI and conditioning sex differences in number and function of natural killer (NK) cells. Independently from sex hormones, *KDM6A*, through its encoded histone demethylase UTX, was found to be responsible for the decrease frequency and increased IFNγ expression characterizing the female NK phenotype (Cheng et al., 2022). For completeness, additional immune-related XCI-escaped genes include *CD99, TLR8, TASL, DDX3X, USP27X, CXCR3, LAMP2, XIAP, CD40*LG, *IRAK1*, and *IL9R* (Carrel and Willard, 2005; Mousavi et al., 2020; Oghumu et al., 2019; Vermeesch et al., 1997).

A seminal work addressing the impact of sex on the genomic landscape of multiple cancers disclosed sex-biased molecular patterns in more than 50% of clinically targetable genes (Yuan et al., 2016). Specifically, *IL2*, *IL6*, *STAT5*, *JAK*, *STAT3*, *IFNα* and *IFNγ*, *TNF-α* and complement, involved in signalling pathways implicated in immune responses, emerged as differentially expressed genes.

These chromosomal and genetic contexts driving a differential immune response to cancer in the two sexes are listed in the visual abstract. However, the translational significance of the indicated groups of immune-related genes which are differentially regulated among the two sexes is still unveiled and necessitates prospective studies.

3.2. Sex hormones and immune profile

The immunomodulatory effect of sex hormones is a long-standing notion. By inhibiting pro-inflammatory (including TNFα, IL-1β and IL-6) (Straub, 2007) and stimulating anti-inflammatory (including IL-4, IL-10 and TGFβ) pathways, estrogens establish a sort of an unbalanced immune response favouring T helper (Th) type 2 *vs* Th1 activity (Roved et al., 2017) and partly explaining the predominance of Th1- and Th2-dependent autoimmune diseases in male and female, respectively (Whitacre, 2001). However, the effects of female hormones are context-dependent as, mainly after menopause, estrogen stimulates NK cell mediated responses (Giglio et al., 1994). Similarly, the decreased NK cytotoxic activity observed during pregnancy (van Nieuwenhoven, et al. 2003) disappears after menopause (Giglio et al., 1994).

While estrogens are associated with enhanced immune reactivity, testosterone has been widely ascribed as immunosuppressive (Foo et al., 2017). This contention is supported by evidence that T cells express androgens receptors (AR), which upon activation suppress IFNγ production, negatively conditioning ICI activity (Guan et al., 2022). Accordingly, clinical trials have documented an increased response rate in patients with advanced prostate cancer treated with AR inhibitors plus PD-1 blockade (Graff et al., 2016, 2020). As programmed exhaustion of CD8+T cells within the TIME is critically regulated by T cell-intrinsic AR signalling (Kwon et al., 2022), the mechanism underlying the positive outcome from immunotherapy might reside in the synergistic effect of AR and PD-1 blockade, respectively preventing CD8 T cells anergy and unleashing their cytotoxic activity (Guan et al., 2022).

Sexual dimorphism in immune response resides also in the differential impact exerted by sex hormones on blood immune cell populations in a quantitative and qualitative manner. In large cohorts of healthy adults, females displayed higher number of $CD4^+$ T cells and macrophages, higher CD4/CD8 ratio and lower NKs and T regulatory cells (Tregs) than males (Abdullah et al., 2012; Ahnstedt et al., 2018; Lee et al., 1996; Scotland et al., 2011). Healthy females also carry more activated CD8 T phenotypes (IFNγ, TNFα, GnZB) and increased B cells number (Abdullah et al., 2012). Higher baseline levels of immunoglobulin M (IgM) (Butterworth et al., 1967) and greater antibody response to vaccination against seasonal and pandemic viruses (influenza, yellow fever, rubella, measles, mumps, hepatitis A and B, herpes simplex 2, rabies, smallpox, and dengue viruses) (Klein et al., 2010), including Sars-Cov2 (Bignucolo et al., 2021), compared to males also characterize female immunity.

In conventional DCs, as opposed to testosterone, estrogens enhance type 2 (IL-4, IL-10, and IL-13) cytokines and may also upregulate the expression of major histocompatibility complex (MHC) class II receptors and co-stimulatory molecules (Hepworth et al., 2010). While both testosterone (Corrales et al., 2009) and estrogens (Relloso et al., 2012) similarly suppress Th17 responses in conventional DCs, estrogens favour the release of type 1 cytokines in plasmacytoid DCs (Laffont et al., 2014; Seillet et al., 2012). Additionally, a higher production and receptor expression of type I IFNs was seen in female plasmocytoid DCs (Mocikat et al., 2003). Of note, single cell RNA sequencing documented upregulation of type I *IFN* stimulated genes in circulating neutrophils from healthy females as compared to male subjects (Gupta et al., 2020). Thus,

the identification of a sex-specific *IFN*-gene signature involving multiple immune-inflammatory phenotypes may offer important insights for personalized therapeutic strategies including immunotherapy.

The notion that estrogens are potent inducers of FOXP3 resulting in expansion of Treg compartment is well recognized (Polanczyk et al., 2004; Polanczyk et al., 2005). Sexual dimorphism on Treg population has been also experimentally documented in melanoma as improved anti-tumor immunity conferred by a reduced Treg function was observed in females (P.-Y. Lin et al., 2010).

Finally, aging in humans is associated with a decline in naïve T cells and $CD8^+$ T cells and a rise in $CD3^+$CD45RA-CCR7+ effector memory, CD4+FOXP3+ Treg and NK cells (Márquez et al., 2020; Yan et al., 2010). However, this effect of aging is attenuated in women which display a relative increased immune reactivity (Takahashi and Iwasaki, 2021). More recently, an age-associated increase in $CD8^+$ T effector memory (TEM) Granzyme K+ (GnZK) and PD-1+ circulating lymphocytes has been reported in humans (Mogilenko et al., 2021), although the impact of sex on this cell population was not investigated.

3.3. Sex differences in PD-1/PD-L1 immune checkpoint

Limited reports are available on the differential expression of PD-1 and PD-L1 in lung cancer according to sex (Pan et al., 2017; Moutafi et al., 2021; Ye et al., 2020). Interestingly, these studies concordantly documented higher PD-L1 levels in tumors from male patients potentially leading to a higher sensitivity to ICIs. Conversely, a lower fraction of PD-1+ $CD8^+$ lymphocytes in female melanoma patients was associated with a lower rate of response to combined ICIs (Loo et al., 2017). Intriguingly, a multiomic molecular analysis conducted on a variety of tumor types, identified a female-bias immune signature in lung squamous carcinoma characterized by higher cytotoxic CD8 T cell activity and PD-1 expression (Ye et al., 2020).

However, in both aforementioned studies the potential confounding role of smoking habit was not evaluated.

Experimental observations made in an animal model revealed that female Tregs display an estrogen-insensitive lower expression of PD-L1 compared to male cells and this phenomenon appears to be coupled with a better response to PD-1 blockade (Lin et al., 2010). Moreover, the potency of Treg-mediated suppressive function has been linked to an increased estrogen-sensitive intracellular expression of PD-1 (Polanczyk et al., 2007; C. Wang et al., 2009) which is translocated to the cell surface upon Treg activation (Raimondi et al., 2006).

Finally, an often disregarded aspect when exploring sex-associated differences in immunity is the transient tolerogenic state that only women intrinsically experience during pregnancy (Barnet et al., 2018). However, this unique immune state engendered by both fetal (Rackaityte and Halkias, 2020) and placental (Murata et al., 2021) cues may evolve during life as chimerism (Bianchi et al., 1996; Jeanty et al., 2014), resulting from long term persistence of fetal DNA in mothers, may constitute an underlying mechanism of the increased incidence of auto-immunity in women (Fugazzola et al., 2011). Most clinical and experimental observations have suggested a rather protective action exerted by fetal microchimerism on the development of cancer, however conflicting results persist on such issue (Sedov et al., 2022; Kallenbach et al., 2011). How immunogenic and tolerogenic pathways in women who have been pregnant are differentially informed with the advent of cancer remains unknown and represent a fascinating area of future investigations in the era of immunotherapy.

4. Concluding remarks

Profound sex differences exist in immune response which are in part constitutive or take place during life as a result of adaptive measures of the organism (Murphy and Weaver, 2016). Genetic, hormonal and environmental factors contribute throughout life to create a divergent metabolic substrate and cytokines/chemokines networking, ultimately conditioning sex specific immune profiles.

How this sexually determined immune dynamic is translated into differential tumor microenvironmental features and ICI response remains largely unknown and prospective data on sex differences in TIME composition are warranted.

Sex intersects with multiple biological, genetic and environmental factors implicated in the onset and evolution of cancer as well as its immune surveillance. So far, studies aimed at predicting ICI efficacy by the adoption of sex as a co-variate to be integrated with age, pregnancy or easily accessible blood immune descriptors are lacking and should represent the focus of shortcoming clinical and experimental observations.

CRediT authorship contribution statement

Giulia Mazzaschi: Writing – original draft. **Federico Quaini:** Writing – original draft, Writing – review & editing. **Sebastiano Buti:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Abdullah, Maha, Chai, Pei Shin, Chong, Mun Yee, Mohd Tohit, Eusni Rahayu, Ramasamy, Rajesh, Pei, Chong Pei, Vidyadaran, Sharmili, 2012. Gender effect on in vitro lymphocyte subset levels of healthy individuals. Cell. Immunol. 272 (2), 214–219. https://doi.org/10.1016/J.CELLIMM.2011.10.009.

Ahnstedt, Hilda, Roy-O'Reilly, Meaghan, Spychala, Monica S., Mobley, Alexis S., Bravo-Alegria, Javiera, Chauhan, Anjali, Aronowski, Jaroslaw, Marrelli, Sean P., McCullough, Louise D., 2018. Sex differences in adipose tissue CD8 + T cells and regulatory T cells in middle-aged mice. Front. Immunol. 9 (APR). https://doi.org/10.3389/FIMMU.2018.00659.

Van Allen, Eliezer M., Miao, Diana, Schilling, Bastian, Shukla, Sachet A., Blank, Christian, Zimmer, Lisa, Antje Sucker, et al., 2015. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 350 (6257), 207–211. https://doi.org/10.1126/science.aad0095.

Altorki, Nasser K., Markowitz, Geoffrey J., Gao, Dingcheng, Port, Jeffrey L., Saxena, Ashish, Stiles, Brendon, McGraw, Timothy, Mittal, Vivek, 2019. The lung microenvironment: an important regulator of tumour growth and metastasis. Nat. Rev. Cancer 19 (1), 9–31. https://doi.org/10.1038/s41568-018-0081-9.

Anagnostou, Valsamo, Smith, Kellie N., Forde, Patrick M., Niknafs, Noushin, Bhattacharya, Rohit, White, James, Zhang, Theresa, et al., 2017. Evolution of neoantigen landscape during immune checkpoint blockade in non-small cell lung cancer. Cancer Discov. 7 (3), 264–276. https://doi.org/10.1158/2159-8290.CD-16-0828.

Anderson, Mark S., Venanzi, Emily S., Klein, Ludger, Chen, Zhibin, Berzins, Stuart P., Turley, Shannon J., Von Boehmer, Harald, et al., 2002. Projection of an immunological self shadow within the thymus by the aire protein. Science (New York, N.Y.) 298 (5597), 1395–1401. https://doi.org/10.1126/SCIENCE.1075958.

Arruvito, Lourdes, Giulianelli, Sebastián, Flores, Ana C., Paladino, Natalia, Barboza, Marcos, Lanari, Claudia, Fainboim, Leonardo, 2008. NK cells expressing a progesterone receptor are susceptible to progesterone-induced apoptosis. J. Immunol. 180 (8), 5746–5753. https://doi.org/10.4049/jimmunol.180.8.5746.

Bajaj, Gaurav, Suryawanshi, Satyendra, Amit, Roy, Gupta, Manish, 2019. Evaluation of covariate effects on pharmacokinetics of monoclonal antibodies in oncology. Br. J. Clin. Pharmacol. 85 (9), 2045–2058. https://doi.org/10.1111/bcp.13996.

Barnet, Megan B., Blinman, Prunella, Cooper, Wendy, Boyer, Michael J., Kao, Steven, Goodnow, Christopher C., 2018. Understanding immune tolerance of cancer: Re-purposing insights from fetal allografts and microbes. Bioessays : News and Reviews in Molecular, Cellular and Developmental Biology 40 (8). https://doi.org/10.1002/BIES.201800050.

Bergström, Beatrice, Lundqvist, Christina, Vasileiadis, Georgios K., Carlsten, Hans, Ekwall, Olov, Ekwall, Anna Karin H., 2019. The rheumatoid arthritis risk gene AIRE is induced by cytokines in fibroblast-like synoviocytes and augments the pro-inflammatory response. Front. Immunol. 10 (JUN). https://doi.org/10.3389/FIMMU.2019.01384.

Bianchi, Diana W., Zickwolf, Gretchen K., Weil, Gary J., Sylvester, Shelley, Ann Demaria, Mary, 1996. Male fetal progenitor cells persist in maternal blood for as long

as 27 Years postpartum. Proc. Natl. Acad. Sci. U.S.A. 93 (2), 705–708. https://doi.org/10.1073/PNAS.93.2.705.
Bignucolo, Alessia, Scarabel, Lucia, Mezzalira, Silvia, Polesel, Jerry, Cecchin, Erika, Toffoli, Giuseppe, 2021. Sex disparities in efficacy in COVID-19 vaccines: a systematic review and meta-analysis. Vaccines 9 (8). https://doi.org/10.3390/VACCINES9080825.
Binnewies, Mikhail, Roberts, Edward W., Kelly, Kersten, Chan, Vincent, Fearon, Douglas F., Merad, Miriam, Coussens, Lisa M., et al., 2018. Understanding the tumor immune microenvironment (TIME) for effective therapy. Nat. Med. 24 (5), 541–550. https://doi.org/10.1038/s41591-018-0014-x.
Brueckl, Wolfgang M., Ficker, Joachim H., Zeitler, Gloria, 2020. Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC). *BMC Cancer*. BioMed Central Ltd. https://doi.org/10.1186/s12885-020-07690-8.
Buder-Bakhaya, Kristina, Hassel, Jessica C., 2018. Biomarkers for clinical benefit of immune checkpoint inhibitor treatment-A review from the melanoma perspective and beyond. Front. Immunol. 9 (JUN). https://doi.org/10.3389/fimmu.2018.01474.
Butterworth, Michael, McClellan, Barbara, Aklansmith, Mathea, 1967. Influence of sex in immunoglobulin levels. Nature 214 (5094), 1224–1225. https://doi.org/10.1038/2141224A0.
Buti, S., Bersanelli, M., Perrone, F., Bracarda, S., Di Maio, M., Giusti, R., Nigro, O., Cortinovis, D.L., Aerts, J.G.J.V., Guaitoli, G., Barbieri, F., Ferrara, M.G., Bria, E., Grossi, F., Bareggi, C., Berardi, R., Torniai, M., Cantini, L., Sforza, V., Genova, C., Chiari, R., Rocco, D., Della Gravara, L., Gori, S., De Tursi, M., Di Marino, P., Mansueto, G., Zoratto, F., Filetti, M., Citarella, F., Russano, M., Mazzoni, F., Garassino, M.C., De Toma, A., Signorelli, D., Gelibter, A., Siringo, M., Follador, A., Bisonni, R., Tuzi, A., Minuti, G., Landi, L., Ricciardi, S., Migliorino, M.R., Tabbò, F., Olmetto, E., Metro, G., Adamo, V., Russo, A., Spinelli, G.P., Banna, G.L., Addeo, A., Friedlaender, A., Cannita, K., Porzio, G., Ficorella, C., Carmisciano, L., Pinato, D.J., Mazzaschi, G., Tiseo, M., Cortellini, A., 2021. Predictive ability of a drug-based score in patients with advanced non-small-cell lung cancer receiving first-line immunotherapy. Eur. J. Cancer 150, 224–231. https://doi.org/10.1016/j.ejca.2021.03.041.
Carrel, Laura, Willard, Huntington F., 2005. X-inactivation profile reveals extensive variability in X-linked gene expression in females. Nature 434 (7031), 400–404. https://doi.org/10.1038/NATURE03479.
Centanni, Maddalena, Moes, Dirk Jan A.R., Trocóniz, Iñaki F., Joseph, Ciccolini, Coen van Hasselt, J.G., 2019. Clinical pharmacokinetics and pharmacodynamics of immune checkpoint inhibitors. Clin. Pharmacokinet. 58 (7), 835–857. https://doi.org/10.1007/S40262-019-00748-2.
Cheng, Mandy I., Riggan, Luke, Li, Joey H., Tafti, Rana Yakhshi, Chin, Scott, Ma, Feiyang, Pellegrini, Matteo, et al., 2022. Sex differences in NK cells mediated by the X-linked epigenetic regulator UTX. bioRxiv. https://doi.org/10.1101/2022.04.21.489076. April, 2022.04.21.489076.
Clocchiatti, Andrea, Cora, Elisa, Zhang, Yosra, Paolo Dotto, G., 2016. Sexual dimorphism in cancer. Nat. Rev. Cancer 16 (5), 330–339. https://doi.org/10.1038/NRC.2016.30.
Conforti, Fabio, Pala, Laura, Bagnardi, Vincenzo, De Pas, Tommaso, Martinetti, Marco, Viale, Giuseppe, Gelber, Richard D., Goldhirsch, Aron, 2018. Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol. 19 (6), 737–746. https://doi.org/10.1016/S1470-2045(18)30261-4.
Cook, Michael B., Dawsey, Sanford M., Freedman, Neal D., Inskip, Peter D., Wichner, Sara M., Quraishi, Sabah M., Devesa, Susan S., McGlynn, Katherine A., 2009. Sex disparities in cancer incidence by period and age. Cancer Epidemiol. Biomark. Prev. 18 (4), 1174–1182. https://doi.org/10.1158/1055-9965.EPI-08-1118.
Cook, Michael B., McGlynn, Katherine A., Devesa, Susan S., Freedman, Neal D., Anderson, William F., 2011. Sex disparities in cancer mortality and survival. Cancer Epidemiol. Biomark. Prev. 20 (8), 1629–1637. https://doi.org/10.1158/1055-9965.EPI-11-0246.
Corrales, Juan José, Almeida, María, Miralles, José Manuel, Alberto, Orfao, 2009. Persistence of androgenic effects on the production of proinflammatory cytokines by circulating antigen-presenting cells after withdrawal of testosterone treatment in aging type 2 diabetic men with partial androgen deficiency. Fertil. Steril. 92 (1), 311–319. https://doi.org/10.1016/j.fertnstert.2008.05.040.
Danaher, Patrick, Warren, Sarah, Lu, Rongze, Samayoa, Josue, Sullivan, Amy, Irena Pekker, Wallden, Brett, Marincola, Francesco M., Cesano, Alessandra, 2018. Pan-cancer adaptive immune resistance as defined by the tumor inflammation signature (TIS): results from the cancer genome atlas (TCGA). Journal for ImmunoTherapy of Cancer 6 (1), 1–17. https://doi.org/10.1186/s40425-018-0367-1.
Desnoyer, Aude, Broutin, Sophie, Julia Delahousse, Maritaz, Christophe, Blondel, Louis, Mir, Olivier, Chaput, Nathalie, Paci, Angelo, 2020. Pharmacokinetic/pharmacodynamic relationship of therapeutic monoclonal antibodies used in oncology: Part 2, immune checkpoint inhibitor antibodies. Eur. J. Cancer 128, 119–128. https://doi.org/10.1016/j.ejca.2020.01.003.
Dosiou, C., Hamilton, A.E., Pang, Y., Overgaard, M.T., Tulac, S., Dong, J., Thomas, P., Giudice, L.C., 2008. Expression of membrane progesterone receptors on human T lymphocytes and jurkat cells and activation of G-proteins by progesterone. J. Endocrinol. 196 (1), 67–77. https://doi.org/10.1677/JOE-07-0317.
Dunford, Andrew, Weinstock, David M., Savova, Virginia, Schumacher, Steven E., Cleary, John P., Yoda, Akinori, Sullivan, Timothy J., et al., 2017. Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias. Nat. Genet. 49 (1), 10–16. https://doi.org/10.1038/NG.3726.
Flak, Magdalena B., Neves, Joana F., Blumberg, Richard S., 2013. Welcome to the Microgenderome." *Science*. American Association for the Advancement of Science. https://doi.org/10.1126/science.1236226.
Foo, Yong Zhi, Nakagawa, Shinichi, Rhodes, Gillian, Leigh, W., Simmons, 2017. The effects of sex hormones on immune function: a meta-analysis. Biol. Rev. 92 (1), 551–571. https://doi.org/10.1111/brv.12243.
Fugazzola, Laura, Cirello, Valentina, Beck-Peccoz, Paolo, 2011. Fetal microchimerism as an explanation of disease. Nat. Rev. Endocrinol. 7 (2), 89–97. https://doi.org/10.1038/NRENDO.2010.216.
Fumet, Jean David, Truntzer, Caroline, Yarchoan, Mark, Ghiringhelli, Francois, 2020. Tumour mutational burden as a biomarker for immunotherapy: current data and emerging concepts. Eur. J. Canc. Elsevier Ltd. https://doi.org/10.1016/j.ejca.2020.02.038.
Gadgeel, Shirish, Rodríguez-Abreu, Delvys, Speranza, Giovanna, Esteban, Emilio, Felip, Enriqueta, Dómine, Manuel, Hui, Rina, et al., 2020. Updated analysis from KEYNOTE-189: pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non–small-cell lung cancer. J. Clin. Oncol. 38 (14), 1505–1517. https://doi.org/10.1200/JCO.19.03136.
Ghosh, Moumita, Gälman, Cecilia, Rudling, Mats, Angelin, Bo, 2015. Influence of physiological changes in endogenous estrogen on circulating PCSK9 and LDL cholesterol. JLR (J. Lipid Res.) 56 (2), 463–469. https://doi.org/10.1194/jlr.M055780.
Giglio, T., Imro, M.A., Filaci, G., Scudeletti, M., Puppo, F., De Cecco, L., Indiveri, F., Costantini, S., 1994. Immune cell circulating subsets are affected by gonadal function. Life Sci. 54 (18), 1305–1312. https://doi.org/10.1016/0024-3205(94)00508-7.
Graff, Julie N., Beer, Tomasz M., Alumkal, Joshi J., Slottke, Rachel E., Redmond, William L., Thomas, George V., Thompson, Reid F., et al., 2020. A phase II single-arm study of pembrolizumab with enzalutamide in men with metastatic castration-resistant prostate cancer progressing on enzalutamide alone. Journal for Immunotherapy of Cancer 8 (2). https://doi.org/10.1136/JITC-2020-000642.
Graff, Julie N., Alumkal, Joshi J., Drake, Charles G., Thomas, George V., Redmond, William L., Farhad, Mohammad, Cetnar, Jeremy P., et al., 2016. Early evidence of anti-PD-1 activity in enzalutamide-resistant prostate cancer. Oncotarget 7 (33), 52810–52817. https://doi.org/10.18632/ONCOTARGET.10547.
Grangeon, Mathieu, Pascale, Tomasini, Chaleat, Solene, Arnaud, Jeanson, Souquet-Bressand, Maxime, Khobta, Nataliya, Bermudez, Julien, et al., 2019. Association between immune-related adverse events and efficacy of immune checkpoint inhibitors in non–small-cell lung cancer. Clin. Lung Cancer 20 (3), 201–207. https://doi.org/10.1016/j.cllc.2018.10.002.
Grassadonia, Antonino, Sperduti, Isabella, Vici, Patrizia, Iezzi, Laura, Brocco, Davide, Gamucci, Teresa, Pizzuti, Laura, et al., 2018. Effect of gender on the outcome of patients receiving immune checkpoint inhibitors for advanced cancer: a systematic review and meta-analysis of phase III randomized clinical trials. J. Clin. Med. 7 (12), 542. https://doi.org/10.3390/jcm7120542.
Gray, Jhanelle E., Villegas, Augusto, Daniel, Davey, David Vicente, Murakami, Shuji, Hui, Rina, Kurata, Takayasu, et al., 2020. Three-year overall survival with durvalumab after chemoradiotherapy in stage III NSCLC—update from PACIFIC. J. Thorac. Oncol. 15 (2), 288–293. https://doi.org/10.1016/j.jtho.2019.10.002.
Guan, Xiangnan, Polesso, Fanny, Wang, Chaojie, Sehrawat, Archana, Hawkins, Reed M., Murray, Susan E., Thomas, George V., et al., 2022. Androgen receptor activity in T cells limits checkpoint blockade efficacy. Nature 606 (7915), 791–796. https://doi.org/10.1038/s41586-022-04522-6.
Gupta, Sarthak, Nakabo, Shuichiro, Blanco, Luz P., O'Neil, Liam J., Wigerblad, Gustaf, Goel, Rishi R., Mistry, Pragnesh, et al., 2020. Sex differences in neutrophil biology modulate response to type I interferons and immunometabolism. Proc. Natl. Acad. Sci. U.S.A. 117 (28), 16481–16491. https://doi.org/10.1073/pnas.2003603117.
Hannah, Michele F., Bajic, Vladimir B., Klein, Sabra L., 2008. Sex differences in the recognition of and innate antiviral responses to seoul virus in Norway rats. Brain Behav. Immun. 22 (4), 503–516. https://doi.org/10.1016/j.bbi.2007.10.005.
Haro, Carmen, Rangel-Zúñiga, Oriol A., Alcalá-Díaz, Juan F., Gómez-Delgado, Francisco, Pérez-Martínez, Pablo, Delgado-Lista, Javier, Quintana-Navarro, Gracia M., et al., 2016. Intestinal microbiota is influenced by gender and body mass index. PLoS One 11 (5). https://doi.org/10.1371/journal.pone.0154090.
Hepworth, Matthew R., Hardman, Matthew J., Grencis, Richard K., 2010. The role of sex hormones in the development of Th2 immunity in a gender-biased model of *trichuris muris* infection. Eur. J. Immunol. 40 (2), 406–416. https://doi.org/10.1002/eji.200939589.
Huang, Alexander C., Postow, Michael A., Orlowski, Robert J., Mick, Rosemarie, Bengsch, Bertram, Manne, Sasikanth, Xu, Wei, et al., 2017. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. Nature 545 (7652), 60–65. https://doi.org/10.1038/NATURE22079.
Huang, Rong, Li, Ting, Ni, Jiajia, Bai, Xiaochun, Gao, Yi, Yang, Li, Zhang, Peng, Gong, Yan, 2018. Different sex-based responses of gut microbiota during the development of hepatocellular carcinoma in liver-specific tsc1-knockout mice. Front. Microbiol. 9 (MAY), 1008. https://doi.org/10.3389/fmicb.2018.01008.
Huang, Lan, Li, Li, Zhou, Yingxu, Yang, Zhaoyang, Wang, Meng, Gao, Yina, Yang, Yang, et al., 2020. Clinical characteristics correlate with outcomes of immunotherapy in advanced non-small cell lung cancer. J. Cancer 11 (24), 7137–7145. https://doi.org/10.7150/jca.49213.
Hussaini, Syed, Chehade, Rania, Gabriel Boldt, Ronald, Raphael, Jacques, Blanchette, Phillip, Maleki Vareki, Saman, Fernandes, Ricardo, 2021. Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors – a systematic review and meta-analysis. Cancer Treatment Reviews. W.B. Saunders Ltd. https://doi.org/10.1016/j.ctrv.2020.102134.
Jeanty, Cerine, Christopher Derderian, S., Mackenzie, Tippi C., 2014. Maternal-fetal cellular trafficking: clinical implications and consequences. Curr. Opin. Pediatr. 26 (3), 377–382. https://doi.org/10.1097/MOP.0000000000000087.
Kallenbach, Lisa R., Johnson, Kirby L., Bianchi, Diana W., 2011. Fetal cell microchimerism and cancer: a nexus of reproduction, immunology, and tumor

biology. Cancer Res. 71 (1), 8–12. https://doi.org/10.1158/0008-5472.CAN-10-0618.
Kalra, Rashi, Bhagyaraj, Ella, Tiwari, Drishti, Nanduri, Ravikanth, Chacko, Anuja P., Jain, Monika, Mahajan, Sahil, Khatri, Neeraj, Gupta, Pawan, 2018. AIRE promotes androgen-independent prostate cancer by directly regulating IL-6 and modulating tumor microenvironment. Oncogenesis 7 (5). https://doi.org/10.1038/S41389-018-0053-7.
Kaneko, Satoshi, Xue, Li, 2018. X chromosome protects against bladder cancer in females via a kdm6a-dependent epigenetic mechanism. Sci. Adv. 4 (6). https://doi.org/10.1126/SCIADV.AAR5598.
Kawai, T., Akira, S., 2006. TLR signaling. Cell Death Differ. 13 (5), 816–825. https://doi.org/10.1038/SJ.CDD.4401850.
Kitagataya, Takashi, Suda, Goki, Nagashima, Kazunori, Katsurada, Takehiko, Yamamoto, Koji, Kimura, Megumi, Maehara, Osamu, et al., 2020. Prevalence, clinical course, and predictive factors of immune checkpoint inhibitor monotherapy-associated hepatitis in Japan. J. Gastroenterol. Hepatol. 35 (10), 1782–1788. https://doi.org/10.1111/jgh.15041.
Klamp, Thorsten, Sahin, Ugur, Bruno, Kyewski, Schwendemann, Jochen, Karl, Dhaene, Türeci, Özlem, 2006. Expression profiling of autoimmune regulator AIRE MRNA in a comprehensive set of human normal and neoplastic tissues. Immunol. Lett. 106 (2), 172–179. https://doi.org/10.1016/j.imlet.2006.06.006.
Klein, Sabra L., Anne, Jedlicka, Pekosz, Andrew, 2010. The xs and Y of immune responses to viral vaccines. Lancet Infect. Dis. 10 (5), 338–349. https://doi.org/10.1016/S1473-3099(10)70049-9.
Kleina, Sabra L., Marriott, Ian, Fish, Eleanor N., 2015. Sex-based differences in immune function and responses to vaccination. Trans. R. Soc. Trop. Med. Hyg. 109 (1), 9–15. https://doi.org/10.1093/TRSTMH/TRU167.
Kwon, Hyunwoo, Schafer, Johanna M., Song, No-Joon, Kaneko, Satoshi, Li, Anqi, Tong, Xiao, Ma, Anjun, et al., 2022. Androgen conspires with the CD8 + T cell exhaustion program and contributes to sex bias in cancer. Sci. Immunol. 7 (73). https://doi.org/10.1126/SCIIMMUNOL.ABQ2630.
la Cuesta-Zuluaga, Jacobo de, Kelley, Scott T., Chen, Yingfeng, Escobar, Juan S., Mueller, Noel T., Ley, Ruth E., McDonald, Daniel, et al., 2019. Age- and sex-dependent patterns of gut microbial diversity in human adults. mSystems 4 (4). https://doi.org/10.1128/msystems.00261-19.
Laffont, Sophie, Rouquié, Nelly, Pascal Azar, Seillet, Cyril, Plumas, Joël, Aspord, Caroline, Guéry, Jean-Charles, 2014. X-chromosome complement and estrogen receptor signaling independently contribute to the enhanced TLR7-mediated IFN-α production of plasmacytoid dendritic cells from women. J. Immunol. 193 (11), 5444–5452. https://doi.org/10.4049/jimmunol.1303400.
Lalani, Aly-Khan A., Daniel, Y C Heng, Basappa, Naveen S., Wood, Lori, Iqbal, Nayyer, McLeod, Deanna, Soulières, Denis, Kollmannsberger, Christian, 2022. Evolving landscape of first-line combination therapy in advanced renal cancer: a systematic review. Ther. Adv. Med. Oncol. 14, 17588359221108684. https://doi.org/10.1177/17588359221108685.
Lee, Bee-Wah, Yap, Hui-Kim, Chew, Fook-Tim, Quah, Thuan-Chong, Prabhakaran, Krishnan, Chan, Georgette S.H., Wong, Siew-Cheng, Seah, Ching-Ching, 1996. Age-and sex-related changes i n lymphocyte subpopulations of healthy asian subjects: from birth to adulthood. Cytometry 262–277. https://doi.org/10.1002/(SICI)1097-0320(19960315)26:1.
Li, Anlin, Chen, Yongjian, Zhang, Wenda, Zhong, Haitao, Ou, Qiyun, Gu, Yang, Xia, Junqing, et al., 2020. Joint association of patients' sex and PD-L1 expression with overall survival benefits and tumor-immune microenvironment in immune checkpoint inhibitors for cancers. Clin. Transl. Med. 10 (2), e92. https://doi.org/10.1002/CTM2.92.
Lin, Pei-Yi, Sun, Lishi, Thibodeaux, Suzanne R., Ludwig, Sara M., Vadlamudi, Ratna K., Hurez, Vincent J., Bahar, Rumana, et al., 2010. B7-H1–Dependent sex-related differences in tumor immunity and immunotherapy responses. J. Immunol. 185 (5), 2747–2753. https://doi.org/10.4049/jimmunol.1000496.
Lin, Pei-Ying, Emily, Hsu, Chih-Yuan, Berry, Lynne, Paul, Bunn, Yu, Shyr, 2022. Analysis of cancer survival associated with immune checkpoint inhibitors after statistical adjustment: a systematic review and meta-analyses. JAMA Netw. Open 5 (8), e2227211. https://doi.org/10.1001/JAMANETWORKOPEN.2022.27211.
Litchfield, Kevin, Reading, James L., Puttick, Clare, Thakkar, Krupa, Abbosh, Chris, Bentham, Robert, Watkins, Thomas B.K., et al., 2021. Meta-analysis of tumor- and T cell-intrinsic mechanisms of sensitization to checkpoint inhibition. Cell 184 (3), 596–614. https://doi.org/10.1016/J.CELL.2021.01.002 e14.
Loo, Kimberly, Tsai, Katy K., Kelly, Mahuron, Liu, Jacqueline, Pauli, Mariela L., Sandoval, Priscila M., Nosrati, Adi, et al., 2017. Partially exhausted tumor-infiltrating lymphocytes predict response to combination immunotherapy. JCI Insight 2 (14). https://doi.org/10.1172/jci.insight.93433.
Lubahn, Dennis B., Joseph, David R., Sullivan, Patrick M., Willard, Huntington F., French, Frank S., Wilson, Elizabeth M., 1988. Cloning of human androgen receptor complementary DNA and localization to the X chromosome. Science (New York, N.Y.) 240 (4850), 327–330. https://doi.org/10.1126/SCIENCE.3353727.
Ma, Xingzhe, Bi, Enguang, Lu, Yong, Pan, Su, Huang, Chunjian, Liu, Lintao, Wang, Qiang, et al., 2019. Cholesterol induces CD8+ T cell exhaustion in the tumor microenvironment. Cell Metabol. 30 (1), 143–156. https://doi.org/10.1016/j.cmet.2019.04.002 e5.
Mantalaris, Athanasios, Panoskaltsis, Nicki, Sakai, Yasuyuki, Bourne, Patricia, Chang, Chawnshang, Messing, Edward M., David Wu, J.H., 2001. Localization of androgen receptor expression in human bone marrow. J. Pathol. 193 (3), 361–366. https://doi.org/10.1002/1096-9896(0000)9999:9999<::AID-PATH803>3.0.CO;2-W.
Markle, Janet G.M., Frank, Daniel N., Mortin-Toth, Steven, Robertson, Charles E., Feazel, Leah M., Rolle-Kampczyk, Ulrike, Von Bergen, Martin, McCoy, Kathy D., Macpherson, Andrew J., Danska, Jayne S., 2013. Sex differences in the gut microbiome drive hormone-dependent regulation of autoimmunity. Science 339 (6123), 1084–1088. https://doi.org/10.1126/science.1233521.
Márquez, Eladio J., Chung, Cheng han, Marches, Radu, Rossi, Robert J., Nehar-Belaid, Djamel, Eroglu, Alper, Mellert, David J., Kuchel, George A., Banchereau, Jacques, Ucar, Duygu, 2020. Sexual-dimorphism in human immune system aging. Nat. Commun. 11 (1). https://doi.org/10.1038/s41467-020-14396-9.
Mazzaschi, Giulia, Madeddu, Denise, Falco, Angela, Bocchialini, Giovanni, Goldoni, Matteo, Sogni, Francesco, Armani, Giovanna, et al., 2018. Low PD-1 expression in cytotoxic CD8 + tumor-infiltrating lymphocytes confers an immune-privileged tissue microenvironment in NSCLC with a prognostic and predictive value. Clin. Cancer Res. : An Official Journal of the American Association for Cancer Research 24 (2), 407–419. https://doi.org/10.1158/1078-0432.CCR-17-2156.
Mazzaschi, G., Minari, R., Zecca, A., Cavazzoni, A., Ferri, V., Mori, C., Squadrilli, A., et al., 2020. Soluble PD-L1 and circulating cd8+pd-1+ and NK cells enclose a prognostic and predictive immune effector score in immunotherapy treated NSCLC patients. Lung Cancer 148 (July), 1–11. https://doi.org/10.1016/j.lungcan.2020.07.028.
McGranahan, Nicholas, Rosenthal, Rachel, Hiley, Crispin T., Rowan, Andrew J., Watkins, Thomas B.K., Wilson, Gareth A., Birkbak, Nicolai J., et al., 2017. Allele-specific HLA loss and immune escape in lung cancer evolution. Cell 171 (6), 1259–1271. https://doi.org/10.1016/j.cell.2017.10.001 e11.
Melhem, Murad, Hanze, Eva, Lu, Sharon, Alskär, Oskar, Visser, Sandra, Gandhi, Yash, 2022. Population pharmacokinetics and exposure-response of anti-programmed cell death protein-1 monoclonal antibody dostarlimab in advanced solid tumours. Br. J. Clin. Pharmacol. 88 (9), 4142–4154. https://doi.org/10.1111/BCP.15339.
Mocikat, Ralph, Braumüller, Heidi, Gumy, Alain, Oliver, Egeter, Ziegler, Heike, Reusch, Uwe, Bubeck, Anja, et al., 2003. Natural killer cells activated by MHC class ILow targets prime dendritic cells to induce protective CD8 T cell responses. Immunity 19 (4), 561–569. https://doi.org/10.1016/S1074-7613(03)00264-4.
Mogilenko, Denis A., Shpynov, Oleg, Andhey, Prabhakar Sairam, Arthur, Laura, Swain, Amanda, Esaulova, Ekaterina, Brioschi, Simone, et al., 2021. Comprehensive profiling of an aging immune system reveals clonal GZMK+ CD8+ T cells as conserved hallmark of inflammaging. Immunity 54 (1), 99–115. https://doi.org/10.1016/J.IMMUNI.2020.11.005 e12.
Moreira-Filho, Alberto, Carlos, Bando, Silvia Yumi, Bernardi Bertonha, Fernanda, Ferreira, Leandro Rodrigues, Freitas Vinhas, Christiana de, Bourguignon Oliveira, Lucila Habib, Zerbini, Maria Claudia Nogueira, Furlanetto, Glaucio, Chaccur, Paulo, Carneiro-Sampaio, Magda, 2018. Minipuberty and sexual dimorphism in the infant human thymus. Sci. Rep. 8 (1), 1–13. https://doi.org/10.1038/s41598-018-31583-3.
Mousavi, Mohammad Javad, Mahmoudi, Mahdi, Ghotloo, Somayeh, 2020. Escape from X Chromosome inactivation and female bias of autoimmune diseases. Molecular Medicine (Cambridge, Mass 26 (1). https://doi.org/10.1186/S10020-020-00256-1.
Moutafi, Myrto K., Tao, Weiwei, Huang, Richard, Haberberger, James, Alexander, Brian, Ramkissoon, Shakti, Ross, Jeffrey S., et al., 2021. Comparison of programmed death-ligand 1 protein expression between primary and metastatic lesions in patients with lung cancer. Journal for ImmunoTherapy of Cancer 9 (4), e002230. https://doi.org/10.1136/JITC-2020-002230.
Murata, Hiromi, Tanaka, Susumu, Okada, Hidetaka, 2021. Immune tolerance of the human decidua. J. Clin. Med. 10 (2), 1–16. https://doi.org/10.3390/JCM10020351.
Murphy, Kenneth, Weaver, Casey, 2016. Janeway's Immunobiology. Janeway's Immunobiology. W.W. Norton & Company. https://doi.org/10.1201/9781315533247.
Naqvi, S, Godfrey, AK, Hughes, JF, Goodheart, ML, Mitchell, RN, Page, DC, 2019 Jul 19. Conservation, acquisition, and functional impact of sex-biased gene expression in mammals. Science 345 (6450), eaaw7317. https://doi.org/10.1126/science.aaw7317.
Nguyen, Kim, Chi Thi, Sawangarun, Wanlada, Mandasari, Masita, Morita, Kei ichi, Harada, Hiroyuki, Kou, Kayamori, Yamaguchi, Akira, Sakamoto, Kei, 2020. AIRE is induced in oral squamous cell carcinoma and promotes cancer gene expression. PLoS One 15 (2). https://doi.org/10.1371/JOURNAL.PONE.0222689.
Nieuwenhoven, Veenstra van, A.L., Heineman, M.J., Faas, M.M., 2003. The immunology of successful pregnancy. Hum. Reprod. Update 9 (4), 347–357. https://doi.org/10.1093/humupd/dmg026.
Nixon, Andrew B., Schalper, Kurt A., Jacobs, Ira, Potluri, Shobha, Wang, I. Ming, Fleener, Catherine, 2019. Peripheral immune-based biomarkers in cancer immunotherapy: can we realize their predictive potential? Journal for ImmunoTherapy of Cancer 7 (1), 1–14. https://doi.org/10.1186/s40425-019-0799-2.
Ntziachristos, Panagiotis, Tsirigos, Aristotelis, Grant Welstead, G., Trimarchi, Thomas, Bakogianni, Sofia, Xu, Luyao, Loizou, Evangelia, et al., 2014. Contrasting roles of histone 3 lysine 27 demethylases in acute lymphoblastic leukaemia. Nature 514 (7523), 513–517. https://doi.org/10.1038/NATURE13605.
Oghumu, Steve, Varikuti, Sanjay, Stock, James C., Volpedo, Greta, Saljoughian, Noushin, Terrazas, Cesar A., Satoskar, Abhay R., 2019. Cutting edge: CXCR3 escapes X chromosome inactivation in T cells during infection: potential implications for sex differences in immune responses. J. Immunol. 203 (4), 789–794. https://doi.org/10.4049/JIMMUNOL.1800931. Baltimore, Md. : 1950.
Pala, Laura, De Pas, Tommaso, Catania, Chiara, Giaccone, Giuseppe, Mantovani, Alberto, Minucci, Saverio, Giuseppe Viale, Gelber, Richard D., Conforti, Fabio, 2022. Sex and cancer immunotherapy: current understanding and challenges. Cancer Cell 40 (7), 695–700. https://doi.org/10.1016/j.ccell.2022.06.005.
Pan, Yunjian, Zheng, Difan, Yuan, Li, Cai, Xu, Zheng, Zongli, Jin, Yan, Hu, Haichuan, et al., 2017. Unique distribution of programmed death ligand 1 (PD-L1) expression in east asian non-small cell lung cancer. J. Thorac. Dis. 9 (8), 2579–2586. https://doi.org/10.21037/jtd.2017.08.61.

Pasello, Giulia, Pavan, Alberto, Attili, Ilaria, Bortolami, Alberto, Bonanno, Laura, Menis, Jessica, Franco Conte, Pier, Guarneri, Valentina, 2020. Real world data in the era of immune checkpoint inhibitors (ICIs): increasing evidence and future applications in lung cancer. Cancer Treat Rev. 87 (March), 102031. https://doi.org/10.1016/j.ctrv.2020.102031.

Paz-Ares, Luis, David Vicente, Ali, Tafreshi, Robinson, Andrew, Parra, Hector Soto, Mazières, Julien, Hermes, Barbara, et al., 2020. A randomized, placebo-controlled trial of pembrolizumab plus chemotherapy in patients with metastatic squamous NSCLC: protocol-specified final analysis of KEYNOTE-407. J. Thorac. Oncol. 15 (10), 1657–1669. https://doi.org/10.1016/j.jtho.2020.06.015.

Polanczyk, Magdalena J., Carson, Bryan D., Subramanian, Sandhya, Afentoulis, Michael, Vandenbark, Arthur A., Ziegler, Steven F., Offner, Halina, 2004. Cutting edge: estrogen drives expansion of the CD4 + CD25 + regulatory T cell compartment. J. Immunol. 173 (4), 2227–2230. https://doi.org/10.4049/jimmunol.173.4.2227.

Polanczyk, Magdalena J., Hopke, Corwyn, Huan, Jianya, Vandenbark, Arthur A., Offner, Halina, 2005. Enhanced FoxP3 expression and Treg cell function in pregnant and estrogen-treated mice. J. Neuroimmunol. 170 (1–2), 85–92. https://doi.org/10.1016/j.jneuroim.2005.08.023.

Polanczyk, Magdalena J., Hopke, Corwyn, Vandenbark, Arthur A., Halina, Offner, 2007. Treg suppressive activity involves estrogen-dependent expression of programmed death-1 (PD-1). Int. Immunol. 19 (3), 337–343. https://doi.org/10.1093/intimm/dxl151.

Poliani, Pietro Luigi, Kisand, Kai, Marrella, Veronica, Ravanini, Maria, Notarangelo, Luigi Daniele, Villa, Anna, Peterson, Pärt, Facchetti, Fabio, 2010. Human peripheral lymphoid tissues contain autoimmune regulator-expressing dendritic cells. Am. J. Pathol. 176 (3), 1104–1112. https://doi.org/10.2353/AJPATH.2010.090956.

Rackaityte, Elze, Halkias, Joanna, 2020. Mechanisms of fetal T cell tolerance and immune regulation. Front. Immunol. 11 (April). https://doi.org/10.3389/FIMMU.2020.00588.

Raimondi, Giorgio, Shufesky, William J., Tokita, Daisuke, Morelli, Adrian E., Thomson, Angus W., 2006. Regulated compartmentalization of programmed cell death-1 discriminates CD4 + CD25 + resting regulatory T cells from activated T cells. J. Immunol. 176 (5), 2808–2816. https://doi.org/10.4049/jimmunol.176.5.2808.

Relloso, Miguel, Aragoneses-Fenoll, Laura, Lasarte, Sandra, Bourgeois, Christelle, Romera, Gema, Kuchler, Karl, Corbí, Angel L., et al., 2012. Estradiol impairs the Th17 immune response against Candida albicans. J. Leukoc. Biol. 91 (1), 159–165. https://doi.org/10.1189/jlb.1110645.

Ribas, Antoni, Wolchok, Jedd D., 2018. Cancer immunotherapy using checkpoint blockade. Science 359 (6382), 1350–1355. https://doi.org/10.1126/science.aar4060.

Rizvi, Naiyer A., Hellmann, Matthew D., Snyder, Alexandra, Kvistborg, Pia, Makarov, Vladimir, Havel, Jonathan J., Lee, William, et al., 2015. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 348 (6230), 124–128. https://doi.org/10.1126/science.aaa1348.

Roved, Jacob, Westerdahl, Helena, Hasselquist, Dennis, 2017. Sex differences in immune responses: hormonal effects, antagonistic selection, and evolutionary consequences. Horm. Behav. 88, 95–105. https://doi.org/10.1016/j.yhbeh.2016.11.017.

Scotland, Ramona S., Stables, Melanie J., Madalli, Shimona, Watson, Peter, Gilroy, Derek W., 2011. Sex differences in resident immune cell phenotype underlie more efficient acute inflammatory responses in female mice. Blood 118 (22), 5918–5927. https://doi.org/10.1182/BLOOD-2011-03-340281.

Sedov, Egor, McCarthy, Jordan, Koren, Elle, Fuchs, Yaron, 2022. Fetomaternal microchimerism in tissue repair and tumor development. Dev. Cell 57 (12), 1442–1452. https://doi.org/10.1016/J.DEVCEL.2022.05.018.

Seillet, Cyril, Laffont, Sophie, Trémollières, Florence, Rouquié, Nelly, Ribot, Claude, Arnal, Jean François, Douin-Echinard, Victorine, Gourdy, Pierre, Guéry, Jean Charles, 2012. The TLR-mediated response of plasmacytoid dendritic cells is positively regulated by estradiol in vivo through cell-intrinsic estrogen receptor α signaling. Blood 119 (2), 454–464. https://doi.org/10.1182/blood-2011-08-371831.

Shankar, Bairavi, Zhang, Jiajia, Rafeh Naqash, Abdul, Forde, Patrick M., Feliciano, Josephine L., Marrone, Kristen A., Ettinger, David S., et al., 2020. Multisystem immune-related adverse events associated with immune checkpoint inhibitors for treatment of non-small cell lung cancer. JAMA Oncol. 6 (12), 1952–1956. https://doi.org/10.1001/jamaoncol.2020.5012.

Sheng, Lili, Kumar Jena, Prasant, Hu, Ying, Wan, Yu-Jui Yvonne, 2021. Age-specific microbiota in altering host inflammatory and metabolic signaling as well as metabolome based on the sex. Hepatobiliary Surg. Nutr. 10 (1), 31–48. https://doi.org/10.21037/hbsn-20-671.

Skoulidis, Ferdinandos, Goldberg, Michael E., Greenawalt, Danielle M., Hellmann, Matthew D., Awad, Mark M., Gainor, Justin F., Schrock, Alexa B., et al., 2018. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. Cancer Discov. 8 (7), 822–835. https://doi.org/10.1158/2159-8290.CD-18-0099.

Souyris, Mélanie, Mejía, José E., Chaumeil, Julie, Guéry, Jean Charles, 2019. Female predisposition to TLR7-driven autoimmunity: gene dosage and the escape from X chromosome inactivation. Semin. Immunopathol. 41 (2), 153–164. https://doi.org/10.1007/S00281-018-0712-Y.

Straub, Rainer H., 2007. The complex role of estrogens in inflammation. Endocr. Rev. 28 (5), 521–574. https://doi.org/10.1210/er.2007-0001.

Su, Maureen A., Stenerson, Matthew, Liu, Weihong, Putnam, Amy, Conte, Felix, Bluestone, Jeffrey A., Anderson, Mark S., 2009. The role of X-linked FOXP3 in the autoimmune susceptibility of turner syndrome patients. Clinical Immunology (Orlando, Fla 131 (1), 139–144. https://doi.org/10.1016/J.CLIM.2008.11.007.

Suzuki, Eriko, Kobayashi, Yoshihiro, Kawano, Osamu, Endo, Katsuhiko, Haneda, Hiroshi, Yukiue, Haruhiro, Sasaki, Hidefumi, Yano, Motoki, Maeda, Masanobu, Fujii, Yoshitaka, 2008. Expression of AIRE in thymocytes and peripheral lymphocytes. Autoimmunity 41 (2), 133–139. https://doi.org/10.1080/08916930701773941.

Takahashi, Takehiro, Iwasaki, Akiko, 2021. Sex differences in immune responses. Science 371 (6527), 347–348. https://doi.org/10.1126/SCIENCE.ABE7199.

Taneja, Veena, 2018. Sex hormones determine immune response. Front. Immunol. 9. https://doi.org/10.3389/FIMMU.2018.01931.

Tray, Nancy, Weber, Jeffrey S., Adams, Sylvia, 2018. Predictive biomarkers for checkpoint immunotherapy: current status and challenges for clinical application. Cancer Immunol. Res. 6 (10), 1122–1128. https://doi.org/10.1158/2326-6066.CIR-18-0214.

Triggianese, Paola, Novelli, Lucia, Galdiero, Maria Rosaria, Chimenti, Maria Sole, Conigliaro, Paola, Perricone, Roberto, Perricone, Carlo, Gerli, Roberto, 2020. Immune checkpoint inhibitors-induced autoimmunity: the impact of gender. Autoimmun. Rev. 19 (8), 102590. https://doi.org/10.1016/j.autrev.2020.102590.

Tukiainen, Taru, Villani, Alexandra Chloé, Yen, Angela, Rivas, Manuel A., Marshall, Jamie L., Satija, Rahul, Aguirre, Matt, et al., 2017. Landscape of X Chromosome inactivation across human tissues. Nature 550 (7675), 244–248. https://doi.org/10.1038/NATURE24265.

Unger, Joseph M., Vaidya, Riha, Albain, Kathy S., Leblanc, Michael, Minasian, Lori M., Gotay, Carolyn C., Henry, N. Lynn, et al., 2022. Sex differences in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials. J. Clin. Oncol. : Official Journal of the American Society of Clinical Oncology 40 (13), 1474–1486. https://doi.org/10.1200/JCO.21.02377.

Vemuri, Ravichandra, Sylvia, Kristyn E., Klein, Sabra L., Forster, Samuel C., Plebanski, Magdalena, Raj, Eri, Flanagan, Katie L., 2019. The microgenderome revealed: sex differences in bidirectional interactions between the microbiota, hormones, immunity and disease susceptibility. Seminars in Immunopathology. Springer Verlag. https://doi.org/10.1007/s00281-018-0716-7.

Vermeesch, Robert, Joris, Petit, Paul, Kermouni, Abdenaïm, Renauld, Jean Christophe, Herman Van Den Berghe, Marynen, Peter, 1997. The IL-9 receptor gene, located in the xq/yq pseudoautosomal region, has an autosomal origin, escapes X inactivation and is expressed from the Y. Hum. Mol. Genet. 6 (1), 1–8. https://doi.org/10.1093/HMG/6.1.1.

Wallis, Christopher J.D., Butaney, Mohit, Raj, Satkunasivam, Freedland, Stephen J., Patel, Sandip P., Hamid, Omid, Pal, Sumanta K., Klaassen, Zachary, 2019. Association of patient sex with efficacy of immune checkpoint inhibitors and overall survival in advanced cancers: a systematic review and meta-analysis. JAMA Oncol. 5 (4), 529–536. https://doi.org/10.1001/jamaoncol.2018.5904.

Wang, Chunhe, Dehghani, Babak, Li, Yuexin, Kaler, Laurie J., Proctor, Thomas, Vandenbark, Arthur A., Offner, Halina, 2009. Membrane estrogen receptor regulates experimental autoimmune encephalomyelitis through up-regulation of programmed death 1. J. Immunol. 182 (5), 3294–3303. https://doi.org/10.4049/jimmunol.0803205.

Wang, Shixiang, Zhang, Jing, He, Zaoke, Wu, Kai, Liu, Xue Song, 2019. The predictive power of tumor mutational burden in lung cancer immunotherapy response is influenced by patients' sex. Int. J. Cancer 145 (10), 2840–2849. https://doi.org/10.1002/ijc.32327.

Whitacre, Caroline C., 2001. Sex differences in autoimmune disease. *Nature Immunology*. Nat Immunol. https://doi.org/10.1038/ni0901-777.

Xiao, Dakai, Pan, Hui, Li, Fuqiang, Wu, Kui, Zhang, Xin, He, Jianxing, 2016. Analysis of ultra-deep targeted sequencing reveals mutation burden is associated with gender and clinical outcome in lung adenocarcinoma. Oncotarget 7 (16), 22857–22864. https://doi.org/10.18632/oncotarget.8213.

Yan, Jun, Greer, Judith M., Hull, Renee, O'Sullivan, John D., Henderson, Robert D., Read, Stephen J., McCombe, Pamela A., 2010. The effect of ageing on human lymphocyte subsets: comparison of males and females. Immun. Ageing 7, 1–10. https://doi.org/10.1186/1742-4933-7-4.

Yatsunenko, Tanya, Rey, Federico E., Manary, Mark J., Trehan, Indi, Gloria Dominguez-Bello, Maria, Contreras, Monica, Magris, Magda, et al., 2012. Human gut microbiome viewed across age and geography. Nature. https://doi.org/10.1038/nature11053.

Ye, Youqiong, Jing, Ying, Liang, Li, Mills, Gordon B., Diao, Lixia, Liu, Hong, Han, Leng, 2020. Sex-associated molecular differences for cancer immunotherapy. Nat. Commun. 11 (1). https://doi.org/10.1038/s41467-020-15679-x.

Yuan, Yuan, Liu, Lingxiang, Chen, Hu, Wang, Yumeng, Xu, Yanxun, Mao, Huzhang, Li, Jun, et al., 2016. Comprehensive characterization of molecular differences in cancer between male and female patients. Cancer Cell 29 (5), 711–722. https://doi.org/10.1016/J.CCELL.2016.04.001.

Zhao, Ruozhu, Chen, Xin, Ma, Weiwei, Zhang, Jinyu, Guo, Jie, Zhong, Xiu, Yao, Jiacheng, et al., 2020. A GPR174-CCL21 module imparts sexual dimorphism to humoral immunity. Nature 577 (7790), 416–420. https://doi.org/10.1038/S41586-019-1873-0.

Zhu, Meng Lei, Nagavalli, Anil, Su, Maureen A., 2013. Aire deficiency promotes TRP-1-specific immune rejection of melanoma. Cancer Res. 73 (7), 2104–2116. https://doi.org/10.1158/0008-5472.CAN-12-3781.