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Review

Immunotherapy Heterogeneity in Pulmonary Arterial Hypertension: Cross-Species Determinants and Sex-Stratified Response Mechanisms

Qian Ma [1,2,3,4], Zhe Lei [4] and Zihua Zhou [1,2,3,*]

[1] Department of Cardiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1277, Jiefang Avenue, Jianghan District, Wuhan 430022, China
[2] Hubei Key Laboratory of Biological Targeted Therapy, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[3] Hubei Provincial Engineering Research Center of Immunological Diagnosis and Therapy for Cardiovascular Diseases, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China
[4] First Department of Cardiology, The First Affiliated Hospital of Shihezi University, Shihezi 830004, China
* Correspondence: zzhua2001@163.com; Tel.: +86-18971029663

Abstract

Pulmonary arterial hypertension (PAH) exhibits substantial biological heterogeneity that may contribute to variable therapeutic responses and complicate the translation of immunotherapies from experimental models to patients. This Review examines how cross-species variation and biological sex may modify PAH immunotherapeutic responses, with particular attention to differences between target-directed biologics and active immunization. Species-related variation in model fidelity, target conservation, and immune biology, together with sex-associated differences in vascular and immune phenotypes, may contribute to heterogeneous therapeutic responses. These effects may be particularly relevant to active immunization because vaccine efficacy depends on multiple host-dependent immune processes. However, direct evidence for species- and sex-associated differences in PAH vaccine efficacy remains limited, and PAH-specific mechanistic evidence should be distinguished from extrapolation based on broader immunology. We therefore discuss a translational strategy integrating mechanism-guided model selection, cross-species validation, sex-stratified study design, human-relevant experimental systems, and multidimensional analysis to improve the design and interpretation of future PAH immunotherapy studies.

Keywords: pulmonary arterial hypertension; interspecies variability; biological sex dimorphism; active immunotherapy; passive immunotherapy

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1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disorder characterized by endothelial dysfunction, abnormal vascular remodeling, increased pulmonary vascular resistance, and eventual right ventricular (RV) failure [1]. Although current therapies targeting the endothelin, nitric oxide–cyclic guanosine monophosphate, and prostacyclin pathways have substantially improved symptoms and clinical outcomes, they primarily modulate vascular tone and disease progression rather than fully reversing

established vascular remodeling [2]. More recently, biologic and immune-directed strategies have expanded the therapeutic landscape of PAH by targeting inflammatory mediators, dysregulated growth-factor signaling, and disease-associated vascular antigens [3,4]. Nevertheless, therapeutic responses remain highly variable across experimental models and patient populations, indicating that target selection alone is insufficient to predict treatment efficacy [5,6].

This variability is particularly relevant to immune-based interventions because their therapeutic effects may depend not only on target engagement but also on the biological context of the host [7]. Interspecies differences in vascular structure, immune-cell composition, inflammatory regulation, target expression, antigen processing, and antibody kinetics may influence therapeutic responses and complicate extrapolation from preclinical models to humans [8]. Likewise, biological sex represents a major source of heterogeneity in PAH [9]. The disease exhibits a well-recognized sex paradox, with higher susceptibility among females but generally poorer outcomes among males, partly reflecting sex-associated differences in vascular remodeling, hormonal regulation, immune homeostasis, and RV adaptation [10]. These biological differences may also modify the magnitude, durability, and safety of immune-mediated therapeutic responses [11]. However, species and biological sex should not be considered isolated determinants of therapeutic response. Their effects may interact with PAH etiology, age, hormonal status, disease severity, comorbidities, concomitant treatment, and baseline immune phenotype, and should therefore be interpreted within a broader multifactorial context. Throughout this Review, human PAH serves as the translational reference against which findings from experimental species and model systems are evaluated.

For the purposes of this Review, we distinguish among conventional PAH-targeted pharmacotherapies, immune-targeted biologic interventions, and active immunization strategies [3]. This distinction is important because the biological sources of response heterogeneity may differ according to therapeutic modality. Antibody-based or other externally administered biologic therapies predominantly depend on target accessibility, molecular compatibility, pharmacokinetics, and tissue exposure [12]. In contrast, active immunization, including vaccine-based approaches, requires coordinated endogenous immune processes involving antigen recognition and presentation, T-cell help, B-cell activation, antibody maturation, and immune-memory formation [4,13]. Active immunization therefore introduces additional host-dependent biological checkpoints through which species background, biological sex, immune repertoire, and baseline immune state may influence immunogenicity and therapeutic durability [8,11]. Direct evidence for sex-specific PAH vaccine responses remains limited, however, and many proposed mechanisms are currently supported by convergence between PAH biology and broader immunological evidence rather than by dedicated comparative vaccine studies [10,14]. Accordingly, this Review distinguishes among direct PAH therapeutic evidence, PAH-specific mechanistic evidence, and extrapolation from broader immunological research. Mechanistic plausibility is therefore not considered equivalent to demonstrated modification of therapeutic response. Against this background, the central question of this Review is not simply how species and biological sex differ, but which of these differences are plausibly relevant to immunotherapeutic response and whether they can help explain discordance between experimental models and human PAH.

Figure 1 presents the conceptual framework of this Review, showing how cross-species differences in disease-model fidelity, immune biology, and target conservation interact with sex-associated variation in PAH susceptibility, vascular remodeling, right ventricular adaptation, and hormonal–immune regulation [15]. We first evaluate species-related differences in PAH pathology, immune regulation, and translational fidelity, fol-

lowed by sex-associated variation in vascular remodeling, RV adaptation, endocrine regulation, and adaptive immunity. We then discuss why active immunization may be especially vulnerable to biological heterogeneity and propose a translational framework integrating cross-species validation, sex-stratified evaluation, immune profiling, and human-relevant experimental systems. Rather than treating biological heterogeneity solely as a source of experimental variability, this framework considers it a set of potentially relevant biological modifiers that can be systematically evaluated during the development of more informative and potentially stratified immunotherapeutic strategies for PAH.

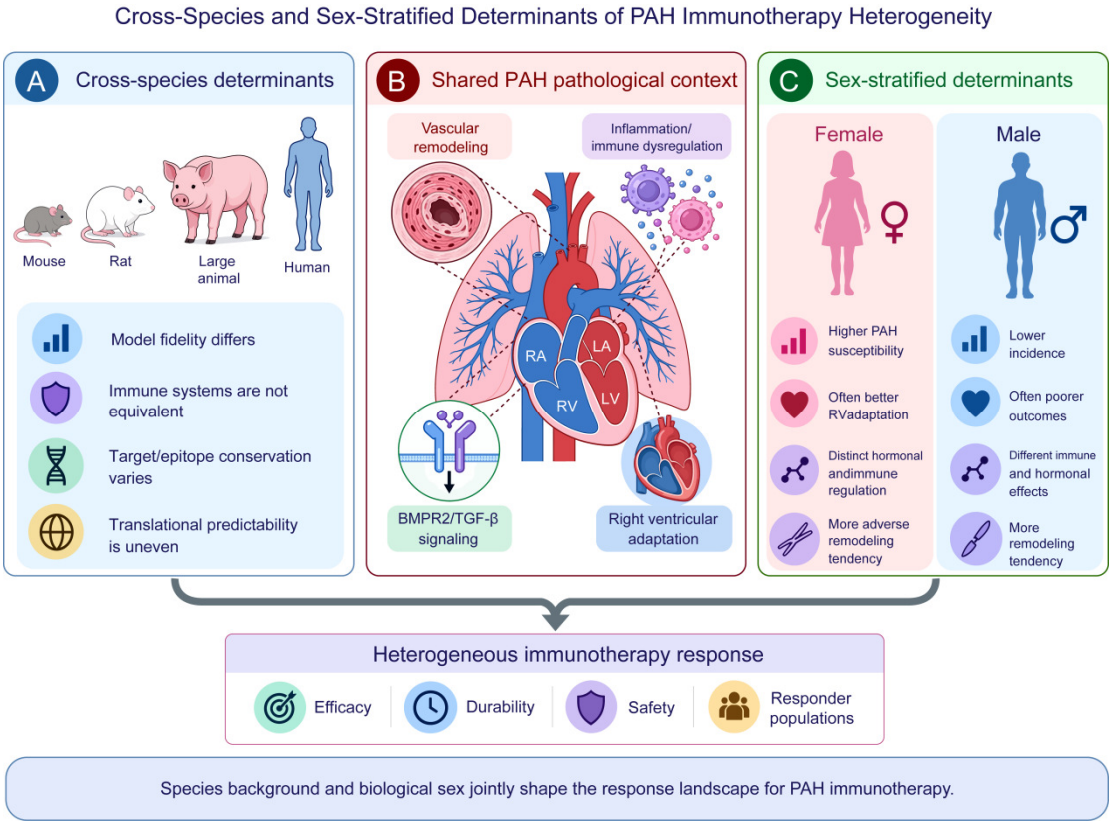


Figure 1. Cross-species and sex-associated determinants of immunotherapy heterogeneity in PAH. Cross-species differences in disease-model fidelity, immune biology, and target conservation interact with sex-associated differences in PAH susceptibility, vascular remodeling, right ventricular adaptation, and hormonal–immune regulation. These factors may modify immunotherapeutic responses against a shared background of PAH pathology, contributing to variability in treatment efficacy, durability, and safety. The framework highlights the importance of considering both species and biological sex when evaluating the translational relevance of PAH immunotherapeutic strategies.

2. Cross-Species Determinants of PAH Immunotherapy Response

2.1. Species-Dependent Differences in PAH Pathology and Translational Fidelity

Animal models remain essential for mechanistic investigation and therapeutic evaluation in pulmonary arterial hypertension (PAH), but no single species fully reproduces the progressive vascular remodeling, immune dysregulation, right ventricular adaptation, and chronic disease course observed in human PAH [16]. Rodent models, particularly mice and rats, are widely used because of their experimental accessibility and suitability for mechanistic studies; however, substantial interspecies variation exists in pulmonary vascular architecture, fibrotic susceptibility, inflammatory responses, and disease severity [17]. These differences directly influence how therapeutic efficacy is interpreted and may

contribute to inconsistent translation from preclinical models to patients [18]. In particular, pathological changes induced by hypoxia, monocrotaline, or Sugen–hypoxia vary considerably across species and strains, and the extent to which these models reproduce advanced vascular occlusion or irreversible remodeling is limited [19].

Large-animal and non-human primate models provide complementary information because of their closer similarity to humans in vascular organization, drug disposition, and selected immune characteristics, but they also differ from human PAH and cannot serve as direct substitutes for clinical studies [20–22]. Their principal value lies in evaluating parameters that are poorly captured in rodents, including target cross-reactivity, biologic pharmacokinetics, sustained antibody exposure, immunogenicity, and species-dependent safety [7]. Accordingly, the translational value of a PAH model should be judged not by its ability to reproduce all aspects of human disease, but by whether it adequately reflects the biological process relevant to the therapeutic mechanism under investigation [16]. This principle is particularly important for immune-based interventions, for which both disease context and host immune biology determine treatment response [23]. Key differences among commonly used experimental species are summarized in Table 1, highlighting variation in vascular remodeling, immune characteristics, and translational relevance.

Table 1. Cross-species comparison of key features relevant to PAH and immunotherapy development.

Feature	Mouse	Rat	Large Animal (e. g., Pig, Dog, Sheep)	Non-Human Primate	Human	Ref.
Pulmonary vascular anatomy	Simple, non-muscularized distal arteries	Similar to mouse, more muscularization than mouse	Closer to human, well-developed muscular arteries	Highly similar to human	Reference standard	[16–22]
Common PAH models	Hypoxia, MCT, Sugen-hypoxia, genetic models	Hypoxia, MCT, Sugen-hypoxia	MCT, hypoxia, embolic, shunt models	Chronic hypoxia, endothelial injury models	Idiopathic, heritable, associated PAH	[5,8,16–20]
Vascular remodeling phenotype	Moderate medial thickening; limited complex lesions	More pronounced muscular remodeling than mouse	Concentric remodeling, plexiform-like lesions (model-dependent)	Complex remodeling similar to human	Medial hypertrophy, intimal lesions, plexiform lesions	[5,8,16–20]
Right ventricular adaptation	Detectable hypertrophy; limited failure	More consistent RV hypertrophy and dysfunction	RV hypertrophy and dysfunction (measurable by imaging)	Similar to human	Variable; often progresses to right heart failure	[5,8,24,25]
Immune system characteristics	Prominent innate and adaptive inflammatory responses, including Th17-associated pathways	Similar to mouse with quantitative and kinetic differences	Closer to human in innate and adaptive immunity	Highly similar to human	Reference standard	[6,23,26,27]
Antibody response kinetics	Species- and context-dependent	Species- and context-dependent	Species- and context-dependent	May approximate selected human responses	Context-dependent; capable of long-term immune memory	[22,26,28]

Target conservation (selected PAH targets)	Target- and epitope-dependent	Target- and epitope-dependent	Target-dependent; selected targets may show greater similarity to humans	High similarity for many conserved biologic targets, but target-dependent	Reference standard	[7,8]
Availability of immunological reagents	Extensive	Extensive	Moderate (increasing)	Limited	Extensive	[6–8,22]
Practical considerations	Low cost, easy handling, genetic tools available	Low-moderate cost, well-established models	Higher cost, greater technical complexity	High cost, ethical constraints	Clinical heterogeneity, limited experimental control	[5,7,8,20,22]
Main advantages for immunotherapy research	Mechanistic studies, genetic manipulation, initial efficacy screening	Validation in a second rodent species; more robust disease phenotype	Human-relevant physiology, pharmacokinetics, and immunogenicity	Closest to human in immune system and target biology	Definitive clinical relevance	[6–8,22,28]
Key limitations	Limited recapitulation of advanced human PAH; species-specific immune traits	Does not fully reproduce severe human disease; some immunological differences	Fewer reagents; higher cost; species-specific differences remain	High cost; ethical and logistic constraints; not identical to human PAH	High heterogeneity; limited access to early disease for mechanistic studies	[5–8,16,20,22,23,26]

Note: Target conservation may vary depending on the specific antigen or epitope. Cross-species features may vary according to the specific PAH model, therapeutic target, antigen/epitope, and experimental context. Abbreviations: ALK, activin receptor-like kinase; BMPR2, bone morphogenetic protein receptor type 2; ET, endothelin; MCT, monocrotaline; PAH, pulmonary arterial hypertension; RV, right ventricular; Th, T helper.

2.2. Species-Specific Immune Biology and Its Relevance to Immunotherapy

Cross-species variability becomes more consequential when therapeutic efficacy depends on endogenous immune responses. Mice, rats, large animals, and humans differ in innate immune activation, antigen presentation, lymphocyte composition, antibody kinetics, and immune-memory formation, creating distinct biological environments in which immunotherapies operate [26]. In PAH models, such differences may interact with species-dependent variation in vascular remodeling and signaling pathways, including endothelin and BMPR2/TGF-β-related networks, thereby modifying the relationship between immune activation and vascular injury [23,27]. Consequently, an intervention that appears effective in one species may produce a different magnitude, durability, or even direction of response in another [28].

These considerations are especially relevant for active immunization. Unlike target-directed biologics, which primarily depend on molecular compatibility and drug exposure, vaccine-based approaches require successful antigen recognition, antigen processing, adaptive immune activation, antibody maturation, and long-term immune memory. Each of these steps may vary across species. Species-dependent differences in immune repertoire, antigen presentation pathways, and humoral response kinetics can therefore alter vaccine immunogenicity and therapeutic durability independently of the biological relevance of the target itself [22]. For this reason, preclinical evidence generated in a single species may either overestimate or underestimate the clinical potential of active PAH immunotherapies [29].

2.3. Implications for Preclinical Evaluation and Cross-Species Validation

Conventional PAH preclinical pipelines place substantial emphasis on rodent models for early efficacy assessment, with larger-animal models often introduced at later stages to address specific questions of physiological relevance and translational validation [8,24]. This approach is practical for many conventional pharmacological agents. However, it may be less informative for immunotherapies whose efficacy depends strongly on host immune biology and species-specific immune responses [30,31]. Single-species evaluation may fail to capture differences in target conservation, immune recognition, antibody persistence, inflammatory responses, and tissue-level remodeling, thereby reducing both reproducibility and translational predictability [5,29]. Methodological rigor, including randomization, blinding, and standardized reporting, remains essential but cannot compensate for intrinsic biological divergence between species.

A more informative strategy is therefore to use cross-species validation as a mechanistic tool rather than as a late-stage confirmatory step. Early comparisons across complementary rodent models can help determine whether therapeutic responses are robust or model-specific, while large-animal or other human-relevant systems can be introduced when target conservation, biologic compatibility, immunogenicity, or long-term safety become critical [25,32]. For active immunization, this framework should additionally assess antigen recognition, antibody magnitude and persistence, immune-memory formation, and vascular remodeling across species [33]. Such a staged but biologically informed approach would reduce uncertainty surrounding species-specific response patterns and improve the translational assessment of next-generation PAH immunotherapies.

3. Sex-Stratified Determinants of PAH Immunotherapy Response

3.1. The PAH Sex Paradox and Divergent Disease Phenotypes

Pulmonary arterial hypertension exhibits a well-recognized sex paradox, with a higher disease prevalence among females but generally poorer clinical outcomes among males [34–36]. This divergence suggests that biological sex influences not only disease susceptibility but also the trajectory of pulmonary vascular remodeling and right ventricular adaptation [10,37,38]. These differences are unlikely to reflect a single pathway and instead arise from interactions among hormonal signaling, vascular biology, immune regulation, and tissue-specific stress responses.

Sex-associated differences are also evident at the vascular and myocardial levels [39]. Female PAH has been linked to relatively greater preservation of right ventricular function under chronic pressure overload, whereas males more frequently develop ventricular dilation, fibrosis, and functional deterioration [40]. At the pulmonary vascular level, sex-associated variation in endothelial injury, smooth muscle proliferation, fibrotic remodeling, and inflammatory activation may contribute to distinct disease phenotypes [41]. However, these patterns should not be interpreted as a simple female-protective versus male-susceptible dichotomy, because sex effects vary according to disease subtype, age, hormonal status, and experimental context [42]. Rather, biological sex should be considered a modifier of the pathological environment in which immunotherapeutic interventions act [10]. The major biological pathways through which sex influences PAH susceptibility and immune responsiveness are summarized in Figure 2.

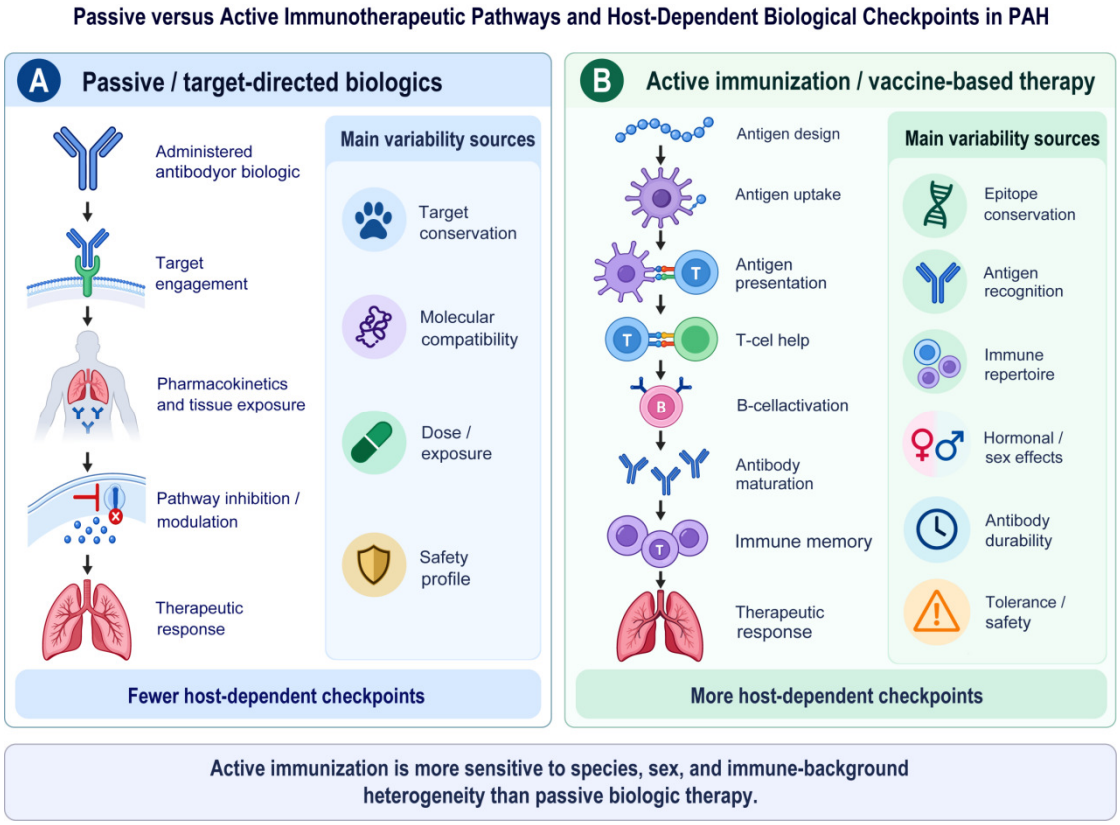


Figure 2. Passive versus active immunotherapeutic pathways and host-dependent biological checkpoints in pulmonary arterial hypertension. Target-directed biologics act primarily through direct target engagement and are influenced mainly by target conservation, molecular compatibility, pharmacokinetics, tissue exposure, and safety. In contrast, active immunization requires a sequential endogenous immune response involving antigen uptake and presentation, T-cell help, B-cell activation, antibody maturation, and immune-memory formation. These additional host-dependent checkpoints increase the potential for variability related to species background, sex-associated immune regulation, immune repertoire, antibody durability, and tolerance. The schematic therefore illustrates why vaccine-based PAH immunotherapy may be more sensitive to biological heterogeneity than externally administered biologic therapies.

3.2. Endocrine and Immune Mechanisms Relevant to Therapeutic Response

Sex hormones represent an important interface between vascular remodeling and immune regulation in PAH. Estrogen receptor-dependent signaling has been associated with endothelial survival, vascular repair, and modulation of inflammatory pathways, whereas androgen-related signaling may contribute to distinct inflammatory and fibrotic responses [43,44]. In parallel, biological sex influences immune-cell activation, cytokine production, antigen-presenting cell function, and adaptive immune responses [45]. These mechanisms may alter the baseline immune environment before treatment and thereby influence the response to immune-directed therapies. In the context of PAH, such effects are particularly relevant because vascular injury and immune dysregulation are closely interconnected [46].

Sex chromosome composition adds an additional regulatory layer. Differential expression of X- and Y-linked immune genes, together with incomplete X-chromosome inactivation and sex-dependent epigenetic programming, can shape immune-cell function independently of circulating hormone levels [47]. These mechanisms may influence antigen sensing, T-cell activation, B-cell responses, and inflammatory resolution [48]. Nevertheless, much of the evidence linking these processes to immunotherapy responsiveness

derives from broader immunology rather than from direct PAH vaccine studies. Therefore, sex-associated immune mechanisms in PAH should currently be viewed as biologically plausible contributors to therapeutic heterogeneity rather than as established modifiers or predictors of treatment response [11]. Sex-associated differences in vascular remodeling, immune regulation, and therapeutic implications are summarized in Table 2.

Table 2. Sex-stratified comparison of key features relevant to PAH and immunotherapy development.

Feature	Females	Males	Key Mechanisms (Proposed or Established)	Implications for Immunotherapy Development	Ref.
PAH prevalence	Higher (≈3–4:1 female-to-male ratio in most cohorts)	Lower	• Estrogen signaling • Genetic factors (X chromosome) • Immune regulation	Consider sex-specific disease susceptibility in target selection and prevention strategies	[42]
Clinical outcomes	Generally better survival	Worse clinical outcomes	• Right ventricular adaptation • Differences in comorbidities • Hormonal and immune factors	Evaluate therapeutic efficacy and survival separately in male and female models/patients	[14]
Pulmonary vascular remodeling	More proliferative/plexiform lesions; relative preservation of RV function	More concentric remodeling; more severe vascular muscularization	• Estrogen-mediated vascular protection • Androgen-related pro-remodeling signaling • Endothelial and smooth muscle cell differences	Assess sex-specific effects on vascular remodeling and right ventricular function	[41]
Right ventricular adaptation	Greater adaptive capacity; more preserved RV function	More prone to RV dilation, fibrosis and dysfunction	• Sex hormones • Metabolic and mitochondrial differences • Inflammatory and fibrotic pathways	Include sex-disaggregated assessment of RV structure and function in preclinical and clinical studies	[40]
Hormonal environment	Estrogen (protective effects on endothelium, anti-inflammatory)	Androgens (may promote inflammation and fibrosis)	• Estrogen receptor signaling • Androgen receptor signaling • Interaction with immune cells	Consider hormonal status (e. g., menstrual cycle, menopause, androgen levels) in study design and interpretation	[45]
Innate immune responses	Stronger innate immune activation (e. g., higher type I interferon responses)	Relatively weaker innate responses	• X-linked immune genes • Hormonal regulation of innate immunity • Epigenetic differences	May influence vaccine adjuvant selection, initial immune activation and risk of adverse inflammatory responses	[48]

Adaptive immune responses	Generally stronger humoral and cellular responses (higher antibody titers, more robust T-cell responses)	Weaker antibody responses, different T-cell polarization (more Th1/Th17 in some contexts)	• Sex hormones • X chromosome-linked immune genes • Differences in cytokine profiles	May affect vaccine immunogenicity, antibody durability and T-cell-mediated mechanisms	[49]
Autoimmunity risk	Higher risk of autoimmune diseases	Lower risk	• Enhanced immune reactivity • X chromosome gene dosage • Hormonal and epigenetic factors	Monitor for autoimmune phenomena, especially in vaccine strategies targeting self-associated antigens	[45]
Response to vaccines (in general population)	Stronger and more durable antibody responses; higher rate of some vaccine-related adverse events	Lower antibody responses; fewer immune-related adverse events	• Hormonal regulation • Immune cell activation and differentiation • Epigenetic and transcriptional differences	Evaluate potential sex-associated differences in vaccine immunogenicity, efficacy, and reactogenicity; dosing or adjuvant strategies require PAH-specific validation	[50]
Relevance to PAH immunotherapy	Higher disease susceptibility; PAH-specific vaccine responsiveness remains uncertain	Lower susceptibility but potentially poorer outcomes and different immune environment	Integration of vascular, hormonal and immune factors	Include both sexes in preclinical and clinical studies; explore candidate biomarkers associated with sex and therapeutic response, together with stratified immunotherapy approaches	[51]

Key message: Biological sex influences PAH pathobiology and immune function and should therefore be incorporated as an important stratification variable in PAH immunotherapy research, particularly for active immunization. Direct evidence for sex-associated differences in PAH vaccine responses remains limited.

3.3. Implications for Sex-Stratified Immunotherapy Evaluation

The relevance of biological sex becomes greater as therapeutic efficacy depends more strongly on the host immune system. For target-directed biologics, sex may influence pharmacology, inflammatory background, and disease severity, but treatment does not require de novo adaptive immune activation. In contrast, active immunization depends on antigen presentation, T-cell help, B-cell maturation, antibody production, and immune-memory formation, all of which may be influenced by sex-related biological factors [52]. Therefore, vaccine-based strategies may be particularly sensitive to sex-associated differences in response magnitude, durability, and safety compared with therapies that rely predominantly on direct target engagement [53].

Current PAH preclinical studies frequently use single-sex designs, limiting the ability to identify sex-dependent therapeutic effects and potentially reducing translational accuracy. Both male and female experimental populations should therefore be incorporated during immunotherapy development, with sex-disaggregated assessment of vascular remodeling, right ventricular function, immune-cell composition, antibody kinetics, and treatment durability [8,15]. Importantly, such analyses should distinguish direct PAH-

specific evidence from mechanistic inference derived from general immunology. This approach would allow biological sex to be incorporated as an experimentally testable variable rather than treated as a secondary demographic characteristic, and would provide a more rigorous basis for future sex-stratified PAH immunotherapy development [54].

4. Differential Sensitivity of PAH Immunotherapeutic Strategies to Biological Heterogeneity

4.1. Distinct Biological Dependencies of Target-Directed Biologics and Active Immunization

Immune-based therapeutic strategies for pulmonary arterial hypertension differ fundamentally in the extent to which their efficacy depends on host immune function. Externally administered antibody-based or other target-directed biologic therapies act primarily through direct engagement of disease-associated molecules and are therefore influenced mainly by target accessibility, molecular compatibility, binding properties, pharmacokinetics, and tissue exposure [55]. Although species-dependent differences in target expression and biologic cross-reactivity remain important, these therapies do not require the host to generate a new adaptive immune response. Their therapeutic effects are consequently more directly linked to the properties of the administered agent and its interaction with the target [56].

Active immunization introduces a substantially greater degree of host dependence. Vaccine-based approaches require sequential antigen uptake and processing, antigen presentation, T-cell activation, B-cell differentiation, antibody maturation, and establishment of long-term immune memory [57]. Therapeutic efficacy therefore depends not only on whether the selected target is biologically relevant, but also on whether the host immune system can generate a sufficiently strong, functionally appropriate, and durable response against that target [58]. This distinction provides a mechanistic basis for why active immunization may be particularly sensitive to variation among species, between sexes, and across individual immune backgrounds [52]. Representative therapeutic strategies and their current developmental status are summarized in Table 3, emphasizing differences in biological dependence and translational requirements among therapeutic modalities.

Table 3. Therapeutic landscape of conventional, biologic, and immune-based strategies relevant to PAH immunotherapy development.

Therapeutic Strategy		Representative Targets/Agents	Mechanism of Action	Stage of Development	Key Findings	Key Gaps and Future Directions	Ref.
Target-directed biologics (externally administered)	Anti-endothelin pathway antibodies/antagonists	Bosentan (small molecule), macitentan (small molecule), anti-ETA antibodies (experimental)	Block endothelin-1 signaling	Approved (small molecules) Preclinical (antibodies)	Proven clinical benefit (small molecules); antibody approaches show efficacy in animal models	Antibody approaches need further validation; species differences in target expression and antibody cross-reactivity	[12]

	Anti-BMPR2 antibodies	Anti-BMPR2 mAbs (experimental/mechanistic tool)	Modulate BMPR2 signaling or prevent pathogenic antibody binding	Preclinical	Efficacy in rodent models; mechanistic support for restoring BMPR2 signaling	Limited in vivo data; potential immunogenicity; species differences in BMPR2 epitopes	[59]
	Anti-IL-6/IL-6R antibodies	Tocilizumab (anti-IL-6R monoclonal antibody)	Inhibition of IL-6-mediated inflammatory signaling	Phase 2 open-label exploratory study	Demonstrated biological target engagement but no consistent improvement in PVR or overall treatment effect	Clinical efficacy remains unestablished; further studies are needed to determine whether specific PAH subgroups may benefit	[60]
	Immune checkpoint modulation	PD-1/PD-L1 pathway; nivolumab, pembrolizumab	Immune checkpoint inhibition	No established therapeutic role in PAH; pharmacovigilance evidence	PAH has been reported during ICI therapy; current clinical evidence does not support therapeutic benefit in PAH	Clarify mechanisms and cardiovascular safety; therapeutic relevance to PAH remains unestablished	[61]
Active immunization (vaccine-based)	Peptide/protein vaccines	ETAR-derived epitope peptide (ETR-002); ETRQβ-002 vaccines	Induce antigen-specific antibodies	Preclinical	Effective in rodent PAH models; target selection influences immune response	Antigen conservation, species differences, immune tolerance, long-term safety	[62]
	DNA/RNA vaccines	BMPR2/BMP–TGF-β pathway nucleic-acid or gene-based constructs (experimental)	Restore or modulate BMPR2/BMP–TGF-β signaling through endogenous transgene expression	Preclinical/proof-of-concept	Proof-of-concept efficacy in animal models	Delivery systems, immunogenicity in large animals/humans, durability of response	[63]
	Autologous dendritic cell vaccines pulsed with PAH-related antigens (conceptual)	Autologous DCs pulsed with PAH-related antigens	Enhanced antigen presentation and T-cell activation	Conceptual/preclinical platform; no direct PAH therapeutic study identified	Efficacy in experimental models; potential for personalized therapy	Complex manufacturing; limited data in PAH; need for human-relevant models	[64]

	Tolerance-modulating vaccines	Modified self-antigens, regulatory vaccine platforms	Induce regulatory immune responses (Tregs, tolerogenic DCs)	Conceptual/preclinical platform; no direct PAH therapeutic study identified	Conceptual approach to reduce autoimmunity risk	Optimal design and balance between efficacy and tolerance remain uncertain	[65]
Cell-based and other immune modulatory approaches	Regulatory T cell therapies	Treg adoptive transfer/restoration	Restore immune tolerance and reduce inflammation	Preclinical	Ameliorates pulmonary vascular remodeling in animal models	Scalability, stability, and long-term effects	[66]
	Mesenchymal stem cells (MSCs)	Bone marrow-or adipose-derived MSCs	Immunomodulation, anti-inflammation, tissue repair	Early clinical (small studies)	Feasible and generally safe in early clinical trials	Heterogeneous results; optimal dosing, timing, and patient selection	[67]
	Cytokine modulation	Anti-TNF-α agents, IL-1 pathway inhibitors, JAK/STAT pathway inhibitors (repurposed or investigational)	Inhibit inflammatory signaling pathways	Preclinical/Early clinical	Some benefit in experimental models	Limited clinical data in PAH; risk of systemic immunosuppression	[68]
Combination and emerging strategies	Multi-target approaches	e. g., vaccine + biologic, immune modulation+ vasodilator therapy	Simultaneous modulation of vascular dysfunction, remodeling, and immune-inflammatory pathways	Conceptual/Preclinical	Improved efficacy in animal models; potential to overcome single-target limitations	Optimal combinations, dosing regimens, and safety profiles	[1]
	Patient-specific immune and molecular profiling; biomarker-guided target selection	Patient-specific immune profiling and candidate antigen/target identification	Tailored immune response based on individual biology	Conceptual/Early exploratory	Rationale supported by disease heterogeneity	Biomarker validation, feasibility, and clinical implementation	[69]

Abbreviations: PAH, pulmonary arterial hypertension; ET, endothelin; BMPR2, bone morphogenetic protein receptor type 2; DC, dendritic cell; MSC, mesenchymal stem cell; Treg, regulatory T cell.

4.2. Host-Dependent Immune Checkpoints as Sources of Therapeutic Variability

The increased sensitivity of active immunization to biological heterogeneity can be understood as a consequence of the multiple immune checkpoints required for vaccine efficacy. Species-dependent differences in antigen processing, immune repertoire composition, lymphocyte activation, antibody kinetics, and immune-memory formation may alter the magnitude and durability of vaccine-induced responses [50,70,71]. Likewise, sex-associated differences in hormonal regulation, antigen-presenting cell function, adaptive immune activation, and antibody production may modify the same sequence of immune events [72–74]. Biological heterogeneity can therefore influence active immunization at multiple stages rather than at a single point of target engagement [70,74].

This effect is particularly relevant for PAH vaccines directed against self-associated vascular antigens or receptor-derived epitopes [62,75]. Such approaches must overcome physiological immune tolerance sufficiently to generate therapeutic antibodies while avoiding excessive immune activation or autoimmune injury [76,77]. Variation in tolerance thresholds, antigen recognition, germinal-center responses, and antibody persistence could therefore produce substantial differences in efficacy and safety among experimental models or patient populations [65].

Importantly, this framework should not be interpreted as implying that active immunization is intrinsically less translatable than target-directed biologics. Rather, it indicates that the determinants of translation are different. For externally supplied biologics, uncertainty is concentrated primarily around target conservation, molecular compatibility, exposure, and safety. For active immunization, uncertainty extends across the entire endogenous immune response, including antigen recognition, antibody quality, response persistence, and immune memory [50,65,70]. Thus, the number of host-dependent biological checkpoints is greater, creating more opportunities for species- and sex-related variability to influence therapeutic outcome [51].

4.3. Translational Implications for PAH Vaccine Development

The differential biological requirements of these therapeutic modalities imply that they should not be evaluated using identical preclinical strategies. Target-directed biologics primarily require confirmation of target conservation, cross-species pharmacological activity, pharmacokinetics, tissue distribution, and toxicity [78–80]. In contrast, evaluation of active immunization should additionally include immunogenicity, antigen-specific antibody magnitude and function, antibody durability, immune-memory formation, and evidence of immune-mediated vascular effects [81–83]. These parameters should be assessed across biologically relevant species and, where feasible, separately in male and female experimental populations.

Such an approach is especially important because direct evidence defining sex-associated differences in responses to PAH vaccines remains limited. Therefore, current expectations regarding sex-associated variation in vaccine responses are supported largely by the convergence of PAH pathobiology with broader evidence on sexual dimorphism in adaptive immunity rather than by extensive head-to-head PAH vaccination studies [84,85]. This uncertainty should be treated as a testable translational question rather than assumed as an established therapeutic pattern [85,86].

Accordingly, biological heterogeneity should not be regarded only as a source of experimental noise. For active immunization, variation in species background, sex, immune phenotype, and antibody-response characteristics may help identify candidate biological features associated with therapeutic responsiveness [87]. Incorporating these variables into preclinical study design may improve translational assessment and facilitate the prospective evaluation of candidate response-associated phenotypes and stratified vaccine-based strategies for PAH [88]. This concept is consistent with the broader proposal that species-aware and sex-stratified immune profiling may support biomarker-guided vaccine development [89].

5. Translational Framework and Future Directions for Precision PAH Immunotherapy

5.1. A Multidimensional Preclinical Framework Integrating Species, Sex, and Immune Phenotype

The biological heterogeneity of pulmonary arterial hypertension indicates that preclinical evaluation of immunotherapy should move beyond conventional single-species

and single-sex designs. A multidimensional translational framework should integrate three complementary dimensions: cross-species validation, sex-stratified assessment, and immune-response profiling [69,90,91]. These variables should not be treated as secondary sources of experimental variation, but as candidate biological modifiers whose associations with therapeutic efficacy, durability, and safety require systematic evaluation [92,93]. This consideration is particularly important for active immunization, in which treatment outcome depends on coordinated endogenous immune responses in addition to target relevance [94].

At the species level, model selection should be guided by the biological requirement of the therapeutic modality rather than by a fixed hierarchical sequence [8,69]. Early rodent studies remain appropriate for mechanistic exploration and initial efficacy testing, but cross-species comparisons should be introduced when target conservation, antigen recognition, antibody responses, or immunogenicity are likely to influence treatment outcome [95]. For biologic agents, relevant endpoints include target expression, molecular cross-reactivity, pharmacokinetics, tissue exposure, toxicity, and the potential for treatment-related immunogenicity [93,94,96,97]. For active immunization, additional assessment of antigen-specific antibody generation, functional neutralization, response durability, immune memory, and vascular remodeling is required. Large-animal or other human-relevant systems may then be used selectively to resolve translational uncertainties that cannot be adequately addressed in conventional rodent models [69].

Sex should be incorporated in parallel rather than evaluated only after efficacy has been established [98]. Both male and female experimental populations should be included where biologically and technically feasible, with sex-disaggregated analysis of hemodynamic outcomes, pulmonary vascular remodeling, right ventricular function, immune-cell phenotypes, and antibody kinetics [99,100]. Where relevant, hormonal status and other modifiers of immune function should be considered during interpretation [101]. Importantly, the objective is not to assume a priori that one sex will respond more favorably, but to determine whether sex modifies the magnitude, durability, or safety of treatment and whether such effects are reproducible across experimental systems [98–101].

5.2. Immune Profiling and Human-Relevant Validation as Translational Bridges

Species and sex stratification alone are unlikely to fully account for heterogeneous therapeutic responses. Immune phenotyping should therefore be incorporated into preclinical and early translational studies to define the biological state in which a therapy is being evaluated [102,103]. Depending on the therapeutic platform, informative parameters may include circulating and tissue immune-cell composition, inflammatory signatures, antigen-specific antibody titers, antibody affinity or neutralizing capacity, T-cell activation, B-cell differentiation, and markers of immune-memory formation [104,105]. For vaccine-based strategies, longitudinal assessment is especially important because therapeutic durability may depend on the persistence and quality of endogenous immune responses rather than on short-term target inhibition alone.

Human-relevant experimental systems may provide an additional bridge between animal studies and clinical translation. Patient-derived vascular cells, multicellular culture systems, organoid-like platforms, and microphysiological models can help assess species-independent aspects of target biology and may be particularly useful when animal cross-reactivity is limited [106–108]. However, these systems should complement rather than replace in vivo evaluation because they cannot fully reproduce systemic immunity, right ventricular-pulmonary vascular coupling, or long-term immune memory [109]. Their greatest value may therefore lie in integrating molecular and immune findings from animal studies with human-specific target expression, cellular responsiveness, and biomarker patterns [103,110].

A translational pipeline based on these principles would thus shift from simple confirmation of efficacy toward systematic evaluation of candidate response modifiers. Instead of asking only whether an intervention improves pulmonary hemodynamics in a given model, studies should also ask which biological features are associated with therapeutic response, whether these associations are conserved across species, and whether they differ between sexes. Such an approach may reduce the risk of advancing therapies whose apparent efficacy depends on a narrow experimental context [102,103].

5.3. Integrative Multivariable and Machine-Learning Approaches

The multifactorial nature of PAH immunotherapy heterogeneity requires analytical approaches that can integrate interacting biological and clinical variables. Conventional multivariable modelling remains important for hypothesis-driven analysis, while machine learning may provide a complementary approach for identifying nonlinear and higher-order interactions. In PAH, such methods have been applied to immune-related molecular signatures and multidimensional clinical data, including XGBoost analysis with SHAP-based interpretation in the Polish BNP-PL registry [90,111]. However, these applications do not establish the ability to predict PAH immunotherapy response. Given the risks of overfitting and limited transportability, machine-learning models require rigorous validation, including independent external validation. Their current role in PAH immunotherapy should therefore be considered complementary and hypothesis-generating rather than a substitute for conventional statistical modelling or prospective validation.

5.4. Evidence Priorities and Future Directions

Several evidence gaps should be addressed before precision PAH immunotherapy can become a realistic clinical strategy. First, direct comparative studies of immunotherapeutic responses across species remain limited, particularly for active immunization. Systematic evaluation of antigen conservation, immunogenicity, antibody quality, immune memory, and safety across complementary models will be necessary to determine which preclinical systems best predict human responses [112]. Second, sex-specific evidence remains insufficient. Although PAH biology and broader immunological research provide strong mechanistic reasons to consider biological sex, dedicated head-to-head studies of male and female responses to PAH vaccines are still sparse [72]. Third, future studies should distinguish clearly between evidence derived directly from PAH immunotherapy and mechanistic inference from general immunology or other disease areas. This distinction is especially important when proposing sex-dependent or species-dependent response mechanisms [113]. Establishing an explicit hierarchy of evidence-ranging from direct PAH therapeutic studies to PAH mechanistic evidence and broader immunological extrapolation would improve interpretation and prevent biologically plausible hypotheses from being presented as established clinical facts. Finally, the long-term objective should be to define the biological and clinical contexts associated with differential therapeutic responses and to evaluate these associations prospectively [1]. For active immunization, this may ultimately involve matching vaccine design and dosing strategies to target conservation, host immune competence, biological sex, and measurable immune-response characteristics [51,92]. For target-directed biologics, translational optimization may depend more heavily on molecular compatibility, exposure, and disease phenotype [114]. In both cases, integrating cross-species validation, sex-aware experimental design, immune profiling, and human-relevant validation may improve translational interpretation and provide a more rigorous foundation for the prospective evaluation of stratified immunotherapy approaches in PAH [1,115–117].

6. Conclusions

Biological heterogeneity represents an important source of variability in pulmonary arterial hypertension immunotherapy and should be considered within the broader clinical and biological context in which therapeutic responses occur. Cross-species differences in vascular pathology, target biology, and immune regulation may influence preclinical efficacy and translational predictability, while biological sex modifies disease susceptibility, right ventricular adaptation, inflammatory context, and adaptive immune function. These effects are particularly relevant to active immunization, whose efficacy depends on multiple host-dependent processes, including antigen recognition, antigen presentation, lymphocyte activation, antibody maturation, and immune-memory formation. In contrast, externally administered target-directed biologics are generally more dependent on molecular compatibility, pharmacokinetics, and tissue exposure, although they remain subject to species- and sex-related biological variation.

The available evidence also highlights an important limitation: direct comparative data on sex- and species-dependent responses to PAH vaccines remain limited, and several proposed mechanisms are currently supported by mechanistic convergence rather than definitive therapeutic studies. Future research should therefore distinguish clearly between direct PAH immunotherapy evidence and inference derived from broader vascular or immunological biology. Integrating cross-species validation, sex-stratified experimental design, immune profiling, and human-relevant models may strengthen the translational value of preclinical studies and help identify candidate biological features associated with therapeutic response.

Ultimately, the goal should not be to eliminate heterogeneity, but to characterize and use it. A translational strategy that accounts for species, sex, and host immune state may provide a more rigorous foundation for developing stratified and potentially more precise immunotherapeutic approaches for PAH, particularly vaccine-based interventions whose success depends most strongly on endogenous immune competence.

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