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REVIEW PAPER

Humanized NSG mice – a modern approach to modelling systemic lupus erythematosus in preclinical modeling

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ABSTRACT

Introduction and aim. Systemic lupus erythematosus (SLE) is a complex autoimmune illness characterized by widespread immune dysregulation and involvement of several organ systems. Conventional mouse models, although crucial for understanding basic immunopathogenic pathways, inadequately mimic human-specific immunological responses, hence constraining translational relevance. This review offers a comprehensive understanding of humanized NSG mice in systemic lupus erythematosus research, outlining techniques for engraftment, model-specific immune reconstitution characteristics, and their respective applications in simulating acute and chronic disease phenotypes.

Literature search. A comprehensive analysis of studies published between 2017 to 2025 was conducted in PubMed, Scopus, Web of Science and Google Scholar database. After removing the duplicates, a total of 87 articles were employed to finalize this study.

Analysis of literature. Humanized NSG mice successfully recapitulate major immunopathological features of systemic lupus erythematosus. Among numerous approaches, $CD34^+$ hematopoietic stem cell models best mimic chronic phenotype, while PBMC and pristane-based systems mimic acute and environmentally triggered forms. Recent advances include cytokine knock-in and HLA transgenic derivatives improving immune reconstitution and translational dependability.

Conclusion. This review provides the first integrative synthesis of humanized NSG mouse models applied to SLE, highlighting their translational potential and methodological advancements from 2017–2025. Collectively, these innovations establish humanized NSG mice as essential preclinical tools bridging experimental immunology with precision medicine in lupus research and therapy development.

Keywords. hematopoietic stem cell, humanized mouse model, immunopathogenesis, NSG mice, SLE

Introduction

Systemic lupus erythematosus (SLE), is a chronic autoimmune illness that is characterized by the dysregulation of the immune system and the development of pathogenic autoantibodies.[1] These autoantibodies target nuclear and cytoplasmic antigens resulting in inflammation and multi-organ damage.[2,3] At the clinical level, SLE is characterized by a wide variety of symptoms, including but not limited to fatigue, joint pain, malar rash, photosensitivity, and more serious consequences such as lupus nephritis, neuropsychiatric lupus, and hematological abnormalities.[4] Multiple factors contribute to the development of SLE, which is characterized by a complex interaction between genetic predisposition, epigenetic alterations, environmental stressors, and hormonal variables.[5,6] Numerous susceptibility loci related

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with immune regulation have been found through the use of genome-wide association studies (GWAS). These loci include genes that are involved in the type I interferon pathway, the HLA complex, and the clearance of apoptotic cells within the body.[7] Certain environmental triggers, such as ultraviolet radiation, infections (especially the Epstein-Barr virus), and certain medications, have the potential to initiate or aggravate illness flares in SLE, while the higher prevalence in females highlights the potential role of estrogen.[8,9] SLE is marked by a loss of immunological self-tolerance, leading to the activation of autoreactive T and B cells and interferon-alpha (IFN-α), responsible for producing immunological complexes, causing tissue deposition, and activating the complement cascade, resulting in chronic inflammation and organ dysfunction.[10,11] Preclinical models are indispensable for the investigation of disease mechanisms and the development of therapeutics. The replication of key features such as lymphoproliferation, autoantibody production (e.g., anti-dsDNA, anti-Sm), and lupus-like kidney pathology has substantially advanced our understanding of SLE in classical murine models such as MRL/lpr, NZB/W F1, and BXSB.[12,13] Despite their significant contributions, classical rodent models are severely constrained by the fundamental differences between the immune systems of mice and humans, as well as the cytokine signaling and gene expression profiles.[14,15] In light of these constraints, a paradigm shift has transpired towards the utilization of humanized mouse models, particularly the NOD-scid IL2Rγ^null (NSG) strain, which, owing to its severely compromised adaptive and innate immunity, has become the benchmark for facilitating the engraftment of the human immune system.[16,17] Humanized NSG mice are progressively utilized to emulate human-specific characteristics of SLE, including autoreactive immune responses, cytokine synthesis, and tissue injury. They provide a significant platform for investigating disease mechanisms, discovering novel therapeutic targets, and evaluating therapy efficacy and safety.[18] In spite of availability of numerous murine model of SLE, no previous review has yet systematically explored the recent advancements in humanized NSG mice and their role in elucidating SLE immunopathogenesis and therapeutic modelling.

Aim

This review aims to provide a thorough understanding of humanized NSG mice in SLE research, detailing the techniques for engraftment, model-specific immune reconstitution characteristics, and their applications in simulating acute and chronic disease phenotypes. Additionally, comparative insights into limitation, challenges recent improvements, and future views are also included.

Literature search

A comprehensive literature study was conducted to identify peer-reviewed studies published between January 2017 and May 2025. This evaluation includes electronic journal articles obtained from esteemed databases such as PubMed, Google Scholar, Web of Science, and Scopus. The search methodology incorporated Medical Subject Headings (MeSH) alongside relevant free-text terms, including "systemic lupus erythematosus" or "SLE," "Humanized NSG mice," "SLE animal model," and "immunological biomarkers," as well as other specialized search expressions (Fig.1). Articles not in English, together with conference abstracts, editorials, and opinion pieces, were excluded. Following the screening and elimination of duplicates, a total of 87 pertinent publications were chosen to inform this comprehensive review.

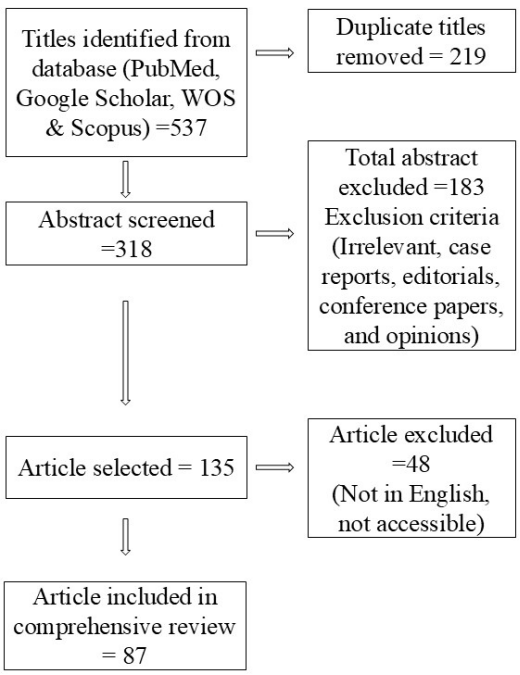

Fig. 1. Schematic representation of the literature search and selection process used in this comprehensive review

Analysis of the literature

Background of NSG mice

The NSG mouse strain is a triple-immunodeficient model that serves as a crucial platform in translational biomedical research, especially for the reconstitution of the human immune system. This model contains compound mutations in the Prkdc gene, which is responsible for the severe combined immunodeficiency (scid) phenotype.[19] The Prkdc mutation leads to a malfunctioning V(D)J recombination system, resulting in the cessation of mature T and B cell maturation, therefore compromising the mouse adaptive immune system.[20] The precise deletion of the interleukin-2 receptor common gamma chain (Il2rg) gene, referred to as IL-2Rγ^null, disrupts signaling through essential interleu-

kins (e.g., IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21) that are vital for lymphoid lineage development and homeostasis, especially regarding the maturation and cytolytic function of natural killer (NK) cells.[21] The combined impact of these mutations results in a significant immunological deficiency, marked by both adaptive and innate immune failure, which incapacitates the host from initiating alloimmune or xenogeneic immune responses. This immunological niche establishes a xenotolerant milieu that facilitates the effective and durable engraftment of human hematopoietic stem and progenitor cells (HSPCs) or peripheral blood mononuclear cells (PBMCs).[22] Post-transplantation, human cells differentiate into several immune cell types, facilitating the development of a human-like immune system in mice, so allowing researchers to examine human-specific immunological responses.[23] Furthermore, the absence of murine major histocompatibility complex (MHC) reduces graft-versus-host and host-versus-graft immunological reactions, facilitating prolonged engraftment, enduring hematopoietic production, and effective immunological responses.[24] Thus, NSG mice function as a biologically pertinent surrogate model for assessing human hematopoiesis, immunopathology, tumor immunoediting, infectious disease dynamics, and immunotherapeutic strategies in physiologically relevant contexts.[25]

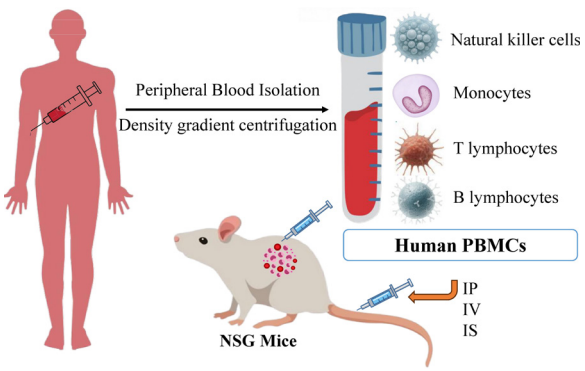

Fig. 2. Schematic representation of human PBMC isolation and engraftment in NSG mice

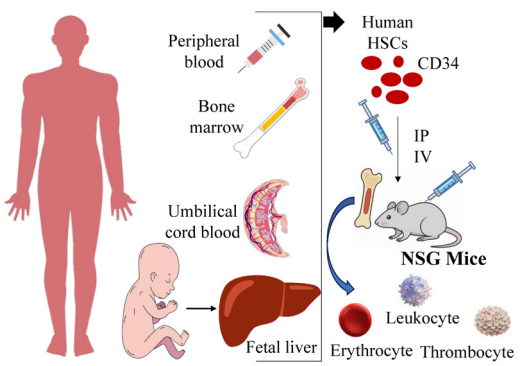

Fig. 3. Schematic representation of human CD34⁺ HSC isolation and engraftment in NSG mice

Types of humanizations

PBMC engraftment

PBMC engraftment is a humanization technique involving the intravenous injection of isolated human immune cells predominantly lymphocytes (T cells, B cells), monocytes, and natural killer (NK) cells into immunodeficient mice, such as NSG mice.[26] Peripheral blood mononuclear cells (PBMCs) are often extracted from the peripheral blood of healthy donors or patients using density gradient centrifugation (Fig. 2) and are subsequently delivered intravenously, commonly via the lateral tail vein of the mice.[27] The significant immunodeficiency of NSG mice allows engrafted human cells to survive, multiply, and partially reconstitute elements of the human immune system within the mouse host. Post-xenotransplantation, human immune cells invade peripheral lymphoid organs, with functional human T cells identifiable within 1–2 weeks.[28] The PBMC model is ideally suited for brief immuno-oncology or infectious disease research that use fast T-cell kinetics without necessitating extended immune monitoring.[29]

CD34⁺ hematopoietic stem cell engraftment

Hematopoietic stem cells (HSCs) are multipotent, immature cells that possess the ability for self-renewal and differentiation into all blood cell lineages, encompassing erythrocytes, leukocytes, and thrombocytes.[30] The expression of the surface glycoprotein CD34 is a defining property of early HSCs and progenitor cells, serving as a crucial marker for their identification and isolation. CD34 facilitates the selective enrichment of these cells from sources including bone marrow, umbilical cord blood, or mobilized peripheral blood (Fig. 3), hence aiding their application in transplantation, regenerative medicine, and the generation of humanized mice models.[31] During the engraftment of CD34⁺ hematopoietic stem cells (HSC), human CD34-positive stem and progenitor cells are transplanted into a recipient, typically an immunodeficient host such as NSG mice. These cells migrate to the bone marrow, establish residence within hematopoietic niches, and differentiate into all principal blood and immune cell lineages.[32] In the context of mobilized peripheral blood, donors undergo pre-treatment with granulocyte colony-stimulating factor (G-CSF), a cytokine that promotes the release of hematopoietic stem cells (HSCs) from the bone marrow into peripheral circulation, thereby enabling their collection via apheresis.[33] Among these sources, umbilical cord blood is preferred for its accessibility, significant proliferative capacity, and reduced occurrence of graft-versus-host disease. Fetal liver-derived HSCs, however less prevalent due to ethical and logistical issues, have high engraftment efficiency and robust hematopoietic reconstitution.[34] This model recapitulates key aspects of human hematopoiesis and adaptive immunity, provid-

ing a strong foundation for exploring immunological development, autoimmune disease mechanisms, immunotherapy effectiveness, and host-pathogen interactions in settings that closely resemble physiology.[35]

Development of humanized NSG mice for SLE

PBMC engraftment protocols: acute SLE modelling via mature immune cell transfer

Peripheral blood mononuclear cells (PBMCs), comprising a diverse array of immunocompetent cells such as T lymphocytes, B lymphocytes, monocytes, and natural killer (NK) cells, are extracted from lupus patients experiencing active disease flares via Ficoll-Hypaque density gradient centrifugation.[36] This xenotransplantation model facilitates rapid immune cell reconstitution, generally occurring within 7 to 14 days following injection. Flow cytometric assessment of human leukocyte antigens (CD45+, CD3+, CD19+, HLA-DR+) in peripheral circulation and lymphoid tissues is utilized to confirm engraftment kinetics and lineage-specific reconstitution.[37] This model resembles acute lupus and facilitates the examination of early immunological irregularities, including skewed TCR repertoires, hyperactive CD4+ T cells, and atypical B cell activation.[38] Furthermore, human-specific proinflammatory cytokines (e.g., IFN-α, IL-6, TNF-α) and immunoglobulins (IgG, IgM, including anti-dsDNA autoantibodies) are identifiable in recipient serum, acting as surrogate biomarkers for disease progression.[39] This substantial T-cell proliferation is often accompanied by the emergence of xenogeneic Graft-versus-Host Disease (xeno-GVHD), a notable confounder in longitudinal investigations. Xeno-GVHD results from the alloreactive T-cell identification of murine major histocompatibility complex (MHC)-deficient tissues within 4-6 weeks, causing multisystem inflammatory disease; this timeframe is ideal for assessing the development of immunological dysregulation associated with SLE before the onset of GVHD.[40]

CD34+ hematopoietic stem cell (HSC) engraftment: chronic SLE and immune ontogeny

The transplantation of human $CD34^+$ hematopoietic stem and progenitor cells (HSPCs) into immunodeficient NSG mice has become an effective method for reconstituting a functional human immune system. This model provides a distinctive platform to investigate the chronic immunopathology of SLE and the development of human immune responses in vivo.[41] As previously mentioned, the pretreatment of donors with granulocyte colony-stimulating factor (G-CSF) is crucial for mobilizing hematopoietic stem cells (HSCs) into the peripheral circulation for effective collection.[42] Before HSC transplantation, recipient NSG mice undergo myeloablative conditioning usually through sublethal total body irradiation (100–250 cGy) or chemotherapeutic agents like busulfan to eliminate endogenous hematopoietic cells and create vacant niches in the bone marrow microenvironment, thus promoting successful engraftment of human stem cells.[43] Following engraftment, $CD34^+$ progenitors migrate to the mouse bone marrow and gradually develop into all principal hematopoietic lineages, encompassing lymphoid (T, B, NK cells) and myeloid (monocytes, dendritic cells, granulocytes) compartments.[44] This framework promotes the advancement of efficient hematopoiesis, immunoglobulin class switching, and the generation of antigen-specific immune responses. Unlike the PBMC-based paradigm, the engraftment kinetics are markedly prolonged, with complete immune reconstitution often requiring 8 to 12 weeks.[45] The danger of xeno-GVHD is significantly reduced due to the naivety of the newly produced immune cells and the lack of pre-primed alloreactive T-cell subsets.[46] This method is especially beneficial for modelling the chronic nature and systemic signs of SLE.[47] It facilitates longitudinal investigations of immunological development, encompassing B cell tolerance checkpoints, somatic hypermutation, class-switch recombination, and the manufacture of high-affinity autoreactive antibodies.[48] When hematopoietic stem cells (HSCs) are obtained from lupus patients or individuals with established predisposing genotypes (e.g., IRF5, STAT4, PTPN22 variants), the resulting human immune system (HIS) mice display patient-specific immune signatures, including modified interferon signaling pathways, plasma blast hyperplasia, and deficiencies in regulatory T cells (Tregs).[49,50] The lack of GVHD facilitates the long-term observation of autoimmune development, therapeutic intervention, and relapse.[51]

Pristane-induced lupus in humanized NSG mice: a dual-hit model of autoimmunity

Pristane (2,6,10,14-tetramethylpentadecane), an environmentally significant hydrocarbon oil, serves as a strong lupus-inducing drug in mouse models by eliciting type I interferon responses through the activation of plasmacytoid dendritic cells (pDCs) and Toll-like receptor 7 (TLR7) signaling.[52] When injected intraperitoneally to humanized NSG mice, namely those reconstituted with CD34+ HSCs, pristane functions as an immunological adjuvant that enhances the autoimmune phenotype by provoking abnormal activation of human immune elements.[53] This combinatorial system simulates gene-environment interactions crucial to SLE pathogenesis, offering a precise platform to assess environmental triggers of illness onset and exacerbation. It amplifies the histological and serological characteristics of lupus, encompassing glomerulonephritis, vasculitis, and circulating immune complexes enriched with anti-RNP and anti-Sm antibodies.[54] Moreover, the pristane model highlights the synthesis of human IFN-α

and BAFF (B-cell activating factor), thereby enhancing B cell viability and autoantibody production.[55] Through the integration of genetic humanization and an environmental stimulus, the pristane-induced model provides a more authentic approach to examining the intricate etiology of lupus.[56] Table 1 presents a comparative analysis of various humanized mouse models employed in SLE research. Each row delineates a specific model type, encompassing the origin of human cells, techniques of engraftment, dynamics of immune reconstitution, and principal scientific applications.

Table 1. A comparison of humanized mouse models in SLE research

Parameter	PBMC engraftment model	CD34⁺ HSC engraftment model	Pristane-induced humanized model
Source of human cells	Peripheral blood from healthy donors or SLE patients	Cord blood, fetal liver, bone marrow, or mobilized peripheral blood	CD34⁺ HSCs or PBMCs
Engraftment site and route	Intravenous (tail vein)	Neonatal intrahepatic or adult intravenous	Intravenous (IV) + Intraperitoneal (Pristane)
Cell types introduced	Mature immune cells (T cells, B cells, NK cells, monocytes)	Hematopoietic stem/progenitor cells (CD34⁺)	Same as PBMC or CD34⁺, plus environmental modulation
Engraftment onset/time to reconstitution	Rapid (1–2 weeks post-injection)	Delayed (8–12 weeks post-conditioning)	Variable (depends on cell source)
Immune components reconstituted	Partial (T cells dominate)	Multilineage (T, B, NK, myeloid)	Multilineage + environmental trigger-induced activation
Immune reconstitution	Primarily T-cell reconstitution	Comprehensive immune system development	Immune response shaped by both human cells and pristane-induced inflammation
Lymphoid organ development	Limited (no thymopoiesis or germinal centers)	Robust (thymic T-cell development, splenic architecture)	Variable; may enhance inflammatory signaling pathways
GVHD risk	High (xeno-GVHD within 3–5 weeks)	Low to negligible	Moderate
Conditioning requirement	None	Required (irradiation or busulfan)	Required (same as PBMC/CD34⁺) + pristane injection
Duration of usefulness	Short-term (typically ≤6 weeks)	Long-term (months to over a year)	Intermediate to long-term
Suitability for autoimmunity models	Limited (T-cell biased, artificial)	High (endogenous repertoire, physiological development)	High (accelerated autoimmunity, gene-environment interactions)
Timeframe for study use	4–6 weeks	≥6 months	Variable depending on design
Best/key applications	T-cell cytotoxicity, early immune activation, xeno-GVHD studies	Vaccine response, chronic lupus phenotypes, personalized immune modeling	Accelerated lupus onset, IFN-I pathway, gene-environment interaction studies

Limitations and challenges of humanized NSG mice for SLE modeling

Incomplete immune system reconstitution and functional disparity

Although CD34⁺ HSC engraftment enables multilineage differentiation, the resulting immune system is still immature in both quantity and function.[57] Central and peripheral tolerance mechanisms are compromised by lymphoid tissue architecture, germinal center development, and thymic selection deficiencies. Human B cells in NSG mice generally have inadequate class-switch recombination and somatic hypermutation, reducing the model's ability to recreate SLE's high-affinity, pathogenic autoantibody profiles.[58] The lack of a completely functional human complement system makes modelling immune complex-mediated end-organ damage like glomerulonephritis more difficult.[59]

Xenogeneic graft-versus-host disease and temporal constraints

Despite its rapidity, PBMC-based humanization is hindered by the premature onset of xenogeneic graft-versus-host disease (xeno-GVHD) occurring within 4–6 weeks post-engraftment. This prevents long-term autoimmune progression and treatment efficacy studies.[60] The alloreactivity of mature human T cells to mice MHC-deficient tissues induces multisystem inflammation that resembles yet obscures lupus pathophysiology. Lupus-specific immune responses and generic xenogeneic reactivity are obscured by this immunological confounder.[61]

Lack of human lymphoid organogenesis and microenvironmental support

NSG mice lack organized secondary lymphoid organs such lymph nodes and functional Peyer's patches. This anatomical gap hinders antigen presentation, T-B cell collaboration, and lymphoid follicle growth. Therefore, autoreactive germinal center reactions and memory responses are greatly reduced.[62] As the murine stromal and cytokine environment is unsuitable for human hematopoiesis and immune cell function, transgenic or cytokine knock-in strains (e.g., NSG-SGM3, MISTRG) are needed to provide complexity and variety.[63]

Limited recapitulation of SLE heterogeneity

Despite better translational platforms than conventional mouse strains, humanized NSG mice still approximate complicated SLE. Gene and epigenetic variability in human SLE is difficult to recreate in single donor cell-engrafted mice.[64] These models cannot reproduce clinical SLE's polygenic vulnerability, stochastic disease flares, and sex-biased prevalence. This restricts research on patient-specific responses and sex hormone–driven immunomodulation, which are critical to SLE pathogenesis.[65]

Technical, ethical, and economic barriers

Humanized NSG mice development is difficult and resource-intensive, requiring quality human biological components, careful pathogen screening, and special-

ized animal facilities. Variations in engraftment, myeloablation, and donor cell survival can dramatically impact immunological outcomes.[66] Ethical problems of using human fetal tissues and regulatory monitoring of human-animal chimaeras further limit these models' acceptability and scalability.[67]

Recent advances in humanized NSG mice models for SLE research

Cytokine knock-in and transgenic NSG derivatives

Transgenic NSG substrains, such as NSG-SGM3, MISTRG, and NSG-IL15, exhibit enhanced hematopoietic production and functional maturity of humanized immune subsets. These strains have human cytokine knock-ins for SCF, GM-CSF, IL-3, M-CSF, and thrombopoietin to establish a xenocompatible cytokine milieu.[68] Myelopoiesis, dendritic cell formation, and monocyte/macrophage activity have improved, which are essential for accurately recreating SLE's myeloid-driven inflammation and interferon-driven immunopathology.[69]

HLA-transgenic NSG mice and autoreactivity modeling

Recent research has focused on developing HLA-restricted NSG mice models that express human MHC molecules (e.g., HLA-DR, HLA-A2). These models enable HLA-restricted positive and negative T cell selection during human hematopoiesis under self-MHC limitations.[70] This breakthrough is crucial for investigating the autoreactive T cell repertoire, antigen-specific tolerance breakdown, and pathogenic T follicular helper (Tfh) cells, a key component of lupus pathogenesis.[71] These platforms provide unmatched insights into autoimmunity's genetic and structural foundation, especially in HLA-associated disease susceptibility regions.[72]

Multi-donor and patient-derived xenografts for precision modeling

Recent studies have used pooled PBMC or $CD34^+$ HSC engraftments from various lupus patients to create a mosaic immune system that accounts for genetic and epigenetic variation.[73] Patient-derived xenograft (PDX) systems have also been modified for lupus modelling, notably using cells from high-risk polymorphism carriers (e.g., IRF5, STAT4, TNFAIP3, TYK2). These methods enable personalized lupus sub phenotype modelling and stratified therapy response evaluation.[74]

Human immune system organoids and hybridized murine platforms

The BLT (bone marrow-liver-thymus) paradigm shows how HSCs can be co-engrafted with human immunological organs such thymic tissue or mesenteric lymph node fragments.[75] These designs improve human immunological ontogeny, T cell education, and mouse tertiary lymphoid structure creation.[76] Hybrid animals with human liver or renal tissues can also examine organ-specific lupus symptoms including lupus nephritis and neuropsychiatric SLE in humanized inflammatory situations. Disease modelling and treatment trials become much more physiologically relevant using these methods.[77]

Human microbiota and environmental triggers in NSG mice models

Recent advances have included human microbiota transplantation (HMT) in NSG mice due to the involvement of microbial dysbiosis and environmental stresses in lupus flares. Mucosal immunity and systemic immune calibration are modulated by this host-compatible microbial ecology.[78] To replicate gene–environment interactions that cause lupus onset and exacerbation, UV radiation, TLR agonists, and pristane are being integrated into humanized systems. These combinatorial systems connect reductionist concepts to real-world autoimmune triggers.[79]

Advanced imaging and intravital immunophenotyping

Modern imaging methods like intravital two-photon microscopy, bioluminescence imaging, and PET are being used on humanized NSG mice models. During lupus development, these methods provide spatiotemporal visualization of immune cell trafficking, tissue infiltration, and microenvironmental interactions.[80,81] Combining high-dimensional flow cytometry and single-cell transcriptomics allows real-time cellular and molecular dynamics analysis at unprecedented granularity.[82] As shown in Fig. 4, a narrative illustration emphasizes recent advances in humanized NSG mouse models for SLE, particularly their role in improving immune system reconstitution and disease modeling.

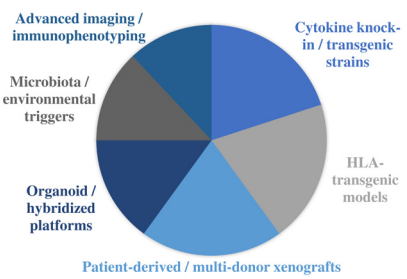

Fig. 4. Narrative illustration emphasizing recent advances in humanized NSG mice models for SLE

Future prospect

Recent advancements in biotechnology may significantly enhance the immunological accuracy and translational applicability of humanized NSG mice utilized in the research of SLE.[19] Engraftment with human thymic tissue can facilitate genuine thymopoiesis and central tolerance, whereas genetically modified strains like NSG-SGM3 and MISTRG, which express human cyto-

kines, are anticipated to enhance hematopoietic reconstitution and the efficacy of antigen-presenting cells.[83] Integrative multi-omics methodologies, encompassing genomes, epigenomics, and spatial transcriptomics, provide robust instruments to elucidate organ-specific immunological anomalies implicated in lupus pathogenesis.[84] Furthermore, the utilization of artificial intelligence and machine learning facilitates data-driven simulations and automated histopathological evaluations, enhancing model refinement and improving therapy predictions.[85] The development of individualized humanization protocols utilizing autologous hematopoietic cells or cells from other ethnic backgrounds facilitates the modelling of individual immunological profiles and genetic vulnerabilities.[86] To translate these innovations into well recognized preclinical platforms effectively, It is imperative to address ethical and regulatory components, Good Laboratory Practice (GLP) adherence, and improve scalability through automation and biofabrication.[87] Fig. 5 provides a narrative-based overview of the emerging applications and future prospects of humanized NSG mouse models in SLE research. These novel methodologies integrate experimental immunology with precision medicine, heralding a new era for lupus research.

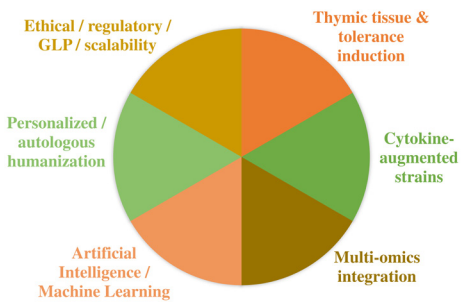

Fig. 5. Narrative illustration highlighting the future prospects of humanized NSG mice models in SLE research

Conclusion

The development of humanized NSG (NOD-scid IL-2Rγ^null) mice has significantly transformed the study environment for SLE, providing an exceptional platform for replicating human-specific immune dynamics with translational significance. These models facilitate the engraftment of patient-derived PBMCs or $CD34^+$ hematopoietic stem cells, offering mechanistic insights into autoimmunity that surpass the constraints of conventional murine systems. Despite significant obstacles, including poor immune development, xeno-GVHD, and inadequate lymphoid architecture, constant advances are enhancing model accuracy. Innovations like human cytokine knock-in strains, co-engraftment of thymic and organoid tissues, HLA-transgenic platforms, and integrative omics technologies synergistically enhance the functional and structural complexity of these models. The integration of AI-driven analytics and personalized engraftment procedures is enhancing precision modelling, facilitating individualized evaluations of pathogenesis and therapy effectiveness. With the progression towards standardization, ethical transparency, and scalable biomanufacturing, humanized NSG mice are set to become essential instruments in connecting laboratory testing with clinical application in lupus research. These advanced platforms clarify the complex foundations of SLE and outline a progressive approach for creating targeted, patient-focused immunotherapies.

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Author contributions

Conceptualization, P.C. and J.M.; Resources, J.M., R.G., P.S.; Data Curation, R.G. and P.S. Validation: P.C.; Original Draft Preparation, J.M. and R.G.; Writing – Review & Editing, J.M. and P.C.; Supervision, P.C.

Conflicts of interest

The authors assert that they have no conflicts of interest.

Data availability

Not applicable

Ethics approval

Not applicable

Use of AI and AI-assisted technologies in the writing process

AI-assisted tools such as ChatGPT, QuillBot, Turnitin, and Mendeley were used for conceptual guidance, language refinement, plagiarism detection, and reference management. The content was reviewed and verified by the author for accuracy.

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