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Article

ANA Serum in a Non-Human Primate (*Macaca fascicularis*) Model of Systemic Lupus Erythematosus Induced by Pristane

Jonny Jonny [1,2,3,*], Pepita Zenia [2], Sanindita Kusumastuti [2], Soetojo Wirjopranoto [1], Chairul Anwar Nidom [1,4,5,6,*], I Ketut Sudiana [1], Elisa Diah Pratiwi [4,5], Tiza Wuri Mawaddah [4,5], Astria Novitasari Nidom [1,5], Reviany Vibrianita Nidom [5], Setyarina Indrasari [5] and Irma Yurita Rosytania [5]

[1] Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya 60132, Indonesia
[2] Indonesia Army Cell Cure Center, Gatot Soebroto Central Army Hospital, Jakarta 10410, Indonesia
[3] Faculty of Military Medicine, Indonesia Defense University, Bogor 16810, Indonesia
[4] Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya 60115, Indonesia
[5] Department of Research and Development Laboratory, Professor Nidom Foundation, Surabaya 60236, Indonesia
[6] Global Biosains Teknologi, Malang 65145, Indonesia
[*] Correspondence: jonny-2023@fk.unair.ac.id (J.J.); nidomca@pnfinstitute.org (C.A.N.)

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Abstract: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease characterized by the production of antinuclear antibodies (ANA). While murine models are widely used for lupus research, their translational value is limited by physiological differences. *Macaca fascicularis*, a non-human primate, offers a closer model due to its genetic and immunological similarities to humans. Pristane (2,6,10,14-tetramethylpentadecane), a hydrocarbon oil, can induce lupus-like manifestations, including ANA production, but evidence in *Macaca fascicularis* remains scarce. This study assessed ANA titers following pristane induction in seven macaques, with one serving as a negative control. A single intraperitoneal dose of pristane (5 mL/kg) was administered, and ANA titers were evaluated biweekly using ELISA. ANA seropositivity (titer ≥1:80) was first detected at week 4, increasing to four macaques by week 8 and persisting at four positives in week 10. The duration of ANA positivity varied across individuals, ranging from a single week to continuous six-week responses, with one showing a biphasic pattern. The control macaque remained negative throughout. Clinical observations included alopecia, weight loss, lymphopenia, hematuria, and proteinuria in ANA-positive animals. In conclusion, pristane induced measurable autoimmunity in *Macaca fascicularis*, supporting its utility as a translational model for lupus research and preclinical testing of therapeutic interventions.

Keywords: *Macaca fascicularis*; Antinuclear Antibody; Systemic Lupus Erythematosus; Non-Human Primate Model; Pristane; Autoimmunity; Lupus

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by the persistent production of antinuclear antibodies (ANA) and immune-mediated damage affecting a broad range of organs [1]. Globally, the prevalence of SLE continues to rise, with an estimated prevalence of 43.7 per 100,000 population, although marked geographic and ethnic variability has been documented across different regions [2,3]. In

low- and middle-income countries, reported prevalence rates range widely from 3.2 to 159 per 100,000, reflecting differences in genetic susceptibility and environmental exposure [2]. In Indonesia, it is estimated that over 1.25 million people are affected [3,4]. This variability, coupled with disparities in disease management, underscores the need for more biologically relevant and representative disease models to improve understanding and treatment strategies [5].

Murine models have long served as the cornerstone of experimental SLE research; however, their translational applicability remains limited due to immunological, genetic, and physiological differences from humans [6]. Although these models have been valuable for dissecting disease mechanisms and testing early-phase interventions, discrepancies in the immune system often restrict the extent to which findings can be extrapolated to human disease [7]. In contrast, non-human primates (NHP), particularly *Macaca fascicularis*, offer a substantially closer genetic and immunological match to humans, including similar lymphocyte subset profiles (CD3, CD4, CD8, CD16, CD20) [8,9]. These similarities enhance the relevance of non-human-primate-based research, making them a valuable platform for studying immune dysregulation and disease pathogenesis underlying SLE [8].

Pristane (2,6,10,14-tetramethylpentadecane) is a hydrocarbon oil widely recognized for its capacity to induce lupus-like autoimmunity in experimental models [10]. Following intraperitoneal administration, pristane integrates into the phospholipid bilayer of resident peritoneal cells, triggering cellular stress response, membrane destabilization, and apoptosis. This causes a release of intracellular and nuclear components, giving a sustained source of autoantigens [11]. Subsequently, these antigens are presented to autoreactive T and B cells, driving autoantibody production and immune complex formation [12]. Pristane also activates plasmacytoid dendritic cells to produce high levels of type I interferons (IFN-α and IFN-β), key mediators in lupus pathogenesis [13,14]. While its effects are well established in mice [15], little is known about its ability to induce SLE in non-human primates [16].

This study aimed to evaluate the capacity of pristane to induce ANA seropositivity and lupus-like clinical manifestations in *Macaca fascicularis* following a single intraperitoneal injection. By characterizing both serological and phenotypic outcomes, we sought to determine the optimal dosage use to elicit immunological signatures that parallel those observed in human SLE, thereby assessing its potential as a translational non-human primate model for future pathogenesis and therapeutic research, particularly in SLE. Given the novelty of the pristane-induced SLE modelling in non-human primates, this work was designed as a pilot exploratory study to generate preliminary observations that may guide to a larger yet powered investigations. A graphical abstract summarizing the study workflow is provided in **Appendix A**, **Figure A1**.

2. Materials and Methods

2.1. Ethical Approval

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Professor Nidom Foundation with approval number 021224/IACUC/VII/2024. All procedures adhered to established national and institutional guidelines for the humane care and ethical use of laboratory animals, ensuring continuous oversight and compliance throughout the study period.

2.2. Animals and Study Design

This study was designed as a pilot investigation aimed at assessing the feasibility of inducing an autoimmune response through pristane administration in a non-human primate model. A total of seven female *Macaca fascicularis,* aged 24–36 months and weighing 3–4 kg, were included in this study. In light of the study's preliminary nature and ethical considerations regarding primate use, only a single macaque was assigned as a negative control. This negative control was intended to confirm baseline antinuclear antibody (ANA) levels and monitor general clinical stability, thereby ensuring assay specificity and allowing initial differentiation from pristane-related changes. The control animal was not intended for formal statistical comparison, but rather to support biological interpretation within an exploratory framework. All animals were maintained under standardized housing conditions with controlled temperature, humidity, and dark/light cycle, and were provided with ad libitum access to food and water to minimize environmental confounders and support animal welfare.

2.3. Pristane Administration

Pristane (2,6,10,14-tetramethylpentadecane; purity ≥ 99%) was administered as a single intraperitoneal (IP) injection at a dose of 5 mL/kg body weight (total volume: 15 mL) to induce lupus-like autoimmunity. The dose selection was based on prior murine studies demonstrating robust autoantibody induction with 0.5 mL IP per 18–20 g mouse, scaled for primate body weight while considering pharmacological safety margins. Animals were monitored daily for general health, behavior, and potential local or systemic adverse effects, including changes in feeding behavior, grooming, and mobility, throughout the 13-week observation period.

2.4. Serum Collection and ANA Measurement

Blood samples (2–3 mL) were collected from the peripheral femoral vein of each macaque every two weeks, starting from baseline (week 0). Serum was subsequently separated and stored under appropriate conditions until analysis. ANA concentrations were quantified using a commercially available Competitive ELISA Kit for Anti-Nuclear Antibody (ANA) in Primates (FineTest, China, Cat. No. EH4161), following the manufacturer's instructions. The assay is based on a competitive binding principle in which ANA from the sample and horseradish peroxidase–conjugated ANA-binding antibody (ANAb-HRP) compete for binding sites on wells pre-coated with nuclear antigen. Briefly, samples and assay buffer were incubated with ANAb-HRP in the coated wells for one hour at room temperature. After incubation, wells were emptied and washed to remove unbound material. Substrate solution was then added, producing a blue color through enzymatic reaction, which turned yellow upon the addition of stop solution. Optical density (OD) was measured at 450 nm using a microplate reader. The color intensity was inversely proportional to ANA concentration, and final concentrations were interpolated from a standard curve generated using the kit-provided standards. In accordance with the kit criteria, a titer of ≥ 1:80 was classified as seropositive.

2.5. Data Analysis

ANA seropositivity patterns were summarized descriptively by documenting the number of macaques exhibiting positive titers, along with the onset week, peak response, and duration of positivity. These observations were visualized using graphs and schematic figures generated with Biorender.com to facilitate clearer interpretation of temporal changes. No formal statistical hypothesis testing was performed due to the small sample size and exploratory nature of the study.

3. Results

3.1. ANA Seropositivity

Following a single intraperitoneal administration of pristane (5 mL/kg body weight), weekly serum analyses were performed to assess ANA titers by competitive ELISA. The temporal progression of ANA seroconversion across the 13-week observation period of the study is summarized in **Figure 1**, illustrating the number of macaques exhibiting ANA positivity at each weekly assessment. As shown in **Figure 1**, ANA seroconversion was detected early in three macaques at week 4, reaching a maximum of five ANA-positive macaques between weeks 6 and 10, before declining toward week 12 and stabilizing thereafter.

To be precise, ANA seropositivity emerged early in the treatment group, with three macaques becoming positive at week 4. The number of ANA-positive animals increased to four at week 5 and peaked at five macaques during weeks 6, 8, 9, and 10. Subsequently, the number of positive animals decreased to four at week 11 and three at week 12, before slightly rebounding to four at week 13. The negative control animal consistently remained ANA-negative throughout the study. **Supplementary Materials Table S1** provides individual seroconversion patterns.

3.2. Duration and Pattern of Seropositivity

Considerable inter-individual variation was observed in the duration and pattern of ANA seropositivity, reflecting heterogeneous susceptibility and immune dynamics among macaques. One macaque demonstrated continuous ANA positivity for seven consecutive weeks, beginning at week 7 until the end of the observation period of the study. Three other macaques became ANA-positive as early as week 4, with two animals remaining positive from week 4 onward, while one macaque showed a biphasic pattern with positivity at weeks 4–11, reverting to negative at week

12, and becoming positive again at week 13. Another macaque also displayed a biphasic seropositivity profile, being positive at weeks 4–6 and 9–13. One animal exhibited delayed seroconversion, with ANA positivity detected just at week 13. These diverse temporal patterns underscore significant inter-individual variability in immune responsiveness to pristane.

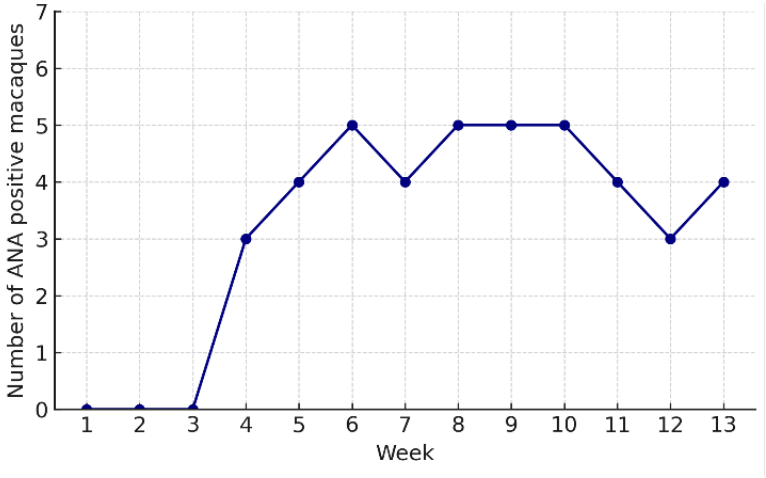

Figure 1. ANA seropositivity dynamics across all macaques during the study period.

3.3. Clinical Observations

Clinical changes observed in this study were minimal. As shown in **Figure 2**, alopecia was documented in one macaque and persisted until the end of the observation period, with its onset temporally coinciding with elevated ANA titers. In addition, some animals exhibited weight loss following lupus induction. Laboratory analyses revealed decreased lymphocyte counts, accompanied by hematuria and proteinuria, indicating renal involvement. These findings were exclusively observed in pristane-treated macaques, with the negative control remaining free of the clinical and laboratory alterations described above. No mortality occurred during the study period.

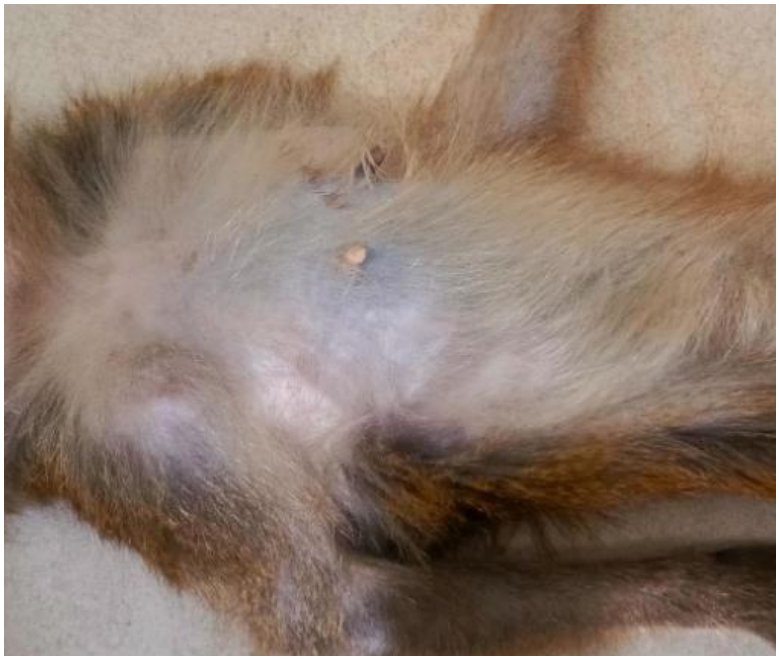

Figure 2. Clinical manifestation of alopecia in an ANA-positive *Macaca fascicularis* at week 8 post-pristane induction.

4. Discussion

The hypothesized immunopathogenic mechanism by which pristane induces autoimmunity, leading to ANA production and lupus-like disease in *Macaca fascicularis*, is illustrated in **Figure 3**. Briefly, pristane acts as a potent inflammatory hydrocarbon that triggers persistent inflammation, recruitment of Ly6C$^+$ monocytes, induction of type I interferons, and release of nuclear antigens [17–19]. The interaction between these antigens and innate immune pathways promotes breakage of immune tolerance and drives autoantibody production [20]. This mechanism, while well-described in murine systems, remains largely hypothetical in non-human primates and requires targeted validation.

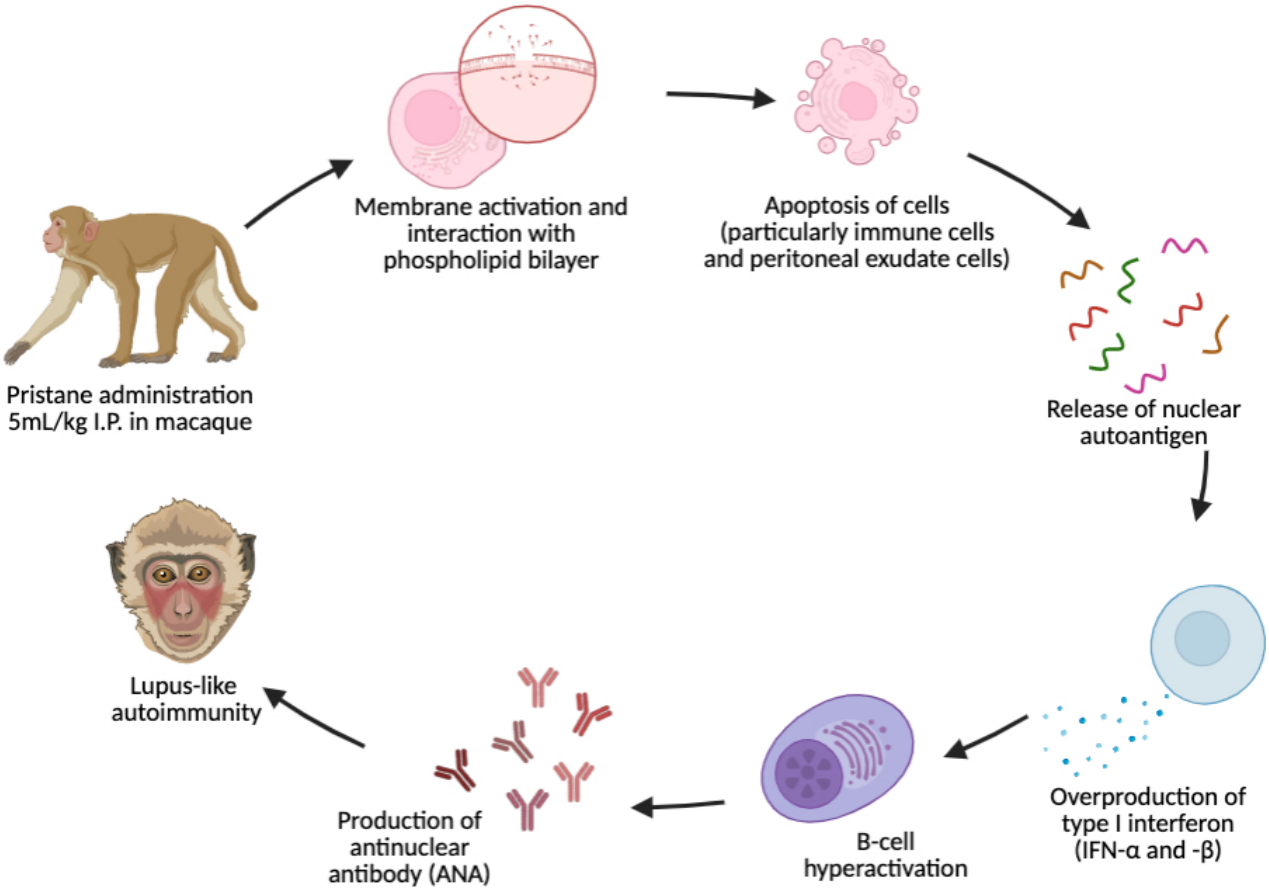

Figure 3. Proposed hypothetical mechanism of pristane-induced autoimmunity. Created in BioRender.
Source: Jonny, J. (2025) https://BioRender.com/0rnm1i2.

The study by Wang et al. [21], used experimental animals of long-tailed monkeys *Macaca fascicularis*, weighing 3–4 kg, injected with pristane via intraperitoneal at a dose of 3.5mL/kg on day 1 and day 120. In the study by Wang et al., the cynomolgus monkeys showed no clinical changes or autoantibodies at week 17 after the first pristane injection. Autoantibodies were detected at week 27, and clinical changes were observed from week 28. Clinical manifestations showed symptoms of systemic lupus that conformed to the criteria for diagnosis of lupus and included not only skin lesions (malar rash and alopecia) but also multi-organ involvement. The time course of clinical onset was consistent with autoantibody formation (weeks 27 to 35), renal function changes (urinalysis changes and renal perfusion imaging at week 30), and hematologic changes (week 32) (**Figure 4**).

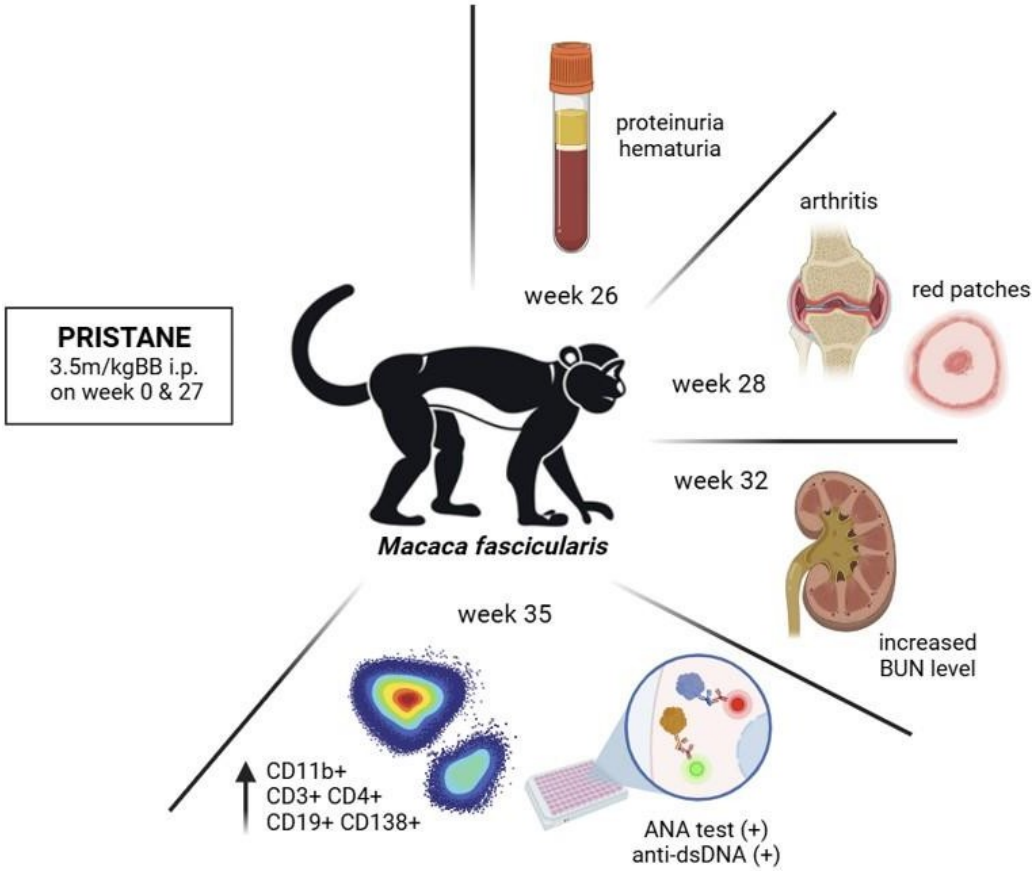

Figure 4. Pathological development in PRISTANE-induced *Macaca fascicularis* as described in the study by Wang et al. [21].

In contrast to the previous study, the present study demonstrated that a single intraperitoneal injection of pristane at a higher dose (5 mL/kg body weight) induced measurable autoimmune responses in *Macaca fascicularis*, as evidenced by the appearance and fluctuation of ANA titers over a 13-week period. ANA seropositivity was detected as early as week 4 post-induction, with peak prevalence involving five macaques between weeks 6 and 10, followed by a gradual decline to three positive animals at week 12 and a slight rebound to four at week 13. These findings indicate that pristane can trigger lupus-like humoral autoimmunity in a non-human primate model, although the response was not sustained in all subjects.

One of the most striking findings was the marked heterogeneity in ANA seroconversion patterns. The macaques exhibited continuous positivity, biphasic response, and even delayed ANA seropositivity. This variability may not only be an incidental observation but also raises several mechanistic questions regarding the individualized immune responses to pristane exposure. Inter-individual variability suggests that host factors, including genetic background and baseline immune state, likely modulate pristane sensitivity [22,23]. This mechanism mirrors human SLE, which is notoriously heterogeneous in clinical course and its respective autoantibody profile [24]. Thus, the macaques used in this study captured not only the immunological directionality of SLE but also its inherent biological heterogeneity

Moreover, the biphasic ANA patterns observed in two macaques closely resemble the flare-remission dynamics of human SLE, indicating an intermittent shift between immune activation and partial regulatory control [25,26]. This shifting activation of innate immune pathway, particularly plasmacytoid dendritic cells activation, drives type I interferon response, combined with antigen release from apoptosis in an episodic manner, can create oscillatory immune responses [27–29]. This mechanism might underlie the biphasic pattern observed in this study. The delayed seroconversion in one macaque raises the possibility of individual kinetic lag in peritoneal inflammation and antigen release. This might parallel the subclinical autoimmunity phase in human, where autoantibody appears

gradually and variably before symptoms emerge [30,31]. These temporal variations underscore the importance of longitudinal follow-up in primate lupus models to capture transient or evolving immunologic phenotypes. This also strengthens the argument that macaques can serve as a refined and clinically relevant model for SLE, capturing the subtleties and heterogeneity that murine models might miss [7].

The use of female macaques should also be considered when interpreting immune response patterns, particularly in SLE settings. The decision to choose females as the only gender used in this study aligns with well-established female predominance in SLE across species, where females exhibit higher susceptibility to SLE due to hormonal and genetic influences that promote a Th2-skewed immune profile, which is one of the key components of SLE pathogenesis [32–34]. Selecting females in this study therefore reduced sex-related biological variability and aligned with established SLE-induction protocols [35, 36]. Nevertheless, future studies incorporating male macaques might be important to delineate sex-based immunological differences and enhance the generalizability of the model. This might be important since a model that incorporates both sexes would be valuable for translational research aiming to generate a novel therapeutic strategy across diverse patient populations.

Clinical manifestations in this model were minimal, with alopecia observed in only one ANA-positive macaque being the most notable finding. This contrasts sharply with murine pristane-induced lupus models, in which pristane administration is associated with a broader spectrum of lupus-like symptoms, including proteinuria, immune complex deposition, and systemic inflammation [14,37]. The clinical manifestations observed were not terminated or therapeutically modulated, as the study design intentionally avoided the use of immunosuppressive agents in order to characterize the natural trajectory of the pristane-induced autoimmunity. Throughout the 13-week observation window, these manifestations remained detectable without evidence of spontaneous remission. Notably, the alopecia documented in one macaque also persisted until study completion. This stability of symptoms is consistent with prior reports in rodent and primate models, which clarified the pristane mechanism to induce autoimmunity [21,22]. Such mechanisms typically sustain disease activity rather than self-resolution, suggesting that the 13-week study period may capture an early-to-intermediate disease phase rather than the full arc of SLE pathology. Whether these abnormalities would eventually regress, remain stable, or progress to more advanced disease cannot be determined from the current study. Also, the limited clinical signs in the present study may be attributable to the single-dose regimen and relatively short observation period. Longer-term follow-up is warranted to delineate chronicity, potential flare-remission dynamics, and the durability of the immunological alterations. Future studies incorporating extended monitoring or therapeutic interventions may help clarify the reversibility of specific manifestations and enhance the translational relevance of this primate SLE model.

The temporal association between alopecia and elevated ANA titers, albeit in a single subject, is noteworthy. Dermatologic manifestations, including hair loss, are common in SLE patients and are often correlated with active disease and elevated autoantibody levels [38]. Although alopecia alone is insufficient to diagnose cutaneous lupus, its temporal alignment with rising ANA titers suggests a localized immune activation coinciding with systemic autoantibody response. Alopecia can occur independently in association with elevated ANA titers, particularly when epithelial barrier disruption enhances exposure of nuclear antigens to the immune system [39,40]. However, this association remains preliminary and cannot be interpreted as evidence of cutaneous lupus without histological confirmation, highlighting an important gap in the present dataset.

A key difference between this study and the previous study is the dosing regimen. In contrast to Wang et al., who employed a two-dose regimen of 3.5 mL/kg body weight administered 120 days apart and reported the onset of autoantibody production only after week 27, the present study demonstrated earlier seroconversion following a single higher dose of 5 mL/kg body weight. The earlier ANA response observed in our macaques may reflect a more rapid initial immune activation triggered by the larger dose of pristane. Pharmacologically, pristane is a hydrophobic hydrocarbon that induces local inflammation, apoptosis, and type I interferon production in a dose-dependent manner. A higher single exposure may therefore accelerate the release of nuclear antigens and innate immune activation without necessarily maintaining prolonged stimulation.

It should be noted that this study did not directly assess the apoptosis marker or type I interferon level, and thus, the proposed mechanism remains hypothetical, inferred from murine models and human immunopathology [41, 42]. The absence of severe clinical symptoms in our study suggests that while the dose was sufficient to trigger humoral autoimmunity, it was also well tolerated without inducing acute systemic toxicity, supporting its use in this exploratory context. Nevertheless, future studies incorporating immunophenotyping, interferon mea-

surements, or apoptosis assays would be essential to validate the mechanistic pathway in non-human primate SLE models research and to determine whether the early autoantibody response may persist ot evolve into multi-organ involvement with longer follow-up.

From a translational perspective, *Macaca fascicularis* offers distinct advantages over rodent models due to its genetic, immunological, and physiological similarities to humans [7]. Demonstrating that pristane reliably induces ANA production and systemic alterations in this species provides an important foundation that immune perturbations triggered by hydrocarbon exposure can reproduce early lupus-like immunopathology in a primate host. This supports the relevance of either danger-signal pathways, type I interferon production, and defective apoptotic clearance as conserved mechanisms across species. However, the present findings represent only an initial step. Translational value will depend on deeper mechanistic characterization, including longitudinal immunophenotyping of circulating immune subsets, interrogation of interferon signatures, and renal or hepatic histopathology to confirm subclinical organ involvement. Such analyses would help determine whether the model recapitulates not only serologic and hematologic abnormalities but also the cellular and molecular hallmarks that define human SLE heterogeneity.

Moreover, the use of a single negative control also limits the comparative inference. Future research should strategically expand control groups, incorporate sham-treated animals, and implement a longer follow-up period to evaluate whether pristane-induced abnormalities progress, stabilize, or remit spontaneously. These refinements are essential to assess model durability, flare dynamics, and therapeutic responsiveness. Despite its limitations, this exploratory study provides a crucial foundation for developing a primate lupus platform that can ultimately support preclinical testing of immunomodulatory therapies, biomarker discovery, and mechanistic dissection of lupus pathogenesis in a physiologically relevant system.

5. Conclusions

This study demonstrates that *Macaca fascicularis* can mount a measurable autoimmune response following pristane induction, as evidenced by the development of ANA seropositivity. The temporal relationship between pristane administration and elevated ANA titers supports the use of this non-human primate species as a potential translational model for investigating the immunopathogenesis of SLE. By applying a pristane-based induction protocol previously validated in rodent models, this research provides an important step toward establishing a primate model that more closely mirrors human immune responses. The findings address a critical gap in lupus research, where physiologically relevant models for preclinical evaluation are limited.

However, the transient nature of ANA expression observed in this study suggests the need for further refinement of the induction protocol. Future studies should investigate repeated or higher doses of pristane, alternative delivery routes, or the incorporation of immune modulators to enhance disease persistence and model reproducibility. Expanding immunophenotyping and histopathological analyses may also help elucidate the underlying mechanisms driving disease development in this model. These findings lay the foundation for developing *Macaca fascicularis* as a robust and translationally relevant non-human primate model for lupus, with the potential to significantly advance therapeutic and mechanistic research in autoimmune disease.

Supplementary Materials

The supporting information can be downloaded at https://ojs.ukscip.com/files/TI-1672-Supplementary-Materials-Table-S1.docx.

Author Contributions

Conceptualization, J.J., S.W., C.A.N., and I.K.S.; methodology, J.J., C.A.N., S.I., and I.Y.R.; software, E.D.P., T.W.M., A.N.N., and S.K.; validation, S.W., C.A.N., I.K.S., and P.Z.; formal analysis, E.D.P., T.W.M., and P.Z.; investigation, E.D.P., T.W.M., A.N.N., R.V.N.; resources, J.J.; data curation, E.D.P., T.W.M., A.N.N., S.I., and P.Z.; writing—original draft preparation, J.J. and P.Z.; writing—review and editing, J.J., P.Z., and S.K.; visualization, P.Z. and S.K.; supervision, J.J., S.W., C.A.N., I.K.S., R.V.N., S.I., and I.Y.R.; project administration, J.J., C.A.N., R.V.N., and S.I.; funding acquisition, J.J. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

All procedures involving animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the Professor Nidom Foundation (IACUC-PNF), in accordance with national and institutional guidelines for the care and use of laboratory animals. The approved protocol is titled "Effects and Regulatory Mechanisms of the Immune System in an Animal Model of Systemic Lupus Erythematosus (SLE) Following Administration of Monocyte-Derived Dendritic Cells (MODCs)" (Ref. No. 021224/IACUC/VII/2024). This study on pristane-induced lupus in *Macaca fascicularis* was conducted under the umbrella of that protocol, which covers multiple approaches to establish and evaluate SLE models, including chemical induction and cell-based interventions. The protocol approval is valid from December 5, 2024, to December 5, 2026, with annual reviews scheduled and ethical oversight maintained throughout the study duration.

Informed Consent Statement

Not applicable. This study did not involve human participants and therefore no informed consent was required.

Data Availability Statement

Data sharing is not applicable to this article as no new datasets were generated or analyzed during the study.

Conflicts of Interest

The authors declare no conflict of interest.

Appendix A

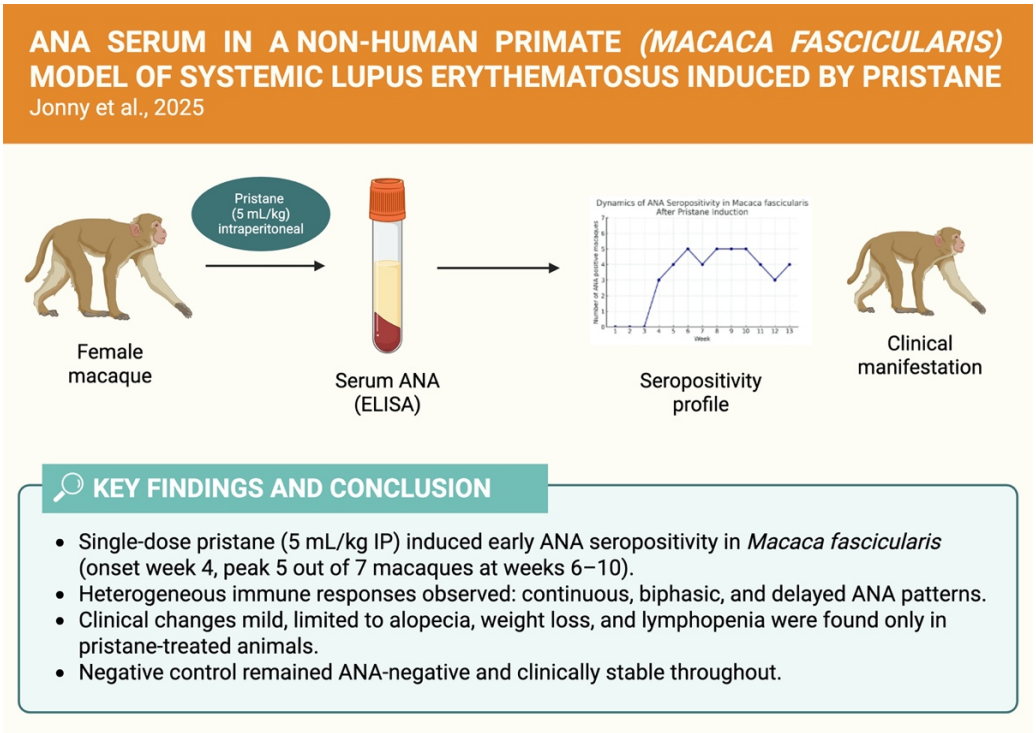

Figure A1. Graphical abstract. Created in BioRender.

Source: Jonny, J. (2025) https://BioRender.com/niqsinx.

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