ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

A Brief Overview on Molecular Aspects of Models for Induction of RA for Target Validation

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Publication Date: 2025/09/02

Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial inflammation, joint destruction, and systemic complications. Understanding its molecular and immunological mechanisms requires robust experimental models that replicate key features of the disease. Various in vivo models, including collagen-induced arthritis (CIA), collagen antibody-induced arthritis (CAIA), antigen-induced arthritis (AIA), SKG mouse model, and pristane-induced arthritis (PIA), provide insights into different aspects of RA pathogenesis. These models mimic processes such as autoantibody generation, T and B cell activation, cytokine-mediated inflammation, pannus formation, and cartilage/bone erosion. While each model has unique advantages such as CIA for adaptive immunity studies, CAIA for innate immune pathways, AIA for localized responses, SKG for genetic predisposition, and PIA for systemic chronicity none fully replicates human RA. Their combined application, along with molecular analyses, allows researchers to dissect immune mechanisms and evaluate novel therapeutic strategies, including biologics, small molecules, and targeted immunotherapies. Ethical considerations, guided by the 3Rs principle (replacement, reduction, refinement), remain integral to animal experimentation. Collectively, these models remain indispensable tools for translational rheumatology and preclinical drug development aimed at improving RA management.

Keywords: *Rheumatoid Arthritis, Collagen-Induced Arthritis, Collagen Antibody-Induced Arthritis, Antigen-Induced Arthritis, SKG Model, Pristane-Induced Arthritis, Autoimmune Disease, Animal Models, Immunopathogenesis, Therapeutic Validation.*

How to Cite: A. Abarnadevika; N. Aravindhan; R. B. Miruthunguptha; Dr. G. Ariharasivakumar (2025) A Brief Overview on Molecular Aspects of Models for Induction of Ra for Target Validation. *International Journal of Innovative Science and Research Technology*, 10(8), 1943-1956. https://doi.org/10.38124/ijisrt/25aug1260

I. INTRODUCTION

A chronic autoimmune condition called rheumatoid arthritis (RA) is characterized by persistent joint inflammation, joint damage, and the presence of specific autoantibodies such rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) [1,2]. About 0.5% to 1% of persons worldwide are afflicted, with women and people between the ages of 40 and 60 being more frequently affected [3]. In addition to lowering quality of life because of pain and joint dysfunction, RA also raises mortality, mostly as a result of related illnesses such infections and cardiovascular disease.[4]. A complex array of environmental and genetic variables contributes to the development of RA. Specific HLA-DRB1 alleles (also referred to as the common epitope) are important genetic risk factors, and environmental variables including smoking and intestinal microbial imbalances can also accelerate the onset of disease [5,6]. When these factors come together, immunological tolerance is compromised, self-reactive T and B cells are activated, aberrant antigen presentation is triggered, and inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17 are produced in greater quantities [7]. This series of immunological responses leads to the development of new blood vessels (angiogenesis), thickening of the synovial lining (synovial hyperplasia), and the growth of invasive tissue known as pannus, which ultimately causes osteoclast activity and enzymes to break down cartilage and bone [8,9]. Animal models that mimic the main characteristics of RA are used extensively by researchers to investigate how the disease progresses and to test possible treatments. The ability of artificially induced in vivo models to replicate important features of RA, such as chronic inflammation, autoimmunity, and joint-specific pathology, makes them popular. Examples of these models include collagen-induced arthritis (CIA), adjuvant-induced arthritis (AIA), and proteoglycan-induced arthritis (PGIA). [10–12]. In these animals, autoantigens or inflammatory chemicals are usually introduced to induce arthritis, frequently in conjunction with adjuvants that strengthen immune responses. Scientists can investigate the role of the innate and adaptive immune systems in RA thanks to this carefully regulated environment. For example, the CIA model has been crucial in revealing how regulatory T cells,

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

Th17 cells, and other cytokine pathways contribute to joint inflammation. [13]

However, a number of variables, including the technique used to generate arthritis, the species and strain of the animal, and the particular emphasis of the study, affect how well these models mimic human RA. The entire picture of human disease cannot be captured by a single model. Each has drawbacks, such as variations in immune system performance, the course of disease, and treatment response in comparison to humans. [14,15]. This study provides a thorough, critical analysis of in vivo artificially produced RA models, emphasizing: The methods employed to cause disease, The main immunological systems at play, a comparison of their advantages and disadvantages as well as their applicability to preclinical drug development. The objective is to advance translational rheumatology research by bringing together the most recent knowledge on various experimental models to assist researchers in selecting the best systems for their work.

➢ *Importance of in-Vivo Models in Rheumatoid Arthritis (RA) Research:*

The chronic autoimmune disease known as rheumatoid arthritis (RA) is characterized by extensive inflammation, thickening of the synovial membrane, and progressive joint degradation. It develops as a result of a complicated interaction between immune system malfunction, environmental factors, and genetic predisposition [16]. In vivo animal models have become crucial for researching RA and evaluating possible treatments before they are used in clinics because direct human experimentation is restricted by ethical concerns. The capacity of these models to mimic the pathological and clinical characteristics of human RA is one of the main factors contributing to their high value. Commonly used models closely resemble important features of the disease, including adjuvant-induced arthritis (AIA), human TNF-α transgenic mice, and collagen-induced arthritis (CIA) in mice and rats. These include bone and cartilage deterioration, pannus development, and joint inflammation [17, 18]. Researchers can study the onset and progression of the disease in a controlled setting using animal models. In vivo systems are crucial for understanding the immunological mechanisms underlying RA, as well as for simulating disease symptoms. They provide information on how B cells aid in the creation of autoantibodies (such as RF and ACPAs), how T cells are stimulated, and how pro-inflammatory cytokines [19,20]. Additionally, these models are essential for testing novel therapies. Any medication must undergo extensive testing in animal trials to determine its safety, effectiveness, and how it acts in the body before being attempted on humans. This involves trying a variety of treatments, including small molecules, traditional disease-modifying antirheumatic medications (DMARDs), biologics including TNF inhibitors, and JAK inhibitors. [21,22]. Lastly, genetically altered models—such as transgenic or knockout mice—have developed into effective instruments for investigating the function of particular genes and signalling networks in RA. These models pave the way for the identification of novel treatment targets and assist in identifying the molecular causes of immune dysfunction [23].

II. DIFFERENT MODELS

A. Collagen-Induced Arthritis (CIA):

The Collagen-Induced Arthritis (CIA) model is most commonly performed in DBA/1 mice, which are particularly susceptible to the disease, though with appropriate protocol adjustments, it can also be adapted for use in C57BL/6 mice and Lewis rats. The model is induced by injecting type II collagen (CII) emulsified in Freund's adjuvant—complete Freund's adjuvant (CFA) for the initial priming and incomplete Freund's adjuvant (IFA) for the booster injection. The main goal of this model is to simulate an autoimmune response in which the immune system mistakenly targets collagen in the joints, leading to cartilage inflammation and destruction. Clinical signs of arthritis typically begin to appear around day 21 after the first immunization, and the disease course usually lasts about 4 to 6 weeks, often resolving spontaneously in many strains. The CIA model is widely used in research to study autoantibody generation, T and B cell activation, and the roles of cytokines and chemokines in joint inflammation. It also serves as a valuable tool for preclinical testing of new anti-inflammatory or immunomodulatory therapies.[24], [25]

➢ *Experimental Protocol (Example: DBA/1 Mouse)*

The Collagen-Induced Arthritis (CIA) protocol typically begins with a primary immunization on Day 0, where 100 µL of type II collagen (CII) emulsified in complete Freund's adjuvant (CFA) is administered via subcutaneous injection, usually at the base of the tail or along the back. The collagen, which is commonly derived from chicken or bovine sources, is dissolved in 0.05 M acetic acid and mixed in a 1:1 ratio with CFA to enhance the immune response. On Day 21, a booster injection of 100 µL of CII combined with incomplete Freund's adjuvant (IFA) is given at a different subcutaneous site. This second immunization serves to re-stimulate the immune system and typically coincides with the onset of clinical arthritis symptoms, initiating joint inflammation in the experimental model.[24], [26]

➢ *Disease Progression: Day-by-Day Breakdown [24], [27], [28]*

Table 1 Immunological Timeline of Experimental Autoimmune Arthritis

Day	Phase	Key Immunological Events	Primary Cells Involved	Cytokines / Markers
0–3	Sensitization	Antigen-presenting cells initiate T cell priming	Dendritic cells, macrophages, naïve CD4+ T cells	↑ IL-12, MHC-II, TGF-β
4–7	T Cell Polarization	CD4+ T cells differentiate into Th1 and Th17 subsets	Th1, Th17, Tregs	↑ IFN-γ, IL-17A, IL-6; ↓ TGF-β

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

8–14	B Cell Activation	B cells present antigen, receive T cell help, and begin producing anti-CII antibodies	B cells, T follicular helper (Tfh) cells	↑ Anti-CII IgG (IgG2a/2b), IL-21
15–20	Immune Complex Phase	Circulating autoantibodies bind cartilage → complement activation	Immune complexes, complement (C3a, C5a), FcγRs	↑ C3, C5a, CRP
21–25	Clinical Onset	Visible joint inflammation, synovial cell activation, infiltration begins	Neutrophils, macrophages, synovial fibroblasts	↑ TNF-α, IL-1β, IL-6, MMP-9
26–35	Peak Inflammation	Aggressive joint damage, pannus formation, and bone erosion	Th17, osteoclasts, FLS	↑ RANKL, IL-17A, GM-CSF, MMPs
36–42	Resolution / Chronicity	Either inflammation resolves or progresses into low-grade chronic arthritis	Tregs, M2 macrophages (or persistent Th17/FLS)	↑ IL-10, TGF-β (resolution) or ↑ IL-6 (chronic)

- *Inference:*

The table outlines the sequential immunological events underlying experimental autoimmune arthritis. Initial antigen priming drives Th1/Th17 polarization, followed by B cell activation and autoantibody production. Immune complex formation and complement activation leads to inflammatory cell infiltration, joint swelling, and peak tissue destruction. The disease outcome depends on whether regulatory mechanisms resolve inflammation or whether persistent effector responses maintain chronic arthritis.

➢ *Histopathological Features [25], [27]:*

Table 2 Histopathological Changes in Experimental Autoimmune Arthritis

Tissue	Observed Pathology
Synovium	Synovial hyperplasia, immune cell infiltration, and pannus formation
Cartilage	Collagen degradation mediated by matrix metalloproteinases (MMPs) and ROS
Subchondral Bone	Bone erosion via osteoclast activation (RANKL-driven)
Vascular Endothelium	Angiogenesis and increased leukocyte trafficking

- *Inference:*

The table highlights the major tissue-level alterations during arthritis progression. Synovial tissue undergoes hyperplasia with immune cell infiltration leading to pannus formation, while cartilage is degraded through MMPs and oxidative stress. Subchondral bone erosion occurs due to osteoclast activation driven by RANKL, and vascular endothelium contributes through angiogenesis and enhanced leukocyte recruitment. Together, these changes underpin joint destruction and chronic inflammation.

➢ *Immunological Mechanisms:*

Both the innate and adaptive arms of the immune system are activated in the Collagen-Induced Arthritis (CIA) model, which closely resembles important aspects of rheumatoid arthritis in humans. Dendritic cells are essential on the innate side because they digest type II collagen (CII), prime CD4+ T cells, and activate the adaptive immune response. Reactive oxygen species (ROS) and pro-inflammatory cytokines like TNF-α and IL-1β are released by activated neutrophils and macrophages, which leads to tissue damage. Early inflammation may also be initiated by mast cells. Additionally, immune complexes activate the complement system, which contributes to the escalation of the local inflammatory response. The robust activation of Th1 and Th17 cells is a hallmark of the adaptive immune response. While Th17 cells release interleukin-17 (IL-17), which promotes neutrophilic infiltration and osteoclastogenesis and damages joints, Th1 cells create interferon-gamma (IFN-γ), which further stimulates macrophages. By generating autoantibodies against CII, B cells help to create immune complexes that exacerbate inflammation.

Despite their existence, regulatory T cells (Tregs) frequently exhibit malfunction, failing to inhibit excessive immunological activation. Many different applications make extensive use of the CIA model. TNF inhibitors (e.g., etanercept, infliximab), IL-6 receptor blockers (e.g., tocilizumab), IL-17 or IL-23 inhibitors, JAK-STAT pathway inhibitors (e.g., tofacitinib, baricitinib), anti-RANKL agents, and other small molecules that target T cells, B cells, or synovial fibroblasts are among the many treatments that it aids in assessing their effectiveness. Furthermore, this model is useful for mechanistic research that examines T-B cell interactions, the function of immune complexes and complement activation, and the mechanisms behind cartilage degradation and synovial inflammation. [25], [29]

➢ *Limitations:*

Despite its widespread use, the Collagen-Induced Arthritis (CIA) model has a number of drawbacks that researchers should take into account. Strain sensitivity is a major problem; DBA/1 mice are the favored strain because they are more sensitive to CIA, while other frequently used strains, such as C57BL/6 or BALB/c, need meticulous protocol adjustment to get reliable results [24]. Furthermore, research into chronic illness causes or the long-term consequences of treatment is complicated by the fact that the sickness is often temporary and self-limiting in many strains. The species-specific difference from human rheumatoid arthritis is another drawback. Although the CIA model closely

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

resembles several joint-specific aspects of RA, it falls short in capturing systemic signs that are frequently observed in clinical illness, such as vasculitis or rheumatoid nodules. Lastly, a great deal of experimental variability exists, as disease.

B. Collagen Antibody-Induced Arthritis (CAIA)

The BALB/c and C57BL/6 mice are frequently employed in the Collagen Antibody-Induced Arthritis (CAIA) model. In order to induce inflammation, a combination of monoclonal antibodies that target type II collagen (CII) is administered. This is frequently followed by an injection of lipopolysaccharide (LPS). The development of immunological complexes causes inflammation in the articular cartilage, which is the main target of immune attack. The illness usually manifests within a day after exposure to LPS, or around Day 4 after antibody delivery. Inflammation peaks between Days 6 and 7 and often subsides by Days 10 to 14, indicating an acute course. Research into innate immune pathways, the functions of Fc receptors, and neutrophil-driven joint injury will particularly benefit from this paradigm. It is also frequently utilized in the preclinical testing of immunomodulatory or anti-inflammatory medications, especially when a quick, repeatable onset of arthritis is sought.

➢ *Experimental Protocol:*

An intravenous injection of 4–5 mg of monoclonal antibodies against type II collagen (CII), usually given via the tail vein, initiates the development of arthritis on Day 0. These antibodies create immunological complexes that start the inflammatory cascade by attaching to collagen in the joints [31]. By Day 3, the intraperitoneal injection of 25–50 µg of lipopolysaccharide (LPS) significantly increases inflammation. By activating Toll-like receptor 4 (TLR4) on innate immune cells, LPS functions as a strong inflammatory stimulus that raises cytokine production and significantly intensifies the inflammatory response.[32].

➢ *Progression of Inflammation (Day-by-Day Breakdown:*

Table 3 Immunological Timeline of Collagen Antibody-Induced Arthritis (CAIA) Model

Day	Phase	Immunological Events	Key Cells Involved	Cytokine and Marker Expression
0–2	Immune Complex Formation	Antibodies bind CII, triggering immune complexes; complement is activated early.	Mast cells, macrophages, neutrophils	↑ C3a, C5a, FcγR signaling [31]
3	Inflammatory Trigger (LPS)	LPS activates TLR4 on immune cells, enhancing cytokine release.	Macrophages, endothelial cells, synovial cells	↑ TNF-α, IL-1β, IL-6, IFN-β [32]
4–5	Acute Inflammation	Joint swelling and neutrophil infiltration; initial cartilage damage.	Neutrophils, macrophages, endothelial cells	↑ CXCL1, MMP-9, IL-6, ROS [33]
6–7	Peak Inflammation	Severe joint swelling, pannus formation, and cartilage erosion.	Neutrophils, osteoclast precursors, mast cells	↑ TNF-α, GM-CSF, IL-1β, RANKL [34]
8–10	Resolution Phase	Inflammation reduces, and neutrophil clearance occurs; macrophages shift towards an anti-inflammatory state.	M2 macrophages, fibroblasts	↑ IL-10, TGF-β, SOCS3 [34]
11–14	Recovery or Residual Damage	In many strains, the disease resolves, though some fibrosis or mild chronic inflammation may remain.	Fibroblasts, tissue macrophages	ECM markers (e.g., IGF-1), fibronectin [35]

- *Inference:*

The table summarizes the sequential immune events in the CAIA model. Disease is initiated by antibody–CII immune complex formation and early complement activation, followed by an LPS-driven inflammatory trigger. This leads to acute inflammation with neutrophil infiltration and progresses to peak pathology characterized by pannus formation and bone erosion. Resolution is mediated by macrophage polarization toward an anti-inflammatory state, though some residual fibrosis or chronic low-grade inflammation may persist depending on strain susceptibility.

➢ *Histopathological Features:*

Table 4 Histopathological Alterations in Collagen Antibody-Induced Arthritis (CAIA)

Tissue Affected	Pathology Observed
Synovium	Acute inflammation, with swelling and infiltration of neutrophils.
Cartilage	Erosion due to immune complexes and protease release from neutrophils.
Subchondral Bone	Mild erosion due to osteoclast activation (mediated by RANKL).
Vascular Endothelium	Increased permeability and angiogenesis in inflamed regions.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

- *Inference:*

The table outlines tissue-specific changes in CAIA. Synovial inflammation with neutrophil infiltration initiates joint pathology, while immune complex deposition and protease release drive cartilage erosion. Subchondral bone shows mild osteoclast-mediated damage, and vascular endothelium contributes through angiogenesis and enhanced permeability. Together, these processes explain the acute joint damage characteristic of CAIA.

➢ *Immunological Mechanisms:*

Neutrophils are important effector cells in the CAIA model's innate immune response phase. They release matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and neutrophil extracellular traps (NETs), all of which exacerbate inflammation and tissue damage [33]. In the acute phase, macrophages have a pro-inflammatory M1 phenotype; however, when inflammation subsides, they change to an anti-inflammatory M2 phenotype [34]. Mast cells enhance the immune response by interacting with Fc gamma receptors (FcγR) [35]. Immune complexes, on the other hand, trigger the complement system, which encourages chemotaxis and releases strong inflammatory mediators including C3a and C5a [36]. Leukocyte recruitment into the inflammatory joint is further aided by endothelial cells' upregulation of adhesion molecules such as ICAM-1 and VCAM-1 [36]. CAIA has a limited dependence on the adaptive immune response. Since the injection of anti-CII antibodies directly causes the disease, T and B cells are not necessary to initiate inflammation, hence avoiding the necessity for an endogenous adaptive immune response [31]. Without priming T or B cells, these injected antibodies cause joint inflammation by imitating harmful autoantibodies. Numerous research areas make extensive use of the CAIA model. It is especially useful for researching the biology of Fc receptors, including analysing how FcγR signalling contributes to arthritis. Additionally, it is a powerful tool for investigating innate immune responses, such as innate cytokine cascades, neutrophil activity, and macrophage polarization [33]. Additionally, CAIA is widely used in preclinical drug testing, particularly for assessing kinase inhibitors that target innate immune pathways, such as SYK and BTK inhibitors, complement inhibitors, anti-cytokine therapies (e.g., anti-TNF, anti-IL-6), and neutrophil-targeted treatments (e.g., CXCR2 inhibitors).

➢ *Limitations*

Although the CAIA model is very helpful for studying innate immune mechanisms, it has a number of drawbacks, including the lack of adaptive immunity, the fact that the model avoids antigen-specific T and B cell responses, and the fact that it is an acute model with inflammation that usually goes away in 10–14 days, which limits its usefulness for studying the chronic, relapsing nature of RA [34], strain sensitivity, where different mouse strains show varying degrees of responsiveness to CAIA induction, which requires careful, strain-specific validation to ensure reproducibility and relevance [33].

C. Antigen-Induced Arthritis (AIA)

Rats, particularly the Lewis strain, and rabbits are the main subjects of the Antigen-Induced Arthritis (AIA) methodology, which aims to trigger a specific immune response in synovial joints. Methylated bovine serum albumin (mBSA) emulsified in Complete Freund's Adjuvant (CFA) is used to start the disease. This model replicates inflammation caused by antigens that is restricted to the joint area. Inflammation peaks soon after the intra-articular challenge, and disease usually manifests 1-2 weeks following vaccination. The illness typically goes away in two to three weeks and has an intense, self-limiting duration. AIA is very useful for researching the immunopathophysiology of arthritis, localized medication delivery, and joint-specific inflammatory processes.

➢ *Protocol (AIA in Rats or Rabbits):*

There are two main steps in the AIA procedure. The first stage is the sensitization phase, during which mBSA emulsified in CFA is administered subcutaneously to the animals. By doing this, the immune system is prepared to identify mBSA as an antigen. The intra-articular challenge involves injecting mBSA directly into the knee joint, which causes a localized inflammatory response, following an incubation period of one to two weeks. This process enables researchers to examine reactions in a confined, controlled environment while accurately simulating the immune-mediated inflammation observed in autoimmune arthritis [37].

➢ *Disease Phases and Inflammatory Events (Day-by-Day Progression):*

Table 5 Immunological Timeline of Antigen-Induced Arthritis (AIA) Model

Day	Phase	Immunopathology	Key Cells/Pathways	Cytokines/Markers
0–2	Sensitization	mBSA in CFA primes immune response, activating T and B cells.	Dendritic cells, T cells, B cells	↑ IL-12, IL-23, IFN-γ [38]
3–7	Initial Immune Activation	APCs activate T cells, triggering immune response and antibody production.	T cells, macrophages, dendritic cells	↑ TNF-α, IL-1β, IL-6, IL-17 [39]
7–14	Acute Inflammation	Joint inflammation; neutrophil and macrophage infiltration.	Neutrophils, macrophages, endothelial cells	↑ CXCL1, IL-6, MMPs, TNF-α [40]
14–21	Resolution or Chronicity	Inflammation resolves or persists as mild chronic inflammation with fibrosis.	Fibroblasts, anti-inflammatory macrophages (M2)	↑ IL-10, TGF-β, collagen deposition [41]

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

- *Inference:*

The table depicts the staged progression of AIA. Sensitization with mBSA in CFA initiates T and B cell priming, followed by APC-driven immune activation and pro-inflammatory cytokine release. This leads to acute joint inflammation with neutrophil and macrophage infiltration, causing tissue damage. The outcome depends on immune regulation—either resolution through anti-inflammatory pathways or progression to mild chronic inflammation with fibrosis.

➢ *Histopathological Features:*

Synovium: Acute synovitis and edema are caused by synovial hyperplasia accompanied by neutrophil and macrophage infiltration, Cartilage: Deterioration brought on by immune cell activity, matrix metalloproteinases (MMPs), and inflammatory cytokines, Bone: In the early phases, there is little to no bone resorption, Vascular Endothelium: In the inflammatory synovium, there is an increase in permeability, leukocyte extravasation, and angiogenesis.

➢ *Immunological Mediators by Type:*

Both the innate and adaptive immune systems actively contribute to the localized inflammation of joints in the Antigen-Induced Arthritis (AIA) model. Neutrophils are the main effector cells on the innate side, generating pro-inflammatory cytokines, reactive oxygen species (ROS), and matrix metalloproteinases (MMPs) that aggravate joint injury. During the resolution phase, macrophages gradually change from a pro-inflammatory (M1) phenotype, which promotes inflammation, to an anti-inflammatory (M2) phenotype [34]. By upregulating adhesion molecules including ICAM-1 and VCAM-1, endothelial cells contribute to the recruitment of immune cells to the inflammatory joint. Additionally, dendritic cells play a role as important antigen-presenting cells that stimulate T cells and aid in the initiation of adaptive immunity.

Both CD4+ and CD8+ T cells are involved in promoting inflammation in adaptive immune responses by generating cytokines such as TNF-α and IL-17. B cells help by generating antibodies against methylation BSA (mBSA), the injected antigen, which create immunological complexes in the joint area and worsen inflammation. Important cytokines that contribute to tissue damage and synovial inflammation are IL-1β, TNF-α, IL-17, and IL-6. There are several uses for the AIA model in arthritis research. It is extremely useful for researching immunological responses unique to joints, particularly those that occur in the synovium. It is perfect for evaluating intra-articular medication delivery systems that are intended to reduce inflammation or encourage tissue repair because of its confined nature. Additionally, it offers important information on the immunopathophysiology of arthritis, such as local cytokine expression, macrophage polarization, and T cell activation dynamics. Additionally, AIA is a useful model for investigating autoimmune responses in an inflammatory setting due to its antigen-specific nature [42].

➢ *Limitations:*

Nevertheless, the model has drawbacks. Inflammation does not mimic the systemic joint involvement observed in conditions such as rheumatoid arthritis because it is usually limited to a single joint, usually the knee. Additionally, it does not exhibit characteristics of systemic autoimmunity, such as distal joint involvement or the detection of circulating autoantibodies [43]. Furthermore, AIA's usefulness for researching chronic disease processes and long-term therapeutic approaches is limited because the inflammation often goes away in two to three weeks.

D. SKG Mouse Model of Autoimmune Arthritis

Genetically altered BALB/c mice in the SKG model have the ZAP-70^W163C mutation, which makes them more susceptible to autoimmune disorders. In order to induce arthritis in these mice, curdlan, a β-1,3-glucan that activates the innate immune system, is usually injected intraperitoneally (i.p.). SKG mice occasionally acquire arthritis on their own as they get older, independent of outside stimuli. Although the disease mostly affects synovial joints, it can also spread to the spleen, lymph nodes, and lungs. After a curdlan injection, arthritis starts 10–14 days later and progresses to a chronic phase, with inflammation peaking between Weeks 3 and 5 and lasting for the rest of the disease. The collapse of central tolerance is commonly studied using the SKG model, with particular attention paid to autoreactive T cell activation and the equilibrium between Th17 and Treg cells. It also aids in the research of how environmental and mucosal factors affect autoimmune arthritis and how rheumatoid arthritis (RA) affects the development of interstitial lung disease (ILD). The model is also useful for preclinical testing of treatments that target innate immune pathways and T cells [44].

➢ *Experimental Protocol:*

On Day 0 of the experiment, mice are given an intraperitoneal injection of 3 mg of curdlan, which activates Dectin-1 on innate immune cells. This sets off the Syk-NF-κB pathway, which in turn causes the production of proinflammatory cytokines such as IL-6 and IL-23 [45]. Around Day 7, clinical monitoring starts, and joint stiffness and swelling are routinely measured. By Weeks 3–5, arthritis usually peaks, and the number of afflicted paws and the degree of swelling are assessed using conventional scoring scales.

➢ *Disease Progression: Week-by-Week Breakdown [46]:*

Table 6 Immunopathological Timeline of SKG Arthritis Model

Week	Phase	Immunopathology	Key Cells / Pathways	Cytokines / Markers
0–1	Innate Priming	Curdlan triggers Dectin-1 → Syk → NF-κB; cytokines promote Th17 skewing	Dendritic cells, macrophages	↑ IL-6, IL-1β, IL-23, GM-CSF

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

1–3	T Cell Expansion	**Autoreactive CD4+ T cells** expand and polarize into Th17 lineage	Th17 cells, CD4+ T cells	↑ IL-17A, IL-22, IFN-γ
3–5	Joint Inflammation	Severe joint swelling, immune infiltration, and bone/cartilage damage	Th17 cells, osteoclast precursors	↑ RANKL, MMPs, TNF-α
6–8+	Systemic Chronic Phase	Extra-articular inflammation: **interstitial lung disease**, splenomegaly	Th17, macrophages, fibroblasts	↑ IL-17, IGF-1, fibronectin

- *Inference:*

The table illustrates the sequential immunopathology in SKG mice. Curdlan stimulation via Dectin-1 initiates innate priming and promotes Th17 skewing. This is followed by expansion of autoreactive $CD4^+$ T cells, leading to Th17-mediated joint inflammation with cartilage and bone damage. In later stages, persistent Th17 activity extends beyond the joints, driving systemic chronic inflammation with extra-articular manifestations such as lung involvement and splenomegaly.

➢ *Histopathological Features [47]:*

Table 7 Tissue-Specific Pathology in SKG Arthritis Model

Tissue	Pathological Features
Synovium	Synovial hyperplasia with dense inflammatory infiltrates and angiogenesis
Cartilage	Erosion and degradation driven by MMPs and inflammatory cytokines
Bone	Subchondral bone resorption through osteoclast activation (via RANKL)
Lung	Interstitial lung inflammation, lymphoid aggregates, and fibrosis resembling ILD
Lymphoid Organs	Enlarged spleen and lymph nodes with active germinal centers

- *Inference:*

The table highlights tissue-level alterations in SKG mice. Synovium exhibits hyperplasia, inflammatory infiltration, and angiogenesis, while cartilage undergoes MMP-mediated erosion. Subchondral bone shows osteoclast-driven resorption, and extra-articular manifestations include interstitial lung inflammation with fibrosis. Lymphoid organs display splenomegaly and active germinal centers, reflecting systemic immune activation.

➢ *Immunological Mechanisms:*

In the SKG model, the recognition of curdlan by dendritic cells and macrophages via Dectin-1 triggers innate immunological activation, which in turn triggers the release of Syk-mediated cytokines, specifically IL-6 and IL-23 [45]. Through the production of neutrophil extracellular traps (NETs), matrix metalloproteinases (MMPs), and reactive oxygen species (ROS), neutrophils contribute to joint injury. Despite not being a major factor, mast cells may have a small impact on sudden flare-ups of the illness. Although it is not necessary for the onset of disease, the complement system promotes inflammation.

Because of the ZAP-70^W163C mutation, CD4+ T cells on the adaptive immunological side are able to avoid thymic deletion, which permits autoreactivity [44]. By producing IL-17, IL-22, and GM-CSF, Th17 cells are important causes of inflammation in the lungs and joints [46]. Although they exist, regulatory T cells (Tregs) are dysfunctional and ineffective at suppressing the aggressive Th17 response [46]. Through the ZAP-70 mutation, the SKG model replicates abnormalities in central tolerance, making it extremely valuable for mechanistic insights. Researching Th17-dominant inflammation, the onset of interstitial lung disease (ILD), and mucosal and microbial causes of autoimmune arthritis is especially pertinent. Pattern recognition receptor (PRR) pathways such Dectin-1, Syk, and Card9 signaling can be studied with this model [47].

➢ *Limitations:*

The SKG model has a number of drawbacks. A major obstacle is strain dependency, which restricts its wider use due to the requirement for homozygous ZAP-70^W163C mutation [44]. Additionally, the model's gradual initiation of illness progression makes it less suitable for quick drug tests. Furthermore, the immunological potency of the curdlan that causes inflammation can differ from batch to batch, which could have an impact on the repeatability of findings [45]. Analysis of joint-specific inflammation may be made more difficult by systemic involvement in the animal, such as lung and lymphoid alterations. Last but not least, the scarcity of SKG mice, which are not extensively marketed, means that long-term research requires meticulous colony management.

E. Pristane-Induced Arthritis (PIA)

The PIA (Pristane-Induced Arthritis) model primarily uses Dark Agouti (DA) rats, although other rat strains can also be utilized with adjusted protocols. The induction agent for this model is pristane, a synthetic alkane (2,6,10,14-tetramethylpentadecane), which targets the synovial joints, causing autoimmune polyarthritis along with systemic features such as splenomegaly and anemia of chronic disease. The onset of disease typically occurs around 10–14 days after pristane injection, and the disease follows a chronic, relapsing-remitting course, lasting several weeks to months. The PIA model is widely used in research to study chronic autoimmune inflammation, explore the interactions between innate and adaptive immune systems, and investigate systemic rheumatoid arthritis features, including extra-articular involvement [49, 51].

➢ *Experimental Protocol (PIA in DA Rats):*

On Day 0, the PIA model is initiated by injecting 150 µL of pristane intraperitoneally (i.p.), without the addition of emulsifiers or adjuvants. In genetically predisposed rats, prinstane is enough to cause arthritis. Clinical symptoms, such as joint swelling, erythema, and impaired mobility,

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

usually manifest between Days 10 and 14. The severity is evaluated using a semi-quantitative scoring system (0–4) that takes into account joint mobility, erythema, and edema. Recurrent inflammation causes relapsing flares throughout the model, with the disease usually peaking around Day 20.[50].

➢ *Disease Phases and Inflammatory Events: Day-by-Day Progression [24],[27],[28]:*

Table 8 Immunopathological Timeline of Pristane-Induced Arthritis (PIA) Model

Day	Phase	Immunopathology	Key Cells/Pathways	Cytokines/Markers
0–3	Priming Phase	Pristane injection activates macrophages and dendritic cells (DCs)	Macrophages, DCs	↑ IL-1β, IL-6
4–10	Autoimmune Initiation	Expansion of Th1 and Th17 cells; B cells begin activation	CD4+ T cells, B cells	↑ IL-17, IFN-γ, autoantibodies (rheumatoid factor)
10–14	Arthritis Onset	Synovitis with mononuclear infiltration and edema	Th1/Th17 cells, macrophages	↑ TNF-α, IL-6, Rheumatoid Factor (RF)
15–30	Peak Disease	Severe joint swelling, cartilage/bone erosion	Neutrophils, osteoclasts	↑ RANKL, MMP-9, TNF-α
30+	Relapse & Chronicity	Disease flares, with persistent low-grade immune activation	Memory T cells, plasma cells	↑ IL-6, IL-1β

- *Inference:*

The table summarizes the staged immunopathology in PIA. Pristane injection initiates innate immune activation, leading to Th1/Th17 expansion and B cell–mediated autoantibody production. This triggers synovitis with mononuclear infiltration and edema, progressing to peak joint inflammation, cartilage, and bone erosion. Later stages involve disease flares and chronic low-grade immune activation mediated by memory T cells and plasma cells.

➢ *Histopathological Features [52]:*

Table 9 Tissue-Specific Pathology in Pristane-Induced Arthritis (PIA) Model

Tissue	Observed Pathology
Synovium	Synovial hyperplasia, mononuclear cell infiltration, pannus formation
Cartilage	Cartilage erosion driven by MMPs and inflammatory cytokines
Subchondral Bone	Osteoclast-driven bone erosion, RANKL-mediated osteoclast activation
Peripheral Organs	Splenomegaly, anemia of chronic disease, lymphadenopathy

- *Inference:*

The table summarizes tissue-level changes in PIA. Synovium exhibits hyperplasia, mononuclear infiltration, and pannus formation, while cartilage undergoes MMP-mediated erosion. Subchondral bone shows osteoclast-driven resorption via RANKL signaling. Peripheral organs demonstrate systemic effects, including splenomegaly, anemia of chronic disease, and lymphadenopathy, reflecting widespread immune activation.

➢ *Immunological Mechanisms:*

Macrophages, which are early makers of important cytokines like IL-1β, IL-6, and TNF-α that are necessary for starting the inflammatory cascade, initiate the innate immune activation in the PIA model. By exposing antigens and encouraging T cell activation, dendritic cells (DCs) serve as a link between the innate and adaptive immune responses. By generating matrix metalloproteinases (MMPs) and reactive oxygen species (ROS), neutrophils contribute to tissue injury. Important cytokines like TNF-α, IL-1β, and IL-6 are essential for starting and maintaining inflammation. By producing pro-inflammatory cytokines like IL-17 and IFN-γ, Th1 and Th17 cells promote tissue degradation and joint inflammation in terms of adaptive immune activation. Autoantibodies, such as rheumatoid factor (RF), are produced by B cells and plasma cells and are essential to the pathophysiology, although Key characteristics of rheumatoid arthritis (RA), such as persistent inflammation accompanied by systemic symptoms like polyarthritis, splenomegaly, and chronic illness anemia, can be accurately simulated using the PIA model. It offers insight into how the innate and adaptive immune systems interact and is helpful for researching the relapsing-remitting nature of autoimmune arthritis. Studying cytokine-driven bone damage (e.g., RANKL and MMPs), testing anti-cytokine therapies (e.g., anti-TNF and anti-IL-6 treatments), analyzing systemic disease manifestations (e.g., anemia and splenomegaly), and investigating T cell and B cell interactions in chronic autoimmunity are some examples of research applications. [53]

➢ *Limitations:*

It is important to take into account the PIA model's many constraints. First, it is less effective in common mouse strains and more effective in Dark Agouti (DA) rats due to its species specificity. Compared to CIA or CAIA, the induction pathway in this model is less well-characterized, which makes it more difficult to comprehend the disease mechanism. Rheumatoid factor (RF) is present, but there are very few anti-CCP antibodies, which limits the model's ability to depict seropositive RA. This is another way that the autoantibody profile varies from clinical RA. Another problem is experimental variability, since the time and severity of sickness can vary depending on the animals' sex, housing conditions, and microbiome composition. Lastly, although

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

the model is helpful for researching systemic RA symptoms, it can make research that just focuses on joint pathology. [49], [50], [54]

➢ *Clinical Evaluation and Scoring in Animal Models:*

Having a clinical evaluation system is crucial when researching diseases like arthritis in animal models since it allows researchers to monitor the disease's progression and the animal's reaction to treatments. This aids in our comprehension of the condition's severity, whether it is getting better or worse, and whether the treatments are working.

➢ *Clinical Scoring System for Mice:*

This scoring system is a simple and effective way to measure the severity of arthritis in animals. It focuses on joint swelling, deformities, and movement limitations, which are the major indicators of arthritis [55], [56].

Table 10 Arthritis Clinical Scoring System in Experimental Models

Score	Criteria	Description
0	No swelling	The joint looks completely normal with no visible signs of swelling.
1	Mild redness or swelling (1 joint)	A slight redness or mild swelling in just one joint, but the animal can still move around without much trouble.
2	Moderate swelling (multiple joints)	Swelling in two or more joints, with visible redness or warmth. The animal might show slight difficulty moving.
3	Severe swelling/impairment	Extensive swelling in multiple joints, making it difficult for the animal to move. You'll notice a clear loss of function.
4	Ankylosis or deformity	The joint is severely damaged—either fused together or deformed—which makes it almost impossible for the animal to move or maintain a normal posture.

- *Inference:*

The table presents a standardized scoring system to assess arthritis severity in animal models. Scores range from 0 (normal joint) to 4 (severe deformity/ankylosis), reflecting progressive joint inflammation, swelling, and functional impairment. This system allows quantification of disease progression and comparison between experimental groups.

➢ *Additional Assessments:*

To obtain a more thorough picture of the animal's health and condition, we use a number of techniques in addition to the primary clinical score. Using calipers to measure paw thickness is a crucial technique for determining the degree of inflammation-induced swelling. Inflammation is indicated by the presence of swelling [57]. The grip strength test measures the animal's ability to hold onto a bar or other object securely in order to assess the forelimbs' functionality. Joint pain or stiffness may be indicated by a weaker grasp [58]. Additionally, we perform a behavioral evaluation that involves gait analysis to look for changes in the animal's gait, such as a limp or a changed stride, which may be signs of arthritis's effect on mobility [59].

➢ *Tissue Collection:*

Collecting joint tissue aims to monitor the course of arthritis and the body's reaction to therapies at different phases of the condition. This is accomplished by euthanizing the animals at several stages of the disease's evolution, which usually comprise baseline, prior to the commencement of the disease; early stage, when the first indications of arthritis occur; and chronic stage, when the disease has reached its full development. The precise stages change based on the experiment's emphasis, but these time points enable us to track the disease's progression throughout time [62]. Tissues are taken from important joints, such as the knee and ankle, during joint harvesting because these joints are essential for examining alterations in synovial tissue, cartilage [64], [65].

➢ *Histological Staining:*

We employ histological staining techniques to identify structural changes and immune cell infiltration in the joints, which helps us better understand the tissue changes that occur during arthritis. Hematoxylin and Eosin (H&E) staining is a frequently employed technique that aids in the examination of tissue structures, with a particular emphasis on inflammation and immunological activity within the joints [66]. In particular, we search for synovial hyperplasia (an increase in cell counts) and the infiltration of immune cells such neutrophils and macrophages, which are indicators of synovitis [67]. Furthermore, rheumatoid arthritis and other conditions are characterized by cellular infiltration, especially by T-cells, macrophages, and neutrophils [68].

Safranin O/Fast Green is another useful staining technique that works very well for assessing the health of cartilage [69]. Because healthy cartilage will stain strongly while deteriorated cartilage would exhibit a loss of this staining, we can determine the integrity of cartilage by measuring the degree of Safranin O staining. By highlighting non-cartilage tissues and creating a sharp contrast, the Fast Green counterstain facilitates improved tissue comparison [70]. Lastly, osteoclast activity, which is crucial in bone loss during arthritis, is evaluated using TRAP (Tartrate-Resistant Acid Phosphatase) staining [71]. Increased osteoclast activity and bone resorption, two important aspects of arthritis-induced bone deterioration, are indicated by elevated TRAP activity [72].

➢ *Molecular Markers:*

To look at the immune response and the particular components causing arthritis, we use molecular techniques in addition to histology methods. These methods enable us to comprehend the role of the immune system in the illness on a deeper level. ELISA and qPCR are two of the most widely used techniques for quantifying cytokines, which are important chemicals involved in inflammation. We can accurately quantify cytokines by using ELISA to identify

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

certain cytokines in tissue or blood samples [76]. Cytokine mRNA levels are measured by qPCR, which shows the amount of cytokine generated in the joints [77]. The cytokines we focus on include TNF-α, which plays a significant role in autoimmune illnesses such rheumatoid arthritis [73], and IL-6, which is frequently raised in inflammatory conditions.

Another effective method we employ to examine immune cell subsets in the joints is flow cytometry. By dissecting the immune cell populations, this technique provides information about how the immune system adapts to arthritis. We especially search for Tregs, which aid in immune system regulation and autoimmunity prevention [80], Th17 cells, which are essential for inflammation in rheumatoid arthritis [79], and CD4+ T cells, which are important for immune response activation [78]. Fluorescently labeled antibodies are used in flow cytometry to identify and examine these immunological cells in great detail [81]. In order to determine which molecules are active during arthritis, immunohistochemistry (IHC) is utilized to visualize particular proteins within tissues. We concentrate on proteins that cause cartilage degradation MMPs [82], promote bone erosion in arthritis RANKL [83], and cause synovial inflammation and joint destruction FLS [84]. We employ particular staining methods to view these proteins after using particular antibodies to detect them using IHC [85].

➢ *Summary Table:*

Table 11 Techniques used to Assess Immunopathology and Tissue Changes in Arthritis Models

Technique	Purpose	Key Molecules/Markers	What We Learn
Hematoxylin & Eosin Staining	Tissue structure; inflammation & immune cells	Synovial tissue, immune cells	Inflammation level, immune cell infiltration
Safranin O/Fast Green Staining	Cartilage integrity	Proteoglycans, cartilage matrix	Cartilage degradation
TRAP Staining	Osteoclast activity	Osteoclasts	Bone resorption activity
ELISA/qPCR for Cytokines	Measure inflammatory cytokines	TNF-α, IL-6, IL-17	Inflammatory profile
Flow Cytometry	Immune cell profiling	CD4+, Th17, Tregs	Immune system breakdown
Immunohistochemistry	Protein expression in tissues	MMPs, RANKL, FLS markers	Protein localization, tissue remodelling

- *Inference:*

The table summarizes commonly used experimental techniques to evaluate arthritis. Histological stains (H&E, Safranin O/Fast Green, TRAP) reveal tissue architecture, cartilage integrity, and osteoclast activity. Molecular assays (ELISA, qPCR) and flow cytometry assess cytokine profiles and immune cell populations, while immunohistochemistry identifies protein localization and tissue remodelling. Together, these methods provide a comprehensive understanding of inflammatory status, joint damage, and immune mechanisms in experimental arthritis.

➢ *Ethical Considerations:*

While studying arthritis in animals can help us better understand the condition and test potential remedies, it also carries a great deal of responsibility. Strict adherence to ethical standards is necessary to guarantee that the animals are treated with dignity and that their welfare is given top priority throughout the study because the procedure can cause pain and misery.

➢ *Institutional Approval:*

An Institutional Animal Care and Use Committee (IACUC) or equivalent ethics board must thoroughly review and approve all experiments before they can start. This ensures that the study conforms with national and international regulations, including the EU Directive 2010/63/EU and the U.S. Animal Welfare Act. The approval process entails assessing the study's design, the experiment's scientific goals, and the potential impact on the animals' well-being. [86], [87].

➢ *Use of Analgesics and Anesthetics:*

Researchers must employ pain-relieving drugs to reduce animal suffering during research, especially when invasive procedures or extreme inflammation are involved. Meloxicam, an anti-inflammatory that helps reduce pain and swelling, and buprenorphine, an opioid for moderate pain, are common choices. But it's important to exercise caution because some medications can alter the immune system, which could impair the experiment's outcome [88], [89]. Effective pain management is crucial for both improving animal welfare and guaranteeing the validity of the research, according to the Guide for the Care and Use of Laboratory Animals [86].

➢ *Humane Endpoints:*

Humane endpoints are precise standards for when an animal's suffering becomes intolerable because, in spite of our best efforts, there are times when the illness progression in an animal model gets too severe. The animal may lose more than 15–20% of its body weight, have serious joint injury, such as swelling, deformities, or necrosis (tissue death), be unable to move about freely enough to get food or water, or exhibit symptoms of a systemic illness, such as lethargy or hypothermia (low body temperature). Upon reaching these endpoints, the animal is put to sleep in a way that causes the least amount of stress and suffering possible. The study protocol has thorough documentation of these requirements, which are upheld by veterinary-assisted trained staff [90], [91].

➢ *Housing and Environmental Enrichment:*

Proper housing arrangements are crucial since the way animals are housed has a big impact on their stress levels and

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

general health. This entails keeping environmental parameters like temperature, humidity, and light cycles constant and, where suitable, provide social housing so that animals can coexist and exhibit their innate social tendencies. Furthermore, enrichment products like chew blocks, nesting materials, and shelters are crucial for lowering stress and fostering psychological well-being. In order to reduce stress and provide more dependable experimental results, it is essential to provide these enrichments [86], [92].

➢ *Applying the 3Rs Principle:*

All ethical animal research is guided by the 3Rs principle: replacement, reduction, and refinement. Reduction, which focuses on using the fewest number of animals required for the experiment, is accomplished through careful study design and statistical planning; Replacement, which involves using alternatives to animal models whenever possible, such as in vitro systems or computational models; and Refinement, which aims to improve procedures to reduce pain or distress, such as using better analgesics, less invasive techniques, and non-terminal sampling (taking samples without euthanizing the animal). These guidelines were first proposed by Russell and Burch. In addition to ensuring that animals are treated ethically, researchers can enhance the quality and dependability of their work and increase its reproducibility by following the 3Rs [93], [94].

➢ *Comparative Summary of Arthritis Models*

By simulating multiple aspects of arthritis, these models offer important insights into the underlying causes of the condition and possible therapeutic approaches. A summary of the main experimental models of arthritis, each with distinct traits, is provided below.

Table 12 Comparison of Common Experimental Arthritis Models

Model	Immune Mechanism	Induction Method	Onset	Chronicity	Key Features	Species Used
CIA (Collagen-Induced Arthritis) [95], [96]	Involves adaptive immunity (Th1/Th17; B cells)	Immunization with collagen type II (CII) mixed with CFA; booster shot on Day 21	Around 21 days	Moderate (3–5 weeks)	Symmetric joint inflammation, cartilage and bone damage, high T and B cell activity, production of anti-CII antibodies	Mice (DBA/1), Rats (Lewis)
CAIA (Collagen Antibody-Induced Arthritis) [97], [98]	Passive, antibody-driven (no immune system activation)	Injection of anti-CII monoclonal antibodies; inflammation is intensified with LPS or other agents	3–5 days	Short (around 2 weeks)	Quick onset, lots of neutrophils, no adaptive immune phase, complement and FcγR dependent	Mice (C57BL/6, BALB/c)
AIA (Antigen-Induced Arthritis) [99], [100]	Antigen-specific, adaptive (Th1/Th17)	Immunization with antigen (e.g., mBSA) mixed with CFA; then direct injection of antigen into joints	1–3 days post injection	Can be local or chronic with repeats	Monoarthritis, heavy neutrophil infiltration, joint inflammation, reliable results	Rats (Wistar, Lewis), Rabbits
SKG (ZAP-70 mutation model)	Genetic autoimmunity (Th17 dominant, ZAP-70 mutation)	Spontaneous or triggered by substances like β-glucan, zymosan, or curdlan	A few weeks	Chronic and progressive	Systemic inflammation, joint and tendon inflammation, features of spondyloarthritis	Mice (SKG strain, BALB/c background)
PIA (Pristane-Induced Arthritis)	Autoimmune (T and B cell involvement)	Single injection of pristane (mineral oil) under the skin	10–14 days	Chronic with flare-ups	Polyarthritis, widespread inflammation, autoantibody production (e.g., RF), synovitis	Rats (DA, Lewis)

- *Inference:*

The table compares five widely used arthritis models based on immune mechanism, induction method, onset, chronicity, key pathological features, and species used. CIA and AIA primarily involve adaptive immunity (Th1/Th17 and B cells), whereas CAIA is antibody-driven with rapid onset and minimal adaptive involvement. SKG reflects genetic autoimmunity with Th17 dominance and systemic chronic inflammation, while PIA models autoimmune polyarthritis with flare-ups. This comparison helps in selecting an appropriate model depending on study goals, such as rapid induction, chronicity, or systemic manifestations.

➢ *Highlights of Each Model:*

A popular model called CIA (Collagen-Induced Arthritis) mimics genuine rheumatoid arthritis by simulating an immune reaction to type II collagen that causes bone loss

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

and joint inflammation. This model is very useful for researching the functions of T and B cells in arthritis as well as immune system involvement. Studying acute inflammation and antibody-driven arthritis is made possible by CAIA (Collagen Antibody-Induced Arthritis), which circumvents the immune system by directly introducing anti-collagen antibodies. This results in a quick onset of joint swelling and neutrophil infiltration. Localized arthritis is frequently studied using AIA (Antigen-Induced Arthritis), which focuses on immune responses specific to antigens. Direct antigen exposure to the joints causes it, and the condition can be controlled by reintroducing the same antigen to cause recurrence. The SKG framework offers an understanding of genetically driven autoimmune illnesses and the function of Th17 cells in inflammation can be gained from the genetic perspective on arthritis, where a mutation in the ZAP-70 gene causes persistent arthritis with characteristics of spondylarthritis. A single injection of pristane (mineral oil) causes PIA (Pristane-Induced Arthritis), an autoimmune condition that leads to persistent joint inflammation and the development of autoantibodies. Systemic inflammation and relapsing-remitting arthritis are frequently studied using this model. With each model giving distinct qualities to investigate various facets of the disease, these models are crucial for developing a deeper knowledge of the causes and course of arthritis. They also provide useful platforms for testing possible medicines and treatments**.**

III. CONCLUSION

Experimental models of rheumatoid arthritis (RA) are crucial for understanding the disease and developing treatments. Each model offers unique insights into the early immune response, inflammation, tissue damage, and disease progression. Researchers can choose the model that best aligns with their focus, and combining multiple models can provide a comprehensive view. Ethical considerations in animal research, adhering to the 3Rs principle, ensure humane treatment and enhance research quality. By selecting appropriate models, using them responsibly, and refining them, significant progress can be made in finding a cure for RA.

- *Conflict of Interest*

There are no conflicts of interest.

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ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25aug1260

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