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REVIEW

# Molecular Targeted Therapy for Chronic Non-Bacterial Mastitis: New Insights into Pathophysiology and Therapeutic Strategies

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**Abstract:** Chronic Non-bacterial Mastitis (CNBM) is a benign and heterogeneous breast disease whose etiology is not yet fully understood and primarily includes plasma cell mastitis and idiopathic granulomatous mastitis. Its management is challenged by limited therapeutic choices, poor treatment outcomes, and considerable adverse effects. The emergence of molecular targeted therapy has presented new alternatives and hope for the treatment of this condition. The marked dysregulation of critical inflammatory pathways, including NF-κB, JAK-STAT, and MAPK, observed during the onset and progression of CNBM, suggests that molecular agents targeting these signaling cascades may hold therapeutic promise. While preclinical studies in animal models have validated the effectiveness of agents such as pathway inhibitors, clinical evidence is still largely confined to case reports and inferences drawn from other autoimmune diseases. A distinct research gap in the molecular targeted treatment of CNBM persists, owing to the absence of large-scale randomized controlled trials. Advancements in future research will hinge on a multi-pronged approach: utilizing multi-omics methods to establish molecular classifications for precision medicine; designing novel, high-selectivity molecular inhibitors and exploring possibilities for drug repurposing; and studying combined therapeutic regimens to improve efficacy while minimizing toxicity. Through interdisciplinary collaboration and sustained investigation, these initiatives are designed to deliver more effective and safer therapeutic solutions for patients, with the ultimate goal of ameliorating the clinical prognosis of this challenging disease and improving their quality of life.

**Keywords:** chronic non-bacterial mastitis, plasma cell mastitis, idiopathic granulomatous mastitis, molecular targeted therapy, inflammatory disease, autoimmunity

## Introduction

Chronic Non-bacterial Mastitis (CNBM) refers to a group of benign, non-neoplastic diseases characterized by chronic inflammation of the breast tissue. The etiology is complex and unrelated to direct infection, involving a multifactorial interplay including autoimmune reactions characterized by aberrant T/B cell activation and elevated interleukin-6 (IL-6), and endocrine dysfunction marked by hyperprolactinemia. Genetic susceptibility involves single nucleotide variants in immune-related genes such as human leukocyte antigen (HLA)-DRB1, while reproductive history acts as the primary trigger. Furthermore, the pathogenesis includes complement activation, evidenced by elevated C3, and M1/M2 macrophage polarization.[1–4] Historically, these conditions were often termed "non-lactational mastitis"; however, this nomenclature is inaccurate as chronic mastitis of non-bacterial origin can also arise during lactation.[5,6]

The incidence of CNBM has risen in recent years, exhibiting distinct demographic and clinical characteristics. The global incidence represents about 0.3% to 1.9% of all breast diseases, while in China, it accounts for about 2% to 5%. The condition predominantly affects women of childbearing age (20–49 years), who comprise approximately 96% of cases. Within this group, the 30–39 age bracket is the most prevalent, accounting for 54.97%, followed by the 20–29 (33.15%) and 40–49 (18.23%) age groups.[7,8] Adolescent females (10–19 years) are rarely affected, representing only

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2.07% of cases, while male cases are exceedingly rare.[9,10] Geographically, distinct variations are observed in the epidemiology of CNBM. Prevalence is notably concentrated in the Americas, with the USA accounting for 37.6% of reported cases in the region. Asia exhibits an upward trend in detection, exemplified by rising annual incidence rates in China. In contrast, while European populations demonstrate a lower overall incidence, they report a higher relapse rate, ranging from 11% to 38.3%. These disparities likely stem from differences in diagnostic capabilities, regional pathogen distribution, and cultural barriers to accessing reproductive health care.[11,12] Notably, epidemiological studies indicate that CNBM may increase the risk of subsequent breast cancer (hazard ratio = 1.73; 95% 1.25–2.40), with a strong association observed in women aged >50 years.[13]

As a heterogeneous disease category, CNBM encompasses several subtypes, primarily Plasma Cell Mastitis (PCM) and Idiopathic Granulomatous Mastitis (IGM). Pathologically, it is characterized by atypical ductal epithelial hyperplasia, inflammatory cell infiltration, progressive fibrosis, and the formation of non-caseating granulomas. The main clinical manifestations include non-cyclical breast pain, palpable breast masses, nipple discharge, breast abscesses, and sinus tract formation.[14–17] It is important to note that although CNBM resembles several related conditions, they have some distinguishing characteristics. Bacterial mastitis, for instance, has an acute onset accompanied by fever and purulent discharge, and usually resolves well with antibiotics. In contrast, breast cancer typically presents as a painless, hard mass with irregular borders, seldom involving inflammation.

CNBM is a challenging benign breast disease that poses significant difficulties in clinical diagnosis and treatment. First, its clinical manifestations and imaging characteristics can be indistinguishable from those of breast cancer, often leading to unnecessary biopsies or surgeries.[18] Consequently, core needle biopsy remains the gold standard for histological diagnosis and is indispensable for excluding malignancy prior to considering inflammatory etiologies. Second, since its pathogenesis is primarily linked to autoimmune reactions, dysregulated inflammatory pathways, or metabolic abnormalities rather than bacterial infection,[19] antibiotic therapy is typically ineffective. Furthermore, the absence of clear therapeutic targets and satisfactory treatments means patients frequently endure recurrent episodes and a chronic disease course, severely affecting psychological health by inducing anxiety and depression, while also compromising quality of life through social isolation and impaired reproductive confidence, as reported in patient surveys.[20]

Current treatment strategies are diverse, yet clinical outcomes remain suboptimal. Pharmacologic regimens include corticosteroids, which are associated with adverse effects such as temporary steroid-induced diabetes mellitus and have a long-term recurrence rate ranging from 28.8% to 40%. Methotrexate fails to achieve remission in 14.9% of cases and carries side effects including nausea and vomiting. Azathioprine's efficacy in special populations, such as pregnant patients, remains insufficiently validated, and it may pose rare risks like cytopenia. Rifampicin-based triple therapy results in a lack of response in 5.96% of patients and a recurrence rate of 8.72%, typically accompanied by mild adverse events.[21–24] Additionally, traditional Chinese medicine options, such as Radix Bupleuri formulations and Yanghe Decoction, lack large-sample randomized controlled trials; partial formulations exhibit an unresponsive rate of 6.5% to 15.38%, and long-term efficacy remains to be fully validated.[25–28] Surgical interventions, which range from lesion excision and quadrantectomy to Mammotome minimally invasive excision and nipple correction, may achieve local control but carry the risk of breast deformity.[29–31] Similarly, physical therapies like microwave ablation, hyperbaric oxygen, and local thermotherapy offer symptomatic relief but no curative effect.[32–34] Collectively, these modalities not only have limited efficacy but also cause significant side effects, contributing to psychological distress such as anxiety and fear.[35–37] While existing research has explored drug administration methods and timing, these efforts are confined to conventional therapies and have yielded no significant improvements in efficacy or side effect management.[38–40] Consequently, there is an urgent and unmet need for the development of novel therapeutic strategies for CNBM (Figure 1).

Unlike conventional pharmacotherapies, research at the molecular level seeks to identify more precise drug targets, thereby enhancing therapeutic efficacy while minimizing adverse effects. Current research indicates that the pathogenesis and progression of CNBM are characterized by significant dysregulation of various inflammatory signaling pathways, with notable aberrant activation of key pathways like Nuclear Factor kappa B (NF-κB), Janus kinase-Signal Transducer and Activator of Transcription (JAK-STAT), and Mitogen-Activated Protein Kinase(MAPK). These discoveries lay

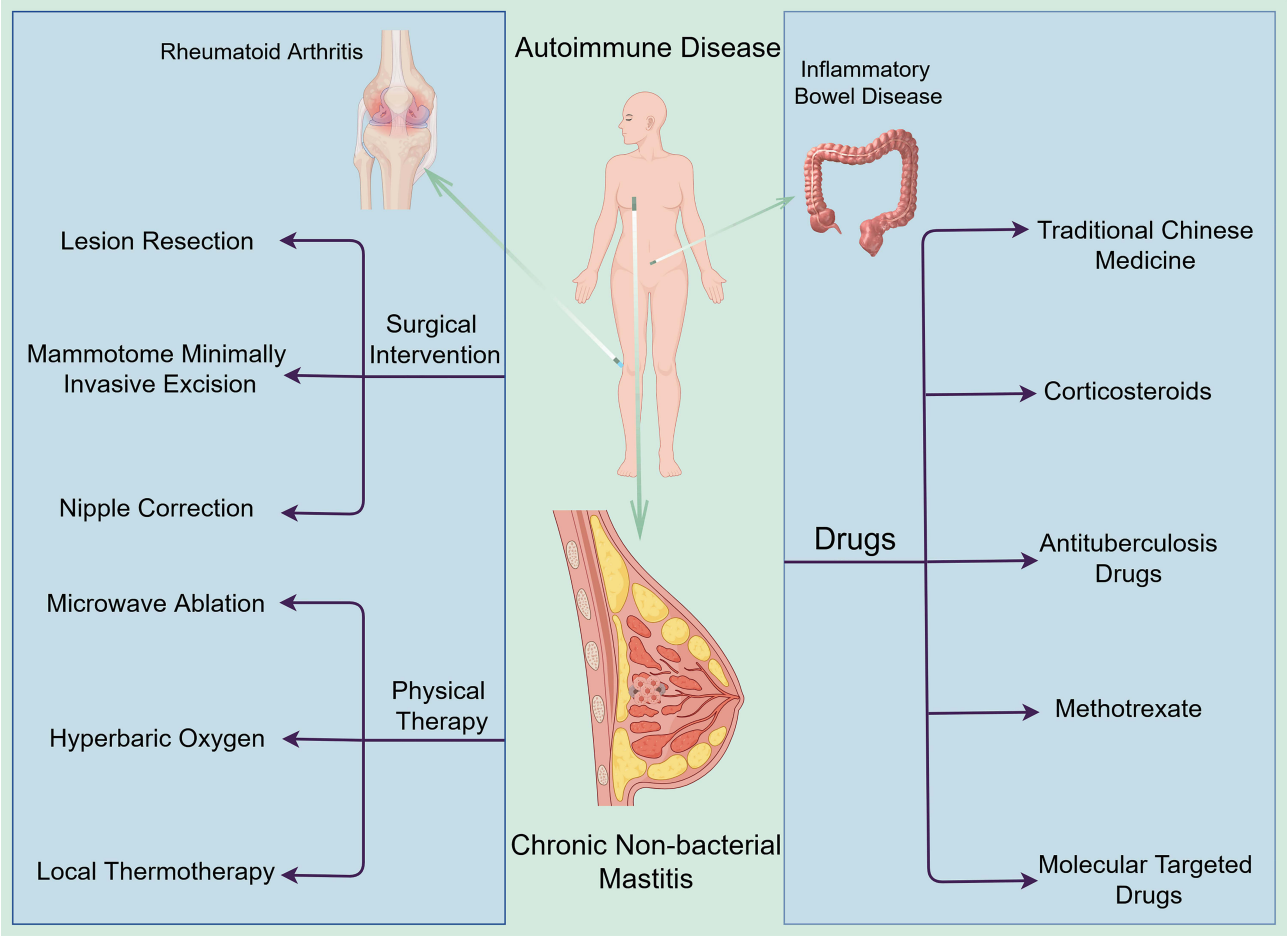


**Figure 1** Current therapeutic approaches for chronic non-bacterial mastitis. The schematic demonstrates that chronic non-bacterial mastitis exhibits parallels with other autoimmune disorders, indicating that therapeutic approaches for the latter may be applicable. It also presents the current primary treatment modalities, encompassing pharmacological therapy, surgical intervention, and physical therapy.

a theoretical foundation for the development of molecular targeted drugs. Emerging technologies such as single-cell RNA sequencing to map immune cell subsets in lesions and dynamic contrast-enhanced MRI to assess treatment response are further advancing target identification and therapeutic monitoring.[41,42]

As the principles of precision medicine gain traction, molecular targeted therapies directed against these dysregulated pathways are emerging as a new frontier in CNBM research. Such therapies represent not merely an alternative, but a potential paradigm shift—moving beyond symptomatic suppression toward interrupting the core pathogenic mechanisms. Additionally, cross-disciplinary collaboration involving immunologists deciphering inflammatory pathways, oncologists adapting targeted therapy platforms, and breast surgeons optimizing combined treatment regimens is accelerating translational research and clinical application. Molecular targeted therapies thus hold the promise of providing more effective and safer treatment options for this challenging condition, ultimately improving patients' long-term outcomes and quality of life.

## Theoretical Rationale

The molecular pathogenesis of CMBM is characterized by the complex interplay of various inflammatory signaling pathways. The aberrant activation of these pathways provides the theoretical foundation for molecular targeted therapy. As research into the disease mechanism has advanced, several key signaling pathways have been identified by researchers as potential therapeutic targets.


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## NF-κB Signaling Pathway

NF-κB signaling pathway is a crucial intracellular pathway governing key biological processes such as inflammation, immune response, and cell survival.[43] It stands as one of the most significantly dysregulated inflammatory pathways in the pathogenesis of mastitis.[44] Research indicates that the NF-κB pathway is persistently activated in IGM tissues. Relative to a control population, patients with IGM exhibit significantly elevated expression levels of interleukin-1β (IL-1β), monokine induced by gamma interferon (MIG), macrophage inflammatory protein (MIP)-1α, MIP-1β, and tumor necrosis factor receptor 2 (TNF RII).[45] Additional studies have reported that, compared with healthy female controls, IGM patients have significantly higher serum levels of IL-6, interleukin-10 (IL-10), and tumor necrosis factor-α (TNF-α).[46] A comparative analysis of IGM lesion tissue versus normal breast tissue using single-cell RNA sequencing (scRNA-seq) has revealed that macrophage subpopulations in IGM tissue undergo a shift towards a pro-inflammatory phenotype. This is evidenced by the enrichment of signaling pathways such as interferon-γ (IFN-γ), IFN-α, IL-6/JAK/STAT3, and TNF-α/NF-κB.[41] This sustained inflammatory response further recruits immune cells, creating a vicious cycle that exacerbates tissue damage and fibrosis. From a therapeutic standpoint, molecular targeted drugs directed against the NF-κB pathway have demonstrated considerable efficacy in other inflammatory diseases,[47] thus providing a strong rationale for their application in CNBM.

## JAK-STAT Signaling Pathway

The JAK-STAT signaling pathway is a crucial conduit for cytokine signal transduction, governing key biological processes such as immune response, cell proliferation, and differentiation.[48] It plays a pivotal role in the pathogenesis of CNBM.[49] The phosphorylation of JAK and STAT governs the transduction of signals to the nucleus, subsequently regulating the production of chronic inflammatory mediators and the activation of immune cells in autoimmune diseases.[50,51] Research indicates that in certain inflammatory conditions, persistent activation of this pathway leads to extensive recruitment of inflammatory cells and overexpression of inflammatory cytokines.[52] Furthermore, studies on PCM have revealed that the IL-6/JAK/STAT3 pathway is significantly activated.[49] Relative to patients with benign breast tumors, those with IGM exhibit significantly elevated levels of IL-6 and C-reactive protein (CRP), suggesting that IL-6 is a key driver in the pathogenesis of IGM.[53] Additional research has confirmed dysregulation of multiple immune molecules—including IL-2, IL-4, IL-6, and IL-10—in the serum and tissue microenvironment of IGM patients. These molecules and their associated pathways represent potential targets and avenues for breakthrough in the future treatment of IGM.[54] Critically, the various components of the JAK-STAT pathway have been validated as ideal targets for small-molecule inhibitors and biologics, presenting a significant opportunity for treating chronic inflammatory diseases.[55]

## MAPK Signaling Pathway

The MAPK signaling pathway is central to the regulation of inflammatory responses and cellular stress.[56] Analysis of IGM lesion tissue using scRNA-seq has revealed that mammary luminal cells from IGM patients exhibit an impaired estrogenic profile while showing upregulation in prolactin's downstream pathways, notably JAK-STAT and MAPK.[41] Acting as an upstream molecule in the MAPK pathway, IL-17 expression is also significantly elevated in IGM patients compared to controls. Moreover, in its capacity as a pro-inflammatory cytokine, IL-17 can serve as a biomarker for assessing inflammatory damage in autoimmune diseases.[57,58] The components of the MAPK pathway, which are key molecules in cellular signal transduction, are regarded as promising targets for drug development. To this end, small-molecule MAPK inhibitors designed for inflammatory diseases have already advanced to clinical trials.[59]

## Toll-Like Receptor (TLR) Signaling Pathway

The TLR signaling pathway serves as a crucial link between the innate and adaptive immune systems, playing a central role in pathogen recognition and immune signal transduction.[60] A comparative analysis of IGM lesion tissue using scRNA-seq has revealed extensive immune cell infiltration, accompanied by the enrichment of the TLR pathway.[41] In comparison with healthy controls, patients with IGM exhibit significantly reduced serum levels of LL-37, IL-36α,

galectin-3 and TLR3. The reduction in LL-37 may, in turn, lead to decreased levels of IL-36α and TLR3, suggesting that these molecules are potentially involved in the pathogenesis of IGM.[61]

### NOD-Like Receptor Family Pyrin Domain-Containing Protein 3 (NLRP3) Signaling Pathway

The NLRP3 signaling pathway mediates innate immune responses and inflammation via the NLRP3 inflammasome. Its overactivation or dysregulation results in the excessive release of inflammatory cytokines, including IL-1β and IL-18, thereby inducing chronic inflammation and autoinflammatory responses. This process is implicated in the pathogenesis of numerous autoinflammatory and autoimmune diseases.[62] Inhibition of the NLRP3 signaling pathway can reduce plasma cell infiltration in breast tissue and downregulate the expression of key pro-inflammatory cytokines such as IL-1β, TNF-α, IL-2 and IL-6.[63]

Evidence suggests that the aforementioned signaling pathways are intimately involved in the pathogenesis and progression of CNBM, thereby providing a theoretical foundation for the development of novel molecular targeted drugs (Table 1). However, these pathways do not function independently; rather, they constitute a complex signaling network. Consequently, a combination inhibition strategy that targets multiple pathways is likely to be more effective than the inhibition of a single pathway.

## Preclinical Research

The preclinical research of molecular targeted drugs for CNBM is primarily dependent on animal models, which serve as a crucial platform for elucidating disease mechanisms and assessing potential therapeutic efficacy. To date, researchers have developed several relevant inflammatory and autoimmune mastitis models for the evaluation of the efficacy and safety of potential therapies.

### Animal Models

Mice and rats are the primary species used for modeling CNBM. A PCM model can be successfully induced in 6–8 week-old female BALB/c mice. This is achieved by co-injecting a water-in-oil emulsion—comprising the supernatant from ground normal mammary tissue mixed with Complete Freund's Adjuvant (CFA)—and recombinant mouse IL-6 into the subcutaneous mammary tissue.[73] A stable, reproducible, and long-lasting rat model that closely mimics

**Table 1** Main Dysregulated Signaling Pathways and Related Potential Molecular Targeted Drugs in Chronic Non-Bacterial Mastitis

| Signaling Pathways | Relevant Constituent Molecules | Relevant Cytokines | Pathway Alteration | Potential Drugs | Drug targets | Related Diseases | Clinical Phase | References |
|---|---|---|---|---|---|---|---|---|
| NF-κB | TRAF, IKKs, NF-κB | IL-1β, IL-6, TNF-α | Activated | Infliximab | TNF-α | RA, CD, AS | Approved | [64] |
| | | | | Adalimumab | TNF-α | RA, Psoriasis, UC | Approved | [65] |
| JAK-STAT | JAKs, STATs | IL-6 | Activated | Tofacitinib | JAKs | RA, PsA, UC | Approved | [66] |
| | | | | Baricitinib | JAK1/ JAK2 | RA, Atopic Dermatitis | Approved | [67] |
| | | | | Tocilizumab | IL-6 | RA, sJIA | Approved | [68] |
| MAPK | MKKs, p38, MAPK | IL-1β, IL-6, TNF-α | Activated | Losmapimod | P38 | Inflammatory Diseases | Preclinical Research | [69] |
| TLR | TLRs, MyD88, IRAK4, TRAF6, TAK1 | IL-1β, IL-6, TNF-α | Activated | PF-06650833 | IRAK4 | Inflammatory Diseases | Preclinical Research | [70] |
| NLRP3 | NLRP3, ASC, caspase-1 | IL-1β, IL-6, TNF-α | Activated | Pralnacasan (VX-740) | Caspase-1 | Inflammatory Diseases | Preclinical Research | [71] |
| | | | | Anakinra | IL-1β | RA, NOMID | Approved | [72] |

**Abbreviations**: RA, Rheumatoid Arthritis; CD, Crohn's Disease; AS, Ankylosing Spondylitis; UC, Ulcerative Colitis; PsA, Psoriatic Arthritis; sJIA, Systemic Juvenile Idiopathic Arthritis; NOMID, Neonatal-Onset Multisystem Inflammatory Disease.

human IGM has been developed using 6–7 week-old female SD rats. This model is established by injecting a tissue homogenate, prepared from breast lesions of IGM patients which contains granulomas or necrotic tissue, in conjunction with CFA.[74]

## Exploration of Therapeutic Targets

To date, several molecular targeted drugs have demonstrated potential therapeutic value in preclinical models of CNBM, with a primary focus on Traditional Chinese Medicine (TCM) and small-molecule inhibitors (Table 2). The involvement of key signaling pathways in the pathogenesis of CNBM, coupled with the availability of numerous molecular targeted drugs against these pathways, presents a compelling opportunity to test and validate a broader spectrum of therapeutics in preclinical CNBM models.

## Challenges in Translational Research

Despite encouraging preliminary results from current preclinical studies, the translation of these findings into clinical practice faces several hurdles. First, the rodents used to model CNBM possess immune systems and mammary gland structures that differ significantly from those of humans, potentially compromising the accuracy of efficacy assessments. Overcoming this challenge necessitates the development of novel models that more closely recapitulate human disease, such as humanized mouse models or 3D organoids.[79,80] Second, CNBM is inherently heterogeneous, encompassing multiple subtypes, and it is hypothesized that each subtype possesses distinct molecular characteristics and dominant signaling pathways. Preclinical models often fail to fully replicate this heterogeneity, thereby limiting the generalizability of corresponding therapeutic strategies. Future research will require more refined disease stratification to facilitate the development of more precise, targeted molecular therapies. Furthermore, the mammary gland tissue exhibits unique drug distribution properties. A critical consideration is ensuring that molecular targeted drugs, even those effective for similar diseases, achieve therapeutic concentrations at the lesion site. Novel drug delivery systems, such as nanoparticles and liposomes, could offer a means to optimize drug distribution and retention within the mammary tissue.[81,82]

# Challenges in Clinical Research

To date, clinical research into molecular targeted therapies for CNBM remains in its nascent stages, with no large-scale randomized controlled trials (RCTs) having been reported. The existing clinical evidence is largely limited to case reports and data extrapolated from studies on other inflammatory conditions, which highlights a significant research gap in the

**Table 2** Molecular-Targeted Drugs Evaluated in Preclinical Studies of Chronic Non-Bacterial Mastitis

| Drug Category | Drugs | Relevant Molecules or Signaling Pathways | Evaluation Model | Subtype | Functional Effect | Reference |
|---|---|---|---|---|---|---|
| TCM | Yanghe decoction | TLR4/Myd88/NF-κB | Mouse, HC11 cells | Mastitis | Reduce the expression of pro-inflammatory factors (TNF-α, IL-6 and IL-1β). | [75] |
| TCM | Sinomenine hydrochloride | IL-6/JAK2/STAT3 | Mouse | PCM | Decrease the percentage of CD138+ plasma cells, suppress the activation of JAK2 and STAT3. | [76] |
| TCM | Shugan Sanjie decoction | JAK-STAT | Mouse | PCM | Reduce the protein expression of p-JAK2/JAK2, p-STAT3/STAT3 and IL-6. | [77] |
| TCM | Broadleaf Mahonia | CCL-5 | Mouse, RAW264.7 cells | IGM | Decrease activity of NF-κB and MAPK signaling, inhibit the expression of IL-1β and IL-6. | [78] |
| Small-molecule inhibitor | MCC950 | NLRP3 | Mouse | PCM | Reduce plasma cell infiltration, decrease the expression of IL-1β, TNF-α, IL-2 and IL-6. | [63] |
| Small-molecule inhibitor | AG-490 | JAK2/3 | Mouse | PCM | Reduce the presence of plasma cells, decrease the levels of IL-6, p-JAK2$^{Y1007/1008}$ and p-STAT3$^{Y705}$ | [73] |

**Abbreviations**: TCM, Traditional Chinese Medicine; PCM, Plasma Cell Mastitis; IGM, Idiopathic Granulomatous Mastitis.

field. Consequently, therapeutic decisions in clinical practice are predominantly guided by physician experience and the off-label application of therapies developed for other inflammatory diseases.

In the absence of dedicated clinical trials, case reports offer valuable clinical insights. For instance, reports indicate that patients with comorbid rheumatoid arthritis (RA) and PCM experienced remission of mastitis symptoms following treatment with TNF-α antagonists. This suggests that TNF-α antagonists may represent a potential therapeutic strategy for mastitis.[83] Certolizumab, a drug commonly used for RA and Crohn's disease (CD), has also demonstrated therapeutic potential in the treatment of IGM.[84] Furthermore, additional research suggests that anti-TNF-α antibodies, such as adalimumab, may be effective against IGM, particularly in cases that are refractory or recurrent.[85,86]

Despite the current lack of clinical trials dedicated to CNBM, relevant pharmacodynamic and safety data can be extrapolated from clinical trials for other inflammatory and autoimmune diseases. Research has explored the potential link between IGM and systemic lupus erythematosus (SLE), indicating a high degree of similarity between the two conditions.[87] The co-occurrence of IGM with erythema nodosum has been observed in some cases, where patients exhibit a higher incidence of breast ulcers and a poorer prognosis, hinting at a shared pathogenic mechanism.[88,89] Given the overlapping clinical features of IGM, erythema nodosum, and arthritis (with or without), along with a positive response to glucocorticoids, it has been proposed that this constellation of symptoms represents an under-recognized systemic autoimmune disease, designated by the acronym "GMENA" (Granulomatous Mastitis, Erythema Nodosum, Arthritis) syndrome.[90] Owing to its immune-mediated pathogenesis, IGM shares similarities with autoimmune rheumatic diseases, wherein cytokines like TNF-α, IL-6, and the Th17 axis play pivotal roles in sustaining granulomatous inflammation.[91] Furthermore, a review of anti-rheumatic drugs in the treatment of IGM has demonstrated that agents such as methotrexate, azathioprine, and mycophenolate mofetil yield favorable therapeutic outcomes.[92] Collectively, these findings suggest that drugs with proven efficacy in other inflammatory or autoimmune conditions are promising starting points for identifying molecular targeted therapies for CNBM. For instance, JAK inhibitors are already clinically applied for a range of inflammatory and autoimmune diseases.[93,94] Several inhibitors of this pathway, such as tofacitinib and baricitinib, have demonstrated clinical efficacy in conditions like RA, psoriasis, and inflammatory bowel disease, thereby enhancing the feasibility of their application in CNBM.[95,96]

## Future Research Directions

With the rapid development of molecular biology technologies and the in-depth advancement of precision medicine concepts, research on molecular targeted therapy for CNBM is ushering in new opportunities.

### Molecular Subtyping and Precision Medicine

Given the inter-patient variability in disease characteristics, genetic backgrounds, and immune statuses, there is a critical need to tailor treatment strategies to the individual. The molecular heterogeneity of CNBM is likely a key contributor to the variable therapeutic responses currently observed. Future research should employ multi-omics approaches, including genomics, transcriptomics, and proteomics, to systematically stratify patients and identify distinct molecular subtypes. Integrated analytical techniques, such as proteogenomics, have been shown to offer a more comprehensive understanding of disease complexity and should be leveraged in CNBM research.[97] Precision therapy guided by molecular subtyping holds the promise of enhancing treatment response rates, minimizing unnecessary drug exposure and adverse effects, and ultimately realizing the goal of truly personalized medicine.

### Novel Drug Development Strategies

Building upon a deeper understanding of CNBM pathogenesis, future research and development of molecular targeted drugs should be directed towards several key areas. First, the development of small-molecule inhibitors with enhanced selectivity and improved safety profiles should target key signaling pathways already identified in CNBM, such as NF-κB, JAK-STAT, and MAPK. Notably, the design of drugs with mammary tissue-specific targeting holds the potential to increase local drug concentrations while minimizing systemic exposure and adverse effects. Second, monoclonal antibodies directed against specific cytokines like IL-6, TNF-α, and IL-1β have demonstrated efficacy in other inflammatory diseases and warrant systematic evaluation in CNBM. Likewise, other molecular targeted agents beyond

monoclonal antibodies, already approved for chronic inflammatory conditions, should be systematically assessed for their potential utility in CNBM. This approach can shorten the timelines and reduce the costs of new drug development, thereby accelerating patient access to therapeutic options.[98] Moreover, given the inherent complexity and redundancy of inflammatory pathways, multi-pathway combination therapies are likely to be more effective than single-pathway inhibition. For instance, combining a JAK inhibitor with low-dose corticosteroids,[99] or pairing inhibitors from different pathways, could yield synergistic effects while simultaneously lowering the dose and associated toxicity of individual agents.[100]

Crucially, to realize these advancements, interdisciplinary collaboration integrating immunology, oncology, breast surgery, and molecular biology will be essential to accelerate translational research and optimize therapeutic strategies. However, despite this promise, it is important to acknowledge potential challenges in adopting molecular targeted therapy for a benign condition like CNBM. Key considerations include the high cost of targeted agents, long-term safety profiles in a predominantly young female population, and the necessity of balancing therapeutic benefits against the self-limiting or steroid-responsive nature of some cases. Therefore, future studies must incorporate cost-effectiveness analyses and long-term follow-up to ensure these therapies are both clinically and economically viable.

## Summary of Findings

CNBM, a heterogeneous benign breast disease of unclear etiology and pathogenesis, currently suffers from limited and variable therapeutic options. This analysis of existing evidence suggests that molecular targeted therapy represents a promising new strategy with the potential to transform the management of this condition.

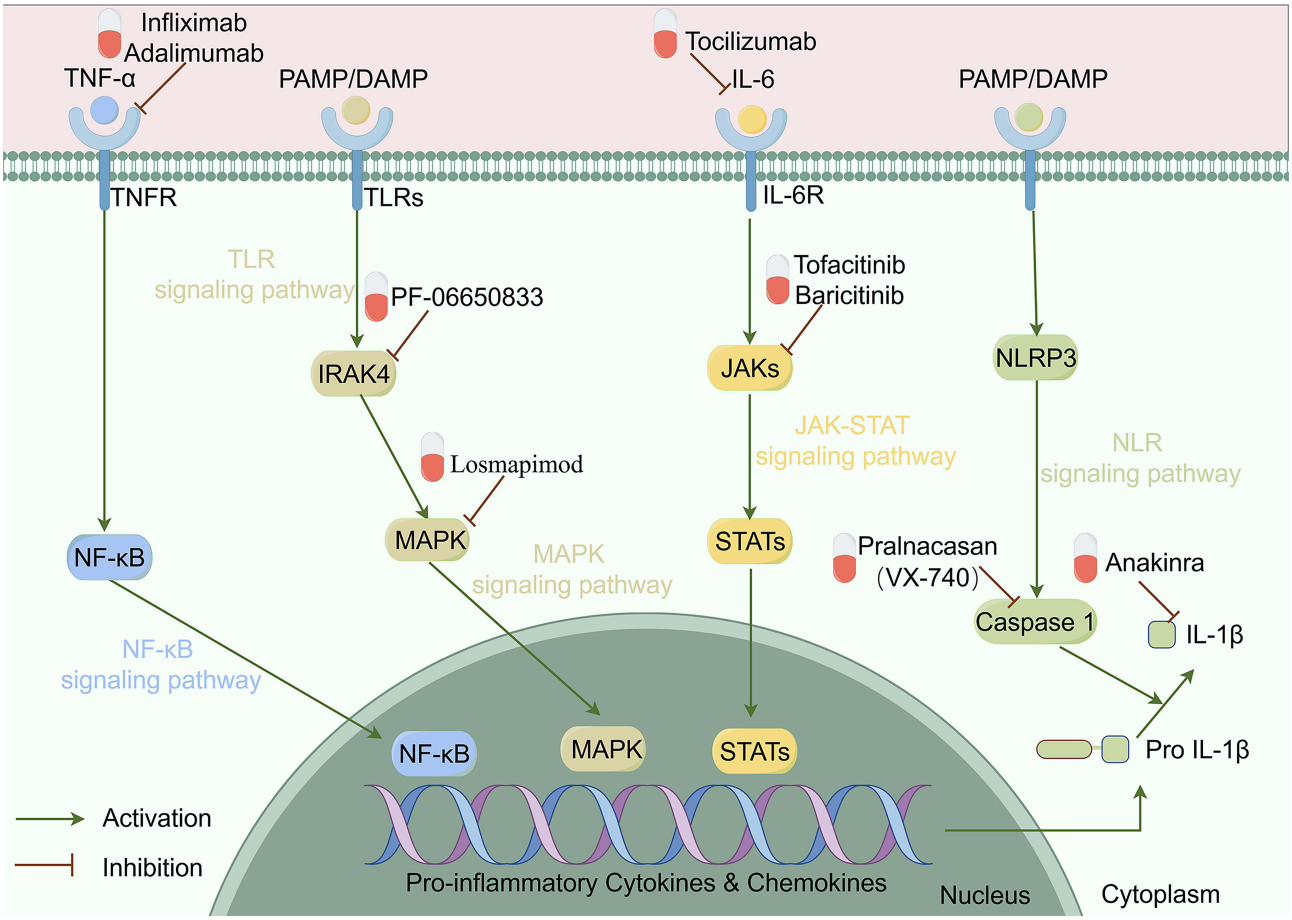


**Figure 2** Main signaling pathway alterations in chronic non-bacterial mastitis. The schematic illustrates key dysregulated pathways, potential intervention targets, and candidate drugs for therapy.

Signaling pathway analyses reveal that CNBM is characterized by significant dysregulation of multiple inflammatory cascades. Preliminary evidence specifically implicates key pathways such as NF-κB, JAK-STAT, and MAPK, thereby providing a strong theoretical foundation for targeted interventions. The efficacy of inhibitors against these pathways has been further corroborated in preclinical animal models (Figure 2). However, a significant translational gap exists, as clinical data are largely confined to case reports. The stark paucity of large-scale, high-quality clinical trials highlights the nascent state of research in this field.

## Conclusion

With the growing adoption of precision medicine and the proven success of molecular targeted drugs in other inflammatory diseases, it is reasonable to anticipate significant advancements in the molecular targeted therapy for CNBM in the coming years. Deepen the understanding of the molecular mechanisms of the disease through multi-omics approaches to achieve precision treatment based on molecular subtyping; develop novel selective inhibitors targeting key pathways and explore combined therapeutic strategies; and ultimately provide patients with more effective and safe treatment options, as well as improve clinical outcomes and quality of life, through interdisciplinary collaboration and sustained research investment.

Molecular targeted therapy offers a new paradigm and a promising opportunity for the management of CNBM. While the path forward is challenging, the outlook is bright. Realizing this potential will require the collective efforts of researchers, clinicians, and patients to drive this field forward, with the ultimate goal of alleviating the disease burden and improving the quality of life for affected individuals.

## Abbreviations

CNBM, Chronic non-bacterial mastitis; IL-6, interleukin-6; HLA, Human leukocyte antigen; PCM, Plasma cell mastitis; IGM, Idiopathic granulomatous mastitis; NF-κB, Nuclear factor kappa B; JAK-STAT, Janus kinase-Signal transducer and activator of transcription; MAPK, Mitogen-activated protein kinase; IL-1β, interleukin-1β; MIG, monokine induced by gamma interferon; MIP, macrophage inflammatory protein; TNF RII, tumor necrosis factor receptor 2; IL-10, interleukin-10; TNF-α, tumor necrosis factor-α; scRNA-seq, single-cell RNA sequencing; IFN-γ, interferon-γ; CRP, C-reactive protein; TLR, Toll-like receptor; NLRP3, NOD-like receptor family pyrin domain-containing protein 3; CFA, Complete freund's adjuvant; TCM, Traditional chinese medicine; RCTs, Randomized controlled trials; RA, rheumatoid arthritis; CD, Crohn's disease; SLE, systemic lupus erythematosus.

## Data Sharing Statement

All the original data of this study belong to the authors. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Disclosure

All authors declare no financial or non-financial competing interests in this work.

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