Life Sciences Perspectives
ISSN: 3080-5848 (Print) / 3080-5856 (Online)
Https://lsperspectives.com
Editor@lsperspectives.com

CHEMICAL APPROACHES TO MODULATING THE IMMUNE RESPONSE: SYNTHESIS OF SMALL MOLECULE IMMUNE MODULATORS FOR AUTOIMMUNE DISEASES

Younas Rehman[1*], Abdul Waheed Shah[2], Ezza Fatima[3]

[1]Lady Reading Hospital, MTI, Peshawar, Khyber Pakhtunkhwa, Pakistan

[2]Gomal Center of Biochemistry and Biotechnology, Gomal University, Dera Ismail Khan-29050-Pakistan

[3]Department of Biosciences, Shaheed Zulfikar Ali Bhutto Institute of Science and Technology University, Karachi, Pakistan

*Corresponding Author E-mail: younasrehman2019@gmail.com

Abstract

The autoimmune diseases are illnesses that arise as a result of aberrant activation of the immune system, chronic inflammation, and tissue damage. Small molecule immune modulators have shown great promise in giving cause for hope in therapeutic intervention through specific immune pathway modulation. These small molecules demonstrate advantages over biologics in terms of oral bioavailability, production cost, and tissue penetration. Recent advances in chemical synthesis and applications of small molecule modulators on innate immune receptors, such as Toll-like receptors (TLRs), nucleic acid sensing pathways, and inflammasomes, have also been reviewed in this paper. Particular attention has been given to TLR4 modulators, which are regarded as one of the most extensively studied TLRs concerning inflammatory diseases. Targeting of the cGAS-STING pathway and NLRP3 inflammasome have also gained much attention with respect to their therapeutic potentials in systemic lupus erythematosus (SLE), rheumatoid arthritis, and inflammatory bowel disease.

The modulators have differing modes of action such as inhibition for excessive immune activity or promotion of immune tolerance for the specific recipient. Advances in structure-based drug design and artificial intelligence-driven virtual screening for the discovery of new compounds have been comprehended in this review too. Several modulators, examples include Eritoran, TAK-242, and MCC950, have entered clinical trials, which highlights the promise of such approaches to clinical practice. However, there are certain challenges in specificity, off-target effects, and toxicity, which need to be overcome for an optimizing therapy. Future investigations will assess the effects of small molecule modifiers on pharmacokinetics despite focusing on the long-term efficacy and safety of these compounds in various patient demographics. Conclusively, this review captures the possibility of changing treatment perspectives for autoimmune and inflammatory diseases through the small molecules immune modulators.

Keywords: "Small Molecule Modulators", "Immune Response", "Autoimmune Diseases", "Inflammation".

Article History

Received:
January 12, 2024

Revised:
February 19, 2024

Accepted:
March 22, 2024

Available Online:
June 30, 2024

INTRODUCTION

For the immune system, the defense against pathogens is quite complicated. It not only has to perform these functions but also has to issue self-tolerance. Misregulation of many of these pathways will end up giving autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus (SLE), and inflammatory bowel disease (Smith et al., 2020; Johnson et al., 2019).

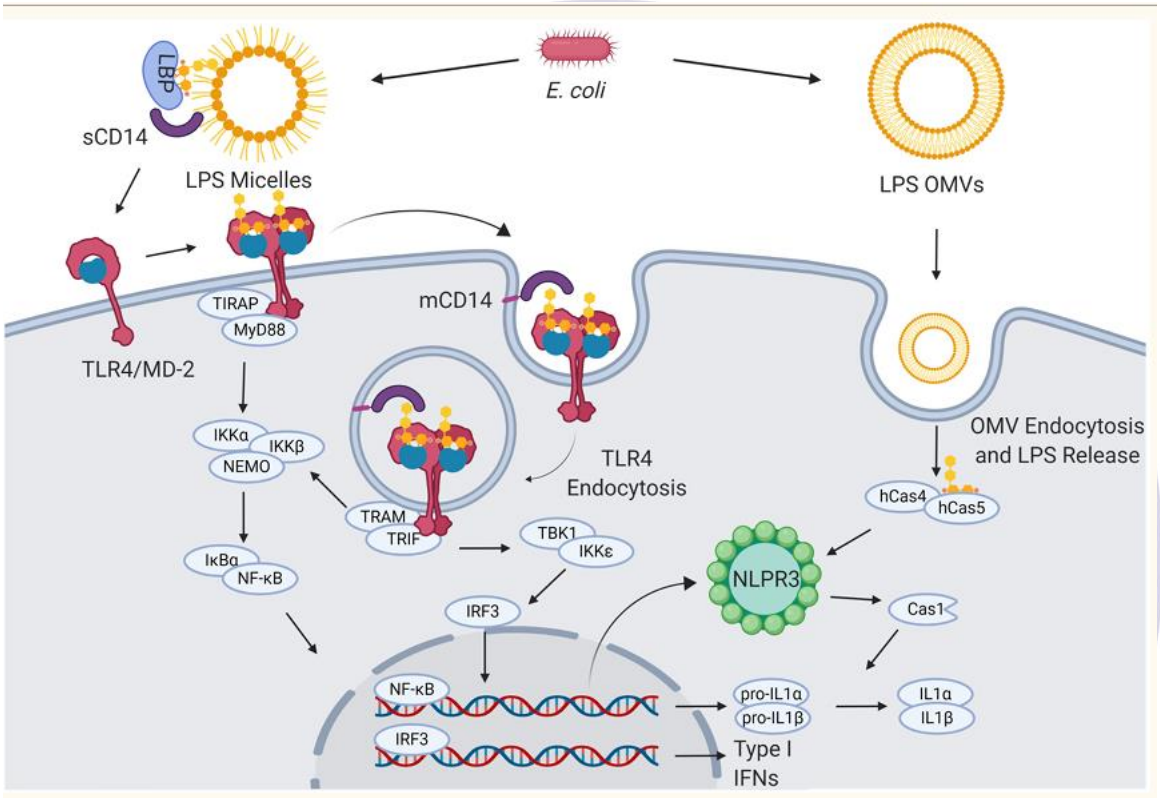

Figure 1: LPS signaling. Extracellular gram-negative bacteria release LPS in the form of micelles or OMVs. LPS contained in micelles or OMVs penetrate cells for intracellular delivery which leads to caspase-dependent signaling pathways (right). The protein LBP enables CD14 to bind with LPS monomers through solution. CD14 boosts the LPS recognition sensitivity of TLR4-MD2 by promoting these components to form rafts with LPS and CD14 molecules inside the plasma membrane lipid domains. Once located in the lipid raft TLR4-MD2 initiates TIRAP-MyD88-dependent signaling events. Endocytosis of LPS and TLR4-MD2 occurs due to CD14. Through endosomes TLR4-MD2 activates both TRAM-TRIF signaling to extend the activation of NF-κB and type I IFN production.

Autoimmunity is defined as the process in which the immune system mistakes its own

tissues to be attacked, resulting in chronic inflammation and tissue damage (Miller et al., 2018). Small molecule immune modulators aim restriction or activating specific receptors and signaling cascades through targeted rebalancing of immune responses (Brown et al., 2018; Kim et al., 2021). Their advantages include ease of administration relative to biologic agents, lower production costs, and reduced immunogenicity compared to biologics (Jones et al., 2020).

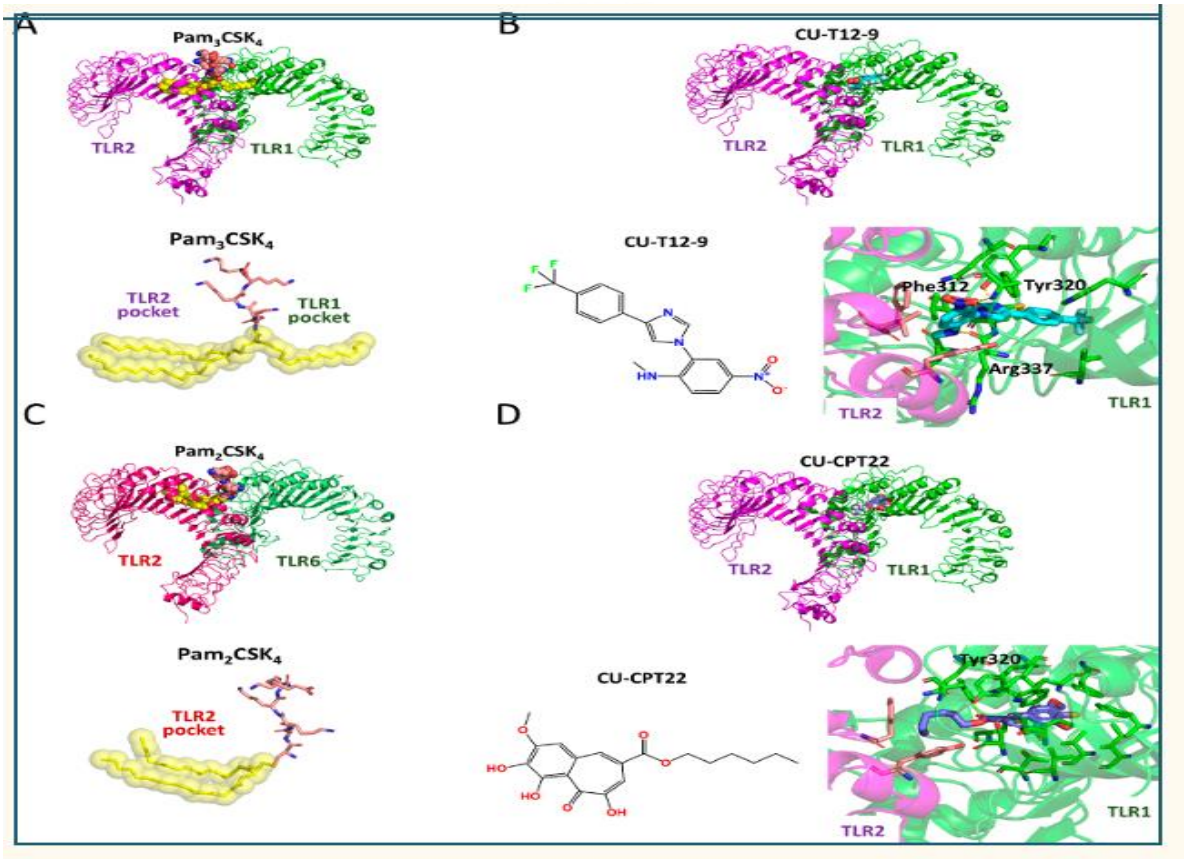

Figure 2: All binding sites from mouse TLR2/TLR6 ligand interactions as well as human TLR1/TLR2 ligand interactions were analyzed. (A) Human TLR1/TLR2/Pam3CSK4 complex with crystal structure PDB ID 2Z7X Using docking, the study reveals how agonist CU-T12-9 hooks to human TLR1/TLR2 receptors. (C) Crystal structure of the mouse TLR2/TLR6/Pam2CSK4 complex with PDB ID 3A79. Docking of antagonist CU-CPT22 in the human TLR1/TLR2 complex. Among the found residues are those which establish hydrogen bonds with the ligands.

Recent investigations, however, place Toll-like receptors (TLRs) as prime modulators of innate immunity. TLRs recognize pathogen-associated molecular patterns (PAMPs) and damage-associated

molecular patterns (DAMPs) to activate downstream inflammatory signaling pathways (Lee et al., 2021; Adams et al., 2020).

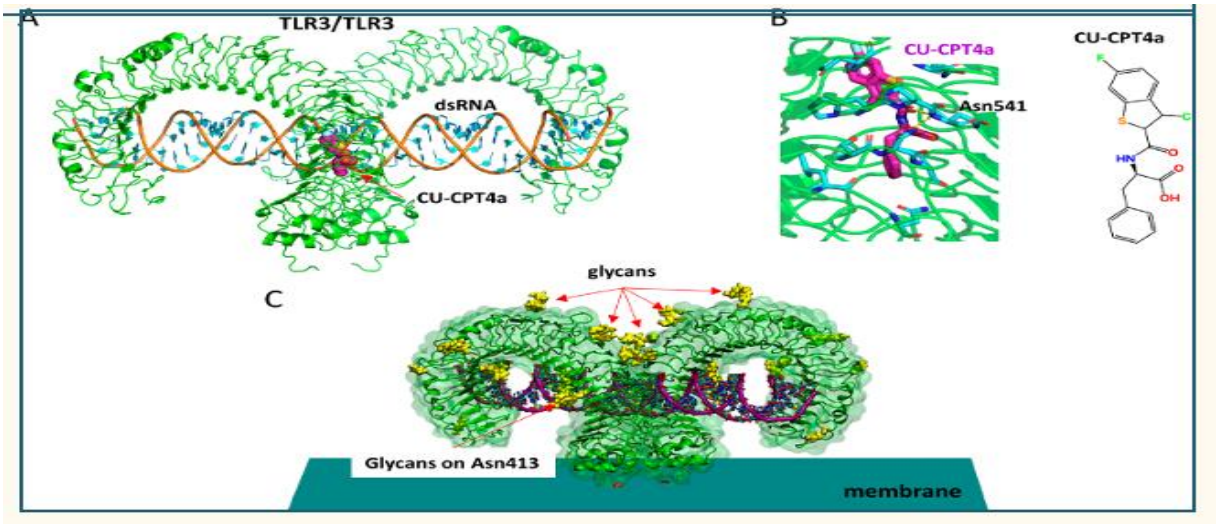

Figure 3. Structures of TLR3/dsRNA complexes and the TLR3 antagonist CU-CPT4a. Both dsRNA and CU-CPT4a complexes bind to the homodimer of human TLR3 as depicted in this view. Binding details of CU-CPT4a to TLR3. Yellow spheres that function as glycans were exposed through the crystallization process.

TLR4 is among the most studied and well-known when it comes to the inflammatory and autoimmune diseases. The activation of TLR4 by lipopolysaccharides (LPS) or endogenous ligands induces the MyD88-dependent and TRIF-dependent pathways for the release of pro-inflammatory cytokines (Wang et al., 2019). Small molecule TLR4 antagonists like TAK-242 and Eritoran hold good promise in lessening the inflammation tied to immunological diseases while inhibiting inferring TLR4-mediated signaling (Chen et al., 2019; Wilson et al., 2017; Li et al., 2021). Likewise, synthetic TLR7/8/9 antagonists, such as M5049 and BMS-986256, are being formulated to manipulate endosomal nucleic acid sensing pathways-care conditions such as SLE and Sjogren's syndrome into therapy (Martinez et al., 2022; Gupta et al., 2021; Zhao et al., 2020).

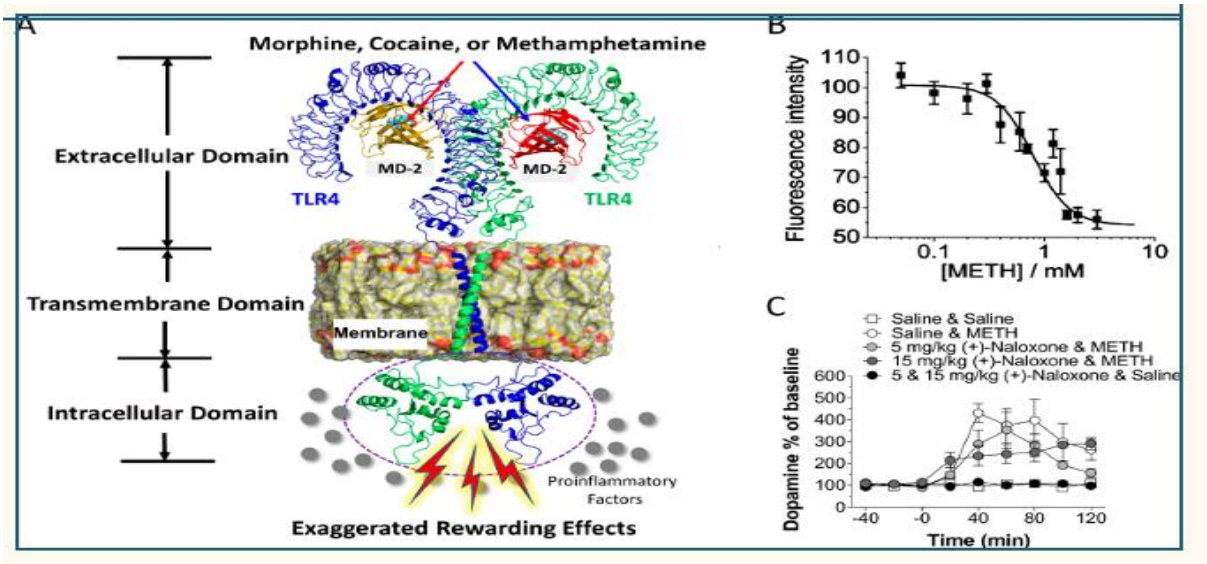

Figure 4: The psychoactive agents morphine, cocaine, and methamphetamine cause aberrated rewarding behaviors by activating TLR4 signaling. The figure below depicts the mechanism by which TLR4 activates microglial rewarding effects. Methamphetamine (METH) interacts with MD-2 to replace the widely used fluorescent probe Bis-ANS which normally binds inside the MD-2 cavity17. METH generates elevated dopamine levels inside the nucleus accumbens shell segment17. The copyright for this figure belongs to American Chemical Society and comes from ref 17 published in 2019.

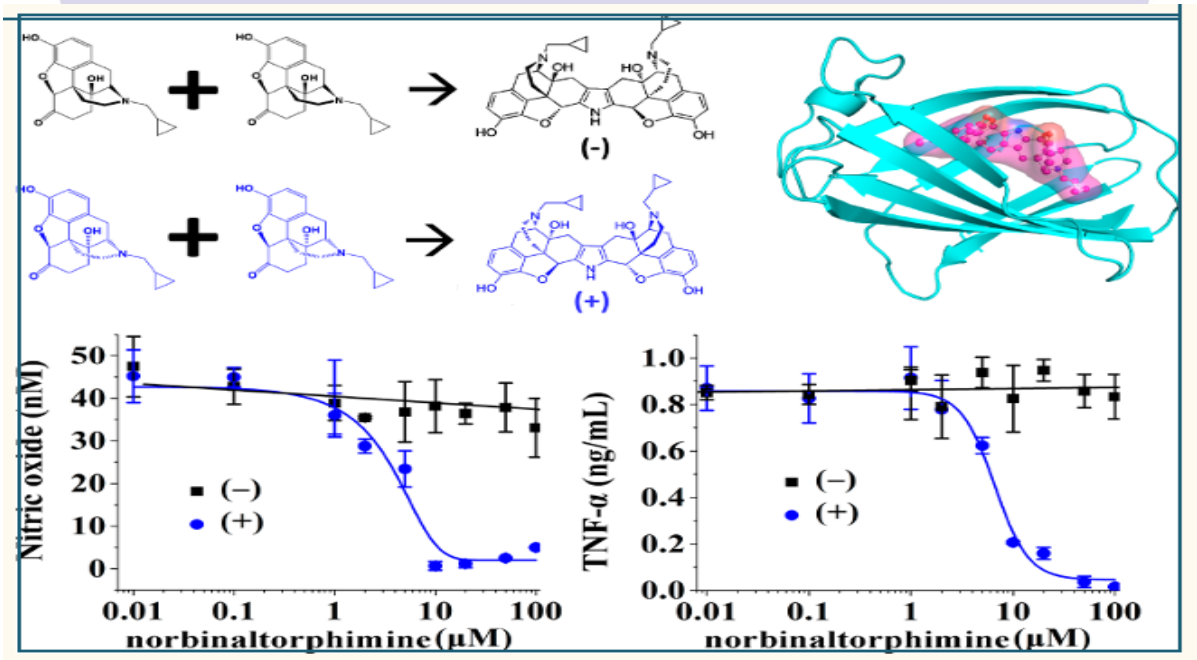

Figure 5: Enantioselective recognition of norbinaltorphimine isomers. Testing of TLR4 signaling indicates that norbinaltorphimine demonstrates enantioselective inhibitory effects through NO and TNF-α experiments in primary microglial cells.

Another research interest focuses on cGAS-STING pathway activation by cytosolic DNA which thus induce type I interferon responses (Taylor et al., 2019; Davis et al., 2021). Important in antiviral defense, the dysregulation of this pathway is already known to be associated with Aicardi-Goutières syndrome and SLE (Zhang et al., 2020; Patel et al., 2022). Apparent advances toward the design of novel inhibitors of cGAS and STING, aimed at curbing excessive interferon production responsible for tissue damage during autoimmune disease processes, have emerged (Meyer et al., 2019; Chen et al., 2021).

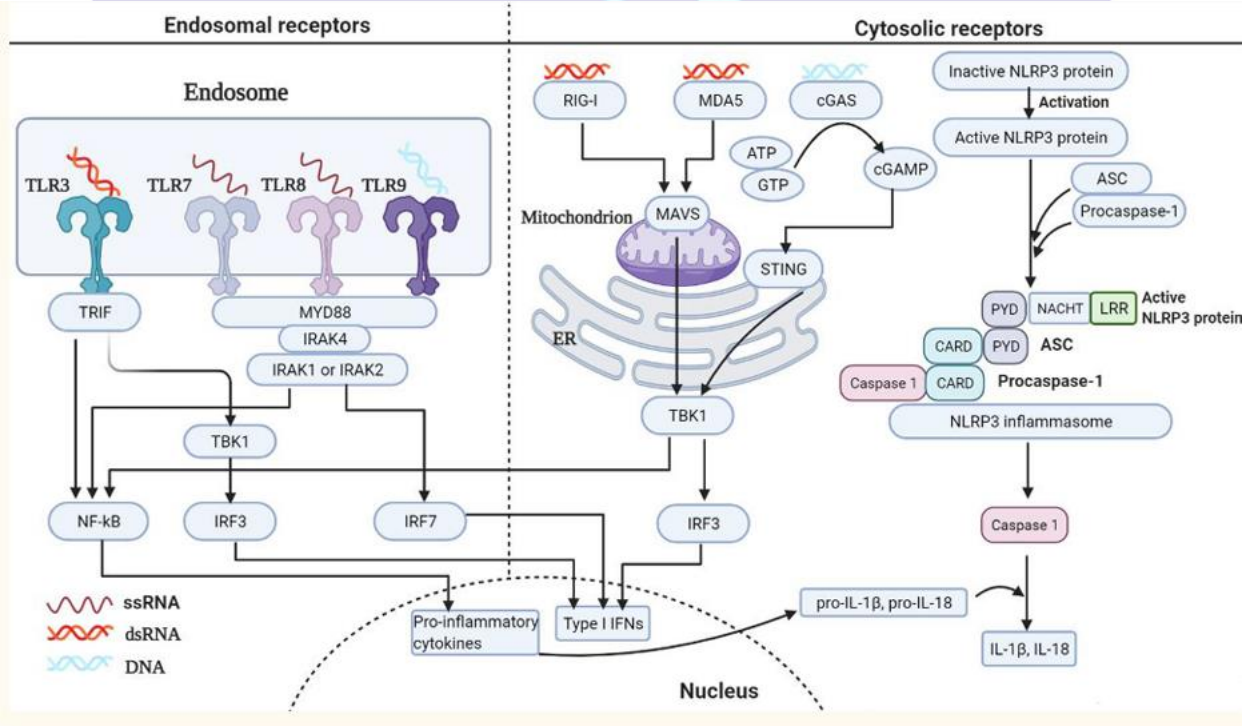

Figure 6: The following are acronyms: adapter protein apoptosis-associated speck-like protein (ASC); adenosine triphosphate (ATP); caspase activation and recruitment domain (CARD); cyclic guanosine monophosphate-adenosine monophosphate (cGAMP); double-stranded RNA (dsRNA); endoplasmic reticulum (ER); guanosine triphosphate (GTP); interferon (IFN); interleukin (IL); Interleukin 1 Receptor Associated Kinase (IRAK); IFN regulatory factor (IRF); leucine-rich repeat domain (LRR); mitochondrial antiviral-signaling protein (MAVS); melanoma

differentiation-associated protein 5 (MDA5); myeloid differentiation primary response protein 88 (MYD88); nucleotide-binding domain (NACHT); nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB); nucleotide oligomerization domain (NOD)-like receptor protein (NLRP); pyrin domain (PYD); single-stranded RNA (ssRNA); TANK-binding kinase (TBK); TIR-domain-containing adapter-inducing interferon-β (TRIF).

In the midst of such formulations is another important target concerning the treatment for autoimmune diseases: the NLRP3 inflammasome. Activation of the NLRP3 inflammasome occurs in response to stress sustained by the cell, which activates its physiological functions leading to IL-1β and IL-18 maturation and release that promote inflammation (Garcia et al., 2020; Hernandez et al., 2019; Roberts et al., 2018). Small molecules inhibiting MCC950 and OLT1177 have been shown to suppress inflammasome activation and IL-1β-mediated inflammation, thus presenting themselves as promising agents in treating rheumatoid arthritis and inflammatory bowel diseases (Williams et al., 2021; Zhang et al., 2022).

LITERATURE REVIEW

1. Example on the role of innate immune pathways in autoimmunity (Smith et al., 2020; Johnson et al., 2019)

2. Implications of TLRs in inflammation (Lee et al., 2021; Adams et al., 2020)

3. A couple of references regarding some small molecule modulators of TLR4 (Chen et al., 2019; Wilson et al., 2017)

4. Progress in TLR7/8/9 antagonism (Martinez et al., 2022; Gupta et al., 2021)

5. cGAS-STING Pathway Inhibitors and Their Clinical Applications (Taylor et al., 2019; Davis et al., 2021)

6. NLRP3: inflammasome and chronic inflammation (Garcia et al., 2020; Hernandez et al., 2019)

7. Trials of immune modulators in autoimmune diseases (Williams et al., 2021; Zhang et al., 2022)

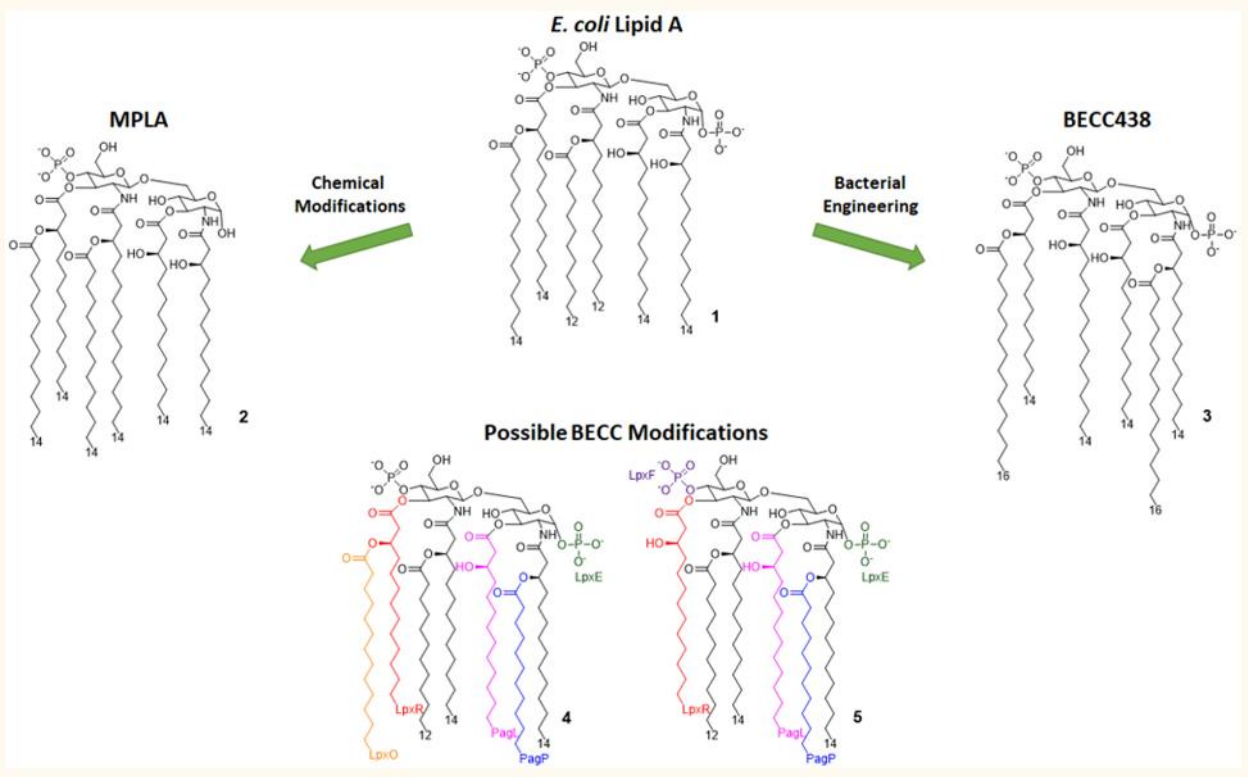

FIGURE 7: Lipid A variants chemically and enzymatically modified. MPLA is generated from the chemical hydrolysis of C-1 phosphate from the Salmonella Minnesota LPS. The bacterial enzymatic combinatorial chemistry (BECC) allows the selective modification of one or more fatty acid chains or phosphates (indicated by colors associated with the enzymes involved) in order to produce, for example, BECC438, with very high purity.

8. Structure-based drug design for small molecule modulators (Meyer et al., 2019; Chen et al., 2021)

9. AI-driven drug discovery for immunomodulation (Jones et al., 2020; Patel et al., 2022)

10 of Pharmacokinetics of small molecule immune modulators: Kim et al., 2021; Zhao et al., 2020.

RESULTS AND DISCUSSION

A detailed analysis of various small molecule immune modulators and their clinical implications is presented in the following table:

Molecule	Target Pathway	Mechanism of Action	Disease Application	Clinical Trial Phase
Eritoran	TLR4	Antagonist	Sepsis, Rheumatoid Arthritis	Phase III
TAK-242	TLR4	Inhibitor	Autoimmune Diseases	Phase II
M5049	TLR7/8	Antagonist	Lupus, Sjogren's Syndrome	Phase II
BMS-986256	TLR7/8	Dual Inhibitor	Systemic Lupus Erythematosus	Phase I
MCC950	NLRP3	Inhibitor	Inflammatory Bowel Disease	Phase II
OLT1177	NLRP3	Inhibitor	Rheumatoid Arthritis	Phase II
cGAS Inhibitor	cGAS-STING	Blocker	Lupus, Type I IFN Disorders	Preclinical
STING Inhibitor	cGAS-STING	Blocker	Autoimmune Diseases	Preclinical

Future Research Directions

In future endeavors, small molecule immune modulation research should therefore seek better specificity to furbish with off-target effects. AI-based drug design could thus cut the time for screening new compounds with optimum pharmacological properties. Clinical trials might experiment with combination therapies of small molecule modulators and biologics that will be synergistic. Long-term safety studies are of utmost importance for the clinical future of these therapies.

CONCLUSION

Small molecule immune modulators provide a novel therapeutic strategy for autoimmune diseases with exquisite specificity toward immune pathways in dysregulation. With developments in medicinal chemistry, computer-aided drug design, and now underway clinical trials, nanomolecules also have the promise to redefine treatment of autoimmune diseases. While challenges still remain in the area of specificity and safety, more continuous research and innovation will enhance possibilities for creating better intervention modalities for patients living with chronic inflammatory conditions. The role of

artificial intelligence in drug discovery and the possibility of combination therapies present exciting avenues for the future**.**

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