

Diverse Biologic Modalities in Systemic Lupus Erythematosus (SLE) Clinical Trials

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ABSTRACT: Systemic Lupus Erythematosus (SLE) is a challenging chronic autoimmune disease that affects patients with a wide range of symptoms, including life-threatening complications. It is difficult to treat because of its heterogeneous nature. Despite available treatment options, there is no cure currently. Over the last few decades, tremendous efforts have been made to understand the biologic mechanisms causing SLE and to explore novel and effective treatment options to better control and eventually cure the disease. In recent years, therapeutic advancements in SLE, particularly the use of diverse biologic modalities, have been exciting and offer new hope for patients. In this review, emerging treatment options in clinical trials using biologic modalities such as therapeutic proteins, cell therapies, and mRNA-LNP are discussed. Meanwhile, representative manufacturing processes for each modality are described along with the associated considerations, which are important for maintaining a robust and reliable supply chain to ensure patient access. The aim is to provide a comprehensive overview, from exciting biological hypotheses to eventual patient usage.

KEYWORDS: Disease Treatment and Therapies, Systemic Lupus Erythematosus (SLE), Biologic Modalities, Manufacturing Processes.

■ Introduction

Systemic lupus erythematosus (SLE) is one of the most difficult-to-treat autoimmune diseases. Due to loss of immune tolerance, SLE patients' immune systems mistakenly attack their own cells and tissues, significantly impacting their health. Individuals with this disease experience a lower quality of life, often suffering from symptoms such as fatigue and pain. Furthermore, it can affect multiple organ systems, presenting a wide range of signs and symptoms that could become life-threatening.^{1,2}

Clinical heterogeneity makes it hard to diagnose and manage SLE because patients can experience very different symptoms and disease courses.³ For example, a defining feature of lupus is the presence of antinuclear antibodies (ANA). However, although more than 97% of cases have a positive ANA test, the specificity of this test is only 20%, making it an unreliable marker for confirming SLE on its own.⁴ Despite diagnostic challenges, the 2019 EULAR/ACR classification system is generally considered a valuable tool, which has shown high sensitivity and specificity.⁵ Using this evaluation system, patients with 10 or more points and meeting at least one clinical criterion are identified as having SLE. Globally, an estimated 3.4 million people are living with SLE.⁶ Statistically, SLE primarily affects females, particularly those of childbearing age.⁷

Considering that SLE has no cure currently, there is a significant unmet medical need. Progress in developing effective treatments for SLE has been slow and challenging. To date, only a limited number of drugs have been specifically approved for the treatment of SLE. Similar to other autoimmune diseases, the standard treatment for SLE relies on immunomodulatory drugs, such as antimalarial therapies. Among these,

hydroxychloroquine (HCQ), approved by the FDA in 1955, is currently considered one of the primary drugs for SLE treatment.⁸ Next, belimumab was approved in 2011 as the first new lupus drug in over 50 years, which selectively inhibits B-cell activating factor (BAFF), also known as BlyS.⁹ SLE patients have an elevated level of this protein in their bodies. Belimumab can neutralize soluble BAFF and then disrupt the survival and maturation signals required for B cells, effectively reducing the population of autoreactive B cells and the subsequent production of harmful autoantibodies. Then, anifrolumab was approved in 2021, which works by binding to the type I interferon receptor (IFNAR1).¹⁰ Most SLE patients tend to overproduce interferons, the signaling proteins that trigger immune system overactivity and persistent inflammation. By blocking this receptor, anifrolumab suppresses the inflammatory signals that lead to organ damage, decreasing the frequency of exacerbations and alleviating symptoms, particularly in the skin and joints. In addition to these three drugs approved for SLE, voclosporin and obinutuzumab were approved for the treatment of lupus nephritis, a major complication of SLE, in 2021 and 2025, respectively.

Despite significant challenges, substantial efforts continue across both academic research and industry to develop new therapies for patients with SLE. In recent years, an upward trend in SLE clinical trial activity has been observed.^{11,12} As of February 8, 2026, a search of ClinicalTrials.gov identified approximately 327 active clinical trials related to SLE, including 70 in Phase 2 and 29 in Phase 3. Most recently, one of the leading emerging strategies for treating SLE is known as immune reset or immune reprogramming, which has shown very promising early clinical results.¹³

With improved understanding of the underlying biological mechanisms causing SLE, scientists can now design diverse therapeutic modalities to slow or stop disease development and progression. As one of the most well-established therapeutic modalities, small-molecule drugs have played an important role in medical treatment since the early 1900s and continue to make significant contributions today.¹⁴ Subsequently, advances in biotechnology, particularly recombinant DNA technology in the 1980s, enabled the development and widespread use of biologic drugs. Among these, monoclonal antibodies have gained particular interest due to their high target specificity and therapeutic versatility. To date, the FDA has approved more than 100 monoclonal antibody therapies for commercial use.^{15,16}

Over the last 20 years, new modalities such as cell therapy and gene therapy have emerged and advanced significantly. Cell therapies use living cells, such as immune cells or stem cells, to repair tissues or modify the body's immune system to better fight disease.¹⁷ Gene therapies utilize state-of-the-art technologies to regulate gene activity within cells, offering long-lasting therapeutic effects.¹⁸ More recently, messenger RNA (mRNA) therapies delivered using lipid nanoparticles (LNPs) have gained attention because they enable the body to produce useful proteins without permanently changing DNA.¹⁹

Despite the urgent need for more effective therapies for SLE, drug development and regulatory approval must go through rigorous processes to ensure patient safety and therapeutic efficacy. To enable clinical evaluation and eventual regulatory approval, the manufacturing strategy is a critical component of the drug development process, ensuring consistent product quality and compliance with regulatory expectations. Notably, the manufacturing processes differ substantially across therapeutic modalities. As therapeutic approaches become increasingly complex, a robust manufacturing process has become essential not only for regulatory approval but also for patient access.

In this review, we focus on several emerging biologic drug candidates currently in clinical trials for the treatment of SLE. They are categorized by their specific modalities (i.e., recombinant protein, cell therapy, and mRNA-LNP) followed by their associated manufacturing processes. By connecting therapeutic innovation with their production requirements, we provide an integrated perspective from scientific hypothesis to supply chain for industrial application.

■ Discussion

Recombinant Proteins – Clinical Advances:

Due to advancements in recombinant DNA technology, therapeutic proteins have become a major modality for disease treatment, including SLE. In addition to belimumab, anifrolumab, and obinutuzumab mentioned above, a considerable number of protein candidates are being tested in clinical trials, particularly monoclonal antibodies (mAbs) or mAb-like proteins. Below are a few highlights of these candidates in late-stage clinical development.

Ianalumab: Ianalumab is a humanized IgG1 monoclonal antibody currently in phase 3 development (SIRIUS-SLE 1 and SIRIUS-SLE 2), which targets the BAFF receptor (BAFF-R).²⁰ While belimumab targets the ligand by neutralizing soluble BAFF, ianalumab blocks the BAFF receptor (BAFF-R) expressed on the surface of B cells, thus inhibiting pro-survival and differentiation signals that are important for autoreactive B cells. In addition, ianalumab engages immune effector cells to induce antibody-dependent cellular cytotoxicity (ADCC), resulting in direct depletion of BAFF-R-expressing B cells. Especially, ianalumab is an afucosylated antibody, a protein structural modification designed to enhance ADCC activity.²¹ The combination of functional pathway blockade and active B cell depletion can lead to a more profound and sustained reduction of pathogenic B cell populations.

Litifilimab: Litifilimab is a humanized IgG1 monoclonal antibody in Phase 3 clinical trials for SLE (TOPAZ-1 and TOPAZ-2), which targets blood dendritic cell antigen 2 (BDCA2), an inhibitory receptor selectively expressed on plasmacytoid dendritic cells (pDCs).²² In SLE, immune complexes containing self-derived DNA or RNA can activate endosomal Toll-like receptors, particularly TLR7 and TLR9, in pDCs, resulting in excessive production of type I interferons. When litifilimab binds to BDCA2, it triggers an intracellular inhibitory signaling cascade that suppresses TLR7 and TLR9-mediated pathways.²³ Specifically, it reduces the activation of downstream transcription factors and decreases the production of type I interferons and other pro-inflammatory cytokines.²³ The mechanism of litifilimab is to reduce pDC responses rather than depleting these cells, which can help preserve broader immune function.

Dapirolizumab pegol: Dapirolizumab pegol is a pegylated, Fc-free monoclonal antibody fragment currently in Phase 3 studies (PHOENYCS GO and PHOENYCS FLY), which targets CD40 ligand (CD40L), a key costimulatory pathway involved in immune activation.²⁴ In SLE, CD40L is overexpressed on activated T cells and promotes pathogenic interactions with CD40 on B cells, dendritic cells, and other antigen-presenting cells, causing autoantibody production and inflammatory cytokine release. By blocking the CD40-CD40L interaction, dapirolizumab pegol inhibits T-cell-dependent B-cell activation and downstream inflammatory signaling.²⁵ The absence of an Fc region reduces the risk of Fc-mediated platelet activation and associated adverse events observed with earlier anti-CD40L antibodies, enabling safer modulation of this immune pathway in patients with SLE. However, without an Fc domain, the remaining Fab fragments will be quickly cleared. Therefore, a 40 kDa PEG chain is added to increase the hydrodynamic radius.²⁶ This design slows clearance and extends the half-life while preserving the intended safety profile.^{25,27}

Telitacicept: Telitacicept is a recombinant, fully human fusion protein approved in China and is currently being evaluated in a Phase 3 global clinical program for SLE (REMESLE-2). It consists of the extracellular domain of TACI (Transmembrane Activator and CAML Interactor) fused to the Fc portion of human IgG. It acts as a soluble binding receptor

that can simultaneously neutralize two key B-cell survival factors, BAFF and a proliferation-inducing ligand (APRIL).²⁸ In SLE, elevated BAFF and APRIL levels promote the antibody production of autoreactive B cells. By binding and neutralizing both ligands important for B-cell maturation and plasma cell survival, telitacept can reduce autoantibody production and immune-mediated inflammation.²⁹

In addition to the late-stage drug candidates discussed above, a significant number of innovative therapeutic proteins are currently under early-stage evaluation. We highlight several of these molecules, focusing on their diverse biological pathways and targets as well as unique molecular design.

CM313: CM313 is a humanized IgG1 monoclonal antibody targeting CD38, a surface marker highly expressed on plasma cells and certain activated immune cells.³⁰ In SLE, long-lived plasma cells play an important role in sustaining autoantibody production and disease activity, which are also relatively resistant to conventional B-cell directed therapies. By binding CD38, CM313 is intended to reduce pathogenic plasma cell populations, which may lead to decreased autoantibody levels and downstream immune complex-mediated inflammation. Unlike anti-CD38 antibodies developed for multiple myeloma (e.g., daratumumab), CM313 is designed for autoimmune applications, where modulation of immune balance is critical. It has been reported that CM313 possesses a significantly higher binding affinity for the CD38 antigen and demonstrates enhanced complement-dependent cytotoxicity (CDC).³⁰

Amulirafusp Alfa: Amulirafusp Alfa is a first-in-class bispecific fusion protein that simultaneously targets CD47 and CD20 on B cells.³¹ CD20 targeting enables selective binding to B cells, while CD47 blockade disrupts the “don’t eat me” signal that normally protects cells from macrophage-mediated phagocytosis. By combining these two mechanisms in a single molecule, Amulirafusp Alfa enhances the clearance of pathogenic B cells while maintaining high target specificity. Therefore, more effective and sustained B-cell depletion, resulting in a deeper immune reset, can be achieved.

A-319: A-319 is a CD19 x CD3 bispecific T cell engager (TCE), which contains an anti-CD3 single-chain variable fragment (scFv) linked to the N-terminal of the heavy chain of an anti-CD19 Fab fragment.³² By simultaneously binding CD3 on T cells and CD19 on B cells, A-319 brings T cells into proximity to pathogenic B cells, leading to T-cell activation and targeted elimination of CD19-positive cells. However, TCE is also known to potentially trigger cytokine release syndrome (CRS), which could be dangerous. Therefore, a balance must be achieved between the desired deep immune reset and unwanted excessive immune activation. Preliminary results indicate that A-319 is well tolerated, with no cases of high-grade CRS or neurotoxicity observed. The initial data demonstrated rapid B-cell depletion and a reduction in autoantibodies alongside measurable improvements in organ function.³³

Last but not least, a recent report showed a promising result of the off-label use of teclistamab, a TCE targeting BCMA and CD3 to deplete plasma and B cells, currently approved for relapsed or refractory multiple myeloma.³⁴ This case in-

volves a 23-year-old woman with refractory SLE unresponsive to multiple conventional therapies.³⁵ Following a five-week step-up dosing regimen, the patient achieved rapid and complete drug-free remission. This was marked by a SLEDAI-2K score of zero (indicating no active lupus disease) by week six, alongside normal kidney function, the disappearance of anti-dsDNA autoantibodies, and the resolution of all other clinical symptoms.³⁵ Although mild CRS and hypogammaglobulinemia occurred, both were manageable, and remission remained sustained at the 16-week follow-up.³⁵

In summary, a wide array of therapeutic proteins, especially mAbs and mAb-like proteins, are being actively explored as potential treatments for SLE. A significant recent trend is the increased interest in bispecific and multispecific antibody modalities, which are specifically engineered to facilitate more sophisticated immune modulation.³⁶ Notably, several of these candidates are being repurposed from hematological oncology for application within the autoimmune space.

Recombinant Proteins – Manufacturing Process:

Since recombinant tissue plasminogen activator (rtPA) became the first mammalian cell-derived therapeutic protein approved in 1987, large-scale cell culture has evolved into the primary platform for biopharmaceutical manufacturing.³⁷ Today, the field has reached a high level of technological maturity, characterized by robust and high-yield production systems along with established regulatory pathways. These platforms now dominate the global biopharmaceutical landscape, including the manufacturing of several blockbuster oncology and immunology drugs.³⁸

Cell Line: The first step in preparing for a manufacturing process is to generate a product-specific cell line, which involves engineering a host cell, most commonly a Chinese Hamster Ovary (CHO) cell, to stably and efficiently express the desired therapeutic protein. Over the years, tremendous efforts have been directed toward constructing high-performance host cell lines to maximize productivity and stability.³⁹ For example, host cells can be engineered to reduce or eliminate their ability to produce the endogenous glutamine synthetase (GS) enzyme. Since glutamine is critical for cell survival and growth, only cells that successfully incorporate the expression plasmid, which carries both the GS gene and the gene of interest (GOI), can survive in glutamine-free media. This method allows for the rapid identification of high-producing clones, significantly shortening timelines and increasing product titers.⁴⁰

A recent advancement in this field is the transition from random integration toward semi-targeted systems using transposases, or to targeted integration (TI), by directing the GOI to “hotspots”, transcriptionally active regions of the genome. High expression levels and greater genetic stability can be achieved.^{41,42} These strategies have demonstrated the capability to increase product titers and significantly reduce the time and resources required for cell line development.

To ensure product consistency, regulatory agencies require that all cell banks used for the production of therapeutic proteins originate from a single cell. Therefore, single-cell cloning

and imaging have become industry standard practices to follow the guidance and provide documented evidence of clonality.⁴³ Once the desired product-specific clone is identified, it is used to generate a GMP-compliant Master Cell Bank (MCB) and a subsequent Working Cell Bank (WCB). These banks must undergo rigorous qualification testing, such as identity verification, genetic stability analysis, and comprehensive safety assessments, including sterility, mycoplasma, and adventitious virus testing. GMP cell banks are typically stored long-term in the vapor phase of a liquid nitrogen tank to maintain maximum stability.

Cell Culture: The manufacturing process begins with thawing a vial from a stored cell bank, followed by a seed train using a series of culture vessels with increasing size to expand the biomass. Finally, the cultures are transferred to a large-scale stirred-tank bioreactor for protein production. To achieve high titers and desired product quality, both cell culture conditions and media components are studied and optimized. For bioreactor operations, process parameters such as agitation speed, temperature, dissolved oxygen (DO) levels, pH setpoints and bandwidth, and cultivation duration are controlled.⁴⁴ In addition, the dissolved CO₂ level (pCO₂) can significantly impact cell culture performance, particularly during scale-up, where gas mass transfer becomes more complex.⁴⁵ Therefore, the pCO₂ levels in the bioreactor are closely monitored and adjusted as needed by optimizing aeration and agitation strategies.

Cell culture media provide the essential nutrients, such as amino acids, glucose, vitamins, and trace metals, required for cell growth and high-quality protein production. The exact composition and concentration of these components are critical. Even minor changes can significantly influence product quality attributes, such as the glycosylation patterns on the protein.⁴⁶ These attributes may have an impact on the safety and efficacy of the product for patients. The majority of industrial mammalian cell culture processes are operated in fed-batch mode. In this approach, concentrated feed media are added periodically to the bioreactor while a lean basal media is used at the start of the culture. This strategy prevents nutrient depletion and extends the culture's longevity, ultimately leading to significantly higher product titers compared to simple batch processes. Nowadays, chemically defined and protein-free basal and feed media are commonly used to enhance performance and batch-to-batch consistency.⁴⁷

Downstream: Following cell culture production, the secreted protein in the culture supernatant is harvested by centrifugation or membrane separation, and then purified through a sequence of downstream unit operations.⁴⁸ This process typically begins with affinity chromatography with high selectivity for primary capture, such as Protein A chromatography for monoclonal antibodies. To further refine the product, subsequent polishing steps, such as ion-exchange (IEX) or hydrophobic interaction chromatography (HIC), are incorporated to remove host cell proteins (HCPs), residual DNA, high molecular weight (HMW) aggregates, and other impurities.⁴⁹ These chromatography steps are operated using either bind-and-elute or flow-through modes, depending on the specific impurity profile and the intended purpose. Process

parameters defining these chromatography unit operations typically include dynamic binding capacity, residence time, flow rate, buffer pH, and conductivity, and gradient slopes.^{50,51} The overall objective of downstream purification is to achieve the target purity and quality attributes while maximizing overall yield.

In addition, the downstream process must incorporate an effective viral clearance strategy to reduce risks from both endogenous retrovirus-like particles and potential adventitious viral contaminants, ensuring the safety of therapeutic proteins derived from a biologics system. The use of multiple unit operations that employ orthogonal mechanisms of action based on distinct physical or chemical principles is required.⁵² These operations typically include viral inactivation, such as low pH incubation or detergent treatment, and viral removal, such as nanofiltration and chromatography. The effectiveness of these steps is quantified by the Log Reduction Value (LRV). The cumulative LRV across the entire downstream process must demonstrate a substantial safety margin for both enveloped and non-enveloped viruses, covering a broad range of physical sizes and biochemical characteristics.⁵³

At the end of the manufacturing process, the purified protein material is concentrated and exchanged into the defined formulation buffer using ultrafiltration/diafiltration (UF/DF). The formulation is established based on development studies demonstrating long-term stability under storage conditions.⁵⁴

The typical manufacturing process for therapeutic proteins with the fed-batch cell culture mode takes 6–8 weeks from vial thaw to completion. Industrial cell culture production bioreactors range from 2,000L to 15,000L. Although specific process definitions vary by product, the fundamental unit operations remain highly similar, enabling the efficient use of existing GMP facilities and common equipment through a platform-based approach.

In recent years, an increasing number of bispecific antibodies are entering clinical trials for potential treatment for SLE, such as amulirafusp alfa, A-319, and teclistamab. Compared to standard monoclonal antibodies, bispecific formats exhibit significant structural diversity. Due to the inherent complexity of assembling two distinct antigen-binding functions within a single molecule, product-related impurities present a significant hurdle for process development. Specifically, downstream purification is more challenging and often requires comprehensive chromatographic strategies to effectively separate assembled bispecific molecules from impurities such as homodimers, half-antibodies, and other misassembled species.⁵⁵ Therefore, manufacturing considerations should be integrated into molecular design at an early stage to minimize the formation of challenging impurities.⁵⁶

Dapirolizumab pegol, mentioned above, uses PEGylation technology in its molecule design. From the manufacturing point of view, PEGylation adds extra unit operations to the workflow. The process parameters, such as PEG reagent purity, molecular weight distribution, and reaction stoichiometry and duration, as well as pH and temperature, are controlled to obtain the desired conjugation efficiency and manage the degree of product heterogeneity.⁵⁷ Furthermore, specialized down-

stream purification steps are developed to separate the target conjugate from unconjugated PEG, sub-optimal PEGylated species, and other process-related byproducts. These steps are essential for achieving the high level of molecular homogeneity and purity demanded by regulatory standards.⁵⁸

Overall, the manufacturing processes of therapeutic proteins for SLE follow established industrial platforms developed over the last 30 years. Utilizing these standardized workflows provides a clear, well-defined path through late-stage development, regulatory approval, and ultimately commercial usage.

Cell Therapy – Clinical Advances:

Cell therapy has been extensively investigated and successfully applied in oncology, particularly in hematologic malignancies, over the past 15–20 years.⁵⁹ Until recent years, its application in severe autoimmune diseases, including SLE, has begun to emerge.⁶⁰ Early clinical experiences, primarily from case reports in patients with refractory disease, have demonstrated encouraging efficacy and durable immunologic responses. These initial results have sparked a growing wave of investigations into diverse cell-based therapeutic strategies.⁶¹ In this section, we highlight several of the main cell therapy modalities currently under evaluation in this field.

Autologous CAR-T cells: The landmark report of the first successful autologous CAR-T cell therapy for SLE emerged in 2021.⁶² In this case, autologous CD19-directed CAR-T cells were used to treat a patient with severe, refractory disease, resulting in profound B-cell depletion, normalization of autoantibody and complement levels, and encouraging clinical improvement within weeks. The therapy was generally well tolerated with manageable acute toxicities. This work provided proof of concept that CAR-T therapy can function as an immune reset in autoimmune disease and laid the foundation for subsequent studies. Follow-up cases published later expanded on this initial finding by reporting treatment of multiple patients with refractory SLE.⁶³ Meanwhile, multiple CD19-directed autologous CAR-T candidates have been rapidly developed by other groups and have advanced into clinical trials, including CC-97540, Relma-cel, and CABA-201 (Rese-cel).^{64–66} This therapeutic approach is also being explored in pediatric patients with remarkable efficacy.⁶⁷

In addition, dual-target CAR-T strategies are being developed to achieve broader and more durable immune reset in SLE by simultaneously eliminating multiple pathogenic B-cell populations, which is similar to the bispecific antibody strategy. For example, AZD0120, a dual-target CAR-T therapy directed against CD19 and B cell maturation antigen (BCMA), is being evaluated.⁶⁸ Meanwhile, C-CAR168, a dual-target CAR-T therapy targeting CD20 and BCMA, is also under investigation in another clinical study.⁶⁹ Collectively, these dual-target CAR-T programs highlight a next-generation strategy designed to prolong immunologic remission by more comprehensively disrupting autoreactive B-cell populations.

On the other hand, the dual-CAR approach can also be achieved by a co-infusion strategy. Co-infusion of autologous CD19 and BCMA CAR-T cells is feasible and clinically active in patients with severe and refractory SLE.⁷⁰ It is worth

noting that this strategy introduces additional manufacturing complexity, as it requires two separate processes for the production and release of two distinct CAR-T cell products, one for each target.

Allogeneic CAR-T cells: Another landmark study published in 2025 provides early clinical evidence that allogeneic anti-CD19 CAR-T cells can achieve meaningful disease control in patients with SLE.⁷¹ Treatment with gene-engineered allogeneic CAR-T cells resulted in rapid and profound depletion of CD19-positive B cells, along with reductions in autoantibody titers and normalization of complement levels. Clinical remission was observed in several patients. Meanwhile, side effects consistent with known adverse events related to CAR-T were observed and manageable.⁷¹ These data provide early proof-of-concept that allogeneic CAR-T therapy may offer a scalable option other than autologous approaches for immune reset in SLE. On the other hand, further studies are needed to understand response durability, immune rejection risk, and long-term safety.

Most recently, a phase 1 study of CB-010, a CRISPR-edited allogeneic anti-CD19 CAR-T cell therapy, was initiated in patients with refractory autoimmune diseases, including SLE, and has been granted Fast Track designation by the FDA.⁷² BMS-986515 is another investigational, healthy donor-derived allogeneic CD19-targeted CAR-T cell therapy currently in phase 1 clinical development (NCT07115745).

Similar to autologous approaches, dual-target CAR-T strategies are also being explored in the allogeneic setting. For example, Allo-329 is an investigational allogeneic dual-target CAR-T cell therapy designed to simultaneously target CD19 and CD70.⁷³ CD70 is an inducible costimulatory ligand expressed on activated immune cells, including subsets of T cells and antigen-presenting cells. It is upregulated in inflammatory and autoimmune settings, including SLE. By targeting both antigens, Allo-329 aims to achieve broader immunomodulation and more effectively control immune escape or incomplete immune reset compared to single-target CAR-T therapies.

CAR-NK cells: While T-cell-based cell therapies remain the dominant approach, natural killer (NK) cells represent another viable option for CAR engineering and disease treatment. KN5501 is an investigational allogeneic anti-CD19 CAR-NK cell therapy being evaluated for the treatment of SLE.⁷⁴ In the ongoing phase 1 study, KN5501 was generally well tolerated, with low-grade CRS observed in some patients and no cases of other adverse events or infections. Most treated patients achieved meaningful disease improvement associated with rapid and complete depletion of CD19-positive B cells and normalization of immunologic markers.⁷⁴ These findings provide early clinical evidence that allogeneic CAR-NK cell therapy may represent a promising off-the-shelf alternative to autologous CAR-T approaches for immune reset in SLE. A similar study was conducted with LB0009 CAR-NK cells.⁷⁵ In addition, the dual-target CD19/BCMA CAR-NK (KN5601) is being tested in a clinical trial (NCT06792799).

Cell Therapy – Manufacturing Process:

As a “living drug,” the manufacturing process for cell therapies is inherently complex. However, since the approval of the first therapy in 2017, these processes have become more streamlined and better defined, particularly for autologous cell therapies. Their indications have also moved toward front-line treatment, benefiting a larger patient population. There are clear signs that this modality, including the manufacturing component, is becoming manageable.

For the autologous CAR-T cell therapy manufacturing process, it begins with leukapheresis, in which white blood cells are collected from the patient's blood and transported to a manufacturing facility. These cells are shipped either fresh or frozen under stringent logistics to ensure cell viability and sample traceability. At the facility, specific immune cells are isolated and then activated with stimulatory reagents to prepare them for genetic modification.⁷⁶ During the genetic engineering step, a viral vector, mainly a lentivirus or retrovirus vector, is used to introduce the genetic material that encodes a CAR into the cells, effectively “reprogramming” them to recognize and target specific markers such as CD19.⁷⁷ Then these genetically modified cells are expanded in culture vessels over several days to achieve a sufficient therapeutic dose. Following that, the cells are harvested, formulated, and cryopreserved as drug products. Finally, these drug products are returned to the clinical site for reinfusion into the patient after passing stringent quality-control testing to verify their identity, purity, and potency. In this scenario, each patient has specific CAR-T batch(s) originating from their own cells. The overall process time, called the “vein-to-vein” journey, could take 3–5 weeks.⁷⁸

Next-generation autologous CAR-T manufacturing is shifting toward a shortened *ex vivo* cell culture timeline, often reduced from the traditional 9–14 days to as few as 24–48 hours, to improve product quality and patient outcomes.⁷⁹ By eliminating or significantly abbreviating the *ex vivo* expansion phase, manufacturers can produce “younger” T-cells that retain a less-differentiated, memory-like phenotype. These minimally cultured cells show enhanced stemness and lower levels of T-cell exhaustion, leading to superior *in vivo* expansion and greater anti-tumor potency compared to cells subjected to long-term culture.⁸⁰ This accelerated workflow not only addresses the risk of disease progression during the “vein-to-vein” waiting period but also simplifies the manufacturing process by reducing the need for larger culture capacity and expensive culture media. Several CAR-T programs using a rapid *ex vivo* manufacturing strategy are being evaluated in clinical trials, such as rapcabtagene autoleucel (YTB323) (NCT05798117).

Allogeneic cell therapy manufacturing represents a paradigm shift from the personalized “scale-out” approach of autologous therapies to a standardized “scale-up” model. It relies on healthy donor-derived cells and a scalable production model rather than patient-specific manufacturing.⁸¹ In allogeneic processes, cells are collected from selected healthy donors and are used as the starting material for multiple patients after extensive characterization. The manufacturing process typically includes genetic modification of donor cells followed by cell expansion and cryopreservation.⁸² Because allogeneic therapies

use donor cells, the risks of immune rejection and graft-versus-host disease (GvHD) must be mitigated through genetic modifications, such as deletion of human leukocyte antigen (HLA) molecules or T-cell receptors.⁸³ Logistically, the allogeneic model eliminates the extreme time sensitivity and complex tracking required for individual patient lots. This transition not only significantly reduces the cost per dose through economies of scale but also allows for more sophisticated genetic engineering when needed.

CAR-NK cell manufacturing involves several specific requirements and challenges that distinguish it from T-cell-based processes.⁸⁴ First, NK cells are more difficult to expand *ex vivo*, requiring carefully optimized cytokines in culture media, and in some cases, feeder cells have been used. It adds complexity to process control, including the removal of residual feeder cells.⁸⁵ Second, genetic modification of NK cells is less efficient than in T cells, as NK cells are relatively resistant to viral transduction and electroporation. Higher vector doses must be used, or alternative gene-delivery platforms are needed, to achieve the desired CAR percentage while maintaining cell viability and function.^{86,87} Third, NK cells are sensitive to over-activation and exhaustion. Therefore, tight control of activation status during manufacturing is required to balance cytotoxic efficacy and premature apoptosis or functional decline. In addition, cryopreservation and thaw recovery present unique challenges for NK cells, as post-thaw viability and functional activity can be more variable than for CAR-T products.⁸⁸ Given the challenges, scientists and researchers have established various ways to optimize the process, enabling CAR-NK cell therapies to advance to clinical trials.^{89,90}

The integration of automation into autologous cell therapy manufacturing is essential for transitioning from manual, labor-intensive processes to a scalable, robust industrial model.⁹¹ Currently, most of the cell therapy manufacturing workflows involve open-system manual interventions in many steps, which increases the risk of human error and contamination. By implementing closed and automated systems such as integrated modular robotic units, greater consistency can be achieved while significantly reducing the cleanroom footprint and addressing capacity challenges. These automated platforms often incorporate real-time monitoring and advanced sensors to capture process parameters so that better control over the complex biological variability coming from patient-derived starting materials can be achieved.⁹² Ultimately, shifting toward an automated component can also reduce manufacturing and release resources and timelines, making these lifesaving “living drugs” more accessible to a larger patient population. Tremendous efforts are being made in this area to dramatically change the landscape of autologous cell therapy manufacturing. This strategy has the potential to become mainstream in the future once compliance with regulatory requirements is demonstrated and robust manufacturing processes are established.

mRNA-LNP – Clinical Advances:

Another emerging and rapidly advancing modality for SLE treatment is mRNA-LNP. Inspired by the strong efficacy of conventional CAR-T therapies, the mRNA-LNP approach

similarly aims to redirect T cells to eliminate pathogenic immune cell populations, such as autoreactive B cells.^{93,94} However, important differences exist between the two strategies. Traditional CAR-T cell therapies, which rely mostly on viral vector-mediated gene transfer and *ex vivo* T-cell expansion, produce long-lived and proliferative CAR-T cells. In contrast, mRNA-LNP technology generates CAR-T cells directly within the patient, so-called *in vivo* CAR-T. Because mRNA expression is transient, which only lasts for several days and does not trigger genomic integration, it provides a potentially safer and more controllable method for modulating the immune system in chronic conditions such as SLE. Different from the systems utilized as COVID-19 vaccines, the application of mRNA-LNP in SLE treatment requires a high level of specificity through active delivery mechanisms. This can be achieved by decorating the nanoparticle surface with T cell targeting ligands to create a targeted nanoparticle (TNP), which can selectively engage T cells rather than relying on passive tissue distribution.⁹⁵

Given the great potential of mRNA-LNP platforms in autoimmune diseases, numerous efforts are underway to advance these approaches into clinical trials for systematic evaluation of safety and efficacy. Among these, HN2301 represents the first wave of *in vivo* mRNA-LNP CAR-T candidates entering clinical trials with SLE patients.⁹⁶ HN2301 encapsulates CD19 CAR encoding mRNA within a proprietary T-cell targeted lipid nanoparticle (EnC-LNP), enabling direct reprogramming of CD8⁺ T cells into functional anti-CD19 CAR-T cells following intravenous administration without the need for lymphodepleting chemotherapy. From a product design perspective, HN2301 incorporates a proprietary anti-CD8 antibody fragment for T-cell targeting and a proprietary ionizable lipid.⁹⁶

According to early clinical data for HN2301, single or repeated administration at the 2 mg per infusion level induced measurable CAR-T cell formation and B-cell reduction. At the 4 mg per infusion level, up to 60% of circulating CD8⁺ T cells were converted into CAR-expressing cells within six hours, resulting in complete depletion of circulating B cells that persisted for approximately 7-10 days.⁹⁶ Preliminary clinical observations also indicated meaningful reductions in SLEDAI-2K scores at three months post-infusion. HN2301 was generally well tolerated, with no grade ≥ 3 CRS, no neurotoxicity, and no other severe treatment-related adverse events reported.⁹⁶

CPTX2309 is another investigational *in vivo* mRNA-LNP CAR-T therapy currently in Phase I clinical development for the treatment of SLE.⁹⁷ It also uses a CD8-targeted lipid nanoparticle, composed of a proprietary lipid and a humanized anti-CD8 targeting binder, to deliver anti-CD19 CAR-encoding mRNA directly into cytotoxic T cells, enabling them to express a CAR and deplete CD19⁺ B cells. Preclinical studies, including those conducted in non-human primates (NHP), demonstrated robust preferential engineering of CD8⁺ CAR-T cells, rapid and profound B-cell depletion in blood and tissues, and subsequent repopulation with predominantly naïve

B cells, suggestive of an immune reset similar to that observed with conventional CAR-T cell therapies.⁹⁷

Compared to other therapeutic modalities, *in vivo* mRNA-LNP platforms for the treatment of SLE remain in the very early stages of clinical development. Nevertheless, the field is gaining significant momentum and attracting substantial interest from both academia and industry. It is driven by the platform's potential to achieve the immune reset observed in successful conventional CAR-T treatments, while offering a more convenient alternative that bypasses the complexities of *ex vivo* manufacturing of cell therapy. The question and potential hurdle for *in vivo* CAR technology is its capability of delivering the CAR gene to the right cells in the human body safely. Driving up transfection efficiency and specificity will be the key to lowering the required dose and expanding the safety window. Consequently, further NHP and human clinical trial data are essential to address these questions and gain a deeper understanding of the overall potential and relative standing of this approach compared with others.

mRNA-LNP – Manufacturing Process:

The manufacturing process of mRNA-LNP therapeutics begins with plasmid DNA (pDNA) production. First, an *E. coli* host strain is used to generate a product-specific cell bank, similar to a mammalian cell bank for protein production. A vial from that microbial cell bank is then thawed and expanded, followed by bioreactor fermentation to produce pDNA encoding the target mRNA sequence. The intracellular pDNA is then harvested through cell lysis, purified, and linearized via restriction enzyme digestion.⁹⁸ In addition to microbial-based production systems, cell-free DNA synthesis has also emerged in recent years as another option.⁹⁹

Once the purified linear pDNA is available, mRNA can be manufactured through *in vitro* transcription (IVT) using it as a template. IVT is a rapid enzymatic reaction that synthesizes the desired mRNA in 2 to 3 hours.

Key process parameters for IVT include the concentration and purity of the pDNA template, T7 polymerase concentration and activity, nucleotide composition and ratios, reaction temperature, pH, magnesium ion concentration, and reaction duration. These parameters directly influence mRNA yield, integrity, and impurity levels, and therefore must be tightly controlled to ensure consistent and high-quality mRNA production.^{100,101} Then, the synthesized mRNA is subsequently purified, typically using chromatography and tangential flow filtration, to remove impurities.

One of the critical impurities to control in mRNA-based products is double-stranded RNA (dsRNA), which is generated as a byproduct during the IVT process. dsRNA is a strong activator of innate immune receptors, leading to type I interferon production and pro-inflammatory signaling. dsRNA levels can be minimized through a holistic control strategy. It includes the optimization of IVT reaction conditions as well as plasmid template design and linearization process to minimize aberrant transcription.¹⁰² In addition, the pDNA quality and T7 enzyme characteristics play an important role and can affect the dsRNA level in IVT.^{103,104} Downstream purification

steps, both chromatography and tangential flow filtration, can also be optimized to reduce residual dsRNA levels following IVT in the manufacturing process development.¹⁰⁵

The LNP manufacturing process is based on the rapid and controlled mixing of an mRNA solution with lipids. Both impingement jet mixing (IJM) and microfluidic mixing technologies are commonly used in the industry.¹⁰⁶ During the manufacturing process, two solutions are prepared first: the first one is the mRNA solution in an acidic aqueous buffer, and the other is the lipid solution in ethanol containing four components (i.e., ionizable lipid, phospholipid, cholesterol, and PEG-lipid). Rapid mixing at the microscale induces spontaneous self-assembly of LNPs through electrostatic interactions between the protonated ionizable lipid and the negatively charged mRNA. Process parameters such as flow rate ratio, total flow rate, buffer pH, and temperature are tightly controlled to achieve reproducible product quality (e.g., particle size, narrow polydispersity, and high encapsulation efficiency).^{106,107} After the encapsulation process, the crude LNP suspension has to go through a series of downstream processing steps such as buffer exchange, concentration, and sterile filtration.

The incorporation of targeting moieties to generate TNPs increases the complexity compared to the traditional LNP manufacturing process and presents unique challenges. For example, it requires conjugating T-cell targeting ligands to the nanoparticle surface. This step requires great control of ligand density and orientation to ensure consistent target function without negatively impacting particle integrity or mRNA encapsulation.¹⁰⁸ From a process standpoint, how to achieve consistent product quality becomes more challenging because surface modification can alter nanoparticle assembly and colloidal stability. Additional risks include increased aggregation and interference with sterile filtration.¹⁰⁹ Given the structural complexity of this type of mRNA-LNPs, advanced analytical tools and robust methods are important to understand the impact of manufacturing processes on product quality, ultimately enabling an effective control strategy that ensures batch-to-batch consistency.

Table 1: The Status of Different Biologics Modalities in Clinical Trials for SLE. The promising new biologic modalities are primarily in the early stages of clinical development, and their manufacturing processes are being further improved.

Modality	Approved drug (General)	Approved drug for SLE	Clinical Stage For SLE	Manufacturing Process
Therapeutic protein	Yes	Yes	Early and late stages	Well-established, large-scale production
Cell therapy – Autologous CAR-T	Yes	No	Early-stage	Established, one batch per patient
Cell therapy – Allogenic CAR-T	No	No	Early-stage	In development
Cell therapy – CAR-NK	No	No	Early-stage	In development
mRNA-LNP	Yes	No	Early-stage	Established for mRNA-LNP; In development for mRNA-TNP

Table 1 summarizes and compares the current status of each modality described above. With a strong interest in finding better treatments for SLE, it is no surprise to see other new modalities or new manufacturing strategies emerging. It is

worth noting that although some initial and limited data from the new modalities are very promising, late-stage clinical trials with large patient populations are needed to demonstrate their true potential.

■ Conclusion

It is exciting to see that the SLE treatment landscape is rapidly advancing after many years of stagnation. The number of clinical trials is growing due to a better understanding of disease biology and a broad range of therapeutic strategies aimed at modulating various immune pathways. Different modalities, from therapeutic proteins to cell therapies to mRNA-LNP, are currently being explored in clinical trials to improve disease control. Importantly, early clinical signals from one modality can rapidly inform and inspire exploration of others. For example, soon after the promising results from autologous CAR-T cell therapies in SLE were published, other modalities, such as bispecific antibodies and mRNA-LNP-based approaches, were developed that seek to achieve similar clinical benefits through distinct and potentially more scalable technologies. Many of these approaches are still in early clinical development, waiting for more clinical data demonstrating overall benefits. On the other hand, differentiation has already extended beyond biological efficacy to the maturity of manufacturing platforms and supply-chain robustness, which are likely to become critical determinants of long-term benefit for patients. Overall, this review highlights the complexity of developing new treatments for patients and the importance of holistic consideration across separate but interconnected areas.

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