BACKGROUND OF THE INVENTION

Conventional ex vivo immune cell expansion protocols rely heavily on static cytokine supplementation, resulting in significant variability in cell product quality, limited therapeutic persistence, T cell exhaustion, Treg overgrowth, and insufficient tumor specificity. This invention overcomes these limitations by introducing a real-time adaptive cytokine modulation system that integrates patient-derived tumor lysate priming, cytokine concentration feedback, and immune phenotype-based logic to produce highly personalized, memory-rich, and therapeutically potent immune cell products.

SUMMARY OF THE INVENTION

This invention represents a substantial advancement in cellular immunotherapy manufacturing, providing an integrated, fully automated system for cytokine regulation and immune education. By coupling real-time cytokine sensing, adaptive dosing algorithms, and personalized tumor-specific antigen priming, the invention significantly improves the quality, safety, and efficacy of expanded immune cell products, facilitating more reliable therapeutic outcomes and streamlined regulatory compliance under GMP conditions.

TECHNICAL ADVANTAGES

This invention enables:
- Dynamic cytokine modulation to avoid exhaustion and Treg expansion
- Personalized immune training via tumor lysate antigens
- GMP-grade automation compatible with existing CAR-T workflows
- Integration of phenotype sensing and cytokine infusion logic
- Immune product consistency across donors and manufacturing sites

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a schematic diagram of the adaptive cytokine regulation system, showing the integration of a bioreactor (100), cytokine infusion module (120), cytokine sensor array (130), phenotype analysis module (140), and the control logic engine (150) which adjusts cytokine delivery in real time.

FIG. 2 illustrates the cytokine feedback control logic system. The input sensors (200) collect IL-2 and IL-7 levels and immune marker data (210), which are used by logic gates (220, 250) and an AI learning module (240) to determine cytokine substitution (e.g., IL-15, IL-21) via a cytokine replacement module (230) and output to infusion command (260).

FIG. 3 depicts the tumor lysate priming workflow used for ex vivo immune cell education. Tumor lysate and patient-derived PBMCs are co-incubated (300), exposed to cytokines (310, 340), with T cell isolation (320), rest period (350), and final collection of primed T cells (360).

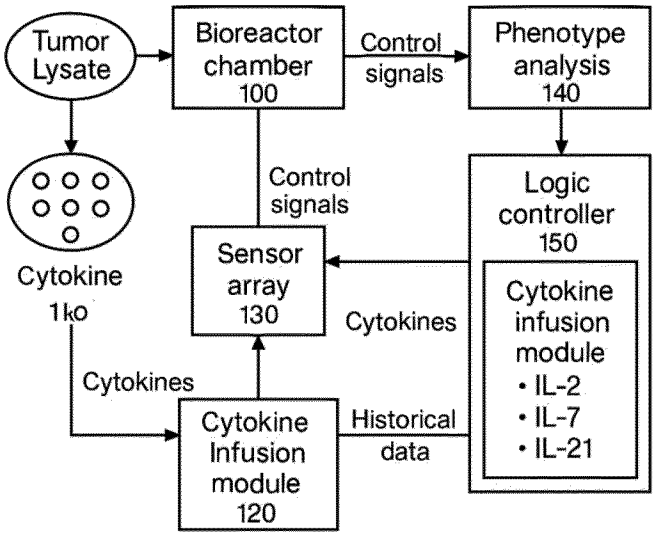

FIGURE 1

FIG. 1– System overview diagram showing cytokine-controlled bioreactor (100), reservoirs (120), cytokine sensors (130), phenotype inputs (140), and logic processor (150).

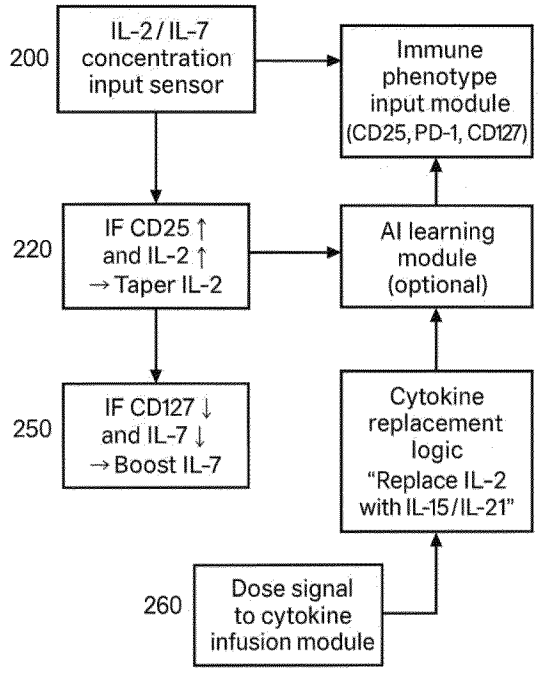

FIG. 2

Alternative cytokine regulation system

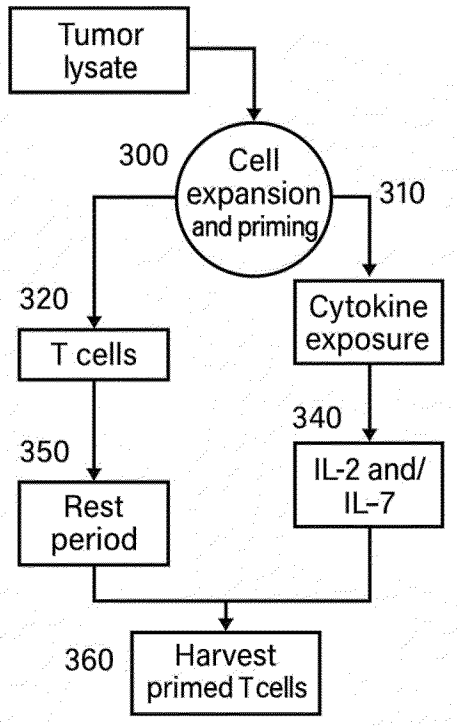

Figure 3

Tumor lysate priming workflow

FIG. 2— Feedback control diagram with input sensors (200), immune marker gate logic (220, 250), AI logic module (240), and cytokine output command (260).

FIG. 3— Tumor lysate priming workflow showing co-incubation chamber (300), cytokine input stages (310, 340), T cell enrichment (320), immune rest (350), and final harvest (360).

DETAILED DESCRIPTION OF THE INVENTION

Cytokine Selection Logic and AI Interpretation Rules

The adaptive cytokine engine described herein leverages immunophenotypic and metabolic inputs to guide cytokine administration dynamically. This logic is implemented either as fixed-rule decision trees or via machine-learning algorithms trained on longitudinal patient response data. Below is the codified matrix for interpreting immune conditions and translating them into cytokine adjustments:

Immune Profile Input	Interpretation	Cytokine Recommendation	Titration Logic / Adjustments
CD8+ T cell low, CD4+ high	Effector cytotoxic response needs boosting	IL-2 (low), IL-15, IL-21	Monitor CD8+/CD4+ ratio increase; reduce IL-2 if CD25+ spikes
NK cells CD56dim low	Poor innate cytotoxicity	IL-15, IL-12	Increase IL-15 if IFN-γ stays low in culture
Tregs (CD25+FoxP3+) high	Immune suppression likely	Avoid IL-2, add IL-12, IFN-γ	Monitor for decrease in Treg frequency; add IL-21 if rebound occurs
High PD-1+, TIM-3+ expression	T cell exhaustion signature	IL-21, low-dose IL-2	Add IL-21 if granzyme B stays low; reduce IL-2 if no CD107a response
Serum IL-6 / IL-10 elevated	Pro-inflammatory or suppressive environment	Avoid IL-2; add IFN-γ + GM-CSF for antigen presentation	Titrate based on IL-6 decay + CRP
Strong IFN-γ gene signature in tumor	T cell inflamed, checkpoint susceptible	IL-15, IL-21 + consider PD-1 inhibitor	Focus on CD8+ expansion, reduce IL-2 if Tregs expand
Cold tumor (low MHC, low TILs)	APC induction needed	GM-CSF + IL-12	Evaluate CD83/CD86 expression in culture
High TGF-β, VEGF, Gal-9 tumor expression	Immunosuppressive microenvironment	IFN-γ, IL-21; avoid IL-2	Add HDACi or TGF-β inhibitor if available
Lactate accumulation in culture	Metabolic overactivation	Reduce cytokine dosing across the board	pH correction; pause IL-2 if sustained acidity
CD25+ rapidly rising (Day 2–4)	T cell overdrive OR Treg expansion	Reduce IL-2, maintain IL-15	Consider short IL-21 pulse or anti-CD25 mAb ex vivo (experimental)
CD107a− / IFN-γ− intracellular cytokine staining low	Poor cytotoxic function despite proliferation	Add IL-21 or IL-12	Verify granzyme B, perforin post Day 6
CD45RO+ memory phenotype lacking	Need for durable T cell memory	IL-7 + IL-21 (post-Day 4)	Assess central vs effector memory on Day 8

This matrix enables programmable AI modules or deterministic logic engines to dynamically select cytokine pathways and adapt to patient-specific immune trajectories. The system supports rule-based overrides, clinical parameter tuning, and model retraining to refine therapeutic decisions over time.

FIG. 1 illustrates the core bioreactor system used to execute adaptive immune cell expansion. Patient-derived peripheral blood mononuclear cells (PBMCs) are introduced into the bioreactor chamber (100), which maintains a sterile and GMP-compliant environment. The system includes a modular cytokine infusion array (120) connected to reservoirs for IL-2, IL-7, IL-15, IL-21, IL-12, IFN-gamma, and GM-CSF. These cytokines are delivered via programmable pumps regulated by feedback data. Cytokine concentration is monitored in real time through biosensors (130) embedded in the fluidic loop of the bioreactor. Immune phenotype detection modules (140) monitor surface markers such as CD25, PD-1, CD127, and CD45RA using flow cytometry or biosensor-based detection. These data streams feed into a programmable control logic processor (150), which continuously recalculates optimal cytokine ratios and adjusts infusion accordingly. Outputs are channeled through the infusion control system (160), delivering tailored cytokine cocktails back into the bioreactor.

FIG. 2 details the logical feedback flow driving cytokine decisions. Sensor modules (200) record IL-2 and IL-7 levels alongside immune phenotypic states (210). This input is parsed through a logic gate (220) evaluating IL-2 concentration against CD25 expression. If CD25 expression is high, indicating overstimulation or regulatory T cell bias, IL-2 is tapered and replaced by IL-15 or IL-21 (230). A secondary gate (250) tracks CD127 expression and IL-7 levels, increasing IL-7 delivery if survival pathways appear compromised. An AI logic module (240) learns from cumulative data across batches to refine future cytokine curves. Final decisions from these gates output to the cytokine infusion control unit (260), ensuring timely and condition-specific cytokine delivery.

FIG. 3 shows the immune education stage using autologous tumor lysates. Tumor fragments or lysates are combined with freshly isolated PBMCs within a controlled co-incubation chamber (300). Initial cytokine support (310) includes low-dose IL-2 and GM-CSF to stimulate early antigen processing. T cells are selectively enriched or isolated into sub-compartments (320) as antigen presentation matures. An immune rest period (350) follows, allowing the downregulation of acute activation markers and promotion of central memory conversion. Cytokine conditioning (340) is resumed with IL-15 and IL-21 to reinforce memory and cytotoxic function. Final cell harvesting occurs from port (360), producing a population of tumor-primed, polyfunctional, and minimally exhausted immune effector cells.

This process enables patient-specific adaptation of immune products while preserving reproducibility and regulatory control under GMP conditions.