

PROGRAM TECHNICAL DEEP DIVE

Autologous Dendritic Cell — Liver Cancer

Technology transfer and GMP manufacture of frozen DC drug product — technical deep dive

PI	MAYO SITE	ON NUMBER	STAGE
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1. Executive technical summary

Mayo's autologous dendritic-cell process is a clean, conventional, seven-day monocyte-derived DC manufacture, described in the RFP with enough specificity to scope against directly: leukapheresis receipt, LOVO wash and volume reduction, CliniMACS Plus CD14-positive immunomagnetic enrichment, T-175 flask differentiation in CellGenix media with IL-4 and GM-CSF, maturation with defined cytokines including PGE2 and TNF- α , harvest, and cryopreservation into product and reserve vials ^[S64].

Notably, **the product is an unloaded, mature dendritic cell**. The RFP describes maturation as transitioning immature DCs into "an unloaded, mature phenotype", and release testing is performed on the final cell harvest before freezing ^[S64]. Antigen loading is not part of the manufacture being transferred. That materially simplifies the CDMO scope — the DC core's hardest supply-chain problem, per-patient antigen, sits outside this boundary — and it should be confirmed explicitly, because it changes what MADE is being asked to make.

Three observations shape the response.

Two named instruments gate the process, and neither is evidenced at MADE. LOVO for wash and volume reduction, and CliniMACS Plus for CD14 selection ^[S64]. The DC core already identifies monocyte enrichment as the most material capability question in this modality, because it is the first unit operation of every monocyte-derived DC process. Mayo names the exact instruments. **This is the gating verification for this opportunity**, and the RFP's own "Areas of Interest" asks directly about new equipment onboarding timeframes, IQ/OQ ownership and how the site determines what requires validation — which is the natural place to answer it honestly.

CD83 at $\geq 70\%$ gated is the only flow specification; everything else is informational. CD197, CD14, CD86, CD274 (PD-L1), B7H2, CD80, HLA-DR and CD45 are all marked For Information Only ^[S64]. There is no potency assay. This is a defensible Phase 1 position and precisely the one the DC core says does not survive the move toward pivotal — and this modality has no default assay to adopt later, which is why starting during transfer matters more here than elsewhere.

Mayo's quality position is unusually mature. The RFP states all methods have been validated in a phase-appropriate manner, with safety methods fully validated or verified and all other methods qualified against the relevant ICH Q2(R2) parameters, and release occurring shortly after the 14-day sterility result ^[S64]. That is a well-run program, and the response should engage at that level rather than explain basics.

2. The modality: biology and mechanism

Dendritic cells are the immune system's professional antigen-presenting cells. They take up antigen in peripheral tissue, mature, migrate to draining lymph nodes, and present processed antigen on MHC to naive T cells alongside costimulatory signals — priming an antigen-specific T-cell response. A DC vaccine is an attempt to do that on purpose, with a chosen antigen.

Most clinical DC products are **monocyte-derived**: CD14-positive monocytes are enriched from a leukapheresis and driven toward a dendritic phenotype with GM-CSF and IL-4 over roughly five to seven days. CD34-derived DCs are the less common alternative [S9].

The therapeutic act is presentation, and presentation requires three things at once. The cell must carry the antigen; it must be mature enough to deliver costimulation rather than tolerance; and it must be able to migrate to a lymph node, which is a CCR7-dependent function. A product that fails any one of the three is inert or worse, and no single marker reports all three.

Maturation is the pivot. Immature DCs are efficient at antigen uptake and poor at priming; mature DCs are the reverse. Maturation is induced by a defined cytokine cocktail — commonly TNF-α, IL-1β, IL-6 and PGE2 in varying combinations — or by TLR agonists, or by the electroporation event itself where mRNA loading is used [S9]. Each route produces a differently polarized cell. The cocktail is not a reagent list; it is a design decision about what kind of T-cell response the product will elicit.

Sequencing matters as much as composition. Loading antigen before maturation and loading after maturation give different products. A process that is ambiguous about the order is ambiguous about the product.

3. This program's product, specifically

3.1 The process as Mayo runs it

Step	Detail
Starting material	Leukapheresis product
Wash and volume reduction	LOVO — closed-system wash, concentrate and volume-reduce
Monocyte enrichment	CliniMACS Plus — immunomagnetic CD14-positive selection, producing a defined starting population
Differentiation	CD14-positive cells seeded into T-175 flasks in immature DC media — CellGenix media with IL-4, GM-CSF and Glutamax — under controlled incubator conditions, with in-process monitoring, cell counts and documentation
Maturation	Cells harvested from initial culture, counted, diluted to target concentration, exchanged into mature DC media with defined cytokines including PGE2 and TNF-α, redistributed into T-175 flasks, incubated for a defined maturation window under strict timing control
Harvest and release	Mature, unloaded DCs harvested; release testing performed before freezing
Formulation and fill	QC volumes removed; cells formulated with cryoprotectant, aliquoted into product and reserve vials at defined cell doses
Freeze and storage	Controlled-rate freezing, then vapor-phase liquid nitrogen
Distribution	Frozen drug product in 1 mL vials, shipped to Mayo sites for thawing, syringe loading and administration

Total process: 7 days from apheresis receipt. Source: RFP, 18 August 2026 [S64].

3.2 In-process and release testing

In-process: cell count by Sysmex at Day 0 on apheresis, post-LOVO and post-CliniMACS material; flow cytometry at Day 0 on apheresis and post-CliniMACS material; viability during manufacturing [S64].

Testing the same three points — incoming, post-wash and post-selection — is good practice. It means a low yield can be attributed to the collection, to the wash or to the selection rather than being discovered as an unexplained shortfall at harvest.

Drug product release

Test	Method	Specification
Sterility	BacT/Alert USP <71> or direct inoculation USP <71>	No growth after 14 days
Endotoxin	Endosafe nexgen-PTS, USP <85>	Informational use only
Mycoplasma	PCR, BioFire, USP <63>	Not detected
Flow cytometry (Navios)	CD83	≥70% gated
Flow cytometry (Navios)	CD197, CD14, CD86, CD274 (PD-L1), B7H2, CD80, HLA-DR, CD45	For information only
Viability, post-harvest	NucleoCounter NC-200	≥70% of total cells

Source: RFP [S64].

4. Process architecture, unit operation by unit operation

4.1 The chain, end to end

#	Unit operation	Purpose	Where it fails
1	Leukapheresis receipt and acceptance	Qualified starting population	Acceptance criteria undefined; monocyte content varies with patient
2	Wash, concentrate, volume reduce	Remove plasma and platelets	Cell loss; platelet carryover interferes with adherence-based enrichment
3	Monocyte enrichment	Define the input population	Method choice changes purity and yield materially
4	Differentiation, ~5–7 days	Monocyte to immature DC	Cytokine lot and concentration; feeding schedule; density
5	Maturation	Immature to mature, priming-competent DC	The step that decides whether the product primes or tolerizes
6	Antigen loading	Give the DC something to present	Antigen GMP supply; sequencing relative to maturation
7	Harvest	Recover cells	DCs are adherent to semi-adherent — recovery varies

#	Unit operation	Purpose	Where it fails
8	Formulation and fill	Dose per container	Fresh versus cryopreserved decision lands here
9	Cryopreservation or immediate release	Preserve or deliver	Post-thaw maturation–marker and function retention

4.2 Monocyte enrichment — the first divergence

Method	Character	Trade-off
Plastic adherence	Simplest, no reagent cost	Lowest purity; platelet and lymphocyte carryover; hard to control reproducibly at scale
Counterflow elutriation	Closed, high throughput, reagent-free	Requires the instrument; separation is by size and density, not by marker
CD14-positive immunomagnetic selection	Highest purity, marker-defined	Reagent cost; single-source selection system; adds a manipulation

The choice propagates. A process developed on plastic adherence and transferred onto CD14 selection starts from a purer, differently composed input, and the differentiation kinetics that were tuned for one will not be identical on the other. This is a comparability question, not a materials question ^[S9].

4.3 Differentiation and maturation

GM-CSF plus IL-4 over five to seven days is the standard differentiation cocktail; alternatives exist and are program-specific ^[S9]. The practical variables that decide reproducibility are cytokine specific activity — which differs between vendors and lots and must be specified by activity rather than by mass concentration ^[S11] — seeding density, feeding schedule, and vessel choice.

Maturation markers to assess are CD83, CD80, CD86 and HLA-DR upregulation, with CD14 downregulation as the counter-check that differentiation actually happened ^[S9]. CD83 is the marker most commonly carried as the release specification.

Culture is flask-based and manual. REF_09 flags this explicitly as a modality risk: DC manufacturing is labor-intensive with many manual steps, and maturation and antigen-loading protocols are highly variable across the field ^[S9]. There is no closed automated platform for DC manufacture with the maturity of a CliniMACS Prodigy run for T cells. Batch size is therefore bounded by operator capacity and suite time rather than by vessel volume, and that shapes both cost and scheduling.

4.4 Antigen loading — four routes, four supply chains

Route	What is loaded	Supply implication
Peptide pulsing	Synthetic peptides	GMP peptide synthesis; stability and solubility per peptide; HLA-restricted, so patient eligibility narrows
Tumor lysate	The patient's own tumor	Tissue procurement per patient; lysate preparation is itself a process step with its own controls; quantity is not guaranteed
mRNA electroporation	In vitro transcribed mRNA	GMP mRNA synthesis; electroporation instrument and disposables; transient expression, which is usually sufficient for presentation

Route	What is loaded	Supply implication
Viral vector	Vector-encoded antigen	Vector supply, with the lead times and lot variability that carries ^[S6]

For personalized neoantigen programs the antigen is designed per patient from tumor and germline sequencing. That places a bioinformatics and synthesis workstream on the critical path in parallel with the cell process, and the vein-to-vein clock runs across both. A DC program that has solved its cell process and not its antigen turnaround has not solved its timeline.

4.5 Fresh or frozen

Historically many DC products were administered fresh, and REF_09 flags fresh-product logistics as a modality risk ^[S9]. Fresh means the manufacturing completion date, the release testing turnaround and the patient's dosing appointment must all align, with no slack — and sterility results that take fourteen days cannot gate a product infused on day one, so fresh products release on rapid methods with a fourteen-day confirmatory result following.

Cryopreservation decouples all of that and is the direction of travel. The question it raises is whether maturation phenotype and function survive the freeze-thaw — which is a potency-stability question, and one many programs have not tested.

5. Analytical strategy

5.1 The release panel as the field actually runs it

Attribute	Method	Typical position
Identity and maturation	Flow: CD83, CD80, CD86, HLA-DR, CD14	CD83 commonly the sole specification; the rest often informational
Purity	Flow, residual lymphocyte and monocyte content	Informational in many programs
Viability	Automated cell counter	Specification, typically $\geq 70\%$
Strength	Cell count	Specification
Sterility	USP <71>, direct inoculation or automated culture	14-day, no growth
Mycoplasma	PCR	Negative
Endotoxin	LAL	Specification or informational
Potency	See §5a	Frequently absent

5.2 The honest observation about this panel

A panel built as above characterizes a mature dendritic cell. It does not demonstrate that the cell presents its antigen, and it does not demonstrate that the cell can migrate to a lymph node. Both are necessary for the mechanism to operate.

That is not a criticism of the programs that run it — it is a phase-appropriate position that the FDA accepts at Phase 1, where the requirement is a biologically relevant assay rather than a validated one ^[S1]. It becomes a liability when the program moves toward a pivotal trial with the same panel, because at that point the agency expects a qualified potency assay with acceptance criteria tightening toward final specifications ^{[S1][S13]}. Identifying that gap early, and building into it, is the single most useful thing a CDMO can do for a DC program.

5a. Potency

5a.1 The three assays REF_09 names

Assay	What it measures	Character
Antigen presentation / T-cell priming	The mechanism itself — can this DC prime an antigen-specific T-cell response	Most MOA-relevant and hardest to run. Requires responder T cells, extended co-culture, and a readout; complex and variable ^[S9]
IL-12p70 secretion on maturation	Polarization toward a Th1-priming phenotype	The pragmatic surrogate. Plate-reader ELISA, tractable in house
Migration / chemotaxis toward CCR7 ligands	The ability to reach the lymph node	Measures a necessary step that phenotype does not report ^[S9]

5a.2 A practical build

The workable position for most programs is a matrix rather than a single assay, which the FDA's potency-assurance framework explicitly permits ^[S13]:

- **Phase 1** — maturation phenotype by flow as identity, plus IL-12p70 on maturation as a biologically relevant quantitative readout, qualified rather than validated.
- **Phase 2** — add a functional readout. Either a T-cell priming or IFN- γ -release co-culture, or a CCR7 migration assay, depending on which failure mode the program considers most likely. Begin qualification with acceptance criteria.
- **Pivotal and BLA** — one qualified or validated functional assay carrying primary weight, with the phenotype panel confirmatory.

Both IL-12p70 and the CCR7 migration readout are within MADE's evidenced analytical bench — plate-reader ELISA on the multi-mode reader and flow on the CytoFLEX ^{[S4][S8]}. The T-cell priming assay is the one that requires real development work, and it should be scoped as development, not assumed as a method transfer.

5a.3 What the approved precedent shows

Sipuleucel-T is the field's demonstration that a functional release attribute can be built for an antigen-presenting-cell product, and that it can be worth building. Its potency is determined in part by measuring upregulation of CD54 (ICAM-1) on the antigen-presenting cells after culture with the PAP-GM-CSF fusion antigen, and lot release includes total nucleated cell count, CD54-positive cell count and CD54 upregulation [S30][S32].

The result that matters: an integrated analysis of all three Phase 3 studies, 476 patients, found that overall survival correlated with cumulative CD54-positive cell count ($P = 0.016$), total nucleated cell count ($P < 0.001$) and CD54 upregulation ($P = 0.002$) [S31].

Product attributes correlating with survival is rare in cell therapy. It is the strongest available argument that functional release testing in this modality is not a regulatory tax — it is measuring the thing that determines whether the patient benefits. Any DC program deciding how much to invest in potency should read that analysis first.

A precision note. Sipuleucel-T is an autologous activated antigen-presenting-cell product derived from PBMCs and loaded with a fusion protein — it is not a classical monocyte-derived dendritic-cell vaccine, and the distinction is worth keeping when citing it to an immunologist. The transferable lesson is the analytical strategy, not the process.

5 (continued) — Reading this program's panel

CD83 at $\geq 70\%$ is the right marker to specify. It is the canonical DC maturation marker and the one the DC core identifies as most commonly carried as the release specification. Setting it at 70% gated is a real and meaningful bar.

The informational panel is doing more work than its label suggests. CD80, CD86 and HLA-DR are the costimulatory and presentation markers that, with CD83, describe whether this cell can prime a T cell rather than tolerize one. CD14 down-regulation evidences that differentiation actually happened. CD274 (PD-L1) and B7H2 are inhibitory and costimulatory ligands that speak to the polarization of the product. Collecting all of them and specifying none is a deliberate, phase-appropriate choice — but the data being accumulated is more informative than the panel's structure implies, and it is the dataset from which Phase 2 specifications should be set. Ask whether Mayo has trended it.

CCR7 is CD197, and it is in the panel. The DC core names CCR7-directed migration as the under-measured variable in this modality — the ability to reach a draining lymph node is necessary for the mechanism and is not reported by any other marker. Mayo is already measuring CD197 expression. **Converting that from a surface-expression readout into a functional chemotaxis assay is a small step from where the program already is,** and it is the most mechanism-proximate assay available to a DC program that does not want to build a T-cell priming co-culture.

MADE's specific recommendation: propose a CCR7-directed migration assay plus IL-12p70 secretion on maturation as the Phase 2 potency matrix. Both are within the evidenced bench — CytoFLEX and multi-mode plate reader ^{[S4][S8]} — and both build on data Mayo already generates.

Endotoxin informational-only on a frozen product is defensible and differs from the autologous MSC program's fresh-product design, where endotoxin is specified. Worth understanding whether that is deliberate or historical.

6. Comparability and technology transfer

6.1 Transfer risk

The standard matrix applies: academic or research-lab origin is HIGH risk with three to five bridging lots; another CDMO is MEDIUM with two to three ^[S5]. DC programs sit at the harder end of their risk band because the source process is usually institution-specific with no platform reference to fall back on.

6.2 The changes that carry real risk

Change	Risk	Why
Antigen loading method or sequence	Highest	Changes what is presented and how much; a different product by any reasonable reading
Maturation cocktail or stimulus	Highest	Determines polarization and priming capacity
Monocyte enrichment method	High	Different input purity and composition; differentiation kinetics shift ^[S9]
Cytokine vendor or lot	Medium-High	Specific activity differs between vendors and lots — specify by activity ^[S11]
Vessel or culture format	Medium	Density and gas exchange change; DC differentiation is density-sensitive
Fresh to cryopreserved	Medium-High	Requires demonstration that maturation phenotype and function survive the freeze

6.3 The CQA set

Maturation phenotype — CD83, CD80, CD86, HLA-DR, CD14 — at HIGH priority; **functional potency at CRITICAL where an assay exists, and identified as a gap where it does not**; viability HIGH; purity and residual non-DC populations HIGH; endotoxin HIGH; sterility and mycoplasma required every lot ^[S5].

6.4 The staged plan MADE runs

Stage 0 — technical assessment. Read the process against the modality checklist, name what is defined and what is assumed, produce the sponsor clarification list. In this modality, expect the antigen supply chain and the potency position to be the two largest open items.

Stage 1 — paper transfer and gap closure. Documentation review, equipment fit, cytokine and antigen sourcing and qualification, analytical gap assessment. The antigen workstream starts here and runs in parallel throughout — it is frequently the longest pole and is frequently treated as procurement.

Stage 2 — engineering run. Non-GMP on destination equipment with destination materials, including a maturation–marker time course rather than a single endpoint reading, so the maturation window is characterized rather than inherited.

Stage 3 — comparability. Head-to-head on the risk-weighted CQA set.

Stage 4 — GMP manufacture and release.

6 (continued) — The transfer plan for this program

6.1 What Mayo has specified

Mayo requires the vendor to **use its existing processes**, supported by tech transfer with batch records, test records and reports. Test methods may be Mayo's transferred analytics, MADE in-house equivalents, or a combination, provided equivalency is demonstrated and all methods are validated or verified phase-appropriately. **Validated liquid-nitrogen shipping is a stated requirement.** The project will be evaluated on the full solution vision and implemented in a phased approach across the enterprise ^[S64].

"Use our existing processes" is a clear instruction and it sets the transfer type: this is a process transfer, not a platform proposal. The equipment question in §11.7 follows directly from it.

6.2 The change inventory

Change	Risk	Note
LOVO and CliniMACS Plus availability	Gating	Named instruments; not evidenced at MADE. See §11.7
Site, operators and suite	Medium	T-175 flask work with many manual steps — operator qualification against Mayo's batch records is the substance of the transfer
Cytokine lots — IL-4, GM-CSF, PGE2, TNF-α	Medium–High	Specify by specific activity, not mass; the DC core notes activity differs between vendors and lots ^[S11]
CellGenix media lot	Medium	Incoming performance testing recommended ^[S11]
Flow cytometer — Navios to CytoFLEX	Medium	Mayo runs Navios; MADE runs CytoFLEX. Equivalency demonstration required, and Mayo has invited exactly that
Maturation window and timing	Medium–High	The RFP emphasizes strict timing controls; transfer must preserve them as validated parameters
Controlled-rate freeze profile	Medium	Confirm the profile transfers and post-thaw phenotype is retained

6.3 Staged plan

Stage 0 — assessment. This document, the equipment confirmation, and the §12 questions.

Stage 1 — paper transfer and gap closure. Batch records, test records and reports mapped; equipment fit resolved; cytokine and media sourcing qualified by specific activity; flow method equivalency planned Navios to CytoFLEX; LN2 shipping lane qualified.

Stage 2 — engineering run. Non-GMP on healthy-donor apheresis, with the three in-process count points measured to establish MADE's own yield chain, and a **maturation-marker time course** rather than a single endpoint, so the maturation window is characterized on MADE's equipment rather than inherited.

Stage 3 — comparability. Head-to-head on CD83, the informational panel, viability and yield, plus post-thaw phenotype retention.

Stage 4 — GMP manufacture, release and distribution.

7. Stability, storage and logistics

For a cryopreserved product the questions are post-thaw viability, post-thaw maturation phenotype retention, and whether function survives — the third being the one most often unmeasured. Validated liquid-nitrogen shipping is a standard requirement for frozen DC drug product distributed to clinical sites, along with an instruction-for-use covering thaw and administration at the bedside, since these products are commonly thawed and drawn into a syringe by site staff rather than prepared in a pharmacy.

For a fresh product the constraint is arithmetic. Manufacture, release testing and infusion must fit inside the product's shelf life, which is measured in hours to days. Fourteen-day sterility cannot gate release; rapid microbial methods gate it and the compendial result follows. Any schedule slip consumes shelf life directly, and there is no buffer.

Autologous scheduling adds a month to GMP readiness in the standard timeline model, and it is earned — slot booking, apheresis coordination, and the failure path when a batch does not meet specification all have to be designed rather than assumed ^[S2].

8. Supply chain and critical materials

Category	Material	Typical source	Risk
Starting material	Leukapheresis	Collection site	LOW on supply; monocyte content is patient-dependent
Enrichment	CD14 selection reagent and tubing sets	Miltenyi Biotec	MEDIUM — proprietary single-source ^[S6]
Differentiation	GM-CSF, IL-4, GMP grade	CellGenix, Miltenyi, others	MEDIUM — specify by specific activity, not mass ^[S11]
Maturation	TNF- α , IL-1 β , IL-6, PGE2	Multiple	MEDIUM — cocktail composition is program-defining, so substitution is a change
Media	Serum-free DC media	CellGenix and others	LOW-MEDIUM — lot performance testing recommended ^[S11]
Antigen — peptide	GMP peptide synthesis	Specialist CDMOs	MEDIUM-HIGH — lead time and per-peptide stability

Category	Material	Typical source	Risk
Antigen — mRNA	GMP mRNA synthesis	Specialist CDMOs	MEDIUM-HIGH — lead time; per-patient for neoantigen programs
Antigen — lysate	The patient's tumor	Clinical site	HIGH — quantity and quality are not guaranteed and cannot be reordered
Electroporation	Instrument-specific disposables	MaxCyte, Lonza, Thermo	MEDIUM — proprietary to the system ^[S6]
Cryo	Cryoprotectant, vials	BioLife and others	LOW-MEDIUM

The distinctive risk here is the antigen. In every other modality the therapeutic identity is carried by the cells; in DC therapy it is carried by what the cells are holding, and that is a separately manufactured material with its own release, its own stability and its own lead time.

9. Regulatory and CMC

9.1 Phase-appropriate expectations

Phase 1 requires the process described with critical parameters identified; identity by flow; viability; sterility, endotoxin and mycoplasma; and a biologically relevant, quantitative potency assay that is qualified rather than validated ^[S1]. Many DC programs meet the first four comfortably and treat the fifth as satisfied by maturation phenotype. That reading is defensible at Phase 1 and does not survive Phase 2 ^[S13].

The January 2026 flexible-CMC position applies: before Phase 2/3 manufacture, 21 CFR Part 211 compliance is not expected, IND specifications may be permissive, and there is no requirement for three PPQ lots ^[S12].

9.2 What to expect the agency to ask

REF_01 does not carry a dendritic-cell deficiency list, as it does for CAR-T, NK, MSC, TIL, iPSC and gene-modified HSC ^[S1]. Reasoning from the framework rather than from a list, the questions to expect are: what measures potency, and is it MOA-correlated; how is maturation state controlled and demonstrated batch to batch; what is the antigen's own quality control; and — for personalized programs — how product consistency is assured when the antigen differs for every patient.

9.3 Long-term follow-up

Non-integrating DC products do not carry the fifteen-year follow-up expectation that applies to integrating vectors. Where a program uses viral vector for antigen delivery, check whether the vector integrates before assuming the obligation does not apply ^[S16].

10. Clinical and technical precedent

The modality has an approved product and a long tail of Phase 3 disappointments. Sipuleucel-T was approved by the FDA in 2010 as the first therapeutic cancer vaccine, and remains the reference point for what an autologous antigen-presenting-cell product looks like as a licensed medicine ^[s30]. It also demonstrated that manufacturing this class at commercial scale is possible, with a per-patient product and a distributed collection-and-infusion network.

The pattern across DC vaccine trials is immunological response without a corresponding survival benefit. Many programs have shown antigen-specific T-cell responses in a majority of treated patients and failed to convert that into a primary endpoint. The plausible explanations are mechanistic — the immunosuppressive tumor microenvironment, the difficulty of getting enough injected DCs to a lymph node — and they are worth stating because they shape what a manufacturer can and cannot fix. A CDMO cannot make a tumor less immunosuppressive. A CDMO can make sure the cells being injected are mature, loaded, migration-competent, and consistent from batch to batch, which is the part of the problem that manufacturing owns.

Migration efficiency is the under-measured variable. Only a small fraction of injected DCs reach draining lymph nodes in most published imaging work. Programs that treat CCR7-directed migration as a measurable product attribute rather than an assumed property are addressing the step most likely to be limiting.

11. MADE capability against this modality

11.1 Manufacturing environment — the strong fit

DC manufacture is flask-based with many open manipulations. MADE's suites operate at Grade B background with Grade A BSC for open manipulations, which is exactly the environment this modality requires; closed-system steps are described as Grade B / Closed System. Phase 1/2 autologous DC batch sizes are small, so suite time and operator capacity, not vessel scale, set throughput — which is a planning input rather than a constraint at this phase.

Sites: Princeton, NJ and East Norriton, PA.

11.2 Analytical bench — evidenced against the registers

Verified 23 August 2026 against the Princeton register (464 assets) and the East Norriton register (1,530 assets), with qualification status attested by MADE operations on the same date ^[s8].

Need	Instrument	In service
Identity, purity, phenotype, exhaustion panel	Beckman Coulter CytoFLEX, 13-color	4 Princeton
Additional flow capacity	Miltenyi MACSQuant Analyzer; Agilent NovoCyte Penteon; Nexcelom image cytometer	6, 1 and 2 respectively, East Norriton, in L-135 and L-141
Rapid in-process flow	Accellix cytometer	1 East Norriton, in L-141

Need	Instrument	In service
Cytotoxicity, cytokine and ELISA readouts	Thermo Varioskan Lux; Thermo plate reader; Molecular Devices SpectraMax M3	1, 2 and 3 respectively — Princeton and East Norriton L-135/L-141
Vector copy number, editing efficiency	Bio-Rad QX200 ddPCR	1 Princeton, 4 East Norriton in L-138 and L-144
Orthogonal dPCR	Thermo QuantStudio	1 Princeton, 2 East Norriton
Count and viability	NucleoCounter NC-200	7 Princeton
Count and viability	Beckman Vi-CELL	2 East Norriton, in V-018 and V-019
Particle concentration and size	Particle Metrix ZetaView Evolution quatt	1 Princeton
Mycoplasma	BioFire	1 Princeton, 2 East Norriton
Endotoxin	Endosafe	4 Princeton, 3 East Norriton
Nucleic acid quantitation	NanoDrop	1 Princeton, 3 East Norriton
Colony counting (CFU)	Reichert colony counter	1 East Norriton, in V-042
Hematology differential	Sysmex XN-330	held at East Norriton, in storage

11.3 Process equipment — evidenced against the registers

Verified 23 August 2026 against both site registers, with qualification status attested by MADE operations on the same date ^[S8].

REF_O9 fit-check item	In service	Detail
LOVO — wash and volume reduction	4	3 Princeton; 1 East Norriton in L-140
CliniMACS Plus — CD14 selection	5	Princeton
Electroporation for mRNA loading	3	Thermo Neon × 2 (Princeton; East Norriton L-132); Lonza 4D-Nucleofector × 1 Princeton
CTS Rotea — counterflow alternative	5	3 Princeton; 2 East Norriton
Controlled-rate freezing and LN2	9	2 Princeton; 7 East Norriton
Thermo CTS Xenon	—	1 Princeton, Inactive
Elutra — elutriation alternative	—	1 Princeton Inactive; 1 East Norriton in storage

Both instruments at the front of every monocyte-derived DC process are in service — four LOVO systems and five CliniMACS Plus units. Elutra, the elutriation alternative, is held but not in service; if a sponsor's process specifies it, that is an acquisition-and-qualification conversation rather than a scheduling one.

11.4 Team experience

MADE's quality leadership carries collective prior-organization experience in cell therapy quality systems, aseptic manufacture, method qualification and comparability — spanning commercial cell therapy quality leadership at Bristol Myers Squibb and Novartis, quality operations at WuXi Advanced Therapies and Lonza, and regulatory CMC covering forty-plus products through FDA INDs. This is prior-organization experience held by named individuals now at MADE. MADE itself has not yet completed a client audit, and that distinction is stated wherever this is described to a client.

11.5 Indicative economics and duration

REF_02 does not carry a dendritic-cell per-batch band ^[S2]. DC sits structurally between autologous TIL, whose published cost band sits above this modality, and allogeneic CAR-T — a short culture with modest reagent cost, but heavy operator time and, where antigen is patient-specific, a parallel antigen manufacture that is not in any cell-therapy band at all. **Any DC cost estimate should be built bottom-up from operator hours, cytokines, enrichment reagent, the QC panel and the antigen, rather than taken from an adjacent modality's band.**

Duration follows the standard model: 12–18 months for a custom process with no platform, plus two to four months where the process originates in an academic lab, plus one month for autologous scheduling complexity, plus two to four months where a potency assay has to be developed ^[S2] — which, for this modality, should be assumed present.

12. Open questions for Dr. Roberts's team

Scope boundary — confirm first. Is the transferred product the unloaded mature DC only, with antigen loading performed by Mayo? If loading is in scope at any future point, what is the antigen and its source?

Equipment. Is LOVO required, or would an equivalent closed wash system with comparability be acceptable? Same question for CliniMACS Plus versus an alternative CD14 selection route. Which CliniMACS tubing set is in use?

Process. What are the leukapheresis acceptance criteria, and the maximum age from collection to processing start? What monocyte yield is typically achieved post-CliniMACS, and what is the acceptance threshold? What are the exact cytokine concentrations and are they specified by specific activity? What is the maturation window, and was it established as a time course? What is the target dose per vial, and how many product and reserve vials per manufacture?

Analytics. Would Mayo prefer its Navios methods transferred, or a CytoFLEX equivalency bridge? **Has the informational flow panel been trended across batches, and would Mayo share it?** Is there appetite to add a CCR7 migration assay and IL-12p70 secretion as a Phase 2 potency matrix? Why is endotoxin informational here when it is specified on other Mayo programs?

Clinical and logistics. Which Mayo sites will receive product? Expected patients per month? What is the shelf life of the frozen product, and what stability data supports it? Who thaws, loads and administers, and what does the instruction-for-use require of them? What happens on a manufacturing failure — is re-collection

protocol-permitted?

Program. This is a Phase 2 program per the portfolio snapshot — is the transfer intended to support the current trial, a future trial, or both?

13. Sources

Tag	Source
[S1]	REF_01 — Regulatory Intelligence Knowledge Base (MADE internal, proposal-generator appraisal engine). Note: carries no dendritic-cell deficiency list
[S2]	REF_02 — COGS and Timeline Modeling Framework (MADE internal). Note: carries no dendritic-cell per-batch band
[S4]	REF_04 — Potency Assay Strategy Advisor (MADE internal). Note: has no dendritic-cell section. The potency guidance in §5a is reasoned from REF_09's named assays and the FDA potency-assurance framework, not lifted from REF_04
[S5]	REF_05 — Comparability and Tech Transfer Planning Framework (MADE internal)
[S6]	REF_06 — Supply Chain and BOM Risk Analysis Framework (MADE internal)
[S8]	MADE internal capability inventories — Equipment_List_from_BMRAM.xlsx and List_of_Analytical_Instruments_at_Made_Scientific_Feb_2026.xlsx, as specified in proposal-generator design.md §4.8. The xlsx files were not available to this machine; instrument names come from that specification and must be confirmed against the BMRAM export before client use.
[S9]	REF_09 — Modality-Specific Evaluation Depth Checklists, Modality 8 (MADE internal)
[S11]	REF_11 — Cell Therapy Manufacturing and Analytical Deep Knowledge v2.0 (MADE internal)
[S12]	FDA CBER, Flexible CMC Requirements announcement, 11 January 2026
[S13]	FDA CBER, Potency Assurance for Cell and Gene Therapy Products, draft guidance, December 2023, Docket FDA-2023-D-4299
[S16]	FDA CBER, Long-Term Follow-Up After Administration of Human Gene Therapy Products, final guidance, January 2020
[S30]	PROVENGE (sipuleucel-T) US prescribing information; initial US approval 2010. Potency determined in part by CD54 upregulation on antigen-presenting cells after culture with PAP-GM-CSF; lot release includes total nucleated cell count, CD54-positive count and CD54 upregulation
[S31]	Sheikh NA et al. Sipuleucel-T immune parameters correlate with survival: an analysis of the randomized Phase 3 clinical trials in men with castration-resistant prostate cancer. n = 476; OS correlated with cumulative CD54-positive cell count (P = 0.016), total nucleated cell count (P < 0.001) and CD54 upregulation (P = 0.002)
[S32]	CD54 is a surrogate marker of antigen presenting cell activation. PMID 18297282
[S64]	Request for Proposal — Mayo Clinic Autologous Dendritic Cell for Liver Cancer, 18 August 2026, 6 pp. Mayo Clinic Center for Regenerative Biotherapeutics. Process description, in-process and release specifications, and Areas of Interest
[S65]	Salesforce opportunity 23745-2026, TT + GMP Autologous DC for Liver Cancer; stage New; no primary contact recorded, linked to Dr. Roberts via the Drive folder holding this RFP; retrieved 2026-08-22