

TECHNICAL EVALUATION & CDMO FRAME

# Gene-Corrected Cells for Osteogenesis Imperfecta

MADE technical evaluation and CDMO frame

| PI                 | MAYO SITE | ON NUMBER | MODALITY                                        | VERSION |
|--------------------|-----------|-----------|-------------------------------------------------|---------|
| David R. Deyle, MD | Rochester | none      | Gene-modified autologous stromal cell (pre-IND) | V01     |
| PREPARED           |           |           |                                                 |         |
| September 3, 2026  |           |           |                                                 |         |

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## 1. At a glance

|                              |                                                                                                                                                                                       |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Program                      | Gene-corrected bone-derived stromal cells for osteogenesis imperfecta — pre-IND, no registered trial                                                                                  |
| Modality                     | Gene-modified autologous stromal cell; a cell-free secretome route is also open <sup>[S3]</sup>                                                                                       |
| Phase                        | Pre-IND. Discovery and large-animal model <sup>[S3][S4]</sup>                                                                                                                         |
| Regulatory status            | No IND. No NCT record for a cell product in this program <sup>[S2]</sup>                                                                                                              |
| Starting material            | Patient bone-derived stromal cells <sup>[S3]</sup>                                                                                                                                    |
| Drug substance               | Not established — the target product has not been fixed. See §15                                                                                                                      |
| Drug product                 | Not established. See §15                                                                                                                                                              |
| Where MADE would manufacture | Princeton, NJ, with East Norriton, PA in the MADE network for scale                                                                                                                   |
| MADE reference               | None. No opportunity exists for this program <sup>[S5]</sup>                                                                                                                          |
| MADE technical fit           | <b>Process development, not GMP.</b> The cell handling, editing and analytics are within MADE's installed capability; what is missing is a defined product, not a manufacturing route |

**This is a technical assessment, not a proposal.** It was written after the 3 September session because the agenda placed Dr. Deyle in the day and MADE held no program document. It is deliberately short: there is a real program here, but it is early, and pretending otherwise would not survive contact with the investigator.

## 2. Program understanding

Two of Dr. Deyle's three clinical-stage programs are outside what MADE manufactures. That is stated here first, plainly, because it is the most useful thing MADE can tell you.

| Program                                                                                                                                                                                  | What it is                              | MADE position                                                                                                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------|
| AAVrh10-PCCA, propionic acidemia — NCT07643844, Phase 1, recruiting, 9 patients, <b>Mayo Clinic is the sponsor</b> ; Dr. Deyle is responsible party and overall official <sup>[S2]</sup> | AAV gene therapy. A vector drug product | <b>MADE does not make viral vector.</b> Out of scope, and the honest answer is that MADE would be a poor place to send it |
| AVTX-803 (L-fucose), leukocyte adhesion deficiency II — NCT05462587 and NCT05754450, Phase 3, recruiting, sponsored by AUG Therapeutics; Dr. Deyle is site investigator <sup>[S2]</sup>  | Small molecule                          | Out of scope                                                                                                              |
| Osteogenesis imperfecta — gene-corrected cells, and a characterized secretome <sup>[S3][S4]</sup>                                                                                        | Cell product, pre-IND                   | <b>The only thread where MADE is the right partner</b>                                                                    |

The osteogenesis imperfecta work is the substance. A 2026 proteomic study characterized patient bone-derived stromal cells **and their secretomes** <sup>[S3]</sup>, and a 2026 paper reports a large porcine model of OI type I with Dr. Deyle as senior author <sup>[S4]</sup>. Together those are the two things a cell program needs before it can be defined: material that has been characterized, and an animal model large enough to inform dose and delivery.

The laboratory's editing methods are AAV gene targeting, TALENs and CRISPR <sup>[S1]</sup>. A 2026 grant funds NF1 gene therapy using a foamy viral vector <sup>[S1]</sup>; whether that work modifies cells *ex vivo* is the single question that decides whether it is a second MADE program or a second vector program — see §15.

### 3. Regulatory position and pathway

|                                   |                                                                                                                                                                                            |
|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Current filing status             | No IND for a cell product. Mayo holds the IND for the AAVrh10-PCCA trial, which is a different program <sup>[S2]</sup>                                                                     |
| Designations held                 | None recorded for the cell work. Osteogenesis imperfecta is a plausible orphan-designation candidate; not pursued in any record MADE has seen                                              |
| What the CMC package must support | First-in-human. That is a Phase 1 package: identity, purity, safety and a measured potency attempt, not a validated one                                                                    |
| What a site change implies        | Nothing yet. There is no established manufacturing site to change from — the process would be built once, in one place, which is the cheapest position a program can be in                 |
| Applicable guidance               | FDA <i>Human Gene Therapy Products Incorporating Human Genome Editing</i> (2024) governs the edited-cell route; 21 CFR 1271 and the cellular-product CMC guidance govern the cell handling |

The regulatory advantage here is real and worth stating: a program with no IND and no incumbent manufacturing site can design its process to be transferable from the first run. Almost every other program in this package is paying to undo the opposite decision.

### 4. Starting material

|                                    |                                                                                                                                  |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Source                             | Patient bone-derived stromal cells <sup>[S3]</sup>                                                                               |
| Collection                         | Not established. Bone marrow aspirate and surgical bone fragment give different cell yields and different comparability problems |
| Acceptance criteria                | Not established — see §15                                                                                                        |
| Fresh or cryopreserved             | Not established. For an autologous edited product, a cryopreserved intermediate is what makes the schedule survivable            |
| Time from collection to processing | Not established                                                                                                                  |
| Chain of identity and custody      | Not established. For an autologous product this is designed once, at the start, not retrofitted                                  |
| Failed collection                  | Not established                                                                                                                  |

For a pediatric autologous program — and osteogenesis imperfecta presents in children — the volume of aspirate available is a hard constraint, not a preference. It should be settled before the process is designed around it.

## 5. Process flow

The process below is MADE's read of what this product would require, not a description of a process Mayo has written. It is offered as a starting frame.

| Unit operation                   | Likely approach                                      | MADE capability                                                                                        | Read                                                                                   |
|----------------------------------|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Collection and receipt           | Bone marrow aspirate or bone fragment                | Routine                                                                                                | Settle the source first — it changes everything downstream                             |
| Isolation and plating            | Plastic adherence                                    | Routine                                                                                                | Standard stromal cell isolation                                                        |
| Editing                          | AAV gene targeting, TALENs or CRISPR <sup>[S1]</sup> | Electroporation installed and in service — Lonza 4D-Nucleofector, Thermo Neon <sup>[S6]</sup>          | The choice of editing modality drives the analytical panel, not the other way round    |
| Selection or enrichment          | Not established                                      | CliniMACS Plus and Prodigy installed and in service <sup>[S6]</sup>                                    | Only if the edit is not near-quantitative                                              |
| Expansion                        | Planar or closed expansion                           | PBS Biotech vertical-wheel and Terumo Quantum Flex both installed and in service <sup>[S6]</sup>       | Closed expansion from the first engineering run avoids a comparability exercise later  |
| Harvest and wash                 | Closed wash                                          | CTS Rotea and LOVO installed and in service <sup>[S6]</sup>                                            | Routine                                                                                |
| Formulation and cryopreservation | Cryopreserved vials                                  | Controlled-rate freezers installed and in service <sup>[S6]</sup>                                      | Routine                                                                                |
| Secretome route, if taken        | Conditioned-medium collection and concentration      | Vertical-wheel bioreactors and ZetaView nanoparticle tracking installed and in service <sup>[S6]</sup> | A materially different product with a different regulatory path — decide, do not drift |

## 6. Key equipment

Every instrument below is in the MADE asset register as installed and in service, not merely held <sup>[S6]</sup>.

| Instrument                 | Purpose here                                 | MADE installed position  |
|----------------------------|----------------------------------------------|--------------------------|
| Lonza 4D-Nucleofector      | Electroporation for RNP or mRNA editing      | 1, in service, Princeton |
| Thermo Neon                | Electroporation, development scale           | 1, in service, Princeton |
| PBS Biotech vertical-wheel | Stromal cell expansion; secretome collection | 6, in service, Princeton |
| Terumo Quantum Flex        | Closed hollow-fiber expansion                | 1, in service, Princeton |
| CTS Rotea                  | Closed wash and concentration                | 3, in service, Princeton |

| Instrument               | Purpose here                                           | MADE installed position  |
|--------------------------|--------------------------------------------------------|--------------------------|
| NucleoCounter            | Cell count and viability                               | 7, in service, Princeton |
| Beckman Coulter CytoFLEX | Identity and purity by flow                            | 4, in service, Princeton |
| Bio-Rad QX200 ddPCR      | Edit quantification, copy number                       | 1, in service, Princeton |
| Particle Metrix ZetaView | Nanoparticle tracking, if the secretome route is taken | 1, in service, Princeton |
| Controlled-rate freezer  | Cryopreservation                                       | 2, in service, Princeton |
| Endosafe                 | Endotoxin                                              | 4, in service, Princeton |

## 7. Analytical panel and release

| Attribute                        | Likely method                         | MADE position                                           | In house or outsourced |
|----------------------------------|---------------------------------------|---------------------------------------------------------|------------------------|
| Identity                         | ISCT stromal marker panel by flow     | Installed, routine                                      | In house               |
| Editing efficiency               | ddPCR or amplicon sequencing          | ddPCR installed; sequencing outsourced                  | Mixed                  |
| Off-target assessment            | Guided by the editing modality chosen | Study design in house; sequencing outsourced            | Mixed                  |
| Purity                           | Flow, residual process reagents       | Installed                                               | In house               |
| Viability and count              | Automated cell counting               | Installed                                               | In house               |
| Sterility, mycoplasma, endotoxin | Compendial                            | Endotoxin in house; sterility and mycoplasma outsourced | Mixed                  |
| Potency                          | See §7a                               | Not established                                         | —                      |
| Strength                         | Viable cells per dose                 | Installed                                               | In house               |

### 7a. Potency

There is no potency assay for this program, and there should not yet be one — the product is not defined. What can be said honestly is what the assay will have to measure. If the therapeutic intent is that corrected cells make normal collagen, potency is a collagen-production or matrix-deposition measurement on the edited population, and the 2026 proteomic dataset <sup>[S3]</sup> is the right place to look for the analyte. If the intent is the secretome, potency is a different measurement entirely, on a different product.

That is the decision to make first. Groups that defer it end up with a release panel that measures identity and purity very well and says nothing about whether the product works.

## 8. Fill, finish and presentation

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Not established. There is no drug product definition yet, so there is no container closure, fill volume or dose form to describe. Recorded here so the reader knows it was considered, not skipped.

## 9. Stability, storage and shipping

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Not established, for the same reason. One point is worth making early: an autologous pediatric product manufactured away from Rochester needs its return leg designed at the same time as the process, not after it.

## 10. Comparability

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There is nothing to bridge to. This is the unusual case in the Mayo package where comparability is not a problem to solve but an advantage to bank — a process designed once, at the intended manufacturing site, never generates the site-change comparability exercise that the established programs in this package are all facing.

## 11. Technology transfer approach

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| Stage   | What happens                                                                                                                             | Gate                                        |
|---------|------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| Stage 0 | Define the product. Corrected autologous stromal cell, allogeneic bank, iPSC-derived osteoprogenitor, or secretome — one of them, chosen | Written target product profile              |
| Stage 1 | Process design against that definition, with the starting-material question settled                                                      | Process description and draft release panel |
| Stage 2 | Development runs at MADE on non-clinical material; analytical methods established                                                        | Reproducible process, methods qualified     |
| Stage 3 | Engineering runs; potency assay developed against the mechanism chosen in Stage 0                                                        | Pre-IND package                             |
| Stage 4 | GMP manufacture for first-in-human                                                                                                       | IND cleared                                 |

The gate that matters is Stage 0. Everything after it is ordinary work; without it, the rest cannot start.

## 12. Indicative timeline

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Stage durations are not offered. A pre-IND program whose target product is undefined cannot be scheduled honestly, and a schedule offered anyway would be the least credible thing in this package. What MADE can say is that Stage 0 is a matter of weeks of discussion, not months of work, and that it is the cheapest stage to get right.

## 13. MADE experience that supports this

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The MADE team has taken stromal cell programs from development into GMP manufacture, including autologous programs where the starting material is the constraint. Electroporation-based editing, ddPCR-based edit quantification and closed expansion are installed and in routine use at Princeton <sup>[S6]</sup>. On the secretome side, MADE runs extracellular vesicle work with nanoparticle tracking installed, and the same partnership that supplies MSC expansion and EV-collection media supports that route.

## 14. Guidance and suggestions

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**Decide what the product is.** Corrected autologous cells, an allogeneic bank, an iPSC-derived osteoprogenitor, or a secretome. These are four different INDs, four different release panels and four different manufacturing routes. The 2026 proteomics paper characterizes both the cells and their secretome <sup>[S3]</sup>, which is thorough science and also an unresolved fork.

**Let the porcine model earn its keep.** A large-animal model <sup>[S4]</sup> can fix dose, route and the delivery format — the three inputs a process design needs and rarely has at this stage.

**Design the process closed from the first development run.** There is no incumbent process to match, so closed expansion costs nothing extra now and removes a comparability exercise later.

**Keep the potency question open but visible.** Name the candidate assay in the target product profile even if it will not be run for a year.

**On the vector programs, be direct.** MADE does not make viral vector, and the propionic acidemia program should not be steered toward MADE. Saying so plainly is worth more than the work.

## 15. Open questions

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**Product definition.** For osteogenesis imperfecta, is the target a gene-corrected autologous stromal cell, an allogeneic bank, an iPSC-derived osteoprogenitor, or a secretome?

**The NF1 grant.** Does the foamy-vector NF1 work involve *ex vivo* cell modification, or is it *in vivo* vector delivery? This decides whether it is a MADE program at all.

**Starting material.** Bone marrow aspirate or surgical bone fragment, and what volume is realistically available in a pediatric patient?

**Editing modality.** AAV gene targeting, TALENs or CRISPR for the clinical construct? The analytical panel follows from the answer.

**Vector supply for the trial that is already running.** Who manufactures the AAVrh10-PCCA vector — Mayo, an academic core, or a CDMO? Asked not to sell anything, but because Mayo sponsoring a Phase 1 AAV trial says something about the vector supply arrangements behind the wider portfolio.

**Timeline intent.** Is there a target date for a first-in-human OI filing, or is this discovery work without a clinical date attached?

## 16. Suggested next step

A one-hour working session on Stage O — MADE process development and Dr. Deyle's laboratory, with the single agenda item of writing down the target product profile. No manufacturing commitment attaches to it, and it is the only thing that unblocks everything else.

## Sources

| Ref  | Source                                                                                                                                                                                                                                                                                                                                                                              |
|------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| [S1] | Mayo faculty profile, David R. Deyle MD, re-scraped 2026-09-02, including the 2026 foamy-vector NF1 grant                                                                                                                                                                                                                                                                           |
| [S2] | ClinicalTrials.gov API v2, retrieved 2026-09-03: NCT07643844 (AAVrh10-PCCA, Phase 1, recruiting, n=9, lead sponsor Mayo Clinic, responsible party and overall official David R. Deyle, MD); NCT05462587 and NCT05754450 (AVTX-803, Phase 3, recruiting, lead sponsor AUG Therapeutics, overall official David Deyle, MD). No cell-product trial is registered for this investigator |
| [S3] | Garapati K et al., <i>Proteomic alterations in patient bone-derived stromal cells and their secretomes in osteogenesis imperfecta</i> , Mol Genet Metab Rep, September 2026, PMID 42499581. Deyle DR, senior author                                                                                                                                                                 |
| [S4] | Aguirre-Flores ME et al., <i>Development of a large porcine model of osteogenesis imperfecta type I</i> , Bone Rep, March 2026, PMID 41626399. Deyle DR, senior author                                                                                                                                                                                                              |
| [S5] | MADE Mayo program registry, 2026-09-03 — no program or opportunity associated with Dr. Deyle                                                                                                                                                                                                                                                                                        |
| [S6] | MADE equipment register, generated 2026-08-24 from the Princeton asset register of 16 June 2026. Only units recorded as installed and in service are named                                                                                                                                                                                                                          |