Are hMSCs (Mesenchymal Stromal/Stem Cells) a Platform of Choice for GENE ENGINEERED CELLULAR THERAPY?

Good Safety Profile — deployed in tens of thousands of patients & hundreds of clinical trials, across two decades

SAFETY FIRST

hMSCs are well-known starting materials for allogeneic, off-the-shelf cell therapy products.

- Low immunogenicity
- Standardized, quality controlled raw materials available
- Transparent regulatory path, already navigated beyond Phase II by BioPharmas
- Consistent CMC Now Possible Across Production Scales

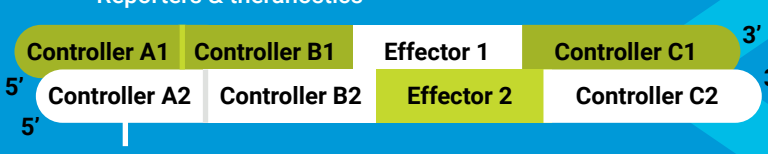
- 1502 hMSC Clinical Trials Posted Between 2011 - 2020
- 126 are Late Stage (Phase 2/3 or later)
- 16 Post Market Trials (Ph 4), Outside of USA

Innate therapeutic properties of hMSCs to harmonize with controlled delivery & expression of novel, programmable gene medicines

THERAPEUTIC POTENTIAL

Combinatorial DNA–Encoded Inputs → *Transfection, transduction, gene transfer* → **MSCs** → *Expansion, cell processing dose-filling, administration* → **Measurable Biological Outputs**

Swappable Molecular Effector Parts
Forward engineer MSCs with molecular therapeutics
- Agonists, ligands, receptors
- Inhibitors & decoys
- Enzymes
- Sensors
- Reporters & theranostics



Swappable Molecular Controller Parts
Modulate function in time & space
- Integration
- Expression
- Stability
- Localization
- Packaging & Targeting (e.g., Exosomes/EVs)

Example "App 1" for Multi-Indication Cell Platform

Cell Therapy Platforms
Plug pre-validated synbio parts & circuits into an industrialized cell "device"
- Targeted genome integration
- Cellular operating systems for improved bioproduction
- Conditional cell fate controls
- Improved survival or homing

Example "App 2" for Specialized Indication Enhanced Therapeutic

Traditional RegenMed Indications with Boost in Potency
Deploy DNA-controlled Rx for unmet medical needs
- Inflammation & autoimmunity
- Cardiovascular
- COVID-19 & ARDS
- Neurodegeneration
- Wound healing & pain
- Tissue / organ engineering

Gene-modified hMSCs can be the ideal cellular "chassis" for rapidly prototyped lead products and a drop-in, accelerated production process

ENGINEERABLE, START TO FINISH

(1) Engineer hMSC product using development-grade materials...

Design, build, test & edit engineered gene sequences → Assemble biofunctional genetic parts into "apps" and app-systems → Deliver & target gene apps into cell genome → Expand & deploy cells w/ enhanced tx function

(2) Engineer a "plug and play" GMP process with off the shelf, clinic-grade hMSC materials...

Obtain donor MSC bank → Transduce/transfect pool of MSCs with your gene apps → Bank frozen, pre-expanded doses → Expand MSCs to final dose → Infuse MSCs into patient

Allogeneic hMSCs can realistically scale at consistent PDLs to meet clinical translation needs, streamlining development time, cost, and regulatory burden

SCALABLE MANUFACTURING

Scale	Working Cell Banks	P3 Expansion	P4 Expansion	Final Harvest*
R&D	1M Cells + 50mL Media	10-15M cells 1 × T-225	3 × CS2 + 1L media	150-250M cells/lot × ~1-5 Mfg. lots
Product Development	10M Cells + 500mL Media	100-150M cells 2 × CS2	5-10 × CS10 + 7-15L media	1.5-2.5B cells/lot × 1-2 Mfg. lots
Phase 1 Clinical	20M Cells + 1.5L Media	200-300M cells 1 × CS10	20 × CS10 + 30L media	3-5B cells/lot ~20 patients × 3-5 Mfg. lots
Phase 2 Clinical	100M Cells + 7.5L Media	1-1.5B cells 5 × CS10	1.2B cells 50L Media Bioreactor	>20B cells/lot ~50 patients × 1-2 Mfg. lots

Product Comparability Across Scales

*Estimate. For more information on bioproduction scale needs for lot-to-dose calculations, please review Building Effective Multi-Year Process Development Programs I: Estimating hMSC Lot Size Ranges for Clinical Manufacturing Through Commercial Demand

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