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

**SAFETY FIRST**

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

**THERAPEUTIC POTENTIAL**

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

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
  - Delivered & targeted 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
  - Transfect/transduce pool of MSCs with your gene apps
  - Bank frozen, pre-expanded doses
  - Expand MSCs to final dose
  - Infuse MSCs into patient

**SCALABLE MANUFACTURING**

- Example “App 1” for Multi-indication Cell Platforms
  - Controller A1
  - Effective A1
  - Controller B1
  - Effective B1
  - Controller C1

- Example “App 2” for Specialized indication Gene Therapy
  - Controller A2
  - Effective B2
  - Controller C2

- Example “App 3” for Translational minded Gene Therapeutics
  - Controller A3
  - Effective B3
  - Controller C3

**Example Cell TheraPays**

- Plug pre-validated synbio parts & circuits into an industrialized cell device
  - Targeted genome integration
  - Improved survival or homing
  - Conditional cell fate controls
  - Improved bioproduction

- Traditional drug indications
  - Inflammation & autoimmunity
  - Cardiovascular
  - COVID-19 & ARDS
  - Neurodegeneration
  - Wound healing & pain
  - Tissue / organ engineering

**BioProcess Factors**

- Product Comparability Across Scales
  - Scale Working Cell Banks
  - P3 Expansion
  - P4 Expansion
  - Final Harvest

- *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 Manufacturing Through Commercial Demand.

**Gene-manipuated hMSCs can realistically scale at consistent PDx to meet clinical transition needs, streamlining development time, cost, and regulatory burden**