In the name of god

Mesenchymal Stem Cell Therapy: From Bench to Bedside in 2025

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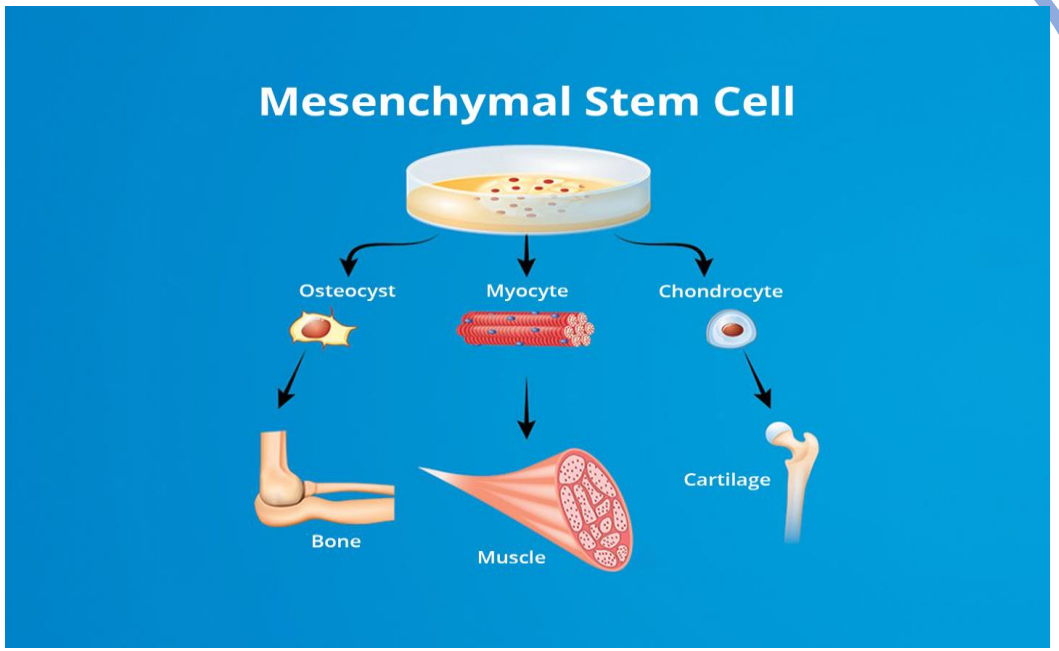
- Introduction
- Mechanism of action
- Clinical applications
- Challenge and limitations
- Conclusion and future outlook

Introduction

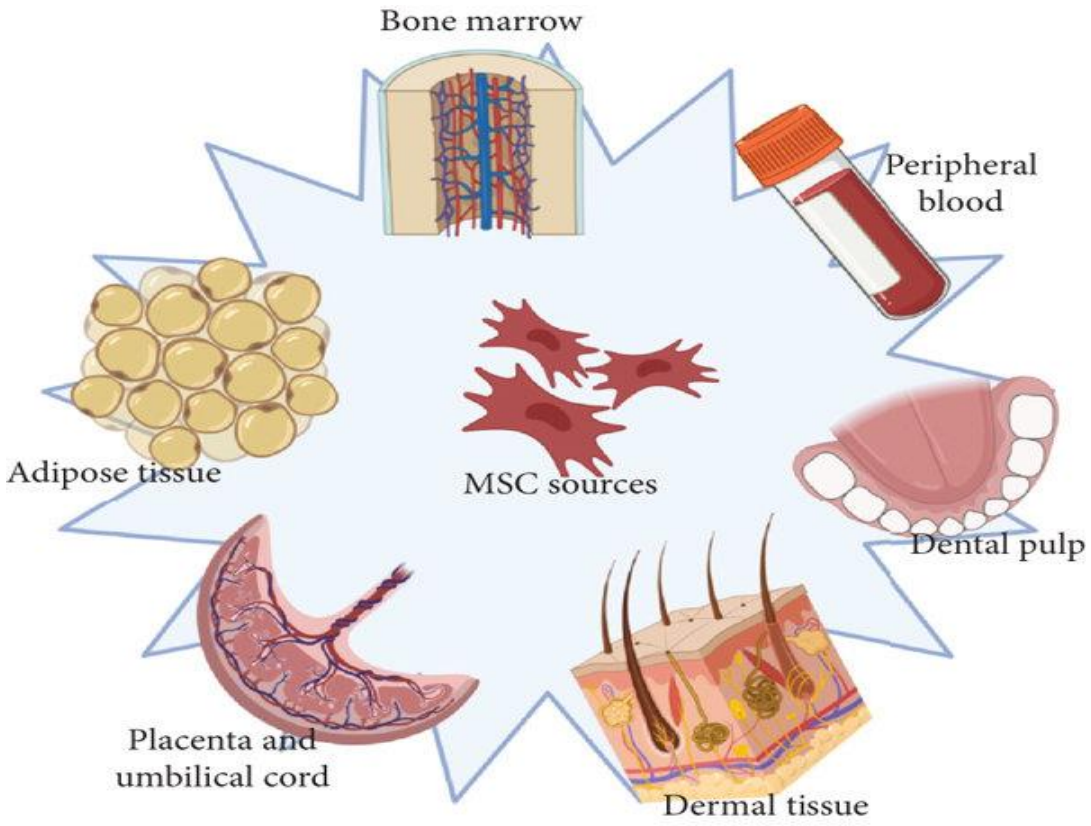
What Are MSCs?



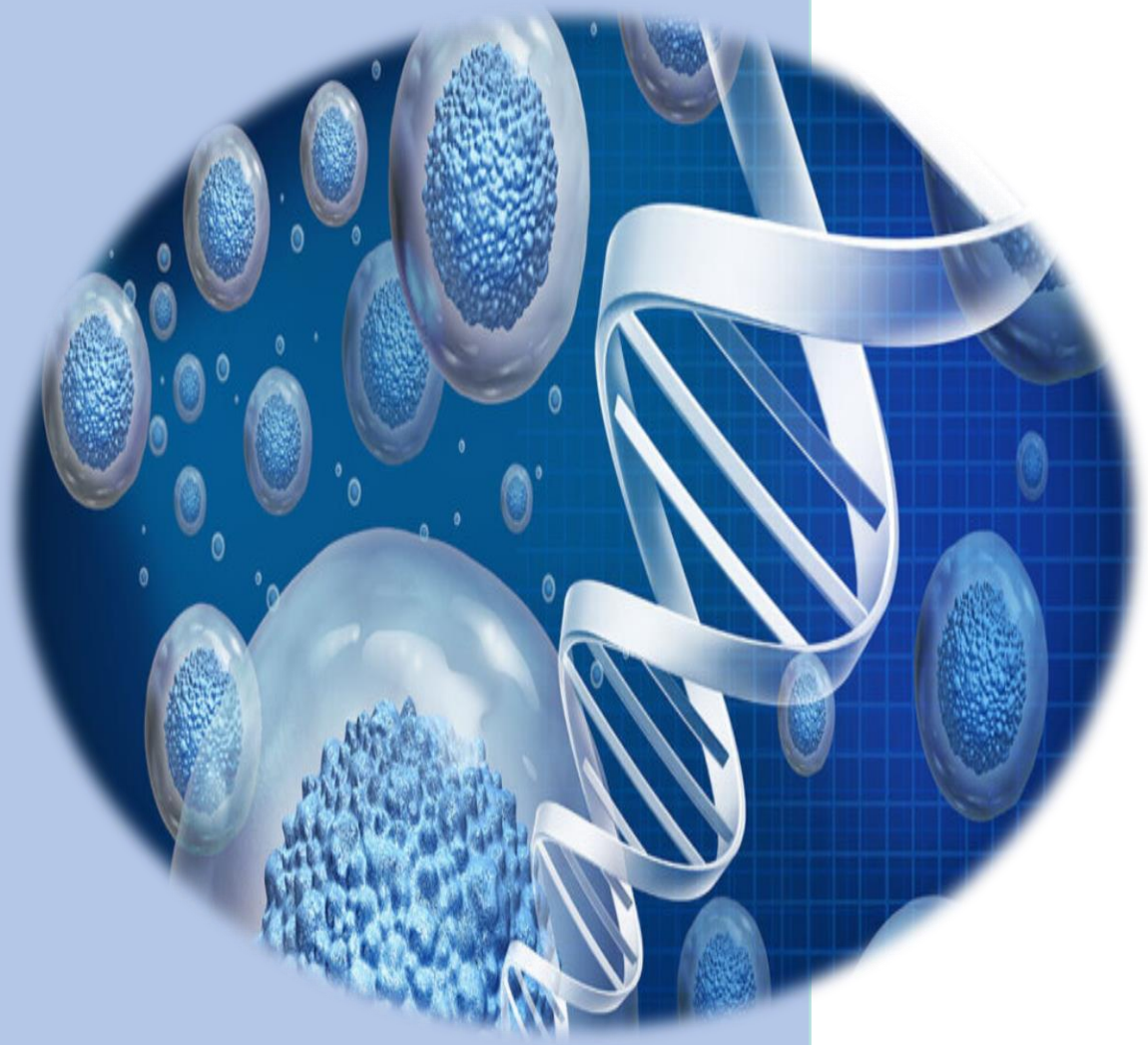
- Adult multipotent stromal cells
- Self-renewing
- Plastic-adherent
- Tri-lineage differentiation: osteogenic, adipogenic, chondrogenic
- Immunomodulatory and trophic properties
- Expression of CD73, CD90, CD105 markers
- Lack of expression CD45, CD34, and CD14 markers

MSC Sources

- Bone marrow (BM-MSC), the first and most commonly used source
- Adipose tissue (AD-MSC), high volume, and easy access
- Umbilical cord (UC-MSC)
- Dental pulp
- Wharton's jelly
- Peripheral blood
- Dermal tissue



Feature	Bone Marrow (BM-MSCs)	Adipose Tissue (AD-MSCs)	Umbilical Cord (UC-MSCs)
Harvest Method	Invasive (aspiration)	Minimally invasive (liposuction)	Non-invasive (medical waste from birth)
MSC Yield	Low	High	Moderate to High
Proliferation Rate	Moderate	High	Very High
Donor Age Dependency	High (declines with age)	Moderate	Low (neonatal source)
Immunomodulatory Capacity	Strong	Moderate to strong	Very strong
Differentiation Potential	Trilineage (osteogenic, chondrogenic, adipogenic)	Trilineage (especially adipogenic)	Trilineage (especially osteo-/chondrogenic)
Immunogenicity	Low	Low	Very Low
Clinical Experience	Extensive (first used in clinical trials)	Growing	Emerging, strong recent interest
Ethical Issues	Minimal	Minimal	Very minimal (no ethical conflict)
Storage and Banking	Not common	Not common	Common (e.g., cord blood/tissue banks)
Applications	Bone, cartilage, autoimmune diseases	Wound healing, cosmetic, metabolic diseases	Inflammatory, immune disorders, regenerative medicine



Mechanisms of Action

- **Paracrine signaling:** cytokines, growth factors

MSCs release a wide range of growth factors and extracellular vesicles (EVs/exosomes) that **promote tissue repair** and **regulate immune responses** (e.g., VEGF, HGF, IGF-1).

- **Immunomodulation:** inhibition of T-cell, NK, and B-cell activity

MSCs secrete **cytokines** (e.g., TGF-β, IL-10, PGE2) that **suppress T-cell proliferation**, shift **macrophages** toward an anti-inflammatory (M2) phenotype, and **modulate** dendritic cell maturation.

- **Homing and tissue repair:** MSCs **migrate** to injured or inflamed tissues via **chemokine receptors** (e.g., CXCR4-SDF1 axis).

- **Exosome-mediated effects**
- **Anti-inflammatory Effects:**

MSCs downregulate pro-inflammatory cytokines (e.g., **TNF-α, IL-1β**) and upregulate anti-inflammatory mediators, **reducing tissue damage** in **inflammatory diseases**.

- **Anti-apoptotic Effects:**

MSC-secreted factors **protect host cells** from apoptosis by activating survival pathways (e.g., PI3K/Akt, ERK).

- **Angiogenesis Promotion:**

Through VEGF and other pro-angiogenic factors, MSCs **enhance** neovascularization in ischemic tissues.

- **Antifibrotic Activity**

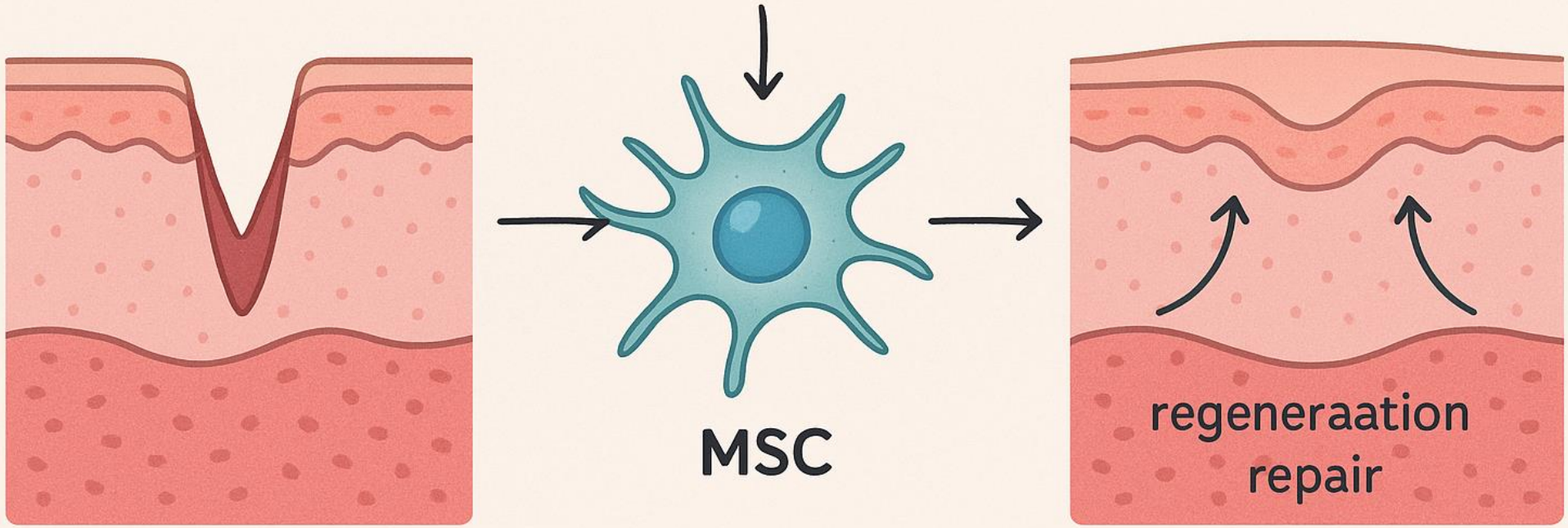
MSCs reduce fibrosis by **downregulating TGF-β1 and collagen** deposition, especially in organs like the lung, liver, and heart.

- **Antimicrobial Effects**

MSCs secrete **antimicrobial peptides** (e.g., LL-37, lipocalin-2), enhancing host defense against **bacterial infections**.

MSC MECHANISM IN WOUND HEALING

- paracine signaling
- immunomodulation
- differentiation



Clinical Applications

Clinical Applications (2024 Updates)

- Autoimmune diseases (Crohn's, RA, SLE)
- Neurodegenerative diseases (Stroke, ALS, MS)
- Orthopedic disorders (OA, cartilage repair)
- GvHD (FDA-approved Prochymal)
- COVID-19-associated Acute Respiratory Distress Syndrome (ARDS) (ongoing trials)

Highlights from Clinical Trials

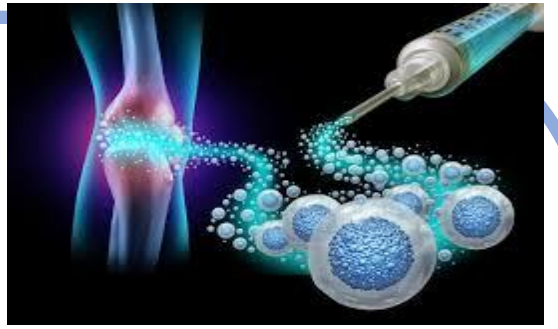
- Over 1200 MSC trials registered (ClinicalTrials.gov)
- Mixed results: success in GvHD, moderate in OA
- **Osteoarthritis** currently has the most clinical trials involving MSCs.

- **Challenges**: dosing, route of administration, variability in cell sources

❑ Cell Characterization and Quality Control

- Confirm **identity, purity, viability**, and **functionality** of cells.
- Use **flow cytometry**, **microscopy**, **gene/protein assays**, etc.
- Ensure **sterility and absence of contaminants.**
- Ensure **test for viability** before transplantation.

How can cells be transferred?



❖ Cell Delivery Methods

•**Local injection** (e.g., into cartilage defects, heart tissue, or skin wounds). Local injection into damaged tissue is the most commonly used method, and the duration of MSC retention and **survival** in the body after injection is typically a few days to a few weeks.

•**Topical gel** for wound.

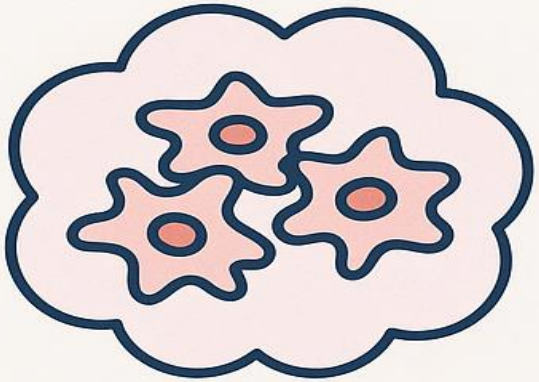
•**Systemic infusion** (e.g., IV for immune modulation). A **limitation** of intravenous injection of mesenchymal stem cells is their **entrapment in the lung**.

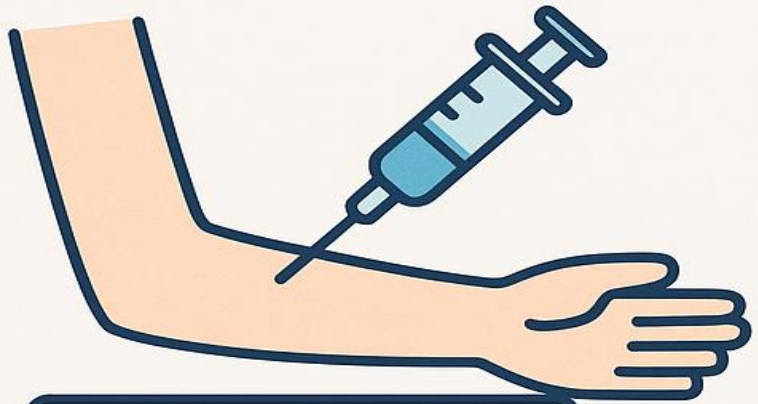
•**Seeding onto scaffolds or biomaterials** (for engineered tissues or implants).

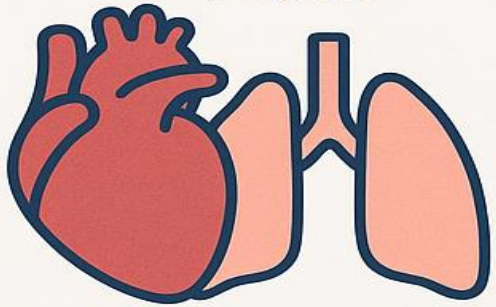
•**Bioprinting** with 3D printing technologies.

MSC IN CLINIC

Time







Preclinical research

Preclinical research

Approved therapies

Early 2000s Clinical trials

Potential therapies

- **Type 2 Diabetes Mellitus**

Year: 2020
Study: Phase II (Stem Cell Res Ther)
MSC Type: Allogeneic umbilical cord MSCs
Results: Significant improvement in HbA1c, fasting glucose, and C-peptide levels.
→ *MSC therapy enhanced insulin sensitivity and beta-cell function*

- **COVID-19 Related ARDS (Acute Respiratory Distress Syndrome)**

Year: 2021
Study: Phase I/II, randomized, double-blind (Lancet Respir Med)
MSC Type: Umbilical cord-derived MSCs
Results: Improved survival, decreased levels of IL-6 and CRP, and better oxygenation. **No** serious adverse events.
→ *MSC therapy showed a 2x higher survival rate compared to placebo in severe ARDS patients.*

•Spinal Cord Injury

Year: 2021
Study: Phase I/II (Cell Transplantation)
MSC Type: Autologous bone marrow-derived MSCs
Results: Neurological improvement (American Spinal Injury Association score, ASIA score) in >40% of patients. No immune rejection or tumor formation observed.
→ *Safe with promising functional recovery..*

•Knee Osteoarthritis

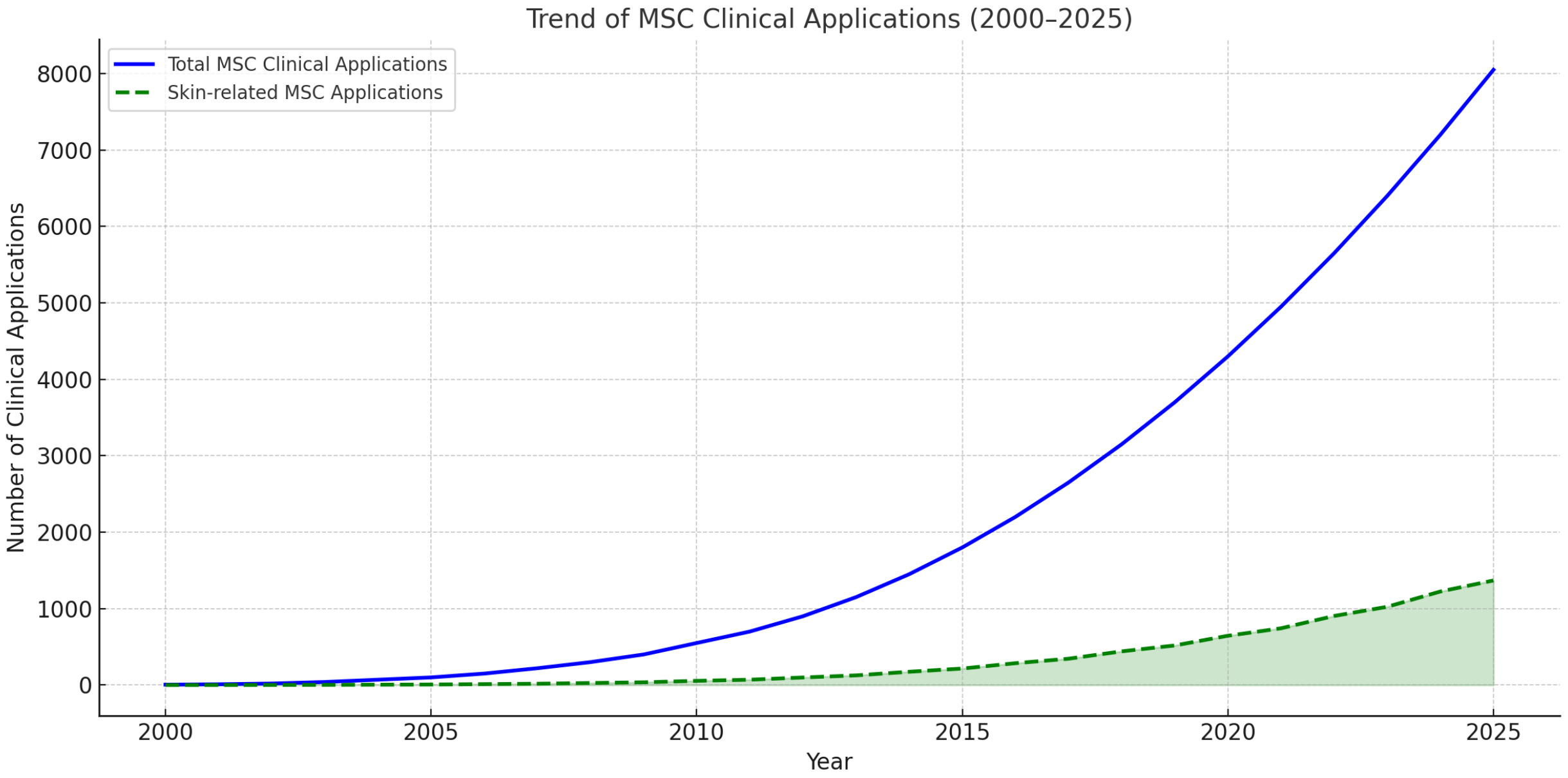
Year: 2022
Study: Phase II RCT (Randomized Controlled Trial) (Stem Cells Translational Medicine)
MSC Type: Bone marrow-derived MSCs (autologous)
Results: Significant reduction in VAS pain scores and improvement in WOMAC function scores **up to 12 months post-injection**
→ *Safe and effective with sustained benefits*.

- **Graft-versus-Host Disease (GvHD) – Steroid-Refractory**
  Year: 2023
  Study: Multicenter Phase III (published in *Blood Advances*)
  MSC Type: Commercial allogeneic MSC product (e.g., remestemcel-L)
  Results: Improved overall response rate at day 28 compared to placebo.
  → *MSC therapy was **approved** or considered for approval in several regions.*

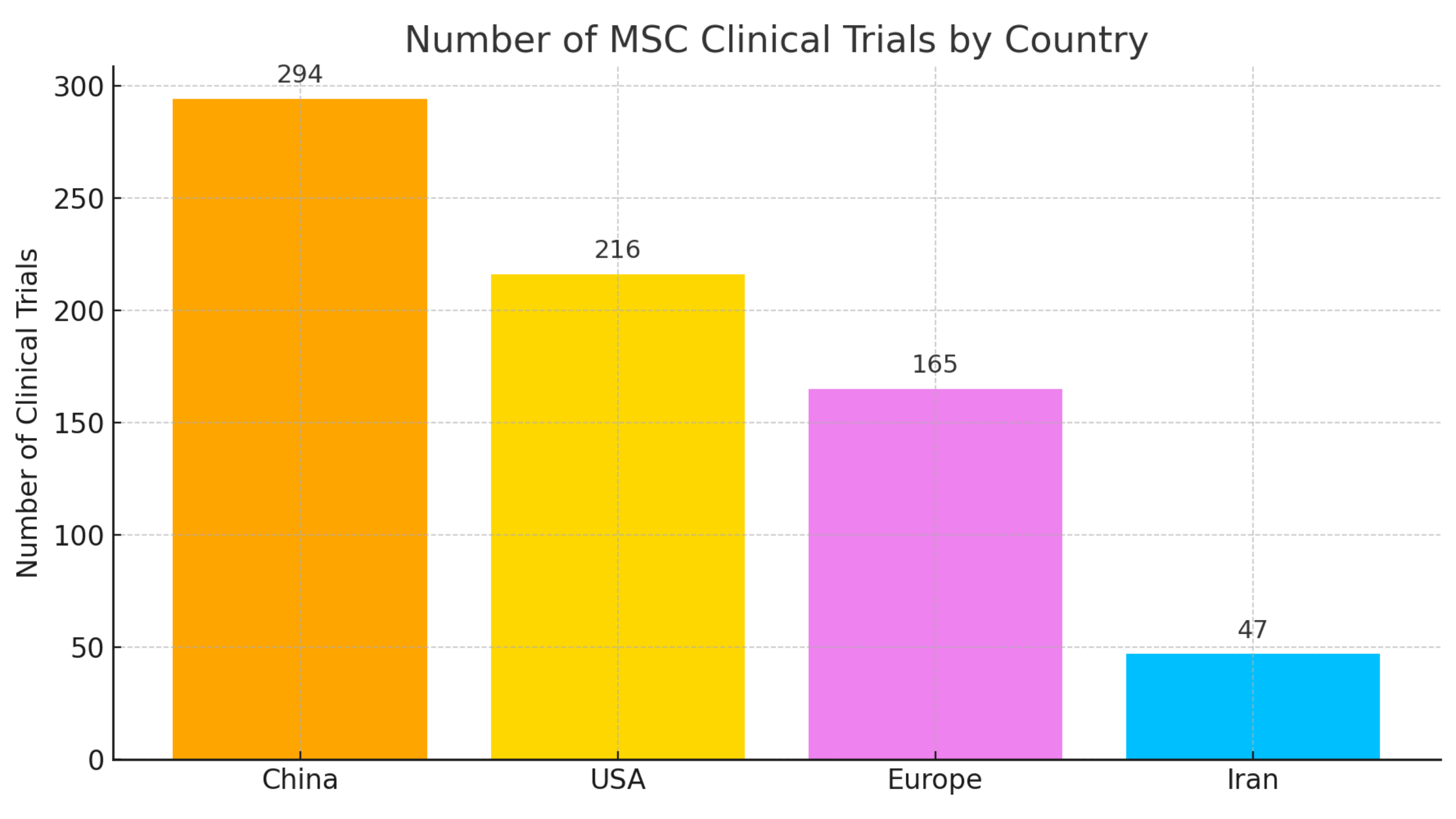
- **Interstitial Lung Disease (ILD) in Systemic Sclerosis**
  Year: 2024
  Study: Phase II trial
  MSC Type: Adipose-derived MSCs
  Results: Stabilization or mild improvement in lung function (FVC, DLCO) and skin fibrosis (mRSS).
  → *Good tolerability and disease-modifying potential.*

Area	Delivery Method	Source of MSC	Common Adjuncts	Main Outcomes
Skin	Topical, injectable	AD-MSC, UC-MSC	PRP, hydrogels	Faster healing, less scarring
Beauty	Injectable, topical	AD-MSC, exosomes	PRP, microneedling	Wrinkle ↓, skin tone ↑, hair ↑

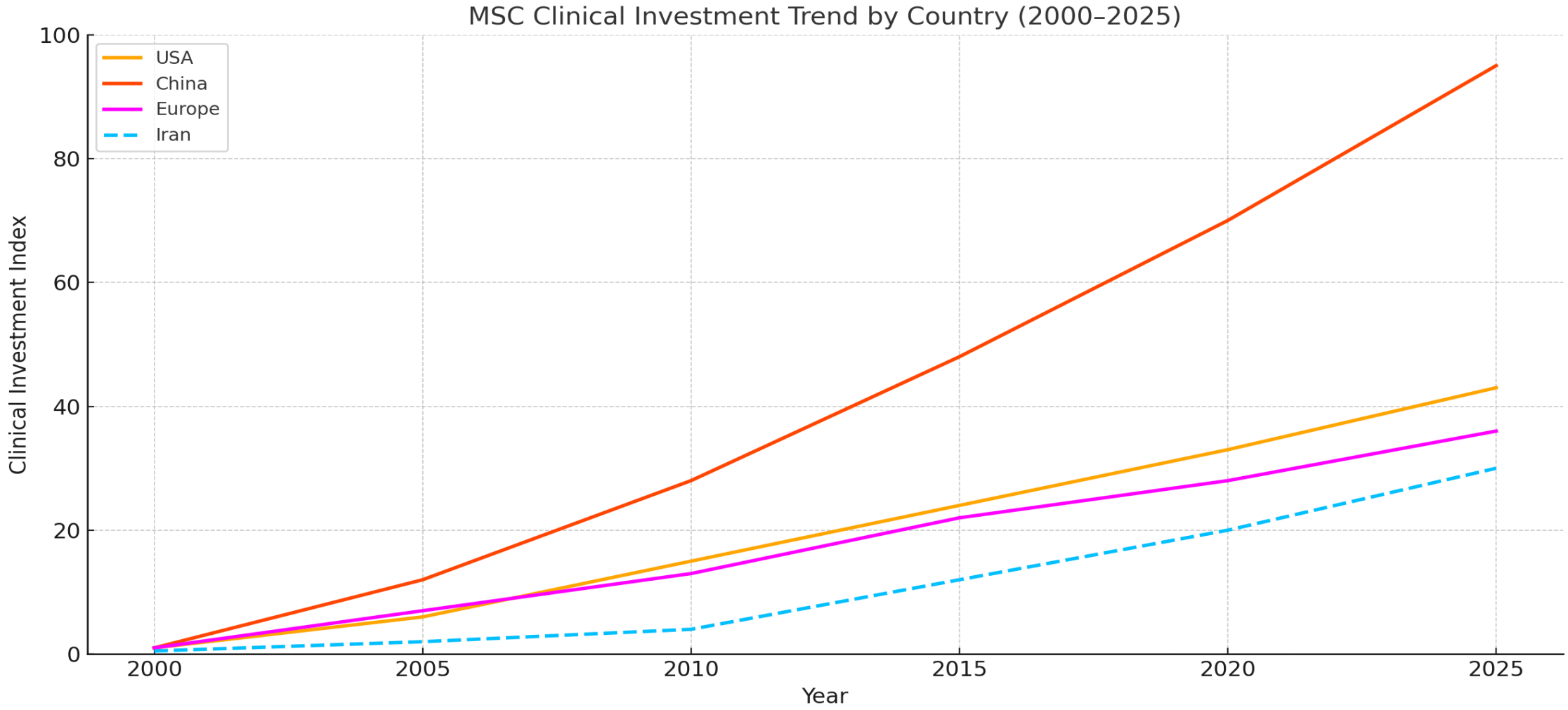
Condition	MSC Source	Route of Administration	Outcomes
Chronic Diabetic Ulcers	AD-MSCs, UC-MSCs	Topical gel, injections	Accelerated healing, reduced inflammation
Burn Wounds	BM-MSCs, AD-MSCs	Spray-on cell suspension, scaffolds	Faster epithelialization, less scarring
Surgical Wounds	UC-MSCs	Injected around wound, Hydrogel scaffold	Improved closure rate
Pressure Ulcers	AD-MSCs	Hydrogel scaffold, injection	Reduced ulcer size, better granulation



Timeline chart showing the increasing trend of Mesenchymal Stem Cell (MSC) **clinical applications from 2000 to 2025**, with skin-related applications highlighted separately.

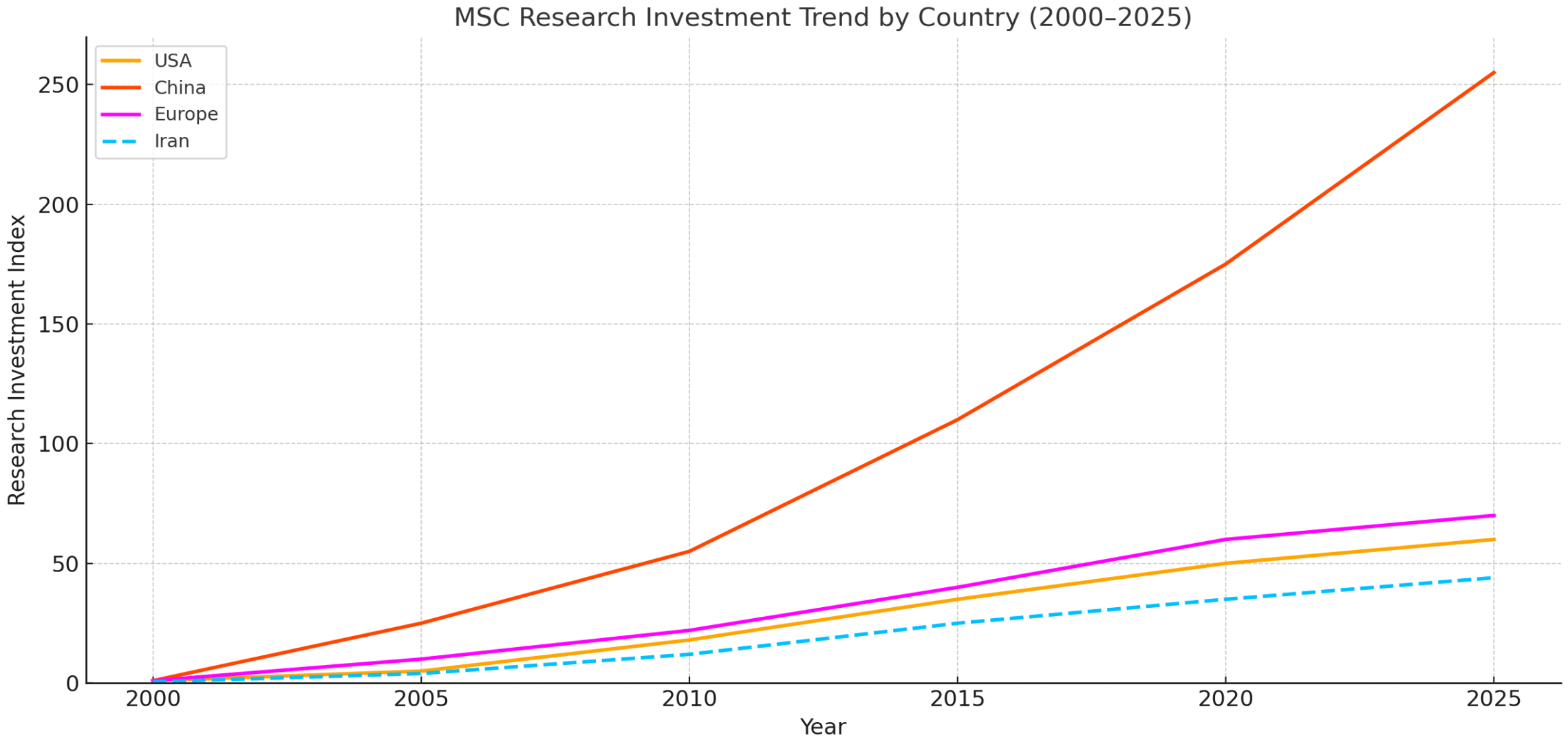

Number of MSC Clinical Trials by Country
Number of Clinical Trials
0
50
100
150
200
250
300
294
216
165
47
China
USA
Europe
Iran

These two charts show the **separate trends** of investment in **clinical application** and **research** of **Mesenchymal Stem Cells (MSCs)** from **2000 to 2025**:



Clinical Investment:

1. The **USA** leads with consistent early investment.
2. **China** shows rapid growth after 2010.
3. **Iran** starts later but is progressing post-2010.



Research Investment:

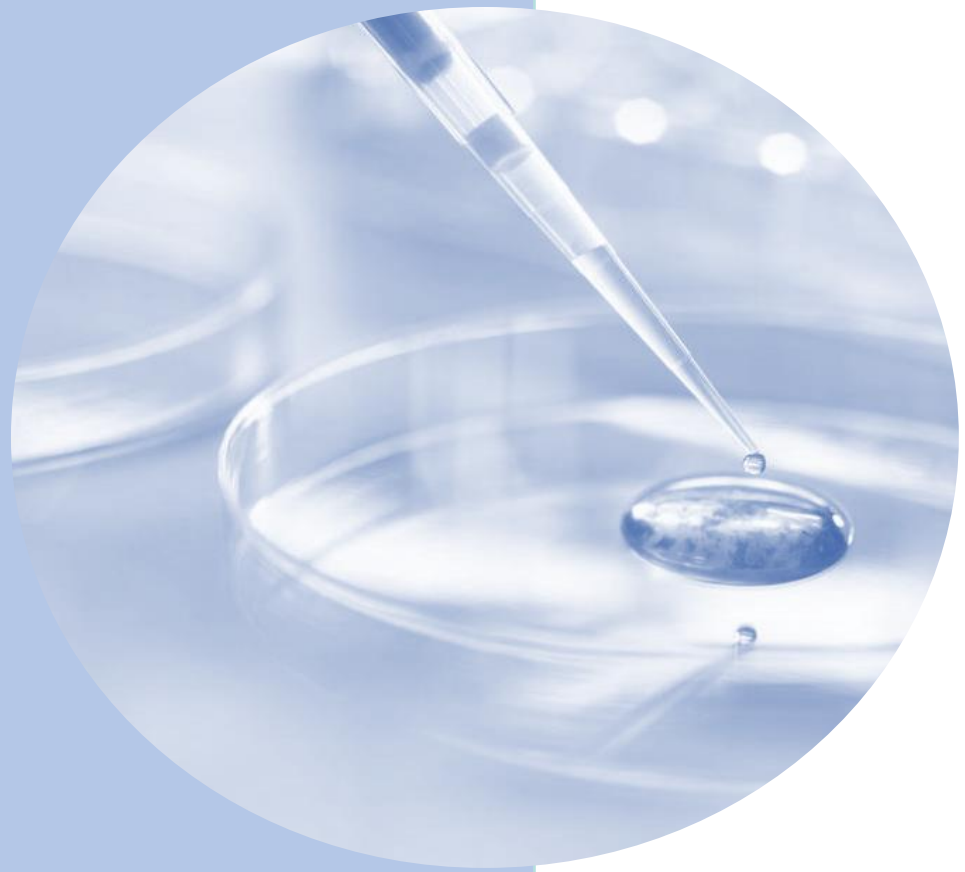
1. **China** has surpassed others in recent years due to aggressive research funding.
2. The **USA** and **Europe** maintain strong academic research.
3. **Iran** shows growing interest in MSC research after 2010.

Global market-available, standardized products based on Mesenchymal Stem Cells (MSCs) for skin regeneration, wound healing, and aesthetics,

Product Name	Company / Country	Application	Cell Source	Approval Status
Alofisel® (darvadstrocel)	Takeda / EU	Perianal fistulas, potential in wound healing	Adipose-derived allogeneic MSCs	EMA approved
Stempeucel®	Stempeutics / India	Diabetic foot ulcers, Critical Limb Ischemia (CLI)	Bone marrow-derived allogeneic MSCs	Indian DCGI approved
Cupistem®	Anterogen / South Korea	Complex fistula, wound healing	Adipose-derived MSCs	KFDA approved
RNL-Bio MSC Therapy	RNL Bio / South Korea	Aesthetic (skin rejuvenation, anti-aging)	Adipose MSCs	Cosmetic clinics (non-drug)
Azficel-T (Laviv®)	Fibrocell Science / USA	Wrinkle reduction (fibroblast + MSC adjunct)	Autologous dermal cells	FDA approved (withdrawn commercially)
MSC-based Dressings (various)	Multiple (e.g., RepliCel, Histogen)	Diabetic wounds, burns (experimental)	MSCs in hydrogel or scaffold	Preclinical / early clinical

Iranian Market MSC-Based Products

Product Name	Institute / Company	Application	Cell Source	Status
CellTech Pharmed MSC Gel	CellTech Pharmed	Wound healing, diabetic ulcers	Allogeneic MSCs (UC/AD)	Clinical use / IR-FDA registered
Royan Cell Therapy Program	Royan Institute	Burn and wound healing (clinical)	Adipose / UC-MSCs	Clinical studies, GMP available
MSC-based creams (cosmetic)	Local biotech / labs	Skin rejuvenation, anti-aging	MSC-conditioned media	Cosmetic license, non-therapeutic



Future perspective

Challenges and Limitations

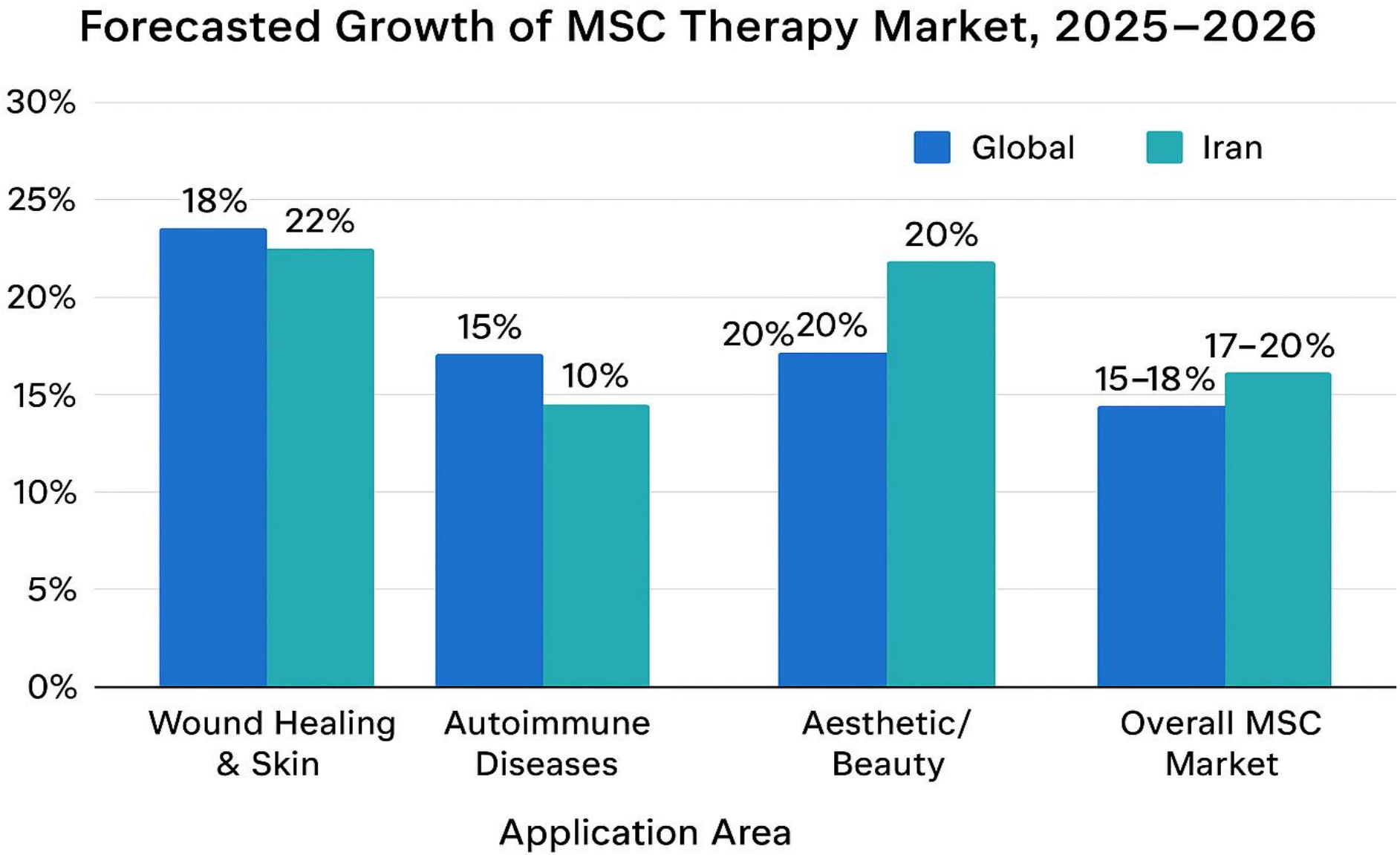
- Biological heterogeneity
- Risk of contamination or senescence
- Tumorigenicity concerns (low but debated)
- Need for standardized potency assays

Future Directions

- Cell-free MSC therapy: exosomes and secretome
- Genetic modification of MSCs
- Tissue-specific MSC lines
- Personalized MSC therapy & AI-driven selection

Key Takeaways

- MSCs are promising tools in regenerative medicine
- Immunomodulation is a key mechanism
- Clinical results are promising but require optimization
- Standardization and regulation are essential


Forecasted Growth of MSC Therapy Market, 2025–2026
30%
25%
20%
15%
10%
5%
0%
Global
Iran
18%
22%
15%
10%
20%
20%
20%
15–18%
17–20%
Wound Healing & Skin
Autoimmune Diseases
Aesthetic/ Beauty
Overall MSC Market
Application Area

References:

- Hu et al., *Stem Cell Research & Therapy* (2022): MSCs in diabetic wound healing
- Walter et al., *Journal of Investigative Dermatology* (2021): Paracrine mechanisms of MSCs
- NIH Clinical Trials
- ISCT Position Paper (2023)
- Nature Reviews Drug Discovery, 2024
- Selected clinical trials on ClinicalTrials.gov
- WHO ICTRP
- *Nature*, *Cell Stem Cell*, *Stem Cells Translational Medicine*

Any questions?

Thank you