

**Lec4\ Mesenchymal stem/stromal cell
secretome for regenerative medicine and drug
delivery**

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Introduction

- **Mesenchymal Stem** Cells are **adult** stem cells capable of self-renewal and differentiation.
- They **play a major** role in **tissue repair** and **regeneration**.
- MSCs are **multipotent stromal cells** that differentiate into bone, cartilage, fat, and connective tissue cells.

Sources of MSCs

- Bone marrow
- Adipose tissue
- Umbilical cord
- Placenta
- Dental pulp

Characteristics

- Self-renewal ability
- Multipotent differentiation
- Plastic adherence in culture
- Immunomodulatory effects
- Growth factor secretion

Differentiation Potential

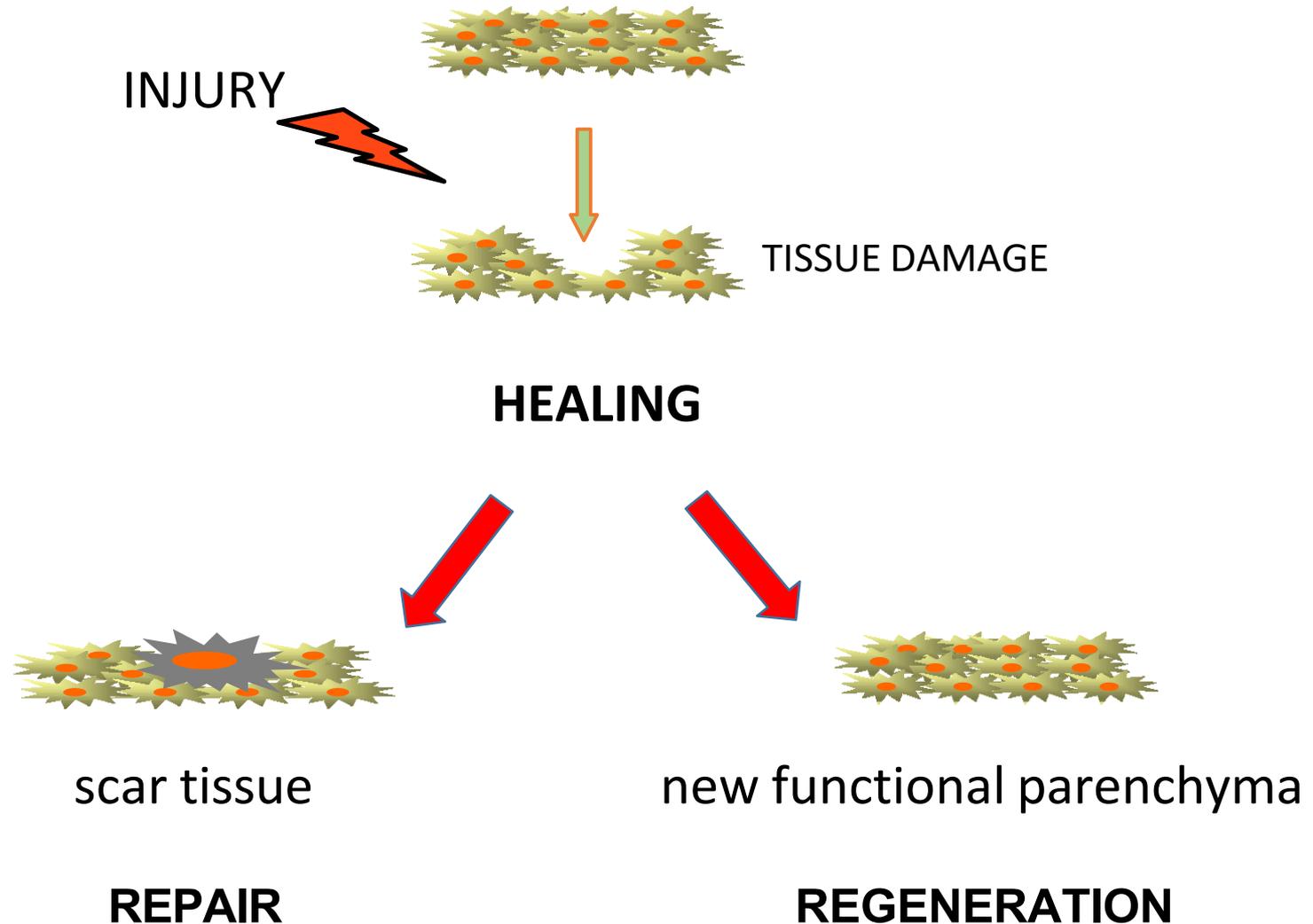
MSCs differentiate into:

- Osteocytes (bone)
- Chondrocytes (cartilage)
- Adipocytes (fat)
- Myocytes (muscle)
- Fibroblasts

Biological Functions

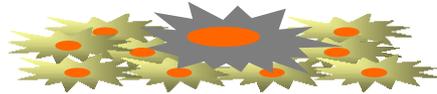
- Tissue regeneration
- Wound healing
- Anti-inflammatory effects
- Immune regulation
- Angiogenesis تكوين الأوعية الدموية

Tissue Regeneration and Repair

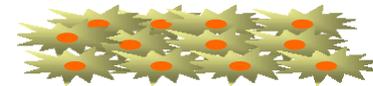


definition of Regenerative Medicine

REPAIR



REGENERATION

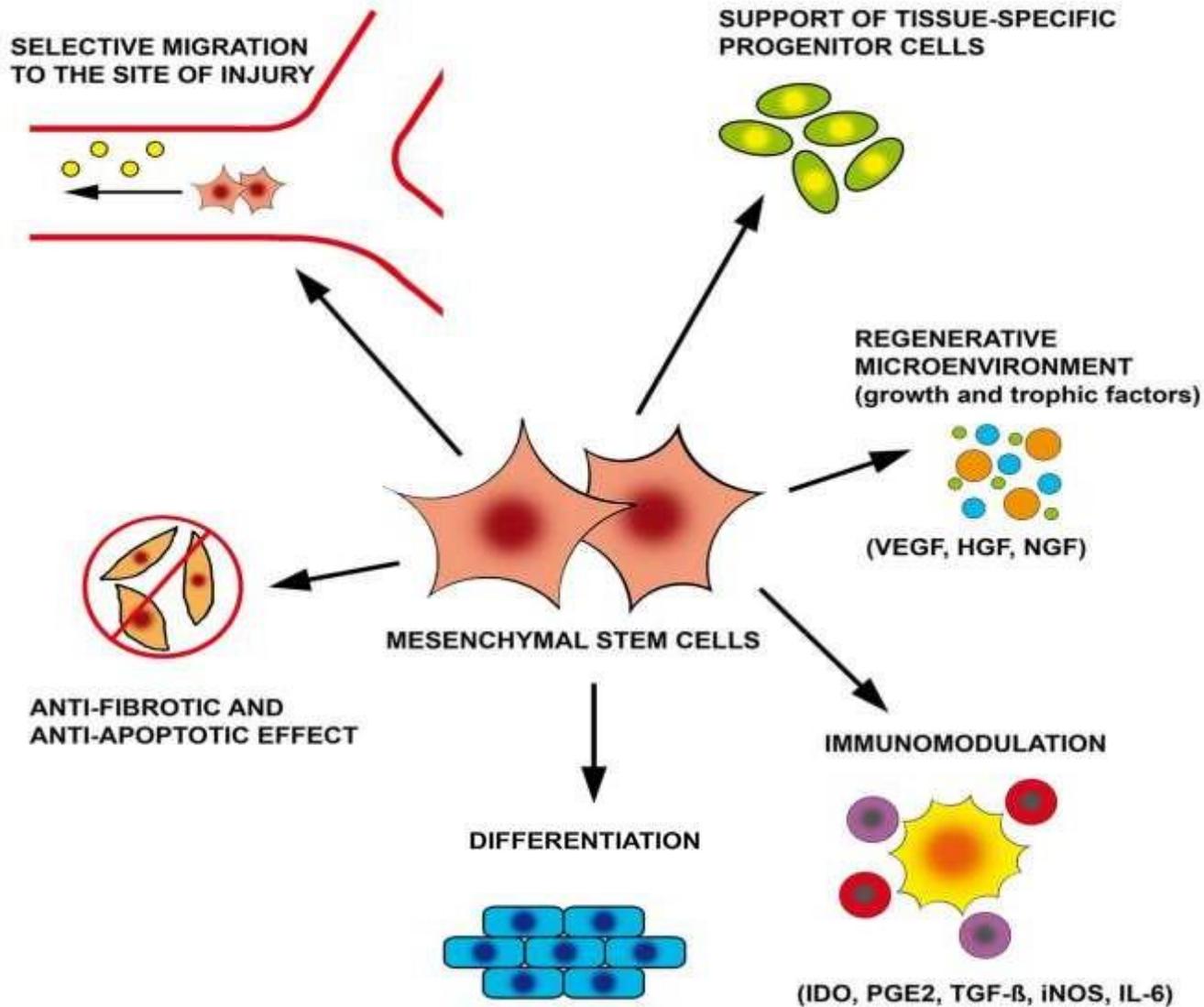


type of tissue
size and the **depth** of damage
individual's health status
age

“Regenerative medicine replaces or regenerates human cells, tissue or organs, to restore or establish normal function”

“These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell therapy, tissue engineering and the reprogramming of cell and tissue types”

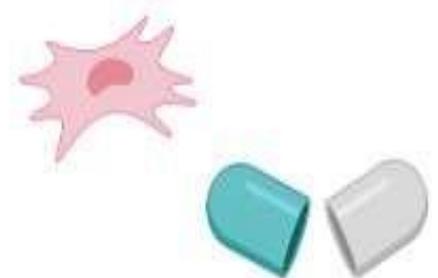
Tissue regeneration and Mesenchymal stem cells (MSC)



MSCs as drugs for regenerative therapy

Current Pharmaceutical Design, 2013, 19, 2459-2473

Mesenchymal Stem/Stromal Cells: A New "Cells as Drugs" Paradigm. *Efficacy and Critical Aspects in Cell Therapy*



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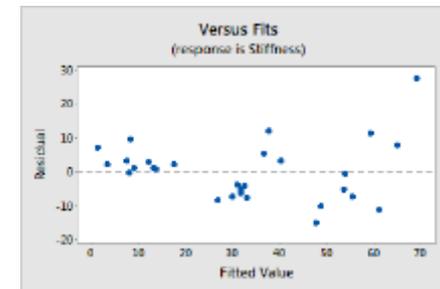
COMPREHENSIVE REVIEW

Ex Vivo Expanded Mesenchymal Stromal Cell Minimal Quality Requirements for Clinical Application

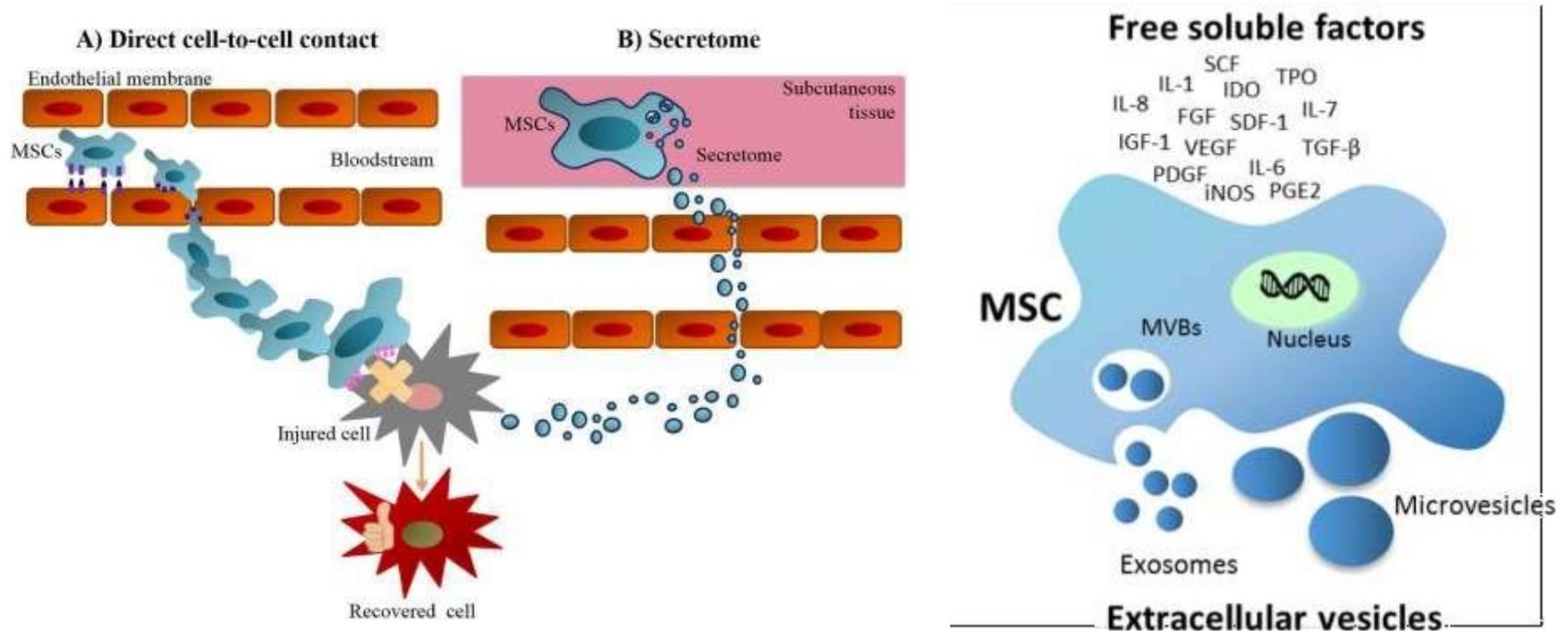
Maria Luisa Torre,^{1,*} Enrico Lucarelli,^{2,*} Simona Guidi,³ Maura Ferrari,⁴
Giulio Alessandri,⁵ Laura De Girolamo,⁶ Augusto Pessina,⁷
Ivana Ferrero,⁸ on behalf of the Gruppo Italiano Staminali Mesenchimali (GISM)

Some of the current issues facing MSCs therapies

1. High cost of products
2. Production/distribution bottlenecks (cryopreservation/logistic)
3. Size of MSC dramatically increases in culture and the expression of adhesion molecules is strongly up regulated. This affects the biodistribution of MSC after e.v. administration (lung accumulation)
4. Variable efficacy (duration/persistence)

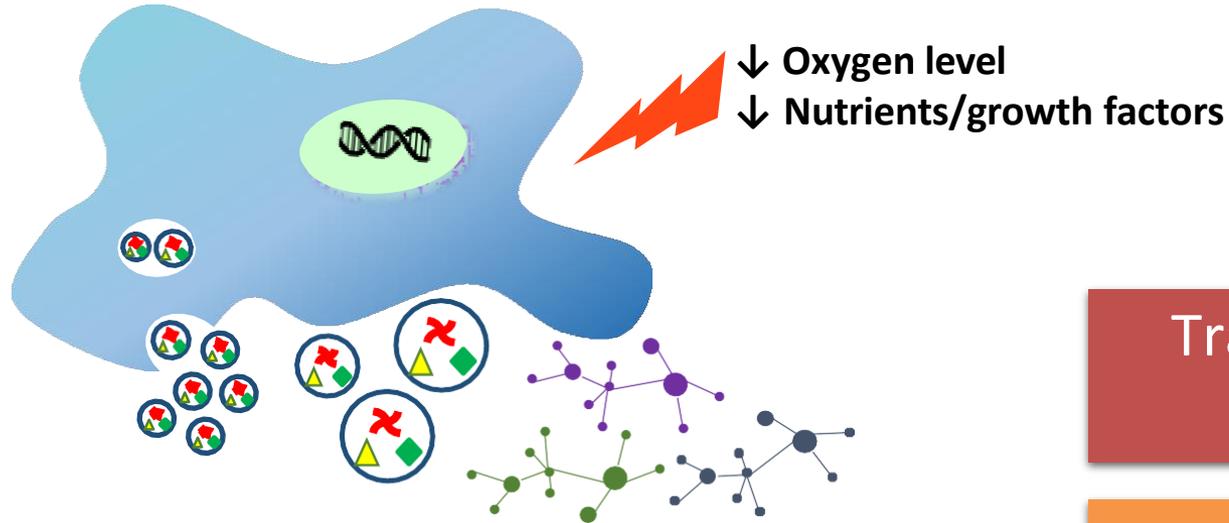


MSC secretome and tissue regeneration



*“MSCs are powerful **site-regulated DRUG STORES** that may serve as modulatory or curative agents for a variety of human maladies”*

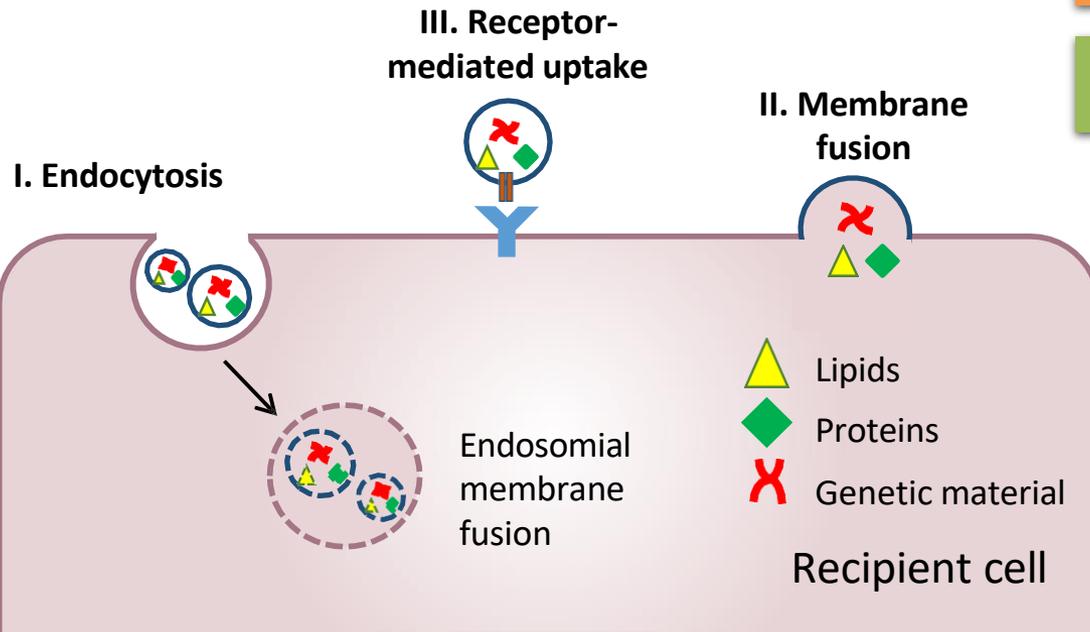
MSC-secretome is a physiological therapeutic agent



Transfer of bioactive compounds

Regulation of receptors

Phenotype changes



Secretome can replace MSC regenerative therapy



Safer (non-living, lower immunogenicity, no vascular clotting)

Ability to adapt and respond to the microenvironment

القدرة على التكيف والاستجابة
للبيئة المحيطة

Nanoscale (enhanced permeability and retention effect) Physiological mediators of tissue regeneration

Effectively cross biological membrane

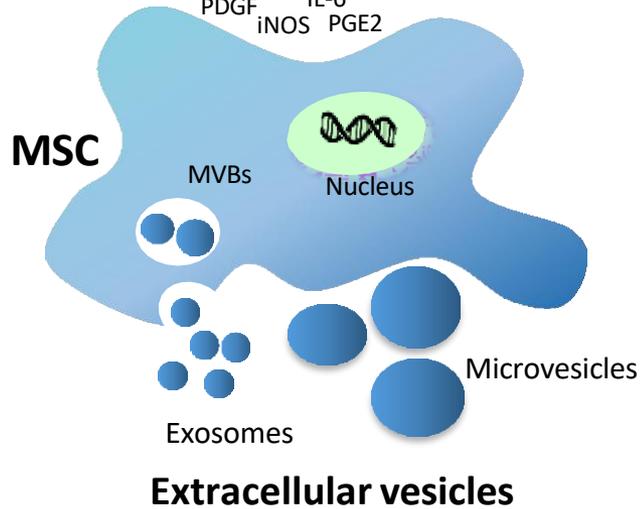
MSC-secretome shows fewer **limitations** than its parental cells

Our challenge: secretome pharmaceuticalization

التحدي الذي يواجهها: تحويل الإفرازات الخلوية إلى أدوية

Free soluble factors

SCF
IL-1 IDO TPO
IL-8 FGF SDF-1 IL-7
IGF-1 VEGF TGF- β
PDGF IL-6
iNOS PGE2



Quality

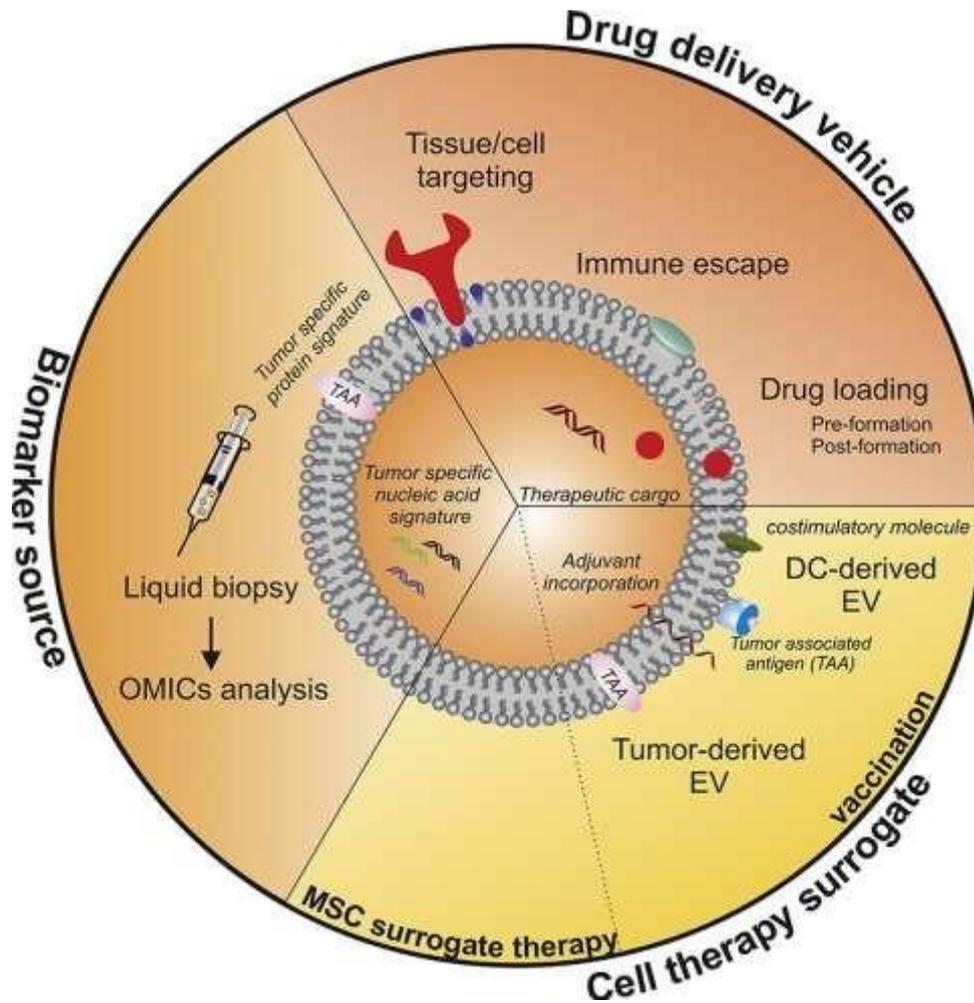
Safety

Efficacy

Industrial scale-up

Diagnostic and therapeutic applications of Evs

التطبيقات التشخيصية والعلاجية خارج الخلية

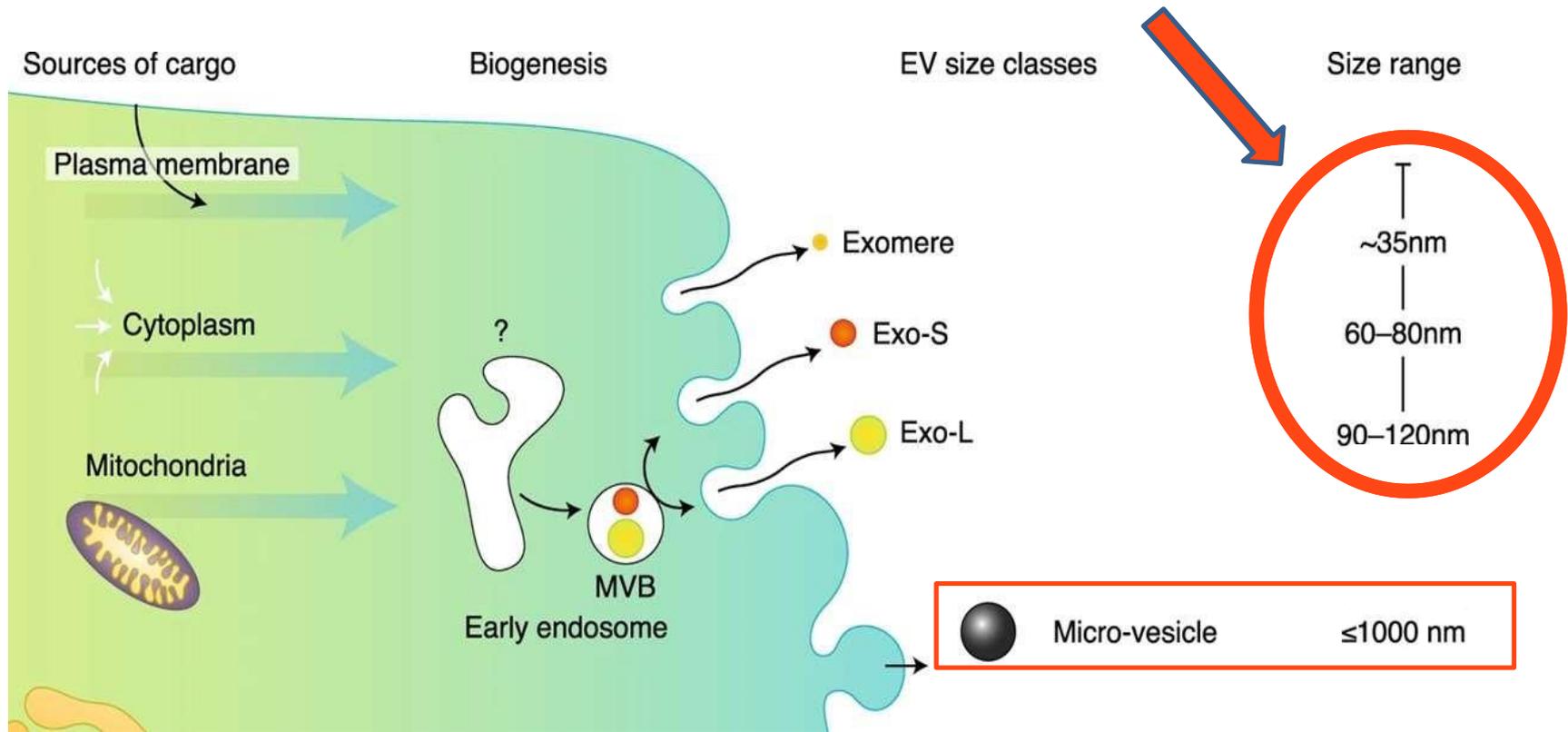


Diagnostic tool

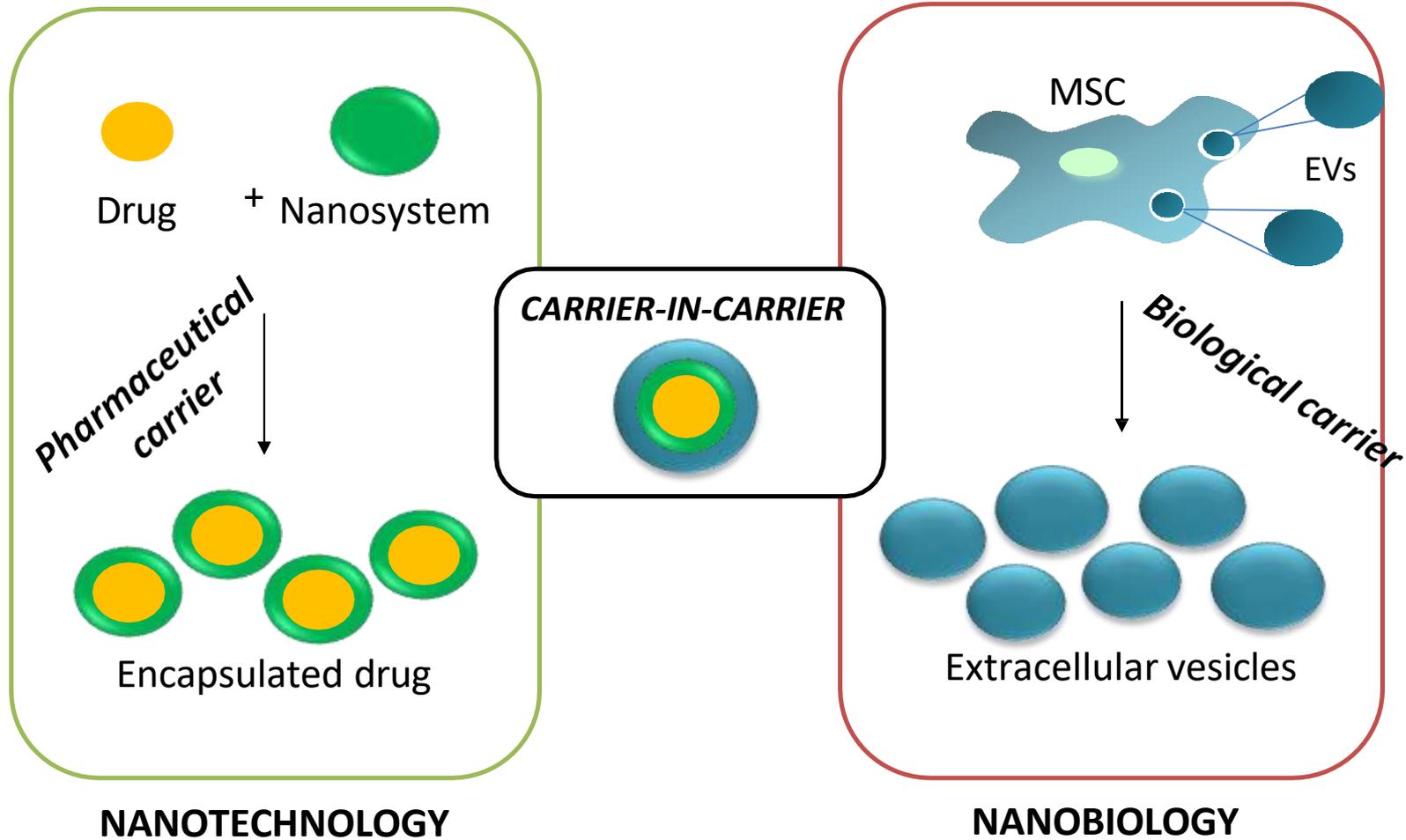
Active Pharmaceutical
Ingredient

Drug Delivery System

MSC-EV Drug Delivery System: a nanocarrier



MSCs-EVs and the “carrier-in-carrier”



Lyosecretome GMP production process at affordable costs is defined



A new API for regenerative medicine is available in large amount



A variety of new Drug Delivery Systems can be designed



Characterization, Composition
Mechanisms of action
Potency/Efficacy

The missing piece for clinical translation

