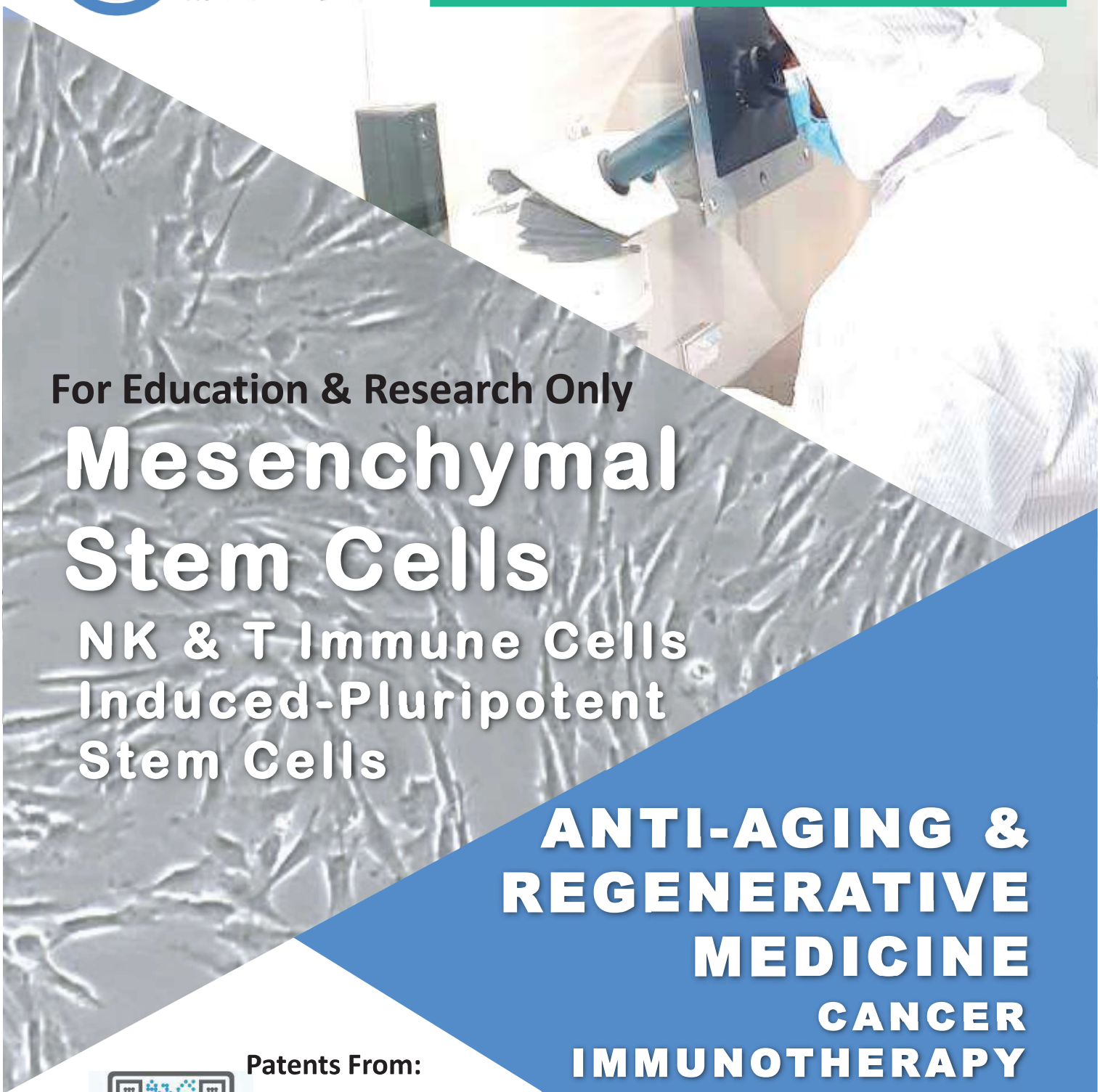
CytoMed Therapeutics
新细胞医学

Pioneering stem cell research and cancer immunotherapy



For Education & Research Only

Mesenchymal Stem Cells

NK & T Immune Cells

Induced-Pluripotent Stem Cells

ANTI-AGING & REGENERATIVE MEDICINE

CANCER IMMUNOTHERAPY

SCAN CYTOMED!

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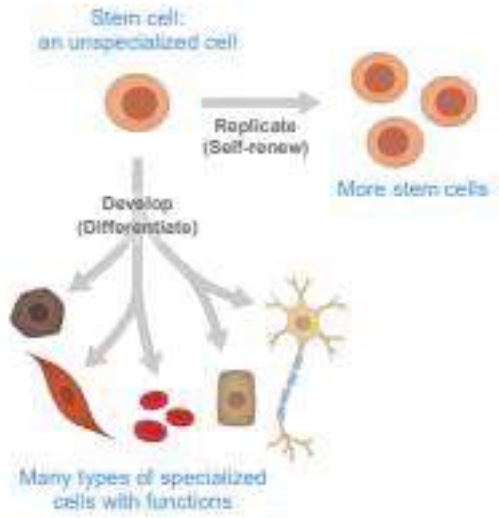
STEM CELL BASICS

Cells Are The New Cure

What are **Stem Cells**?

Stem cells are an unspecialized type of cells which can replicate and are able to develop into different types of specialized cells.

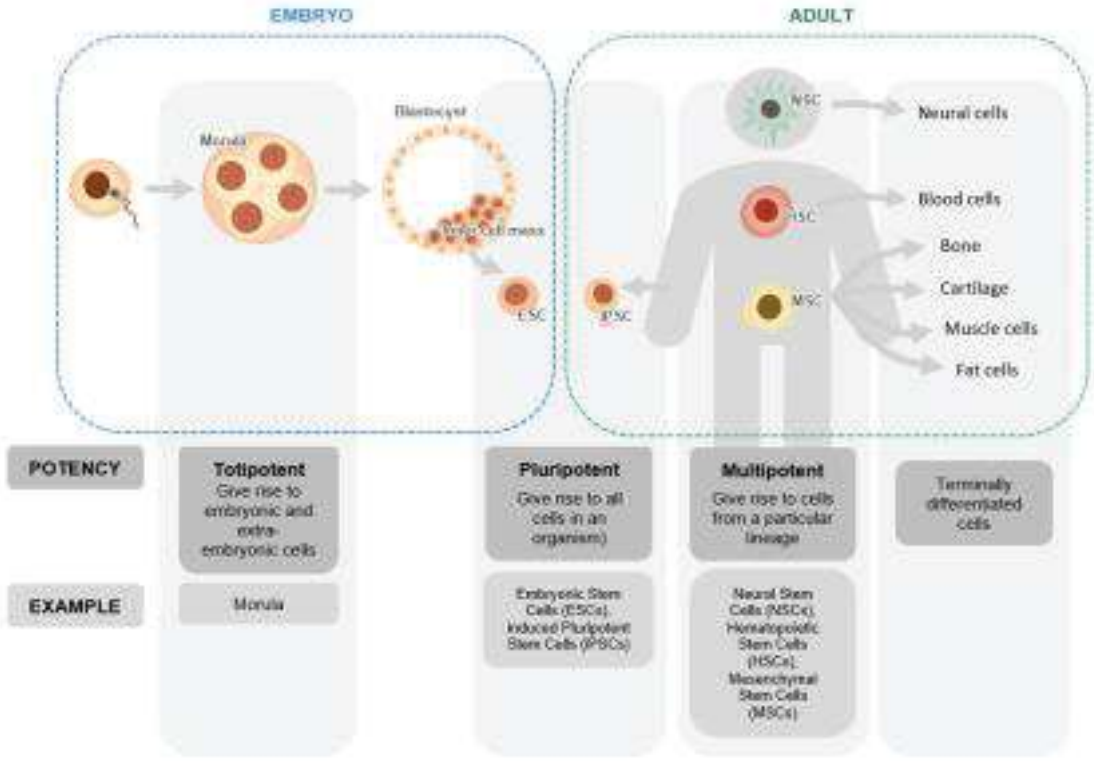


Why are Stem Cells **Important**?

Stem cells directed to differentiate into specific cell types, offer a renewable source of replacement cells and tissues to treat many diseases.

Type and **Potency** of Stem Cells

Different stem cell types possess different capacity of differentiation depending on their 'potency'.



What are **Mesenchymal Stem Cells**?

Mesenchymal stem cells (MSCs) are multipotential adult stem cells that can be found in the stroma of all organs and are the building blocks for tissue renewal and repair following injury.

MSCs have the ability to differentiate into multiple cell types of mesenchymal lineage, such as bone, cartilage, fat, and muscle cells as well as those of non-mesenchymal lineage depending on the environment in which they are cultured.

Why are MSCs **Unique**?

MSCs are extensively studied for clinical applications due to their unique properties:

- **Multilineage differentiation** makes MSCs a valuable cell source to treat many diseases.
- **Secreting factors** including cytokines, chemokines and growth factors can be harnessed for regenerative treatments.
- **Immunomodulation** being the ability to modulate immune response may reduce inflammation.
- **Homing ability** allows MSCs to travel to specific injury sites.

Health is Wealth!

MSC THERAPY

Potential Benefits of MSC Therapy

MSCs cultured for therapy, accompanied by a host of growth factors and cytokines, have the collective potential of regenerating and replacing damaged body cells and tissues, thus restoring vitality and functionality of organs and systems.

MSC therapy in clinical trials has shown much promise in anti-aging and regenerative medicine.

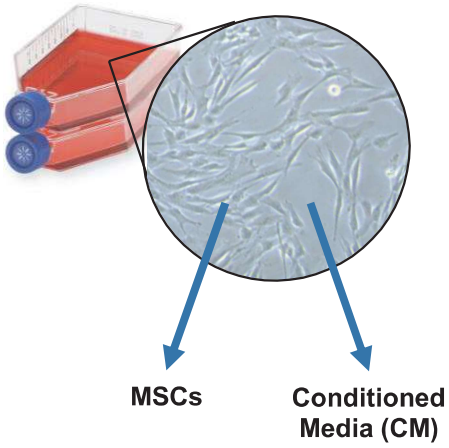
Sources of MSC

Bone marrow, umbilical cord (UC) and adipose tissue (AT) are among the most studied sources of MSCs.

General Benefits of MSC Infusion

Production of MSCs

UC or AT samples obtained from our clinical partners are processed in our laboratory. All samples are handled by well-trained health professionals and scientists, in a highly sterile manner, using state-of-the art technologies, facilities and equipment to culture high-quality MSCs.



Specific Medical Conditions Under Global Research

- Age-related Macular Degeneration
- Aging Frailty
- Alzheimer's Disease
- Autoimmune Diseases
- Cerebral Palsy
- Diabetes Mellitus (Types I&II)
- Heart Disease and Failure
- Intervertebral Disc Degenerative Disease
- Motor Neuron Disease
- Multiple Sclerosis
- Osteoarthritis
- Parkinson's Disease
- Skin Conditions (e.g., Acne, Eczema, Psoriasis)
- Spinal Cord Injury
- Stroke

Route of Administration

MSCs can be applied to the body via:
1. Infusion into bloodstream or muscles
2. Direct application on skin or wounds

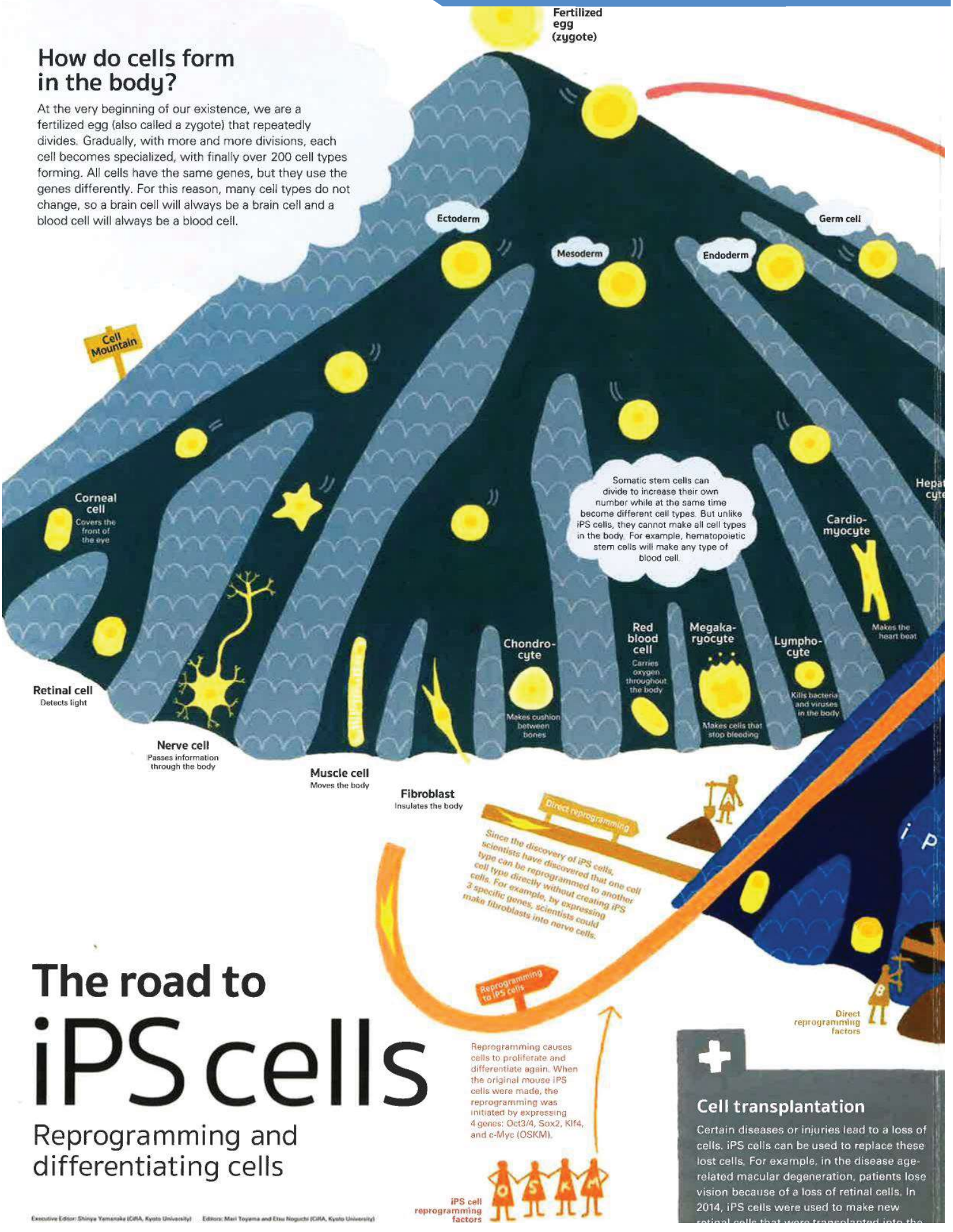
CM containing beneficial factors can be applied via:
1. Topical application as skin/hair care

The road to iPS cells

Reprogramming and differentiating cells

How do cells form in the body?

At the very beginning of our existence, we are a fertilized egg (also called a zygote) that repeatedly divides. Gradually, with more and more divisions, each cell becomes specialized, with finally over 200 cell types forming. All cells have the same genes, but they use the genes differently. For this reason, many cell types do not change, so a brain cell will always be a brain cell and a blood cell will always be a blood cell.



Cell transplantation

Certain diseases or injuries lead to a loss of cells. iPS cells can be used to replace these lost cells. For example, in the disease age-related macular degeneration, patients lose vision because of a loss of retinal cells. In 2014, iPS cells were used to make new

Executive Editor: Shinya Yamanaka (CiRA, Kyoto University) Editors: Mari Toyama and Etsu Noguchi (CiRA, Kyoto University)

The road to ~

IPS CELLS

What is so special about iPS cells?

In 2006, Dr. Shinya Yamanaka and his team of scientists showed that mouse fibroblasts (a type of skin cell) could be changed to a different cell type by expressing in them 4 specific genes. They did the same with human skin cells in 2007. These new cells, which they called induced pluripotent stem cells (iPS cells), could become any cell type in the body. The ability to make iPS cells shocked scientists around the world, because it was thought impossible. For this discovery, along with Dr. John Gurdon, Dr. Yamanaka was awarded the 2012 Nobel Prize in Physiology or Medicine.

The zygote divides many times to make different cell types. After the first few divisions, it forms into a structure called the blastocyst. The blastocyst includes a region called the inner cell mass. Cells from the inner cell mass can be made into embryonic stem cells (ES cells). ES cells can be made into any type of cell in the body.

Ovum

Becomes a zygote when fertilized

ES cell

iPS cell

iPS cells can be made into any cell type in the body

iPS cells can be multiplied many, many times

Pancreatic cell

Makes insulin

Cleans the body of toxins

iPS Mountain

S cells can become any cell type

New drugs

Because iPS cells can be made from patient cells, they provide a new way to study drugs and medicines.

How do we progress iPS cell research?

iPS cells are still a relatively new technology with great potential in science and medicine. But with this potential comes many ethical questions. For example, will it be acceptable to make sperm and eggs from iPS cells and then use them to fertilize eggs that can be grown to babies? How about growing human organs in different animals, like pigs. These and other questions cannot be answered only by scientists, but must also consider the opinions of all of society.

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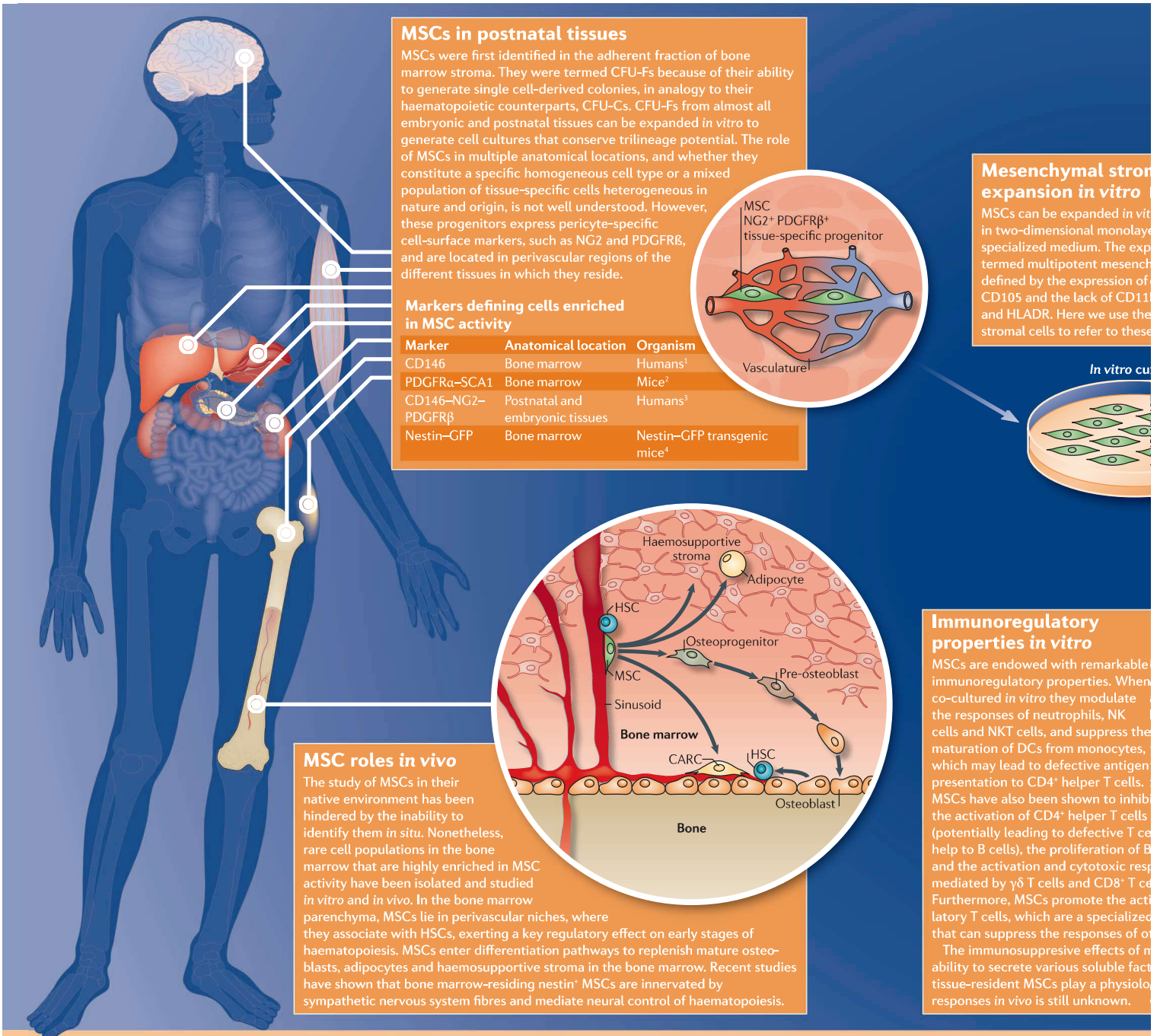
nature REVIEWS
MOLECULAR CELL BIOLOGY

The identity and properties

César Nombela-Arrieta a

MSCs are self-renewing, multipotent precursors. They were originally found to reside in the stromal adherent fraction of the bone marrow, where they sustain the homeostatic turnover of non-haematopoietic stromal cells, regulate HSC maintenance and might contribute to vascular stability. The physiological roles of MSCs in anatomical locations other than the bone marrow remain largely undefined. MSCs can be expanded *in vitro* to generate mesenchymal stromal cell cultures, which, under appropriate conditions, can differentiate into



MSCs in postnatal tissues

MSCs were first identified in the adherent fraction of bone marrow stroma. They were termed CFU-Fs because of their ability to generate single cell-derived colonies, in analogy to their haematopoietic counterparts, CFU-Cs. CFU-Fs from almost all embryonic and postnatal tissues can be expanded *in vitro* to generate cell cultures that conserve trilineage potential. The role of MSCs in multiple anatomical locations, and whether they constitute a specific homogeneous cell type or a mixed population of tissue-specific cells heterogeneous in nature and origin, is not well understood. However, these progenitors express pericyte-specific cell-surface markers, such as NG2 and PDGFRß, and are located in perivascular regions of the different tissues in which they reside.

Markers defining cells enriched in MSC activity

Marker	Anatomical location	Organism
CD146	Bone marrow	Humans[1]
PDGFRα–SCA1	Bone marrow	Mice[2]
CD146–NG2–PDGFRβ	Postnatal and embryonic tissues	Humans[3]
Nestin–GFP	Bone marrow	Nestin–GFP transgenic mice[4]

Mesenchymal stro expansion *in vitro*

MSCs can be expanded *in vit* in two-dimensional monolaye specialized medium. The exp termed multipotent mesench defined by the expression of CD105 and the lack of CD11 and HLADR. Here we use the stromal cells to refer to these

In vitro cu

MSC roles *in vivo*

The study of MSCs in their native environment has been hindered by the inability to identify them *in situ*. Nonetheless, rare cell populations in the bone marrow that are highly enriched in MSC activity have been isolated and studied *in vitro* and *in vivo*. In the bone marrow parenchyma, MSCs lie in perivascular niches, where they associate with HSCs, exerting a key regulatory effect on early stages of haematopoiesis. MSCs enter differentiation pathways to replenish mature osteoblasts, adipocytes and haemosupportive stroma in the bone marrow. Recent studies have shown that bone marrow-residing nestin$^+$ MSCs are innervated by sympathetic nervous system fibres and mediate neural control of haematopoiesis.

Immunoregulatory properties *in vitro*

MSCs are endowed with remarkable immunoregulatory properties. When co-cultured *in vitro* they modulate the responses of neutrophils, NK cells and NKT cells, and suppress the maturation of DCs from monocytes, which may lead to defective antigen presentation to CD4$^+$ helper T cells. MSCs have also been shown to inhibit the activation of CD4$^+$ helper T cells (potentially leading to defective T ce help to B cells), the proliferation of B and the activation and cytotoxic resp mediated by γδ T cells and CD8$^+$ T ce Furthermore, MSCs promote the acti latory T cells, which are a specialized that can suppress the responses of o

The immunosuppresive effects of m ability to secrete various soluble fact tissue-resident MSCs play a physiolo responses *in vivo* is still unknown.

MesenCult™: Your High-Performance Platform for MSC Derivation, Culture and Differentiation

STEMCELL Technologies is committed to serve scientists along the basic to translational research continuum by providing high-quality, standardized media and reagents for MSC (also known as mesenchymal stromal cell) research. Choose from a range of MesenCult™ specialty products to derive, expand, differentiate and characterize human and mouse MSCs. This platform is optimized to standardize your cell culture system and minimize experimental variability.

MPC Generation from hPSCs:

STEMdiff™ Mesenchymal Progenitor Kit (Catalog #05240): animal component-free kit for the differentiation and culture of mesenchymal progenitor cells (MPCs) from human ES or iPS cells. MPCs generated using STEMdiff™ Mesenchymal Progenitor Kit have a robust proliferation rate and maintain trilineage differentiation capacity.

MSC Derivation and Expansion:

- *MesenCult™-ACF Plus Culture Kit* (Catalog #05448): animal component- and serum-free culture kit for derivation and culture of human MSCs. Cells cultured in MesenCult™-ACF Plus expand faster compared to cells cultured in serum-based media and demonstrate robust differentiation potential. Human platelet lysate- and serum-based media for human MSC derivation and expansion are also available.
- *MesenCult™ Expansion Kit* (Mouse: Catalog #05513): enrich for and expand mouse MSCs in culture without serial passaging and generate purified MSC cultures as early as passage 0.

Human MSC Differentiation and Characterizat

Differentiate human MSCs into chondrogenic, ad using *MesenCult™-ACF Chondrogenic Differentiat MesenCult™ Adipogenic Differentiation Medium* (h *MesenCult™ Osteogenic Differentiation Kit* (Huma

Mouse MSC Differentiation and Characterizatio

Differentiate mouse MSCs into adipogenic and os *MesenCult™ Adipogenic Differentiation Kit* (Mouse *MesenCult™ Osteogenic Stimulatory Kit* (Mouse; C

For more information on how STEMCELL Technol please visit our website: https://www.stemcell.co

s of mesenchymal stem cells

a and Leslie E. Silberstein

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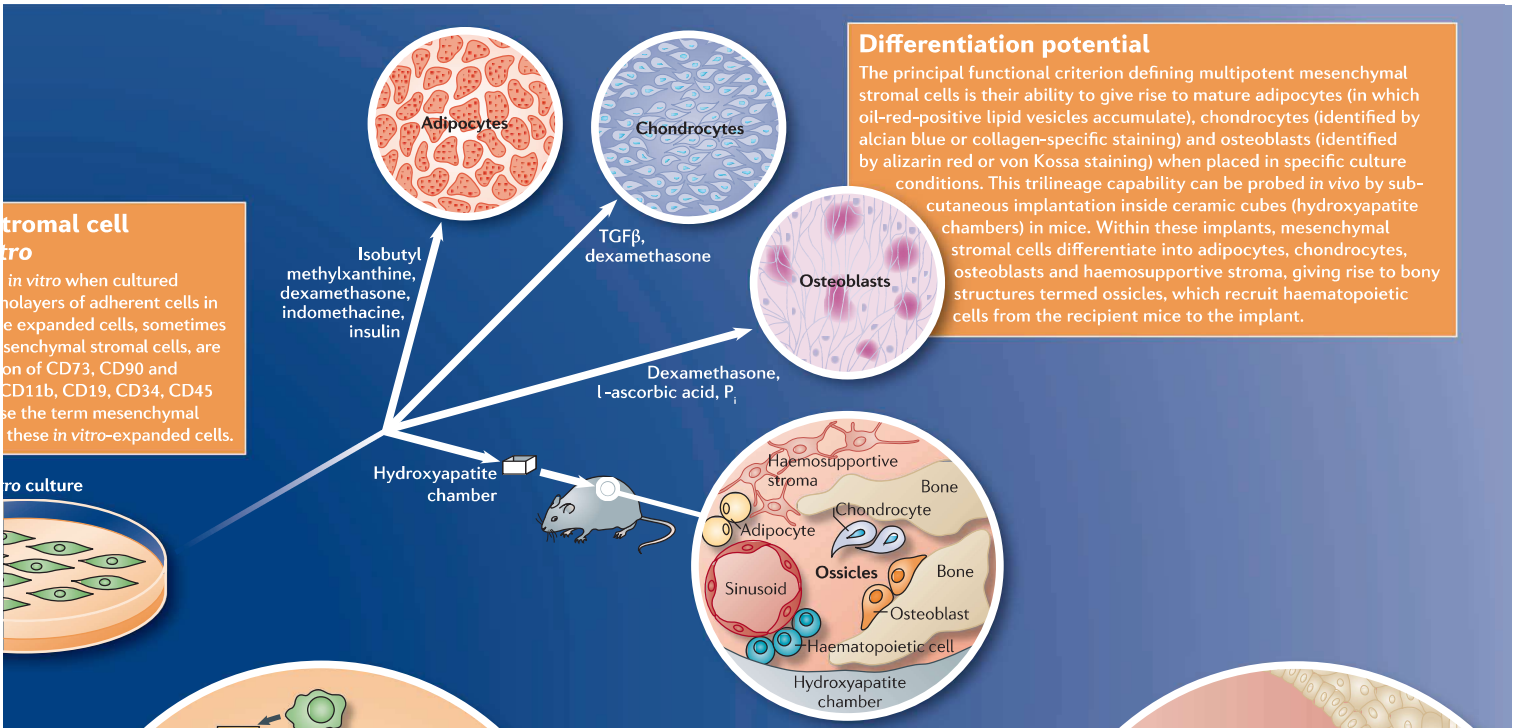
adipocytes, chondrocytes and osteoblasts. In more recent studies multipotent mesenchymal stromal cell cultures have been derived from perivascular stem cells expressing pericyte markers in many postnatal tissues. The differentiation capabilities, extraordinary paracrine potential and ease of isolation of *in vitro*-expanded mesenchymal stromal cells have attracted great interest into, and efforts towards, the exploitation of MSCs and their expanded progeny as therapeutic agents for tissue regeneration and repair.



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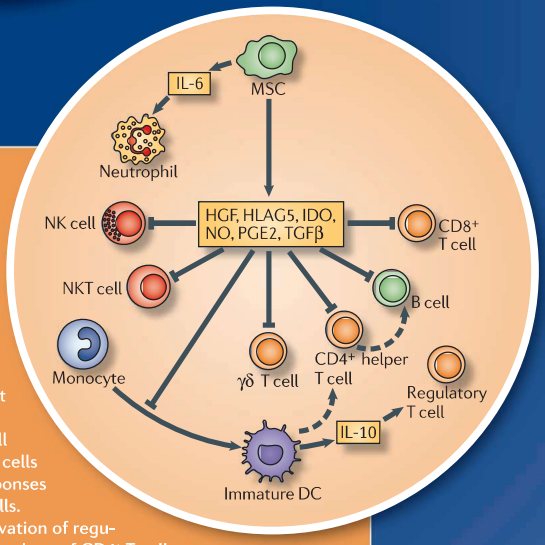
ro culture

Differentiation potential

The principal functional criterion defining multipotent mesenchymal stromal cells is their ability to give rise to mature adipocytes (in which oil-red-positive lipid vesicles accumulate), chondrocytes (identified by alcian blue or collagen-specific staining) and osteoblasts (identified by alizarin red or von Kossa staining) when placed in specific culture conditions. This trilineage capability can be probed *in vivo* by subcutaneous implantation inside ceramic cubes (hydroxyapatite chambers) in mice. Within these implants, mesenchymal stromal cells differentiate into adipocytes, chondrocytes, osteoblasts and haemosupportive stroma, giving rise to bony structures termed ossicles, which recruit haematopoietic cells from the recipient mice to the implant.



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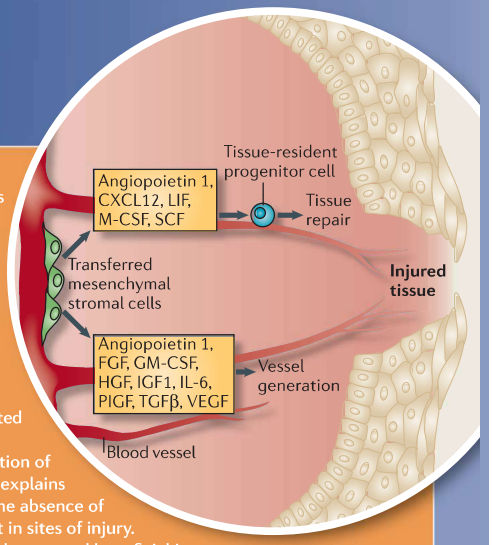
Therapeutic potential

Expanded multipotent mesenchymal stromal cells are being extensively studied for their possible therapeutic properties in numerous pre-clinical and clinical settings. Studies initially focused on using their stem cell-like properties for tissue regeneration and repair. However, it is now well established that their beneficial effects are mostly derived from the secretion of immunomodulatory and cytoprotective factors that contribute to the regeneration of injured tissues. The current hypothesis is that paracrine factors secreted by mesenchymal stromal cells provide protective microenvironmental cues and promote the activation of local tissue-resident progenitor populations. This explains why favourable effects can be observed even in the absence of prolonged mesenchymal stromal cell engraftment in sites of injury.



Systemic infusion of mesenchymal stromal cells has proved beneficial in different pre-clinical models of acute lung injury, myocardial infarction, diabetes as well as renal and hepatic failure. Some of the human conditions for which the safety and efficacy of mesenchymal stromal cell-based therapies are being, or will soon be, studied in clinical trials include acute graft-versus-host disease, multiple sclerosis, osteogenesis imperfecta, stroke, spinal injury, systemic lupus erythematosus and cardiovascular disease.

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cell.com/products/brands/mesencult.html.

Abbreviations

CARC, CXCL12-abundant reticular cell; CFU-Cs, colony-forming unit-cells; CFU-Fs, colony-forming unit-fibroblasts; CXCL12, CXC-chemokine ligand 12; DC, dendritic cell; FGF, fibroblast growth factor; GFP, green fluorescent protein; GM-CSF, granulocyte macrophage colony-stimulating factor; HGF, hepatocyte growth factor; HLA, human leukocyte antigen; HSC, haematopoietic stem cell; IDO, indoleamine 2,3-dioxygenase; IGF1, insulin growth factor 1; IL, interleukin; LIF, leukaemia inhibitory factor; NG2, nerve/glial antigen 2; NK, natural killer; NKT, natural killer T; NO, nitric oxide; PGE2, prostaglandin E2; MSC, mesenchymal stem cell; PDGFR; platelet-derived growth factor receptor; P_i, inorganic phosphate; PlGF, placental insulin growth factor; SCA1, surface cell antigen 1; SCF, stem cell factor; TGFβ, transforming growth factor-β; VEGF, vascular endothelial growth factor.

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ABOUT US

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CytoMed, a spin-off from A*STAR, Singapore, is a deep technology company specializing in cell therapy. It owns and built an international PIC/S standard Good Manufacturing Practice (GMP) facility for research and manufacturing of cell therapy products. The GMP compliant facility is NEBB certified Grade A cleanroom facility and is subject to stringent internal and external audits to ensure it functions at the highest quality standards and conform to the regulatory requirements.

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iPSCbank The Future of Medicine

IPSCbank is a subsidiary of CytoMed which mainly focuses on the banking of our customers' cells such as PBMCs, iPSCs and MSCs for future usage.

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Landmark Medical Centre is a Ministry of Health certified hospital, collaborating with CytoMed to administer this novel CTM-N2D therapy, pending regulatory approval. A clinical trial – 'REGEN Trial', has been registered with the National Malaysian Research Registry (Research ID: NMRR-19-2594-50562).

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