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EDITORIAL

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'Cells as tools' to 'Cell-s produced tools' - An evolving paradigm in Regenerative Medicine

Internal milieu or niche of biological mechanisms on how reparative solutions take shape to control a damage as well as repair the damages caused in any organ within mammalian body are not fully known. Recent data in the evolving era of regenerative medicine in which, cells, stem cells and adult cells have been used as tools to repair, restore, rejuvenate or regenerate the lost/damaged/dysfunctional cells, tissues and organs indicate that there could be several means with which such regenerative medicine based applications work viz, fusion, differentiation, trans-differentiation and paracrine; whilst the paracrine mechanisms are numerous[1] in which several cell produced factors[2], some are seemingly known while many yet to be explored. This phenomena might look something new, but a careful analysis of literature doesn't say so. Embryo culture supernatant has been used clinically for improving embryo implantation rates in *in vitro* fertilization (IVF) procedures from 2007[3]. This procedure of injecting embryo culture supernatant (ECS) into the uterus before blastocyst transfer (BT) has been reported to improve implantation and pregnancy rates in different randomized clinical trials[3,4]. Conditioned Media (CM) obtained by culturing cells and stem cells form another avenue of cell-free regeneration. Mesenchymal stem cell-derived CM (MSC-CM) have been reported to have potential for cell-free regeneration of bone[5]. CM from adipose-derived stem cells (ADSCs) applied in pilot human clinical studies for hair regeneration[6] and human exfoliated deciduous teeth-CM has been used for bone regeneration around teeth implants in *in vivo* experiments[7] form some of such clinical applications using CM.

A significant advantage to use the cell-secreted factors sans cells, if considered rationally should:

I. Avoid issues of antigenicity and immunogenicity during clinical translation[8], and
II. Have maximum gains where paracrine effects contribute mainly to regeneration[1].

This concept of cell-free regeneration has gained further significance by the use of exosomes, which are extracellular vesicles released from cells upon fusion of the intermediate endocytic compartment, the multivesicular body (MVB), with the plasma membrane[9]. Cell-derived exosomes from different types of cells and stem cells have been reported to be useful in several regenerative medicine applications, including myocardial regeneration[10], anti-cancer therapies[11] and hind limb ischemia[12].

Amidst the existing debate and translational constraints based on regulatory approaches in different countries on whether cell based therapies should be considered as drugs or products[13], such cell-free regeneration approaches may pave way for faster translation of the technology to the bedside. Still, the nature and functions of such cell-produced tools including exosomes are likely to have several variables based on the cell source, age of the donor, *in vitro* environmental conditions etc., [14] which needs further research to ascertain the effects of such variability in clinical contexts.

Nevertheless, looking into cells as factories to produce solution-oriented products or components, the domain of regenerative medicine has been only gaining strength by virtue of such novel strategies in yielding exciting solutions. This is not a simple paradigm shift of cells as tools to cell-produced tools, rather an added responsibility on the shoulders of the scientific community to ensure the right kind of *in vitro* environments where the cells are nurtured, enable them produce the right tools for cure.

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