TRANSCELL BIOLOGICS

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INSIDE

CREDITS

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HIGHLIGHTS

Patient derived

Stem cells

RPE treatment

Parkinson's disease

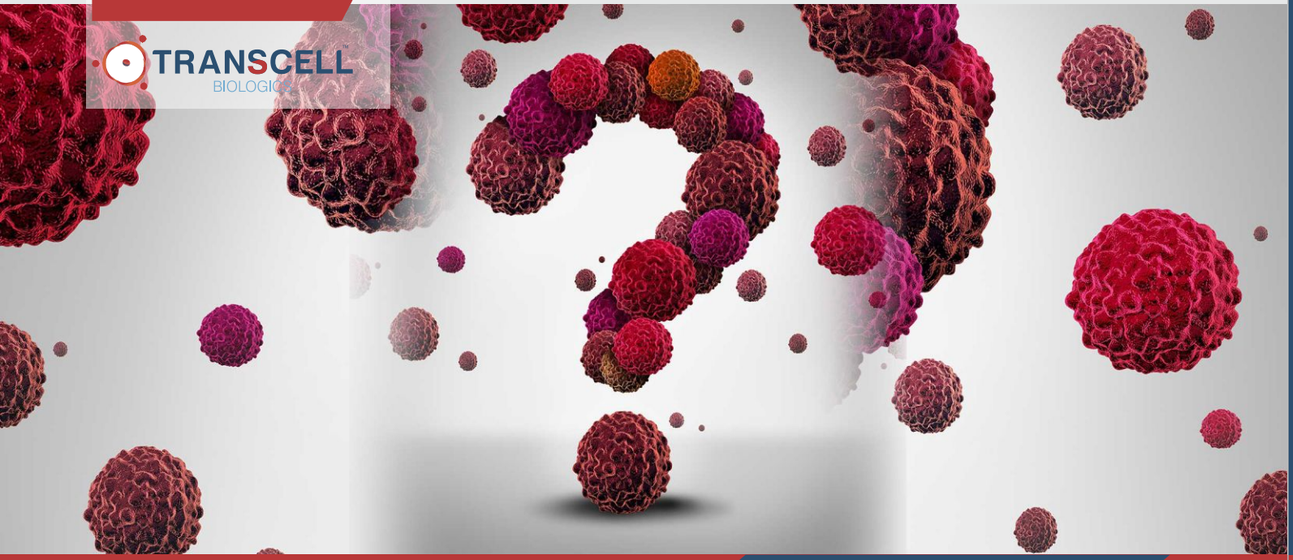
FROM THE EDITOR

In developing countries like India, despite the advancements in medical sciences research, a plethora of diseases continue to take their toll on the health of the population. If we look at the list of killer diseases in India, cardiovascular diseases top the list being responsible for a whopping 24.8% of the deaths followed by Diabetes silently killing. Majority of these cardiovascular diseases are due to dietary habits, smoking, high cholesterol levels and obesity. Respiratory diseases are responsible for about 10% of the deaths. Rapid industrialization and resultant pollution, smoking etc. are the culprits behind these respiratory illnesses. Tuberculosis, malignancies and unintentional injuries also contribute to the overall death toll in India. While drugs for treating the symptoms of some of the above mentioned diseases and conditions are available, chronically ill patients afflicted by these diseases do not stand a chance of survival. Conventional therapies could help alleviate the temporary pain but may not be successful in curing the disease in its entirety. Novel approaches to treat these life threatening diseases is the need of the hour. Stem cell therapy which is a relatively new form of treating and managing diseases has been slowly gaining popularity in public and medical fraternity alike. One of the reasons for the widespread consensus on stem cell based therapies is due to the fact that it is a wholistic approach resolving the root cause. Clinically relevant and therapeutic stem cells can be sourced from either the patient's own body or a donor depending on the ailment and the treatment required. The field of stem cell clinical research is progressing towards integrating this regenerative medicine into traditional practice. This could be achieved by a collective effort by the scientific, clinical/medical practitioners and regulatory communities. Effective communication of the data and cooperation between these communities would help many patients with debilitating conditions take advantage of this novel, effective method of treatment. Organizations like Tran-Scell continue to strive to make sure the normal public and healthcare providers are equally aware of the advantages of embracing regenerative medicine for treating ailments that were hitherto considered hopeless and in some cases fatal. Tran-Scell calls for a unique and real ecosystem built in India where the local breakthroughs/advancements in biotech/healthcare is seemlessly applied to treat the diseases of Indian population with regultory congnizance with less or no dependence on foreign pharma.

This newsletter focusses on the fascinating and captivating topic of patient derived stem cells and the applications to treat.

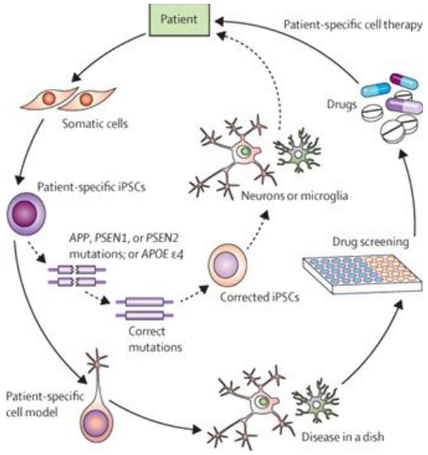
Now, it is your turn and I wish you a happy reading!

Anand Soorneedi



PREFACE

Patient derived stem cells in Regenerative Medicine are precision tools to cure certain disorders of the mankind. Depending on the methods used, reprogramming of patient derived adult cells to correct the abberation and use in cell therrapy approaches is close to reality.



STEM CELLS: WHAT ARE THEY

Stem cells are the progenitor cells for various tissues and organs in our body. The specialized cells that make up various tissues and organs are initially derived from a pool of stem cells that have the capacity to divide and differentiate shortly. The role stem cells play in replacing and replenishing the cells in the body over the course of life have made them a subject of immense interest for researchers all over the world. Stem cells have two important properties. (i) self-renewal and (ii) ability to differentiate into a wide variety of cells, depending on their place of origin inside the human body.

Depending on the stage of development at which the stem cells are sourced, they can be broadly classified into (i) Embryonic, (ii) Fetal and (iii) Adult stem cells.

Embryonic stem cells as the name suggests are derived from the early blastocyst stage of an embryo. These kinds of stem cells have the capacity of differentiating into all types of cells in the body i.eTotipotency. Fetal stem cells are the type found in a developing fetus. Adult stem cells are tissue and organ specific stem cells meaning they are found in specialized tissues and organs. These special kind of stem cells are pluripotent and multipotent depending on the type they belong to. Eg: A hematopoietic stem cell can only generate a red/white blood cell or platelets. Neuronal stem cells can differentiate into a specific type of nerve cell. Mesenchymal stem cells derived from limbus can differentiate into all the three lineages. Induced pluripotent stem cells (iPSCs) are a new league discovered in 2006 that are reprogrammed to behave like embryonic stem cells in their genetic expression.

NOVEL CONCEPTS AND MECHANISMS:

The field of stem cell therapy has been gaining much momentum with patient derived autologous applications as integrated options in disease management. Thanks to advances in the field of genome editing. Using iPSCs for developing disease models is also gaining popularity, owing to the ease with which they can be employed in vitro. Techniques like CRISPR (for precise genome editing) are being used to tackle the problem of unpredictable variability in differentiation of adult stem cells derived from a patient. Since the progenitor cells are derived from the patient if for clinical transplantations, the challenge is to make sure that the mutations responsible for causing the disease are edited.

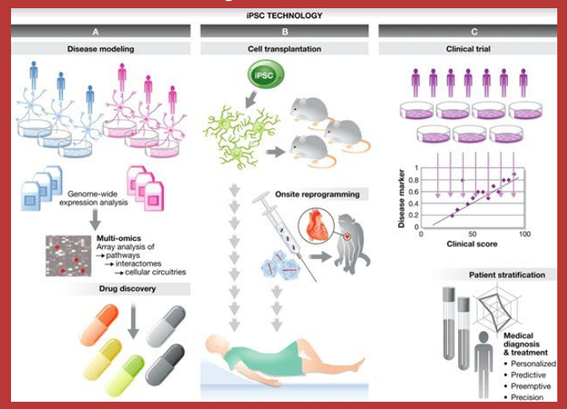
ADVANCEMENTS - HYPOTHESIS - CLINICAL APPLICATIONS:

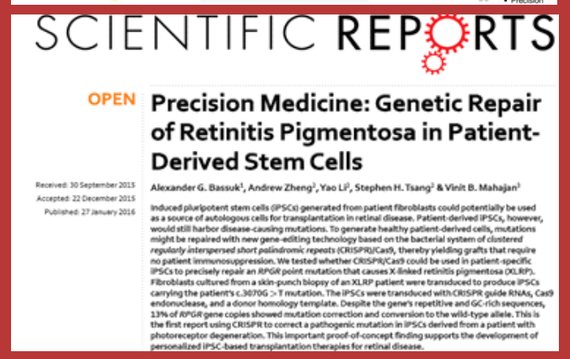
Induced Pluripotent Stem Cells and their significance in treating various disorders

The reason why researchers are interested in handling iPSCs is because they can be derived from the patient themselves (autologous), reducing the risk of immune-rejection and that they could be programmed to make pluripotent stem cells that are disease specific. These disease specific stem cell lineages are advocated as invaluable tools for studying the mechanism of disease cause and progression.

A fairly recent groundbreaking study was on the treatment on Retinitis Pigmentosa using stem cells derived from the skin of patient and using CRISPR to repair the defective gene.

The corrected cells were then transdifferentiated to retinal cells and transplanted into the same patient to treat loss of vision.





SCIENTIFIC REPORTS

OPEN

Precision Medicine: Genetic Repair of Retinitis Pigmentosa in Patient-Derived Stem Cells

Alexander G. Bassuk[1], Andrew Zheng[2], Yao Li[2], Stephen H. Tsang[2] & Vinit B. Mahajan[1]

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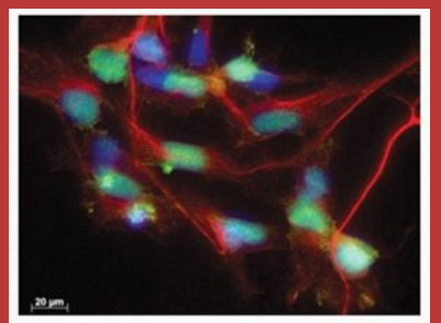
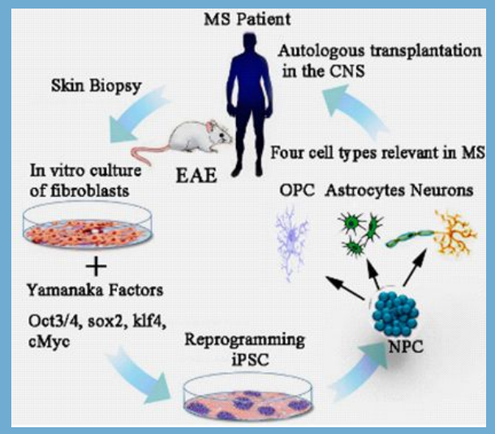
Induced pluripotent stem cells (iPSCs) generated from patient fibroblasts could potentially be used as a source of autologous cells for transplantation in retinal disease. Patient-derived iPSCs, however, would still harbor disease-causing mutations. To generate healthy patient-derived cells, mutations might be repaired with new gene-editing technology based on the bacterial system of clustered regularly interspersed short palindromic repeats (CRISPR/Cas9, thereby yielding grafts that require no patient immunosuppression. We tested whether CRISPR/Cas9 could be used in patient-specific iPSCs to precisely repair an *RPGR* point mutation that causes X-linked retinitis pigmentosa (XLRP). Fibroblasts cultured from a skin-punch biopsy of an XLRP patient were transduced to produce iPSCs carrying the patient's c.3070G > T mutation. The iPSCs were transduced with CRISPR guide RNAs, Cas9 endonuclease, and a donor homology template. Despite the gene's repetitive and GC-rich sequences, 13% of *RPGR* gene copies showed mutation correction and conversion to the wild-type allele. This is the first report using CRISPR to correct a pathogenic mutation in iPSCs derived from a patient with photoreceptor degeneration. This important proof-of-concept finding supports the development of personalized iPSC-based transplantation therapies for retinal disease.



A research team spanning the New York Stem Cell Foundation and the Ying Liu Laboratory at the University of Texas Health Science Center at Houston optimized the targeting efficiency of the CRISPR/Cas9 system in a stem cell application. Specifically, they generated a dual knockin reporter in human induced pluripotent cells. Here, mCherry (red) expression faithfully reflects endogenous neurogenin 2 (green) expression during neural induction. Nuclei are revealed by DAPI staining. Scale bar: 20?µm. CRISPR/Cas9 reporter cell lines can be used to determine the role of transcription factors in human development and to purify neural lineage specific populations. [Ying Liu Laboratory]

CRISPR: A new weapon in the stem cell therapy arsenal

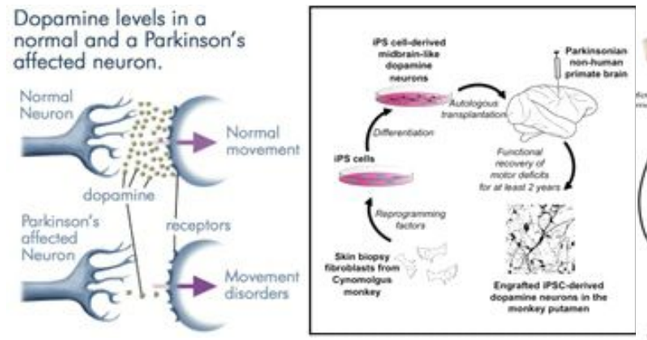


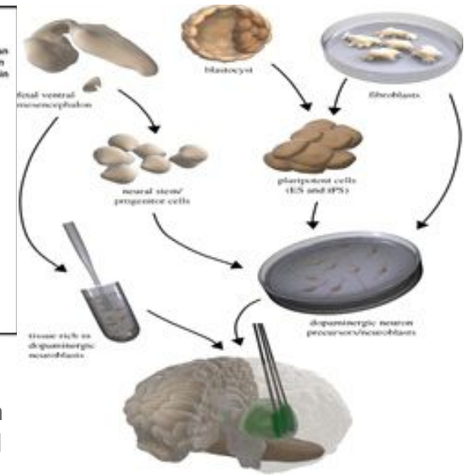
Microglia can be derived from patient-specific human induced pluripotent stem cells and may help modulate the course of central nervous system diseases.

On April 29, 2013, American Association of Neurological Surgeons (AANS) reported that when mouse and human iPSCswere co-cultured with OP9 cells, differentiate into hematopoietic progenitor cells (HPCs). HPCs in turn co-cultured with astrocytes, generate cells that express CD11b, Iba-1 and CX3CR1; secrete the cytokines IL-6, IL-1ß and TNF-a; generate reactive oxygen species; and phagocytose fluorescent particles, all consistent with a microglial phenotype. Gene expression clustering using self-organizing maps indicates that iPSC-derived microglia more closely resemble normal microglia than other inflammatory cell types. The iPSC-derived microglia engraft and migrate to areas of injury within the brain. These finding have led researchers to conclude that iPSC-derived microglia may one day be useful as gene and protein delivery vehicles to the CNS.

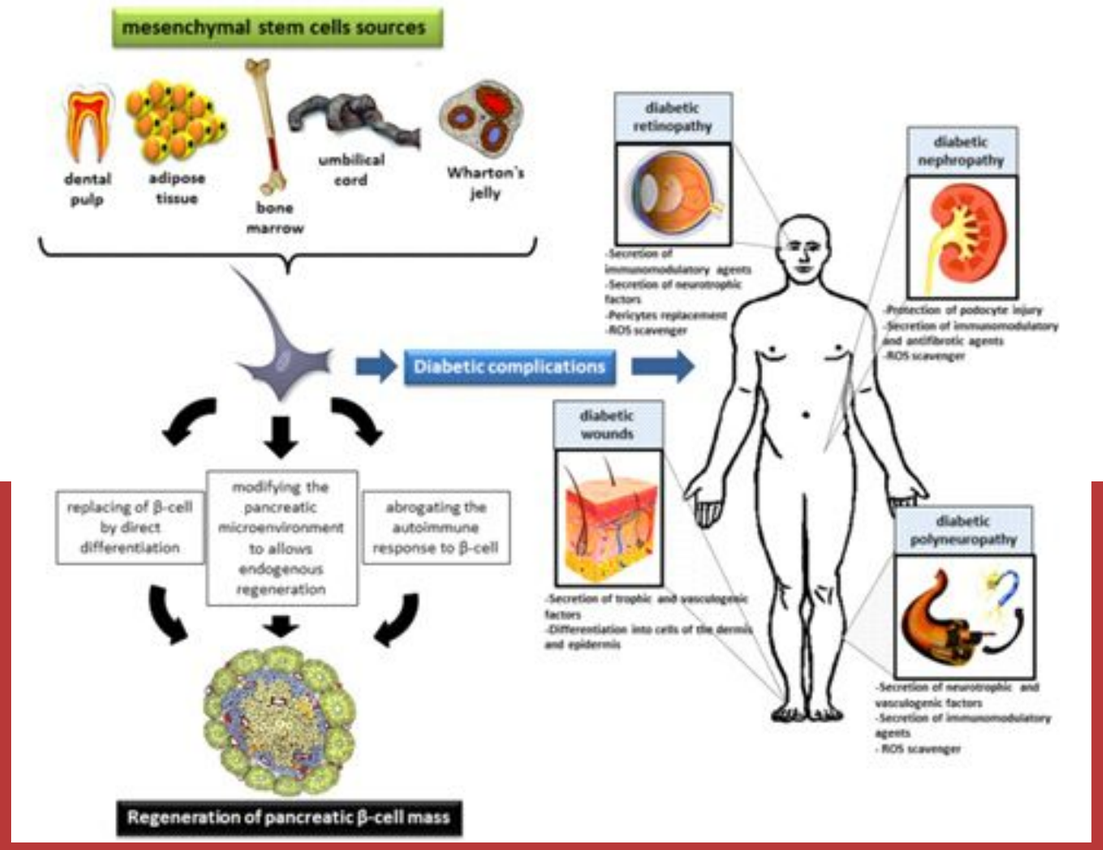
CNS NeurolDisord Drug Targets, 2011 Jun reported the potential application of induced pluripotent stem cells in cell replacement therapy for Parkinson's disease.

Parkinson's disease (PD), a degenerative disease in humans, is known to result from loss of dopamine neurons in the substantia nigra and is typically characterized by severe motor symptoms of tremor, rigidity, bradykinsia along with postural instability. Although levodopa administration, surgical neural lesion, and deep brain stimulation have been shown to be effective in only improving parkinsonian symptoms, cell replacement therapy such as transplantation of dopamine neurons or neural stem cells has shed new light on an alternative treatment strategy for PD addressing the root cause. While the difficulty in securing donor dopamine neurons and the immuno-rejection of neural transplants hinder application of neural transplants in clinical treatment, iPSCs derived from somatic cells may represent a powerful source for replacement therapies in this neurodegenerative disease. Animal studies have further shown that iPSCs from fibroblasts could be induced into dopamine neurons and transplantation of these cells within the central nervous system improved motor symptoms in the 6-OHDA model of PD. Also, neural stem cells or fibroblasts from patients can be efficiently reprogrammed and subsequently differentiated into dopamine neurons. Derivation of patient-specific iPSCs and subsequent differentiation into dopamine neurons would provide personalized stem cell therapy for PD.





Patient derived adult pluripotent mesenchymal stem cells are another category of stem cells derived from bone marrow, tooth pulp, fat tissue, peripheral blood being advocated as therapeutic tools for autologous applications treating other than genetic diseases.



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