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Edison Explains

Stem cells

How do we produce stem cells without using human embryos?

Why are stem cells controversial?

Stem cells derived from human embryos have been controversial since the discovery that these unspecialised cells could be harvested from fertilised embryos and used to replicate human cells.

Ethical concerns regarding the sanctity and definition of life due to the destruction of embryos required in the harvesting of stem cells created public and presidential opposition to their use, especially in the US; that is, until Shinya Yamanaka identified how to reprogramme specialised cells into their unspecialised variants.

Yamanaka determined that by adding a set of genetic instructions in mouse fibroblasts, he could reprogramme tissue to create stem cells. He later used the same technique on human cells, and the resulting induced pluripotent cells could replicate a variety of human tissues, while skirting the issue of ethical controversy.

How are cells reprogrammed into a pluripotent state?

During his Nobel Prize-winning research, Yamanaka fashioned an engineered retrovirus that introduced new genetic instructions into cells, in the process reverting them to an unspecialised state. In the retrovirus family, lentiviruses are most commonly used in the production of induced pluripotent stem cells (iPSCs).

Unfortunately, retroviral vectors have a few associated hurdles that make them difficult to implement in treatment.

These range from a tendency to mutate, to lingering effects post treatment and the unintended reactivation of reprogramming factors. These are all issues that make retroviral reprogramming difficult to implement in a clinical setting with strict safety requirements.

Edison Insight

"There are some indications, typically serious and often inherited, which cannot be treated by small molecule drugs, monoclonal antibodies or even antisense molecules. For these undruggable indications, and where tissue needs to be regenerated, engineered stem cells appear to be the only way to help patients currently." Andy Smith, healthcare analyst.

How can cells be reprogramed to reduce the risk of mutagenesis?

Adenoviruses are an alternative to retrovirals, as they do not use RNA but a version of DNA to alter a cell's genes. The Sendai RNA virus is another solution, as it does not integrate into a host's genome, reducing the risk of insertional mutagenesis.

Plasmid-based expression, in which a small double-stranded, free-floating DNA molecule, separate from a patient's genome, is used to reprogramme cells, can also create iPSCs.

The technique reduces the risk of mutation, as it fails to affect the cell's underlying genome. Minicircles, smaller variants of a plasmid with some distinctive features, can also be used to this effect.

Non-virus RNA delivery is another technique that limits the risk of mutagenesis. It works by inserting DNA-altering RNA, often through the use of peptides or lipids.

Reprogramming proteins can also be used, with the aid of cell-penetrating peptides. The peptides, made up of amino acids, guide large reprogramming proteins, which tend to find it difficult to penetrate into cells past cell membranes.

Are induced pluripotent cells the only non-embryonic source of stem cells?

Naturally occurring stem cells are not found exclusively in embryos, and are present in the umbilical cord. Stem cells are not the sole domain of the very young either and adults also produce stem cells, albeit in smaller quantities.

Unlike embryonic stem cells, adult stem cells lack the ability to differentiate into any type of tissue. For example, mesenchymal stem cells found in bones and blood will only replicate into bone, cartilage or fat.

Furthermore, not all embryonic cells are harvested from fertilised eggs. In fact, somatic cell nuclear transfer (SCNT) predates Yamanaka's discoveries, but lacked the ability of scale found in iPSCs.

SCNT removes the nucleus of an egg, then replaces it with differentiated stem cells to create artificial embryonic cells.

How are stem cells used in treatment?

Today, stem cells are, by and large, used in the lab to replicate tissues for experimentation.

Of the few treatments that use stem cells, bone marrow transplants are the most common. Here, donor mesenchymal cells are used to generate new marrow for implantation. Umbilical cord blood, and its stem cells, have also been used to treat children with certain rare blood diseases since 1989.

There has also been some recent success in corneal repair, with Holoclar, an induced pluripotent stem cell corneal repair treatment, approved for use in the EU in 2015.

Which companies are currently conducting stem cell clinical trials?

Stem cell research is a fertile field for clinical trials, with many ongoing studies. For example, International Stem Cell is developing a pluripotent cell treatment for Parkinson's disease in a Phase I trial that is nearing its end, while ReNeuron, BrainStorm Cell Therapeutics and Neuralstem are all conducting trials in neural disease.

ReNeuron is conducting a Phase II study on stem cells in chronic stroke disability and a Phase I/II study in retinitis pigmentosa, a rare genetic condition of the eyes, while BrainStorm is proceeding with a multi-dose Phase III trial for amyotrophic lateral sclerosis (ALS).

Pluristem Therapeutics, for its part, has announced a Phase II study for the treatment of muscle injury in hip arthroplasty, due to femoral neck fracture.

Other researchers, like Cellular Biomedicine Group, have begun stem cell clinical trials in knee osteoporosis, or, in the case of Regeneus, in knees osteoarthritis, with its proprietary adipose (fat) derived allogeneic stem cells, which have shown signs of efficacy in their Phase I study.