Universal donor cells – a revolution against rejection

Dr Claudia Mitchell (CEO of Universal Cells) and her team are focused on the commercialisation of an innovative gene-editing technology to develop universal donor stem cells that are not subject to immune system rejection.

Pluripotent stem cells offer huge therapeutic potential. These undifferentiated cells can give rise to almost any specialised cell type, acting as a natural repair system for damaged tissues or as novel therapeutics that can be further engineered to treat diseases.

Scientists have exploited the unique properties of stem cells to treat diseases associated with dying or damaged cells. Currently, in Europe, 26,000 patients per year receive stem cell therapy to treat blood disorders and some cancers, including leukaemia. However, currently human donors are the main source of stem cells, limiting the treatment’s success due to rejection by the patient’s immune system.

In order to achieve the full therapeutic potential of pluripotent stem cells, the issue of rejection must be solved: Universal Cells Inc. aims to achieve this goal. Founded by Dr Claudia Mitchell and Dr David Russell in 2013, the company focuses on the use of a pioneering gene-editing technology to develop Universal Donor Cells (UDCs) – modified pluripotent stem cells that are refractory to rejection by a patients’ immune system.

**The Molecular Basis of Rejection**

Each individual has a unique set of human leukocyte antigens (HLAs) – cell surface protein markers that signal to the immune system that they are that individual’s own cells. In the population, the genes that encode HLA molecules are hypervariable – meaning each individual has a specific barcode of HLA molecules that are custom-fit for their immune system. There are 2 classes of HLA molecules: HLA class I molecules, which are expressed on all cells and HLA class II molecules, which are expressed on a subset of cells associated with the immune system. Both class I and class II molecules are made up of two parts. Class I molecules are formed when the hypervariable HLA class I protein binds another protein called Beta-2-microglobulin (B2M), which is required for the HLA molecule to reach the surface of the cell. HLA class II molecules get to the surface of the cell when two hypervariable HLA class II molecules bind together. Both types of HLA molecules serve the role of presenting pieces of other proteins to the immune system.

HLA molecules are closely monitored by the immune system. Differences in either HLA class I or HLA class II proteins lead to the identification and rapid destruction by cytotoxic T-cells (cells that ‘kill’ other cells).
How are Universal Donor Cells (UDCs) developed using recombinant adeno-associated virus (rAAV) technology?

Universal Cells, Inc. uses rAAV-mediated genome-editing technology to engineer the HLA molecules of pluripotent stem cells and thus create cells that are universally compatible. First, a single-chain, non-polymorphic HLA class I transgene composed of the HLA-E molecule fused to the beta 2-microglobulin (B2M) transgene described above is encoded within the rAAV and is knocked-in at the B2M gene via homologous recombination. Additionally, in order to knock-out HLA class II expression, another rAAV vector is used to eliminate the expression of a transcription factor that is necessary for the expression of all HLA class II molecules.

ADVANTAGES OF UDCs AND RAAV TECHNOLOGY

There are multiple strategies that can be employed to reduce the rejection of stem cells, including: i) HLA-typed stem cell banks, where hundreds of separate HLA-specific cell lines are produced, ii) allogeneic donor stem cells, where a single line is produced and transplanted but requires toxic immunosuppressive drugs and iii) autologous induced pluripotent stem cells (iPSCs), where a patient’s own cells are isolated and manipulated to behave like a pluripotent stem cell.

A major advantage of UDCs over HLA-typed stem cell banks is that only one cell line is required. This significantly reduces the cost, complexity and time required to undertake clinical trials and eventual commercialisation. HLA-typed banks also do not solve the problem of HLA class II matching or the presentation of foreign proteins by the matched HLA molecules.

Although allogeneic donor cells also entail just a single cell line, they require the use of immunosuppressants, which weaken the immune system. This reduces the incidence of rejection but also results in severe side-effects, which complicate the clinical outcome: UDCs, however, do not require immunosuppression, as there are no foreign proteins to trigger an immune response.

Compared to UDCs, autologous iPSCs are very expensive to manufacture. Furthermore, there is enormous variability between different preparations of iPSCs, leading to potentially unpredictable cell differentiation potential, manufacturing capacity and ultimately unpredictable clinical outcomes.

CURRENT AND FUTURE USES OF UDCs

UDCs are an exciting product that will enable a new class of therapeutics to treat a variety of life-threatening diseases. For example, Universal Cells, Inc. has recently established partnerships to develop cancer therapies using universal donor T-cells (with Adaptimmune) and universal donor retinal pigment epithelium cells for the treatment of adult macular degeneration (with Healios). Other examples of applications include the development of UDC-derived keratinocytes therapies which could be applied to treat skin wounds and burn injuries, or the development of UDC-derived beta pancreatic cells to treat type 1 diabetes.

Overall, rAAV-mediated gene-editing technology and UDCs can have a huge impact in the healthcare industry, overcoming the obstacle of transplant rejection, revolutionising stem cell therapies and changing the way we treat genetic diseases.

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