CD133 Clinical Trials: Safety and Efficacy

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Introduction
A single human body contains trillions of cells made up of several types based on physiology and function. There are types of cells that are linked to the fulfillment of specific physiological roles, for example neurons are signaling cells, bone cells are specialized in maintaining the integrity of the skeletal structure, while muscle cells are specialized in coordinating body movements. In addition to these specialized cells, there are other types of cells that apparently have no specific function. These cells can be led to acquire specific functions by differentiation. These cells are known as stem cells and can be defined as cells that have the ability to self-divide as well as to differentiate into specialized cells.

The term "stem cell" finds its first mention in scientific literature by a German biologist Ernst Haeckel. He used the term "Stammzelle" to describe the single-celled organism presumed to be the ancestor of the multi-cellular organism. Haeckel also used the same word to describe the fertilized egg that gives birth to a more complex multicellular organism [1]. Later, at the end of the 19th century, Weismann proposed a theory of the continuity of the germplasm. The theory suggests a separate cell type that remains separate in embryonic development known as germ cells. Boveri, in 1892, proposed that germ cells are those that can lead to primordial germ cells and where other primordial somatic cells come from, giving a definition of stem cells that is fairly close to their modern definition.

The modern concepts in stem cells come from the advancement of research in the hematopoietic system. Specially, the boost to the stem cell research was provided by the development of staining for various kinds of blood cells by Ehrlich. Although, Peppenheim in 1896, suggested the common precursor of red blood cells and white blood cells, yet Maximow is credited for coining the term of stem cells in 1909 [3,4]. The definitive evidence was finally provided by Till and McCullough in 1963 when they published about the cells in hematopoietic tissue giving rise to colonies that contain cells of different lineages i.e. erythrocytes, granulocytes and megakaryocytes.

Stem cell types and characteristics
Stem cells can be divided either on the basis of origin or on their characteristic ability to produce other type of cells. On the basis of origin, Stem cells are divided into two types: embryonic stem cells, isolated from embryo, and adult stem cells obtained from the adult tissues [8].

On the basis of ability to generate different lineages of cells, stem cells can be: Totipotent, producing every type of cells including germ cells, Pluripotent: that can produce all type of cells except embryonic germ cells, Multipotent: the stem cells that have the ability to differentiate into different types of mature cells, Self-regenerating stem cells: that can divide and produce large quantity of stem-cells and Plastic stem cells, that can differentiate into type other than they were originally isolated from.

Stem cell therapy
As the name suggests, stem cell therapy is the use of stem cells to treat disease. The use of stem cells, because of their ability to regenerate and differentiate, to treat physiological disorders seems to have promising prospects. Stem cell therapy is used in a number of disorders. Various clinical trials are underway to establish the safety and efficacy of the stem cell therapy as presented.

Stem cell therapy is of great interest because of its applications in tissue engineering, regenerative medicine and gene therapy because of their therapeutic potential. The main objectives in the field of stem cell research for the years to come are to identify therapeutic targets, cell differentiation and physiological mechanisms, the safety and efficacy of the use of stem cells as therapy.

The most important practical application is in the treatment of patients with leukemia or lymphoma using stem cells derived from bone marrow. Chemotherapy can kill rapidly dividing cells without distinguishing between neoplastic cells and healthy cells. This is a major problem inherent in the use of chemotherapy. The side effect of conventional chemotherapy can be reversed by stem cell transplantation by administering functional healthy bone marrow stem cells to replace damaged stem cells in the host body. One of the main side effects associated with such a transplant is that these stem cells (especially if the cells are of heterogeneous origin) have the ability to elicit an immune response which can lead to graft versus host disease.

A total of eight hematopoietic stem cell products derived from umbilical cord blood have already been approved by the FDA for the treatment of blood and immunological diseases. The European Medicines Agency approved in 2014 the use of limbic stem cells for people suffering from a serious deficiency in vital limbic stem cells for the epithelial regulation of the cornea.

CD133 or Prominin-1
Hematopoietic stem cells express a pentaspan glycoprotein present on membrane known as CD133 or Prominin-1. The role of Prominin-1 is well established in organizing membrane structural integrity [21]. In human, a gene on chromosome 4 encodes Prominin-1. CD133 is a transmembrane glycoprotein. It has five transmembrane domains, two extracellular loops and two cytoplasmic loops an N-terminal chain which is extracellular and a C-terminal cytoplasmic tail, comprising total of 865 amino acids and have a molecular weight of 120 kDa. The N-terminal chain consists of 105 amino acids, two extracellular loops (one

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larger than other) contain around 258 and 279 amino acids, while two intracellular domains that are smaller in size compared to extracellular loops, have only 29 and 21 amino acids and a cytoplasmic tail is of 59 amino acids. These loops are connected by transmembrane domains containing 23 amino acids each (Figure 1). There are seven different isoforms of CD133 has been reported that are distributed in different parts of the body [22-24]. CD133 distribution in human body.