

## Cloning Technologies and Stem Cell Research

### The Issue

In February 1997 scientists at the Roslin Institute in Edinburgh announced that they had successfully 'cloned' an adult sheep. A number of additional developments in cloning higher animals were subsequently reported. These developments, coupled with the isolation, in late 1998, of human embryonic stem cells, generated considerable public interest in cloning and stem cell research. Particular attention has focussed on the potential for cloning entire human beings and the benefits of cloning for therapeutic (rather than reproductive) purposes. This paper outlines GSK's views on the importance of these technologies in medical research and our uses of them.

### GSK's Position

#### Cloning Technologies

- GSK uses cloning technologies to replicate molecules and cells for drug discovery and development. This technology has accelerated the testing of life-saving compounds and is critical to future advancements in biomedical research.
- GSK does not use cloning technologies with the intention of reproducing entire human beings and we do not see a medical or research case for doing so.

#### Stem Cell Research

- GSK recognises that recent advances in stem cell research herald a new approach for producing human tissues for transplantation and for the treatment of many debilitating diseases and injuries, including Parkinson's disease, Alzheimer's disease, diabetes and spinal cord injuries.
- GSK currently uses adult human stem cells to advance research in our own research centres and in collaboration with academic centres of excellence. For example, stem cells from human blood are used by GSK to evaluate the safety of medicines. GSK's use of adult stem cells, like that of other pharmaceutical companies, has been conducted for many years and is recognised as an integral element of research for new medicines.
- Foetal stem cells and other foetal material can have a role in discovering therapies for serious and debilitating diseases. GSK has external collaborative agreements in place where these materials are used to advance research into medicines for serious medical disorders.
- GSK believes that human embryonic stem cells (HESCs) have a promising place in medical research and drug discovery. In appropriate instances, GSK makes use of such cells in its own research and in collaboration with academic institutions or other external partners.
- Induced Pluripotent Stem cells (iPS) are genetically and functionally similar to embryonic stem cells. However, scientific understanding of iPS cells is still very young. Parallel research using both HESCs and iPS cells is therefore needed to ensure that this area of stem cell technology can be fully leveraged. GSK makes use of iPS cells in its own research and in collaboration with our academic institutions.

# GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

- Any current, or future, use of human embryonic or foetal material, including stem cells, by GSK or by outside collaborators follows established ethical requirements and rigorous scrutiny, including confirmation that the provider of the material has obtained informed consent from the donor.
- The use of embryonic and/or foetal material by GSK R&D or in collaboration with an external partner requires the approval of the Chairman of R&D.

## Legislative Environment

- GSK is committed to working with governments to support appropriate legislation or regulation that addresses societal concerns while allowing research to continue so the full potential of cloning technologies and stem cell research can be realised.
- An all-embracing ban on “human cloning” must be avoided. Any ban should be specifically restricted to the “cloning of entire human beings”; otherwise, there is a real danger of inhibiting research into currently untreatable or incurable diseases and medical conditions.

## BACKGROUND

### GSK and Cloning Technologies

Cloning is the process of producing an identical copy of something – in the case of biomedical research, a gene, cell, or entire organism. Biomedical researchers have used cloning technology for a number of decades. The technology has improved our understanding of human biology and led to innovative medical breakthroughs.

There are three main applications of cloning technology in biomedical research: molecular cloning, cellular cloning, and animal cloning. There is also a distinction between “therapeutic” and “reproductive” cloning. Research is also underway in some quarters using cybrid embryos.

Molecular cloning: Molecular cloning is an essential tool in research at GSK and other research institutions. Molecular cloning involves placing a new piece of DNA into a cell in such a way that every time the cell divides, the DNA is reproduced. This process generates many copies of identical genetic material that can be studied and used in the research process. It also enables production in industrial quantities of the specific protein encoded by a gene.

One important example of a disease application of molecular cloning is the production of a human protein needed to treat a disease. Since the discovery of the gene associated with insulin production, for example, molecular cloning has been used to enable bacteria to produce human insulin. The human gene is inserted into bacterial cells that in turn mass-produce human insulin. Prior to this breakthrough, patients with diabetes had to rely on cow or pig insulin, often requiring higher doses and increasing the risk of adverse reactions.

Cellular cloning: Cellular cloning is used to produce and perpetuate cell lines of identical cells and is also a fundamental tool in research and development used by GSK. A combination of cellular cloning and molecular cloning enabled the sequencing of the human genome, which is providing researchers with the ability to investigate the underlying causes of diseases in order to develop better prevention, treatments and cures.

# GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

Animal cloning: Animal cloning involves a wholly different technique called somatic cell nuclear transfer (SCNT). This technique removes the nucleus of an unfertilized egg cell, replaces it with material from the nucleus of a "somatic cell" (a skin cell, for example), and then stimulates this hybrid cell to begin dividing. The technique is the basis for cloning animals and in theory could be used to clone humans.

GSK does not clone animals. However, in common with biomedical researchers in universities and other research institutions, we do use genetically modified rodents (i.e. rats & mice) as research models for Alzheimer's disease, cancer, diabetes, obesity and cardiovascular disease. Specific genes in these rodents are targeted and then either turned off or increased in number to achieve a better understanding of metabolic pathways and discover potential drug targets. GSK sources these rodents from external suppliers as well as producing some in-house.

Cybrid Embryos: GSK notes the UK Government's decision to allow research into life-saving diseases using cytoplasmic embryos, or cybrids. These are made by using eggs from animals, such as rabbits or cows, which have had their nuclei replaced with genetic code from human cells. This is not an area of research currently conducted by GSK; however, we recognise its potential value in supporting discovery of novel medicines. Any decision to apply the technology to future GSK research programmes, or those of its academic partners, would be made following the same stringent internal guidelines established for embryonic and foetal stem cell use.

"Therapeutic" and "Reproductive" Cloning: The main distinction between these two types of cloning - both of which involve SCNT - is intent. "Reproductive cloning", as currently practiced, seeks to produce entire animals, whereas "therapeutic cloning" produces human embryonic stem cells for use in research.

## Stem Cell Research

Stem cells are unspecialised cells that can renew themselves indefinitely and develop into specialised, more mature cells. For example, stem cells give rise to blood, skin, liver, muscle and a variety of other tissues and organs.

The two defining features of stem cells – their potential for differentiating into various specialised cells and their capacity for self-renewal – make them the logical focus of research into tissue regeneration.

A better understanding of how these cells develop, divide and give rise to differentiated cells, could lead to innovative ways to treat burns, stroke, spinal-cord injuries, neurodegenerative disease, cancer and diabetes, among other medical conditions.

## Stem Cell Definitions

Embryonic Stem Cells: Embryonic stem cells, which come from the inner cell mass of an early stage embryo, have the potential to develop into all or nearly all of the tissues in the body. The scientific term for this characteristic is "pluripotentiality." This unique feature of embryonic stem cells gives scientists optimism that human stem cell research will result in new ways of treating disease.

# GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

A common source of human embryos from which stem cells are obtained are surplus embryos from in vitro fertilisation (IVF) programmes. Another potential source is human SCNT as described above. GSK's approach allows for the use of SCNT-sourced cells if they are required for research intended to lead to new medicines. Currently, however, GSK and its academic collaborators only make use of embryonic stem cell lines originating from IVF programmes. These are primarily obtained or derived from a number of cell banks, including those overseen by the Medical Research Council in the UK and the National Institutes of Health in the US.

Foetal Stem Cells: Foetal stem cells are derived from foetal tissue, the transition from embryo to foetus in humans being generally defined as at 9 weeks. Scientists in many research institutions use foetal stem cells because of the scientific limitations of animal cells and adult human stem cells. For example, scientists have found a way of implanting human foetal stem cells into the brains and spinal cords of rats as a step toward creating new therapies for neurodegenerative diseases like Parkinson's disease and Alzheimer's disease.

Foetal stem cells and other foetal material used by GSK and its external collaborators are obtained from hospitals and/or clinics with the consent of the woman. The process for obtaining informed consent to use the foetal material is completely separate from her decision whether to terminate her pregnancy. The informed consent process is initiated only after the woman's decision to terminate and does not compromise her freedom to change that decision.

Adult Stem Cells: Adult stem cells are "multipotent". After cells differentiate to become tissues and organs in a human body, some tissues retain a group of these versatile cells to replace mature cells that are damaged or aged. Adult stem cells can divide in two, one cell differentiating into the cell type needed by the damaged tissue, the other cell remaining undifferentiated (as a stem cell). One example is blood stem cells serving to replenish mature blood cells, which are short lived.

Although scientists believe that some adult stem cells from one tissue can develop into cells of another tissue, no adult stem cell has been shown in culture to be "pluripotent". It is hoped that once the processes of cell differentiation and tissue regeneration are understood more clearly, researchers will be able to work directly with stem cells derived from adults, or perhaps to induce differentiated cells to 'redifferentiate' in a new direction.

Adult derived stem cells can be collected from both adults and children, they include blood stem cells, which are found in the bone marrow continuously replenish the body's red blood cells, white blood cells, and platelets.

GSK is a founding member of the Stem Cells for Safer Medicine (SC4SM) initiative in the UK, which brings together pharmaceutical companies and public sector organisations. SC4SM aims to develop a bank of human cell lines for use in early medicine discovery that can help to identify and eliminate potential toxicity issues before medicines are tested in people. In 2010, SC4SM investigations focused on the use of stem cells to generate cardiac and liver cells.

Adult vs Embryonic and Foetal Stem Cells: Based on scientific understanding to date, it appears unlikely that human adult stem cells alone will provide all the necessary cell types required for the most clinically important areas of research. These uncertainties are such that work should continue on all fronts (that is with adult, embryonic and foetal stem cells) to ensure that the full potential of stem cell research is realised for the benefit of patients.

# GLOBAL PUBLIC POLICY ISSUES

GlaxoSmithKline's Position

Induced Pluripotent Stem cells: iPSs are created by the introduction of 3-4 genes into the somatic cells. They have an advantage over HESCs because they can potentially be created from any human cell, for example skin cells, and used to create all the cell types that HESCs can create. They can then be transplanted back into the person from whom they were taken, via a process called autologous cell therapy and thereby avoid tissue rejection. For drug discovery purposes, iPS technology allows the creation of banks of human cells with defined genotypes of interest to multiple diseases. As such, they are set to provide a highly sophisticated platform to support preclinical drug development.

## **GSK and Stem Cell Technologies**

GSK is using two distinct scientific approaches to develop new medicines using adult and embryonic stem cells:

1. Regenerative therapeutics – identifying medicines which activate stem cells in patients and regenerate cells lost in the disease process e.g. pancreas cells in diabetes or brain cells in Parkinson's disease. GSK's first regenerative medicine, Promacta™, a bone marrow stem cell activating drug, was approved in 2008 for treating platelet loss in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP).
2. Cellular tools – using stem cells to generate a range of cell types (many of which cannot be safely or physically collected from patients) to determine drug activity and toxicity, e.g. liver hepatocytes, brain neurons or cultures of contracting heart cells.

In 2010, we announced a new strategic alliance with the Italian Fondazione Telethon and Fondazione San Raffaele which specialise in research into rare genetic disorders, to develop novel treatments for such conditions using gene therapy carried out on stem cells taken from a patient's bone marrow. Under this agreement, we will develop an investigational gene therapy for Adenosine Deaminase Deficiency – Severe Combined Immune Deficiency (ADA-SCID), a very rare and life-threatening disorder that affects approximately 350 children worldwide. We will also co-develop further stem cell therapies to treat six other rare disorders.

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