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Research Article

# HEADWAY INTO THE INSIGHTS AND APPLICATIONS OF XENOGENIC CELL THERAPY

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**ABSTRACT**

Xenogenic cellular therapy is a novel technology with a wide scope for development and management of human degenerative diseases. Obstinate diseases, injuries and disorders are pigeonholed by abnormal cellular function or cell death. Xenogenic transplantation can restore diseased or lost tissue to provide curative therapy for such conditions. Regardless of the benefits offered there exists a lacuna with regards to the safety concerns to the host environment. Nonetheless, the availability of organs, tissues and cells from animals remains a significant advantage of the treatment. This has led to the development of a number of products and researchers in the area of life sciences are showing profound interest to come up with newer advancements and products with diverse applications. The review focuses on highlighting the basic concepts of the therapy so as to get an insight into its methodology, applications and the commercialised products available.



## INTRODUCTION

Xenogenic cell therapy, also called live cell therapy is the use of viable animal somatic or organ cells that are especially cultured for transplantation or implantation in or administration to the human body for treatment of certain abnormalities in the normal functioning of the human body (Edge *et al*. 1998). The genetic constitution of the cells is altered if necessary, by isolation of specific cells of an organ or tissue. These isolated cells are then cultured in laboratories and are suitably modified to suit the treatment requirements (Dylla *et al.* 2008). Steps are taken to not let the xenogenic cell preparation trigger the immune system of the human recipient as far as possible. The use of live animal cells was first demonstrated by Nobel laureate Dr. Alex Carrel who showed the influence of live cells on dying ones in late 19th century. Years later in 1931, Dr. Paul Niehans successfully used this therapy to save a patient's life, by chance. The patient had an injured parathyroid gland whose function affected the thyroid gland which regulates calcium metabolism. The dysfunction caused severe convulsions in the patient. Niehans macerated the parathyroid gland of an ox and prepared a suspension of the cells in physiological saline solution and injected it into the pectoral muscles of the patient. The convulsions miraculously diminished and ceased within hours. The effect of recovery lasted for over 20 years (Lauren 2001).

**Benefits of the therapy**

i. It is easier to obtain xenogenic cell products than human cell products.
ii. In case of carefully chosen source animal for the cell preparation, there is minimum immunological response.
iii. It has generally been observed that it revitalizes the 'old' cells of the recipient.
iv. It can be administered as a cell suspension intravenously or intra arterially to avoid surgical implantation as in case of organ transplants.
v. It is possible to target organs like brain where surgical implantation is difficult to perform.

**Risks and disadvantages**

i. Immunological rejection of the administered animal cells.
ii. Infection by known and unknown bacterial and viral diseases that infect animals.

iii. In case the patient is immune-suppressed for the treatment, there is risk of secondary infections.
iv. Cancers due to excessive proliferation of tissue
v. In case of pregnant women, this therapy may affect the growth of the foetus.

**Indications**

i. Organ disorders of heart, kidneys, lung, urine bladder, prostate, stomach, chronic digestive disorders, emphysema
ii. Chronic diseases of vascular system, skeleton and joints, reduced blood circulation, insufficient blood circulation in the brain
iii. Arthritis (joint degeneration) of various joints and spinal columns (osteochondritis), chronic joint rheumatism, osteoporosis
iv. Adult onset diabetes (type II)
v. Retarded development of infant or child, genetic / hereditary diseases
vi. Diseases of the brain or spinal cord
vii. Alzheimer's disease
viii. Parkinson disease
ix. Paralysis
x. Thalassemia and Hemoglobinopathies
xi. Renal insufficiency
xii. Male impotence or disorders male function of endocrine systems
xiii. Early menopauses, climacteric complaints
xiv. Neuritis (Nerve infections) inflammations
xv. MS (multiple sclerosis)
xvi. Migraine
xvii. Premature degeneration or lack of vitality
xviii. Exhaustion
xix. Weak body defences
xx. Premature aging and loss skin elasticity

**The manufacturing process life cycle**

The process of xenogenic cell therapy involves selection of the source animals, breeding of the animals in isolation, selection of donor animal, extraction of required organ or tissue, cell culture, cell modification, manufacture of cell product and quality testing followed by preclinical and clinical trials.

**Selection, breeding and isolation of animals**

Animals that are used for production of xenogenic cell products are those bred in captivity under stringent conditions maintaining health specifications. They are bred under pathogen free conditions called Specific Pathogen Free (SPF) conditions. These animals are not given any antibiotics or vaccines as trace residues of these may cause problems in the human recipient. Under certain circumstances if vaccines are given, records of the same are to be maintained. When cells, tissues or organs are harvested from these source animals, a complete histological and pathological test is performed to ensure that the sample is free of any known pathogens as far as possible. An aliquot of these samples are archived for future reference. Therapy can also be done by cells/ tissues of genetically modified animals or by cells that have been modified after extraction under laboratory conditions (Wright 2005). Such modifications are done by incorporation of the required genes into the genetic make-up of the acquired cell culture. Genetic modification also helps to alter the antigenic properties of the xenogenic cell product which will help to administer the product without immune suppression of the patient and with minimum chances of the rejection of the infused cells. Specific pathogen free conditions that are maintained in the breeding of the animals are recorded systematically.

Records for the following activities are to be maintained:

- Containment and isolation conditions of animals
- Water used for drinking and cleaning
- Feed given along with feeding techniques used
- Bedding
- All movements by the animal from the point of entry to exit in the facility
- Interactions of the animal with others in the herd or with any other species
- Health checkups, medication or vaccines, if given
- Microbiological testing
- Tests for infection by other parasites
- Disposal of animal waste products
- Disposal of dead animal

Sheep (bovine) or cow (ovine) tissue or organs are generally used. Sheep are free of cancer, AIDS with best immune response. These cells may be taken from the brain, pituitary gland, thyroid gland, thymus gland, liver, kidney, pancreas, spleen, heart, ovaries, testicles, or even from whole embryos.

**Required facilitates for animal breeding include:**

- Certain strict conditions are to be maintained in the breeding of source animals:
- Separate containments for all animals ensuring minimum interactions
- All materials that come in contact with the animals must be sterilised
- Water and feed provided to the animals must be of approved quality
- The environment within the containments are highly controlled with the use of bio filters like HEPA filters that ensure microbe-free air the animals so that there is no risk of infection
- Personnel handling the animals also must follow required conditions while interacting with the animals
- There should be facilities easily available for testing of the animals for any infection by bacteria, virus or parasite
- Aliquot samples of all extracted cell products from all animals must be archived for a long period

Cells that are isolated from the fresh tissues of the animals are further processed in such a way that the cells of choice are isolated with no contamination by cells of other types. The cell cultures are monitored for their function, integrity, viability, microbiological limits, purity, and cell longevity.

**Manufacturing of xenogenic cell products**

Xenogenic cell products used for therapy may be injected intravenously or intra arterially or surgically implanted. For injectable products, a specific number of cells from a stock culture are suspended in a medium. The medium used must be immunologically safe for the recipient. Hence human plasma or serum derived products are used. The final form for administration can be

microencapsulated in biopolymers and prepared as capsules (Jones *et al.* 2012). For surgical implants, the products may be combined with medical devices in order to make them more recipient-compliant. Other materials added like immune-modulating agents or other biological products have to be tested for their safety in the preparation by in-vitro tests (Gaskin *et al*. 2014). The shelf life of the products has to be determined by experimental stability studies. Storage conditions like temperature, freezing temperature etc have to be pre determined and specified for xenogenic products. These products are usually stored at $-70^0$C in suitable media or in paraffin blocks. After manufacturing, the cell products are tested for their biological potency by non-clinical *in vivo* as well as *in vitro* methods for various applications and findings like pharmacokinetics, immunological studies, toxicity studies, cell distribution, metabolism mechanism, carcinogenicity, genotoxicity and so on.

**Mechanism of action of the therapy**

Xenogenic cells when given as an infusion rapidly disperse in the body through the blood stream. They retain their viability and hence show the desired pharmacological effect. As there is cell specificity in these products, they go to the tissue or organ that they have targeted towards. For example, liver cells go to liver, kidney cells to kidney. Since embryonic cells of sheep or cows have undeveloped immunological makeup (Untitled authors 1991), they do not cause toxic immune responses in the human recipients hence, these are mostly preferred. These cells are incorporated in the recipient as per the need of the body. These incorporated cells then cause revitalization of the damaged cells of the recipient. There are gradual changes in the body after the administration of live cells. After immediate infusion of the cells, the cells are rapidly absorbed in to the blood stream. To avoid any shrinkage or bursting of the xenogenic cells in the blood, the isotonicity of the cell suspension is adjusted and the immunobiological reaction are observed over the next couple of weeks (Hunt-Burri *et al.* 2011). In some cases there may be fever and generalised weakness. Following this, the required therapeutic action is noted which leads to an overall improvement in the health and improved vitality. In case of organ targeted therapy, there is improvement in the functioning of the organ and the body recovers from the ailment.

Revitalization is believed to occur in two ways:

i. The genetic makeup of the newly incorporated cells helps revive the damaged genetic makeup of the damaged cells, thus revitalizing them. The correct genetic codes within the new xenogenic cells help to alter the damaged DNA of old cells. Once, the DNA is corrected the organ begins to function normally.
ii. The xenogenic cells supply the old cells with physiological substrates and enzymes necessary for their repair and proliferation. These substances are found in abundance in the cell suspension administered as these are fresh, young and viable cells.

**Applications**

Many new formulations of xenogenic origin are under clinical trials currently (Prakash and Soe-Lin 2004). The applications mentioned below are not currently used as pharmaceutical products. These are mostly under clinical trials to ensure their pharmacological safety.

1. **Long term induction of analgesia using bovine chromaffin cells**
   Semi permeable biopolymer encapsulated bovine adrenal chromaffin cells when implanted into rat subarachnoid space produced antinociceptive action. This action is believed to be due to production of opiod peptides i.e. Met – enkephalin and catecholamines by the transplanted cells. This action is induced upon stimulation by administration of low doses of nicotine. The transplanted cells were found to retain their viability and continue to release the above neuroactive substances for period over 3 months following transplantation. This effect has also been contradicted by certain other studies i.e. consistent results were not obtained by different independent studies.
2. **Treatment for ovarian cancer**
   Xenogenic nonimmune fibroblast cells release HStk transgene retroviruses at site of tumour which transduce toxin producing suicide gene in the proliferating tumour cells rendering them vulnerable to Ganciclovir treatment.
3. **Symptomatic treatment of Parkinson's disease**
   Encapsulated xenogenic dopaminergic tumour cells on transplantation into CNS showed attenuation of behavioural anomalies in patients of Parkinson's disease. The probable cause of this action can be the revitalization of the degenerated neurons by the rapidly proliferating tumour cells.
4. **Rapid hypoglycemic action**
   Porcine islet cells combined with fibrin as a composite transplanted into subcutaneous space of mouse has shown to control of blood glucose levels within a period of 3-4 days with sustained action. This can be used in diabetes mellitus I.
5. **Cosmeticological use**
   Capsules and serums containing animal cell proteins and enzymes are been used effectively as treatment for premature aging, wrinkles, scars and overall revitalization of skin.

Due to the risks associated and cases where use of xenogenic therapy endangered the lives of patients, the US FDA banned the use of all xenogenic products in the United States of America in 1985. However, this therapy is widely used by physicians across Europe especially in Britain, Germany, Switzerland, etc. European Medicines Agency has published guidelines on Xenogenic cell-based medicinal products (EMEA, 2009). The guideline addresses the scientific requirements for xenogeneic cell-based medicinal products for human use. The guideline is intended for products entering the marketing authorisation procedure. However, the principles laid down in the guideline are to be considered by applicants entering into clinical trials.

**CONCLUSION**

Though xenogeneic cellular therapies offer advantages over other cellular therapies, they possess a number of potential safety issues that need to be addressed to ensure safe development. A growing body of work now exists on the non-clinical testing strategies for xenogeneic products, and these studies have enabled the safe

progression of early products from animal models into clinical studies where they are showing promise in the treatment of various diseases. As the technology and understanding of how to mitigate risks develops, this form of therapy will definitely prove to be miraculous treatment in years to come and it seems likely that other products will follow these first line products into clinical trials. Concisely, xenogenic cell therapy appears to be a growing industry in the field of medicine especially as it gives a holistic cure with long lasting effects.

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