



## REGENERATIVE MEDICINE-A FUTURE MEDICINE

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### ABSTRACT

Regenerative Medicine is the process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects. Regenerative medicine also empowers scientists to grow tissues and organs in the laboratory and safely implant them when the body cannot heal itself. Importantly, regenerative medicine has the potential to solve the problem of the shortage of organs available for donation compared to the number of patients that require life-saving organ transplantation, as well as solve the problem of organ transplant rejection, since the organ's cells will match that of the patient. It refers to a group of biomedical approaches to clinical therapies that may involve the use of stem cells. Examples include; the injection of stem cells or progenitor cells (cell therapies); another the induction of regeneration by biologically active molecules; and a third is transplantation of *in vitro* grown organs and tissues (Tissue engineering).

### KEYWORDS

Future medicine, Regenerative medicine, Stem cells, Cellular therapy, Tissue engineering

### INTRODUCTION

“Regenerative Medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging.” Importantly, regenerative medicine has the potential to solve the problem of the shortage of organs available for donation compared to the number of patients that require life-saving organ transplantation.

Clinical procedures that aim to repair damaged tissue or organs, most often by using tissue engineered scaffolds and stem cells to replace cells and tissues damaged by aging and by disease. It includes tissue engineering, genetic engineering and molecular activators<sup>[1]</sup>. Regenerative Medicine is working to improve the quality of life for patients all over the world. Scientists work with this powerful technology to create new body parts from a patient's own cells and tissues. The goal of regenerative medicine is to



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one day be capable of maintaining the body in such a way there will be no need to replace whole organs.

### ***HISTORY***

This report features chapters written by experts in several areas of enormous potential for regenerative medicine. Drs. Junying Yu and James A. Thomson explain the basic features of embryonic stem cells, how they are being used in research, and how they may lead to human therapies. Drs. Jos Domen, Amy Wagers, and Irving Weissman describe the historical origins of blood-forming stem cell research, basic features of these adult stem cells, progress on using these cells for human therapies, and future possibilities. Dr. David Panchision explores ways to use cell-based therapies to restore lost function in the human nervous system. Dr. Thomas Zwaka explains how stem cells may be used for gene therapy, and Dr. Mark L. Rohrbach explains the current state of intellectual property issues associated with research using human embryonic stem cells <sup>[2]</sup>.

### ***FIELDS OF REGENERATIVE MEDICINE***

#### ***1. Medical devices and artificial organs:***

According to the FDA a medical device is defined, in part, as any health care product that does not achieve its primary intended purposes by chemical action or by being metabolized. Medical devices include, among other things, surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, intraocular lenses, and orthopedic pins. Medical devices also include diagnostic aids such as reagents and test kits

for in vitro diagnosis (IVD) of disease and other medical

#### ***2. Tissue engineering and biomaterials:***

The definition of tissue engineering is attributed to Drs. Langer and Vacanti who stated it to be "an interdisciplinary field that applies the principles of engineering and life sciences toward the development of biological substitutes that restore, maintain, or improve tissue function or a whole organ".

#### ***3. Cellular Therapies:***

Stem cell research offers unprecedented opportunities for developing new medical therapies for debilitating diseases and a new way to explore fundamental questions of biology. Stem cells are unspecialized cells that can self-renew indefinitely and also differentiate into more mature cells with specialized functions. Cellular therapies are used mostly as regenerative medicine.

#### ***4. Clinical Translation:***

Clinical translation puts promising therapies into active trials. The Clinical Translation Team provides a seamless transition from bench top to bedside with the goal of providing excellence in clinical care for patients with end-stage, end-organ disease through mechanisms of repair, recovery and replacement <sup>[3]</sup>.

### ***STEM CELL TREATMENTS***

Stem cell treatments are a type of cell therapy that introduces new cells into damaged tissue in order to treat a disease or injury. Many medical researchers believe that stem cell treatments have the potential to change the face of human disease and alleviate suffering. The ability of stem cells to self-renew and



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give rise to subsequent generations that can replace diseased and damaged tissues in the body, without the risk of rejection and side effects.

Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can be induced to become tissue- or organ-specific cells with special functions.

### **Bio artificial Liver:**

Currently in a Phase I Trial, the bio artificial liver support system employs a hollow-fiber bioreactor cartridge that is loaded with hepatocytes. In one version of the reactor the hollow fibers act as an immunoisolation barrier, serving to prevent direct contact of patient blood flowing on the interior of the fibers with the hepatocytes on the exterior of the fibers<sup>[4]</sup>.

### **Heart damage:**

Several clinical trials targeting heart disease have shown that adult stem cell therapy is safe and effective, and is equally efficient in old as well as recent infarcts.

### **Generation of heart muscle cells<sup>[5]</sup>:**

- Stimulation of growth of new blood vessels that repopulate the heart tissue

- Secretion of growth factors, rather than actually incorporating into the heart
- Assistance via some other mechanism

### **Artificial Blood:**

Currently research is being conducted to examine blood soluble drag-reducing polymers and their potential clinical applications. Such polymers may be used in substances such as artificial blood/transfusion fluids for critical care medicine, surgery and organ preservation, blood additive for improvement of microcirculation impaired by diabetes, atherosclerosis and sickle cell disease.

### **Haematopoiesis (Blood cell formation):**

Diseases of haematopoietic cells are called hematopathology. The specificity of one's immune cell repertoire, which allows it to recognize foreign antigen, causes further challenges in the treatment of immune disease. Identical matches between donor and recipient must be made for successful transplantation treatments, while matches are uncommon, even between first-degree relatives. Research using both hematopoietic adult stem cells and embryonic stem cells has contributed great insight into possible mechanisms and methods of treatment for many of these ailments<sup>[6]</sup>.

### **Bio hybrid Lung:**

This bio hybrid oxygenator has the potential to provide functionality and durability unachievable with its fully synthetic predecessors. Endothelial cells and micro fabrication technology as used in the semiconductor industry to develop artificial alveolar-



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capillary modules, which may become the building blocks of bio hybrid artificial lungs <sup>[7]</sup>.

### *Brain damage:*

Healthy adult brains contain neural stem cells, these divide and act to maintain general stem cell numbers or become progenitor cells. Stem cells may also be used to treat brain degeneration, such as in Parkinson's and Alzheimer's disease.

### *Spinal cord injury:*

Multipotent adult stem cells from an umbilical cord blood can be transplanted to a patient suffering from a spinal cord injury without difficulty. Also researchers injected human embryonic stem cells, human blastocyst stem cells into neural stem cells, then into the beginnings of motor neurons, and finally into spinal motor neuron cells were used <sup>[8]</sup>.

### *Diabetes:*

Diabetes patients lose the function of their insulin-producing beta cells of their pancreas. Human embryonic stem cells may be grown in cell culture and stimulated to form insulin-producing cells that can be transplanted into the patient <sup>[9]</sup>.

### *Cancer:*

Bone marrow, and more recently, umbilical cord blood stem cells have been used to treat cancer patients with conditions such as leukemia and lymphoma. During chemotherapy, most growing cells are killed by the cytotoxic agents. These agents

not only kill the leukemia or neoplastic cells, but also the haematopoietic stem cells within the bone marrow <sup>[10]</sup>.

### *Deafness:*

There has been success in re-growing cochlea hair cells with the use of stem cells <sup>[11]</sup>.

### *Blindness and vision impairment*

Researchers have successfully transplanted retinal stem cells into damaged eyes to restore vision. Using embryonic stem cells, scientists are able to grow a thin sheet of totipotent stem cells in the laboratory. When these sheets are transplanted over the damaged retina, the stem cells stimulate renewed repair, eventually restoring vision <sup>[12]</sup>.

### *Amyotrophic lateral sclerosis*

Stem cells have cured rats with an Amyotrophic lateral sclerosis-like disease. The rats were injected with a virus to kill the spinal cord motor nerves related to leg movement, succeeded by injections of stem cells into their spinal cords. These migrated (passed through many layers of tissues) to the sites of injury where they were able to regenerate the dead nerve cells restoring the rats which were once again able to walk <sup>[13]</sup>.

### *Baldness:*

Hair follicles also contain stem cells, and researchers predict research on these follicle stem cells may lead to successes in treating baldness through "hair



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multiplication", also known as "hair cloning". This treatment is expected to work through taking stem cells from existing follicles, multiplying them in cultures, and implanting the new follicles into the scalp<sup>[14]</sup>.

### *Missing teeth:*

Stem cells taken from the patient could be coaxed in the lab into turning into a tooth bud which, when implanted in the gums, will give rise to a new tooth, which would be expected to take two months to grow. It will fuse with the jawbone and release chemicals that encourage nerves and blood vessels to connect with it. The process is similar to what happens when humans grow their original adult teeth<sup>[15]</sup>.

### *Graft vs. host disease and Crohn's disease:*

Prochymal, derived from adult bone marrow. The target disorders of this therapeutic are graft-versus-host disease and Crohn's disease.

### *Wound healing:*

Stem cells are used to stimulate the growth of human tissues. In an adult, wounded tissue is most often replaced by scar tissue, which is characterized in the skin by disorganized collagen structure, loss of hair follicles and irregular vascular structure. In the case of wounded fetal tissue, however, wounded tissue is replaced with normal tissue through the activity of stem cells. A possible method for tissue regeneration in adults is to place adult stem cell "seeds" inside a tissue bed "soil" in a wound bed and allow the stem

cells to stimulate differentiation in the tissue bed cells<sup>[16]</sup>.

### *Neural and behavioral birth defects:*

This was done by direct neural stem cell transplantation into the brains of the offspring. The scientists found that before they die the neural stem cells succeed in inducing the host brain to produce large numbers of stem cells which repair the damage. Researchers also developed the methods to take cells from the patient's own body, turn them into stem cells, and then transplant them back into the patient's blood via the blood stream<sup>[17]</sup>.

### *Orthopedics:*

Clinical case reports in the treatment of orthopedic conditions have been reported. Centeno et al. have published MRI evidence of increased cartilage and meniscus volume in individual human subjects, though it is unclear how the MRI results compare to clinical response<sup>[18]</sup>.

### **Stem cell use in animals:**

Veterinary applications Veterinary research can contribute to human medicine:

Research currently conducted on horses, dogs, and cats can benefit the development of stem-cell treatments in veterinary medicine, but may also contribute to developing those in human medicine for a range of injuries and diseases such as myocardial infarction, stroke, tendon and ligament damage, osteoarthritis, osteochondrosis and muscular dystrophy. Companion animals may be superior



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models than typical mouse models for human disease. <sup>[19]</sup>

Veterinary research has developed regenerative treatment models, particularly involving mesenchymal stem cells:

Veterinary applications of stem cell therapy as a means of regenerating new tissue as an alternative to scar (less functional tissue) formation have developed from research that has been conducted since 1998 using adult-derived mesenchymal stem cells to treat animals with injuries or defects affecting bone, cartilage, ligaments and/or tendons. Because mesenchymal stem cells can differentiate into the cells that make up bone, cartilage, tendons, and ligaments. (as well as muscle, fat, and possibly other tissues) The two main sources of mesenchymal stem cells used are adipose tissue or bone marrow <sup>[20]</sup>.

There is scientific evidence supporting that stem cells can improve healing by five main means:

1) providing an anti-inflammatory effect, 2) homing to damaged tissues and recruiting other cells, such as endothelial progenitor cells, that are necessary for tissue growth, 3) supporting tissue remodeling over scar formation, 4) inhibiting apoptosis, and 5) differentiating into bone, cartilage, tendon, and ligament tissue <sup>[21]</sup>.

## PRESERVATION OF PRTABLE ORGANS

Using current technology, prior to transplant organs are packed in coolers filled with ice and special solutions and can only be preserved safely for limited periods of time. However, POPS preserves the heart and other organs by mimicking the actions and

environmental conditions of the internal body, such as perfusing it with blood and a proprietary maintenance solution <sup>[22]</sup>.

## FEATURES OF REGENERATIVE MEDICINE

Past:

- Successful transplantation of bone, soft tissue, and corneas occurred early in the 20<sup>th</sup> century.
- Real progress in organ transplantation began in 1954 with the first successful kidney transplant.
- During the 1960s, successful transplantation of pancreas/kidney, liver, isolated pancreas and heart occurred.
- Transplant surgery success continued into the 1980s with successful heart-lung, single lung, double lung, living-donor liver, and living-donor lung transplants <sup>[23] [24]</sup>.

Today:

- The rapid development of transplant medicine along with the aging of the baby boomer generation has caused an increased demand for tissues and organs far exceeding the available donor organs.
- Approximately 500,000 Americans benefit from a transplant each year.
- As of May 2006, there were over 90,000 people on the waiting list for donor organs. Many of these individuals will die before a suitable organ can be found.





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- Tissue-engineered skin has been used for skin replacement, temporary wound cover for burns, and treatment for diabetic leg and foot ulcers.
- Tissue-engineered bladder, derived from a patient's own cells, can be grown outside the body and successfully transplanted.
- A material developed from the small intestines of pigs is increasingly used by surgeons to restore damaged tissues and support the body's own healing processes. Physicians rely on the material, called small intestinal submucosa (SIS), for everything from reconstructing ligaments to treating incontinence. Today, SIS is most commonly used to help the body close hard-to-heal wounds such as second-degree burns, chronic pressure ulcers, diabetic skin ulcers, and deep skin lacerations.
- Tissue-engineered products are used to induce bone and connective tissue growth, guide long bone regeneration, and replace damaged knee cartilage.
- Tissue-engineered vascular grafts for heart bypass surgery and cardiovascular disease treatment are at the pre-clinical trial stage<sup>[25] [26]</sup>.

## CONCLUSION

By providing tissues and organs "on demand," regenerative medicine will improve the quality of life for individuals and reduce healthcare costs. Imagine a world where there is no donor organ shortage, where victims of spinal cord injuries can walk, where weakened hearts are replaced. This is the long-term promise of regenerative medicine, a rapidly developing field with the potential to transform the treatment of

human disease through the development of innovative new therapies that offer a faster, more complete recovery with significantly fewer side effects or risk of complications.

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## REFERENCES

1. Weissman IL. Stem cells: units of development, units of regeneration and units in evolution, *Cell*, 100(1):157-168 (2000).
2. Gurtner GC, Callaghan MJ and Longaker MT. Progress and Potential for Regenerative Medicine, *Annu. Rev. Med*, 58: 299-312 (2007).
3. Singec I, Jandial R, Crain A, Nikkhah G and Snyder EY. The leading edge of stem cell therapeutics, *Annu Rev Med* ,58: 313-328 (2007).
4. Alison MR, Islam S and Lim S. Stem cells in liver regeneration, fibrosis and cancer: the good, the bad and the ugly, *J Pathol* , 217(2): 282-98 (2009).
5. Strauer BE, Schannwell CM, Brehm M. Therapeutic potentials of stem cells in cardiac diseases, *Minerva Cardioangiol*, 57 (2): 249-67 (2009).
6. Giarratana MC, Kobari L, Lapillonne H, *et al*. Ex vivo generation of fully mature human red



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- blood cells from hematopoietic stem cells, *Nat Biotechnol*, 23 (1): 69–74 (2005).
7. Sueblinvong V and Weiss DJ. Cell therapy approaches for lung diseases: current status, *Curr Opin Pharmacol*, 9 (3): 268-273 (2009).
  8. Chen J, Wang L, Zhang Z, et al. Therapeutic benefit of intravenous administration of bone marrow stromal cells after cerebral ischemia in rats, *Stroke*, 32: 1005-1011 (2001).
  9. McCall MD, Toso C, Baetge EE and Shapiro AM. Are stem cells a cure for diabetes? *Clin Sci*, 118 (2): 87-97 (2009).
  10. Wang X, Julio M, Economides KD, Walker D, et al. A luminal epithelial stem cell that is a cell of origin for prostate cancer, *Nature*, 461: 495-500 (2009).
  11. Boer JC, Carney KE, and Van der Zee S. Differentiation of mouse embryonic stem cells into spiral ganglion neurons: a therapeutic approach to deafness, *J Neuroscience*, 29 (18): 5711-5712 (2009).
  12. Pribila JT, Ronan SM and Trobe JD. Multiple intracranial meningiomas causing papilledema and visual loss in a patient with nevoid Basal cell carcinoma syndrome, *J Neuroophthalmol*, 28 (1): 41-46 (2008).
  13. Schippling S, Heesen C, Zander A and Martin R. Stem cell transplantation in multiple sclerosis, *J Neurology*, 255: 43-7 (2008).
  14. Busuttil DP. Alopecia areata universalis and acute lymphoblastic leukemia, *Am J Hematol*, 82 (9): 860 (2007).
  15. Yen AH and Sharpe PT. Stem cells and tooth tissue engineering *Cell Tissue Res*, 331 (1): 359–72 (2008).
  16. Jettanacheawchankit S, Sasithanasate S, Sangvanich P, et al. Acemannan stimulates gingival fibroblast proliferation; expressions of keratinocyte growth factor-1, vascular endothelial growth factor, and type I collagen; and wound healing, *J Pharmacol Sci*, 109 (4): 525-531 (2009).
  17. Nathan S, Das De S, Thambyah A, et al. Cell-based therapy in the repair of osteochondral defects: A novel use for adipose tissue, *Tissue Eng*, 9 (4): 733-744 (2003).
  18. Awad HA, Butler DL, Boivin GP, et al. Autologous mesenchymal stem cell-mediated repair of tendon, *Tissue Eng*, 5 (3): 267 (1999).
  19. Taylor SE, Smith RK, and Clegg PD. Mesenchymal stem cell therapy in equine musculoskeletal disease: scientific fact or clinical fiction? *Equine Veterinary Journal*, 39 (2): 172-180 (2007).
  20. Sampaolesi M, et al. Mesoangioblast stem cells ameliorate muscle function in dystrophic dogs, *Nature*, 444: 574-579 (2006).
  21. Richardson LE, et al. Stem cells in veterinary medicine-attempts at regenerating equine tendon after injury, *Trends Biotechnol*, 25 (9): 409-416 (2008).
  22. Yamada Y, et al. Autogenous injectable bone for regeneration with mesenchymal stem cells and platelet-rich plasma: tissue engineered bone regeneration, *Tissue Engineering*, 10 (5-6): 955-964 (2004).
  23. Csaki C, et al. Chondrogenesis, osteogenesis and adipogenesis of canine mesenchymal stem cells: a biochemical, morphological and ultrastructural study, *Histochemistry & Cell Biology*, 128 (6): 507-520 (2007).
  24. Oedayrajsingh M, Breuls R, Schouten T, et al. Phenotypical and functional characterization of





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- freshly isolated adipose tissue-derived stem cells, Stem Cells Dev, 16: 91-104 (2007).
25. Fraser JK, Wulur I, Alfonso Z, et al. Fat Tissue: an underappreciated source of stem cells for biotechnology, Trends Biotechnol, 24 (4): 150-154 (2006).