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History of Tissue Engineering and Regeneration with Modern Day Applications in Medicine

Review Article

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Abstract

Regenerative medicine is a scientific process of growing living, functional tissues to repair or replace tissue or organ function that has been depleted due to age, disease, injury, or congenital defects. Regenerative medicine can also be referred to as a group of biomedical approaches to clinical therapies that may involve the use of stem cells. This branch in medicine enables scientists to grow tissues and organs in the laboratory which could be surgically implanted into specific locations in the human body to progressively heal itself to restore depleted organs function. Regenerative medicine has the potential to solve broad ranged medical issues like shortage of organs available for donation compared with the number of patients that require them. Furthermore, it could be used in transplantation, in particular, in complex organ transplant rejection which is slowly but surely being pedestaled for the common-sense practical reason that the organ's cells must match that of the patient. Examples include injection of stem cells or progenitor cells (i.e., cell therapies); induction of regeneration by biologically active molecules (i.e., immunomodulation); and transplantation of in vitro grown organs and tissues (i.e., tissue engineering).

Abbreviations: ASC's: Adult Stem Cells, STAP cells: Stimulus-triggered Acquisition of Pluripotency Cells, iPSC's: induced Pluripotent Cells, ESC's: Embryonic Stem Cells, SCNT: Somatic Cell Nuclear Transfer, CSSC's: Corneal Stromal Stem Cells, LESC's: Limbal Epithelial Stem Cells, PSC's: Pluripotent Stem Cells, NIH: National Institutes of Health, NHGRI: National Human Genome Research Institute, NIBIB: National Institute of Biomedical Imaging & Bioengineering

Introduction

Now patients with diseased and injured organs are treated with transplanted organs when deemed appropriate. Nevertheless, there is a shortage of donor organs due to the aging population compounded by a stark rise in the number of new cases of organ failure [1]. Due to the limited number of organs, scientists are forced to rely on other innovative approaches such as the principles of cell transplantation, material science and bioengineering to construct biological silhouettes capable of replicating and restoring normal function of affected tissues [1]. Stem cell harvesting is a rapidly advancing part of regenerative medicine leading to new discoveries and novel stem cells, such as amniotic fluid and placental stem cells that can avoid the ethical dilemma associated with embryonic stem cells [1].

The processes of therapeutic cloning and creation of induced pluripotent cells (iPSC's) provides potential sources of stem cells desperately needed for cell-based tissue engineering applications. Consensus about stem cells still being in the rudimentary research phase is widely acknowledged but some tissue engineering therapies involving autologous and adult stem cells have breached numerous clinical settings. This clearly signals the promise and scope of regenerative medicine for futuristic medical and pharmaceutical therapies is humongous [1].

An Elaborate historical timeline from 600 BC to 2016 AD

Ancient practice of surgery in India, 600 BC: Ancient documented texts of surgery and anatomy in south Asia were given

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the titles of Sushruta Samhita (6th century BC) and Charaka samhita (4th century BC) with various methods to repair torn earlobes with cheek skin and reconstruction of nose from flap of forehead skin [2]. The important information mentioned in both references was sourced through animal sacrifice, improperly buried human bodies and direct patient examination as depicted in figure 1 [3].

Freshwater Hydra regeneration discovered, 1740: A research uncovered how hydra regrows lost heads, its ability to regenerate and constantly replace damaged body parts, replace all the cells every 20 days and 27,000 genes that play a critical role in these transformative biological processes [4].

Demonstration of artificial embryo twinning in Sea urchins, 1885: The first ever significant demonstration of cloning was performed by a German philosopher and biologist Hans Dreish, by shaking a 2 celled sea urchin embryo to split the cells and proved that each individual cell grew into a healthy adult sea urchin. Therefore, clearly determines that each cell has its set of genetic information [5].

Starfish regeneration, 1901: Regeneration (originally published in 1901) was a path breaking book developed by putting together a series of lectures delivered by Thomas H. Morgan on embryology and a diversity of organisms that had the innate ability to regenerate along with experimental evidence (e.g. starfish diagram shown below in figure 2 regenerating 4 new limbs from the tip of a severed limb). He argued that regeneration was a fundamental aspect of the growth process of an individual organism [6].

Figure 1: Sushruta is shown examining a patient's radial pulse & clinic workers are shown compounding various types of medications [3].

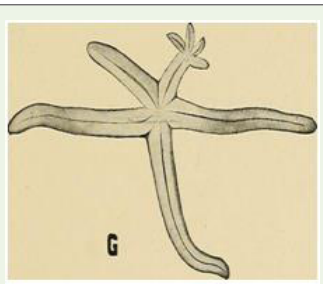

Figure 2: Starfish showed growing tiny new limbs on the tip of the severed limb itself [7].

Embryo cloning in a Vertebrate, 1902: Hans Spemann separated two salamander embryos at a very early stage and they both grew into healthy adult salamanders. This experiment also proved that if the embryo had already matured, then cloning of the same would not have been possible [8].

Frog embryonic cells grown in lab, 1907: Embryologist Ross Harrison was credited for developing the first technique of cell culture in vitro in 1907 at Yale University where small pieces of living frog embryonic tissue were isolated and successfully grown outside the body [9].

Salamander embryos developed from cell nucleus experiment, 1928: Spemann continued his lab experiment on salamanders and pushed the nucleus of a fertilized egg to one side of the cytoplasm and after four cell divisions, resulted in 16 cells. The same nucleus was allowed to slide back into the non-dividing side of the egg which resulted in 16 separate salamander embryos [10].

Successful nuclear transfer from tadpole embryo, 1952: Robert Briggs and Thomas King proved that the nucleus derived from an early embryo into a nucleus deprived frog egg resulted in a developed tadpole. This established that nuclear transfer was a viable cloning technique and reinforced that it is the nucleus that directs cell growth and also early embryonic cells are preferred for cloning [11].

Nuclear transfer from tadpole intestinal cells, 1958: John Gurdon reported growing adult South African clawed toads after transferring nuclei from tadpole intestinal epithelial cells. He also observed that the same was not possible when intestinal cells were isolated from adult frogs of the same species [12].

Cloning via somatic cell nuclear transfer succeeds, 1962: A scientifically developed method termed as somatic cell nuclear transfer (SCNT) was found to confer totipotency; defined as the ability of a cell to give rise to all cell types of an entire organism. John Gurdon demonstrated the same by isolating differentiated frog somatic cells [13].

Self-renewing stem cells in mouse bone marrow, 1963: Toronto researcher's duo Jim Till and Ernest McCulloch were the first to observe hematopoietic stem cells in mouse bone marrow and proved their existence via a series of lab experiments [14]. This research laid the foundation for further studies to isolate, analyze characteristics and develop stem cell applications in medicine [15].

Nuclear transfer rabbit embryo successful, 1975: First scientist to report developing a rabbit embryo in vitro was Derek Bromhall. This was achieved by transferring rabbit nuclei into nucleus free rabbit eggs in spite of the smaller size of mammalian somatic cells and challenges that come with microscopic level lab experiments [11].

Lab grown embryonic mouse stem cells & lab skin heals wounds, 1981: Gail Martin grew embryonic stem cells in the lab medium by isolating single cells of mice. These were later harvested to conclusively demonstrate the pluripotency by observation of these very same cell lines that grew into a wide variety of cell types [16].

In a separate research study conducted in the same year, cells isolated from skin biopsies stem cells were derived and clinically applied to treat severe wounds (Figure 3) [18].

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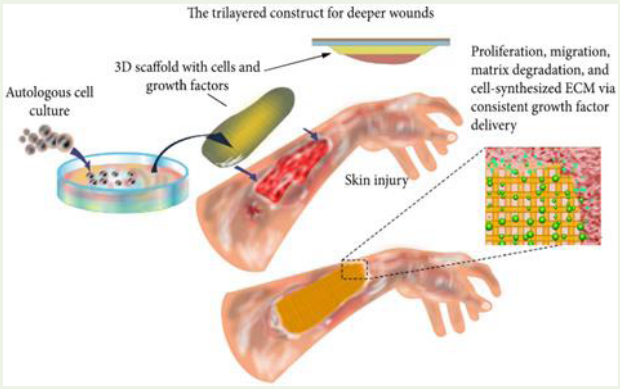

Figure 3: Several stages of skin tissue engineering using biomaterials and stem cells [17].

Nuclear transfer creation of first mammal, 1984: Research work by Steen Willadsen resulted in the very first normal cloned lambs being born [19]. This was achieved by nuclear transfer from an eight celled lamb embryo that was the cornerstone for further research due to the possibility of clones from single embryos of other farm animals. The initial experiments in mammals that inspired sheep cloning were earlier conducted by Solter and McGrath by applying nuclear transfer methods to mouse embryos [20].

Nuclear transfer from an embryonic cell to produce calves, 1987: The first team of dairy scientists to achieve success by nuclear cell transfer into a bovine embryo was Prather et al [21]. Although only 2 healthy live calves were born out of 19 bovine embryos that were being studied, the results encouraged further investigation of nuclear transfer transplants.

Nuclear transfer done from lab cultured sheep cells, 1996: Wilmut and Campbell based in scotland, totally avoided donor nuclei from cells of early embryos which was the standard norm. They demonstrated that nuclei from cells that had been isolated from an adult sheep, transferred and multiplied in a petri dish in the lab implanted into sheep egg cells resulted in a normal lamb being born [22].

Somatic cell nuclear transfer mammal created, 1996: Sheep were the first large animal model in nuclear transfer research projects and the first mammal to be ever cloned in 1996 by Wilmut and Campbell. They transferred the nucleus from an adult sheep udder cell and implanted them into early embryos. Of the 29 early embryos which developed only one pregnancy went to full term [20].

First primate created from embryonic nuclear transfer, 1997: Meng et al transferred early-stage embryonic cells into monkey egg cells and the resulting embryos were then implanted into surrogate mothers out of which 2 rhesus monkeys were born [23]. This conclusively proved that primates which are human species's closest relatives could be cloned.

First transgenic mammal created from genetic engineered lab cells, 1997: Schnieke et al introduced the human factor IX gene, a plasma protein with a role in blood clotting in humans into the genome of sheep skin cells grown in a petri dish, to create transgenic sheep. The process involved donor DNA from the cultured transgenic cells. Of the 7 lambs that were born only one lamb produced factor IX protein in her milk. This helped to prove that mammals could be engineered to make therapeutic and other useful proteins [24].

Human embryonic stem cells isolated, and lab organs approved, 1998: H1, H7, H9, H13, and H14 were the very first human embryonic stem cell lines that were isolated in the year 1998 in a confidential lab research facilities due to lack of federal funds and lack of widespread general consensus (Figure 4) [25].

Somatic cell nuclear transfer cloning of mammals, 1999: The several kinds of somatic cells employed for these highly successful and result oriented livestock cloning were: mammary epithelial cells, ovarian cumulus cells, skin fibroblast cells, various internal organ cells from liver, testis, skin, ear, macrophages, leukocytes, cumulus and oviductal cells. Statistical analysis of the data revealed that cumulus and oviduct epithelial cells were the most suited for creating healthy and viable cattle [27].

Endangered species cloned via somatic cell nuclear transfer, 2001: One of the unexpected beneficial applications of somatic cell transfer was revival of endangered species through inter-species cloning and examining the potential of the same for reproductive and therapeutic cloning. Examples of such include gaur, mouflon, zebu, gray wolf, bactrian camel etc (Table 1) [13]. In the same year, i.e. 2001, the European Union (EU) eased many of the restrictions on embryonic stem cell research. However, the government funding was still not approved yet [2,28].

Lab grown bladders for kids & embryonic cells cultured, 2006: The very first human recipients of lab engineered bladders were reported by Wake Forest researchers in a report that was published in Lancet Journal together with the long-term success in pediatric

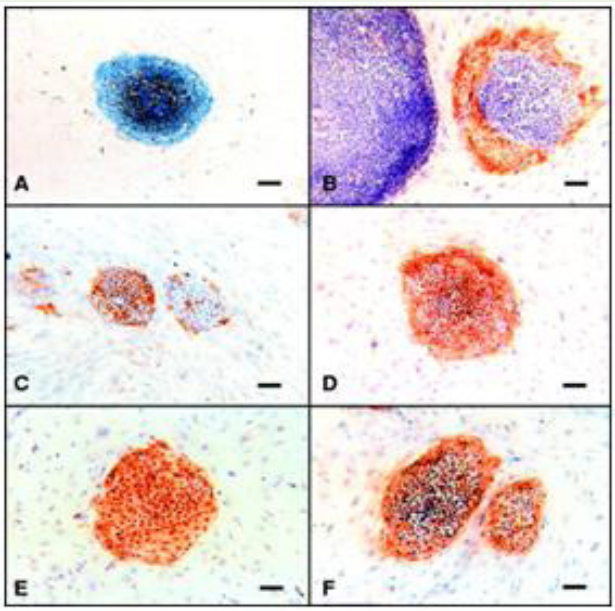

Figure 4: Undifferentiated proliferation of embryonic stem cell lines from blastocysts in vitro for 4 to 5 months [26].

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Table 1: List of endangered species revived via mammalian somatic nuclear cell transfer cloning [29].

Interspecies cloning	2000	Gaur (*Bos gaur*)
	2001	Mouflon (*Ovis orientalis musimon*)
	2001	Zebu (*Bos indicus*)
	2004	African Wildcat (*Felis lybica*)
	2007	Gray wolf (*Canis lupes*)
	2009	Pyrenean ibex (*Capra pyrenaica pyrenaica*)
	2013	Coyote (*Canis lactrans*)
	2017	Bactrian camel (*Camelus bactrianus*)

and adolescent patients, between the ages of 4 and 19, who received bladders grown from their own cells (Figure 5). Therefore, avoiding the risks of rejection and establishing tissue engineering as a viable tool to solve medical problems of complex magnitude [30]. Furthermore, research data demonstrated in the same year that embryonic stem cells can be directly generated from mouse adult cells by inducing few but specific cell culture transcription factors [31].

Rhesus monkey embryonic stem cells created, 2007: Derivation of embryonic stem cells genetically identical to a primate by somatic cell nuclear transfer was achieved and results represented successful reprogramming of adult somatic cells into embryonic stem cells. This proved that therapeutic cloning in primates is practical, and it also holds enormous potential to cure several degenerative diseases by nullifying concerns about rejection by the host immune system [33].

Human embryonic stem cell lines approved, 2009: Federal funding and grants were first approved for research on human embryonic stem cells in 2009. After several years of debate and legal challenges, a new era emerged (Figure 6) with the potential for breakthrough in health and medicine [34]. 2009 was also the year when for the first time an extinct goat species of Spain was cloned from cryopreserved skin biopsy samples that were collected in 1999 (Figure 7) [35].

Breakthrough cures for spinal cord injury and cornea repair, 2010: Novel biomaterials were designed to develop hydrogel scaffolds for clinical cure of the most debilitating and complex injuries of the spinal cord. These scaffolds could stimulate cellular regeneration and functional recovery and involved the combinatorial approach of integrating biomaterial scaffolds with cell transplantation and molecule delivery [38]. The unique challenge of corneal tissue injury was delved deeply after the discovery of the two types of stem cells that were given the names (Figure 8): CSSC's & LESC's; the full versions being corneal stromal stem cells and limbal epithelial stem cells respectively; and both types of stem cells were found to have huge implications to invent clinical cures for Cornea related health conditions [39].

Human stem cell lines created by virtue of therapeutic cloning, 2013: After many years of trying, researchers at Oregon health sciences university harvested skin cells from a baby with a congenital health condition. They succeeded in fusing them with donated human eggs to create human embryos that were genetically identical to the donor baby and then efficiently derived stem cells from the embryos [41]. Image below shows the somatic cell nuclear transfer to obtain embryonic stem cells with the potential to be grown into pancreas (Figure 9), heart (Figure 10), liver, brain and red blood cells in vitro.

Figure 5: Lab grown bladder shaped biodegradable mold [32].

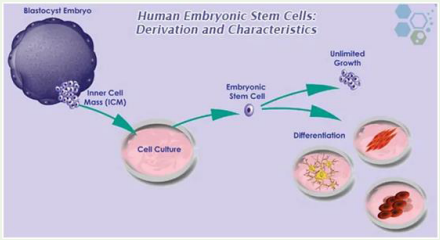

Figure 6: Embryonic stem cells isolated from the inner cell mass of a blastocyst at the earliest stage [36].

Figure 7: Extinct Spanish mountain goat species called the bucardo cloned via cryopreserved skin biopsy sample [37].

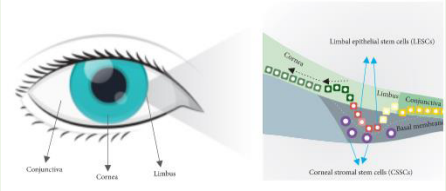

Figure 8: Localization and markers of corneal stromal & limbal epithelial stem cells for regenerative therapy [40].

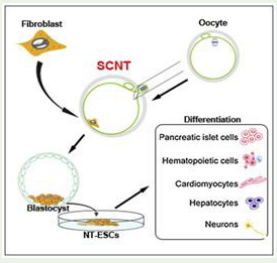

Figure 9: Somatic cell nuclear transfer to obtain embryonic stem cells that can be grown into different organs [42].

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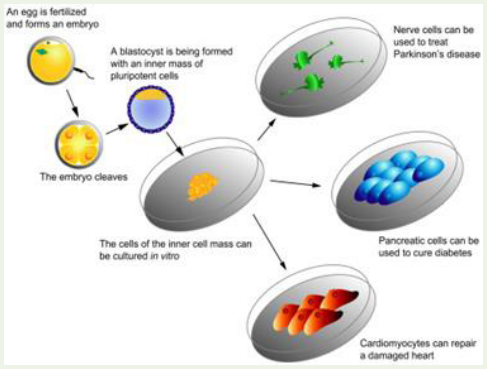

Figure 10: Potential applications of embryonic stem cells to cure chronic medical conditions illustrated [43].

Patient specific stem cells created by STAP technique, 2014: A unique and simple cellular reprogramming method was invented by Obokata et.al. Termed as stimulus-triggered acquisition of pluripotency (STAP), which eliminated the need for both nuclear transfer and transcription factors in order to grow stem cell lines in the lab [44]. The discovery was that a low ph. medium triggers somatic cells to give rise to STAP cells by reprogramming rather than selection. This also proved that STAP cells efficiently contribute to chimeric embryos and off springs. Further derivation of robustly expandable pluripotent cell lines was also demonstrated [45].

Stem cell therapy to cure severely damaged cornea, 2015: Promises and ambitions to repair severely and deeply hurt corneal tissue due to physical or chemical burns were fueled when EU approved a limbal stem cell treatment developed by researchers at Modena University in Italy. The outer layers of the cornea deteriorate causing limbal stem cell deficiency [46]. This novel therapy heals by transplanting corneal sheets which could be grown from the limbal stem cells derived from the undamaged part of the limbus. This was found to be good enough to restore the sight to both the eyes and resulted from over 2 decades of basic, pre-clinical and clinical research studies [47].

Healthy and fertile mice created from mouse skin cells and surrogacy, 2016: A team of stem cell biologists at Kyushu University were able to generate healthy mouse pups by maturing skin-cell-derived eggs inside the mouse mother where the maturation took place in a lab dish [48]. The initial hypothesis was published in 2011 [49], the actual lab experiments took 4 years and resulted in the birth of 6 baby mice that were fertile, healthy and had normal lifespans, despite only 1 % of the implanted cells being live births (Figure 11). The research clearly suggests that women who lack eggs or for men without sperm, can get replacement cells made from their own skin therefore extending human fertility by decades, and may also help preserve endangered animal species and even allow same-sex couples to have their own genetic children [50].

Regenerative Medicine

Regenerative medicine can be viewed as a promising interdisciplinary field of research and clinical applications that focus on the repair, replacement, regeneration of cells, tissues, organs to restore impaired function resulting from causes such as congenital defects, disease, injury and aging [52]. Clinical procedures aimed to repair damaged tissue or organs, by clinically engineered tissue scaffolds, stem cells to replace cells & tissues damaged by aging/disease via tissue engineering, genetic engineering and molecular activators; are considered techniques to make new body parts from a patient's own cells and tissues (Figure 12). This therefore reduces the goal of treating depleted organs in the human body to restore normal function in such a way that there is no need to replace whole organs [53].

Regenerative medicine integrates the process of self-healing where the human body uses its own repair mechanisms, or sometimes with help foreign biological material to recreate cells, rebuild tissues and organs (Figure 12). Tissue engineering and regenerative medicine are considered synonymous as scientists and clinicians utilize this approach with the hope to focus on cures for complex chronic diseases [54]. Regenerative medicine encompasses three domains (i.e., tissue engineering, stem cells and cloning).

Tissue Engineering: Tissue engineering is a field which progressed from biomaterials development and combines scaffolds, cells, biologically active molecules into functional tissues. The holistic goal is to assemble functional constructs that restore, maintain, improve damaged tissues or whole organs like artificial skin or lab engineered cartilage that have been approved by the Food and Drug Administration (FDA) with limited clinical applications [45]. Tissue engineering's principles can be characterized into cell transplantation,

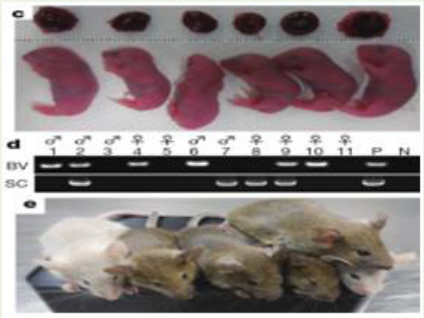

Figure 11: 4 year experiment on mouse skin cells results in 6 healthy & fertile mice with a full life span [51].

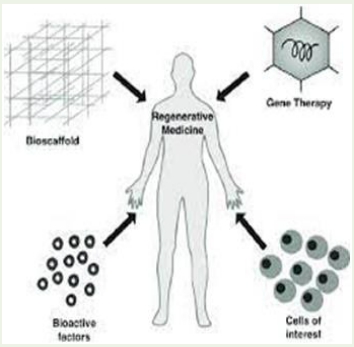

Figure 12: Various inputs from interdisciplinary fields needed for designing personalized medicine [55].

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science of biomaterials or engineering biological substitutes [56]. Tissue engineering's clinical application strategies can be classified as acellular scaffolds (i.e., highly dependent on the body's natural ability usually prepared via 3d printing artificial scaffolds or by removing cellular components from tissues) or scaffolds seeded with stem cells i.e., deployed stand-alone via direct injection or clubbed with carriers such as hydrogels [56]. Tissue engineering is also considered an interdisciplinary field that brings together bioengineering, material science and life sciences to accelerate healing processes through the assembly of biological substitutes [57]. These biological mockers are often three dimensional constructs with the function, structure and mechanics better than the tissue that is to be replaced and such 3-D constructs demand wise selection of four key materials i.e., scaffold, growth factors, extracellular matrix and cells [57].

Stem cells in tissue engineering: Native cells can be described as a variety of primary human cells (e.g., bladder urothelial cells). In patients with extensive end-stage organ disease, tissue biopsies may not yield enough normal cells required for growing in vitro cell lines. In other instances primary autologous human cells cannot expand or grow from a particular organ (e.g., pancreas). This is where stem cells come to the rescue as viable alternative sources from which the needed tissues can be grown in the lab medium and harvested [56]. These procedures involve growing organs in the lab medium through selection and seeding of the right kind of stem cells that are skillfully placed onto a scaffold and allowed to mature in a bioreactor, before surgical implantation with the goal of replacing a malfunctioning organ.

Stem Cells & Therapeutic Cloning: High quality samples of autologous cells from the diseased organ of the host are the primary source for tissue/organ replacement therapy and it is not a viable option for extensive end-stage organ failure; and hence embryonic stem cells (ESC) are the alternative from which the desired tissue can be lab grown through combination of tissue engineering methods employed over the past few decades [58]. ESC isolated by immune-surgery of the embryo have demonstrated longevity in culture by maintaining their undifferentiated state for at least 80 generations under standard protocols and in addition possess two remarkable advantages (i.e., the ability to proliferate into an undifferentiated pluripotent or self-renewal state and to differentiate into many specialized cell types) [58]. Differentiation into cells of various types has also been established in skin, neurons, blood, cardiac cells, cartilage, endothelial cells, urethra, bladder, blood vessels, trachea, muscle, pancreas etc. & further evidence of their pluripotency was noticed through cell aggregations both in vivo as well as in vitro lab cultures [58]. Timely legal, ethical and political barriers to progress in ESC research have led to the search for alternate sources. Therapeutic cloning can fill this huge void (Figure 13).

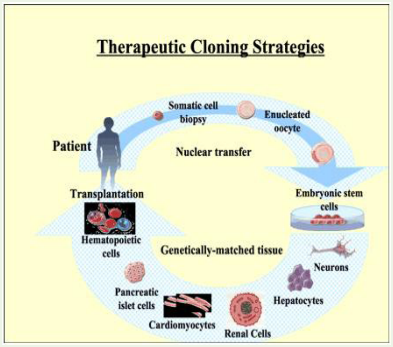

Figure 13: Various strategies from initial biopsy to transplantation into the same patient [59].

Biomaterials in tissue engineering

Synthetic materials such as Teflon and silicone that were introduced to replace or to rebuild diseased tissues or parts in the human body, led to the development of a wide array of devices. However, the functional aspect of the original tissue was not restored. This led scientists in cell biology, molecular biology, and biochemistry to further investigate and as a result novel biomaterials were discovered and designed [56]. These newly developed biomaterials were able to replicate the biological and mechanical function of human and animal tissues/organs in a simulated 3-D format in which cells can attach, grow, form new tissues with appropriate structure and function and also providing the appropriate cell-adhesion substrate, growth factors and bioactive factors critical for most mammalian cell types while allowing delivery of cells with high loading efficiency under desirable condition in vivo forces so that the predefined 3-D structure of a specific tissue-engineered organ is attained as a most desirable clinical as well as public health outcome (58). Classes of biomaterials found to be most ideally biocompatible for both in vitro and in vivo engineering of tissues include [58]: naturally derived materials like collagen and alginate; acellular tissue matrices (bladder submucosa and small intestinal submucosa); and synthetic polymers like poly glycolic acid (PGA), poly lactic acid (PLA), poly lactic-co-glycolic acid (PLGA)

Cost & Insurance challenges in translating regenerative therapies to clinics

Unsolved funding issues linger in the domain of innervation of tissues and organs which is critical for full in vivo functionality [56]. Several clinical trials involving stem cells and cloning have been paused due to limited funding [56]. As the cost that the medical health care system can allow for advanced therapies is limited; insurance plans are not ready to reimburse for the same [56]. Lowering the costs of bioengineered products will be addressed and realized as the technologies gradually advance with time, and the volume of stem cell clinical impact applications increase [56].

Promising areas of tissue engineering

Researchers at the National Institute of Biomedical Imaging and Bioengineering (NIBIB) are focused on several areas to rapidly develop novel clinical therapies by [54]: quality control of stem cells by regulating their lab culture environment; implanting human livers in mice to save time and costs of developing new drugs and allow for monitoring critical drug interactions; engineering mature bone stem cells to tackle abnormal bone growth; sugar lattices to help engineered tissue survive isotonic body fluids; solutions like bio gels and bio adhesives for bum knee; and regenerating new kidneys from patients own sells to overcome problems of donor shortages and drastically reduce morbidity associated with immunosuppression in organ transplants.

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Applications in health and medicine

2002 executive summary report prepared by the National research council's review committee calculated the number of potential americans that could benefit from tissue regenerative therapeutic treatments to be more than 134 million as shown in the break down based on their individual medical conditions below (Table 2) [60]:

Bioartificial liver (BAL): BAL support system was designed and developed as a bioreactor cartridge, loaded with detoxifying hepatocytes and hollow nanofibers acting as an immunoisolation barrier. This enabled the prevention of direct contact of patient blood flowing on to the nanofibers with the hepatocytes [61].

Generation of heart muscle cells: Clinical trials targeting stimulation of growth of new blood vessels that repopulate heart tissue instead of complex surgical interventions have proved to be safe & effective (Figure 14) [61].

Hematopathology: Research of hematopoietic or blood forming cells involving both adult and embryonic stem cells gave great insights into mechanisms of transfusion fluids for critical care medicine, surgery, organ preservation and improvement of microcirculation in diabetes, atherosclerosis and sickle cell disease [61].

Neurodegenerative conditions: Clinical trials that harvested neural stem cells from healthy adult brains were found to be capable of maintaining stem cell numbers or become progenitor cells with promise of treating Parkinson's and Alzheimer's disease [61].

Spinal cord: Adult stem cells transplanted by scientists into spinal cord injury patients led to the exciting discovery that human embryonic stem cells & human blastocyst stem cells can also be injected into neural stem cells and further probing shed light on clinical solutions by experimenting with motor neurons & spinal motor neuron cells [61].

Diabetes: Human embryonic stem cells were grown through cell cultures and tweaked in vitro to form insulin producing cells that were transplanted directly into the pancreas. This restored the function of their insulin producing beta cells [61].

Cancer: Bone marrow and umbilical cord stem cells have been successfully used to treat conditions such as leukemia and lymphoma by recouping hematopoietic stem cells killed by the cytotoxic chemotherapy agents within the bone marrow [61].

Blindness and vision impairment: Researchers achieved success via transplanted retinal stem cells into damaged eyes (Figure 15), again by employing embryonic stem cells. Thin sheets of totipotent stem cells grown in the lab were transplanted over the damaged retina stimulating renewed repair and subsequently restoring vision [61].

Amyotrophic lateral sclerosis (ALS): Clinical benefits of stem cells were proven in curing rats with ALS like disease by injections of stem cells into their spinal cords which then passed through many layers of tissues to the specific sites of injury, regenerating the dead nerve cells. This restores the patient's abilities to walk again [61].

Baldness: Researchers predict and expect that research on hair follicle stem cells may lead to successes in treating baldness through hair cloning performed by harvesting stem cells from existing follicles and multiplying the same through in vitro cultures further leading to implanting the new follicles [61].

Dental cures: Stem cells collected from the patient were worked on in the lab to grow new tooth buds and surgically implanted into the gums, giving rise to new healthy teeth by jawbone fusing through releasing chemical messengers that encouraged growth of new oral nerves and blood vessels [61].

Graft versus host disease and Crohn's disease: Novel breakthrough intravenous therapies developed by stem cells derived from adult bone marrow of 18- to 30-year-olds, abundant in mesenchymal stem cells (63), have enabled researchers to successfully target disorders related to both graft versus host and Crohn's disease [61].

Neural and behavioral birth defects: Direct neural stem cell transplantation into the brains of the offspring was found to bear fruit in inducing the host brain to produce large numbers of stem cells which repaired the neuronal and congenital damage [61]. Series of steps included taking cells from the patient's own body, turning them into stem cells, and then transplanting them back into the patient's blood [61].

Orthopedics: Clinical case reports in the treatment of orthopedic conditions have been reported. Centeno et al. Have published MRI

Table 2: Disease wise break up of 134 million american patients eligible for regenerative therapy benefit [60].

Condition	Number of patients
Cardiovascular Disease	58 million
Autoimmune diseases	30 million
Diabetes	16 million
Osteoporosis	10 million
Cancers	8.2 million
Alzheimer's disease	5.5 million
Parkinson's disease	5.5 million
Burns (Severe)	0.3 million
Spinal-cord injuries	0.25 million
Birth defects	0.15 million/year

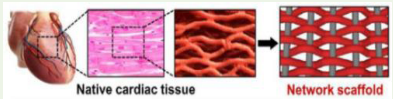

Figure 14: Interwoven/aligned conductive nanofiber yarn or hydrogel hybrid cardiac scaffold [67].

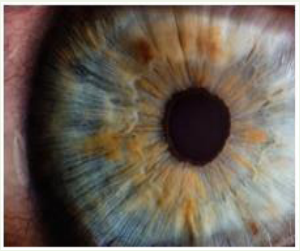

Figure 15: Damaged retina scan shows age related macular degeneration [62].

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evidence of increased cartilage and meniscus volume in individual human subjects, though it is unclear how the MRI results compare to clinical response.

Veterinary applications: Research conducted on horses, dogs, and cats has shown potential to develop stem-cell treatments in veterinary medicine and may contribute to human medicine cures for myocardial infarction, stroke, tendon and ligament damage, osteoarthritis, osteochondrosis and muscular dystrophy [61]. Companion animals were found to be superior models than typical mouse models and armed with relevant Veterinary research since 1998; regenerative treatment models sprouted involving mesenchymal stem cells harvested primarily from adipose tissue or bone marrow in order to treat animals with injuries or defects affecting bone, cartilage, ligaments and tendons [61].

Mechanisms of action: Scientific evidence has supported encouraging facts that stem cells improve healing through below observed mechanisms: anti-inflammatory effect; homing to injured tissues; recruiting tissue growth factors; supporting tissue remodeling over scar formation; inhibiting apoptosis and differentiation into bone, cartilage, tendon, ligament, muscle, fat and other tissues [61].

Limitations & ethical considerations

There are some limitations of the research work on tissue engineering and regeneration that have been done to date.

1) Data cited in research studies are mostly not reproducible [64].

2) Designing appropriate capillary networks to allow gas exchange, provide nutrition, and remove metabolic waste from the implants [64].

3) Different cell types require unique culture mediums which makes it quite challenging to design a multilayered organ system scaffold [64].

4) Designing and creating a scaffold capable of supporting various cell types [64].

5) In order to maximize ESCs in tissue growth & maintenance of the pluripotent state; expression sequence, dosing, and duration for growth factors have to be pre-defined accurately [64].

The ethical considerations in stem cell research include:

1) Adult stem cells (little controversial)

2) ESC's from discarded embryos produced in vitro (most controversial)

3) ESC's obtained through therapeutic cloning (extent of controversy related to type of research)

4) ASC's (adult stem cells) may as well avoid the ethical problem of ESC's but not a great deal of scientific data is published regarding their replication and differentiation patterns [64]

5) ESC's have clear cut technical advantages over ASC's as they can be generated in abundant quantities in the lab and in undifferentiated state for many generations [64]

6) Researchers face great adversity in creating ideal lab conditions for adult hematopoietic stem cells that can proliferate without becoming specialized; thereby limiting the avenues to explore ASC's to generate specialized cells in abundance needed for transplantation [64]

7) Despite impressive progress in the field of tissue engineering, further work toward organ and tissue replacement is crucial and optimal cell sources, 3-D designs, and microfabrication technology are still being investigated [57]

8) The search for ideal mammalian multipotent or pluripotent stem cells in tissue engineering has been emerging rapidly and also associated with controversies [57]

Future with stem cell therapy

Human ESC have proved their ability to differentiate into somatic cell types that can grow the entire human body and potential benefits to health and medicine are very wide ranging, from generating neurons for Parkinson's patients to learning about the underlying molecular biology and biochemistry of tumor development [Figure 16] [65]. A highly cited 2002 report by the National Academies of Science estimated that the potential patient population in the US eligible for stem cell-based therapies are more than 100 million [60].

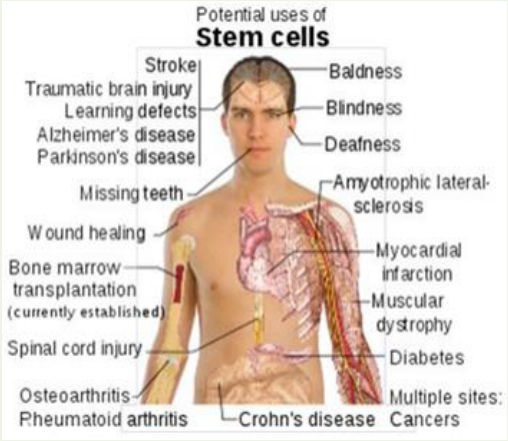

Figure 16: Medical applications of stem cells that can be grown into complete body parts for transplantation [66].

Conclusion

After reviewing progress that has been made in the several domains of regenerative medicine, scientists are constantly improving and expanding these cost effective therapies. The shortage of donors increasing along with increasing patient populations each year, the boomer generation's needs and demands for surgical implants and increased life expectancy, regenerative medicine will become more appealing as a therapeutic solution in the future. The acceptance of regenerative medicine as a therapeutic option could have both public health and economic implications in the healthcare system. Regenerative medicine has the potential to improve health outcome and quality of lives; reduce healthcare costs; reduce or eliminate the risk of immune system rejection; eliminate the search

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for a matching donor or the need of a donor itself completely; by pass immunosuppression medicines and related adverse events; shorten the rehabilitation periods and expenses; ease the burden of inpatient and outpatient visits in super busy hospital and clinics; design/ engineer and print 3-D tissues and organs in shorter time frames; and shorten the phases of clinical trials. As more research work is done, regenerative medicine will be more recognized and would be considered as a treatment option.

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