Review (Narrative)

Developmental Perspective on Regenerative Medicine: An Update

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SUMMARY

Regenerative medicine is an 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 ageing. The main focus of regenerative medicine is the human cells. In order to achieve the purpose of regenerative medicine, several scientists and clinicians have been stimulated to focus on regenerative ideas when dealing with tissue failure due to rapid success seen with early tissue engineering. Recently, financial meltdown has choked biotech by devastating its already floundering inflow of investment funds. However, regenerative medicine is a hope for future medicine as big pharmaceutical corporations have been acquiring some of the most significant biotech, possibly marking a new era where regenerative medicine. This results in making the academic labs of universities and the small boundaries of SMEs opportunity for gainful applications in the marketplace. The quest for regeneration is one of the dreams of mankind, like flying and setting foot on the moon. Stem cells have been becoming the promising way for being induced to differentiate into different purpose cells even some thorny problems are still there. It can be predicted that it is the destiny of mankind to reach for its visions, and therefore regenerative medicine is bound to be the hope for future medicine.■

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"Abuse they say is inevitable when use is not known"
--Anonymous.

THE above quote shows that if one does not understand what regenerative medicine means how then can one start to talk about it being the hope for future medicine? Hence, we need to have an inept understanding of what regenerative medicine is and what it entails and how it can be seen as the hope for future medicine.

THE CONCENTRATION OF REGENERATIVE MEDICINE

Regenerative Medicine can be defined in several ways. Breaking down the words into literal meaning, regenerative can be said to renew or re-grow what has been used up or exhausted. Medicine means a treatment or cure.

There are already a lot of definitions, but all are lengthy and not the sort of things scientists, start-ups or advocates can say swiftly when a pharmaceutical executive, government minister or member of the public asks for solid clarification. While it could be said that regenerative medicine is what most of the interested people in the field understands what it entails, it is also important to carry along several institutions such as government, Non-governmental organizations and the general public with the development.

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. This field holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves. 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.

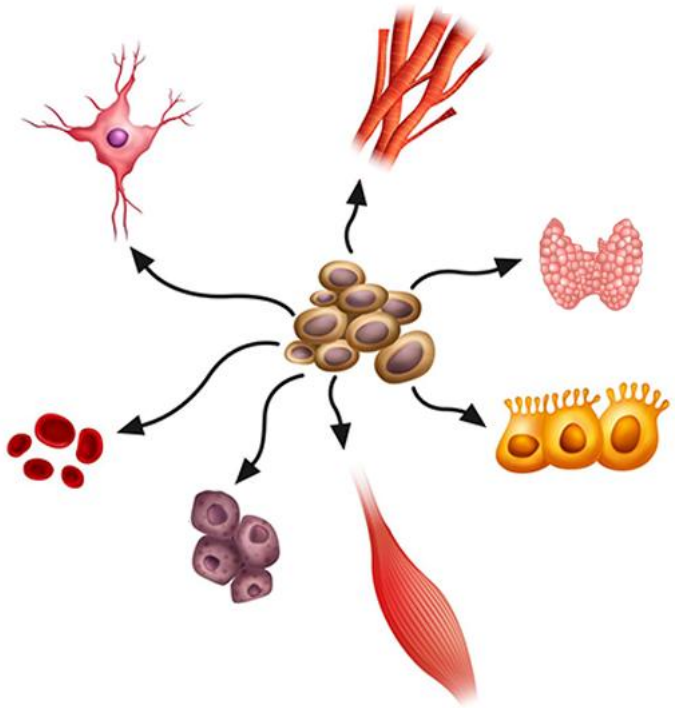
Furthermore, regenerative medicine is an interdisciplinary field of medical research and clinical applications that focuses mainly on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and ageing. It makes use of a combination of several converging technological measures, both existing and newly discovered, this moves it beyond indigenous transplanting and replacement therapies. This includes surgery, surgical implantations, such as artificial hips, and increasingly sophisticated biomaterial scaffolds. Also, it involves hospital procedures such as bone marrow and organ transplants and it relates to tissue engineering. There is no absolute cut-off in the transformation of these into fully developed regenerative medicine but they each leave residues of their input that can mean the patient is not capable of being termed "of natural health" with respect to the treated condition.

The main focus of regenerative medicine is human cells. These may be somatic, adult stem or embryo-derived cells and now there are versions of the latter cells that have been reprogrammed from adult cells so that both can be collected conveniently under the heading of "pluri-potent cells". Also, tremendous research developments and advantages in the stem cell arena have shed new lights on future therapeutic possibilities and it seems logical that actively modulating or guiding repair processes holds the promise of regenerating damaged tissues and organs in the body by stimulating previously irreparable organs to heal themselves (1-4). The prospect of transplanting in vitro grown organs and tissues has been widely investigated in the field of regenerative medicine (5).

Several scientists and clinicians have been stimulated to focus on regenerative ideas when dealing with tissue failure due to rapid success seen with early tissue engineering (6). A brief review of recent literatures concerning advancements in Regenerative Medicine would raise the impression that regenerative medicine is the hope of future medicine because it will help to produce tissue replacement "off the shelf", in the near future for everyone in need (7). It would interest you to know that some persons have proclaimed that the time must come to "stop tissue engineering and start engineering tissues". A brief history of regenerative medicine will help us to know what it has been overtime and resultantly discover its potential to be a hope for future medicine.

A BRIEF HISTORY OF REGENERATIVE MEDICINE

The myth of the great Titan Prometheus, as introduced by Hesiod in his theogony (8th century B. C.) provides a foothold for regenerative medicine. In early research on regeneration, Descartes (1596–1650) in his "L" Homme", was the first to defy a divine meaning in biological phenomena and stated that the function of the human body can be interpreted by means of its physical and chemical properties. However, it was not until the middle of the 18th century that the idea of an abstract motive power of biological organisms was dismissed by the general public and the scientific elite, when Lavoisier (1743–1794) postulated that the chemical processes governing life could be reproduced and studied in the laboratory. During the same time naturalists were taking sides on the phenomena of generation and regeneration: Pre-formationists supported that appendages to be regenerated and organisms to be born pre-existed as miniatures at the site of interest. So, at the base of a severed lizard tail, in their conception a miniature tail was pre-formed and waited to be "activated" by an amputation. Likewise, in the sperm or in the ovum of the human there existed a miniature "homunculus" that grew into a new born infant. This theory was in accordance with the Christian beliefs of creation and prevailed until the middle of the 18th century. On the contrasting end, came the Aristotelean thesis that undifferentiated matter was able to give rise to life. This theory had been actually named "epigenesis" by William Harvey (1578–1657) in his work "on the generation of animals" grossly repeating on Aristotle"s works. Abraham Trembley (1710–1784) produced several publications on the regenerative phenomena on freshwater polyps. He managed to obtain a clone of 50 polyps from one organism that he had quartered. He performed sections at every conceivable plane, contradicting pre-formational beliefs of the time. The question was posed: If the animal soul was the organizing and unifying element of life, how could a newly regenerated form arise? Until the end of the 18th century philosophical and religious debate linked to the science of regeneration was set aside, and epigenesis gained acceptance with the eventual ascendancy of epigenetic and developmental embryology bringing about a revolution in natural sciences.



Once the religious and social burdens had fallen, the 19th century was marked by a rapid succession of developments. Schleiden and Schwann described in 1838–1839 the cell theory. In 1858, Rudolf L. K. Virchow stated the famous omnis cellula ex cellula and through microscopic observations he confirmed the cell theory and established the idea of cells being the elementary units of life able to replicate themselves by division. In 1867, the eminent German pathologist Julius Cohnheim postulated what became known as the "Cohnheim hypothesis". He suggested that all of reparative cells taking part in the regeneration of wounds come from the bloodstream (and therefore from the bone marrow) (8). Finally, at the end of the 19th century, Barth observed that upon autologous bone transplantation in hounds the vast majority of cells die and leave scaffolding behind to be slowly repopulated by new host cells and an adequate neovascular network.

In 1912, Alexis Carrel, a French scientist working at the Rockefeller Research Institute in New York, started a culture from a small slice of heart muscle taken from a chick embryo. This culture continued for several decades, outliving the normal chicken"s lifespan. His belief that cells in culture were inherently immortal dominated the early 20th century until in the 1960s Leonard Hayflick and Paul Moorhead defied this dogma and proposed the "Hayflick limit", according to which differentiated cells in culture are not able to replicate more than 40–60 times and are bound to display signs of senescence with successive passages.

However, some mutated lines possessed the capacity to replicate themselves forever, if kept undifferentiated in culture. By 1967 Leroy Stevens had developed a strain of mice, with a high incidence of spontaneous

testicular teratomas. These neoplasias displayed a characteristic mixture of different tissues lined up next to each other randomly. By the end of the 1960s it was established that they originated from germ cells that were able to give rise to a plethora of different tissues. So the concept of pluripotency of germinal cells was introduced and this tumour cell was named embryonal carcinoma stem cell (EC). Research with EC stem cells expanded considerably in the 1970s. In a series of experiments, chimeric mice were produced by injecting ECs into early blastocysts. Because ectopic blastocyst injections were also found to generate teratomas it became soon evident that pluripotent cells could also be derived from blastocysts directly (9). Soon the next logical step was undertaken, when Gail Martin (10) in the United States and Martin Evans (11) in England generated in 1981 a stable diploid cell line that could generate every tissue of the adult body, including germ cells. Gail Martin referred to her cells as "embryonic stem cells" and gave them the nickname "ES cells".

However, the human equivalent was not available at that time. Researchers performed studies on cells obtained from blastocysts of primates, including rhesus monkeys and marmosets (12) as well as human EC stem cell lines isolated from a rare tumour of the male testes, after orchiectomy procedures. However, in 1998 some couples undergoing treatment for extracorporeal fertilization donated a surplus of blastocysts for experimental purposes. James Thomson isolated and cultivated a human ES line from these blastocysts (13). A new era had dawned and the prospects of this technology seem overwhelming.

THE ERA OF REGENERATIVE MEDICINE

The transition from tissue engineering into regenerative medicine was justified by dramatic developments in the financial, scientific and political landscape. From a financial point of view, the first years of the 21st century, anticipated to bring the biotechnological revolution, were characterized by a disconnect between expectations and reality. As Lysaght noted in 2004: "although aggregate development costs exceed $4.5 billion, the field has yet to produce a single profitable product".

On the scientific arena new technologies had come into play, with the very term tissue engineering being unable to accommodate them: The availability of human embryonic stem cells was bringing the cellular therapy at the front line of the field. Gene technology had come to a point, where a whole mammal could be cloned or genetically manipulated (the Monsanto swine case). Drug delivery systems and nanotechnology were developed and integrated in the design of biomaterials. The paramount significance of angiogenic processes for homeostasis, biointegration and upscaling of tissue engineered constructs became clear. Experimental activities were directed to encompass integrative strategies towards generation of autonomously vascularized bioartificial tissue elements. In addition tumour research was further advanced with the prospect of revolutionizing cancer treatment to round up progress in the biotechnological arena (13).

The course of regenerative medicine was also shaped by a political event. The US legislature had frozen most of federal granting for stem cell research. Robert Nicholas Klein II, a lawyer and real-estate developer, whose son suffered from diabetes mellitus type I, and whose mother suffered from Alzheimer"s invested over $3 million of his own money, and organized a public effort to put pressure on the government of California to change policy on stem cell research and regenerative medicine. On November 2, 2004, the Proposition No. 71 passed through a public ballot initiative with a 59.05% to 40.95% majority. As a response to that, the California Institute of Regenerative Medicine was established to supervise a huge funding of more than $3 billion over 10 years.

STEM CELLS: THE POTENTIAL HOPE FOR REGENERATIVE MEDICINE

Stem cells refer to a cell that has the ability to self-regenerate and replicate, and can induce differentiation into a wide variety of cells in a proper environment. Therefore, it is an ideal method to use stem cells to induce differentiated cells as a source of transplantation. Stem cells exist in many places, mainly embryonic stem cells and adult stem cells.

Embryonic stem cells are pluri-potent or totipotent, and can induce differentiation into all cells of the three germ layers in vivo under appropriate circumstances. However, embryonic stem cells have ethical issues of scarce source, difficulty, and controversy, because embryonic stem cells need to be separated from early embryos. Although adult stem cells are less ethical and controversial, they are also rare in number, poor in

function after differentiation, allogeneic immune rejection, and difficult to survive after transplantation. Therefore, the direct production of pluri-potent stem cells from their own somatic cells has become an attractive method. There are many methods for making stem cells, but they are all achieved by techniques of reprogramming. Reprogramming refers to the ability to change the state of a differentiated cell, usually to a similar or complete state of the embryonic cell, to obtain pluri-potency. The state of differentiation of cells is usually closely related to the expression of specific genes.

Therefore, the reprogramming program usually shuts down the gene expression of the original differentiated cells, and then opens up new gene clusters, which are generally related to embryonic development, and thus interact with gene expression. It is very important for the transcriptional pattern to be linked, which is why stem cell production and induced differentiation now involve many specific transcription factors.

REGENERATIVE MEDICINE: ITS PROSPECTS FOR FUTURE MEDICINE

Recently, financial meltdown has choked biotech by devastating its already floundering inflow of investment funds. It has been noted that from the end of 2007 until 2010 the industry had no initial public offering. The few survivors have turned their back to research altogether because in science, excellent scientific ideas and discoveries that provoke enthusiastic expectations turn out to be more difficult when it comes to routine clinical applications. When no immediate clinical results are visible, industrial research funding becomes a problem. Investors are taking their money out of the industry thus driving stock price floors lower and by the end of 2009 as many as 79% of the biotech firms were trading under their opening price (14). No big hope for a cyclical recovery in funding exists momentarily because, as mentioned, investors have snubbed biotech for a decade. Vivid fantasies of lifesaving new cures and tantalizing financial forecasts in the 1990s have made space for tight fists and raised eyebrows among investors.

However, this is hardly a phenomenon limited to the life sciences. Since 1995 the Gartner Advisory Group has devised a methodology to describe the "ups and downs of new technologies and relate them to business considerations (15).

These common general observations from the financial world seem to be also worthwhile to be considered by life science researchers, because of their analogy to scientific developments and their relevance to potential research funding sources. According to the hype cycles theory, a new technology is bound to undergo a series of five phases. As a first event there is a "technology trigger". During this step, the new technology draws considerable attention by a breakthrough or a major press release. Soon thereafter, there is a "peak of inflated expectations" during which over enthusiasm and overt publicity initiates a rage of investments. During this period there is a disconnection between expectations and performance. In the "trough of disillusionment" failure to meet the expectations, renders the technology unfashionable and unattractive in the public mind and for investors. During the "slope of enlightenment" although public interest has grossly deteriorated, in some centres the practical application and commercial potential is reassessed.

Understanding innovative technologies is pivotal to developing successful investment strategies in the biotech sector and hence is influential in developing the field of regenerative medicine. In a European conference held in May 2010 in Brussels on innovation in healthcare with focus on small and medium enterprises (SME) relevant to the sector, there was a consensus that there are serious socio-economical barriers to be overcome, before the European landscape becomes nearly as favourable as in the United States (16). Until then European grown talent will be constantly "crossing the Atlantic" not only in respect to bioengineering expertise, but also in terms of talented fund managers. Nevertheless, within the European Framework Programme (FP7) some 15% of a total of €6 billion dedicated to health research were funnelled into SMEs. Another €2 billion has been separately invested in the Innovative Medicines Initiative, a public–private group that enhances collaboration between companies and experts on pre-competitive research projects. In autumn 2010 the European commission is about to publish the research and innovation strategy for the coming decade.

The Innovative Medicines Initiative represents an issue important to the ecosystem of health related research and development. Although state funding is key to the foundling steps of innovative health technologies, eventually these advances will translate into products and services and will be integrated into the regular system of investment and revenue. There is a grey area,

however, where the biotechnological advances escape the level of basic academic research but are also a step behind from becoming a proven concept ready for clinical application. This area has been described by several authors as the "death valley" and it is dictated not only by a "financial gap" but equally by a technical one as well as a gap of information and trust. Specifically for regenerative medicine one could add legal and ethical problems into this metaphor (17). Small enterprises are unlikely to support a tedious effort of bringing an innovative technology to the point of applicability and profitability, whereas large-capital companies are better equipped, with a robust financial and political backbone.

Despite any financial up and downs and the driving forces of various funding sources regenerative medicine will definitely play a major role in the future of medicine. Besides the ever growing knowledge of adult or embryonic stem cells and their regulation many patients might profit from new insights in the near future (18). As an example, preservation of cord blood stem cells is gaining popularity after promising results on their use for brain injury (19) and type 1 diabetes mellitus (20) as well as stroke and hearing loss.

These data engender a new direction in regenerative medicine basic research – the necessity to discover the natural microenvironment and consequently, to engineer the artificial support essential for stem cells to act (20). Under the light of such recent achievements of research in regenerative medicine one might come back to the saga of Prometheus to find out that it seems likely that not only the liver may carry the ability to regenerate in itself but also other vital organs like the heart might well be able to renew themselves.

DIRECTIONALLY INDUCED DIFFERENTIATION: THE OBSTACLE WE NEED TO CONQUER

Many treatments for damaging, dysfunctional, and degenerative diseases usually require mature and functionally intact somatic cells, so how to induce differentiated stem cells to become the somatic cells we need is another major theme of regenerative medicine.

When stem cells are cultured alone and without the addition of factors such as Leukemia Inhibitory Factor, Bone Morphogenesis Protein and Wnt, random differentiation is easy, so in order to induce efficiently for stem cell differentiation, stem cells can generally be cultured in suspension, or stem cells can be directly cultured on a stromal cell or an extracellular matrix. Suspension culture forms a globular embryoid body and slowly differentiates into three germ layer progenitors, while stem cells cultured using stromal cells or extracellular matrix are due to stromal cells or cells. The outer matrix differentiates into various precursor cells by different effects. These precursor cells, after adding many cocktail-like induction factors, can differentiate in various directions that we want to develop

Majorly, three problems we are facing in practical application: (i) The success rate of induced differentiation is low; (ii) The cells that induce differentiation have not survived for a long time after transplantation; (iii) The cells that induce differentiation are not as functional as mature somatic cells. Therefore, the current stage of efforts is to better understand the mechanism of the differentiation system, more perfect regulation of gene expression and induction factors, in order to obtain regenerative cells that can repair damaged tissues or degenerative diseases.

CONCLUSIONS

Regenerative medicine is a hope for future medicine as big pharmaceutical corporations have been acquiring some of the most significant biotech, possibly marking a new era where regenerative medicine. This results in making the academic labs of universities and the small boundaries of SMEs opportunity for gainful applications in the marketplace. The quest for regeneration is one of the primordial dreams of mankind, like flying, remote communication and setting foot on the moon. It is the destiny of mankind to reach for its visions, and therefore regenerative medicine is bound to be the hope for future medicine. Stem cell induced differentiation has a promising future when reliable methods were used without inferring with the potential of its regeneration.■

ARTICLE INFORMATION

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Study concept and design: Barr & Kelly
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