Regenerative Medicine requires a Paradigm Shift in Outcome Measures

Gordon Slater*

Orthopaedic Surgeon, Private Practice, Level 2, Suite 2.01, 376 New South Head Rd, Double Bay, NSW 2028; Australia

*Corresponding author: Gordon Slater, Orthopaedic Surgeon, Private Practice, Level 2, Suite 2.01, 376 New South Head Rd, Double Bay, NSW 2028; Australia

Citation: Slater G. (2021) Regenerative Medicine requires a Paradigm Shift in Outcome Measures. J Stem Cell Res. 2(1):1-15.

Received: February 10, 2021 | Published: March 30, 2021

Copyright © 2021 by Slater G. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Regenerative medicine is an emerging multidisciplinary science that endeavours to replace or regenerate human cells, tissues and organs to establish or restore normal function. The regenerative medicine field results from the convergence of multiple scientific avenues, including the successful growth of cells in the laboratory, identification, characterization and differentiation of stem cells and the improved understanding and development of molecular biology. This allows for the control of the intracellular and extracellular environment to promote tissue and organ formation in the lab. Regenerative medicine consists of three factors: cell, chemical substance and scaffolds from this point of view the process resembles anti-aging medicine. And offers the potential to revolutionize patient care in the twenty-first century, and thus a reset of outcome measures and basic principles in medicine must be considered.

Keywords

Biologics; Regenerative medicine; Stem cell; Minimally invasive surgery; Anti-Aging; Slater
Introduction

Quality vs Quantity

Advancement in medicine is increasing the longevity and enhancing the quality of life of people around the world [5]. Currently the average western life expectancy is 72.6 years [12], and the average western quality of life is around 60% [79]. We appear to be living longer but with more alignments, our medicine allows us to live with disease rather than curing or reversing. Anti-ageing and regenerative medicine has the potential to increase life expectancy by up to 500% [94]. I propose that true regeneration should not only increase the quantity but also the quality. Included in quality would be the potential invasiveness of the intervention and potential side effects. What do we need to go through in order to achieve the desired outcome. Is the treatment worse than the cure?

Regenerative medicine has emerged as a multidisciplinary field to potentially address the limitations in both the quality and the quantity of life. Restoration of normal function with minimal invasiveness to maximise the efficacy of the treatment for the patient [112]. The aim to make the risks of the treatment pale in comparison to the rewards derived from the treatment.

In order to achieve this combinations of treatments will be required including stem cells, molecular biology and the use of adjuvants [112,77]. This will allow for the development of tissues both in vivo and in vitro [77].

Three broad avenues involving cells, adjuvants and scaffolds need to be brought together as in anti-aging medicine [34]. Disease is generally the result of aging in western society. Its arrest and/or reversal offer the potential to revolutionise patient care in the 21st century [91].

Biologics

A biologic drug (biologic) is a product that is produced from or contains components of living organisms [6]. Use of products that are made from animal hosts is not new. Vaccinations have been used for many years and have revolutionised the delivery of medicine largely eliminating many diseases that where a scourge to the mankind. As internal modifiers, biologic drugs either enhance or inhibit biological processes that are part of the key mechanisms of action for critical pathways in healing. Perhaps the most prevalent and advanced example of biologics is CRISPR [17,63,70]. CRISPR-Cas9 is a versatile tool used for genome engineering that has revolutionized biotechnology. This gene manipulation technique provides a widely available tool for altering and even correcting DNA, thus preventing a wide range of diseases [17,70].

Regeneration Vs Anti-aging

Aging can be defined as a progressive deterioration of physiological function accompanied by an increase in vulnerability and mortality with age [35,27], it is a complex and heterogenous process as its rate varies considerably between diverse species, between organisms of the same species and even between tissues and cells of the same organism [27]. Currently the leading cause of death worldwide and notably in industrialized countries, are age related conditions such as cancer and cardiovascular and neurodegenerative diseases [23,29]. As result of the relationship between the aging process and age-
related diseases, the benefits emerging from anti-ageing science have enormous potential to both increase life expectancy and financial savings [33]. Harvard professor David Sinclair has recently proposed a new radical theory of aging suggesting that aging hallmarks are symptoms of epigenetic changes that occur over time, but that the original genetic code remains very much intact, he suggests the idea that if we can rest these codes we could slow, stop or even reverse aging.

Regeneration is perhaps an isolated example of anti-aging. Regeneration focusses on regional loss of cells leading too conditions such as osteoarthritis. As cells become increasingly senile the tissue becomes exposed to disease and failure. Osteoarthritis is a prime example of this process.

**Future anti-aging treatment: the role of stem cells**

Stem cell therapies contain live cells that have the ability to generate a whole new organism. As they are pluripotent (meaning they are capable of turning into many different cell types), stem cells have the potential to help patients to restore their tissue, and therefore increase their longevity. Emerging stem cell-based therapies to combat the function decline associated with aging has recently attracted attention, due to their ability to differentiate [68,11] (Figure 1) and give rise to all cellular types proving opportunity for regenerative medicine [21,24,94]. The trick is to encourage the stem cell to become the cell that is needed at the host site.

![Figure 1: Chondrocyte Differentiation](image_url)

**Figure 1**: Chondrocyte Differentiation. Strobach, et al. “Gene therapy Applications in fracture repair”.

*Research Article* | Slater G. J Stem Cell Res 2021, 2(1)-18.

*DOI*: [https://doi.org/10.52793/JSCR.2021.2(1)-18](https://doi.org/10.52793/JSCR.2021.2(1)-18)
Catastrophic biologic failure
The beginning of the end

The beginning points of biologic failure are:
1. The end of growing
2. The end of stem cell multiplication
3. The decline of adjuvant hormones HGH etc
4. Critical loss of stem cell/adjuvant hormones. Excess capacity loss, tipping point
5. Catastrophic failure. Death

The aftermath of death follows a set sequence: autolysis, bloat, active decay and skeletonization [68,111]. Note that different tissues are beyond salvage at different time intervals.

Stage one- Autolysis
The first stage of death autolysis otherwise known as self-digestion begins immediately after death. This stage occurs due a lack of blood and oxygen circulation. As the body has no way of receiving oxygen and removing waste there is a built up of excessive carbon dioxide, this excess causes an acidic environment which results in the rupture of cell membranes. These membranes release enzymes that begin eating the cells from the inside out [68,111].

Stage two- Bloat
Leaked enzymes from stage one begins to produce various gases, causing the human body to potentially double in size. Additionally, microorganism and bacteria produce unpleasant odours called putrefaction [68,111].

Stage Three- active decay
Fluids are released through orifices indicating the beginning of the process of active decay. During this process organs, muscles and skin becomes liquefied. Once all of the body’s tissue decomposes, hair, bones, cartilage and other by-products of decay remain. Throughout this process the cadaver loses most of its mass[68,111].

Stage Four- Skeletonization
There is no set framework throughout which skeletonization occurs, as the decomposition rate of collagen and inorganic components varies [111]. In medicine allograft is used regularly to provide a scaffold in healing.

Reverse engineering
Lets look at death than look how it relates to limb reconstruction/regeneration. In salvage we start with debridement which is the removal of dead, infected contaminated tissues. This generally means resection to a margin of safety similar to tumour surgery. The problem with this in the foot is that the
resultant limb is left dysfunctional as important tissue is removed. The remnant foot has excess pressures applied to areas which were not designed to receive this load and can in turn fail. This can lead to a cycle of amputation until the entire foot is removed. In reconstruction we have no compunction in using allograft or other tissues which are by their nature already dead. Here we are after the structure and the hopeful incorporation by the body with creeping substitution. My contention is that structures such as bone even if dead can perhaps be recolonised by native cells and salvaged. Structures that liquefy earlier as above have to be removed. But other structures that die slower can perhaps be reclaimed.

**Principles of Regeneration**

**Surgical principles of regeneration**

As noted above in a threatened extremity we can see that some tissues get to the point of no return quicker than others.

Reconstruction of threatened limb.
1. Ensure skeleton structure stable and joints. Protection/movement/?exo skeleton minimise detrimental environment maximise overall health i.e heart
2. Tissue envelope repair
3. Introduction of new cells/Activation
4. Ongoing maintenance/proliferation [94,78]

**Principle of regeneration**

- tissues to be regenerated should be at a critical number and quality to allow regenerative threshold. Tissues and functions regenerate at different rates. They need to be protected during this time,
- stem cell can be recruited or introduced to diseased zones to achieve a regenerative threshold. There abundance in blood vessels leads peripheral tissues to be able to regenerate quicker than other less vascular tissues. i.e. Toes better than heels
- regeneration is a slow process, there may be multiple treatments required to regenerate tissues. Treatment should shift to injection therapies rather than invasive treatments.
- proliferation of cells is not necessarily required to cure a disease, as local cells can be augmented e.g. chondrocytes increase matrix or the quality of the matrix [77,82,112].

Even though the process of death is different in many respects to regeneration there is a likeness in the way it relates. Slowly metabolising tissues will regenerate slowly. Previous views have considered the process of regeneration as a continuum [56,82]. However, an emerging view supports the idea the process of regeneration can be split into major constituent cellular events [56]. These phases I propose can be likened to the stages of death, and thus considering the process of death and the events that occur at each stage can aid in dissecting the essential mechanisms of regeneration.
Tissue engineering

Image Credit: Medgadget. tissue injuring example

All injuries is a cause of concern to the patient from various perspectives. First, there’s the inconvenience of potential immobility, coupled with the economic stress of having to pay for healing and recovery. Some orthopaedic conditions require the utilization of surgical procedures in order to restore the patient to optimal health, and the healing time can be extensive and take up to a few months.

Orthopaedic surgery requires the utilization of methods that aim to restore the mechanical integrity of the body. With time, there are some aspects of the body’s healing mechanisms that revert, and the healing of tissues such as cartilage and ligaments is difficult to achieve. Some bone and tissue functions that do have the ability to restore do not do this to the original strength.

According to medical studies the healing of orthopaedic tissues is directly correlated to the incorporation of four main elements: cells, morphogenetic signals, scaffolds and mediums that will support the mechanical structure of the body. Bioengineering procedures have enabled the development of tissue regenerative materials that will restore both the mechanical integrity of bone, and also facilitate the restoration of the ligaments, cartilage and even blood vessels that are associated with particular regions of the body such as the ankles and the knees.

Via medical research, source tissues for tissue engineering is sourced from various bodily sources and the importance of each of the differing cell sources is yet to be identified. In the medical realm:

1) Stem cell research is understudy to identify the most effective cells to introduce to specific healing sites.
2) For morphogenetic signals their influence by growth factors or other sources such as platelet rich plasma is currently being elucidated
3) Smart scaffolds that integrate with the body are also under investigation

As medical knowledge on a topic expands, it will be possible to overcome the obstacles to the current
incorporation of engineered tissue into the orthopaedic treatment plan. In the future, as synthetic and biologic material properties are better understood it will be possible to combine all of these elements in order to apply them to therapies. Industry best practices and federal approvals still have to be established before the full implementation can be accepted globally.

**Regenerative Treatments**
The human body is designed to heal itself. As aging occurs this capability declines with stem cell depletion. The body’s skeleton is one prime example of a mechanism that has to heal itself in situ. Bone cells regenerate spontaneously, and new cells are always being regenerated, to replace the ones that have been absorbed by the body. One of the beautiful things about bone is that in its natural state, bone will heal without scarring.

**Regeneration of the Skeletal System**
The skeleton bears mechanical loads and it moves with mechanical stimuli. Tissue engineering technologies have been incorporated that will enable the restoration of the relevant tissues that will keep the bone function at peak. The generation of these tissues involves the utilization of patient autologous cells, growing them in a culture, and then seeding them onto a scaffold. Bioreactors are the incubators of our cell cultures. Success of this method is a promising technique that will lead to proliferation of regenerative methods in orthopaedic care.

As the ideal methods for culturing cells is under debate, the truth of the application cannot be overseen. Practicality will result in an initial focus on minimally invasive procedures that will incorporate these engineered tissues. With time, and better understanding, more sophisticated applications can be identified. (114)

**Outcome Measures**
Classification systems in orthopaedics have been used extensively in orthopaedics for a variety of different applications. Notably in research, for descriptive purposes, and attempts to classify disease and injury to predict pathology and treatment outcomes [1-25]. A good classification system should be easily reproducible so that inter observer reliability is high. With the advent of minimally invasive techniques of surgery in the forefoot it has become more necessary to be accurate in planning surgery.

Current surgical treatments are often end stage and “procedures of desperation”. For example after conservative treatments have failed and pain killers the pressure is for surgery to be offered as a last resort. By this stage there is often a decline in the overall health of the individual and loss of lifestyle and conditioning.

By definition than regenerative surgery is offered when there is something to regenerate. many patients are told to “come back when you can’t walk.

“If there is complete loss of cartilage cells than regenerative technology with a simple adjuvant or
accelerant is unlikely to work. In this case the base cells would need to be added.” Regenerative medicine works best in the earlier components of disease.

Intervention in this case occurs earlier than salvage and perhaps treatment length is longer as tissues regrow slower. The aspiration of the patient in terms of restoration of function can perhaps be met rather than long term limitations placed (Table 1).

**Outcome Measurement of Treatment**

A. Level of invasiveness:
- Risk vs reward.
- Salvage. Has there an invasive procedure such as loss of organ (joint replacement).
- Minimally invasive with joint preservation
- Regenerative injection therapy

B. Result:
- Outcome compared to age matched control
- Outcome compared to “youthful result”

C. Longevity of result:
- Deteriorating leading to catastrophic failure and revision. Secondary salvage
- Deteriorating resulting in primary salvage procedure

D. Maintenance:
- Long term result but requires further interventions. But these are RIT (regenerative injection therapies).

E. Benefits outside of primary treatment target:
- The future regenerative medicine blending with anti-aging.

| LEVEL  | Outcome                                      |
|--------|----------------------------------------------|
| One    | • Better than before treatment (>30%)        |
|        | • Invasive treatment with replacement of organ|
|        | Patient satisfied outcome but not with the   |
|        |   treatment.                                 |
|        | Result is deteriorating                      |
|        | **Limitations on activity**                 |
| Two    | • Better than before treatment minimally invasive|
|        | • Result is deteriorating                    |
|        | • Limitations on activity                    |
|        | • Patient satisfied with result and treatment|
Discussion

Regenerative medicine offers the possibility to both restore function avoiding salvage operations and also to turn the clock back to function when compared to age-matched controls.

Formally it has been thought that it not possible to regrow cartilage however it is clear that mammalian chondrocytes can proliferate in the right circumstances. The paradigm shift to regenerative techniques continue with the constant question of can we ultimately turn the clock back on disease increasing the

Table 1: With a regenerated ankle joint for example.

|   |   |
|---|---|
| **three** | • Better than before treatment but not fully active  
Treatment outcome declines.  
• Minimally invasive.  
• Limitations on activity |
| **four** | • Regenerative Rp  
• Age matched return of function  
• Treatment outcome Declines  
• Not invasive |
| **Five** | • Regenerative  
• Restoration of normal function  
• Not just good for age now a youthful outcome  
• Better than before procedure + increasing benefits.  
• Local effect only.  
• No restrictions in activity |
| **Six** | • Anti-aging  
• Single Rx  
• Multi positive effects outside target organ  
• No restrictions in activity |

*Research Article* | Slater G. J Stem Cell Res 2021, 2(1)-18.  
*DOI:* [https://doi.org/10.52793/JSCR.2021.2(1)-18](https://doi.org/10.52793/JSCR.2021.2(1)-18)
quality of life and perhaps ultimately life extension. Orthopedic practice sees a continued shift to keyhole image guided surgical techniques. Except the ‘key hole’ is slightly longer now then the tip of a ball point pen. This is leading to reduced recovery times, pain, and complications. Of course, these need to be balanced against enthusiasm and learning curves. These techniques combine well with regenerative techniques.

Previously we have written a paper on the foetal healing cascade. The message is that it was once possible, even as humans, to heal quickly without scaring; it was even possible to heal and repair complex organs. Just as the Mexican salamander is able to regenerate entire complex limbs into adulthood. Our humble starting point is to heal failed tissue of a single cell type to the point where the effects of disease reverse.

Some definitions may need to be changed or at least modified in their assessment. For example debridement. The definition of dead tissue can be challenged in some circumstances as for example dead bone can be used as a scaffold.

I propose now that in the future virtually all disease processes can be reversed with regenerative techniques which can be likened to the first incremental steps in anti-aging medicine. Most chronic adult diseases are a result of aging.

Our rationale is outcome measures need to evolve raising the bar on treatment outcomes and the way in which the treatment is delivered. Regeneration in the adult is slow. Advances are needed to shorten the duration of treatments. This will likely be in the form of the use of more adjuvants for example after initial distraction therapies. A possible outcome measurement would be both objective and subjective. The patients experience being the pivotal in the result. Not merely survivorship of the initial operation. Regenerative medicine will continue to evolve in the management of many conditions and become compelling as an alternative to traditional treatments.

References
1. A brief definition of regenerative medicine | Regenerative Medicine. Futuremedicine.com. 2020. https://www.futuremedicine.com/doi/10.2217/17460751.3.1.1
2. Ackerman IN, Bucknell A, Page RS, Broughton NS, Roberts C, Cavka B, et al. The substantial personal burden experienced by younger people with hip or knee osteoarthritis. OsteoarthrCartil.2015;23(8):1276-84.
3. Allsop D and Kennett K. “Skull and facial bone trauma“. In Nahum AM, Melvin J. Accidental injury: Biomechanics and prevention. Ber-
4. Abhaykumar S and Elliot DS. “Percutaneous plate fixation for periprosthetic femoral fractures: a preliminary report“. Injury 31.8 (2000): 627-630.
5. Aigner T, Vornehm SI, Zeiler G, Dudhia J, von der Mark K, et al. Suppression of cartilage matrix gene expression in upper zone chondrocytes of osteoarthritic cartilage. Arthritis Rheum. 1997;40(3):562-9.
6. Aitken SA. “The epidemiology of upper limb, lower limb and pelvic fractures in adults“. Department of Trauma and Orthopaedics, University of Edinburgh, Edinburgh (2013).
Aigner T, Gebhard PM, Schmid E, Bau B, Harley V, Poschl E. SOX9 expression does not correlate with type II collagen expression in adult articular chondrocytes. Matrix Biol. 2003;22(4):363-72.

Allied Market Research. Allied Market Research. 2017.

Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect. 1998;47:487-504.

Bland JM and Altman DG. “Statistical methods for assessing agreement between two methods of clinical measurement”. Lancet 1.847

Baek GH. “Duplication”. In: Abzug JM, Kozin SH, Zlotolow DA, eds. The Pediatric Upper Extremity. New York, NY: SpringerVerlag (2015) 325-368.

Bini S. Artificial Intelligence, Machine Learning, Deep Learning, and Cognitive Computing: What Do These Terms Mean and How Will They Impact Health Care? J Arthroplasty. 2018;33(8):2358-61.

Bishop YMM., et al. “Discrete multivariate analysis”. MIT Press, Cambridge (1975).

Beaty JH and Kasser JR. “The elbow: Physeal fractures, apophyseal injuries of the distal humerus, avascular necrosis of the trochlea, and T-condylar fractures”. In Rockwood and

Berenbaum F. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). Osteoarthritis Cartilage. 2013;21(1):16-21.

Berterame S, Erthal J, Thomas J, Fellner S, Vosse B, Clare P, et al. Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study. Lancet. 2016;387(10028):1644-56.

Cyranoski D. Acid bath offers easy path to stem cells. Nature. 2014;505(7485):596-596. doi:10.1038/505596a

Chrisman OD. The effect of growth hormone on established cartilage lesions. A presidential address to the Association of Bone and Joint Surgeons, 1974. Clin OrthopRelat Res. 1975(107):232-8

Clifford R. Wheelless III. “Frykman Classification” (2013).

Crecenete-Campo J, Borrajo E, Vidal A, Garcia-Fuentes M. New scaffolds encapsulating TGF- β3/BMP-7 combinations driving strong chondrogenic differentiation. Eur J Pharm Biopharm. 2017;114:69-78.

Centre MS. Further Research Melbourne: Melbourne Stem cell Centre; 2019.

Duscher D, Barrera J, Wong VW, et al. Stem Cells in Wound Healing: The Future of Regenerative Medicine? A Mini-Review. Gerontology. 2015;62(2):216-225. doi:10.1159/000381877

Das R, Timur UT, Edip S, Haak E, Wruck C, Weinans H, et al. TGF-β2 is involved in the preservation of the chondrocyte phenotype under hypoxic conditions. Annals of Anatomy - AnatomischerAnzeiger. 2015;198:1-10.

Diamanti-Kandarakis E, Dattilo M, Macut D, et al. MECHANISMS IN ENDOCRINOLOGY: Aging and anti-aging: a Combo-Endocrinology overview. European Journal of Endocrinology. 2017;176(6):R283-R308. doi:10.1530/eje-16-1061

Dunn AR. Intra-articular growth hormone injections regrow cartilage, increase motion and reduce pain in 93 per cent. of arthritic ankles. Osteoarthritis and Cartilage. 2012;20:S295-S6.

Fukumoto T, Sperling JW, Sanyal A, Fitzsimmons JS, Reinholz GG, Conover CA, et al. Combined effects of insulin-like growth factor-1 and transforming growth factor-beta1 on periosteal mesenchymal cells during chondrogenesis in vitro. Osteoarthritis Cartilage. 2003;11(1):55-64.
29. Ganceviciene R, Liakou AI, Theodoridis A, Makrantonaki E, Zouboulis CC. Skin anti-aging strategies. Dermato-Endocrinology. 2012;4(3):308-319. doi:10.4161/derm.2280
30. García-Rubíño M, Lozano-López C, M. Campos J. Inhibitors of Cancer Stem Cells. Anticancer Agents Med Chem. 2016;16(10):1230-9
31. Gato-Calvo L, Magalhaes J, Ruiz-Romero C, Blanco FJ, Burguera EF. Platelet-rich plasma in osteoarthritis treatment: review of current evidence. Ther Adv Graham M. What’s the Best Anti Aging Vitamins and Supplements for Men and Women? Youngevity Australia Distributor. December 28, 2019.
32. Gordon. S. Minimally Invasive Forefoot Surgery-Slater Planning Classification System. July 2018
33. Gordon. S. Foetal Healing Cascade - Can We Duplicate It In Adults? October 2019
34. Gordon. S. The Future of Medicine - Biologics and Artificial Intelligence October 2019
35. Gordon. S. Growth Factors and Articular Cartilage Rejuvenation: Where are we up to with reversing OA?. December 2019
36. Grande D, Schwartz J, Brandel E, Chahine N, Sgaglione N. Articular Cartilage Repair: Where We Have Been, Where We Are Now, and Where We Are Headed. Cartilage. 2013;4(4):281-5.
37. Gregory T, Gregory J, Sledge J, Allard R, Mir O. Surgery guided by mixed reality: presentation of a proof of concept. Acta Orthopaedica. 2018;89(5):480-3.
38. “Growth Plate Fractures”. orthoinfo.aaos.org, by the American Academy of Orthopaedic Surgeons (2014)
39. GB Monteggia. “Istituzioni Chirurgiche”. Volume 5. Milano, Pirotta and Maspero (1814).
40. Gautier H, Guicheux J, Grimandi G, Faivre-Chauvet A, Daculsi G, Merle C. In vitro influence of apatite-granule-specific area on human growth hormone loading and release. J Biomed Mater Res. 1998;40(4):606-13
41. Gill T, Safran M, Mandelbaum B, Huber B, Gambardella R, Xerogeanes J. (2018) A Prospective, Blinded, Multicenter Clinical Trial to Compare the Efficacy, Accuracy, and Safety of In-Office Diagnostic Arthroscopy With Magnetic Resonance Imaging and Surgical Diagnostic Arthroscopy. Arthroscopy. 2018;34(8):2429-35.
42. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, et al. Osteoarthritis. Lancet
43. Haeberle H, Helm J, Navarro S, Karnuta J, Schaffer J, Callaghan J, et al. Artificial Intelligence and Machine Learning in Lower Extremity Arthroplasty: A Review. J Arthroplasty. 2019;34(10):2201-3.
44. Hayashi M, Muneta T, Ju YJ, Mochizuki T, Sekiya I. Weekly intra-articular injections of bone morphogenetic protein-7 inhibits osteoarthritis progression. Arthritis Res Ther. 2008;10(5):R118.
45. Han Y, Huang H, Pan J, Lin J, Zeng L, Liang G, et al. Meta-analysis Comparing Platelet-Rich Plasma vs Hyaluronic Acid Injection in Patients with Knee Osteoarthritis. Pain Medicine. 2019;20(7):1418-29.
46. Im HJ, Li X, Muddasani P, Kim GH, Davis F, Rangan J, et al. Basic fibroblast growth factor accelerates matrix degradation via a neuro-endocrine pathway in human adult articular chondrocytes. J Cell Physiol. 2008;215(2):452-63.
47. Islam MM, McRae IS, Mazumdar S, Taplin S, McKetin R. Prescription opioid analgesics for pain management in Australia: 20 years of dispensing. Intern Med J. 2016;46(8):955-63.
48. John J Callaghan., et al. “The Adult Hip, Volume 1”. Lippincott Williams & Wilkins (2007): 958.
49. Jayabalan P, Hagerty S, Cortazzo MH. The use of platelet-rich plasma for the treatment of Osteoarthritis. The Physician and Sportsmedicine. 2014;42(3):53-62. doi:10.3810/psm.2014.09.2076
50. Karanges EA, Blanch B, Buckley NA, Pearson SA. Twenty-five years of prescription opioid use in Australia: a whole-of-population analysis using pharmaceutical claims. Br J Clin Pharmacol 2016;82(1):255-67.
51. Knippenberg M, Helder MN, Zandieh-Doulabi B, Wuisman PIJM, Klein-Nulend J. Osteogenesis versus chondrogenesis by BMP-2 and BMP-7 in adipose stem cells. Biochem Biophys Res Commun. 2006;342(3):902-8.
52. Lozada CJ. Osteoarthritis. Medscape 2019.
53. Liu-Bryan R, Terkeltaub R. Emerging regulators of the inflammatory process in osteoarthritis. Nat Re Rheumatol. 2015;11(1):35-44.
54. Lagasse E, Shizuru J, Uchida N, Tsukamoto A. Toward Regenerative Medicine Review requirement the demonstration that a clonogenic cell is. Immunity. 2001;14:425-436.
55. Landge AN, Radhakrishnan D, Kareem A, Prasad K. Intermediate Developmental Phases During Regeneration. Plant and Cell Physiology. 2018;59(4):707-712. doi:10.1093/pcp/pcy011
56. Lower Extremity Trauma - Board Review". OrthoConsult (2017).
57. Le ADK, Enweze L, DeBaun MR, Dragoo JL. Current Clinical Recommendations for Use of Platelet-
58. Rich Plasma. Curr Rev Musculoskelet Med. 2018;11(4):624
59. Liu MM, McIntyre L, Pugliese C, Fergusson D, Winston BW, Marshall JC, et al. Safety of cell therapy with mesenchymal stromal cells (SafeCell): a systematic review and meta-analysis of clinical trials. PLoS One. 2012;7(10):e47559.
60. Lee B. INVOSSA, a first-in-class of cell and gene therapy for osteoarthritis treatment: the phase III trial. OsteoarthrCartil. 2018;26:543-54.
61. Lew S, Cho J, Kim T, Lee M. Long-term follow-up assessment of the safety and efficacy of INVOSSA-K INJ., a novel cell mediated gene therapy for treatment of osteoarthritis. OsteoarthrCartil. 2019;27:5212.
62. Lohmander LS, Hellot S, Dreher D, Krantz EFW, Kruger DS, Guermazi A, et al. Intraarticular Spirifermin (Recombinant Human Fibroblast Growth Factor 18) in Knee Osteoarthritis: A Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis Rheum. 2014;66(7):1820-3
63. Malemud CJ. Biologic basis of osteoarthritis: state of the evidence. CurrOpinRheumato 2015;27(3):289-94.
64. Mayfield JK., et al. “Carpal dislocations: pathomechanics and progressive perilunar instability”. Journal of Hand Surgery 5.3 (1980):
65. Martin LM, G; Larssen, K; McDonald, G; Briggs, A; Whitfort, T; Brooks, P; Relf, I. Arthritis an
66. Mesko, Bertalan. Robotics in Robotics in Healthcare —— Get Ready. The Medical Futurist. 2019.
67. Mobasher A, Batt M. An update on the pathophysiology of osteoarthritisAnn Phys Rehabil Med. 2016;59(5):333-9.
68. Mo Costandi. Life after death: the science of human decomposition. the Guardian. May 5, 2015.
69. Miyakoshi N, Kobayashi M, Nozaka K, Okada K, Shimada Y, Itoi E. Effects of intraarticular administration of basic fibroblast growth factor with hyaluronic acid on osteochondral defects of the knee in rabbits. Arch Orthop Trauma Surg. 2005;125(10):683-92.
70. Markhardt B., et al. “Schatzker Classification of Tibial Plateau Fractures: Use of CT and MR Imaging Improves Assessment”. Radio
71. Nagao M, Hamilton JL, Kh R, Berendsen AD, Duan X, Cheong CW, et al. Vascular Endothelial Growth Factor in Cartilage Development and Osteoarthritis. Scientific Reports. 2017;7(1):13027.
72. National Health Survey: Australian Bureau of Statistics; 2017-18.
73. Otero M, Favero M, Dragomir C, Hachem KE, Hashimoto K, Plumb DA, et al. Human chondrocyte cultures as models of cartilage-specific gene regulation. Methods Mol Biol. 2012;806:301-36.
74. Osteoarthritis of the Knee Clinical Care Standard – Case for Improvement. Sydney, Care. ACoSaQiH; 2018.
75. Presnell E. Postmortem Changes: Overview, Definitions, Scene Findings. Medscape.com. July 7, 2020. https://emedicine.medscape.com/article/1680032-overview
76. Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A. Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 2013;41(2):356-64.
77. Phull AR, Eo SH, Abbas Q, Ahmed M, Kim SJ. Applications of Chondrocyte-Based Cartilage
78. Rayegani SM, Raeissadat SA, Taheri MS, Babaee M, Bahrami MH, Eliaispour D, et al. Does intra-articular platelet rich plasma injection improve function, pain and quality of life in patients with osteoarthritis of the knee? A randomized clinical trial. Orthop Rev (Pavia). 2014;6(3):5405.
79. Reinke JM, Sorg H. Wound Repair and Regeneration. Eur Surg Res. 2012;49:35-43.
80. Reznik AM, Urish K. Understanding the impact of artificial intelligence on orthopaedic surgery. AAOS Now. 2018;21
81. Rahmati M, Mobasher A, Mozafari M. Inflammatory mediators in osteoarthritis: A critical review of the state-of-the-art, current prospects, and future challenges. Bone. 2016;85:81-90.
82. Salomi M, Maciel R. Document Management and Process Automation in a Paperless Healthcare Institution. Technology and Investment. 2017;08(03):167-178
83. Shimono K, Oshima M, Arakawa H, Kimura A, Nawachi K, Kuboki T. (2010) The effect of growth factors for bone augmentation to enable dental implant placement: A systematic review. Japanese Dental Science Review. 46(1):43-53
84. Slater G, Huckstep R, Kirwan D. Management of Chondrosarcoma Including Modular Ceramic and Alumina Prosthetic Replacement. Aust N Z Surg. 1993
85. Sharma N, Slater G. Pantalar Arthrodesis Using the Fuse It Arthrodesis Plug in Charcot. EC Orthopaedics. 2019;10(2): 84-9
86. Scherne H and Oestern HJ. “A new classification of soft-tissue damage in open and closed fractures”. Unfallheilkunde 85.3 (1982):
87. Somashekar S, Sepúlveda M, Norden A, Rauthan A, Arun K, Patil P, et al. Early experience with IBM Watson for Oncology (WFO) cognitive computing system for lung and colorectal cancer treatment. JClinOncol.2017;35:8527.
88. Sophia Fox AJ, Bedi A, Rodeo SA. The basic science of articular cartilage: structure, composition, and function. Sports Health. 2009;1(6):461-8.
89. Scientists Are Developing A Gene Therapy That Could Delay Aging. WorldHealth. 2021.
90. Sereisky JB, Flatow EL, Andarawis-Puri N. Musculoskeletal regeneration and its implications for the treatment of tendinopathy. Int J Exp Pathol. 2013;94(4):293-303.
91. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012;51(2):249-
92. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. 2010;6(11):625-35.
93. Stem Cell Research and Regenerative Medicine | Principles of Rehabilitation Medicine | AccessMedicine | McGraw-Hill Medical. Mhmedical.com. 2021.
94. Spakova T, Rosocha J, Lacko M, Harvanova D, Gharaibeh A. Treatment of knee joint osteoarthritis with autologous platelet-rich plasma in comparison with hyaluronic acid. Am J Phys med Rehabil. 2012;91(5):411-7.
95. Singh NK, Shiwani S, Singh GR, Jeong D, Kinjavedkar P, Amarpal A, et al. TGF-β1 improves articular cartilage damage in Rabbit Knee. Pak Vet JI. 2012;32:412-7.
96. Schneider MC, Chu S, Randolph MA, Bryant SJ. An in vitro and in vivo comparison of cartilage growth in chondrocyte-laden matrix metalloproteinase-sensitive poly (ethylene glycol) hydrogels with localized transforming growth factor β3. Acta Biomaterialia. 2019;93:97-110.
97. Smith RL. Degradative enzymes in osteoarthritis. Front Biosci. 1999;4:D704-12.
98. Stages of decomposition. Stages of decomposition. The Australian Museum. 2020.
99. Top Regenerative Medicine Services. Exponent.com. 2020.
100. The Stages of Human Decomposition | Aftermath Services. Aftermath Services | Crime Scene Clean Up & Death Cleanup Professionals. August 31, 2017.
101. The Principles of Regenerative Medicine | Stem-cell therapy 1: Potential treatment of cerebral infarcts and spinal cord injury with mesenchymal stem cell transplantation | TRI Advances. Tri-kobe.org. 2019.
102. van der Kraan PM. Differential Role of Transforming Growth Factor-beta in an Osteoarthritic or a Healthy Joint. J Bone Metab. 2018;25(2):65-72.
103. van Lente H, Rip A. The Rise of Membrane Technology. Social Studies of Science. 1998;28(2):221-254. doi:10.1177/030631298028002002
104. Wang X, Hunter D, Xu J, Ding C. Metabolic triggered inflammation in osteoarthritis. Osteoarthritis Cartilage. 2015;23(1):22-30
105. Winquist RA., et al. “Closed intramedullary nailing of femoral fractures. A report of five hundred and twenty cases”. Journal of Bone and Joint Surgery. American Volume 66.4 (1984): 529-539.
106. https://www.medicaleconomics.com/technology/top-4-healthcare-trends-2019
107. https://www.medicinenet.com/biologics_biologic_drug_class/article.htm#what_is_a_biologic_drug_(biologics)?.2019
108. https://www.inc.com/james-paine/3-disruptive-technologies-shaping-future-of-healthcare.html. 2017.
109. https://www.ibm.com/watson-health/learn/artificial-intelligence-medicine (January 1, 2019)
110. https://www.bristolroboticslab.com/medical-robotics
111. https://www.mayoclinic.org/tests-procedures/bone-marrow-transplant/in-depth/stem-cells/art-20048117. 2019.
112. http://web.mit.edu/scicom/www/stemcells.html. 2005.
113. https://www.mayoclinicproceedings.org/article/S0025-6196(13)00477-1/pdf

This article was originally published in a special issue entitled “Regenerative medicine will need a reset of outcome measures and basic principles in medicine”, handled by Editor. Dr. Gordon Slater.