REVIEW ARTICLE

Japanese Laws and the Current Status of Regenerative Medicine in the Tohoku Region

Yuya Kamano[1], Noboru Terajima[2], Yuta Chiba[3], Venkata Suresh V[4], Masahiro Saito[5]

Abstract

Aim: The aim of this study was to review Japanese laws regarding regenerative medicine and the current status of clinical application of regenerative medicine, to learn about the advantages and problems, and to thereby serve as a reference for measures necessary for the development of regenerative medicine.

Background: Regenerative medicine started in 1957 with the transplantation of hematopoietic stem cells, followed by the establishment of embryonic stem cells in 1981 and induced pluripotent stem cells in 2006, and continues to evolve progressively. At the same time, however, problems have emerged due to lax legal regulations, such as the use of treatments that lack scientific evidence.

Review results: The Japanese government enacted two laws to regulate regenerative medicine: the Law to Ensure the Safety of Regenerative Medicine and the Amend the Pharmaceutical Affairs Law in 2013. These laws were enacted with the aim of providing safe regenerative medicine promptly and smoothly and developing many regenerative medicine products. In these laws, regenerative medicine is defined as medical treatment that restores lost functions of damaged organs and tissues with the help of cellular and tissue-based products. Nowadays, there are two major methods of regenerative medicine. One representative method involves the transplantation of devices that activates self-regenerative ability by introducing living cells into patients' body. The other method is the activation and differentiation of endogenous stem cells with cell growth and differentiation factors.

Conclusion: The current status of regenerative medicine in the Tohoku region after the enactment of these laws is described in detail. This clarified the advantages and disadvantages associated with regenerative medicine as it is currently practiced in Japan.

Clinical significance: Development of regenerative medicine in dentistry will be advanced by learning about its clinical application in medicine.

Keywords: Japanese Laws on Regenerative Medicine, Regenerative medicine, Tohoku region.

The Journal of Contemporary Dental Practice (2023): 10.5005/jp-journals-10024-3487

Background

Regenerative medicine is a promising technology that can provide a new approach to treating diseases and defects for which there were no treatment options available in the past.[1–3] On the other hand, ethical considerations are often required due to the use of cells and genes. In Japan, the discovery of induced pluripotent stem (iPS) cells has led to particularly high public expectations for regenerative medicine, but the technology is undeniably a mixed bag.[4,5] To rectify this situation, the Act on Comprehensive Promotion of Measures for Ensuring Prompt and Safe Access to Regenerative Medicine for the public was enacted on April 26, 2013. In addition, the following two laws were enacted in conjunction with each other, depending on the differences in the method of providing regenerative medicine:

- Law for Ensuring the Safety of Regenerative Medicine: This law was enacted for medical treatment at one's own expense and clinical research. It was enacted on November 20, 2013 and took effect on November 25, 2014 to establish standards for institutions providing regenerative medicine and cell culture processing facilities in order to ensure the safety of regenerative medicine.
- Pharmaceutical Affairs Law Revision Act: It was enacted on November 20, 2013 and enforced on November 25, 2014 to establish a new approval and licensing system based on the characteristics of regenerative medical products in order to accommodate the practical application of regenerative medicine.

Although these laws have made it possible to obtain some assurance regarding safety, however, it is true that questions remain regarding scientific validity. One reason for this is the flow of the Law for Ensuring the Safety of Regenerative Medicine.

Regenerative medicine using specific cellular processed materials, which is mainly performed as medical treatment at one's own expense, can be performed by applying to the Ministry of Health, Labour and Welfare based on the Law for Ensuring the Safety of Regenerative Medicine. The risk classification is based on the type of specific cell-processed products used and the method of administration, and the application procedure differs according to the risk classification. Type I regenerative medicine is high-risk medicine that uses cells whose safety has not been adequately established, which includes using embryonic stem (ES) cells, iPS cells, iPS cell-like

[1–3]Tohoku Health and Welfare Bureau, Ministry of Health, Labour and Welfare, 1-1-20 Kakyoin, Aoba-ku, Sendai, Miyagi, 981-0952, Japan

[4,5]Division of Operative Dentistry, Department of Ecological Dentistry, Graduate School of Dentistry, Tohoku University, 4-1 Seiryo-machi, Aoba-ku, Sendai, Miyagi, 980-8575, Japan

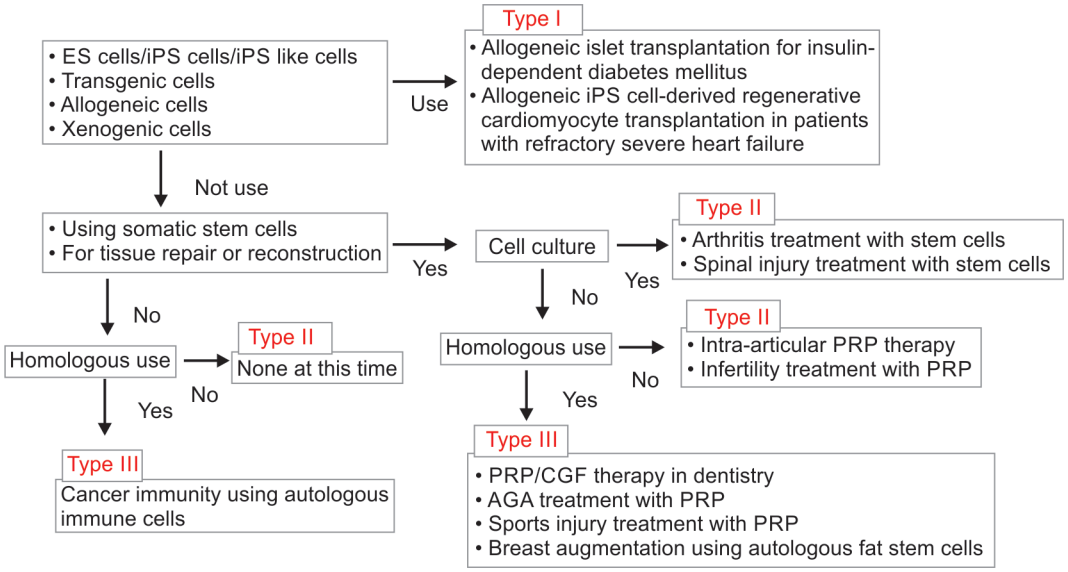
Corresponding Author: Yuya Kamano, Tohoku Health and Welfare Bureau, Ministry of Health, Labour and Welfare, 1-1-20 Kakyoin, Aoba-ku, Sendai, Miyagi, 981-0952, Japan, Phone: +81 227269263, e-mail: kamano-yuuya.3t9@mhlw.go.jp

How to cite this article: Kamano Y, Terajima N, Chiba Y, *et al.* Japanese Laws and the Current Status of Regenerative Medicine in the Tohoku Region. J Contemp Dent Pract 2023;24(2):120–128.

Source of support: Nil

Conflict of interest: None

Flowchart 1: Risk classification of regenerative medicine in Japan. The Japanese regenerative medicine is risk classified using the flowchart. What kinds of cells were used, what is the purpose of regenerative medicine, whether cell culture was performed, and whether it is a homologous use are taken into consideration. The classification is made from type I to type III, and a typical example of the treatment is described in each flowchart



cells, and allogeneic cells (Flowchart 1). Type II regenerative medicine is a medium-risk medicine that uses cells with relatively assured safety. Most medical treatments using autologous somatic stem cells are included in this category, but the risk classification is divided according to whether the cells are cultured or homologous used (Flowchart 1). Homologous use refers to a method of administering cells that have the same function as the cells in the area where the harvested cells are to be used for regenerative medicine. For example, fat cells are harvested from the abdomen and administered to the affected area after breast cancer surgery for the purpose of breast reconstruction. Type III regenerative medicine is a relatively low-risk treatment that uses processed somatic cells. Platelet-rich plasma (PRP) and concentrated growth factor (CGF), which are commonly used in dentistry, are included in this category, and are performed by many general practitioners (Flowchart 1). Regenerative medicine is further divided into clinical research and treatment, where applications submitted as treatment are already safe and scientifically valid, and applications submitted as clinical research are safe but scientific validity is not yet clear. If the safety and scientific validity of the treatment have been sufficiently established through clinical research, it is reapplied as a treatment. Type I regenerative medicine is subject to review by the Specified Authorized Committee for Regenerative Medicine, and then submitted to the Health Sciences Council, which decides whether or not it can be offered. These technologies have undergone multiple reviews, and it is believed that their safety and scientific validity have been thoroughly reviewed and implemented. On the other hand, although type II and type III regenerative medicines have been submitted to a review committee, a small number of committee members review a large number of diseases, and the current situation is that they have not been sufficiently reviewed. In addition, although the medical plan is supposed to be prepared by a representative of the provider institution, the representative often lacks legal knowledge, and sometimes inadequate provision plans are submitted.

In this review article, we would like to discuss the problems and points for improvement based on actual cases of regenerative medicine currently being performed in the Tohoku region, which falls within the author's jurisdiction. The Tohoku region consists of six prefectures: Aomori, Iwate, Akita, Yamagata, Fukushima, and Miyagi, and the central city is Sendai, Miyagi Prefecture. It is home to one of Japan's major universities, Tohoku University, and although it has the background to promote regenerative medicine, it has not yet advanced as far as other regions. In this review article, we will explore the reasons for this situation.

Review Results

Applications of Regenerative Medicine in the Tohoku Region

Data Collection Methods

The Tohoku Regional Bureau of Health and Welfare, of which the author is member, is an agency of the Ministry of Health, Labour and Welfare, and provision plans for regenerative medicine to be performed in the Tohoku region are submitted. The author is also in a position to check for any deficiencies in the submitted provision plans. Statistics on the number of provision plans for regenerative medicine in Japan have begun since 2016, and the data used in this review are a compilation of data published by the Ministry of Health, Labour, and Welfare on its website and in handouts.

Number of Regenerative Medicine Registrations in Japan and the Tohoku Region

As of November 2022, 7 provision plans for type I regenerative medicine as treatment and 17 as research have been registered in Japan, and 1 provision plan as treatment and 0 as research have been registered in the Tohoku region (Table 1).

As of November 2022, a total of 1,224 provision plans for type II regenerative medicine that are being conducted as treatment and 43 provision plans that are being conducted as research have been registered nationwide. Themes range from knee arthritis to infertility treatment. In the Tohoku region, 19 provision plans conducted as treatment and 1 provision plan conducted as research are registered (Table 1).

Table 1: The number of registered regenerative medicine provision plans by year

		2016		2017		2018		2019		2020		2021		2022	
		Tohoku	*Japan*	*Tohoku*	*Japan*	*Tohoku*	*Japan*	*Tohoku*	*Japan*	*Tohoku*	*Japan*	*Tohoku*	*Japan*	*Tohoku*	*Japan*
Type I	Treatment	0	2	0	0	0	0	0	0	0	0	1	3	1	7
	Research	1	10	1	17	1	17	1	19	0	19	0	18	0	17
Type II	Treatment	0	35	0	82	0	127	6	226	9	457	13	727	19	1,224
	Research	0	25	2	40	2	59	2	65	1	69	1	54	1	43
Type III	Treatment	173	2,456	162	3,321	169	3,403	153	3,344	134	3,354	130	3,360	138	3,717
	Research	1	42	0	51	0	55	1	62	1	64	1	57	1	44

- Treatment: It has already been scientifically validated and is used as a treatment
- Research: The safety of the treatment has been ensured, but the scientific validity is not sufficient and the treatment is still in the research stage
- JAPAN: The number of applications for Japan as a comparison

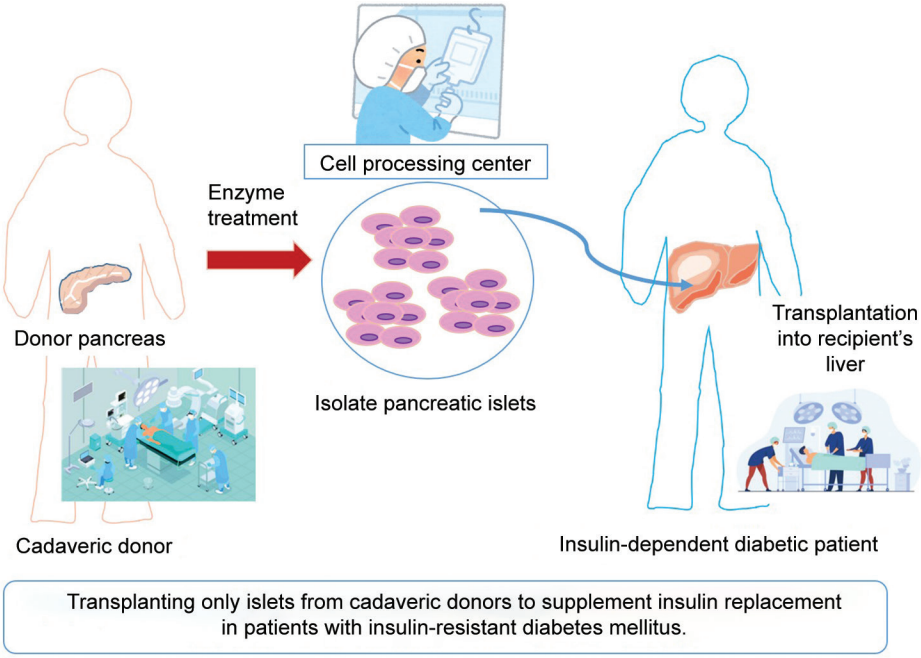


Fig. 1: Flow of allogeneic pancreatic head transplantation for insulin-resistant diabetes mellitus. The pancreas is removed from a cadaveric donor, and only the pancreatic head is isolated by enzymatic treatment to remove impurities. The isolated pancreatic head is transplanted into the liver of an insulin-resistant diabetic patient. A single pancreas can be transplanted into multiple patients, reducing the frequency of insulin administration and weaning patients from dialysis

As of November 2022, 3,717 provision plans for type III regenerative medicine for cancer immunology and sports injuries and 44 provision plans for research have been registered in Japan. Most of these registrations are made by dental clinics. Concentrated growth factor and platelet-rich plasma are the main treatment modalities performed in the dentistry. In the Tohoku region, 138 provision plans are registered as treatment and one as research (Table 1).

Type I Regenerative Medicine in the Tohoku Region

Allogeneic Islet Transplantation for Insulin-dependent Diabetes Mellitus

It is estimated that about 115,000 people in Japan suffer from insulin-dependent diabetes mellitus. The disease occurs when β cells in the pancreas collapse and cease to function due to autoantibodies. Insulin replacement is necessary to control blood glucose, and if left untreated, causes retinopathy, nephropathy, and neuropathy.[6] In this treatment, islets that are from the pancreas of an organ donor are isolated and transplanted after brain death or cardiac arrest, with the expectation of therapeutic effects on diabetes, such as stabilization of blood glucose levels, disappearance of hypoglycemic attacks, and reduction of insulin requirements (Fig. 1). Compared to pancreas transplantation, islet transplantation has advantages, including the possibility of isolating many islets from a single donor pancreas and transplanting them into multiple recipients, but it also has the disadvantage that the clinical outcome is worse than that of pancreas transplantation.[7] Therefore, pancreas transplantation has become the first choice at

present. It is hoped that the clinical outcome of islet transplantation will be improved, or that islets will be produced from iPS cells and transplanted.[8] Plans are also underway to transplant pig islets.[9]

Allogeneic islet transplantation began at the University of Minnesota in 1974,[10] and 267 allogeneic islet transplants were performed from 1990 to 1998.[11] As a result, insulin withdrawal for more than one week was achieved in 12.7% of patients and more than one year was achieved in 8.2% of patients.[11] In Japan, islet transplantation began in 2004, and by 2007, 18 islet transplantations had been performed with favorable results.[12] Subsequently, the efficacy of allogeneic islet transplantation was confirmed through a multicenter collaborative study, and the procedure was listed on the health insurance list in 2020. In the Tohoku region, islet transplantation is currently available only at Tohoku University Hospital, but the number of patients is small due to donor problems. The other six clinics offering this treatment are the National Center for Global Health and Medicine in Tokyo, Fujita Medical University Hospital in Aichi Prefecture, Kyoto University Hospital in Kyoto Prefecture, Osaka University Hospital in Osaka Prefecture, Fukuoka University Hospital in Fukuoka Prefecture, and Nagasaki University Hospital in Nagasaki Prefecture. Another medical institution currently preparing to apply for allogeneic islet transplantation is Hokkaido University Hospital in Hokkaido. These medical institutions were multicenter research facilities when islet transplantation was in the research phase and became treatment provider institutions after the research was completed. However, the shortage of donors is severe, as only about four transplants have been performed cumulatively since the year the provision plan was submitted: two at Kyoto University Hospital and two at Fukuoka University Hospital. The results of each transplant are under follow-up and are not available in detail. Since allogeneic cells are used, this is a type I regenerative medicine (Flowchart 1).

Type II Regenerative Medicine in the Tohoku Region

Platelet-rich Plasma Therapy for Osteoarthritis

Osteoarthritis occurs when the cartilage in joints wears away due to various causes. This results in limited joint mobility and pain. The knee and hip joints are most commonly affected, but it can also occur in the elbow and finger joints. Treatment has so far included anti-inflammatory medications, intra-articular steroid and hyaluronic acid injections, and joint replacements, but now, as an intermediate treatment, PRP is being used.

Platelet-rich plasma is produced by centrifugation of autologous blood and is known to contain high levels of growth factors.[13] When PRP is injected into a damaged joint, the growth factors are thought to repair the surrounding tissue and relieve pain. In a study comparing hyaluronic acid injections with PRP treatment for knee osteoarthritis, about 60% of patients experienced significant improvement in visual analogue scale (VAS) scores after 6 months.[14] On the other hand, there was no clear difference in tissue repair. This suggests that PRP contributes to the improvement of joint function mainly through its anti-inflammatory effect, but further research is needed to understand the mechanism of action.

The number of clinics offering this treatment is gradually increasing in the Tohoku region, with 10 clinics offering the treatment. Currently, there are no safety issues, and there have been numerous reports of pain relief and improved joint mobility. It is expected that this area will be further promoted in the future. Although PRP is produced using autologous peripheral blood, it is not considered a homologous use because it is injected into the joint cavity with poor blood flow and is defined as a type II regenerative medicine (Fig. 1).

Somatic Stem Cell Therapy for Osteoarthritis

Adipose[15] and bone marrow[16] mesenchymal stem cells are the main stem cells used in stem cell therapy, and recently dental pulp stem cells are also used in some cases.[17] Stem cells are characterized by their ability to modulate inflammation and are expected to alleviate inflammation when administered.[18–24] Unlike PRP, some reports indicate that stem cells are directly involved in cartilage tissue repair, but the number of reports are insufficient, and further accumulation of such data is expected.

In the Tohoku region, the only stem cell therapy for osteoarthritis is the use of fat stem cells, and there is only one clinic that offers this therapy. Adipose-derived stem cells are isolated from abdominal fat tissue and cultured to increase their number. Once a sufficient number of adipose stem cells are obtained, they are mixed with Ringer's solution and injected into the joint cavity where the cartilage tissue has been destroyed (Fig. 2). Although the procedure has only been in use for less than a year, there have already been more than 100 cases, where pain relief and improvement in range of motion have been reported. Although it uses autologous stem cells, it is classified as type II regenerative medicine because it involves cell culture (Flowchart 1).

Platelet-rich Plasma Therapy for Infertility

Pregnancy is achieved through the processes of fertilization and implantation. Infertility is caused by each of these processes. Currently, there are two types of PRP treatment for infertility: one for the ovaries (Fig. 3A) and the other for the endometrium (Fig. 3B). Oocyte number and quality are important in the treatment of infertility, but both are known to decline with age. Recent reports on PRP in the ovary have shown that intracytoplasmic PRP injection is effective in patients with low ovarian response and greatly improved hormonal profiles and ovarian reserve. Approximately 60% of patients with premature ovarian dysfunction recovered menstruation and showed statistically significant improvements in ovarian reserve, follicle-stimulating hormone, and follicular follicle count. Approximately 40% of perimenopausal patients responded positively to PRP treatment. Approximately 80% of perimenopausal patients had regular menstrual periods, improved hormone levels, and follicular follicle counts.[25] The ovary is an active structure for angiogenesis, and various platelet factors are known to activate angiogenesis. Based on these findings, it is expected that the application of PRP to the ovaries will promote tissue regeneration by the essential factors for angiogenesis and normal vascular function contained in PRP, thereby strengthening dysfunctional pre- and postmenopausal ovarian tissue and improving the number and quality of oocytes.

The endometrium plays an important role in implantation, and it has been reported that implantation is difficult when the thickness of the endometrium is less than 7 mm.[26–28] Endometrial thinning can be caused by a variety of factors, but lack of blood flow to the endometrium is one factor. In a report of PRP applied to the endometrium, a comparison of blood flow in the endometrium before and after administration showed that PRP administration improved blood flow in the endometrium. The authors concluded that this was the result of tissue regeneration due to the effects of cytokines and growth factors contained in PRP.[29] On the other hand, it was also reported that six out of nine pregnancies were achieved

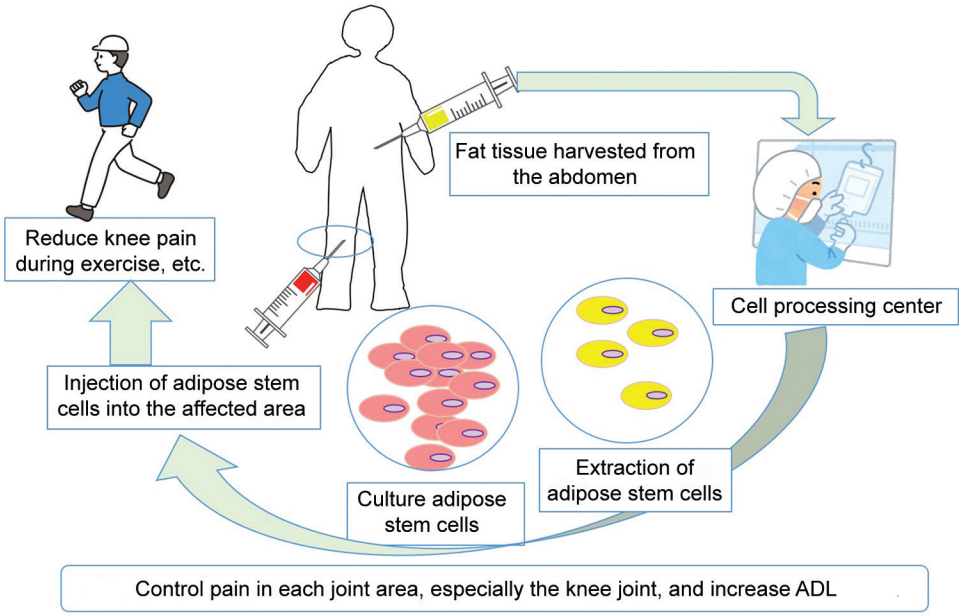


Fig. 2: Treatment flow of osteoarthritis of the knee with fat stem cells. Extract fat from the abdomen and isolate only adipose stem cells. Isolated adipose stem cells are cultured and increased to a sufficient number. The increased number of fat stem cells is injected into the affected area. The pain during exercise is reduced, leading to improvement of activities of daily living (ADL). Some clinics claim that worn-out cartilage tissue can be regenerated, but the scientific evidence is still weak

after PRP administration followed by embryo transfer in patients with secondary implantation failure.[30] Based on these results, it is expected that the application of PRP to the endometrium improves blood flow in the endometrium and is effective in improving implantation failure (Fig. 4).

In the Tohoku region, there are two medical institutions that offer PRP treatment for the ovaries and four clinics offering PRP for the endometrium. With the advancements of infertility treatment in recent years, both the number of patients receiving and the number of clinics performing PRP treatment have increased. However, this treatment is a treatment at one's own expense and is not covered by advanced medical treatment, so it cannot be used for infertility treatment covered by insurance. We hope that in the future, we can do more research and that this treatment can be included in advanced medical treatment and eventually under health insurance. Although PRP is used, it is not considered a homologous use because it is applied to the ovaries, which have poor blood flow, and thus is classified as type II regenerative medicine. On the other hand, the endometrium is not a considered homologous use even though it has abundant blood flow. Therefore, it is a type II regenerative medicine (Flowchart 1), suggesting that the definition of homologous use is ambiguous.

Type III Regenerative Medicine in the Tohoku Region

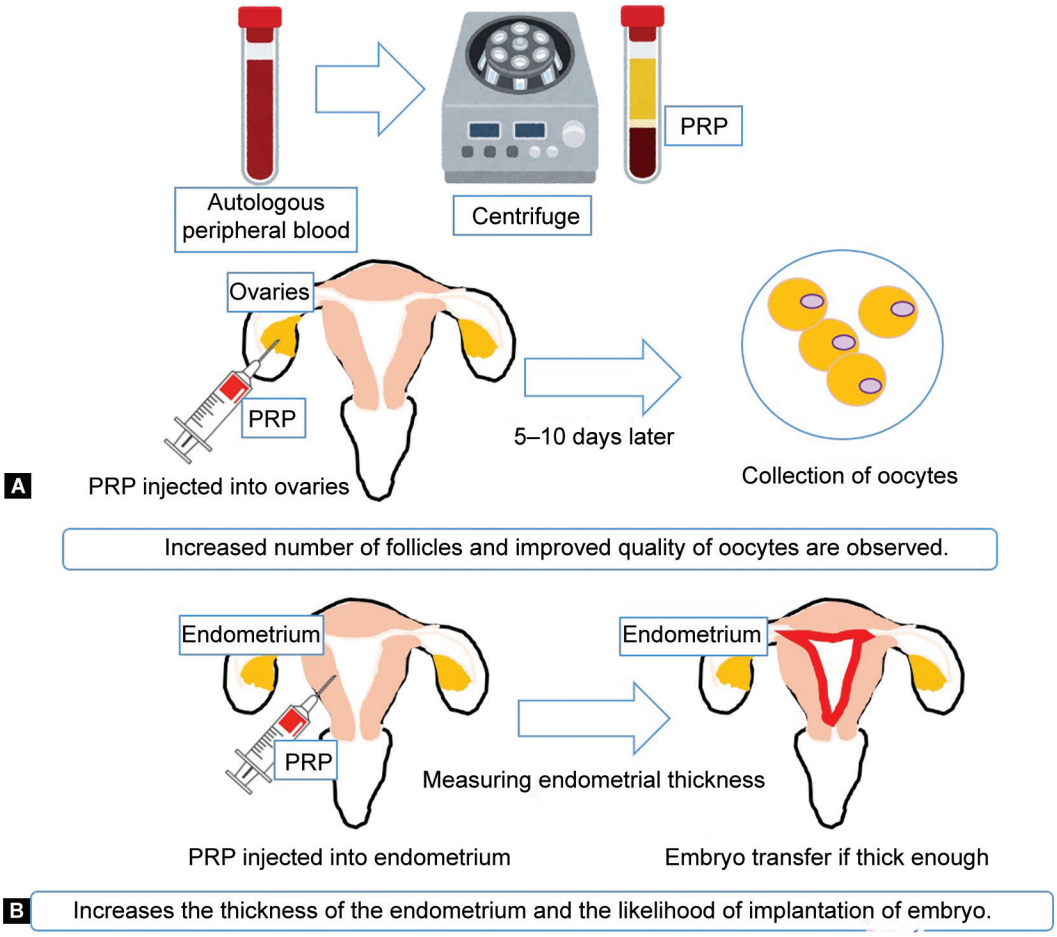
PRP Therapy for Sports Injuries (Muscle, Tendon, and Ligament Injuries)

The goal of PRP therapy for sports injuries is early recovery of the affected area. Soft tissues such as muscles, tendons, and ligaments are damaged by overuse during sports or by temporary strong external pressure. All of these injuries heal over time if they are mild, but they are known to become intractable if the patient continues to play sports while enduring pain. Especially for professional athletes, a quick recovery from injury is directly related to their own success, and an early recovery is desirable. There are numerous reports on PRP treatment of sports injuries, inflammation of the Achilles tendon, patellar tendon, and external epicondyle of the elbow and have been shown to be effective in improving pain in all cases compared to the administration of local anesthetics.[31–33] Platelet-rich plasma has also been shown to be effective in ligament injuries, with 88% of 34 athletes with partial tears of the medial collateral ligament of the elbow reported to benefit from PRP treatment.[34]

Platelet-rich plasma is considered to be a homologous use because it is injected into tissues with high blood flow and is classified as a type III regenerative medicine. There are six clinics in the Tohoku region where this treatment is available, and most of these clinics also offer intra-articular administration, a type II regenerative medicine (Flowchart 1).

Cancer Immunotherapy

Cancer immunotherapy is becoming increasingly important as a fourth treatment modality following surgical resection, radiation therapy, and chemotherapy. Cancer immunotherapy can be broadly classified into those included in standard treatments such as immune checkpoint inhibitors including Programmed death receptor-1 (PD-1) inhibitors and other therapies.[35] Cancer immunotherapies covered by the Law for Ensuring the Safety of Regenerative Medicine are included in other therapies and mainly include effector T-cell therapy (CAR-T therapy) and therapies that activate autologous natural killer (NK) cells and dendritic cells.[36] Cancer immunotherapy using CAR-T cells is classified as type I regenerative medicine because it uses genetically engineered cells, while type III regenerative cancer immunotherapy in the Tohoku region mainly uses NK cells and dendritic cells. The CAR-T therapy has already been approved by insurance in Japan for the treatment of some hematologic cancers. Cancer immunotherapy using NK cells and dendritic cells, on the other hand, is offered as an uninsured treatment. In addition, cancer immunotherapy using induced



Figs 3A and B: Plasma-rich platelet infertility treatment. (A) PRP for the ovaries: PRP obtained by centrifugation of autologous peripheral blood is injected transvaginally into the ovary. After 5–10 days, the follicles are removed from the ovaries. Increased number of follicles and increased maturity of oocytes are observed with PRP indication; (B) PRP for endometrial application: PRP obtained by centrifugation of autologous peripheral blood is injected transvaginally into the endometrium. Thickening of the thickened endometrium is measured, and if sufficient thickness is obtained, embryo transfer is performed. It is believed that the thickness of the endometrium must be at least 7 mm for implantation in the uterus, and it has been observed that the thickness of the endometrium increases when PRP is injected, resulting in an increased chance of pregnancy

pluripotent stem cell-derived natural killer T cells (iPS-NKT cells) differentiated from iPS cells is in the research stage.[37] Incidentally, iPS-NKT cells and CAR-T cells are treated as regenerative medical products and are therefore restricted in many cases not by the Law for Ensuring the Safety of Regenerative Medicine, but by the Law to Amend the Pharmaceutical Affairs Law.

Cancer immunotherapy using NK cells and dendritic cells is the only cancer immunotherapy being offered in the Tohoku region. A total of 25 provision plans were submitted by 5 medical institutions. The scientific validity of these therapies is mainly based on their effectiveness in treating prostate cancer.[38] However, the range of indications for treatment extends mainly to solid tumors in general, and some doubts remain. It is a homologous use because it uses autologous immune cells to use them as immune cells, and it is not intended to regenerate or reconstruct tissue. Therefore, it is classified as type III regenerative medicine (Fig. 1).

PRP/CGF Therapy in Dental Treatment

Currently, PRP and CGF, which are applied by extracting platelet components from autologous blood, are the main regenerative medicines used in dentistry (Flowchart 1). Platelet-rich plasma (PRP)/concentrated growth factor (CGF) is applied to patients with inadequate jawbone, either alone or in combination with a bone replacement material, for implant placement or maxillary sinus floor elevation. Although there are many reports showing that it suppresses inflammation and relieves pain in the surgical site,[39–41] there are few reports related to bone regeneration in the same area. On the other hand, some reports suggest that controlling inflammation is important for bone regeneration,[42] and PRP/CGF may help in regeneration of new bone.[43] For PRP and CGF, many manufacturing kits are available and often do not require special aseptic areas such as clean benches. Many general practitioners can prepare and provide PRP and CGF using only a dedicated kit and a centrifuge, and many general practitioners do so. Despite the fact that these therapies are widely used throughout Japan, data collection is insufficient and continuous investigation is considered necessary. They are also widely indicated in the Tohoku region and are often used in conjunction with implant placement. In addition, some studies have applied CGF to the treatment of apical periodontitis, and the results of these studies are awaited for publication. Platelet-rich plasma (PRP)/concentrated growth factor (CGF) is used, and because it is applicable to areas with abundant

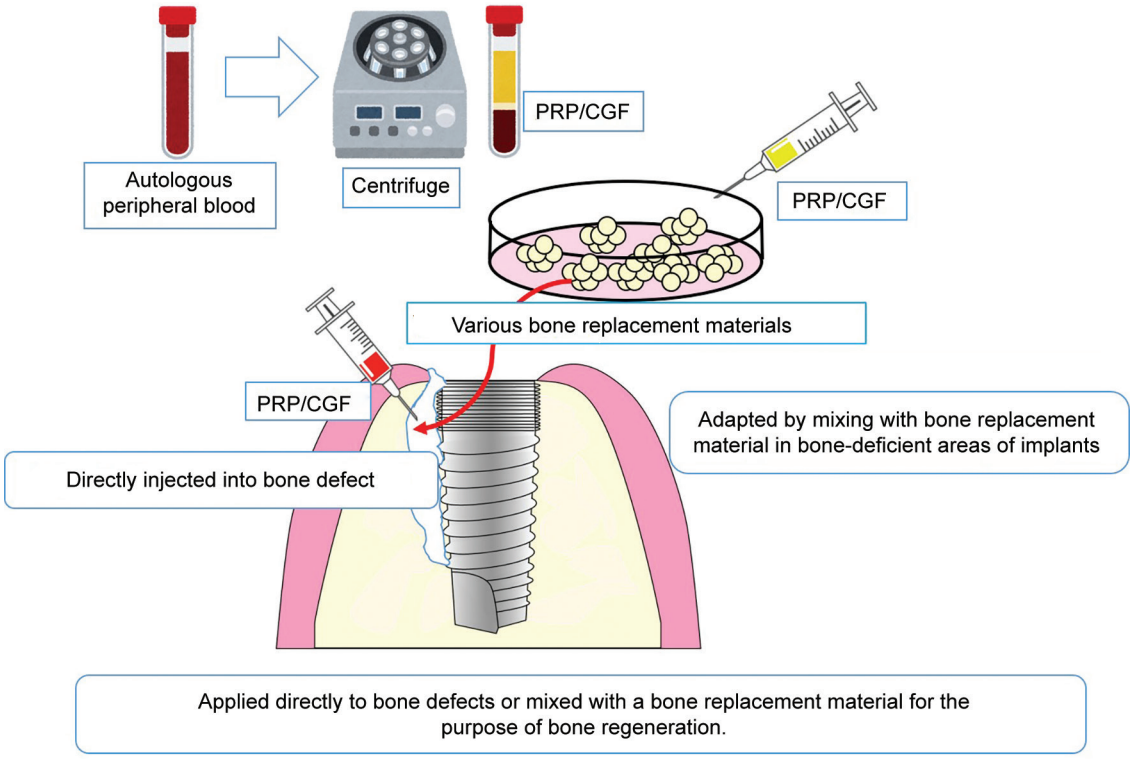


Fig. 4: Platelet-rich plasma (PRP)/concentrated growth factor (CGF) is indicated during implant treatment. In dental implant treatment, the bond between the implant and the alveolar bone is important, but the bone volume is often insufficient. Platelet-rich plasma (PRP)/concentrated growth factor (CGF) can be applied directly to areas where bone volume is insufficient, or PRP/CGF can be mixed with various bone replacement materials to secure sufficient bone volume. Although PRP/CGF seems to reduce inflammation and pain in the surgical site, it is unclear whether PRP/CGF contributes to bone regeneration in the same area

blood flow, and is considered a homologous use and classified as a type III regenerative medicine (Flowchart 1).

Discussion

Problems with the Regenerative Medicine Law

Although the law was enacted in 2013 and is still in its infancy, technological developments in regenerative medicine have overcome the law in some areas. When the law was first enacted, it covered so-called *ex vivo* cellular therapies, but many therapies that affect the differentiation and proliferation of cells within cells, such as *in vivo* gene therapy[44,45] and exosome therapy,[46,47] have also become more common. These therapies are undoubtedly also cell-based therapies and can be considered a type of regenerative medicine. Platelet-rich plasma-freeze dry (PRP-FD), in which PRP is freeze-dried[48] and only growth factors are administered, has also become popular in recent years.[49] This treatment is not covered by the law because the cellular component is removed. The mechanism of action is considered to be similar to that of PRP, but the scientific basis is unclear compared to PRP, and it is important to gather more knowledge in the future. In addition, some regulation may be required as it falls outside the scope of the law by removing the cellular component. A similar product used in the field of cosmetic surgery is a stem cell culture solution in which mesenchymal stem cells are cultured and the cellular components are removed.[50] Although it does not contain cells, it is believed to be effective in skin regeneration due to growth factors that are eluted during culture.

Another issue is the documentation to be submitted to the Ministry of Health, Labour and Welfare by the medical institution providing the product. Medical institutions submit the documents to the Ministry of Health, Labour and Welfare after the committee's review, but currently, the regenerative medicine is so diverse that the committee may not be able to adequately review the documentation. We are seeking to ensure the quality of the committee and at the same time feel that some sort of specialized administrative body is needed.

Issues in Regenerative Medicine

The problem with Type I regenerative medicine is the small number of providing medical institutions. However, there are already some treatments covered by health insurance, such as allogeneic pancreatic islet transplantation for insulin-dependent diabetes mellitus. It is also true that there are many hurdles to overcome, such as the small number of donors and difficulties in processing technology and facilities. To this end, it might be useful to establish a new system to overcome the barrier from basic research to clinical research.

The problem with type II regenerative medicine is the small number of institutions offering it and the resulting lack of scientific evidence. The number of institutions providing this type of regenerative medicine is increasing steadily, and it is expected to continue to develop in the future.

The problem with type III regenerative medicine is the growing number of providers. The most important of these procedures are related to dentistry and since many general practitioners are

involved in this field, I believe that there is not enough assurance of their skills and knowledge. In addition, although there are many cases of regenerative medicine being performed by individual practitioners, it is thought that there are not enough studies on the effectiveness of regenerative medicine. We understand that it is difficult to obtain sufficient data in the busy clinical schedule, but we hope to see further studies on the efficacy of regenerative medicine

Issues of Regenerative Medicine in the Tohoku Region

As shown in Table 1, there are fewer institutions providing regenerative medicine in the Tohoku region than in other regions of Japan. This may be partly due to the fact that the Kanto regions, where there are many institutions, is home to the University of Tokyo and Keio University, while the Kinki region has Kyoto University and Osaka University. Another reason is regional characteristics. Perhaps because of the heavy snowfall in the region, many people are basically reluctant to try new things. Although the safety and scientific validity of many regenerative medicines have already been recognized, whether or not the general public accepts is another matter. More importantly, regenerative medicine is mostly medical treatment at one's own expense, and many of these therapeutic procedures are expensive. Therefore, although regenerative medicine tends to be avoided by the general public, there are many useful techniques, and it would be desirable if they could first be performed in large medical institutions such as university hospitals.

Nevertheless, the number of type II regenerative medicine, for which the scientific basis is relatively well established, is gradually increasing, while the number of type III regenerative medicine, for which the scientific basis is weak, is slightly decreasing (Table 1). This is a good trend in itself, but it is unfortunate that the number of type I regenerative medicine is not increasing (Table 1). Since Tohoku University is a top public university in the Tohoku region, it would be great if it could promote cutting-edge research in regenerative medicine through industry–academia collaboration.

Conclusion

While the field of regenerative medicine has made dramatic progress since the discovery of ES cells and iPS cells, there have also been institutional problems. Therefore, in 2013, Japan enacted a law on regenerative medicine with the aim of providing regenerative medicine in a timely and safe manner. As a result, new treatment methods and regenerative medicine products have been developed for cases that were previously difficult to treat. However, there are still some regenerative medicines that lack scientific evidence, and further research is needed. In addition, it is necessary to revise the law for new therapies that did not exist when the law was established, such as *in vivo* gene therapy, therapies that do not include cellular components and are therefore not covered by the law, such as PRP-FD and stem cell culture media.

Clinical Significance

There are few examples of clinical applications of regenerative medicine in dentistry, and the scope could be expanded by referring to medical science.

Limitation

The opinion is solely that of the authors and does not reflect the views of Ministry of Health, Labour and Welfare or any related institutions.

Acknowledgments

The authors appreciate the support of Ministry of Health, Labour and Welfare, Tohoku Regional Bureau of Health and Welfare, Medical Affairs Division.

References

1. Thomas ED, Lochte HL Jr, Lu WC, et al. Intravenous infusion of bone marrow in patients receiving radiation and chemotherapy. N Engl J Med 1957;257(11):491–496. PMID: 13464965.
2. Sawa Y, Miyagawa S. Cell sheet technology for heart failure. Curr pharm biotechnology. 2013;14(1):61–66. PMID: 23437937.
3. Mandai M, Kurimoto Y, Takahashi M. Autologous induced stem-cell-derived retinal cells for macular degeneration. N Engl J Med 2017;377(8):792–793. PMID: 28834478.
4. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 2006;126(4):663–676. PMID: 16904174.
5. Takahashi K, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131(5):861–872. PMID: 18035408.
6. Ikegami H, Noso S, Babaya N, et al. Genetics and pathogenesis of type 1 diabetes: Prospects for prevention and intervention. J Diabetes Invest 2011;2(6):415–420. PMID: 24843523.
7. Shapiro AM, Lakey JR, Ryan EA, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343(4):230–238. PMID: 10911004.
8. Yabe SG, Fukuda S, Nishida J, et al. Induction of functional islet-like cells from human iPS cells by suspension culture. Regener Ther 2019;10:69–76. PMID: 30623004.
9. Kano M, Mizutani E, Homma S, et al. Xenotransplantation and interspecies organogenesis: Current status and issues. Front endocrinol 2022;13:963282. PMID: 35992127.
10. Najarian JS, Sutherland DE, Matas AJ, et al. Human islet transplantation: A preliminary report. Transplant Proc 1977;9(1):233–236. PMID: 405770.
11. Nagata H, Matsumoto S, Okitsu T, et al. In situ cooling of pancreata from non-heart-beating donors prior to procurement for islet transplantation. Transplant Proc. 2005;37(8):3393–3395. PMID: 16298604.
12. Saito T, Gotoh M, Satomi S, et al. Islet transplantation using donors after cardiac death: report of the Japan Islet Transplantation Registry. Transplantation 2010;90(7):740–747. PMID: 20811319.
13. Alves R, Grimalt R. A review of platelet-rich plasma: History, biology, mechanism of action, and classification. Skin Appendage Dis 2018;4(1):18–24. PMCID: 5806188.
14. Shen L, Yuan T, Chen S, et al. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: Systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res 2017;12(1):16. PMCID: 5260061.
15. Si Z, Wang X, Sun C, et al. Adipose-derived stem cells: Sources, potency, and implications for regenerative therapies. Biomed pharmacother 2019;114:108765. PMID: 30921703.
16. Arthur A, Gronthos S. Clinical application of bone marrow mesenchymal stem/stromal cells to repair skeletal tissue. Int J Mol sc 2020;21(24):9759. PMCID: 7767389.
17. Bar JK, Lis-Nawara A, Grelewski PG. Dental pulp stem cell-derived secretome and its regenerative potential. Int J Mol sci 2021;22(21): 12018. PMCID: 8584775.
18. Pers YM, Rackwitz L, Ferreira R, et al. Adipose mesenchymal stromal cell-based therapy for severe osteoarthritis of the knee: A phase I dose-escalation trial. Stem Cells Transl med 2016;5(7):847–856. PMCID: 4922848.
19. McIntyre JA, Jones IA, Han B, et al. Intra-articular mesenchymal stem cell therapy for the human joint: A systematic review. Am J Sports Med 2018;46(14):3550–3563. PMID: 29099618.

20. Yokota N, Hattori M, Ohtsuru T, et al. Comparative clinical outcomes after intra-articular injection with adipose-derived cultured stem cells or noncultured stromal vascular fraction for the treatment of knee osteoarthritis. Am J Sports Med 2019;47(11):2577–2583. PMID: 31373830.
21. Mardones R, Jofre CM, Tobar L, et al. Mesenchymal stem cell therapy in the treatment of hip osteoarthritis. J Hip Preserv Surg 2017;4(2): 159–163. PMID: 28630737.
22. Emadedin M, Ghorbani Liastani M, Fazeli R, et al. Long-term follow-up of intra-articular injection of autologous mesenchymal stem cells in patients with knee, ankle, or hip osteoarthritis. Arch Iran Med 2015;18(6):336–344. PMID: 26058927.
23. Freitag J, Wickham J, Shah K, et al. Effect of autologous adipose-derived mesenchymal stem cell therapy in the treatment of acromioclavicular joint osteoarthritis. BMJ Case Rep 2019;12(2): e227865. PMCID: 6398814.
24. Centeno CJ, Freeman MD. Percutaneous injection of autologous, culture-expanded mesenchymal stem cells into carpometacarpal hand joints: A case series with an untreated comparison group. Wien Med Wochenschr 2014;164(5-6):83–87. PMID: 23949564.
25. Sfakianoudis K, Simopoulou M, Grigoriadis S, et al. Reactivating ovarian function through autologous platelet-rich plasma intraovarian infusion: Pilot data on premature ovarian insufficiency, perimenopausal, menopausal, and poor responder women. J Clin Med 2020;9(6):1809. PMCID: 7355907.
26. Pettersson G, Andersen AN, Broberg P, et al. Pre-stimulation parameters predicting live birth after IVF in the long GnRH agonist protocol. Reprod biomed 2010;20(5):572–581. PMID: 20236862.
27. Kasius A, Smit JG, Torrance HL, et al. Endometrial thickness and pregnancy rates after IVF: A systematic review and meta-analysis. Human reprod 2014;20(4):530–541. PMID: 24664156.
28. Liu KE, Hartman M, Hartman A, et al. The impact of a thin endometrial lining on fresh and frozen-thaw IVF outcomes: an analysis of over 40 000 embryo transfers. Human reprod 2018;33(10):1883–1888. PMCID: 6145412.
29. Tandulwadkar SR, Naralkar MV, Surana AD, et al. Autologous intrauterine platelet-rich plasma instillation for suboptimal endometrium in frozen embryo transfer cycles: A pilot study. J Hum Reprod Sci 2017;10(3):208–212. PMCID: 5672727.
30. Nazari L, Salehpour S, Hosseini MS, et al. The effects of autologous platelet-rich plasma in repeated implantation failure: A randomized controlled trial. Hum Fertil (Camb) 2020;23(3):209–213. PMID: 30714427.
31. Mishra AK, Skrepnik NV, Edwards SG, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: A double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sports Med 2014;42(2):463–471. PMID: 23825183.
32. Podesta L, Crow SA, Volkmer D, et al. Treatment of partial ulnar collateral ligament tears in the elbow with platelet-rich plasma. Am J Sports Med 2013;41(7):1689–1694. PMID: 23666850.
33. MS AH, Mohamed Ali MR, Yusof A, et al. Platelet-rich plasma injections for the treatment of hamstring injuries: A randomized controlled trial. Am J Sports Med 2014;42(10):2410–2418. PMID: 25073598.
34. Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: A meta-analysis of randomized controlled clinical trials. Am J Sports Med 2017;45(1): 226–233. PMID: 27268111.
35. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. J Exp Med 2000;192(7):1027–1034. PMCID: 2193311.
36. Melenhorst JJ, Chen GM, Wang M, et al. Author correction: Decade-long leukaemia remissions with persistence of CD4(+) CAR T cells. Nature 2022;612(7941):E22. PMID: 36477542.
37. Motohashi S, Iinuma T, Kurokawa T, et al. [Application of iPS Cell-Derived NKT Cells to Cancer Immunotherapy]. Gan to kagaku ryoho Cancer chemother 2020;47(10):1411–1414. PMID: 33130731.
38. Yang YJ, Park JC, Kim HK, et al. A trial of autologous ex vivo-expanded NK cell-enriched lymphocytes with docetaxel in patients with advanced non-small cell lung cancer as second- or third-line treatment: phase IIa study. Anticancer Res 2013;33(5):2115–2122. PMID: 23645763.
39. Firouzi N, Yavari HR, Rahimi S, et al. Concentrated growth factors combined with lipopolysaccharide stimulate the in vitro regenerative and osteogenic activities of human dental pulp stem cells by balancing inflammation. Int J dent 2022;2022:2316666. PMCID: 9780000.
40. Chu J, Duan W, Yu Z, et al. Intra-articular injections of platelet-rich plasma decrease pain and improve functional outcomes than sham saline in patients with knee osteoarthritis. Knee surg sports traumatol arthroscop 2022;30(12):4063–4071. PMID: 35124707.
41. Russo F, D'Este M, Vadala G, et al. Platelet rich plasma and hyaluronic acid blend for the treatment of osteoarthritis: Rheological and biological evaluation. PloS one 2016;11(6):e0157048. PMCID: 4911091.
42. Yamada M, Watanabe J, Ueno T, et al. Cytoprotective preconditioning of osteoblast-like cells with N-acetyl-L-cysteine for bone regeneration in cell therapy. Int J Mol sci 2019;20(20):5199. PMCID: 6834301.
43. Anitua E. The use of plasma-rich growth factors (PRGF) in oral surgery. Pract Proced Aesthet Dent 2001;13(6):487–493. PMID: 11544821.
44. Chilcott EM, Muiruri EW, Hirst TC, et al. Correction: Systematic review and meta-analysis determining the benefits of in vivo genetic therapy in spinal muscular atrophy rodent models. Gene ther 2023;30(1-2):188. PMID: 36437357.
45. Fu Z, Lai Y, Zhuang Y, et al. Injectable heat-sensitive nanocomposite hydrogel for regulating gene expression in the treatment of alcohol-induced osteonecrosis of the femoral head. APL Bioeng 2023;7(1):016107. PMCID: 9862308.
46. Salehpour A, Balmagambetova S, Mussin N, et al. Mesenchymal stromal/stem cell-derived exosomes and genitourinary cancers: A mini review. Front Cell Development Biol 2022;10:1115786. PMCID: 9845763.
47. Littig JPB, Moellmer R, Agrawal DK, et al. Future applications of exosomes delivering resolvins and cytokines in facilitating diabetic foot ulcer healing. World J Diab 2023;14(1):35–47. PMCID: 9850797.
48. Freeman FE, Browe DC, Nulty J, et al. Biofabrication of multiscale bone extracellular matrix scaffolds for bone tissue engineering. Eur cell mater 2019;38:168–187. PMID: 31602629.
49. Nakatani Y, Agata H, Sumita Y, et al. Efficacy of freeze-dried platelet-rich plasma in bone engineering. Arch oral biol 2017;73:172–178. PMID: 27771585.
50. Szablowska-Gadomska I, Rudzinski S, Dymowska M. Secretome of mesenchymal stromal cells as a possible innovative therapeutic tool in facial nerve injury treatment. BioMed res int 2023;2023:8427200. PMCID: 9867597.