

Progress in STEM CELL

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Review



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Author for correspondence:

Phuc Van Pham

e-mail: pvphuc@hcmuns.edu.vn

An evolution of stem cell research and therapy in VietNam

Phuc Van Pham^{1,2}, Ngoc Bich Vu², Oanh Thuy Huynh², Mai Thi-Hoang Truong², Truc Le-Buu Pham², Long Thanh Dang², Ngoc Kim Phan¹ and Kiet Dinh Truong³

¹Laboratory of Stem Cell Research and Application, VNUHCM University of Science, Viet Nam

²Stem Cell Institute, VNUHCM University of Science, Viet Nam

³Ho Chi Minh City Stem Cell Society, Ho Chi Minh City, Viet Nam

Abstract

Stem cell research is among the most exciting, attractive, and rapidly growing fields in biomedicine. Besides the popularity of stem cell research at the bench, stem cell therapy has become a bustling interest in the clinic and industry. In Vietnam, biomedical scientists have studied stem cells since 1995. From that time on, Vietnamese scientists have obtained significant achievements in stem cell research and therapy, especially with regards to stem cell therapy for disease treatment. This report aims to provide an overview of stem cell research and therapy from 1995 to date. Stem cell research activities were collected by questionnaire and analyzed based on publications and projects about stem cells in various databases, including Pubmed, Web of Science, Google Scholar, Embase, as well as from national scientific information. The results showed that stem cell research and therapy significantly increased from 2009 to date with greater publications on stem cells and clinical applications. With this growth rate, Vietnam is poised to continue developing in the stem cell industry. The potential goal for Vietnam is to advance as one of the countries in the Southeast Asian region and in the world that continues to push the frontier in stem cell research and therapy.

1. About stem cells

Stem cells are un-specialized cells in organisms, including humans [1]. They are characterized by two properties, namely self-renewal and differentiation. Self-renewal is a special process by which stem cells can produce at least a copy via mitosis. By this process, stem cells can maintain the stem cell pool in the body, which helps to maintain homeostasis. Differentiation is the process by which stem cells become various functional cells which mediate various processes in the body [1].

There are about four different kinds of stem cells in the human body. These include embryonic stem cells (ESCs), adult stem cells (ASCs), cancer stem cells (CSCs), and induced pluripotent stem cells (iPSCs). The latter cells are produced from epigenetic reprogramming of adult somatic cells. ESCs were firstly isolated from human blastocysts by James Thomson in 1998 [2]. ESCs are pluripotent and can be differentiated into all cells of the body, except for cells of the amniotic membrane and the umbilical cord. Adult stem cells are collected from human tissues after birth [3].

Adult stem cells have been widely studied for use as disease treatments in recent years, in Vietnam and worldwide. Hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) are the most popular adult stem cells that are currently used in the clinic. Around the world, HSCs have been studied and used to treat hematopoietic malignancies since the 1950s [4]. From that time til now, more than 100,000 patients have been transplanted with HSCs to treat hematopoietic diseases [5]. HSCs can be isolated from bone marrow, umbilical cord blood, or from peripheral blood.

Meanwhile, MSCs are anew type of stem cells that were first discovered in the bone marrow [6]. Unlike HSCs, MSCs can adhere to plastic dishes, and differentiate into various functional cells from the mesoderm [7]. Several therapeutic mechanisms of MSCs have been discovered since the 2000s [8,9]. Moreover, the application of MSCs has been rapidly advanced worldwide with the use of off-the-shelf MSC products [10,11]. Unlike HSCs, MSCs express low major histocompatibility complexes (MHCs) and can modulate the host immune system [12]. Therefore, they can be used in allogeneic transplantation setting without the need for immune suppression(as is the case in HSC transplantation). MSCs can be isolated from a variety of tissues, such as bone marrow, adipose tissue, umbilical cord blood, umbilical cord tissue, and dental pulp... [6,13,14]

2. Stem cell milestone in Viet Nam

Studies on stem cell research and its application in Vietnam started since 1995 and since then have achieved some favorable results with respect to disease treatment applications [15]. The first hematopoietic stem cell transplantation was performed by Dr. Tran Van Be in 1995 at the Blood Transfusion & Hematology Hospital, in Ho Chi Minh City (HCMC) to treat leukemia. HSC transplantation now can be carried out by several different hospitals, in North and South Vietnam [16]. These hospitals include the Blood Transfusion & Hematology Hospital (HCMC), Hue Centre Hospital (Hue), National Institute of Hematology and Blood Transfusion (Hanoi, Vietnam), Vinmec Hospital (Hanoi, Vietnam), and Cho Ray Hospital (HCMC) **Figure 1** [15]. To date, over the past decade in Vietnam, there have been about 500 cases of HSC transplantation to treat malignant hematopoietic diseases **Table 1**.

In the next year, at the 103 Military Hospital, for the first time, autologous expanded keratinocytes were grafted to treat the burn [17,18]. This is the first study to use *in vitro* expanded cells in the clinic, even though the cells are not stem cells. The applications of stem cells in clinic slowed down from 1996 to 2006. During these ten years, there were no new reported applications of stem cells. However, in 2007, several clinical applications of stem cells were performed using HSCs and other stem cells. Bone marrow transplantation was used to treat diseases, including non-union or delay fractures, and heart failure [19–22]. Limbal stem cells and cheek epithelial cells were transplanted to treat Steven Johnson Syndrome at Eyes Hospital (HCMC) [23]. Moreover,

Table 1. Some hematopoietic stem cell transplantation centers in Viet Nam (updated to 10-2016)

Areas	Center/Hospital	Cases
South	Blood Transfusion and Hematology Hospital HCM	222
	Cho Ray Hospital	30
	National Blood Transfusion and Hematology	225
North	108 Military Hospital	16
	Pediatric Institute	20
	Bach Mai Hospital	5
Middle	Nghe An Hospital	5
	Hue Central Hospital	7
Total		530

this year, the first allogeneic expanded MSCs were used to treat ulcers at Saint Paul Hospital and Traditional Medicine Hospital (Hanoi, Vietnam) [24]. In 2009, the new approach in burn treatment using allogeneic expanded fibroblasts was performed at the Vietnam National Institute of Burn (Hanoi, Vietnam) [25].

The clinical application of stem cells has achieved new milestones since 2012. Since that time, more clinical trials have been performed using MSCs to treat common diseases, such as knee osteoarthritis [26,27], chronic obstructive pulmonary disease (COPD) [28], cerebral palsy [29], autism [30] and type 1 diabetes mellitus (unpublished data). In 2017, the first clinical trial using allogeneic expanded MSCs from umbilical cord tissues was performed to treat type 1 diabetes mellitus by vein transfusion.

The stem cell research activities were further advanced by the establishment of the Stem Cell Laboratory (SCL) (now Stem Cell Institute, <http://www.sci.edu.vn>), first key laboratory of stem cell research and application at the University of Science, Vietnam National University (VNUHCM) in HCMC. At this laboratory, basic procedures were established for *in vitro* animal and human cell cultures for fibroblasts, keratinocytes, and other cell types. Procedures for stem cell isolation, proliferation and differentiation of MSCs from murine bone marrow and umbilical cord blood were developed there since 2007. After that, the laboratory made various achievements in the development of new technologies for isolation, characterization, differentiation, and cryopreservation of various stem cells from different tissues, including adipose tissue, umbilical cord blood, and bone marrow [31–35]. This laboratory succeeded to differentiate MSCs into adipocytes, osteoblasts, chondrocytes, cardiomyocytes, insulin-producing cells, and neuron-like cells [36–39]. Moreover, various animal models of different diseases were also developed in order to execute pre-clinical trials [32,37,40]. The animal disease models treated by stem cell transplantation have included femoral head necrosis, type 1 and 2 diabetes mellitus [32], bone marrow failure, injured knee cartilage [41], aged skin, liver cirrhosis [37], hindlimb ischemia [42, 43], heart failure [44], and spinal cord injury [45]. Besides the use of normal stem cells, the SCL has also focused on the use of cancer stem cells [46], has developed assays to evaluate drug resistance, and has investigated cancer stem cell-based targeted therapy, gene therapy [47,48], and immune cell therapy [49].

Besides this group, some other groups in Vietnam have also been involved in stem cell research. One stem cell group, headed by Dr. Tran Cong Toai, at Pham Ngoc Thach Medicine University (HCMC), has investigated procedures to collect and expand stem cells *in vitro* from bone marrow and adipose tissues [50–52]. This group has also conducted studies on culturing and differentiating MSCs on scaffold in order to produce bone [53]. This group has also learned and applied the cheek epithelial cell culture for Steven Johnson Syndrome treatment from Eyes Hospital, HCMC (data unpublished).

In Hanoi, some stem cell research groups have also been formed and developed since the 2000s. Regarding basic research, there are two groups; one is headed by Dr. Bui Xuan Nguyen (Biotechnology Institute, Vietnam Academy Science and Technology) and the other by Dr.

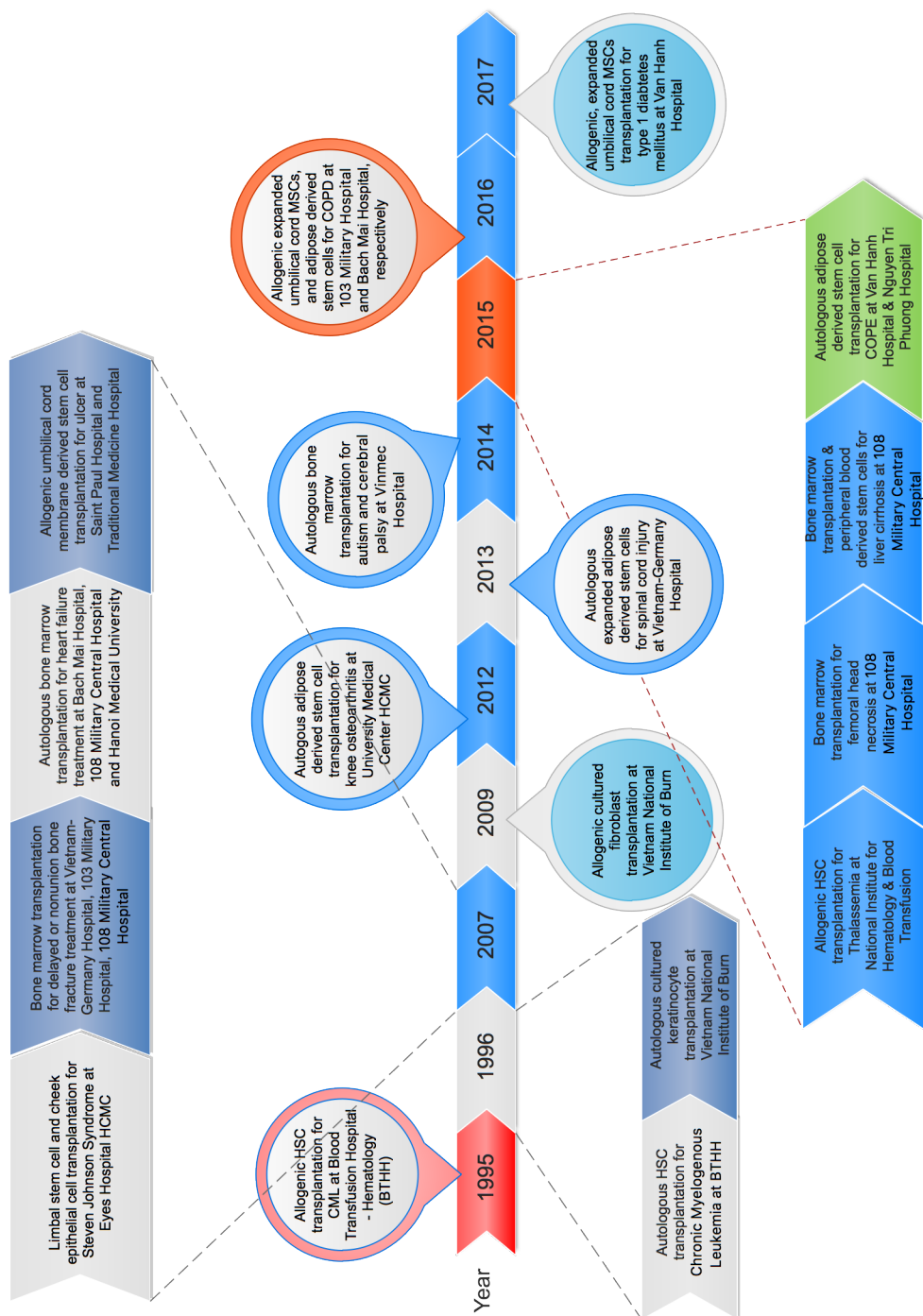


Figure 1. Stem cell clinical application milestones in Viet Nam. Clinical application of stem cells began in 1995 in Vietnam with the first clinical application of hematopoietic stem cell transplantation for chronic myeloid leukemia. The clinical application of stem cells rapidly grew from 2007 to date with about ten diseases treated by stem cell transplantation.

Nguyen Mong Hung (at the University of Science, VNU, Hanoi). Dr. Bui Xuan Nguyen developed the technique of animal cloning with the success of Sao La cloned embryos [54] while Dr. Nguyen Mong Hung used ESCs from chicken embryos to create chimera chickens [55]. He also transplanted murine ESCs to treat mice irradiated with a dose of 900 r. About translational medicine research, the group at Biotech Institute, Vietnam Academy Science and Technology also started some translational studies to isolate, culture and differentiate various kinds of stem cells [56,57].

Regarding clinical research, some centers have focused on the isolation, growth, and preservation of stem cells for clinical trials; these include the 103 Military Hospital, 108 Military Hospital, Vinmec Hospital, Vietnam National Institute of Hematology and Blood Transfusion, and National Hospital of Pediatrics (*data unpublished*).

3. Current applications of stem cells in various fields

Similar to other countries, in Vietnam, stem cells can be applied in many areas, from medicine to pharmacy to agriculture. Although stem cells have been studied in medicine, pharmacy, and agriculture, only a few applications of stem cells have been approved, for anti-aging purposes and some disease treatments **Figure 2**.

In medicine, stem cell-enriched fraction from bone marrow, umbilical cord blood and adipose tissues, or non-expanded stem cells (e.g. purified HSCs), have been approved to treat certain diseases [22,24,26,27,30]. *In vitro* expanded stem cells are still used in clinical trials since engineered tissues, differentiated stem cells, stem cell drugs, and gene-modified stem cells have not been well-studied in Vietnam. The clinical applications of stem cells in aesthetics or anti-aging in Vietnam is usually limited by transfusion, injection of certain stem cell-derived cellular products, and/or growth factors can stimulate endogenous stem cells.

In pharmacy, stem cells have been applied in drug production as well as drug screening in recent years. Stem cells, especially cancer stem cells, have been used to screen anti-tumor drugs [58,59]. Stem cell drugs were first studied at the Stem Cell Institute (SCI) at VNU-HCMC, beginning in 2015, with the first products being CartilatistTM, which act as a stem cell-based drug for knee osteoarthritis (*data unpublished*), and ModulatistTM, which treats certain immune system-related diseases [28].

Regarding biological research, agriculture, and conservation, there have not been any studies using stem cells in developmental biology research. However, some start-up studies have explored the use of stem cells in the production of transgenic animals and animal cloning [54, 55,60–62], but these applications are only under the initial review phase.

4. Current stem cell technologies

Stem cell technology consists of four main types of techniques: isolation, culture and expansion, differentiation and modification, and preservation. With a 20-year history of establishment and development of stem cells, Vietnam now holds patents for some essential techniques. As shown in **Figure 3**, Vietnam has studied most of the above stem cell technologies. At present, all state-of-the-art stem cell isolation techniques in the world are imported and used by certain laboratories and hospitals in Vietnam, especially in HCMC and Hanoi. Vietnam own all techniques to enrich, isolate and purify stem cells from both fluids and solid tissues. Some modern methods, such as stem cell sorting via flow assisted cell cytometry (FACS), magnetic assisted cell sorting (MACS), and laser capture micro-dissection, are also available at some of the laboratories in Vietnam.

In Vietnam, a major strength in stem cell technology is the cryo-preservation of stem cells. The commercialization of stem cell banks and their services have enabled stem cell cryo-preservation to flourish in Vietnam. Indeed, at present, there are seven stem cell banks in Vietnam which store umbilical cord blood and umbilical cord tissues.

However, many other techniques in stem cell culture, such as cell expansion, differentiation, and modification have not been used or developed at most stem cell laboratories or hospitals in



Figure 2. Current applications of stem cells in various fields at Viet Nam. At Viet Nam, stem cells were studied to be applied into medicine (regenerative medicine), pharmacy and also agriculture or biological research. Most studies focus on the application of stem cells in medicine and pharmacy. There are a few applications of stem cells and stem cell-derived products in disease treatment as well as aesthetics. Almost clinical applications were approved relating to the transplantation of stem cell-enriched bone marrow. Green color: Applied; Yellow color: In Research; Red color: Not yet research.

Vietnam. Regarding stem cell culture, most laboratories have cultured stem cells in T-flasks or Petri dishes. Therefore, the stem cell manufacturing scale-up has not yet been done. The use of 3-dimensional (3-D) culture systems or stem cell suspension culture have been recently investigated at the SCI (*data unpublished*). In the entire country, very few laboratories can culture and expand stem cells. Similarly, stem cell differentiation, modification, and epigenetic reprogramming have all mainly been done at the SCI. Regarding iPSCs, from 2015, there have been studies at the SCI and Reprogramming Laboratory (International University, VNUHCM) on reprogramming to produce iPSCs or endothelial progenitor cells from fibroblasts [62–67].

5. Clinical application of stem cells

As introduced in **Figure 4**, more than 40 major diseases have been treated by stem cells in the world. In Vietnam, about 20 different diseases have been treated by stem cell transplantation.

HSC transplantation for hematological malignancies has had a long history in Vietnam with the first transplantation being performed more than 20 years ago. Although there have been some cases that used purified HSCs with CD34+ stem cells, most of the cases have used stem cell-enriched fraction from bone marrow, umbilical cord blood, or stem cell-mobilized peripheral blood. To date, there are now more than 500 cases of HSC transplantation to treat different hematopoietic malignancies, including acute myeloid leukemia (AML), chronic myeloid leukemia (CML), anemia, and beta thalassemia. These applications are part of routine treatment in Vietnam. The treatment efficacy has varied among the different hospitals.

For musculoskeletal diseases, stem cells (mainly stem cells enriched from bone marrow) have been used to treat various bone conditions, such as clinically included delayed or nonunion of fracture, nonunion fracture of the tibia, femoral head necrosis, and bone healing. All treatments now being investigated in clinical trials of pilot or phase I/II. Some reports suggest that the therapy is feasible, but thus far, no treatment has been approved by the Ministry of Health as a routine treatment. This is different from adipose-derived stem cell transplantation, which showed significant impact for knee osteoarthritis and was approved as a standard treatment in hospitals. The success of the adipose-derived stem cell transplantation was a result of multi-centered clinical trial, with the participation of Van Hanh Hospital (HCMC) and Nguyen Tri Phuong Hospital (HCMC, Vietnam). These clinical trials used the technologies developed by the SCI to isolate stromal vascular fractions (SVFs) from adipose tissue and platelet-rich plasma (PRP) from peripheral blood. The cocktail of SVF and PRP were injected into the knee in combination with microfracture. The results showed that the treated patients significantly improved in VAS score, Lysholm score, and cartilage regeneration [27]. Up to now, about 1000 patients have been treated for knee osteoarthritis by this therapy; this number continues to increase daily (*data unpublished*).

Another disease investigated in an ongoing multi-centered clinical trial is COPD. Here, the stem cells being investigated are expanded umbilical cord tissue-derived MSCs. This clinical trial was performed at the 103 Military Hospital and Van Hanh Hospital from 2017 onward. This study represented the first time that stem cell expansion technology, invented by Vietnamese scientists, was approved by the Ministry of Health for treatment of COPD patients. The preliminary results showed that patients significantly improved in COPD symptoms after six months of treatment [28].

Stem cell transplantation has shown success for some diseases. In other trials, as the investigation of stem cell treatment is still underway, it is too early to predict outcome. All studies in Vietnam, at present, have ended in Phase I/II stage due to limited patients.

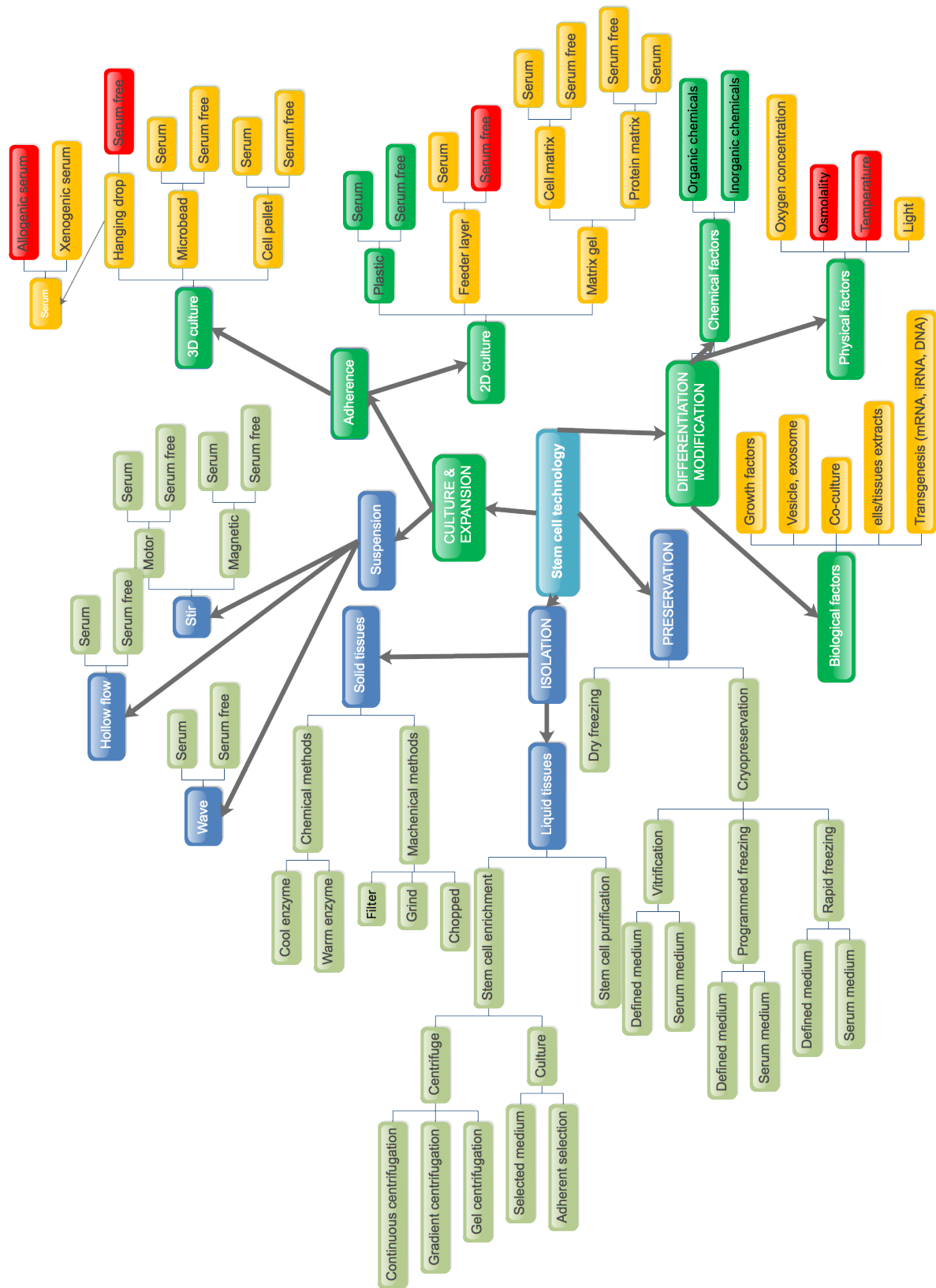


Figure 3. Current stem cell technologies in Vietnam. Vietnamese scientists owned some essential techniques in isolation, culture & expansion, differentiation and modification, and preservation of stem cells. Almost owned methods belong to the isolation and cryopreservation. While the culture, expansion as well as differentiation or modification techniques have not been researched yet in Viet Nam. Green color: Applied; Yellow color: In Research; Red color: Not yet research.

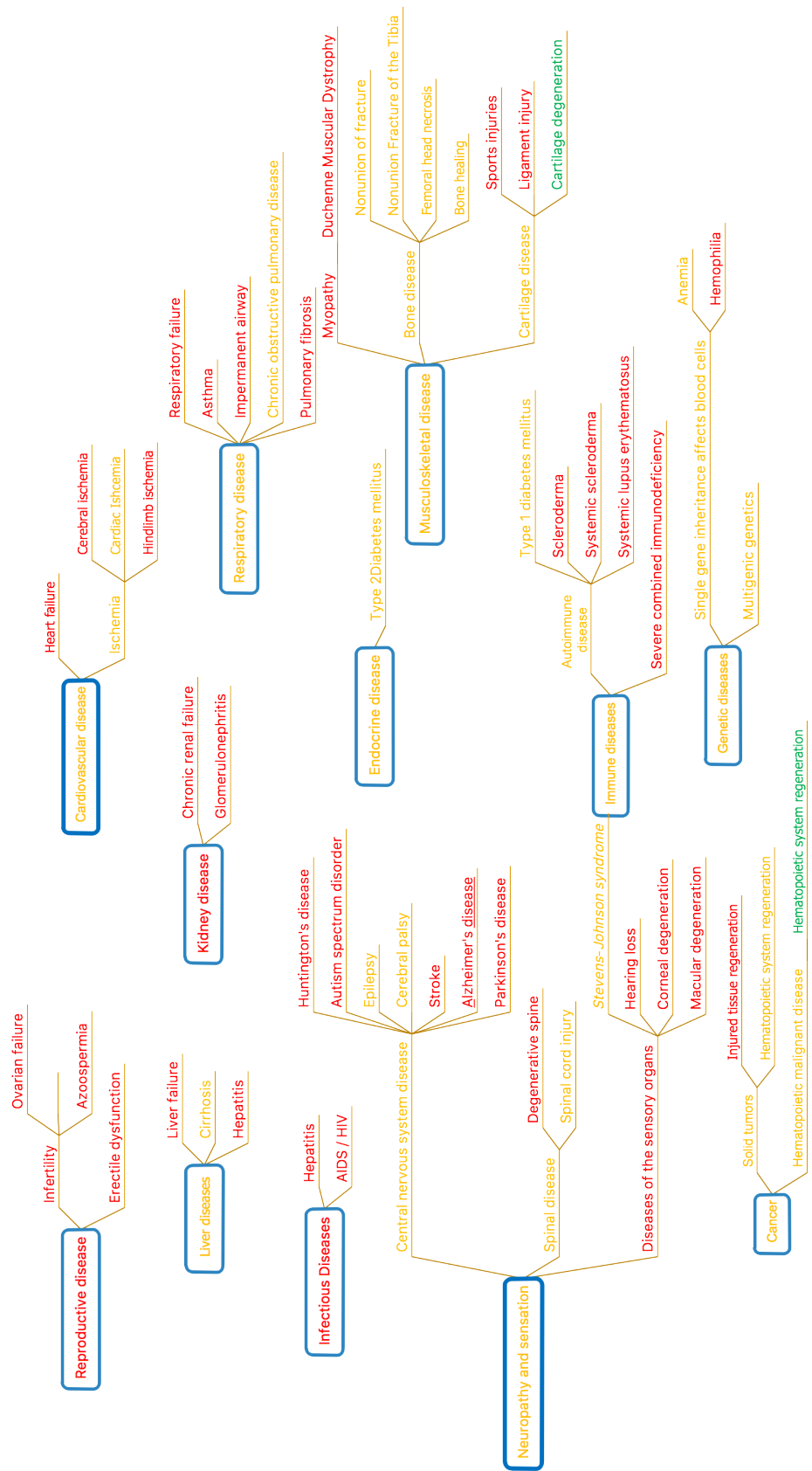


Figure 4. Current applications of stem cells in disease treatment. In more than 40 different diseases are treated by stem cell transplantation, at Viet Nam stem cell transplantation, at Viet Nam stem cell transplantation are used to treat about 20 disease conditions. However, to date, only two disease conditions are approved by Ministry of Health to treat as routine treatment included knee osteoarthritis and hematopoietic system regeneration in hematopoietic malignancies. Green color: Applied; Yellow color: In Research; Red color: Not yet research.

6. A suggestion for stem cell technology and products in Vietnam

Based on the present techniques and demands of the market, some products should be developed in Vietnam to expand stem cell research and application to the year 2030 (Figure 5).

An analysis about the demand of hospitals and companies in Vietnam showed that market demand for stem cell-based products are arranged by different levels of technology. The level technology of stem cell technology is classified based on evaluations of experts, and range from 0 to 100 points. Currently, some products that can be produce at low to medium of technology levels with high demand are non-expanded stem cells, stem cell extraction kits, stem cell extracts, and secretomes of stem cells.

Non-expanded stem cells are the stem cell-enriched fraction that can be isolated from bone marrow, umbilical cord blood, peripheral blood, and adipose tissue. These products can simply be produced by equipment to concentrate the mononuclear cells (MNCs) and remove undesired cells (including red blood cells and mature lymphocytes). Applications of non-expanded HSCs from bone marrow, peripheral blood, and umbilical cord blood were approved to treat some malignant hematopoietic conditions, which increased the demand for these products. Moreover, from 2016, application of non-expanded stem cells from adipose tissue was permitted by the Ministry of Health for knee osteoarthritis; thus, one more product was added to the stem cell market in Vietnam.

Regarding the non-expanded stem cell products, stem cell extraction kits have become the most exciting products from 2013 to date. These kits are used to facilitate stem cell extraction process. The products from the procedures are compliant with clinical usage. Some stem cell extraction kits are being commercialized in the Vietnamese market; although most kits are imported, there are a few kits that were developed and produced locally (Table 2).

Stem cell extracts or secretome of stem cells are widely used in aesthetics in Vietnam. These products are mainly imported from Korea, Japan, Singapore, and other countries. Stem cell supernatant obtained from the culture media of stem cells contains various components, especially certain growth factors that are produced by stem cells during in vitro culture. These growth factors exhibit some biological effects on wound healing, collagen synthesis, and cell proliferation. In addition to the products from stem cell extracts or secretome of stem cells, there are other stem cell-based cosmetic products which only contain certain recombinant proteins (e.g. growth factors) to stimulate endogenous stem cells or other kinds of cells when they are used.

7. Conclusion

Stem cell research at the bench, in medicine and in industry in Vietnam has achieved major milestone with some significant development in stem cell technology and application since 1995. There are now more than 20 diseases treated by stem cell transplantation in clinical trials, with two diseases in which stem cells are approved as standard therapy. Moreover, stem cell technology has made huge strides in technique development, such as stem cell isolation and cryo-preservation. However, some important techniques in stem cell culture (such as expansion, modification, and differentiation) have not been well developed or widely used in Vietnam. Therefore, currently, Vietnam has only developed and owned some stem cell-based products, made at low- or medium-level of technology. Therefore, Vietnam should focus on and further advance stem cell culture and differentiation techniques so the researchers can patent and produce high-quality stem cell products, such as stem cell drug products. With a rapid development in stem cell research and therapy, Vietnam is poised to make further advances in the stem cell industry, with the goal of advancing as a stem cell research leader in the Asian region and worldwide.



Figure 5. The relation of market demand and technology levels at Viet Nam. The market demand is high for some products related to non-expanded stem cells, stem cell extraction kits, stem cell extracts, secretomes for aesthetics, stem cell drugs. ... These products required the technology level from low to high. With the current technologies, Viet Nam should rapidly develop some products as stem cell extractions, non-expanded stem cells for commercialization and satisfied the market demand; moreover, the developing the stem cell culture, expansion to produce the stem cell drugs, stem cell extracts, stem cells derived secretomes. ... are the new directions at Viet Nam.

Table 2. Some stem cells based products at Viet Nam market

Trade name	Usage	Supplier/producer
ADSC Extraction kit	Extract the SVF from adipose tissue.	GeneWorld Ltd. (produced based on the technology of Laboratory of Stem Cell Research and Application, VNUHCM University of Science, HCMC)
Cell Extraction kit	Extract SVFs, single cells from adipose tissue, umbilical cord tissue	Regenmedlab (produced based on the technology of Stem Cell Institute, VNUHCM University of Science, HCMC)
MNC Isolation Kit	Isolate the MNCs from peripheral blood, umbilical cord blood, and bone marrow	Regenmedlab (produced based on the technology of Stem Cell Institute, VNUHCM University of Science, HCMC)
Biosafe Sepax Single Use Kit	Separate the cells from umbilical cord blood, bone marrow, peripheral blood or other blood derivatives	Biosafe Sepax, GE Healthcare
Auto Xpress (AXP)	Automated, functionally closed system that consistently and efficiently harvests the stem cell-rich buffy coat from umbilical cord blood.	Thermogenesis
Auto Xpress (Marrowxpress)	Isolating and concentrating stem cells from bone marrow aspirate	Thermogenesis
AdiStem™ Small / Large Kit	Extracting SVFs from adipose tissue	AdiStem Pty Ltd.
Beauty Cell Celution®800/ CRS	Extracting SVFs from adipose tissue Extracting SVFs from adipose tissue	N-Biotek, Inc. Cytori Therapeutics, Inc.

8. Open Access

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9. List of abbreviations

ASC/ADSC: Adipose derived stem cells; **BM**: Bone marrow; **CSC**: Cancer stem cell; **ESC**: Embryonic stem cell; **HSC**: Hematopoietic stem cell; **iPSC**: Induced pluripotent stem cell; **MNC**: Mononuclear cells; **MSC**: Mesenchymal stem cell; **SCI**: Stem Cell Institute; **SVF**: Stromal Vascular Fraction; **UCB**: Umbilical cord blood; **VNUHCM**: Viet Nam National University Ho Chi Minh City.

10. Competing interests

The authors declare that they have no conflict of interest.

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12. Authors' contributions

PVP suggested the idea, collected data and corrected the manuscript, NBV, OTH, MTTT, TLBP, LTD, NKP, KDT collected the data, analyzed the data, visualized the data. All author wrote, read and approved the final manuscript.

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