

# Fight for Regulation and its Enforcement on Stem Cell Therapy in China



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## Abstract

The article begins with Chinese attention to the fight for regulation on stem cell therapy in USA. The main body of this article is a try to provide an overview on the unruly situation of stem cell therapy in which is a fight between humanist culture of medical tradition and capitalist culture of the market manifested. Then the article discusses clinico-ethical and research ethical issues as well as regulatory issues in clinical research and translations of stem cell therapy. Finally, this article concludes that the fight between humanist culture of medical tradition and capitalist culture of the market will be still going on not only in the field of stem cell therapy but also in the fields of gene editing and somatic cell therapy.

**Keywords:** Stem cell therapy; Clinical trial; Medical professionalism; Medical commercialism; Informed consent; Humanist culture; Capitalist culture; Clinical ethics; Research ethics; Regulation; Gene editing; Somatic cell therapy.

## Introduction

Chinese academics including scientists, physician and bioethicists are attentively watching the lawsuits of FDA vs Stem Cell Company and hailed FDA wins it [1,2]. As we have experienced a10 years fight against the unproven and unregulated stem cell therapy from 2005 to 2015 when Ministry of Health (MOH promulgated the Interim Regulation on the Clinical Trials of Stem Cells [3,4]. The episode of unruly situation of stem cell therapy (SCT) which seems miraculous but eventually unproven is a cluster of symptoms stemming from the pervasive medical commercialism, the degeneration of medical professionalism, the diseased health system and policy, as well as the prevailing corruption in medical care and the society at large. In this article we will review this maybe untended episode related with the debates on ethical and regulatory issues may become is a lesson pitiful but useful for future efforts to regulate the clinical translation of stem cells as well as gene editing and somatic cells or other biological products in mainland China (below China for abbreviation) as well as in other countries. In this article the term stem cell therapy refers to an unproven and unregulated therapy with use of stem cells. "Unproven" means that this therapy is not proven by clinical trials. "Unregulated" means that the providers of this therapy exploited existing regulatory gaps or loopholes for avoiding or evading the

regulation and oversight by regulatory body. In the strict sense, stem cell therapy should be:

1. Possessing the knowledge of the mechanism of stem cell differentiation and regulation, and mastering the techniques of oriented differentiation, and obtaining the cells or tissues for transplantation on the basis of adequate basic research.
2. Conducting clinical trials and obtaining the evidence of safety and efficacy of SCT on the basis of pre-clinical studies.
3. Being approved by regulatory body.

Now these formal clinical trials are being conducted in China as well as in other countries. When the Ministry of Science and Technology (MOST) and Ministry of Health (MOH) jointly promulgated Ethical Guidance on Human Embryonic Stem Cell Research (bellow Ethical Guidance for abbreviation) [5] scientists and regulators envisioned that after creating immortal stem cell lines and mastering the mechanism of stem cell regulation and differentiation, specific cells and tissues could be harvested and used for transplantation so as to treat diseases. Some experts estimated it would take 50 years. However, unexpectedly, SCT suddenly emerged and rapidly transmitted to all over the country as an epidemic. The unruly situation of SCT refers to a special social phenomenon unique to China in the 21

century and constitutes a more notorious scandal than today's He Jiankui Incident [6].

### An Overview of the Unruly Situation of Stem Cell Therapy in China

What is the real unruly situation of SCT in China during the period of 2005-2015? It is hard to be found out because it was unregulated and never transparent. Very few academic reports were published in academic journal. What follows is an overview we try to describe on the basis of reports in media and our personal experiences. It is certain that the picture described is incomplete and inaccurate. It may be only the tip of iceberg [Foot note 1-3].

### When and who is the first conducting this therapy in China?

Probably it began after 2003, maybe in 2006. In the period of 1999-2003 when scientists and bioethicists in Beijing and Shanghai were drafting the recommendations on regulating stem cell research, nobody raised the question about SCT up to the promulgation of Ethical Guidance. The first report about SCT was published on Xinmin Weekly, a magazine in Shanghai, in September 2007 [7]. Hu Xiang, the CEO of Beike Biotech Company said they started this therapy in 1999 but without providing evidence. One of the hospitals associated with Beike company said it began with 2006 [7]. It was reported that there was a debate on developing neural stem cell therapy, and then several doctors at Xuanwu Hospitals (leading internal neurology) in Beijing expressed their dissenting opinions on it. Probably, it started in 2005 or earlier and definitely after 2003.

### How many medical institutions provide "SCT"?

In 2009 Italian TV Station came to China to do investigation and was told by a medical institution which provided "SCT" that there were 400. Suppose 100 were added in 2009-2011, the guess of about 500 institutions altogether is reasonable. The representatives include: Beijing Tiantan Puhua Hospital, Beijing Xishan Hospital, Jilin Tongyuan Hospital, 261 Military Hospital, Liaoning Air Force Hospital, Kunming Military Police Hospital and Beike Company and its associated hospitals. All of them can be searched at website google or baidu. According to the report by Dr. Dominique McMahon, Munk School of Global Affairs, Toronto University who did site investigation for 8 weeks in China (6 weeks in 2007 and 2 weeks in the autumn of 2011), she found that among the medical institutions which provides "stem cell therapy" 36% are hospitals affiliated with Chinese Liberation Army or Military Police [8-10]. The number of companies related with stem cells production or marketing in 2009 was about 100.

Beike Company of Biotechnologies and its associate hospitals are one of the most influential institutions in stem cells preparation and clinical application. Beike was founded in June 2005, registered capital CNY 10 million. "Stem cell" is its major

products. Hu Xiang is a biologist returning from oversea. He was graduated from Guiyang Medical College, obtained Ph.D. in University of Gotteburg and Chalmers University of Technology, Sweden and did Post Doc in British Colombia University. He has founded a pharmaceutical company in Guiyang, served as agency for medical equipment company or hospital manager. Later he focuses on the emerging area of stem cells. He said: "If we develop stem cell technology as medicine according to traditional model, such as upstream research, middle trials, waiting approval, 3 phases of clinical trials, finally obtaining certificate etc. it would take more than 10 years, and investment no less than USD 1000 billion." Hu concluded that it is a choice with maximum risk. He put his bet on creating a network with rapid application of stem cells in clinics, i.e. he sells stem cell products to hospitals where these products be applied to patients, he and hospitals share the income paid by patients. Thanks to Beike's advertising tactics, with promotional agencies in Europe, North America, and Turkey, the company has attracted 400 patients from overseas during the past 2 years, and now treats up to 50 foreign and 130 Chinese patients each month. The company is aggressively expanding its business and aims to recruit a further 14 Chinese hospitals and to set up centers in India, Bulgaria, Romania, and Panama [11] [Foot note 4-6].

### Why to provide SCT?

Almost everybody said: Patients urgently need it we must consider for patients! "We cannot wait!" Hu Xiang said [12]. It sounds compelling! But how patients know stem cells can cure their disease Is there any scientific or clinical grounds for SCT? How do you know SCT would not bring about harms to patients?

### Industrialization of SCT

With the investment of commercial capitals an industrial chain of stem cell retrieval, preparation, production and treatment at hospitals etc. has been formed. SCT will be potentially a golden mine of USD 80 billion in the two years globally. In China the income of stem cell industry will grow to CNY 30 billion from present CNY 2 billion, the annual growth rate is 170%. The huge space of profits promotes the "octopus" of stem cells to grow out many "tentacles", such as process, storage or R&D of stem cell product. A Biotechnology Services Company in Beijing receives more than 10 order forms from hospitals or cosmetic clinics each month. They ask the company to culture stem cells to treat all kinds of disease (i.e. diabetes) and remove wrinkles. CNY 10,000 has to be paid for one therapeutic unit (cell number 50 million). Sales amount of some salesmen reach CNY millions per month [13].

### What kind of stem cells doctors used?

Some disclosed to clients, some not, keeping confidential. Without the test by authentic third-party institution nobody knows what they used. Perhaps, in some cases there is no stem cell, only general cell. Those disclosed include autogenous stem

cells; adult stem cells (e.g. mesenchymal cells); heterogeneous stem cells; umbilical blood cells; fetal cells (e.g. olfactory ensheathing cells).

### Where the stem cells came from?

Some were produced by hospital itself; or by registered biotech companies, such as Beike where umbilical blood in vitro cultured and proliferated 7-10 days; or from private companies with unknown identity; or cheated: "imported from overseas" but perhaps just general cells; or derived from patient's own stem cells, and inject back to her/his body after culturing (variation may occur during culturing, and cause risks e.g. tumor) [11,14] [Foot note 7-9].

### What kind of diseases was treated?

Any disease includes Lou Gehrig disease, traumatic brain and spinal injuries, diabetes (I and II types), ataxia, multiple sclerosis, autism, amyotrophic lateral sclerosis, Parkinson disease, Alzheimer disease, optic atrophy, stroke, heart muscle injuries, ischemic heart disease, liver diseases; neurological disorders etc.

### What is the procedure?

In Beike cultured and proliferated umbilical blood stem cells or bone marrow stem cells derived from operation were injected into spinal fluids. One course covers 4-5 days, during this period stem cells were injected 4 times, each time stem cells were input into body intravenously. Apart from stem cells they also provided rehabilitation therapy, electric stimulus, massage, acupuncture, and herbs. (Global Business 2007) Two kinds of treatment were provided by the Center for Stem Cell Research affiliated with Beijing Tiantan Hospital for Neurological Science:

- a. Administer activated and proliferated human neural stem cells orally or by injection.
- b. Inject autogenous bone marrow stem cells, fetus' neural stem cells or adult retinal pigment epithelium stem cells to improve symptoms of stroke, cerebral palsy, Parkinson disease and other diseases of neural system.

In Beijing Xishan Hospital (West Mountain Institute of Neural Regeneration and Function Rebuilding) olfactory ensheathing colloid cells from aborted fetus were injected to treat spinal injuries and other central neural system diseases [12,15].

### How many patients have been treated by SCT?

In 2009 colleagues from University of Toronto estimated 6,000 patients have been treated, apart from thousands of foreigners [8,9]. However, then Beike claimed they have already treated 6,000 patients. Almost at the same time Huang Hongyun at Xishan Hospital claimed he has treated 500 patients, 3,000 Chinese patients and 1,000 foreign patients on the queue [16]. The staff at Tongyuan Hospital in Jilin Province said they have treated 15,000 patients [17]. Since 2005 seven years elapsed, during this time how many patients were treated by, say, 500

hospitals? Perhaps it is not overestimated to say that the number of those patients who underwent "SCT" may amount to 100-200 thousand. However, it is an estimate, not proved by evidences.

### How much money has to be paid by a patient?

For Chinese patient, one course (4 injections) cost CNY 50,000. For foreign patients, one course cost USD 20,000. In Puhua, 4-5 times injection to treat autism cost CNY 205,000 [17,18].

### How much cost?

According to the estimate by hematological expert Professor Han Zhongchao, the cost of preparing umbilical blood stem cells may be CNY 1,000, proliferation may increase the cost several times (may be CNY 5,000!) [15]. If so, it is really a small investment bringing a ten thousand-fold profits. Extremely excessive profits! [Foot note 10-12]

### How is the efficacy?

Doctors, hospitals and companies involved in SCT all said it is "efficacious". But the evidence supporting their claim is scarce, instead, there were so many complaints from patient [7,17,19]. In a dialogue between the authors of this article and Principal Investigator of SCT, staff from Jilin Biotech Company and doctors from Jilin People Hospital they all claimed the treatment of II type of diabetes by SCT is efficacious. When the woman doctor was asked to provide data to prove SCT better than mushroom soup in treating diabetes, she admitted that she has no data, only relying on patients' statements. Beike's strategy in the hospitals associated with Beike is that they used a hodgepodge to treat patients: stem cell injection, rehabilitation therapy, massage, acupuncture, herbs. Even the treatment is efficacious, which of them works? Because Beike operates a "treat and discharge" policy, none of the doctors at any cooperating hospitals follow the progress of their patients, how they know its efficacy or not. So, after so many years there is no compelling evidence to prove the efficacy of SCT even for a single case. Hu Xiang admitted that SCT may only have nutritional or supportive function".

### Patients' Response

Although you can read at Beike's website a huge number of patients' positive response which patients may feel at the early stage of SCT, however, eventually many Chinese patients felt tricked, some of them formed an organization at internet to fight against the cheating by use of SCT [17,19]. However, many patients are farmers from poor villages, they are vulnerable, and don't know how to protect their rights/interests [19]. Foreign patients made complaints too. A US patient Rochard Jewell, 54 years old Parkinson's sufferer, said 4 days before the start of the 5-week course: "I've spent my life savings to come out here. I wish I could have just had this treatment in the US", and he have already paid almost CNY 220,000 for the treatment." The decision to come to China was difficult but he was willing to do almost anything to improve his quality of life. However, these

desperate patients were exploited by those advocates of SCT [18]. Italian patients felt no better when returning home after SCT in China, even worse. They made complaints to Beike, Beike asked them to go there to treat again. Later Italian TV Station sent a team to do investigation and interviews. After their report was shown on TV, no Italian comes to do stem cell tourism.

### Comments by chinese experts

Professor Jing Naihe (Deputy Director, Institute of Biochemistry and Cell Biology, Shanghai Academy of Life Sciences) commented that the improvement of symptoms after SCT is all a short-term effect. It is simply an effect of neural system to external stimulants. The long-term improvement is impossible. We extremely lack clinical evidences to support long-term benefits from SCT [17]. It should be added to the comment that in the short-term effect there is a placebo effect. Professor Qi Guoming (Vice President of Chinese Medical Association) said it is another chicken blood therapy! Unfortunately, his words may prove to be prophetic.

### Comments by US experts

Neurological experts from State University of California Los Angeles (UCLA), Dobkin et al. [20] examined 7 returned patients treated by Huang Hongyun (Xishan Hospital) and found no one had significant improvement, 5 among them suffered complications including meningitis [20,21]. Professor Susan Perlman, an ataxia expert at UCLA examined a US patient Chin who had been treated by Beike/Hospital. She said in one month after treatment there was certain quantifiable improvement, however, in about 6 months all these improvement disappeared. The same are other 2 patients with ataxia and spinal injuries. Professor Perlman said if stem cells reach the lesion and differentiate into neurons and integrate with the tissue there, they should have long-term efficacy. She compared SC injection with doping [11]. As early as in 2008 SCT was ranked as one of 10 major frauds in science and technology in 2007 by Beijing Newspaper of Science and Technology [22]. It is not without reason. In November 2012 a meeting on stem cell therapy and medical tourism was held in Harvard University, the conclusion is that the efficacy of stem cells is not scientifically verified yet; stem cell tourism leads to health risks, and the accurate information on stem cell therapy should be provide to the public. The conclusion holds true to China too [23].

### How is the risk?

In mainland China all data on SCT are largely not reported and inaccessible, so it is difficult to know the risks brought about by SCT. However, it is absolutely not the case that there is no risk as SCT advocates boasted. In January 2009 an Israel boy underwent SCT from fetus in Russia and was found tumor in brain and spine when returned to the country. Genetic test showed the tumor cells came from transplanted cells [24,25]. In 2010 a patient, Mr. Hong Chun came from Jinhua, Zhejiang Province to a hospital in Shanghai to undergo SCT. He had grave

adverse effect after 2 injection of stem cells and died after back home [13].

### Explanations of the unruly situation of "SCT"

How to explain the unruly situation of SCT in China? Several plausible explanations could be provided as follows:

**Explanation 1:** High profit margin: Because SCT is a practice which makes big profits with small capital, it caused a great number of doctors to provide such unproven and unregulated therapy. In the ubiquitous market doctors are not sages transcending vanity fair, but homo economicus too. The cost for unproven stem-cell therapies in China paid by patients is sky-rocketing. The prices of SCT for diabetes range from CNY 100,000 to 400,000 and "SCT" for Parkinson's disease normally costs at least CNY 50,000 in several hospitals. These high prices have led to the trade becoming vastly profitable [17]. However, for doctors, especially those who work at public hospitals there are moral, regulatory and legal constraints, how is possible to provide unproven and unregulated therapy in such unprecedentedly large scale? It seems that the explanation in term of doctors' individual conduct is inadequate.

**Explanation 2:** Asymmetry in information and power exploited: Doctors who provide SCT exploited the asymmetry in information and power between doctors and patients, took advantage of desperate patients to sell this unproven and unregulated therapy in order to make profits from these patients. It may partly explain why hundreds public hospitals provided such SCT. It is not purely doctors' individual conduct, but a conduct which was permitted tacitly by medical community at least partly. Except Chinese Society for Diabetes (Chinese Society for Diabetes 2010), there is no medical society which came out to reject SCT. However, this explanation may not account for why the society and government tolerated this conduct for such a long time.

**Explanation 3:** Corruption of medical community and deterioration of medical professionalism: Unruly situation of SCT in such large scale indicated the degeneration of medical professionalism and corruption of medical community. So far Chinese Medical Association and Chinese Medical Doctors Association failed to recognize medicine is not an occupation in general, but a profession which shoulders responsibilities to the society. The fact that these associations and regulatory body only talked about "occupational spirit" not "professionalism" is a factor which tolerated doctors and hospitals making huge profits from SCT in such large scale [Foot note 13-16].

**Explanation 4:** Periodic hype therapy syndrome: In China there has been a social epidemic which may be called "periodic hype therapy syndrome". Since the Cultural Revolution there has been a therapy prevailing in the public all the fashion which was advocated by doctors or health officials, such as bitten therapy (advocated by then Minister of Health during the Cultural Revolution), chicken blood therapy, swing arm therapy, qigong

therapy up to now green bean therapy in lesser scale and getting through blood vessel therapy in locals (advocated by Gansu Provincial health officials) etc. However, in comparison with those hype therapies the prevailing of SCT is unparalleled in the scale and in length of time. One factor is: SCT is labeled as high-tech. However, if there is no institutional support, it is impossible for SCT to become such far too cumbersome.

**Explanation 5:** Rampant medical commercialism: Since the first round of health care reform which was market-oriented in China, attempts were made to solve health care financing problem with market mechanism and to increase the quantity and improve quality of health care services with market competition. Underlying these attempts is the conception of taking health care as general goods but not the public good. There is no controversy on medicines and medical equipment's taken as goods, however health services provided by health professionals such as diagnosis, treatment, nursing, prevention as well as public health are public good. Market-oriented reform introduced market and capital into health care services, and turned professional institution – public hospitals into enterprise, where fundamental principles of medical ethics and medical professionalism with the first principle of patient's interest first are all thrown away. The priority is on making profits. This runs in the direct opposition to the value of traditional Chinese medicine that looks medicine as the art of ren (humaneness, care, compassion, empathy, doing good to patients) not the art of making money.

**Explanation 6:** Wrong and stupid policy: The policy what refers to is “selling medicine to nurture hospital” and connecting doctors' income with patient's payment. Since China embraced the market economy in the early 1980s, the government has provided limited financial support to its public hospitals (only 3-8% of total income) and hospitals are left to fend for them. To generate income, many doctors prescribe expensive medications, order unnecessary medical tests, over-treatment, and make exaggerated claims about unproven therapies. Entering the 21st century China decided to make a U-turn in health care reform for emphasizing government guidance instead market orientation. Apart from making commitments to cover basic health care of all citizens in urban and rural areas with various medical insurance programs, public hospitals will be returned to public good. Now the reform of public hospitals at county level is quite successful. But tertiary public hospitals are at stake. To the disappointment of many public health researchers and practitioners, the government still does not commit to cover the staff salaries of tertiary public hospitals although promising to inject more money into them. Consequently, there will continue to be a direct connection between payments by patients and doctors' income. As long as this situation does not change, clamping down on unregulated medical practice including unproven SCT in China will remain challenging [26] [Foot note 17-20].

### Ethical Issues in SCT

#### Clinico-ethical Issues

Providing unproven and unregulated SCT violates the principles of patient's interest first, respect for patient's autonomy and social justice. Instead, doctor and hospital's interests first in the practices of providing unproven SCT. The advocates of SCT repeatedly said providing SCT is for releasing patients' suffering. But is providing unproven therapy in the patients' best interest? The fact is that unproven therapy caused great physical, mental and financial harms to patients. In SCT the first is not patient's interests, but doctors and hospitals' interests – making profits [27].

Understating risk, overstating benefit. The providers of SCT disclosed information to patients only by advertisement, always exaggerated benefits and covered risks. For instance, at Beike's website where is full of patients' positive responses without mentioning any negative effects. It is not only immoral but also illegal, for it violates China's Tort Law in which Article 55 stipulates that “medical staff shall disclose medical risks, alternatives etc. to patient and obtain written consent from her/him.” (NPC China 2009) Timothy Caulfield, a biomedical ethics researcher at the University of Alberta in British Columbia, and his colleagues, analyzed 19 stem cell clinics around the world, which have English-language websites including Beike. All websites advertise improvements as a result of stem cell therapies, but few indicate any potential risks except procedural risks and side effects such as nonspecific fever or tingling. This asymmetric portrayal of risks and benefits leaves an overall impression that the therapies are readily available to the public rather than experimental. After a comprehensive search of scientific literature, the researchers could not find any evidence to back up such claims. Increasingly, such misinformation on unproven procedures has been allowed to proliferate on the internet with relative immunity from legal and ethical constraints, causing much confusion among patients considering such interventions [21,28-31]. Exploitation of patients. Is it fair to require patients of paying so high cost for “SCT”? The cost of SCT for hospitals or biotech companies is about CNY 1,000 or at most CNY 5,000 only, but patients have to pay CNY 50,000-200,000. It is not only excessive profits but also an exploitation of patients [32].

#### Research ethical issues

All people who are high on SCT never ever did lab or animal research and opposed to clinical trials. In early 2008, Beike and the Minneapolis Heart Institute Foundation in Minnesota discussed jointly pursuing clinical trials on using stem cells to mitigate certain heart disorders. The foundation offered to help Beike set up a clinical-trial protocol that would include creating a registry of patient outcomes. However, Beike declined the offer “because of their inability to fund the venture” [33]. Why they are not willing even oppose to conduct clinical trials? [Foot note 21-23]

**Reason 1:** The safety of SCT has already been proven. Hu Xiang says that the transfusion of umbilical stem cells is a proven procedure to treat diseases such as leukemia [11]. "So, we know it's safe." Here, he confused unproven SCT with already proven hematopoietic stem cell therapy.

**Reason 2:** Only the patients know which therapy is efficacious. Hu Xiang said: "We can write up our data for publication. But what's the point? Patients know whether they have improvements or not [34]. Statement made by patient or even by doctor is subjective experience, and it cannot form objective evidences to prove whether the therapy is safe and efficacious or not. Only positive data obtained from clinical trials designed by scientific method can form scientific evidences. According to Popper, only the data obtained in this way can form basic statement by which a certain hypothesis (whether a therapy is safe or efficacious) is tested inter-subjectively [35].

**Reason 3:** It is immoral. Huang Hongyun said: "Clinical trials are unethical because the trials only pretend to treat them...I wouldn't do it. Double-blind trials only harm the patient." He also said that in clinical trials 50% patients would suffer. If we give them placebo, we only do harms to them. This is not in patients' interest. It is enough for us to do innovative therapy or to have patients themselves in previous years as in control arm [12,16,36,14]. Later Hu Xiang accepted our suggestion to conduct clinical trials in a few hospitals including Nanjing Drum Building Hospital where they used Beike stem cell products to treat lupus erythematoses. However, they did not use controlled group, and only compared the past (not use of SCT 3 years ago) and the present (use of SCT) of same group of patients.

- i. Huang's argument is question begging apart from his ignorance of randomized controlled trials. Before clinical trials SCT and existing therapy are in equipoise, then there is no data which prove as well as medical community does not accept which is better. Which is safer or which brings less risk to patients remains to be proven by clinical trials. So, before the trials it cannot be claimed that patients assigned in control arm would suffer, whereas patients assigned in SCT arm won't suffer. Actually, providing unproven SCT to patients brought higher physical, mental and financial risks/harms than those in control arm [Foot note 24-26].
- ii. Huang confused clinical trials with innovative therapy, so he does not understand the difference between research and treatment. Innovative therapy is an unproven treatment which is permitted only in rare and limited cases. It is illegitimate to provide such unproven therapy to hundreds or even thousands of cases as Huang did. And innovative therapy cannot generate objective evidence to prove its safety and efficacy although it may provide some useful clues to scientists.
- iii. The comparison between the past and the present of same group of patients is not clinical trials at all. The inner

and outer environment of patients in the past and in the present are different, so if the condition is improved, it may be due to some factor in the difference of inner and outer environment, rather than the injection of stem cells. The approval of this project by IRB of Nanjing Drum Building Hospital indicates the gap of its research review capacity [37].

Why they are not willing to conduct clinical trials? Cell biologist Duanqing Pei, director-general of the Guangzhou Institute of Biomedicine and Health, said: "I can understand why they wouldn't want to do a trial. They might spend millions of dollars to prove that the treatment isn't effective [33]". The unfold history demonstrates that it may be true that they knew the truth of how much effect SCT can have, and clinical trials will reveal the truth, but they don't want the public to know the truth.

However, some scientist took clinical trials seriously. In 2002 Zhu Jianhong, a neurosurgeon at the Shanghai-based Fudan University Huashan Hospital, and his colleagues were able to derive adult neural stem cells from 16 of 22 such patients. After rigorous cell biology and animal studies, Zhu and co-workers undertook a randomised controlled clinical trial to test the safety and efficacy of the autologous transplantation of those stem cells for functional recovery after brain injury. Later in the trial there were 20 patients in the control and treatment groups, who were matched for age, the location of the lesion, and the severity of the injury; the patients have been followed up for 2-5 years. In one patient, Zhu labelled the stem cells with magnetic nanoparticles and found that the injected cells migrated towards the injured regions. "The preliminary results are encouraging, but the size of the trial is too small to be conclusive", cautions Zhu. "And the issue of spontaneous recovery remains to be resolved." (Qiu J: 2008b)

### Regulatory Issues

SCT is unregulated and its proponents steadily resistance to the regulation for a long time. The regulatory body should promote biomedical scientist to study, develop and apply innovative therapies which will be safer and more efficacious than existing. However, it should be conducted responsibly which means the requirement scientists and physicians of adhering integrity and fighting misconduct as well as protecting patients/research participants' rights and interests. The regulation of such research develop, and application should be institutionalized. However, there are cognitive, moral and regulatory gaps in China [38,39].

### Cognitive gap

A considerable number of scientists and physicians still do not know why clinical trials must be conducted before clinical application and the protocol of the clinical trials must be reviewed and approved independently by IRB. Some geneticist said: "science is the most ethical, and scientists should be protected as emperor".

## Moral gaps

A considerable number of scientists, ethicists or lawyers claim that “international ethical guidelines are Western, not applicable to China”; “Informed consent is a principle of individualism and liberalism, we are adhering the principle of collectivism or societal interest first”; “Only we, physicians, knew how to protect patients”; “The cost is too high to explain our project to illiterate farmers”; “In the era of high tech individual privacy should be given up” etc.

## Regulatory gaps

Needed regulations not developed and promulgated regulations not enforced, and violation of regulations not penalized. Many scientists criticized the regulatory gaps. Professor Pei Duanqing said that foreign patients came to China to undergo stem cell transplantation not because the techniques in China are advanced, but there are many legal loopholes [12]. At the meeting of BIONET Final Conference Chinese and European scientists and bioethicists jointly called for enhancing regulations of stem cell treatment [40,41].

In 2009 Ethics Committee of Ministry of Health developed Ethical Guidelines on Clinical Trials and Application of Adult Stem Cells (Ethical Committee 2009) as recommendations submitted to MOH. The Ethical Guidelines includes chapters of ethical principles, ensuring the quality of and safety of adult stem cells, review of protocols and innovative therapy or experimental treatment. A considerable part of the Ethical Guidelines is to elucidate the relationships between clinical trials and clinical application, and between pre-clinical research and clinical research/trials. Pre-clinical (lab and animal) research is the premise of clinical trials and a clinical trial is the necessary condition for clinical application. Sufficient evidence of safety and efficacy is only obtained during the two steps of scientific research (pre-clinical research and clinical trials); the results are evaluated scientifically and ethically and if the application is approved by the health administration, adult stem cells are permitted to be translated into clinical application [42].

In December 2009 Ministry of Health tried to regulate SCT with the promulgation of Regulations on Clinical Application of Medical Technologies [43] in which SCT is classified as the 3rd type of medical technology, which is required that clinical trials must be conducted before clinical application and both clinical trials and application should be approved by MOH. However, the hospitals and companies which provide SCT ignored this requirement [44]. In January 2012 MOH has to promulgate the Notification on Self Inspection and Correction of Stem Cell Clinical Research and Application (MOH 2012) in which SCT would be suspended for one year. In 2013 MOH published two drafts online for comments from the public: Regulations on Clinical Trials and Research of Stem Cells and Regulations on Research of Medical Science and Technology Involving Human Subjects. Finally MOH promulgated Interim Regulations on

Clinical Trials of Stem Cells in which investigators and their institution are required of applying to the regulatory body, being reviewed by IRB, adhering informed consent, and protecting subjects as well as not permitting to receive any payment from subjects, operating in the market and using advertisement [4]. Now there are 102 institutions of stem cell clinical research which are all affiliated with some of the best hospitals classified as first class hospitals at third level in China. Clinical applications of SCT have not been approved.

## Revival of Unruly Situation of SCT, Somatic Cell Therapy and Gene Editing?

We have to not forget we are living a society where capital and market are pervasive in every fields and sectors including health care and biotechnologies. Health care and innovation, R%D and clinical translations of biotechnologies need support or assistance from market mechanism. When the tendrils of the market is extending to health care, it will unavoidably collide with traditional values of medicine: patient interest first or medicine being the art of ren. The capital and market tend to be greedy. They will recklessly make money without beneath attention to the regulation and even with willfully resistance to it. So even there exists regulation, the biotech companies and hospitals, private for-profit hospitals in particular colluded with them always manage to exploit the non-existence of the regulation or the loophole of it and covertly violate it without the attention of regulatory body. So, we have to aware that the tension between patient's good in medicine/health care and drive for profits in the market and capital permanently exist. It should be said that after the regulatory efforts made by MOH (now named as National Health Commission) since 2009 the unruly situation of SCT has been largely corrected. However, there are still some institutions, private ones in particular tried to break through the regulation. In Pengpai News the journalists successively reported that a private company named as the Life Pool Center for Health Care Ltd claims to provide “stem cell anti-aging comprehensive treatment program” and “stem cell treatment diabetes program”, including multi-stem cell injection”. The prices of the above treatment schemes range from CNY 298,000 (about USD 45,000/person to CNY 960,000(about USD 140,000)” for making money from stem cells, and many big players in the capital and market are getting involved in. Later, Hainan Health Commission said the regulation on stem cell translation is still not loosen up for Hainan Province [45,46].

We predict that the fight between fundamental values in medicine and profit pursuing in the market will be in the fields of gene editing and somatic cell therapy. In the website of Xinlang a blog was published on February 6, 2018, and the title is “China is already ahead of the United States in gene therapy, and the next \$100 billion market is on the eve of its explosion [47].” The author of the blog claimed that the first case of clinical trial on human gene editing using CRISPR-Cas9 was conducted at the 105th Military Hospital in 2105, then at

Huaxi Hospital of Sichuan University in 2016, and at Hangzhou City Cancer Hospital in 2017, although all of them are illegal [47] and at the Hangzhou City Cancer Hospitals 15 patients died among 86 human subjects who are all cancer patients. None of the Chinese trials mentioned above has published results [48]. So, it is not surprise that He Jiankui dared to violate regulations to create two genome edited babies in such a culture in which profit pursuing overrides the value of Patient Interest First and Medicine Being the Art of Ren.

Furthermore, on March 29, 2019 National Health Commission (NHC, i.e. Ministry of Health) promulgated Interim Regulations on Clinical Research and Translational Applications (draft).in which the clinical trials and translations of somatic cell therapy will be managed by regulatory body only with records. As long as the health institution is approved to be permitted to conduct clinical trials and then the clinical translations or applications are automatically delivered by the institution without the need of the review and approval by regulatory body except of sending a report to it [49-60]. The draft causes strong negative responses from many scientists, physicians, bioethicists, lawyers, and other scholars in the humanities and social sciences. They will gather to discuss the draft and submit recommendations to NHC. This will be another round of the fight between these two cultures: humanist culture of medical tradition and capitalist culture of the market [61-95].

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