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# Stem Cells - Great Adjunct In Regeneration

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**Abstract**
Cell is the structural and functional unit of life. A living cell is a true representative of life with its own organisation and specialised functions. Stem cells are defined as clonogenic, unspecialised cells capable of both self renewal for long periods and multilineage differentiation contributing to regenerate specific tissues. Stem cells are dormant untill called into action by proper set of chemical signals, where upon they differentiate to form required tissues. The cells are research tools and they open many doors of opportunity for biomedical & transplantation research, & restoring vital body functions. Stem cells may hold the key to replacing cells lost in many devastating diseases. There is little doubt that this potential benefit underpins the vast interest about stem cell research.What is clear about stem cells is that a tremendous amount of work is still required to identify and maintain multipotentialmesenchymal stem cells in vitro, in order to complement the recent advances in tissue engineering and gene manipulation technology.

**Key Words**
stem cells, pulp,cementum, bone, oral mucosa, craniofacial.

## Introduction

Cut a stem of a plant and stick it on ground. Chances are it will grow into a new plant. The cells in the plant stem have ability to do so. Do we humans have this same ability to do so? Research findings during the last two decades suggest that we might, depending on which of our cells we start from. Scientists have been interested in cell biology since the advent of microscopes in 18th century. Cell propagation and differentiation were witnessed for the first time and cells were recognized as the building blocks of life capable of giving rise to other cells and key to understanding human development in 19th century. [1],[2],[3]

Cell is the structural and functional unit of life. A living cell is a true representative of life with its own organisation and specialised functions.[4],[5] The human body has a remarkable capacity for regeneration. Cells in tissues such as blood and epithelia divide rapidly and are regenerated continually throughout life, whereas cells in most other tissues turn over more slowly and respond only to specific biological signals. The unique cells that give rise to specialised cells are called stem cells.[6],[7]

Stem cells are defined as clonogenic, unspecialised cells capable of both self renewal for long periods and multilineage differentiation contributing to regenerate specific tissues.They can theoretically divide without limit to replenish other cells as long as the person is still alive. Stem cells could be of embryonic, or adult type. Recently stem cells are also obtained from umbilical cord blood. Adult tissues reported to contain stem cells include brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, periodontal ligament and more recently, in the pulp. In tooth and its supporting structures, stem cells are identified in adult human dental pulp, human primary teeth (stem cells from primary exfoliated deciduous teeth) and periodontal ligament.[8],[9]

Dead cells of any kind, no matter the type of injury or disease, can be replaced with new healthy cells due to the amazing flexibility of stem cells. Thus any disease in which there is tissue degeneration, could be a potential source for stem cell therapies including skin diseases, anaemias, bone diseases, cancers, cartilaginous diseases, liver diseases, myocardial diseases, immuno deficiences, stroke, eye diseases, gastrointestinal disorders, neural disorders and the list goes on.[10],[11]

Stem cells are dormant untill called into action by proper set of chemical signals, where upon they differentiate to form required tissues. They are known to play a role in dentinogenesis and amelogenesis. Various bone regenerative procedures and pulpal regeneration is thought to be induced by stem cells. More recently tooth and periodontal tissue regeneration has been done by taking stem cells from third molar tooth in California.[12],[13],[14]

Research on stem cells and their application to treat various diseases is still at a preliminary stage. However, results from animal models are very promising and many researchers believe that it is only a matter of time before the same results can be achieved with human stem cell. But stem cells are very complex in themselves. Agreat amount of work is still required to identify and maintain multipotentialmesenchymal stem cells in vitro, in order to complement the recent advances in tissue engineering and gene manipulation

technology.[1],[15],[16]

**Regenerative Potential**

The craniofacial region mainly consists of bone, cartilage, adipose tissue, muscle, nerve, and dental tissue. Many of these tissues have originated from either mesoderm- derived cells or ectoderm-derived neural crest cells during development. Bone marrow derived mesenchymal stem cells have been reported to differentiate, at least into mesoderm derived tissues including bone, cartilage, adipose tissue and muscle. Therefore, bone marrow derived mesenchymal stem cells may be the ideal candidates for the regeneration of multiple tissue types in different craniofacial region.[5],[6]

A multinational team headed by University of California school of Dentistry researcher DrSongtao Shi, has successfully regenerated tooth root and supporting periodontal ligament to restore human tooth in animal model utilising stem cells harvested from the extracted wisdom teeth of 18-20 year old. The technique relies on stem cells harvested from the root apical papilla, which is responsible for the development of tooth's root and periodontal ligament.So for the tooth regeneration, there should be availability of stem cell for every structure present in the teeth like cementum, dentin, enamel, pulp, and so on with supporting bone.[2]

**Bone**

Tremendous amount of work has been done on the abilityofbone marrow derived stem cells to differentiate in to the bone. When cultured in the presence of dexamethasone, inorganic phosphate and ascorbic acid, bone marrow derived stem cells can differentiate into osteoblast-like cells with capacity to synthesize mineralised nodules(Gronthos et al.1994, Pittenger et al.1999).[1],[8],[17] Under these conditions uncommitted Bone marrow derived stem cells begin to express many osteogenic markers such as CBFA/Runx2,Osterix,Osteopontin, Parathyroid hormone receptor and Osteocalcin.In addition, optimal outcomes have been achieved in studies by using autologous Bone marrow derived stem cells to treat human patients with different bone defects(Quarto et al.2001,Warnke et al.2004).For example the study by Warnke et al.2004 designed a custom made biomaterial scaffold that contained BMP-7 and autologous bone marrow in order to generate a functional mandible. Although the origin of cells (presumed to be bone marrow derived stem cells) responsible for the regeneration of the mandible was not defined, the patient developed an improved masticatory function and was reported to be satisfied with the esthetic outcome.

Another important feature of in vivo osteogenesis of Bone marrow derived stem cells is the capacity of these cells to facilitate formation of organised haematopoietic marrow elements, which originate from recipient cells, when transplanted into immunocompromised mice with hydroxyapatite tricalcium phosphate ceramic powder as a carrier (Ashton et al. 1980, Friedenstein et al.1982, Bab et al. 1988, Goshima et al. 1991).[18],[19]

So after successful Bone marrow derived stem cells transplantation, donor cells actively form Bone on the surface of the carrier vehicle and the recipient cells are induced to form haematopoietic marrow elements, leading to a bone marrow organ like structure. However the mechanism by which osteogenic differentiation of Bone marrow derived stem cells influences the organisation of recipient marrow components, is yet to be elucidated.[14],[20]

**Cementum**

Although there are differences in the organisation of Bone and Cementum, it is not clear if they are formed by distinct cell types or by bone forming cells that have different environment clues. Distinguishing between two possibilities has been difficult, because to date, there is no specific marker for Cementum and Cementocytes.Cultures of murine or Primary Human Derived stem cells have been established from healthy teeth using a Collagenase pre-treatment as had been established previously for the culture of trabecular bone cells. With primary human cementum-derived cells, discrete colonies that contained cells exhibiting fibroblast- like morphology formed, and when the colonies became sufficiently large, cells from individual colonies were isolated and sub cultured. Cementum-derived cells exhibit low alkaline phosphatase activity and mineralize in vitro to a lesser degree than Bone marrow derived stem cell cultures.[17]

To study the differentiation capacities, Human Cementum derived cells were attached to the hydroxapatite/tricalcium phosphate ceramic and transplanted subcutaneously into immuno compromised mice. Like individual colonies of Human Bone marrow derived stem cells approximately 50 percent of the clonal human cementum derived cells tested, formed a bone like tissue that featured osteocyte/cementocyte-like cells embedded with in a mineralised matrix. However mineralised tissue was lined with a layer of cells that were somewhat more elongated than osteoblasts and the human derived cementum cell matrix was somewhat less cellular than that produced by Bone marrow derived stem cells. Unlike Bone marrow derived skeletal cell transplants which developed lamellar bone, the Human cementum derived cell matrix was found to contain unorganised collagen bundles, as seen in cementum.[18]

Cells in the Human cementum derived cell matrix were positive for Fibromodulin and Lumican. While Osteocytes in Bone marrow derived skeletal cell matrix were negative. The Human cementum derived cells were devoid of haematopoietic marrow. These results show that cells from normal Human cementum can be isolated and expanded in vitro. Furthermore, these cells are capable of differentiating and forming a cementum–like tissue when transplanted into immunocompromised mice.[2],[3]

**Dentin-Pulp Complex**

The Dentin-pulp complex displays an exquisite regenerative potential in response to injury. The post-natal dental pulp contains a variety of potential progenitor/stem cells(Gronthos 2002).Potential derivatives suggested for these stem/progenitor cells include the cell-rich layer of Hohl adjacent to odontoblasts(Cotton 1968), perivascular cells, undifferentiated mesenchymal cells, and fibroblasts(Ruch 1998).

In dental tissues it has been suggested that the newly generated odontoblast-like cells are the pulp cells and undifferentiated mesenchymal cells, which had de-differentiated from pulp-cells and Pericytes (Yamamura 1985).Recently, Gronthos (2000-2002) have attempted to characterize a unique population of post-natal human dental

pulp-stem cells. These cells have shown the capacity for self-renewal and differentiation into odontoblast-like cells, which formed the dentin matrix with some tubular features in vivo.[6]

The same group has also identified a potential mesenchymal stem cell population derived from Exfoliated decidous human teeth (SHED), capable of extensive proliferation and multipotential differentiation (Miura et al.2003).The possible role for post-natal human dental pulp stem cells in vitro differentiation into odontoblast-like cells and deposition of mineraliseddeposits after treatment with dentin matrix extracts in association with a mineralization supplement of B-Glycerophosphate and ascorbic acid (Liu et al. 2005). [7]

Further studies to identify a stem cell niche in the dental pulp suggested that the putative stem cell marker, STRO-1 is expressed by dental derived stem cells using immunomagnetic activated cell selection(Shi and Gronthos 2003, Shi et al 2005).It has also been reported that postnatal human dental pulp stem cells express the perivascular cell marker CD146 and a proportion of these cells also positively co-express alpha smooth muscle actin and the pericyte associated antigen 3G5(Gronthos et al.2003, Muira et al. 2004).These findings concur with co-localisation studies of these markers to perivascular cells in situ, and it is possible that post natal human dental pulp stem cells may reside in this perivascular niche with in the adult pulp derived from outside the tooth.

It is interesting to note that expansion cultures of rodent mature dental pulp cells give rise to cells of myofibroblast appearance and strong expression of smooth muscle alpha actin( Smith et al 2005).This may be simply due to a stronger competitive growth by myofibroblast progenitors in the cell population being cultured, however it has been speculated that myofibroblast are form of 'default' differentiation as the neural crest phenotype has been suggested to be unstable with schwann cells able to trans-differentiate into this cell type(Real et al 2005, Smith et al 2005).This also raises interesting questions regarding the 'site' specificity of any primary explant of dental pulp which may contain more or less vascular-derived progenitors or myofibroblast progenitors. Should we really be isolating and culturing a mixed population of primary cells or is it better to select cells, early, on the basis of surface antigens prior to culturing on?

The use of the cell surface marker low-affinity nerve growth factor receptor to identify possible postnatal stem progenitor cells from mature rodent dental pulp using flow cytometery has yielded a small population of cells whose potentiality is now being examined(Smith 2005).

It has been shown that post natal human dental pulp stem cells and stem cell population derived from Exfoliated decidous human teeth express Dentin Sialophosphoproteins in xenogenic transplants and that this expression is not present in bone formed by bone marrow stromal cells in similar transplants suggesting that the clonogenic dental pulp derived cells represent an undifferentiated pre-odontogenic phenotype in vitro.

Despite a gene expression, profile of post natal human dental pulp stem cells have been compared with bone marrow stromal cells, only relatively few differentially expressed genes(including collagen 18 and 1,IGF-2 cyclin –dependent kinase6) were highly expressed in post natal human dental pulp stem cells and there are still no specific markers for post natal human dental pulp stem cells(Shi and Gronthos 2003).Thus it appears that there are potentially several niches of stem/ progenitors cell with in the dental pulp, more information is required to further understand whether all clonogenic cells are derived from a single highly proliferative pluripotent stem cell population or from committed progenitors belonging to distinct lineages. Post natal human pulp stem cells like osteoblasts express markers such as bone sialoprotein, alkaline phosphatase, type 1 collagen, and osteocalcin (Kuo et al. 1992, Tsukamoto et al. 1992, Buurma et al. 1999, Buchuille et al.2000).

Dentin matrix can be considered a reservoir of growth factors since growth factors such as transforming growth factor-beta, Bone morphogenic protein, Fibroblast growth factor and Insulin like growth factor are secreted by functional Odontoblasts and pulp fibroblasts (Frinkelman et al.1990, Ruch et al. 1995). These factors are released after Dentin demineralisation by caries process and seem to be involved in the proliferation and differentiation of pulp cells, providing chemotactic signals to recruit progenitor pulp cells at injury site and to initiate tissue repair (Martin et al.19997, D'Souza et al. 1998).

The dental pulp is a naturally highly vascularised tissue and conservative pulp procedures like pulp capping and pulpotomy result in the injury of blood vessels. The injured endothelial cells release chemotactic factors, signaling molecules necessary for the recruitment of inflammatory and progenitors for initiating the healing process (Martin 1997, Tedder et al 1995). It is suggested that endothelial injury is involved in the recruitment of odontoblast–like cells at the site of injury (Matheinet al.2005).This information raises the speculations about the use of stem cells and signal molecules in conservative pulp therapies and in trauma to teeth, with incomplete root formation, leading to more biological approach.

The odontogenic potential of individual single-colony derived human dental pulp stem cells was determined. In this, two-third of single colony derived human dental pulp stem cell strains generated abundant ectopic dentin in vivo, while only a limited amount of dentin was detected in the remaining one-third. These results indicate that single-colony derived human dental pulp stem cells differ from each other with respect to their rate of odontogenesis.

Further studies must be focused on the molecular and cellular events that play an important role in tooth regeneration, physiology, embryology, treatment related events and therapies related with stem cells, contributing to a better clinical dental practice. Taken together these results indicate that human dental pulp stem cells possess stem cell like qualities including self-renewal capability and multilineage differentiation.[9],[10]

**Periodontal Ligament Attachment Apparatus**

The functional periodontal ligament apparatus anchors the tooth and consists of periodontal fibres that run between alveolar bone and cementum lining the

root surface. Following conventional periodontal therapy involving debridement of root surface, the periodontal tissues heal by repair and migration of the epithelium along the previously contaminated root surface.

Periodontal regeneration requires new connective tissue attachment to the root surface, a process that involves the regeneration of periodontal fibres and the insertion of these fibres into newly formed cementum. Unfortunately currently available regeneration techniques are clinically unpredictable, resulting in only partial regeneration at best (Bartoldet al.2000, Wang et al.2005).[11]

From a biological perspective, current and future prospects for improved regeneration of periodontal tissues are dependent on our ability to facilitate the repopulation of the periodontal wound by cells capable of promoting regeneration. It has been demonstrated that only the periodontal ligament, but not gingival connective tissue or bone, contains cells capable of establishing new attachment fibres between cementum and bone. The ability of Periodontal ligament cell populations to achieve regeneration has implied that progenitor cells, and possibly stem cells reside in Periodontal ligament.[12]

Although it is clear that cells residing in the periodontal ligament can achieve regeneration and this population is heterogenous (Limebacket al.1983), it is not known that which subpopulations are capable of achieving regeneration. Indeed, cells derived from regenerating defects are found to have specific properties such as increased proliferation rates, representative of a 'regenerative phenotype and distinct from PDL cells(Ivanovski et al.2001).Therefore in order to identify progenitor and stem cells from the periodontium, identifying markers should be there to distinguish these types of cells.

In order to understand the cellular origin of developing PDL apparatus, transplanted tooth buds were used to show that the mesenchymal-derived dental follicle surrounding the developing tooth root is the source of progenitor cells for Cementum,Alveolar bone and PDL(Tencate et al 1971, Tencate and Mills 1972, Palmer and Lumsden 1987).

More recently, the dental follicle associated with third molars has been shown to contain precursor cells which are clonogenic and have the ability to differentiate under in vitro conditions to a membrane-like structure containing calcified nodules (Marsezecket al.2005).

The source of post-natal progenitor cells which may be capable of regenerating the periodontium has been investigated for a number of years. Cell kinetic experiments in mice and rats (McCulloch and Melcher 1983, McCulloch et al.1989) have shown that PDL fibroblast populations represent a steady-state renewal system with number of new cells generated by mitosis equal to the number of cells lost through apoptosis and migration. This capacity of self-renewal, which is further evidenced by the rapid turn over of the PDL, supports the notion of progenitor/stem cell populations. Furthermore, a significant number of periodontal cells do not enter the cell cycle (McCulloch and Melcher 1983) suggesting that cells may act in a similar manner to quiescent, self-renewal and multipotent stem cells.[13]

The relationship between progenitor cells in regenerating tissues and normally functioning (steady-state) tissues has been investigated in studies performed in normal mouse PDL(McCulloch 1985), rounded mouse PDL(Gould et al.1980), normal rat gingiva(Nemeth et al. 1993).These studies have identified a common paravascular location for fibroblast progenitors. These cells exhibit some of the classical cytological features of stem cells, including small size, responsiveness to stimulating factors and slow cycle (Gould et al 1980, McCullloch and Melcher 1983, McCulloch 1985).

Furthermore, these paravascular cells exhibit spatial clustering which suggests a possible clonal distribution of progenitors and their progeny (McCulloch 1985).Other possible sources of osteoblast and cementoblast precursors are the endosteal spaces of alveolar bone from which cells have been observed to adopt a paravascular location in the PDL of mice (McCulloch et al 1987).

However, based on these studies, paravascular cells in PDL cannot be designated as stem cells because the clonogenic capacity of these cells and their ability to differentiate into multiple cell types were not demonstrated. Additional identification and isolation of these cells using membrane surface for stem cells and demonstration of their clonogenic as well as multilineage properties, has subsequently been sought in order to consolidate the hypothesis that stem cells reside in PDL.

Additional challenges have been encountered when trying to extract mesenchymal stem cells from connective tissue composed largely of fibroblastic cells, such as PDL. As stated earlier, a single specific antigenic marker for mesenchymal stem cells is not available, and hence a combination of markers must be used in order to achieve their isolation. Thus it appeared or demonstrated that PDL stem cells can be isolated using STRO-1 and CD146 markers. The presence of mesenchymal stem cells in the PDL is also supported by the findings of Trubian et al 2005, who isolated and characterised a population of mesenchymal stem cells from PDL which expressed a variety of stromal cell markers CD90, CD29, CD44, CD166, CD105, and Cd13.

The clinical potential for the use of PDL derived stem cells has been further enhanced by the demonstration that these cells can be isolated from cryopreserved PDL's thus providing a ready source of mesenchymal stem cells (Sec et al 2005).

From a biological perspective, in order for periodontal regeneration to occur, the aviability of appropriate cell types, together with favourable local environment promoting cell migration, adhesion, proliferation and differentiation, all need to be precisely coordinated both temporarily and spatially. Thus a tissue engineering strategy for periodontal regeneration that exploits the regenerative capacity of stem cells residing in the periodontium, grown in three-dimensional construction and subsequently implanted into the defect may help to overcome many limitations with current regenerative modalities (Bartold et al.2000).In doing so, the need for recruitment of various different cells to site is negated and the predictability of outcome may be enhanced.[15]

**Cartilage**

Craniofacial tissue contains several areas which consist of Cartilage, such as nose, ear, and temporomandibular ligament. Surgery, Congenital deformity, trauma or some types of temporomandibular ligament disorders may lead to a loss or destruction of the cartilage matrix. It is anticipated that cartilage regeneration may offer an alternative approach to the treatment of these disorders.

Bone marrow derived mesenchymal stem cells can differentiate into chondrocytes when cultured under a three dimensional serum-free setting in the presence of transforming growth factor-beta(Pittenger et al 1999), which was confirmed by the expression of type 2 collagen and Aggrecan (Pittenger et al 1999, Gronthos et al 2003).

When bovine bone marrow derived mesenchymal stem cells were receded into biodegradable scaffolds and subsequently implanted into fetal tracheas, they showed a significant chondrogenic differentiation (Fuchs et al 2003)

Moreover, improved cartilage repair in patellar groove defects was observed following implantation of rabbit bone marrow derived mesenchymal stem cells (Wakitani et al 1994, Im et al 2001). At the molecular and cellular levels, recent studies have demonstrated that Wnt beta-catenin may play a crucial role in regulating chondrogenesis of Bone marrow derived mesenchymal stem cells (Day et al 2003, Hill et al 2005).

Ectopic canonical Wntsignalling leads to enhanced ossification and suppression of chondrocyte formation, while genetic inactivation of beta-catenin causes ectopic formation of chondrocytes while the requirement of high- quality cell preparations, growth factors and ideal scaffolds possess many challenges for cell-based therapies. Bone marrow derived mesenchymal stem cells have shown a great therapeutic potential to repair cartilage defect (Magne et al 2005, Raghunath et al 2005).[17]

**Adipose Tissue**

Adipose tissue in different craniofacial regions may have a considerable impact on the appearance of facial structures. Bone marrow derived mesenchymal stem cells can differentiate into adipocytes when cultured with the inductive medium, which contains hydrocortisone, indomethacin, insulin and isobutyl methyl xanthenes(Pittenger et al 1999, Gimble and Guilak 2003).The adipocytes derived from bone marrow derived mesenchymal stem cells show cytoplasmic lipid vacuoles positively stained with Oil red O.The differentiation can be genetically confirmed by the expression of the fat- associated markers, Peroxisone proliferators activated receptor(PPAR) gamma 2 and leptin(Gronthos et al 2003). On the other hand, adipose-derived adult mesenchymal cells have also been demonstrated as a population of multipotent stem cells, which can differentiate into adipogenic, osteogenic, chondrogenic, myogenic and neuronal strains to regenerate adipose tissue for cosmetic purpose and tissue repair in craniofacial reconstructive surgery.[18]

**Muscular Tissue**

It has been shown that demethylation compounds such as 5-azacytidine or amphotericin B can induce myogenic differentiation of bone marrow derived mesenchymal stem cells in vitro(wakitani et al 1995, Makino et al 1999, Phinney et al 1999).Many reports have demonstrated that implantation of cultured bone marrow mononuclear cells by intracoronary injection improves left ventricular function(Assmus et al 2002, Strauer et al 2002, Wollest et al 2004) although the question of transdifferentiation of bone-marrow derived cells into cardiomyocytes has been raised(Balson et al 2004).

Recently, several clinical trials have reported an improvement of myocardial function by an autologous bone marrow derived mesenchymal stem cells transplantation after acute myocardial infaraction (Chin et al 2004, Price et al 2006). Collectively, these studies demonstrate a potential therapeutic use of Bone marrow derived mesenchymal stem cells for regeneration of cardiac and perhaps skeletal muscles, particularly for patients who have undergone a radical surgery or trauma, including patients having problems in mastication.[17],[18]

**Oral Mucosa**

Trans et al (2003) reported an example of transdifferentiation of human bone marrow derived stem cells into buccal epithelial cells. Using fluorescence in situ hybridisation and immuno histochemistry, they identified Y-chromosome-positive buccal cells in five female patients who had received either a bone marrow transplant or an allogenic mobilized peripheral blood stem cell transplant from male donors.Y-chromsome–positive cells in these female patients were morphologically distinguishable as buccal epithelial cells and they also expressed cytokeratin 13, a recognized epithelial marker located in the superficial layer of the cheek. The donor-derived buccal epithelial cells were identified by morphologic characteristics, cytokeratin expression, positive Y-chromosome and negative CD45.

The plasticity of adult bone marrow-derived cells has been questioned by studies suggesting that fusion between donor and host cells gave an appearance of transdifferentiation (Teradaet al.2002, Ying et al.2002).However in vivo they did not observe cell fusion. Trans et al examined more than 9700 buccal cells and reported no evidence of fusion. These findings were also confirmed by Metaxas et al 2005 who reported that none of the buccal cells examined had more than one chromosome, which excludes fusion as the answer to cell plasticity.[16],[20]

**Conclusion**

There has been much written about the new discoveries of various stem cell types and their properties. Importantly, these cells are research tools and they open many doors of opportunity for biomedical & transplantation research, & restoring vital body functions. Stem cells may hold the key to replacing cells lost in many devastating diseases. There is little doubt that this potential benefit underpins the vast interest about stem cell research.

What is clear about stem cells is that a tremendous amount of work is still required to identify and maintain multipotentialmesenchymal stem cells in vitro, in order to complement the recent advances in tissue engineering and gene manipulation technology.

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