The potential of stem cell therapies for neurological diseases

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As a novel neurotherapeutic strategy, stem cell transplantation has received considerable attention, yet little of this attention has been devoted to the probabilities of success of stem cell therapies for specific neurological disorders. Given the complexities of the cellular organization of the nervous system and the manner in which it is assembled during development, it is unlikely that a cellular replacement strategy will succeed for any but the simplest of neurological disorders in the near future. A general strategy for stem cell transplantation to prevent or minimize neurological disorders is much more likely to succeed. Two broad categories of neurological disease, inherited metabolic disorders and invasive brain tumors, are among the most likely candidates.

By current estimates, over 100 million Americans could benefit from stem cell therapies. Targets of stem cell therapies include cardiovascular and autoimmune diseases, diabetes, multiple sclerosis, osteoporosis, cancer, Alzheimer’s disease (AD) and Parkinson’s disease (PD) [1]. Stem cell therapy has been used for over 30 years as a therapy for disorders of the hematopoietic system. For example, transplantation of stem cells derived from bone marrow have been used to dramatically decrease the death rate in leukemia [2], and this success has fostered high expectations for this expanding branch of clinical medicine. The complexities of some of the neurological diseases proposed as targets for stem cell therapy, however, may be such that stem cell therapy as a restorative approach may be much less likely to succeed than when used as a preventive approach [3]. That is, it is much less likely that novel stem cell therapies will be successfully used to repair a brain that has been ravaged by stroke, trauma, genetic disease, or a neurodegenerative process. Indeed, there can be little doubt that only palliative or minimally restorative care might ever be possible after massive brain damage has occurred. This concept is supported by experience with bone marrow transplant for some metabolic diseases affecting the brain (e.g., x-linked adrenoleukodystrophy or mucopolysaccharidosis type 1) where early treatment can prevent the progression of the disease and no benefit is seen after severe brain damage has occurred [4]. A similar effect is noted in animal models of spinal cord injury where only early treatment is beneficial [5].

Sources of stem cells for neurotherapy

There are three main sources of human stem cells for neurotherapy: the brain itself, bone marrow or cord blood and the preimplantation embryo. Neural stem cells (NSCs), defined by their clone-forming ability, self-renewal capability and multipotency, can be isolated from fetal [6], neonatal [7] and adult human brain [8], where they are localized to the hippocampus and subventricular zone (SVZ) in stem cell niches [9]. NSCs can give rise to the three brain cell types: neurons, astrocytes and oligodendrocytes. The presence of NSCs in the adult brain accounts for the finding that neurons are generated constantly, even into adulthood [10], in some regions of the brain, especially the SVZ and the dentate gyrus of the hippocampus. Importantly, only a very small percentage of the brain is replenished by this activity; thus, the brain has only minimal capacity to repair itself after disease or injury. The biological reason for the presence of this
stem cell population has yet to be determined with certainty, but one reason might be for neuronal replacement in long-term memory [11]. Although NSCs represent a logical first choice as a cell population to use for neural cell replacement and have been very useful for proof-of-principle in animal studies and preclinical trials [12], it is unlikely that they will ever be clinically useful. The primary reason for this is that the very small numbers of donors that are ever likely to be available would not present a sufficient pool to allow immunological matches to be made with any but a very small proportion of possible recipients. For current therapy of the hematological disorders, for example, there are approximately 6–7 million potential donors for bone marrow transplants [13]. These donors collectively provide immunological matches for approximately 70% of the possible recipients. A bank of NSCs to approach this level of matching ability would be extremely laborious, expensive and time-consuming and is unlikely ever to be created. It is possible, however, that NSCs possess only a weak capacity to stimulate immune rejection [14,15] and, when implanted into an immune-privileged site, such as the brain, might evade the immune system altogether [16].

An alternate approach to NSC transplantation, however, is suggested by several studies that indicate that the endogenous pool of NSCs may be recruited under the appropriate conditions. Thus, exercise, for example, has been demonstrated to stimulate neurogenesis [17]. Furthermore, intracranial administration of trophic factors, coincident with a neuropathological process, can elicit a substantial neurogenic response with the newly generated cells migrating en masse toward the site of injury [18]. These data suggest that it may be possible to harness endogenous processes and obviate transplantation [19]. It remains to be seen, however, whether or not such an approach will be sufficient and, importantly, safe.

In addition to the hematopoietic system, bone marrow also contains a supporting tissue called stroma [20]. It was originally thought to simply provide a structural framework for the hematopoietic system; however, it has now been found to contain a population of mesenchymal stem cells (MSCs), which are strongly adherent and can therefore be isolated by culturing marrow on an appropriate substrate and washing other cells off [21]. MSCs can give rise to many kinds of connective tissue cells and are easily differentiated into chondrocytes, osteocytes and adipocytes [22]. A related stem cell population, the multipotent adult progenitor cell, has also been isolated from bone marrow [23].

Recent studies by a number of laboratories have suggested that MSCs have two additional properties that make them attractive for stem cell transplantation: they appear to provide a degree of immune tolerance when transplanted concurrently with bone marrow [24,25], possibly decreasing the incidence or severity of graft versus host disease, and they may have the potential to differentiate into additional cell types, including neural cells [26–29]. Current clinical trials are examining both of these properties [201]. Although controversial [30], these data suggest that not only might MSCs improve engraftment after conventional bone marrow transplantation, they may also provide precursors for other organ systems besides blood. The implication, especially for the short-term, is that bone marrow, from a single immune-matched donor, may potentially be used for multiple purposes for the recipient. In addition, this putative stem cell plasticity offers the potential for use in autologous transplantation to treat certain extramedullary diseases [31,32].

Human embryonic stem cells (ESCs) are usually obtained from the inner cell mass of embryos produced by in vitro fertilization (IVF) [33]. Under certain conditions, ESC populations can divide indefinitely while undifferentiated, while under other conditions they can differentiate into virtually any cell type in the body, (i.e., they are pluripotent) [33]. When cultured in the laboratory, ESCs grow as compact colonies and usually require the presence of feeder cells for their survival. When undifferentiated ESC colonies are detached from the feeder layer and transferred into serum-containing medium, they form multicellular aggregates called embryoid bodies, which can contain cell types representing all three germ layers of the body: endoderm, mesoderm and ectoderm [33,34].

Several groups have produced neural precursors from human ESCs and have tested them by injection into the rodent brain or spinal cord [35–39]. The transplanted cells were incorporated into the host nervous system, migrated along appropriate tracks, differentiated into neurons in a region-specific manner, made synaptic contacts with host neurons, or gave rise to oligodendroglia or astroglia.

These data suggest that ESCs may be used to provide transplantable cell types for any tissue or organ system, including the brain. However, the issue of immune-matching remains, although it may be solvable with somatic cell nuclear transfer or induction of immune tolerance and some studies suggest that ESCs possess a degree of immune privilege [40].

Current stem cell therapies

Before considering novel stem cell therapies, it is worth reviewing what stem cell therapies are currently in use and how those therapies work. To date, approximately 70 different disorders of hematopoiesis have successfully been treated with bone marrow transplantation [202]. Umbilical cord blood (UCB) and mobilized peripheral blood stem cells can also be used. As mentioned above, approximately 70% of transplant patients can find an appropriate immunologically matched donor through the national marrow donor program and other similar entities that have a combined pool of 6–7 million potential donors [13]; the remaining 30% are either transplanted with a less-than-ideal match and/or die [41].

In general, successful engraftment of donor hematopoietic stem cells (HSCs), be they from bone marrow, cord blood, or peripheral blood, requires myeloablation (destruction of the patient’s hematopoietic system) followed by rescue with the donor cells. There is significant mortality and morbidity associated with this technique and it is currently reserved for the very sickest of patients that cannot be managed in any other
The rescue of the patient’s hematopoietic system is dependent on the innate ability of the donor cells to home to and repopulate the bone marrow niche. Homing to the bone marrow is accomplished by host marrow stromal cell secretion of stromal-derived-factor 1 (SDF)-1, a chemokine that attracts the injected stem cells through its interaction with the CXC receptor, CXCR-4, present on the donor cells [45]. The success of this therapeutic approach, therefore, rests on the facts that:

- Blood components have a short half-life and must be constantly replenished
- There is a pool of stem cells that constantly replenishes the blood system
- This pool of stem cells can be more-or-less selectively destroyed
- Donor stem cells, simply injected intravenously, have the innate ability to home to the stem cell niche and repopulate it, thus replacing the destroyed stem cell pool

Therefore this form of stem cell therapy, can accurately be described as cellular replacement therapy. Few organ systems have such a comprehensive, innate, cellular replacement system that can be destroyed and replaced (skin and intestinal epithelia being possible examples); therefore, it is unlikely that a similar strategy can be used for most of the diseases for which stem cell therapies have been proposed. Thus, although stem cell therapies have been used successfully for more than 30 years, entirely new strategies must be devised for most of the novel therapies proposed.

Another group of diseases being treated with HSC transplantation is the lysosomal storage disorders (LSDs), including the mucopolysaccharidoses such as Hurler’s syndrome [4,46]. These diseases, many of which are lethal in early childhood or lead to severe mental retardation, involve the harmful accumulation of specific cell components due to the absence or inactivity of a specific enzyme normally involved in their degradation [47]. In these cases, stem cell therapy functions primarily as enzyme replacement by providing cells containing an active form of the missing or defective enzyme. Since disease progression may lead to extensive damage, early diagnosis and treatment are essential [48]. HSC transplantation in the LSDs is effective primarily for soft tissue, non-CNS organs such as spleen and liver, with only limited effectiveness for bone and cartilage and little to no effectiveness for the CNS for most of the LSDs tested [46]. This means that HSC transplantation can only be used for some LSDs that affect the brain and, even with these, must be instituted before brain damage has progressed.

Although the same basic strategy is used for stem cell therapy of LSDs, HSC transplantation, and its outcome in terms of cellular replacement is the same, the goal of HSC transplantation in the LSDs is not the cellular replacement per se but replacement of the enzyme that the replacing cells provide [4]. The cells merely act as the living vehicle for, and producer of, the enzyme. Peculiar to many lysosomal enzymes is the fact that they can be transferred between cells; thus, enzymes can physically move from the donor’s cells to the recipient’s cells [49]. The critical issue, however, is the extent to which the transplanted cells can stably populate the various organ systems of the recipient, not the extent to which the transplanted cells can differentiate into the tissues of the various organ systems of the recipient.

### Possible novel stem cell therapies

As mentioned earlier, HSC therapy for metabolic diseases has had some success, albeit limited. This limit is particularly true for the CNS. In animal models of some of the LSDs, however, implantation of NSCs [50–52] or genetically engineered NSCs [53] directly into the brain significantly ameliorates the detrimental effects of the disease on the brain. In addition, transplantation of MSCs may provide added benefit for the bone and cartilage defects found in these diseases. Indeed, some clinical studies have suggested that MSC transplantation does have an added beneficial effect in patients previously transplanted with bone marrow [54]. These data suggest that combination stem cell therapy, using intravenous HSCs and MSCs for the periphery and intracerebroventricular NSCs for the brain might be an effective treatment strategy for these patients. As many of the LSDs are childhood lethal, they are prime targets for such an experimental approach. Importantly, Stanford university has just received FDA approval for the intracranial implantation of fetal-derived NSCs for the treatment of Battet’s disease, a uniformly fatal lysosomal storage disorder [55]. However, as NSCs may be unlikely to be available for widespread application without serious immune system problems, a strategy more likely to succeed might include MSCs that have been primed for neural differentiation (neutralized) in place of the NSCs [56]. An important implication here is that a single donor may be able to act as the source for multiple stem cell types for the recipient – HSCs, MSCs and neutralized MSCs – thus minimizing immune-matching considerations. A possible strategy, therefore, would be to establish engraftment with BMT followed by, or coinciding with, MSC transplantation. This would be followed by the intracerebral implantation of neutralized MSCs from the same donor, obviating rejection. It remains to be seen, however, if such cells are able to establish long-term residence in the brain parenchyma. The point in this approach is that, whatever the stem cell source, the cells are not being transplanted as a replacement cell population and thus are not required to differentiate into neurons or glia, but rather, to act as a population of cells that simply provides enzyme and prevents brain (and other organ) damage.

Critical to the approach of NSC or MSC transplantation in the LSDs is the ability of these cells to extensively migrate into the brain parenchyma. Indeed, in animal models, it has been demonstrated convincingly that NSCs can migrate out from the ventricles after a simple, single intracerebroventricular injection to take up residence in the entire cortical mantle [57]. This is not surprising given that these cells express the CXCR4 receptor [7] and that CXCR4 homing to SDF-1 is an important component of the development of the cerebral and cerebellar cortices during normal brain development [58–60]. MSCs also appear to have this homing capacity [61], although the mechanism is less clear as their CXCR4 expression is less...
robust than that seen in NSCs [UNPUBLISHED OBSERVATIONS]. Germ cell transplantation to the treatment of the LSDs is on the going inflammatory process that is one of the components of these diseases [62,63] and that further acts as a stimulus to NSC migration from the ventricles into the parenchyma [64]. Indeed, any brain disease or injury that has inflammation as one of its components might well be a target for NSCs, including multiple sclerosis, AD, traumatic brain injury, spinal cord injury and ischemia [15,64–68].

Although the LSDs potentially benefit from a unique biochemical mechanism wherein the enzyme of interest may be transferred between cells [49], it does not necessarily follow that this type of mechanism must be present for cellular therapy of any enzyme defect to be effective. If the mortality and morbidity of bone marrow transplantation [2] can be substantially decreased (clinical trials are currently underway) [201], then it is not unreasonable to predict that this type of therapy could also be used for enzyme deficiencies for which alternative therapies already exist. For instance, some of the disorders of intermediary metabolism [69–71], where easily transportable small molecules are primarily affected, may well be quite responsive to having a cell population that can metabolize the substrate in question, even at a lower than normal rate. Whereas an enzyme deficiency must be 85% or more below normal to have a clinical effect, only a small increase in enzyme activity might be necessary to have significant beneficial clinical effects [72,73]. Patients with organic acidemias, for example, can be treated with dietary restriction, although it is well known that even with this treatment they may develop brain damage [74]. Cellular therapy may, therefore, play an important adjunctive role in these and many other metabolic diseases.

The second neurological disease category likely to benefit from stem cell therapy comprises the invasive brain tumors. These diseases, which have a very high mortality rate and for which there are no effective treatment strategies, are prime targets for such an experimental approach. Using a variety of different NSCs, several different laboratories have demonstrated that NSCs have a remarkable ability to migrate through the body and through normal tissues to accumulate in various types of tumors, both neural and non-neural [75–78]. This migratory ability again appears to be related to the same SDF-1/CXCR4 mechanism responsible for HSC homing [66,77]; participation of other mechanisms, such as MCP-1/CCR2 may also be important [79–81]. This provides a potential avenue for developing radically new types of cancer treatment, especially for tumors that infiltrate the brain so extensively that they cannot be effectively removed by surgery or are unresponsive to chemotherapy. In such cases, it may be possible to use the homing ability of NSCs to deliver chemotherapeutic agents accurately and exclusively to the tumor cells as they appear to secrete SDF-1 and other chemokines in large quantities [66,79]. This would have the added advantage of decreasing total body burden of the toxic chemotherapeutic agents usually used to treat these diseases.

Both NSCs and MSCs have been genetically engineered to produce various products that could be delivered directly to the tumor [82,83]. They can be designed to release cytolytic viruses that destroy adjacent cells, to produce antitumor proteins, or to secrete enzymes that will locally convert prodrugs into active chemotherapeutic compounds.

Again, the stem cells are not being used as a cellular replacement, although that may be an added benefit. In this case, the cells are being used as delivery vehicles to target a pathological process. Given that the invasive brain tumors, such as glioblastoma multiforme, present significant clinical challenges, including being fatal in most cases, a concerted effort to design a strategy to use NSCs for diseases such as these appears warranted.

Although the principle of preventive neurotherapy can, in theory, be applied to other nervous system disorders, such as spinal cord injury, stroke and traumatic brain injury, the variability of the injury among patients and the likelihood of only partial amelioration of injury make the statistical design and interpretation of such clinical studies more challenging. Stem cell neurotherapy in PD will likely have the same problems as current therapy based on fetal-derived tissue, such as lack of feedback regulation of dopamine secretion [84]. AD may, however, fall into the same category as the neurometabolic diseases assuming that the very earliest stages of the disease can be reliably diagnosed and that an appropriate interaction of stem cells with the disease can be identified [32,68]. One potential area for successful neurotherapy may be the demyelinating diseases. In these diseases, stem cells would be asked to remyelinate rather than rewire, a potentially tractable scenario. Unfortunately, multiple sclerosis, although a candidate for stem cell neurotherapy aimed at remyelination, presents the double confounds of being an intermittent disease with variable anatomical disease localization and concurrent axonal pathology in the more severe cases [85,86]. Similarly, spinal cord injury, while having demyelination as a component of the pathological process, still has at its core major axonal injury, with concurrent secondary degeneration at locations quite distant to the injury [87].

Potential pitfalls associated with novel stem cell therapies

One of the major problems with transplantation of any kind is the possibility of immune rejection of the transplanted tissue. Currently, two strategies are used to prevent or reduce the extent of the destructive immune response: suppression of the immune system with drugs and careful histocompatibility leukocyte antigen (HLA)-matching of the donor to the recipient. However, immune suppression may put the patient at risk for infection and matching may not always be successful. Should life-long immunosuppression begin in early childhood, the risks are greatly magnified [88,89]. Autologous transplantation provides another solution, although in the case of genetic diseases such as the lysosomal disorders this would have to be combined with gene therapy to correct the genetic defect. Recently, advances in ESC research have
suggested a new approach: somatic cell nuclear transfer (SCNT), which is used to produce an ESC line that is derived from, and therefore theoretically immune matched to, the patient [90]. The potential of SCNT has been demonstrated in animal models [91]. Since bone marrow transplants can be used successfully for treatment of some of the hematological malignancies and given the constraints of HLA-matching, a first clinical application of ESCs produced by SCNT might well be the treatment of patients with hematological disorders for whom a matched bone marrow donor cannot be found. Three confounds, however, threaten the apparent simplicity of this approach:

- To date, only two laboratories have been successful with human SCNT [90,92], suggestive of its technical difficulty
- Matching of the mitochondrial genome, which contributes to the minor histocompatibility complexes, is not solved with this approach [93,94], suggesting that immune rejection problems may persist after SCNT
- The availability of egg donors is unlikely to satisfy the potential demand [95,96]

Another potential approach, however, may solve all of these issues: pretransplantation induction of immune tolerance with a HSC subpopulation, namely dendritic cells, derived from the same ESC line to be used to derive the cells needed for therapy [97,98,99].

Another potential problem with using cells expanded ex vivo in the laboratory is the current need to use animal cells or products during cell culture. Many ESCs, for example, are grown on feeder layers of mouse embryonic fibroblasts [100], while MSCs are expanded in the presence of fetal bovine serum [21]. Although it has been suggested that the use of animal cells or products may obviate the use of cells for therapeutic applications [101], the clinical use of similarly treated cells or other implantable products has been underway for many years. In addition, it is possible to significantly reduce the animal components simply by culture of the cells for a period of time in nonanimal–based systems [101]. Therefore, the animal component concerns appear to be resolving.

Implantation of undifferentiated ESCs does, however, carry a substantial risk because of their propensity to form teratomas. Teratoma formation is, in fact, the gold standard by which one shows that a given ESC line is pluripotent [33,102,103]. Thus undifferentiated ESCs are unlikely to be used directly in therapeutic applications. As differentiation of an ESC eliminates its capacity to form a tumor [33,102,103], ESCs will be used to generate lines of cells that are at least partially differentiated, and it is these derived cells that may be used therapeutically. Unequivocal demonstration of the complete elimination of undifferentiated ESCs after differentiation, however, will be a difficult but necessary step for moving these cells toward therapeutic use.

Finally, the technique of IVF itself, which provides the starting material for the derivation of ESCs, often produces genetically abnormal embryos [104], and ESCs themselves are notoriously genetically unstable [105]. It is likely that ESCs produced by SCNT will suffer from these same problems. There is currently no way of knowing whether ESCs are completely genetically normal and would be safe to use in stem-cell therapy. Indeed, long-term safety studies may well take decades to complete. Moreover, there is emerging data that suggests that each ESC line possesses a differing capability for differentiation toward a specific lineage and that this capability varies with passage number [106]. Thus, it is not clear that ESCs produced by SCNT will, in fact, have an appropriate ability to differentiate toward the specific lineage needed for the patient for whom they were produced.

In conclusion, treatment of most brain injuries and diseases presents considerable challenges, not least of which is the unlikely prospect of being able to restore complex neurological functions after they have been irrevocably lost due to death of the associated neurons. The complexity of the nervous system in all likelihood precludes all but minimal restorative therapy.

Expert commentary

Neurotherapy using stem cells is a nascent field that has considerable promise but also daunting challenges. The complexity of the nervous system is such that, at least in the near term, strategies designed to confer neuroprotection, rather than neurorestoration, will be most likely to show significant, beneficial clinical effects. Stem cell neurotherapy of two broad categories of neurological disease, both of which are associated with significant mortality and morbidity, is likely to be successful: the neurometabolic diseases and the neuromalignancies. These therapies will initially be based on bone marrow-derived stem cell populations and may set the stage for eventual use of immune-matched or immune-tolerated, embryo-derived stem cells.

Five-year view

Since MSCs are already in Phase I clinical trials for therapy of cardiac muscle after myocardial infarction and since HSCs are currently being used for therapy of non-CNS tissues in the LSDs, it is not unreasonable to predict that MSCs will soon enter clinical trials as adjunctive therapies with HSCs for non-CNS tissues in the LSDs. Further, as MSCs are in the development phase for clinical trials testing, their therapeutic efficacy in spinal cord injury, stroke and traumatic brain injury trials addressing the efficacy of MSCs in treating the CNS in the LSDs should be, in the final planning stages within 5 years if not already underway.
Key issues

- Given the complexities of the CNS, use of stem cells as a therapy to prevent irreversible CNS damage may be more likely to succeed than use as a restorative therapy.
- The lysosomal storage disorders (LSDs) and the invasive brain tumors represent two diseases wherein stem cell therapy designed to protect the nervous system or remove tumor cells, respectively, may have a significant impact.
- Hematopoietic stem cells from bone marrow are successfully being used as a therapy for the non-CNS manifestations of the LSDs.
- Animal studies suggest that neural stem cells (NSCs) may significantly abrogate the CNS pathology caused by the LSDs.
- Animal studies also suggest that NSCs home to tumors allowing the possible delivery of tumoricidal agents, on a cellular level, selectively to tumor cells.
- Although NSCs have provided proof-of-principle in preclinical studies, mesenchymal stem cells, derived from the recipient or immune-matched donors, may be more clinically useful.

References

Papers of special note have been highlighted as:
- of interest
- of considerable interest

23. Excellent review of mesenchymal stem cells.
Hallmark paper for the derivation of human embryonic stem cells.


Hallmark paper for the derivation of human embryonic stem cells.


As the cells described by Pittenger et al., are currently in clinical trials, this paper is a particularly important read.


Good review of stem cells and their scientific controversies.


Hallmark paper for the derivation of human embryonic stem cells.


First paper to demonstrate the large-scale differentiation of a purified population of transplantable cells from human embryonic stem cells.


Suggests that stem cells are not necessarily immune privileged.


Good proof-of-principle paper.


Clinical study of the additive effects of mesenchymal stem cells after successful bone marrow engraftment.

Cooper JD. Progress towards understanding the neurobiology of Batten disease or neuronal ceroid lipofuscinosi. Curr. Opin. Neurol. 16, 121–128 (2003).

Deng J, Petersen BE, Steindler DA, Jorgensen ML, Laywell ED. Mesenchymal stem cells spontaneously express neural proteins in culture, and are neurogenic after transplantation. Stem cells [In Press].

Proof-of-principle paper for mesenchymal stem cells in neurological disease.
160

Schnitzler


76 Good review on the application of stem cells in the neuro malignancies.


78 • Proof-of-principle paper for the homing of neural stem cells to brain tumors.


80 Blockade of CXCR4 significantly inhibits homing of neural stem cells to tumors.


94 • Hallmark paper for human somatic cell nuclear transfer.


Stem cell-based neurotherapy


• Description of a novel way to address immune system issues with human embryonic stem cells.


• Suggests that in vitro fertilization may lead to a higher incidence of genetic disorders.


• Documents the genetic instability of embryonic stem cells.


• Documents the genetic instability of embryonic stem cells.

Websites

201 ClinicalTrials.gov U.S. National Library of Medicine.
www.clinicaltrials.gov

202 National marrow donor program. Learning more about your disease
www.marrow.org/PATIENT/learning_abo ut_disease.html

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