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### RESEARCH ARTICLE

## TRANSPLANTATION OF GOLD NANOPARTICLES WITH OR WITHOUT BONE MARROW STEM CELLS FOR REGENERATION OF SURGICALLY INDUCED TONGUE DEFECT IN RATS

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### Abstract

The ultimate goal of tongue reconstruction is restoring the tongue integrity while preserve its critical functions(i.e., articulation, mastication, and deglutition) and minimize the morbidity profile of a selected reconstructive technique. Mesenchymal stem cells (MSCs) used in tissue engineering became a therapeutic selection due to numerous advantages as regeneration of damaged tissues with high quality without the formation of fibrous tissue, minimal donor site morbidity in comparison with autografts and a low risk of disease transmission and autoimmune rejection. Bone marrow stem cells (BMSCs) are expandable stem, self-renewing, embedded at the site of injury and motivate tissue regeneration and wound healing. In oral wounds, they reveal greater re-epithelialization, intracellular matrix formation, cellularity, and neoangiogenesis, thus speed up wound healing. Gold nanoparticles (GNPs) application in medical fields is growing due to the chemical and physical properties like biocompatibility, optical properties, facile surface modification and stability. GNP usage in regenerative medicine is safe if the implanted tissue is replacing a tissue/organ resected because of tumor.

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### Introduction:-

#### Tongue

Tongue is a movable organ inside the oral cavity with several utilities, and it guides for underlying systemic diseases. It is a movable muscular structure contributes in the functions of speech and swallowing. It is responsible for mastication and turning over the food in the mouth propelling it inward<sup>(1)</sup>. The morphological structure of tongue and its papillae vary extensively in dissimilar types of mammals due to the functional actions, surrounding environment effect, manipulation of food manner, swallowing, the animal care, and animals' vocal modulations<sup>(2)</sup>.

#### Histology of tongue

The tongue superior surface is rough and irregular. A V-shaped line sulcus terminalis divides it into anterior part (body), and posterior part (base). The tongue is roofed with a keratinized stratified squamous epithelium which is dense on the upper surface, while over the inferior surface is smooth and thin. The epithelium on lateral sides and upper surfaces of tongue display a large amount of projecting papillae that covers epithelium and a central core of connective tissue. Papillae are less settled or absent on inferior surface<sup>(3)</sup>.

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### Tongue disorders

Tongue disorders are mostly seen in individuals wearing dentures and use tobacco. The greatest public tongue complaints are geographic tongue, then hairy tongue and fissured tongue. Tongue overgrowths usually necessitate tissue removal and biopsied to differentiate benign tumors such as granular cell tumors, fibromas, lymphoepithelial cysts from premalignant leukoplakia or malignant tumors as squamous cell carcinoma<sup>(4)</sup>. Tongue may be injured by mechanical, thermal, electrical or chemical means<sup>(5)</sup>. Tongue is susceptible to numerous diseases such as glossitis and inflammatory diseases like geographic tongue, oral thrush and median rhomboid glossitis, black hairy tongue, oral hairy leukoplakia, fissured tongue and burning mouth syndrome. Numerous types of oral cancer mainly disturb the tongue. The most common is squamous cell carcinoma<sup>(6)</sup>.

### Tongue regeneration

Defects in any living tissues are regained by a natural sequence of activities for healing done for repair or regeneration. Though, natural repair and regeneration can lose tolerability and regulation in case of large trauma or surgery, causing undesirable outcomes as fibrosis and aging. Restoring the living tissue using renewable cells is named tissue regeneration technology<sup>(7)</sup>.

Several studies have been made in animals for tissue regeneration for example; stem cells and extracellular matrix scaffolds to improve the theory of oral tissue regeneration to apply clinically in dentistry,<sup>(8)</sup>.

### Stem cells

Stem cells are undifferentiated cells that have the character of self-renewal. They have the possibility to progress into numerous cell lines via differentiation. Different categories of stem cells are known, dependent on type of cells that it can generate and the position in body. Oral tissues are presented to be a source of stem cells<sup>(9)</sup>.

Tissue engineering using MSCs became a good selection for regeneration with numerous benefits as elevated regeneration quality for impaired tissues devoid of fibrous tissue formation, minimal donor site morbidity in comparison with autografts that demonstrate autoimmune rejection and disease transmission<sup>(10)</sup>.

### Bone Marrow Stem Cells

Bone marrow stem cells have the ability to self-renew, differentiate into adipocytes, osteoblasts, and chondrocytes in expandable stem cells. They are able to be embedded at the injury site and enhance tissue regeneration and healing of wounds due to synergistic downregulation of proinflammatory cytokines and improved production of soluble factors with antiapoptotic, proangiogenic, and antioxidant properties. In oral wounds, they display greater re-epithelialization, cellularity, intracellular matrix formation and neoangiogenesis, so speed up wound healing<sup>(11)</sup>.

### Nanotechnology

A nanoparticle or ultrafine particle is known as a particle of matter that is between 1 to 100 nanometres diameter. In nanotechnology, a particle is known as a minor body which acts as an entire element taking in consideration its transport and properties<sup>(12)</sup>. Nanotechnology is used recently in different fields as electrical, optical, and magnetic fields as well as structural performance at the molecular and sub molecular level. Their features of being safe, cheap, easily carried and administered, give them the capability of remodeling a range of medical and biotechnology applications<sup>(13)</sup>. Restoration of tissue function and defect site by tissue engineering include implantation of biomaterial scaffolds that are porous, biodegradable and implanted with adequate amount of normal cells<sup>(14)</sup>.

### Gold nanoparticles (GNPs)

Gold nanoparticles are studied nowadays for application clinically in nanomedicine. In spite of great number of researches done in cancer therapy applying GNP; their application in regenerative medicine and tissue engineering is still progressing. When comparing GNP with other nanoparticles, GNPs' properties as colloidal stability, little toxicity, and physicochemical properties led to making them appropriate multifunctional for phototherapy, drug delivery, cell imaging and diagnosis purposes. Moreover, researches studying GNPs capability to enhance stem cell differentiation for bone tissue engineering, to increase the mechanical and adhesive characters of scaffolds and surface topography guiding cell behaviors are required<sup>(15)</sup>.

**Table 1:-** Researches collected from PubMed database estimating the impact of MSCs on oral mucosa regeneration in vivo and in vitro:

Author		Study design	Aim	Result
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(publication year)				
El-Menoufy et al. 2010 <sup>(16)</sup>	In vivo	Animal dog model	I. TO EVALUATE THE ROLE OF BMSCs IN TREATING INDUCED ORAL ULCERS.	BMSCs transplantation accelerates healing of oral ulcer, due to angiogenesis stimulation via VEGF and raised intracellular matrix formation by increasing releasing of collagen gene.
Zhang et al. 2012 <sup>(17)</sup>	in vivo	Animal rat model	To study the therapeutic benefits of GMSCs on chemotherapy-induced oral mucositis to be embedded at site of injury and survival.	Seeding of GMSCs reduced the aggressiveness and prevalence of ulceration and repaired papillae configuration, and epithelial layer thickness.
Qilin et al 2017 <sup>(18)</sup>	In vivo	Animal rat model	To investigate viability of manufacturing combined construct of small intestinal submucosal extracellular matrix (SIS-ECM) with human gingival mesenchymal stem cells a GMSC/SIS-ECM tissue graft for regeneration of tongue.	Embedding the GMSC/SIS-ECM speeds up healing of wounds and muscle restoration, and preserves tongue shape by improving the role of endogenous skeletal progenitor cells and decreasing fibrosis.
Fakhr et al 2017 <sup>(19)</sup>	In vivo	Animal rat model	to evaluate the effect of SC versus simvastatin on the mucous membrane and salivary glands of the tongue of rats with streptozotocin-induced DM	Tongue of rats treated with SC showed almost normal histology This indicates that bone marrow-derived SC are responsible for repairing the tissues and replacing them when injured or exposed to tear, wear or diseases.
Zhang et al 2019 <sup>(20)</sup>	In vivo	Animal rat model	To evaluate the effect of combined seeding of small intestinal submucosa-extracellular matrix (SIS-ECM) with gingival mesenchymal stem cells (GMSCs) in a critically dimensioned tongue defect model.	Tongue lingual papillae treated with SIS-ECM \ GMSCs retrieval and taste bud restoration by increasing release of CK14, CK8, and markers for taste bud cells. This also raises BDNF expression; a growth factor with a significant effect on the proliferation and differentiation of basal progenitor cells into taste bud cells.

**Table 2:-** Researches collected from PubMed database estimating the impact of gold nanoparticles on tissue regeneration in vitro and in vivo:

Author (publication year)		Study design	Aim	Result
Heo et al 2014 <sup>(21)</sup>	in vitro and in vivo		To improve a novel method for bone	The in vitro results showed that the hydrogels loaded with

			regeneration depending on application of a biodegradable hydrogel overloaded with GNPs.	GNPs stimulates differentiation, proliferation, and alkaline phosphate (ALP) action on human adipose-derived stem cells (ADSCs) because they differentiate into osteoblast cells in a dose-dependent way. The in vivo studies revealed that these hydrogels overloaded with high concentrations of GNPs had an important role on new bone regeneration.
PikSuan et al 2017 <sup>(22)</sup>	In vivo	Animal model rat	To investigate the effect of GNP in photobiomodulation therapy on wound healing process.	The presentation of GNPs in photobiomodulation therapy has a great effect in accelerating wound healing because of increased epithelialization, collagen deposition and rapid vascularization.
Marza et al 2019 <sup>(23)</sup>	In vivo	Animal model rat	To estimate the power of using bioactive glass (BG) and BG-GNPs composites on skin wound regeneration in investigational rats for 14 days.	18% BG-GNPs-Vaseline ointment is a favorable applicant for wound healing submissions with strong vascular proliferation and complete wound regeneration
El-Halwagy et al 2020 <sup>(24)</sup>	In vivo	Animal model rat	To evaluate the potential impacts of gold nanoparticles on the mucous membrane of the albino rats' tongues	Exposure to gold nanoparticles solution caused atrophic and degenerative changes of both the dorsal and ventral surfaces of the tongue. A recovery period of one-month can lead to regeneration and improvement in the histological picture.

**Table 3:-** Researches collected from PubMed database determining the gold nanoparticles influence on stem cell differentiation in vitro and in vivo:

Author (publication year)		Study design	Aim	Result
Changqing et al 2010 <sup>(25)</sup>	In vitro		To investigate the cellular effects of GNPs on the mesenchymal stem cells differentiation (MSCs) and the related cellular mechanisms.	GNPs are adopted by MSCs causing increase in their migration rate to osteoblast cells over adipocyte cells through encouraging osteogenic transcriptional outline.
Volkova N et al 2017 <sup>(26)</sup>	In vivo	Animal rat model	To study the effect of different concentrations of 15nm gold nanoparticles on features of mesenchymal stem cells.	It was established that GNPs with concentrations of 1.5–6 $\mu\text{g/ml}$ are nontoxic for MSCs, whereas increasing to 9 $\mu\text{g/ml}$ is toxic, demonstrated by the decreased synthesis of collagen

				type I and adipogenic differentiation.
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### Conclusions:-

GNP is a promising candidate for tongue defect regeneration. BMSCs therapy is considered as a promising choice for regeneration of tongue defect. We suggest that GNPs enhance stem cell therapy therefore; combination of BMSc and GNP is of great interest and importance for tongue repair.

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