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# Oral Rehabilitation of Patients Sustaining Orofacial Injuries: The UPenn Initiative

Q Z. Zhang
*University of Pennsylvania*

C Chen
*University of Pennsylvania*

M B. Chang
*University of Pennsylvania*

R M. Shanti
*University of Pennsylvania*

S B. Cannady
*University of Pennsylvania*

*See next page for additional authors*



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## Abstract

Tissue injuries in the oral and maxillofacial structures secondary to trauma, warfare, ablative cancer, and benign tumor surgery result in significant losses of speech, masticatory and swallowing functions, aesthetic deformities, and overall psychological stressors and compromise. Optimal oral rehabilitation remains a formidable challenge and an unmet clinical need due to the influence of multiple factors related to the physiologic limitations of tissue repair, the lack of site and function-specific donor tissues and constructs, and an integrated team of multidisciplinary professionals. The advancements in stem cell biology, biomaterial science, and tissue engineering technologies, particularly the 3-dimensional bioprinting technology, together with digital imaging and computer-aided design and manufacturing technologies, have paved the path for personalized/precision regenerative medicine. At the University of Pennsylvania, we have launched the initiative to integrate multidisciplinary health professionals and translational/clinical scientists in medicine, dentistry, stem cell biology, tissue engineering, and regenerative medicine to develop a comprehensive, patient-centered approach for precision and personalized reconstruction, as well as oral rehabilitation of patients sustaining orofacial tissue injuries and defects, especially oral cancer patients.



## Keywords

3D printing; personalized/precision medicine; reconstruction; regenerative medicine; stem cell(s); tissue engineering, Bioprinting; Esthetics, Dental; Humans; Mouth; Printing, Three-Dimensional; Regenerative Medicine; Tissue Engineering, bioprinting; dental procedure; human; injury; mouth; regenerative medicine; three dimensional printing; tissue engineering

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## Author(s)

Q Z. Zhang, C Chen, M B. Chang, R M. Shanti, S B. Cannady, B W. O'Malley, S Shi, and A D. Le

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# Oral Rehabilitation of Patients Sustaining Orofacial Injuries: The UPenn Initiative

**Q.Z. Zhang[1], C. Chen[1], M.B. Chang[1,2], R.M. Shanti[1,3,4], S.B. Cannady[3], B.W. O'Malley[3], S. Shi[1], and A.D. Le[1,4]**

**Abstract**

Tissue injuries in the oral and maxillofacial structures secondary to trauma, warfare, ablative cancer, and benign tumor surgery result in significant losses of speech, masticatory and swallowing functions, aesthetic deformities, and overall psychological stressors and compromise. Optimal oral rehabilitation remains a formidable challenge and an unmet clinical need due to the influence of multiple factors related to the physiologic limitations of tissue repair, the lack of site and function-specific donor tissues and constructs, and an integrated team of multidisciplinary professionals. The advancements in stem cell biology, biomaterial science, and tissue engineering technologies, particularly the 3-dimensional bioprinting technology, together with digital imaging and computer-aided design and manufacturing technologies, have paved the path for personalized/precision regenerative medicine. At the University of Pennsylvania, we have launched the initiative to integrate multidisciplinary health professionals and translational/clinical scientists in medicine, dentistry, stem cell biology, tissue engineering, and regenerative medicine to develop a comprehensive, patient-centered approach for precision and personalized reconstruction, as well as oral rehabilitation of patients sustaining orofacial tissue injuries and defects, especially oral cancer patients.

**Keywords:** regenerative medicine, personalized/precision medicine, reconstruction, stem cell(s), tissue engineering, 3D printing

## Introduction

Orofacial injuries sustained by trauma, warfare, ablative tumor and cancer surgeries, inflammatory and infectious diseases, congenital defects, and others have resulted in major loss of tissues and constitute a challenge in the reconstruction of the dental, oral, and maxillofacial tissues (Hunter et al. 2016; Zhang and Yelick 2018). Oral cancer surgeries contribute a significant cohort of orofacial injuries due to the fact that surgery with postoperative (adjuvant) radiation and/or chemotherapy remains the mainstay of treatment for these patients (Petrovic et al. 2018; Shanti and O'Malley 2018). Because of the complex anatomy in the oral and maxillofacial regions, injuries usually result in alterations in esthetic appearance (deformities); bone and soft tissue defects; fibrosis; oral infection; significant pain; difficulties in mastication, swallowing, and speech; and negative psychosocial and financial effects, all of which may contribute to a significant decline in quality of life of patients to an unacceptable level (Valdez and Brennan 2018). Therefore, reconstruction of oral and maxillofacial defects presents unique clinical challenges, mainly because of their complex and unique 3-dimensional (3D) geometry (Nyberg et al. 2017). The management of patients with oral cancer is even more complicated because it not only addresses the tumor or cancer itself but also fulfills the complete rehabilitation of all oral functions (Petrovic et al. 2018; Valdez and Brennan 2018). As such, it remains a great challenge to achieve these goals due to multiple factors related to cancer, patient, treatment modality, and, most apparently, a lack of multidisciplinary efforts and patient-centered approaches (Petrovic et al. 2018).

Precision medicine has emerged as a new approach to treat complex diseases with consideration of genetic, proteomic, transcriptomic, and metabolomic variability as well as environmental and lifestyle influences that are unique to each individual patient (Snyderman et al. 2016). For the application of precision medicine in cancer patients, including those with oral cancers, the integration of large-scale biological databases and advances in both bioscience and technologies promises new discovery of comprehensive biomarkers and treatment-specific targets, thus enabling more accurate diagnoses, customizing more precise strategies for prevention and treatment, reliably predicting responses to therapy, and, consequently, contributing to optimal health care outcome (Polverini et al. 2018). Most recently, the advancements in stem cell biology, biomaterial science, and tissue engineering (TE) technologies,

[1]Department of Oral & Maxillofacial Surgery & Pharmacology, University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA
[2]Division of Restorative Sciences, University of Pennsylvania School of Dental Medicine, Philadelphia, PA, USA
[3]Department of Otorhinolaryngology–Head and Neck Surgery, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[4]Department of Oral & Maxillofacial Surgery, Penn Medicine Hospital of the University of Pennsylvania, Philadelphia, PA, USA

**Corresponding Author:**
A.D. Le, Department of Oral & Maxillofacial Surgery and Pharmacology, University of Pennsylvania School of Dental Medicine, 240 South 40th Street, Philadelphia, PA 19104, USA.
Email: Anh.Le@uphs.upenn.edu

particularly the 3D bioprinting and 3D imaging technologies, have brought the concept of personalized medicine to a new level, including the development and advancement of personalized/precision regenerative medicine (Gomes et al. 2017). These advanced technologies and tools have paved the path to personalized/precision regenerative medicine therapies and enabled a multidisciplinary, patient-centered approach for reconstruction and oral rehabilitation of patients sustaining oral and maxillofacial defects.

## Unmet Clinical Needs

Patients who encounter loss of both soft and hard oral and maxillofacial tissues due to severe trauma-related injuries or resection of benign and malignant head and neck tumors desperately need rehabilitative management with the goals to restore oral function, as well as improve esthetics and patient well-being and quality of life (Barclay et al. 2018; Petrovic et al. 2018; Zhang and Yelick 2018). Despite advances in surgical approaches to reconstruction of oral and maxillofacial defects, progress in maxillofacial prosthetic rehabilitation remains suboptimal and insufficient in restoring lost and disabling oral functions resulting from a hard or soft tissue defect, partly due to compromised vascularization and neural functions. Successful rehabilitation of oral functions for these patients relies on multiple factors related to the type of injury, individual patient, tumor itself, treatment modality, and health professionals (Petrovic et al. 2018). The collaboration of medical, dental, and translational research specialties will allow for a more comprehensive and innovative approach to management of these complex patients. Therefore, a team of multidisciplinary professionals is required, which may include pathologists, radiation and medical oncologists, oral and reconstructive surgeons, maxillofacial prosthodontists, endodontists, and other health professionals such as vocational rehabilitation counselors, physical therapists, speech pathologists, dental hygienists, nurses, nutritionists, psychologists, and social workers. However, successful assembly of such a team of multidisciplinary health professionals for comprehensive rehabilitation of oral functions is typically limited to designated medical/cancer centers, particularly at major teaching institutes. According to patient-reported outcome data, many of their continued and unmet needs are related to their oral and dental rehabilitation (Petrovic et al. 2018). Therefore, oral rehabilitation remains a formidable challenge and an unmet clinical need for this cohort of patients with oral and maxillofacial injuries (Petrovic et al. 2018).

## Program Development

With the established goal to improve the unmet clinical need of reconstruction and rehabilitation of the dental, oral, and maxillofacial structures, our multidisciplinary team of dentists, surgeons, and other professionals at the University of Pennsylvania (UPenn) has initiated a patient-centered approach to provide safer, more precise, personalized, or precision treatments that will result in faster functional recovery, improved esthetics and health, and, overall, a better quality of life for patients with oral and maxillofacial injuries, including those being treated for a tumor in the orofacial region. On the clinical side, this approach has been fostered by launching the initiatives of 4 clinical centers that focus on temporomandibular joint disorders (TMDs), orthognathic and corrective surgery, trauma and reconstructive surgery, and oral/dental rehabilitation (Fig. 1). Many faculty members hold joint appointments at both Penn Dental Medicine and Penn Medicine, which further facilitates a high level of interaction with other specialists and fosters the interdisciplinary and collaborative approach to achieve optimal and patient-centered care.

In the realm of research, our basic and translational scientists will work closely with clinicians to address the special areas of unmet clinical focuses and concentrate efforts on translational/clinical research in tissue engineering and regenerative medicine (TE/RM) of the oral and maxillofacial tissues, particularly on mesenchymal stem cells from adult oral gingival tissues (GMSCs), dental pulp stem cells (DPSCs), and others, and how they might aid wound healing and regenerating lost tissues sustained from orofacial injuries (Figs. 1 and 2). Our goal is to launch the initiative to establish a translational/clinical research center in regenerative dental medicine that will be well integrated with the clinic centers and provide state-of-the-art technologies and personalized TE/RM products to meet increasing clinical demand. All these promising areas of research will support the department's overarching goal to provide a "comprehensive and integrated approach to deliver the highest quality and personalized care to patients" (Figs. 1 and 2).

## Clinical Focuses: Multiple Centers Integrated with Interdisciplinary Specialists and Advanced Technologies

The goal for our clinical initiative is to provide an optimal oral reconstruction and rehabilitation patient-centered care. To this purpose, many faculty members in the Department of Oral & Maxillofacial Surgery who hold joint appointments at both Penn Dental Medicine and Penn Medicine have actively participated in the development of the 4 clinical centers with a focus on temporomandibular joint disorders, orthognathic/corrective surgery, trauma/reconstructive surgery, and oral/dental rehabilitation (Fig. 1). They will foster interaction and collaboration with multidisciplinary specialists from Otolaryngology/Head and Neck Surgery, Pathology, Radiation/Medical Oncology, Oral Medicine, Prosthodontics, Orthodontics, Endodontics, and other professionals, including nurses, nutritionists, dental hygienists, physical/speech therapists, psychologists, and social workers. They will also closely interact with research scientists at the initiative Center for Translational Research in Regenerative Dental Medicine and explore new approaches using a combination of traditional and state-of-the-art technologies such as magnetic resonance imaging (MRI)/computed tomography (CT) imaging, 3D digital scanning, computer-aided design (CAD)/computer-aided manufacturing

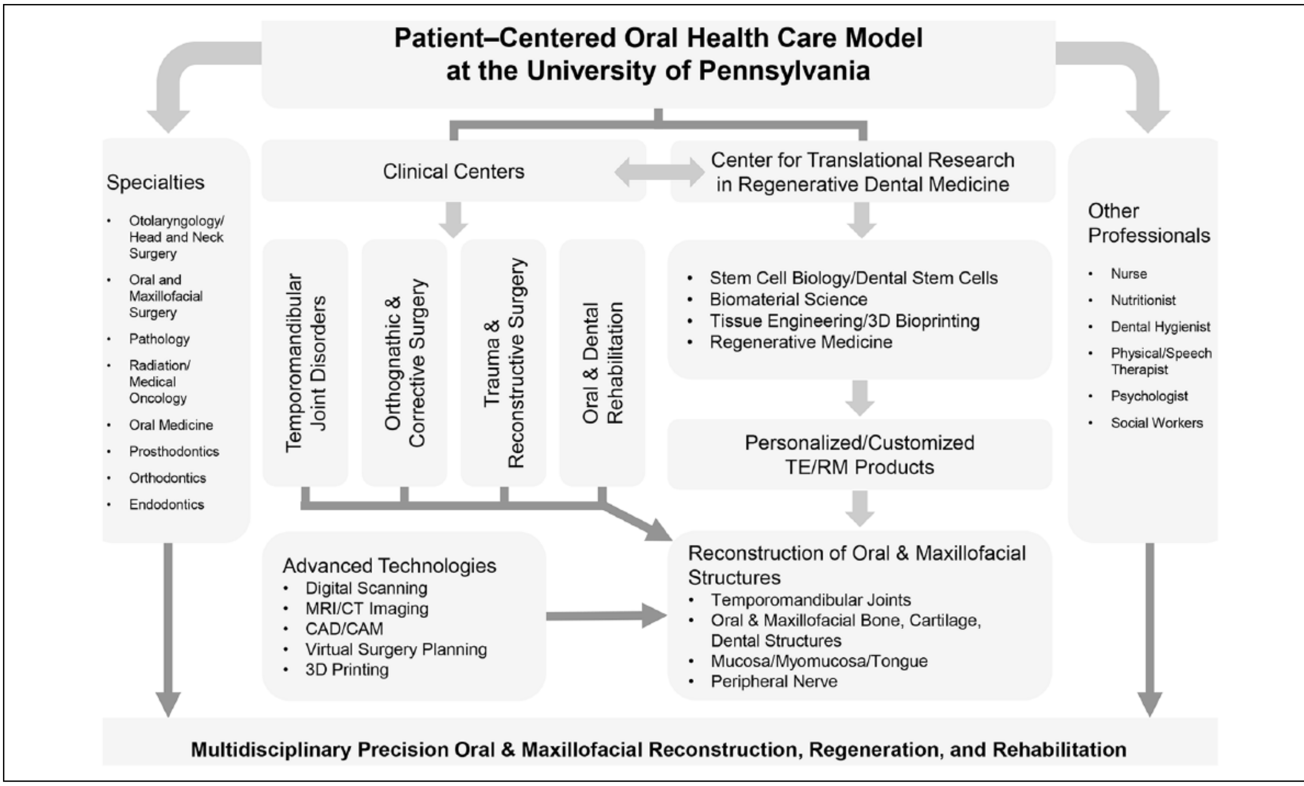


**Figure 1.** Initiatives for the development of a multidisciplinary patient-centered oral health care model at the University of Pennsylvania for precision oral and maxillofacial reconstruction, regeneration, and rehabilitation.

(CAM), 3D printing techniques, virtual surgical preplanning (VSP), and stem cell–based TE/RM products to deliver personalized, precision reconstruction, regeneration, and rehabilitation of the oral and maxillofacial structures and enhance patient care (Fig. 1).

Advanced care for patients sustaining severe orofacial injuries needs to integrate surgical reconstructive techniques with maxillofacial prosthodontic rehabilitation to optimize the functions and esthetics (Urken et al. 2015). Accurate preoperative planning of the surgical reconstruction is required because a correct positioning of the bone is important to allow for dental implant placement in the preferred anatomical positions. When the bone is incorrectly positioned, the postoperative function and esthetics of the implant-supported prosthesis are often disappointing. CAD is the process of creating, modifying, analyzing, or optimizing a design using computer systems. CAM is the process of planning, managing, or controlling manufacturing using computer systems (Bhatia and Sowray 1984). In recent years, 3D digital planning and additive manufacturing have become widely available and reliable technologies for VSP (Fig. 3A, B). VSP technique is a useful tool to help surgeons visualize the maxillofacial defects of the mandible and/or maxilla, perform virtual ablation, and plan reconstruction procedures on the computer before implementation in the operating room (Chim et al. 2014). The advantages of CAD/CAM technology include improvement of accuracy of esthetic results and restoration, reduction of operation time, accurate fitting of osseous implants, and performance of resection and reconstruction in 1 step (Kang et al. 2016).

Currently, vascularized osseous free flaps remain the most feasible option for the reconstruction of maxillofacial defects due to their abundant blood supply and flexibility for transplant orientation and insertion (Kumar et al. 2016). To enhance the esthetic, functional outcome and quality of life of patients, placement of endosseous dental implants is commonly accepted as a part of the treatment planning for optimal prosthodontic rehabilitation (Fig. 3C, D). A recent retrospective study showed an overall cumulative survival rate (CSR) of implants in the mandible as high as 92.6% (Balshi et al. 2015), whereas another systematic review reported that the survival rate of implants placed in bone flaps in jaw rehabilitation ranged from 82.4% to 100% with a CSR of 93.2% (Zhang et al. 2016), thus supporting the use of endosseous dental implants as a reliable modality in oral and dental rehabilitation.

The 3D printing technique in the head and neck reconstruction allows for fabricating 3D printed implants or prostheses and creating accurate replicas of patient-specific anatomy, patient-specific templates that guide precise cutting and drilling, and surgical splints for the virtual postoperative position of the patient structure (Jacobs and Lin 2017; Zhang and Yelick 2018). The use of CAD/CAM technology for the fabrication of surgical resection guides and mandibular reconstruction plates resulted in an accurate surgical result (Fig. 3C, D) (Foley et al. 2013). Implant-supported titanium frameworks made with

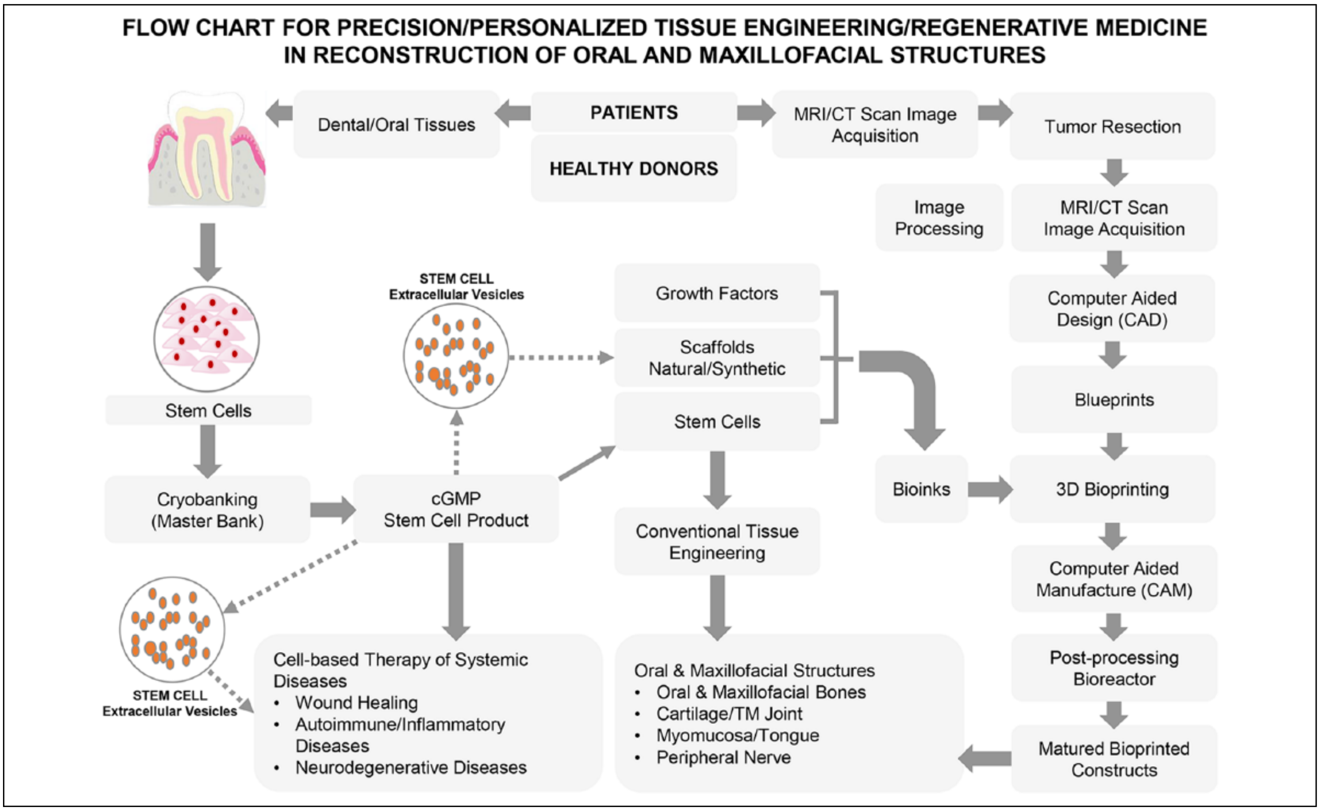


**Figure 2.** Flowchart for precision reconstruction, regeneration, and rehabilitation of the oral and maxillofacial structures using stem cell–based tissue engineering/regenerative medicine approach.

CAD/CAM technology have been reported to fit significantly better than frameworks made with the conventional lost wax technique (Drago et al. 2010). With new developments in 3D printing and CAD-CAM techniques, it will be possible to virtually plan and fabricate customized dental prostheses to achieve the favorable clinical outcomes for oral and dental rehabilitation of patients sustaining orofacial injuries.

## Research Focuses: Application of Stem Cell–Based TE/RM Strategies

In the realm of research, our goal is to integrate regenerative dental medicine in precision reconstruction, regeneration, and rehabilitation of the oral and maxillofacial structures. To this purpose, our research team with expertise in stem cell biology will collaborate with experts in tissue engineering and biomaterials within and/or outside the university and well integrate our clinical teams to focus our translational/clinical research on generation of personalized TE/RM products from dental stem cells (e.g., GMSCs and DPSCs) for regeneration of lost tissues from oral and maxillofacial injuries (Figs. 1 and 2). Particularly, we will launch initiatives to establish a biobank of dental stem cells of current Good Manufacturing Practice (cGMP) quality and integrate the use of growth factors, biomaterials, stem cells, and/or their extracellular vesicle products as optimal "bioinks" for 3D-bioprinting different types of bioengineered constructs applicable for reconstruction of the oral and maxillofacial structures (Fig. 2).

Our research team was the first to isolate and characterize a subpopulation of multipotent mesenchymal stem cells (MSCs) from human gingival tissues (GMSCs) (Zhang et al. 2009). Afterward, a similar subpopulation of MSCs in gingival connective tissues was reported by several other groups (Fournier et al. 2010; Mitrano et al. 2010; Tang et al. 2011). In comparison to MSCs derived from other adult tissues such as bone marrow and adipose, GMSCs are highly proliferative and also possess potent immunomodulatory, anti-inflammatory, and regenerative potentials in a variety of human oral and nonoral disease models (Zhang et al. 2012). Local transplantation of GMSCs could promote bone regeneration in mandibular and calvarial defects (Moshaverinia et al. 2014; Diomede et al. 2018; Shi et al. 2019) and cartilage formation (Ferre et al. 2014), thus supporting the potential use of GMSCs in craniofacial bone regeneration. Systemic administration of GMSCs facilitates the regeneration of epithelial layers in colitis, skin, and oral mucosal healing models (Zhang et al. 2009; Zhang et al. 2010). Our recent studies showed that local implantation of porcine small intestine submucosa extracellular matrix (SIS-ECM) laden with GMSCs or GMSC-derived exosomes promotes regeneration of tongue muscle, epithelial layer, and taste buds in a critical-sized rat tongue defect model, possibly via activating the endogenous skeletal muscle, epithelial, and

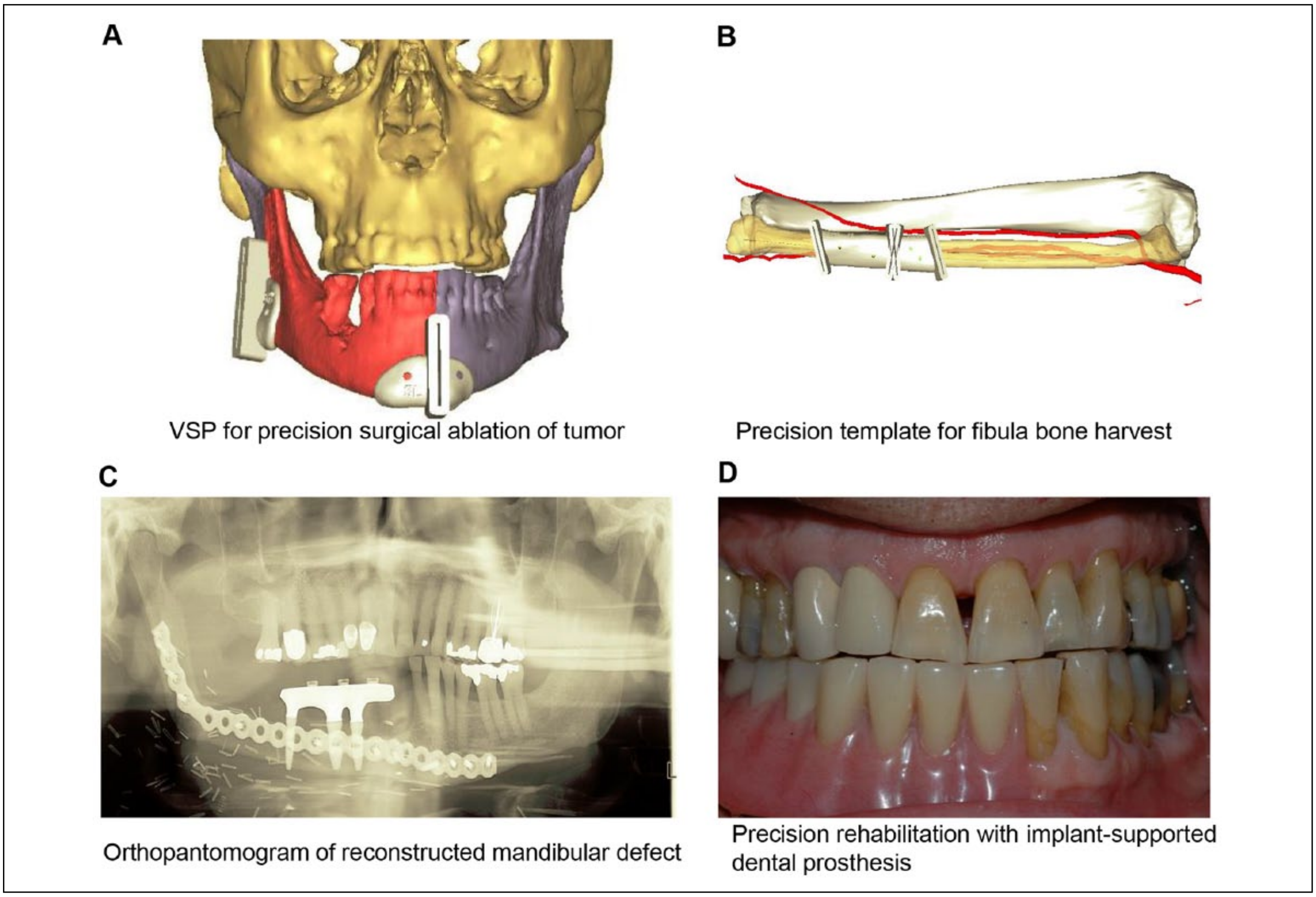


**Figure 3.** Clinical application of virtual surgical planning (VSP) and computer-aided design (CAD)/computer-aided manufacturing (CAM) technologies. (**A**) VSP images for precision surgical ablation of tumor. (**B**) Precision template for fibula bone harvest. (**C**) Orthopantomogram of reconstructed mandibular defect. (**D**) Clinical photographs showing precision rehabilitation with implant-supported dental prosthesis.

taste bud progenitor cells (Xu et al. 2017; Zhang et al. 2019). Several lines of evidence have implicated the potential use of GMSCs in repair/regeneration of gingival and periodontal defects (Fawzy El-Sayed et al. 2012; Li et al. 2018). Due to their neural crest origin (Xu et al. 2013; Isaac et al. 2018), the ex vivo expanded GMSCs could be reproducibly induced into neural progenitor–like or neural crest stem–like cells (NCSCs) through nongenetic approaches, which displayed enhanced beneficial effects on nerve regeneration in rat sciatic nerve crush injury and facial nerve defect models (Zhang et al. 2017; Zhang, Nguyen, Shi, Burrell, Xu, et al. 2018). Meanwhile, GMSC-derived extracellular vesicles or exosomes could activate the repair phenotype of Schwann cells and promote repair/regeneration of crush-injured sciatic nerves of mice (Mao et al. 2018).

The regeneration of dental pulp with vital vasculature and nerve components is still one of the most challenging in stem cell–based dental tissue engineering. Recently, we showed that DPSCs and stem cells from human exfoliated deciduous teeth (SHED) possessed potential for neurovascularization. In a clinical study, pulp-derived stem cells have shown neurogenesis, angiogenesis, and neurovascular regenerative activities to rebuild the complex pulpal structure in situ. Significantly, scaffold-free transplantation of pulp-derived stem cells is able to regenerate de novo pulpal tissue with highly organized physiological patterns, which is equipped with blood vessels and nerves. In addition, pulp-derived stem cell transplantation increases the length of the root and reduces the width of the apical foramina of recipient teeth, indicating the regenerated pulpal tissue possesses normal function and maintains dynamic root development (Xuan et al. 2018). These findings documented the first clinical evidence that pulp-derived stem cell transplantation has the capacity to regenerate functional dental pulp with recovery of neurovascularization.

Conventional TE approaches have some major limitations for fabricating vascularized and functional tissues and organs (Ozbolat and Hospodiuk 2016). In the past decade, advancements in stem cell biology, biomaterial science, and TE technologies, particularly the emerging 3D bioprinting technologies, have significantly advanced the fabrication of implantable artificial tissue complexes for regeneration of both soft and hard tissues (Gomes et al. 2017). Three-dimensional bioprinting is a computer-driven, rapid prototyping technology, which uses CAD software to generate blueprints that can guide the precise assembly of the printable materials or "bioinks" to fabricate highly accurate biomimetic tissue constructs as desired (Kang et al. 2016). Due to the easiness to modulate the design parameters; the flexibility to incorporate various types of biomaterials, cells, and growth factors; the rapid and precise replication of tissue/organ structures with a micro-scale resolution; and the high degree of reproducibility, 3D bioprinting technologies have shown great promise in revolutionizing personalized/precision regenerative medicine by enabling the fabrication of customized, multicomponent, and implantable tissue constructs with respect to patient-specific anatomy (e.g., size and shape), pathology, and biomechanical properties, which are particularly relevant to be applied in the field of craniofacial reconstruction because of the unique and complex anatomical features of this region (Kang et al. 2016; Arrigoni et al. 2017; Nagarajan et al. 2018; Zhang and Yelick 2018). Due to their multipotent differentiation capability and potent regenerative potentials, MSCs of different origins have been extensively explored as the seed cells for generation of TE/RM products, such as the cellular component of "bioinks" for 3D bioprinting of different types of biomimetic tissue constructs (Snyder et al. 2015). Using a state-of-the-art 3D bioprinting system, we have generated scaffold-free nerve grafts using GMSC spheroids enriched with NCSC properties as the only cellular "bioink," which showed beneficial effects on regeneration and functional recovery of defected rat facial nerves (Zhang, Nguyen, Shi, Burrell, Cullen, et al. 2018).

Taken together, our approach to combine the 4 focused clinical centers and our expertise in stem cell biology, especially our pioneering work in GMSCs and DPSCs, has positioned our multidisciplinary team to launch the initiative to establish a translational/clinical research center in regenerative dental medicine, which will provide the state-of-the-art technologies and personalized dental stem cell–based TE/RM products for precision reconstruction of the dental, oral, and maxillofacial defects and oral functional rehabilitation. These initiatives will allow us to have more opportunities to collaborate with clinicians and researchers from other institutes and to further develop multicenter clinical trials, with the ultimate goal to continue to improve the care of patients sustaining severe orofacial injuries.

## Future Directions

The initiatives of this multidisciplinary and patient-centered program for reconstruction and oral rehabilitation of patients sustaining orofacial injuries at the University of Pennsylvania are novel in several aspects. The unique approach to integrate the focused clinical centers of interdisciplinary clinical teams with the translational/clinical research center with expertise in stem cell biology, the emphasis on the unmet clinical need in management of patients with orofacial injuries, the amalgamation of state-of-the-art technologies in both clinical and research realms, and the overarching goal to generate dental stem cell–based TE/RM products for customized, precision reconstruction, regeneration, and oral rehabilitation of patients sustaining lost or injured orofacial tissues will allow a more complete rehabilitation of all oral functions, a more optimal cosmesis, improved psychological well-being, and, consequently, a significant improvement in quality of life of each individual patient. Albeit our initiatives hold great promise, they are still in infancy and in a developmental phase with recognizable challenges. On the clinical side, we will strengthen the interaction among multidisciplinary specialties (e.g., setting up meetings and discussions at a regular base, to accelerate the introduction of more advanced technologies, to initiate both national and international collaboration with other institutes, and to set up survey questionnaires to obtain patient feedback with the service provided by our program). In the realm of research, we will continue to engage collaboration, both nationally and internationally, with scientists in biomaterial science, tissue engineering, and preclinical large animal models, to accelerate the establishment of standard operating procedures (SOPs) for tissue collection, cell isolation and culture, and storage; to develop capabilities for banking of dental stem cells; and to accelerate the preclinical studies in large animal models. The successful resolution of these challenges will pave the way to execute the goals set in our program initiatives.

### Author Contributions

Q.Z. Zhang, C. Chen, M.B. Chang, R.M. Shanti, A.D. Le, contributed to conception and design, drafted and critically revised the manuscript; S.B. Cannady, B.W. O'Malley, S. Shi, contributed to conception and design, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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