

# Dental, Oral, and Craniofacial Regenerative Medicine: Transforming Biotechnologies for Innovating Patient Care

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Regenerative medicine (RM) is an emerging medical field aimed at replacing or repairing human cells, tissues, or organs for the restoration of normal structure and function (Cossu et al. 2018). This is an exciting time to translate RM innovations to clinical practice due to recent advances in stem cell science, the development of tools for genetic manipulation of cells, and bioengineered systems to program cell fate and function in the body. In 2012, the National Institutes of Health established the intramural Center for Regenerative Medicine (currently, the Stem Cell Translational Laboratory) with the goal of finding ways to reduce or remove obstacles that have impeded the clinical translation of RM therapies (Rao and Collins 2012). Even before the development of the National Institutes of Health's Center for Regenerative Medicine, the National Institute for Dental and Craniofacial Research (NIDCR) long recognized that despite significant advances in the basic sciences and engineering for dental, oral, and craniofacial (DOC) RM, very few advances ever make it to the clinic to enhance patient health care delivery.

In 2017, under the leadership of its director, Martha Somerman, the NIDCR launched 2 U.S. national cooperative agreements (U24s) to support resource centers for developing the DOC Tissue Regeneration Consortium (DOCTRC; NIDCR 2017). This is the second stage of a 3-stage initiative designed to propel novel therapeutics from preclinical investigation to Food and Drug Administration submissions for eventual human clinical trials. "By establishing this research consortium, the NIDCR seeks to lead national efforts to accelerate the translation of promising DOC regenerative medicine therapies into the clinic," said Dr. Somerman. "DOCTRC is designed as a model for optimizing translation of scientific advances in this field." This approach will balance the clinical needs with technology and translational constraints to bring some of the most promising technologies through the developmental pathway (Figs. 1, 2). This strategy is consistent with the NIDCR's strong history of support for RM through the R01 mechanism, but this U24 program takes a key next step. It is anticipated that practicing clinicians, engineers, and scientists will come together with corresponding clinical dental practice, academia, and industry leaders to transform patient care.

The goal of this perspective is to create awareness of this exciting new NIDCR initiative and continue to solicit technologies from researchers through the interdisciplinary translational project (ITP) program offered by the DOCTRC. The ITP program was developed to fund and translate promising RM technologies addressing unmet clinical needs with market potential in the DOC space. The program encourages researchers from academia and private industry to participate and partner through the resource centers with a final call for proposals by mid-2018. It is believed that the continued evolution of the field of RM requires collaboration of key stakeholders to develop new DOC clinical therapies. The RM resource centers are designed as national service centers that will support innovative approaches from research teams worldwide to promote a national and international collaboration in RM.

The 2 DOCTRC resource centers are

- 1) the Center for Dental, Oral, and Craniofacial Tissue and Organ Regeneration (C-DOCTOR), which represents a group of California institutions, including the University of California–San Francisco, the University of Southern California, the University of California–Berkeley, the University of California–Davis, Stanford University, and the University of California–Los Angeles, and

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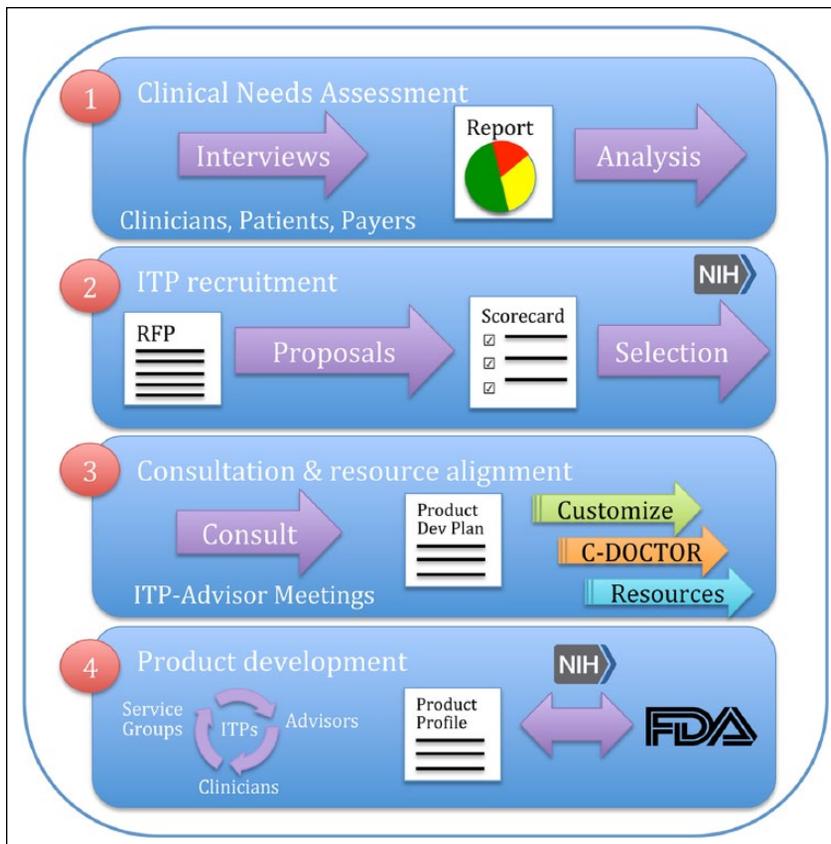
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**Figure 1.** Center for Dental, Oral, and Craniofacial Tissue and Organ Regeneration (C-DOCTOR) ITP pipeline. C-DOCTOR will develop an ITP team pipeline through a process of structured innovation, during which recruitment, selection, and advancement of technologies optimally align with the priorities of 4 key stakeholder groups: providers (clinicians and health care networks), producers (industry), payers, and patients. FDA, Food and Drug Administration; ITP, interdisciplinary translational project; NIH, National Institutes of Health; RFP, request for proposal.

- 2) the Michigan-Pittsburgh-Wyss Resource Center: Supporting Regenerative Medicine in Dental, Oral, and Craniofacial Technologies (MPWRM TechDOC), composed of the University of Michigan, University of Pittsburgh, and the Wyss Institute of Harvard University.

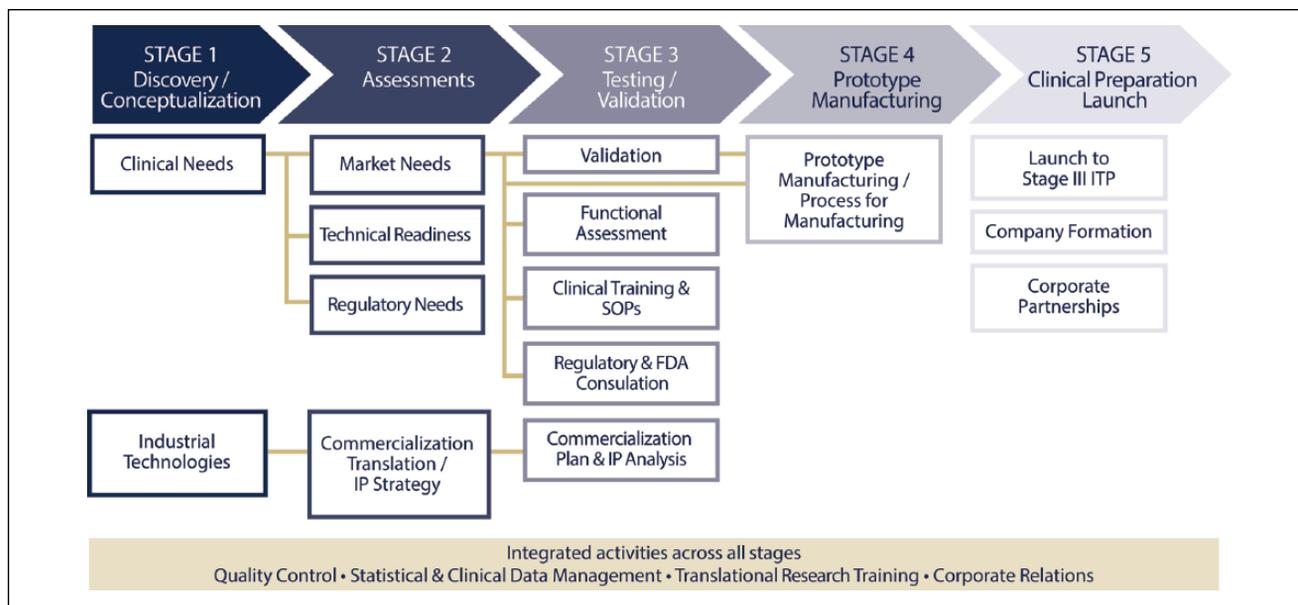
Although major advances in RM over the past several decades have illuminated the possibilities for repairing tissue and organ defects or deficiencies, including those of the craniofacial complex, the conversion of discoveries to the clinic and improvement of patient care is slow, expensive, and failure prone (Collins 2011). The recent Lancet Commission stated that “a combination of poor quality science, unclear funding models, unrealistic hopes, and unscrupulous private clinics threatens regenerative medicine’s social license to operate.” To address these limitations, this ambitious NIDCR initiative to translate technologies in the DOC space offers a comprehensive and systematic approach for the support of technology development in the oral health sciences, an area that has traditionally been underrepresented in the developmental pipeline due to its relatively small market size and niche focus when compared with broader medical applications. The reimbursement

structure in dentistry has also hampered many clinical and translational efforts because of contrasting third-party payer mechanisms and costly drug, device, and biologic development costs (Giannobile and Joskow 2012). Despite these obstacles and challenges of developing new technologies for clinical practices that rely on solo practitioners, group practices, and hospital-based models, researchers in the DOC space have a strong history of collaborative science that has catapulted innovations in medicine and medical device development fields, such as orthopedics, vascular surgery, and plastic surgery, among others. It is hoped that the innovative technologies developed through the collaboration between the resource centers and the ITPs will demonstrate not only clinical benefits but patient economic benefits as well.

Multiple technical considerations will also be crucial for the advancement of RM as a field and for bringing technologies to the clinic through the DOCTRC. First, the use of stem cells or other cellular therapies, whether isolated from autologous or allogeneic tissues, will require tight control over cell behavior, safety, and efficacy after transplantation. Second, the assembly of large replacement tissues or organs will require integration of vascular networks between engineered tissues and the surrounding host vasculature. Finally, the interaction of implant biomaterials, cells,

and biological agents will require exquisite control and understanding of the host system to ensure cell engraftment and tissue responsiveness to the engineered constructs (Mao and Mooney 2015). These 3 components must be carefully considered and optimized through systematic preclinical development with subsequent transfer to first-in-human phase I clinical trials for the repair of DOC-related structures. Preclinical development is facilitated by the organization of core facilities and standardized procedures developed at the resource centers to ensure their rigor and reproducibility.

RM biotechnologies will have a better chance of being translated to the clinical arena thanks to this new national initiative. It will be important for our AADR and cooperating IADR stakeholders to embrace this unique opportunity to leverage the innovative scientific investments made in the DOC field to help transform clinical care for our patients. C-DOCTOR and the MPWRM TechDOC both strongly encourage interested teams to submit applications for ITP team awards and to partner with the resource centers to help develop and translate their RM technologies to clinical applications prior to the posted deadlines on the websites. We are also eager to engage with corporate partners to facilitate the commercialization of technologies.



**Figure 2.** Michigan-Pittsburgh-Wyss Resource Center: Supporting Regenerative Medicine in Dental, Oral, and Craniofacial Technologies (MPWRM TechDOC) organization and process. The MPWRM TechDOC is organized to be in line with the process of technology development and the ITP program. Projects are initially evaluated in the discovery/conceptualization stage (stage 1), followed by a more in-depth assessment in stage 2. For technologies that show promise, the MPWRM TechDOC contributes support and funding (stages 3 and 4) to position technologies for FDA submission and commercialization. In stage 5 of the process, it is anticipated that the clinical launch of successful projects into therapies for the regeneration or restoration of functional dental, oral, and craniofacial tissues will occur via advancement to the next phase of the NIDCR DOCTRC initiative or other follow-on funding or through commercialization by corporate partners. DOC, dental, oral and craniofacial; DOCTRC, DOC Tissue Regeneration Consortium; FDA, Food and Drug Administration; IP, intellectual property; ITP, interdisciplinary translational project; NIDCR, National Institute for Dental and Craniofacial Research; SOP, standard operating procedure.

Further information about C-DOCTOR can be found at <http://c-doctor.org> and the MPWRM TechDOC at <https://doctrc.com>. These programs have ongoing initiatives for funding ITPs.

### Author Contributions

W.V. Giannobile, D.H. Kohn, contributed to data analysis, drafted and critically revised the manuscript; Y. Chai, Y. Chen, K.E. Healy, O. Klein, N. Lane, M.T. Longaker, J.C. Lotz, D.J. Mooney, C.S. Sfeir, M. Urata, W.R. Wagner, B.M. Wu, contributed to data analysis, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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