Critical Reviews in Oral Biology & Medicine

Journal of Dental Research
1–8

DOI: 10.1177/00220345211009502
journals.sagepub.com/home/jdr

Translating Dental, Oral, and Craniofacial Regenerative Medicine Innovations to the Clinic through Interdisciplinary Commercial Translation Architecture

D.P. Taylor[1,2,3*], M. Yoshida[4*], K. Fuller[5], W.V. Giannobile[6], C.S. Sfeir[2,7], W.R. Wagner[2], and D.H. Kohn[4]

Abstract

Few university-based regenerative medicine innovations in the dental, oral, and craniofacial (DOC) space have been commercialized and affected clinical practice in the United States. An analysis of the commercial translation literature and National Institute for Dental and Craniofacial Research's (NIDCR's) portfolio identified barriers to commercial translation of university-based DOC innovations. To overcome these barriers, the NIDCR established the Dental Oral Craniofacial Tissue Regeneration Consortium. We provide generalized strategies to inform readers how to bridge the "valley of death" and more effectively translate DOC technologies from the research laboratory or early stage company environment to clinical trials and bring needed innovations to the clinic. Three valleys of death are covered: 1) from basic science to translational development, 2) from translational technology validation to new company formation (or licensing to an existing company), and 3) from new company formation to scaling toward commercialization. An adapted phase-gate model is presented to inform DOC regenerative medicine teams how to involve regulatory, manufacturability, intellectual property, competitive assessments, business models, and commercially oriented funding mechanisms earlier in the translational development process. An Industrial Partners Program describes how to conduct market assessments, industry maps, business development processes, and industry relationship management methods to sustain commercial translation through the later-stage valley of death. Paramount to successfully implementing these methods is the coordination and collaboration of interdisciplinary teams around specific commercial translation goals and objectives. We also provide several case studies for translational projects with an emphasis on how they addressed DOC biomaterials for tissue regeneration within a rigorous commercial translation development environment. These generalized strategies and methods support innovations within a university-based and early stage company-based translational development process, traversing the many funding gaps in dental, oral, and craniofacial regenerative medicine innovations. Although the focus is on shepherding technologies through the US Food and Drug Administration, the approaches are applicable worldwide.

Keywords: translational research, translational development, industry collaborations, translational medical research, technology transfer, biomaterials

Introduction

The term *valley of death* generally characterizes a period of time in which a commercial translation project has a specific set of goals and milestones to reach a value inflection point but lacks the resources to achieve that point (Truebel and Thurston 2020). These valleys (or funding gaps) can occur throughout an early stage innovation's life span with 3 prominent phases: 1) from basic science to translational development, 2) from translational technology validation to new company formation (or licensing to an existing company), and 3) from new company formation to scaling toward commercialization. Major goals and milestones that oftentimes are inhibited by these funding gaps include in vitro validation, preclinical research, clinical trials (with first in human being particularly challenging), and US Food and Drug Administration (FDA) clearance or approval (Linton and Xu 2021). Adding to the complexity, those goals and milestones have different funding models and value propositions to the funding sources depending on whether the innovation remains within the university for continued development or if the innovation is licensed out to a commercial entity. As an example, many university-based innovations reach the stage of having compelling preclinical

[1]Department of Biomedical Informatics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
[2]McGowan Institute for Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, USA
[3]sciVelo, University of Pittsburgh Health Sciences, Pittsburgh, PA, USA
[4]Department of Biologic and Materials Sciences & Prosthodontics, University of Michigan School of Dentistry, Ann Arbor, MI, USA
[5]Medical Device Regulatory Solutions LLC, Ann Arbor, MI, USA
[6]Harvard School of Dental Medicine, Boston, MA, USA
[7]Department of Periodontics and Preventive Dentistry, School of Dental Medicine, University of Pittsburgh, Pittsburgh, PA, USA
*Authors contributing equally to this article.

A supplemental appendix to this article is available online.

Corresponding Author:
D.H. Kohn, School of Dentistry and Professor of Biomedical Engineering, University of Michigan, 1011 N. University Ave., Ann Arbor, MI 48109-1078, USA.
Email: dhkohn@umich.edu

animal data showing promising efficacy that have been built upon many years of federal funding to elucidate mechanism and proof of concept. However, traditional government funding may not be available to support pivotal preclinical studies, manufacturing, toxicity testing, or phase I/II or pilot human clinical trials, and potential industry sponsors may only be interested at the stage of larger-scale human results (Voices 2018).

There are certain clinical indications and technology types that are less sensitive to funding gaps by the nature of their significant market upsides. For example, clinical indications such as cancer immunotherapy and technologies such as CRISPR/Cas9 have a large diversity of funding sources that may ease the burden of follow-on funding. Other clinical indications or technology types may require a higher degree of technology and market de-risking due to a lack of a market track record. The dental, oral, and craniofacial regenerative medicine (DOC RM) space is replete with all 3 valleys of death given factors including novel combination devices with biologics and biomaterials, limited preclinical model systems, smaller patient cohorts for clinical trials, and overall market sizes that are smaller than other clinical indications. As a result, converting the potent scientific discoveries into sustainable commercial products to address the DOC RM space is not yet well established (Giannobile 2015).

One way to measure the valley of death of DOC RM technologies is to assess the number of patent filings that emerge from National Institutes of Health (NIH) grant funding. We queried the National Institute for Dental and Craniofacial Research's (NIDCR's) database for granted patents (2014–2020) stemming from dental biomaterials, tissue engineering, and RM grant awards. This subset identified 45 NIDCR grants that led to 26 patents over approximately 200 awarded grants using the same grant selection criteria and timeframe. Consequently, less than 25% of the grants resulted in patented intellectual property, which is a marker of commercialization potential. These statistics are consistent with other biomedical research areas, where approximately 10% of NIH-funded grants generated patents (Li et al. 2017). Moreover, fewer than 5 NIDCR-funded projects resulted in FDA submissions. With patent rights often being the central component of academic license agreements to commercial entities, thoughtful patent strategies and technology marketing are also critical to commercialization and bridging the funding gap. Certainly, there is a timing consideration as patents and FDA submissions can take years to issue, and not all awarded grants have specific aims that would lead to translatable work. However, these data illustrate that commercial orientation of the DOC RM research can be improved, and with more commercially oriented projects will come greater need for systematic approaches to de-risk the science and marketability of these innovations.

Although some funding gaps in the DOC RM space mark terminal limitations in the science, technology, or market sustainability, many gaps can be overcome with careful preplanning (Giannobile et al. 2018). At the earliest stages of DOC RM product conceptualization—even during the basic science stage—planning for events such as regulatory, manufacturability, preclinical validation, market segmentation, reimbursement strategy, business models, and intellectual property can reduce or eliminate many valleys of death. To overcome this, it is critical to establish unique partnerships with university-based core services as well as industry collaborations. The Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center (MPWRM RC, or the Center) of the Dental Oral Craniofacial Tissue Regeneration Consortium (DOCTRC) has developed such partnerships, including with The Avenues Company (marketing), Medical Device Regulatory Solutions (regulatory), and the University of Pittsburgh program, sciVelo (academic commercial translation). These partnerships are highly integrated to support de-risking of both the science and the commercial application, and we describe such integration further in this article. Principal investigators are also encouraged to work with their institution's technology transfer offices early in the innovation process. This is important to help ensure that no enabling information about the inventions is prematurely disclosed that could obviate the potential intellectual property. The Center helps principal investigators with these technology transfer office connections if those investigators are new to the process of invention disclosure development and submission. More information about the Center's core services, including connectivity with technology transfer, can be found on the website https://mpwrm-doctrc.pitt.edu.

This article aims to inform readers about the significance of the valley of death in university- and early stage company-based DOC RM translational research in the United States and how to build a transdisciplinary infrastructure to guide and propel projects through their commercial translation stages. We will also describe how to structure commercial translation project management and how to position university-based projects for FDA submissions, industry partnerships, and clinical adoption. We briefly introduce the MPWRM RC and provide details about a roadmap tool that this Center innovated to guide projects through their translational journey. We conclude with 3 translational project case studies with an emphasis on their commercial orientation, biomaterials and other technologies, and how the projects implemented an adapted phase-gate model specific to DOC RM devices and drugs. These early stage commercial translation approaches are relevant across many global geographies; however, reaching the clinic outside of the United States (such as the European Economic Area) would require other regulatory bodies, and those considerations should be involved in the early phases.

Academic Commercial Translation Center Structure and Purpose

A multidisciplinary center was assembled in 2017 from academia, industry, and the private sector to provide domain expertise to guide early stage DOC RM projects from translational research projects into preclinical validation studies and to FDA filing and clinical implementation. The strategies presented in this article are derived from practices of the MPWRM RC.

There was a primary focus on clinical needs validation, technology assessment, and commercial translation support throughout early to late-stage project development. This

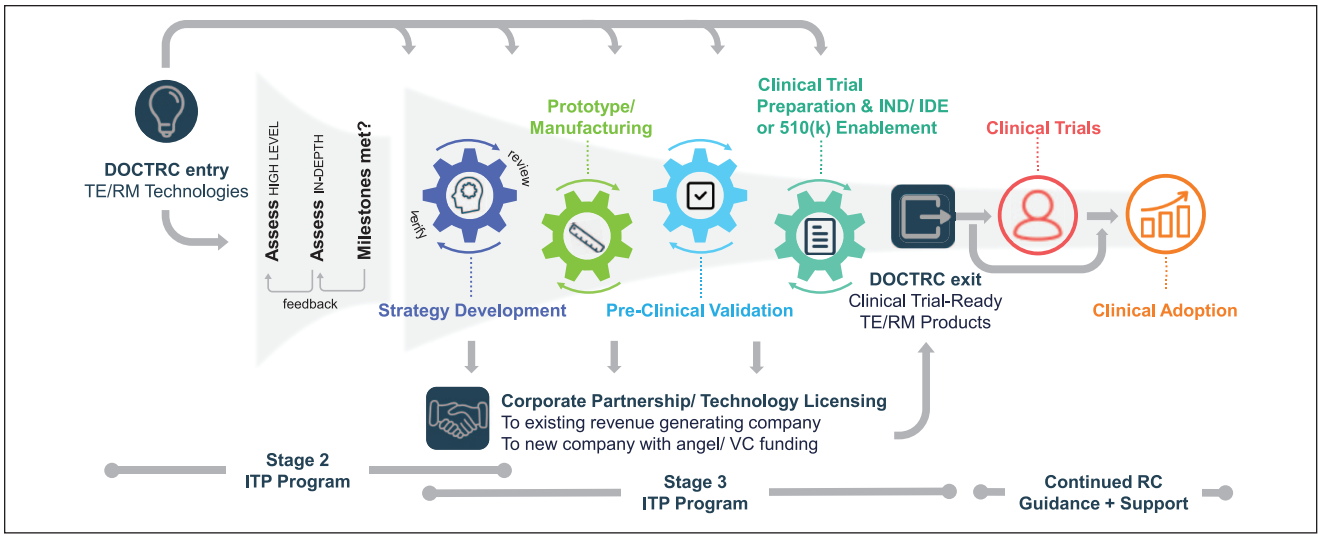

Figure 1. Stages of the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center. Translational projects are evaluated in stage 2 (Stage 2 ITP Program) based on their scientific, technical, and commercialization merit. Interdisciplinary teams of experts conduct these quantitative assessments. Stage 3 (Stage 3 ITP Program) consists of a series of phases to further de-risk the technical and commercial aspects of the translational projects. Note that aspects of commercialization such as technology licensing considerations and corporate partnerships are introduced early in the process. Project teams exit stage 3 when the projects are sufficiently advanced to attract follow-on funding, licensing to an incumbent company, or new company formation. The ultimate goal of this process is to generate translational projects that have a higher degree of clinical trial and clinical adoption success due to the involvement of interdisciplinary teams early in the projects' life span.

approach was important because much earlier in the translational process, the teams were exposed to concepts such as regulatory, manufacturability, intellectual property prior art, business models from incumbent companies, and other later-stage commercialization factors such as competitive developments and the existence of customers with a clinical need. Contemplating the concepts at the start of translational projects allows project teams to pivot and adapt early and to account for these considerations well before preclinical trials when quality system design controls, Good Laboratory Practices (GLP), and other standards will narrow and constrain the project scope.

Three Center stages were created: Planning (stage 1), Project Curation and Selection (stage 2), and Acceleration to Clinical Impact (stage 3). A framework was developed (Fig. 1) to manage projects throughout these stages with an emphasis on a transdisciplinary approach, an adapted phase-gate model, and establishment of an Industrial Partners Program (IPP). This approach enabled the involvement of commercial aspects well before later-phase milestones such as patent filing and product design freeze. These are important resources, especially for nonindustry inventors who sometimes overestimate market potential due to lack of market reports and expertise in projecting total addressable markets.

Developing Projects for Successful Translational Exits

Many of the translational projects needed support throughout the DOC RM phase-gate process. In this phase-gate approach, the developmental stage of a project ("phase") is punctuated by a decision point ("gate"), thus providing interventions to critically evaluate whether projects should continue. The phase-gate model we developed has roots in the technology management field, including from the Stage Gate Review from the Department of Health and Human Services Enterprise Performance Life Cycle Framework (2008). To illustrate a strategy to support translational projects using this approach, we will focus on the Preclinical Development phases (Fig. 2). There is a need for a coaching tool to guide project teams in navigating the preclinical development process as these preclinical development activities are one of the valleys of death stages within the translational development process. Therefore, the Center created 2 translational development status questionnaires, one for medical device development requirements (Appendix Fig. 1) and one for drug development requirements (Appendix Fig. 2). These questionnaires provide an overview of the translational development process divided into 5 key phases, whereby each phase has a go/no-go decision gate to determine whether a particular stage's key deliverables were met. Regulatory and commercialization experts implement these questionnaires to achieve 3 objectives: 1) as an educational tool to inform project teams about key deliverables that must be navigated and delivered throughout the translational process, 2) to gain a more accurate assessment of a particular project team's translational development status and to better illuminate how experts should be allocated to support the projects, and 3) to provide a comprehensive project status reporting tool to help make project oversight decisions.

The Center involved practice-based research networks to create access to a large group of recognized clinical opinion leaders for their input on clinical needs and high-value indications to improve decisions about preclinical models and regulatory pathways. These networks aim to de-risk the translational projects and prime markets for downstream clinical adoption. Furthermore, such a network is leveraged for customer discovery efforts starting at earlier stages to confirm the clinical need

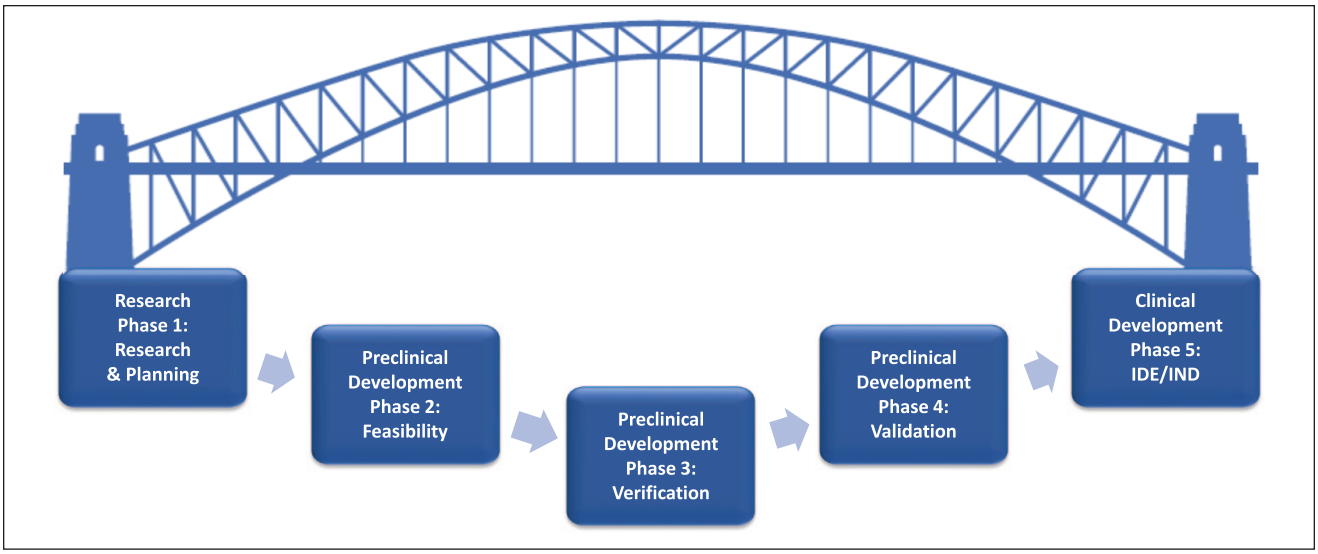

Figure 2. Phase-gate process overview. Translational projects are managed through a phase-gate process spanning 5 phases from Research and Planning to Clinical Development (Investigational Device Exemption [IDE]/ Investigational New Drug [IND]) submission. At the end of each phase, an evaluation process (gate) is conducted by transdisciplinary teams to assess the completeness of each phase before proceeding to the next phase. Some projects do not succeed in passing a gate and either remain in that phase to address certain limitations or cease progression altogether. This is an important process in academic commercial translation so that only those projects that have adequately addressed each phase are advanced—allowing for the most potent projects to move into clinical development and clinical impact.

and to understand the key barriers and drivers for the successful clinical adoption (Ulwick 2002).

An IPP was also established to support the integrative and collaborative involvement of industry in the early and late-stage life cycles of translational projects. The IPP is organized into 4 components: Assessment, Commercial Translation Planning, Business Development, and Relationship Management (Fig. 3). As an example, the IPP assisted a project team that was developing a hydrogel-based protein delivery technology for regenerative endodontics. The IPP created a high-fidelity market map to inventory potential licensees and created a commercial translation pitch deck to assist with the initial industry discussions. Moreover, the IPP served as a bridge with the technology transfer team of the project's home institution to proactively engage prospective licensees. This IPP example resulted in a greater number of relevant industrial stakeholders that better understood the commercial potential and is now in active discussions to license out the technology for further commercial advancement.

Commercial Translation Project Case Studies

In this section, several Center biomaterials-based projects that exemplify the interdisciplinary approach to translational project development are presented as case studies. As a translational research initiative, the projects were assessed to have demonstrated proof of concept and clinical relevance prior to entry into the program. A multidisciplinary advisory team was formed and tailored to the needs of each project. Assembled expertise included the scientific, technical, clinical, regulatory, and commercialization aspects of the project. In collaboration with the advisory team and support from the home institution, project milestones were refined for each project period to address key elements that would support an eventual FDA submission. These elements were designed with the entire product development and commercial translation process in mind (Fig. 1). Accordingly, the success criteria against which the milestones were measured, and relevant go/no-go decisions were specified, and a phase-gate model was applied (Fig. 2), with the next tranche of Center funding dependent on the successful meeting of prior milestones. Industry partnerships were established early in the process (Fig. 3), providing the projects with important commercialization insights while there was ample time to adjust product development plans and creating networks of high-potential licensees.

Case Study 1: Facial Nerve Guide

One of the projects supported by the Center encompasses the development of a polymeric guide for long-gap nerve repair. Composed of biodegradable poly(caprolactone), the conduit provides sustained release of a glial cell line–derived neurotrophic factor, which is encapsulated in double-walled poly(lactic-co-glycolic acid)/poly(L-lactic acid) microspheres embedded in the conduit. Prior to entry into the Center, in vitro characterization of the conduit was completed, providing an understanding of parameters that control critical nerve guide properties, including luminal porosity, suture retention, and growth factor concentration and elution rate (Kokai et al. 2009). Furthermore, the nerve guide was evaluated in a 5-cm nerve defect in a nonhuman primate model, where it resulted in

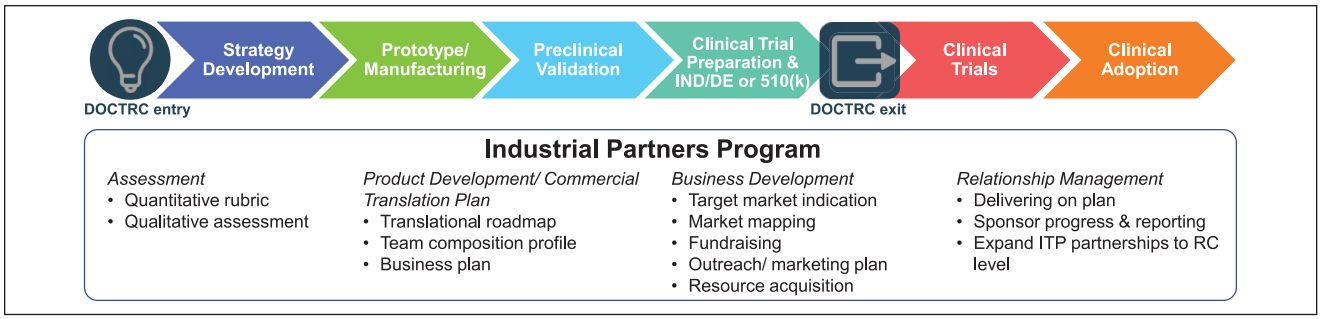

Figure 3. Industrial Partners Program (IPP) stages. Aligned with the stages of the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center (Fig. 1), the IPP supports the involvement on industry throughout this translational development life cycle. The IPP consists of 4 components: Assessment, Product Development/Commercial Translation Plan, Business Development, and Relationship Management. The IPP supports the codevelopment and management of the Translational Development Status Questionnaires (Appendix Figs. 1, 2) and extends the project support into developing early stage business plans, market mapping, outreach to industry partners, and helping to sustain the industry relationships to create a virtuous cycle of industry collaboration with the translational projects.

an 80% return to function after 1 y (Fadia et al. 2020). With substantive scientific work supporting the prospective product, along with corresponding patent protection, the project had completed the Research and Planning stage of the translational process (Fig. 2), and the peripheral nerve injury market was being explored as a potential first clinical indication. This project was selected for funding to explore commercialization opportunities in the DOC space, where injuries resulting in facial paralysis often result in significant physiological and psychosocial morbidity. However, solutions for nerve injuries in the DOC space are typically repurposed from nerve repair approaches in the extremities despite the unique anatomical setting and disease etiologies due to the much smaller procedural volume and thus market size.

Studies executed focus on Preclinical Development phase activities, including mechanical and biocompatibility testing of the nerve guides toward the initial prototype design and fabrication. In parallel, Research and Planning activities were specifically related to the DOC indications, such as regulatory strategy development and activities geared toward product commercialization, including new company formation. The project and its advisory teams developed a commercial translation roadmap that integrates regulatory, commercialization, and market adoption strategies. Toward this end, the team consulted with regulatory experts to explore approaches for FDA submissions. The regulatory roadmap was guided by the learnings from DOC-specific market research and customer discovery, taking into account the time to market and scenarios of clinical adoption in the markets being considered. Interviews with both adult and pediatric clinicians in the oral surgery, plastic surgery, and otolaryngology specialties were conducted to home in on a patient segment who would most benefit from the nerve guide and identify possible barriers to adoption specific to craniofacial applications. With these Research and Planning activities of the first phase of the translational development process feeding into the commercialization plans, the project team successfully founded a new company to further commercialize activities of the nerve guide. Through the leadership of this new company, the team is in iterative communications with the FDA for guidance. This process will continue to shape the roadmap toward commercialization and clinical application of this technology.

As the prospective device is being explored for other indications, the company proceeded with activities associated with later phases of the translational development process, including the implementation of design control and quality management systems under the Preclinical Development Verification phase. A new manufacturing process to increase the production rate of the nerve guides was developed and refined and is planned for transfer to a facility capable of producing the nerve guides under Good Manufacturing Practices (GMP). The GMP-grade nerve guides will be evaluated to confirm that the design criteria, including the previously established functional properties and characteristics of human facial nerves, are met. It is anticipated that guides will be used in future preclinical testing in a GLP-regulated environment, where data from such studies will support a submission to the FDA to initiate clinical studies.

Case Study 2: Gene Therapy for Radiation-Induced Xerostomia

In the treatment of head and neck cancers, radiotherapy is commonly prescribed in conjunction with surgery and/or chemotherapy. Because of the anatomical proximity, the salivary glands receive secondary damage from radiotherapy, where xerostomia is one of the common side effects. While intensity-modulated radiotherapy partially reduces the incidence of radiation-induced xerostomia, more than half of patients whose salivary glands are exposed to radiation develop xerostomia, equating to 50,000 patients annually in the United States. Currently available treatments, such as amifostine, pilocarpine, and/or other palliative routes, are unable to address this complication in a way that is satisfactory for patients. Consequently, gene therapy was put forward as potential alternative therapy (Baum et al. 2012). Due to the potential side effects of viral vectors, an ultrasound-assisted gene transfer (UAGT) technique to deliver the aquaporin 1 gene (*AQP-1*) for the

amelioration of radiation-induced xerostomia was developed to address this need. This nonviral gene delivery is based on sonoporation generated by the ultrasound, which transiently alters cell membrane permeability, enabling gene transfer into salivary gland cells surviving radiation.

Prior to entry into the Center, the project established proof of concept in a mini-swine model, where the delivery of *AQP-1* to the parotid glands restored salivary flow to pretreatment levels (Wang et al. 2015). The operation parameters to induce the acoustic field required to effectuate UAGT were established, and the candidate vector for the application was tested also in a mini-swine salivary parotid gland. In this evaluation, UAGT therapy restored the stimulated salivary flow to preinjury levels comparable to that achieved by an adenoviral delivery, which was evaluated in a phase I clinical trial to establish *AQP-1* gene therapy safety.

While the benefit of obviating the use of an adenovirus is compelling, the UAGT technique is uniquely complex, with multiple components needed to effectuate. The technique uses a device to deliver ultrasound to induce cavitation of microbubbles for transient sonoporation of epithelial cells of the salivary gland to deliver a gene therapy. Given this multifaceted approach, the need to establish a clear understanding of the regulatory pathway emerged as a priority. With significant portions of the scientific work under the Research and Planning phase completed (Appendix Fig. 1), the project team worked with the Center's regulatory core experts to identify key experiments that would be required to demonstrate safety (with preliminary efficacy) to obtain approval to conduct first-in-human studies. Given that substantial work was completed prior to the Center's support, the key studies were determined to be performed under GLP regulations for increased study quality and rigor. The first study was to demonstrate the safety of ultrasound-induced cavitation alone, in the absence of any vectors, in a relevant swine model. To maximize the effort and minimize financial commitment that would be required for such a GLP study, the study protocol was developed by the investigators and reviewed by the Center's regulatory and quality assurance core experts and statisticians to ensure that the study was designed to demonstrate the safety of ultrasound-induced cavitation with sufficient power. Upon iterative revisions, the study was finalized with a contract research organization (CRO), at which the protocol was performed, with support from the project team investigators. In addition to the assigned study director and the quality units from the CRO, regulatory and quality assurance experts were also consulted and kept abreast of modifications and amendments to the study, following the documentation requirements, as specified by the GLP requirements. Other activities under Preclinical Development include feasibility and verification, including establishing and refining specifications for all the components necessary to actuate the UAGT and validating them under GLP conditions.

In parallel, the project team also collaborated with market assessment and commercialization advisers to delineate how this treatment would be implemented in a clinical setting. The team interviewed stakeholders, including clinicians who would ultimately administer this treatment, including otolaryngologists, head and neck surgeons, oral surgeons, and interventional radiologists, and clinicians who interface with the patients and hear firsthand the unmet needs from the patients' perspective. From these interviews, the team was able to glean how irradiation-induced xerostomia is currently managed and how this new therapy may fit into the existing workflow, as well as the patients' attitude toward their willingness to pay higher out-of-pocket costs for improvement to their quality of life.

As the team designs the first clinical trials for UAGT treatment of irradiation-induced xerostomia in preparation for the Clinical Development phase, these learnings will be incorporated to facilitate patient recruitment and a successful trial outcome. The clinical trial design, along with the results from the abovementioned GLP studies and other requisite elements, will be composed in collaboration with the regulatory experts toward an FDA submission to enable a first-in-human study for this unique therapy.

Case Study 3: Biomaterial for Bone Grafting Adhesive

In addition to the translational research projects from academic institutions, these strategies may also support startup companies to address critical elements of their product development to help reach the FDA submissions for the initiation of clinical trials.

A last example highlights the development of a biocompatible biomaterial as a bone adhesive product by a small startup company. The development of a successful bone grafting technology with sufficient adhesive properties was limited. Osteoconductive materials, such as loose particulates of soft putties that can support bone regeneration, often lack structural integrity. As a result, ancillary fixation (e.g., screws, tacks) or containment (e.g., membranes, meshes) devices are required to prevent graft migration and the ingrowth of fibrous tissue that impedes bone regeneration and remodeling, compromising the bone graft. The company developed an injectable, cohesive, self-setting, mineral-organic wet-field adhesive, comprising 2 naturally occurring compounds, tetracalcium phosphate and O-phospho-L-serine, in an aqueous medium for bone grafting and dental implant stabilization applications. As this biomaterial can conform and adhere to complex defect sites, with requisite mechanical properties, its implementation as a bone graft strives to enable implant placement simultaneous to the bone augmentation procedure, saving significant healing time currently required in advance of implant installation.

Prior to the Center's engagement, activities under the Research and Planning phase were largely accomplished, as the company had completed significant characterization of its biomaterial, including in vitro, characterization of its components and their effect on the formulation and physical/handling properties. Optimization of mechanical and structural properties, as well as preliminary biocompatibility testing under recognized standards, such as American Society of Testing and Materials (ASTM) International and International Organization for

Standardization standards, was also performed. Early in vivo studies demonstrated the ability of this material to resorb and form new bone in a critical-size defect model and in a canine maxillary onlay and inlay graft model.

Studies were designed to de-risk the project toward clinical trial initiation specifically for bone graft applications. Additional in vivo studies were conducted to compare several variations of the material to select the most promising formulation based on predefined primary outcomes and measures of success, completing the Research and Planning phase of the translational process. The Preclinical Development phases for feasibility and verification ensued. Biocompatibility studies, packaging development, sterilization and shelf-life validation, and other studies to ensure that device designs are acceptable are currently under way. In combination with the results from the biomaterial formulation evaluated under GLP conditions by a CRO (Preclinical Development: GLP Validation), these results will support an FDA submission as the team progresses to the Clinical Development stage. In parallel, the accessory delivery device is also being developed; upon prototype development, the team engaged external firms to conduct user-handling trials with surgeons to understand key elements that will influence the adoption of the product by clinicians. This assessment was also guided by FDA expectations and in accordance with American National Standards Institute and human factors engineering standards. As a caveat, there are regulatory differences outside of the United States (FDA), and if a global marketplace is contemplated, those corresponding regulatory bodies should be factored in during this early stage analysis.

Customer discovery efforts were also conducted by the IPP team prior to the program matriculation. In particular, a group of experts in the dental bone graft field was interviewed to understand the current paradigm and the course of treatment for the intended indication and associated costs. Equally important, the clinicians shared their perspective on other considerations for adopting such new technology into their practice, including the effect on existing workflow and revenue streams. Through these discussions, specific indications that can most opportunely capitalize on the benefits of this biomaterial both from scientific/clinical and commercialization perspectives were explored.

While stakeholder discovery revealed that this bone adhesive biomaterial product, unlike many in the DOC space, was likely to be reimbursed by medical insurance, the small patient population and cutting-edge technological approach require close attention to nontraditional sources of development funding and investment such as seed capital firms or venture capital groups.

Redirecting Projects. While the 3 cases above illustrate how the interdisciplinary machinery assisted in project advancement, there are projects that did not succeed through the funnel for various reasons (Fig. 1). At the earliest stages of project reviews, proposals with strong scientific merit but with unclear clinical needs, ambiguous regulatory paths, or high-risk intellectual property potential were not selected for support. For selected projects, failure to meet milestones resulted in off-ramping from the program. Most of the challenges at this stage were technical (e.g., biomaterials unable to withstand sterilization procedures for mass production, inability to reproduce efficacy in a critical animal model, or lack of clear functional superiority over current standards of care). While basic research programs may enable further investigation of the outcomes, these key phase-gate decisions are required to guide the translational development and provide further project de-risking for clinical adoption. Projects that exited were guided toward alternative funding sources to strengthen basic and/or translational potential.

Conclusion

The valley of death in DOC RM–based projects spans a wide band of project development stages. To help overcome these valleys, it is advantageous to assemble interdisciplinary teams to help de-risk the science, technology, intellectual property, business models, and commercial funding in an adapted phase-gate model specific to RM therapies and devices. A major factor in successfully advancing these projects is the highly integrative and interdisciplinary nature of bridging scientific and business disciplines early in the project life cycles—leading to project teams contemplating late-stage commercial translation factors early in the development process when it is easier and less expensive to make important development adjustments. The adapted phase-gate process has broad applications to translational project teams, whether they are early in the concept and planning phases or later in the development phases. These efforts are all with the purpose of helping these technologies successfully exit a university-based translational development process and overcoming the many funding gaps associated with DOC RM innovations.

Author Contributions

D.P. Taylor, contributed to conception, design, data analysis, and interpretation, drafted and critically revised the manuscript; M. Yoshida, K. Fuller, contributed to data analysis and interpretation, drafted and critically revised the manuscript; W.V. Giannobile, W.R. Wagner, contributed to conception and design, critically revised the manuscript; C.S. Sfeir, contributed to data analysis and interpretation, critically revised the manuscript; D.H. Kohn, contributed to conception, design, data analysis, and interpretation, critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

Acknowledgments

We thank Dr. Dave Mooney from the Harvard Wyss Institute for his counsel in helping teams through the phase-gate process. We also thank the project teams assisting with the case studies, including Dr. Kacey Marra (University of Pittsburgh); Dr. Michael Passineau (Allegheny General Hospital); Dr. Isabelle Lombaert (University of Michigan); Brian Hess (RevBio, Inc.); and D. Grayson Allen (RevBio, Inc.), as well as Dr. Andrew Brown, for his contributions to the Industrial Partners Program.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work and research reported in this publication were supported by the National Institute of Dental and Craniofacial of the National Institutes of Health under Award Numbers U24 DE026915 and U24 DE029462.

ORCID iDs

D.P. Taylor https://orcid.org/0000-0002-2146-8804
C.S. Sfeir https://orcid.org/0000-0003-3163-3292

References

Baum BJ, Alevizos I, Zheng C, Cotrim AP, Liu S, McCullagh L, Goldsmith CM, Burbelo PD, Citrin DE, Mitchell JB, et al. 2012. Early responses to adenoviral-mediated transfer of the aquaporin-1 cdna for radiation-induced salivary hypofunction. Proc Natl Acad Sci USA. 109(47):19403–19407.

Department of Health and Human Services Enterprise Performance Life Cycle Framework. 2008. Stage Gate Reviews [accessed 2021 Mar 24]. https://www2.cdc.gov/cdcup/library/hhs_eplc/56%20-%20Stage%20Gate%20Reviews/EPLC_Stage_Gate_Reviews_Practices_Guide.pdf.

Fadia NB, Bliley JM, DiBernardo GA, Crammond DJ, Schilling BK, Sivak WN, Spiess AM, Washington KM, Waldner M, Liao HT, et al. 2020. Long-gap peripheral nerve repair through sustained release of a neurotrophic factor in nonhuman primates. Sci Transl Med. 12(527):eaav7753. Erratum in: Sci Transl Med. 2020;12(542):eabc4054.

Giannobile WV. 2015. Improving clinical trials in dentistry. J Dent Res. 94(3 Suppl):6s–7s.

Giannobile WV, Chai Y, Chen Y, Healy KE, Klein O, Lane N, Longaker MT, Lotz JC, Mooney DJ, Sfeir CS, et al. 2018. Dental, oral, and craniofacial regenerative medicine: transforming biotechnologies for innovating patient care. J Dent Res. 97(4):361–363.

Kokai LE, Lin YC, Oyster NM, Marra KG. 2009. Diffusion of soluble factors through degradable polymer nerve guides: controlling manufacturing parameters. Acta Biomater. 5(7):2540–2550.

Li D, Azoulay P, Sampat BN. 2017. The applied value of public investments in biomedical research. Science. 365(6333):78–81.

Linton JD, Xu W. 2021. Understanding and managing the biotechnology valley of death. Trends Biotechnol. 39(2):107–110.

Truebel H, Thurston T. 2020. Danger in the valley of death: how the transition from preclinical research to clinical trials can impact valuations. Drug Discov Today. 25(12):2089–2094.

Ulwick A. 2002. Turn customer input into innovation. Harvard Business Rev [accessed 2021 Mar 17]. https://hbr.org/2002/01/turn-customer-input-into-innovation.

Voices: crossing the valley of death. 2018. Cell Stem Cell. 23(5):639–641.

Wang Z, Zourelias L, Wu C, Edwards PC, Trombetta M, Passineau MJ. 2015. Ultrasound-assisted nonviral gene transfer of AQP1 to the irradiated minipig parotid gland restores fluid secretion. Gene Ther. 22(9):739–749.