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Craniomaxillofacial Disorders and Solutions in Humans and Animals

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Abstract

Cross-disciplinary collaborations have initiated translational studies in an effort to harness naturally occurring diseases in companion animals to accelerate the development of new treatment modalities, drugs, and device inventions. These synergistic collaborations can identify clinically relevant models that offer the opportunity to conduct rigorous translational investigations. However, the relationship between craniomaxillofacial diseases in companion animals and humans has been widely overlooked. We report here an innovative and visionary 2-d symposium that was organized to gather professionals working on craniomaxillofacial disorders and solutions in humans and/or animals from multiple disciplines, including veterinary physicians, basic scientists, biomedical engineers, physicians, and dentists. The symposium provided a platform for junior and senior investigators and basic science and clinical researchers to network, collaborate, and develop a new clinical and translational framework for accelerated therapy development.

Keywords: veterinary dentistry, oral and maxillofacial surgery, companion animals, one health initiative, comparative dentistry, clinical and translational science

Introduction

Humans and companion animals, particularly dogs and cats, develop similar diseases, such as cancers, orthopedic degenerative diseases, and certain metabolic diseases. Whereas anatomic and physiologic features may differ between humans and companion animals, these naturally occurring diseases have essentially identical pathogeneses and thus potentially respond, as well as not respond, to similar therapeutic interventions. In 2015, the Institute of Medicine published a seminal book entitled *The Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research: Workshop Summary* (Nass et al. 2015), which highlighted the important opportunity to explore the disease mechanism and therapeutic options through a collaboration with veterinary medicine.

Wild and companion animals share our susceptibility to some diseases and environmental hazards. According to the Centers for Disease Control and Prevention, the health of people is connected to the health of animals and the environment (https://www.cdc.gov/onehealth/index.html). The One Health Initiative encourages the collaborative efforts of multiple disciplines to achieve the best health for people, animals, and the environment. Historic and ongoing collaborations between scientists and clinicians in the human and veterinary areas are paving innovative roads in translational studies through naturally occurring disease models in companion animals, domesticated large animals, and wild animals. Importantly, these synergistic collaborations are yielding clinically relevant models of human diseases, as they reflect the complex genetic, environmental, and physiologic variation present in humans. Historically, veterinary dentistry was born through interactions with human dentists, and comparative dentistry and oral pathology have come a long way; however, its integration into a clinical and translational science still awaits future development. Here we report the first such attempt to foster the future collaboration between human and veterinary dentists and craniomaxillofacial researchers.

Inaugural Conference Combining Human and Veterinary Dentistry

The inaugural Craniomaxillofacial Disorders and Solutions in Man and Animals Conference was held at the Luskin Conference Center of the University of California Los Angeles (UCLA) campus on November 11 to 13, 2016 (Fig. 1). The conference was created to provide a unique opportunity for clinicians and scientists to discuss craniomaxillofacial disorders occurring in humans and animals and the challenges that they pose for the patient and the clinician.

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Figure 1. The inaugural Craniomaxillofacial Disorders and Solutions in Man and Animals Conference was held at the Luskin Center, University of California, Los Angeles (UCLA), during November 11 to 13, 2016. (**A**) The participants were drawn from human and veterinary dentistry, oral and maxillofacial surgery, basic and clinical/translational science, industry, and the Food and Drug Administration (FDA). (**B**) Conference organizers (from left): Dr. Nishimura, Dr. Moshaverinia (UCLA School of Dentistry), Dr. Arzi (University of California Davis School of Veterinary Medicine), Dr. Fiani (Cornell University College of Veterinary Medicine) and Dr. Verstraete (University of California Davis School of Veterinary Medicine). (**C**) Keynote speaker, Dr. Barbara Natterson-Horowitz (David Geffen School of Medicine at UCLA), author of *Zoobiquity*. (**D**) Discussion in the lecture hall, Dr. Mao (Columbia University College of Dental Medicine). (**E**) Discussion outside the lecture hall. (**F**) Panel discussion on new paradigm of translational science (from left): Dr. Runner (FDA), Dr. Jarrahy (David Geffen School of Medicine at UCLA), Dr. Nishimura, Dr. Macura (FDA), Dr. Maki (VetCell Therapeutics). (**G**) A panelist, Dr. Dunham (George Washington University, formerly FDA), continued discussion.

The global objective of this conference was to bring together dedicated clinicians and scientists who work on the craniomaxillofacial region and who are interested in learning about similar disorders and solutions in humans and animals. A further objective of this conference was to build new connections and to strengthen the continuity among scientists, veterinarians, and medical doctors.

Oral Diseases in Humans and Companion Animals and in Experimental Animal Models

The National Health and Nutrition Examination Survey of the U.S. civilian noninstitutionalized population revealed that 46% of dentate adults, representing 64.7 million people, presented for periodontitis (Eke et al. 2015). The prevalence of periodontitis was positively associated with increasing age and with 8.9% of the people having developed severe periodontitis. Similarly, periodontitis is the most widely experienced oral disease in companion dogs (Fig. 2A). According to the American Veterinary Dental College, periodontal disease is the most common clinical conditions affecting adult dogs and cats (https://www.avdc.org/periodontaldisease.html). The severity of the disease increases with age (Kortegaard et al. 2008), and the prevalence may reach >90% in some breeds (Hoffmann and Gaengler 1996), resulting in discomfort and inflammation in the oral cavity. Diagnostic approaches in dogs and cats affected by periodontitis mirror those applied in humans and include dental radiography and periodontal charting. Similarly, the therapeutic approach includes periodic periodontal treatments, dental extractions, and occasionally more advanced therapies, such as guided tissue regeneration.

To understand the pathogenesis and to design effective therapeutic options, experimental animal models play a pivotal role. The requirements for a good experimental animal model include anatomic similarity, low cost, and genetic stability, as well as easy care, feeding, and husbandry. Rodent periodontitis models have been frequently used; however, they require disease induction stimuli from exogenous sources (Struillou et al. 2010). In 1956, Gupta and Shaw reported that among the rodents that they investigated, only representatives of the rice rat (*Oryzomys palustris*) species had a high incidence of periodontal lesions without any induction stimuli. The

rice rats naturally developed periodontal abnormalities, ranging from gingivitis, ulceration of gingival epithelium, and accumulation of bacterial plaque to moderate inflammation, disruption of periodontal ligament, migration of junctional epithelium, and alveolar bone resorption. The severity of periodontitis in rice rats progressed by age, to which metabolic factors did not contribute (Aguirre et al. 2017). The rice rats were a unique rodent model to investigate the pathogenesis (Dick and Shaw 1966) and therapeutic modulation of periodontitis (Shaw and Dick 1966; Cohen and Meyer 1993). Rice rats were recently reported to develop osteonecrosis of the jaw-like lesions associated with periodontitis when zoledronate, a potent nitrogen-containing bisphosphonate, was administered (Aguirre et al. 2012). The disease progression of naturally occurring periodontitis in rice rats mirrors that of humans and companion animals (Fig. 2A).

While small animals such as rodents are typically helpful for initial studies that provide a basic understanding of disease pathogenesis, larger animal models such as dogs are used in preclinical efficacy and safety studies for human therapeutic development (Struillou et al. 2010; Giannobile et al. 2011). There has been a concerted effort to move away from preclinical evaluations that use nonrodent species, particularly dogs, for human therapies (Baumans 2004; Conole 2004; Hasiwa et al. 2011). Instead of generating experimental animal models, recent efforts have helped investigators working with naturally occurring disorders establish guidelines for translational science (Devireddy et al. 2017). This conference fostered dialogues to explore how companion animals such as dogs, cats, and horses should serve as naturally occurring large animal models to study aspects of not only periodontitis but other craniomaxillofacial disorders, such as malocclusion and temporomandibular disorders, for understanding disease processes and new treatment modalities delivered on a clinical trial basis.

Reconstructive/Regenerative Therapy for Oral and Maxillofacial Cancer in Animals

Neoplasia is common in dogs and accounts for almost 50% of all mortalities in dogs >10 y of age (Craig 2001). A variety of neoplastic disorders occur in the oral and maxillofacial region of dogs and cats, including odontogenic and nonodontogenic tumors, with malignant tumors representing approximately 6% of all tumors in dogs (Verstraete et al. 1992). In animals, as in humans, cancer is a complex multifactorial disorder that develops over a long period. These fundamental similarities in disease complexity and progression contribute to the power of pets with naturally occurring cancer to become an excellent model for translation (Nass et al. 2015). These values were also recognized by veterinary and human oncologists and basic cancer researchers who jointly formed the Comparative Oncology Trials Consortium within the National Cancer Institute, which functions to design and execute multi-institutional clinical trials in companion animals with naturally occurring tumors (Gordon et al. 2009).

In that regard, advanced surgical procedures, such as the regeneration of critical-size mandibular defects in dogs following mandibulectomy for cancer removal, has received attention by the human and veterinary scientific community and the public. Dogs with mandibular tumors, such as squamous cell carcinoma or odontogenic tumors, may receive anatomically correct reconstruction of the mandible through a combination of intra- and extraoral approaches, a locking titanium reconstruction plate (Synthes Maxillofacial; Paoli), and a compression-resistant matrix infused with recombinant human bone morphogenetic protein-2 (rhBMP-2) (Fig. 2B). Furthermore, surgical planning consisting of computed tomographic imaging and 3-dimensional model printing is routinely utilized (Arzi, Cissell, et al. 2015). This technique effectively restores the biomechanics and normal function of the patient following mandibulectomy. The current protocol involves utilizing 0.5 mg/mL of rhBMP-2 at a 50% soak volume infused on a compression resistant matrix (Mastergraft Matrix, Medtronic; Arzi, Verstraete, et al. 2015). The same regenerative principle is also performed routinely for mandibular defect nonunion fractures (Verstraete et al. 2015). This is important, as the use of rhBMP-2 has been U.S. Food and Drug Administration (FDA)–approved for few applications, such as spinal fusion, but not for regenerating mandibular bone in humans. It has been reported that the off-label use of rhBMP-2 in cervical fusion surgery resulted in life-threatening complications, such as dysphagia, dysphonia, and airway stenosis due to soft tissue swelling (Leach and Bittar 2009). However, this clinically relevant dog therapy may prove instrumental for paving the way for the establishment of a defined clinical protocol for the safe use of rhBMP-2 for bone regeneration in humans.

Inflammatory Mucosal Lesions and Stem Cell Therapy

Chronic inflammation of the oral mucosa is clinically characterized by the presence of inflamed, ulcerated, and erythematous mucosa. Oral mucositis is seen most frequently in human disorders such as lichen planus, stomatitis, and pemphigus, which may result in serious consequences include pain requiring opioid analgesia and potentially life-threatening infections. Oral pain may also result in malnutrition, often requiring the prolonged hospitalization (Sonis et al. 2001). Chronic oral mucosa inflammation is a common side effect of cancer treatment (Scully et al. 2004). High-dose chemotherapy and radiotherapy, followed by bone marrow transplantation, have been used to treat hematologic cancers. During this treatment, oral mucositis develops in >70% of patients (Woo et al. 1993). Oral mucositis is also frequently experienced by patients with solid organ transplantation and immunosuppression therapy (Nappalli and Lingappa 2015).

These inflammatory disorders have a complex pathogenesis that involves mucosal infiltration by T and B cells (Joly and Litrowski 2011; Di Stasio et al. 2014). In the case of ulcerative oral mucositis in medication-related osteonecrosis of the jaw, oral mucosal barrier immunity is altered by disproportionate

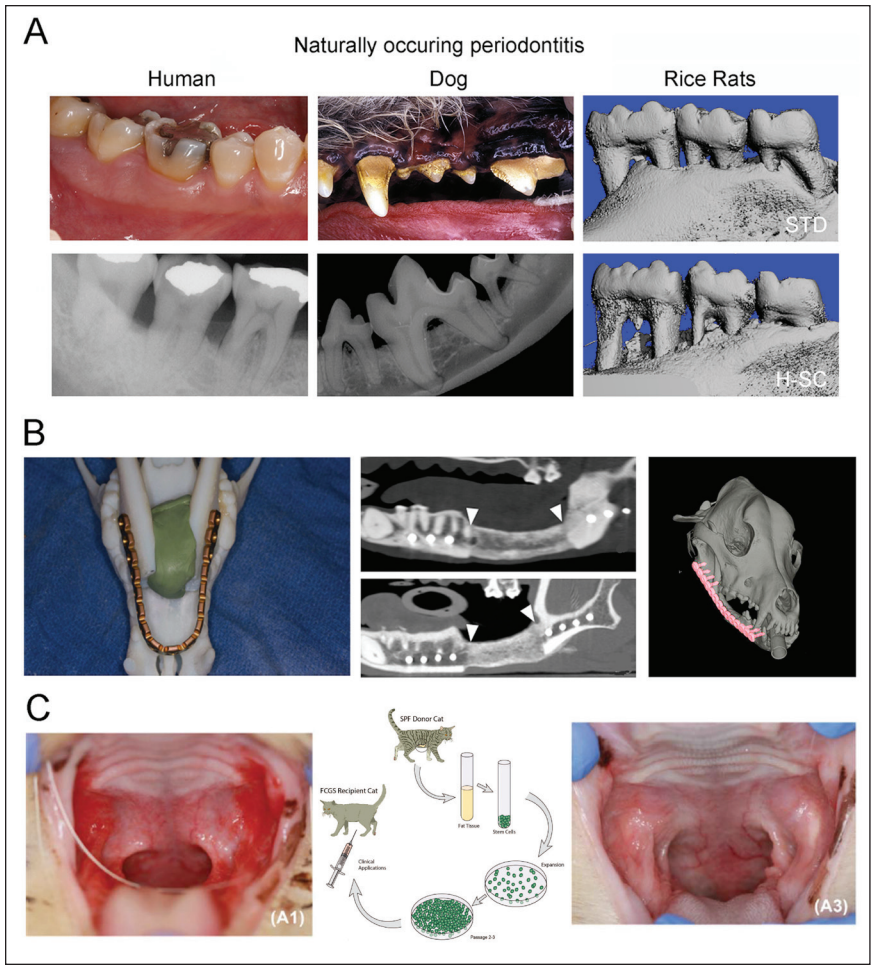

Figure 2. Naturally occurring diseases affecting craniomaxillofacial tissues and new therapeutic modalities. (**A**) Naturally occurring periodontitis is common in humans and companion animals. The disease phenotype is similar in their oral cavity. Disease phenotypes include gingival inflammation and alveolar bone resorption. Rice rats similarly develop naturally occurring periodontitis with a standard diet (STD), but advanced alveolar bone resorption was observed with a high-sucrose (H-SC) diet. Micro–computed tomography images of rice rats through the courtesy of Dr. Aguirre and Dr. Messer, University of Florida, Gainesville. (**B**) Oral cancer is experienced by humans and companion animals. Veterinary oral and maxillofacial surgery has uniquely developed advanced treatment: a regenerative approach to mandibular reconstruction in dogs with 3-dimensional modeling for surgical planning and rhBMP-2 infused on a compression-resistant matrix for regenerating bone (between arrowheads) following mandibulectomy or for defect nonunion fractures (Arzi, Cissell, et al. 2015). (**C**) The treatment of severe feline refractory chronic gingivostomatitis via allogeneic adipose-derived mesenchymal stem cells exhibited substantial clinical improvement (Arzi et al. 2017). FCGS, feline chronic gingivostomatitis; SPF, specified pathogen-free.

infiltration and retention of granulocytic myeloid neutrophils (Hokugo et al. 2010; Sun et al. 2016). While new biological therapeutic approaches such as keratinocyte growth factor (i.e., palifermin) have been investigated for treating cancer therapy–induced oral mucositis (Barasch et al. 2009), a standard treatment protocol has not been established.

Cats exhibit a severe and debilitating chronic mucosal disease termed *feline chronic gingivostomatitis* (FCGS). The etiology of FCGS, while currently being studied, is elusive, and it is generally accepted that FCGS arises from an inappropriate immune response to oral antigenic stimulation, potentially multifactorial in nature and possibly with varying inciting causes (Winer et al. 2016). A clinical trial performed over the past 5 y is focusing on the immune-modulatory effect of adipose-derived stem cells administered systemically to cats affected by gingivostomatitis (Arzi et al. 2016; Arzi et al. 2017). The clinical trial is focusing on autologous or allogeneic adipose-derived stem cells administered intravenously at a dose of 20 million cells (Fig. 2C). Two administrations are given 1 mo apart, and an extensive immune characterization is performed before treatment and at defined time points (i.e., 1, 3, and 6 mo) and includes peripheral blood mononuclear cell proliferation assay, hematology and protein analysis, cytokine enzyme-linked immunosorbent assays, and flow cytometry, just to name a few. Importantly, histology and immunohistochemistry are performed before treatment and at exit from the clinical trial, 6 mo later. A recent study demonstrated that human and feline adipose-derived mesenchymal stem cells have comparative phenotypes for immunomodulatory functions (Clark et al. 2017). Therefore, the results of this trial are encouraging and may lead to human clinical trials for the treatment of human oral mucosal disorders such as lichen planus, stomatitis, and pemphigus, which often lead to serious life quality implications, including pain, severe discomfort malnutrition, and potentially life-threatening infections.

A New Clinical/Translational Framework

The treatment of craniomaxillofacial disorders holds a significant value to those affected patients and health care teams. In humans and companion animals, the manifestations of these disorders account for physical, nutritional, neurologic, and psychological impairments and create a significant financial burden. The development of new medical formulations and medical devices plays a critical role in addressing this challenge. The gap analysis conducted by the University of California Biomedical Research Acceleration, Integration and Development revealed the strong basic science research in University of California academic institutions, such as the investigation on mechanistic disease mechanisms in animal models, the development of therapeutic targets and options, and early translational studies (Fig. 3A). By contrast, clinical trials adhering the FDA protocol are disproportionately less conducted.

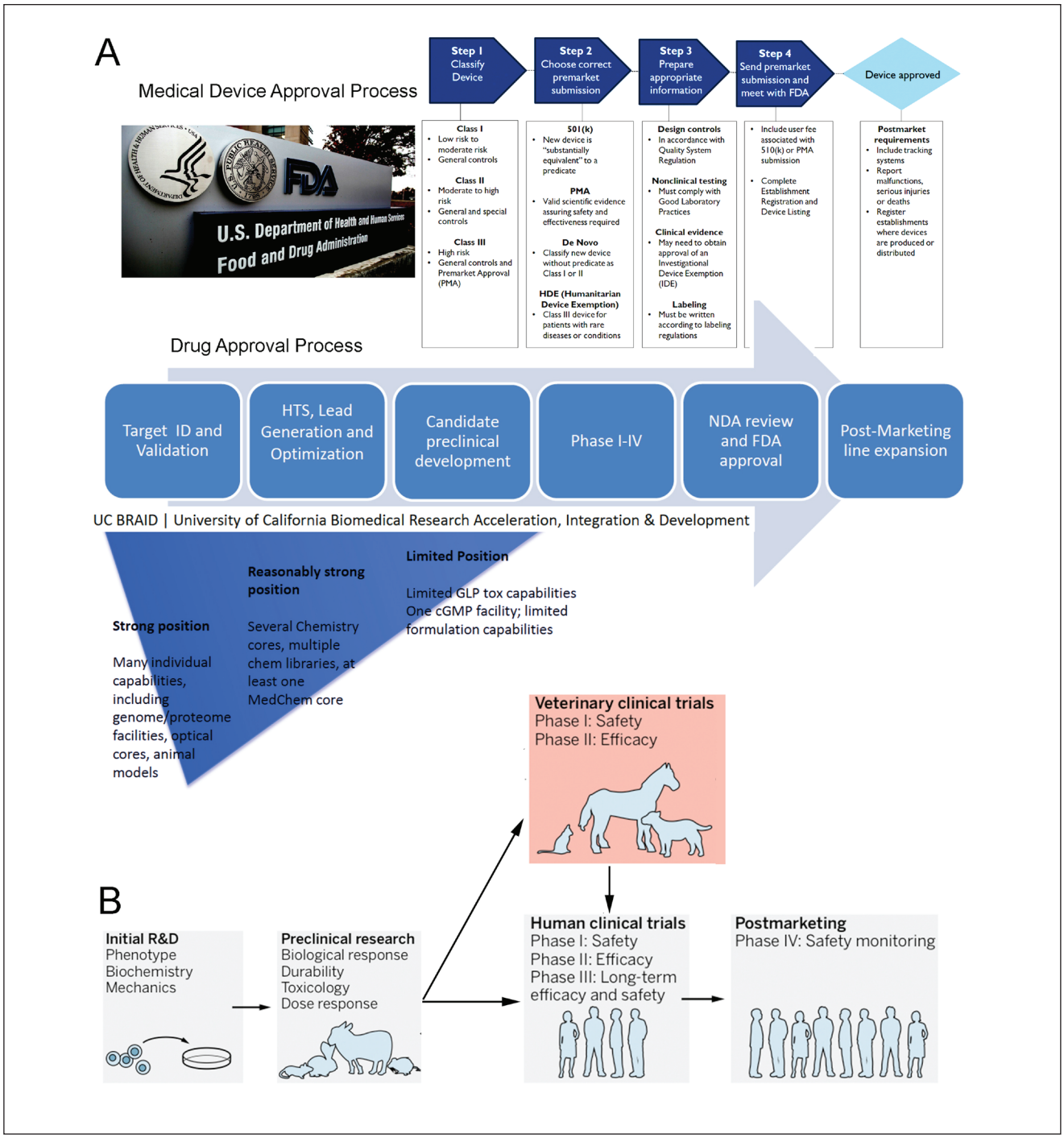

Figure 3. Regulatory framework involving companion animals and humans. (**A**) The flow of basic science, clinical and translational science, and regulatory processes. (**B**) An alternative approach of the clinical and translational process, including clinical trials for companion animals (modified from Kol et al. 2015). cGMP, current good manufacturing practices; FDA, Food and Drug Administration; GLP, good laboratory practices; HTS, high-throughput screening; NDA, new drug application.

Conventional preclinical mouse models have been widely used for studies of disease mechanisms and therapeutic intervention. Preclinical animal models for oral, periodontal, and craniofacial disorders include canine and nonhuman primates (Giannobile et al. 2011). After the preclinical animal studies, the candidate new medical formulation or medical device will undergo rigorous clinical trials (Fig. 3A). The FDA provides a number of early interaction opportunities—specifically, a pre-submission meeting, an informational meeting, a study risk determination meeting, an agreement meeting, a determination

meeting, a submission issue meeting, and a day 100 meeting. Each meeting provides the agency feedback in a set timeline. University scientists are entitled to communicate with the FDA, without the commitment by a commercial entity.

Even with these supports from the FDA, only 1 of every 1,000 compounds that undergoes the initial phase of testing will reach the next phase of testing in humans (Giannobile et al. 2011). It is widely known that induced disease in experimental animal models often lacks key characteristics of human diseases, such as aging, long latency, heterogeneity among pathologic agents, and genetic variations. This may contribute to late-stage drug development failures (Kol et al. 2015; Nass et al. 2015). Sections of the conference explored the possibility of combining clinical trials in companion animals as a planned part of therapy development for animals and humans (Kol et al. 2015; Fig. 3B).

The benefit of naturally occurring diseases in companion animals and their treatment has been recognized as a translational opportunity to human disease and treatment. The National Cancer Institute supports the Comparative Oncology Trials Consortium, a network of academic comparative oncology centers, which functions to design and execute clinical trials in dogs with cancer to assess novel therapies (Gordon et al. 2009). The approach of comparative biology between humans and companion animals has been applied for cancer immunogenic therapy (Finocchiaro and Glikin 2017), metabolic disorders (Chandler et al. 2017), and stem cells therapy (Hoffman and Dow 2016).

This conference presented a panel discussion for the comparative biology and clinical trials in companion animals for craniomaxillofacial disorders. The importance of comparative dentistry was shared among the conference attendees. However, it was recognized that the regulatory protocol of using the information of companion animal clinical trials was not established. In other words, the current regulatory format does not accept the therapeutic and safety data on naturally occurring diseases in companion animals. The industry participants pointed out a financial challenge in therapeutic agents for companion animals, which should cost far less than those for human patients.

Conclusion and Future Directions

The conference attracted the attention and enthusiasm of >70 researchers and clinicians from the veterinary and human medical fields who dedicated an intensive 2-d conference to a plethora of clinically-relevant subjects.

The following objectives were achieved: 1) the recognition of several similarities and differences in craniomaxillofacial disorders occurring in humans and animals; 2) productive discussion regarding research and clinical efforts for the treatment of craniomaxillofacial disorders in humans and animals; and 3) an open discussion among academic institutions, private industry, and representatives from the FDA.

The conference was evaluated by means of an anonymous questionnaire to plan pathways to sustain and strengthen future meetings. The results of the questionnaire identified future directions:

- The conference unequivocally tapped a relatively unexplored collaborative platform, which should be critical among academic institutions and interprofessional disciplines. We recommend the establishment of a Comparative Dentistry Research Group under the International Association for Dental Research.
- As the One Health Initiative has started to influence the regulatory framework, the participation of government and private entities must be important. We recommend the establishment of a Comparative Dentistry Trial Consortium under the National Institute of Dental and Craniofacial Research.
- To facilitate future directions, the continuation of joint conferences may play a critical role in further strengthening our efforts.

Author Contributions

B. Arzi, A. Moshaverinia, and I. Nishimura, contributed to conception, drafted and critically revised the manuscript; F.J.M. Verstraete, N. Fiani, contributed to conception, critically revised. All authors gave final approval and agree to be accountable for all aspects of the work.

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3D Printing, Special Designs, and Beyond: Ben Wu (UCLA), Jay Jaynetti (UCLA), Ali Khademhosseini (Harvard), Jason Soukup (University of Wisconsin)

Oral Immune Disorders and Solutions: Boaz Arzi (UC Davis), Nasim Fazel (UC Davis)

Tissue Engineering and Stem Cells for Craniofacial and TMJ Defects: Alireza Moshaverinia (UCLA), Cun-yu Wang (UCLA), Jeremy Mao (Columbia)

Oral and Maxillofacial Cancer, Cysts and Clefts: José Ignacio Aguirre (University of Florida), Anahid Jewett (UCLA), Eric Carlson (University of Tennessee), Frank Verstraete (UC Davis), Santiago Peralta (Cornell), Arnaud Bewley (UC Davis)

Jaw Reconstruction and BMP Strategies: Frank Verstraete (UC Davis), Min Lee (UCLA), Alexander Reiter (University of

Pennsylvania), Homa Zadeh (University of Southern California)

Nanotechnology and Drug Delivery Systems: Ichiro Nishimura (UCLA), Varghese John (UCLA), Paul Weiss (UCLA), Wenyuan Shi (UCLA)

New Imaging and Diagnostic Technology and Design: David Hatcher (UC Davis; University of California, San Francisco), Derek Cissell (UC Davis)

Clinical and Translational Science: Ichiro Nishimura (UCLA), Susan Runner (Food and Drug Administration), Bernadette Dunham (George Washington University), Sherrill Macura (Food and Drug Administration), Chad Maki (VetCell Therapeutics), Reza Jarrahy (UCLA)

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