

UC Davis

UC Davis Previously Published Works

Title

The oromaxillofacial region as a model for a one-health approach in regenerative medicine.

Permalink

<https://escholarship.org/uc/item/8mh2m1bn>

Journal

American Journal of Veterinary Research, 83(4)

ISSN

0002-9645

Authors

Arzi, Boaz
Nolta, Jan A
Vapniarsky, Natalia

Publication Date

2022

DOI

10.2460/ajvr.21.12.0208

Peer reviewed

The oromaxillofacial region as a model for a one-health approach in regenerative medicine

Boaz Arzi, DVM^{1,2*}; Jan A. Nolta, PhD^{3,4}; Natalia Vapniarsky, DVM, PhD^{2,5}

¹Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California-Davis, Davis, CA

²Veterinary Institute for Regenerative Cures, School of Veterinary Medicine, University of California-Davis, Davis, CA

³Department of Cell Biology and Human Anatomy, School of Medicine, University of California-Davis, Davis, CA

⁴Institute for Regenerative Cures, School of Medicine, University of California-Davis, Davis, CA

⁵Department of Pathology, Microbiology and Immunology, School of Veterinary Medicine, University of California-Davis, Davis, CA

*Corresponding author: Dr. Arzi (barzi@ucdavis.edu)

<https://doi.org/10.2460/ajvr.21.12.0208>

ABSTRACT

The concept of a one-health approach in regenerative medicine has gained tremendous momentum in the scientific and public communities in recent years. Knowledge derived from this approach informs innovative biomedical research, clinical trials, and practice. The ultimate goal is to translate regenerative strategies for curing diseases and improving the quality of life in animals and people. Building and fostering strong and enthusiastic interdisciplinary and transdisciplinary collaboration between teams with a wide range of expertise and backgrounds is the cornerstone to the success of the one-health approach and translational sciences. The veterinarian's role in conducting clinical trials in client-owned animals with naturally occurring diseases is critical and unique as it may potentially inform human clinical trials. The veterinary regenerative medicine and surgery field is on a steep trajectory of discoveries and innovations. This manuscript focuses on oromaxillofacial-region regeneration to exemplify how the concept of interdisciplinary and transdisciplinary collaboration and the one-health approach influenced the authors' work experience at the University of California-Davis.

As we are adjusting to the new normal following a turbulent pandemic on the planet, we truly recognize the fundamental importance of a global perspective and approach to understanding and improving the health and well-being of people and animals.^{1,2} The concept of one health and the connection between human and animal health has never been so clear to understand and explain (**Figure 1**). The concept of one health, albeit with different terms, can be traced back in history. For example, Egyptian papyri treated human and animal diseases similarly to “the flock of God” in 1,800 BC.³ Another example is the Zhou Dynasty in China that developed an integrated public health system that included medical doctors and veterinarians in the 11th through 13th centuries.³ Fast forward to the 19th century and scientists such as Rudolf Virchow linked human and veterinary medicine as a form of comparative medicine based on discovering similarities in disease process between species.⁴ This concept of naturally occurring disease in animals that may serve as a model of human disease was also proposed by August Krogh, a winner of the Nobel Prize in Physiology or Medicine, in a *Science* paper in 1929.⁵ In this paper, he recognized the significance of naturally occurring diseases. Further, he emphasized that collaborative work with zoologists was critical.



Figure 1—An illustration of the oromaxillofacial region as a potential and promising model for a one-health global approach in regenerative medicine and tissue engineering.

When these concepts were realized in the 1950s, oncologic clinical trials in client-owned dogs with naturally occurring cancer were begun, and such trials are

currently at the forefront of novel anticancer therapeutics translational efforts.⁶⁻⁸ The valuable experience gained from using canine cancer models has inspired other disciplines. Specifically, regenerative medicine and tissue engineering integrate this approach to yield a more effective and rapid translation of novel discoveries to advance human and animal well-being.

The present narrative review focuses on the oromaxillofacial region as a potential and promising model for a one-health approach in regenerative medicine and tissue engineering (Figure 1). We will also reflect on our collective experience and achievements with interdisciplinary and transdisciplinary collaborations at the University of California-Davis.

Regenerative Medicine in Clinical Practice

A regenerative approach to inflammatory mucosal disease

Chronic oral mucosal inflammatory disorders occur in people and pets and are characterized by ulcerated and proliferative inflamed mucosa.⁹⁻¹¹ Typically, these lesions are chronic and result in considerable morbidity. Depending on the treatment, the lesions may be nonremissive. The diagnosis is usually made by clinical and histological examination in humans and pets.^{9,11}

In that context, our group has proposed feline chronic gingivostomatitis (FCGS) as a novel, naturally occurring disease model of human chronic oral inflammatory diseases (including oral lichen planus, stomatitis, oral Crohn disease, and pemphigus).^{12,13} However, while several similarities exist, we recognize the importance of not overlooking the differences between feline immune-mediated oral mucosal inflammatory disease and human autoimmune inflammatory disease. Regardless, it is plausible that regenerative therapies proven successful in cats may be beneficial to people with oral lichen planus, for example. Therefore, in the past 10 years, our transdisciplinary group embarked on a clinical trial in cats with nonresponsive FCGS using autologous or allogeneic, adipose-derived, mesenchymal stromal (stem) cells (ASCs) administered systemically.¹⁴⁻¹⁶

FCGS is a severe and painful oral inflammatory disease that has 2 phenotypes: ulcerative and proliferative. This condition is estimated to affect 0.7% to 12% of cats presented to veterinary practices and is typically managed by full-mouth tooth extractions or extraction of the premolar and molar teeth.¹⁷ However, about 30% of cats are refractory to treatment, requiring lifelong therapy with antibiotics, corticosteroids, and analgesics.¹⁸ Because the disease is typically debilitating, owners of severely affected cats refractory to treatment may elect euthanasia.¹⁷

Recent studies have illuminated part of the pathogenesis of FCGS. They suggested a complex and multifactorial immune-mediated mechanism led by CD8+ cytotoxic T cells that likely results from underlying viral disease (ie, calicivirus), loss of self-tolerance to antigens, and alterations in innate and adaptive immunity.^{19,20} Histologically, lesions in cats are characterized

by lymphocyte-rich inflammation with a predominance of effector T cells present primarily in the epithelial mucosa and B cells exclusively in the submucosa.¹⁹

The finding of the roles of T- and B-cell activation in FCGS and the knowledge that ASCs have a potent ability to downregulate immune cell activation drove our motivation to use ASCs to treat FCGS in 4 separate clinical trials.²¹⁻²⁴ In the first 3 trials, FCGS-affected cats with teeth previously extracted received 2 IV injections of 2×10^7 ASCs 4 weeks apart.¹⁴⁻¹⁶ In the first trial, 7 cats received autologous ASCs; in the second trial, 9 cats received unmatched, allogeneic ASCs from specific pathogen-free donor cats. In the third trial, we embarked on a multi-institutional pilot study that included both autologous and allogeneic ASCs and studied the potential of shipped ASCs to reproduce the success rate of the initial 2 trials. Finally, in the fourth trial, we examined the efficacy of allogeneic ASCs on FCGS cats prior to full-mouth tooth extractions (an early-intervention study).²⁵

In the first clinical trial (ie, autologous ASCs), we demonstrated safety and approximately 70% efficacy (Figure 2).¹⁵ Cats that responded to systemic ASC

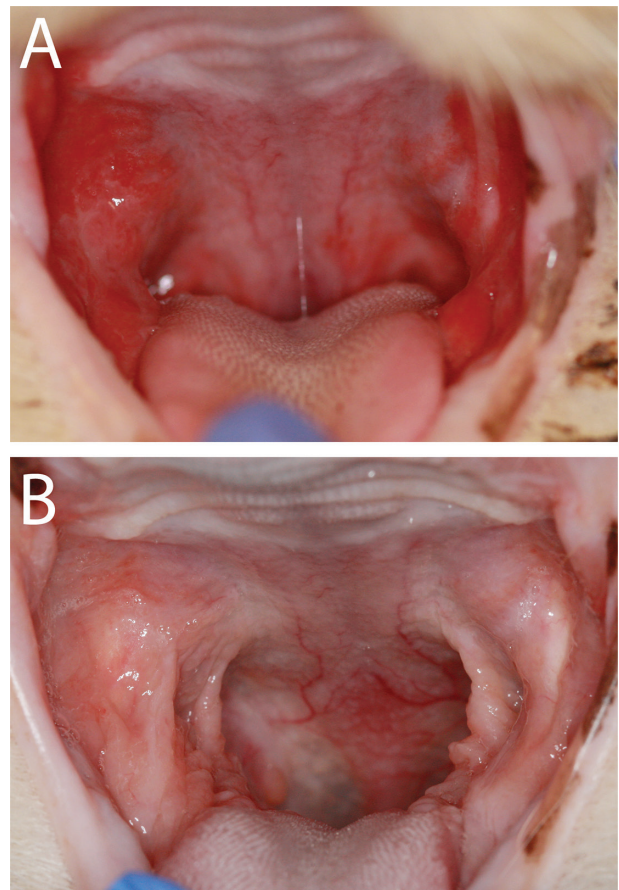


Figure 2—Photographs of a cat with nonresponsive feline chronic gingivostomatitis (A) that was enrolled in a clinical trial, received 2 IV injections of 2×10^7 ASCs 4 weeks apart, and responded with a cure (B). (Adapted from Quimby JM, Borjesson DL. Mesenchymal stem cell therapy in cats: current knowledge and future potential. *J Feline Med Surg*. 2018;20[3]:208–216. Reprinted with permission.)

therapy exhibited either complete clinical resolution or a substantial reduction in clinical disease severity complemented by histological resolution or profound improvement of the oral lesions. We detected reduction of total circulating CD8+ T cells, resolution of neutrophilia, and reduction of serum proinflammatory cytokines (IL-1 β and IFN γ). This initial study demonstrated the clinical potential of ASCs as a therapeutic method for oral inflammatory lesions.

An unexpected discovery was made during the initial phase of the clinical trials. Approximately 50% of the cell lines obtained from the fat of cats developed giant foamy multinucleated cells (syncytial cells).¹² These alterations were associated with proliferation arrest and death of the cells, rendering them unsuitable for autologous application. We determined that syncytial cell formation and proliferation arrest were caused by the feline foamy virus, a spuma-retrovirus present in approximately 50% of cats.¹² Upon expansion of ASCs, the virus becomes active and its proliferation induces a cytopathic effect in the cell cultures, slowing down and eventually hindering ASC proliferation. This unexpected discovery hindered the large-scale expansion of autologous ASCs and inspired us to embark on an allogeneic ASC clinical trial.

In the second clinical trial, we investigated the use of fresh allogeneic ASCs for treatment of FCGS in a similar fashion as was done in the first trial.¹⁴ We also radiolabeled the cells and tracked them systemically. We demonstrated that allogeneic ASCs administered systemically are safe and have approximately 57% clinical efficacy and that clinical resolution took longer, compared with the autologous ASCs clinical trial. The radiolabel tracking revealed that most cells were entrapped by the lungs promptly after administration, as was observed by other groups.^{14,26-28} A higher fraction of radiolabeled cells were identified in the oral cavity of FCGS-affected cats, compared with healthy control cats.^{14,26-28} We concluded that fresh allogeneic ASCs are safe but appear to have lower clinical efficacy with a delayed response as compared with autologous ASCs and that the mechanism of action for autologous and allogeneic ASCs may differ in this model of oral inflammation.¹⁴

In the third trial, we expanded our work to multicenter settings. We determined that feline ASCs can be commercially shipped to distant locations while maintaining their viability, function, and phenotype.¹⁶ Here, we reproduced our findings and demonstrated that shipped feline ASCs administered systemically resulted in favorable clinical, histological, and systemic responses in approximately 70% of cats with FCGS. We repeatedly confirmed that ASCs induced immunomodulation in cats with chronic oral mucosal inflammatory lesions characterized by CD8+ T-cell inflammation and T-cell activation.¹⁶

Finally, a clinical question was raised: can we treat cats with ASCs as an early intervention and avoid full-mouth tooth extractions? Inspired by this question, we performed a pilot study on 5 cats with FCGS before tooth extractions. We adhered to the same approach as in the previous 3 studies.²⁵ While the treatment was determined to be clinically

safe, we did not observe a meaningful clinical response. Furthermore, none of the cats exhibited immune modulation, as noted in the previous studies. We concluded that systemic administration of ASCs before full-mouth tooth extraction lacks substantial clinical efficacy, and we do not recommend it at this time.²⁵

Apart from the clinical ramifications of these trials on feline health, our group investigated the mechanisms of ASC immune modulation with the prospect of translating these findings to a clinical trial in human patients suffering from oral inflammatory conditions, such as lichen planus. We found that feline ASCs modulate lymphocyte proliferation through soluble mediators that mirror human ASC secretion patterns.²⁹ We determined that feline ASCs have similar gene expression profiles to human ASCs, as revealed by transcriptome analysis (unpublished data). In a different study, we demonstrated that feline ASCs utilize PGE₂ and an intracellular adhesion molecule-1/leukocyte function-associated antigen-1 ligand interaction to inhibit T-cell proliferation with a resultant cell cycle arrest in G0-G1.³⁰ These data elucidate some of the mechanisms by which feline ASCs interact with T cells and help define other T cell-mediated disease targets in cats that may be amenable to ASC therapy. These data will also inform human clinical trials in regenerative medicine.

Regeneration of critical-size mandibular bone defects

Regenerating critical-size mandibular bone defects in dogs has received attention from the medical community and the general public in the past several years.³¹⁻³⁵ Mandibular critical-size defects typically occur due to trauma or amputation secondary to cancer or as a sequela of severe periodontitis. The ideal treatment to restore jaw functionality and the patient's well-being is to provide anatomically correct mandibular reconstruction. The latter can potentially be achieved through bone regeneration to allow appropriate biomechanics and pain-free mastication. The use of recombinant human bone morphogenetic protein 2 (rhBMP-2) delivered via absorption onto collagen matrices has been FDA approved for spinal fusion and for some dental applications. Based on selected reports describing extralabel use of rhBMP-2 for mandibular reconstruction in humans^{36,37} and anecdotal reports on its use in dogs,^{33,38} our group has refined and instituted the routine use of rhBMP-2 in dogs. The strategy we developed was used in canine patients following tumor excision, defect nonunion fractures, and trauma necessitating mandibular reconstruction (**Figure 3**). In our work, the use of rhBMP-2 applied onto a scaffold has been highly successful and predictable for bone regeneration. Dogs experiencing naturally occurring mandibular defects, similar to human conditions, may be instrumental in refining techniques, understanding the regenerative process, and obtaining valuable information on potential complications. Lessons learned in canine patients can pave the road toward solving this intractable problem in humans.

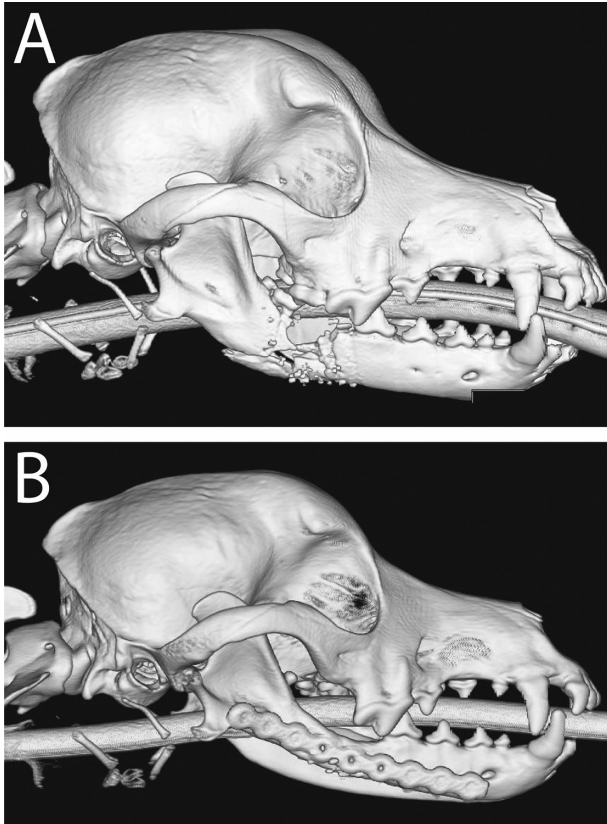


Figure 3—Reconstructed CT images of a dog that sustained a gunshot injury to its right mandible, creating a critical-size bone defect (A). The injury and bone defect were repaired with a regenerative approach with a titanium locking miniplate and recombinant human bone morphogenetic protein-2 infused on a compression-resistant matrix (ie, scaffold), resulting in complete regeneration and remodeling of the mandibular defect (B)

The temporomandibular joint

Laboratory animals are traditionally used as models for temporomandibular joint (TMJ) research and are crucial to the study of basic disease mechanisms and potential therapeutics.³⁹ With that in mind, TMJ disorders such as degenerative joint disease, osteoarthritis, septic arthritis, and ankylosis seen in the TMJ of companion animals may better reflect the disease complexity. Specifically, factors such as genetic diversity and the environmental and physiological effects that play a role in the disease's pathogenesis may be very similar in companion animals sharing the same habitat as their human owners.³⁹ In addition, the medical standards of care, surgical approaches, and specialist training in humans and companion animals have many similarities.²

We studied naturally occurring TMJ disorders in companion animals for over 10 years. We discovered that degenerative TMJ disease is the most common TMJ disorder in dogs and the second most common in cats.⁴⁰ Importantly, the clinical manifestation of TMJ degeneration in dogs and cats is very similar if not identical to that seen in humans (**Figure 4**).^{41,42} In both dogs and people, clinical signs may not correlate with the presence and severity of CT



Figure 4—Computed tomographic images of the temporomandibular joint of a human (A) and a dog (B) that both had chondral and subchondral bone defects in the mandibular head of the condylar process, demonstrating that degenerative or arthritic changes of the temporomandibular joint in dogs are similar if not identical to those seen in humans.

findings. This is clinically relevant, as regenerative therapeutics for improving TMJ degeneration can be used in clinically affected dogs on a clinical trial basis and may provide an excellent model based on the information elaborated on earlier. However, as in other models of diseases, there are anatomical and structure-function differences between dogs and humans, such as the thin and relatively poorly developed TMJ disk in dogs, the kinematic of the joint, and the joint space limitation in dogs.³⁹ Other disorders of the TMJ in dogs and cats that may be excellent candidates for regenerative solutions that are similar to conditions in humans include fractures and septic arthritis.

Challenges of a One-Health Approach in Regenerative Medicine

Diversity is innate to all species, and with that in mind, all naturally occurring animal models have limitations. Our regenerative work is no exception, and results from the clinical trials should always be interpreted with caution regarding the predictive value for translation. For example, multiple breeds of dogs or cats from various geographic locations and backgrounds increase variability and would require

longer study time for recruiting cases, execution of the study, and follow-up time. Specifically for regenerative medicine, there is also known variability in cell function between species.^{30,43} These limitations are difficult to overcome.

Veterinary clinical trials focus on providing a therapeutic solution to companion animals and may not be designed with considerations of informing human clinical trials. Many trials also lack statistical power, randomization, appropriate control groups, and blinding. There is also a tendency to report such studies as a pilot study with no follow-up. These deficiencies may discourage funding agencies from supporting veterinary clinical trials that are based on the concept of a one-health approach and give a base for a critique on using naturally occurring animal models for translation.

Finally, not all diseases that naturally occur in animals have human counterparts. For example, human diseases that are a major cause of morbidity and mortality such as coronary heart disease, Parkinson disease, and Huntington disease do not currently have a naturally occurring animal model.²

Ethical Considerations

First and foremost, providing regenerative therapeutics to animals with naturally occurring disease should aim to benefit the animal. With cutting-edge innovative work that is often experimental, we emphasize the ethical aspects of protecting both pets and their owners. In addition, like clinical trials in children or incapacitated adults, pets depend on their owners to make medical decisions on their behalf and to accept or decline a clinical trial or experimental treatment.^{2,44}

Although the regulations and standards are well-defined for humans and laboratory animals, the rules on clinical research in client-owned animals are not as clear.⁴⁴ To address this shortcoming, the AVMA has put forth a clear policy statement. It states that clinical veterinary research should be conducted with oversight ensuring the safe and ethical treatment of veterinary patients while providing appropriate disclosure to and soliciting informed consent from clients.⁴⁵ In this regard, each clinical trial involving client-owned animals should be thoroughly reviewed by an institutional animal care and use committee and a clinical trial review board. Clients should clearly understand their role and sign an informed consent form. Finally, all available diagnostic and treatment options, risks, benefits, and prognoses should be explained, and conflicts of interests must be disclosed. Importantly, economically challenged pet owners should not be exploited. All possible standard-of-care treatment options should be available to their pets before enrolling in a clinical trial.

Future Opportunities

As was discussed at the beginning of this review, it is now more apparent than ever that a one-health

approach to medicine recognizes the interconnectedness of human and animal health. The latter should be leveraged by academic and funding entities to foster stronger interdisciplinary and transdisciplinary collaborations between teams with a wide range of expertise and backgrounds. Importantly, since these aspects begin with appropriate education, including clinical research in veterinary training, curricula should strengthen the role and impact of veterinary medicine in the one-world, one-health approach. Looking beyond the horizon, creating dual-degree educational programs for veterinary and human medicine degrees may produce a new group of clinician-scientists who can lead the one-health approach. Dual-degree training programs such as MD-PhD and DVM-PhD are already being offered at multiple institutions. Also, postgraduate research training fellowships and career development awards are effectively solicited by the NIH.

Creating innovative and visionary symposia focusing on specific areas of clinical research is of strategic benefit. For example, the Craniomaxillofacial Disorders and Solutions in Humans and Animals Symposium created among leaders in the field from the University of California-Davis, University of California-Los Angeles, and Cornell University gathered professionals working in the field of oromaxillofacial disorders such as veterinarian clinician-scientists, basic scientists, biomedical engineers, physicians, and dentists.⁴⁶ This symposium was an outstanding display of networking and collaborations that resulted in new and translational collaborations and therapy developments. Another multidisciplinary example that works in the spirit of one health is the Temporomandibular Joint Bioengineering Conference, which comprises an international forum of bioengineers, scientists, physicians, and veterinarians aiming to advance technology and therapy related to TMJ disorders in humans and animals.⁴⁷ There are already several other symposia such as the Integrated Human and Veterinary Aerodigestive Team Symposium, the Joint Human and Veterinary Cardiology Symposium, and the Zoobiquity conference. These team symposia have proven to be exceptional forums for developing and fostering collaborations and engaging colleagues outside their narrow disciplinary community.

Finally, to overcome the challenges of supporting the one-health approach in regenerative medicine, it is the task of the leaders in the field to steer public opinion and raise public awareness. Changes in public opinion may, in turn, encourage major funding entities such as various institutions of the NIH, the California Institute for Regenerative Medicine, and the Department of Defense in supporting multi-institutional companion animal clinical trials led by transdisciplinary regenerative medicine research teams.

Conclusions

In recent years, we have witnessed substantial advances in veterinary regenerative medical research

and clinical trials. Approaching this work from the perspective of one health is instrumental for improving the lives of animals and humans. Veterinarian clinician-scientists have a strategic role in forming and fostering interdisciplinary and transdisciplinary collaborations. Incorporating veterinary regenerative clinical trials on novel therapeutic approaches may provide unique predictive data and accelerate the development of drugs that address pressing needs in human health. Importantly, advocating for funding from local and government agencies to support these clinical trials led by transdisciplinary regenerative medicine research teams is of major importance.

Acknowledgments

The authors thank Dr. Chrisoula Toupadakis Skouritakis for assistance with the illustrations and figures and Drs. Alireza Moshaverinia, David Hatcher, Arnaud F. Bewley, and Nsim Fazel for contributing images.

The authors report no conflicts of interest related to this report.

References

- Conrad PA, Meek LA, Dumit J. Operationalizing a One Health approach to global health challenges. *Comp Immunol Microbiol Infect Dis*. 2013;36(3):211–216.
- Kol A, Arzi B, Athanasiou KA, et al. Companion animals: translational scientist's new best friends. *Sci Transl Med*. 2015;7(308):308ps21. doi:10.1126/scitranslmed.aaa9116
- Zinsstag J, Schelling E, Waltner-Toews D, Tanner M. From “one medicine” to “one health” and systemic approaches to health and well-being. *Prev Vet Med*. 2011;101(3-4):148–156.
- Conrad PA, Mazet JA, Clifford D, Scott C, Wilkes M. Evolution of a transdisciplinary “One Medicine-One Health” approach to global health education at the University of California, Davis. *Prev Vet Med*. 2009;92(4):268–274.
- Krogh A. The progress of physiology. *Science*. 1929;70(1809):200–204.
- McCoy JR. Trial of chemotherapeutic agents in spontaneous tumors in dogs. *Ann N Y Acad Sci*. 1958;76(3):850–853; discussion 853–854.
- Pursell RT. Treatment of cancer in dogs by intravenous methylene blue. *Nature*. 1957;180(4597):1300. doi:10.1038/1801300a0
- Paoloni M, Khanna C. Translation of new cancer treatments from pet dogs to humans. *Nat Rev Cancer*. 2008;8(2):147–156.
- Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: a literature review and update. *Arch Dermatol Res*. 2016;308(8):539–551.
- Lee DB, Verstraete FJM, Arzi B. An update on feline chronic gingivostomatitis. *Vet Clin North Am Small Anim Pract*. 2020;50(5):973–982.
- Lommer MJ. Oral inflammation in small animals. *Vet Clin North Am Small Anim Pract*. 2013;43(3):555–571.
- Arzi B, Kol A, Murphy B, et al. Feline foamy virus adversely affects feline mesenchymal stem cell culture and expansion: implications for animal model development. *Stem Cells Dev*. 2015;24(7):814–823.
- Arzi B, Murphy B, Cox DP, Vapniarsky N, Kass PH, Verstraete FJ. Presence and quantification of mast cells in the gingiva of cats with tooth resorption, periodontitis and chronic stomatitis. *Arch Oral Biol*. 2010;55(2):148–154.
- Arzi B, Clark KC, Sundaram A, et al. Therapeutic efficacy of fresh, allogeneic mesenchymal stem cells for severe refractory feline chronic gingivostomatitis. *Stem Cells Transl Med*. 2017;6(8):1710–1722.
- Arzi B, Mills-Ko E, Verstraete FJ, et al. Therapeutic efficacy of fresh, autologous mesenchymal stem cells for severe refractory gingivostomatitis in cats. *Stem Cells Transl Med*. 2016;5(1):75–86.
- Arzi B, Peralta S, Fiani N, et al. A multicenter experience using adipose-derived mesenchymal stem cell therapy for cats with chronic, non-responsive gingivostomatitis. *Stem Cell Res Ther*. 2020;11(1):115. doi:10.1186/s13287-020-01623-9
- Winer JN, Arzi B, Verstraete FJ. Therapeutic management of feline chronic gingivostomatitis: a systematic review of the literature. *Front Vet Sci*. 2016;3:54. doi:10.3389/fvets.2016.00054
- Jennings MW, Lewis JR, Soltero-Rivera MM, Brown DC, Reiter AM. Effect of tooth extraction on stomatitis in cats: 95 cases (2000–2013). *J Am Vet Med Assoc*. 2015;246(6):654–660.
- Vapniarsky N, Simpson DL, Arzi B, et al. Histological, immunological, and genetic analysis of feline chronic gingivostomatitis. *Front Vet Sci*. 2020;7:310. doi:10.3389/fvets.2020.00310
- Fried WA, Soltero-Rivera M, Ramesh A, et al. Use of unbiased metagenomic and transcriptomic analyses to investigate the association between feline calicivirus and feline chronic gingivostomatitis in domestic cats. *Am J Vet Res*. 2021;82(5):381–394.
- Carrade DD, Lame MW, Kent MS, Clark KC, Walker NJ, Borjesson DL. Comparative analysis of the immunomodulatory properties of equine adult-derived mesenchymal stem cells. *Cell Med*. 2012;4(1):1–11. doi:10.3727/215517912X647217
- Mata M, Vera JF, Gerken C, et al. Toward immunotherapy with redirected T cells in a large animal model: ex vivo activation, expansion, and genetic modification of canine T cells. *J Immunother*. 2014;37(8):407–415.
- Nasef A, Mathieu N, Chapel A, et al. Immunosuppressive effects of mesenchymal stem cells: involvement of HLA-G. *Transplantation*. 2007;84(2):231–237.
- Rodríguez-Fuentes DE, Fernández-Garza LE, Samia-Meza JA, Barrera-Barrera SA, Caplan AI, Barrera-Saldaña HA. Mesenchymal stem cells current clinical applications: a systematic review. *Arch Med Res*. 2021;52(1):93–101.
- Arzi B, Taechangam N, Lommer MJ, Walker NJ, Loscar MR, Borjesson DL. Stem cell therapy prior to full-mouth tooth extraction lacks substantial clinical efficacy in cats affected by chronic gingivostomatitis. *J Feline Med Surg*. 2021;23(6):604–608.
- Saat TC, van den Engel S, Bijman-Lachger W, et al. Fate and effect of intravenously infused mesenchymal stem cells in a mouse model of hepatic ischemia reperfusion injury and resection. *Stem Cells Int*. 2016;2016:5761487. doi:10.1155/2016/5761487
- Spiet M, Hunt GB, Walker NJ, Borjesson DL. Scintigraphic tracking of mesenchymal stem cells after portal, systemic intravenous and splenic administration in healthy Beagle dogs. *Vet Radiol Ultrasound*. 2015;56(3):327–334.
- de Witte SFH, Luk F, Sierra Parraga JM, et al. Immunomodulation by therapeutic mesenchymal stromal cells (MSC) is triggered through phagocytosis of MSC by monocytic cells. *Stem Cells*. 2018;36(4):602–615.
- Clark KC, Fierro FA, Ko EM, et al. Human and feline adipose-derived mesenchymal stem cells have comparable phenotype, immunomodulatory functions, and transcriptome. *Stem Cell Res Ther*. 2017;8(1):69. doi:10.1186/s13287-017-0528-z
- Taechangam N, Iyer SS, Walker NJ, Arzi B, Borjesson DL. Mechanisms utilized by feline adipose-derived mesenchymal stem cells to inhibit T lymphocyte proliferation. *Stem Cell Res Ther*. 2019;10(1):188. doi:10.1186/s13287-019-1300-3
- Arzi B, Verstraete FJ, Huey DJ, Cissell DD, Athanasiou KA. Regenerating mandibular bone using rhBMP-2: part 1-

- immediate reconstruction of segmental mandibulectomies. *Vet Surg*. 2015;44(4):403–409.
32. Verstraete FJ, Arzi B, Huey DJ, Cissell DD, Athanasiou KA. Regenerating mandibular bone using rhBMP-2: part 2-treatment of chronic, defect non-union fractures. *Vet Surg*. 2014;44(4):410–416.
 33. Boudrieau RJ. Initial experience with rhBMP-2 delivered in a compressive resistant matrix for mandibular reconstruction in 5 dogs. *Vet Surg*. 2014;44(4):443–458.
 34. Freinkel S. Rebuilding our badly broken pets. The New York Times Well Blog. Accessed February 2, 2022. https://well.blogs.nytimes.com/2014/01/13/rebuilding-our-badly-broken-pets/?_php=true&_type=blogs&r=2
 35. Arzi B, Cissell DD, Pollard RE, Verstraete FJ. Regenerative approach to bilateral rostral mandibular reconstruction in a case series of dogs. *Front Vet Sci*. 2015;2:4. doi:10.3389/fvets.2015.00004
 36. Cicciú M, Herford AS, Cicciú D, Tandon R, Maiorana C. Recombinant human bone morphogenetic protein-2 promote and stabilize hard and soft tissue healing for large mandibular new bone reconstruction defects (Erratum published in *J Craniofac Surg*. 2014;25[4]:1563). *J Craniofac Surg*. 2014;25(3):860–862.
 37. Herford AS, Boyne PJ. Reconstruction of mandibular continuity defects with bone morphogenetic protein-2 (rhBMP-2). *J Oral Maxillofac Surg*. 2008;66(4):616–624.
 38. Boudrieau RJ, Mitchell SL, Seeherman H. Mandibular reconstruction of a partial hemimandibulectomy in a dog with severe malocclusion. *Vet Surg*. 2004;33(2):119–130.
 39. Almarza AJ, Brown BN, Arzi B, et al. Preclinical animal models for temporomandibular joint tissue engineering. *Tissue Eng Part B Rev*. 2018;24(3):171–178.
 40. Arzi B, Cissell DD, Verstraete FJ, Kass PH, DuRaine GD, Athanasiou KA. Computed tomographic findings in dogs and cats with temporomandibular joint disorders: 58 cases (2006–2011). *J Am Vet Med Assoc*. 2013;242(1):69–75.
 41. Lin AW, Vapniarsky N, Cissell DD, et al. The temporomandibular joint of the domestic dog (*Canis lupus familiaris*) in health and disease. *J Comp Pathol*. 2018;161:55–67.
 42. McKay RM, Vapniarsky N, Hatcher D, et al. The diagnostic yield of cone-beam computed tomography for degenerative changes of the temporomandibular joint in dogs. *Front Vet Sci*. 2021;8:720641. doi:10.3389/fvets.2021.720641
 43. Arzi B, Koch TG, Volk SW, et al. Cell therapy in veterinary medicine as a proof-of-concept for human therapies: perspectives from the North American Veterinary Regenerative Medicine Association. *Front Vet Sci*. 2021;8:779109. doi:10.3389/fvets.2021.779109
 44. Bertout JA, Baneux PJR, Robertson-Plouch CK. Recommendations for ethical review of veterinary clinical trials. *Front Vet Sci*. 2021;8:715926. doi:10.3389/fvets.2021.715926
 45. Establishment and use of Veterinary Clinical Studies Committees. AVMA. Accessed February 2, 2022. <https://www.avma.org/resources-tools/avma-policies/establishment-and-use-veterinary-clinical-studies-committees>
 46. Arzi B, Moshaverinia A, Verstraete FJM, Fiani N, Nishimura I. Craniomaxillofacial disorders and solutions in humans and animals. *J Dent Res*. 2018;97(4):364–370.
 47. Almarza AJ, Mercuri LG, Arzi B, et al. Temporomandibular Joint Bioengineering Conference: working together toward improving clinical outcomes. *J Biomech Eng*. 2020;142(2):020801. doi:10.1115/1.4044090