



4-2015

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### Recommended Citation

Hajishengallis, G., Lamont, R. J., & Graves, D. T. (2015). The Enduring Importance of Animal Models in Understanding Periodontal Disease. *Virulence*, 6 (3), 229-235. <http://dx.doi.org/10.4161/21505594.2014.990806>

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# The Enduring Importance of Animal Models in Understanding Periodontal Disease

## Abstract

Whereas no single animal model can reproduce the complexity of periodontitis, different aspects of the disease can be addressed by distinct models. Despite their limitations, animal models are essential for testing the biological significance of in vitro findings and for establishing cause-and-effect relationships relevant to clinical observations, which are typically correlative. We provide evidence that animal-based studies have generated a durable framework for dissecting the mechanistic basis of periodontitis. These studies have solidified the etiologic role of bacteria in initiating the inflammatory response that leads to periodontal bone loss and have identified key mediators (IL-1, TNF, prostaglandins, complement, RANKL) that induce inflammatory breakdown. Moreover, animal studies suggest that dysbiosis, rather than individual bacterial species, are important in initiating periodontal bone loss and have introduced the concept that organisms previously considered commensals can play important roles as accessory pathogens or pathobionts. These studies have also provided insight as to how systemic conditions, such as diabetes or leukocyte adhesion deficiency, contribute to tissue destruction. In addition, animal studies have identified and been useful in testing therapeutic targets.

## Keywords

animal models, dysbiosis, immune subversion, inflammation, periodontitis, systemic disease

## Disciplines

Dentistry

# The enduring importance of animal models in understanding periodontal disease

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Whereas no single animal model can reproduce the complexity of periodontitis, different aspects of the disease can be addressed by distinct models. Despite their limitations, animal models are essential for testing the biological significance of *in vitro* findings and for establishing cause-and-effect relationships relevant to clinical observations, which are typically correlative. We provide evidence that animal-based studies have generated a durable framework for dissecting the mechanistic basis of periodontitis. These studies have solidified the etiologic role of bacteria in initiating the inflammatory response that leads to periodontal bone loss and have identified key mediators (IL-1, TNF, prostaglandins, complement, RANKL) that induce inflammatory breakdown. Moreover, animal studies suggest that dysbiosis, rather than individual bacterial species, are important in initiating periodontal bone loss and have introduced the concept that organisms previously considered commensals can play important roles as accessory pathogens or pathobionts. These studies have also provided insight as to how systemic conditions, such as diabetes or leukocyte adhesion deficiency, contribute to tissue destruction. In addition, animal studies have identified and been useful in testing therapeutic targets.

## Introduction

Animal models for the study of human disease have limitations that are inherent in the very definition of the term “model,” *i.e.*, an approximation or simulation of a real system that is under investigation. It is thus obvious that no one single model reproduces all aspects of a human disease. However, the strengths of animal models more than compensate for the simulation. First, cause-and-effect relationships can be tested conclusively in animal models but are difficult to prove in human studies.

Moreover, results from animal studies provide initial information on the safety and potential efficacy of novel therapeutic compounds. Furthermore, animal models have less serious limitations than *in vitro* models, which cannot replicate the complexity of cross-interactions that occur between the immune response, the microbiome, and the host tissue. The appropriateness of a given animal model lies in its capacity to test a specific hypothesis rather than its fidelity to all aspects of disease pathogenesis. Therefore, different models of the same disease can be used to test discrete aspects of its pathogenesis.<sup>1</sup> In essence, animal models represent a point on a spectrum of assay systems that span the more experimentally tractable *in vitro* models, through the biological complexity of animals, to clinically valid human studies (Fig. 1).

The most common periodontitis models involve procedures for oral gavage and placement of ligatures. The reader is referred to previous publications for a detailed description of these models and their successful application in a large number of studies.<sup>1–3</sup> Briefly, in the oral gavage model, gingival inflammation and bone loss can be induced following oral inoculation with bacteria associated with human periodontitis. In the ligature-induced periodontitis model, the placement of silk ligatures around posterior teeth facilitates local accumulation of indigenous bacteria and enhances bacteria-mediated gingival inflammation and bone loss. Although irrelevant for studying bone loss, the so-called “chamber” and “abscess” models have been used to study specific virulence aspects of periodontal organisms *in vivo*. In the chamber model, bacteria are injected into the lumen of a subcutaneously implanted titanium-coil chamber and *in vivo* bacterial interactions with recruited inflammatory cells can be assessed accurately and quantitatively.<sup>1,4,5</sup> In the abscess model, bacteria are injected subcutaneously into the dorsum and then scored for impact on systemic health or localized abscess characteristics.<sup>6,7</sup>

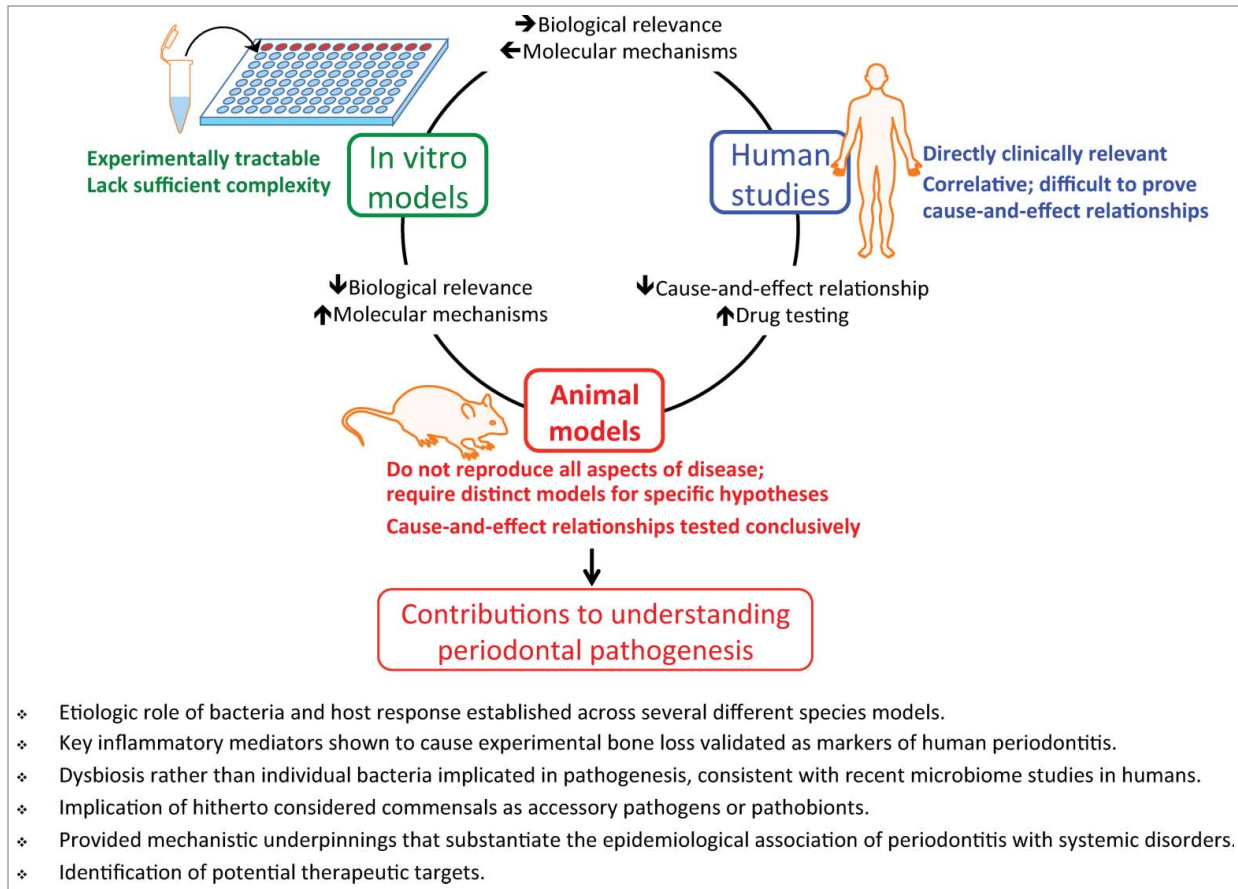
It is now well established that periodontitis is triggered by pathogenic microbial communities forming on subgingival tooth surfaces while the host response is responsible for the tissue damage in periodontitis; moreover, systemic conditions have an impact on periodontal disease by affecting pathologic mechanisms and host immune status.<sup>8,9</sup> Animal studies have greatly contributed to these critical principles which have been reproduced across several different animal species models demonstrating a consistency that lends support for the validity of the overall concept, as well as the utility of animal models to study periodontal disease processes. The latter reflects the enduring usefulness of *in vivo* studies.

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Submitted: 10/13/2014; Revised: 11/17/2014; Accepted: 11/19/2014  
<http://dx.doi.org/10.4161/21505594.2014.990806>

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**Figure 1.** Animal models of periodontitis: characteristics and contributions. Animal models are contrasted with in vitro models and human studies in terms of their advantages and disadvantages, followed by a summary of key animal model-based contributions to understanding periodontal disease pathogenesis. It should be noted, however, that animal model-based research benefits from both in vitro models and human studies for obtaining mechanistic insights in finer molecular detail and for determining clinical relevance, respectively. The cycle connecting the 3 experimental systems is meant to demonstrate this interrelationship. For instance, the arrows emanating from “Animal models” and “Human studies” to “In vitro models” indicate the reliance of the former systems on the more tractable in vitro system for dissecting plausible molecular mechanisms. Conversely, the reverse arrows indicate that in vitro model-based mechanisms depend on animal and human systems for testing potential biological relevance. One of the greatest contributions of animal models is the testing of cause-and-effect relationships that cannot be typically addressed in human studies, most of which are correlative. Conversely, candidate drugs identified in animal models require the ultimate test in human clinical trials before they can be validated and enter the clinic.

We will review studies that have provided a durable framework for understanding periodontal disease, as well as the most common and important issues that have been raised over the years with regard to the relevance of animal models, in particular mice which are widely used in mechanistic studies. Moreover, we will discuss whether these models maintain the potential to generate further knowledge for an in-depth understanding of periodontal disease pathogenesis.

### The Role of Bacteria

The concept that bacteria are an important etiologic factor in periodontal tissue destruction first came from studies of gnotobiotic rats and gnotobiotic mice.<sup>10,11</sup> The role of bacteria was further demonstrated by topical application of antiseptics or systemic application of antibiotics reducing bone loss in animal

models involving dogs, mice, rats and non-human primates.<sup>12-15</sup> The role of bacteria is further supported by findings that osteoclastogenesis and alveolar bone resorption are enhanced by the application of bacteria.<sup>16,17</sup> Thus loss of function (gnotobiotic animals or use of anti-bacterials) and gain of function (the addition of bacteria) in a number of animal models (non-human primates, dogs, mice and rats) consistently establish a common role of bacteria in initiating the disease process.

More recently, mouse models have additionally facilitated a complete reappraisal of the role of certain organisms, such as *Streptococcus gordonii*, which have traditionally been considered as oral commensals. In vitro evidence indicates that *S. gordonii* can contribute to community pathogenicity by providing an attachment substratum for colonization by *P. gingivalis*.<sup>18</sup> Hence co-infection with *S. gordonii* and *P. gingivalis* in vivo would be predicted to enhance both *P. gingivalis* colonization and alveolar bone loss compared to mono-infection with *P. gingivalis*. Results

from the oral gavage model support these predictions. Moreover, blocking attachment of *P. gingivalis* to *S. gordonii* ameliorates bone loss, thus opening a new avenue of research into therapeutic agents in periodontal disease.<sup>19,20</sup>

In the murine abscess model, bacteria are delivered directly into the animal without the need for specialized colonization factors and the alveolar bone is not involved. Despite the limited applicability for periodontitis, the model does allow assessment of an organism's ability to resist immune killing, grow in vivo, and spread systemically. A recent successful use of the abscess model was to establish synergistic interactions between *S. gordonii* and *Aggregatibacter actinomycetemcomitans*. In vitro, growth of *A. actinomycetemcomitans* is enhanced through utilization of L-lactate produced as a metabolic by-product by *S. gordonii*.<sup>21</sup> In order for *A. actinomycetemcomitans* to cross-feed with *S. gordonii*, it produces catalase by which it overcomes the adverse effects of hydrogen peroxide released extracellularly by oral streptococci. The murine abscess model not only confirmed the importance of catalase but also established that dispersin B (DspB), an enzyme that dissolves *A. actinomycetemcomitans* biofilms, is necessary for nutritional synergism between *A. actinomycetemcomitans* and *S. gordonii*.<sup>22</sup> Specifically, 3D image analysis of the abscess material revealed that DspB is required for an optimal spatial organization of *A. actinomycetemcomitans* cells at >4  $\mu\text{m}$  from *S. gordonii* cells, a distance that minimizes exposure to peroxide but allows access to L-lactate. Hence, provided the experimental questions are framed to fit the model system, even a rudimentary model such as abscess formation can provide valuable in vivo verification of processes identified in vitro.

A potential issue regarding the use of mouse models to study periodontal disease pathogenesis is that the periodontitis-associated microbiotas in mice and humans differ considerably. However, this is not a prohibitive factor for using mouse models since periodontitis is fundamentally a dysbiotic inflammatory disease precipitated by disruption of host-microbe homeostasis.<sup>9,23</sup> Dysbiosis is not dependent so much on the particular microbial roster but rather on the specific gene combinations or collective virulence activity within the altered microbial community.<sup>24,25</sup> This notion is supported by a recent metatranscriptomic study which showed that disease-associated microbial communities exhibit conserved metabolic and virulence gene expression profiles, despite high inter-patient variability in terms of microbial composition.<sup>26</sup> Therefore, a conserved periodontitis-associated microbiota is not a requirement for the pathogenesis of human periodontitis. This realization and the fact that periodontitis is not uniquely a human disease<sup>27</sup> and involves common pathogenic mechanisms among different mammalian species (see above) validates the use of animal models to study periodontitis. In a similar context, intestinal health requires maintaining a balance between the colonic epithelium, the immune system, and the resident microbiota, whereas the breakdown of this homeostatic relationship leads to inflammatory bowel disease (IBD).<sup>28</sup> As with periodontitis, this concept confers relevance to the use of mice as models for IBD pathogenesis despite the differences between the mouse and human microbiotas.

Animal models can also provide insights into better understanding of data from human microbiome studies. A recent study

in the murine oral gavage model has shown that the oral commensal microbiota is absolutely required for induction of inflammatory bone loss by *P. gingivalis*, which has traditionally been considered a causative agent in human periodontitis.<sup>29</sup> Such commensals can act as pathobionts in a dysbiotic microbial community,<sup>30,31</sup> and in human periodontitis are likely represented by hitherto underappreciated species that have now been shown to have as good or better a correlation with disease as *P. gingivalis* (or other long-established pathogens).<sup>32-35</sup> Therefore, a concept first established in mice is consistent with and has explanatory power for results obtained from metagenomic analyses of human periodontitis. Moreover, the commensal-turned-pathobiont concept is supported by a recent metatranscriptomic study, which revealed that a plethora of virulence factors upregulated in the microbiome of periodontitis patients is primarily derived from the previously underappreciated species that were not traditionally associated with periodontitis.<sup>36</sup>

## The Role of the Host Immune Response

A controversy that has flared from time to time in the annals of periodontal research involves the role of the host response in periodontal destruction. That the host response and elements of innate or adaptive immunity can be protective has been shown by several studies. For instance, immunization of gnotobiotic rats against *P. gingivalis*, protects against bone loss induced by inoculation of this bacterium<sup>37</sup> as does immunization in non-human primates and in mice.<sup>38-41</sup> Similar results have been obtained by adoptive transfer of T-helper lymphocytes.<sup>42</sup> Moreover, both humans and mice that fail to recruit neutrophils to the periodontal tissue (e.g., due to leukocyte-adhesion deficiency) develop an aggressive form of periodontitis early in life.<sup>43</sup> However, animal models also provide conclusive evidence that the host response is intimately involved in the destructive process. Both systemic and topical application of non-steroidal anti-inflammatory drugs that inhibit prostaglandin synthesis reduce periodontal bone loss in spontaneously occurring periodontal disease in dogs and in ligature-induced periodontal disease in non-human primates.<sup>44,45</sup> Similarly, application of factors that inhibit cytokines, including tumor necrosis factor [TNF], interleukin [IL]-1, IL-17, complement, and RANKL reduce periodontal tissue destruction whether induced by *A. actinomycetemcomitans* oral gavage or by ligatures in mice or non-human primates, providing additional evidence that the host response mediates bone loss.<sup>46-55</sup> Moreover, such studies have offered promising therapeutic targets for the treatment of human periodontitis. In contrast, application of IL-1 or TNF, or genetic over-expression, enhances bone loss triggered by bacteria.<sup>56-58</sup> Likewise, attenuation of the host response by genetic ablation generally lessens bacteria-induced bone loss.<sup>59-63</sup> Thus, animal studies consistently demonstrate that bacteria alone are not sufficient to induce periodontal bone loss, a conclusion that would be difficult to make solely from in vitro studies or human studies.

Recent studies have questioned the reliability of murine models for the investigation of human inflammatory disease, a broad

conclusion which, if validated, would have a significant impact on the use of mouse models of periodontal disease. Specifically, gene expression profiling of C57BL/6J mice and humans during endotoxemia revealed poor correlation between the human genes and mouse orthologues and vice versa.<sup>64</sup> However, this shortcoming in fact does not apply to periodontitis where the same inflammatory mediators (e.g., prostaglandin E2, TNF, IL-1 $\beta$ , and IL-17) mediate inflammatory bone loss in various species including mice, rats, dogs, non-human primates, and humans.<sup>43,46,54,55,63,65-68</sup> Moreover, important innate or adaptive immune players implicated in experimental mouse periodontitis have been confirmed in higher animals. For instance the central complement component C3 promotes inflammatory periodontal bone loss in both mice and non-human primates,<sup>55</sup> whereas regulatory T cells mediate protection against the same condition in both mice and dogs.<sup>67</sup>

When mouse models are used in an appropriate context to address specific hypotheses in periodontal disease pathogenesis, the results obtained have been consistent with in vitro observations using human cells. For instance, studies in the oral gavage model have confirmed the capacity of *P. gingivalis* to inhibit the expression of E-selectin and neutrophil-recruiting chemokines,<sup>29</sup> as predicted by the local chemokine paralysis model first established in vitro using endothelial and gingival epithelial cells.<sup>69,70</sup> Moreover, consistent with the requirement of intact C5a receptor (C5aR) signaling in human leukocytes for successful evasion of killing by *P. gingivalis*, the organism fails to colonize the periodontium of C5aR-deficient mice, in contrast to wild-type mice where *P. gingivalis* can persist and cause disease.<sup>29,71,72</sup> Moreover, local treatment of *P. gingivalis*-colonized mice with a C5aR antagonist essentially eliminates *P. gingivalis*, reverses its dysbiotic effect, and inhibits development of periodontitis.<sup>29,71,73</sup> In line with in vitro evidence that *P. gingivalis* can escape TLR4 recognition or activation,<sup>74</sup> TLR4-deficient neutrophils display normal inflammatory responses to *P. gingivalis* in the chamber model, comparable with wild-type neutrophils (but not TLR2-deficient neutrophils which exhibit a poor response).<sup>5</sup> Furthermore, the lipid A phosphatase activity of *P. gingivalis*, which is required for modulation of lipid A structure and hence evasion of TLR4,<sup>74</sup> was shown to contribute to the capacity of *P. gingivalis* for oral colonization and enhancement of the commensal bacterial load in a rabbit model of ligature-induced periodontitis.<sup>75</sup> These studies also justify the characterization of *P. gingivalis* as a keystone pathogen, a concept that is relevant also in other inflammatory dysbiotic diseases.<sup>76,77</sup> The consistency between in vivo animal and in vitro human experimental systems not only confers biological significance to the in vitro findings but also lends further support and validation of these animal models.

One potential limitation of rodent models is that the cells and effector molecules of the immune system can differ from their human counterparts as is the case with the neutrophil chemokine CXCL8/IL-8. Mice and rats do not produce IL-8, but they do produce functionally equivalent homologs that are controlled by the transcription factor NF- $\kappa$ B.<sup>78-80</sup> *P. gingivalis* can inhibit neutrophil transmigration toward human epithelial cells in vitro<sup>81</sup> through production of a serine phosphatase, SerB, that inhibits

NF- $\kappa$ B activation by dephosphorylating its p65 subunit.<sup>69,70</sup> An important test of the relevance of rodent models then was to assess the functionality of SerB in vivo. In the rat oral gavage model, a SerB-deficient mutant of *P. gingivalis* incited greater neutrophil infiltration in gingival tissues.<sup>82</sup> Thus, even though specific immune effectors may differ between rodents and humans, similarity in the command and control pathways ensures that mice and rats can indeed model the human immune systems in many important ways.

In addition to inducing periodontitis via oral gavage or ligature placement, the disease can develop in mice spontaneously as a result of the aging process, a factor that also contributes to human periodontitis.<sup>83</sup> The use of the aging-associated periodontitis model led to the identification of a novel molecule involved in periodontal tissue homeostasis, namely the endothelial cell-derived glycoprotein Del-1.<sup>54</sup> Del-1 engages in reciprocal antagonistic interactions with IL-17 in terms of their expression and function in neutrophil recruitment and inflammation. This reciprocal relationship has been confirmed in humans, with Del-1 dominating in healthy gingiva and IL-17 prevailing in inflamed gingiva.<sup>54</sup>

Importantly, the induction of periodontitis in mice involves more physiological means as compared to other widely used mouse models of other human diseases. For instance, chemically-induced models of IBD have limitations in understanding events that initiate gut inflammation in human IBD.<sup>84</sup> Psoriasis, a T-cell-mediated chronic inflammatory skin disease, is generally not seen in animals other than humans, yet, various mouse models including transgenics and knockouts have been developed that mimic psoriasis.<sup>85</sup> Despite their serious limitations, these models have established that psoriasis is a T-cell-mediated disease and have been used to dissect novel pathways of disease pathogenesis. In experimental autoimmune encephalomyelitis, a model of human multiple sclerosis, the disease is often induced artificially after injection of autoantigen emulsified in complete Freund's adjuvant. This promotes the induction of CD4+ T cell-mediated autoimmune mechanisms, whereas CD8+ T cells prevail in multiple sclerosis lesions.<sup>86</sup> Similarly, collagen-induced arthritis in mice, a commonly used model of rheumatoid arthritis, is elicited by immunization with type II collagen formulated in complete Freund's adjuvant.<sup>87</sup> Nevertheless, imperfect as they may be, these models have significantly enhanced our understanding of disease pathogenesis.

## Impact of Systemic Disease

It is well documented in human studies that systemic conditions such as diabetes mellitus increase the risk and severity of periodontal disease.<sup>88</sup> Animal models have established a mechanistic basis for this phenomenon. Both type 1 and type 2 diabetic mice exhibit a greater inflammatory response than normal mice to the same inoculation of *P. gingivalis* into connective tissue.<sup>89,90</sup> If TNF is blocked in diabetic rats or diabetic mice, much of the diabetes-enhanced bone resorption is reversed, indicating that diabetes-enhanced inflammation, particularly TNF, is

problematic.<sup>91-93</sup> Interestingly, diabetes appears to cause a particular problem in the resolution of inflammation which leads to dysregulation of a number of pathways that both enhance bone resorption and reduce coupled bone formation.<sup>94,95</sup> A number of factors may enhance inflammation in diabetic animals including increased formation of advanced glycation end products (AGEs).<sup>8</sup> When AGE signaling is blocked in a periodontal disease model both diabetes-enhanced TNF levels and periodontal bone loss are reduced.<sup>96</sup> Therefore, human studies have provided evidence of an association between diabetes, AGEs, inflammation and periodontal disease, but animal studies with the use of specific inhibitors provide conclusive evidence of functional relationships between these parameters and identify specific processes affected. Conversely, the notion that periodontitis exerts an adverse impact on systemic health is substantiated by mechanistic animal studies linking periodontitis or periodontal pathogens to disorders such as atherosclerosis, adverse pregnancy outcomes, and rheumatoid arthritis.<sup>97,98</sup>

## Conclusion

In summary, whereas no one animal model can recapitulate the complexity of periodontal disease, different aspects of the disease can be represented by different models, which have contributed considerably in dissecting the mechanistic underpinning of periodontitis. Of course, the synthesis and integration of findings from all available experimental systems (in vitro, animal, human) are required for better understanding of disease pathogenesis (Fig. 1). A good example of the interconnectivity and relevance of each experimental system is provided by the treatment of periodontitis with local delivery of tetracyclines. Tetracyclines have been shown to inhibit periodontal disease in rats and to alter the subgingival microflora in humans.<sup>15,99</sup> However, experiments with germ-free rats demonstrated that tetracyclines can reduce

periodontal breakdown in a non-antimicrobial manner involving inhibition of matrix metalloproteinases (MMPs).<sup>100</sup> This led to a number of *in vitro* studies to investigate the precise mechanisms involved and the development of new drugs that inhibit MMP activity.<sup>100</sup> MMP-blocking drugs first discovered in rat models of periodontal disease have been subsequently marketed as Periostat<sup>®</sup> to prevent periodontitis in humans<sup>101</sup> and are being further developed for treatments of other tissue-breakdown diseases including cardiovascular disease.<sup>102</sup>

When using animal models, what matters is not only the species but primarily the ways in which the chosen model is used. For instance, whereas non-human primate models are closer to human periodontitis than any dog, rabbit, or rodent model, no model can be discounted if used appropriately and the data are interpreted within the limitations of the model. It is the opinion of these authors that the dismissal of animal models on the grounds that they do not faithfully represent all aspects of human periodontitis does not constitute serious scientific criticism and, in the absence of better mechanistic alternatives, represents an impediment to scientific progress. Needless to add, however, that it is important to strive to optimize existing models or invent new and improved ones based on new experimental results and constructive criticism.

## Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

## Funding

The authors' research is supported by NIH grants; DE015254, DE017138, DE021685, DE024716, AI068730 (GH); DE011111, DE012505, DE016690, DE017921, DE022867, DE023193 (RJL); and DE017732, DE021921 (DTG).

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