

Preventing Periodontitis or Controlling its Progression Reduces the Development of Medication-Related Osteonecrosis of the Jaw (MRONJ) in Rice Rats (*Oryzomys Palustris*)

EJ Castillo¹, JG Messer¹, JM Jiron¹, AM Abraham¹, SM Thomas¹, JF Yarrow², DB Kimmel¹, JI Aguirre¹

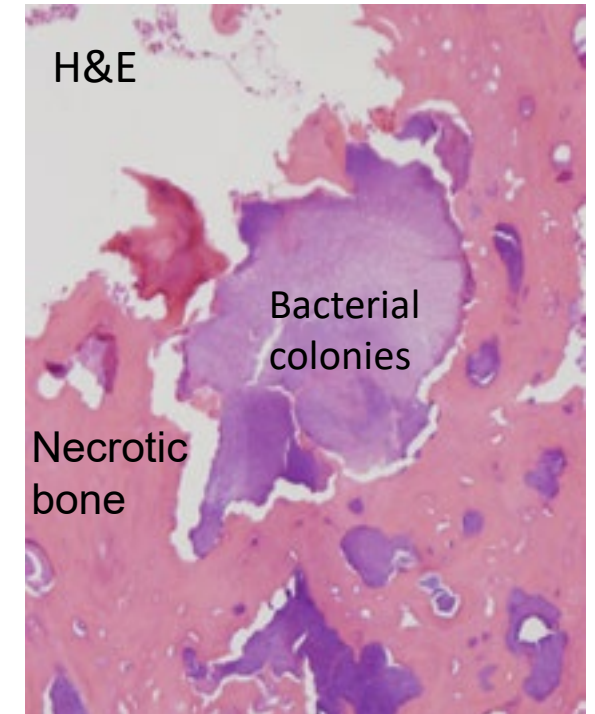
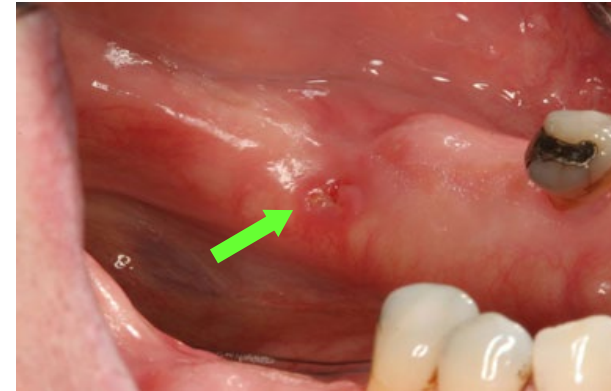
¹University of Florida, Department of Physiological Sciences Gainesville, FL, USA

²VA Medical Center, Research Service, VA Medical Center, Gainesville, FL

MRONJ

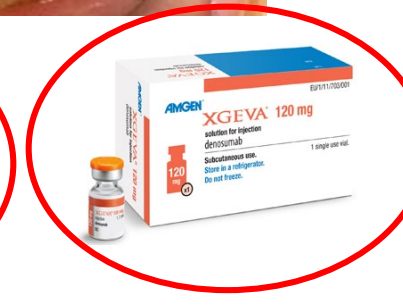
- **Exposed necrotic bone in the oral cavity**

- >8 wk without healing
- Systemic medications
 - Powerful anti-resorptives [(pARS) eg. Bisphosphonates (Zoledronic acid, ZOL) or anti-RANKL inhibitors]
 - Anti – angiogenics (eg. anti-vascular endothelial growth factors.
- No history of radiation therapy or apparent metastases to head and neck



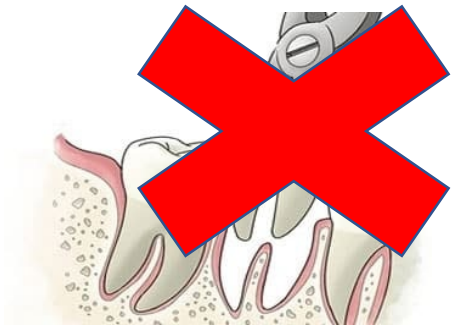
- **Local oral risk factors**

- Recent tooth extractions
- Periodontitis (PD), periapical infection
- Mucosal trauma



Preventative Measures can reduce MRONJ

- Elimination/Reduction of oral and dental risk factors



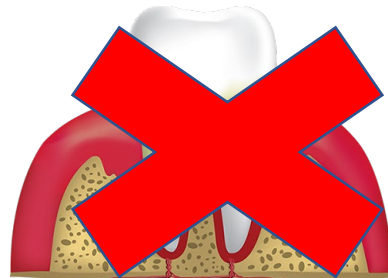
Tooth Extraction



Unfitting Removable Denture



Peri-implantitis



Periodontitis

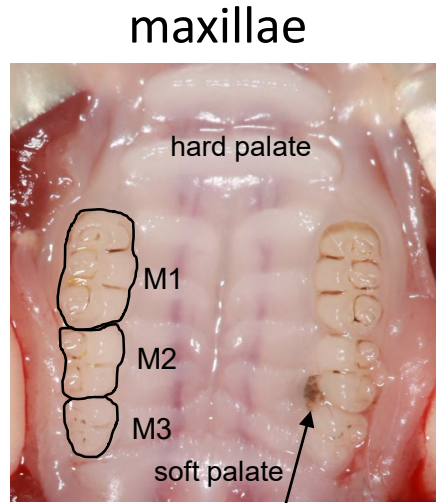
Preclinical Model of PD and MRONJ



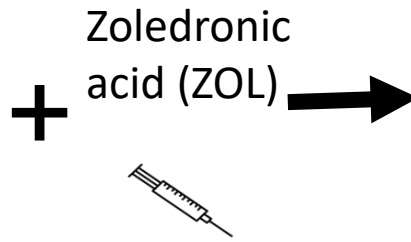
Rice rat (*O. palustris*)



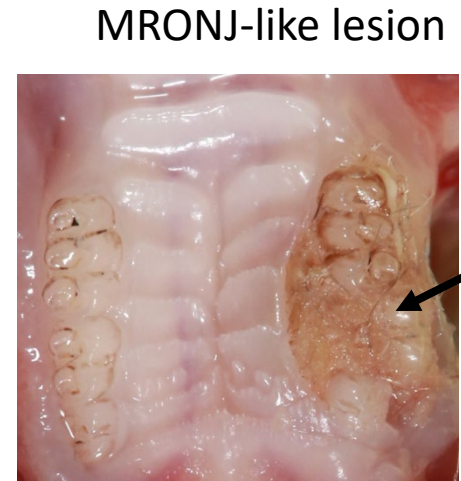
STD rodent chow



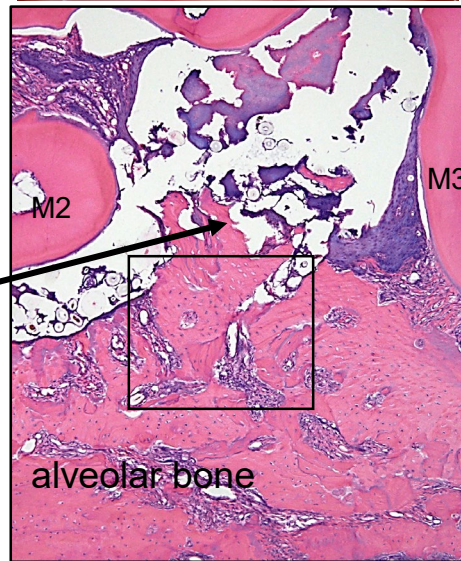
Food-impaction induced localized PD (FILP) lesions



Zoledronic acid (ZOL)

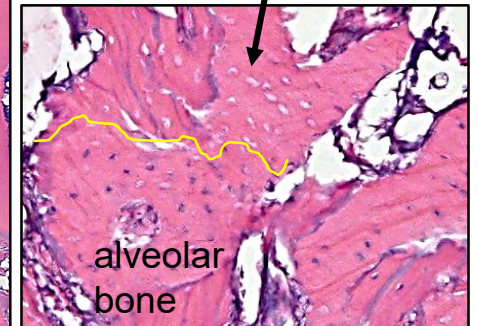


MRONJ-like lesion



Oral cavity

alveolar bone



necrotic bone

alveolar bone

60-80% rice rats develop FILP lesions at 16-34 wks of age

Around 94% of FILP lesions occur in the maxilla

(Messer et al 2017)

(Messer et al 2018)

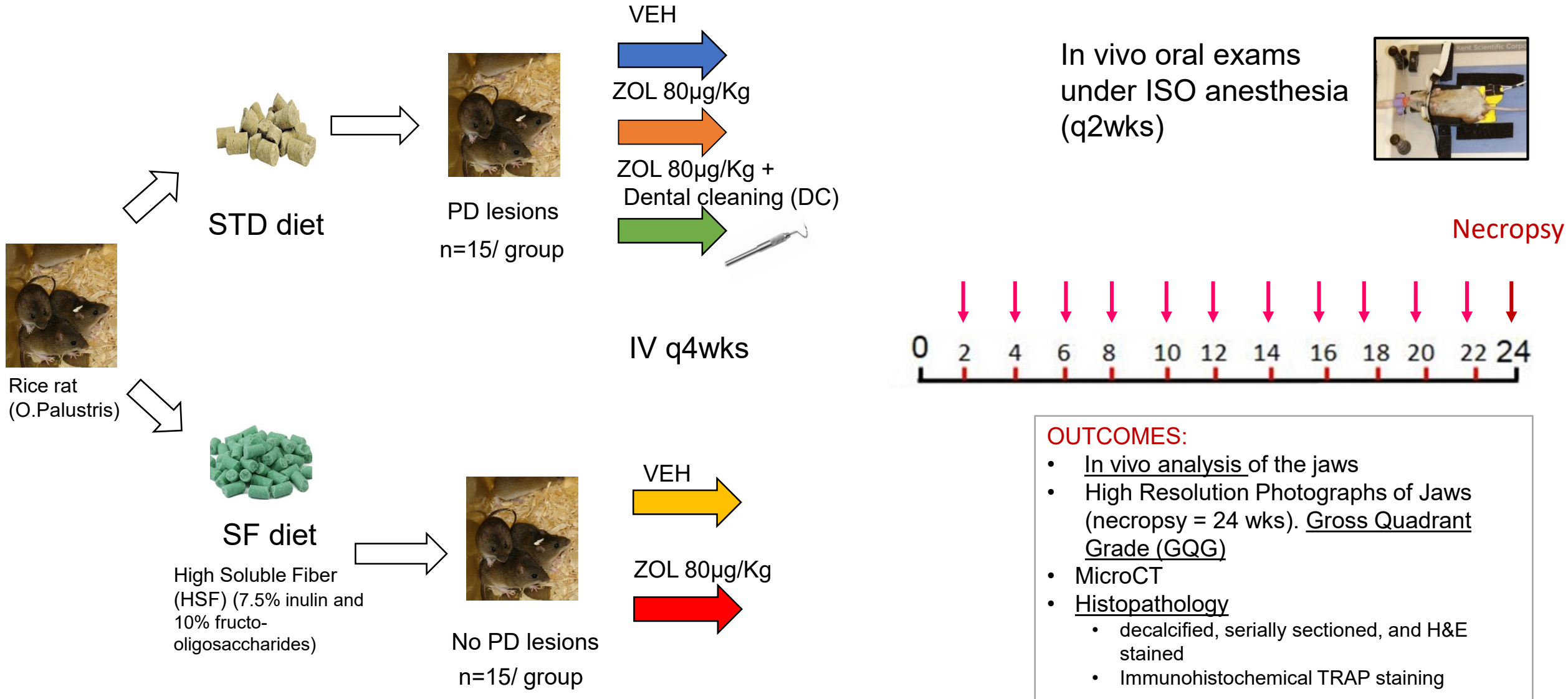
Hypothesis

A dietary modification or mechanical dental cleaning in rice rats will prevent or control PD, and hence will reduce the prevalence of MRONJ

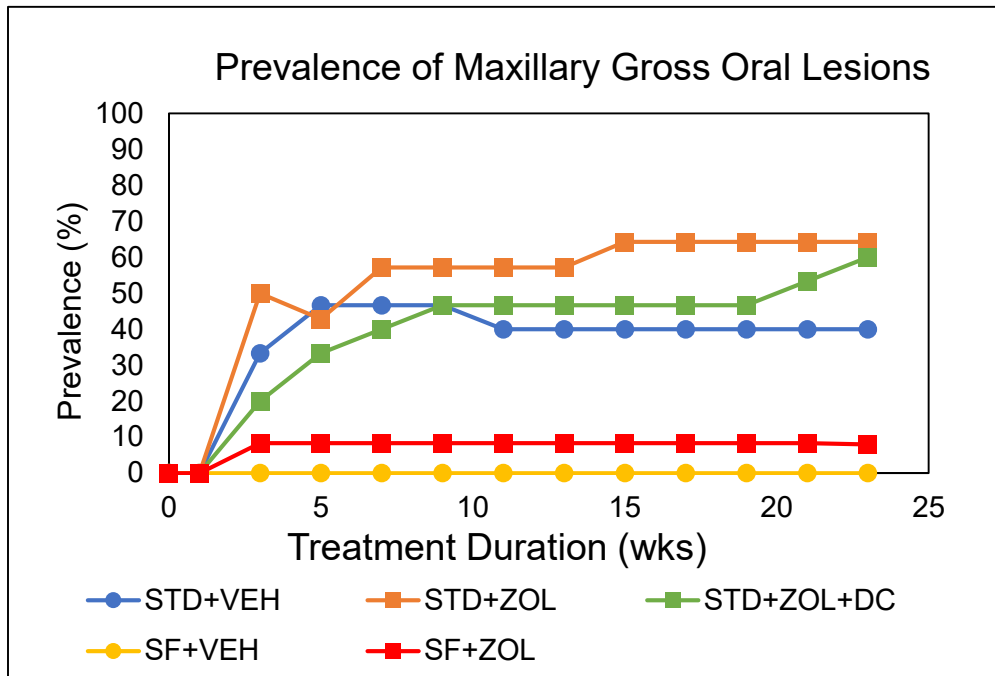
Determine the efficacy of preventing or controlling PD in the development of MRONJ by:

- 1) Oral mechanical cleaning of Lesions
- 2) Diet modification

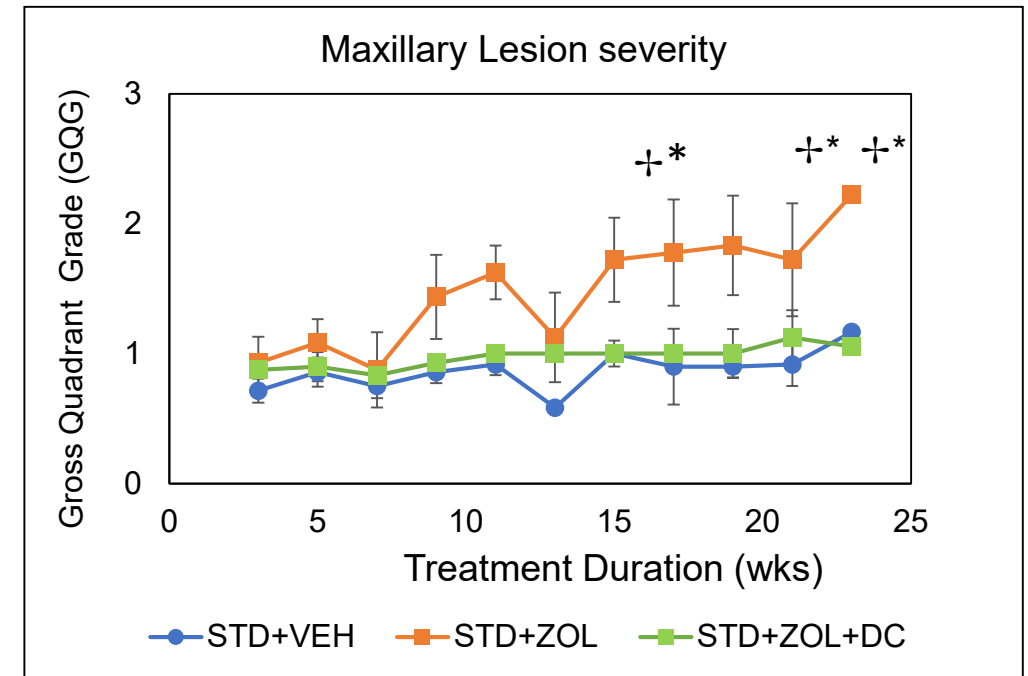
Materials and Methods



In Vivo Analysis of Maxillary Quadrants

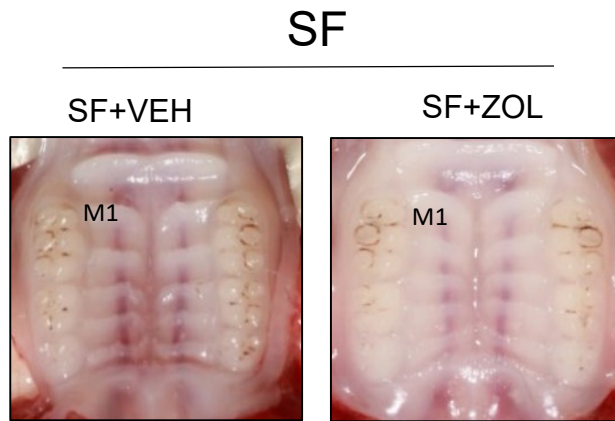
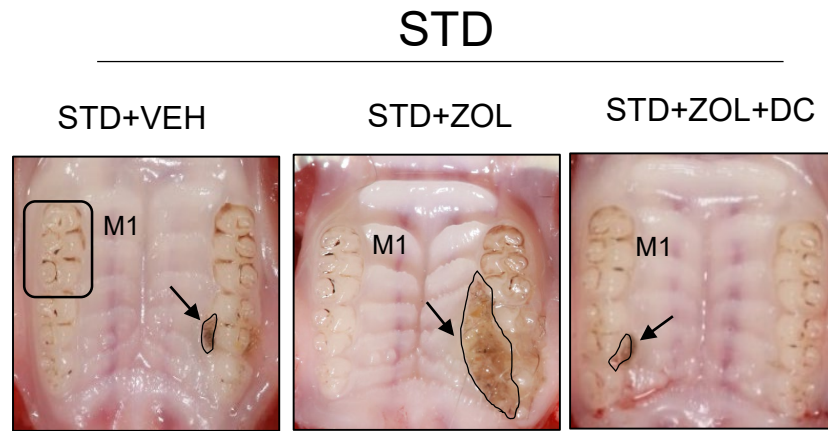


- SF+VEH and SF+ ZOL rats had significantly lower prevalence of oral lesions than STD rats

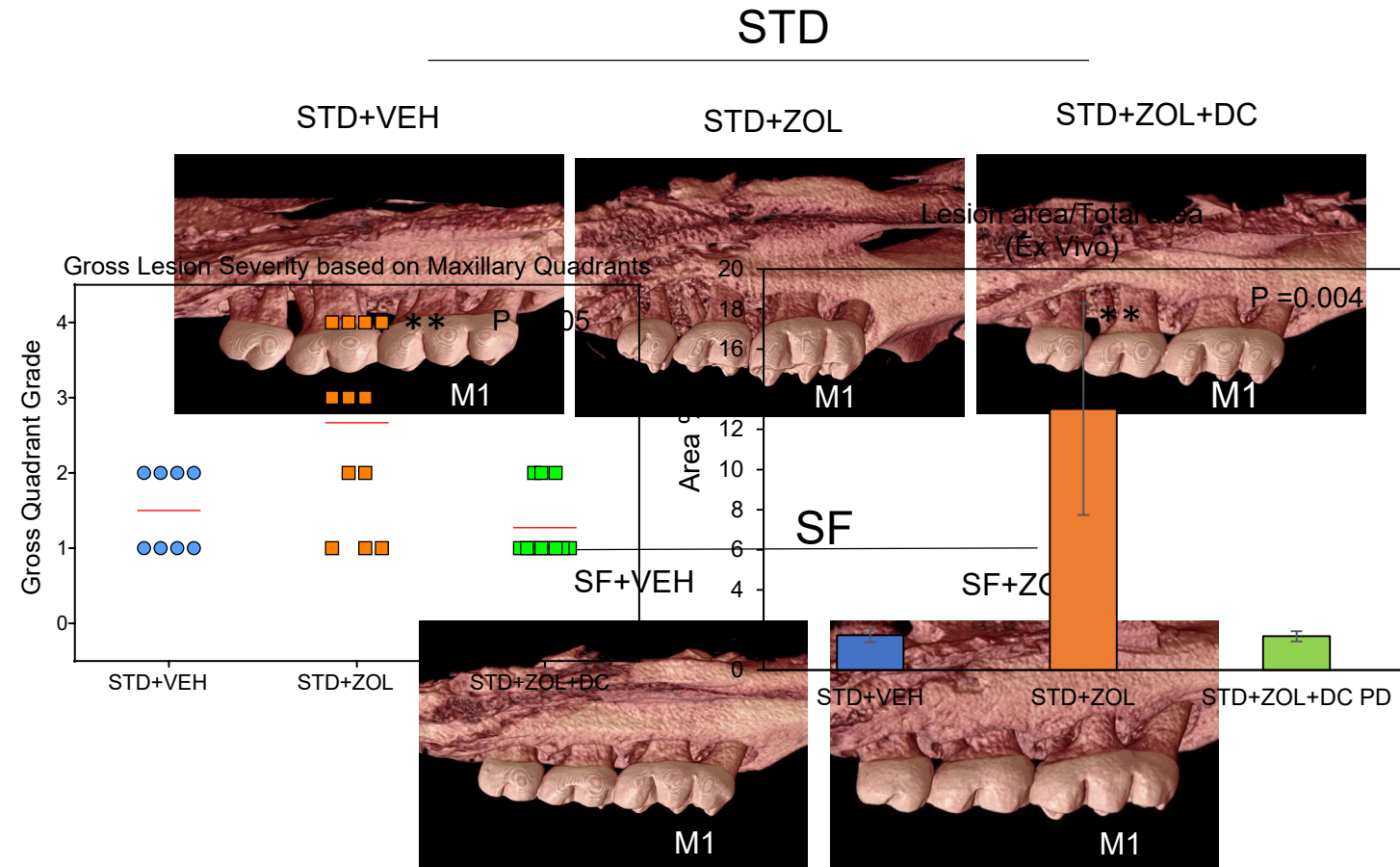


- STD+ZOL rats that received dental cleanings had significantly reduced severity of PD lesions.

Ex-Vivo Gross Analysis of Oral Lesions

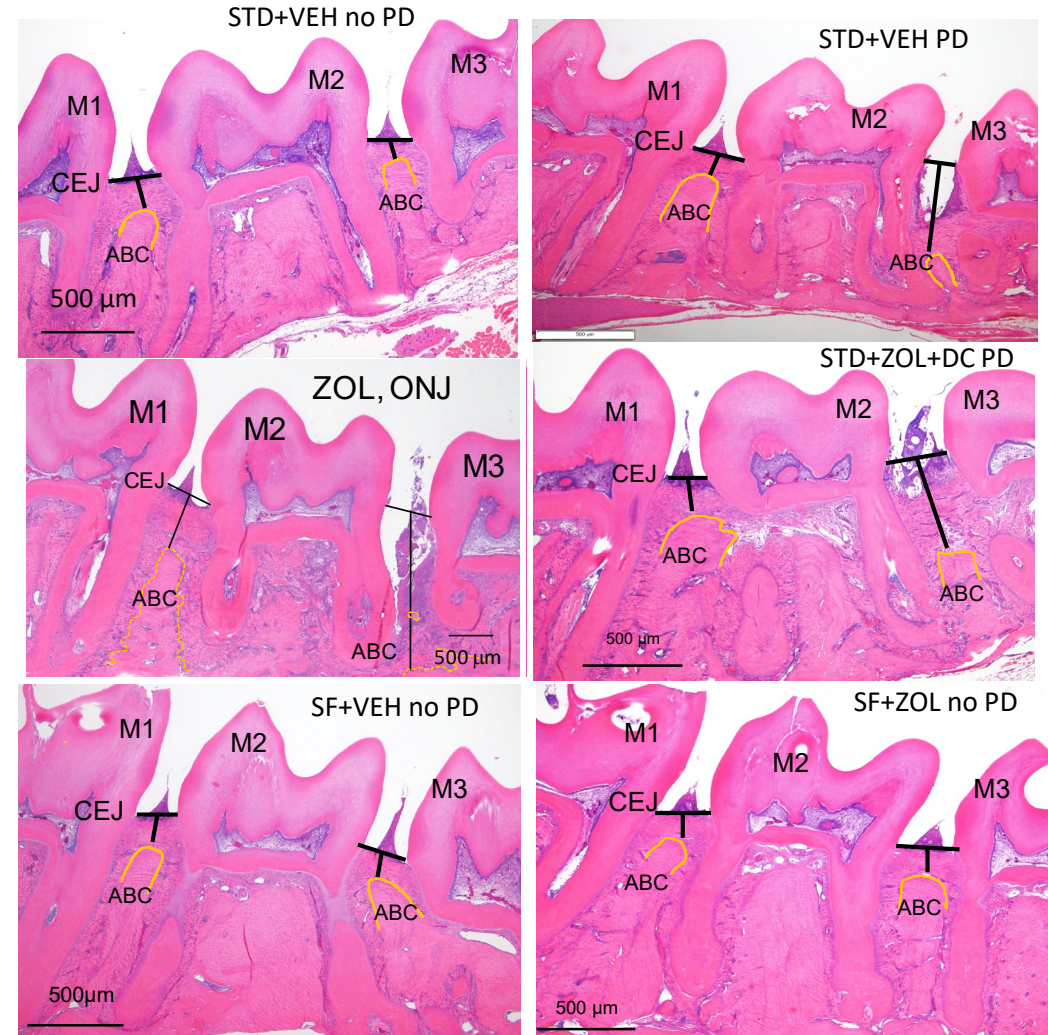
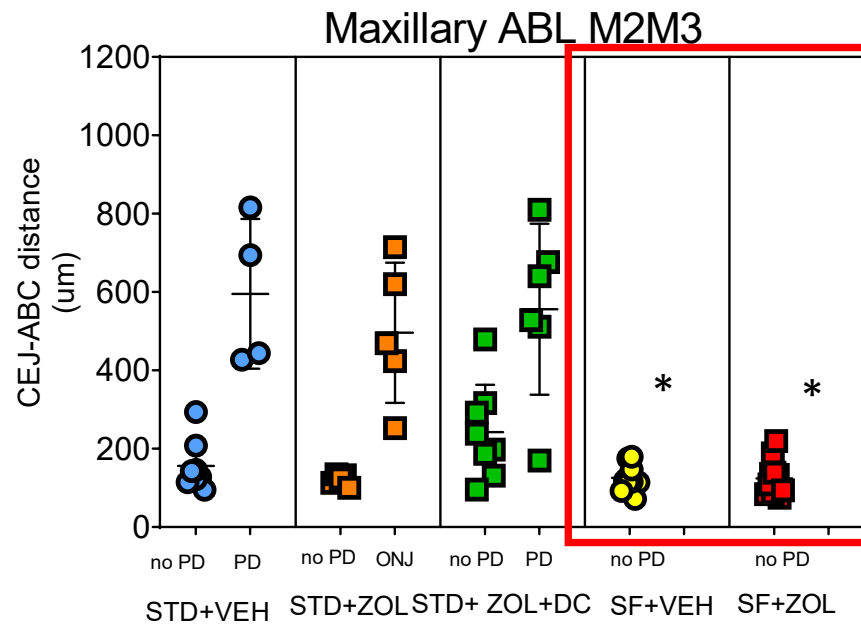


High Resolution Photographs

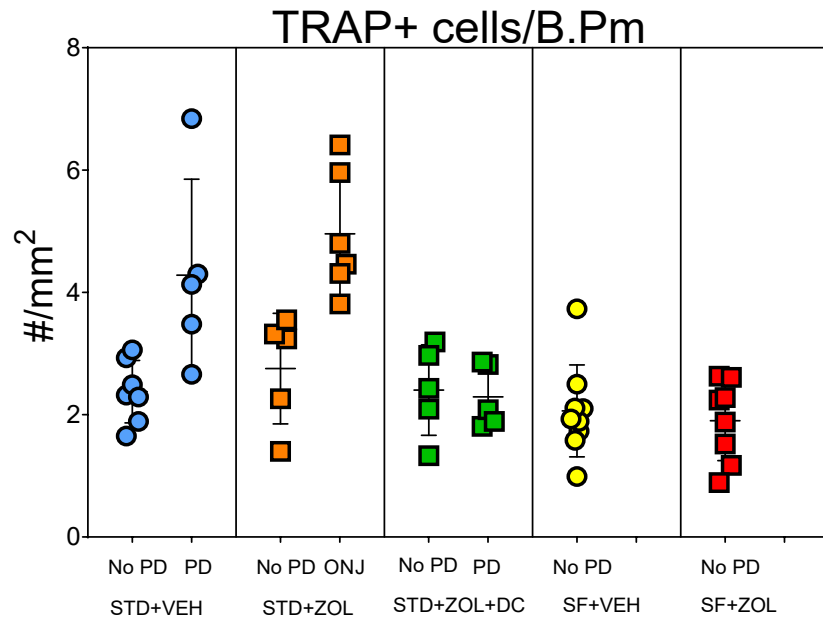


3D reconstruction of MicroCT slices

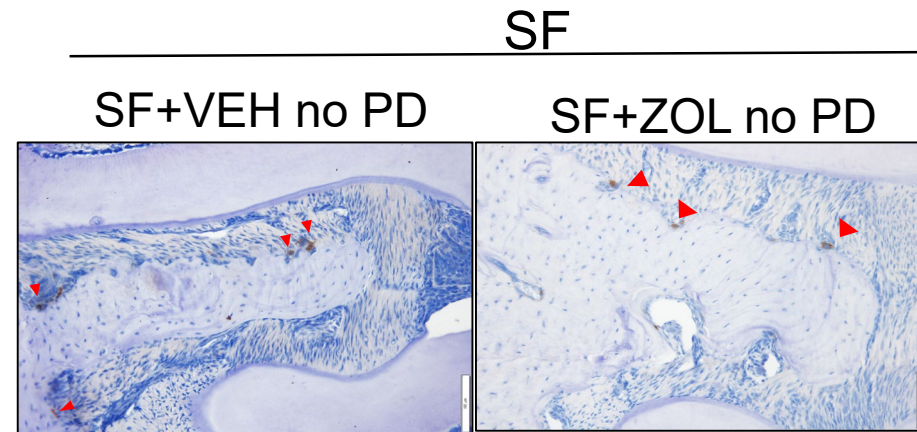
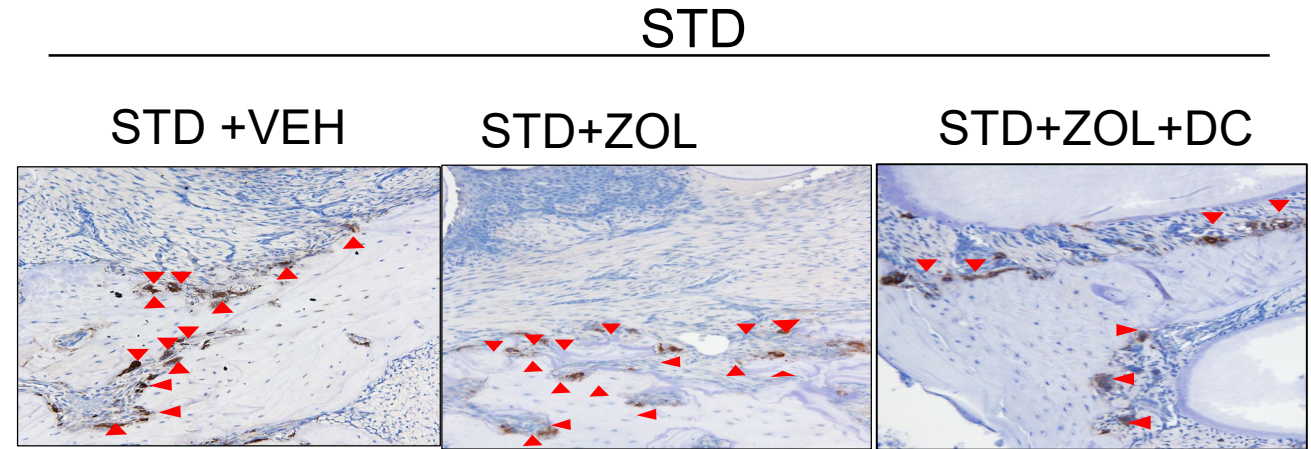
Alveolar Bone Loss



Immunohistochemical staining of TRAP⁺ Cells



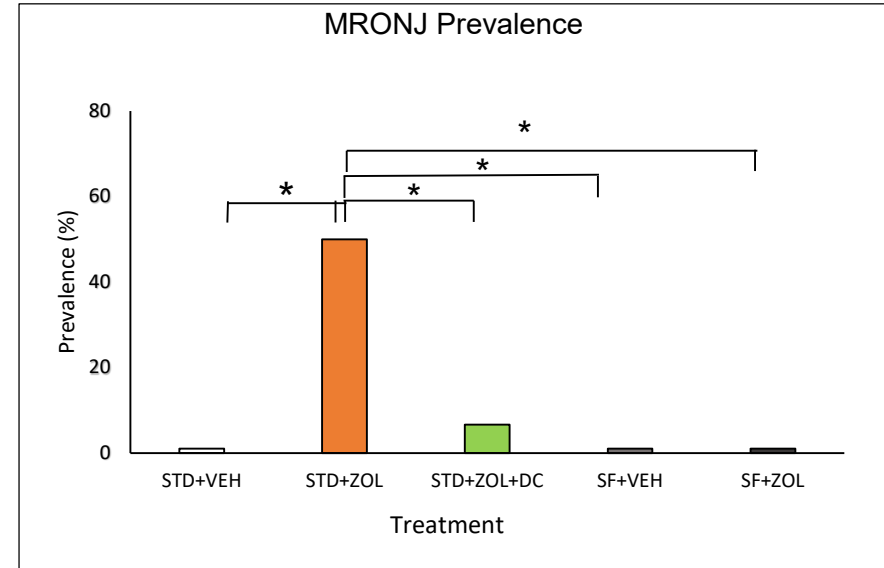
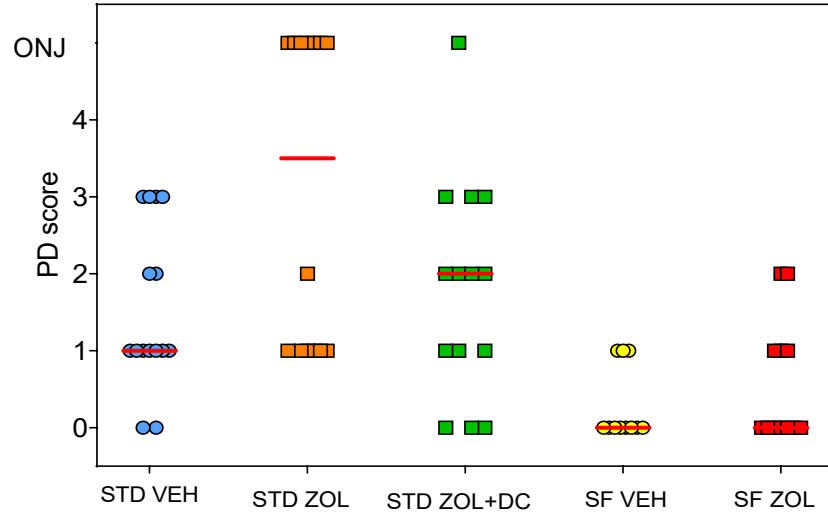
Quantification of osteoclast number/mm²



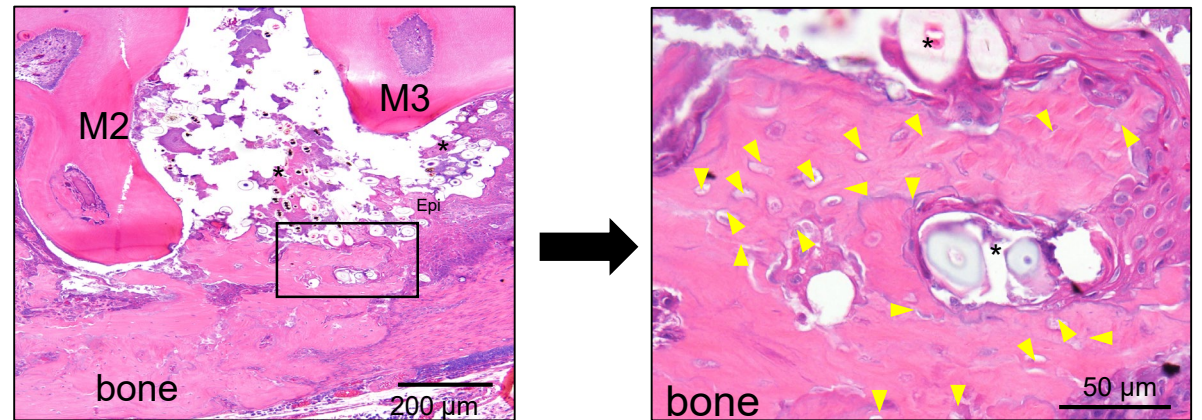
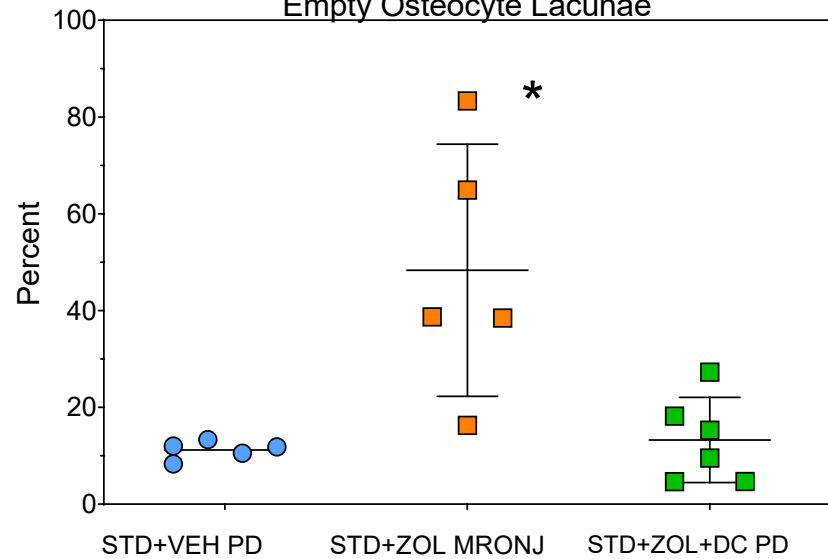
Immunohistochemical TRAP stained sections. Red arrow indicates TRAP⁺ osteoclast

Histopathologic Assessment

Maxillary Histological PD Scores at 24 weeks (M2M3)



Empty Osteocyte Lacunae



- Exposed necrotic bone
- Lack of overlying gingival epithelium
- ≥ 10 confluent empty osteocyte lacunae

Conclusions

- Dental cleaning reduces gross severity and extension but does not resolve PD lesions in rice rats.
- Preventing progression of PD reduces occurrence of MRONJ.
- SF diet prevented the development of PD and MRONJ regardless of treatment
- These findings provide direct preclinical evidence to support current guidelines² concerning maintenance of good oral hygiene in pAR patients.