Role of Osteocytes in Regulating Orthodontic Tooth Movement

2021 Grants

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FollowUp Form

Award Information

In an attempt to make things a little easier for the reviewer who will read this report, please consider these two questions before this is sent for review:

- *Is this an example of your very best work, in that it provides sufficient explanation and justification, and is something otherwise worthy of publication? (We do publish the Final Report on our website, so this does need to be complete and polished.)*
- *Does this Final Report provide the level of detail, etc. that you would expect, if you were the reviewer?*

Title of Project*

Role of Osteocytes in Regulating Orthodontic Tooth Movement

Award Type

Biomedical Research Award (BRA)

Period of AAOF Support

July 1, 2021 through June 30, 2023

Institution

University of California San Francisco

Names of principal advisor(s) / mentor(s), co-investigator(s) and consultant(s)

Dr. Tamara Alliston

Amount of Funding

$30,000.00

Abstract

(add specific directions for each type here)

Respond to the following questions:

Detailed results and inferences:*

If the work has been published, please attach a pdf of manuscript below by clicking "Upload a file".
OR
Use the text box below to describe in detail the results of your study. The intent is to share the knowledge you have generated with the AAOF and orthodontic community specifically and other who may benefit from your study. Table, Figures, Statistical Analysis, and interpretation of results should also be attached by clicking "Upload a file".

2023 AAOF final report.pdf
Please see attached.

Were the original, specific aims of the proposal realized?*

Yes

Were the results published?*

No

Have the results of this proposal been presented?*

Yes

To what extent have you used, or how do you intend to use, AAOF funding to further your career?*

AAOF funding has led me to explore a new area of research regarding the role of osteocytes in orthodontic tooth movement and to build a new collaborative relationship with a renewed scientist Dr. Tamara Alliston. Especially because of my recent move to UCSF, AAOF funding was essential in continuing my translational research in orthodontics as it has supported me through many different projects. This funding has led to an R21 and R01 submissions. Recent submission is getting reviewed. I will continue to submit NIH grants on this topic using the results from this grant.

Accounting: Were there any leftover funds?

$0.00

Not Published

Are there plans to publish? If not, why not?*

Yes!

Presented

Please list titles, author or co-authors of these presentation/s, year and locations:*

Osteocyte-Intrinsic TGFβ Regulation of Alveolar Bone Remodeling Under Orthodontic Forces.
Zhao B, Ngo A, Faldu J, Suh J, Alliston T, Hong C
June 2023 IADR Bogota, Colombia

Was AAOF support acknowledged?

If so, please describe:

Yes.

Internal Review

Reviewer Comments

Reviewer Status*

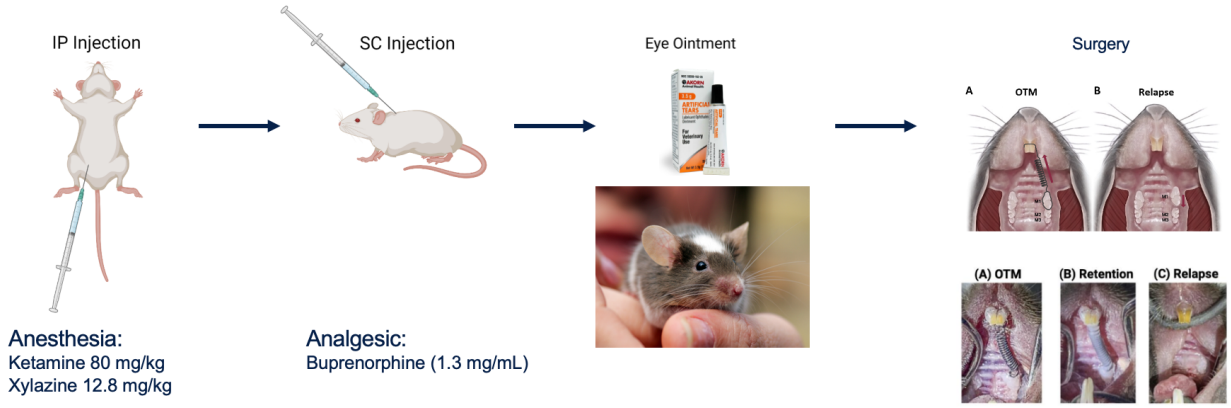
File Attachment Summary

Applicant File Uploads

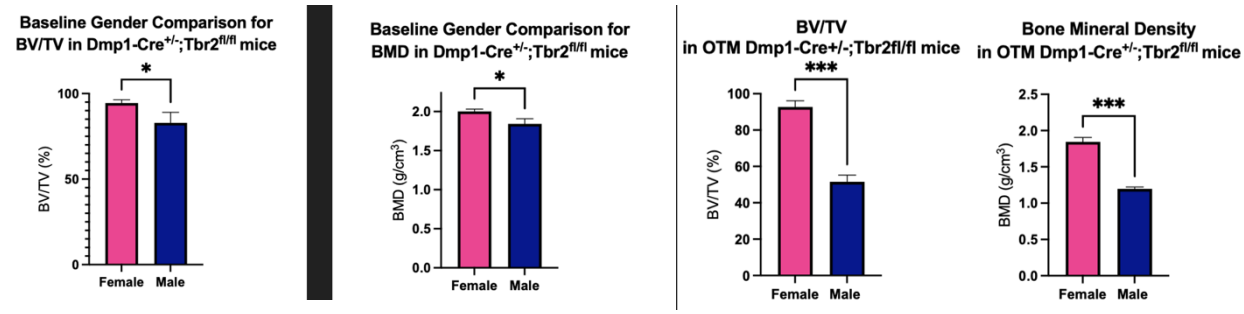
- 2023 AAOF final report.pdf

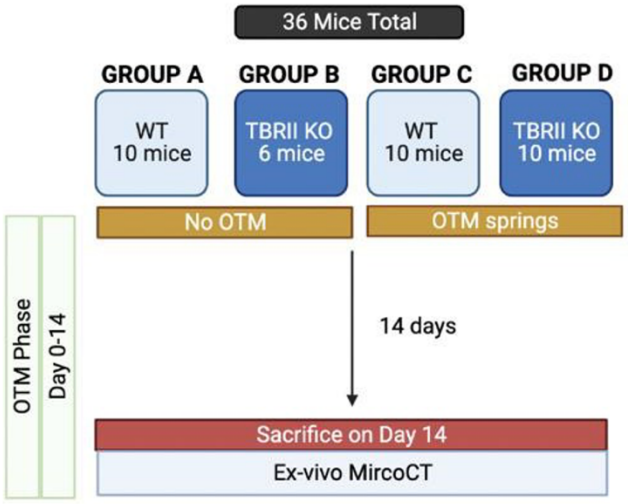
Detailed Results and Inferences

A. We have established orthodontic tooth movement model in mice through many trials and errors. A handpiece was used to make retention grooves on the distal surfaces of the maxillary incisors, 0.5mm from the gingival margin. 0.008” SS ligature wire was used to tie in the NiTi CCS spring to the incisors from the first molar. .010”x.030” delivering 5g of force at 3.5mm activation was used and standardized.

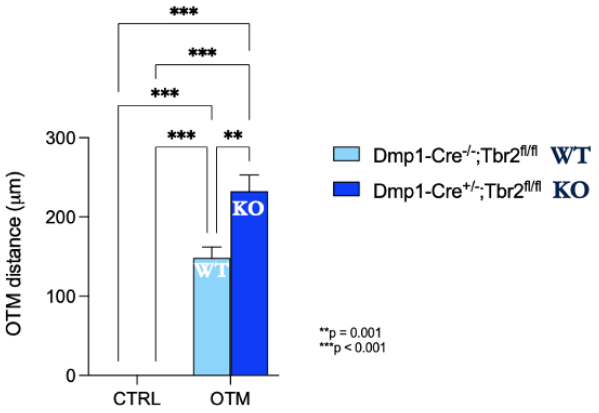


B. 12-week-old osteocyte-specific TGF-β receptor II KO mice TBRII$^{ocy-/-}$(Dmp1-Cre$^{+/-}$;TBRII$^{fl/fl}$) and WT mice (Dmp1-Cre$^{-/-}$;TBRII$^{fl/fl}$) mice were divided into 4 groups as shown below and underwent 3 days and 14 days of OTM. Although this proposal was originally aimed for a study in males only, we additionally studied the effect of sex as this genotype was recently reported to have sex difference in long bones. Therefore, both males and females were used and separated within the groups. We performed a preliminary study using n=3-5 per group per sex. We found that there was lower bone volume and bone mineral density in male mice without OTM. This difference between males and females was more pronounced following OTM. Accordingly, OTM was significantly greater in males compared to females. This was an unexpected finding, highlighting the sex differences in bone remodeling and response to OTM. We also examined the OTM between 3 days and 14 days. 14 day OTM exhibited clear differences in OTM amount.

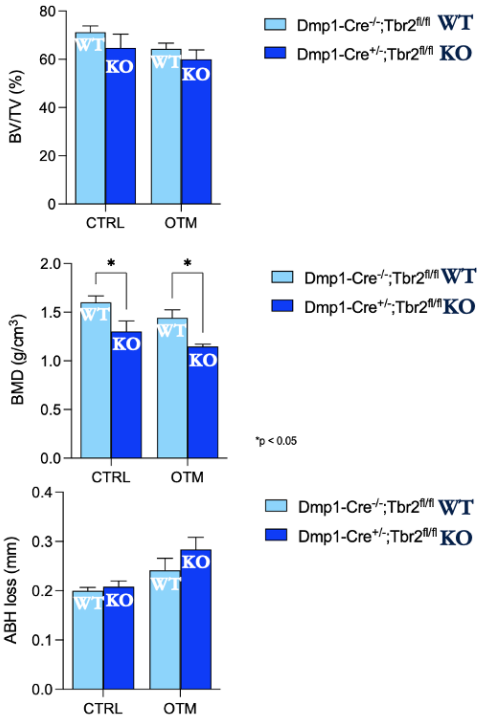


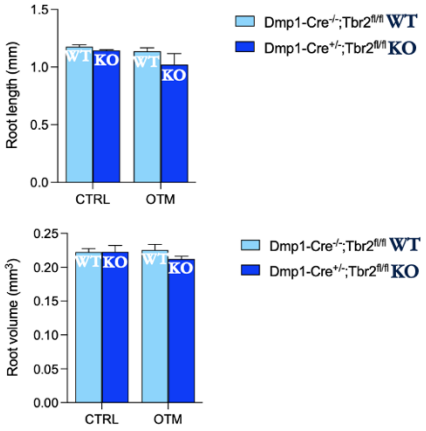


C. After the preliminary studies, in order to determine the extent to which TGF-β signaling in osteocytes affects rate of orthodontic tooth movement, 12-week-old **male** osteocyte-specific TGF-β receptor II KO mice TBRII$^{ocy-/-}$(Dmp1-Cre$^{+/-}$;TBRII$^{fl/fl}$) and WT mice (Dmp1-Cre$^{-/-}$;TBRII$^{fl/fl}$) mice were divided into 4 groups as shown below and underwent 14 days of OTM. In the OTM group, KO mice had statistically significantly more OTM (57%) than WT mice (**p=0.001). KO OTM mice on average measured 232μm and WT OTM mice on average measured 148μm, which is comparable value to those found in OTM literature. Control mice in the KO and WT group showed no OTM. The control represents mice that did not receive the orthodontic spring appliance, therefore the distances between the first and second maxillary left molar is zero. Initially in this proposal, we hypothesized that osteocyte-intrinsic TGFβ signaling is critical in the regulation of alveolar bone remodeling directly via perilacunar/canalicular remodeling and indirectly via mechanosensitive induction of sclerostin and RANKL production by osteocytes. For this reason, we expected that the disrupted osteocyte-intrinsic TGFβ signaling to inhibit OTM by decreased alveolar bone remodeling as in our previous studies with long bones. However, our results showed that osteocyte-intrinsic TGFβ signaling impairment had an opposite effect. It is exciting to see this result as this highlights the uniqueness of alveolar bone, which often acts very differently from long bones. In addition, our results show that TGF-β is a complex signaling molecule with pleiotropic effects on multiple cell types. The signaling pathway of TGF-β is very intricate, as previous studies have shown TGF-β to be secreted by osteoblasts, osteoclasts, and osteocyte cells. It is possible that since TGF-β is so complex and broad-acting in its function, any disruption in its signaling pathway can cause dysregulation in bone homeostasis and perilacunar remodeling. Overall, our studies elucidated that osteocyte-intrinsic TGFβ signaling plays a key role in modulating OTM.



D. In order to determine the extent to which TGF-β signaling in osteocytes affects alveolar bone remodeling and root volume, we analyzed bone volume (BV/TV), bone mineral density (BMD), and alveolar bone height (ABH). BV/TV measurements (%) showed that KO mice had less BV/TV than WT mice in both the CTRL and OTM groups, although not statistically significant. BMD measurements (g/cm^3) showed that KO mice had statistically significantly less BMD compared to WT mice in both control and OTM groups (*p<0.05). ABH loss measurements (mm) showed that KO mice had similar ABH levels as the WT mice in the control group. In the OTM group, KO mice had more ABH loss than WT mice, although not statistically significant. These results are consistent with increased OTM in KO mice. The root length (RL) and root volume (RV) measurements (mm^3) showed that KO mice had similar RL/RV as WT mice in the control group. In the OTM group, KO mice had smaller RL/ RV than WT mice, although not statistically significant.





E. We also established an OTM-retention-relapse model for future studies in the role of osteocytes in orthodontic relapse. We used WT male mice. There were 4 groups each with a sample size of 3. Group 1 was the OTM control group that underwent OTM for 28 days. Group 2 was the 14 day OTM group, Group 3 was the Retention group (14 days OTM followed by 14 days retention), and Group 4 was the Relapse group (14 days OTM, 14 days retention, followed by 7 days relapse). Group 4 had 80% reduction in OTM compared to Group 1 and 60% reduction compared to Group 3. Group 2 and Group 3 did not have significant changes confirming the efficacy of retainer placement.