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AAO Foundation Final Report Form (a/o 5/30/2020)

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?*

Please prepare a report that addresses the following:

Type of Award, e.g., Orthodontic Faculty Development Fellowship Award, Postdoctoral Fellowship Award, Biomedical Research Award, Center Award, Educational Innovation Award, Program Award, Research Aid Award

Orthodontic Faculty Development Fellowship Award

Name(s) of Principal Investigator(s): **Eliane H Dutra**

Institution: **University of Connecticut Health**

Title of Project: **The effects of intermittent administration of PTH and Alendronate on the mandibular condylar cartilage.**

Period of AAOF Support (e.g. 07-01-19 to 06-30-20): **07-01-19 to 12/31/21**

Amount of Funding: **$20,000**

Summary/Abstract :

Aim 1: Objectives: To characterize the effects of parathyroid hormone (PTH) and alendronate (Alend) on the osteochondral tissue of temporomandibular joint.
Materials and Methods: Ninety six male and female transgenic reporter mice, 4 to 5 weeks old were divided into 6 groups: (1) Control group: saline was injected daily for 14 days; (2) PTH: PTH was injected daily for 14 days; (3) Alend: Alend was injected every alternate days for 14 days; (4) Combined PTH and Alend: PTH was injected daily and Alend injected every alternate days for 14 days; (5) PTH then Alend: PTH was injected daily for 14 days followed by Alend injections in alternate days for 14 days; (6) PTH wait Alend: PTH was injected daily for 14 days. There was a waiting period of a 1-week before administration of Alend in alternate days for 14 day. Mice were injected with 5-ethnyl-2'-deoxyuridine (EdU), 48 hours and 24 hours prior to euthanization.
Results: There was significant increase in bone volume and decrease in osteoclastic activity in groups in which Alend was administered after PTH in both genders. There was significant increase in cartilage thickness with PTH or Alend alone in females, whereas in males PTH alone led to increase in cartilage thickness. Chondrocyte apoptosis was significantly decreased with PTH or Alend alone in both male and female. Matrix metallopeptidase 13, and aggreganase-2 (ADAMTS5) expression were significantly decreased with PTH and Alend alone in both genders.
Conclusion: PTH and Alend administration causes anabolic effects in the osteochondral tissue of TMJ.

Aim 2: Objectives: There is an urgent need for the development of therapeutic agents that are anabolic for the Temporomandibular Joint (TMJ) cartilage as chondrogenerative treatments for TMJ osteoarthritis. The goal of this study was to evaluate *in vitro* gene expression changes in chondrocytes from the TMJ from mice when different regimens of the anabolic agent Parathyroid Hormone (PTH) and the antiresorptive drug Alendronate (alone and concurrent) are used.
Material and Methods: Cells from the TMJ cartilage of 4-week-old BL6 mice were isolated and plated. Cells were treated daily for 10 days: **1)** Control (no treatment, only media), **2)** I-PTH (50ng/ml intermittent-PTH treatment only), **3)** Alendronate (20uM Alendronate treatment only), **4)** I-PTH + Alendronate (concurrent administration for 10 days), **5)** I-PTH alternated with Alendronate (I-PTH treatment for 5 days and Alendronate treatment for the following 5 days). RNA extraction and qPCR for genes relevant for chondrogenesis was performed.
Results: A substantial increase in FGF2 was observed with I-PTH treatment, but addition of Alendronate reduced the stimulated expression. FGFR3 expression was enhanced by PTH and inhibited by Alendronate, while the combined treatments induced a similar increase induced by I-PTH alone. Alendronate inhibited the expression of ALN, RUNX2 and MMP13, while the combined treatment with I-PTH had an opposite effect. BMP2 expression was increased with Alendronate and decreased with I-PTH, and the combination of drugs has diminished the Alendronate effects. I-PTH increased PRG4 expression, and addition of Alendronate in different regimens has significantly enhanced this effect. No significant difference was found for VEGF and SOX9 between groups.
Conclusion: Although PRG4 expression seems to be enhanced when the two agents were combined, these results suggest lack of synergism between PTH and Alendronate in the induced effects in chondrocytes.

Detailed results and inferences: **Complete manuscript has been submitted for publication and is under review for Aim 1. Abstract has been submitted for the 2022 AADR meeting with Aim 2 results.**

1. If the work has been published please attach a pdf of manuscript OR
2. 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 be included.

Respond to the following questions:

1. Were the original, specific aims of the proposal realized? **Yes**
2. Were the results published? **Manuscript has been submitted and is under revision for Aim 1. Abstract has been submitted for Aim 2.**
    a. If so, cite reference/s for publication/s including titles, dates, author of co-authors, journal, issue and page numbers: **N/A**
    b. Was AAOF support acknowledged? **Yes**
    c. If not, are there plans to publish? If not, why not? **N/A**
3. Have the results of this proposal been presented? **No**
    a. If so, list titles, author or co-authors of these presentation/s, year and locations:
    b. Was AAOF support acknowledged? **N/A**
    c. If not, are there plans to do so? If not, why not? **Results will be presented at the 2022 AADR meeting.**

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

The AAOF funding has helped me to generate data for NIH/NIDCR and AAOF grant submission and to publish relevant manuscripts.

Accounting for Project; i.e., any leftover funds, etc.

There was no leftover funds left.