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**AAO Foundation Final Report Form  
(a/o 5/31/2016)**

Date: June 7, 2017

Type of Award: Center Award

Name(s) of Principal Investigator(s): Laura R. Iwasaki

Co-Investigator: Jeffrey C. Nickel

Secondary Investigators: Larry D. Crouch, Janardan P. Pandey, Mark Johnson

Title of Project: Biomechanical, developmental, and genetic determinants for rate of orthodontic tooth movement in humans

Period of AAOF Support: July 1, 2005 with approved request to transfer (from UNMC to UMKC in 2007) and no-cost extension to June 30, 2016

Amount of Funding: \$69,407

Summary/Abstract of Completed Project (250 word maximum)

**Objectives:** To test rates of tooth translation for optimal stresses and effects of developmental stage, gingival crevicular fluid (GCF) levels of cytokines, and Interleukin-1 (IL-1) gene cluster polymorphisms.

**Methods:** Subjects requiring maxillary first premolar extractions were recruited to this randomized split-mouth study that used segmental mechanics. Height and cephalometric superimposition changes determined growing (G) and non-growing subjects (NG). DNA was collected by cheek-wipes or saliva and stored frozen until ready for genotyping. Subjects were appointed for 9-11 visits over 84 days for maxillary dental impressions to measure three-dimensional tooth movement and check retraction forces. Calibrated springs were selected to apply two different stresses of 4, 13, 26, 52, or 78 kPa to maxillary canines in each subject. Statistical analyses ( $\alpha=0.050$ ) included ANOVA, effect size (partial  $\eta^2$ ), Tukey's HSD, two-group t-tests and full linear regression modeling.

Results: Forty-six subjects consented to participate. Distolateral translation rates were  $0.034\pm 0.015$ ,  $0.047\pm 0.019$ ,  $0.066\pm 0.025$ ,  $0.068\pm 0.016$ , and  $0.079\pm 0.030$  mm/day for 4, 13, 26, 52, and 78 kPa, respectively. Rates were significantly affected by stress (all  $p\leq 0.022$ ; partial  $\eta^2=0.38$ ) and significantly higher ( $p=0.001$ ) in G ( $0.062\pm 0.026$  mm/day) than NG ( $0.041\pm 0.019$  mm/day). Three factors were significant for faster tooth movement ( $R^2=51\%$ ):  $\geq 1$  copy of allele 2 at IL-1B gene, G with high levels of IL-1 $\beta$ , and higher stresses with high levels of IL-1 $\beta$ .

Conclusions - Stress, growth status, GCF levels of IL- $\beta$ , and IL-1 genotype were significant factors for tooth translation rate. In particular, optimal stresses were 26-52 kPa and overall rates were 1.5-fold faster in G compared to NG.

Response to the required questions are as follows:

1. Were the original, specific aims of the proposal realized?

Yes, the original specific aims were realized. As a result of the most recent no-cost extension (NCE) and re-budgeting request approved on May 7, 2014, we were permitted to change the protocols for gingival crevicular fluid (GCF) analyses to expand the number of analytes to 9, including the 2 originally proposed (IL-1 $\beta$ , IL-1RA) by using more current technology than originally proposed. The results of secondary analyses involving the expanded number of analytes, genotyping, combined with the tooth movement results are still in progress but are beyond the original aims.

2. Were the results published?

a.) If so, was AAOF support acknowledged?

b.) If not, are there plans to publish? If not, why not and will AAOF support be acknowledged?

Yes, the results have been published and are listed below. All these publications acknowledge the support of the AAOF.

1. Iwasaki LR, Liu Y, Liu H, Nickel JC (in press): Speed of tooth movement in growers and non-growers: Selection of applied stress matters. *Orthod Craniofac Res*
2. Nickel JC, Liu H, Iwasaki LR (2015): Effects of mechanical stress and growth on velocity of human tooth movement. In *Expedited Orthodontics: Improving the Efficiency of Orthodontic Treatment Through Novel Technologies*, Kapila SD, Nervina J, Hatch N, (eds), Monograph 51, Craniofacial Growth Series, Department of Orthodontics and Pediatric Dentistry and Center for Human Growth and Development, The University of Michigan, Ann Arbor, MI, pp 27-46.
3. DeForest WN, Hentscher-Johnson JK, Liu Y, Liu H, Nickel JC, Iwasaki LR (2014): Human tooth movement by continuous high and low stresses. *Angle Orthod* 84:102-8.
4. Iwasaki LR, Chandler JR, Marx DB, Pandey JP, Nickel JC (2011). IL-1 Genetic polymorphisms and IL-1 protein secretion in gingival crevicular fluid predict the speed of human orthodontic tooth movement. In *Effective and Efficient Orthodontic Tooth Movement*, McNamara JA Jr, Hatch N, Kapila SD (eds), Monograph 48, Craniofacial Growth Series, Department of Orthodontics and Pediatric Dentistry and

- Center for Human Growth and Development, The University of Michigan, Ann Arbor, MI, pp 93-116.
5. Iwasaki LR, Chandler JC, Marx DB, Pandey JP, Nickel JC (2009): IL-1 gene polymorphisms, secretion in gingival crevicular fluid, and speed of human orthodontic tooth movement. *Orthod Craniofac Res* 12:129-140.
  6. Iwasaki LR, Gibson CS, Crouch LD, Marx DB, Pandey JP, Nickel JC (2006): Speed of human tooth movement is related to stress and IL-1 gene polymorphisms. *Am J Orthod Dentofac Orthop* 130:698.e1-e9.

Some results from this study also appear in:

Iwasaki LR (2015). Markers of paradental tissue remodeling in the gingival crevicular fluid and saliva of orthodontic patients. Chapter 10 in *Biological Mechanisms of Tooth Movement*, Second Edition, Davidovitch Z, Krishnan V (eds), Wiley Blackwell, John Wiley & Sons Ltd., West Sussex UK, pp. 138-144.

Nickel JC, Liu H, Marx DM, Iwasaki LR (2014): Effects of mechanical stress and growth on velocity of human tooth movement. *Am J Orthod Dentofac Orthop* 145:S74-81.

DeForest W, Nickel J, Liu Y, Liu H, Iwasaki L (2012): Human tooth movement by continuous high and low stresses. *J Dent Res*, 91(SI A):697.

Hentscher-Johnson JK, Williams KB, Ye L, Walker MP, Nickel JC, Iwasaki L (2012): Pain quality and intensity during tooth translation by two stresses. *J Dent Res*, 91(SI A):698.

Iwasaki LR, Nickel JC (2009). Markers of paradental tissue remodeling in the gingival crevicular fluid of orthodontic patients. In *Biological Mechanisms of Tooth Movement*, Davidovitch Z, Krishnan V (eds), Blackwell Publishing Co, pp 123-142.

Iwasaki LR, Crouch LD, Nickel JC (2008): Genetic factors and tooth movement. *Seminars in Orthodontics* 14:135-145.

Iwasaki LR, Marx DB, Nickel JC (2006): Stress magnitude and growth status affect human tooth movement velocity. *J Dent Res*, 85(SI A):1640.

3. Have the results of this proposal been presented?
  - a.) If so, when and where? Was AAOF support acknowledged?
  - b.) If not, are there plans to do so? If not, why not and will AAOF support be acknowledged?

Yes, the results have been presented as listed below. All these presentations acknowledged the support of the AAOF.

1. Sept. 10, 2016 “Speed of human tooth movement: What the data show,” 2016 Innovators’ Workshop on Personalized and Precision Orthodontic Therapy, organized

- by the Consortium for Orthodontic Advances in Science and Technology and co-sponsored by the Federation of American Societies for Experimental Biology, West Palm Beach, Florida
2. Feb. 20, 2016: "The speed of human teeth: Factors that matter," 25th Australian Orthodontic Congress, Melbourne, Australia
  3. July 17-21, 2015: "Factors that affect the speed of human tooth movement," College of Diplomates of the American Board of Orthodontics 2015 Annual Meeting, Avon, Colorado
  4. Mar. 20, 2014: "GCF biomarkers of orthodontic tooth movement," Symposium: Biomarkers in Gingival Crevicular Fluid (GCF): Current Paradigm Shifts in Dentistry, AADR Annual General Session, Charlotte, North Carolina
  5. Mar. 8-9, 2014: "The speed of teeth in orthodontics: Mechanical limitations and enhancements," invited speaker for the 41st Annual Moyers Symposium: Expedited Orthodontics: Improving Efficiency of Orthodontic Treatment Through Novel Technologies, Ann Arbor, Michigan.
  6. May 4, 2013: "Applied biomechanics reveals factors that affect the speed of human tooth movement," invited speaker for Doctors Scientific Program: Biomechanics Group, 113th AAO Annual Session, Philadelphia, Pennsylvania
  7. Oct. 9, 2012: "Factors that affect the speed of human tooth movement," invited lecture to Facultad de Odontologia, Pontificia Universidad Javeriana, Bogota Columbia.
  8. Feb. 26, 2010: "The speed and nature of human canine retraction," 36th Annual International Conference on Craniofacial Research (Pre-symposium), University of Michigan, Ann Arbor, Michigan.
  9. Oct. 18, 2008: "The speed of teeth," Symposium 50: Horizons of Change in Dental Education, Faculty of Dentistry, University of Manitoba, Winnipeg, Manitoba.
  10. Sept. 12, 2008: "IL-1 gene polymorphisms, secretion in gingival crevicular fluid, and speed of human orthodontic tooth movement," in "Biomedicine in Orthodontics: From Tooth Movement to Facial Growth", 2008 Conferences on Orthodontic Advances in Science and Technology, Pacific Grove, California.
  11. Sept. 12, 2007: "Determinants of the speed of human tooth movement," Oral Biology Seminar Series, UMKC School of Dentistry, Kansas City, Missouri.
  12. May 22, 2007: "Stress and the speed of teeth," American Association of Orthodontists 107th Annual Session, Seattle, Washington.
  13. Feb. 8, 2006: "Factors that affect the speed of orthodontic tooth movement," Georgia Section of the American Association for Dental Research, Medical College of Georgia, Augusta, Georgia.
4. To what extent have you used, or how do you intend to use, AAOF funding to further your career?

The funding provided by this Center Award has provided data for 6 peer-reviewed publications, 4 book chapters, 2 published abstracts and 14 invited presentations, to date. Thus, the outcomes of this award have been helpful to further my academic career and that of my collaborators. In addition, this award has supported the work of three former Master of Science students and a

former Dental Summer Scholar who are now practicing orthodontists (Drs. Jeff Chandler, Jodi Hentscher-Johnson, Matthew McCoy and Whitney (DeForest) Hewitt). Consideration is being given to using the data obtained via this award to apply for further funding to continue research in this area.

Accounting for Project, i.e., any left-over funds, etc.

All funds from this award have been spent on the project, according to the approved budget and with the oversight of the UMKC School of Dentistry Research Office.

Please return to AAOF via email attachment to [aaofevp@aaortho.org](mailto:aaofevp@aaortho.org)