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# AAO Foundation Final Report Form
**(a/o 6/30/2020)**

*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, Biomedical Research Award

Name(s) of Principal Investigator(s): Carlos Flores-Mir, Daniel Graf

Institution: University of Alberta

Title of Project: An exploration into the paradox of midfacial hypoplasia and pediatric upper airway obstruction: probing intrinsic defects in bone/cartilage differentiation

Period of AAOF Support (e.g. 07-01-20 to 06-30-21): 07-01-21 to 06-30-22

Amount of Funding: 30,000 USD

Summary/Abstract:

Midfacial hypoplasia is often associated with severe morbidities that require surgical intervention, such as upper airway obstruction (manifested as sleep-disordered breathing [SDB]), malocclusion or craniosynostosis. Surgical intervention in children with severe hypoplasia is prone to complications and a high relapse rate. Our understanding of midfacial growth is incomplete; there is disagreement about whether midfacial growth is driven by the nasal septum, frontonasal suture, or both. Furthermore, controversy about whether upper airway obstruction leads to reduced midfacial growth reflects intrinsic complex changes to bone formation. This results in uncertainty regarding the best type of surgical approach and the appropriate timing for surgical intervention. It also hampers optimal non-surgical management in milder cases.

Our research team recently identified that children with sleep-disordered breathing show a significant reduction in their mandibular cortical width, which is already evident in children younger than five. This provides a clinical suggestion that intrinsic changes to craniofacial bone formation capacity might be associated with severely altered sleep breathing disorders. We recently completed the first genetic mouse model's phenotypic characterization for midfacial hypoplasia that developed upper airway obstruction during rapid midfacial growth (funded through AAOF). We noted changes to cartilage, bone, and sutures that preceded upper airway obstruction, suggesting that those tissues' intrinsic defects directly predispose to growth anomalies.

**We hypothesize that intrinsic defects to bone/cartilage formation and growth are associated with midfacial hypoplasia.** Understanding these defects will allow for better diagnostics and improve clinical management options in the long term. This project addresses a significant **gap of knowledge** highly relevant for maxillofacial and ENT surgeons, sleep medicine specialists and orthodontists to develop better patient-specific interventions with an increased success rate.

**This project aims** to understand to what degree bone, cartilage, and suture anomalies might contribute to midfacial hypoplasia and airway obstruction. We will address this in three objectives, each grounded on foundational observations from our mouse model and correlate those findings to affected children.

Objective 1: Nasal cartilage – substantial deviation of the nasal septum in mice, is accompanied by osteoarthritic-like changes to the nasal cartilage. We will investigate these changes in detail and extend our findings to biopsies from septoplasties in children with upper airway obstruction.

Objective 2: Bone – children and mice show reduced bone formation (mandibular cortical width). We will investigate whether this reduction is associated with intrinsic bone formation and remodelling differences and whether systemic markers for bone remodelling can identify this fact.

Objective 3: Sutures – our mouse model shows changes in suture organization and growth, raising the possibility that midfacial hypoplasia could also be reflected in changes in surrounding suture physiology. We will test whether the process of intramembranous ossification is altered in our mouse model, how this affects interdigitation of midpalatal and palatine sutures, and whether changes to interdigitation are also evident in children with airway obstruction.

Impact and significance: The proposed work investigates to what degree intrinsic changes to bone/cartilage formation are associated with midfacial hypoplasia and airway obstruction. A better understanding of how the various factors contribute to these malformations should enable an improved differential diagnosis and better-personalized treatment plans based on these etiologies.

Respond to the following questions:

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

   To understand to what degree bone, cartilage, and suture anomalies might contribute to midfacial hypoplasia and airway obstruction. Three objectives, each grounded on foundational observations from the proposed mouse model and correlate those findings to affected children, were planned over a period larger than the length of the AAOF funding cycle.

Current status:

**Objective 1a**: Nasal cartilage – Identify molecular and cellular changes associated with septum deviation – Determine which chondrocyte/cartilage properties are controlled by BMP7 in the nasal cartilage.
Objective completed and published in:
Baddam P, Roth DM, Biancardi V, Eaton F, Thereza-Bussolaro C, Mandal R, Wishart DS, Barr A, MacLean J, Flores-Mir C, Pagilardini S, Graf D. Neural crest-specific deletion of Bmp7 leads to midfacial hypoplasia, nasal airway obstruction, and disordered breathing modelling Obstructive Sleep Apnea. Disease Models & Mechanisms 2021; 14: dmm047738. Doi: 10.1242/dmm.047738
**Objective 1b**: Nasal cartilage – Identify molecular and cellular changes associated with septum deviation – Identify proteome changes in biopsies from children undergoing septoplasty with/without nasal septum deviation.
Human ethics approved. A new MSc student in the lab will start investigating human cartilage samples in 2023.

**Objective 2a**: Bone – Identify molecular and cellular changes associated with reduced bone formation - Deciphering the molecular control of midfacial growth in BMP7-deficient mice.
The objective in progress – significant data already collected.
**Objective 2b:** Bone – Identify molecular and cellular changes associated with reduced bone formation - Deciphering the molecular control of midfacial growth in children with midfacial hypoplasia.

Human ethics approval is in progress.

**Objective 3a:** Sutures – Identify molecular and cellular changes associated with midfacial hypoplasia - Identification of cellular changes in sutures from BMP7-deficient mice
The objective in progress – significant data already collected. Preparation of two manuscripts in progress: one primary research paper based on the suture phenotype in BMP7-deficient mice and one clinical review paper discussing suture anomalies associated with *delayed* suture fusion. Both manuscripts are expected to be submitted by the end of 2022.

**Objective 3b**: Sutures – Identify molecular and cellular changes associated with midfacial hypoplasia - Assessment of sutures of children at risk of OSA
Human ethics approval is in progress. Identified DDS student willing to perform analysis on CBCT scans.

2. Were the results published?
    a. If so, cite reference/s for publication/s including titles, dates, author or co-authors, journal, issue and page numbers

Baddam P, Roth DM, Biancardi V, Eaton F, Thereza-Bussolaro C, Mandal R, Wishart DS, Barr A, MacLean J, Flores-Mir C, Pagilardini S, Graf D. Neural crest-specific deletion of Bmp7 leads to midfacial hypoplasia, nasal airway obstruction, and disordered breathing modelling Obstructive Sleep Apnea. Disease Models & Mechanisms 2021; 14:

dmm047738. Doi: 10.1242/dmm.047738 (AAOF funding, leveraged funding acknowledged)

Baddam P, Bayona-Rodriguez F, Campbell SM, ElHakim H, Graf D. Properties Of The Nasal Cartilage, From Development To Adulthood: A Scoping Review. Cartilage 2022; 13: 19476035221087696 . doi: 10.1177/19476035221087696/ ID: CART-21-0241.R1

b. Was AAOF support acknowledged? Acknowledged noted.

c. If not, are there plans to publish? If not, why not? Two additional publications are in preparation (see objective 3)

3. Have the results of this proposal been presented?
   a. If so, list titles, author or co-authors of these presentation/s, year and locations
      Due to COVID restrictions, several relevant conferences were postponed. Results were presented in invited presentations by:
      Daniel Graf:
      1) University of Missouri-Kentucky, Nov 10, 2021, Midfacial hypoplasia: lessons from a mouse model
      2) University of Alberta, Medical Genetics Grand Rounds, Jan. 12, 2022, Midfacial hypoplasia: lessons from a mouse model
      3) University of British Columbia, School of Dentistry, Sept 8, 2022, Midfacial hypoplasia: How changes to cell properties lead to developmental anomalies

   b. Was AAOF support acknowledged? Yes
   c. If not, are there plans to do so? If not, why not?

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

   AAOF funding was critical for initiating the career of Pranidhi Baddam, who is now a PDF in a prestigious USA institution. AAOF also supported the work of the PhD candidate Daniela M Roth, who spearheaded the suture review and is preparing two further publications concerning objective 3.

   AAOF funding helped to directly leverage funding:

- Women and Children Health Institute (WCHRI), University of Alberta CAD$ 50,000
- G & R Sperber Fund in Craniofacial Research, University of Alberta CAD$ 30,000
- NSERC PhD Studentship (Pranidhi Baddam) CAD$ 63,000

In addition, AAOF-funded research indirectly contributed to the acquisition of 2 major grants:

- National Sciences and Engineering Research Council (NSERC), Canada CAD$ 160,000
- Canadian Institute for Health Research (CIHR), Canada CAD$ 740,000

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

All funds have been spent.