Objectives

- Appreciate the principles of craniofacial epigenetics, which includes epigenetic orthopedics as well as the concept of epigenetic orthodontics
- Introduce the principles of Pneumopedics®
- Gain knowledge of biomimetic oral appliances
- Apply these concepts as a potential cure for Obstructive Sleep Apnea in a multi-disciplinary, dental setting
What about teeth?

Epigenetics is the study of phenotypic changes that occur via mechanisms other than DNA sequence alteration. These changes are mediated by covalent attachments of chemical groups to the DNA and its associated proteins, histones and chromatin.

Types of epigenetic modification include: ADP-riboylation, acetylation, methylation, phosphorylation, sumoylation and ubiquitination.


Researchers release most complete mapping of the Human Epigenome to date

The New York Times (February 19, 2015) reports that 200 scientists working on an ambitious federal project have begun to understand the complicated system of switches that regulates genes, turning some on and others off. The scientists hope these discoveries will eventually lead to a deeper understanding of diseases and new ways to treat or cure them. Their findings are published in 24 papers in Nature and other journals.

WHAT IS EPGENETICS?

WHAT IS BIOMIMETICS (BIOMIMICRY)?

A science that studies natural models and then uses these designs and processes to solve human problems.

WHAT IS CRANIOFACIAL EPIGENETICS?

Craniofacial epigenetics uses a person’s natural genes to correct and straighten the jaws, teeth, soft tissues and functional spaces, painlessly, using biomimetic appliances.

Epigenetic orthodontics
Cosmetic treatment with health benefits

Includes epigenetic orthopedics for bone formation and remodeling

PNEUMOPEDICS® Non-surgical upper airway remodeling
Pre-Distraction osteogenesis

Post-Distraction osteogenesis

Improved facial soft tissue profiles

Results from midfacial distraction osteogenesis alone showed similarity to maxillo-mandibular advancement

Spatial Matrix Hypothesis

- During growth, spatial and functional alignment of skeletal elements is maintained through remodeling of bony surfaces (including the periodontium) to permit function
- Environmentally-(or genetically-) induced changes (e.g., tooth extraction, digit-sucking etc.) produce changes in early morphologic relationship → new solution (phenotypic variation)
- This 'new solution' represents Departure from the genetically encoded 'developmental body plan' (Temporo-Spatial Patterning)
- Developmental compensation occurs to permit compromised function → malocclusion, TMD, OSA, tori, etc
- Decompensation required through treatment with appropriate spatial signaling to re-establish (genomic) pattern formation for optimal form and function

Singh, GD. British Dental Journal, 2007

Singh, GD. Michigan Craniofacial Growth Series, 2004
What is the dental arch morphology in adults with OSA?

Mean upper arch OSA configuration 7-11% narrower
Mean lower arch OSA configuration 10-11% narrower

N = 108

Craniofacial effects following DNA appliance treatment: 38 year old adult diagnosed with OSA

After 10 months of active treatment the minimum transpalatal width increased from 34mm to 39mm

Singh, Wendling et al. Dent Today 2011

Case progress with biomimetic DNA appliance

October, 2010
October, 2011

July, 2015
August, 2016

3D CBCT scan transverse sections

Change in upper airway after 15 months

Singh, Wendling et al. Dent Today 2011

71% increase in upper airway volume from 12889mm³ to 22024mm³
Decrease in AHI from 24/hr to 2.8/hr after 10 months with no device in the patient’s mouth

38 year old: 12 months DNA appliance therapy

**Enhanced craniofacial homeostasis**

Singh GD et al. Dent Today 2011

**Abstract**

Purpose: The aim of this study was to review studies using cavo plane computed tomography (CBCT) to assess differences in the upper airway after appliance or surgical therapy in subjects with obstructive sleep apnea and to correlate CBCT findings with treatment outcomes. Helical tomographic data were matched. Studies for patient-specific outcomes were evaluated using a customized evaluation tool.

Results: Parameters were not in seven articles. Fifty studies were assessed using CBCT 12 or 16 months after an appliance therapy or orthognathic maxillary advancement surgery with or without geniobuccal advancement. Areas (parameters measured were linear, cross-sectional (CS) area, volume or airway function). Finally two additional surgical case reports, airway volume increased by 6.8 – 8.7 cm³ (+87%) and navigation by 6.0% (±2.8 cm²) and 7.4% (±4.8 cm²).

Conclusions: The available published studies show evidence of CBCT measured anatomic changes with surgical and dental appliance treatment in OSA. There is insufficient data to develop a consensus for treatment outcomes in real life. High-quality evidence based studies, with statistically appropriate sample size and data collection methodology, are needed to determine the CBCT airway dimensional changes are suitable for outcomes of treatment outcomes.

Singh and Cress, Dent Today, 2013

**Case study:**

Non-surgical cosmetic treatment with health benefits

Singh and Cress, Dent Today, 2013
Upper arch: Orthodontic changes

Initial 12 Months

Singh and Cress, Dent Today, 2013

Lower arch: Orthodontic changes

Initial 12 Months

Singh and Cress, Dent Today, 2013

3D CBCT SUPERIMPOSITION

POST = BLUE  PRE = GREY

Singh and Cress, 2013

UPPER AIRWAY ANALYSIS

Pneumopedic® effect with no appliance in mouth

Singh and Cress, Dent Today, 2013

Biomimetic effects in adults following epigenetic orthodontic treatment with the DNA appliance

Is there an increased transpalatal bone width after DNA appliance therapy in adults?

Singh, Heit et al., J Ind Orthod Soc. 2014

Patient Pre-treatment Post-treatment

<table>
<thead>
<tr>
<th></th>
<th>Transpalatal bone width (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASE</td>
<td>28.71</td>
</tr>
<tr>
<td>FE</td>
<td>31.12</td>
</tr>
<tr>
<td>HF</td>
<td>33.44</td>
</tr>
<tr>
<td>CH</td>
<td>32.95</td>
</tr>
<tr>
<td>KH</td>
<td>35.44</td>
</tr>
<tr>
<td>NN</td>
<td>30.12</td>
</tr>
<tr>
<td>KR</td>
<td>32.57</td>
</tr>
<tr>
<td>JD</td>
<td>39.91</td>
</tr>
<tr>
<td>Mean</td>
<td>33.03</td>
</tr>
</tbody>
</table>

P value = 0.002
Is there an increased maxillary bone volume after DNA appliance therapy in adults?

Biomimetic effects in adults following epigenetic orthodontic treatment with the DNA appliance

Singh, Heit et al., J Ind Orthod Soc. 2014

<table>
<thead>
<tr>
<th>Patient</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASE</td>
<td>14143</td>
<td>15121</td>
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<tr>
<td>FE</td>
<td>15218</td>
<td>19823</td>
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<tr>
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<td>19374</td>
<td>21289</td>
</tr>
<tr>
<td>CH</td>
<td>20036</td>
<td>20609</td>
</tr>
<tr>
<td>KH</td>
<td>18884</td>
<td>19572</td>
</tr>
<tr>
<td>NN</td>
<td>16689</td>
<td>16869</td>
</tr>
<tr>
<td>KR</td>
<td>12389</td>
<td>17287</td>
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<tr>
<td>JD</td>
<td>21536</td>
<td>21858</td>
</tr>
<tr>
<td>Mean</td>
<td>17.3 cm$^3$</td>
<td>19.1 cm$^3$</td>
</tr>
<tr>
<td>P value</td>
<td>= 0.02</td>
<td></td>
</tr>
</tbody>
</table>

Singh, Heit et al., J Ind Orthod Soc 2014

Example of Non-surgical procedure:

Pre-treatment and progress comparison

Pre-treatment conditions

Example of Non-surgical procedure:
**WHAT IS PNEUMOPEDICS?**

Pneumopedics is the process of non-surgical, upper airway remodeling that may result from treatment with a biomimetic oral appliance.

**How does Pneumopedics work?**

The biomimetic oral appliance system uses the principles of Epigenetics to activate a person’s naturally-occurring genes to correct deficiencies in the craniofacial region. The tissues in the craniofacial region are slowly redeveloped and remodeled over time, making corrections to the structure of the upper airway, non-surgically. It is a pain-free, minimally invasive process, which uses no drugs, medication or injections.

During the Pneumopedic process, the craniofacial region undergoes structural changes so that the functional space of the upper airway increases volumetrically, allowing for improved function of basic, physiologic processes, such as breathing during sleep. This is the reason that this system of biomimetic oral appliances can be used to treat, reduce and eventually eliminate OSA.

**Further research questions**

- Is there an increased nasal cavity **widths** after DNA appliance therapy in children/adults?
- Is there an increased nasal airway **volume** after DNA appliance therapy in children/adults?
The aim of this study is to evaluate changes in nasal airway volume in adult patients following biomimetic oral appliance therapy.

**Objective**

**Methods**

After obtaining informed consent, we undertook 3D cone-beam (CBCT) scans of 11 consecutive, adult patients (mean age approx. 38 years) prior to and 18 months after biomimetic oral appliance therapy. These cases had all been diagnosed with clinical midfacial hypoplasia without congenital malformation.

To acquire the nasal cavity volume, volumetric, 3-D reconstruction of the nasal cavity was undertaken between the anterior and posterior nasal spines, extending superiorly from the palatine process of the maxilla and the palatine bone to the cribriform plate of the ethmoid bone. Laterally, the maxillary sinuses were trimmed out at their junction with the nasal cavity on the 3D CBCT data.
Volumetric reconstruction of the nasal cavity

Measurement of nasal airway volume

The nasal cavity volume was calculated in all cases. The findings were subjected to statistical analysis, using paired t-tests.

Improved nasal symmetry and functional space

Nasal airway volume changes in adults (cm$^3$) after 18 months

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pre-Treatment</th>
<th>Post-Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASE</td>
<td>33.596</td>
<td>33.596</td>
</tr>
<tr>
<td>FE</td>
<td>56.001</td>
<td>56.001</td>
</tr>
<tr>
<td>HF</td>
<td>50.067</td>
<td>50.067</td>
</tr>
<tr>
<td>CH</td>
<td>55.534</td>
<td>55.534</td>
</tr>
<tr>
<td>KH</td>
<td>43.624</td>
<td>43.624</td>
</tr>
<tr>
<td>NN</td>
<td>30.381</td>
<td>30.381</td>
</tr>
<tr>
<td>KR</td>
<td>36.765</td>
<td>36.765</td>
</tr>
<tr>
<td>JB</td>
<td>23.083</td>
<td>23.083</td>
</tr>
<tr>
<td>JD</td>
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<td>68.923</td>
</tr>
<tr>
<td>EA</td>
<td>33.515</td>
<td>33.515</td>
</tr>
<tr>
<td>TK</td>
<td>29.460</td>
<td>29.460</td>
</tr>
<tr>
<td>AT</td>
<td>47.114</td>
<td>47.114</td>
</tr>
</tbody>
</table>

Mean $39.8cm^3$ | $42.3cm^3$

p value $P < 0.05$

Table Clinic Prize 2014


Example of Non-surgical procedure:

Courtesy: Dr Tammarie Heit, DDS

Further research questions

What are the effects of increased nasal airway volume after DNA appliance therapy in adults diagnosed with OSA?

The aim of this study is to test the hypothesis that the upper airway can be enhanced in adults diagnosed with OSA so that CPAP therapy might potentially become avoidable.
Methods

- 11 consecutive adults aged >21yrs.
- Diagnosed with mild to moderate OSA, following HST interpreted by a Board certified sleep physician.
- Each subject was treated using biomimetic oral appliance therapy by a dentist (TG) with advanced training in dental sleep medicine.
- The mean AHI of the study sample was calculated prior to and after treatment with no appliance in the mouth when both sleep studies were done.

Results

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pre-AHI</th>
<th>Post-AHI</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5.4</td>
<td>3.1</td>
<td>16</td>
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<td>B</td>
<td>10.9</td>
<td>7.1</td>
<td>19</td>
</tr>
<tr>
<td>C</td>
<td>21.9</td>
<td>2.5</td>
<td>13</td>
</tr>
<tr>
<td>D</td>
<td>13.7</td>
<td>1.1</td>
<td>7</td>
</tr>
<tr>
<td>E</td>
<td>8.2</td>
<td>3.7</td>
<td>4</td>
</tr>
<tr>
<td>F</td>
<td>21.3</td>
<td>12.8</td>
<td>4</td>
</tr>
<tr>
<td>G</td>
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<td>3.7</td>
<td>4</td>
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<tr>
<td>H</td>
<td>5.1</td>
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<td>I</td>
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<td>13.3</td>
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<tr>
<td>Std</td>
<td>5.9</td>
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</tr>
<tr>
<td>p value</td>
<td>&lt; 0.01</td>
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<td></td>
</tr>
</tbody>
</table>

Mean AHI Improvement 68.4%

Singh, Griffin et al. World Association of Sleep Medicine, 2015 doi:10.1016/j.sleep.2015.02.020

Patient History and Physical Findings

- A 27 year old female reported to our office with TMD symptoms, was screened for OSA and was diagnosed with severe obstructive sleep apnea with an initial AHI of 105/hr
- Level 1 sleep study showed AHI 118/hr
- Referred to ENT for tonsillectomy.
- Reduced AHI 70/hr and controlled on CPAP, which she did not like.
- Initiated DNA appliance therapy for 9 months (combined with CPAP).
- Resulted in AHI of 1/hour without CPAP or DNA appliance in situ.

Oropharyngeal appearance: Before and after tonsillectomy

Courtesy: Dr Tammarie Heit, DDS
Follow up study on severe OSA treated by different dentists, using DNA appliance or mRNA appliance therapy

Singh, Griffin and Cress, J Sleep Disorders Therapy, 2016

More recent data: Long-term (5yr) follow-up

Singh, Liao, Stevens, ENT 2017
Case study 1: Non-surgical cosmetic treatment with health benefits

These correlations of form and function support the notion of Craniofacial Homeostasis.

Pre-treatment

Mid-treatment

Post-treatment

Finished Case: 14 months
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**CONCLUSIONS**

- Non-surgical upper airway remodeling can be obtained in both children and adults, and suggests that genetically-encoded developmental mechanisms may be epigenetically-modulated by biomimetic oral appliances to enhance the upper airway in patients with OSA.

- These findings may help dentists in the management of adults and children diagnosed with obstructive sleep apnea, using Pneumopedics® and craniofacial epigenetics.