Craniofacial Biology Research Informs Health Care: Past, Present & Future

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USA – Japan Biomedical Scientific Research Cooperation and Collaborations
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Niigata, Showa, Okayama, Kyoto, Kyushu, Kagoshima, Tokai, Tohoku, Notre Dame Seishin Universities
The Burden of Congenital and Acquired Craniofacial Anomalies

- 1 out of every 10 people in industrial countries present craniofacial-oral-dental disease or disfigurements.

- 1 million people in USA have severe congenital craniofacial-oral-dental disfigurements (e.g. non-syndromic and syndromic clefts, birth marks, hemangiomas, oligodontia, severe malocclusions).

- Acquired craniofacial-oral-dental diseases and disorders include severe facial burns, head and neck trauma, head & neck cancers, hypertrophic scars, and severe acne with facial scars impact many millions of people.

- Total direct & indirect global health care costs are $500 billion per year.
Vertebrate fossils show craniofacial birth defects
Aristotle and biological observations
Anatomy, embryology, surgery, and facial deformities
Synthesis of biology, genetics, biochemistry, embryology, histology to become “Developmental Biology” (Evo-Devo)
Hans Spemann receives Nobel Prize in 1935
Herbert Cooper creates first craniofacial team (1938)
World War II and the derivatives of ultrasound, antibiotics, anesthesiology, and craniofacial surgery and rehabilitation
Vannevar Bush and the modern creation of the NIH (cancer, dental, and heart) in 1948
NIDR creates “1st” Genetics Branch at NIH (1950)
NIDR first grants for craniofacial in 1957
Thalidomide Epidemic & Teratogen-Induced Dysmorphology (10,000 infants with dysmorphology in 1957)
Landmark Conference December 6-9, 1959 called “Gatlinburg Conference” or “Congenital Anomalies of the Face and Associated Structures”
Paul Tessier, John Converse, Peter Randal, Bob Gorlin, Michael Cohen, Jr. & Sam Pruzansky Exemplars of Clinical Scholars
Basic, translational & clinical research in craniofacial diseases and disorders (genetics, teratogens, nutrition, hearing, speech, vision, occlusion & orthodontics) in USA, Japan, UK and Beyond (1980s)
NIDR to NIDCR in 1998 (budget doubles) “50 Year Anniversary”
NIDCR sponsors “Face Base Initiative” 2004-present
Gordon Conferences establish “Craniofacial Morphogenesis and Tissue Engineering” conference every two years
Customized or personalized craniofacial medicine and dentistry
From Fish to Philosopher: “Evo-Devo” Evolution & Developmental Biology

Slavkin *Birth of a Discipline: Craniofacial Biology*, Aegis Communications 2012
“A Tipping Point:” Thalidomide Tragedy Informs Teratology & Craniofacial Birth Defects (1950s – 1970s; Accutane in 1980s)

Slavkin *Birth of a Discipline: Craniofacial Biology, Aegis Communications 2012*
Highly Conserved Homeotic Genes Discovered that Control Craniofacial and Body Form (1980s)

From flies to pediatrics, HOX genes regulate the entire body segmentation plan, from head to toe

Slavkin *Birth of a Discipline: Craniofacial Biology*, Aegis Communications 2012
From Chromosome Discovery
To Karyotyping
To Genomics
To Proteomics
To Metabolomics
To Pharmacogenomics and Systems Approaches
To Biomimetics and Tissue Engineering
To Regeneration and Nano-bio-informatics
And Beyond
SELECTED EVENTS

- Social Security Act included funds for the care of children with congenital birth defects-1935
- 1st Cleft Palate Clinic- (Dr Herbert Cooper); 1st Craniofacial Team-1938 (creation of Inter Professional Teams for Health Care)
- NIDR created-1948
- Thalidomide Epidemic (10,000 babies) – October 1957
- NIDR first genetics branch at NIH; March of Dimes -1958
- NIDR supports Gatlinburg Conference-December 1959
- 1st March of Dimes Conference-1960
- Dr Sam Pruzansky coins term “craniofacial biology” – 1968 (synthesis of embryology, biochemistry, clinical)
- Japanese, USA, UK, France, Australia, Canada, Scandinavia Cleft lip and Cleft Palate Centers for Clinical Services as well as Research Institutes created at many Universities in the 1970s and 1980s
- NIDR becomes NIDCR in 1998; leads Surgeon General’s Report on Oral Health
- Regenerative medicine & dentistry, tissue engineering, clinical trials for ED, Gordon Conferences, NIDCR FaceBase, Personalized Health Care, Genomics, Saliva as diagnostic fluid, 3-D Imaging, Nanotechnology, $1,000 for patient’s complete genome, and microbiome in 21st Century
Composition of Craniofacial Interprofessional Health Teams
(100s CF Teams in USA, Japan, Europe & Beyond, 2014)

Surgeon, Pediatrician, Pedodontist, Prosthodontist, Orthodontist, Speech Therapist, Audiologist/ENT, Geneticist, Clinical Psychologist, Social Services, Physical Therapy for Feeding Disorders, Nursing, Psychiatry, Nutrition and Education, Dental Hygiene, Anesthesiology
Craniofacial (Multidisciplinary) Teams

Fundament research investments provides fuel for craniofacial biology in post-genomic era.
Examples of Research Opportunities in Craniofacial Biology

- Predications of patients in terms of repair, wound healing, and/or regeneration (phenomics: as genotype connects with phenotype)
- Advances in osseoinduction, osseointegration, and future growth patterns (e.g. “Does lip repair affect midface growth? Speech?”)
- Gene Therapy (e.g. saliva production with gland regeneration)
- Cell Therapy (e.g. immunomodulation, drug delivery, tissue and organ regeneration)
- Protein Therapy (e.g. X-linked ectodermal dysplasia using protein ectodysplasin A to rescue clinical EDX phenotype)
- Cell, Tissue & Organ Regeneration (Biomaterials)
- Advances towards understanding genotype/phenotype relationships (Phenomics) and drug/genotype interactions (pharmacogenomics)
- Quantitative and Systems Biological approaches
- Innovations for digital 3-D imaging & impressions, speech & hearing
Craniofacial-Oral-Dental Genomics! Will Dentistry Ride the Wave or Watch From the Beach? Now is the time!
A call for increased education in genetics for dental health professionals. Collins & Tabak, 2004 JDE


A view of the future: dentistry and oral health in America. Garcia & Tabak, 2009 JADA
Larry Tabak and Francis Collins

A call for increased education in genetics for dental health professionals. Collins & Tabak, 2004 JDE
One of thousands of innovative clinicians

Dr. Paul Tessier

A French Surgeon who created a major transformation of craniofacial surgery; consulted for NIDCR in 1960s-1980s; provided training for many craniofacial surgeons such as Dr. Henry Kawamoto; close friends with Drs. Sam Pruzansky and John Converse
Calls To Action for “Personalized Oral Health” (2012-2014)

Personalized Medicine: Will Dentistry Ride the Wave or Watch from the Beach? Kornman & Duff, 2012 JDR

Personalized Oral Health Care: Providing “–omic” Answers to Oral Health Queries. Glick, 2012 JADA


Patient Stratification for Preventive Care in Dentistry. Giannobile, Braun, Caplis, et al. 2013 JDR

Personalized Medicine Enters Dentistry: What Might This Mean for Clinical Practice? Giannobile, Kornman & Williams. 2013 JADA

Revising the scope of practice for oral health professionals in health care: Enter Genomics. The Santa Fe Group (Primary Author Slavkin). 2014 JADA

From phenotype to genotype: enter genomics and transformation of health care. Slavkin. 2014 J Dent Res
Expanding the foundation for personalized medicine: implications and challenges for dentistry (Garcia, Kuska & Somerman, 2013 in JDR “Clinical Reviews in Oral Biology & Medicine 92(suppl 1):3-10s)

- Personalized health care aims to individualize care based on a person’s unique genetic (genotype), environmental, and clinical profile (phenotype).

- The completion of the Human Genome Project (2004), and cost-effective whole genome-wide sequencing methods and bioinformatics (2013), now enable clinicians to formulate decisions based upon the patient’s genotype and phenotype (e.g. risk assessment, diagnosis, treatment, prognosis).

- Now is the time for oral health professionals to prepare for the arrival of personalized health care.
Strategic Plan 2014-2019

“Enable Precise and Personalized Oral Health Care”

Martha Somerman
DDS, PhD.
Director, NIDCR,
Science fuels engine of technology & informs clinical health care (21st Century)

Post-Genomic Era, Stem Cells, Systems Biology, Nanotechnology

“Live Longer, Live Better” (Prevention & Behavioral Sciences)

Non-Invasive Imaging (functional MRI, 3-D imaging), Biomedical Engineering

Biomimetics & Regenerative Medicine/Dentistry (cells, tissues, organs)

Major Revisions of Health Professional Education

Multidisciplinary “Team” Primary Health Care
Types of CI/CP
(in California 1:500 live births)

The burden of craniofacial conditions cause $95.9 billion per year in medical and wage/household work costs (1999 dollars). A baby is born every hour with CL/CP in USA, every minute world-wide, and often requires surgery, speech, hearing, learning, orthodontics, dental, feeding needs, social services & psychosocial health care needs
Human genetics very successful at explaining diseases caused by single gene mutation (Mendelian Inheritance)

Genotype

Phenotype

Environment
PHENOTYPE + GENOTYPE
from single nucleotide polymorphisms to patient, family & population craniofacial phenotypes

Phenomics
- Cleft lip and/or Cleft palate
- Male vs female
- Isolated and/or Syndromic

Genomics
- TGFalpha, RARA, IRF6 and Other Gene Networks (e.g., BMPs, TGF-betas, Wnts, Shh)
Examples of the Regulatory Genes that Control Craniofacial-Oral-Dental Morphogenesis

• Anhydrotic Ectodermal Dysplasia: TNF-alpha ligand and receptor genes

• A Novel Oligodontia: PAX9 transcription factor gene

• Cleidocranial Dysplasia (supernumerary teeth): CBFA-1 transcription factor gene

• Rieger Syndrome (tooth number, size and shape): PitX2 transcription factor genes

• 700 genes identified in mice and 200 in humans (see Inborn Errors of Development)
Phenotype of the X-linked Anhidrotic Ectodermal Dysplasia (ED) child
Can we correct single gene mutations?

- X-linked Anydrotic Ectodermal Dysplasia
- Human defects include sweat and lacrimal glands, hair, nails and teeth
- Mouse animal models
- Dog animal models
- Define and measure clinical phenotype features

- Therapeutic Strategies
- Inject TNF-alpha (EDA) during pregnancy
- Inject TNF-alpha (EDA) after birth
- “Proof of Principle”
- FDA approvals
- Public/private partnerships
- First patient injected with ED1200 protein in 2013; with clinical trial in progress
WHAT IS EDA1200?

It is a fusion protein which combines a portion of the EDA1 protein (which, in XLHED patients, is not produced correctly) with a portion of an antibody molecule.

EDA1200 is called ectodysplasin A or EDA. In ‘replacement therapy’ clinical studies EDA1200 rescues clinical mutant phenotype in mice and dogs.

In dog studies, ‘replacement therapy’ with EDA1200 two days after birth was most effective to eliminate mutant phenotype. If two weeks after birth, there was no benefit.
Permanent correction of an inherited ectodermal dysplasia with recombinant EDA (TNF-alpha receptors) Gaide & Schneider Nature Medicine 9:614, 2004

- X-linked hypohidrotic ectodermal dysplasia
- Absent or deficient hair, teeth and sweat glands
- The mouse strain *Tabby* shares phenotypic characteristics with human EDA
- Treat pregnant *Tabby* with recombinant form of EDA1, that crosses the placenta, and it “rescues” the phenotype in all offspring
- The first example of a developmental defect that can be permanently corrected
Ectodysplasin-A1 can rescue hair and tooth growth, and sweat gland development in *Tabby* mice (Oliver Gaide, 2009) & dogs (Margaret Casal)

- Mutations in ADA-A1 cause ectodermal dysplasia in mice, dogs and humans
- EDA splice isoforms are EDA-A1 and EDA-A2; they both bind to EDAR and XEDAR (receptors) and promote transcription
- EDA-A1 used in gene and protein therapy to administer to mammals (mice and dogs) to rescue genetic defects by producing “normal” phenotype (hair, sweat glands and teeth)
- 2001-2009: first time a genetic defect was rescued and produced “normal” clinical phenotype
In utero exposure to recombinant FcEDA1 results in complete reversion of the Tabby clinical phenotype.
1990, Jonathan Zonana and Juha Kere discovered XLHED [X-linked hypohidrotic (anhydrotic) ectodermal dysplasia].

2000-2009, Oliver Gaide and Pascal Schneider identified ED1200 protein and showed that this protein rescued mutant mice with HED.

2006-2009, Margaret Casal rescued HED in dogs.

2010, FDA approval for EDIMMER COMPANY to begin ‘replacement therapy’ clinical trials with the National Foundation Ectodermal Dysplasia.

2012-2013 Studies to better define and quantitate phenotypes.

2013 First ED infant injected with ED 1200.
Key References:

http://www.genecards.org (2013)

National Foundation for Ectodermal Dyslasia (see www.nfed.org and info@nfed.org)
Tissue Engineering Applications for Challenges of Craniofacial-Oral-Dental Birth Defects, Head and Neck Trauma, and Head and Neck Cancers
Biomimetic Approach for Nose Replacement: Stem Cells, Scaffolds, Tissue Engineering and Biomaterials

Robert Langer MIT
Biomimetic Solutions for Nasal Carcinoma
Design and Fabricate Human Roots Using Stem Cells

Dental implant

Porcelain Crown

Stem cell-mediated Root/Perio-complex regeneration

Bio-root implant

Songtao Shi 2006
George Washington’s false teeth were crafted from gold, ivory, lead, human and animal teeth in 18th century.

Possibilities for tooth regeneration in 21st century?
Biomimetic Opportunities

- Tooth, muscle, cartilage, bone and nerve regeneration
- Stem cells and tissue/organ engineering - - -soft and hard tissues (birth defects? Bone augmentation?)
- Improve dental & medical implant technology
- Understand soft and hard tissue inflammation and wound healing processes
- Antimicrobial resistance and discovery of new pathogens (microbial genomics)
- Innovative diagnostics (saliva and bioimaging)
- Pharmacogenomics to design “personal” therapeutics
Science is the fuel that drives the engine of technology and informs clinical health care

Stem cells
Nanobiotechnology
Haptics and related informatics
Synthetic biology
Biomimetics
HapMaps and SNPs (bioinformatics)
Systems Biology (e.g. “Diseasome”)
...ACGTATTGCTAAT
CGATTCGGCAT...

Genetic Code=Triplets or Codons (CGG, ATA)
Human Genomic Math: 21,000 genes & 19,000 pseudogenes
Human Genetic Variations, and Variation in DNA Sequences (less than 0.1% of Human Genome)

3.2 billion letters of human DNA encoded within 21,009 genes
1 Base per 1,000 Shows Single Nucleotide Polymorphism
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Human Biome = Genome + Mitochondrial DNA + Microbiome
The Decreasing Cost of Genotype Information

NextSeq 500 Desktop Sequencer (from Illumina, San Diego)

- Faster (complete genome 8-12 hrs)
- Cheaper ($1,000 per human genome)
- Smarter (precise, efficient, accurate)
- DNA and RNA sequencing
- FDA approved in late 2013
- In 2014, now utilized in inherited disease detection, genetic variance and risk assessments, stratification of patients within large populations, and cancer diagnostics for treatment/chemotherapy selections
PHENOTYPE + GENOTYPE
from single nucleotide polymorphisms to patient, family & population phenotypes
Systems Biology & Phenomics are Transforming How We Understand, Diagnosis, Treatment & Prognosis for Craniofacial-Oral-Dental Diseases and Disorders
The Next Frontier: Changing & Emerging Opportunities

The Next Ten Years

- Science-Based Health Care
- Major Revisions in Professional Health Care Education
- Advocacy For Health Promotion, Risk Assessment & Disease Prevention
- Increased Cost Effectiveness & Clinical Efficacy
- Human Genome-Wide Scans for $1,000 per person
- Cellular, Molecular and Tissue and Organ Engineering
- Virtual Surgery and Nanoinstrumentation
- Bioimaging
- Emphasis on Diagnostics, Therapeutics & Rehabilitation of “Aging Populations”
- Access to Quality and Comprehensive Health Care for all People and Reduce Costs in USA and beyond
“Knowing is not enough; we must apply.

Willing is not enough; we must do.”

Goethe