BIOGRAPHICAL SKETCH

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NAME: David H. Kohn

eRA COMMONS USER NAME (credential, e.g., agency login): dhkohn

POSITION TITLE: Natalie C. Roberts Endowed Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Tulane University, New Orleans, LA	BSE	05/1983	Biomedical Engineering
University of Pennsylvania, Philadelphia, PA	MSE	05/1985	Bioengineering
University of Pennsylvania, Philadelphia, PA	Ph.D.	05/1989	Bioengineering

A. Personal Statement

I have 3 decades of research, teaching, service and administrative experience in the bioengineering/ biomaterials/tissue engineering fields. Since starting my lab at the University of Michigan 30 years ago, significant contributions to the fields of biomaterials, biomechanics and tissue engineering have been made. My lab has: 1) generated important insights into the behavior of synthetic biomaterials used clinically that have led to modified implant designs; 2) developed biomimetic materials that can communicate with their biological microenvironment; 3) engineered cell-cell communication to form larger and spatially uniform volumes of tissue in-vivo; 4) engineered peptides to selectively adhere specific cell populations, enhance tissue formation in-vivo, inhibit pathological calcification, and serve as adhesives. We also have extensive experience phenotyping tissues and assessing the functionality of engineered tissues. Towards this end, we have: 1) measured mechanical properties of tissues at various levels of hierarchy and established relationships between morphological, compositional and mechanical properties; 2) investigated mechanically-mediated tissue adaptation and how mechanical loading alters the structure and composition of tissue and the phenotype of genetically compromised mice; 3) demonstrated that tissues can respond to mechanical loading and genetic alterations via mechanical changes that are mediated by compositional changes. This body of work has resulted in over 145 peer-reviewed papers, 10 patents and over 130 invited presentations. I have served as PI on NIH grants continuously for the past 24 years, successfully administering projects, collaborations and student mentoring. In my laboratory, I have trained 45 graduate students, 6 post-docs, 49 undergraduates, 14 clinical fellows and 5 visiting scholars, and many of my past trainees are now funded independent investigators. In addition to directing the Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center, I serve as PI of an NIH T32 in tissue engineering. Other leadership experience includes service as Graduate Chair in Biomedical Engineering and as President of the Society for Biomaterials. As a result of my experiences directing my lab and administering programs that extend beyond my lab, I am able to interact and communicate effectively with colleagues from a variety of engineering, biological and clinical backgrounds, as well as help develop research plans and organize and manage timelines and budgets.

a. Rossello RA, Wang Z, Kizana E, Krebsbach PH, **Kohn DH** (2009). Connexin 43 as a signaling platform for increasing the volume and spatial distribution of regenerated tissue. *PNAS* 106(32): 13219–24. PMCID: PMC2726403.
b. Ramaswamy J, Nam HK, Ramaraju H, Hatch NE, **Kohn DH** (2015). Inhibition of osteoblast mineralization by phosphorylated phage-derived apatite-specific peptide. *Biomaterials* 73: 120-130. PMCID: PMC4605886.

c. Gardinier JD, Al-Omaishi S, Rostami N, Morris MD, **Kohn DH** (2018). Examining the influence of PTH(1-34) on tissue strength and composition, *Bone,* 117: 130-137. PMCID: PMC6202137.
d. Ramaraju H, **Kohn DH** (2019). Cell and material-specific phage display peptides increase iPS-MSC mediated bone and vasculature formation in vivo, *Adv Healthcare Mater* 8(9): e1801356, PMCID: PMC6508981.

B. Positions and Honors

Positions and Employment

1982 – 1983	Research Assistant, Biomechanics Laboratory Tulane University, New Orleans, LA
1983	Research Assistant, Dept. of Biomechanics, Hospital for Special Surgery, New York, NY
1984 – 1989	Research Fellow, Dept. of Bioengineering, University of Pennsylvania, Philadelphia, PA
1987 – 1989	Health Science Specialist, Veteran's Administration, Philadelphia, PA
1989 – 1996	Assistant Professor, Dept. of Biologic & Materials Sciences, Univ. of Michigan, Ann Arbor, MI
1990 – 1996	Assistant Professor, Graduate Program in Bioengineering, University of Michigan
1992 -	Director, Bioengineering Consulting, Inc., Ann Arbor, MI
1996 - 2004	Associate Professor (w/ tenure), Dept. of Biologic & Materials Sciences, University of Michigan
1996 - 2004	Associate Professor, Dept. of Biomedical Engineering, University of Michigan
2000 – 2001	Visiting Professor, Craniofacial and Skeletal Diseases Branch, NIDCR, NIH
2002 - 2008	Chair, Graduate Committee, Dept. of Biomedical Engineering, University of Michigan
2004 -	Professor, Depts. of Biologic & Materials Sciences; Biomedical Engineering, Univ. of Michigan
2007 -	Co-Director (2007-2011), Director (2011-), NIH Training Program in Tissue Engineering
2017 -	Director, Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center
2020 -	Natalie C. Roberts Endowed Professor

Other Experience and Professional Activities (Selected)

1996 - 1999	Chair, Society for Biomaterials - Oral/Craniofacial Biomaterials Special Interest Group
1996 - 2000	NIH, Orthopaedics Study Section for SBIR/STTR Grants; Chair 1998 - 2000
1998 – 2001	Arthritis Foundation - Biomechanics/Biotechnology Study Section
1998 - 2003	NIH, Oral Biology and Medicine II Study Section, Ad-Hoc member
2001 - 2002	President, International Association for Dental Research, Implantology Research Group
2006 - 2009	NIH, Skeletal Biology Structure and Regeneration, Ad-Hoc Member
2006 - 2007	Member-at-Large, Society for Biomaterials
2007	Hunter Distinguished Lecturer, Dept. of Bioengineering, Clemson University
2009 - 2011	NSERC (Canada), Strategic Projects Panel on Biomedical Technologies
2009 – 2013	NIH, Skeletal Biology Development and Disease, Chartered Member
2011 – 2015	Society for Biomaterials, Board of Directors and Council, Secretary-Treasurer
2017 - 2018	Society for Biomaterials, President

Honors (Selected)

1994 – 1997	The Whitaker Foundation - Biomedical Research Award,
1994 – 1998	National Science Foundation, Research Initiation Award
2000 – 2001	NIH IPA Award
2005	Fellow, American Institute for Medical and Biological Engineering
2012	Fellow, International Union of Biomaterials Scientists and Engineers
2012	International Association for Dental Research, Distinguished Scientist Award
2013	Fellow, American Association for the Advancement of Science
2017	Fellow, American Association for Dental Research
2020	Distinguished Faculty Research Mentoring Award, University of Michigan

C. Contributions to Science

1. Biomimetic Biomaterials

A limitation in translating tissue engineering to the clinic is an inability to reproducibly achieve a significant volume of tissue. To better control cells' response to biomaterials and guide tissue regeneration, we mimic aspects of nature's biomineralization strategies as a basis for biomaterials design. We developed biomaterials

based on the self-assembly of biological mineral onto 3D organic templates. We also demonstrated that the function of stem cells and amount and spatial distribution of bone regenerated *in-vivo* were enhanced by controlling the nucleation and growth of bioimimetic mineral onto an organic template. The combination of material chemistry and substrate rigidity provide substrate-mediated cues for control of cell behavior, but soluble signals from a biomaterial can also influence cell differentiation, demonstrating that a biomaterial can influence cells without being in direct contact. This finding led us to engineer cell-cell communication as a strategy to enhance regeneration. We have shown that alterations in cell-cell communication via overexpressing gap junction proteins leads to significantly greater volumes of bone formed *in-vivo* and more uniform spatial distribution, potentially overcoming a critical barrier in tissue engineering.

a. Rossello RA, Wang Z, Kizana E, Krebsbach PH, **Kohn DH** (2009). Connexin 43 as a signaling platform for increasing the volume and spatial distribution of regenerated tissue, *PNAS* 106(32): 13219–24. PMCID: PMC2726403.
b. Shin K, Jayasuriya AC, **Kohn DH** (2007). Effect of ionic activity oroducts on the structure and composition of mineral formed on 3-dimensional poly(lactide-co-glycolide) scaffolds, *J Biomed Mater Res*. 83A: 1076-86. PMCID: PMC2744813.
c. Leonova EV, Pennington KE, Krebsbach PH, **Kohn DH** (2006), Substrate mineralization stimulates focal adhesion contact redistribution and cell motility of bone marrow stromal cells, *J Biomed Mater Res* 79: 263-70..
d. Rossello RA, **Kohn DH** (2010). Cell communication and tissue engineering, *Communicative and Integrative Biology*, 3: 53-56. PMCID: PMC2881242.

2. Biomaterials that Communicate with the Biological Milieu

We have developed organic/inorganic hybrid biomaterials in which proteins direct biological response to the material either passively or actively. The former technique capitalizes on Nature's mechanisms of controlling crystal growth via protein/crystal binding, while in the later technique, therapeutic agents are integrated into the mineral in a spatially controlled manner, allowing for spatial and temporal delivery of active biological molecules. We developed high throughout combinatorial approaches to discover novel peptides and investigate peptide/biomaterial interactions, Using phage display, we discovered peptides that exhibit preferential affinity to specific material chemistries and a second set of peptides with affinity to specific cells. We combined these sequences to create dual-functioning peptides that have material and cell-specific binding domains, serving as tethers between the material and biological worlds and enabling spatially directed tissue formation. Capitalizing on the peptides' apatite-binding binding ability, we next demonstrated their ability to bind to cell-secreted mineral, and these peptides are now used to inhibit pathological calcification and bind to bone for targeted delivery of drugs.

a. Luong LN, McFalls KM, **Kohn DH** (2009). Gene delivery via DNA incorporation within a biomimetic apatite coating, *Biomaterials* 30: 6996-7004. PMCID: PMC2783865.
b. Segvich SJ, Smith HC, **Kohn DH** (2009). The adsorption of preferential binding peptides to apatite-based materials, *Biomaterials,* 30: 1287-1298. PMCID: PMC2744811.
c. Ramaraju H, Miller SJ, **Kohn DH** (2017). Dual-functioning peptides discovered by phage display increase the magnitude and specificity of BMSC attachment to mineralized biomaterials, *Biomaterials,* 134: 1-12. PMCID: PMC5492996.
d. Ramaraju H, **Kohn DH** (2019). Cell and material-specific phage display peptides increase iPS-MSC mediated bone and vasculature formation in vivo, *Adv Healthcare Mater*, 8(9): e1801356, PMCID: PMC6508981.

3. Structure-Function Relations in Mineralized Tissues Across Hierarchy

To develop structure-function relations in mineralized tissues and define metrics for bone quality across dimensional scale, we have used acoustic emission, Raman spectroscopy, NMR and HPLC to detect and predict damage, and identify ultrastructural changes associated with compromised bone quality. In collaboration with Dr. Michael Morris, we were the first to couple mechanical and compositional analyses of tissues using Raman spectroscopy, and relate mechanical deformation at the ultrastructural level to compositional changes. Using NMR, we are amongst the first to identify the important role of water in mediating mechanical stability of bone, and the first to demonstrate that there are 3 distinct water compartments in bone, each mediating a different functional response. Most recently, we developed a new animal model of lathyrism and HPLC methods for the direct quantification of immature and mature cross-links. We identified significant positive correlations between pyridinoline cross-link content and tissue strength and we are the first to report a correlation between bone fracture toughness and cross-link maturity. A significant

outcome of this work is the recognition that a critical determinant of bone quality is cross-link type, rather than total quantity, and the cross-links that exist in lower abundance are the best predictors of bone quality.

a. Timlin JA, Carden A, Morris MD, Rajachar RM, **Kohn DH** (2000). Raman spectroscopic markers for fatigue related bovine bone microdamage, *Analytical Chemistry*, 72: 2229-2236.
b. Carden A, Rajachar RM, Morris MD, **Kohn DH** (2003). Ultrastructural changes accompanying the mechanical deformation of bone tissue: a Raman imaging study, *Calcified Tissue Int* 72:166-175.
c. Wilson EE, Awonusi A, Morris MD, **Kohn DH,** Tecklenburg MMJ, Beck LW (2006). Three structural roles for water in bone observed by solid-state NMR, *Biophysical Journal*, 90: 3722-3731. PMCID: PMC1440753.
d. McNerny EM, Gong B, Morris MD, **Kohn DH** (2015). Bone fracture toughness and strength correlate with collagen cross-link maturity in a dose-controlled lathyrism mouse model. *J Bone Miner Res* 30(3): 455-64. PMCID: PMC4333018.

4. Functional Adaptation in Bone

Building on our ex-vivo based structure-function findings, we developed a short-term, weight-bearing rodent exercise model. Using this model with mice of different ages, genders, background strains and genetic modifications, we identified significant location and gender-specific differences in phenotype and mechanical responsiveness of the skeletal system. We also determined that exercise can rescue deficiencies in function caused by gene deletion, suggesting that mechanical stimulation can compensate for genetically-induced deficiencies in bone quality. However, we found that the phenotype resulting from targeted deletion of bone matrix genes is dependent on the background strain on which transgenic mice are bred. Using the exercise model, we also demonstrated that in-vivo mechanical loading can increase resistance to fatigue damage, and defined compositional changes in collagen cross-linking guiding the increased resistance. Most recently, using exercise in conjunction with enhancement or inhibition of PTH signaling, we demonstrated that bone adaptation during exercise is not only a function of dynamic loading, but also PTH release, and that PTH signaling contributes differently to bone adaptation at the structural and tissue levels.

a. Wallace JM, Rajachar RM, Allen MR, Bloomfield SA, Robey PG, Young MF, **Kohn DH** (2007). Exercise induced changes in the cortical bone of growing mice are bone and gender specific, *Bone*, 40: 1120-27. PMCID: PMC2729655.
b. Wallace JM, Golcuk K, Morris MD, **Kohn DH** (2009). Inbred strain-specific response to biglycan deficiency in the cortical bone of C57BL6/129 and C3H/He mice, *J Bone Min Res*, 24: 1002-12. PMCID: PMC3276349.
c. Gardinier JD, Mohamed F, **Kohn DH** (2015). PTH signaling during exercise contributes to bone adaptation. *J Bone Miner Res* 30: 1053-1063. PMCID: PMC4734644.
d. Gardinier JD, Al-Omaishi S, Morris MD, **Kohn DH** (2016). PTH signaling mediates perilacunar remodeling during exercise, *Matrix Biology*, 52-54: 162-175. PMCID: PMC4875803.

5. How Mechanical Competence of Bone Can be Explained by Compositional Changes

It has long been assumed that bone adapts to mechanical loading and improves its strength by turning over or adding material. We demonstrated that bone can also respond to exercise, as well as genetic alterations and other stimuli/insults, via mechanical changes that are not mediated by the addition of new bone, but via compositional changes. We have further demonstrated that these compositional changes occur predominantly in the perilacunar zone around osteocytes. We also demonstrated that exercise can shift cross-link chemistry toward the pyridinoline pathway and counter the effects of cross-link inhibition on mechanical properties. Also of significance is our finding that cross-link inhibition and rescue can result in changes in modulus without changes in mineral density, challenging the tenet that modulus is controlled by the mineral component of bone.

a. Wallace JM, Golcuk K, Morris MD, **Kohn DH** (2010). Inbred strain specific effects of exercise in wild type and biglycan deficient mice, *Ann Biomed Eng* 38: 1607-17, PMCID: PMC2865557.
b. Raghavan M, Sahar ND, **Kohn DH,** Morris MD (2012). Age-specific profiles of tissue-level composition and mechanical properties in murine cortical bone, *Bone,* 50: 942-53. PMCID: PMC3299845.
c. McNerny EM, Gardinier JD, **Kohn DH** (2015). Exercise increases pyridinoline cross-linking and counters the mechanical effects of concurrent lathyrogenic treatment. *Bone,* 81: 327-337. PMCID: PMC4640975.
d. Gardinier JD, Al-Omaishi S, Rostami N, Morris MD, **Kohn DH** (2018). Examining the influence of PTH(1-34) on tissue strength and composition, *Bone*, 117: 130-137, 2018; PMCID: PMC6202137.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/collections/bibliography/40436505/

D. Research Support

Ongoing Research Support

T32 DE07057-44 (Kohn PI/Director) 7/1/17 - 6/30/22
Tissue Engineering and Regeneration
The objective of this training program is to provide an interdisciplinary research-intensive environment for individuals who wish to pursue careers in the oral sciences, with focus on restoring oral-craniofacial tissues.

U24 DE026915-03 (Kohn Multi-PI/Lead PI) 3/1/17 – 2/28/21 (NCE)
Michigan-Pittsburgh-Wyss Resource Center: Supporting Regenerative Medicine in Dental, Oral and Craniofacial Technologies
The goal of this Resource Center is to translate TE/RM innovations that address the ongoing clinical need to restore or create healthy, functional DOC tissues. To achieve this goal, we will implement the structure (Aim 1) and operations (Aim 2) of the RC to identify technologies for clinical application that will navigate through the translational pipeline in Phase III of the DOCTRC Program.

U24 DE029462-01 (Kohn Multi-PI/Lead PI) 4/1/20 - 3/31/25
Michigan-Pittsburgh-Wyss Regenerative Medicine Resource Center: Advancing Dental, Oral, and Craniofacial Regeneration to Clinical Trial Initiation
The goals of this cooperative agreement for stage 3 of the Dental-Oral-Craniofacial Tissue Regeneration Consortium (DOCTRC) are to: 1) implement the Resource Center structure and processes developed in stage 2 to catalyze Interdisciplinary Translational Projects (ITPs) towards clinical adoption; 2) direct clinical translation and commercialization of ITP technologies; and 3) broaden DOCTRC impact and build sustainability. This grant represents the next stage of U24 DE026915 and Y1 of U24 DE029462, will coincide with a NCE of U24 DE026915.

R01 DE026116-04 (Kohn PI w/ T Scott) 8/1/16 to 7/31/21
Engineering Anti-Fragile Interfaces
Work in this grant will test the central hypothesis that incorporating tethering oligomers that bond to collagen and/or apatite in mineralized tissue and functional groups on the surface of a biomaterial will increase the bond strength over time and under acidic conditions.

P30 AR069620-04 (Kohn PI Core C; Overall PI K Jepsen) 8/1/16 to 7/31/21
Structural and Compositional Assessment Core of Michigan Integrative Musculoskeletal Health Core Center
The aims of this Core are to provide scientific guidance on: 1) the best use of technologies and experimental design for quantifying composition, architecture, and structure of musculoskeletal tissues; 2) standardization and training in technologies to quantify tissue composition, architecture, and structure; 3) data analysis, interpretation of results and recommendations for future studies.

R01 AR065424-05 (Co-I Kohn; PI K Jepsen) 7/15/14 to 6/30/20
Bone Robustness as a Biomarker of Skeletal Aging and Fragility
The objectives of this R01 are to study bone as a complex adaptive system using the natural variation in robustness as an experimental model to predict inter-individual differences in BMU-based remodeling (Aim 1), fracture resistance (Aim 2), and skeletal aging (Aim 3).

University of Michigan BSI 2019 SRI (Kohn PI) 1/1/20 – 12/31/25
Biosciences Scientific Research Initiative
Engineering Cell Programmable Biomaterials for Dental and Musculoskeletal Health
The objective of this initiative is to develop advanced materials that control the programming of cells and development and spatio-temporal organization of tissue, while also providing feedback on tissue function