BIOGRAPHICAL SKETCH

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NAME: Cohen, Pinchas

eRA COMMONS USER NAME (credential, e.g., agency login): Cohenp2

POSITION TITLE: Dean and Executive Director, USC Leonard Davis School of Gerontology

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
Technion, Haifa, Israel	MD	06/1986	Medicine
Stanford University, California		06/1992	Pediatrics & Endocrinology

A. Personal Statement

Dr. Cohen is an international leader in the fields of aging and mitochondrial biology. He has made important contributions to the area of growth factors and their roles in longevity, metabolism and carcinogenesis, and has made major advancements in the understanding of the role of nutrition in human aging. In the last several years his laboratory discovered a novel family of mitochondrial-derived peptides that signal to regulate cellular metabolism and survival. His recent discoveries implicating the mitochondrial peptides, humanin, SHLPs and MOTS-c, as novel cyto-protective factors and metabolic regulators have created a new direction in the field of mitochondrial biology and aging research. He has been awarded both a Transformative RO1 and an NIA EUREKA grant for exploring the role of the novel family of mitochondrial-derived peptides in health and disease. His lab continues to discover additional novel peptides, define their physiological roles and identify potential therapeutic and diagnostic potential. Dr. Cohen manages a program of translational research with multiple collaborations. Dr. Cohen's lab has also developed novel assays for these recently discovered proteins (including humanin, SHLPs and MOTS-c, and additional novel peptides) and they serve the research community in terms of novel assay development, a role that is critical for translational research. Dr. Cohen has extensive experience in training students, fellows and junior faculty and has led multiple institutional training efforts and training grants. Dr. Cohen's lab has focused on understanding how mitochondrial peptides may explain the mechanism of action of interventions that modulate aging including diet, exercise and drugs such as metformin. Over the last several years, the Cohen lab has focused on the discovery of the MDPs that are involved in prostate cancer pathogenesis, and therapy.

B. Positions and Honors.

Professional Experience:

1986-1989 **Intern and Resident**, Department of Pediatrics, Stanford University, Stanford, California
1989-1992 **Endocrine Fellow**, Department of Pediatrics, Stanford University
1992-1997 **Assistant Professor**, Department of Pediatrics, University of Pennsylvania
1997-1999 **Associate Professor** *(with tenure)*, Department of Pediatrics, University of Pennsylvania
1999-2012 **Professor and Director of Endocrine Research**, Mattel Children's Hospital at UCLA
2001-2012 **Chief of Endocrinology**, Mattel Children's Hospital at UCLA
2008-2012 **Co-Director** (2008-2010) **and Director**, (2010-2012) UCSD/UCLA Diabetes Research Center
2011-2012 **Vice Chair for Research**, Mattel Children's Hospital at UCLA
2012- **Dean,** Davis School of Gerontology, USC
2012- **Executive Director,** Ethel Percy Andrus Gerontology Center, USC

Honors and Awards:

1984	The Israeli Diabetes Foundation Young Investigator of the Year
1986	Graduated from Medical School with highest honors
1990	Lawson Wilkins Society Research Fellow (Lilly Award)
1991	WSPR-David W. Smith Pediatric Trainee Award (Ross Award)
1993	American Diabetes Association Career Development Award
1995	Elected member: Society for Pediatric Research (SPR)
1999	CaPCURE Research Award
2000	Pfeiffer Foundation Research Award
2006	Elected member: American Pediatric Society (APS)
2007	APS Outstanding Science Award
2009	NIH director Transformative RO1 Award
2011	Glenn Award for Research in Biological Mechanisms of Aging
2012	William & Sylvia Kugel Gerontology Dean's Chair at USC
2013	Milken Institute Associate
2014	President, The Growth Hormone Research Society
2017	Elected Member, National Academy of Inventors
2019	Irving S. Wright Award of Distinction (AFAR)
2019	Elected: Fellow of the Gerontological Society of America

National Advisory, Editorial, and Study Section Service

Associate Editor:

2003-2011 *Pediatric Research, 2006-2009 PLoS Computational Biology*

Editorial Board Member:

Journal of Clinical Endocrinology and Metabolism; Endocrinology; Cancer Biology and Therapy; Molecular Genetics and Metabolism, GH & IGF Research

Study Section Member (selected list):

1995-7 NIH GCRC study section Ad Hoc Reviewer
1997-9 Doris Duke Foundation Grant Program.
2003 NCI Urology Special Emphasis Programs.
2006-9 Tumor Cell Biology Study Section.
2007 NIA PO1 Special Study section.
2008-12 Neurological, Aging and Musculoskeletal Epidemiology Study Section.
2009 RC1/RC2 study sections.
2009-19 AFAR grant review study section (Chair)
2010 NICHD Special Emphasis panel
2012-18 NIA CMAD study Section

Executive Council Member:

1997-2009 International IGF Society Council member.
1998-2018 Growth Hormone Research Society Council member (**President 2014-2016**)
2003-2006 Endocrine Society Steering Committee
2009-2012 National Diabetes Centers Directors Executive Committee

C. Contributions to Science

Since I started my career, I published **Nearly 300 peer-reviewed publications (cited over 25,000 times)**.
(Comprising an *h-index* of 90 and an *i10 index* of 259)
MyBibliography can be accessed at http://1.usa.gov/1FL6bOu
My **Google-Scholar Page** can be accessed at: http://scholar.google.com/citations?user=W1wn0zAAAAAJ&hl=en

My research spans basic discovery to translational research to clinical science and has a diverse scope relevant to Aging, Cancer, Diabetes, growth factor physiology, and mitochondrial biology. Below are key areas where I have made important contributions. There has been a natural evolution of my research from IGF-biology in cancer and aging to IGFBP-science to the characterization of IGFBP3-partners, to the discovery of the mitochondrial peptide humanin culminating with the recognition of additional mitochondrial-derived peptides

including MOTS-c and SHLPs, which together created a new field within mitochondrial science.

A. The role of insulin-like growth factors in aging, longevity, and cancer

I have performed extensive studies over the years demonstrating the relationship between growth hormone, IGF-1 and the aging process as well as carcinogenesis. My lab has linked the reduced IGF system activity to familial longevity and healthspan in humans.

1. Guevara-Aguirre J, Balasubramanian P, Guevara-Aguirre M, Wei M, Madia F, Cheng CW, Hwang D, Martin-Montalvo A, Saavedra J, Ingles S, de Cabo R, Cohen P, Longo VD. Growth Hormone Receptor Deficiency is Associated With a Major Reduction in Pro-aging Signaling, Cancer and Diabetes in Humans. *Science Translational Medicine*. 2011; 3:70ra13. PMCID: PMC3357623

2. Levine ME, Suarez JA, Brandhorst S, Balasubramanian P, Cheng CW, Madia F, Fontana L, Mirisola MG, Guevara-Aguirre J, Wan J, Passarino G, Kennedy BK, Wei M, Cohen P, Crimmins EM, Longo VD. Low Protein Intake Is Associated with a Major Reduction in IGF-1, Cancer, and Overall Mortality in the 65 and Younger but Not Older Population. *Cell Metab*. 2014; 19:407-17. PMCID: PMC3988204

3. Ben-Avraham D, Govindaraju DR, Budagov T, Fradin D, Durda P, Liu B, Ott S, Gutman D, Sharvit L, Kaplan R, Bougnères P, Reiner A, Shuldiner AR, Cohen P, Barzilai N, Atzmon G. The GH receptor exon 3 deletion is a marker of male-specific exceptional longevity associated with increased GH sensitivity and taller stature. *Sci Adv*. 2017; 3:e1602025. PMCID: PMC5473676

4. Mao K, Quipildor GF, Tabrizian T, Novaj A, Guan F, Walters RO, Delahaye F, Hubbard GB, Ikeno Y, Ejima K, Li P, Allison DB, Salimi-Moosavi H, Beltran PJ, Cohen P, Barzilai N, Huffman DM. Late-life targeting of the IGF-1 receptor improves healthspan and lifespan in female mice. *Nat Commun*. 2018; 9:2394. PMCID: PMC6008442

B. The role of nutritional interventions in aging and longevity

Our studies demonstrated the relationship between dietary components that determine IGF levels and human disease incidence (especially cancer).

1. Brandhorst S, Choi IY, Wei M, Cheng CW, Sedrakyan S, Navarrete G, Dubeau L, Yap LP, Park R, Vinciguerra M, Di Biase S, Mirzaei H, Mirisola MG, Childress P, Ji L, Groshen S, Penna F, Odetti P, Perin L, Conti PS, Ikeno Y, Kennedy BK, Cohen P, Morgan TE, Dorff TB, Longo VD. A Periodic Diet that Mimics Fasting Promotes Multi-System Regeneration, Enhanced Cognitive Performance, and Healthspan. *Cell Metab*. 2015; 22:86-99. PMCID: PMC4509734

2. Mitchell SJ, Madrigal-Matute J, Scheibye-Knudsen M, Fang E, Aon M, González-Reyes JA, Cortassa S, Kaushik S, Gonzalez-Freire M, Patel B, Wahl D, Ali A, Calvo-Rubio M, Burón MI, Guiterrez V, Ward TM, Palacios HH, Cai H, Frederick DW, Hine C, Broeskamp F, Habering L, Dawson J, Beasley TM, Wan J, Ikeno Y, Hubbard G, Becker KG, Zhang Y, Bohr VA, Longo DL, Navas P, Ferrucci L, Sinclair DA, Cohen P, Egan JM, Mitchell JR, Baur JA, Allison DB, Anson RM, Villalba JM, Madeo F, Cuervo AM, Pearson KJ, Ingram DK, Bernier M, de Cabo R. Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice. *Cell Metab*. 2016; 23:1093-112. PMCID: PMC4911707

3. Wei M, Brandhorst S, Shelehchi M, Mirzaei H, Cheng CW, Budniak J, Groshen S, Mack WJ, Guen E, Di Biase S, Cohen P, Morgan TE, Dorff T, Hong K, Michalsen A, Laviano A, Longo VD. Fasting-mimicking diet and markers/risk factors for aging, diabetes, cancer, and cardiovascular disease. *Sci Transl Med*. 2017 Feb 15;9(377). Doi: 10.1126/scitranslmed.aai8700

4. Cheng CW, Villani V, Buono R, Wei M, Kumar S, Yilmaz OH, Cohen P, Sneddon JB, Perin L, Longo VD. Fasting-Mimicking Diet Promotes Ngn3-Driven β-Cell Regeneration to Reverse Diabetes. *Cell*. 2017; 168:775-788. PMCID: PMC5357144

C. The discovery of Humanin and MOTS-c

As part of our quest to identify IGFBP3 partners that are important in mediating the effects of this molecule we cloned (using a yeast-two-hybrid system with IGFBP3 as a bait) a peptide encoded from a small open reading frame sORF within the mitochondrial chromosome at the 16S rRNA region. This peptide, called humanin, has unique cytoprotective and healthspan-enhancing features. Humanin has also emerged as an important insulin-

sensitizing agent that has atherosclerosis-preventing effects and, using a novel ELISA assay we have developed, has been shown to be associated with markers of health and longevity.

Over the last several years, we began to re-examine mitochondrial physiology to understand the processes by which the mitochondrial-derived peptides humanin is expressed and regulated. At the same time, we began to recognize that additional MDPs are expressed from the mitochondrial DNA. Recently we published the existence of a peptide (MOTS-c) derived from the 12S region of the mtDNA, that has weight-loss inducing effects and acts as a muscle-specific, exercise-mimetic insulin sensitizer.

1. Ikonen M, Liu B, Hashimoto Y, Ma L, Lee KW, Niikura T, Nishimoto I, Cohen P. Interaction between the Alzheimer's survival peptide humanin and insulin-like growth factor-binding protein 3 regulates cell survival and apoptosis. *Proc Natl Acad Sci U S A*. 2003; 100:13042–13047. PMCID: PMC240741.

2. Yen K, Wan J, Mehta HH, Miller B, Christensen A, Levine ME, Salomon MP, Brandhorst S, Xiao J, Kim SJ, Navarrete G, Campo D, Harry GJ, Longo V, Pike CJ, Mack WJ, Hodis HN, Crimmins EM, Cohen P. Humanin Prevents Age-Related Cognitive Decline in Mice and is Associated with Improved Cognitive Age in Humans. *Nature Scientific Reports*. 2018; 8:14212. doi: 10.1038/s41598-018-32616-7. PMCID: PMC6154958

3. Lee C, Zeng J, Drew BG, Sallam T, Martin-Montalvo A, Wan J, Kim SJ, Mehta H, Hevener AL, de Cabo R, Cohen P. The mitochondrial-derived peptide MOTS-c promotes metabolic homeostasis and reduces obesity and insulin resistance. *Cell Metabolism*. 2015; 21, 443–454. PMCID: PMC4350682

4. Kim SJ, Miller B, Mehta HH, Xiao J, Wan J, Arpawong TE, Yen K, Cohen P. The mitochondrial-derived peptide MOTS-c is a regulator of plasma metabolites and enhances insulin sensitivity. Physiol Rep. 2019; 7:e14171 PMCID: PMC6640593

D. The discovery of multiple additional mitochondrial peptides

Recently, we cloned and described multiple other mitochondrial peptides with a fascinating array of biological effects:

1. Cobb LJ, Lee C, Xiao J, Yen K, Wong RG, Nakamura HK, Mehta HH, Gao Q, Ashur C, Huffman DM, Wan J, Muzumdar R, Barzilai N, Cohen P. Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers. *Aging* (Albany NY). 2016; 8:796-809. PMCID: PMC5706922

2. Xiao J, Howard L, Wan J, Wiggins E, Vidal A, Cohen P, Freedland SJ. Low circulating levels of the mitochondrial-peptide hormone SHLP2: novel biomarker for prostate cancer risk. *Oncotarget*. 2017; 8:94900-94909. PMCID: PMC5706922

3. Nashine S, Cohen P, Nesburn AB, Kuppermann BD, Kenney MC. Characterizing the protective effects of SHLP2, a mitochondrial-derived peptide, in macular degeneration. *Nature Scientific Reports*. 2018; 8:15175. doi: 10.1038/s41598-018-33290-5.

4. Mehta HH, Xiao J, Ramirez R, Miller B, Kim SJ, Cohen P, Yen K. Metabolomic profile of diet-induced obesity mice in response to humanin and small humanin-like peptide 2 treatment. Metabolomics. 2019; 15:88 PMCID: PMC6554247

E. Understanding the regulation of mitochondrial peptides

We are describing and characterizing the regulation of mitochondrial peptides at the genomic, epigenetic and transcriptomic level.

1. Kim SJ, Wan J, Cohen P, Yen K. Mitochondrial derived peptides as novel regulators of metabolism. Physiol Rep. 2019; 7:e14171. PMCID: PMC5663826

2. Kim SJ, Mehta HH, Wan J, Kuehnemann C, Chen J, Hu JF, Hoffman AR, Cohen P. Mitochondrial peptides modulate mitochondrial function during cellular senescence. *Aging* (Albany NY). 2018; 10:1239-1256. PMCID: PMC6046248

3. Breton CV, Song AY, Xiao J, Kim SJ, Mehta HH, Wan J, Yen K, Sioutas C, Lurmann F, Xue S, Morgan TE, Zhang J, Cohen P. Effects of air pollution on mitochondrial function, mitochondrial DNA methylation, and mitochondrial peptide expression. *Mitochondrion*. 2019; 46:22-29. PMCID: PMC6506186

4. D'Souza RF, Woodhead JST, Hedges CP, Zeng N, Wan J, Kumagai H, Lee C, Cohen P, Cameron-Smith D, Mitchell CJ, Merry TL. Increased expression of the mitochondrial derived peptide, MOTS-c, in skeletal muscle of healthy aging men is associated with myofiber composition. Aging (Albany NY). 2020 Mar 17;12. doi: 10.18632/aging.102944. Online ahead of print. PMID: 3218220

D. Additional Information: Research Support

Ongoing Research Support

R01AG061834 Cohen (PI) 09/01/2018 - 08/31/2023
Humanin is an AD resilience factor through its interaction with APOE4
The major goals of this project are to define the physical and genomic interactions between humanin and APOE4 and demonstrate the effects of this phenomenon on the stability and toxicity of APOE4 in AD models.

1R56AG062693-01 (Cohen/Crimmins) 08/01/2019 - 07/31/2020
Ethnic-Specific Mitochondrial DNA Variations that Contribute to Dementia
This project will evaluate the effects of mitochondrial SNPs on the risk of developing cognitive disfunction in subjects enrolled in the Health and Retirement Study.

DOD PC160353 Cohen (PI) 09/01/2017 – 08/31/2020
Ethnic Disparity of Mitochondrial Peptides and Prostate Cancer Risk
This project will evaluate the potential of SHLP2 levels to predict the outcome of prostate cancer biopsies in African American and Caucasian men recruited from North Carolina and Los Angeles and determine the relative contribution of mtDNA and nDNA to the ethnic-related risk.

P01AG034906 PI: Longo, Role: Project #2 PI 08/01/2011 - 07/31/2022
Dietary Restriction, GH/IGF-I & Mechanisms of Differential Cellular Protection
The major goals of this project are to understand the role of diet in aging and longevity.

U54CA233465 PI: Carpten, Role: Project #1 PI 11/01/2018 – 10/30/2021
FLORIDA-CALIFORNIA CANCER RESEARCH, EDUCATION HEALTH EQUITY CENTER
Project-1: Disparities in Mitochondrial Peptidomics and Transcriptomics in Prostate Cancer
This project will examine MDPs, mtDNA and mtRNA variations in prostate cancer.

R01CA231219 PI: Aronson, Role: subcontract PI 09/01/2018 - 08/31/2023
GPR120 and Macrophages in Dietary Omega-3 Inhibition of Prostate Cancer
This project will determine the role of fish oil derivatives in prostate cancer prevention.

R01EY27363 PI: Kenney, Role: subcontract PI 09/01/2018 - 08/31/2023
Protective Effects of Humanin on AMD Mitochondria
This project will determine the role of mitochondrial peptides in AMD prevention.

Completed Research Support

AFAR PC2017-1 Cohen (PI) 07/01/2017 – 06/30/19
Characterization of the Healthspan promoting Activity of the Mitochondrial Peptide Humanin.
This AFAR BIG Award addressed humanin levels in samples from human, primate, and murine trials of caloric restriction and other interventions intended to increase healthspan.