BIOGRAPHICAL SKETCH

NAME: Edward K. L. Chan

eRA COMMONS USER NAME: eklchan

POSITION TITLE: Professor, Department of Oral Biology and Department of Anatomy and Cell Biology

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date	FIELD OF STUDY
University of British Columbia, Vancouver, British Columbia, Canada	B.Sc.	1976	Biochemistry
University of Calgary, Calgary, Canada	M.Sc.	1980	Clinical Chemistry
University of Calgary, Calgary, Canada	Ph.D.	1984	Immunopathology
Scripps Clinic and Research Foundation, La Jolla, California	Research Fellow	1984-88	Immunochemistry and Molecular Biology

A. Personal Statement

My research interests in immunity have always been broad from immune hypersensitivity leading to autoimmune-mediated diseases to the other extreme of the spectrum when presumably inefficiency in the immune response can contribute to the development of cancer. The significance in periodontal disease is that it is the most common chronic infection in adults and can lead to many other systemic diseases. This exciting proposal addresses some of the important factors that are driving the periodontal disease and gives us an opportunity to look into novel therapy.

In 2000, my lab identified and cloned the protein GW182, a macromolecular marker of the novel cytoplasmic foci known as GW bodies (GWBs) discovered in my laboratory during the studies of autoantibody to these foci. These highly conserved structures were first considered as both storage centers for a specific subset of mRNAs and degradation sites for these mRNAs. GWBs are now also known as the mammalian counterpart of processing bodies (P bodies) identified in yeast. My laboratory demonstrated a link of RNA interference (RNAi) function to GWBs (1); specifically, disruption or disassembly of GWB impairs short interference RNA (siRNA) and microRNA (miRNA)-mediated translational silencing activity. Furthermore, we showed that the biogenesis of miRNA is closely linked to GWB formation; specifically these foci disassembled in HeLa cells made deficient of mature miRNA. They re-assembled when these same cells were transfected with surrogate miRNA. We have continued to examine the cell biology of GWB in siRNA and miRNA function, and the roles of specific miRNA in innate immunity, autoimmunity, and cancer. miRNAs are currently considered key regulators of gene expression by negative feedback control of the half-lives of important mRNAs. Most relevant to the current proposal, our laboratory demonstrated the critical role of miR-146a in endotoxin-induced tolerance, cross-tolerance (2), and IL-1-induced cross-tolerance (3). Together with the co-PI, we identified up-regulated miR-146a in mice with periodontal disease (PD) induced by polymicrobial infection with three major periodontal pathogens, *P. gingivalis*, *T. denticola*, and *T. forsythia* (4). All these work together form the basis for the current proposal.

1. Jakymiw A, Lian S, Eystathioy T, Li S, Satoh M, Hamel JC, Fritzler MJ, Chan EKL. Disruption of GW bodies impairs mammalian RNA interference. Nat Cell Biol. 2005;7:1267-74. Cited >365 times
2. Nahid MA, Pauley KM, Satoh M, Chan EKL. miR-146a is critical for endotoxin-induced tolerance: Implication in innate immunity. J Biol Chem. 2009;284:34590-9. PMC:2787321. Cited >251 times
3. Nahid MA, Satoh M, Chan EKL. Interleukin-1β-responsive miR-146a is critical for the cytokine-induced tolerance and cross-tolerance to toll-like receptor ligand. J Innate Immun. 2015; 7:428-40. Cited >4 times
4. Nahid MA, Rivera M, Lucas A, Chan EKL, Kesavalu L. Polymicrobial infection with periodontal pathogens specifically enhances microRNA miR-146a in ApoE-/- mice during experimental periodontal disease. Infect Immun. 2011;79:1597-605. PMC:3067556. Cited >59 times

B. Positions and Honors

Positions and Employment: 1984-8, Research Associate; 1988-90, Senior Research Associate, Scripps Clinic and Research Foundation; 1990-6, Assistant Member; 1991–2002, Director, DNA Core Laboratory for Structural Analysis; 1997-2002, Associate Professor, Department of Molecular & Experimental Medicine, The Scripps Research Institute, La Jolla, California; 2002-, Professor, Department of Oral Biology, College of Dentistry; 2004-, Professor, Department of Anatomy and Cell Biology, College of Medicine, University of Florida, Gainesville, Florida; 2009-, Joint Member, Immunology Program, Moffitt Research Institute, Tampa, FL

Professional Societies: American Society for Cell Biology, American College of Rheumatology, American Association for Cancer Research, American Society for Biochemistry and Molecular Biology, International Endotoxin and Innate Immunity Society

Honors and Awards: 1983-6, Alberta Heritage Foundation for Medical Research Fellowship Award; 1985 and 1986, American Rheumatism Association Western Region Fellows Awards; 1986-9, Arthritis Foundation Fellowship Award; 1987, American Rheumatism Association Senior Rheumatology Scholar Award; 1989-91, Arthritis Foundation Investigator Award; 1995, elected member, The Henry Kunkel Society; 2008-10 and 2013-6, University of Florida Research Foundation Professorship; 2009 and 2013, Doctoral Mentoring Award, University of Florida Colleges of Medicine & Dentistry Interdisciplinary Program in Biomedical Sciences; 2013, UF-Howard Hughes Medical Institute program Science for Life Distinguished Mentor Award for Undergraduates; 2016, Addgene's Blue Flame Award

Federal Committees and Service:

Veterans Affairs, Medical Research Service Grant Review 1991, 1993, 2000, 2002
NIAMS, NIH, Study Section Member, General Medicine A-1, 1995-9
NIH CSR Special Emphasis Panel ZRG1 SSSG 03, 1998
NSF Electronic Proposal Review, 2002
NIH CSR Special Emphasis Panel, 2002
NIH CSR Special Emphasis Panel, Dermatology and Rheumatoid Sciences, 2004
NIH CSR Immunology Special Study Section for SLE, 2005
NIH CSR Immunology Study Section, 2006
NIH CSR Special Emphasis Panel, Musculoskeletal, Oral and Skin Sciences Integrated Review Group, 2010
NIDCR, NIH, Ad hoc review panel, Intramural Research Program in the Molecular Physiology and Therapeutics Branch, Board of Scientific Counselors, 2011
NIH CSR Special Emphasis Panels, Musculoskeletal, Oral and Skin Sciences Integrated Review Group, June and Dec, 2012
NIAID, NIH, U.S.-India Bilateral Collaborative Research Grants on Human Immune Phenotyping and Infectious Disease Initiative, Human Immunology Project Consortium, 2012
Congressionally Directed Medical Research Program (CDMRP), Review Panel, Investigator Initiated Research Award and Technology/Therapeutic Development Award in lupus and rheumatoid arthritis research, 2013
NIAID, NIH, Review Panel, Autoimmunity Centers of Excellence, 2013
NIH CSR Special Emphasis Panel, Musculoskeletal, Oral and Skin Sciences, 2014
NIDCR, NIH, Ad hoc review panel, Intramural Research Program in the Molecular Physiology and Therapeutics Branch, Board of Scientific Counselors, 2017

Non-Federal Committees and Service:

Arthritis Society of Canada, Medical and Scientific Programs, 1990, 1993-4, 1998, 2000
Wellcome Trust, London; Infection and Immunity program, 1992; Molecular & Physiological Sciences, 2009
Medical Research Council of Canada, 1993, 97-00
Research Council of Canada, Natural Sciences and Engineering, 1995-6
Arthritis Foundation, Study Section Member, Molecular Biology and Genetics Study Section, 1999-2001
West Virginia University, Reviewer for the Office of Sponsored Programs, 2000
Netherlands Organization for Scientific Research, Council for Chemical Sciences, 2003
United States-Israel Binational Science Foundation, 2008
Singapore Agency for Science, Technology and Research Biomedical Research Council, 2008
Austrian Science Fund, Biology and Medicine, 2008
Alberta Heritage Foundation for Medical Research Investigator Award, 2008

French National Research Agency, the Integrated Mechanisms of Inflammation program, 2010, 2012
Health Research Board, Dublin, Ireland, Clinical and Biomedical Research Unit, 2010, 2011
Israel Science Foundation, 2011
Lupus Foundation of America, Grant Review Committee, 2012
Qatar National Research Foundation, State of Qatar, National Priorities Research Program, 2013, 2014
Netherlands Organization for Scientific Research, Council for Chemical Sciences, The Hague, The Netherlands 2013
Prinses Beatrix Spierfonds, The Hague, The Netherlands, 2015
Molecular and Cellular Medicine Board, Medical Research Council, UK, 2015
Lupus Research Institute, Grant Review Committee, 2010-6

Editorial Boards: 1991-2003, Molecular Biology Reports; 1999-2014, Arthritis Research and Therapy; 2009-11, Journal of Dental Research; 2010-, Frontiers Editorial Board, Review Editor of Frontiers in Non-Coding RNA; 2011-4, MicroRNA; 2013-, Journal of Autoimmunity; 2014-6, Guest editor, Frontiers in Immunology; 2017-, Review Editor in Cytokines and Soluble Mediators in Immunity, part of Frontiers in Immunology

C. Contributions to Science

Our use of human autoantibodies in molecular characterization leading to the discovery of functional markers for three novel subcellular structures. My laboratory (1984-2002) was highly successful, using human autoantibodies as unique probes, in the identification and cloning of more than 20 novel autoantigens, including SS-B/La, Ro52/TRIM21, NOR-90/hUBF, PM-Scl-75, p80-coilin, HCC1/RBM39, p62/IGF2BP2, SG2NA, DFS70/LEDGF, golgin-97, golgin-160, golgin-245, p90/CIP2A, and GW182.

1. Year 1990-1, **p80-coilin as functional marker for Coiled body** (later renamed Cajal body). The identification and cloning of p80-coilin provided a highly novel marker for the nuclear body and this has started a new field of investigation. To date, a PubMed search with keyword “p80-coilin” or “Cajal body” shows 358+ publications.
   a. Andrade LE, **Chan EKL**, Raska I, Peebles CL, Roos G, Tan EM. Human autoantibody to a novel protein of the nuclear coiled body: immunological characterization and cDNA cloning of p80-coilin. J Exp Med. 1991;173:1407-19. PMCID: 2190846. Cited 354 times.
   b. Andrade LE, Tan EM, **Chan EKL**. Immunocytochemical analysis of the coiled body in the cell cycle and during cell proliferation. Proc Natl Acad Sci U S A. 1993;90:1947-51. PMCID: 45997. Cited 187 times.

2. Year 2000-2, **GW182 as a functional marker for GW bodies** (GWB). Our interests in miRNA work stem from the identification and cloning of the protein GW182 in our lab. We examine the cell biology of GWB in siRNA and miRNA function and establish that GW182 is the key effector downstream in miRNA-Ago-mRNA complex, and the roles of specific miRNA in innate immunity, autoimmunity, and cancer. miRNAs are currently considered by some investigators as key regulators of gene expression via negative feedback control of the half-lives of critically important mRNAs, such as classical oncogenes and tumor suppressors. Our initial identification of GW182 as a marker for GWBs has contributed significantly. PubMed search for “GW182” alone shows 160+ publications to date.
   a. Eystathioy T, **Chan EKL**, Tenenbaum SA, Keene JD, Griffith K, Fritzler MJ. A phosphorylated cytoplasmic autoantigen, GW182, associates with a unique population of human mRNAs within novel cytoplasmic speckles. Mol Biol Cell. 2002;13:1338-51. PMCID: 102273. Cited 339 times.
   b. Yang Z, Jakymiw A, Wood MR, Eystathioy T, Rubin RL, Fritzler MJ, **Chan EKL**. GW182 is critical for the stability of GW bodies expressed during the cell cycle and cell proliferation. J Cell Sci. 2004;117:5567-78. Cited 183 times.
   c. Jakymiw A, Lian S, Eystathioy T, Li S, Satoh M, Hamel JC, Fritzler MJ, **Chan EKL**. Disruption of GW bodies impairs mammalian RNA interference. Nat Cell Biol. 2005;7:1267-74. Cited 376 times

3. Year 2006-, **Rods and Rings (RR)** are conserved, non-membrane-bound intracellular polymeric structures composed in part of inosine monophosphate dehydrogenase (IMPDH), a key enzyme in GMP and GTP biosynthesis. We show that RR formation is induced by IMPDH inhibitors as well as glutamine deprivation. Depriving cells of serine and glycine promotes RR formation and we have traced these effects to dihydrofolate reductase (DHFR) and serine hydroxymethyltransferase-2 (SHMT2), pivotal enzymes in one-carbon metabolism and nucleotide biosynthesis. RR assembly is likewise induced upon DHFR inhibition by methotrexate or aminopterin as well as siRNA-mediated knockdown of DHFR or SHMT2. Because RR assembly occurs when guanine nucleotide biosynthesis is inhibited, and because RR rapidly disassembles

after the addition of guanine nucleotide precursors, RR formation may be an adaptive homeostatic mechanism, allowing IMPDH to sense changes in the one-carbon folate pathway. Autoantibodies to RR are found primarily in chronic hepatitis C patients who have undergone interferon/ribavirin therapy, but not prior to therapy. Ribavirin is a strong IMPDH inhibitor. Clearly this is a new area that will attract a lot of interests.

a. Carcamo WC, Satoh M, Kasahara H, Terada N, Hamazaki T, Chan JY, Yao B, Tamayo S, Covini G, von Muhlen CA, **Chan EKL**. Induction of cytoplasmic rods and rings structures by inhibition of the CTP and GTP synthetic pathway in mammalian cells. PLoS One. 2011;6:e29690. PMCID: 3248424. Cited 57 times
b. Covini G, Carcamo WC, Bredi E, von Muhlen CA, Colombo M, **Chan EKL**. Cytoplasmic rods and rings autoantibodies developed during pegylated interferon and ribavirin therapy in patients with chronic hepatitis C. Antivir Ther. 2012;17:805-11. Cited 34 times
c. Calise SJ, Purich DL, Nguyen T, Saleem DA, Krueger C, Yin JD, **Chan EKL.** Rod and ring formation from IMP dehydrogenase is regulated through the one-carbon metabolic pathway. J Cell Sci. 2016;129:3042-52. Cited 2 times

4. Year 2009-, **Dominant miRNA in innate immune response regulating endotoxin tolerance.** Our 2009 JBC article was the first to define the critical role of miR-146a in endotoxin tolerance and we have followed up with several studies to document that miR-146a has a dominant role in IL-1β-induced tolerance and cross-tolerance to toll-like receptor (TLR) ligands. TLR and IL-1R signaling activates the MyD88-dependent pathway with the formation of the myddosome, involving the helical assembly of the MyD88-IRAK4-IRAK2/IRAK1 complex. TLR/IL-1R signaling leads to activation of NF-κB, which is known to activate miR-146a production. TLR2 and TLR5 ligands also activate transcription factor CREB and miR-132/-212 production. miR-132/-212 targets IRAK4, whereas miR-146a targets IRAK2/1 and TRAF6. IRAK4 and IRAK2/1 are critical components of the myddosome, which is in turn critical for activation of the pathway. Thus, these miRNA operate as negative regulatory feedback mechanism to prevent the destructive consequences of uncontrolled cytokine production during the IL-1β/TLR signaling cascade. One of our most highly cited work is the early identification of elevated miR-146a in peripheral blood mononuclear cells of patient with rheumatoid arthritis and the high level of this microRNA correlated with disease activities.

a. Nahid MA, Pauley KM, Satoh M, **Chan EKL**. miR-146a is critical for endotoxin-induced tolerance: Implication in innate immunity. J Biol Chem. 2009;284:34590-9. PMC:2787321. Cited 254 times
b. Nahid MA, Satoh M, **Chan EKL**. Mechanistic role of microRNA-146a in endotoxin-induced differential cross-regulation of TLR signaling. J Immunol. 2011;186:1723-34. PMC:3608687. Cited 144 times
c. Pauley KM, Satoh M, Chan AL, Bubb MR, Reeves WH, **Chan EKL**. Upregulated miR-146a expression in peripheral blood mononuclear cells from rheumatoid arthritis patients. Arthritis Res Ther. 2008;10:R101. PMC:2575615. Cited 505 times

Summary of Publications *(Feb., 2017)*

Peer-Reviewed Articles: 214 (2016:8; 2015:7)
Review Articles, Editorials, and Letters: 35 (2016:3; 2015:4)
Book Chapters and Symposium Proceedings: 55 (2016:7; 2015:2)
Books Co-edited: 7

Google Scholar Bibliography ("Edward K.L. Chan"):

Citation indices	*All*	*Since 2012*
Citations	*17,313*	*6,497*
h-index	*72*	*44*
i10-index	*205*	*136*

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40277181/?sort=date&direction=descending

D. Research Support

Ongoing Research Support
Pfizer RA ASPIRE -US 2012 Chan, E.K.L. (PI) 9/1/2012-8/31/2017 (No cost extension)
Ethnic heterogeneity in microRNA expression as a biomarker in rheumatoid arthritis
The major goal of this project is to examine miRNA expression in RA patients with Hispanic background. No overlap.
Role: PI

University of Florida Seed Grant 2/1/2015-1/31/2017
MicroRNA biomarkers in oral cancer outcome
The goal of the proposal is to collaborate with clinical investigators in Orlando Health to study multiple populations based on miRNA signature to predict oral cancer outcome. No overlap
Role: PI, Chan, E.K.L.

DoD Medical Discovery Award 1/1/2016-6/31/2017
Oral metagenomic biomarkers in rheumatoid arthritis
The goal of this collaborative proposal will examine microbiome from patients with rheumatoid arthritis. No overlap.
Role: PI, Chan, E.K.L.

R01 ES021464-02S1 (Pollard, K.M.) 6/1/2015-5/31/2018
NIEHS/NIH
Virtual Consortium for Translational/Transdisciplinary Environmental Research (ViCTER)
Subproject title: Influence of Innate Immunity on Xenobiotic-Induced Systemic Autoimmunity
The subproject will focus on miRNA analyses in the xenobiotic mouse models of autoimmunity. No overlap.
Role: Subproject PI, Chan, E.K.L.

NIEHS/NIH 6/1/2015-5/31/2017
NHANES antinuclear antibody assay
The goal of this contract is to determine changes in autoantibody in different NHANES populations. No overlap.
Role: PI, Chan, E.K.L.

UF Research Foundation 6/1/2015-5/31/2017
Nanoparticle-mediated microRNA therapy for oral cancer
The goal of this internally-funded project is to optimize delivery of miRNA/anti-miRNA to oral cancer via nanoparticles. No overlap.
Role: PI, Chan, E.K.L.

<u>Completed Research Support</u>
R01 AI47859 Chan (PI) 12/27/2006 - 12/26/2013
NIH / NIAID
Antigens of the RNA-induced silencing complex in autoimmunity
The major goals of this project are to define the role of RNA interference associated autoantigens in human autoimmune disease and mouse model of autoimmunity.

Chan, EKL (PI) 4/1/2009 - 3/31/2012
Lupus Research Institute
miRNA biomarkers affecting the interferon pathway in SLE
The major goals of this project are to identify miRNA relevant to human SLE.

Chan, E.K.L. (PI) 7/15/2010-7/14/2015
Andrew J Semesco Foundation for Oral Cancer Research
Fellowship: **MicroRNA and the suppression of cellular activity to prevent oral cancer tumor formation**
The funding support stipend of a PhD graduate student to work on oral cancer investigation.

Chan, E.K.L. (PI) 4/2013-3/2015
UF-HHMI Science for Life Distinguished Mentor Award
This award was given for mentoring of undergrads over the past 10 years in my lab.

DE019644-01 Cha, Seunghee (PI) 7/01/2010- 6/30/2016
NIH / NIDCR
Expression and function of microRNA in autoimmune Sjögren's syndrome
The major goals of this project are to identify miRNA relevant to Sjögren's syndrome. Role: co-Investigator