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.	05/1976	Biochemistry
University of Calgary, Calgary, Canada	M.Sc.	11/1980	Clinical Chemistry
University of Calgary, Calgary, Canada	Ph.D.	06/1984	Immunopathology
Scripps Clinic and Research Foundation, La Jolla, California	Research Fellow	1984-88	Immunochemistry and Molecular Biology

A. Personal Statement

The PI's research interests in cancer research started with studies in the diversity of the autoantibody responses in cancer during his tenure at the Scripps Research Institute, La Jolla, CA. His laboratory cloned many autoantigens, including CIP2A (or p90), which was identified later as a highly important inhibitor of PP2A in oral cancer, through collaboration with Dr. Westermarck in Finland (*Junttila et al., CIP2A Inhibits PP2A in Human Malignancies. Cell. 2007;130:51-62*).

Since joining the University of Florida College of Dentistry in 2002, his lab continues to focus on head and neck and oral cancers. In 2018, 51,540 new cases in oral cavity and pharynx cancer are expected in the United States and 10,030 deaths estimated from these cancers. In Florida, cancer of the oral cavity and pharynx is one of two cancers (other being cancer of the cervix) that have both higher incidence and mortality rates than the national average. There is clearly a need to improve the diagnosis and treatment of oral cancer as it represents significant burden to society.

Early research focus of the lab was the characterization of microRNA (miRNA) differentially expressed in human oral cancer. The interests in miRNA work stem from the identification and cloning of the protein GW182, a macromolecular marker of the novel cytoplasmic foci known as GW bodies (GWBs) in the PI's lab. GWBs are now also known as the mammalian counterpart of processing bodies (P bodies) first identified in yeast. The PI's laboratory demonstrated a link of RNA interference (RNAi) function to GWBs; specifically, disruption or disassembly of GWB impairs short interference RNA (siRNA) and microRNA (miRNA)-mediated translational silencing activity (1). Furthermore, they showed that the biogenesis of miRNA is closely linked to GWB assembly; specifically these foci disassembled in HeLa cells made deficient in mature miRNA or from the knockdown of Drosha or DGCR8 to inhibit maturation of endogenous miRNA. GWBs re-assembled when these same cells were transfected with surrogate miRNA. The laboratory continued to examine the cell biology of GWB in siRNA and miRNA function establishing that GW182 is the key effector downstream in miRNA-Ago-mRNA complex, and the roles of specific microRNA in oral cancer (2). 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.

The PI's lab has a record of accomplishment in the analysis of oral tumors. They have shown that high expression of miR-21 is a major factor related to the poor prognosis of patients (3). miR-7 and miR-21 are both upregulated in oral cancer and they negatively regulate the tumor suppressor gene RECK (3). On the other hand, miR-375 is a key tumor suppressor miRNA that is underexpressed in oral cancer. The lab has demonstrated that miR-375 regulates a number of important genes, including CIP2A, E6AP, 14-3-3ζ, and HPV

viral protein E6 and E7. More importantly, they have established and published a mouse model of oral cancer that can be used to test for efficacy in therapy (4).

The current focus is the development of CAR-T cell based immunotherapy for oral cancer and an *in vitro* demonstration of feasibility was published earlier this year from the PI's laboratory (5). As shown in preliminary data, there is ongoing testing of anti-CD70 CAR-T in a mouse xenograft model using human tumor cells implanted into the flank in NSG mice, which are genetically designed to be immunodeficient and able to accept these tumors. Additional tumor models have been developed using tumor cells injected in the tongue to examine the effect of CAR-T cell delivery under different tumor environment.

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 >428 times
2. Jung HM, Phillips BL, Chan EKL. miR-375 activates p21 and suppresses telomerase activity by coordinately regulating HPV E6/E7, E6AP, CIP2A, and 14-3-3zeta. Mol Cancer. 2014;13:80. PMC:4021670. Cited >47 times
3. Jung HM, Phillips BL, Patel RS, Cohen DM, Jakymiw A, Kong WW, Cheng JQ, Chan EKL. Keratinization-associated miR-7 and miR-21 regulate tumor suppressor reversion-inducing cysteine-rich protein with kazal motifs (RECK) in oral cancer. J Biol Chem. 2012;287:29261-72. PMC:3436145. Cited >65 times
4. Jakymiw A, Patel RS, Deming N, Bhattacharyya I, Shah P, Lamont RJ, Stewart CM, Cohen DM, Chan EKL. Overexpression of dicer as a result of reduced let-7 microRNA levels contributes to increased cell proliferation of oral cancer cells. Genes Chromosomes Cancer. 2010;49:549-59. PMC:2859695. Cited >120 times
5. Park YP, Jin L, Bennett KB, Wang D, Fredenburg KM, Tseng JE, Chang LJ, Huang J, Chan EKL. CD70 as a target for chimeric antigen receptor T cells in head and neck squamous cell carcinoma. Oral Oncol. 2018;78:145-50.

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

Professional Societies: American Association for Cancer Research, American Society for Cell Biology, American College of Rheumatology, 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; 2017, University of Florida Term Professorship

Federal Committees and Service (*last 10 years only*):

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 (*last 10 years only*):

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, 2017
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, 2010-7

Editorial Boards:

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

C. Contributions to Science

1. The PI's laboratory use of human autoantibodies in molecular characterization leading to the discovery of functional markers for three novel subcellular structures: Coiled body (later renamed Cajal body); **GW bodies** (GWB, also known as mammalian P bodies); and **Rods and Rings (RR)**. The 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. For example, in 2000-2, we cloned and identified GW182 as a functional marker for GW bodies and subsequently we demonstrated its associated RNAi function. Our interests in miRNA work stem from the identification 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. Our initial identification of GW182 as a marker for GWBs has contributed significantly. PubMed search for "GW182" alone shows 199+ publications to date.

a. 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. PMC:45997. Cited >190 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 >200 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 >426 times.

d. 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. PMC:3248424. Cited >67 times.

2. Critical microRNAs in oral cancer. Our laboratory has published a series of articles on the different important microRNA differentially expressed in oral cancer, mostly focusing on the major subtype tongue cancer. This was initiated initially with collaboration with Dr. Jin Q Cheng at the Moffitt Cancer Center, which provide tumor samples. microRNAs are considered as key regulators of gene expression via negative feedback control of the half-lives of critically important mRNAs, including oncogenes and tumor suppressors. We have shown that high expression of oncogenic miR-21 is a major factor related to the poor prognosis of patients. On the other hand, miR-375 and miR494 are key tumor suppressor microRNAs that are underexpressed in oral cancers. Our lab is establishing microRNA biomarkers for early diagnosis of pre-oral cancer and has published a recent review on emerging microRNAs in cancer.

a. Jung, H.M., Phillips, B.L., Patel, R.S., Cohen, D.M., Jakymiw, A., Kong, W.W., Cheng, J.Q., and **Chan, E.K.L.** (2012) Keratinization-associated miR-7 and miR-21 regulate tumor suppressor reversion-inducing-cysteine-rich protein with kazal motifs (RECK) in oral cancer. J. Biol. Chem. 287:29261-72. PMC3436145

b. Jung, H.M., Patel, R.S., Phillips, B.L., Wang, H., Reinhold, W.C., Cohen, D.M., Chang, L.J., Yang, L.J., and **Chan, E.K.L.** (2013) Tumor suppressor miR-375 regulates MYC expression via repression of CIP2A coding sequence through multiple miRNA-mRNA interaction. Mol. Biol. Cell 24:1638-48. PMC3667718

c. Jung, H.M., Phillips, B.L., and **Chan, E.K.L.** (2014) miR-375 activates p21 and suppresses telomerase activity by coordinately regulating HPV E6/E7, E6AP, CIP2A, and 14-3-3ζ. Mol. Cancer 13:80.

d. Libório-Kimura, T.N., Jung, H.M., and **Chan, E.K.L.** (2015) miR-494 represses HOXA10 expression and inhibits cell proliferation in oral cancer. Oral Oncol. 51:151-7.

e. Harrandah, A.M., Mora, R.A., and **Chan, E.K.L.** (2018). Emerging microRNAs in cancer diagnosis, progression, and immune surveillance. Cancer Lett 438, 126-132.

3. Dominant microRNA 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 >346 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 >187 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 >642 times

d. Nahid, M.A., Satoh, M., and **Chan, E.K.L.** (2015). Interleukin-1β-responsive miR-146a is critical for the cytokine-induced tolerance and cross-tolerance to toll-like receptor ligand. J. Innate immune. 7:428-40.

SUMMARY of Published Work *(Jan., 2019)* Complete List in MyBibliography:
http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40277181/?sort=date&direction=descending
Number of Peer-Reviewed Papers: 224
Number of Reviews, Editorials, Opinions, and Letters: 40
Number of Book Chapters and Symposium Proceedings: 57
Number of Books Edited: 7
Number of Scientific Abstracts: 358
Google Scholar Bibliography ("Edward K.L. Chan"):

Citation indices	*All*	*Since 2014*
Citations	*21,396*	*6,921*
h-index	*82*	*43*