BIOGRAPHICAL SKETCH

NAME: Anson W. Lowe

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

POSITION TITLE: Associate Professor of Medicine

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
University of California, Berkeley, CA	A.B.	1976	Physiology
Mt. Sinai School of Medicine, New York, N.Y.	M.D.	1980	Medicine
Intern & Resident in Internal Medicine, The Columbia-Presbyterian Hospital, New York, N.Y.		1983	Medicine
Research Fellowship in Nephrology, Columbia University, New York, N.Y. (Mentor: Qais Al-Awqati)		1984	Nephrology
Fellowship in Gastroenterology, UCSF		1985	Gastroenterology
Postdoctoral fellow in the Dept. of Biochemistry & Biophysics, UCSF (Mentor: Regis B. Kelly)		1989	Cell Biology

A. Personal Statement

I have been NIH funded and active in gastroenterology and cell biology for 35 years, and served as a PI and faculty member at Stanford University for the past 30 years. For my entire scientific career, I am experienced in both the biology and clinical aspects of human disease. I would consider my laboratory as the leader in the field concerning the regulation of EGFR signaling by AGR2. My major active focus is development of therapeutic interventions focused on AGR2.

B. Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.

1980 - 1983	Intern and Resident in Internal Medicine, The Presbyterian Hospital, Columbia-Presbyterian Medical Center, New York, N.Y.
1983 - 1984	Fellowship in the Division of Nephrology, Department of Medicine, College of Physicians & Surgeons, Columbia University, New York, N.Y. Research performed the laboratory of Qais Al-Awqati.
1984-1989	Fellowship in the Division of Gastroenterology, Department of Medicine, University of California, San Francisco
1985-1989	Associate Research Biochemist, Department of Biochemistry & Biophysics, University of California, San Francisco (Research performed in the laboratory of Regis B. Kelly).
1989-1996	Assistant Professor, Department of Medicine, Division of Gastroenterology, Stanford University School of Medicine, Stanford, California
1995-1996	Assistant Professor, Department of Molecular & Cellular Physiology (by courtesy), Stanford University School of Medicine, Stanford, California
1996-2020	Associate Professor, Department of Medicine, Division of Gastroenterology, Stanford University School of Medicine, Stanford, California
1996-2016	Associate Professor, Department of Molecular & Cellular Physiology (by courtesy), Stanford University School of Medicine, Stanford, California

2001-2012	Associate Director, Stanford Digestive Disease Center
2020-present	Associate Professor, Emeritus (active), Medicine

Other Professional Activities

2011-2016	Special Sections Editor, *Gastroenterology*
2000-2004	Associate Editor, *The American Journal of Medicine*
2004-2007	AGA Research Review Panel
2010-2013	AGA Research Review Panel

C. Contribution to Science

1. My early publications focused on the mechanisms of secretory granule biogenesis in the pancreatic exocrine cell. At the time, the mechanisms underlying the formation of secretory granules and how proteins were sorted to these organelles were unknown. I discovered a set of membrane proteins shared between exocrine, neural, and endocrine secretory granules derived from different tissues. I also discovered that the pancreatic zymogen granule possessed an integral membrane protein, VAMP2, which was also present in neural and endocrine secretory granules, and was later determined to be responsible for vesicle targeting and fusion.

    a) Clift O'Grady, L., Linstedt, A.D., Lowe, A.W., Grote, E. and Kelly, R.B. Biogenesis of synaptic vesicle-like structures in a pheochromocytoma cell line PC-12. *J.Cell Biol.* 110:1693-1703, (1990). PMID:2110571, PMCID:PMC2200166
    b) Lowe, A.W., Madeddu, L. and Kelly, R.B. Endocrine secretory granules and neuronal synaptic vesicles have three integral membrane proteins in common. *J.Cell Biol.* 106:51-59, (1988). PMID: 3276713, PMCID:PMC2114944
    c) Matsuuchi, L., Buckley, K.M., Lowe, A.W. and Kelly, R.B. Targeting of secretory vesicles to cytoplasmic domains in AtT-20 and PC-12 cells. *J.Cell Biol.* 106:239-251, (1988). PMID: 2828380, PMCID:PMC2114966
    d) Braun, J.E.A., Fritz, B., Wong, S.M.E. and Lowe, A.W. Identification of a VAMP-like membrane protein in rat zymogen granules of the exocrine pancreas. *J.Biol.Chem.* 269:5328-5335, (1994). PMID:8106518
    e) Mandic, R., and A. W. Lowe. Characterization of an alternatively spliced isoform of vesicle-associated membrane protein-2 (VAMP-2). . *FEBS Letts* 451:209-213, (1999). PMID:10371166
    f) Mandic, R., Trimble, W.S., and A. W. Lowe. Tissue-Specific Alternative RNA Splicing of VAMP-1. *Gene* 199:173-179, (1997). PMID: 9358054
    g) Gaisano, H.Y., Sheu, L., Grondin,G., Ghai,M., Bouquillon, A., M., Lowe, A., Beaudoin, A., and W.S. Trimble. The vesicle-associated membrane protein (VAMP) family of proteins in rat pancreatic and parotid acinar cells. *Gastroenterology* 111: 1661-1669, (1996). PMID:8942747
    h) Rodepeter FR, Wiegand S, Luers HG, Bonaterra GA, Lowe AW, Bette M, Jacob R, Mandic R. Indication for differential sorting of the rat v-SNARE splice isoforms VAMP-1a and -1b. Biochem Cell Biol. 2017; 95(4):500-509. PubMed PMID: 28314111.

2. Following my work on proteins involved in vesicle targeting and fusion, I focused on the dominant membrane protein of the pancreatic exocrine secretory granule, GP2, as potentially functioning in the sorting and packaging of digestive enzymes into the secretory granule. I established, by generating a knockout mouse that GP2 did not function in secretory granule biogenesis or protein sorting. The work resolved a major hypothesis in the field as many other laboratories had also proposed that GP2 served as a protein sorting receptor. My subsequent work pursued the true function of GP2 and established that it bound a large class of pathogenic bacteria that express Type I fimbriae, which supported a potential role in innate immunity that protects the pancreas from ascending infections. GP2 was also found in M cells of the intestine where it bound Salmonella and underwent transcytosis to a compartment where dendritic cells reside. GP2 is now an established biomarker for intestinal M cells and studies continue on its role in the immune system.

From a translational perspective, I established that GP2 serves as a useful clinical marker for the diagnosis of acute and chronic pancreatitis.

a) Lowe, A.W., Luthen, R.E., Wong, S.M.E. and Grendell, J.H. The zymogen granule protein, GP-2, is elevated in a rat model for acute pancreatitis. *Gastroenterology* 107:1819-1827, (1994). PMID:7525398
b) Wong, S.M.E. and Lowe, A.W. Nucleotide sequence of human GP-2, the major membrane protein in the secretory granule of the exocrine pancreas. *Gene* 171 (2): 311-312, (1996). PMID:8666297
c) Fritz, B.A. and Lowe, A.W. Polarized GP-2 secretion via glycosylphosphatidylinositol targeting and apical membrane restricted proteolysis. *Am. J. Physiol.* 270:G176-G183 (1996). PMID:8772516
d) Fritz, B.A., Fei, M. and Lowe, A.W. Processing of the zymogen granule membrane protein, GP2. *Pancreas* 24:336-43, (2002). PMID: 11961485
e) Hao, Y., J. Wang, N. Feng, and A.W. Lowe. 2004. Determination of plasma glycoprotein 2 levels in patients with pancreatic disease. *Arch Pathol Lab Med*. 128:668-74. PMID: 15163232
f) Yu, S., Y. Hao, and A.W. Lowe. 2004. Effects of GP2 expression on secretion and endocytosis in pancreatic AR4-2J cells. *Biochem Biophys. Res. Commun*. 322:320-5. PMID:15313209
g) Yu, S., S. A. Michie, and A.W. Lowe. Absence of the Major Zymogen Granule Membrane Protein, GP2, Does Not Affect Pancreatic Morphology or Secretion. *J. Biol. Chem*. 26;279(48):50274-9 (2004). PMID:15385539
h) Terahara K, Yoshida M, Igarashi O, Nochi T, Pontes GS, Hase K, Ohno H, Kurokawa S, Mejima M, Takayama N, Yuki Y, Lowe, AW, Kiyono H: Comprehensive gene expression profiling of Peyer's patch M cells, villous M-like cells, and intestinal epithelial cells. *J Immunol* 2008, 180(12):7840-7846. PMID:18523247
i) Yu S, Lowe AW. The pancreatic zymogen granule membrane protein, GP2, binds Escherichia coli type 1 Fimbriae. *BMC Gastroenterol*. 2009;9(1):58. PMID:19627615, PMCID:PMC2726147
j) Koji Hase, K., Kawano, K., Nochi, T., *Pontes, G.S.*, Fukuda, S., Ebisawa, M., Kadokura, K., Tobe,T., Fujimura, Y., Kawano, S., Nakato, G., Kimura, S., Murakami, T., Iimura, M., Hamura, K., Fukuoka, S-I., Lowe AW, Waguri, S., Itoh, K., Kiyono, H., and Ohno, H. Uptake via Glycoprotein 2 of $FimH^+$ bacteria by M cells initiates mucosal immune response. *Nature.* 2009: 462(7270):226-230. PMID:19907495

3. With the advent of DNA microarrays at Stanford University, I conducted early studies that characterized the gene expression profile of pancreatic, esophageal, and gallbladder cancers, and Barrett's esophagus. The result was the identification of unique gene signatures for these cancers. A remarkable feature among both pancreatic and esophageal adenocarcinomas was the uniformity in their respective gene expression profiles, which was unlike many other cancers such as those derived from the breast. The invariability of the gene expression profile was consistent with the relatively uniformity of their natural history. The work provided a comprehensive assessment of the differentially expressed genes in pancreatic and esophageal cancer and serves as a valuable public resource.

a) Iacobuzio-Donahue,C.A., Maitra,A., Olsen, M., Lowe, A.W., Van Hee, N.T., Rosty, C., Walter, K., Sato, N., Parker, A., Ashfaq,R., Jaffee, E., Ryu, B., Jones, J., Eshleman, J.R., Yeo, C.J., Cameron, J.L., Kern, S.E., Hruban, R.H., Brown, P.O., Goggins, M. Exploration of global gene expression patterns in pancreatic adenocarcinoma using cDNA microarrays. *Am J Pathol*. Apr;162(4):1151-62 (2003). PMID:12651607, PMCID:PMC1851213
b) Lowe, A.W., Olsen, M., Hao, Y., Lee, S.P., Lee, K-T., Chen, X., van de Rijn, M., and P.O. Brown. Gene Expression Patterns in Pancreatic Tumors, Cells and Tissues. *Plos One* 2007 Mar 28;2:e323. PMID:17389914, PMCID:PMC1824711
c) Hao, Y., Triadafilopoulos, G., Sahbaie, P., Young, H., Omary, M.B., and A. W. Lowe. Gene Expression Profiling Reveals Stromal Genes Expressed in Common Between Barrett's Esophagus and Adenocarcinoma. *Gastroenterology* 2007 131:925-933 (2007). PMID:16952561, PMCID:PMC2575112
d) Kim, H.N., Choi, D.W., Lee, K.T., Lee, J.K., Heo, J.S., Choi, S-H., Paik, S.W., Rhee, J.C., and A.W. Lowe. Gene expression profiling in lymph node-positive and lymph node-negative pancreatic cancer. *Pancreas* 2007 Apr;34(3):325-34. PMID: 17414055
e) Hao Y, Sood S, Triadafilopoulos G, Kim JH, Wang Z, Sahbaie P, Omary MB, Lowe AW. Gene expression changes associated with Barrett's esophagus and Barrett's-associated adenocarcinoma cell lines after acid or bile salt exposure. *BMC Gastroenterol*. 2007 Jun 27;7(1):24. PMID:17597535, PMCID:PMC1925102

f) Kim JH, Kim HN, Lee KT, Lee JK, Choi SH, Paik SW, ...Lowe, AW. Gene Expression Profiles in Gallbladder Cancer: The Close Genetic Similarity Seen for Early and Advanced Gallbladder Cancers May Explain the Poor Prognosis. *Tumour Biol.* 2008;29(1):41-9. PubMed PMID: 18497548

4. The work on gene expression profiling led to a search for novel, unstudied genes that were highly expressed in pancreatic and esophageal cancers and vital for cancer pathogenesis. The effort led to my current focus on the gene *Anterior Gradient 2* (AGR2). AGR2 attracted my interest because of its widespread expression in all adenocarcinomas, but absence from normal tissues. Using lung and esophageal adenocarcinoma cell lines, my laboratory was the first to establish that AGR2 expression is required to maintain the transformed phenotype of adenocarcinoma cell lines. Subsequent studies established that AGR2 expression affected both the Hippo and EGFR signaling pathways by respectively activating the coactivator YAP1 and inducing expression of the EGFR ligand *Amphiregulin.* We then proceeded to define the mechanism of action for AGR2 and discovered that it serves as a thioredoxin within the endoplasmic reticulum, and that its major substrate is the Epidermal Growth Factor Receptor (EGFR). Within the endoplasmic reticulum, AGR2 physically interacts with EGFR and enables its transport to the cell surface where cell signaling is initiated. Without AGR2 expression, we established that EGFR signaling is not possible, and thus represents a novel and likely dominant mechanism for regulating EGFR signaling. The finding represented a major advance for both AGR2 and EGFR, and provided valuable insights in cancer pathogenesis. Our most recent work defined AGR2 function in normal tissues. We established in a murine pancreatitis model that AGR2 expression is induced and is responsible for initiating EGFR signaling and tissue regeneration, without which the mice die. The work represents the first definitive assessment of EGFR function in adult vertebrates, namely tissue regeneration. The work also supported a close relationship between tissue regeneration and the development of pancreatic cancer. I consider our laboratory to be the leader in AGR2 biology and its role in regulating EGFR in health and disease.

   From a translational perspective, we have used genes whose expression is induced by AGR2 expression, as biomarkers for pancreatic cysts and cancer.

   a) Wang, Z., Hao, Y., Lowe, A.W. The adenocarcinoma-associated antigen, *AGR2*, promotes tumor growth, cell migration, and cellular transformation. *Cancer Res*. 2008:68(2):492-497. PMID:18199544
   b) Dong A, Gupta A, Pai RK, Tun M, Lowe AW. The Human Adenocarcinoma-associated Gene, AGR2, Induces Expression of Amphiregulin through Hippo Pathway Co-activator YAP1 Activation. *J Biol Chem* 2011;286(20):18301-10. PMCID: PMC3093902. PMID:21454516, PMCID:PMC3093902
   c) Tun MT, Pai RK, Kwok S, Dong A, Gupta A, Visser BC….Lowe, AW, Park, WG. Diagnostic accuracy of cyst fluid amphiregulin in pancreatic cysts. *BMC Gastroenterol.* 2012;12(1):15. PubMed PMID: 22333441. PMID:22333441, PMCID:PMC3305641 (corresponding and co-senior author)
   d) Gupta A, Dong A, Lowe AW. AGR2 gene function requires a unique endoplasmic reticulum localization motif. *J Biol Chem.* 2012;287(7):4773-82. PMID: 22184114, PMCID:PMC3281655
   e) DiMaio MA, Kwok S, Montgomery KD, Lowe AW, Pai RK. Immunohistochemical panel for distinguishing esophageal adenocarcinoma from squamous cell carcinoma: a combination of p63, cytokeratin 5/6, MUC5AC, and anterior gradient homolog 2 allows optimal subtyping. *Hum Pathol.* 2012;43(11):1799-807. PMID: 22748473, PMCID:PMC3465493
   f) Gupta A, Wodziak D, Tun M, Bouley DM, Lowe AW. Loss of anterior gradient 2 (agr2) expression results in hyperplasia and defective lineage maturation in the murine stomach. *J Biol Chem.* 2013;288(6):4321-33. PubMed PMID: 23209296, PMCID:PMC3567683
   g) Foygel K, Wang H, Machtaler S, Lutz AM, Chen R, Pysz M, Lowe AW, Tian L, Carrigan T, Brentnall TA, Willmann JK. Detection of pancreatic ductal adenocarcinoma in mice by ultrasound imaging of thymocyte differentiation antigen 1. *Gastroenterology*. 2013;145(4):885-94 e3. PMID: 23791701; PMCID: PMC3783557.
   h) Park WG, Wu M, Bowen R, Zheng M, Fitch WL, Pai RK, et al. Metabolomic-derived novel cyst fluid biomarkers for pancreatic cysts: glucose and kynurenine. *Gastrointest Endosc*. 2013. PubMed PMID: 23566642, PMCID:PMC3780566
   i) Dong A, Wodziak D, Lowe AW. Epidermal Growth Factor Receptor (EGFR) Signaling Requires a Specific Endoplasmic Reticulum Thioredoxin for the Post-translational Control of Receptor Presentation

to the Cell Surface. *J Biol Chem*. 2015;290(13):8016-27. PubMed PMID: 25666625, PMCID:PMC4375459.

j) Wodziak D, Dong A, Basin MF, Lowe AW. Anterior Gradient 2 (AGR2) Induced Epidermal Growth Factor Receptor (EGFR) Signaling Is Essential for Murine Pancreatitis-Associated Tissue Regeneration. *PLoS One*. 2016;11(10):e0164968. PubMed PMID: 27764193.

Patents

a) Lowe, Anson W. and Dong, Aiwen, inventors; The Board of Trustees of the Leland Stanford Junior University, assignee, Use of AGR3 for Treating Cancer. US patent 9,415,088. August 16, 2016.

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