BIOGRAPHICAL SKETCH

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NAME: Deborah J Andrew

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

POSITION TITLE: Professor, Department of Cell Biology

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 Central Florida; Orlando, FL	B.S.	1976-1979	Limnology
University of Central Florida; Orlando, FL	M.S.	1979-1981	Genetics
University of California, San Diego, CA	Ph.D.	1981-1987	**Genetics/Molecular Biology**
University of Colorado; Boulder, CO	Post-doc	1988-1990	Developmental Biology
Stanford University; Stanford, CA	Post-doc	1990-1993	Developmental Biology

A. PERSONAL STATEMENT

My research has focused on Drosophila developmental genetics since 1979, when I began my Master's thesis. Since that time, my lab (either me or someone in my group) has done almost every manipulation reported for this organism, ranging from imaginal disc transplantation to creating targeted gene knockouts by homologous recombination and CRISPR/CAS9. My lab has done microarrays, co-immunoprecipitations, chromatin immunoprecipitations, Southerns, Northerns, Westerns, EMSAs, qRT-PCR, library screens, and enzyme assays. We have done immunostaining, histolology, in situs, scanning and transmission electron microscopy, confocal imaging, and we have developed the tools for live multiphoton imaging of deep tissues. We have done chemical mutagenesis screens, generated both loss-of-function and overexpression clones, and created numerous transgenic fly lines, including transformations with heat shock, Gal4, UAS, reporter lacZ and genomic [cosmid] constructs. We have generated antibodies to several proteins (Scr, Trachealess, CrebA, Sage, Ribbon, Pasilla, Dsc73, WRS, Titin, PH4αSG1, PH4αSG2, Sano, Dmt, Tbc-1, Jbug, Outspread), which has helped our research and that of many other labs. We have mapped both genes and proteins to salivary gland polytene chromosomes and have worked with Drosophila S2, human HeLa and Hep2 cells. We have the technical abilities to carry out the proposed studies.

I have taught in both graduate and medical school courses every year since arriving at Hopkins, directing a course in Developmental Biology for both groups for several years. I also teach graduate genetics and medical school cell physiology. I have trained eleven post-docs (five current), ten graduate students (one current), six technicians (one current) and numerous undergraduates (three current), working closely with all of them, since my lab size has always been reasonably small – eight people maximum and often fewer at any given time. I have served as a regular member of the CDF5/Dev-2 study section and as an ad hoc reviewer for other study sections/special emphasis panels, as well as participating in NIH in-house reviews. Thus, I feel confident that I can direct the studies outlined in this proposal.

Since establishing my own lab in 1993, my studies have focused on the specification, morphogenesis and cell type specialization of two tubular organs, the Drosophila salivary gland and trachea. We have published many primary papers describing the roles of several transcription factors and their downstream targets in organ development. I have been invited to write reviews on organ formation in major developmental and cell biology journals, including Mechanisms of Development, BioEssays, Trends in Cell Biology, Developmental Biology, Journal of Cell Science, Differentiation, WIRES Developmental Biology, and Frontiers in Biology. I

am a regular reviewer for several general (Cell, Science, Nature, PLoS Genetics, PLoS Biology), cell biology (JCB, MCB, JCS) and development-specific (Development, Dev.Biol., MOD, Differentiation) journals and I served on the editorial board for Developmental Dynamics from 2008 - 2015. This past year I was co-editor on a special issue of Current Opinion in Genes and Development on Organogenesis.

B. POSITIONS AND HONORS

Experience:

1979-1981: M.S. Thesis Research; Advisor: Dr. David T. Kuhn; University of Central Florida, Orlando, FL
1982-1987: Ph.D. Thesis Research; Advisors: Dr. Bruce S. Baker, Dr. James A. Posakony; University of California San Diego, La Jolla, CA
1988-1993: Postdoctoral Research; Advisor: Dr. Matthew P. Scott, CU Boulder and Stanford University
1993-1999: Assistant Professor, Dept. of Cell Biology, Johns Hopkins University SOM, Baltimore, MD
1994-1997: Mid-Atlantic Representative, Drosophila Board of Directors
1999-2004: Associate Professor, Dept. of Cell Biology, Johns Hopkins University SOM, Baltimore, MD
1999-2001: Ad hoc reviewer National Institutes of Health Study Section OBM-1, OBM-2, CDF-5
2002-2006: Regular reviewer National Institutes of Health Study Section CDF5/DEV-2
2006: Co-organizer, Santa Cruz Developmental Biology Meeting
2004-2008: Faculty of 1000, Developmental Biology
2004-now: Professor, Dept. of Cell Biology, Johns Hopkins University SOM, Baltimore, MD
2007-2015: Editorial Board, Developmental Dynamics
2010-2013: Reviewer, NIDCR review of in-house faculty
2014: Reviewer, NICHD review of in-house faculty
2010-2014: Organizational Committee, Biennial EMBO Workshop " Molecular and Developmental Biology of Drosophila", Crete, Greece
2010: Special Emphasis Panel, NIAID International Centers of Excellence for Malaria Research
2010: Co-organizer, 51st Annual Drosophila Research Meeting
2010-2011: Fly Board Elections Committee Member
2011-2015: Ad hoc reviewer, F05 Graduate student and Post-doctoral NIH Fellowships
2013: Co-organizer: Gordon Research Conference on Salivary Glands and Exocrine Biology
2013-present: Drosophila Genetics Resource Center Advisory Board
2013-2016: Treasurer of the Drosophila Board
2015: Organizer: Gordon Research Conference on Salivary Glands and Exocrine Biology
2015: Co-editor for special issue of "Current Opinion in Genes and Development on "Organogenesis"
2016: President-elect of the Drosophila Board (term to be served in 2018)

Awards, fellowships and grants:

1981-1984: National Science Foundation Graduate Fellowship
1983-1984: Cal Biochem Award for Molecular Research
1987-1988: Martin Kamen Award for Best Biochemistry Thesis, UC San Diego
1988-1991: American Cancer Society Postdoctoral Fellowship
1993-1994: American Cancer Society Institutional Research Grant
1994-1995: Johns Hopkins University Institutional Research Grant
1994-1999: National Institutes of Health RO1 Research Grant 1RO1 GM51311
1999-2002: March of Dimes Research Grant
1999-2016: National Institutes of Health RO1 Research grant NIH RO1 DE12873
2000-2001: Professor's Award for Distinction in Teaching the Basic Sciences JHMI
2001-2016: National Institutes of Health RO1 Research grant 1 RO1 DE13899
2015-2016: Johns Hopkins Malaria Research Pilot Grant

C. CONTRIBUTION TO SCIENCE

1. Specification of salivary gland (SG) cell fates in Drosophila requires integration of multiple patterning inputs SG specification in Drosophila was shown by Steve Beckendorf's lab to require the Hox gene *Sex combs reduced* (*Scr*) acting in combination with the dorsal-ventral patterning genes. We showed that Scr can induce SG fates in all segments of the embryo that are also not expressing the trunk gene *teashirt* or the posterior Hox gene *Abdominal-B.* We further showed that expression of other more posteriorly expressed Hox genes can also block Scr-dependent SG fate specification. We demonstrated that Scr requires two more generally expressed cofactors for SG specification, Exd and Hth, and that once SGs are specified, all three

proteins – Scr, Exd and Hth – are no longer expressed (Scr and Hth) or no longer localize to nuclei (Exd) in SG cells. Thus, although Scr specifies the SG fate decision, it is not required to maintain SG fates or control SG differentiation. Scr and its cofactors activate expression of several downstream transcription factors, including Fkh, Sage, CrebA and Hkb, which are required to both maintain and implement SG fates. In related work, we identified the signaling components downstream of Dpp that prevent SG fates in dorsal cells that express Scr and its cofactors. We showed that Fkh blocks expression of duct genes in secretory cells and that Notch activation at the boundary between duct and secretory cells is required to specify the precursors to the adult SGs, known as imaginal ring cells. Collectively, these studies have made the Drosophila SG one of the best-understood model organs in terms of cell fate specification and maintenance.

Haberman, A.S., Isaac, D.D. and **Andrew, D.J.** (2003) Specification of cell fates within the salivary gland primordium. *Developmental Biology* 258: 443-453. PMID: 12798300

Henderson, K.D., and **Andrew, D.J.** (2000) Regulation and function of *Scr*, *exd*, and *hth* in the Drosophila salivary gland. *Developmental Biology* 217: 362-374. PMID: 10625560

Henderson, K.D., Isaac, D.D. and **Andrew, D.J.** (1999) Cell fate specification in the Drosophila salivary gland: The integration of homeotic gene function with the DPP signaling cascade. *Developmental Biology* 205: 10-21. PMID: 9882494

Andrew, D.J., Horner, M.A., Petitt, M.G., Smolik, S.M. and Scott, M.P. (1994) Setting limits on homeotic gene function: restraint of *Sex combs reduced* activity by *teashirt* and other homeotic genes. *EMBO J.* 13: 1132-1144. PMID: 7900989

2. Cell shape change and cell rearrangement drive epithelial tube morphogenesis Many organs critical for viability of multicellular organisms are epithelial tubes, which comprise tightly adherent polarized cells that keep apical (lumenal) materials separate from materials outside the tube and allow for the rapid transport of molecules from one place in the body to another. The Drosophila SG and trachea are ideal epithelial tubes to study since the primordia are polarized prior to specification and because regular mitotic divisions cease either once the tissue has internalized to form incipient tubes (in the case of the trachea) or once the tissue is specified (in the case of the SG). Thus, both epithelial tissues are ideal for uncovering the contributions of cell shape change, cell rearrangement and tissue migration to tissue elongation. To that end, we have identified and characterized roles for several transcription factors and their downstream targets in this process. We have discovered that cellular events, largely at the apical surface, play a major role in overall tube architecture. For example, the BTB-containing transcription factor Ribbon mediates tube elongation by increasing the flexibility of the apical surface. It does so by upregulating expression of Crumbs, an apical transmembrane protein that drives apical membrane expansion, and downregulating phosphorylation of Moesin, a protein that in its active phosphorylated state links the apical plasma membrane to the underlying actin cytoskeleton. Similarly, we showed that Hkb is critical for SG elongation; in *hkb* mutants, the glands form short “hockey-puck” shaped tubes instead of the elongated “cigar-shaped” tubes of WT embryos. We demonstrated that Hkb controls SG tube elongation via two downstream targets that mediate growth and delivery of apical membrane: *crumbs*, the same gene also regulated by Rib, and *klarsicht*, which encodes a protein that mediates minus end-directed microtubule-dependent organelle transport. In the trachea, our work characterizing the Trh target gene *Serrano* resulted in the original discovery that the PCP pathway is required to limit tube elongation in Drosophila. As final example, we showed that the atypical Cadherin - Cad99C, which localizes to the apical plasma membrane, controls cell rearrangement during tube elongation by linking the apical plasma membrane to the apical extracellular matrix, thus providing forces that counteract those driving cell rearrangement during tube elongation. We also showed that high-level expression of Cad99C confers apical character to other plasma membrane domains, an activity previously thought to be limited to Crb.

Chung, S.-Y. and **Andrew, D.J.** (2014) Cadherin 99C regulates apical expansion and cell rearrangement during epithelial tube elongation. *Development* 141: 1950-1960. PMCID: PMC3994772

Chung, S.-Y., Vining, M.S., Bradley, P.L., Chan, C.-C., Wharton, K.A. and **Andrew, D.J.** (2009) Serrano (Sano) functions with the planar cell polarity genes to control tracheal tube length *PLoS Genetics* 5(11): e1000746. PMCID: PMC2776533

Kerman, B.E., Cheshire, A.M., Myat, M.M., and **Andrew, D.J.** (2008) Ribbon modulates apical membrane during tube elongation through Crumbs and Moesin. *Developmental Biology* 320: 278-288. PMC2562552

Myat, M.M. and **Andrew, D.J.** (2002) Epithelial tube morphology is determined by the polarized growth and delivery of apical membrane. *Cell* 111: 879-891. PMID: 12526813

3. CrebA/Creb3L bZip transcription factors coordinately upregulate secretory capacity Secretion occurs in all cells, with relatively low levels in most cells and extremely high levels in professional secretory cells, such as those of the pancreas, salivary and mammary glands. How secretory capacity is selectively upregulated in specialized secretory cells was unknown. Through our work in the Drosophila SG and other tissues, we discovered that Drosophila CrebA is both necessary and sufficient to upregulate expression of the protein components of the entire early secretory pathway. CrebA-regulated genes encode proteins involved in targeting nascent polypeptides to the ER, proteins required for cotranslational translocation, proteins that remove the N-terminal signal sequences, proteins required for ER morphology, proteins required for N-linked glycosylation, disulfide bond formation, prolyl hydroxylation and sugar modifications, as well as proteins that mediate trafficking between the ER and Golgi, Golgi and ER, and within the Golgi. Moreover, CrebA also boosts levels of expression of genes encoding tissue-specific cargo proteins, thus enhancing secretory capacity by coordinately upregulating the secretory machinery as well as tissue-specific secreted cargo. We have shown, on our own and as part of a collaborative study, that the mammalian proteins – the five members of the Creb3L family of bZip transcription factors, which were previously best known for their roles in the unfolded protein response - have the same activity, both in flies and in mammals. Altogether, these findings highlight the value of studying model organisms in which the reduced levels of functional redundancy can be used to discover ancient and fundamental roles of entire gene families.

Fox, R.M. and **Andrew, D.J.** (2015) Changes in organelle position and epithelial architecture associated with loss of *CrebA*. *Biology Open* 4: 317-330. PMCID: PMC4359738

Barbosa S, Fasanella G, Carreira S, Llarena M, Fox R, Barreca C, **Andrew D**, and O'Hare P. (2013) An orchestrated program regulating secretory pathway genes and cargos by the transmembrane transcription factor CREB-H. *Traffic*. 14: 382-398. PMCID: PMC3593995

Fox, R.M., Hanlon, C.D. and **Andrew, D.J.** (2010) The CrebA/Creb3-like transcription factors are major and direct regulators of secretory capacity. *Journal of Cell Biology* 191: 479-492. PMCID: PMC3003312

Abrams, E.W. and **Andrew, D.J.** (2005) CrebA regulates secretory activity in the salivary gland and epidermis. *Development* 132: 2743-2758. PMID: 15901661

4. Achieving tissue-specific gene expression: Sage and Fkh coordinately activate expression of SG-specific cargo genes and the enzymes that modify that cargo The single Drosophila FoxA family member known as *fork head* (*fkh*) is expressed early, continuously, and to high levels in the SG, where it controls major aspects of SG development. We have shown that Fkh prevents expression of duct-specific genes in the secretory portion of the SG, maintains its own SG expression as well as that of *Sage* and *CrebA*, keeps the non-dividing SG cells alive, and drives the cellular events required to convert the two-dimensional SG placode into a three-dimensional elongated and internalized epithelial tube. Indeed, *fkh* has been shown to affect expression of ~60% of the more than 100 SG genes whose expression we have examined in WT and *fkh* mutant embryos. An important question was how Fkh could control such major activities in the SG when it is also expressed and required in multiple other embryonic tissues. We discovered that Fkh partners with Sage, a bHLH protein expressed in only the SG, to control expression of genes encoding SG-specific cargo as well as genes encoding enzymes that modify that cargo. These findings support a model wherein FoxA proteins are also likely to partner with similar tissue-specific factors (likely including other Sage-related bHLH proteins) to control formation and specialization of the many mammalian tissues that require FoxAs for their formation.

Fox, R.M., Vaishnavi, A., Maruyama, R., and **Andrew, D.J.** (2013) Organ-specific gene expression: the bHLH protein Sage provides tissue-specificity to Drosophila FoxA. *Development* 140: 2160-71. PMCID: PMC3640219

Maruyama, R., Grevengoed, E., Stempniewicz, P., **Andrew, D.J.** (2011) Genome-wide analysis reveals a major role in cell fate maintenance and an unexpected role in endoreduplication for the Drosophila FoxA gene *fork head*. *PLoS One* 6(6): e20901. PMCID: PMC3116861

Abrams, E.W., Mihoulides, W.K. and **Andrew, D.J.** (2006) Fork head and Sage maintain a uniform and patent salivary gland lumen through regulation of two downstream target genes, *PH4αSG1* and *PH4αSG2*. *Development* 133: 3517-3527. PMID: 16914497

Myat, M.M. and **Andrew, D.J.** (2000) FORK HEAD prevents apoptosis and promotes cell shape change during formation of the Drosophila salivary glands. *Development* 127: 4217-4226. PMID: 10976053

5. Trachealess functions as a "master regulator" of tracheal development Ours was one of two labs (mine and Benny Shilo's) to clone the *trachealess* (trh) gene as one of the first transcription factors known

to be required for epithelial tube formation. Trh, which encodes a bHLH-PAS domain transcription factor, controls formation of multiple embryonic tubes, including the trachea, the filzkörper (an air filter found at the interface between the trachea and outside world) and the salivary duct. In *trh* mutants, the primordia for all three tissues are present but fail to undergo any of the events of initial tube formation. Several labs, including ours, have since discovered tracheal targets of Trh that are required for internalization of the primordia, branch migration and tube length control. Based on studies of other early-expressed tracheal transcription factors by other groups, models had suggested that Trh was one of a few transcription factors whose combined activities controlled expression of different subsets of tracheal genes. Our recent analysis of tracheal gene expression by in situ and microarray analysis revealed that Trh is required for the expression of all tracheal genes. Indeed, Trh maintains its own tracheal expression as well as that of the other major early expressed tracheal transcription factor, known as Drifter/Ventral veinless, which affects expression of only an estimated 25-30% of tracheal genes. This work indicates that activation of Trh by the early patterning genes is the major event in tracheal specification, maintenance of tracheal cell fates as well as terminal differentiation of the entire system. Recent

Cheng, Y.L., and **Andrew, D.J.** (2015) Extracellular Mipp1 activity confers migratory advantage to epithelial cells during collective migration. *Cell Reports* 13: 1-15. PMID: 26628373

Chung, S.-Y., Chavez, C. and **Andrew, D.J.** (2011) Trachealess (Trh) regulates all tracheal genes during Drosophila embryogenesis. *Developmental Biology* 360: 160-172. PMCID: PMC3215829

Jin, J., Anthopoulos, N., Wetsch, B., Binari, R.C., Isaac, D.D., **Andrew, D.J.**, Woodgett, J.R. and Manoukian, A.S. (2001) Regulation of *Drosophila* tracheal system development by protein kinase B. *Developmental Cell* 1: 817-827. PMID: 11740943

Isaac, D.D. and **Andrew, D.J.** (1996) Tubulogenesis in Drosophila: A requirement for the *trachealess* gene product. *Genes and Development* 10: 103-117. PMID: 8557189

My full Bibliography can be found at
http://www.ncbi.nlm.nih.gov/sites/myncbi/deborah.andrew.1/bibliography/40434451/public/?sort=date&direction=ascending

D. RESEARCH SUPPORT

ONGOING RESEARCH SUPPORT

5 R01 DE013899 **PI: Deborah J. Andrew** **02/01/01 – 06/30/16**
NIH/NIDCR **Formation of the Drosophila salivary gland**
The goals of this proposal are (Aim 1) to characterize the molecular machinery that coordinates apical constriction, a cell shape change required for the formation of many organs; (Aim 2) to identify other key regulators that function with CrebA to achieve high-level secretory capacity in specialized secretory organs; (Aim 3) to identify tissue-specific gene products to learn how their expression is coordinated with morphogenesis and acquisition of secretory capacity. This study is expected to provide new paradigms for how organ morphogenesis and physiological specialization are coupled during development.

5 R01 DE012873 **PI: Deborah J. Andrew** **02/01/99 – 04/30/16**
NIH/NIDCR **Role of Trachealess in embryonic tube formation**
The goals of this proposal are (Aim 1) to unravel the roles of new Trh target genes that are expressed early and encode molecules with domain structures that suggest a role in mediating tube invagination; (Aim 2) to explore the mechanisms whereby Sano and the PCP regulators control tube size through effects on cell shape; (3) To link the molecular activity of an unusual enzyme encoded by *mipp1* to tube size control and migration.

JHMRI Pilot Grant **PI: Deborah J. Andrew** **09/01/15 – 08/31/2015**
Johns Hopkins **Exploring strategies for transmission compromised mosquitoes**
The goals of this grant are to (1) characterize the morphology of the adult salivary glands and (2) leverage what we have learned about the function of major players in Drosophila salivary gland development and maintenance (Fkh, Sage and CrebA) to disrupt the salivary glands of adult mosquitoes using CRISPR/CAS mediated strategies.