BIOGRAPHICAL SKETCH

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NAME: Katherine J.D. Ashbourne Excoffon

eRA COMMONS USER NAME (credential, e.g., agency login): EXCOFFON1

POSITION TITLE: Associate Professor

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 Guelph, Guelph, Ontario, Canada	B.Sc.	04/1994	Honors Biochemistry
University of British Columbia, British Columbia, Canada	Ph.D.	08/2000	Genetics
University of Iowa, Roy J. and Lucille A. Carver College of Medicine, Iowa City, IA (Prof. Joseph Zabner)	PostDoc	01/2003	Viral-mediated gene transfer/airway biology

A. Personal Statement

I bring all of the qualifications and characteristics required to successfully mentor Hannah Shows and ensure completion the proposed research. I discovered the apical adenovirus receptor (CAR^{Ex8}) and cellular interactions that both upregulate and downregulate its apical levels, and hence adenovirus infection at the apical surface of polarized epithelia. A patent for the peptides described in a recently funded R01 has recently been submitted. Importantly, 32 of my 40 publications concern the biology and vectorology of adenovirus, as well as several other viruses, using diverse biochemical, molecular, cellular, and microscopy approaches. I have *in vitro* experience to produce and analyze airway epithelia from multiple species (human, mouse, rat, pig), and *in vivo* small and large animal model experience (9 publications). During my training and in my current faculty position, I have had the opportunity to work with and mentor numerous undergraduate and graduate students, clinical fellows, post-docs, technicians, and junior faculty – many of these studies resulting in publications. I have also successfully led numerous national and international collaborations. This F31 Ruth L. Kirschstein National Research Service Award (NRSA) Individual Predoctoral Fellowship proposal will significantly enhance the research performed in conjunction with the newly funded R01 to build a pipeline of novel small molecules that may have highly potent antiviral activity. While Hannah and I have mapped out at least 5 potential peer-reviewed publications, I expect that given her high level of experience, fantastic hands in the laboratory, and writing skills, there may be several more. In addition, Hannah and I have research synergy as alumni of University of Iowa and by previously performing impactful research on lipoprotein lipase. Mentoring Hannah in this research builds logically on my prior experience, and will lead this research and our careers in an exciting and translational direction.

1. Sharma P, Kolawole AO, Core SB, Kajon AK, Excoffon KJDA. (2012) Sidestream Smoke Exposure Increases the Susceptibility of Airway Epithelia to Adenoviral Infection. PLoS One. 7(11):e49930. PMID: 23166798
2. Yan R, Sharma P, Kolawole AO, Martin S, Readler J, Kotha PNL, Hostetler HA, and Excoffon KJDA. (2015) The PDZ3 domain of the cellular scaffolding protein MAGI-1 interacts with the coxsackievirus and adenovirus receptor (CAR). The International Journal of Biochemistry & Cell Biology. 61:29-34. PMID 25622559.
3. Kotha PNL, Sharma P, Kolawole AO, Yan R, Alghamri MS, Brockman TL, Gomez-Cambronero J, and Excoffon KJDA. (2015) Adenovirus Entry from the Apical Surface of Polarized Epithelia is Facilitated by the Host Innate Immune Response. PLoS Pathogens. 11(3): e1004696. PMID 25768646.

4. Sharma, P., Martis, P., and Excoffon, KJDA. (2017) Adenovirus transduction: More complicated than receptor expression. Virology. 502: 144-151. PMID: 28049062

B. Positions and Honors

Positions and Employment

2003-2006	Assistant Research Scientist, Department of Internal Medicine, University of Iowa
2006-2009	Associate Research Scientist, Department of Internal Medicine, University of Iowa
2009-2013	Assistant Professor, Department of Biological Sciences, Wright State University
2013-	Associate Professor with tenure, Department of Biological Sciences, Wright State University

Other Experience and Professional Memberships

05/1998-	American Society for Gene and Cellular Therapy – member, Abstract review committee (2015), Respiratory & GI Tract Committee 2017-present)
12/2001-	American Society of Cell Biology - member
05/2006-	American Society for Virology – member, Abstract review committee (2016-18)
04/2012-	American Society for Microbiology - member
10/2012	Grant Reviewer – NIH/NIAID ZRG1 ad hoc study section member
09/2013	Grant Reviewer – NIH/NIAID, ZAI1-DR-A-C1 ad hoc study section member
11/2014	Grant Reviewer – NIH/NIDDK, ZDK1 GRB-7 ad hoc study section member
06/2014, 2015	Grant Reviewer – VA IMMA ad hoc study section member
09/2015-	Scientific Advisory Board, 4D Molecular Therapeutics (AAV-based therapeutics)
11/2015	NIH, ZRG1 IDM-S (81), AREA applications in Infectious Diseases and Microbiology
06/2016	NIH, VIRA, Virology Study Section
07/2016	NIH, ZRG1 IDM-S (81), AREA applications in Infectious Diseases and Microbiology

Honors

1990-1994	Canada Scholarship and Dean's List, University of Guelph
1991	NSERC Undergraduate Student Research Award, University of Guelph
1992	Dean's Scholarship, University of Guelph
1993	Floyd Roadhouse Prize in Analytical Chemistry, University of Guelph
1995-1998	1967 Natural Science and Engineering Scholarship, University of British Columbia
1999	University Graduate Fellowship, University of British Columbia
1999-2000	Li Tse Fong University Graduate Fellowship Award, University of British Columbia
2003-2006	Parker B. Francis Pulmonary Fellowship, University of Iowa
2004	Carver College of Medicine Research Week Poster Award, University of Iowa
2010	Women's Giving Circle Research Award, Wright State University
2012	Southwestern Ohio Council for Higher Education (SOCHE) Faculty Excellence Teaching Award
2012	Wright State University President's Award for Excellence: Early Career Achievement
2013	International Scholar Advocate Award, Wright State University
2015	American Society for Virology 34th Annual Meeting State-of-the-Art Lecture

C. Contribution to Science

1. Glybera, the first clinically approved gene therapy in the Western world.

Although I formally entered the fields of virology and gene therapy when I started my PhD in 1995, I was inspired long before by my older sister who has Rubinstein-Taybi syndrome. As I learned about the genetic and biochemical changes that caused her characteristic phenotypic changes, I fostered the dream of reversing the symptoms of such genetic diseases through the delivery of genes and proteins that complement the deficiency. My PhD studies were performed with Dr. Michael Hayden at the University of British Columbia, Vancouver, Canada. I discovered that gene transfer of a specific variant of the *lipoprotein lipase* gene (LPL^{S447X}) resulted in highly efficient disease correction in murine and feline models of lipoprotein lipase deficiency. Although patent delays caused these findings to be published after I graduated, the discovery formed the basis for my PhD thesis and I am listed as an inventor, along with my mentors, on the patent. This gene variant, in an AAV1 backbone, is now the first gene therapy fully approved for clinical use in Europe (Glybera; alipogene tiparvovec).

a. Ashbourne Excoffon, K.J., Liu, G., Miao, L., Wilson, J.E., McManus, B.M., Semenkovich, C.F., Coleman, T., Benoit, P., Duberger, N., Branellec, D., Denefle, P., Hayden, M.R. and Lewis, M.E.S. (1997) Correction of Hypertriglyceridemia and Impaired Fat Tolerance in Lipoprotein Lipase Deficient Mice by Adenoviral-Mediated Expression of Human Lipoprotein Lipase. *Arteriosclerosis, Thrombosis and Vascular Biology*, 17:2532-2539. PMID: 9409224.
b. Liu G., Ashbourne Excoffon K.J., Wilson J.E., McManus B.M., Rogers Q.R., Miao L., Kastelein J.J., Lewis M.E. and Hayden M.R. (2000) Phenotypic correction of feline lipoprotein lipase deficiency by adenoviral gene transfer. *Human Gene Therapy*, 11(1):21-32. PMID: 10646636.
c. Ross CJ, Liu G, Kuivenhoven JA, Twisk J, Rip J, van Dop W, Ashbourne Excoffon KJ, Lewis SM, Kastelein JJ, Hayden MR. (2005) Complete rescue of Lipoprotein Lipase-deficient mice by somatic gene transfer of the naturally occurring LPLS447X beneficial mutation. *Arteriosclerosis, Thrombosis and Vascular Biology*. 25(10):2143-50. PMID: 16002740
d. Lipoprotein Lipase (LPL) Variant Therapeutics, Ref: 00-039; PCT/CA2000/000762, WO2001/000220 US, Canadian, Japanese and European Patent Application. Patent Granted August 13, 2008

2. The apical adenovirus receptor.

During my PhD studies, the first and only gene therapy death occurred due to the proinflammatory effects of acute high-dose adenovirus administration. I *hypothesized* that upregulation of the adenovirus receptor, CAR, would reduce the dose of adenovirus required for efficient gene therapy – and decrease toxicity. During my postdoctoral period in the laboratory of Dr. Joseph Zabner at the University of Iowa, the site of the first gene therapy trials for cystic fibrosis, I began to study basic questions in virology and cell biology. This approach has continued in my independent faculty position at Wright State University. One of my goals was to identify the cellular mechanisms, and agonists, that upregulate CAR in order to increase the efficacy of adenovirus-mediated gene therapy. The corollary is that antagonists for the same cellular targets would downregulate CAR and protect people from the potentially devastating consequences of wild type adenovirus or coxsackievirus infection. This has led to several important discoveries that have made us rethink our understanding of adenovirus biology, such as alternative routes of adenovirus entry, including the one described in this application – apical localization of an alternative splice form, CAR^{Ex8}. Given my recent discovery of MAGI-1 targeted peptide agonists and antagonists for CAR^{Ex8}, I am finally poised to test my hypothesis.

a. Excoffon KJDA, Gansemer ND, Mobily ME, Karp PH, Parekh KR, Zabner J. (2010) Isoform-specific regulation and localization of the Coxsackie and adenovirus receptor in human airway epithelia. PLoS One. Mar 26;5(3):e9909. PMID: 2845650.
b. Kolawole AO, Sharma P, Yan R, Lewis KJ, Hostetler HA, Ashbourne Excoffon KJ. (2012) The PDZ1 and PDZ3 Domains of MAGI-1 Regulate the Eight Exon Isoform of the Coxsackievirus and Adenovirus Receptor. Journal of Virology. Sept; 86(17):9244-54. PMID: 22718816.
c. Sharma P, Kolawole AO, Core SB, Kajon AK, Excoffon KJDA. (2012) Sidestream Smoke Exposure Increases the Susceptibility of Airway Epithelia to Adenoviral Infection. PLoS One. 7(11):e49930. PMID: 23166798.
d. Kotha PNL, Sharma P, Kolawole AO, Yan R, Alghamri MS, Brockman TL, Gomez-Cambronero J, and Excoffon KJDA. (2015) Adenovirus Entry from the Apical Surface of Polarized Epithelia is Facilitated by the Host Innate Immune Response. PLoS Pathogens. 11(3): e1004696. PMID 25768646.

3. Polarized viral entry and egress in epithelia

To initially understand the biology of viral entry and egress in polarized epithelia, I turned to genetically modified forms of CAR and non-CAR binding viruses. Swapping the cytoplasmic and transmembrane domains for CAR with a glycophosphatidyl-inositol (GPI) tail caused apical localization of CAR and significantly enhanced apical adenovirus infection. This provided the first proof that increased CAR at the apical surface would enhance viral infection. In contrast to most adenoviruses (Groups A, C-G), Group B adenoviruses do not use CAR as a receptor, but instead can use CD46 which localizes at the apical surface. Accordingly, group B adenoviruses have greater infection efficiency and are attractive potential gene therapy vectors. Reoviruses use a basolateral adhesion protein that is in the same gene family as CAR. Similar to CAR-binding adenoviruses, reovirus infection is much more efficient from the basolateral surface than the apical surface. In contrast to adenovirus, I discovered that reovirus egresses from the apical surface and does not break the tight junctions or kill epithelial cells. Importantly, our molecules that increase apical CAR have the potential to reveal mechanisms that regulate the localization of other basolateral adhesion proteins that function as viral receptors. This

work also highlights highly successful national and international collaborations that have advanced our understanding of viral infection.

a. Davis, B., Nguyen, J., Stoltz, D., Depping, D., Excoffon, K.J.D. and Zabner, J. (2004) Adenovirus-mediated gene transfer to airway epithelia is enhanced by apical localization of the Coxsackie-Adenovirus Receptor by GPI In Vivo. Molecular Therapy. 10(3):500-6. PMID: 15336650
b. Excoffon K.J.D.A., Guglielmi, K.M., Wetzel, J.D., Gansmer, N, Campbell, J.A., Dermody, T.S. and Zabner, J. (2008) Reovirus preferentially infects the basolateral surface and is released from the apical surface of polarized human respiratory epithelial cells. Journal of Infectious Diseases 197(8):1189-97. PMID: 18419529. (Cover Image)
c. Granio, O., Norez, C., Excoffon, K.J.D.A., Karp, P.H., Lusky, M., Becq, F., Boulanger, B., Zabner, J. and Hong, S.S. (2007) Cellular localization and Cl- channel activity of GFP-CFTR in airway epithelial and tracheal cells. American Journal of Respiratory Care and Critical Medicine 37(6):631-9. PMID: 17641299.
d. Granio O, Ashbourne Excoffon KJ, Henning P, Melin P, Norez C, Gonzalez G, Karp PH, Magnusson MK, Habib N, Lindholm L, Becq F, Boulanger P, Zabner J, Hong SS. Adenovirus 5-fiber 35 chimeric vector mediates efficient apical correction of the cystic fibrosis transmembrane conductance regulator defect in cystic fibrosis primary airway epithelia. Human Gene Therapy. 2010 Mar;21(3):251-69. PMID: 19788389.

4. Directed evolution of novel AAVs with enhanced entry into airway epithelia

One of the reasons I was attracted to the University of Iowa for Postdoctoral studies was their expertise in adeno-associated virus (AAV). This small, single-stranded DNA, helper-dependent, non-integrating virus has moved to the forefront of gene therapy as the favored vector (e.g. Glybera). However, at that time, none of the known AAV serotypes could efficiently infect airway epithelia from the apical surface. In collaboration with Dr. David Schaffer at UC Berkeley, we used directed evolution to identify a hybrid AAV with ~500 X greater efficiency of apical airway transduction. Interestingly this virus did not have increased apical infection in mouse or pig airway epithelia highlighting the fact that optimization of vectors in animal models is unlikely to yield clinically relevant vectors for humans. Directed evolution of AAV in pig airway yielded distinct AAV variants that have successfully treat pigs with cystic fibrosis. I am currently serving as a member of the scientific advisory board for 4D Molecular therapeutics, a company formed to take our human optimized AAV2.5T vector into clinical trials.

a. Excoffon K.J.D.A., Koerber, J.T., Dickey, D.D., Murtha, M., Keshavjee, S., Kaspar, B., Zabner, J. and Schaffer, D.V. (2009) Directed evolution of adeno-associated virus to an infectious respiratory virus. Proceedings of the National Academy of Science USA. Mar 10;106(10):3865-70. PMID: 19237554.
b. Dickey DD, Excoffon KJ, Koerber JT, Bergen J, Steines B, Klesney-Tait J, Schaffer DV, Zabner J. (2011) Enhanced sialic acid-dependent endocytosis explains the increased airway epithelia infection efficiency of a novel adeno-associated virus. Journal of Virology. Sep;85(17):9023-30. PMID: 21697483.
c. Dickey DD, Excoffon KJ, Young KR, Parekh KR, Zabner J. (2012) Hoechst increases adeno-associated virus-mediated transgene expression in airway epithelia by inducing the cytomegalovirus promoter. Journal of Gene Medicine. Jun; 14(6):366-73. PMID: 22610695.
d. Steines, B., Dickey, DD., Bergen, J., Excoffon, KJDA., Weinstein, J., Li, X., Yan, Ziying., Abou Alaiwa, M., Shah, VS., Bouzek, DC., Powers, LS., Gansemer, ND., Ostedgaard, LS., Engelhardt, JF., Stoltz, DA., Welsh, MJ., Sinn, PL., Schaffer, DV., and Zabner, J. (2016) CFTR gene transfer with AAV improves early cystic fibrosis pig phenotypes. Journal of Clinical Investigations Insight. 1(14):e88728. PMID 27699238.

5. The physiological importance of a polarized epithelium.

A polarized epithelium is a primary barrier between the microbe-infested outer world and the sterile inner world of an individual. It turns out that many proinflammatory moledules are ineffective at the apical surface and require a breach in the tight junctions in order to access their receptors. Breaches can be induced by many stimulants, from the release of histamine associated with hypersensitivity reactions to direct invasion by various bacteria. In contrast, the apically localized cystic fibrosis transmembrane regulator (CFTR) chloride channel has a novel thiocyanate transport function which plays an important role in host defense.

a. Ostedgaard LS, Randak C, Rokhlina T, Karp P, Vermeer D, Ashbourne Excoffon KJ, Welsh MJ. (2003) Effects of C-terminal deletions on cystic fibrosis transmembrane conductance regulator function in cyst-

ic fibrosis airway epithelia. Proceedings of the National Academy of Science, USA. 100(4):1937-42. PMID: 12578973.

b. Zabner J, Winter M, Excoffon KJ, Stoltz D, Ries D, Shasby S, Shasby M. (2003) Histamine alters E-cadherin cell adhesion to increase human airway epithelial permeability. Journal of Applied Physiology, 95(1):394-401. PMID: 12794099.
c. Moskwa, P., Lorentzen, D., Excoffon, K.J., Zabner, J., McCray Jr, PB., Nauseef, WM., Dupuy, C., Banfi, B. (2006) A novel host defense system of airways is defective in cystic fibrosis. American Journal of
d. Humlicek, A.L. Manzel, L.J., Chin, C.L., Shi, L, Excoffon, K.J.D.A., Winter, M.C., Shasby, D.M., and Look, D.C. (2007) Paracellular permeability restricts airway epithelial responses to selectively allow activation by mediators at the basolateral surface. Journal of Immunology 178(10):6395-403. PMID: 17475869.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/katherine.excoffon.1/bibliography/45776087/public/?sort=date&direction=descending

D. Research Support

Ongoing Research

NIH R01/NIAID, Excoffon (PI) 09/25/2017-08/31/2022
Prevention of adenovirus pathogenesis through downregulation of the apical adenovirus receptor
The goal of this R01 is to determine the mechanism of action and *in vivo* efficacy of peptides that decrease the apical adenovirus receptor and adenovirus infection.
Role: PI
No overlap

Department of Defense, Congressionally Directed Medical Research Programs (CDMRP), Medvedev (PI)
2016 Peer Reviewed Medical Research Program (PRMRP) Discovery Award 5/1/17-10/31/18
Real-Time Detection of Cellular Respiratory Biomarkers of Early-Stage Infections Using Terahertz Sensing;
The identification of tissue specific respiratory bio-markers would allow real time detection of metabolic changes that occur during disease. We will study variability of respiration associated with viral infections (adenovirus) and basic metabolic changes in primary airway cells in comparison to liver cells.
Role: Co-PI
No overlap

NIH R15/NIAID, Excoffon (PI) 09/23/2010 - 12/31/2018
Isoform-specific regulation and localization of the Coxsackie and adenovirus receptor in polarized airway epithelia; This is a renewal of the previous R15 award and the major goal of this grant is to identify the mechanism by which an interaction with full length MAGI-1 directly regulates CAR^{Ex8}.
Role: PI
No overlap

Completed Research

Boonshoft School of Medicine Translational Research Grant (WSU) 09/01/14 - 8/31/17
Bioengineering novel solutions to chronic wounds
The major goal of this grant is to develop a novel organotypic multidimensional chronic wound model culture system in order to evaluate potential therapeutics to accelerate wound healing.
Co-PI: Katherine Excoffon and Michael Johnson
No overlap

NIH R21/NIAID 07/01/2011 - 06/30/2013
Molecular evolution of AAV vectors for anti-HIV gene therapy
The major goal of this grant is to use directed molecular evolution of AAV to tailor make HIV and T cell-specific AAV vectors in order to treat HIV infection with gene-based therapeutics.
PI: Katherine Excoffon, Co-Investigator: Dawn Wooley (WSU), Collaborator: David Schaffer (UCBerkeley)