BIOGRAPHICAL SKETCH

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NAME: Lee, Adrian V.

eRA COMMONS USER NAME (agency login): avlee1

POSITION TITLE: Professor of Pharmacology and Chemical Biology

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
University of Kent, Canterbury, UK	BSc	05/89	Biochemistry
ICRF, University of Surrey, Guildford, UK	PhD	1993	Breast Biology
UT Health Science Center at San Antonio	Postdoc	1997	Breast Cancer

A. Personal Statement

I am an established investigator having published over 120 peer-reviewed manuscripts and a history of collaborative efforts (both wet and dry lab). The outstanding environment at the University of Pittsburgh will provide all the necessary facilities and resources needed to complete the research. The goal of my laboratory is translational breast cancer research, particularly research involving human specimens with the ultimate goal of moving basic science discoveries to the clinic. The laboratory has a long standing interest in targeting the insulin-like growth factor (IGF) pathway in breast cancer. This work has been continuously funded by NIH for 14 years and has provided fundamental insight into how IGFs regulate mammary gland development and tumorigenesis in the mouse and the therapeutic importance of this to human breast cancer. For example, we generated transgenic mice overexpression IGF1R or its downstream adaptors IRS1 and IRS2 and showed that all three mouse models developed mammary cancer. We characterized the ability of IGF1R overexpression to transform MCF10A mammary epithelial cells and cause EMT. Important to the clinical translation of IGF1R inhibitors, we developed an IGF gene expression signature that correlates with IGF activity, is repressed by IGF1R inhibitors, and highlighted a TNBC PDX model that is especially sensitive to IGF1R inhibition.

A more recent area of research involves genomic profiling of breast cancer. While at Baylor College of Medicine (BCM), Dr Lee collaborated with Dr. Aleks Milosavljevic and the Human Genome Center to develop new methods to characterize DNA structural rearrangements in breast cancer, and they were the first to map all structural rearrangements at the base pair level in a breast cancer cell line. Since moving to the University of Pittsburgh, Dr. Lee has now transferred these technologies and expanded this line of research. For example, the laboratory has measured ESR1 mutations by ddPCR in 44 primary breast cancers, 72 metastatic brain, 15 metastatic bone, and 32 cfDNA samples. We found a significant rate of mutation (~25% in blood), this work was recently reported in *Clinical Cancer Research*. Dr. Lee is a well-established investigator with a history of collaborative efforts involving numerous laboratory and clinical researchers.

B. Positions and Honors

Positions and Employment

1997-1999	Instructor, Dept. of Medicine, University of Texas Health Science Center, San Antonio, TX
1999-2005	Assistant Professor, Breast Center, Dept. of Medicine, and Dept. of Mol. & Cellular Biology, Baylor College of Medicine, Houston, TX
2005-2010	Associate Professor, Breast Center, Dept. of Medicine, and Dept. of Mol. & Cellular Biology, Baylor College of Medicine, Houston, TX
2010-present	Professor, Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA
2010-present	Director, Women's Cancer Research Center, University of Pittsburgh Cancer Institute, Pittsburgh, PA
2012-present	Professor, Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA
2014-present	Co-leader, Breast and Ovarian Cancer Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA

Other Experience and Professional Memberships

1998-2008	Member, Department of Defense study sections; Endocrinology III (1998), Endocrinology II (2000-02), Pathobiology II (2005), Endocrinology I (2006), Integration Panel (2008, 2012, 2014)
1999-2002	Permanent Member, Tumor Cell Biology study section, Komen Foundation
1999-2010	Organizing Committee, San Antonio Breast Cancer Symposium
2000-2001	Scientific Advisor, Komen Research Foundation
2001-2002	Member, Massachusetts Department of Public Health Breast Cancer study section
2003-2007	Permanent member, California Breast Cancer Research Program, Etiology and Prevention
2005-2012	Section Editor (Viewpoints), Breast Cancer Research
2006	Ad hoc member, NCIC Program Project Review – IGF as a therapeutic target
2007-2012	Permanent member, NIH Molecular Oncogenesis study section (MONC)
2008	Susan G Komen for the Cure; Pathobiology study section (2008), Chair, Postdoctoral awards Tumor Cell Biology (2011), Chair/member – Basic Science (2013-present)
2010-2012	Executive Committee (2010-12); Chair, Abstract review committee (2010); SABCS
2013	2014 AACR Program Committee - Tumor Biology Subcommittee
2005-present	Ad hoc member NIH study sections; SEP – Molecular Targets for Cancer Drug Discovery (2003), P01– Molecular Carcinogenesis (2005), Molecular Oncogenesis (MONC) (2005-2007), SEP ZRG1 EMNR-E (02) (2009), SEP ZCA1 PCRB-B (2009), NCI intramural MTBL program review (2010), ZCA1 SRLB-C – SEP: Cancer Biology-2 (2012), SEP: ZCA SRB-C (2014)
2009-present	Editorial Board, Hormones and Cancer; Hormone Molecular Biology and Clinical Investigation
2010-present	Scientific Advisory Council, Susan G Komen for the Cure
2012-present	Annual Meeting Steering Committee, Endocrine Society
2013-present	Editor, Endocrinology
2014-present	Editorial Board, npj Breast Cancer

Honors

1990	Imperial Cancer Research Fund, graduate scholarship
1998	New Faculty Start Up Award, Howard Hughes Medical Institute
1998	NCI/SPORE Career Development Award in Breast Cancer
2003	T.T. Chao Scholar Award

C. Contribution to Science (selected from 127 publications)

C.1) IGF-IR regulation of transformation and breast cancer

There has been great interest in understanding the role of IGFs in breast cancer, and this has led to therapeutic targeting. In collaboration with Bristol-Myers Squibb, we originally developed the first transgenic model of IGF-IR-mediated tumorigenesis. We subsequently showed that IGF-IR transforms mammary epithelial cells and causes EMT via a novel pathway involving NF-kB and snail regulation of E-cadherin (a pathway now validated by others).

a. Litzenburger BC, Kim HJ, Kuiatse I, Carboni JM, Attar RM, Gottardis MM, Fairchild CR, **Lee AV**. BMS-536924 reverses IGF-IR-induced transformation of mammary epithelial cells and causes growth inhibition and polarization of MCF7 cells. *Clinical cancer research.* 2009 Jan 1;15(1):226-37. PMID: 19118050. PMCID: PMC2819349.

b. Kim HJ, Litzenburger BC, Cui X, Delgado DA, Grabiner BC, Lin X, Lewis MT, Gottardis MM, Wong TW, Attar RM, Carboni JM**, Lee AV**. Constitutively active type I insulin-like growth factor receptor causes transformation and xenograft growth of immortalized mammary epithelial cells and is accompanied by an epithelial-to-mesenchymal transition mediated by NF-kappaB and snail. *Molecular and cellular biology.* 2007 Apr;27(8):3165-75. PMID: 17296734. PMCID: PMC1899918.

c. Carboni JM, **Lee AV**, Hadsell DL, Rowley BR, Lee FY, Bol DK, Camuso AE, Gottardis M, Greer AF, Ho CP, Hurlburt W, Li A, Saulnier M, Velaparthi U, Wang C, Wen ML, Westhouse RA, Wittman M, Zimmermann K, Rupnow BA, Wong TW. Tumor development by transgenic expression of a constitutively active insulin-like growth factor I receptor. *Cancer research.* 2005 May 1;65(9):3781-7. PMID: 15867374.

C.2) Biomarkers of IGF action

Recent studies targeting the IGF-IR pathway in cancer have shown limited success. This is in part due to redundancy and cross-talk in the system (e.g. with insulin receptor) and a lack of biomarkers for defining IGF driven tumors. We initially developed an IGF gene expression signature consisting of genes regulated by IGF-I which highlighted tumors with active IGF signaling. We subsequently showed that this signature was reversed by IGF-IR inhibitors and identified a triple-negative breast cancer patient-derived xenograft (TNBC PDX) that

was sensitive to an IGF-IR inhibitor
a. Erdem C, Nagle AM, Casa AJ, Litzenburger BC, Wang YF, Taylor DL, Lee AV, Lezon TR. Proteomic screening and lasso regression reveal differential signaling in insulin and insulin-like growth factor I pathways. Mol Cell Proteomics. 2016 Jun 30. pii: mcp.M115.057729. PMID: 27364358
b. Litzenburger BC, Creighton CJ, Tsimelzon A, Chan BT, Hilsenbeck SG, Wang T, Carboni JM, Gottardis MM, Huang F, Chang JC, Lewis MT, Rimawi MF, Lee AV. High IGF-IR activity in triple-negative breast cancer cell lines and tumorgrafts correlates with sensitivity to anti-IGF-IR therapy. Clin Cancer Res. 2011 Apr 15;17(8):2314-27. Central PMCID: 3926653.
c. Creighton CJ, Casa A, Lazard Z, Huang S, Tsimelzon A, Hilsenbeck SG, Osborne CK, **Lee AV**. Insulin-like growth factor-I activates gene transcription programs strongly associated with poor breast cancer prognosis. Journal of Clinical Oncology. 2008 Sep 1;26(25):4078-85. PubMed PMID: 18757322. Pubmed Central PMCID: 2654368.
d. Boone DN, **Lee AV**. Targeting the insulin-like growth factor receptor: developing biomarkers from gene expression profiling. Critical reviews in oncogenesis. 2012;17(2):161-73. PMID: 22471706.

C.3) Insulin receptor substrates in breast cancer

Our group has provided fundamental insight into the role of insulin receptor substrates in human breast cancer. We initially discovered that IRSs underwent dramatic hormonal regulation in the mouse mammary gland, and overexpression was sufficient to cause tumorigenesis. IRS levels were found to correlate with tamoxifen resistance in a large (~1,600) cohort of breast cancer patients. More recent work has shown that the IRSs are a central scaffold for multiple signaling pathways and this has led to the development of inhibitors of IRSs which are in preclinical development and testing.
a. Migliaccio I, Wu MF, Gutierrez C, Malorni L, Mohsin SK, Allred DC, Hilsenbeck SG, Osborne CK, Weiss H, **Lee AV**. Nuclear IRS-1 predicts tamoxifen response in patients with early breast cancer. *Breast cancer research and treatment.* 2010 Oct;123(3):651-60. PMID: 19924529. PMCID: PMC2891842.
b. Dearth RK, Cui X, Kim HJ, Hadsell DL, **Lee AV**. Oncogenic transformation by the signaling adaptor proteins insulin receptor substrate (IRS)-1 and IRS-2. *Cell cycle.* 2007 Mar 15;6(6):705-13. PMID: 17374994.
c. Dearth RK, Cui X, Kim HJ, Kuiatse I, Lawrence NA, Zhang X, Divisova J, Britton OL, Mohsin S, Allred DC, Hadsell DL, **Lee AV**. Mammary tumorigenesis and metastasis caused by overexpression of insulin receptor substrate 1 (IRS-1) or IRS-2. *Molecular and cellular biology.* 2006 Dec;26(24):9302-14. PMID: 17030631. PMCID: PMC1698542.
d. **Lee AV**, Zhang P, Ivanova M, Bonnette S, Oesterreich S, Rosen JM, Grimm S, Hovey RC, Vonderhaar BK, Kahn CR, Torres D, George J, Mohsin S, Allred DC, Hadsell DL. Developmental and hormonal signals dramatically alter the localization and abundance of insulin receptor substrate proteins in the mammary gland. *Endocrinology.* 2003 Jun;144(6):2683-94. PMID: 12746333.

C.4) Cross-talk between growth factors and ER

Studies of estrogen receptor (ER) action in breast cancer have shown a tight link with growth factor action, and growth factors play a major role in hormone resistance. I first showed that IGF can activate ER. Subsequently I also showed that ER enhanced IGF signaling, thus setting up a positive feedback loop. Microarray analysis revealed the complexity of this crosstalk indicating both synergism and repression. We have further characterized this complex interaction at the level of progesterone receptor and PI3K signaling. The concepts of growth factor action in hormone resistant breast cancer have been translated to the clinic where anti-growth factor inhibitors are showing promise.

a. Fu X, Creighton CJ, Biswal NC, Kumar V, Shea M, Herrera S, Contreras A, Gutierrez C, Wang T, Nanda S, Giuliano M, Morrison G, Nardone A, Karlin KL, Westbrook TF, Heiser LM, Anur P, Spellman P, Guichard SM, Smith PD, Davies BR, Klinowska T, **Lee AV**, Mills GB, Rimawi MF, Hilsenbeck SG, Gray JW, Joshi A, Osborne CK, Schiff R. Overcoming endocrine resistance due to reduced PTEN levels in estrogen receptor-positive breast cancer by co-targeting mammalian target of rapamycin, protein kinase B, or mitogen-activated protein kinase kinase. Breast cancer research : BCR. 2014;16(5):430. PubMed PMID: 25212826. Pubmed Central PMCID: 4303114.
b. Casa AJ, Potter AS, Malik S, Lazard Z, Kuiatse I, Kim HT, Tsimelzon A, Creighton CJ, Hilsenbeck SG, Brown PH, Oesterreich S, **Lee AV**. Estrogen and insulin-like growth factor-I (IGF-I) independently down-regulate critical repressors of breast cancer growth. Breast cancer research and treatment. 2012 Feb;132(1):61-73. PubMed PMID: 21541704. Pubmed Central PMCID: 3936881.
c. **Lee AV**, Jackson JG, Gooch JL, Hilsenbeck SG, Coronado-Heinsohn E, Osborne CK, Yee D. Enhancement of insulin-like growth factor signaling in human breast cancer: estrogen regulation of insulin

receptor substrate-1 expression in vitro and in vivo. Molecular endocrinology. 1999 May;13(5):787-96. PubMed PMID: 10319328.

d. **Lee AV**, Weng CN, Jackson JG, Yee D. Activation of estrogen receptor-mediated gene transcription by IGF-I in human breast cancer cells. The Journal of endocrinology. 1997 Jan;152(1):39-47. PubMed PMID: 9014838.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/adrian.lee.1/bibliography/41359038/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

NIH/NCI R01CA94118 (1yr NCE) Lee (PI) 01/15/02-02/01/17
IRS-1 and -2 Signaling in Mammary Development and Cancer
The main goals of this project are better understand the role of signaling adaptors, termed insulin receptor substrates (IRSs), in breast cancer. We will determine if IRS levels affect breast cancer patient outcome and if they predict response to recently developed anti-IGF-IR inhibitors.

Susan G Komen for the Cure – SAC110021 Lee (PI) 04/01/15-03/30/17
Genomic changes in breast cancer metastasis to the brain
The main goal of this project is to determine the genetic changes in breast cancers that metastasize to the brain using DNA and RNA-seq.

DOD BC150894 Lee (PI) 01/01/16-01/01/18
A 3D bioprinted model for the study of premalignant disease
The goal of this proposal is to 3D bioprint a mouse mammary gland in vitro and then grow human DCIS cell lines and primary cells inside the mouse mammary ductal system.

DOD BC150095 Lee (PI) Awarded, pending
Transcriptomic profiling and functional characterization of fusion genes in recurrent ovarian cancer
The goal of this proposal is to identify and characterize fusion genes using RNA sequencing of recurrent ovarian cancers.

BCRF Research grant Lee (PI) 10/01/13-09/30/16
Impact of Intratumor Transcriptomic Heterogeneity on Breast Cancer Prognosis and Response to Therapy
We will directly compare transcriptomic levels in different regions of breast cancers and provide the first evidence that ITH has a significant impact up on prediction of prognosis. We will develop methods to quantify and account for ITH in whole crushed up specimens

NIH/NCI P50CA159981 Odunsi (PI), Lee (Pilot Proj PI) 07/01/15-06/30/16
Transcriptomic profiling and functional characterization of fusion genes in recurrent ovarian cancer
The goal of this SPORE pilot project is to perform RNA-sequencing on matched primary-recurrent serous ovarian cancer and identify novel fusion transcripts. The award only includes supply money for the project and thus doesn't overlap with this application for salary support for Nolan Priedigkeit.

Pennsylvania Department of Health (CURE) Cooper (PI), Lee (Proj Ldr) 07/01/15-06/30/18
BD4BH: Big Data for Better Health
The goal of this joint Pitt and CMU award (in collaboration with UPMC and Pittsburgh Supercomputer) is to apply advanced machine learning approaches to identify novel drivers of breast and lung cancer. Dr Lee is Project Leader of a team focused on validating novel drivers of breast cancer.

BCRF Research Award Lee (PI) 04/01/15-04/01/17
Aurora Program
Provide administrative oversight and co-ordination of the Aurora Program at Pitt, which is collecting primary and metastatic breast cancer for genomic sequencing

NIH/NCI R01CA183976 Wang (PI), Lee (co-inv) 09/01/14-06/01/19
Characterization of Recurrent Adjacent Gene Translocations in Breast Cancer
Dr. Lee will validate lead AGT candidates identified bioinformatically by Dr Wang using Nanostring analysis of a panel of breast cancer cell lines and tissues

NIH/NCI U24CA184407 Crowley (PI), Lee (co-inv) 05/06/14-04/30/19

Cancer Deep Phenotype Extraction from Electronic Clinical Records
We will extend existing software with new methods for cancer deep phenotyping. Several aims propose investigation of biomedical information extraction where there has been little or no previous work

NIH/NCI P50 CA047904 Davidson (PI), Lee (Pgm co-ldr) 08/01/15–08/01/20
UPCI Cancer Center Support Grant: Breast and Ovarian Cancer Program Co-leader
Program co-leader for the breast and ovarian cancer program (BOCP) designed to stimulate and foster translational research

NIH U54HG0084500 Cooper (PI), Lee (co-inv) 09/30/14-08/31/19
BD2K: Center for Causal Modeling and Discovery of Biomedical Knowledge from Big Data
To conduct research to advance the science and utility of Big Data in the context of biomedical and behavioral research, and to create innovative new approaches, methods, software, tools, and related resources.

NIH/NCI R0101CA190766 Tseng (PI), Lee (co- inv) 07/07/15-06/30/19
Power Calculation and Design Issues in Next-Generation Sequencing
The objective is to develop power calculation tools for differential expression analysis from RNA-seq. Optimal sample size and sequencing depth are jointly determined by power function and budget constraints.

NCATS Supplement to 5UH2TR000503 Taylor (PI), Lee (co-inv) 08/01/15-07/30/16
Measuring the temporal-spatial responses of dormancy and drug resistance in a human breast cancer niche with a liver-on-a-chip microphysiological platform

Mentored awards

Era of Hope DOD Postdoctoral fellowship Farabaugh 06/30/14-06/30/17
Oncogene Induced Changes in Mammary Cell Fate and EMT in Breast Tumorigenesis
Dr Lee mentors a postdoctoral fellow (Dr Susan Farabaugh) who is studying how IGF1R alters cell fate in the mammary gland and in tumorigenesis.

NCI F30CA203095 Priedigkeit 06/30/16-06/30/20
Role: Mentor MSTP
Transcriptomic profiling and functional characterization of fusion genes in recurrent ovarian cancer
Dr Lee mentors an MSTP student (Nolan Priedigkeit) who is examining fusion RNAs in recurrent ovarian cancer using RNA sequencing