BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

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	1989	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 160 manuscripts with an H-index of 52. I have a history of collaborative efforts (both wet and dry lab). 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. I have previously served as PI on an R01, project leader on a P01 and P50, and am currently program leader on a P30, co-investigator on a U54, and have successfully led many research teams and holds numerous other leadership positions. My lab generates numerous large datasets, and I collaborate with computational/system biologists to develop knowledge that can be tested in the wet lab. We are thus in an excellent position to collaborate with Drs. Schwartz, Ma and Wang and provide data for analysis and consult on the biological importance of any findings.

A major recent focus of my laboratory has been a systems biology approach to interrogate metastatic tissues, using molecular profiling and experimental validation. Pitt has one of the largest tumor banks in the country (it was the largest contributor of tissue to Breast TCGA), and combined with one of the largest academic breast cancer clinics means we are in a unique situation to address the challenge of metastatic breast cancer. I recently participated in the TCGA panCan Clinical Working Group which has collated, integrated and quality checked clinicopathologic data on >10,000 TCGA cases and produced a new clinical data resource.

In this

Four references below are most closely linked to the subject of this current proposal:

1. Smith NG, Gyanchandani R, Shah OS, ***Lee AV***. Targeted mutation detection in breast cancer using MammaSeq™. Breast Cancer Res. 2019 Feb 8;21(1):22.
2. Priedigkeit N, Hartmaier RJ, Chen Y, ….. **Lee AV**. Breast cancer brain metastases show limited intrinsic subtype switching, yet exhibit acquired ERBB2 amplifications and activating mutations. *JAMA Oncol.* 2017;3(5):666-671.
3. Hartmaier RJ, Trabucco SE, Priedigkeit N, ….**Lee AV**. Recurrent hyperactive ESR1 fusion proteins in endocrine therapy resistant breast cancer. Ann Oncol. 2018 Jan 19. doi: 10.1093/annonc/mdy025. [Epub ahead of print] PMID: 29360925.
4. Priedigkeit N, Watters RJ, Lucas PC, …. **Lee AV**. Exome-Capture RNA-Sequencing Of Decade-Old Breast Cancers And Matched Decalcified Bone Metastases Identifies Clinically Actionable Targets. *JCI Insight*. 2017 Sep 7;2(17). PMID: 28878133

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
2010-2018 Director, Women's Cancer Research Center, University of Pittsburgh Cancer Institute, Pittsburgh, PA

2014-2018 Co-leader, Breast and Ovarian Cancer Program, University of Pittsburgh Cancer Institute, Pittsburgh, PA
2010-present Professor, Department of Pharmacology and Chemical Biology, University of Pittsburgh, Pittsburgh, PA
2012-present Professor, Department of Human Genetics, University of Pittsburgh, Pittsburgh, PA
2016-present Director, Institute for Precision Medicine, University of Pittsburgh
2017-present Pittsburgh Foundation Chair in Precision Medicine

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, 2017, 2018, 2019)
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)
2010-2012 Executive Committee (2010-12); Chair, Abstract review committee (2010); SABCS
2013 2014 AACR Program Committee – Tumor Biology Subcommittee
2012-2016 Annual Meeting Steering Committee, Endocrine Society
2013-2017 Associate Editor, Endocrinology
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), SEP ZCA1 SRB-X (J2) S (2016); ZCA1TCRBVO1 (2017)
2008-present Susan G Komen for the Cure; Pathobiology study section (2008), Chair, Postdoctoral awards Tumor Cell Biology (2011), Chair/member – Basic Science (2013-present)
2009-present Editorial Board, Hormones and Cancer; Hormone Molecular Biology and Clinical Investigation
2012-present Scientific Advisory Council, Susan G Komen for the Cure
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
2006-2012 NIH permanent member, Molecular Oncogenesis study section
2012-present Susan G. Komen Scholar
2014-present Breast Cancer Research Foundation awardee
2018 Terri L. Chapman Award, Susan G. Komen Greater Pennsylvania Affiliate
2018` PNC Elsie Hillman Distinguished Scholar Award
2018 Biomedical Graduate Scholar Association (BGSA) Distinguished Mentor Award

C. Contribution to Science (selected from 170 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. We 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). Recently we performed a large proteomic screen of response to IGF1 in breast cancer cell lines and identified E-cadherin as a modulator of IGF action.

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.
d. 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 (IGF1) Pathways. Mol Cell Proteomics. 2016 Sep;15(9):3045-57. doi: 10.1074/mcp.M115.057729. Epub 2016 Jun 30. PMID: 27364358

C.2) Insulin receptor substrates in breast cancer
My group has provided fundamental insight into the role of insulin receptor substrates in human breast cancer. We initially discovered that IRSs are turned over by the proteasome following IGF activation, and that IRSs underwent dramatic hormonal regulation in the mouse mammary gland. 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. Surprisingly, while others have suggested a crosstalk between ErbB2 and IRSs, we didn't find this using both murine and human cell lines, and mouse models. 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. **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. Endocrinol. 2003;144:2683-94. PMID: 12746333.
b. 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. Mol Cell Biol. 2006;26:9302-14. PMID: 17030631. PMCID: PMC1698542.
c. 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;123:651-60. PMID: 19924529. PMCID: PMC2891842.
d. Farabaugh SM, Chan BT, Cui X, Dearth RK, **Lee AV**. Lack of interaction between ErbB2 and insulin receptor substrate signaling in breast cancer. Cell Commun Signal. 2016 Oct 21;14(1):25. PMID: 27765041; PMCID: PMC5073819

C.3) Intratumor heterogeneity (ITH) and molecular evolution in breast cancer
A recent focus of study in the laboratory is ITH and molecular evolution in breast cancer progression. We recently reported on ITH of the five major gene expression prognostic tests in breast cancer, and the effect ITH has on risk prediciton. We examined intrinsic gene signatures in patient matched primary breast cancer and brain metastases and identified a high rate (~20%) of swtiching to HER2 amplified. Whole-exome capture RNA seqeuncing analysis of bone metastases also indentified both subtype swtiching and several novel putative therapetic targets.
a. Gyanchandani R, Lin Y, Lin HM, Cooper KL, Normolle DP, Brufsky AM, Fastuca M, Crosson W, Oesterreich S, Davidson NE, Bhargava R, Dabbs DJ, **Lee AV**. Intra-tumor heterogeneity affects gene expression profile test prognostic risk stratification in early breast cancer. *Clin Cancer Res*. 2016;22(21):5362-5369
b. Priedigkeit N, Hartmaier RJ, Chen Y, Vareslija D, Basudan A, Watters RJ, Thomas R, Leone JP, Lucas PC, Bhargava R, Hamilton RL, Chmielecki J, Puhalla SL, Davidson NE, Oesterreich S, Brufsky AM, Young L, **Lee AV**. Breast cancer brain metastases show limited intrinsic subtype switching, yet exhibit acquired ERBB2 amplifications and activating mutations. JAMA Oncol. 2017 May 1;3(5):666-671.
c. Priedigkeit N, Watters RJ, Lucas PC, Basudan A, Bhargava R, Horne W, Kolls JK, Fang Z, Rosenzweig MQ, Brufsky AM, Weiss KR, Oesterreich S, **Lee AV**. Exome-Capture RNA-Sequencing Of Decade-Old Breast

Cancers And Matched Decalcified Bone Metastases Identifies Clinically Actionable Targets. JCI Insight. 2017 Sep 7;2(17). PMID: 28878133
d. Varešlija D, Priedigkeit N, Fagan A, Purcell S, Cosgrove N, O'Halloran PJ, Ward E, Cocchiglia S, Hartmaier R, Castro CA, Zhu L, Tseng GC, Lucas PC, Puhalla SL, Brufsky AM, Hamilton RL, Mathew A, Leone JP, Basudan A, Hudson L, Dwyer R, Das S, O'Connor DP, Buckley PG, Farrell M, Hill ADK, Oesterreich S, **Lee AV**, Young LS. Transcriptome Characterization of Matched Primary Breast and Brain Metastatic Tumors to Detect Novel Actionable Targets. J Natl Cancer Inst. 2018 Jun 28. PMID: 29961873

C.4) Detection of ESR1 mutations in advanced breast cancer
We collaborated with Dr. Oesterreich to measure ESR1 mutations in cfDNA and recently reported on ESR1 mutations in breast cancers treated with aromatase inhibitors and palbociclib. In a unique case report we noted the identification of an ESR1 amplification in an advanced ER+ breast cancer, and response to high dose estradiol.
a. Wang P, Bahreini A, Gyanchandani R, Lucas P, Hartmaier RJ, Watters RJ, Jonnalagadda AR, Trejo Bittar HE, Berg A, Hamilton RL, Kurland BF, Weiss KR, Mathew A, Leone JP, Davidson NE, Nikiforova MN, Brufsky AM, Ambros T, Stern AM, Puhalla SL, **Lee AV** and Oesterreich S (2015). Sensitive detection of mono- and polyclonal ESR1 mutations in primary tumors, metastatic lesions and cell free DNA of breast cancer patients Clin Cancer Res. 2015 Oct 23. pii: clincanres.1534.2015. PMID: 26500237 PMCID: PMC4775406
b. Gyanchandani R, Kota KJ, Jonnalagadda AR, Minteer T, Knapick BA, Oesterreich S, Brufsky AM, **Lee AV**, Puhalla SL. Detection of ESR1 mutations in circulating cell-free DNA from patients with metastatic breast cancer treated with palbociclib and letrozole. Oncotarget. 2016 Aug 19. doi: 10.18632/oncotarget.11383.
c. Kota K, Brufsky A, Oesterreich S, **Lee A**. Estradiol as a Targeted, Late-Line Therapy in Metastatic Breast Cancer with Estrogen Receptor Amplification. Cureus. 2017 Jul 6;9(7):e1434. doi: 10.7759/cureus.1434. PMID: 28924522

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/adrian.lee.1/bibliography/public/

D. Research Support
Ongoing Research Support

Pennsylvania Department of Health (CURE) — Lee (PI) — 06/01/18-05/31/22
Estrogen Receptor Dependency in Metastatic Breast Cancer
The purpose of this proposal is to develop a mechanistic understanding of *ESR1* fusions, to provide new concepts for the treatment of endocrine-resistant breast cancer.

BCRF Research grant — Lee (PI) — 10/01/13-09/30/20
Role of E-cadherin in regulating IGF1R in breast cancer
The goal of this award is to understand the role of E-cadherin in repressing IGF1R action and if this is key to targeting IGF1R in E-cad low breast cancers.

BCRF Aurora Data Coordinating Center — Lee (PI) — 02/01/18-01/01/21
Aurora Program
Collect and harmonize clinical and genomic data from the Aurora project sequencing primary and metastatic breast cancer. Make this data available to all investigators.

Susan G Komen for the Cure – SAC110021 — Lee (PI) — 04/01/15-03/30/20
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

Breast Cancer Alliance — Lee (PI) — 02/01/19-02/10-20
Therapeutic targeting of novel pathways in breast cancer brain metastases
The goal of this study is to understand the role of RET in breast cancer metastasis to brain.

NIH/NCI R01CA224909 — Oesterreich (PI), Lee (co-I) — 12/15/17-12/14/22
FGFR4 – A new druggable target in endocrine resistant breast
This project if focused on the analysis of FGFR4, a less well studied member of the FGFR family, in ER+ metastatic disease using in vitro and in vivo models, and clinical specimens.

NIH/NCI R01CA221303 — Oesterreich (PI), Lee (co-I) — 04/01/18-03/31/23
Mechanism-based target of ER-mutant breast cancer

The goal of this project is to understand the mechanism of endocrine resistance in breast tumors with mutations in the estrogen receptor genes.

NIH/NCI P50 CA047904 Ferris (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

Previous

NIH/NCI R01CA94118 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.