BIOGRAPHICAL SKETCH

NAME: Knudsen, Beatrice S.

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

POSITION TITLE: Professor and Director

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 Vienna, Austria	MS	1984	Chemistry
Cornell Graduate School of Medical Sciences	PhD	1988	Cell Biology
Cornell University Medical College	MD	1989	

A. Personal Statement

My laboratory has a long history of important publications and funding from the NIH, DOD and the Prostate Cancer Foundation on signal transduction mechanisms in prostate cancer, with a particular focus on the role of the HGF-MET axis. A rationale for the study of MET is the realization that a major defect in prostate cancer formation and progression is the derangement of the mechanisms controlling branching morphogenesis. HGF-MET signaling is a critical mediator of this process. My basic science studies of molecular and cellular mechanisms in cancer formation and progression have been aligned with translational studies on biomarker discovery and development. Because the majority of patient cancer tissues are small formalin-fixed biopsies, we have worked in collaboration with industry to improve the in-situ detection of multiple parallel protein and RNA biomarkers in single cells and to overcome the lack of biomarker stability during the tissue collection process.

I have always embraced multi-disciplinary research and have been fortunate to contribute my knowledge in pathology and oncogenic kinases to collaborative projects with the most talented basic scientists, epidemiologists and biostatisticians at the Fred Hutchinson Cancer Research Center and now at Cedars-Sinai Medical Center. Recently, I assumed the directorship of the Division of Translational Pathology at Cedars-Sinai and am overseeing the creation of a state-of-the-art biobank and molecular pathology core. The strength of this program, which is unique in the United States, lies in the integration of diagnostic and molecular pathology with digital image analysis and software development. By converting images from patient cancer tissues into 'omics' datasets we provide novel opportunities for morphometric biomarker discoveries. In addition, knowledge of precise cellular composition of tissue samples improves the interpretation of genomic and proteomic data. My overall goal is to work closely with basic scientists, urologists, oncologists and computational biologists to close the gap between laboratory research and clinical care and to make major strides in the treatment of cancer patients.

Akfirat C, …… Knudsen BS ***Tumour cell survival mechanisms in lethal metastatic prostate cancer differ between bone and soft tissue metastases.*** J Pathol. 2013;230(3):291-7. PMCID: 3926514.

Yan D, Wang P, Knudsen BS, Linden M, Randolph TW. ***Statistical Methods for Tissue Array Images - Algorithmic Scoring and Co-training.*** Ann Appl Stat. 2012;6(3):1280-305. PMCID: 3441061.

Putzke AP, …… Knudsen BS ***Metastatic progression of prostate cancer and E-cadherin regulation by ZEB1 and SRC family kinases.*** Am J Pathol. 2011;179(1):400-10. PMCID: 3123858.

Risk MC, Knudsen BS, Coleman I, Dumpit RF, Kristal AR, LeMeur N, Gentleman RC, True LD, Nelson PS, Lin, DW. ***Differential gene expression in benign prostate epithelium of men with and without***

prostate cancer: evidence for a prostate cancer field effect. Clin Cancer Res. 2010;16(22):5414-23. PMCID: 2992073.

B. Positions and Honors

Positions and Employment

1989-1990 Internship (Medicine), The New York Hospital
1990-1995 Postdoctoral Fellow, Rockefeller University, Laboratory of Molecular Oncology
1995-1998 Visiting Scientist, Rockefeller University
1995-1998 Resident, Anatomic Pathology, The New York Hospital
1998-2002 Assistant Professor, Department of Pathology, Cornell Medical College
1998-2002 Assistant Attending, Department of Pathology, The New York Presbyterian Hospital
2002-2008 Assistant Member, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
2004-2009 Affiliate Assistant Professor, Department of Pathology, University of Washington
2005-present Associate Member, Prostate Centre, Vancouver General Hospital
2008-2011 Associate Member, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center
2009—2011 Affiliate Associate Professor, Department of Pathology, University of Washington
2011-present Affiliate Investigator, Fred Hutchinson Cancer Research Center, Seattle, WA
2011-present Professor of Biomedical Sciences and Pathology & Laboratory Medicine
Director of Translational Pathology and Medical Director of Biobank
Departments of Pathology & Laboratory Medicine and Biomedical Sciences
Cedars-Sinai Medical Center, Los Angeles
2015-Present Associate Editor the Editorial Board of Genitourinary Oncology, a specialty of Frontiers in Oncology

Patent

2011 United States Patent 7,892,770
"Monoclonal antibody which binds cMet (HGFR) in formalin-fixed and paraffin embedded tissues and related methods"

Honors

1986 Julian Rachele Prize for paper publication
1987 Duvigneau Prize for oral paper presentation
1990 Revson Fellowship
2011 Prostate Cancer Foundation Creativity Award
2014 Movember Central-Coordinating PI GAP1 project

Licensure

2003 - 2012 Washington State Medical License
2012 - California State Medical License

C. Contribution to Science

1. Development of Prognostic and Predictive Cancer Biomarkers

As a post-doctoral scholar at the Rockefeller University, I worked on the structural analysis and biological function of the SH3 protein domain and was involved in the discovery of a complex between the CRK and CRKL adaptor proteins and the ABL tyrosine kinase. The phosphorylation of CRK in this complex became the major biomarker for monitoring the response the Gleevec in CML. Following this fundamental discovery, and throughout my carrier, I worked in the field of biomarker development. As faculty at Cornell Medical College, I focused on urological cancers and demonstrated that the prostate specific membrane antigen (PSMA) is expressed on microvascular endothelial cells of many organs and thus a target of in-vivo tumor imaging and anti-angiogenic therapy. In my current position, I am directing a program in digital pathology in which we are developing novel biomarkers by applying computer vision to histopathological tissue preparations.

Feller SM, Knudsen B, Hanafusa H. ***c-Abl kinase regulates the protein binding activity of c-Crk.*** EMBO J. 1994;13(10):2341-51. PMCID: 395099.

Liu H, Moy P, Kim S, Xia Y, Rajasekaran A, Navarro V, Knudsen B, Bander NH. ***Monoclonal antibodies to the extracellular domain of prostate-specific membrane antigen also react with tumor vascular endothelium.*** Cancer Res. 1997;57(17):3629-34.

Gertych A, Mohan S, Maclary S, Mohanty S, Wawrowsky K, Mirocha J, Knudsen BS. ***Effects of tissue decalcification on the quantification of breast cancer biomarkers by digital image analysis.*** Diagn Pathol. 2014;9(1):213. PMCID: 4252006.

Gertych A, Ma Z, Tajbakhsh J, Velasquez-Vacca A, Knudsen BS. ***Rapid 3-D delineation of cell nuclei for high-content screening platforms.*** Comput Biol Med. 2015. PMCID: 4440328.

2. Functional Analysis and Clinical Relevance of the MET Receptor Kinase in Prostate Cancer

The MET receptor tyrosine kinase stimulates cell migration, branching morphogenesis, invasion and metastasis and high expression in cancer is associated with adverse patient outcome. We demonstrated high MET expression in prostate cancer bone metastasis, which led to the testing of the MET/VEGFR2 inhibitor, cabozantinib, in patients and the observation of dramatic tumor shrinkage after treatment. We analyzed the HGF-MET receptor/ligand axis both in primary prostate cancer cells and in patient cohorts with clinical outcomes annotation. These studies have now culminated in an analysis of the MET axis with 7 antibodies in 18 different cancer types to determine cancer-type specific biomarker panels of MET pathway activation (manuscript in preparation). Furthermore, the expertise in primary cell culture that we developed in conjunction with the MET project has been applied to other cancer types, in particular ovarian cancer.

Gmyrek GA, Walburg M …. Knudsen BS. ***Normal and malignant prostate epithelial cells differ in their response to hepatocyte growth factor/scatter factor.*** Am J Pathol. 2001;159(2):579-90. PMCID: 1850543.

Knudsen BS, Gmyrek GA, Inra J, Scherr DS, Vaughan ED, Nanus DM, et al. ***High expression of the Met receptor in prostate cancer metastasis to bone.*** Urology. 2002;60(6):1113-7.

Knudsen BS, Vande Woude G. ***Showering c-MET-dependent cancers with drugs.*** Curr Opin Genet Dev. 2008;18(1):87-96.

Ventura AP …… Knudsen BS. ***Activation of the MEK-S6 pathway in high-grade ovarian cancers.*** Appl Immunohistochem Mol Morphol. 2010;18(6):499-508. PMCID: 2989426.

3. Assay Development

A major challenge in measurements of tissue-based biomarkers is the typically small amount of tissue and the instability of analytes, in particular RNA and phosphoproteins biomarkers. Therefore, assay platforms have to be adjusted and multiple biomarkers analyzed concurrently. We demonstrated that the Quantigene™ RNA analysis platform was well suited to overcome the RNA degradation problems in formalin-fixed and paraffin-embedded (FFPE) tissues. We continue to use the principle of this assay in our in-situ hybridization approach with RNAscope®. Another assay system that my laboratory developed was the multiplex imaging with Raman-active and silver impregnated spheres conjugated to antibody probes.

Knudsen BS et al. ***Evaluation of the branched-chain DNA assay for measurement of RNA in formalin-fixed tissues.*** J Mol Diagn. 2008;10(2):169-76. PMCID: 2259472.

Lutz BR ……. Knudsen BS ***Spectral analysis of multiplex Raman probe signatures.*** ACS Nano. 2008;2(11):2306-14. PMCID: 2662378.

Knudsen BS, et al. ***A novel multipurpose monoclonal antibody for evaluating human c-Met expression in preclinical and clinical settings.*** Appl Immunohistochem Mol Morphol. 2009;17(1):57-67. PMCID: 2952101.

Complete List of Published Work in My Bibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/18omlXeSVORAj/bibliography/48052593/public/?sort=date&direction=ascending

D. Research Support

Active Research Support

UCLA Spore in Prostate Cancer Reiter (PI) 10/1/15 – 08/31/16
Title: Protein phosphorylation changes in the DNA damage response checkpoint as biomarkers and drug targets in advanced prostate cancer
The goal of the project is to develop a mass spectrometry/proteomics biomarker panel that measures the extent of DNA damage in prostate cancer needle biopsies. The biomarker panel will be tested for stratification of patients with advanced prostate cancer for treatment with drugs that synergize with DNA damage.
Role: PI of developmental research project

5 R01CA182438-01A1 Kim/Knudsen (Co-PI) 08/01/14 – 07/31/19
Title: Biomarkers for active surveillance stratification in prostate cancer
This project will test RNA expression biomarker signatures in human Exon arrays for their ability to predict aggressive cancer in prostate needle biopsies. The goal is to identify a biomarker panel that can be used for recommendation of enrolment in an active surveillance program and delay of surgery or radiation.
Role: co-PI

PC131996 DoD Health Disparity Award Garraway (PI) 8/01/14 – 6/30/16
Title: Biologic and genomic indicators of metastatic prostate cancer progression in African-American Men
This project profiles high-grade prosteta cancers in AA men on the Genechip and interrogates gene signatures for their ability to predict metastatic progression to lethal prostate cancer.
Role: co-I

Spielberg Discovery Fund in Prostate Res, Knudsen/Freeman (Co-PI) 10/01/12-09/30/16
Title: *The Ecosystem of Lethal Prostate Cancer*
The goal of this interdisciplinary project is to reduce overtreatment by developing a series of assays that allow for a non-invasive assessment of disease.
Role: Co-PI

2R01CA108646-07A1 Bhowmick (PI) 09/12/12-06/30/17
Title: TGF Beta Signals in Prostate Stromal-Epithelial Interactions
The goal of this project is to specifically identify the TGFß-mediated signals in the stroma that mediate prostate androgen responsiveness.
Role: Co-Investigator

Creativity Award Knudsen (PI) 05/23/11-08/31/16
Prostate Cancer Foundation
Title: Biomarkers of Response to Treatment with XL184 in the Bone
This project aims to identify metabolic imaging biomarkers to monitor treatment responses to the c MET/VEGFR2 inhibitor, Cabozatinib (XL184) in prostate cancer bone metastases.
Role: PI

Completed Research Support

5 R01CA131255-01A1 Knudsen/Lin (Co-PI) 07/13/09 –05/31/15
Title: In Vivo Effects of Sulforaphane Supplementation on Normal Human Prostate
This dual PI project will identify intermediate biomarkers of prostate cancer prevention by sulphorafane supplementation prior to radiacal prostatectomy. The biomarkers are based on novel molecular hypotheses and measured in human tissues that are obtained in a double blinded randomized nutritional intervention trial.
Role: Co-PI

2P01CA98912 Chung (PI) 09/29/09-07/31/14
Title: Prostate Cancer Bone Metastasis: Biology and Targeting
This program project grant focuses on the elucidation of the biology and molecular pathways involved in the interaction between stromal cells of the bone or the prostate and malignant prostate cancer cells.
Role: Co-Investigator

R01CA138639 Neuhouser (PI) 04/01/10 – 01/31/13
Title: Vitamin D and Prostate Cancer: Biomarkers & Genetic Variation
The overall objective of this proposal is to elucidate mechanisms by which vitamin D influences prostate cancer risk.
Role: Co-Investigator

W81XWH-08-1-268 Knudsen (PI) 05/01/08-08/31/13
Title: Gp140/CDCPI in the Development of Prostate Cancer Metastasis
The aims of this dual PI project are to determine the role of Gp140 in adhesion and invasion of cells and phosphorylation of the androgen receptor as well as its role as a biomarker and treatment target of prostate cancer metastasis, and to determine whether inhibition of Gp140 prevents metastases of PC3-GFP xenografts.
Role: PI