BIOGRAPHICAL SKETCH

NAME: Marker, Paul C.

eRA COMMONS USER NAME (credential, e.g., agency login): marke032

POSITION TITLE: 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
Grinnell College, Grinnell, IA	B.A.	05/1991	Biology
Stanford University, Palo Alto, CA	Ph.D.	05/1998	Developmental Biology
University of California-San Francisco, CA	Postdoctoral	08/2002	Prostate Cancer

A. Personal Statement

Research in my laboratory is focused on understanding the biology of the prostate gland at the molecular level. Interest in understanding the biology of the prostate is driven both by the fascinating nature of the developmental processes that function during organogenesis of the prostate and by the high incidence in humans of prostatic diseases including prostatic adenocarcinoma and benign prostatic hyperplasia (BPH). I am particularly interested in the role of intercellular communication between epithelial and stromal cells during normal prostate function, during the progression of BPH and associated lower urinary tract symptoms, and during the progression of prostatic cancer. For the current proposal, I will oversee the proposed mouse studies for Project 3 of the U54 renewal application "Cellular and Molecular Mediators of fibrosis in the development of lower urinary tract dysfunction" that propose to test the role of IL-4 receptor signaling in lower urinary tract dysfunction. This role fits well within the past accomplishments of my laboratory that has used mouse genetic models to discover and investigate molecular pathways involved in various aspects of the normal and diseased biology of the prostate gland. My experience with mouse genetics, prostate biology, and prostate cancer make me well suited to perform this role in the proposed project.

Highlighted peer review publications:

a) Joesting MS, Perrin S, Elenbaas B, Fawell SE, Rubin JS, Franco OE, Hayward SW, Cunha GR, **Marker PC**. Identification of SFRP1 as a candidate mediator of stromal-to-epithelial signaling in prostate cancer. *Cancer Research* 2005; 65:10423-10430.

b) Rahrmann EP, Collier LS, Knutson TP, Doyal ME, Kuslak SL, Green LE, Malinowski RL, Roethe L, Akagi K, Waknitz M, Huang W, Largaespada DA, **Marker PC**. Identification of PDE4D as a proliferation promoting factor in prostate cancer using a Sleeping Beauty transposon based somatic mutagenesis screen. *Cancer Research*, 2009; 69:4388-4397. PMCID: PMC2710962

c) Powers GL, Hammer KDP, Domenech M, Frantskevich K, Malinowski RL, Bushman W, Beebe DJ, and **Marker PC**, Phosphodiesterase 4D Inhibitors Limit Prostate Cancer Growth Potential, *Molecular Cancer Research*, 2015, 13: 149-60 published OnlineFirst August 22, PMCID: PMC4312503

d) Le B, Powers GL, Tam YT, Schumacher N, Malinowski RL, Steinke L, Kwon G, and **Marker PC**. Multi-drug loaded micelles delivering chemotherapy and targeted therapies directed against HSP90 and the PI3K/AKT/mTOR pathway in prostate cancer, *PLoS One,* 2017, 12: e0174658. PMCID: PMC5370140

B. Positions and Honors

1989 - 1991	Undergraduate Research Assistant, Charles Sullivan's laboratory, Grinnell College
1992 - 1998	Graduate Research Assistant, David Kingsley's laboratory, Stanford University
1998 - 2002	Postdoctoral Fellow, Gerald Cunha's laboratory, University of California San Francisco
2002 - 2007	Assistant Professor, Department of Genetics, Cell Biology, and Development, University of Minnesota
2007- 2010	Assistant Professor, Division of Pharmaceutical Sciences, University of Wisconsin-Madison
2010 - 2016	Associate Professor, Division of Pharmaceutical Sciences, University of Wisconsin-Madison
2016 - present	Professor, Division of Pharmaceutical Sciences, University of Wisconsin-Madison
2011 - present	Vice Chair, Division of Pharmaceutical Sciences, University of Wisconsin-Madison
2014 - present	Associate Dean for Research, School of Pharmacy, University of Wisconsin-Madison

C. Contribution to Science

1. Mobile DNA elements such as transposons have been useful genetic tools in multiple models organisms both as insertional mutagens for forward genetic screens and as gene transfer vectors. My laboratory pioneered the use of the Sleeping Beauty transposon system as a genetic tool for studying prostate cancer. Our work has included somatic mutagenesis screens to discover new genes important for prostate cancer. This work identified *phosphodiesterase 4d (Pde4d)* as a candidate prostate cancer driver gene and as a candidate drug target in prostate cancer. In related studies, we have also pioneered the use of Sleeping Beauty transposon system as a gene transfer vector for investigating candidate prostate cancer genes.

   a) Rahrmann EP, Collier LS, Knutson TP, Doyal ME, Kuslak SL, Green LE, Malinowski RL, Roethe L, Akagi K, Waknitz M, Huang W, Largaespada DA, **Marker PC**. Identification of PDE4D as a proliferation promoting factor in prostate cancer using a Sleeping Beauty transposon based somatic mutagenesis screen. *Cancer Research*, 2009; 69:4388-4397. PMCID: PMC2710962

   b) Hammer KDP, Alsop J, Buresh-Stiemke RA, Frantskevich K, Malinowski R, Roethe L, Powers GL, and **Marker PC**, A novel method for somatic transgenesis of the mouse prostate using the Sleeping Beauty transposon system, *The Prostate*, 2014, 74:781-91 PMCID: PMC4089518

   c) Powers GL, Hammer KDP, Domenech M, Frantskevich K, Malinowski RL, Bushman W, Beebe DJ, and **Marker PC**, Phosphodiesterase 4D Inhibitors Limit Prostate Cancer Growth Potential, *Molecular Cancer Research*, 2015, 13: 149-60 published OnlineFirst August 22, PMCID: PMC4312503

2. Development of the prostate gland during embryonic and early postnatal life is a process driven by androgens in males. Many years of experimental embryologic studies also made clear that paracrine signaling between the developing prostatic mesenchyme and prostatic epithelium is crucial for prostate development. An important area of current research on prostate development is identifying and characterizing the specific paracrine signaling pathways that drive prostate development. One important contribution of my laboratory to this effort is research on the role of Fibroblast growth factor receptor 2 (Fgfr2), the modification of heparan sulfate proteoglycans that act as Fgfr2 co-receptors, and downstream signal transduction pathways during prostate development.

   a) Kuslak SL, Thielen JL, **Marker PC**. The mouse seminal vesicle shape mutation is allelic with Fgfr2. *Development* 2007; 134:557-565.

   b) Kuslak SL, **Marker PC**. Fibroblast growth factor receptor signaling through MEK-ERK is required for prostate bud induction. *Differentiation* 2007; 75:638-651.

c) Buresh RA, Kuslak SL, Rusch MA, Vezina CM, Selleck SB, and **Marker PC**, Sulfatase 1 is an inhibitor of ductal morphogenesis with sexually dimorphic expression in the urogenital sinus, *Endocrinology*, 2010, 151(7):3420-31 PMCID: PMC2903932

d) Buresh-Stiemke RA, Malinowskia RL, Keil KP, Vezina CM, Oosterhofc A, van Kuppevelt TH, and **Marker PC**, Distinct expression patterns of Sulf1 and Hs6st1 spatially regulate heparan sulfate sulfation during prostate development, *Developmental Dynamics*, 2012, 241: 2005-2013 PMCID: PMC3677568

3. Development of the prostate gland during embryonic and early postnatal life is a process driven by androgens in males. Many years of experimental embryologic studies also made clear that paracrine signaling between the developing prostatic mesenchyme and prostatic epithelium is crucial for prostate development. An important area of current research on prostate development is identifying and characterizing the specific paracrine signaling pathways that drive prostate development. One important contribution of my laboratory to this effort is research on the role of components of the WNT/beta-catenin signaling pathway including Sfrp1 and Wif1 in this process. In this case, we have also identified potential roles for this pathway during the progression of prostatic diseases.

   a) Joesting MS, Perrin S, Elenbaas B, Fawell SE, Rubin JS, Franco OE, Hayward SW, Cunha GR, **Marker PC**. Identification of SFRP1 as a candidate mediator of stromal-to-epithelial signaling in prostate cancer. *Cancer Research* 2005; 65:10423-10430.

   b) Joesting MS, Cheever TR, Volzing KG, Yamaguchi T, Wolf V, Naf D, Rubin JS, and **Marker PC**, Secreted frizzled related protein 1 is a paracrine modulator of epithelial branching morphogenesis, proliferation, and secretory gene expression in the prostate, *Developmental Biology* 2008; 317:161-173 PMCID: PMC2435376

   c) Keil KP, Mehta V, Branham AM, Abler LL, Buresh RA, Joshi PS, Schmitz CT, **Marker PC**, Vezina CM, Wnt inhibitory factor 1 (Wif1) is regulated by androgens and enhances androgen-dependent prostate development, *Endocrinology*. 2012 Dec;153(12):6091-103 PMCID: PMC3512059

   d) Wegner KA, Mehta V, Johansson JA, Mueller BR, Keil KP, Abler LL, **Marker PC**, Taketo MM, Headon DJ, and Vezina CM, Edar is a downstream target of beta-catenin and drives collagen accumulation in the mouse prostate, Biol Open, epub ahead of print 02/13/2019

4. The study of prostatic diseases including prostate cancer and benign prostatic hyperplasia using mouse models is desirable because of the genetic and other molecular tools available in mice. However, the significant anatomic and molecular differences between the prostates of mice and humans create challenges for using mouse models to study prostatic diseases. My laboratory has contributed several studies that have included development of new mouse models and/or facilitated the use of existing mouse models for the study of prostatic diseases.

   a) Thielen JL, Volzing KG, Collier LS, Green LE, Largaespada DA, **Marker PC**. Markers of prostate region-specific epithelial identity define anatomical locations in the mouse prostate that are molecularly similar to human prostate cancers. *Differentiation* 2007;75: 49-61.

   b) Nicholson TM, Ricke EA, **Marker PC**, Miano JM, Mayer RD, Timms BG, vom Saal FS, Wood RW, Ricke WA, Testosterone and 17ß estradiol induce glandular prostatic growth, bladder outlet obstruction, and voiding dysfunction in male mice, *Endocrinology*, 2012, 153(11):5556-5565 PMCID: PMC3473198

   c) Le B, Powers GL, Tam YT, Schumacher N, Malinowski RL, Steinke L, Kwon G, and **Marker PC**. Multi-drug loaded micelles delivering chemotherapy and targeted therapies directed against HSP90 and the PI3K/AKT/mTOR pathway in prostate cancer, *PLoS One,* 2017, 12: e0174658. PMCID: PMC5370140

   d) Wegner KA, Abler LL, Oakes SR, Mehta GS, Ritter KE, Hill WG, Zwaans BM, Lamb LE, Wang Z, Bjorling DE, Ricke WA, Macoska J, **Marker PC**, Southard-Smith EM, Eliceiri KW, and Vezina CM, Void spot assay procedural optimization and software for rapid and objective quantification of rodent voiding function, including overlapping urine spots, Am J Physiol Renal Physiol, 2018, 315: F1067-F1080

5. The molecular mechanisms that control patterning of the vertebrate skeleton are fundamental to understanding the morphologic variation among species. As a graduate student, I contributed to understanding these molecular mechanisms by using the techniques of positional cloning to identify genes affected by spontaneous mutations that altered skeletal patterning in mice and humans.

   a) Kingsley DM, Bland AE, Grubber JM, **Marker PC**, Russell LB, Copeland NG, Jenkins NA. The mouse *short ear* skeletal morphogenesis locus is associated with defects in a bone morphogenetic member of the TGF beta superfamily. *Cell*, 1992, 71: 399-410.

   b) **Marker PC**, Seung K, Bland AE, Russell LB, and Kingsley DM. Spectrum of *Bmp5* mutations from germline mutagenesis experiments in mice. *Genetics*, 1997, 145: 435-443

   c) [Clark RM, **Marker PC**]*, Kingsley DM. A novel candidate gene for mouse and human preaxial polydactyly with altered expression in limbs of *hemimelic extra-toes* mutant mice. *Genomics*, 2000, 67: 19-27. *equal contribution with first author

   d) Clark RM, **Marker PC**, Roessler E, Dutra A, Schimenti JC, Muenke M, and Kingsley DM. Reciprocal mouse and human limb phenotypes caused by gain- and loss-of-function mutations affecting *Lmbr1*. *Genetics,* 2001, 159: 715-726

Public URL:
http://www.ncbi.nlm.nih.gov/sites/myncbi/1zWdjnynYDrAg/bibliography/44071028/public/?sort=date&direction=ascending

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

Grant U54DK104310 (Ricke, PI), George M O'Brien Center of Excellence, 12/01/14-11/30/19
Title: Mediators of fibrosis in the development of lower urinary tract dysfunction
Principal Investigator: William A Ricke, my role Project PI
The major goals are to investigate molecular and cellular biological mechanisms driving fibrosis in the prostates of mice and men and to investigate the relationships of hormonal, developmental, metabolic, and inflammatory processes in development of fibrosis associated with lower urinary tract dysfunction using functional urological testing. This is a Center grant that includes 3 projects and core facilities.
My role: Co-leader of project 2

Completed Research Support

Grant 1R21 CA195313, NIH/NCI 12/01/2015-11/30/2018
Title: Magi2 in aggressive prostate cancer
Principal Investigator: Paul C. Marker
This project investigates the role of Magi2 as a candidate driver of castration resistant prostate cancer.