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: Christine Ann Cartwright

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

POSITION TITLE: Professor of Medicine and Gastroenterology, Stanford University

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
Stanford University	B.S	6/73	Biology
University of Utah	M.D.	6/78	Medicine
University of California, San Diego	Residency	6/81	Internal Medicine
University of Utah	Residency	6/82	Chief Medical Resident
University of California, San Diego	Fellowship	6/84	Gastroenterology
The Salk Institute	Postdoctoral	5/89	Cancer Biology

A. Personal Statement

My early training in cancer biology and protein phosphorylation at The Salk Institute together with my broad background in medicine and gastroenterology and my clinical focus on cancer in inflammatory bowel diseases, provides the expertise needed for the proposed studies on molecular mechanisms of intestinal cell growth control.

B. Positions and Honors

Faculty Appointments:

1984-87 Instructor in Medicine (Clinical), University of California, San Diego
1987-89 Assistant Professor of Medicine (Clinical), University of California, San Diego
1989-95 Assistant Professor of Medicine/Gastroenterology, Stanford University
1995-05 Associate Professor of Medicine/Gastroenterology, with tenure, Stanford University
2005- Professor of Medicine/Gastroenterology, Stanford University
1989-07 Director, Center for Inflammatory Bowel Diseases, Stanford University
1994- Cancer Biology Faculty, Stanford University

Research Awards:

1983-84 AGA Interdisciplinary Research Training Award, University of California, San Diego
1984-85 Giannini Foundation Medical Research Fellow, The Salk Institute
1989-91 Merck Faculty Development Award, Stanford University
1989-91 Hume Faculty Scholar, Stanford University
1989-91 Named Investigator Award, Digestive Disease Center Grant, NIH/NIDDK, P30-DK38707

1989, 93 Katharine McCormick Fund for Women, Stanford University
1989, 94 Pilot/Feasibility Awards, Digestive Disease Center Grant, NIH/NIDDK, P30-DK38707
1992 AGA/SmithKline Beecham Clinical Research Award
1995- Election into the American Society for Clinical Investigation
2008 Outstanding AGA Women in Science Award (1 of 25 honored)

Professional Activities:

1995-99 Member, Tumor Biochemistry/Endocrinology Study Section, American Cancer Society
1998 Member (Ad Hoc), General Medicine A-2 Study Section, National Institutes of Health
1997-00 Editorial Board, *American Journal of Physiology: Gastrointestinal and Liver Physiology*
1994-06 Editorial Board, *Inflammatory Bowel Diseases*
2007-09 Member, Gastrointestinal Cell/Molecular Biology Study Section, National Institutes of Health

Research Grants: Principal Investigator: Christine A. Cartwright:

1985-88 NIH, NCI, 1 K08 CA01040, Clinical Investigator Award
1989-91 American Cancer Society, Faculty Research Grant, CD-400
1991-96 NIH, R29 – DK43743
1994-96 Crohn's and Colitis Foundation of America
1996-99 American Cancer Society, #BE-246
2003-06 Broad Medical Research Foundation, IBD-0068
2003-09 NIH, NCI, R01-CA97020
1996-18 NIH, NIDDK, R01-DK43743

Invited Speaker at National Scientific Meetings:

Topic: *Intestinal Cell Growth Control: Regulation of Src Tyrosine Kinases*

11/6/93 Thirty-seventh Annual Clinical Conference and Twenty-sixth Annual Special Pathology Program: Advances in the Biology and Therapy of Colorectal Cancer, The University of Texas MD Anderson Cancer Center, Houston, Texas

2/8/95 Plenary Session, Western Association of Physicians, Fortieth Annual Meeting, Carmel, California

5/13/97 American Gastroenterological Association Research Symposium: Cell and Molecular Biology of Gastrointestinal Cancers: Growth Factors, Tyrosine Kinases and Signal Transduction, Washington DC

8/7/97 FASEB Summer Research Conference on Gastrointestinal Tract VII: Development, Differentiation and Adaptation, Copper Mountain, Colorado

5/19/99 American Gastroenterological Association Research Symposium: Compartmentalization: Kinases, Phosphatases and their Anchoring Proteins, Orlando, Florida

5/20/08 American Gastroenterological Association/GI Oncology Research Symposium: Protein Kinases and GI Cancers, San Diego, California

Invited Chairperson at National Scientific Meetings:

5/21/96 Co-Chairperson, American Gastroenterological Association Research Forum Gastrointestinal Oncology: "Molecular and Cellular Biology of Colonic Neoplasia"

5/12/97 Co-Chairperson, American Gastroenterological Association Research Forum Gastrointestinal Oncology: "Molecular Biology of Gastrointestinal Cancer"

5/21/00 Co-Chairperson/Organizer, American Gastroenterological Association / Gastroenterology Research Group Symposium on “Colon Carcinogenesis”

5/22/02 Co-Chairperson, American Gastroenterological Association Research Forum Gastrointestinal Oncology: "Inflammatory Bowel Diseases and Neoplasia"

5/16/04 Co-Chairperson/Organizer, American Gastroenterological Association / GI Oncology / Gastroenterology Research Group Symposium on "Stem Cells – Biology and Cancer"

5/15/05 Co-Chairperson for the AGA/GI Oncology State of the Art Lecture: "Ras Signaling and Therapeutics", Dr Frank McCormick. 106th Annual Meeting of the American Gastroenterological Association, May15, 2005, Chicago, Ill.

5/18/13 Co-Chairperson, American Gastroenterological Association Research Forum Gastrointestinal Oncology: "Tumor and Cell Biology"

Faculty Teaching Awards:

2003 GI/Medicine Faculty Teaching Award
2009 GI/Medicine Faculty Teaching Award (voted by the GI Fellows)
2009 GI/Medicine Faculty Teaching Award (voted by the GI Faculty)

C. Contributions to Science

1. We are interested in understanding how normal intestinal cells regulate their growth and how loss of that regulation results in malignant transformation. Our research focuses on molecular mechanisms by which the Src family of tyrosine kinases and their inhibitors contribute to the regulation. When Src activity is appropriately restrained, the kinase participates in diverse signaling pathways that control cell division, proliferation, differentiation, adhesion and survival. When Src activity is unrestrained, the kinase is oncogenic. Thus, it is important to search for mechanisms that regulate Src activity. We discovered that one fundamental mechanism by which Src is regulated is by addition of a phosphate to a highly conserved tyrosine, 527, in the C-terminal tail. Mutation of this site converts the normal cellular Src into a transforming protein.

   a. **Cartwright CA**, MA Hutchinson and W Eckhart. Structural and functional modification of pp60$^{c\text{-}src}$ associated with polyoma middle tumor antigen from infected or transformed cells. *Mol Cell Biol* 5:2647-2652, 1985.
   b. Cooper JA, KL Gould, **CA Cartwright** and T Hunter. Tyr^{527} is phosphorylated in pp60$^{c\text{-}src}$: implications for regulation. *Science* 231:1431-1434, 1986.
   c. **Cartwright CA**, PL Kaplan, JA Cooper, T Hunter and W Eckhart. Altered sites of tyrosine phosphorylation in pp60$^{c\text{-}src}$ associated with polyomavirus middle tumor antigen. *Mol Cell Biol* 6:1562-1570, 1986.
   d. **Cartwright CA**, W Eckhart, S Simon and PL Kaplan. Cell transformation by pp60$^{c\text{-}src}$ mutated in the carboxy-terminal regulatory domain. *Cell* 49:83-91, 1987.

2. We demonstrated that the specific activity of Src is elevated in most malignant and premalignant lesions of the colon. We found striking activation of Src (20-fold) in malignant and premalignant epithelia of ulcerative colitis, a chronic inflammatory disease of the colon that carries an increased risk for colon cancer. Conversely, we found that the specific activity of cytoskeletal Src decreases as intestinal crypt cells differentiate. Together, our results indicate that downregulation of Src activity is important for differentiation, and upregulation for growth and transformation of intestinal cells.

   a. **Cartwright CA**, MP Kamps, AI Meisler, JM Pipas and W Eckhart. pp60$^{c\text{-}src}$ activation in human colon carcinoma. *J Clin Invest* 83:2025-2033, 1989.
   b. **Cartwright CA**, AI Meisler and W Eckhart. Activation of the pp60$^{c\text{-}src}$ protein kinase is an early event in colonic carcinogenesis. *Proc Natl Acad Sci USA* 87:558-562, 1990.

c. **Cartwright CA**, S Mamajiwalla, SA Skolnick, W Eckhart and DR Burgess. Intestinal crypt cells contain higher levels of cytoskeletal-associated pp60$^{c\text{-}src}$ protein tyrosine kinase activity than do differentiated enterocytes. *Oncogene* 8:1033-1039, 1993.
d. **Cartwright CA**, CA Coad and BM Egbert. Elevated c-Src tyrosine kinase activity in premalignant epithelia of ulcerative colitis. *J Clin Invest* 93:509-515, 1994.

3. We discovered that another major mechanism by which Src activity is regulated is by interaction with Rack1 (receptor for activated C kinase 1). Using a yeast two-hybrid assay, we identified Rack1 as a novel substrate and binding partner of Src and an inhibitor of Src kinases and cell growth. The significance of these findings is defining a major mechanism by which Src activity is repressed. While a number of interacting proteins have been identified that upregulate Src activity, few have been identified that downregulate Src activity. Because it is the repression of c-Src activity rather than the elevation of v-Src activity that accounts for differences in their transforming abilities, it is important to search for cellular mechanisms that repress c-Src. In doing so, we will learn about how normal cells regulate their growth and how loss of that regulation results in uncontrolled cell growth and malignant transformation.

   a. Chang BY, KB Conroy, E Machleder and **CA Cartwright**. RACK1, a receptor for activated C kinase and a homolog of the β subunit of G proteins, inhibits activity of Src tyrosine kinases and growth of NIH 3T3 cells. *Mol Cell Biol* 18:3245-3256, 1998.
   b. Chang BY, M Chiang and **CA Cartwright**. The interaction of Src and RACK1 is enhanced by PKC activation and tyrosine phosphorylation of RACK1. *J Biol Chem* 276:20346-20356, 2001.
   c. Chang BY, R Harte and **CA Cartwright**. RACK1: a novel substrate for the Src protein-tyrosine kinase. *Oncogene* 21:7619-7629, 2002.
   d. Miller LD, KC Lee, D Mochly-Rosen and **CA Cartwright**. RACK1 regulates Src-mediated Sam68 and p190RhoGAP signaling. *Oncogene* 23:5682-5686, 2004.

4. We revealed a novel function of Rack1 in regulating the cell cycle in late G_1 and mitosis. By overexpressing Rack1, depleting Src with siRNAs or utilizing cell-permeable peptides that enhance or disrupt Rack1's interaction with Src, we showed that Rack1 regulates G_1/S progression by suppressing Src activity and thereby a major, mitogenic, signaling pathway that culminates in activation of Myc. Consequently, cell cycle progression is restrained. The significance of this finding is that kinase inhibitors that work by "braking the cycle" before cells are fated to divide, would wield powerful and pervasive control over cell growth. Such inhibitors are tumor suppressors and represent exciting new targets for cancer therapy.

   a. Park J and **CA Cartwright**. Src activity increases and Yes activity decreases during mitosis of human colon carcinoma cells. *Mol Cell Biol* 15:2374-2382, 1995.
   b. Mamidipudi V, J Zhang, KC Lee and **CA Cartwright**. RACK1 regulates G_1/S progression by suppressing Src kinase activity. *Mol Cell Biol* 24:6788-6798, 2004.
   c. Mamidipudi V, LD Miller, D Mochly-Rosen and **CA Cartwright**. Peptide modulators of Src activity in G_1 regulate entry into S phase and proliferation of NIH 3T3 cells. *Biochem Biophys Res Commun* 352:423-430, 2007.
   d. Mamidipudi V, NK Dhillon, T Parman, LD Miller, KC Lee, and **CA Cartwright**. RACK1 inhibits colonic cell growth by regulating Src activity at cell cycle checkpoints. *Oncogene* 26:2914-24, 2007.

5. We discovered other novel functions of Rack1. We identified a proapoptotic function of Rack1: suppressing Src activity in the intrinsic and Akt pathways. We showed that Rack1 is required for staurosporin-induced mitochondrial cell death, the activation and translocation of Bax and Bim to mitochondria, the oligomerization of Bax and caspase activation. This discovery is significant because almost all cytotoxic anticancer drugs currently in use induce apoptosis of malignant cells. Thus, understanding apoptotic triggers is important for new drug discovery in cancer therapy.

   We identified a function of Rack1 in maintaining junctional homeostasis of intestinal epithelia by regulating Src- and HGF-induced endocytosis of E-cadherin. We found that Rack1 promotes cell-cell adhesion and reduces invasive properties of colon cancer cells by regulating E-cadherin tyrosine phosphorylation and endocytosis and by diverting E-cadherin from a degradative to a recycling

pathway. The significance of these findings lies in the potential therapeutic application of Rack1 mimetics to inhibit invasion of cancer cells.

Our recent *in vivo* studies revealed that Rack1 regulates growth of intestinal epithelia by suppressing crypt cell proliferation and regeneration, promoting differentiation and apoptosis and repressing development of neoplasia. They identified a novel function for Rack1 in maintaining intestinal homeostasis by protecting the epithelial barrier. Rack1 loss resulted in a patchy, erosive, hemorrhagic, inflammatory enterocolitis, which resembles that of inflammatory bowel diseases (IBD) in humans. Understanding mechanisms that protect barrier function in normal intestine and how loss of that protection contributes to the pathogenesis of IBD could lead to improved therapies for these and other erosive diseases of the gastrointestinal tract.

a. Mamidipudi V and **CA Cartwright**. A novel pro-apoptotic function of RACK1: suppression of Src activity in the intrinsic and Akt pathways. *Oncogene* 28:4421-4433, 2009.
b. Swaminathan G and **CA Cartwright**. Rack1 promotes epithelial cell-cell adhesion by regulating E-cadherin endocytosis. *Oncogene* 31:376-389, 2012.
c. Cheng Z-F, RK Pai and **CA Cartwright**. Rack1 function in intestinal epithelia: regulating crypt cell proliferation and regeneration and promoting differentiation and apoptosis. *Am Journal Physiol Gastrointest Liver Physiol.* 2018 Jan 1;314(1):G1-G13. doi: 10.1152/ajpgi.00240.2017. Epub 2017 Sep 21. PMID: 28935684
d. Cheng Z-F and **CA Cartwright**. Rack1 maintains intestinal homeostasis by protecting the integrity of the epithelial barrier. *Am Journal Physiol Gastrointest Liver Physiol*. 2018 Feb 1;314(2):G263-G274. doi: 10.1152/ajpgi.00241.2017. Epub 2017 Nov 14. PMID: 29025732

D. Research Support

Ongoing Research Support:

5 R01 DK43743 Cartwright (PI) 06/15/91 – 01/31/18

NIH/NIDDK

Intestinal Cell Growth Control: Role of Tyrosine Kinases

The goal of this project is to investigate mechanisms by which intestinal epithelial cells regulate their growth.

Completed Research Support:

5 R01 CA097020 Cartwright (PI) 07/03/03 – 06/30/09

NIH/NCI

Human Colon Cancer: Role of the Src Tyrosine Kinase

The goals of this project are to investigate RACK1's influence on cell transformation by v-Src, and to identify mutations, post-translational modifications and subcellular translocations of Src and Rack1 that deregulate their function in colon cancer cells.