## BIOGRAPHICAL SKETCH

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| NAME<br>Cartwright, Christine Ann | POSITION TITLE<br>Professor of Medicine and Gastroenterology |
|---|---|
| eRA COMMONS USER NAME (credential, e.g., agency login)<br>cartwright.christine | |

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)* | MM/YY | FIELD OF STUDY |
|---|---|---|---|
| Stanford University | B.S. | 1973 | Biology |
| University of Utah | M.D. | 1978 | Internal Medicine |
| University of California, San Diego | Residency | 1981 | Internal Medicine |
| University of California, San Diego | Fellow | 1984 | Gastroenterology |
| The Salk Institute for Biological Studies | Research Associate | 1989 | Cancer Biology |

### A. Personal Statement

The focus of my research is on understanding how normal intestinal cells regulate their growth and how loss of that regulation results in malignant transformation. We study molecular mechanisms by which the Src tyrosine kinases and their inhibitors contribute to the regulation. We discovered two fundamental mechanisms whereby Src activity is regulated. One is by addition of a phosphate to a highly conserved tyrosine in the C-terminal tail. Mutation of this site converts the normal cellular Src into a transforming protein. The other is by interaction with Rack1, an endogenous substrate and inhibitor of Src kinases and colonic cell growth. Our recent *in vitro* studies demonstrate that Rack1 regulates colonic cell growth by suppressing Src activity at critical cell cycle checkpoints and during apoptosis. We are now examining the function of Rack1 *in vivo*, and during mitochondrial cell death. If Rack1 works *in vivo* as it does *in vitro*, by suppressing an oncogenic kinase at critical checkpoints in the cycle and during apoptosis, then we will have discovered a major mechanism by which intestinal cells regulate their growth. Exploitation of this discovery could lead to novel colon cancer therapies that mimic Rack1 function.

### B. Positions and Honors

Postdoctoral Training:

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| 1978-81 | Intern and Resident in Internal Medicine, University of California, San Diego |
| 1982 | Chief Medical Resident, University of Utah |
| 1982-84 | Fellow in Gastroenterology, University of California, San Diego |
| 1984-89 | Research Associate, Molecular Biology and Virology Laboratory<br>The Salk Institute for Biological Studies, San Diego, California |

Faculty Appointments:

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|---|---|
| 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:

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| 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 |
| 1992 | AGA/SmithKline Beecham Clinical Research Award |
| 1989, 94 | Pilot/Feasibility Awards, Digestive Disease Center Grant, NIH/NIDDK, P30-DK38707 |
| 2008 | Outstanding AGA Women in Science Award |

Professional Activities:

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| 1995- | Member, American Society for Clinical Investigation |
| 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:

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|---|---|
| 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 |
| 1996-16 | NIH, NIDDK, R01-DK43743 |

**C. Selected Publications (39 of 58)**

1. Schulz R, CA Cartwright and A Goldstein. Reversibility of morphine tolerance and dependence in guinea pig brain and myenteric plexus. *Nature* 251:329-331, 1974.
2. Schulz R and CA Cartwright. Effect of morphine on serotonin release from myenteric plexus of the guinea pig. *J Pharmacol Exp Ther* 190:420-430, 1974.
10. Cartwright CA, JA McRoberts, KG Mandel and K Dharmsathaphorn. Synergistic action of cyclic adenosine monophosphate- and calcium-mediated chloride secretion in a colonic epithelial cell line. *J Clin Invest* 76:1837-1842, 1985.
11. Dharmsathaphorn K, P Huott, CA Cartwright, JA McRoberts, KG Mandel and G Beuerlein. Inhibition of ATP levels by quinidine in a human colonic epithelial cell line. *Am J Physiol* 250:G806-G813, 1986.
12. 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.
13. 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.
14. 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.
15. Kaplan PL, S Simon, CA Cartwright and W Eckhart. cDNA cloning with a retrovirus expression vector: generation of a c-*src* cDNA clone. *J Virol* 61:1731-1734, 1987.
16. 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.
17. Cartwright CA, R Simantov, PL Kaplan, T Hunter and W Eckhart. Alterations in pp60$^{c\text{-}src}$ accompany differentiation of neurons from rat embryo striatum. *Mol Cell Biol* 7:1830-1840, 1987.
18. Cartwright CA, R Simantov, WM Cowan, T Hunter, and W Eckhart. pp60$^{c\text{-}src}$ expression in the developing rat brain. *Proc Natl Acad Sci USA* 85:3348-3352, 1988.

19. Tack LC, CA Cartwright, JH Wright, W Eckhart, KW Peden, A Srinivasan and JM Pipas. Properties of a simian virus 40 mutant T antigen substituted in the hydrophobic region: defective ATPase and oligomerization activities and altered phosphorylation accompany an inability to complex with cellular p53. *J Virol* 63:3362-3367, 1989.
20. 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.
21. Peden KW, SL Spence, LC Tack, CA Cartwright, A Srinivasan and JM Pipas. A DNA replication-positive mutant of simian virus 40 that is defective for transformation and the production of infectious virions. *J Virol* 64:2912-2921, 1990.
22. Bjelfman C, G Meyerson, CA Cartwright, K Mellstrom, U Hammerling and S Pahlman. Early activation of endogenous pp60$^{c\text{-}src}$ kinase activity during neuronal differentiation of cultured human neuroblastoma cells. *Mol Cell Biol* 10:361-370, 1990.
23. Wu JY, Z-Y Zhou, A Judd, CA Cartwright and WS Robinson. The hepatitis B virus-encoded transcriptional *trans*-activator hbx appears to be a novel protein serine/threonine kinase. *Cell* 63:687-695, 1990.
24. 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.
26. 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.
27. Park J, AI Meisler and CA Cartwright. c-Yes tyrosine kinase activity in human colon carcinoma. *Oncogene* 8:2627-2635, 1993.
29. 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.
31. Peña SV, MF Melhem, AI Meisler and CA Cartwright. Elevated c-Yes tyrosine kinase activity in premalignant lesions of the colon. *Gastroenterology* 108:117-124, 1995.
32. 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.
33. Peng Z-Y and CA Cartwright. Regulation of the Src tyrosine kinase and Syp tyrosine phosphatase by their cellular association. *Oncogene* 11:1955-1962, 1995.
34. Kumble S, MB Omary, CA Cartwright and G Triadafilopoulos. Src activation in malignant and premalignant epithelia of Barrett's esophagus. *Gastroenterology* 112:348-356, 1997.
35. Cartwright CA. Intestinal cell growth control: Role of Src tyrosine kinases. *Gastroenterology* 114:1335-38,1998.
36. 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.
37. Walter AO, Peng Z-Y and CA Cartwright. The Shp-2 tyrosine phosphatase activates the Src tyrosine kinase by a non-enzymatic mechanism. *Oncogene* 18:1911-1920, 1999.
38. 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.
39. Chang BY, R Harte and CA Cartwright. RACK1: a novel substrate for the Src protein-tyrosine kinase. *Oncogene* 21:7619-7629, 2002.
42. Chang BY, and CA Cartwright. Detection of protein kinase binding partners by the yeast two-hybrid analysis. *Methods in Molecular Biology* 233:327-343, 2003.
43. Kambham N, R Vij, CA Cartwright and T Longacre. Cytomegalovirus infection in steroid-refractory ulcerative colitis: a case-control study. *Am J Surg Pathol* 8:365-373, 2004.
44. Mamidipudi V, BY Chang, R Harte, KC Lee and CA Cartwright. RACK1 inhibits the serum- and anchorage-independent growth of v-Src transformed cells. *FEBS Letters* 567:321-326, 2004.
45. Miller LD, KC Lee, D Mochly-Rosen and CA Cartwright. RACK1 regulates Src-mediated Sam68 and p190RhoGAP signaling. *Oncogene* 23:5682-5686, 2004.
46. 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.

49. 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.
50. 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* 26:2914-2924, 2007.
54. 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.
56. Zhou Q, NT Snider, J Liao, DH Li, A Hong, N-O Ku, CA Cartwright and MB Omary. Characterization of in vivo keratin 19 phosphorylation on tyrosine-391. *PLoS One* 5(10): e13538, 2010.
58. Swaminathan G and CA Cartwright. Rack1 promotes epithelial cell-cell adhesion by regulating E-cadherin endocytosis. *Oncogene* 31:376-389, 2012.

**D. Research Support**

Ongoing Research Support:

5 R01 DK43743 Cartwright (PI) 06/15/91 – 07/31/16

NIH/NIDDK

Intestinal Cell Growth Control: Role of Tyrosine Kinases

The goal of this project is to investigate mechanisms whereby normal intestinal 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.