

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME PAUL DENT, Ph.D.	POSITION TITLE PROFESSOR		
eRA COMMONS USER NAME PAUL_DENT			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
University of Newcastle upon Tyne, England	B.Sc. (1 st)	1988	BIOCHEMISTRY
University of Dundee, Scotland	Ph.D.	1992	BIOCHEMISTRY

A. POSITIONS AND HONORS

1988-1991 Graduate Student, (Professor Sir P. Cohen, F.R.S.), University of Dundee, Scotland
1992-1996 Postdoctoral (Professor T. W. Sturgill), University of Virginia, Charlottesville, Virginia
1996-2000 Assistant Professor, Department of Radiation Oncology, VCU, Richmond, Virginia
2000-2004 Associate Professor, Department of Radiation Oncology, VCU, Richmond, Virginia
2004-2006 Associate Professor, Department of Biochemistry, VCU, Richmond, Virginia
July 2006- Professor, Department of Biochemistry, VCU, Richmond, Virginia.

Permanent Member, ET-1/DMP Study Section 2000-2005; Permanent Member, BMCT Study Section 2005-2009; Ad-Hoc Member: invited permanent Radiation Study Section (June '01, Feb '02); Chairman and Member, multiple Dept. of Defense and SEP NIH review 2002-; Program Project reviewer, 2003-; Assistant Editor; The Journal of Biological Chemistry; Associate. Editor, Cancer Biology & Therapy; Molecular Pharmacology.

B. SELECTED PEER-REVIEWED PUBLICATIONS

1. **Dent, P.**, Haser, W., Haystead, T. A., Roberts, T. M., and Sturgill, T. W. Activation of mitogen-activated protein kinase kinase by v-Raf in NIH 3T3 cells and in vitro. *Science*, 257: 1404-1407, 1992.
2. **Dent, P.**, Jelinek, T., Morrison, D. K., Weber, M. J., and Sturgill, T. W. Reversal of Raf-1 activation by purified and membrane-associated protein phosphatases. *Science*, 268: 1902-1906, 1995.
3. Kasid, U., Suy, S., **Dent, P.**, Ray, S., Whiteside, T. L., and Sturgill, T. W. Activation of Raf by ionizing radiation. *Nature*, 382: 813-816, 1996.
4. Suy, S., Anderson, W. B., **Dent, P.**, Chang, E., and Kasid, U. Association of Grb2 with Sos and Ras with Raf-1 upon gamma irradiation of breast cancer cells. *Oncogene*, 15: 53-61, 1997.
6. Auer, K. L., Park, J. S., Seth, P., Coffey, R. J., Darlington, G., Abo, A., McMahon, M., Depinho, R. A., Fisher, P. B., and **Dent, P.** Prolonged activation of the mitogen-activated protein kinase pathway promotes DNA synthesis in primary hepatocytes from p21Cip-1/WAF1-null mice, but not in hepatocytes from p16INK4a-null mice. *Biochem J*, 336 (Pt 3): 551-560, 1998.
7. **Dent, P.**, Reardon, D. B., Park, J. S., Bowers, G., Logsdon, C., Valerie, K., and Schmidt-Ullrich, R. Radiation-induced release of transforming growth factor alpha activates the epidermal growth factor receptor and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death. *Mol Biol Cell*, 10: 2493-2506, 1999.
11. Vrana, J. A., Grant, S., and **Dent, P.** Inhibition of the MAPK pathway abrogates BCL2-mediated survival of leukemia cells after exposure to low-dose ionizing radiation. *Radiat Res*, 151: 559-569, 1999.
13. Park, J. S., Qiao, L., Benz, C., Darlington, G., Firestone, G., Fisher, P. B., and **Dent, P.** A role for both Ets and C/EBP transcription factors and mRNA stabilization in the MAPK-dependent increase in p21 (Cip-1/WAF1/mda6) protein levels in primary hepatocytes. *Mol Biol Cell*, 11: 2915-2932, 2000.
14. Qiao, L., Valerie, K., El Deiry, W., Schmidt-Ullrich, R., Fisher, P. B., Grant, S., Hylemon, P. B., and **Dent, P.** Deoxycholic acid (DCA) causes ligand-independent activation of epidermal growth factor receptor (EGFR) and FAS receptor in primary hepatocytes: inhibition of EGFR/mitogen-activated protein kinase-signaling module enhances DCA-induced apoptosis. *Mol Biol Cell*, 12: 2629-2645, 2001.

Principal Investigator/Program Director (Last, First, Middle):

16. Yacoub, A., Qiao, L., **Dent, P.**, and Hagan, M. P. MAPK dependence of DNA damage repair: ionizing radiation and the induction of expression of the DNA repair genes XRCC1 and ERCC1 in DU145 human prostate carcinoma cells in a MEK1/2 dependent fashion. *Int J Radiat Biol*, 77: 1067-1078, 2001.
17. Qiao, L., Yacoub, A., Fisher, P. B., Hagan, M. P., Grant, S., and **Dent, P.** Pharmacologic inhibitors of the mitogen activated protein kinase cascade have the potential to interact with ionizing radiation exposure to induce cell death in carcinoma cells by multiple mechanisms. *Cancer Biol Ther*. 1: 168-176, 2002.
18. Amorino GP, Hamilton VM, Valerie K, **Dent, P.**, Lammering G, and Schmidt-Ullrich RK. Epidermal growth factor receptor dependence of radiation-induced transcription factor activation in human breast carcinoma cells. *Mol Biol Cell*. 13: 2233-2244, 2002.
19. Qiao, L., McKinstry, R., Gupta, S., Gilfor, D., Windle, J. J., Hylemon, P. B., Grant, S., Fisher, P. B., and **Dent, P.** Cyclin kinase inhibitor p21 potentiates bile acid-induced apoptosis in hepatocytes that is dependent on p53. *Hepatology*. 36: 39-48, 2002.
20. Yacoub A, Han SI, Caron R, Gilfor D, Mooberry S, Grant S, **Dent P.** Sequence Dependent Exposure of Mammary Carcinoma Cells to Taxotere and the MEK1/2 Inhibitor U0126 Causes Enhanced Cell Killing In Vitro. *Cancer Biol Ther*. (2003) 2: 670-676.
21. Fang, Y, Han, SI, Gupta, S, Studer, E, Grant, S, Hylemon, PB and **Dent, P.** Bile acids induce mitochondrial ROS which promote activation of receptor tyrosine kinases and signaling pathways. *Hepatology*, (2004) 40: 961-971.
22. Carón RW, Yacoub A, Mitchell C, Zhu X, Hong Y, Sasazuki T, Shirasawa S, Hagan MP, Grant S, **Dent P.** Radiation-stimulated ERK1/2 and JNK1/2 signaling can promote cell cycle progression in human colon cancer cells *Cell Cycle* (2005) 4: 60-72.
23. Carón RW, Yacoub A, Zhu X, Mitchell C, Han SI, Sasazuki T, Shirasawa S, Hagan MP, Grant S, **Dent P.** H-RAS V12 induced radioresistance in HCT116 colon carcinoma cells is heregulin dependent. *Molecular Cancer Therapeutics*, (2005) 4: 243-255.
24. Carón RW, Yacoub A, Li M, Zhu X, Mitchell C, Hong Y, Hawkins W, Sasazuki T, Shirasawa S, Kozikowski AP, Dennis PA, Hagan MP, Grant S, **Dent P.** Activated forms of H-RAS and K-RAS differentially regulate membrane association of PI3K, PDK-1 and AKT and the impact of therapeutic kinase inhibitors on cell survival. *Molecular Cancer Therapeutics*, (2005) 4: 256-270.
25. **Dent P.**, Han SI, Mitchell C, Studer E, Yacoub A, Grandis J, Grant S, Krystal GW, Hylemon PB. Inhibition of insulin/IGF-1 receptor signaling enhances bile acid toxicity in primary hepatocytes. *Biochem Pharmacol*. 2005 Nov 25;70(11):1685-96.
26. Hawkins W, Mitchell C, Yacoub A, Grant S, **Dent P.** Transient exposure of mammary tumors to PD184352 and UCN-01 causes tumor cell death in vivo and prolonged suppression of tumor re-growth. *Cancer Biology and Therapy*, 2005. 4: 1275-1284.
27. Yacoub A, Hawkins W, Hanna D, Hong Y, Park MA, Grant M, Roberts JD, Curiel DT, Fisher PB, Valerie K, Grant S, Hagan MP, **Dent P.** Human chorionic gonadotropin (hCG) modulates prostate cancer cell survival after irradiation or HMG CoA reductase inhibitor treatment. *Mol Pharmacol*. 2007 Jan;71(1):259-75.
28. Yacoub A, Gilfor D, Hawkins W, Park MA, Hanna D, Hagan MP, Curiel DT, Fisher PB, Grant S, **Dent P.** MEK1/2 Inhibition Promotes Taxotere((R)) Lethality in Mammary Tumors in Vivo. *Cancer Biol Ther*. 2006 Oct;5(10):1332-9.
29. Yacoub A, Park MA, Hanna D, Hong Y, Mitchell C, Pandya AP, Harada H, Powis G, Chen CS, Koumenis C, Grant S, **Dent P.** OSU-03012 promotes caspase-independent but PERK-, cathepsin B-, BID-, and AIF-dependent killing of transformed cells. *Mol Pharmacol*. 2006 Aug;70(2):589-603.
30. Golding SE, Rosenberg E, Neill S, **Dent P.**, Povirk LF, Valerie K. Extracellular signal-related kinase positively regulates ataxia telangiectasia mutated, homologous recombination repair, and the DNA damage response. *Cancer Res*. 2007 Feb 1;67(3):1046-53.
31. Hagan MP, Yacoub A, **Dent P.** Radiation-induced PARP activation is enhanced through EGFR-ERK signaling. *J Cell Biochem*. 2007 Aug 15;101(6):1384-93.
32. Park MA, Yacoub A, Rahmani M, Zhang G, Hart L, Hagan M, Calderwood S, Sherman M, Koumenis C, Spiegel S, Chen CS, Graf M, Curiel D, Fisher P, Grant S, **Dent P.** OSU-03012 stimulates PERK-dependent increases in HSP70 expression, attenuating its lethal actions in transformed cells. *Mol Pharmacol*. 2008 Apr;73(4):1168-84.
33. Hamed, H, Hawkins, W, Mitchell, C, Gilfor, D, Zhang, G, Pei, XY, Dai, Y, Hagan, MP, Roberts, JD, Yacoub, A, Grant, S and **Dent, P.** Transient exposure of transformed cells to RAS / MEK inhibitors and UCN-01 causes cell death in vitro and in vivo. *Mol. Cancer Ther*. 2008 Mar;7(3):616-29.

Principal Investigator/Program Director (Last, First, Middle):

34. Yacoub, A, Hamed, H, Emdad, L, Dos Santos, W, Broaddus, WC, Ramakrishnan, V, Sarkar, D, Shah, K, Curiel, DT, Grant, S, Fisher, PB and **Dent, P**. MDA-7/IL-24 Plus Radiation Enhance Survival in Animals with Intracranial Invasive Primary Human GBM Tumors. *Cancer Biol and Ther*. 2008 Jun;7(6):917-33..
35. Zhang, G, Park, MA, Mitchell, C, Rahmani, M, Hamed, H, Martin, AP, Curiel, DT, Yacoub, A, Graf, M, Lee, M, Roberts, JD, Fisher, PB, Grant, S and **Dent, P**. Vorinostat and sorafenib synergistically kill tumor cells via FLIP suppression and CD95 activation. *Clin Cancer Res*. 2008 Sep 1;14(17):5385-99.
36. Martin, AP, Miller, A, Emad, L, Park, MA, Rahmani, M, Walker, T, Mitchell, C, Ihle, N, Hagan, MP, Yacoub, A, Powis, G, Fisher, PB, Grant, S and **Dent, P**. Lapatinib resistance in HCT116 cells is mediated by elevated MCL-1 expression, decreased BAK activation, and not by ERBB receptor mutation. *Mol. Pharm*. 2008 Sep;74(3):807-22.
37. Zhang G, Park MA, Mitchell C, Walker T, Hamed H, Studer E, Graf M, Rahmani M, Gupta S, Hylemon PB, Fisher PB, Grant S, **Dent P**. Multiple Cyclin Kinase Inhibitors Promote Bile Acid-induced Apoptosis and Autophagy in Primary Hepatocytes via p53-CD95-dependent Signaling. *J Biol Chem*. 2008 Sep 5;283(36):24343-58.
38. Lebedeva IV, Su ZZ, Vozhilla N, Chatman L, Sarkar D, **Dent P**, Athar M, Fisher PB. Mechanism of In vitro Pancreatic Cancer Cell Growth Inhibition by Melanoma Differentiation-Associated Gene-7/Interleukin-24 and Perillyl Alcohol. *Cancer Res*. 2008 Sep 15;68(18):7439-47
39. Singhal J, Singhal SS, Yadav S, Suzuki S, Warnke MM, Yacoub A, **Dent P**, Bae S, Sharma R, Awasthi YC, Armstrong DW, Awasthi S. RLIP76 in Defense of Radiation Poisoning. *Int J Radiat Oncol Biol Phys*. 2008 Oct 1;72(2):553-61.
40. Park MA, Zhang G, Martin AP, Hamed H, Mitchell C, Hylemon PB, Graf M, Rahmani M, Ryan K, Liu X, Spiegel S, Norris J, Fisher PB, Grant S, **Dent P**. Vorinostat and sorafenib increase ER stress, autophagy and apoptosis via ceramide-dependent CD95 and PERK activation. *Cancer Biol Ther*. 2008 Oct 12;7(10).
41. Rosato RR, Almenara JA, Maggio SC, Coe S, Atadja P, **Dent P**, Grant S. Role of histone deacetylase inhibitor-induced reactive oxygen species and DNA damage in LAQ-824/fludarabine antileukemic interactions. *Mol Cancer Ther*. 2008 Oct;7(10):3285-97.

C. RESEARCH SUPPORT

Ongoing Research Support

R01 DK52825 Dent (PI) 08/01/04-07/31/09
NIH/NIDDK

Signaling Pathways in Epithelial Cells

The aims of this project are to understand how bile acids modify the survival of primary cultures of hepatocytes when these cells are exposed to chemotherapeutic agents.

Role: PI

R01 CA108520 Dent (PI) 09/01/05-08/31/10
NIH/NCI

MDA-7/IL-24 and Free Radicals in Renal Cancer Therapy.

The major goals of this project are studying the role of agents that generate ROS in enhancing the toxicity of MDA-7 / IL-24 in kidney cancer. There is no overlap with any of the above applications.

Role: PI

P01 CA104177 P. Fisher (PI) 09/01/05-08/31/10
NIH/NCI

MDA-7 and Glioma Therapy.

The major goals of this project are studying the role of MDA-7 / IL-24 as a radiosensitizer in human glioma.

Role: PI, Project 2

Grant # N/A (Grant) 11/01/07 to 10/31/10

The V Foundation

Reestablishing the Leukemia Cell Death Program with Sorafenib and Bcl-2 Antagonists

Principal Investigator/Program Director (Last, First, Middle):

The goal of this project is to define further the mechanisms by which sorafenib interacts synergistically with Bcl-2 antagonists in leukemia, and to extend these findings to animal models and primary human leukemia cells. Role: Co-Investigator

R01 CA093738-06 (Grant) 08/01/07 – 07/31/12
NIH/NCI

NF-KappaB Inhibitors and Differentiation-Inducers in Leukemia

The major goal of this proposal is to develop a rational basis for a novel antileukemic strategy combining agents that inhibit the NF-kappaB pathway with clinically relevant differentiation-inducers (DIs).

Role: Co-Investigator

Completed Research Support

R01 CA88906 Dent (PI) 08/01/01-07/31/07
NIH/NCI

Radiosensitization of Carcinoma Cells by Inhibition of MAPK.

The central goal of this application is to develop a rational basis for employing agents that disrupt the mitogen activated protein kinase (MAPK) signaling pathway in order to potentiate the anti-tumor activity of ionizing radiation. This strategy is based upon recent evidence indicating that prolonged incubation of tumor cells with specific inhibitors of the MAPK pathway interact synergistically with radiation to initiate the apoptotic protease cascade several days after exposure, and overcome blockade of the cell death pathway conferred by over expression of Bcl-2. We postulate that this phenomenon stems from perturbations in cell cycle regulation and a reduced ability to survive radiation-induced DNA damage. The studies in this proposal neither examine the role of H-RAS and K-RAS signaling in the multiple signaling responses of tumor cells, nor the impact of RAS signaling on the behavior of tumor cells after irradiation.

Role: PI

P01 CA72955 K. Valerie (PI) 07/01/03-06/30/08
NIH/NCI

Genetic Modulation of RAS Dependent Radiation Responses.

The major goals of this project are studying the role of RAS oncogenes as an immediate early response to radiation and differential control of growth regulatory pathways and cellular radiosensitivity. There is no overlap with the current application.

Role: PI, Project 2

R01 CA100866-04 Grant (PI) 05/01/03 to 10/31/08
NIH/NCI

Checkpoint abrogation and MEK1/2 inhibition in myeloma

The major goal of this project is to develop a novel strategy for multiple myeloma treatment employing checkpoint abrogators in combination with inhibitors of the MEK1/2/ERK1/2 pathway. The present application represents a competitive renewal of this award Role: Co-Investigator