© PAUL S. ANDERSON 2013

INTRAVENOUS ASCORBATE AND ONCOLOGIC AGENTS

Updated Data Review and Policies for concurrent use at Anderson Medical Specialty Associates, Southwest College of Naturopathic Medicine Research Institute and Medical Center and Bastyr University Clinical Research Center

Paul S. Anderson

05/01/2013

© Paul S. Anderson – All rights reserved – Reproduction and redistribution only allowed with proper attribution.

Abstract:

Intravenous application of ascorbic acid (IVAA) has a long history in adjunctive oncology communities. Its use has stimulated much debate regarding efficacy, safety and appropriate inclusion in oncologic practice. The potential for both antagonistic and synergistic interactions between IVAA and chemotherapies or radiation has existed for some time as an unanswered or confusing question in the naturopathic and allopathic oncology community. The purpose of this publication is to summarize and update the state of understanding of this complicated topic for clinicians employing either standard or integrative oncology care.

INTRAVENOUS ASCORBATE AND ONCOLOGIC AGENTS

Introduction:

Intravenous ascorbate has been used in oncology practice by naturopathic and alternative allopathic physicians for decades. Published data regarding this therapy shows that it continues to be one of the most commonly employed alternative IV therapies. This popularity has both stimulated awareness of this therapy and concern regarding not only the safety and efficacy of IVAA in the oncology patient but also for the potential of antagonistic reactions with standard therapies.

Publications regarding the postulated mechanisms of action, safety profile, pharmacokinetics and pharmacodynamics were sparse for many years. This led to a highly varied understanding as well as application of IVAA in oncology. In the past five, and especially two, years published data has supported many of the postulated actions of IVC, its pharmacokinetics and dynamics and particularly how those kinetic and dynamic properties can antagonize or synergize the effects of various chemotherapy agents as well as radiation therapies. This data will be presented and summarized.

The goal of this publication is to summarize and update our understanding of the science and practice surrounding this popular and potentially powerful therapeutic agent and how it may interact with standard oncology therapies.

The initial presentation of this basic data was made in February 2013 and the appropriate citation is:

Anderson P. "Intravenous Ascorbic Acid and Oncology Agents." Scientific Presentation. Oncology Association of Naturopathic Physicians Second Annual Meeting. Phoenix, Arizona. February, 2013.

Format:

Agents are grouped by commonly accepted pharmacologic mechanisms. Each group will have footnotes germane to any data currently known regarding ascorbate and that agent. Additionally a grid denoting the reference number and type of response and data set will precede each set of footnotes.

Agents with no currently available published data will have the notation "No direct data" following their name.

Policy:

Agents with positive data, including those with limited negative data combined with multiple positive references, are considered safe to administer in conjunction with ascorbic acid for IV use. Those with no direct data but positive data for other agent class members are considered safe for concurrent use as well. Those with negative data have notations based on published pharmacokinetic data, which outline the specific timing for which intravenous ascorbic acid use is compatible.

Concurrent administration includes administration as close as the same day as the agent mentioned.

© 2013 Paul S. Anderson – All Rights Reserved

CONTENTS:

© 2013 Paul S. Anderson – All Rights Reserved

© 2013 Paul S. Anderson – All Rights Reserved

© 2013 Paul S. Anderson – All Rights Reserved

© 2013 Paul S. Anderson – All Rights Reserved

© 2013 Paul S. Anderson – All Rights Reserved

Chemotherapy Types:

I. Polyfunctional alkylating agents

A. Triazines:

Dacarbazine (DTIC)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

1. Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA. Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. Nutr Cancer. 1994;22(3):233-45. PMID: 7877893

Temozolomide (Temodar)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			[1]
Positive Response			

1. Bael TE, Peterson BL, Gollob JA. Phase II trial of arsenic trioxide and ascorbic acid with temozolomide in patients with metastatic melanoma with or without central nervous system metastases. Melanoma Res. 2008 Apr;18(2):147-51. doi: 10.1097/CMR.0b013e3282f2a7ae. PMID: 18337652

B. Nitrosoureas :

Lomustine (CCNU)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

1. Prasad K, Sinha P, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. Proc Natl Acad Sci USA 1979;76:829–32.

© 2013 Paul S. Anderson – All Rights Reserved

Carmustine (BCNU)

Potential class synergy with ascorbate suggested in:

Cullen J. Ascorbate induces autophagy in pancreatic cancer. Autophagy. 2010 April ; 6(3): 421–422.

Streptozocin (STZ, Zanosar) **[No direct data]**

Semustine (methyl CCNU) **[No direct data]**

C. Nitrogen mustards:

Melphalan (Alkeran)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2	

1. Gokhalé P, Patel T, Morrison MJ, Vissers MC. The effect of intracellular ascorbate on the susceptibility of HL60 and Jurkat cells to chemotherapy agents. Apoptosis. 2006 Oct;11(10):1737-46. PMID: 16951922

2. Verrax J, Dejeans N, Sid B, Glorieux C, Calderon PB. Intracellular ATP levels determine cell death fate of cancer cells exposed to both standard and redox chemotherapeutic agents. Biochem Pharmacol. 2011 Dec 1;82(11):1540-8. doi: 10.1016/j.bcp.2011.07.102. Epub 2011 Aug 9. PMID: 21843513

Mechlorethamine (Mustargen) **[No direct data]:**

D. Oxazaphosphorines

Cyclophosphamide (Cytoxan)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1	2

© 2013 Paul S. Anderson – All Rights Reserved

Cyclophosphamide (Cytoxan) - continued

1. Nichold BM et al. The effects of cyclophosphamide alone and in combination with ascorbic acid against murine ascites Dalton's lymphoma. Indian J Pharmacol 2006; 38:4:260-265

2. Taper H, de Gerlache J, Lans M, Roberfroid M. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. Int J Cancer 1987;40:575–9.

Ifosphamide (Mitoxana and Ifex)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response	[1,2]		

1. Multhoff G, et.al. Differential Effects of Ifosfamide on the Capacity of Cytotoxic T Lymphocytes and Natural Killer Cells to Lyse Their Target Cells Correlate With Intracellular Glutathione Levels .Blood, Vol 85, No 8 (April 15). 1995: pp 2124-2131

2. This effect via the same mechanism mentioned here: Bahlis N, McCafferty-Grad J, Jordan-McMurry I, Neil J, ReisI, Kharfan-Dabaja M, et al. Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. Clin Cancer Res 2002;8:3658–68.

Chlorambucil (Leukeran) **[No direct data]:**

Thiopeta (Thioplex) **[No direct data]:**

Trofosfamide (Ixoten) **[No direct data]:**

E. Alkyl sulfonates:

Busulfan (Myleran) **[No direct data]:**

© 2013 Paul S. Anderson – All Rights Reserved

F. Other Alkylating Drugs

Procarbazine (Matulane)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response			1

1. Taper H, de Gerlache J, Lans M, Roberfroid M. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. Int J Cancer 1987;40:575–9.

Altretamine (Hexalen) **[No direct data]:**

II. Platinums

Cisplatin (Platinol)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,4,5,6,7	8,9

1. Kurbacher C, Wagner U, Kolster B, Andreotti P, Krebs D, Bruckner H. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 1996;103:183–9.

2. Reddy V, Khanna N, Singh N, Vitamin. C augments chemotherapeutic response of cervical carcinoma HeLa cells by stabilizing P53. Biochem Biophys Res Commun 2001;282:409–15.

3. Abdel-Latiff MM et al. Vitamin C enhances chemosensitization of esophageal cancer cells in vitro. J Chemother 2005; 17:5:539-49 vitamin C enhances the antitumor activity of 5-Fu and cisplatin, in part by inhibiting translocation of NF-kappaB and AP-1, and sensitizes cancer cells to drug-induced cell death

4. Reddy VG et al. Vitamin C augments chemotherapeutic response of cervical carcinoma HeLa cells by stabilizing p53. Biochem Biophys Res Commun 2001; 282:2:409-15 …… then sensitized HeLa cells to cell-cycle arrest, cell death/apoptosis induced by cisplatin, and etoposide

© 2013 Paul S. Anderson – All Rights Reserved

5. Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA. Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. Nutr Cancer. 1994;22(3):233-45. PMID: 7877893

6. Sarna S et al. Chemo-immunotherapeutical studies on Dalton's lymphoma mice using cisplatin and ascorbic acid: synergistic antitumor effect in vivo and in vitro. Arch Immunol Ther Exp (Warsz) 1993; 41:5-6:327-33

7. Prasad SB et al. Use of subtherapeutical dose of cisplatin and Vitamin C against murine Dalton's lymphoma. Pol J Pharmacol Pharm 1992; 44:4:383-91

8. Yam D et al. Suppression of tumor growth and metastasis by dietary fish oil combined with vitamins E and C and cisplatin. Cancer Chemother Pharmacol 2001; 47:1:34-40

9. Weijl NI et al. Supplementation with antioxidant micronutrients and chemotherapy-induced toxicity in cancer patients treated with cisplatin-based chemotherapy: a randomised, double-blind, placebo-controlled study. Eur J Cancer 2004;40:10:1713-23.

Carboplatin (Paraplatin and Paraplatin-AQ)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response			1,2,3

1. Sullivan, G. et. al. (2011, November). Prospective Randomized Phase I/IIa Pilot Trial to Assess Safety and Benefit Administering High Dose Intravenous Ascorbate in Combination with Chemotherapy in Newly Diagnosed Advanced Stage III or Stage IV Ovarian Cancer. Moderated Abstract [6] presented at the Society for Integrative Oncology, Cleveland, OH.

2. Ma, Y. Drisko, J. Poilreddy, K. (2011, November). Synergistic Effects of Ascorbate with Carboplatin against Human Ovarian Cancer in Vitro and in Vivo. Moderated Abstract [20] presented at the Society for Integrative Oncology, Cleveland, OH.

3. Pathak A, Bhutani M, Guleria R, Bal S, Mohan A, Mohanti B, et al. Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr 2005;24:16–21.

Oxaliplatin (Eloxatin) **[No direct data]:**

© 2013 Paul S. Anderson – All Rights Reserved

III. Antimetabolites

A. Purine antagonists:

Mercaptopurine (6-MP) **[No direct data]:**

Thioguanine (6-TG) **[No direct data]:**

Fludarabine Phosphate (Fludara, Oforta) **[No direct data]:**

Cladribine (Leustatin) **[No direct data]:**

Pentostatin (Nipent) **[No direct data]:**

B. Pyrimidine antagonists:

Fluorouracil (5-FU)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,4	5

1. Fromberg, A, et.al. Ascorbate Exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol, 67:1157-1166, 2011. DOI 10.1007/s00280-010-1418-6 (Springer online).

2. Prasad K, Sinha P, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. Proc Natl Acad Sci USA 1979;76:829–32.

3. Nagy B et al. Chemosensitizing effect of Vitamin C in combination with 5-fluorouracil in vitro. In Vivo 2003; 17:3:289-92

4. Abdel-Latiff MM et al. Vitamin C enhances chemosensitization of esophageal cancer cells in vitro. J Chemother 2005; 17:5:539-49 vitamin C enhances the antitumor activity of 5-Fu and cisplatin, in part by inhibiting translocation of NF-kappaB and AP-1, and sensitizes cancer cells to drug-induced cell death

5. 5-FU ASC with K3 Positive in vivo: Taper H, de Gerlache J, Lans M, Roberfroid M. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. Int J Cancer 1987;40:575–9.

© 2013 Paul S. Anderson – All Rights Reserved

Gemcitabine (Gemzar)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,4,5	5,6,7

1. Monti DA, et. al. Phase I evaluation of intravenous ascorbic Acid in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. PLoS One. 2012;7(1):e29794. Epub 2012 Jan 17.

2. Espey MG, Chen P, Chalmers B, Drisko J, Sun AY, Levine M, Chen Q. Pharmacologic ascorbate synergizes with gemcitabine in pre-clinical models of pancreatic cancer. Free Radic. Biol. Med. 2011; 51

3. Martinotti S, Ranzato E, Burlando B. In vitro screening of synergistic ascorbate-drug combinations for the treatment of malignant mesothelioma. Toxicol In Vitro. 2011 Dec;25(8):1568-74. Epub 2011 May 27. PMID:21645609

4. Joseph J. Cullen, Douglas R. Spitz, and Garry R. Buettner . Comment on "Pharmacologic ascorbate synergizes with Gemcitabine in pre-clinical models of pancreatic cancer" i.e. All we are saying is, give C a chance. Free Radic Biol Med. 2011 June 15; 50(12): 1726–1727. doi:10.1016/j.freeradbiomed.2011.03.030.

5. Ma, Y. et. al. (2011, November). Pharmacologic Ascorbate Synergizes with Gemcitabine in Pre-Clinical Models of Pancreatic Cancer. Moderated Abstract [19] presented at the Society for Integrative Oncology, Cleveland, OH.

6. Martinotti S, Ranzato E, Burlando B. In vitro screening of synergistic ascorbate-drug combinations for the treatment of malignant mesothelioma. Toxicol In Vitro. 2011 Dec;25(8):1568-74. Epub 2011 May 27. PMID: 21645609

7. Kassouf W, Highshaw R, Nelkin G, Dinney C, Kamat A, Vitamins C. K3 sensitize human urothelial tumors to gemcitabine. J Urol 2006;176:1642–7.

Capecitabine (oral pro-5-Fluorouracil) **[No direct data]:**

Cytarabine (ARA-C) **[No direct data]:**

Azacitidine (Vidaza) **[No direct data]:**

© 2013 Paul S. Anderson – All Rights Reserved

C. Competitive inhibitor of dihydrofolate reductase:

Methotrexate (Trexall)

	Basic Science	In Vitro	In Vivo
Negative Response		[1]	
Neutral Response			
Positive Response			

1. Prasad K, Sinha P, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. Proc Natl Acad Sci USA 1979;76:829–32.

IV. Plant alkaloids

A. Camptothecins:

Topotecan (Hycamtin) **[No direct data]:**

Irinotecan (Camptosar)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

1. Fromberg, A, et.al. Ascorbate Exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol, 67:1157-1166, 2011. DOI 10.1007/s00280-010-1418-6 (Springer online).

© 2013 Paul S. Anderson – All Rights Reserved

B. Epipodophyllotoxins:

Etoposide (VP-16,VePe-sid)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2	

1. Gokhalé P, Patel T, Morrison MJ, Vissers MC. The effect of intracellular ascorbate on the susceptibility of HL60 and Jurkat cells to chemotherapy agents. Apoptosis. 2006 Oct;11(10):1737-46. PMID: 16951922

2. Reddy VG et al. Vitamin C augments chemotherapeutic response of cervical carcinoma HeLa cells by stabilizing p53. Biochem Biophys Res Commun 2001; 282:2:409-15

Teniposide (Vumon) **[No direct data]:**

C. Non- Epipodophyllotoxins:

Amsacrine (Amsidine) **[No direct data]:**

Mitoxantrone (Novantrone) **[No direct data]:**

D. Vinca Alkaloids:

Vinblastine (Velban)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1	

1. Taper H, de Gerlache J, Lans M, Roberfroid M. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. Int J Cancer 1987;40:575–9.

© 2013 Paul S. Anderson – All Rights Reserved

Vincristine (Oncovin)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,4,5	

1. Chiang C, Song E, Yang V, Chao C. Ascorbic acid increases drug accumulation and reverses vincristine resistance of human non-small-cell lung-cancer cells. Biochem J 1994;301(Pt 3):759–64.

2. Song E, Yang V, Chiang C, Chao C. Potentiation of growth inhibition due to vincristine by ascorbic acid in a resistant human non-small cell lung cancer cell line. Eur J Pharmacol 1995;292:119–25.

3. Pathak AK et al. Potentiation of the effect of paclitaxel and carboplatin by antioxidant mixture on human lung cancer h520 cells. J Am Coll Nutr. 2002 Oct;21:5:416-21.

4. Pathak A, Bhutani M, Guleria R, Bal S, Mohan A, Mohanti B, et al. Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr 2005;24:16–21.

5. Taper HS et al. Non-toxic sensitization of cancer chemotherapy by combined Vitamin C and K3 pretreatment in a mouse tumor resistant to oncovin. Anticancer Res. 1992; 5:1651-4.

Vinorelbine (Navelbine) **[No direct data]:**

E. Taxanes:

Paclitaxel (Taxol)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,4,5,6	7

1. Kurbacher C, Wagner U, Kolster B, Andreotti P, Krebs D, Bruckner H. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 1996;103:183–9.

© 2013 Paul S. Anderson – All Rights Reserved

Paclitaxel (Taxol) - continued

2. Pathak AK et al. Potentiation of the effect of paclitaxel and carboplatin by antioxidant mixture on human lung cancer h520 cells. J Am Coll Nutr. 2002 Oct;21:5:416-21.

3. Pathak A, Bhutani M, Guleria R, Bal S, Mohan A, Mohanti B, et al. Chemotherapy alone vs. chemotherapy plus high dose multiple antioxidants in patients with advanced non small cell lung cancer. J Am Coll Nutr 2005;24:16–21.

4. D'Souza GG, Wang T, Rockwell K, Torchilin VP. Surface modification of pharmaceutical nanocarriers with ascorbate residues improves their tumor-cell association and killing and the cytotoxic action of encapsulated paclitaxel in vitro. Pharm Res. 2008 Nov;25(11):2567-72. Epub 2008 Jul 11. PMID: 18618230

5. Sawant RR, Vaze OS, Rockwell K, Torchilin VP. Palmitoyl ascorbate-modified liposomes as nanoparticle platform for ascorbate-mediated cytotoxicity and paclitaxel co-delivery. Eur J Pharm Biopharm. 2010 Aug;75(3):321-6. Epub 2010 Apr 28. PMID: 20433922

6. Sawant RR, Vaze OS, Wang T, D'Souza GG, Rockwell K, Gada K, Khaw BA, Torchilin VP. Palmitoyl ascorbate liposomes and free ascorbic acid: comparison of anticancer therapeutic effects upon parenteral administration. Pharm Res. 2012 Feb;29(2):375-83. Epub 2011 Aug 16. PMID: 21845505

7. Sullivan, G. et. al. (2011, November). Prospective Randomized Phase I/IIa Pilot Trial to Assess Safety and Benefit Administering High Dose Intravenous Ascorbate in Combination with Chemotherapy in Newly Diagnosed Advanced Stage III or Stage IV Ovarian Cancer. Moderated Abstract [6] presented at the Society for Integrative Oncology, Cleveland, OH.

Docetaxel (Taxotere)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

1. Fromberg, A, et.al. Ascorbate Exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol, 67:1157-1166, 2011. DOI 10.1007/s00280-010-1418-6 (Springer online).

© 2013 Paul S. Anderson – All Rights Reserved

F. Other mitotic inhibitors - Epothilones:

Ixabepilone (Ixempra) **[No direct data]:**

Estramustine (Emcyt) **[No direct data]:**

V. Polyfunctional Agent

Arsenic trioxide (Arsenox)

	Basic Science	In Vitro	In Vivo
Negative Response		1	
Neutral Response			
Positive Response	2	3,4,5	6

1. Karasavvas N, Ca´rcamo J, Stratis G, Golde D. Vitamin C protects HL60 and U266 cells from arsenic toxicity. Blood 2005;105:4004–12.

2. Lu, J.; Chew, E. H.; Holmgren, A. (2007). "Targeting thioredoxin reductase is a basis for cancer therapy by arsenic trioxide". Proc. Natl. Acad. Sci. U.S.A. 104 (30): 12288–12293. doi:10.1073/pnas.0701549104. PMC 1940330. PMID 17640917. //www.ncbi.nlm.nih.gov/pmc/articles/PMC1940330/.

3. Bahlis N, McCafferty-Grad J, Jordan-McMurry I, Neil J, ReisI, Kharfan-Dabaja M, et al. Feasibility and correlates of arsenic trioxide combined with ascorbic acid-mediated depletion of intracellular glutathione for the treatment of relapsed/refractory multiple myeloma. Clin Cancer Res 2002;8:3658–68.

4. Dalton W. The Biology Behind: Targeting the Mitochondria: An Exciting New Approach to Myeloma Therapy - Commentary re: N. J. Bahlis et al., Feasibility and Correlates of Arsenic Trioxide Combined with Ascorbic Acid-mediated Depletion of Intracellular Glutathione for the Treatment of Relapsed/Refractory Multiple Myeloma. Clin. Cancer Res., 8: 3658-3668, 2002. Clinical Cancer Research 3643 Vol. 8, 3643–3645, December 2002

5. Grad J, Bahlis N, Reis I, OshiroM, DaltonW, Boise L. Ascorbic acid enhances arsenic trioxide-induced cytotoxicity in multiple myeloma cells. Blood 2001;98:805–13.

6. Arsenic trioxide induced apoptosis was not enhanced by ascorbic acid in normal cells, suggesting that this combination may be selectively toxic to some malignant cells – Dai, J.; Weinberg, R. S.; Waxman, S.; Jing, Y. (January 1999). "Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system". Blood 93 (1): 268–277. PMID 9864170. http://bloodjournal.hematologylibrary.org/cgi/content/abstract/93/1/268.

© 2013 Paul S. Anderson – All Rights Reserved

VI. Antibiotics

A. Anthracyclines:

Doxorubicin (Adriamycin, Rubex, Doxil)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,4,5,6,7	8

1. Kurbacher C, Wagner U, Kolster B, Andreotti P, Krebs D, Bruckner H. Ascorbic acid (vitamin C) improves the antineoplastic activity of doxorubicin, cisplatin, and paclitaxel in human breast carcinoma cells in vitro. Cancer Lett 1996;103:183–9.

2. Wells WW et al. Ascorbic acid and cell survival of Adriamycin resistant and sensitive MCF-7 breast tumor cells. Free Radic Biol Med 1995; 18:4:699-708

3. Marian M et al. Potentiation of the biological activities of daunomycin and Adriamycin by ascorbic acid and dimethylsulfoxide. Experientia 1982. 38:5:573-4

4. Shimpo K et al. Ascorbic acid and adriamycin toxicity. Am J Clin Nutr. 1991;54:6 Suppl:1298S-1301S

5. Woz'niak G et al. Influence of vitamins C and E on cytotoxic activity of adriamycin in chosen cell cultures. Acta Pol Pharm. 2002;59:1:31-5.

6. Casciari JJ, Riordan NH, Schmidt TL, Meng XL, Jackson JA and Riordan HD. Cytotoxicity of ascorbate, lipoic acid, and other antioxidants in hollow fibre in vitro tumours. British Journal of Cancer (2001) 84(11), 1544–1550 doi: 10.1054/ bjoc.2001.1814

7. Costa WF, Nepomuceno JC. Protective effects of a mixture of antioxidant vitamins and minerals on the genotoxicity of doxorubicin in somatic cells of Drosophila melanogaster. Environ Mol Mutagen. 2006 Jan;47(1):18-24. PMID: 16010670

8. Taper H, de Gerlache J, Lans M, Roberfroid M. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. Int J Cancer 1987;40:575–9.

© 2013 Paul S. Anderson – All Rights Reserved

Daunorubicin (DaunoXome)and Epirubicin (Ellence)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2	

1. Marian M et al. Potentiation of the biological activities of daunomycin and Adriamycin by ascorbic acid and dimethylsulfoxide. Experientia 1982. 38:5:573-4

2. Fromberg, A, et.al. Ascorbate Exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol, 67:1157-1166, 2011. DOI 10.1007/s00280-010-1418-6 (Springer online).

Mitoxantrone (Novantrone) **[No direct data]:**

Idarubincin (Idamycin) **[No direct data]:**

B. Polypeptide:

Dactinomycin / Actinomycin-D (Cosmegen) **[No direct data]:**

C. DNA Crosslink alkylator:

Mitomycin (Mutamycin)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2	

1. Kammerer C, Getoff N. Synergistic Effect of Dehydroascorbic Acid and Mixtures with Vitamin E and ,-Carotene on Mitomycin C Efficiency Under Irradiation In Vitro. in vivo 18: 795-798 (2004)

2. Kammerer C et al. Enhancement of mitomycin C efficiency by Vitamin C, E-acetate and beta-carotene under irradiation. A study in vitro. Anticancer Res 1999; 19:6B:5319-21

© 2013 Paul S. Anderson – All Rights Reserved

D. Glycopeptide:

Bleomycin (Blenoxane)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

1. Prasad K, Sinha P, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. Proc Natl Acad Sci USA 1979;76:829–32.

E. RNA Synthesis inhibitor:

Plicamycin (Mithramycin) **[No direct data]:**

VII. Hormonal agents

A. Anti-estrogens:

Tamoxifen (Nolvadex)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response	[1]		
Positive Response		[2]	

1. Garba, Nana Aisha, "The Role of Redox Signaling in the Molecular Mechanism of Tamoxifen Resistance in Breast Cancer" (2012). FIU Electronic Theses and Dissertations. Paper 551.

© 2013 Paul S. Anderson – All Rights Reserved

2. Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA. Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. Nutr Cancer. 1994;22(3):233-45. PMID: 7877893

Fulvestrant (Faslodex) **[No direct data]:**

Toremifene (Fareston) **[No direct data]:**

B. Aromatase inhibitors:

Exemestane (Aromasin)

	Basic Science	In Vitro	In Vivo
Negative Response	[1]		
Neutral Response			
Positive Response			

1. Bharath Konda, Ravi N. Tiwari, and Harshal Fegade. Development and Validation of Stability Indicating Method for the Determination of Exemestane by Reverse Phase High Performance Liquid Chromatography .Journal of Chromatographic Science, Vol. 49, September 2011

[At most upon coadministration of HDIVC with daily po drug there would be a 6-12 hour window of possible inhibition.] 2013 Datapharm Communications Ltd.http://www.medicines.org.uk/emc/medicine /2484/SPC

Aminoglutethimide (Cytadren) **[No direct data]:**

Anastrozole (Arimidex) **[No direct data]:**

letrozole (Femara) **[No direct data]:**

C. Progestins:

Megestrol acetate (Megace) **[No direct data]:**

© 2013 Paul S. Anderson – All Rights Reserved

D. Anti-androgens:

Bicalutamide (Casodex) **[No direct data]:**

Flutamide (Eulexin) **[No direct data]:**

Nilutamde (Nilandron) **[No direct data]:**

E. GnRH / LHRH agonists or analogs:

Leuprolide (Lupron) **[No direct data]:**

Goserelin (Zoladex) **[No direct data]:**

IIX. Multi Agent Therapies

A. **ASC and FOLFIRI**

FOL= Leucovorin Calcium (Folinic Acid), F= Fluorouracil, IRI= Irinotecan Hydrochloride

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

1. Frömberg A, Gutsch D, Schulze D, Vollbracht C, Weiss G, Czubayko F, Aigner A. Ascorbate exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol. 2011 May;67(5):1157-66. Epub 2010 Aug 8.

B. **ASC and FOLFOX**

FOL– Folinic acid (leucovorin) F – Fluorouracil (5-FU) OX – Oxaliplatin (Eloxatin)

As Ascorbate is not detrimental to the efficacy of FOLFIRI [1] and the major change in therapy between FOLFIRI and FOLFOX is a Platin (instead of a tecan), and as ascorbate appears synergistic with Platins [2] it would be reasonable to assume that Ascorbate would only improve efficacy of FOLFOX or FOLFIRI.

[1] Frömberg A, Gutsch D, Schulze D, Vollbracht C, Weiss G, Czubayko F, Aigner A.. Ascorbate exerts anti-proliferative effects through cell cycle inhibition and sensitizes tumor cells towards cytostatic drugs. Cancer Chemother Pharmacol. 2011 May;67(5):1157-66. Epub 2010 Aug 8.

© 2013 Paul S. Anderson – All Rights Reserved

[2] Sung Ho An, Jung Hoon Kang, Dong Heui Kim2 & Myeong Seon Lee. Vitamin C increases the apoptosis via up-regulation p53 during cisplatin treatment in human colon cancer cells. BMB reports 2011; 44(3): 211-216]

IX. Miscellaneous anticancer drugs

Hydroxyurea (Hydrea)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2	

1. Koç A, Wheeler LJ, Mathews CK, Merrill GF (January 2004). "Hydroxyurea arrests DNA replication by a mechanism that preserves basal dNTP pools". J. Biol. Chem. 279 (1): 223–30. doi:10.1074/jbc.M303952200. PMID 14573610. http://www.jbc.org/cgi/pmidlookup?view=long&pmid=14573610.
2. 5-FU, Cyclophosphamide, Procarbazin, Asparginase, Vinblastine, Adriamycin: ASC with K3 Positive in vivo: Taper H, de Gerlache J, Lans M, Roberfroid M. Non-toxic potentiation of cancer chemotherapy by combined C and K3 vitamin pre-treatment. Int J Cancer 1987;40:575–9.

Asparaginase (El-spar) **[No direct data]:**

Mitotane (Lysodren) **[No direct data]:**

X. Targeted therapies

A. BCR-ABL tyrosine kinase inhibitor:

Imatinib (Gleevec) – Positive in vitro

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1	

1. Tarumoto T et al. Ascorbic acid restores sensitivity to imatinib via suppression of Nrf2-dependent gene expression in the imatinib-resistant cell line. Exp Hematol 2004; 32:4:375-81

© 2013 Paul S. Anderson – All Rights Reserved

B. Inhibitor of cellular signaling by targeting multiple receptor tyrosine kinases; all receptors for (PDGF-Rs) and (VEGFRs):

Sunitinib (Sutent) **[No direct data]:**

C. Proteasome inhibitor:

- Bortezomib (Velcade)

Concern: <u>Potential inhibition in vitro by ascorbate [1]</u>

IVC Administration Note:

Given the pharmacokinetics of (Maximum proteasome inhibition occurs within 1 hour, and most effective inhibition wanes throughout the 12-24 hours following administration[2]) and IV Ascorbate we (BORC and AMSA Tx guidelines) recommend IVC as appropriate the day prior to, or 24 - 48 hours following bortezomib dosing.

Oral ascorbate?

Conclusions: No antagonism of bortezomib is seen in preclinical in vivo experiments, where EGCG or ascorbic acid plasma concentrations are commensurate with dietary or supplemental intake. The data suggest that patients receiving bortezomib treatment do not need to avoid normal dietary consumption of green tea, vitamin C-containing foods, or EGCG or vitamin C dietary supplements. [3]

1. G Perrone, T Hideshima, H Ikeda, Y Okawa, E Calabrese, G Gorgun, L Santo, D Cirstea, N Raje, D Chauhan, M Baccarani, M Cavo and K C Anderson. Ascorbic acid inhibits antitumor activity of bortezomib in vivoVitamin C supplement in multiple myeloma. Leukemia 23, 1679-1686 (September 2009) doi:10.1038/leu.2009.83

2. Schwartz R, Davidson T. Pharmacology, pharmacokinetics, and practical applications of bortezomib. Oncology (Williston Park). 2004 Dec;18(14 Suppl 11):14-21.

3. Bannerman B, et.al. Preclinical evaluation of the antitumor activity of bortezomib in combination with vitamin C or with epigallocatechin gallate, a component of green tea. Cancer Chemother Pharmacol (2011) 68:1145–1154 DOI 10.1007/s00280-011-1591-2

- Bortezomib, Ascorbic acid and Melphalan (BAM) therapy: Positive synergy

1. Berenson JR, Yellin O, Woytowitz D, Flam MS, Cartmell A, Patel R, Duvivier H, Nassir Y, Eades B, Abaya CD, Hilger J, Swift RA. Bortezomib, ascorbic acid and melphalan (BAM) therapy for

© 2013 Paul S. Anderson – All Rights Reserved

patients with newly diagnosed multiple myeloma: an effective and well-tolerated frontline regimen. Eur J Haematol. 2009 Jun;82(6):433-9. Epub 2009 Feb 17.

D. VEGF Inhibitors:

Bevacizumab (Avastin)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response	1,2	3,4	

1. Nespereira, B. et.al. Vitamins C and E downregulate vascular VEGF and VEGFR-2 expression in apolipoprotein-E-deficient mice. Atherosclerosis. 2003 Nov;171(1):67-73. PMID: 14642407
2. Kim HN. Et.al. Vitamin C down-regulates VEGF production in B16F10 murine melanoma cells via the suppression of p42/44 MAPK activation. J Cell Biochem. 2011 Mar;112(3):894-901. doi: 10.1002/jcb.22997. PMID: 21328462
3. Pathi S, et. al. PHARMACOLOGIC DOSES OF ASCORBIC ACID REPRESS SPECIFICITY PROTEIN (Sp) TRANSCRIPTION FACTORS AND Sp-REGULATED GENES IN COLON CANCER CELLS.Nutr Cancer. 2011 ; 63(7): 1133–1142. doi:10.1080/01635581.2011.605984.
4. Mikirova et.al. Anti-angiogenic effect of high doses of ascorbic acid. Journal of Translational Medicine 2008, 6:50 doi:10.1186/1479-5876-6-50

E. Multi target - Inhibitor of VEGFR phosphorylation, glycosylation, mTOR signaling:

Itraconazole (Sporanox, Onmel) **[No direct data]:**

© 2013 Paul S. Anderson – All Rights Reserved

F. EGFR Inhibitors:

Tyrosine kinase inhibitors of EGFR.

Erlotinib (Tarceva)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		2	1

1. Monti DA, et. al. Phase I evaluation of intravenous ascorbic Acid in combination with gemcitabine and erlotinib in patients with metastatic pancreatic cancer. PLoS One. 2012;7(1):e29794. Epub 2012 Jan 17.

2. Pathi S, et. al. PHARMACOLOGIC DOSES OF ASCORBIC ACID REPRESS SPECIFICITY PROTEIN (Sp) TRANSCRIPTION FACTORS AND Sp-REGULATED GENES IN COLON CANCER CELLS.Nutr Cancer. 2011 ; 63(7): 1133–1142. doi:10.1080/01635581.2011.605984.

Gefitinib (Iressa) **[No direct data]:**

Vandetanib (Caprelesa) **[No direct data]:**

Lapatinib (Tykerb) **[No direct data]:**

EGFR competitive receptor binders.

Conatumumab - TRAIL Ligand

	Basic Science	In Vitro	In Vivo
Negative Response		1	
Neutral Response			
Positive Response			

© 2013 Paul S. Anderson – All Rights Reserved

Negative in vitro study with cells preloaded with ASC:

1. Perez-Cruz I, Ca´rcamo J, Golde D. Caspase-8 dependent TRAIL-induced apoptosis in cancer cell lines is inhibited by vitamin C and catalase. Apoptosis 2007;12:225–34.

Panitumumab (Vectibix) **[No direct data]:**

Cetuximab (Erbitux) **[No direct data]:**

(In development: Zalutumumab, Nimotuzumab, and Matuzumab.) **[No direct data]:**

G. Specific monoclonal antibody therapy:

Rituximab (Rituxan) **[No direct data]:**

Alemtuzumab (Campath) **[No direct data]:**

H. mTOR inhibitors:

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response	1,2		

1. Cullen J. Ascorbate induces autophagy in pancreatic cancer. Autophagy. 2010 April ; 6(3): 421–422.

2. Chen L, et. al. Hydrogen peroxide inhibits mTOR signaling by activation of AMPKα leading to apoptosis of neuronal cells.Lab Invest. 2010 May ; 90(5): 762–773. doi:10.1038/labinvest.2010.36.

Temsirolimus (Torisel) **[No direct data]:**

© 2013 Paul S. Anderson – All Rights Reserved

Everolimus (Afinitor) **[No direct data]:**

(Ridaforolimus – in development) **[No direct data]:**

XI. Non-specific immunotherapies and adjuvants:

BCG **[No direct data]:**

Interleukin-2 (Aldesleukin)

	Basic Science	In Vitro	In Vivo
Negative Response			[1]
Neutral Response			
Positive Response			

IVC Lowers IL-2 levels [1] – Use apart from IL-2 Tx t1/2 is roughly 7 minutes [2] and clearance is practically complete at 45 minutes.

1. Mikirova N, et. Al. Effect of High Dose Intravenous Vitamin C on Inflammation in Cancer Patients. Journal of Translational Medicine 2012, 10:189. DOI 10.1186/1479 – 5876-10-189

2. Lotze MT, et.al. In vivo administration of purified human interleukin 2. II. Half life, immunologic effects, and expansion of peripheral lymphoid cells in vivo with recombinant IL 2. J Immunol. 1985 Oct;135(4):2865-75. PMID: 2993418

Interferon-alpha

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		[1]	

Positive in vitro study:

© 2013 Paul S. Anderson – All Rights Reserved

1. Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA. Modification of the effect of tamoxifen, cis-platin, DTIC, and interferon-alpha 2b on human melanoma cells in culture by a mixture of vitamins. Nutr Cancer. 1994;22(3):233-45. PMID: 7877893

XII. Immunomodulating drugs:

Thalidomide / lenalidomide (Revlimid)

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response	[1]		

Positive basic science:

1. Anderson, K. C. (2005). "Lenalidomide and Thalidomide: Mechanisms of Action—Similarities and Differences". Seminars in Hematology 42 (4 Suppl 4): S3–S8. doi:10.1053/j.seminhematol.2005.10.001. PMID 16344099.

XIII. Radiation Therapy:

	Basic Science	In Vitro	In Vivo
Negative Response			
Neutral Response			
Positive Response		1,2,3,10	4,5,6,7,8,9,11

© 2013 Paul S. Anderson – All Rights Reserved

1. In Vitro Positive pre / co-treatment with ascorbate+Vit K(3)

    – "In addition, cell death caused by VC+VK(3) treatment as well as by prolonged VC treatment is consistent with cell demise by autoschizis, not apoptosis. This report confirms and complements previous observations about this new mode of tumor cell death. It supports the contention that a combination of VC+VK(3), also named Apatone, could be co-administered as a nontoxic adjuvant with radiation and/or chemotherapies to kill bladder tumor cells and other cancer cells without any supplementary risk or side effects for patients."

    – Gilloteaux J, et.al. Cell damage and death by autoschizis in human bladder (RT4) carcinoma cells resulting from treatment with ascorbate and menadione. Ultrastruct Pathol. 2010 May;34(3):140-60.

2. In Vitro positive:

    – Prasad K, Sinha P, Ramanujam M, Sakamoto A. Sodium ascorbate potentiates the growth inhibitory effect of certain agents on neuroblastoma cells in culture. Proc Natl Acad Sci USA 1979;76:829–32.

3. In Vitro positive:

    – "In conclusion, pharmacological concentrations of ascorbate radiosensitize GBM primary cells to a much greater extent than astrocytes; this large therapeutic ratio may be of clinical significance in radiation-resistant cancers."

    – Herst, P. M. et al., Pharmacological concentrations of ascorbate radiosensitize glioblastoma multiforme primary cells by increasing oxidative DNA damage and inhibiting G2/M arrest. Free Radic. Biol. Med. (2012), doi:10.1016/j.freeradbiomed.2012.01.021

4. Positive ASC and K3 in vivo:

    – Taper H, Keyeux A, Roberfroid M. Potentiation of radiotherapy by nontoxic pretreatment with combined vitamins C and K3 in mice bearing solid transplantable tumor. Anticancer Res 1996;16:499–503.

5. Radiation was targeted better toward cancer cells and less toward normal cells in one mouse study

    • Tewfik FA, Tewfik HH. et al. The influence of ascorbic acid on the growth of solid tumors in mice and on tumor control by X-irradiation. Int J Vitam Nutr Res Suppl. 1982;23:257-63.

6. A randomized human trial of 50 patients evaluated the effect of combined Vitamin C 5gms/day and radiotherapy in different tumor types and noted more complete responses to radiation in the vitamin C group

    – Hanck AB.Vitamin C and cancer. Progress in Clinical & Biological Research 259:307-20,1988.

© 2013 Paul S. Anderson – All Rights Reserved

7. Murine fibrosarcoma mouse model showing increased radiation efficacy in ascorbate pre-treated animals. "The data suggest that after high-dose ascorbic acid the radiation dose given to cancer patients could be increased without increasing acute complications but with an expected increase in tumor-control probability." "Although a single dose of ascorbic acid delivered at a dose of *4.5 g/kg body wt ip (50 min before* irradiation) significantly increased the radiation tolerance of both skin and bone marrow, tumors were not protected." [Human equivalent doses would be 35 to 325 grams of ascorbate].

- Okunieff P. Interactions between ascorbic acid and the radiation of bone marrow, skin, and tumor. Am J Clin Nuir 1991;54:1281S-3S.

8. Mouse model of BMT Radiation Tx: pre- and post-treatment with human equivalent of 15 grams ASC prevented fatal gastrointestinal syndrome.

- Yamamoto T, et.al. Pretreatment with Ascorbic Acid Prevents Lethal Gastrointestinal Syndrome in Mice Receiving a Massive Amount of Radiation. J. Radiat. Res., 51, 145–156 (2010)

9. Ascorbate and radiotherapy outcomes in head and neck cancer: The results of the present study indicate that the patients having better response to the treatment (All the patients received chemo-radiotherapy in the form of concurrent cisplatin (35mg/m2 weekly) and radiation to a total dose of 7,000 cGy by a Cobalt-60 machine, daily single dose comprising of 200 cGy, five days a week regimen over a period of seven weeks.) had higher plasma levels of ascorbic acid, while the patients showing partial or no response had lower levels of ascorbic acid.

- Gupta A, et.al. Redox Status and Ascorbic Acid in Carcinoma of Head and Neck is Correlated to Clinical Response. The Open Clinical Cancer Journal, 2010, 4, 1-2

10. This study was conducted to examine the utility of the combined use of ascorbic acid (AsA) and radiation in clinical applications. We investigated cell survival, DNA fragmentation, and caspase activation after X-ray irradiation and AsA treatment of human leukemia HL60 cells. The number of living cells decreased after combined X-ray irradiation and AsA treatment (2 Gy + 5 mM) in comparison with that after X-ray irradiation (2 Gy) or AsA treatment (5 mM) alone. DNA fragmentation was more in the cells subjected to combined X-ray irradiation and AsA treatment than in those subjected to X-ray irradiation alone. Caspase-3, caspase-8, and caspase-9 were highly activated following combined X-ray irradiation and AsA treatment, but caspase-8 activity was not markedly increased after X-ray irradiation alone. Bax levels in the mitochondrial membrane fractions were increased after AsA treatment alone and after combined X-ray irradiation and AsA treatment. However, there was no apparent increase in the Bax levels after X-ray irradiation treatment alone. Thus, this study confirmed that supplementing X-ray irradiation with AsA treatment results in increased apoptosis in HL60 cells. With regard to the apoptosis-inducing factors, we hypothesized that Bax and caspase-8 were activated after combined X-ray irradiation and AsA treatment compared with either treatment alone.

- Shinozaki K, Hosokawa Y, Hazawa M, Kashiwakura I, Okumura K, Kaku T, Nakayama E. Ascorbic acid enhances radiation-induced apoptosis in an HL60 human leukemia cell line. J Radiat Res (Tokyo). 2011;52(2):229-37. Epub 2011 Feb 19.

© 2013 Paul S. Anderson – All Rights Reserved

11. Conclusions:

- GBM cells are sensitive to ascorbate in clinically achievable concentrations
- Ascorbate toxicity is mediated through the production of hydrogen peroxide and is at least in part dependent upon the presence of metals
- Ascorbate sensitizes GBM cell lines to ionizing radiation
- Ascorbate sensitizes GBM xenografts to ionizing radiation and temozolomide.
    - Allen BG et.al. High-dose ascorbate enhances chemo-radio-sensitization in GBM. Poster Presentation, American Society for Radiation Oncology2012

© 2013 Paul S. Anderson – All Rights Reserved