

140 East Church Street, Sellersville PA 18960 USA

Tel: 215-453-2507 Fax: 215-257-9781

www.sodiumphenylbutyrate.com

SCIENTIFIC ARTICLES/ CLINICAL STUDIES

Sodium Phenylbutyrate

(4-Phenylbutyric Acid, Sodium Salt)

CANCER

Lee Sy, Hong EH, Jeong JY, Cho J, Seo JH, K HJ, Cho HJ. Esterase-sensitive cleavable histone deacetylase inhibitor-coupled hyaluronic acid nanoparticles for boosting anticancer activities against lung adenocarcinoma. *Biomater Sci* Nov 2019;7(11):4624-4635. <https://pubs.rsc.org/en/content/articlelanding/2019/bm/c9bm00895k>

Tanaka T, Kojima K, Yokota K, Tanaka Y, Ooizumi Y, Ishii S, Nishizawa, Yokoi K, Ushiku H, Kikuchi M, Kojo K, Minatani N, Katoh H, Sato T, Nakamura T, Sawanobori, Watanabe M, Yamashita K. Comprehensive Genetic Search to Clarify the Molecular Mechanism of Drug Resistance Identifies ASCL2-LEF1/TSPAN8 Axis in Colorectal Cancer. *Ann Surg Oncol* May 2019;26(5):1401-1411. <https://pubmed.ncbi.nlm.nih.gov/30706227/>

Qian K, Sun L, Zhou G, Ge H, Meng Y, Li J, Li X, Fang X. Sodium Phenylbutyrate Inhibits Tumor Growth and the Epithelial-Mesenchymal Transition of Oral Squamous Cell Carcinoma In Vitro and In Vivo. *Cancer Biother Radiopharm* May 2018;33(4):139-145.

<https://www.liebertpub.com/doi/10.1089/cbr.2017.2418>

Al-Keilani MS, Alzoubi KH, Jaradat SA. The effect of combined treatment with sodium phenylbutyrate and cisplatin, erlotinib or gefitinib on resistant NSCLC cells. *Clin Pharmacol* Oct 2018;10:135-140.

 <https://www.dovepress.com/getfile.php?fileID=45127>

Jin X, Wu N, Dai J, Li Q, Xiao X. TXNIP mediates the differential responses of A549 cells to sodium butyrate and sodium 4-phenylbutyrate treatment. *Cancer Med* Feb 2017;6(2):424-438. <https://pubmed.ncbi.nlm.nih.gov/28033672/>

Xu YW, Xheng SB, Chen BS, Wen Y, Zhu SW. Effect of sodium phenylbutyrate on the sensitivity of PC3/DTX-resistant prostate cancer cells to docetaxel. *Nan Fang Yi Ke Da Xue Xue Bao* Nov 2017;37(1):130-134.

<https://pubmed.ncbi.nlm.nih.gov/28109113/>

Xu, X., Zheng, S., Chen, B., Wen, Y., Zhu, S. sodium Phenylbutyrate antagonizes prostate cancer through the induction of apoptosis and attenuation of cell viability and migration. *Onco Targets & Therapy*, May 12, 2016, 9: 2825-2833.

<https://pubmed.ncbi.nlm.nih.gov/27274278/>

Kikuchi, M., Yamashita, K., Waraya, N., Ushiku, H., Kojo, K., Ema, A., Kosaka, Y., Katoh, H., Sengoku, N., Enomoto, T., Tanino, H., Sawanobori, M., Watanabe. Epigenetic regulation of ZEB1-RAB25/ESRP1 axis plays a critical role in phenylbutyrate treatment-resistant breast cancer. *Oncotarget,* 7(2): 1741-1753 January 2016

Shi S, Tan P, Yan B, Gao R, Zhao J, Wang J, Gup J, Li N, Ma Z. ER stress and autophagy are involved in the apoptosis induced by cisplatin in human lung cancer cells. *Oncol Rep* May 2016;35(5):2606-14

Fadeev NP, Kharisov RI, Kovan’ko EG, Pustovalov YI. Study of Antitumor Activity of Sodium Phenylbutyrate, Histon Deacetylase Inhibitor on Ehrlich Carcinoma Model. *Bull Exp Biol Med* Sep 2015;159(5):652-4.

<https://read.qxmd.com/read/26468021/study-of-antitumor-activity-of-sodium-phenylbutyrate-histon-deacetylase-inhibitor-on-ehrlich-carcinoma-model>

Welsch, L., Welsch, T., Dovzhanskiy, I., Felix, K., Giese, N.A., Krysko, D. Impact of the histone deacetylase inhibitor 4-phenylbutyrate on the clearance of apoptotic pancreatic carcinoma cells by human macrophages. *International Journal of Oncology*, 2012, 40(2). P. 427-435

Chen WQ, Feng FL, Gu HB, et al. Effect of sodium phenylbutyrate on the apoptosis of human tongue squamous cancer cell line and expression of p21 and surviving genes. *Zhonghua Kou Qiang Yi Xue Za Zhi*, July 2010; 45(7):416-20

De-shum, Pan, Wei-qiang, Chen. The effects of sodium phenylbutyrate (SPB) on the expression of p21 and survivine genes on human tongue squamous cancer cell line Tca8113. *Chinese Pharmacological Bulletin,* February 2010

Steinmann, J., Halldórsson, S., Agerberth, B., Gudmundsson, G.H. Phenylbutyrate Induces Antimicrobial Peptide Expression. *Antimicrobial Agents and Chemotherapy*, Page. 5127-5133, Vol. 53, December 2009

Holm, E; Schade, I. Effects of short-chain and saturated long-chain fatty acids on tumor growth-in vitro and experimental in vivo effects. Aktuelle Ernahrungsmedizin 2008;33(5):225-230.

Cortez, CC; Jones, PA. Chromatin,cancer and drug therapies. Mutat Res-Fundam Mol Mech Mutagen 2008;647(1-2):44-51.

Murahari, S; Jalkanen, AL; Kulp, SK; Chen, C-S; Jubala, CM; Fosmire, SP; Modiano, JF; Fossey, SL; London, CA, Kisseberth, WC.OSU-HDAC42, a novel histone deacetylase inhibitor with potent antitumor effects on human and canine osteosarcoma cells. Proceedings of the American Association for Cancer Research Annual Meeting 2008;49:578.

Wang, C., Meng, M., Zhang, J., Jin, C., Jiang, J., Ren, H., Jiang, J., Qin, C., and Yu, D. *Chinese Medical Journal* 2008; 121(17):1707-1711*.*

Burkitt, Kyunghee and Ljungman, Mats. Phenylbutyrate interferes with the Fanconi anemia and BRCA pathway and sensitizes head and neck cancer cells to cisplatin. *Molecular Cancer* 7:24, March 2008.

Svechnikova, Irina, Almqvist, Per M., Ekström, Tomas J. HDAC inhibitors effectively induce cell type-specific differentiation in human glioblastoma cell lines of different origin. *International Journal of Oncology* 32:821-827, 2008

Huynh, L; Grant, J; Leroux, JC; Delmas, P; Allen, C. Prediction the solubility of the anti-cancer agent docetaxel in small molecule excipients using computational methods. Pharm Res 2008; 25:147-157.

Hurtubise, A; Bernstein, ML; Momparler, RL. Preclinical evaluation of the antineoplastic action of 5-aza-2’-deoxycytidine and different histone deacetlylase inhibitors on human Ewing’s sarcoma cells. Cancer Cell Int 2008;8:16.

Koutsourea, Al; Fousteris, MA; Arsenou, ES; Papageorgiou, A; Pairas, GN; Nikolaropoulos, SS. Rational design, synthesis and in vivo evaluation of the antileukemic activity of six new alkylating steroidal esters. Bioorg Med Chem 2008; 16(9):5207-5215.

Estey, E. New drugs in acute myeloid leukemia. Seminars in Oncology 2008;35(4):439-448.

Picard, V; Bergeron, A.; Larue, H; Fradet, Y. MAGE-A9 mRNA and protein expression in bladder cancer. Int J Cancer 2007; 120 (10):2170-2177.

Vila-Carriles, WH; Zhou, Z-H; Bubien, JK; Fuller, CM; Benos, DJ. Participation of the chaperone Hsc70 in the trafficking and functional expression of ASIC2 in glioma cells. J Biol Chem 2007;282(47):34381-34391.

Entin-Meer, M; Rephaeli, A; Yang, X; Nudelman, A; Haas-Kogan, DA. AN-113, a novel prodrug of 4-phenylbutyrate with increased anti-neoplastic activity in glioma cell lines. Cancer Lett 2007; 253(2):205-214.

Christov, Konstantin, Grubbs, Clinton J; Shilkaitis, Anne, Juliana, M Margaret; Lubet, Ronald A. Short-term modulation of cell proliferation and apoptosis and preventive/therapeutic efficacy of various agents in a mammary cancer model. Clin Cancer Res 2007; 13(18 Part. 1):5488-5496.

Christov, K; Grubbs, C; Juliana, M; Luber, R. Correlation of the preventive/therapeutic efficacy of agents in the methylnitrosourea (MNU) mammary cancer model with changes in cell proliferation and apoptosis following short-term treatment. Proceedings of the American Association for Cancer Research Annual Meeting 2007; 48:997.

Sung, MW; Waxman, S. Combination of cytotoxic-differentiation therapy with 5-fluorourcail and phenylbutyrate in patients with advanced colorectal cancer. Anticancer Res 2007;27(2):995-1001.

Caraway, HE; Gore, SD. Addition of histone deacetylase inhibitors in combination therapy. J. Clin Oncol 2007; 25(15):1955-1956.

Verheul, HMW; Qian, DZ; Carducci, MA; Pili, R. Sequence-dependent antitumor effects of differentiation agents in combination with cell cycle-dependent cytotoxic drugs. Cancer Chemother Pharmacol 2007; 60(3):329-339.

Ammerpohl, O; Trauzold, A; Schniewind, B; Griep, U; Pilarsky, C; Grutzmann, R; Saeger, H-D; Janssen, O; sipos, B; Kloppel, G; Kalthoff, H. Complementary effects of HDAC inhibitor 4-PB on gap junction communication and cellular export mechanisms support restoration of chemosensitivity of PDAC cells. Br J Cancer 2007; 96(1):73-81.

Jiemjit, A; Fandy, TE; Baylin, SB; Carraway, H; Herman, JG; Gore, SD. Sequential administration of DNA methyltransferase inhibitors (DNMTi) and histone deacetylase inhibitors (HDACi) induces apoptosis with caspase and reactive oxygen species (ROS)-dependent synergy. Proceedings of the American Association for Cancer Research Annual Meeting 2007; 48:249.

Hattori, Y; Fukushima, M; Maitani, Y. Non-viral delivery of the connexin 43 gene with histone deacetylase inhibitor to human nasopharyngeal tumor cells enhances gene expression and inhibits in vivo tumor growth. Int J Oncol 2007;30(6):1427-1439.

Lyon, CM; Klinge, D; Liechty, KC; Grimes, MJ; Grimes, J; Thomas, C; March, T; Stidley, C; Keith, R; Belinsky, SA. Rosiglitazone prevents the progression of pre-invasive lung cancer in a murine model. Proceedings of the American Association for Cancer Research Annual Meeting 2007; 48:395.

Cunha De Santis , G; de barros Tamarozzi, M; Sousa, RB; Moreno, Se; Secco, D; Garcia, AB; Lima, ASG; Faccioli, LH; Falcoao, RP; Cunha, FQ; Rego, EM. Adhesion molecules and Differentiation Syndrome: phenotypic and functional analysis of the effect of ATRA, As203, phenylbutyrate, and G-CSF in acute promyelocytic leukemia. Haematologica 2007; 92(12):1615-1622.

Meng, M; Wang, C-T; Jiang, J-M; Zhang, J-C; Jiang, J-J; Jin, C-J. Expression of histone deacetylase 4 in human liver carcinoma cell line Bel-7402 and its significance. Chinese Journal of Cancer Biotherapy Chin. J. cancer Biother 2007; 14(2):153-157.

Lu, Y-S; Kashida, Y; Kulp, SK; wang, Y-C; Wang, D; Hung, J-H; Tang, M; Lin, Z-Z; Chen, T-J; Cheng, A-L; Chen, C-S. Efficacy of a novel histone deacetylase inhibitor in murine models of hepatocellualr carcinoma. Hepayology 2007; 46(4):1119-1130.

Svechnikova, I; Ammerpohl, O; Ekstroem, TJ. P21waf1/Cip1 partially mediates apoptosis in hepatocellular carcinoma cells. Biochem Biophys Res Commun 2007; 354(2):466-471.

Lu, Y-S; Kashida, Y; Jung, J-H; Chen, C-S; Wang, Y-C; Cheng, A-L; Chen, C-S. In vivo efficacy of OSH-HDAC42, a novel phenylbutyrate-based histone deacetylase inhibitor, in human hepatocellular carcinoma animal models. Proceedings of the American Association for Cancer Research Annual Meeting 2007; 48:169.

Lubbert, M; Claus, R. Epigenetic inactivation of gene expression. New therapeutic targets in hematology. Onkologe 2007;13(1):46-55. lindsay@customvite.com or service@nutrilab.com.

Claus, R; Router, B, Loubbert, M. Targets of epigenetics therapy-Gene reactivation as a novel approach in MDS treatment. Cancer Treat Rec 2007; 33(Suppl. 1):S47-S52.

Luebbert, M. Which myelodysplastic syndromes patients are candidates for treatment with decitabine. Leukemia Research 2007; 31(Suppl. 1):S20.

Gore, SD. Do histone deacetylase inhibitors have a place in the treatment of myelodysplastic syndromes? Leukemia Research 2007; 31(Suppl. 1):S21.

Phillips, JA; Griffin, BE. Pilot study of sodium phenylbutyrate as adjuvant in cyclophosphamide-resistant endemic Burkitt’s lymphoma. Trans R Soc Trop Med Hyg 2007; 101(12):1265-1269.

Milkevitch, M; Jeitner, TM; Beardsley, NJ; Delikatny, EJ. Lovastatin enhances phenylbutyrate-induced MR-visible glycerophosphocholine but not apoptosis in DU145 prostate cells. Biochim Biophys Acta 2007; 1771(9):1166-1176.

Phillips John A., Griffin, Beverly E. Pilot study of sodium Phenylbutyrate as adjuvant in cyclophosphamide-resistant endemic Burkitt’s lymphoma. *Royal Socity of Tropical Medicine and Hygiene* doi: 10.1016/j.trstmh.2007.06.0200.

Lopez, CA, Feng, FY, Herman, JM, Nyati, MK, Lawrence,TS, Ljungman, M. Phenylbutyrate Sensitizes Human Glioblastoma Cells Lacking Wild-Type P53 Function To Ionizing Radiation. *Int. J. Radiation Oncology Biol. Phys,* Vol. 69, No. 1, PP. 214-220, 2007.

L.H. Camacho, J. Olson, W.P. Tong, .W. Young, D.R. Spriggs, M.G. Malkin. Phase I dose escalation clinical trial of phenylbutyrate sodium administered twice daily to patients with advanced solid tumors. *Invest. New Drugs,* 2007 25:131-138.

Vila-Carriles, WH; Kovacs, GG; Bubien, JK; Gillespie GY; Fuller, CM; Benos, DJ. Cellular localization of acid sensing ion channels in human astrocytes and gliomas. FASEB Journal 2006; 20(4, Part1):A325.

Christov, K; Grubbs, C; Lubet, R; Altered cell proliferation and apoptosis as biomarkers for identifying preventive/therapeutic agents against chemically induced mammary cancers. Breast Cancer Research and Treatment 2006; 100(Suppl. 1):S58.

Lea, MA; Ibeh, C; Shah, N; Moyer, MP. Enhanced differentiation of colon cancer cells induced by combinations of inhibitors of kinases and of historic deacetylases. Proceedings of the American Association for Cancer Research Annual Meeting 2006; 47:1184.

Gore, SD;, Jiemjit, A; Silverman, LB; Aucott, T; Baylin, S; Carraway, H; Douses, T; Fandy, T; Herman, J; Karp, JE; Licht, JD.; Murgo, AJ.; Odchimar-Reissig, R; Smith, BD; Zwiebel, JA.; Sugar, E. Cimbined methyltransferase/Histone deacetylase inhibition with 5Azacitidine and MS-275 in patients with MDS, CMMoL and AML: Clinical response, Histone Acetylation and DNA damage. Blood 2006; 108(11, part 1):156A-157A.

Sun, J; Liu, S; Yu, J; Wei, M; Mao, C; Ding, H; Kearney, J; Huynh, L; Paschka, P; Wang, D; Klisovic, RB; Perrotti, D; Chen, C-S; Blum, WG; Marcucci, G. Characterization of HDACI OSU42 as a novel histone deacetylase inhibitor in AML cell lines. Blood 2006; 108(11 Part 1):563A.

Gore, SD; Baylin, S; Sugar, E; Carraway, H; Miller, CB; Carducci, M; Grever, M; Galm, O; Dauses, T; Karp, JE; Rudek, MA; Zhao, M; Smith, BD; Manning, J; Jiemjit, A; Dover, G; Mays, A; Zwiebel, J; Murgo, A; Weng, L-J; Herman, JG. Combined DNA methyltransferase and histone deacetylase inhibition in the treatment of myeloid neoplasms. Cancer Res 2006; 66(12):6361-6369.

Brock, MV. Clinical aspects of molecular biology for the diagnosis and treatment of esophageal cancer. Esophagus 2006; 3(3):91-94.

Beyer, SJ; Kulp, SK; Baird, M; Auer, H; Kornacker, K; Chen, C-S; Beer, DG; Kresty, LA. The effects of a phenylbutyrate-drived histone deacetylase inhibitor (HDAC-42) on acid-induced gene expression patterns of SEG-1 human esophageal adenocarcinoma cells. Proceedings of the American Association for Cancer Research Annual Meeting 2006; 47:1128-1129.

West, DA; Lucas, DM; Davis, ME; De lay, MD; Johnson, AJ; Guster, SE; Freitas, MA; Parthun, MR; Wang, D; Kulp, SK; Grever, MR; Chen, C-S; Byrd, JC. The novel histone deacetylase inhibitor OSU-HDAC42 has class I and II histone deacetylase (HDAC) inhibitory activity and represents a novel therapy for chronic lymphocytic leukemia. Blood 2006; 108(11 Part 1): 794A-795A.

Lyon, CM; Klinge, D; Liechty, KC; Belinsky, SA. DNA demethylating agents and a PPA-gamma agonist cooperate to induce apoptosis in lung cancer cell lines. Proceedings of the American Association for Cancer Research Annual Meeting 2006; 47:10.

Meletis, J; Viniou, N; Terpos, E. Novel agents for the management of myelodysplastic syndromes. Med Sci Monit 2006; 12(9):RA 194-RA206.

Kulp, SK; Chen, C-S; Wang, D-S; Chen, C-Y; Chen, C-S. Antitumor effects of a novel phenylbutyrate-based histone deacetylase inhibitor, (S)-HDAC-42, in prostate cancer. Clin Cancer Res 2006; 12(17):5199-5206.

Wanda H. Vila-Carriles, Gergely Gy Kovacs, Biljana Jovov, Zhen-Hong Zhou, Amit K. Pahwa, Garrett Colby, Ogenna Esimai, G. Yancey Gillespie, Timothy B. Mapstone, James M. Markert, Catherine M. Fuller, James K. Bubien, Dale J. Benos. Surface Expression of ASIC2 Inhibits the Amiloride-sensitive Current and Migration of Glioma Cells. *The Journal of Biological Chemistry* VOL. 281, NO> 28, pp. 19220 – 19232, July 14, 2006.

Mack, GS. Epigenetic cancer therapy makes headway. Journal of the National Cancer Institute 2006;98(20):1443-1444.

Fouladi, M. Histone deacetylase inhibitors in cancer therapy. Cancer Investigation 2006;24(5):521-527.

Galm, O; Herman, JG; Bbaylin, SB. The fundamental role of epigenetics in hematopoietic malignancies. Blood Rev 2006;20(1):1-13.

P. Malask, S. Chanel, L.H. Camacho, S. Soignet, P.O. Dandolfi, I. Guernah, R. Warrell, S. Nimer. Pilot study of combination transcriptional modulation therapy with sodium phenylbutyrate and 5-azacytidine in patients with acute myeloid leukemia or myelodysplastic syndrome. *Leukemia* 2006, 20, 212-217.

Schniewind B., Heintz K., Kurdow R., Ammerpohl O., Trauzold A., Emme D., Dohrmann P., Kalthoff H. Combination Phenylbutyrate/gemcitabine therapy effectively inhibits in vitro and in vivo growth of NSCLC by intrinsic apoptotic pathways. *Journal of Carcinogenesis* 2006,1477-3163-5-25.

Jin C., Park J.W., Choi J.W., Kang H., Jin G.B., Choi S.M., Park S.S., Ryu D., Jang L.C. Antiproliferative Effect of Phenylbutyrate in AsPC-1 Pancreatic Cancer Cell Line. *Korean J. Hepatobiliary Pancreat Surg.* 2006 Mar: 10(1):1-9. Korean

Kouraklis G., Theocharis S. Histone deacetylase inhibitors: A novel target of anticancer therapy (Review). *Oncology Reports* 15: 489-494, 2006.

Sampathkumar S-g, Jones MB, Meledeo MA, Hida K, Sheh T, Gomatputra P, Yarema KJ. Carbohydrate-based small molecules as anti-cancer drugs: Short chain fatty acid-hexosamine hybrids. *Glycobiology* 2005; 15 (11): 1249-1250.

Lu Q, Wang D-S, Chenm C-S, Hu Y-D, Chen C-S. Structure-based optimization of phenylbutyrate-derived histone deacetylase inhibitors. *J Med Chem* 2005; 48 (17): 5530-5535.

Gao, J; X-y; Xu F-I; Liu D-y; Lei D-p. Effects of sodium phenylbutyrate alone or in combination with fluorouracil or cisplatin on laryngeal carcinoma Hep-2 cell line. Zhongguo Xinyao yu Linchuang Zazhi 2005; 24(10):778-781.

Gao, J; Ruan, X; Pan, X; Xu, F; Lei, D; Liu, D. The effect of sodium phenylbutyrate to agents used in induction chemotherapy on laryngeal carcinoma cells Hep-2 in vitro. Lin Chuang Er Bi Yan Hou Ke Za Zhi 2005; 19(15):680-682.

Luebbert, M. Combined targeting of the epigenetic silence in leukemia: Cooperating activities of DNA methylation and histone deacetylation inhibitors. Leukemia Research 2005; 29(7):727-728.

Wang, H-E; Wu, H-C; Kao, S-J; Tseng, F-W; Wang, Y-S; Yu, H-M; Chou, S-L; Yen, S-H; Chi, K-H. Modulation of 5-fluorouracil cytotoxicity through thymidylate synthase and NF-kappaB down-regulation and its application on the radiolabelled iododeoxyuridine therapy on human hepatoma cell. Biochem Pharmacol 2005; 69(4):617-626.

Milkevitch, M; Shim, H; Pilatus, U; Pickup, S; Wehrle, JP; Samid, D; Poptani, H; Glickson, JD; Delikatny, EJ. Increases in NMR-visible lipid and glycerophosphocholine during phenylbutyrate-induced apoptosis in human prostate cancer cells. Biochim Biophys Acta 2005; 1734(1):1-12.

Rudek MA, Zhao M, He P, Hartkle C, Gilbert J, Gore SD,. Carducci MA, Baker SD. Pharmacokinetics of 5-Azacitidine Administered With Phenylbutyrate in Patients With Refractory Solid Tumors or Hematologic Malignancies. *Journal of Clinical Oncology* Vol 23 #17 June 10, 2005.

Belinsky S.A., Silencing of genes by promoter hypermethylation: key event in rodent and human lung cancer. *Carcinogenesis* Vol. 26, No. 9 (1481-1487) 2005.

Mortazavi, A.; Hoot, DR; Carlton, PS; Wang, S; Degroff, VL.; Lu, Q; Kulp, S; Chen, C-S; Clinton, SK. Inhibition of cell growth and induction of apoptosis in bladder cancer cell lines by a novel histone deacctylase inhibitor derived from phenylbutyrate. Proceedings of the American Association for Cancer Research Annual meeting 2005; 46(Supplement S): 422.

Hao, C-I; Tang, K-j; Chen, S, Xing, H-y; Wang, M; Wang, J-x. 5-Aza-2’-deoxycytidine enhances differentiation and apoptosis induced by phenylbutyrate in Kasumi-1 cells. Zhonghua Zhong Liu Za Zhi 2005;27(3):148-151.

Meng M., Jiang J.M., Liu H., In C.Y., Zhu J.R. Effects of sodium phenylbutyrate on differentiation and induction of the P21WAF1/CIP1 anti-oncogene in human liver carcinoma cells lines. *Chinese Journal of Digestive Diseases* 2005; 6; 189-192.

Garcia-Manero, G; Issa, J-P. Histone deacetylase inhibitors: A review of their clinical status as antineoplastic agents. Cancer Investigation 2005;23(7):635-642.

Phuphanich S, Baker SD, Grossman SA, Carson KA, Gilbert MR, Fisher JD, Carducci MA. Oral sodium phenylbutyrate in patients with recurrent malignant gliomas: A dose escalation and pharmacologic study. Neuro-Oncology Vol 7 pg 177-182, April 2005.

Munshi A, Kurland JF, Nishikawa T, Tanaka T, Hobbs Ml, Tucker SL, Ismail S, Stevens C, Meyn RE. Histone deacetylase inhibitors raidosensitize human melanoma cell by suppressing DNA repair activity. *Clin Cancer Res* 2005; 11 (13): 4912-4922.

Siitonen, T., Koistinen, P., Savolainen, E. Increase in Ara-C cytotoxicity in the presence of valproate, a histone deacetylase inhibitor, is associated with the concurrent expression of cyclin D1 and p27Kip1 in acute myeloblastic leukemia cells. *Leukemia Research* 29 (2004) 1335-1342*.*

Liu M., Brusilow W.S.A., Needleman R., Activity of the yeast Tat2p tryptophan permease is sensitive to the anti-tumor agent 4-phenylbutyrate. *Curr Genet* 46:256-268 (2004).

Emionite L., Galmozzi F., Grattarola M., Boccardo F., Vergani L, Toma S., Histone Deacetylase Inhibitors Enhance Retinoid Response in Human Breast Cancer Cell Lines. *Anticancer Research 24:* 4019-4024 (2004).

Zhang X., Wei L., Yang Y., Yu Q. Sodium 4-Phenylbutyrate Induces Apoptosis of Human Lung Carcinoma Cells Through Activating JNK Pathway. *Journal of Cellular Biochemistry* 93:819-829 (2004).

Sachs M.D., Ramamurthy M., van der Poel H., Wickham T.J., Lamfers M., Gerritsen W., Chowdhury W., Li Y., Schoenberg M.P., Rodriguez R. Histone deacetylase inhibitors upregulate expression of the coxsackie adenovirus receptor (CAR) preferentially in bladder cancer cells. *Cancer Gene Therapy* (2004) 11, 477-486.

Kim, Y.H., Park, J.W., Lee, J.Y., et al. Sodium Phenylbutyrate sensitizes TRAIL-mediated apoptosis by induction of transcription from the DR5 gene promoter through Ap1 sites in colon Cancer cells. *Carcinogenesis.* 2001; 25:1813-20

Nakagawa H., Intrathecal or intracavitary administration of sodium butyrate to treat neoplastic meningitis and malignant glioma *Proceedings of the AACR,* Vol. 45:5241, March 2004.

X.-N. Li, S. Parikh, Q. Shu, H.-L. Jung, C.-W. Chow, L. Perlaky, H.-C. E. Leung, J. Su, S. Blaney, and C. C. Lau Phenylbutyrate and Phenylacetate Induce Differentiation and Inhibit Proliferation of Human Medulloblastoma Cells *Clin. Cancer Res.,* February 1, 2004; 10(3): 1150 - 1159.

Burzynski, SR, Lewy, RI, Weaver, R, Janicki, T, Jurida, G, Khan, M, Larisma, CB, Paszkowiak, J, , Szymkowski, B. Long-Term Survival and Complete Response of a Patient With Recurrent Diffuse Intrinsic Brain Ctem Glioblastoma Multiforme. *Integrative Cancer Therapies,* 3(3); 2004 pp. 257-261.

Appelskog I.B., Ammerpohl O., Svechnikova I.G., Lui W-O., Almqvist P.M., Ekström T.J. Histone deacetylase inhibitor 4-phenylbutyrate suppresses GAPDH mRNA expression in glioma cells. *International Journal of Oncology* 24:1419-1425, 2004.

Linz, Uta, Complete response of a recurrent, multicentric malignant glioma in a patient treated with Phenylbutyrate. *Journal of Neuro-Oncology* 66:251, 2004.

Asklune, T., Appelskog I.B., Ammerpohl O., Ekstron T.J., Almqvist, P.M. Histone deacetylase inhibitor 4-phenylbutyrate modulates glial fibrillary acidic protein and connexin 43 expression, and enhances gap-junction communication in human glioblastoma cells. *European Journal of Cancer,* 2004 Vol 40, No. 7.

Gray S.G., Quian C.-N., Furge K., Guo X., The B.T., Microarray profiling of the effects of histone deacetylase inhibitors on gene expression in cancer cell lines. *Int. J of Onc.* 24:773-795, 2004.

Chung, Yih-Lin, Wang, Ae-June, Yao, Lin-Fen, Antitumor Histone deacetylase inhibitors suppress cutaneous radiation syndrome: Implications for increasing therapeutic gain in cancer radiotherapy. *Molecular Cancer Therapeutics* 2004; 3(3):317-325

Belinsky S.A., Klinge D.M., Stidley C.A., Issa J-P., Herman J.G., March T.H., Baylin S.B., Inhibition of DNA Methylation and Histone Deacetylation Prevents Murine Lung Cancer. *Cancer Research* (63) 7089-7093, November 1, 2003.

Sun Li-Jun, Huang Qiang, Lan Qing, Du Zi-wei, Hu Geng-xi, Wang Ai-dong, Gene Expression Profiling of Phenylbutyrate Induced Differentiation of Glioma Cells by cDNA Array. *Chinese Journal of Cancer Research 15(1):38-42,* 2003*.*

Thompson P., Balis F., Baruti M., Berg S.S., Adamson P., Klenk R., Aiken A., Packer R., Murry D.J., Jakacki R., Blaney S.M. Pharmacokinetics of phenylacetate administered as a 30-min infusion in children with refractory cancer. *Cancer Chemother Pharmacol* (2003) 52:417-423.

Finzer P., Stöhr M., Seibert N., Rösl F., Phenylbutyrate inhibits growth of cervical carcinoma cells independent of HPV type and copy number *J. Cancer Res. Clin. Oncol.* (2003) 129:107-113.

Witt O, Mönkemeyer S, Rönndahl G, Erdlenbruch B, Reinhardt D, Kanbach K, and Pekrun A. Induction of fetal hemoglobin expression by the histone deacetylase inhibitor apicidin*. Blood*, Mar 2003; 101: 2001 - 2007.

Svechnikova I, Gray S.G, Kundrotiene J, Ponthan F, Kogner P, Ekström T. Apoptosis and tumor remission in liver tumor xenografts by 4-phenylbutyrate. *Int. Journal of Oncology* 22: 579-588, 2003*.*

Gray S.G., Iglesias A.H., Teh B.T., Dangond F., Modulation of Splicing Events in Histone Deacetylase 3 by Various Extracellular and Signal Transduction Pathways *Gene Expression*, Vol. 11, pp. 13-21. Oct. 2002.

Baker M J, Brem S, Daniels S, Sherman B, Phuphanich S. Complete response of a recurrent, multicentric malignant glioma in a patient treated with phenylbutyrate. *J Neuro-Oncology*; 59:239-242, 2002.

Boivin A-J., Momparler L.F., Hurtubise A., Momparler R.L.. Antineoplastic action of 5-aza-2’-deoxycytidine and phenylbutyrate on human lung carcinoma cells. *Anti-Cancer Drugs*. Vol 13 (869-874) 2002.

Dyer E.S., Paulsen M.T., Markwart S.M., Goh M., Livant D.L. and Ljungman M. Phenylbutyrate inhibits the invasive properties of prostate and breast cancer cell lines in the sea urchin embryo basement membrane invasion assay. *Int. J. Cancer*: 101, 496-499 (2002).

Shi M-G, Huang Q., Dong J, Sun Z-F., Lan Q. Experimental Study of Combination Therapy against Human Glioma Xenograft by Differentiation-Inducing Agent and Cytotoxic Chemotherapeutic Drug. *Chinese Journal of Cancer*, 2002, 21(10): 190-1094.

Du H-L., Qi Y., Shi Y-J., Bu D-F., Wu S-L. Apoptosis and Re-expression of p16 Gene in the Myeloma Cell Line U266 Induced by Synergy of Histone Deacetylase Inhibitor and Demethylating Agent.  *Chinese Journal of Cancer,* 2002, 21(10):1057-1061.

Kennedy C., Byth K., Clarke C.L., DeFazio A., Cell Proliferation in the Normal Mouse Mammary Gland and Inhibition by Phenylbutyrate. *Molecular Cancer Therapeutics* Vol. 1, 1025-1033, Oct. 2002.

Sirchia S.M., Ren M., Pili R.ironi E., Somenzi G., Ghidoni R., Toma S., Nicolo G., Sacchi N.. Endogenous Reactivation of the RARß2 Tumor Suppressor Gene Epigenetically Silenced in Breast Cancer *Cancer Research 62,* 2455-2461, May 1, 2002.

Gore SD, Weng LJ, Zhai S, Figg WD, Donehower RC, Dover GJ, Grever M, Griffin CA, Grochow LB, Zabalena Y, Hawkins AL, Burks K and Miller CB. Impact of prolonged infusions of the Putative Differentiating Agent Sodium Phenylbutyrate on Myelodysplastic Syndromes and Acute Myeloid Leukemia. *Clinical Cancer Research* Vol. 8, 963-970, April 2002

Clarke K.O., Ludeman S.M., Springer J.B., Colvin O.M., Lea M.A., Harrison L.E. Exposure to a deuterated analogue of Phenylbutyrate retards S-phase progression in HT-29 colon cancer cells. *Journal of Pharmaceutical Sciences, Vol. 91, No. 4*, April 2002.

Chang T-H, Szabo E., Enhanced Growth Inhibition by Combination Differentiation Therapy with Ligands of Peroxisome Proliferator-activated Receptor-y and Inhibitors of Histone Deacetylase in Adenocarcinoma of the Lung. *Clinical Cancer Research* Vol. 8, 1206-1212, April 2002.

Shao N, Huang Q, Sun J, Dong J, Wang A, Wang F, Zhu W, A putative pathway in differentiation of SHG-44 glioma cells induced by sodium phenylbutyrate. The Human Genome Organization, HGM2002, Poster 451.

Zhu Q, Zhang J-W, Zhu H-Q, Shen Y-L, Flexor M, Jia P-M, Yu Y, Cai X, Waxman S, Lanotte M, Chen S-J, Chen Z, and Tong J-H. Synergic effects of arsenic trioxide and cAMP during acute promyelocytic leukemia cell maturation subtends a novel signaling cross-talk. *Blood*, Feb 2002; 99: 1014 - 1022.

D-C Zhou, Kim SH, Ding W, Schultz C, Warrell R P, Jr, and Gallagher R E. Frequent mutations in the ligand-binding domain of PML-RAR after multiple relapses of acute promyelocytic leukemia: analysis for functional relationship to response to all-trans retinoic acid and histone deacetylase inhibitors in vitro and in vivo*. Blood*, Feb 2002; 99: 1356 - 1363.

Feinman R., Clarke, K.O., Harrison LE. Phenylbutyrate-Induced Apoptosis is Associated with Inactivation of Nf-кB in HT-29 colon cancer cells. *Cancer Chemother Pharmacol* (2002) 49:27-34.

Goh M., Chen F., Paulsen M.T., Yeager A.M., Dyer E.S., Ljungman M. Phenylbutyrate Attenuates the Expression of Bcl-XL, DNA-PK, Caveolin-1, and VEGF in Prostate Cancer Cells1. *Neoplasia* Vol. 3, No. 4, 2001, pp. 331-338.

Cosentini E, Haberl I, Pertschy P, Teleky B, Mallinger R, Baumgartner G, Wenzl E and Hamilton G. The differentiation inducers phenylacetate and phenylbutyrate modulate camptothecin sensitivity in colon carcinoma cells in vitro by intracellular acidification. *International Journal of Oncology* 19: 1069-1074, 2001

Calvaruso G, Carabillo M, Guiliano M, Lauricella M, D’Anneo A, Vento R, Tesoriere G. Sodium phenylbutyrate induces apoptosis in human retinoblastoma Y79 cells: The effect of combined treatment with the topoisomerase I-inhibitor topotecan. *Int. Journal of Oncology* 18: 1233-1237, 2001.

Gilbert J, Baker SD, Bowling MK, Grochow L, Figg WD, Zabelina Y, Donehower RC, Carducci MA: A Phase I Dose Escalation and Bioavailability Study of Oral Sodium Phenylbutyrate in Patients with Refractory Solid Tumor Malignancies. *Clin Cancer Res*. 7: 2292-2300, 2001.

Gore SD, Weng LJ, Zhai S, Figg WD, Donehower RC, Dover GJ, Grever M, Griffin CA, Grochow LB, Rowinsky EK, Zabalena Y, Hawkins AL, Burks K, Miller CB: Impact of the Putative Differentiating Agent Sodium Phenylbutyrate on Myelodysplastic Syndromes and Acute Myeloid Leukemia. *Clin Cancer Res.* 7: 2330-9, 2001

Carducci MA, Gilbert J, Bowling MK, Noe D, Eisenberger MA, Sinibaldi V, Zabelina Y, Chen TL, Grochow LB, Donehower RC. A Phase I clinical and pharmacological evaluation of sodium phenylbutyrate on an 120-h infusion schedule. *Clin Cancer Res*. 7(10):3047-55, Oct 2001

Pili R, Kruszewski MP, Hager BW, Lantz J, Carducci MA. Combination of phenylbutyrate and 13-cis retinoic acid inhibits prostate tumor growth and angiogenesis. *Cancer Research* 61, 1477-85, Feb. 15, 2001.

Berg S., Serabe B., Aleksic A., Bomgaars L., McGuffey L., Dauser R., Durfee J., Nuchtern J., Blaney S. Pharmacokinetics and cerebrospinal fluid penetration of phenylacetate and phenylbutyrate in the nonhuman primate. *Cancer Chemother Pharmacol*. 47: 385-390. February 2001.

**BLOOD**

Huang A, Young TL, Dang T, Shi Y, McAlpine CS, Werstuck GH. 4-phenylbutyrate and valproate treatment attenuates the progression of atherosclerosis and stabilizes existing plaques. *Atherosclerosis*, Vol 266, Pages 103-112, November 2017.

<https://pubmed.ncbi.nlm.nih.gov/29024862>

Almeida, A., Murakami, Y., Baker, A., Maeda, Y., Roberts, I., Kinoshita, T., Layton, DM, Karadimitria, A. Targeted Therapy for Inherited GPI Deficiency. *The New England Journal of Medicine* 2007; 356:1641-7.

 <https://www.nejm.org/doi/full/10.1056/nejmoa063369>

Tveten K, Holla OL, Ranheim T, Berge KE, Leren TP, Kulseth MA. 4-Phenylbutyrate restores the functionality of a misfolded mutant low-density lipoprotein receptor. *FEBS J* 2007;274(8):1881-1893.

<https://febs.onlinelibrary.wiley.com/doi/full/10.1111/j.1742-4658.2007.05735>

TvetenK, Holla OL, Renheim T, Berge KE, Leren TP, Kulseth MA. Rescue of the low-density lipoprotein receptor 2A mutant G544V by 4-Phenylbutyrate. *Molecular chaperones and the heat shock response* 2006;187.

 <https://pubmed.ncbi.nlm.nih.gov/17408384/>

#### SICKLE CELL ANEMIA, THALASSEMIA & COOLEY’S ANEMIA

Perrine SP. Fetal globin stimulant therapies in the beta-hemoglobinopathies: principles and current potential. *Pediatr Ann* 2008; 37 (5): 339-346.

<https://pubmed.ncbi.nlm.nih.gov/18543545/>

Hines P, Dover GJ, Resar LMS. Pulsed-dosing with oral sodium Phenylbutyrate increases hemoglobin F in a patient with sickle cell anemia. *Pediatr Blood Cancer* 2008; 50 (2): 357-359. <https://onlinelibrary.wiley.com/doi/abs/10.1002/pbc.21104>

Xing H, Zhang S, Koeffler HP, Fung, MC. Cucurbitacin D Upregulataes fetal hemoglobin expression in K562 cells and human erythroid progenitors. *Blood* 2007; 110 (11, Part 2): 26B-27B.

<https://ashpublications.org/blood/article/110/11/3833/58328/Cucurbitacin-D-Upregulates-Fetal-Hemoglobin>

Odièvre M, Brun M, Krishnamoorthy R, lapouméroulie and Elion J. Sodium Phenylbutyrate Down regulates Endothelin-1 Expression in Cultured Human Endothelial Cells: Relevance to Sickle-Cell Disease. *American Journal of Hematology*, 82:357-362, 2007.

Perrine S, Trudel M, Castaneda SA, Mankidy R, Boosalis MS, Mpollo M-SEM, White GL, Bohacek R, Faller DV. A new generation of gamma globin gene inducers act on novel molecular and cellular targets. *Blood* 2006; 108 (11, Part 1): 453A.

Thompson AA. Advances in the management of sickle cell disease. *Pediatr Blood Cancer* 2006; 45 (5): 533-539.

Singer ST, Kuypers FA, Olivieri NF, Weatherall DJ, Mignacca R, Coates TD, Davies S, Sweeters N, Vichinsky EP. Fetal haemoglobin augmentation in E/β0 thalassaemia: clinical and haematologival outcome. *British Journal of Haematology,* 2005, 131, 378-388

Witt, Olaf, Mönkemeyer, Sven, Rönndahl, Gabi, Erdlenbruch, Bernhard, Reinhardt, Dirk, Kanbach, Katrin and Pekrun, Arnulf. Induction of fetal hemoglobin expression by the histone deacetylase inhibitor apicidin. *Blood,* March 1, 2003, Volume 101, Number 5

Pace BS, White GL, Dover GJ, Boosalis MS, Faller DV, and Perrine SP. Short-chain fatty acid derivatives induce fetal globin expression and erythropoiesis in vivo. *Blood,* 15 December 2002, Vol. 100, No. 13, pp. 4640-4648

# UREA CYCLE DISORDER/ ORNITHINE TRANSCARBAMYLASE DEFICIENCY

Peña-Quintana, L., Llarena, M., Reyes-Suárez D., Aldámiz-Echevarria, L. Profile of sodium phenylbutyrate granules for the treatment of urea-cycle disorders: patient perspectives. *Patient Preference and Adherence* September 6, 2017, 11: 1489-1496. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5593420/>

Lee B, Rhead W, Diaz GA, et al. Phase 2 comparison of a novel ammonia scavenging agent with sodium phenylbutyrate in patients with urea cycle disorders: safety, pharmacokinetics and ammonia control. *Mol Genet Metab* 2010 Jul; 100(3):221-08

Tuchman M, Lee B, Lichter-Konecki U, Summar ML, Yudkoff M, Cederbaum SD, Kerr DS, Diaz GA, Seashore MR, Lee HS, McCarter RJ, Batshaw ML. Cross-sectional multicenter study of patients with urea cycle disorders in the United States. Urea Cycle Disorders Consortium of the Rare Diseases Clinical Work Network, *Mol Genet Metab* 2008: 94 (4): 397-402.

Leonard JV, Ward P, Martin P, Morris AAM. Hypothesis: proposals for the management of a neonate at risk of hyperammonaemia due to a urea cycle disorder. *Eur J Pediatr* 2008; 167 (3): 305-309.

Lee B, Garovoy MR, Gargosky SE, Berry SA. Preliminary data on adult patients with urea cycle disorder (UCD) in an open-label, switch-over, does-escalation study comparing a new ammonia scavenger glyceryl tri (4-phenylbutyrate) (HPN-100), to buphenyl (sodium phenylbutyrate – PBA). *Journal of Inherited Metabolic Disease* 2008; 31 (Suppl. 1): 91.

Dobbelaere DD. Sodium phenylbutyratae (Ammonaps) in the treatment of patients with urea cycle disorders – European post-approval data. *Journal of Inherited Metabolic Disease* 2008; 31 (Suppl. 1): 92.

Maillot F, Crenn P. Urea cycle disorders in adult patients. *Revue Neurologique (Paris)* 2007; 163 (10): 897-903.

Bhattacharya K, Briddon A, Lee PJ. A review of biochemical outcomes of adults with OTC deficiency. *Journal of Inherited Metabolic Disease* 2007; 30 (Suppl. 1): 82.

Wright GA, Davies NA, Ytrebo LM, Stadlbaure V, Fuskevag O-m, Zwigmann C, Hodges S, Jalan R. L-ornithine Phenylacetate reduces arterial ammonia, improves brain osmolytes and reduces brainwater in a bile duct ligated pat model of cirrhosis. *Hepatology* 2007; 46 (4, Suppl S): 604A-605A.

Kern RM, Yang Z, Kim PS, Grody WW, Iyer RK, Cederbaum SD. Arginase induction by sodium phenylbutrate in mouse tissues and human cell lines. *Molecular Genetics and Metabolism* 90 (2007) 37.41.

Eather G, Coman D, Lander C, J. McGill Carbamyl phosphate synthase deficiency: Diagnosed during pregnancy in a 41-year-old. *Case Reports/Journal of Clinical Neuroscience 13* 2006: 702-706.

Singh RH, Acosta PB, Kennedy MP, Longo N, Elsas LJ. Potassium retention in patients treated for argininosuccinate lyase deficiency. *Journal of Inherited Metabolic Disease* 2006; 29 (1): 48.

Wuebbels BH. Outcomes among male OTC patients treated with Ammonaps. *Journal of Inherited Metabolic Disease* 2006: 29 (Suppl 1): 129.

Saha AS, Langridge P, Playfor SD. The pattern of intravenous drug administration during the transfer of critically ill children by a specialist transport team. *Paediatr Anaesth* 2006: 16 (10):1063-1067

C Vilatoba M, Eckstein C, Bilbao G, Smyth CA, Jenkins S, Thompson JS, Eckhoff De, Contreras JL. Sodium 4-phenylbutyrate protects against liver ischemia reperfusion injury by inhibition of endoplasmic reticulum stress mediated apoptosis. *Surgery* 2005; 138 (2): 342-351.

Bachmann C. Long-term outcome of urea cycle distorders. *Acta Gastroenterol Belg* 2005; 68 (4): 466-468.

Horslen S.P., McCowan T.C., Goertzen T.C., Warkentin P.I., Cai H.B., Strom S.C., Fox I.J. Isolated Hepatocyte Transplantation in an Infant with Severe Urea Cycle Disorder. *Pediatrics* Vol. 111 No. 6 June 2003.

Legras A., Labarthe F., Maillot F., Garrigue M-A,. Kouatchet A., Ogier de Baulny H., Late diagnosis of ornithine transcarbamylase defect in three related female patients: Polymorphic presentations. *Crit. Care Med.* 2002 Vol. 30, No. 1.

Burlina A.B., Ogier H., Korall H., Trefz F.K. Long-term treatment with Sodium Phenylbutyrate in ornithine transcarbamylase-deficient patients. *Molecular Genetics and Metabolism* 72, 3512-355 March 2001

Batchaw ML., MacArthur RB, Tuchman M., Alternative pathway therapy for urea cycle disorders: twenty years later. *J Pediatr.,* 138 (1 Suppl):S46-54; discussion S-54-5. Jan 2001.

Summar M., Current strategies for the management of neonatal urea cycle disorders. *J. of Pediatrics,* (138: S30-S39) Jan. 2001.

CYSTIC FIBROSIS

Chanoux RA, Rubenstein RC. Molecular chaperones as targets to circumvent the CFTR defect in cystic

Fibrosis. *Front. Pharmacol* July 17, 2012.

<https://www.frontiersin.org/articles/10.3389/fphar.2012.00137/full>

Suaud L, Mikker K, Panichelli AE, et al. 4-Phenylbutyrate stimulates Hsp 70 expression through the Elp2 component of elongator and STAT-3 in cystic fibrosis epithelial cells. *Journal Biol Chem* 2011, Dec 30; 286(52):45083-92.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3247989/>

Roque, T.,Boncoeur, E., Saint-Criq, V., Bonvin, E., Clement, A., Tabary, O., Jacquot, J. Pro-inflammatory effect of sodium 4-phenylbutyrate in ΔF508-CFTR lung epithelial cells: Involvement of ERK1/2 and JNK signaling. *JPET,* June 23, 2008, DOI:10.1124/jpet.107.135186. <https://pubmed.ncbi.nlm.nih.gov/18574003/>

Singh OV, Pollard HB, Zeitlin, PL. Chemical Rescue ofΔF508-CFTR Mimics Genetic Repair in Cystic Fibrosis Bronchial Epithelial Cells. *Molecular & Cellular Proteomics* 7.5, February, 2008.

Virginie Prulièr-Escabasse, Carole Planés, Estelle Escudier, Pascale Fanen, André Coste, Christine Clerici. Modulation of Epithelial Sodium Channel Trafficking and Function by Sodium 4-Phenylbutyrate in Human Nasal Epithelial Cells. *JBC Papers in Press,* September 21, 2007, DOI 10.1074/jbc.M702384200.

Claudiu Iordache, Marek Duszyk. Sodium 4-Phenylbutyrate upregulates EnaC and sodium absorption in T84 cells. *Experimental Cell Research* 313 (2007) 305-311

Prulière-Escabasse, V., Planès, C., Escudier, E., Fanen, P., Coste, A., Clerici, C.Modulation of Epithelial Sodium Channel Trafficking and Function by Sodium 4-Phenylbutyrate in Human Nasal Epithelial Cells. *Journal of Biological Chemistry* September 2007

Vij, Neeraj, Fang, Shengyun and Zeitlin, Pamela L. Selective Inhibition of Endoplasmic Reticulum-associated Deradation Rescues ΔF508-Cystic Fibrosis Transmembrane Regulator and Suppresses Interleukin-8 Levels. *The Journal of Biological Chemistry*, Vol. 281, No. 25 pp. 17369-17378, June 23, 2006.

Singh O.V., Vij N., Mogayzel Jr. P.J., Jozwik C., Pollard H.B., Zeitlin P. L., Pharmacoproteomics of 4-Phenylbutyrate-treated IB3-1 Cystic Fibrosis Bronchial Epithelial Cells. *Journal of Proteome Research* 2006, 5, 562-571.

Kerem E. Pharmacological Induction of CFTR Function in Patients with Cystic Fibrosis: Mutation-Specific Therapy. *Pediatric Pulmonology* 40:183-196 (2005).

Céline René, Magali Taulan, Florence Iral, Julien Doudement, Aurore L’Honoré, Catherine Gerbon, Jacques Demaille, Mireille Claustres and Marie-Catherine Romey, Binding of serum response factor to cystic fibrosis transmembrane conductance regulator CArG-like elements, as a new potential CFTR transcriptional regulation pathway. *Nucelic Acids Research,Vol. 33, No. 16, 5271-5290,* 2005.

Suaud L, Rubenstein RC. Activation of STAT-3 in CF epithelial cell by Sodium 4-Phenylbutyrate. *FASEB Journal* 2005; 19 (4, Suppl. S, Part 1): A658.

Wright J.M., Zeitlin P.L., Cebotaru L., Guggino S.E., Guggino W.B., Gene expression profile analysis of 4-phenylbutyrate treatment of IB3-1 bronchial epithelial cell line demonstrates a major influence on heat-shock proteins. *Physiol Genomics 16:204-211*, 2004*.*

Lim M., McKenzie K., Floyd A.D., Kwon E., Zeitlin P.L. Modulation of ΔF508 Cystic Fibrosis Transmembrane Regulator Trafficking and Function with 4-Phenylbutyrate and Flavonoids. *Am.* *J. Respir. Cell Mol. Biol*. Vol. 31, pp. 351-357, 2004.

Wang W-J., Mulugeta S., Russo S.J., Beers M.F., Deletion of exon 4 from human surfactant protein C results in aggresome formation and generation of a dominant negative, *Journal of Cell Science* 116, 683-692, 2003.

Roomans G.M. Pharmacological Approaches to Correcting the Ion Transport Defect in Cystic Fibrosis. *Am J. Respir Med.* 2003; 2(5):413-431

Poschet J.F., Skidmore J., Bouchjer J.C., Firoved A.M., Van Dyke R.W., Deretic V. Hyperacidification of Cellubrevin Endocytic Compartments and Defective Endosomal Recycling in Cystic Fibrosis Respiratory Epithelial Cells, *The Journal of Biological Chemistry* Vol. 277, No. 16, April 2002

.

Zeitlin, P., Diener-West, M., Rubenstein, R., Boyle, M., Lee, C., Brass-Ernst, L. Evidence of CFTR Function in Cystic Fibrosis after Systemic Administration of 4-Phenylbutyrate. *Molecular Therapy*, Vol. 6, No. 1, July 2002

Farinha Carols M., Nogueira, Paulo, Mendes, Filipa, Penque, Deborah and Amaral, Margarida D. The human Dnaj homologue (Hdj)-1/heat-shock protein (Hsp) 40 co-chaperone is required for the *in vivo* stabilization of the cystic fibrosis transmembrane conductance regulator by Hsp70. *Biochem. J.* (2002) 366, 797-806.

# ADRENOLEUCODYSTROPHY (ALD)

Brose RD, Shin G, McGuinness MC, Schneidereith T, Purvis S, Dong GX, Keefer J, Spencer F, Smith KD. Activation o the stress proteome as a mechanism for small molecule therapeutics. *Hum Mol Genet* Oct 2012 1;21(19):4237-52.

<https://pubmed.ncbi.nlm.nih.gov/22752410/>

Baarine M, Ragot K, Genin EC, Hajj HE, Trompier D, Andreoletti P, Ghandour MS, Menetrier F, Cherkaoui-Malki M, Savary S, Lizard. Peroxisomal and mitochondrial status of two murine oligodendrocytic cell lines (158N,158JP): potential models or the study of peroxisomal disorders associated with dysmyelination processes. *J Neurochem* Oct 2009;111(1):119-31. <https://pubmed.ncbi.nlm.nih.gov/19659692/>

Gondcaille C., Depreter M. Fourcade S., Lecca M.R., Leclercq S., Martin P.G.P., Pineau T., Cadepond F., ElEtr M., Bertrand N., Beley A., Duclos S., De Craemer D., Roels F., Savary S., Bugaut M., Phenylbutyrate up-regulates the adrenoleucodystrophy-related gene as a nonclassical peroxisome proliferator. *The Journal of Cell Biology*, Vol. 169, No. 1, 93-104, April 2005. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2171887/>

Girard S, Bruckert E, Turpin G. Endocrine disease in adrenoleukodystrophy. *Ann Med Intern (Paris)* Feb 2001;152(1):15-26.

McGuinness MC, Zhang HP, Smith KD Evaluation of pharmacological induction of fatty acid beta-oxidation in X-linked adrenoleukodystrophy. *Mol Genet Metab* Sept-Oct 2001;74(1-2):256-63

Wei H., Kemp S, McGuinness MC, Moser AB, Smith KD. Pharmacological induction of Peroxisomes in Peroxisome Biogenesis Disorders. *Ann Neurol,* 47:286-296. 2000.

# KIDNEY/RENAL

Bonnemaison ML, Marks-Nelson ES, Boesen EI. Sodium 4-phenylbutyrate treatment protects against renal injury in NZBWF1 mice. *Clin Sci (Lond)* Jan 2019;133(2):167-180. <https://www.meta.org/papers/sodium-4-phenylbutyrate-treatment-protects/30617186>

Randhawa R, Bhardwaj R, Kaur T. Amelioration of hyperoxaluria-induced kidney dysfunction by chemical chaperon 4-phenylbutyric acid.  *Urolithiasis* Apr 2019;47(2):171-179

Guo J, Zhu J, Ma L, Shi H, Hu J, Zhang S, Hou L, Xu F, An Y, Yu H, Ge J. Chronic Kidney Disease Exacerbates Myocardial Ischemia Reperfusion Injury; Rol of Endoplasmic Reticulum Stress-Mediated Apoptosis. *Shock* Jun 2018;49(6):712-720

Bhardwaj R, Tandon C, Dhawan DK, Kaur T. Effect of endoplasmic reticulum stress inhibition of Hyperoxaluria-induced oxidative stress; influence on cellular ROS sources. *World J Urol* Dec 2017;35(12):1955-1965

Liu SH, Yang CC, Chan DC, Wu CY, Chen LP, Huang JW, Hung KY, Chiang CK. Chemical chaperon 4-phenylbutyrate protects against the endoplasmic reticulum stress-mediated renal fibrosis *in vivo* and *in vitro. Oncotarget*a Apr 19, 2016, 7(16): 22116-22127

Karoui Ke, Viau A, Dellis O, Bagattin A, Nguyen C, Baron W, Burtin M, Broueilh M, Heidet L, Mollet G, Druilhe A, Antignac C, Knebelmann B, Friedlander G, Bienaime F, Gallazzini M, Terzi F. Endoplasmic reticulum stress drives proteinuria-induced kidney lesions via Lipocalin 2. *Nat Commun* Jan 2016; 7:10330

Mohammed-Ali Z, Lu C, Marway MK, Carlisle RE, Ask K, Lukic D, Krepinsky JC, Dickhout JG. Endoplasmic reticulum stress inhibition attenuates hypertensive chronic kidney disease through reduction in proteinuria. *Sci Rep* Feb 2017; 7:41572

Uggenti C, Briant K, Streit AK, Thomson S, Koay YH, Baines RA, Swanton E, Manson FD.  *Dis Model Mech* Nov 2016;9(11):1317-1328

Kolb PS, Ayaub EA, Zhou W, Yum V, Dickout JG, Ask K. The therapeutic effects of 4-phenylbutyric acid in maintaining proteostasis *Int J Biochem Cell Biol* Apr 2015;1:45-52

Carlisle RE, Brimble E, Werner KE, Cruz GL, Ask K, Ingram AJ, Dickhout JG. 4-Phenylbutyrate inhibits tunicamycin-induced acute kidney injury via CHOP/GADD153 repression. *PLoS One* Jan 2014;9(1):e84663

Kemter E, Sklenak S, Rathkolb B, de Angelis MH, Wolf E, Aigner B, Wanke R. No amelioration of uromodulin maturation and trafficking defect by sodium 4-phenylbutyrate in vivo: studies in mouse models of uromodulin-associated kidney disease. *J Biol Chem* Apr 2014;289(15):10715-26

Choi S.W., Ryu O.H., Choi S.J., Song I.S., Bleyer A.J., Hart T.C. Mutant Tamm-Horsfall Glycoprotein Accumulation in Endoplasmic Reticulum Induces Apoptosis Reversed by Colchicine and Sodium 4-Phenylbutyrate. *J. Am. Soc. Nephrol.* 16:3006-3014, 2005.

Liu Xiao Li, Nephrin cellular trafficking and intracellular interactions, Division of Matrix Biology Dept. of Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden, May 2004.

Liu X.L., Cotta Done S., Yan K., Kilpelainen P., Pikkarainen T., Tryggvason K. Defective Trafficking of Nephrin Missense Mutants Rescued by a Chemical Chaperone. *J. Am. Soc. Nephrol.* 15:1731-1739, 2004.

# AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Corman A, Jung B, Häggblad, Bräutigam, Lafarga V, Lindemalm L, Hühn, Carreras-Puigvert J, Fernandez-Capetillo O. A Chemical Screen Identifies Compounds Limiting the Toxicity of C9ORF72 Dipeptide Repeats. *Cell Chem Biol*. Feb 2019;26(2):235-243.e5.

[**cell-chemical-biology/pdf/S2451-9456(18)30380-5.pdf**](http://www.cell.com/cell-chemical-biology/pdf/S2451-9456%2818%2930380-5.pdf)

Del Signore, S.J., Amante, D.J., Kim, J., Stack, E.C., Goodrich, S., Cormier, K., Smith, K., Cudkowicz, M.E., Ferrante, R.J. Combined riluzole and sodium phenylbutyrate therapy in transgenic amyotrophic lateral sclerosis mice. *Amyotrophic Lateral Sclerosis,* Volume 10,, Issue 2, April 2009.

Cudkowicz, M.E., Aneres, P.L., et al. Macdonald, S.A., et al. Phase 2 study of sodium Phenylbutyrate in ALS. *Amyotroph Lateral Scler.* 2009; 10(2):99-106

Scott, S, Kranz, JE, Cole, J, Lincecum, JM, Thompson, K, Kelly, N, Bostrom, A, Theodoss, J, Al-Nakhala, BM, Vieira FG, Ramasubbu, J, Heywood, JA. Design, power and interpretation of studies in the standard murine model of ALS. *Amyotroph Lateral Scler* 2008; 9 (1): 4-15.

Cudkowicz, ME, Andres, PL, Choudry, R, MacDonald, SA, Zhang, H, Schoenfeld, D, Ferrante, RJ. Safety and dose escalating study of oral sodium phenylbutyrate in subjects with ALS *Neurology* 2007; 68 (12, Suppl. 1): A90.

Traynor BJ, Bruijn L, O’Neill F, Fagan G, Cudkowicz ME. Neuroprotective agents for clinical trials in ALS: a systematic assessment. *Neurology* 2006; 67(1):20-27

Petri S., Kiaei M., Kipiani K., Chen J., Calingasan N.Y., Crow J.P., Beal M.F., Additive neuroprotective effects of a histone deacetylase inhibitor and a catalytic antioxidant in a transgenic mouse model of amyotrophic lateral sclerosis. *Neurobiology of Disease* 22, 40-49 (2006).

Carri, MT, Grignaschi, G, Bendotti, C. Targets in ALS: designing multidrug therapies. *Trends Pharmacol Sci* 2006; 27 (5): 267-273.

Traynor, BJ, Bruijn, L, Conwit, R, Beal, F, O’Neill, G, Fagan, SC, Cudkowicz, ME. *Neurology* 2006; 67 (1): 20-27.

Bruijn LI, Cudkowizc, M. Therapeutic targets for amyotrophic lateral sclerosis: Current treatments and prospects for more effective therapies. *Expert Rev Neurother* 2006: 6 (3): 417-428.

DiBernardo, A.B., Cudkowicz, M.E. Translating preclinical insights into effective human trials in ALS. *Biochimica et Biophysica Acta* 1762 (2006) 1139-1149.

Ryu H, Smith K, Camelo S.I., Carreras I., Lee J., Iglesias A.H., Dangond F., Cormier K.A., Cudkowicz M.E., Brown Jr. R.H., Ferrante R.J. Sodium phenylbutyrate prolongs survival and regulates expression of anti-apoptotic genes in transgenic amyotrophic lateral sclerosis mice. *Journal of Neurochemistry,* 2005, 93, 1087-1098.

 [pubmed.ncbi.nlm.nih.gov/15934930/](https://pubmed.ncbi.nlm.nih.gov/15934930/)

**CEREBRAL ISCHEMIC INJURY**

Lei J., Wang, B., Feng, D., Huang, L., Li, Y., Li, T., Zhu, G., Li, C., Li, F., Gao, G., Li, G. Pretreatment with Sodium Phenylbutyrate Alleviates Cerebral Ischemia/Reperfusion Injury by Upregulating DJ-1 Protein. *Frontiers Neurol.,* June 9, 2017.

Krishnamoorthy S, Sharma SS. Sodium phenylbutyrate ameliorates focal cerebral ischemic/reperfusion injury associated with comorbid type 2 diabetes by reducing endoplasmic reticulum stress and DNA fragmentation. *Behav Brain Res* Nov 2011;225(1):110-6

Qi X., Hosoi T., Okuma Y., Kaneko M., Nomura Y., Sodium 4-Phenylbutyrate Protects against Cerebral Ischemic Injury, *Molecular Pharmacology* 66:899-908, 2004.

**EPILEPSY**

Sánchez-Elexpuru G, Serratosa JM, Sanz P, Sánchez MP. 4-Phenylutyric acid and metformin decrease sensitivity to pentylenetetrazol-induced seizures in a malin knockout model of Lafora disease. *Neuroreport* Mar 2017;28(5):268-271

Loron AG, Sardari S, Narenjkar J, Sayyah M. In silico Screening and Evaluation of the Anticonvulsant Activity of Docosahexaenoic Acid-Like Molecules in Experimental Models of Seizures. *Iran Biomed J* Jan 2017;21(1):32-9

Berthier A, Payá M, Garcia-Cabrero AM, Ballester MI, Heredia M, Serratosa JM, Sánchez MP, Sanz P. Pharmacological Interventions to Ameliorate Neuropathological Symptons in a Mouse Model of Lafora Disease. *Mol Neurobiol* Mar 2016;53(2):1296-1309

Weise S, Syrbe S, Preuss M, Bertsche A, Merkenschlager A, Bernhard MK. Pronounced reversible hyperammonemic encephalopathy associated with combined valproate-topiramate therapy in a 7-year old girl. *Springerplus* June 2015;4:276

Yokoi N, Fukata Y, Kase D, Miyazaki T, Jaegle M, Ohkawa T, Takahashi N, Iwanari H, Mochinzuki Y, Hamakubo T, Imoto K, Meijer D, Watanabe M, Fukata M. Chemical corrector treatment ameliorates increased seizure susceptibility in a mouse model of familial epilepsy. *Nat Med* Jan 2015;21(1):19-16

Bogdanovic, M.D., Kidd, D., Briddon, A., Duncan, J.S., Land, M.M. Late onset heterozygous ornithine transcarbamylase deficiency mimicking complex partial status epilepticus. *J. Neurol. Neurosurg Psychiatry,* 2000, 69:813-815

**CARDIAC INJURY**

Zhang Z, Zhao L, Zhou Y, Lu X, Wang Z, Wang J, Li W. Taurine ameliorated homocysteine-induced H9C2 cardiomyocyte apoptosis by modulating endoplasmic reticulum stress. *Apoptosis* May 2017;22(5):647-661

Takatori O, Usui S, Okajima M, Kaneko S, Ootsuji H, Takashima SI, Kobayashi D, Murai H, Furusho H, Takamura M. Sodium 4-Phenylbutyrate Attenuates Myocardial Reperfusion Injury by Reducing the Unfolded Protein Response. *J Cardiovasc Pharmacol Ther* May 2017;22(3):282-292

Jain K, Suryakumar G, Ganju L, Singh SB. Amelioration of ER stress by 4-phenylbutyric acid reduces chronic hypoxia induced cardiac damage and improves hypoxic tolerance through upregulation of HIF-1a. *Vascul Pharmacol* Aug 2016;83-36-46

Jian L, Lu Y, Lu S, Lu C. Chemical Chaperone 4-Phenylbutyric Acid Reduces Cardiac Ischemia/Reperfusion Injury by Alleviating Endoplasmic Reticulum Stress and Oxidative Stress. *Med Sci Monit* Dec 2016;22.5218-5227

Okajima, M., Takamura, M., Usui, S., Kaneko, S. Sodium 4-phenylbutyrate protects against myocardial ischemia-reperfusion injury by reducing unfolded protein response-mediated apoptosis in mice. *30th International Symposium on Intensive Care and Emergency Medicine, Brussels, Belgium* March 9-12, 2010

Daosukho,C., Chen, Y., Noel, T., Sompol, P., Nithipongvanitch, R., Velex, J.M., Oberley, T.D., St. Clair, D.K. Phenylbutyrate, a histone deacetylase inhibitor, protects against Adriamycin-induced cardiac injury. *Free Rauduc Bio Med.* 42(12):1818-1825 June 15, 2007.

# HUNTINGTON’S DISEASE

Naia L, Cunha-Oliveria T, Rodrigues J, Rosenstock TR, Oliveria A, Ribeiro M, Carmo C, Oliveria-Sousa S, Duarte A, Hayden MR, Rego AC. Histone Deacetylase Inhibitors Protect Against Pyruvate Dehydrogenase Dysfunction in Huntington’s Disease *J Neurosci* Mar 2017;37(10):2776-2794. <https://www.jneurosci.org/content/jneuro/37/10/2776.full.pdf>

Upagupta C, Carlisle RE, Dickhout JG. Analysis of the potency of various low molecular weight

chemical chaperones to prevent protein aggregation. *Biochem Biophys Res Commun* Apr 2017; 486(1):163-170.

Ebbel, E.N., Leymarie, N., Schiavo, S., etal. Identification of Phenylbutyrate-generated metabolites in Huntington disease patients using parallel liquid chromatography/electrochemical arran/mass spectrometry and off-line tandem mass spectrometry. *AnalyticalBiochem.* 2010; 399(2):153-61

Hogarth, P, Lovrecic, L, Kraine, D. Sodium Phenylbutyrate in Huntington ’s disease: A Dose-Finding Study. *Movement Disorders,* 2007, Vol. 22, No. 13.

Sadri-Vakili, Ghazaleh and Cha, Jang-Ho J. Mechanisms of Disease: histone modifications in Huntington’s disease. *Nature Clinical Practice Neurology,* June 2006, Vol. 2, No. 61.

Borovecki F., Lovrecic L. Zhou J., Jeong H., Then F., Rosas H.D., Hersch S.M., Hogarth P., Bouzou B., Jensen R.V., Krainc D. Genome-wide expression profiling of human blood reveals biomarkers for Huntington’s disease. *PNAS* August 2, 2005, Vol. 102 No. 31 (11023-11028).

Gardian G., Browne S.E., Choi D-K., Klivenyi P., Gregorio J., Kubilus J.K., Ryus H., Langley B., Ratan R.R., Ferrante R.J., Beal M.F. Neuroprotective Effects of Phenylbutyrate in the N171-82Q Transfenic Mouse Model of Huntington’s Disease. *The Journal of Biological Chemistry* Vol. 280, No.1, Jan. 7, 2005 (556-563).

Tolchin, E. Biomarkers of Huntington’s Disease Found in Blood 7/26/05. *Bioscience Technology,* [*http://www.biomedical*](http://www.biomedical)*products.com*

Ferrante R.J., Kubilus J.K., Lee J., Ryu Hl, Beesen A., Zucker B., Smith K., Kowall N. W., Ratan R. R., Luthi-Carter R., Hersch S.M., Histone Deacetylase Inhibition by Sodium Butyrate Chemotherapy Ameliorates the Neurodegenerative Phenotype in Huntington’s Disease Mice. *J Neurosci* 2003; 23 (28): 9418-9427.

**MULTIPLE SCLEROSIS (MS)**

Dasgupta S, Zhou Y, Jana M, Banik NL, Pahan K. Sodium Phenylacetate Inhibits Adoptive Transfer of Experimental Allergic Encephalomyelitis in SJL/J Mice at Multiple Steps. *J Immunology* 2003, 170:3874-3882.

**PARKINSON’S DISEASE**

Chompoopong S, Jarungjitaree S, Punbanlaem T, Rungruang T, Chongthammakun S, Kettawan, A, Taechowisan T. Neuroprotective Effects of Germinated Brown Rice in Rotenone-Induced Parkinson’s-Like Disease Rats. *Neuromolecular Med* Sept 2016; 18(3):334-46

Roy, A., Ghosh A., Jana A., Liu X., Brahmachari S., Gendelman HE., Pahan K. Sodium Phenylbutyrate controls neurinflammatory and antioxidant activities and protects dopaminergic neurons in mouse models of Parkinson’s disease. *PLoS*, 2012:7(6):e38113.doi:10.1371/journal.pone.0038113.

 <https://pubmed.ncbi.nlm.nih.gov/22723850/>

Zhou, W., Bercury, K., Cummiskey, J., Luong, N., Lebin, J., Freed, C.R. Phenylbutyrate Upregulates DJ-1 and Protects Neurons in Cell Culture and in Animal Models of Parkinson’s Disease. *JBC Papers.* March 3, 2011.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3083206/>

Tamaki A, Yanagida T, Kitamura Y, Takata K, Taniguchi T. Neuroprotective effect of chemical chaperone 4-Phenylbutyrate on rotenone-induced dopaminagic neurodegeneration. *Journal of Pharmacological Sciences* 2008;106 (suppl. 1);233P.

Inden M, Kitamura Y, Takeuchi H, Yanagida T, Takata K, Kobayashi Y, Taniguchi T, Yoshimoto K, Kaneko M, Okuma Y, Taira T, Ariga H, Shimohama S. Neurodegeneration of mouse nigrostriatal dopaminergic system induced by repeated oral administration of rotenone is prevented by 4-phenylbutyrate, a chemical chaperone. *J Neurochem* 2007; 101(6):1491-1504.

Kubota, Kyoko, Niinuma, Yoshifumi, Kaneko, Masayuki, Okuma, Yasunobu, Sugai, Mami, Omura, Tomohiro, Uesugi, Mai, Uehara, Takashi, Hosoi, Toru, Nomura, Yasuyuki. Suppressive effects of 4-Phenylbutyrate on the aggregation of Pael receptors and endoplasmic reticulum stress. *Journal of Neurochemistry*, 2006, 97, 1259-1268

Gardian, G., Yang, L., Cleren, C., Calingasan, N.Y., Klivenyi, P., and Beal, N.F. Neuroprotective Effects of Phenylbutyrate Against MPTP Neurotoxicity. *NeuroMolecule Medicine*, 2005 Volume 5

# SPINAL MUSCULAR ATROPHY

Hauke, J, Riessland, M, Lunke, S, Eyoupoglu, IY, Bloumche, I, El-Osta, A, Wirth, B, Hahnen E. Survival motor neuron gene 2 silencing by DNA methylation correlates with spinal muscular atrophy disease severity and can be bypassed by histone deacetylase inhibition. *Hum Mol Genet* 2009 ; 18 (2) : 304-317.

Bosboom, WM, Vrancken, AF, van den Berg, LH, Wokke, JH, Iannaccone, ST. Drug treatment for spinal muscular atrophy types II and III. *Cochrane Database Syst Rev* 2009 ; 1 : CD006282.

Dayangaoc-Erden, D, TopaloAlu, H, Erdem-Yurter, H. A preliminary report on spinal muscular atrophy lymphoblastoid cells lines : are they an appropriate tool for drug screening  *Adv Ther* 2008 ; 25 (3) : 274-279.

Dayangaç-Erden, Topaloğlu, Haluk, Erdem-Yurter, Hayat, A Preliminary Report on Spinal Muscular Atrophy Lymphoblastoid Cell Lines : Are They an Appropriate Tool for Drug Screening ? *Adv Ther* 2008 ;25(3) :274-279.

Lunn, M.R., Wang, C.H. Spinal Muscular Atrophy. *Lancet* 2008 ; 371 (9630) :2120-33

Mercuri, E., Bertini E., Messina S., Solari, A. etal. Randomized, double-blind, placebo-controlled trial of phenylbutyrate in spinal muscular atrophy. *Neurology* 2007; 68:1-1

Darras, BT, Kang, PB. Clinical trials in spinal muscular atrophy. *Curr Opin Pediatr* 2007; 19 (6): 675-679.

Swoboda, KJ. Prospective evaluation of pre-symptomatic infants with spinal muscular atrophy: Implications for early therapeutic intervention. *Annals of Neurology* 2007; 62 (Suppl. 11): S2.

Davies S.L., Moral M.A. Spinal muscular atrophies – distinctions and therapeutic progress. *Drugs of the*

Wirth, B, Brichta, L, Schrank, B, Lochmouller, H, Blick, S, Baasner, A, Heller, R. Mildly affected patients with spinal muscular atrophy are partially protected by an increased SMN2 copy number. *Hum Genet* 2006; 119 (4): 422-428

Wirth, B, Brichta, L, Hahnen, E. Spinal muscular atrophy: from gene to therapy. *Semin Pediatr Neurol* 2006; 13 (2): 121-131.

Wirth, B, Brichta, L, Hahnen, E. Spinal muscular atrophy and therapeutic prospects. *Prog Mol Subcell Biol* 2006; 44: 109-132.

Ganta M, Grzeschik SM, Heavlin WD, Wang CH. Phenylbutyrate modulates multiple neuronal survival ene expression in SMA cells. *Annals of Neurology* 2006; 60 (Suppl. 10): S140.

Brahe C., Vitali T., Tiziano F.D., Amgelozzi C., Pinto A.M., Borgo F., Moscato U., Bertini E., Mercuri E., Neri G. Phenylbutyrate increases SMN gene expression in spinal muscular atrophy patients. *European J. of Human Genetics* (2005) 13, 256-259.

Schwartz, M. The molecular-genetic background of spinal muscular atrophy: Diagnosis, prognosis and future treatments. *Ugeskr Laeg* 2005: 167 (7): 745-748.

Mercuri E., Bertini E., Messina S., Pelliccioni M., D’Amico A., Colitto F., Mirabella M., Tiziano F.D., Vitali T., Angelozzi C., Kinali M., Main M., Brahe C. Pilot trial of phenylbutyrate in spinal muscular atrophy. *Neuromuscular Disorders* Vol 14, Issue 2,(130-135) Feb 2004.

Andreassi C., Angelozzi C., Tiziano F.D., Vitali T., De Vincenzi E., Boninsegna A., Villanova M., Bertini E., Pini A., Nmeri G., Brahe C. Phenylbutyrate increases SMN expression in vitro: relevance for treatment of spinal muscular atrophy. *European Journal of Human Genetics* (2004) 12, 59-65

# ALZHEIMER’S DISEASE

Barbero-Camps E, Fernandez A, Baulies A, Martinez L, Fernandez-Checa J, Colell A. Endoplasmic reticulum stress mediates amyloid ß neurotoxicity via mitochondrial cholesterol trafficking. *Am J Pathol* July 2014;184(7):2066-81

Corbet, G., Roy A., Pahan K. Sodium Phenylbutyrate Enhances Astrocytic Neurotrophin Synthesis via Protein Kinase C (PKC)-mediated Activation of cAMP-esponse Element-binding Protein (CREB) Implications for Alzheimer Disease Therapy. *The American Society for Biochemistry and Molecular Biology* 2013

Cuadrado-Tejefor, M., Ricobaraza A., Torrijo R., Franco R., Garcia-Osta, A., Phenylbutyrate is a

# Multifaceted Drug that Exerts Neuroprotective Effects and Reverses the Alzheimer’s Disease-like Phenotype of a Commonly Used Mouse Model. *Current Pharmaceutical Design,* Vol.19, No. 28, pp. 5076-5084(9). November 28, 2013.

# <https://www.ingentaconnect.com/content/ben/cpd/2013/00000019/00000028/art00006>

# Ricobaraza A., Cuadrado-Tejefor M., Marco S., Perez-Otano I., Garcia-Osta A. Phenylbutyrate rescues

#  dendritic spine loss associated with memory deficits in a mouse model of Alzheimer disease.

#  *Hippocampus.*2012 May: 22(5): 1040-50.doi: 10.1002/hipo.20883.Epub 2010 Nov 10.

Cuadrado-Tejedor M, Garcia-Osta A, Ricobaraza A, Oyarzabal J, Franco R. Defining the mechanism of action of 4-phenylbutyrate to develop a small-molecule-based therapy for Alzheimer’s disease. *Curr Med Chem* 2011;18(36):5545-53.

Ricobaraza, A., Cuadrado-Tejedor, M., Pérez-Mediavilla, A., Frechilla, D., Del Río, J., García-

 Osta, A. Phenylbutyrate Ameliorates Cognitive Deficit and Reduces Tau Pathology in an Alzheimer’s disease Mouse Model. *Neuropsychopharmacology* January 14, 2009;doi:10.1038/nnp.2008.229

Liu N, Qiang W, Kuang X, Thuillier P, Lynn WS, Wong Paul KY. The peroxisome proliferator phenylbutyric acid (PBA) protects astrocytes from ts1 MoMuLV-induced oxidation cell death. *J Neurovirol* Aug 2002;8(4):318-25

**MUSCLE**

Hayashi G, Labelle-Dumais C, Gould DB. Use of sodium 4-phenylbutyrate to define therapeutic parameters for reducing intracerebral hemorrhage and myopathy in Col4a1 mutant mice. *Dis Model Mech*Jul 2018;11(7):dmm034157. <https://pubmed.ncbi.nlm.nih.gov/29895609/>

Begam M, Abro VM, Mueller AL, Roche JA. Sodium 4-phenylbutyrate reduces myofiber damaabe in a mouse model of Duchenne muscular dystrophy. *Appl Physiol Nutr Metab* Oct 2016;41(10):1108-1111. <https://pubmed.ncbi.nlm.nih.gov/27628198/>

Nogalska, A., D’Agostine, C., Engel, W.K., Askanas, V. Sodium Phenylbutyrate reverses lysosomal dysrunction and decreases amyloid-β42 in an in vitro-model of inclusion-body myositis. *Neurobiology of Disease,* Volume 65, Pages 93-101, May 2014

# AGING

Ono K, Nakashima M. Sodium 4-phenylbutyrate inhibits protein glycation. *Biomed Rep*, December 2020; 13(6):61.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7605125/>

Wagner, G. Towards a life prolonging pill? Small molecules with anti-ageing properties. *Current Drug Targets* 2006: 7 (11): 1531-1537

Burzynski, S.R. Aging:gene silencing or gene activation? *Med Hypotheses* 2005: 64 (1): 201-208

Kang H-L., Benzer S., Min K-T. Life extension in *Drosophila* by feeding a drug. *PNAS* Jan 22, 2002, Vol. 99 No. 2, (838-843).

**EYE**

Zode GS, Bugge KE, Mohan K, et al. Topical ocular sodium 4-phenylbutyrate rescues glaucoma in a myocilin mouse model of primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2012 Mar; 53(3):1557-65.

 <https://pubmed.ncbi.nlm.nih.gov/22328638/>

Christopher Kai-shun Leung, Chinese University of Hong Kong, Sodium 4-Phenylbutyrate has the ability to prevent steroid-induced glaucoma. *Press Release* August 17, 2010

Gong Bo, Zhang Li-Yun, Lam Dennis Shun-Chiu, Pang Chi-Pui, Yam Gary Hin-Fai. Sodium 4-phenylbutyrate ameliorates the effects of cataract-causing mutant gammaD-crystallin in cultured cells. *Molecular Vision 2010* June 4, 2010

Yung-Yue Jeng, Nien-Ting Lin, Pen-Heng Chang, Yuan-Ping Huang, Victor Fei Pang, Chen-Hsuan Liu, Chung-Tien Lin. Retinal ischemic injury rescued by sodium 4-phenylbutyrate in a rat model. *Experimental Eye Research* (84 (2007) 486-492.

Gary Hin-Fai Yam, Katarina Gaplovska-Kysela, Christian Zuber, Jürgen Roth. Sodium 4-Phenylbutyrate Acts as a Chemical Chaperone on Misfolded Myocilin to Rescue Cells from Endoplasmic Reticulum Stress and Apoptosis. *Investigative Ophthalmology & Visual Science,* April 2007, Vol. 48, No.4.

Roth J, Yam GH-F, Gaplovska-Kysela K, Zuber C. Russell body formation and apoptosis in myocilin-caused primary open-angle glaucoma; rescue by the chemical chaperone sodium 4-phenylbutyrate. *FASEB Journal* 2007; 21 (5): A182.

Jeng Y-Y, Lin N-T, Chang P-H, Huang Y-P, Pang VF, Liu C-H, Lin C-T. Retinal ischemic injury rescued by sodium 4-phenylbutyrate in a rat model. *Exp Eye Res* 2007; 84 (3): 486-492.

**RHEUMATOID ARTHRITIS**

Yih-Lin Chung, Ming-Yuan Lee, Ae-June Wang, Lin-Fen Yao. Therapeutic Strategy Uses Histone Deacetylase Inhibitors to Modulate the Expression of Genes Involved in the Pathogenesis of Rheumatoid Arthritis. *Molecular Therapy* Vol. 8, No. 5, November 2003. [https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(03)00235-1](https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016%2803%2900235-1)

**DIABETES**

Vanweert F, Neinast M, Rapis E E, van de Weijer T, Hoeks J, Schrauwen-Hinderling, V B, Blair M C, Bornstein M R, Hesselink M K C, Schrauwen P, Arany Z, Phielix E. Therapeutic Efficiency of Lowering Branched-Chain Amino Acid Levels in Patients with Type 2 Diabetes Using Sodium Phenylbutyrate: A Randomized Placebo Controlled Clinical Intervention Study. *The LANCET* November 2, 2021.

 <https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3944597>

Ono K, Nakashima M. Sodium 4-phenylbutyrate inhibits protein glycation. *Biomed Rep* 10.3892/br.2020.1368 December 2020; 13(6):61

 <https://pubmed.ncbi.nlm.nih.gov/33149906/>

Reddy SS, Shruthi K, Joy D, Reddy B. 4-PBA prevents diabetic muscle atrophy in rats by modulating ER stress response and ubiquitin-proteasome system. *Chem Biol Interact* Jun 2019;306:70-77. <https://pubmed.ncbi.nlm.nih.gov/30980806/>

Kato A, Tatsumi Y, Yako H, Sango K, Himeno T, Kondo M, Kato Y, Kamija H, Nakamura J, Kato K. Recurrent short-term hypoglycemia and hyperglycemia induce apoptosis and oxidative stress via the ER stress response in immortalized adult mouse Schwann (IMS 32) cells. *Neurosci Res* Oct 2019;147:26-32

Zhou Q, Guo W, Jia Y, Xu J. Effect of 4-Phenylbutyric Acid and Tauroursodeoxycholic Acid on Magnesium and Calcium Metabolism in Streptozotocin-Induced Type 1 Diabetic Mice. *Biol Trace Elm Res* June 2019;189(2):501-510.

<https://link.springer.com/article/10.1007/s12011-018-1494-8>

Smith K, Reddy SS, Chitra PS, Reddy GB. Ubiquitin-proteasome system and ER stress in the brain of diabetic rats. *J Cell Biochem* Apr 2019;120(4):5962-5973

Gadallah SH, Ghanem HM, Abdel-Ghaffar A, Metwaly FG, Hanafy LK, Ahmed EK. 4-Phenylbutyric acid and rapamycin improved diabetic status in high fac diet/streptozotocin-induced type 2 diabetes through activation of autophagy. *Arch Physiol Biochem*. June 2019;1-10

Huang Kh, Suan SS, Lin WH, Wu CT, Sheu ML, Chiang CK, Liu SH. Role of Calbindin-D28k in Diabetes-Associated Advanced Renal Proximal Tubule Cell Injury. *Cells* June 2019;8(7):660

Kalpana K, Priyadarshini E, Sreeja S, Jagan K, Anuradha CV. Scopoletin intervention in pancreatic endoplasmic reticulum stress induced by lipotoxicity. *Cell Stress Chaperones* Sep 2018;23(5):857-869

Kong FJ, Ma LL, Guo JJ, Xu LH, Li Y, Q S. Endoplasmic reticulum stress/authophagy pathway is involved in diabetes-induced neuronal apoptosis and cognitive decline in mice. *Clin Sci (Lond)* Jan 2018;132(1):111-125

He Z, Zou S, Yin J, Gao Z, Liu Y, Wu Y, He H, Z Y, Wang Q, Li J, Wu F, Xu A, Jia X, Xiao J. Inhibition of Endoplasmic Reticulum Stress Preserves the Integrity of Blood-Spinal Cord Barrier in Diabetic Rats Subjected to Spinal Cord Injury. *Sci Rep* Aug 2017;7(1):7661

Liu H, Yin JJ, Cao MM, Liu GD, Su Y, Li YB. Endoplasmic reticulum stress induced by lipopolysaccharide is involved in he association between inflammation and autophagy in INS-1 cells. *Mol Med Rep* Nov 2017;(16(5):5787-5792

Cheang WS, Wong WT, Zhao L, Xu J, Wang L, Lau CW, Chen ZY, Ma RCW, Xu A, Wang N, Tian XY, Huang Y. PPARδIs Required for Exercise to Attenuate Endoplasmic Reticulum Stress and Endothelial Dysfunction in Diabetic Mice. *Diabetes* Feb 2017;66(2):519-528

Pomozi V, Brampton C, Szeri F, Dedinski D, Kozák E, van de Wetering K, Hopkins H, Martin L, Váradi A, LeSaux O. Functional Rescue of ABCC6 Deficiency by 4-Phenylbutyrate Therapy Reduces Dystrophic Calcification in Abcc6 -/- Mice. *J Invest Dermatol* Mar 2017;137(3):595-602

Montane J, de Pablo S, Castaño C, Rodríguez-Comas J, Cadavez L, Obach M, Visa M, Alcarras-Vizán G, Sanchez-Martinez M, Nonell-Canals A, Parizas M, Servitja JM, Novials A. Amyloid-induced ß-cell dysfunction and islet inflammation are ameliorate by 4-phenylbutyrate (PBA) treatment. *FASEB J* Dec 2017;(12):5296-5306

Guo R, Wu Z, Jiang J, Liu C, Wu B, Li X, Li T, Mo H, He S, Li S, Yan H, Huang R, You Q, Wu K. New mechanism of lipotoxicity in diabetic cardiomyopathy: Deficiency of Endogenous H2S Production and ER stress. *Mech Ageing Dev* Mar 2017; 162:46-52

Lombardi A, Tomer Y. Interferon alpha impairs insulin production in human beta cells via endoplasmic reticulum stress. *J Autoimmun* Jun 2017;80:48-55

Chiang CK, Wang CC, Lu TF, Huang KH, Sheu ML, Liu SH, Hung KY. Involvement of Endoplasmic Reticulum Stress, Autophagy, and Apoptosis in Advanced Glycation End Products-Induced Glomerular Mesangial Cell Injury. *Sci Rep* Sep 2016;6:34167

Hattori S, Kamiya T, Hara H, Ninomiya M, Koketsu M, Adachi T. CoCl2 Decreases EC-SOD Expression through Histone Deacetylation in COS7Cells. *Bio Pharm Bull* 2016;39(12):2036-2041

Zheng P, Lin Y, Wang F, Luo R, Zhang T, Hu S, Feng P, Liang X, Li C, Wang W. 4-PBA improves lithium-induced nephrogenic diabetes insipidus by attenuating ER stress. *Am J Physiol Renal Physiol* Oct 2016;311(4):F763-F776

Cao AL, Wang L, Chen X, Wang YM, Guo HJ, Chu S, Liu C, Zhang XM, Peng W. Ursodeoxycholic acid and 4-Phenylbutyrate prevent endoplasmic reticulum stressed-induced podocyte apoptosis in diabetic nephropathy. *Lab Invest* June 2016;96(6):610-22

Toma L, Sanda GM, Deleanu M, Stancu CS, Sim AV. Glycated LDL increase VCAM-1 expression and secretion in endothelial cells and promote monocyte adhesion through mechanisms involving endoplasmic reticulum stress. *Mol Cell Biochem* June 2016;417(1-2):169-79

Gu H, Yu J, Don D, Zhou Q, Wang JY, Fang S, Yang P. High Glucose-Repressed CITRD2 Expression Through miR-200b Triggers the Unfolded Protein Response and Endoplasmic Reticulum Strett. *Diabetes* Jan 2016;65(1):149-63

Sharma D, Singh JN, Sharma SS. Effects of 4-phenylbutyric acid on high glucose-induced alterations in dorsal root ganglion neurons. *Neurosci Lett* Dec 2016;635:83-89

Tanis RM, Piroli GG, DaySD, Frizzel N. The effects of glucose concentration and sodium Phenylbutyrate treatment on mitochondrial bioenergetics and ER stress in 3T3-L1 adipocytes. *Biochimica et Biophysica Acts (BBA) – Molecular Cell Research* Volume 1853, Issue 1, Pages 213-221, January 2015.

<https://pubmed.ncbi.nlm.nih.gov/25448036/>

Roy D, Kumar V, James J, Shihabudeen MS, Kulshrestha S, Goel V, Thirumurugan K. Evidence that Chemical Chaperone 4-Phenylbutyric Acid binds to Human Serum Albumin at Fatty Acid Binding Sites. *PLoS One* Jul 2015;10(7):e0133012

Ji X, Yao L, Wang M, Liu X, Peng S, Li K, Xu M, Shen N, Luo L, Sun C. Cystatin C attenuates insulin signaling transduction by promoting endoplasmic reticulum stress in hepatocytes. *FEBS Lett* Dec 2015;589(24Pt B):3938-44

Srinivasan K, Sharma SS. Sodium Phenylbutyrate ameliorates focal cerebral ischemic/reperfusion injury associated with comorbid bype 2 diabetes by reducing endoplasmic reticulum stress and DNA fragmentation. *Behav Brain Res* Nov 20, 2011; 225(1); 110-6

Xiao, C., Giacca, A., Lewis, G.F. Sodium Phenylbutyrate, a Drug With Known Capacity to Reduce Endoplasmic Reticulum Stress, Partially Alleviates Lipid-Induced Insulin Resistance and β-Cell Dysfunction in Humans. *Diabetes Journal,* December 2010

Brend Ray-Sea Hsu, Sxu-Tan Chen, Shin-Huei Fu. Enhancing engraftment of islets using perioperative sodium 4-phenylbtyrate. *International Immunopharmacology* 6 (2006) 1952-1959

Ozcan U., Yilmax E., Ozcan L., et al. Chemical chaperones reduce ER stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science* 2006; 313:1137-40.

Fu S.H., Chen S.T., Hsu B.R.S, Attenuation of Primary Nonfunction for Syngeneic Islet Graft Using Sodium 4-Phenylbutyrate. *Transplantation Proceedings,* 37, 1830-1831 (2005).

**PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY**

Ferriero R, Manco G, Lamantea E, Nusco E, Ferrante MI, Sordino P, Stacpoole PW. Phenylbutyrate Therapy for Pyruvate Dehydrogenase Complex Deficiency and Lactic Acidosis. *Science Translational Medicine,* Volume 5, Issue 175, pp.175ra21, March 6, 2013

**LIVER**

Morinaga M, Kon K, Saito H, Arai K, Uchiyama A, Yamashina S, Ikejima K, Watanabe S. Sodium 4-phenylbutyrate prevents murine dietary steatohepatitis caused by *trans*-fatty acid plus fructose. *Journal of Clinical Biochemistry and Nutrition*, Pages 183-191, 2015.

Van der Velden, L.M., Stapelbroek, J.M., Krieger, E., et al. Folding defects in P-type ATP 8B1 associated with hereditary cholestasis are ameliorated by 4-phenylbutyrate. *Hepatology.*2010;51(1):286-96.

Hayashi H, Sugiyama Y. Short-chain ubiquitination is associated with degradation rate of a cell-surface-resident bile salt export pump (BSEP/ABCB11). *Mol Pharmacol 2009;75(1):143-150.*

Lam P, Soroka CJ, Boyer JL. Chemical chaperones partially reverse the misprocessing of a BRIC2 mutant of the bile sale export pump, ABCB11. *Hepatology 2007;* 46(4, Suppl. S):330A.

Lam P, Pearson CL, Soroka CJ, Xu S, Mennone A, Boyer JL. Levels of plasma membrane expressive and benign mutations of the bile salt export pump (Bsep/Abcb11) correlate with severity of cholestatic diseases.  *Am J Physiol Cell Physiol 2007; 293(5):C1709-1716*

Hayashi, Hisamitsu and Sugiyama, Yuichi. 4-Phenylbutyrate Enhances the Cell Surface Expression and the Transport Capacity of Wild-Type and Mutated Bile Salt Export Pumps. *Hepatology* 2007.45:1506-1516.

Tveten K, Holla OL, Ranheim T, Berge KE, Leren TP, Kulseth MA. 4-Phenylbutyrate restores the functionality of a misfolded mutant low-density lipoprotein receptor. *FEBS J* 2007; 274 (8): 1881-1893.

Tveten K, Holla OL, Ranheim T, Berge KE, Leren TP, Kulseth MA. Rescue of the low-density lipoprotein receptor 2A mutant G544V by 4-phenylbutyrate. *Molecular chaperones and the heat shock response* 2006; 187.

Vilatoba M., Eckstein C., Bilbao G., Smyth C.A., Jenkins S. Thompson J.A., Eckhoff D.E., Contreras J.L. Sodium 4-phenylbutyrate protects against liver ischemia reperfusion injury by inhibition of endoplasmic reticulum-stress mediated apoptosis. *Surgery* Aug 2005; 138:342-51.

**ADDICTION**

Romieu P, Host L, Gobaille S, Sandner G, Aunis D, Zwiller J. Histone deacetylase inhibitors decrease cocaine but not sucrose self-administration in rats. *J Neurosci* 2008; 28 (38): 9342-9348. <https://www.jneurosci.org/content/28/38/9342>

**ISCHEMIC SPINAL CORD DAMAGE**

Mizukami, T., Orihashi, K., Hertambang, B., Takahashi, S., Hamaishi, M., Okada, K., Sueda, T. Sodium 4-Phenylbutyrate protects against spinal cord ischemia by inhibition of endoplasmic reticulum stress. *Journal of Vascular Surgery,* Vol. 52, Issue 6, Page 1580-1586, December 2. <https://pubmed.ncbi.nlm.nih.gov/20843623/>

 **MAPLE SYRUP URINE DISEASE**

Köse M, Canda E, Kagnici M, Uçar SK, Çoker M. A Patient with MSUD: Acute Management with Sodium Phenylacetate/Sodium Benzoate and Sodium Phenylbutyrate. *Case Rep Pediatr* 2017; 2017:1045031.

<https://www.hindawi.com/journals/cripe/2017/1045031/>

Brunetti-Pierri, N., Lanher, B., Erez, A., Ananieva, E.A., Islam, M., Marini, J.C., Sun, Q., Yu, C., Hegde, M., Li, J., Wynn, R.M., Chuang, D.T. Hutson, S., Lee, B. Phenylbutyrate Therapy for Maple Syrup Urine Disease. *Hum. Mol. Genet.*November 23, 2010.

 <https://pubmed.ncbi.nlm.nih.gov/21098507/>

Lee B. Use of Sodium Phenylbutyrate for Treatment of Maple Syrup Urine Disease (MSUD) *American Society of Human Genetics Annual Meeting and the 11th International Congress on Inborn Errors of Metabolism Meeting,* 2009.

**ENDOPLASMIC RETICULUM STRESS**

Choi SW, Ryu OH, Choi SJ, Song IS, Bleyer AJ, Hart TC. Mutant tamm-horsfall glycoprotein accumulation in endoplasmic reticulum induces apoptosis reversed by colchicines and sodium 4-phenylbutyrate. *J Am Soc Nephrol* 2005; 16 (10): 3006-3014.

Kubota K, Niinuma Y, Kaneko M, Okuma Y, Sugai M, Omura T, Uesugi M, Uehara T, Hosoi T, Nomura Y. Suppressive effects of 4-phenylbutyrate on the aggregation of Pael receptors and endoplasmic reticulum stress. *J Neurochem* 2006; 97 (5): 1259-1268.

Yam GF-F, Gaplovska-Kysela K, Zuber C, Roth J. Sodiium 4-phenylbutyrate acts a a chemical chaperone on misfolded myocilin to rescue cells from endoplasmic reticulum stress and apoptosis. *J Invest Ophthalmol Vis Sci* 2007; 48 (4): 1683-1690.

Jang H-J, Jung J, Ha E-S, Choi S-E, Jung S, Kim H, Kim F, Kang Y, Lee K-W. 4PBA (4-phenylbutyrate) reduced palmitate-induced endoplasmic reticulum stress and apoptosis in HUVEC. *Diabetologia* 2007; 50 (1): S278.

**SCHIZOPHRENIA**

He M., Huang X-F., Gao G., Zhou T, Li W., Hu J., Chen J., Li J., Sun T. Olanzapine-induced endoplasmic reticulum stress and inflammation in the hypothalamus were inhibited by an ER stress inhibitor 4-phenylbutyrate. *Psychoneuroendocrinology* June 2019 104:286-299 doi: 10.1016/j.psyneuen.2019.03.017. Epub 2019 Mar 21doi: 1. <https://pubmed.ncbi.nlm.nih.gov/30927713/>

Patel S., Sharma D., Kalia, K., Tiwari, V. Crosstalk between endoplasmic reticulum stress and oxidative stress in schizophrenia: The dawn of new therapeutic approaches. *Neurosci Biobehav Rev.* December, 2017 doi: 10.1016. <https://pubmed.ncbi.nlm.nih.gov/28890198/>

Hasan A., Mitchell A., Schneider A., Halena, T., Akbarian S. Epigenetic dysregulation in schizophrenia: molecular and clinical aspects of histone deacetylase inhibitors. *Eur Arch Psychiatry Clin Neurosci*, June 2013 263 (4): 273-84doi:10.1007/s00406-013-0395-2. <https://pubmed.ncbi.nlm.nih.gov/23381549/>

Weïwer M., Lewis, M.C., Wagner F.F., Holson, E.B. Therapeutic potential of isoform selective HDAC inhibitors for the treatment of schizophrenia. *Future Med Chem*Sept, 2013, 5 (13):1491-508 doi/104155/fmc. 13.141.

<https://pubmed.ncbi.nlm.nih.gov/24024943/>

# OBESITY

He M., Huang X-F., Gao G., Zhou T, Li W., Hu J., Chen J., Li J., Sun T. Olanzapine-induced endoplasmic reticulum stress and inflammation in the hypothalamus were inhibited by an ER stress inhibitor 4-phenylbutyrate. *Psychoneuroendocrinology* June 2019 104:286-299 doi: 10.1016/j.psyneuen.2019.03.017. Epub 2019 Mar 21doi: 1. <https://pubmed.ncbi.nlm.nih.gov/30927713/>

Min, G-K, Kang H-j, Choi B-J, Jeon YH, Cho J-Y, Lee I-K, Kim D.W. Phenylbutyrate Ameliorates High-Fat Diet-Induced Obesity via Brown Adipose Tissue Activation. *Bio Pharm Bull* 2019; 42(9): 1554-1561. Doi: 10.1248/bpb.b 19-00346.

<https://pubmed.ncbi.nlm.nih.gov/31474715/>

Tanis, RM, Piroli, GG, Day, SD, Frizzel, N. The effects of glucose concentration and sodium Phenylbutyrate treatment on mitochondrial bioenergetics and ER stress in 3T3-L1 adipocytes. *Biochimica et Biophysica Acts (BBA) – Molecular Cell Research* Volume 1853, Issue 1, Pages 213-221, January 2015.

 <https://pubmed.ncbi.nlm.nih.gov/25448036/>

# INFECTION AND IMMUNITY

Jellbaure, S., Lopez, A.R., Behnsen, J., Gao, N., Nguyen, T., Murphy, C., Edwards, R.A., Raffatellu, M. Beneficial Effects of Sodium Phenylbutyrate Administration during Infection with Salmonella enterica Serovar Typhimurim. *IAI Journal,* June 2016. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4995890/>

Kulkarni NN, Yi Z, Huehnken C, Agerberth B, Gudmundsson GH. Phenylbutyrate induces cathelicidin expression via the vitamin D receptor: Linkage to inflammatory and growth factor cytokines pathways. *Moleculat Immunology,* Volume 63, Issue 2, Pages 530-539, February 2015. <https://pubmed.ncbi.nlm.nih.gov/25458314/>

# DEPRESSION

Jangra, Ashol, Sriram, Chandra Shaker, Dwivedi, Shubham, Gurjar, Satendra Singh, Hussainm Md Iftikar, Borah, Probodh, Lahkar, Mangala. Sodium Phenylbutyrate and Edaravone Abrogate Chronic Restraint Stress-Induced Behavioral Deficits: Implication of Oxido-Nitrosative, Endoplasmic Reticulum Stress Cascade and Neuroiflammation *Cellular and Molecular Neurobiology,* January 2017, Vol 37, Issue 1, pp65-81.

 <https://pubmed.ncbi.nlm.nih.gov/26886752/>

Jangra, Ashok, Sriramm Chandra Shaker, Lahkar, Mangala Lipopolysaccharide-Induced Behavioral

Alterations Are Alleviated by Sodium Phenylbutyrate via Attenuation of Oxidaive Stress and Neuroinflammatory Cascade. *Inflammation* August 2016, Vol 39 Issur 4, pp1441-1452. <https://pubmed.ncbi.nlm.nih.gov/27192986/>

**AFRICAN SWINE FEVER VIRUS**

Frouco, G., Freitas, F.B., Martins, C., Ferreira, F. Sodium Phenylbutyrate abrogates African Swine Fever Virus replication by disrupting the virus-induced hypoacetylation status of histone H3K9/K14. *Virus Research,* Vol 242, Pages 24-29, October 2017.

 <https://pubmed.ncbi.nlm.nih.gov/28916365/>

**SPERM DISORDERS**

Wang EH, Yao SQ, Tao L, Xi,JY. Sodium 4-Phenylbutyrate Attenuates High-ft Diet-induced Spermatogenesis [J]. *Biomedical and Environmental Sciences,* 2018, 31 (12):876-882. <https://pubmed.ncbi.nlm.nih.gov/30636657/>

Dai L, Endo D, Akiyana N, Yamamoto-Fukuda T, Koji T. Aberrant levels of histone H3 acetylation induce spermatid anomaly in mouse testis. *Histochem Cell Biol* Feb 2015;143(2):209-24. <https://pubmed.ncbi.nlm.nih.gov/25326673/>

**MUSCLE DISEASES**

Brown DM, Jones S, Daniel ZCTR, Brearley MC, Lewis JE, Ebling FJP, Parr T, Brameld JM. Effect of Sodium 4-Phenylbutyrate on Clenbuterol-mediated Muscle Growth. *PLoS,* July 27, 2018; 13(7):e0201481.

 <https://pubmed.ncbi.nlm.nih.gov/30052661/>

**SLC6A1**

Sucic, S, El-Kasaby A, Freissmuth, M. 4-Phenylbutyrate rescues folding-deficient creating transporter-1 variants linked to the creatine transporter deficiency syndrome. *The FASEB Journal, Biochemistry and Molecular Biology*, April, 2019. <https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.2019.33.1_supplement.780.12>

**TREATMENT OF BOVINE MASTITIS**

Wang X, Zhang M, Jiang N, Zhang A. Sodium Phenylbutyrate Ameliorates Inflammatory Response Induced by Staphylococcus aureus Lipoteichoic Acid via Suppressing TLR2/NF-kB/NLRP3 Pathways in MAC-T Cells. *Molecules,* November 22, 2018;23(12). Pii E3026. Doi: 10.3390/molecules 23123056.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6321250/>

# MISCELLANEOUS RESEARCH & ARTICLES

Iannitti T, Palmieri B. Clinical and experimental applications of sodium phenylbutyrate. *Drugs R D* 2011 Sept 1; 2011(3):227049.

Rougé,C, Des Robert, C, Robins, A, Le Bacquer, O, Volteau, C, DeLaCochetière, M-F, Darmaun, D. Manipulation of Citrulline Availability in Humans. *Am J Physiol Gastrointest Liver Physiol* 293: G1061-G1067, 2007.

Caruthers R.L., Johnson C.E. Stability of extemporaneously prepared sodium phenylbutyrate oral suspensions. *Am J Health-Syst Pharm –* Vol 64, July 15, 2007.

Caruthers RL. Stability of sodium phenylbutyrate in two oral liquid vehicles. *ASHP Midyear Clinical Meeting.* 2006; 41.

Kasumov T., Brunengraber L.L., Comte B., Puchowicz M., Jobbins K., Thomas K, David F., Kinman R., Wehrli S., Dahms W., Kerr D., Nissim I., Brunengraber H. New Secondary Metabolites of Phenylbutyrate in Humans and Rats. *Drug Metabolism and Disposition* Vol. 32, No. 1 32:10-19, 2004.

DISCLAIMER: The information presented is intended for educational purposes only for investigators and sponsors of clinical trials that are the subject of an investigational new drug application.