

BIOGRAPHICAL SKETCH

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NAME Georg T. Wondrak, Ph.D.	POSITION TITLE Associate Professor of Pharmacology & Toxicology		
eRA COMMONS USER NAME wondrak			
EDUCATION/TRAINING (Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)			
INSTITUTION AND LOCATION	DEGREE (if applicable)	YEAR(s)	FIELD OF STUDY
Swiss Federal Institute of Technology, Zurich, Switzerland	dipl.Nat.ETH	1987	Biochemistry
Institute of Biotechnology, Technical University, Berlin, Germany	Ph.D.	1997	Biotechnology

A. Personal Statement:

My drug discovery research examines the pathological role of oxidative and proteotoxic stress in melanoma and nonmelanoma skin cancer and solar photodamage. Based on genomic and proteomic target identification efforts, we are designing molecular strategies for chemotherapeutic and chemopreventive intervention:

(I) Our recent research suggests that redox dysregulation (originating from metabolic alterations and dependence on mitogenic and survival signaling through reactive oxygen species) represents a specific vulnerability of cancer cells that can be targeted by apoptogenic prooxidant chemotherapeutics. We are therefore aiming at discovery and target identification of small molecule redox drugs (e.g. synthetically-lethal endoperoxides and genotype-directed modulators of oxidative stress) displaying anti-cancer activity *in vitro* and *in vivo*. We are also testing feasibility of repurposing clinically used antimalarials (including artemisinin-endoperoxides) as therapeutic modulators of oxidative and proteotoxic stress response pathways for cancer cell chemosensitization.

(II) For pharmacological cancer chemoprevention and antioxidant tissue protection from environmental insult, we are aiming at the discovery and design of redox-directed activators of biological stress response pathways. Screening synthetic and food factor-derived compound libraries, we engage in the identification of small molecule cytoprotectants including (i) inducers of the Nrf2/Keap1-orchestrated antioxidant defense and (ii) activators of the HSF1 (heat shock factor 1)-orchestrated heat shock response in epithelial cells. We are particularly interested in the chemopreventive development of cytoprotective biofactors derived from cinnamon (cinnamaldehyde) and edible plants of the American Southwest (e.g. betalain-pigments from prickly pear and saguaro fruits).

B. Positions and Honors:

1988 Research Assistant, Centro de Biología Molecular, Universidad Autónoma, Madrid, Spain
 1989-1992 Medical Manager, Janssen Pharmaceutica, Neuss, Germany
 1993-1997 Research and Teaching Assistant, Ph.D. dissertation "Glycation-damage of nucleic acids", Institute of Biotechnology, Technical University, Berlin, Germany
 1998-2000 Research Postdoctoral Scholar and Scientist III, College of Pharmacy, University of Kentucky,
 2001-2002 Assistant Research Scientist, Department of Pharmacology & Toxicology, Division of Medicinal Chemistry, College of Pharmacy, University of Arizona
 2002-2005 Associate Research Scientist, Department of Pharmacology & Toxicology, Division of Medicinal Chemistry, College of Pharmacy, University of Arizona
 9/2005-5/2011 Assistant Professor, Tenure Track, Department of Pharmacology and Toxicology, Division of Drug Discovery and Development, College of Pharmacy, University of Arizona; Comprehensive Member, Arizona Cancer Center, Therapeutic Development Program
 2008 Annual Sydney E. Salmon Distinguished Junior Investigator award recipient
 6/2011-pres. Associate Professor, Department of Pharmacology and Toxicology, College of Pharmacy, University of Arizona

other service:

- 2009-pres. Councilor, American Society for Photobiology (ASP)
2013 reviewer, 'Omnibus R03/R21: Therapeutics', Special Emphasis Panel, Scientific Review Group 2013/05 ZCA1 RTRB-Z, NIH-NCI
2014 reviewer, NCI Program Project (P01) Special Emphasis Panel (SEP) III, NIH-NCI
2014-2016 President elect, American Society for Photobiology (ASP)

editorial board membership:

- (i) *Free Radical Research*, (ii) *Redox Biology*, (iii) *Photodermatology, Photoimmunology & Photomedicine*

C. Peer-reviewed Publications:

- Williams J.D., Bermudez Y., Park S.L., Stratton S.P., Uchida K., Hurst C.A., and **Wondrak G.T.** Malondialdehyde-derived epitopes in human skin result from acute exposure to solar UV and occur in nonmelanoma skin cancer tissue. (2014) *J. Photochem. Photobiol. B* 132:56-65.
- Qiao S., Tao S., Rojo de la Vega M., Park S.L., Vonderfecht A.A., Jacobs S.L., Zhang D.D., and **Wondrak G.T.** The antimalarial amodiaquine causes autophagic-lysosomal and proliferative blockade sensitizing human melanoma cells to starvation- and chemotherapy-induced cell death. (2013) *Autophagy* 9(12):2087-102.
- Tao S., Justiniano, R., Zhang D.D., and **Wondrak G.T.** The Nrf2-inducers tanshinone I and dihydrotanshinone protect human skin cells and reconstructed human skin against solar simulated UV. (2013) *Redox Biol.* 1(1):532-41.
- Lamore, S.D. and **Wondrak, G.T.** UVA causes dual inactivation of cathepsin B and L underlying lysosomal dysfunction in human dermal fibroblasts. (2013) *J. Photochem. Photobiol. B* 123:1-12.
- Davis A.L., Cabello C.M., Qiao S., Azimian S., **Wondrak G.T.** Phenotypic identification of the redox dye methylene blue as an antagonist of heat shock response gene expression in metastatic melanoma cells. *Int J Mol Sci.* 2013 Feb 19;14(2):4185-202.
- Whitman S.A., Long M., **Wondrak G.T.**, Zheng H., and Zhang D.D. Nrf2 modulates contractile and metabolic properties of skeletal muscle in streptozotocin-induced diabetic atrophy. *Exp Cell Res.* 2013 Oct 15;319(17):2673-83.
- Tao S., Zheng Y., Lau A., Jaramillo M.C., Chau B.T., Lantz R.C., Wong P.K., **Wondrak G.T.**, Zhang D.D. Tanshinone I activates the Nrf2-dependent antioxidant response and protects against As(III)-induced lung inflammation in vitro and in vivo. *Antioxid Redox Signal.* 2013 Nov 10;19(14):1647-61.
- Cabello, C.M., Lamore, S.D., Bair 3rd, W.B., Qiao, S., Azimian, S., Lesson, J.L., and **Wondrak, G.T.** The redox antimalarial dihydroartemisinin targets human metastatic melanoma cells but not primary melanocytes with induction of NOXA-dependent apoptosis. (2012) *Invest. New Drugs* 30(4):1289-301.
- Qiao, S., Cabello, C.M., Lamore, S.D., J.L., Lesson, J.L., and **Wondrak, G.T.** D-Penicillamine targets metastatic melanoma cells with induction of the unfolded protein response (UPR) and Noxa (PMAIP1)-dependent mitochondrial apoptosis. (2012) *Apoptosis* 17:1079-94.
- Qiao, S., Lamore, S.D., Cabello, C.M., Munoz-Rodriguez, J.L., Lesson, J.L., and **Wondrak, G.T.** Thiostrepton is an inducer of oxidative and proteotoxic stress that impairs viability of human melanoma cells but not primary melanocytes. (2012) *Biochem. Pharmacol.* 83(9):1229-40.
- Lamore, S.D. and **Wondrak, G.T.** Autophagic-lysosomal dysregulation downstream of cathepsin B inactivation in human skin fibroblasts exposed to UVA. (2012) *Photochem. Photobiol. Sci.* 11:163-72.
- Wondrak G.T.** and Jacobson E.L. Vitamin B6: beyond coenzyme functions. (2012) *Subcell. Biochem.* 56:291-300.
- Lamore, S.D. and **Wondrak, G.T.** Zinc pyrithione impairs zinc homeostasis and upregulates stress response gene expression in reconstructed human epidermis. (2011) *Biometals*, 24(5):875-90.
- Cabello, C.M., Lamore, S.D., Bair 3rd, W.B., Davis, A.L., Azimian, S., and **Wondrak, G.T.** DCPIP (2,6-Dichlorophenolindophenol) as a genotype-directed redox chemotherapeutic targeting NQO1*2 breast carcinoma. (2011) *Free Radic. Res.* 45(3):276-92.
- Zheng H., Whitman, S.A., Wu, W., Wong, P.K., **Wondrak, G.T.**, Fang, D., and Zhang, D.D. Therapeutic Potential of Nrf2 activators in Streptozotocin-induced diabetic nephropathy. (2011) *Diabetes* 60:3055-66.
- Wondrak G.T.**, Villeneuve NF, Lamore SD, Bause AS, Jiang T, Zhang DD. The Cinnamon-Derived Dietary Factor Cinnamic Aldehyde Activates the Nrf2-Dependent Antioxidant Response in Human Epithelial Colon Cells. (2010) *Molecules* 15:3338-3355.

- Lamore, S.D., Qiao, S., Horn, D., and **Wondrak, G.T.** Proteomic Identification of Cathepsin B and Nucleophosmin as Novel UVA-Targets in Human Skin Fibroblasts. (2010) *Photochem. Photobiol.* 86(6):1307-17. **(This publication was featured on the cover of the issue.)**
- Papoutsis, A.J., Lamore, S.D, **Wondrak G.T.**, Selmin, O.I., and Romagnolo, D.F. Resveratrol prevents epigenetic silencing of BRCA-1 by the aromatic hydrocarbon receptor in human breast cancer cells. (2010) *J. Nutr.* 140(9):1607-14.
- Bair WB 3rd, Cabello CM, Uchida K, Bause AS, **Wondrak G.T.** GLO1-Overexpression in human malignant melanoma. (2010) *Melanoma. Res.* 20(2):85-96.
- Lamore, S.D., Azimian, S., Horn, D., Anglin, B.L., Uchida, K., Cabello, C.M., and **Wondrak, G.T.** The Malondialdehyde-derived Fluorophore DHP-lysine is a Potent Sensitizer of UVA-induced Photooxidative Stress in Human Skin Cells. (2010) *J Photochem Photobiol B*, 101(3):251-64.
- Lamore SD, Cabello CM, **Wondrak G.T.** The topical antimicrobial zinc pyrithione is a heat shock response inducer that causes DNA damage and PARP-dependent energy crisis in human skin cells. (2010) *Cell Stress Chaperones* 15(3):309-22.
- Lamore, S.D., Cabello, C.M., and **Wondrak, G.T.** HMGB1-directed drug discovery targeting cutaneous inflammatory dysregulation. (2010) *Curr Drug Metab.* 11(3):250-65.
- Cabello CM, Bair WB 3rd, Bause AS, **Wondrak GT.** Antimelanoma activity of the redox dye DCPIP (2,6-dichlorophenolindophenol) is antagonized by NQO1. (2009) *Biochem. Pharmacol.* 78(4):344-54.
- Wondrak G.T.** Redox-directed Cancer Therapeutics: Molecular Mechanisms and Opportunities. (2009) *Antioxid. Redox Signal.* 11(12):3013-3069. **(This publication was featured on the cover of the issue.)**
- Cabello CM, Bair WB 3rd, Lamore SD, Ley S, Azimian S, **Wondrak GT.** The experimental chemotherapeutic N6-furfuryladenine (kinetin-riboside) induces rapid ATP depletion, genotoxic stress, and CDKN1A (p21) upregulation in human cancer cell lines. (2009) *Biochem. Pharmacol.* 77(7):1125-38.
- Cabello CM, Bair WB 3rd, Lamore SD, Ley S, Bause AS, Azimian S, **Wondrak GT.** The cinnamon-derived Michael acceptor cinnamic aldehyde impairs melanoma cell proliferation, invasiveness, and tumor growth. (2009) *Free Radic. Biol. Med.* 15:46(2):220-31.
- Wang, X.J., Sun, Z., Villeneuve, N.F., Zhang, S., Zhao, F., Li, Y., Chen, W., Zheng, W., **Wondrak, G.T.**, Wong, P.K., and Zhang, D. Nrf2 enhances resistance of cancer cells to chemotherapeutic drugs: the dark side of Nrf2. (2008) *Carcinogenesis* 29(6):1235-43.
- Wondrak, G.T.** Reactivity-based Drug Discovery using Vitamin B₆-derived Pharmacophores. (2008) *Mini Rev. Med. Chem.* 8:519-528.
- Wondrak, G.T.**, Cabello, C.M., Villeneuve, N.F., et al. Cinnamoyl-based Nrf2 Activators targeting Human Skin Cell Photo-oxidative Stress. (2008) *Free Radic. Biol. Med.* 45(4):385-95.
- Cabello, C.M., Bair, W.B, and **Wondrak, G.T.** Experimental Therapeutics Targeting the Redox Achilles Heel of Cancer. (2007) *Curr. Opin. Investig. Drugs* 8(12):1022-37.
- Wondrak, G.T.** Let the sun shine in: Mechanisms and Potential for Therapeutics in Skin Photodamage. (2007) *Curr. Opin. Investig. Drugs* 8(5):390-400.
- Wondrak, G.T.** NQO1-activated Phenothiazinium Redox Cyclers for the Targeted Bioreductive Induction of Cancer Cell Apoptosis. (2007) *Free Radic. Biol. Med.*, 43(2):178-90.
- Wondrak, G.T.**, Jacobson, M.K. and Jacobson, E.L. Endogenous UVA Photosensitizers: Mediators of Skin Photodamage and Novel Targets for Skin Photoprotection. (2006) *Photochem. Photobiol. Sciences* 5:215-237.
- Wondrak, G.T.**, Jacobson, M.K., and Jacobson, E.L. Anti-Melanoma Activity of Apoptogenic Carbonyl Scavengers. (2006) *J. Pharmacol. Exp. Ther.* 316:805-814.
- Wondrak, G.T.**, Jacobson, M.K. and Jacobson, E.L. Identification of Quenchers of Photoexcited States as Novel Agents for Skin Photoprotection. (2005) *J. Pharmacol. Exp. Ther.* 312:482-491
- Wondrak, G.T.**, Jacobson, M.K., and Jacobson, E.L. An Emerging Molecular Target in Melanoma: Cellular Carbonyl Stress and the Inhibition of Mitochondrial Survival Pathways by Carbonyl Scavenger Agents. (2005) *Curr. Cancer Ther. Rev.* 1:271-276.
- Wondrak, G.T.**, Roberts, M.J., Jacobson, M.K. and Jacobson, E.L. 3-Hydroxypyridine Chromophores are Endogenous Sensitizers of Photooxidative Stress in Human Skin Cells. (2004) *J. Biol. Chem.* 279, 30009-30020.
- Wondrak, G.T.**, Roberts, M.J., Cervantes Laurean, D., Jacobson, M.K. and Jacobson, E.L. Proteins of the Extracellular Matrix are Sensitizers of Photooxidative Stress in Human Skin Cells. (2003) *J. Invest. Dermatol.*, 121, 578-586.
- Roberts, M.J., **Wondrak, G.T.**, Jacobson, M.K. and Jacobson, E.L. DNA Damage by Carbonyl Stress in Human Skin Cells. (2003) *Mutat. Res.*, 522, 45-56.

- Wondrak, G.T.**, Cervantes-Laurean, D., Roberts, M.J., Qasem, J.G., Kim, M., Jacobson, E.L. and Jacobson, M.K. Identification of α -Dicarbonyl Scavengers for Cellular Protection against Carbonyl Stress. (2002) *Biochem. Pharmacol.*, 7105, 1-13.
- Wondrak, G.T.**, Jacobson, E.L. and Jacobson, M.K. Photosensitization of DNA Damage by Glycated Proteins. (2002) *Photochem. Photobiol. Sciences* 1, 355-363.
- Wondrak, G.T.**, Roberts, M.J., Jacobson, M.K. and Jacobson, E.L. Photosensitized Growth Inhibition of Cultured Human Skin Cells: Mechanism and Suppression of Oxidative Stress from Solar Irradiation of Glycated Proteins. (2002) *J. Invest. Dermatol.*, 119, 489-498.
- Jacobson, E.L., Giacomoni, P.U., Roberts, M.J., **Wondrak, G.T.**, and Jacobson, M.K. Optimizing the Energy Status of Skin Cells during Solar Irradiation. (2001) *J. Photochem. Photobiol. B* 63, 141-147.
- Wondrak, G.T.**, Varadarajan, S., Butterfield, D.A., and Jacobson, M.K. Formation of a Protein-Bound Pyrazinium Free Radical Cation during Glycation of Histone H1. (2000) *Free Radic. Biol Med.* 29, 557-567.
- Wondrak, G.T.**, Cervantes-Laurean, D., Jacobson, E.L., and Jacobson, M.K. Histone Carbonylation *in vivo* and *in vitro*. (2000) *Biochem. J.* 351, 769-777.
- Tressl, R., **Wondrak, G.T.**, Kruger, R., and Rewicki, D. New Melanoidin-like Maillard Polymers from 2-Deoxypentoses. (1998) *J. Agric. Food Chem.* 46, 104-110.
- Tressl, R., **Wondrak, G.T.**, Garbe, L., Kruger, R., and Rewicki, D. Pentoses and Hexoses as Sources of New Melanoidin-like Maillard Polymers. (1998) *J. Agric. Food Chem.* 46, 1765-1776.
- Wondrak, G.T.**, Tressl, R., and Rewicki, D. Maillard Reaction of Free and Nucleic Acid-Bound 2-Deoxy-D-ribose and D-Ribose with ω -Amino Acids. (1997) *J. Agric. Food Chem.* 45, 321-327.
- Wondrak, G.T.**, Pier, T., and Tressl, R. Light from Maillard Reaction: Photon Counting, Emission Spectrum, Photography and Visual Perception. (1995) *J. Biolumin. Chemilumin.* 10, 277-84.
- Tressl, R., **Wondrak, G.T.**, Kersten, E. and Rewicki, D. Structure and Potential Crosslinking Reactivity of a New Pentose Specific Maillard Product. (1994) *J. Agric. Food Chem.* 42, 2692-2697.

D. Book Chapters:

- 'Sunscreen-Based Skin Protection Against Solar Insult: Molecular Mechanisms and Opportunities'. **Wondrak GT**, (2014) in: 'Fundamentals of Cancer Prevention'; ISBN 978-3-642-38983-2; publisher: Springer; pp. 301-320.
- Bause, A.S., Lamore, S.D., and **Wondrak, G.T.** More Than Skin Deep: The Human Skin Tissue Equivalent as an Advanced Drug Discovery Tool. (2009) in: *Frontiers in Drug Design and Development*, Caldwell and Attar-Rahman, Co-Eds., Bentham Science Publishers, Bussum, The Netherlands; 4:pp135-161
- Jacobson, E.L., Giacomoni, P.U., Roberts, M.J., **Wondrak, G.T.** and Jacobson, M.K. 'Metabolic Effects of Solar Radiation and Enhancers of Energy Metabolism', (2001) in: *Sun Protection in Man*, Comprehensive Series in Photosciences, P. Giacomoni, Ed., Donat-P. Häder, Giulio Jori (Series eds.), European Society for Photobiology Press, Erlangen, Germany, pp 677-690.
- Tressl, R., **Wondrak, G.T.**, Kersten, E., Kruger, R.P., Rewicki, D. 'Identification of Maillard Type Polymers with Antioxidative Activity', (1998) in: *Functional Foods for Disease Prevention*, ACS Symposium Series 702, Shibamoto, Terao, Osawa editors, Oxford University Press, pp 209-220.

E. Research SupportACTIVE

1 R03 CA167580-01 (PI: Wondrak) 04/01/2012 – 03/31/2014 1.20 calendar

NIH/NCI \$ 100,000 (direct)

'Testing feasibility of artemisinin-based synthetic-lethal suppression of skin photocarcinogenesis'

The major goal of this project is to perform a pilot study targeting murine skin photocarcinogenesis using a library of synthetic-lethal endoperoxide drugs optimized for topical cutaneous delivery.

1 R21 CA166926-01 (Wondrak,Zhang; co-PIs; MPI) 01/01/2013 – 12/31/2014 1.20 calendar

NIH/NCI \$275,000 (direct)

'Targeting Colorectal Carcinogenesis Using a Cinnamon-Derived Food Factor'

The major goal of this project is to perform a pilot study using a cinnamon-derived food factor to prevent colorectal cancer in a murine model of the human disease.

L'OREAL C130820 (PI: Wondrak) 11/01/2013 – 10/31/2014 1.20 calendar

L'Oréal Advanced Research \$ 100,000 (direct)

'Comparative dermal stress response profile of topical treatments'

The major goal of this project is to perform a comparative dermal stress response study of topical treatments using organotypic skin models including reconstructed human epidermis.

To be resubmitted

1 R21 CA175650-01 (PI: Wondrak) 01/01/2014 – 12/31/2015 1.20 calendar

NIH/NCI \$ 275,000 (direct)

'c-Myc-directed synthetic-lethal intervention targeting malignant melanoma'

The major goal of this project is to test the hypothesis that c-myc-driven dysregulation of iron homeostasis mediated by overexpression of transferrin receptor 1 (TfR1) represents a molecular Achilles heel of melanoma cells amenable to synthetic-lethal intervention using iron-activated peroxide drugs. [The project was reviewed as follows: Impact score: 28; Percentile: 19; this application will be resubmitted].

1 R01 ES023786-01 (co-PIs: Wondrak; Zhang) 01/01/2014 – 12/31/2018 1.20 calendar

NIH/NIEHS \$ 1,250,000 (direct)

'Cinnamon-based Nrf2 activation targeting arsenic-potential of solar skin carcinogenesis'

This project tests the hypothesis that environmental skin carcinogenesis caused by the combined action of arsenic and solar photons can be suppressed using cinnamon-derived small molecule Nrf2 activators. [The project was reviewed as follows: Impact score: 38; Percentile: 35; this application will be resubmitted].

COMPLETE

1 R01 CA122484-05 (PI: Wondrak) 07/01/2007 – 5/31/2013

6/01/2012 – 5/31/2013 (no cost extension)

NIH/NCI \$ 760,000 (direct)

'Targeting Glycolytic Control of Melanoma Cell Survival'

ABRC490890 (PI: Wondrak), AZ Biomedical Research Commission, 7/1/2006 – 6/30/09
(\$150,000 total)

'Melanoma Cell Survival Signaling by Glycolytic Intermediates'