

BIOGRAPHICAL SKETCH

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NAME Dlugosz, Andrzej A.	POSITION TITLE Professor		
eRA COMMONS USER NAME (credential, e.g., agency login) dlugosza			
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
Franklin and Marshall College	BA	1975-79	Biology
Pennsylvania State University College of	MD	1980-84	Medicine
National Cancer Institute	Fellow	1988-97	Keratinocyte Biology
Franklin and Marshall College	BA	1975-79	Biology

A. Positions and Honors. A.**Positions and Employment**

- 1984-85 Medical Intern, Roger Williams General Hospital, Providence, RI
 1985-88 Dermatology Resident, Hospital of the University of Pennsylvania, Philadelphia, PA
 1987-88 Chief Resident, Dermatology, Hospital of the University of Pennsylvania, Philadelphia, PA
 1988-95 Guest Researcher/Biotechnology Fellow, LCCTP/NCI/NIH, Bethesda, MD
 1995-97 Senior Staff Fellow, LTVB/NCI/NIH, Bethesda, MD
 1997-04 Associate Professor, Department of Dermatology, University of Michigan
 2004- Professor, Department of Dermatology, University of Michigan
 2009- Professor, Department of Cell & Developmental Biology, University of Michigan

Other Experience, Committee Service, Honors, and Awards

- 1988 Dermatology Foundation Research Fellowship
 1988 American Cancer Society Physician Research Training Fellowship
 1993 Thomas B. Fitzpatrick-Kao Corporation Research Award
 1997- Scientific Director, Cutaneous Oncology Program, U-Michigan Comprehensive Cancer Center
 2001-05 University of Michigan Institutional Review Board
 2000- General Medicine A1 Study Section, Ad Hoc Member
 2002- NCI Program Project Review Panels
 2002- American Society for Clinical Investigation, Elected Member
 2005- American Dermatological Association, Elected Member
 2008- Poth Professor of Cutaneous Oncology
 2008- Associate Director, Cellular & Molecular Biology Graduate Training Program, U-Michigan
 2009 Chair, Medical and Scientific Committee, Dermatology Foundation
 2009- Member, Arthritis, Connective Tissue and Skin (ACTS) Study Section
 2009- Co-director, Cancer Cell Biology Program, U-Michigan Comprehensive Cancer Center

B. Selected peer-reviewed publications (in chronological order, of a total of 64)

- Croop J, Toyama Y, **Dlugosz AA**, Holtzer H. Selective effects of phorbol 12-myristate 13-acetate on myofibrils and 10-nm filaments. *Proc Natl Acad Sci USA* 77:5273-5277, 1980. PMID 350040.
- Croop J, Dubyak G, Toyama Y, **Dlugosz A**, Scarpa A, Holtzer, H. Effects of 12-O-tetradecanoylphorbol-13-acetate on myofibril integrity and Ca²⁺ content in developing myotubes. *Dev Biol* 89:460-474, 1982.
- Dlugosz AA**, Tapscott SJ, Holtzer H. Effects of phorbol 12-myristate 13-acetate on the differentiation program of embryonic chick skeletal myoblasts. *Cancer Res* 43:2780-2789, 1983.
- Dlugosz AA**, Antin PB, Nachmias VT, Holtzer H. The relationship between stress fiber-like structures and nascent myofibrils in cultured cardiac myocytes. *J Cell Biol* 99:2268-2278, 1984. PMID 2113583.
- Hietala O, Dzubow L, **Dlugosz, AA**, Pyle JA, Jenney F, Gilmore SK, O'Brien TG. Activation of human squamous cell carcinoma ornithine decarboxylase activity by GTP. *Cancer Res* 48:1252-1257, 1988.

6. **Dlugosz AA**, Yuspa SH. Staurosporine induces protein kinase C agonist effects and maturation of normal and neoplastic mouse keratinocytes in vitro. *Cancer Res* 51:4677-4684, 1991.
7. **Dlugosz AA**, Yuspa SH. Coordinate changes in gene expression which mark the spinous to granular cell transition in epidermis are regulated by protein kinase C. *J Cell Biol* 120:217-225, 1993. PMCID 2119499.
8. Denning MF, **Dlugosz AA**, Howett MK, Yuspa SH. Expression of an oncogenic *ras*^{Ha} gene in murine keratinocytes induces tyrosine phosphorylation and reduced activity of protein kinase C δ . *J Biol Chem* 268:26079-26081, 1993.
9. **Dlugosz AA**, Cheng C, Williams EK, Dharia AG, Denning MF, Yuspa SH. Alterations in murine keratinocyte differentiation induced by activated *ras*^{Ha} genes are mediated by protein kinase C- α . *Cancer Res* 54:6413-6420, 1994.
10. **Dlugosz AA**, Cheng C, Williams EK, Darwiche N, Dempsey PJ, Mann B, Dunn AR, Coffey RJ Jr, Yuspa SH. Autocrine transforming growth factor α is dispensible for *v-ras*^{Ha}-induced epidermal neoplasia: potential involvement of alternate epidermal growth factor-receptor ligands. *Cancer Res* 55:1883-1893, 1995.
11. Threadgill DW, **Dlugosz AA**, Hansen L, Tennenbaum T, Lichti U, Yee D, LeMantia C, Mourton T, Herrup K, Harris RC, Barnard JA, Yuspa SH, Coffey RJ Jr, Magnuson T. Targeted disruption of mouse EGF receptor- effect of genetic background on mutant phenotype. *Science* 269:230-234, 1995.
12. Denning MF, **Dlugosz AA**, Threadgill DW, Magnuson T, Yuspa SH. Activation of the epidermal growth factor receptor signal transduction pathway stimulates tyrosine phosphorylation of protein kinase C δ . *J Biol Chem* 271:5325-5331, 1996.
13. Stanwell C, Denning MF, Rutberg SE, Cheng C, Yuspa SH, **Dlugosz AA**. Staurosporine induces a sequential program of mouse keratinocyte terminal differentiation through activation of PKC isozymes. *J Invest Dermatol* 106:482-489, 1996.
14. Rutberg SE, Saez E, Glick A, **Dlugosz AA**, Spiegelman BM, Yuspa SH. Differentiation of mouse keratinocytes is accompanied by PKC-dependent changes in AP-1 proteins. *Oncogene* 13:167-176, 1996.
15. Chiang C, Swan RZ, Grachtchouk M, Bolinger M, Litingtung Y, Robertson E, Cooper MK, Gaffield W, Westphal H, Beachy PA, **Dlugosz AA**. Essential role for *Sonic hedgehog* during hair follicle morphogenesis. *Dev Biol* 205:1-9, 1999.
16. Ding Q, Fukami S-i, Meng X, Nishizaki Y, Zhang H, Sasaki H, **Dlugosz A**, Nakafuku M, Hui C-c. Mouse suppressor of fused is a negative regulator of Sonic hedgehog signaling and alters the subcellular distribution of Gli1. *Curr Biol* 9:1119-1122, 1999.
17. Grachtchouk M, Mo R, Yu S, Zhang X, Sasaki H, Hui CC, **Dlugosz AA**. Basal cell carcinomas in mice overexpressing Gli2 in skin. *Nat Genet* 24:216-217, 2000.
18. McBride AA, **Dlugosz A**, Baker CC. Production of infectious bovine papillomavirus from cloned viral DNA by using an organotypic raft/xenograft technique. *Proc Natl Acad Sci USA*, 97:5534-5539, 2000.
19. Sheng H, Goich S, Wang A, Grachtchouk M, Mo R, Lowe L, Sasaki H, Mo R, Kui L, de Sauvage F, Hui C-c, **Dlugosz AA**. Dissecting the oncogenic potential of Gli2 in skin: deletion of an NH(2)-terminal fragment alters tumor phenotype. *Cancer Res* 62:5308-5316, 2002.
20. Mill P, Mo R, Fu H, Grachtchouk M, Kim PCW, **Dlugosz AA**, Hui CC. Sonic hedgehog-dependent activation of Gli2 is essential for embryonic hair follicle development. *Genes Dev* 17:282-94, 2003. PMCID195973.
21. Van Mater D, Kolligs FT, **Dlugosz A**, Fearon ER. Transient activation of β -catenin signaling in cutaneous keratinocytes is sufficient to trigger the active growth phase of the hair cycle in mice. *Genes Dev* 17:1219-1224, 2003. PMCID196062.
22. Grachtchouk V, Grachtchouk M, Lowe L, Johnson TJ, Wei L, Wang A, de Sauvage F, **Dlugosz AA**. The magnitude of hedgehog signaling activity defines skin tumor phenotype. *EMBO J* 22:2741-2751, 2003. PMCID156767.
23. Allen M, Grachtchouk M, Sheng H, Grachtchouk V, Wang A, Wei L, Liu J, Ramirez A, Metzger D, Chambon P, Jorcano J, **Dlugosz AA**. Hedgehog signaling regulates sebaceous gland development. *Amer J Pathol* 163:2173-2178, 2003. PMCID1892397.
24. Brancaccio A, Minichiello A, Grachtchouk M, Antonini D, Sheng H, Parlato R, Dathan N, **Dlugosz AA**, Missero C. Requirement of the forkhead gene *Foxe1*, a target of sonic hedgehog signaling, in hair follicle morphogenesis. *Hum Mol Genet* 13:2595-606, 2004.
25. Hutchin ME, Kariapper MST, Grachtchouk M, Wang A, Wei L, Cummings D, Liu J, Michael LE, Glick A, **Dlugosz, AA**. Sustained Hedgehog signaling is required for basal cell carcinoma proliferation and

- survival: conditional skin tumorigenesis recapitulates the hair growth cycle. *Genes Dev* 19:214-23, 2005. PMID545881.
26. Roessler E, Ermilov AN, Grange DK, Wang A, Grachtchouk M, **Dlugosz AA**, Muenke M. A previously unidentified amino-terminal domain regulates transcriptional activity of wild-type and disease-associated human GLI2. *Hum Mol Genet* 14:2181-2188, 2005.
 27. Grachtchouk M, Liu J, Wang A, Wei L, Bichakjian CK, Garlick J, Paulino AF, Girodano T, **Dlugosz AA**. Odontogenic keratocysts arise from quiescent epithelial rests and are associated with deregulated hedgehog signaling in mice and humans. *Am J Pathol* 169 (3):806-14, 2006. PMID1698812.
 28. Pasca di Magliano M, Sekine S, Ermilov A, Ferris J, **Dlugosz AA**, Hebrok M. Hedgehog/Ras interactions regulate early stages of pancreatic cancer. *Genes Dev* 20:3161-73, 2006. PMID1635150.
 29. Vasireddy V, Uchida Y, Salem N, Kim SY, Mandal MN, Reddy GB, Bodepudi R, Alderson NL, Brown JC, Hama H, **Dlugosz A**, Elias PM, Holleran WM, Ayyagari R. Loss of functional ELOVL4 depletes very long-chain fatty acids (\geq C28) and the unique $\{\omega\}$ -O-acylceramides in skin leading to neonatal death. *Hum Mol Genet* 16:471-82, 2007.
 30. Mosher JT, Yeager KJ, Kruger GM, Joseph NM, Hutchin ME, **Dlugosz AA**, Morrison SJ. Intrinsic differences among spatially distinct neural crest stem cells in terms of migratory properties, fate determination, and ability to colonize the enteric nervous system. *Dev Biol* 303:1-15, 2007. PMID 1910607.
 31. Liu F, Thirumangalathu S, Gallant NM, Yang SH, Stoick-Cooper CL, Reddy ST, Andl T, Taketo MM, **Dlugosz AA**, Moon RT, Barlow LA, Millar SE. Wnt-beta-catenin signaling initiates taste papilla development. *Nat Genet* 39:106-12, 2007.
 32. Dentice M, Luongo C, Huang S, Ambrosio R, Elefante A, Mirebeau-Prunier D, Zavacki AM, Fenzi G, Grachtchouk M, Hutchin M, **Dlugosz AA**, Bianco AC, Missero C, Larsen PR, Salvatore D. Sonic hedgehog-induced type 3 deiodinase blocks thyroid hormone action enhancing proliferation of normal and malignant keratinocytes. *Proc Natl Acad Sci USA* 104:14466-71, 2007. PMID1964817.
 33. Pasca di Magliano M, Biankin AV, Heiser PW, Cano DA, Gutierrez PJ, Deramaudt T, Segara D, Dawson AC, Kench JG, Henshall SM, Sutherland RL, **Dlugosz A**, Rustgi AK, Hebrok M. Common activation of canonical wnt signaling in pancreatic adenocarcinoma. *PLoS ONE* 2:e1155, 2007.
 34. Zavros Y, Waghray M, Tessier A, Bai L, Todisco A, L Gumucio D, Samuelson LC, **Dlugosz A**, Merchant JL. Reduced pepsin A processing of sonic hedgehog in parietal cells precedes gastric atrophy and transformation. *J Biol Chem* 282:33265-74, 2007.
 35. Liu F, Chu EY, Watt B, Zhang Y, Gallant NM, Andl T, Yang SH, Lu MM, Piccolo S, Schmidt-Ullrich R, Taketo MM, Morrisey EE, Atit R, **Dlugosz AA**, Millar SE. Wnt/beta-catenin signaling directs multiple stages of tooth morphogenesis. *Dev Biol* 313:210-24, 2008.
 36. Zhang Y, Andl T, Yang SH, Teta M, Liu F, Seykora JT, Tobias JW, Piccolo S, Schmidt-Ullrich R, Nagy A, Taketo MM, **Dlugosz AA**, Millar SE. Activation of $\{\beta\}$ -catenin signaling programs embryonic epidermis to hair follicle fate. *Development* 135:2161-72, 2008. PMID2516408.
 37. Michael LE, Westerman BA, Ermilov AN, Wang A, Ferris J, Liu J, Blom M, Ellison DW, van Lohuizen M, **Dlugosz A**. Bmi1 is required for Hedgehog-pathway driven medulloblastoma expansion. *Neoplasia* 10:1343-1349, 2008. PMID2586685.
 38. Yang SH, Andl T, Grachtchouk V, Wang A, Liu J, Syu L, Ferris J, Wang TS, Glick AB, Millar SE, **Dlugosz AA**. Pathological responses to oncogenic Hedgehog signaling in skin are dependent on canonical Wnt/ β -catenin signaling. *Nat Genet* 40:1130-5, 2008. PMID: PMC2688690
 39. Gudjonsson JE, Aphale A, Grachtchouk M, Ding J, Nair RP, Wang T, Voorhees JJ, **Dlugosz AA**, Elder JT. Lack of evidence for activation of the Hedgehog pathway in psoriasis. *J Invest Dermatol* 129:635-40, 2009. NIHMSID: NIHMS89356
 40. Sharov AA, Mardaryev AN, Sharova TY, Grachtchouk M, Atoyian R, Byers HR, Seykora JT, Overbeek P, **Dlugosz A**, Botchkarev VA. BMP antagonist Noggin promotes skin tumorigenesis via stimulation of the Wnt and Shh signaling pathways. *Amer J Pathol* 175:1303-14, 2009. Epub 2009 Aug 21. PMID: PMC2731148
 41. Han YG, Kim HJ, **Dlugosz AA**, Ellison DW, Gilbertson RJ, Alvarez-Buylla A. Dual and opposing roles of primary cilia in medulloblastoma development. *Nat Med* 15:1062-5, 2009. Epub 2009 Aug 23.
 42. Wong SY, Seol AD, So PL, Ermilov AN, Bichakjian CK, Epstein EH Jr, **Dlugosz AA**, Reiter JF. Primary cilia can both mediate and suppress hedgehog pathway-dependent tumorigenesis. *Nat Med* 15:1055-61, 2009. Epub 2009 Aug 23.
 43. **Dlugosz AA**, Talpaz M. Following the Hedgehog to New Cancer Therapies. *N Engl J Med* 361:1202-1205, 2009.

C. Research Support.**Ongoing Research Support****R01 AR45973-10 Dlugosz (PI)**

03/07/00-02/28/10

NIH/NIAMS

"Molecular Regulation of Hair Follicle Morphogenesis"

The major goals of this grant are to ascertain whether Hh signaling stimulates hair follicle growth by acting directly on stem cells, their progeny, or both; to determine the function of Hh signaling in sebaceous gland development and maintenance; and to explore the mechanism by which ectopic, focal activation of Hh signaling leads to formation of de novo epithelial buds. Role: PI

R01 CA87837-10 Dlugosz (PI)

07/01/00-02/28/10

NIH/NCI

"Molecular Basis of Epithelial Skin Cancer"

The major goals of this grant are to gain further insight into Hh pathway mediated tumorigenesis by identifying tumor progenitor cells, exploring the involvement of Hh signaling in extracutaneous tumors, and assessing the collective function of Gli proteins in Hh pathway mediated tumorigenesis. Role: PI

R01 CA118875-03 Dlugosz (PI)

07/13/07-05/31/12

NIH/NCI

"Hedgehog Signaling in Upper Digestive Tract Malignancy"

The major goals of this grant are to define the role of Hh signaling in normal and abnormal stomach, and using a novel mouse model of Hh pathway-driven gastric adenocarcinoma, investigate signaling alterations underlying the development of these tumors, identify their cellular origin, and assess whether continued Hh signaling is required for tumor maintenance. Role: PI

2 P01 DK062041-07 Merchant (PI)

08/01/08-07/31/13

NIH/NIDDK

"Cellular Decisions of Differentiation in the GI Tract"

Project 2: *Hedgehog Signaling in Stomach Homeostasis and Pathology*

The major goals of this project are to identify cell types expressing Hh pathway components in stomach, and establish the functions of Hh signaling in gastric epithelium versus mesenchyme. Progeny of embryonic and postnatal Hh-activated cells will be identified using a genetic-inducible fate-mapping approach, and acute and chronic responses to Hh pathway modulation will be examined using conditional transgenic mouse models. Role: Project Director

2 T32 AR007197-32 (Elder)

05/01/08-04/30/13

NIH/NIAMS

"Training Grant in Cell and Molecular Dermatology"

The major goal of this grant is to offer training for postdoctoral research fellows in cell and molecular dermatology at the University of Michigan. Role: Mentor

Helen L. Kay Charitable

01/01/09-12/31/10

Private Foundation (Dlugosz)

"The Hedgehog Pathway in Cancer Development and Maintenance"

Funds from this gift will help cover the cost of producing, characterizing, and maintaining mouse models of human cancer linked to uncontrolled activation of the Hedgehog pathway. Role: PI

Completed Research Support**T32 HD007505 Gumucio (PI)**

05/01/02-04/30/07

NIH/NICHHD

"Training Program in Organogenesis"

The major goal of this grant is to support a pre-and post-doctoral training program in organogenesis, emphasizing a two-mentor structure to facilitate cross-disciplinary training in basic, clinical and applied aspects of organ formation and maintenance. Role: Mentor