

BIOGRAPHICAL SKETCH

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NAME Anton Wellstein, M.D., Ph.D.	POSITION TITLE Professor, Oncology & Pharmacology		
eRA COMMONS USER NAME wellstea			
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
J.Gutenberg-University, Mainz/Germany	MD	1973	Medicine
J.Gutenberg-University, Mainz/Germany	Dr. med.	1977	Clin. Chemistry/Patho
J.W. Goethe-University, Frankfurt/M. Germany	PhD (Habil)	1985	Pharmacology

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

1974-80	Internship and residency training in Internal Medicine, Tropical Medicine, Surgery
1980-87	Fellow; Department Pharmacology, J.W. Goethe-Universität, Frankfurt/M.
1985	Habilitation in Pharmacology (PhD), J.W. Goethe-Universität, Frankfurt/M.
1986	Privatdozent (Res Assist. Professor) Pharmacology, J.W. Goethe-Universität, Frankfurt/M.
1987-89	sabbatical Medicine Branch NCI/NIH, Bethesda (with Marc E. Lippman, MD)
1989	associate Professor, Pharmacology & Medicine, Georgetown University, Washington DC
1994	tenure as Professor, Pharmacology & Medicine, Georgetown University, Washington DC
2000	Chief Division of Biochemistry & Pharmacology, Dept of Oncology Georgetown University

Study Sections

1994-2001	Member, NIH Study Sections NCI SPORE (Skin, Prostate, GI, Brain), SEPs
2001-present	Member, NIH Study Section CAMP, interim Chair MONC (2005)
2002-present	NCI Program for the Assessment of Clinical Cancer Tests (PACCT); Committee Member

Honors

1984, Award for outstanding research at the J.W. Goethe-Universität, Frankfurt/M., Germany; 1985, International Paul-Martini Award for "Novel Approaches in Clinical Pharmacology"; 1987, National Award: Translation of Basic Pharmacology into Therapy. "Preis der Therapiewoche"; 1988 International Boehringer Ingelheim Research Award, "Muscarinic Receptors in vivo"; 1993, Esther-Zoller Breast Cancer Research Lectureship. U.C.S.F.; 1995, 18th San Antonio Breast Cancer Symposium, Plenary Speaker; 1998, Basic Research Award, 18th annual meeting, French Cancer Society, Paris

B. Selected peer-reviewed publications. (selected from >140 peer-reviewed publications)

1. Czubayko F., Smith R.V., Chung H.C., Wellstein A. (1994) Tumor growth and angiogenesis induced by a secreted binding protein for fibroblast growth factors. J Biol Chem 269:28 243-48
2. Liaudet-Coopman E.D.E., Wellstein A. (1996) Regulation of gene expression of a binding protein for fibroblast growth factors by retinoic acid. J Biol Chem 271:21303-308
3. Schulte A.M., Lai S., Kurtz A., Czubayko F., Riegel A.T., Wellstein A. (1996) Human trophoblast and choriocarcinoma expression of the growth factor pleiotrophin attributable to germ line insertion of an endogenous retrovirus. Proc Natl Acad Sci USA 93:14759-64
4. Czubayko F., Schulte A.M., Berchem G.J., Wellstein A. (1996) Melanoma angiogenesis and metastasis modulated by ribozyme-targeting of the secreted growth factor pleiotrophin Proc Natl Acad Sci USA 93:14753-58
5. Czubayko F., Liaudet-Coopman E.D.E., Aigner A., Tuveson A.T., Berchem G., Wellstein A. (1997) A secreted FGF-binding protein can serve as the angiogenic switch in human cancer. Nature Medicine 3:1137-40

6. Czubayko F., Downing S.G., Hsieh S.S., Goldstein D.J., Lu P.Y., Trapnell B.C., Wellstein A. (1997) Adenovirus-mediated transduction of ribozymes abrogates HER-2/neu and pleiotrophin expression and inhibits tumor cell proliferation. Gene Therapy 4:943-49
7. Souttou B., Ahmad S., Riegel A.T., Wellstein A. (1997) Signal transduction pathways involved in the mitogenic activity of pleiotrophin: Implication of MAP kinase and PI3 kinase pathways. J Biol Chem 272: 19588-93
8. Kurtz A., Wang H.L., Darwiche N., Harris V., Wellstein A. (1997) Expression of a binding protein for FGF is associated with epithelial development and skin carcinogenesis. Oncogene 14:2671-2681
9. Schulte A.M., Wellstein A. (1998) Structure and phylogenetic analysis of an endogenous retrovirus inserted into the human growth factor gene pleiotrophin. J Virology 72:6065-72
10. Harris V., Liudet-Coopman E.D.E., Boyle B.B., Wellstein A., Riegel A.T. (1998) Complex transcriptional regulation of an FGF-binding protein gene by phorbol esters. J Biol Chem 273:19130-139
11. Souttou B., Juhl H., Hackenbruck J., Vigny M., Raulais D., Rockeisen J., Klemp J., Wellstein A., (1998) Elevated serum levels of the growth factor pleiotrophin reflect pleiotrophin-positive tumors in patients. J Natl Cancer Inst 90:1468-73
12. Harris VK, Cotticchia CM, List HJ, Wellstein A, Riegel AT (2000) Mitogen-induced expression of the FGF binding protein is transcriptionally repressed through a non-canonical E-box element. J Biol Chem 275:28539-548
13. Weber D, Klomp HJ, Czubayko F, Wellstein A, Juhl H (2000) Pleiotrophin can be rate-limiting for pancreatic cancer cell growth. Cancer Res 60:5284-8.
14. Harris VK, Cotichia CM, Kagan BL, Ahmad S, Wellstein A, Riegel AT (2000). Induction of the angiogenic modulator FGF-BP by epidermal growth factor is mediated through both MEK/ERK and p38 signal transduction pathways. J Biol Chem 275:10802-11
15. Boyle BB, Harris VK, Liudet EDE, Riegel AT, Wellstein A (2000) Differential regulation of a FGF-binding protein by receptor-selective analogs of retinoic acid. Biochem Pharmacol 60:1677-1684
16. List HJ, Lauritsen KJ, Reiter R, Powers C, Wellstein A, Riegel AT (2001) Ribozyme-targeting demonstrates that the nuclear receptor coactivator AIB1 is a rate limiting factor for estrogen-dependent growth of human MCF-7 breast cancer cells. J Biol Chem 276:23763-8
17. Reiter R, Wellstein A, Riegel AT (2001) An isoform of the coactivator AIB1, that increases hormone and growth factor sensitivity, is overexpressed in breast cancer. J Biol Chem 2001, 276:39736-41
18. Tassi E, Al-Attar A, Aigner A, Swift MR, McDonnell K, Karavanov A, Wellstein A. (2001) Enhancement of fibroblast growth factor (FGF) activity by an FGF-binding protein. J Biol Chem 276:40247-53
19. Stoica GE, Kuo A, Aigner A, Sunitha I, Souttou B, Malerczyk C, Caughey DJ, Wen D, Karavanov A, Riegel AT, Wellstein A. (2001) Identification of ALK (anaplastic lymphoma kinase) as a receptor for the growth factor pleiotrophin. J Biol Chem 276:16772-79
20. Harris VK, Kagan BL, Ray R, Coticchia CM, Liudet-Coopman ED, Wellstein A, Riegel AT. (2001) Serum induction of the fibroblast growth factor-binding protein (FGF-BP) is mediated through ERK and p38 MAP kinase activation and C/EBP-regulated transcription. Oncogene 20(14):1730-1738
21. Aigner A, Butscheid M, Kunkel P, Krause E, Lamszus K, Wellstein A, Czubayko F. (2001) An FGF-binding protein (FGF-BP) exerts its biological function by parallel paracrine stimulation of tumor cell and endothelial cell proliferation through FGF-2 release. Int J Cancer 92:510-7
22. Liu XH, Aigner A, Wellstein A, Ray PE (2001). Upregulation of a FGF-binding protein in HIV-1 associated nephropathies. Kidney Internat 59:1717-28
23. Bowden E, Stoica GE, Wellstein A (2002) Anti-apoptotic signaling of pleiotrophin through its receptor, anaplastic lymphoma kinase. J Biol Chem 277:35862-8
24. Stoica GE, Kuo A, Powers C, Bowden ET, Buchert Sale E, Riegel AT, Wellstein A (2002) Midkine binds to Anaplastic Lymphoma Kinase (ALK) and acts as a growth factor for different cell types. J Biol Chem 277:35990-8
25. Powers C, Aigner A, Stoica GE, McDonnell K, Wellstein A (2002) Pleiotrophin signaling through anaplastic lymphoma kinase (ALK) is rate-limiting for glioblastoma growth. J Biol Chem 277:14153-58
26. Aigner A, Ray PE, Czubayko F, Wellstein A (2002) Immunolocalization of an FGF-binding protein reveals a widespread expression during different stages of mouse embryo development. Histochem Cell Biol (2002) 117:1-11
27. Ray R, Cabal-Manzano R, Moser AR, Waldman T, Zipper LM, Aigner A, Byers SM, Riegel AT, Wellstein A (2003) Upregulation of Fibroblast Growth Factor-Binding Protein by beta-catenin during colon carcinogenesis. Cancer Res 63:8085-89

28. Kagan BL, Cabal R, Henke RT, Stoica GE, Nguyen Q, Wellstein A, Riegel AT (2003) Complex regulation of the fibroblast growth factor-binding protein (FGF-BP) in MDA-MB-468 breast cancer cells by CCAAT/enhancer-binding protein beta. Cancer Res 63:1696-705
29. Kurtz A, Aigner A, Cabal R, Butler RE, Hood D, Sessions RB, Czubayko F, Wellstein A (2004) Differential regulation of an FGF-binding protein during skin carcinogenesis and wound healing. Neoplasia 6:595-602
30. Oh A, List HJ, Reiter R, Zhang Y, Gehan E, Wellstein A, Riegel AT (2004) The nuclear receptor coactivator AIB1 mediates IGF-1 induced phenotypic changes in human MCF-7 breast cancer cells. Cancer Res 64:8299-308
31. Henke RT, Haddad BR, Kim SE, Rone JD, Marni A, Jessup JM, Wellstein A, Maitra A, Riegel AT (2004) Overexpression of the nuclear receptor coactivator AIB1 (SRC-3) during progression of pancreatic adenocarcinoma. Clin Cancer Res 10:6134-42
32. Reiter R, Oh A, Wellstein A, Riegel AT (2004) Impact of the Nuclear Receptor Coactivator AIB1 isoform AIB1-Delta3 on estrogenic ligands with different intrinsic activity. Oncogene 23:403-409
33. McDonnell K, Bowden ET, Cabal-Manzano R, Hoxter B, Riegel AT, Wellstein A (2005) Vascular leakage in chick embryos after expression of a secreted binding protein for fibroblast growth factors. Lab Investigation 85:747-755
34. Malerczyk C, Schulte AM, Czubayko F, Bellon L, Macejak D, Riegel AT and Wellstein A (2005) Ribozyme targeting of the growth factor pleiotrophin in established tumors, a gene therapy approach. Gene Therapy 12:339-46
35. Henke RT, Maitra A, Paik S, Wellstein A (2005) Gene expression analysis in sections and tissue microarrays of archival tissues by mRNA in situ hybridization. Histol Histopathol 20:225-37.
36. Tassi, E, Henke, RT, Bowden, ET, Swift, MR, Kodack, DP, Kuo, AH, Maitra, A, and Wellstein, A (2006) Expression of a fibroblast growth factor-binding protein during the development of adenocarcinoma of the pancreas and colon. Cancer Res, 66: 1191-1198
37. Modlinger, P, Chabrashvili, T, Gill, PS, Mendonca, M, Harrison, DG, Griendling, KK, Li, M, Raggio, J, Wellstein, A, Chen, Y, Welch, WJ, and Wilcox, CS (2006) RNA silencing in vivo reveals role of p22phox in rat angiotensin slow pressor response. Hypertension, 47: 238-244
38. Ray, PE, Tassi, E, Liu, XH, and Wellstein, A (2006) Role of fibroblast growth factor-binding protein in the pathogenesis of HIV-associated hemolytic uremic syndrome. Am J Physiol, 290: R105-113
39. Henke, RT, Eun Kim, S, Maitra, A, Paik, S, and Wellstein, A (2006) Expression analysis of mRNA in formalin-fixed, paraffin-embedded archival tissues by mRNA in situ hybridization. Methods, 38: 253-262.
40. Xie, B, Tassi, E, Swift, MR, McDonnell, K, Bowden, ET, Wang, S, Ueda, Y, Tomita, Y, Riegel, AT, and Wellstein, A (2006) Identification of the fibroblast growth factor (FGF)-interacting domain in a secreted FGF-binding protein by phage display. J Biol Chem, 281: 1137-1144
41. Kuo AH, Stoica GE, Riegel AT, Wellstein A (2007) Recruitment of insulin receptor substrate-1 and activation of NF-kappaB essential for midkine growth signaling through anaplastic lymphoma kinase. Oncogene 26:859-69.
42. Tassi E, Walter S, Aigner A, Cabal-Manzano RH, Ray R, Reier PJ, and Wellstein A (2007) Effects on neurite outgrowth and cell survival of a secreted Fibroblast Growth Factor binding protein upregulated during spinal cord injury. Am J Physiol. Epub Jun 6, 2007

Patents / Patent Applications

1. Wellstein A (1998) A retro-peptide that blocks the fibroblast growth factor receptor. US Patent #578 9382.
2. Riegel AT, Harris VK, Wellstein A (1999) FGF-BP promoter sequences as sensors of drug effects. Provisional PCT/US99/16544; international 014749.0104
3. Wellstein A (2000) Identification of a receptor for the growth factor pleiotrophin. Filed 6/2001.
4. Wellstein A, Czubayko F (2001) Inhibition of an FGF-binding protein using ribozymes. USP #6245748
5. Riegel AT, Reiter R, Wellstein A (2002) Coactivators in the diagnosis and treatment of breast cancer. filed
6. Wellstein A, McDonnell K, Ngaiza J (2002) Phage display discovery of metastasis genes.
7. Tso JY, Wellstein A, Chao D (2004) Anti-pleiotrophin antibodies. Filed 3/2004; #10/812,366
8. Wellstein A, Bowden E, Tassi ET (2005) Agonists and antagonists of ALK. filed

C. Research Support

Ongoing Research Support

A. The family of secreted FGF binding proteins.

Over the past 12 years we have pursued expression studies, ribozyme targeting studies, molecular cloning of the human gene, the mouse cDNA and gene, and the rat cDNA as well as characterization of new FGF-BP homologues, BP2 and BP3. In the course of the studies we have characterized the retinoid downregulation of the BP1 gene and have demonstrated its upregulation in some malignant tissues and in models of carcinogenesis. Furthermore, we were able to elucidate molecular mechanisms underlying the transcriptional upregulation of the BP1 gene by tumor promoters and growth factors. In addition to the evaluation of the function and differential regulation of BP1 we have run more detailed mechanistic studies of the activity of BP1 at the protein structure protein / protein, cellular and whole organism levels. In the next phase of this project we will expand these studies and compare BP2 and BP3 with BP1 as well as study the interactions with FGFs other than FGF-1 and FGF-2. This work is supported by one RO1 that was renewed in 2006.

RO1 CA71508-09 (P.I. Wellstein) Biology and Pathology of FGF-binding proteins 06/97 to 11/11

PO1 HL-68686 (Program Director Wellstein) Oxidative stress, Hypertension and an FGF-binding protein (Project #3) 9/01 to 9/11

The goal is to understand, how an FGF-binding protein induces oxidative stress and hypertension.

B. The growth factor pleiotrophin and its signaling through the ALK kinase receptor

The P.I. initially purified this growth factor from breast cancer cell supernatants (Wellstein et al JBC 1992) and the laboratory has worked on expression, ribozyme-targeting, regulation, gene structure and detection of this gene product in the past decade. Most recently, we identified the receptor for pleiotrophin, the ALK kinase receptor and characterized the signal transduction pathway. This work was supported through for some 10 years through an NIH/SPORE grant in Breast Cancer. It is now supported under two RO1s, one on drug discovery and one on the role of PTN in pancreatic cancer metastasis:

RO1 CA101811-01 (P.I. Wellstein – Co-P.I. Kozikowski) Inhibition of the ALK receptor kinase 8/03 to 7/07
Small-molecule ALK kinase inhibitors are studied under this RO1 that proposes structure-based drug design in synthetic chemistry laboratory (Dr. Kozikowski) in a collaborative effort with biological studies in a tumor biology laboratory (Dr. Wellstein). Both investigators are equal P.I.s one for the synthetic chemistry (Dr. K.) and one for biology (Dr. W.).

RO1 CA108440-01 (P.I. Wellstein) Pleiotrophin modulation of pancreatic cancer metastasis 9/03 to 8/08
The contribution of PTN to pancreatic cancer metastasis is studied under this RO1.

C. Proteomics analysis of signal transduction

DAMD W81XWH-06-1-0590. (P.I. Georgetown site Wellstein) 9/06 to 8/11
DOD Center of Excellence Breast Cancer Research
A new Therapeutic Paradigm for Breast Cancer Exploiting Low-Dose Estrogen-Induced Apoptosis
This is a subcontract to the Georgetown University site to run proteomics analysis and data integration of the Program. The overall, national P.I., Dr. Jordan is at FoxChase, Philadelphia.

D. NIH/NCI CCSG, Cancer Center Support grant

Dr. Wellstein has headed the Angiogenesis, Invasion Metastasis Program of the Cancer Center since 1998. This is part of the NCI CCSG grant to the Lombardi Comprehensive Cancer Center infrastructure. The CCSG was last recomputed in 2002.