

## BIOGRAPHICAL SKETCH

**Name:** MARINA ZICHE

**Position Title:** Professor of Pharmacology

**Affiliation:**

Dept. Life Sciences  
University of Siena  
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**Education**

Medical Doctor, Univ. of Florence Medical School, Italy (1977)  
ECFMG examination, USA (1980)  
Board Member of Endocrinology, Univ. of Florence Medical School, Italy (1983)

**Research and professional experience**

1979-81 Fogarty fellow, Lab. Pathophysiology, National Cancer Institute, National Institute of Health, Bethesda, USA  
1984-98 Senior Research Scientist, Dept. Preclinical and Clinical Pharmacology Univ. Florence.  
1985 Guest Scientist, Dept. Hormone Res., Weizman Institute of Science, Rehovot, Israel  
1987 Guest Scientist, Dept. Pharmacology, Karolinska Institutet, Stockholm, Sweden.  
1990-98 Visiting Professor, Microcirculation Research Institute, Dept. Medical Physiology, Texas A&M University, College Station, Texas, USA.  
1998-2000: Associate Professor, Inst. Pharmacological Sciences, Univ. Siena, Siena.  
2000-01 Visiting Professor, University of Texas Southwestern Medical Center, Dallas, TX (USA)  
2000-present: Professor of Pharmacology, School of Pharmacy, Univ. Siena.  
2000-2012: Head, Laboratory of Angiogenesis, Section of Pharmacology, Department of Biotechnology, Univ. Siena.  
Present: Head, Laboratory of Angiogenesis, Department of Life Sciences, Univ. Siena.

**Awards**

1983: "Massimo Lupo" award, Nobile Collegio Caccia di Novara, Italy.  
1997: Alberico Benedicenti Award (Italian Society of Pharmacology)  
Invited speaker in over 60 international meetings over the last 10 years

**Institutional activity**

President, Ethical Committee for the Clinical Evaluation of Drugs, Azienda USL 10 Florence, Italy (1999-2001).  
President and member (2001-2008), School of Biotechnologies for Human Health, University of Siena.  
Coordinator of the II level Master "Governo clinico del farmaco e dispositivo medico" of the University of Siena (2010-2012)  
Member of the Commissione Terapeutica Regione Toscana (from 2013)

## **Grant reviewer**

Deutsche Forschungsgemeinschaft (DFG) (Germany) special project "Angiogenesis: Molecular mechanisms and functional interaction" (1999-2006).

EEC proposal reviewer for the the Framework Programmes (since 1999-2007).

Italian Ministry for University and Research (MIUR) grant evaluator (since 2004)

## **Editorial board**

American Journal of Physiology, Heart and Circulatory Physiology (1994-1998)

British Journal of Pharmacology (2002-2005)

Endothelium (1999-2008)

Laboratory Investigations (2001-2004)

Angiogenesis (since 1997)

Journal of Vascular Research (since 2003)

## **Research fundings (last 10 years):**

### **Non profit agencies and private organizations**

- Title: Interplay between microsomal Prostaglandin E synthase type-1 and tyrosine kinase receptor signaling in tumor progression and angiogenesis. Funding agency: ITT, Firenze, 2012-15.
- Title: Role of bradykinin B2 receptor in the activation of inflammatory angiogenesis. Funding agency: Menarini Ricerche, Florence, 2011-2013
- Title: Microsomal Prostaglandin E synthase type I and EGFR/k-ras in controlling tumor progression and angiogenesis (IG10731). Funding agency: AIRC, 2010-2013
- Title: Role of PGE-2 in tumor progression and angiogenesis. Funding agency: ITT, Firenze, 2008-09.
- Title: mPGES-1, EGFR, prostanoids and growth factors interactions in tumor progression and angiogenesis. Funding agency: Angelini ACRAF SpA, Roma, 2007-10
- Title: Characterization of the functional responses of cells of the vascular wall exposed to nanostructured metallic alloys. Funding agency: Lima Lto SpA, San Daniele del Friuli, 2007-08
- Title: Cerebral vascular pathology: molecular mechanisms of endothelial dysfunction. Funding agency: Telethon, 2007-09
- Title: New Therapeutic strategies for senile dementia: role of beta amyloid on microcirculation. Funding Agency: Fondazione MPS, Siena, 2006-2008.
- Title: Evaluation of PKC antagonists in modulating VEGF induced angiogenesis in a rabbit corneal eye model. Funding Agency: KAI Pharmaceuticals San Francisco USA, 2005-2006.
- Title: Pharmacology of beta amyloid peptides on the cardiovascular system. Funding Agency: SienaBiotech, Siena, 2004.
- Title: Set up of a pilot study to evaluate the proangiogenic effects on coronary microvessels of drugs resulting from the combination of NO and statins. Funding agency: Nicox Research Institute, Bresso (Milano) 2004.

### **Institutional agencies**

-Title: Copper and angiogenesis: study of the mechanisms of cell regulation and development of new angiogenesis modulators. Funding agency: MIUR research project (PRIN), 2010-2012.

-Title: Characterization of prognostic markers in vascular pathologies. Funding agency: Ricerca Finalizzata-Ministero della Salute, 2007-2009

- Title: Role of PGE-2 in tumor progression and angiogenesis. Funding agency: University of Siena, 2007-08.
- Title: Cell senescence and vascular remodeling. Funding agency: MIUR research project (PRIN), 2005-2006.
- Title: Eicosanoids and nitric oxide. Mediators of Cardiovascular, Cerebral and Neoplastic Diseases. Funding Agency: EEC, Sixth Framework programme, Integrated project: EICOSANOX, 2004-2008.
- Title: Angiogenic properties of beta amyloid peptides. Funding agency: University of Siena, 2004-2005.
- Title: Optimization of endothelial responses on nanostructured surfaces to promote angiogenesis. Funding Agency: MIUR research project (FIRB), 2003-2006.
- Title: Interplay of COX-2 and NOS in the mechanisms controlling angiogenesis. Funding Agency: MIUR research project (FIRB), 2003-2006.
- Title: Interaction of microvascular endothelium and activated monocytes as target of novel therapeutic approach in Leishmania Infantum infection. Funding Agency: MIUR research project (FIRB), 2003-2006.

## **Patents**

1) 12 April 1999 patent n. "Angiobalance" F199/A/000086 in collaboration with Prof. M. Pazzagli, University of Florence.

Title: "Plasmids containing multiple competitors and their application for angiogenic factor quantification"

2) 15 April 1999 patent n. MI99A 000777, 11.04.2000 patent n PCT/EP00/03236 in collaboration with Prof. F. Chillemi, University of Milan.

Title: "Polypeptides derived from endostatin exhibiting antiangiogenic activity".

3) 1 March 2001 patent n. MI2001A000426, patent USA n.10/399, 408 in collaboration with Prof. L. Casella, University of Pavia.

Title: "Nitric oxide donor drugs based on metallic centers".

4) December 2000, Patent n. PCT/EP01/14727 in collaboration with Prof. M. Pazzagli, Univ. Florence,

Title: "Extracts of serum of snake, their preparation and use as antitumors"

5) 28 May 2003 patent n. RM 2003 A000264 in collaboration with Prof. M. Botta, University of Siena.

Title: "Derivatives 4 substituted of 1-(2-chloro-2-phenyl)-1H-pyrazolo(3,4-d) pyrimidines and their use"

6) 05/02/2007 patent n. 2007A19D in collaboration with Alessandro Facchini.

Title: "Nanostructured titanium alloys to be used as biomaterials for the preparation of medical-surgical devices".

## **Research topics and experience**

The laboratory of Marina Ziche focuses on research of the endothelium with particular emphasis on angiogenesis, one of the principal functions of this tissue. Angiogenesis, a process which leads to formation of new vessels, has a relevant physiological role during development and in adult life. The involvement of angiogenesis in pathologies, particularly cancer, but also cardiovascular and chronic degenerative diseases, has sparked an intense research interest in this phenomenon.

The laboratory of Prof. Ziche has contributed to research on angiogenesis by characterising molecules (growth factors, cytokines...) which exert important effects on the formation of new blood vessels in pathologies such as cancer and vascular diseases. Other significant contributions deal with the elucidation of signalling pathways involved in angiogenesis (NO/cGMP, COX/prostanoids, FGF-2) and with the control of the acquisition of the angiogenic phenotype by endothelial cells during cancer progression and degenerative processes.

Other topics running in the lab are drug discovery (2 patents) and pharmacogenetics to improve safety and efficacy of prescription in cancer research and host-immune response.

## **Techniques**

The above studies are grounded on a long established repertoire of cell biology, biochemical and molecular biology techniques. The laboratory has a solid and internationally recognized experience on ex-vivo and in vivo techniques to assess angiogenesis (rabbit cornea and matrigel plug in mice), tumor growth (in nude mice), and cardiovascular functions (aorta rings and isolated heart).

The group has expertise in the maintenance and breeding of genetically modified mice (transgenic and KO) and Zebrafish, and assays for pharmacogenetics.

## **Scientific publications**

Author of over 170 publications as scientific papers in peer review journals and invited reviews and chapters in books

All the publications: H index= 48

Last 10 years: H index= 22

### Publications on peer review journals (2008-2013)

Corti F, Finetti F, Ziche M, Simons M. The Syndecan-4/Protein Kinase C $\alpha$  Pathway Mediates Prostaglandin E<sub>2</sub>-induced Extracellular Regulated Kinase (ERK) Activation in Endothelial Cells and Angiogenesis in Vivo. *J Biol Chem*. 2013 May 3;288(18):12712-21. doi: 10.1074/jbc.M113.452383.

Focardi M, Picchi A, Donnini S, Cameli M, Ziche M, Marzilli M, Mondillo S. Hydrogen peroxide mediates endothelium-dependent dilation of coronary arterioles in obese rats on low carbohydrate diet. *Microcirculation*. 2013 Mar 20. doi:10.1111/micc.12058.

Solito R; Federico Corti, Chen CH, Mochly-Rosen D, Giachetti A, Ziche M, Donnini S. Mitochondrial aldehyde dehydrogenase-2 activation prevents  $\beta$  amyloids induced endothelial cell dysfunction and restores angiogenesis. *J Cell Sci*. 2013 Feb 27. [Epub ahead of print]

Donnini S, Giachetti A, Ziche M. Assessing vascular senescence in zebrafish. *Methods Mol Biol*. 2013;965:517-31. doi: 10.1007/978-1-62703-239-1\_34.

Finetti F, Terzuoli E, Bocci E, Coletta I, Polenzani L, Mangano G, Alisi MA, Cazzolla N, Giachetti A, Ziche M, Donnini S. Pharmacological inhibition of microsomal prostaglandin E synthase-1 suppresses epidermal growth factor receptor-mediated tumor growth and angiogenesis. *PLoS One*. 2012;7(7):e40576.

Bellou S, Karali E, Bagli E, Al-Maharik N, Morbidelli L, Ziche M, Adlercreutz H, Murphy C, Fotsis T. The isoflavone metabolite 6-methoxyequol inhibits angiogenesis and suppresses tumor growth. *Mol Cancer*. 2012 May 14;11:35.

Finetti F, Basile A, Capasso D, Di Gaetano S, Di Stasi R, Pascale M, Turco CM, Ziche M, Morbidelli L, D'Andrea LD. Functional and pharmacological characterization of a VEGF mimetic peptide on reparative angiogenesis. *Biochem Pharmacol*. 2012 Aug 1;84(3):303-11.

Donnini S, Finetti F, Terzuoli E, Giachetti A, Iñiguez MA, Hanaka H, Fresno M, Rådmark O, Ziche M. EGFR signaling upregulates expression of microsomal prostaglandin E synthase-1 in cancer cells leading to enhanced tumorigenicity. *Oncogene*. 2012 Jul 19;31(29):3457-66.

Donnini S, Finetti F, Francese S, Boscaro F, Dani FR, Maset F, Frasson R, Palmieri M, Pazzagli M, De Filippis V, Garaci E, Ziche M. A novel protein from the serum of *Python sebae*, structurally homologous with type- $\gamma$  phospholipase A(2) inhibitor, displays antitumour activity. *Biochem J*. 2011 Dec 1;440(2):251-62.

Pisanti S, Picardi P, Prota L, Proto MC, Laezza C, McGuire PG, Morbidelli L, Gazzo P, Ziche M, Das A, Bifulco M. Genetic and pharmacologic inactivation of cannabinoid CB<sub>1</sub> receptor inhibits angiogenesis. *Blood*. 2011 May 19;117(20):5541-50.

Giuliani G, Cappelli A, Matarrese M, Masiello V, Turolla EA, Monterisi C, Fazio F, Anzini M, Pericot Mohr G, Riitano D, Finetti F, Morbidelli L, Ziche M, Giorgi G, Vomero S. Non-peptide NK<sub>1</sub> receptor ligands based on the 4-phenylpyridine moiety. *Bioorg Med Chem*. 2011 Apr 1;19(7):2242-51.

Yeh JC, Cindrova-Davies T, Belleri M, Morbidelli L, Miller N, Cho CW, Chan K, Wang YT, Luo GA, Ziche M, Presta M, Charnock-Jones DS, Fan TP. The natural compound n-butylidenephthalide derived

from the volatile oil of *Radix Angelica sinensis* inhibits angiogenesis in vitro and in vivo. *Angiogenesis*. 2011 May;14(2):187-97.

Terzuoli E, Puppo M, Rapisarda A, Uranchimeg B, Cao L, Burger AM, Ziche M, Melillo G. Aminoflavone, a ligand of the aryl hydrocarbon receptor, inhibits HIF-1 $\alpha$  expression in an AhR-independent fashion. *Cancer Res*. 2010 Sep 1;70(17):6837-48.

Terzuoli E, Donnini S, Giachetti A, Iñiguez MA, Fresno M, Melillo G, Ziche M. Inhibition of hypoxia inducible factor-1 $\alpha$  by dihydroxyphenylethanol, a product from olive oil, blocks microsomal prostaglandin-E synthase-1/vascular endothelial growth factor expression and reduces tumor angiogenesis. *Clin Cancer Res*. 2010 Aug 15;16(16):4207-16.

Palumberi D, Aldi S, Ermini L, Ziche M, Finetti F, Donnini S, Rosati F. RNA-mediated gene silencing of FUT1 and FUT2 influences expression and activities of bovine and human fucosylated nucleolin and inhibits cell adhesion and proliferation. *J Cell Biochem*. 2010 Sep 1;111(1):229-38.

Lund N, Henrion D, Tiede P, Ziche M, Schunkert H, Ito WD. Vimentin expression influences flow dependent VASP phosphorylation and regulates cell migration and proliferation. *Biochem Biophys Res Commun*. 2010 May 7;395(3):401-6.

Donnini S, Solito R, Cetti E, Corti F, Giachetti A, Carra S, Beltrame M, Cotelli F, Ziche M. Abeta peptides accelerate the senescence of endothelial cells in vitro and in vivo, impairing angiogenesis. *FASEB J*. 2010 Jul;24(7):2385-95.

Ziche M, Morbidelli L. Molecular regulation of tumour angiogenesis by nitric oxide. *Eur Cytokine Netw*. 2009 Dec;20(4):164-70.

Morbidelli L, Pyriochou A, Filippi S, Vasileiadis I, Roussos C, Zhou Z, Loutrari H, Waltenberger J, Stössel A, Giannis A, Ziche M, Papapetropoulos A. The soluble guanylyl cyclase inhibitor NS-2028 reduces vascular endothelial growth factor-induced angiogenesis and permeability. *Am J Physiol Regul Integr Comp Physiol*. 2010 Mar;298(3):R824-32.

Donnini S, Terzuoli E, Ziche M, Morbidelli L. Sulfhydryl angiotensin-converting enzyme inhibitor promotes endothelial cell survival through nitric-oxide synthase, fibroblast growth factor-2, and telomerase cross-talk. *J Pharmacol Exp Ther*. 2010 Mar;332(3):776-84.

Monti M, Donnini S, Giachetti A, Mochly-Rosen D, Ziche M.  $\delta$ PKC inhibition or varepsilonPKC activation repairs endothelial vascular dysfunction by regulating eNOS post-translational modification. *J Mol Cell Cardiol*. 2010 Apr;48(4):746-56.

Finetti F, Donnini S, Giachetti A, Morbidelli L, Ziche M. Prostaglandin E(2) primes the angiogenic switch via a synergic interaction with the fibroblast growth factor-2 pathway. *Circ Res*. 2009 Sep 25;105(7):657-66.

Donnini S, Solito R, Monti M, Balduini W, Carloni S, Cimino M, Bampton ET, Pinon LG, Nicotera P, Thorpe PE, Ziche M. Prevention of ischemic brain injury by treatment with the membrane penetrating apoptosis inhibitor, TAT-BH4. *Cell Cycle*. 2009 Apr 15;8(8):1271-8.

Ziche M, Morbidelli L. The corneal pocket assay. *Methods Mol Biol*. 2009;467:319-29.

Solito R, Corti F, Fossati S, Mezhericher E, Donnini S, Ghiso J, Giachetti A, Rostagno A, Ziche M. Dutch and Arctic mutant peptides of beta amyloid(1-40) differentially affect the FGF-2 pathway in brain endothelium. *Exp Cell Res*. 2009 Feb 1;315(3):385-95.

Aldi S, Della Giovampaola C, Focarelli R, Armini A, Ziche M, Finetti F, Rosati F. A fucose-containing O-glycoepitope on bovine and human nucleolin. *Glycobiology*. 2009 Apr;19(4):337-43.

Lodovici M, Caldini S, Morbidelli L, Akpan V, Ziche M, Dolaro P. Protective effect of 4-coumaric acid from UVB ray damage in the rabbit eye. *Toxicology*. 2009 Jan 8;255(1-2):1-5.

Pezzatini S, Morbidelli L, Gristina R, Favia P, Ziche M. A nanoscale fluorocarbon coating on PET surfaces improves the adhesion and growth of cultured coronary endothelial cells. *Nanotechnology*. 2008 Jul 9;19(27):275101.

Ziche M, Donnini S, Morbidelli L, Monzani E, Roncone R, Gabbini R, Casella L. Nitric oxide releasing metal-diazeniumdiolate complexes strongly induce vasorelaxation and endothelial cell proliferation. *ChemMedChem*. 2008 Jul;3(7):1039-47.

Donnini S, Monti M, Roncone R, Morbidelli L, Rocchigiani M, Oliviero S, Casella L, Giachetti A, Schulz R, Ziche M. Peroxynitrite inactivates human-tissue inhibitor of metalloproteinase-4. *FEBS Lett*. 2008 Apr 2;582(7):1135-40.

Soro S, Orecchia A, Morbidelli L, Lacal PM, Morea V, Ballmer-Hofer K, Ruffini F, Ziche M, D'Atri S, Zambruno G, Tramontano A, Failla CM. A proangiogenic peptide derived from vascular endothelial growth factor receptor-1 acts through alpha5beta1 integrin. *Blood*. 2008 Apr 1;111(7):3479-88.

Finetti F, Solito R, Morbidelli L, Giachetti A, Ziche M, Donnini S. Prostaglandin E2 regulates angiogenesis via activation of fibroblast growth factor receptor-1. *J Biol Chem*. 2008 Jan 25;283(4):2139-46.