

## BIOGRAPHICAL SKETCH

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NAME Enzo AGOSTINELLI	POSITION TITLE Professor of Biochemistry & Molecular Biology		
eRA COMMONS USER NAME (credential, e.g., agency login) eagostinelli			
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	MM/YY	FIELD OF STUDY
SAPIENZA University of Rome	Master degree	12/1976	Biology
SAPIENZA University of Rome	Ph.D.	02/1980	Biochemistry
Université du Québec à Montréal (Canada)	Posdoc	11/1984	Biochemistry & Molecular Biology

### A. Personal Statement

Since 1985, DrAgostinelli has been instrumental in uniting basic and applied biochemistry-pharmacology-toxicology together with experimental evaluation of new natural anticancer agents. Thus, main research interests are in cancer research with special focus on developing new anticancer therapies using copper-enzymes amine oxidases from natural sources, both animal and plant, in the presence of exogenous/endogenous polyamines. Their mechanism of action has been studied at the subcellular level also in combination with heat (hyperthermia), radiations or therapeutic agent currently used against malignant cell growth (doxorubicin, docetaxel, interferon) and lysosomotropic compounds such as chloroquine. The research has been focalized on the development of new anticancer strategies with the aim of identifying subcellular targets, using advanced methodologies. DrAgostinelli is interested in cancer types that display intrinsic resistance to pro-apoptotic stimuli, especially to conventional chemotherapy and radiotherapy, and/or that develop multidrug resistance during chronic chemotherapy, with special interest in melanomas, colon adenocarcinomas, and osteosarcomas. These studies culminated in the formation of the Cancer Research Laboratory at the Department of Biochemical Sciences of the Sapienza University of Rome. This laboratory provides access and expertise in a range of technologies, instrumentations and methodologies for the ultrastructural and cytochemical analysis of human cancer cells, both sensitive and MDR; by transmission electron microscopy, laser scanning confocal microscopy, flow cytometry and RT-PCR. The laboratory also makes possible for the research group to carry out studies in molecular biology and to isolate copper-enzymes amine oxidases performing their characterization with spectrophotometric, fluorimetric and electron paramagnetic resonance assays.

DrAgostinelli's group currently focus on two areas. The first concerns studies on natural products, how these can best be applied for the development of novel therapeutic and preventive anticancer strategies and the relationship between inflammation and its progression to malignant disease. The second area involves therapeutic nanotechnology studies for drug delivery and targeting. With the aim of improving the system effectiveness by exploiting a nanotech approach, bovine serum amine oxidase (BSAO) was covalently immobilized onto poly(ethylene glycol) (PEG) or injectable nanohydrogels (NHs) based on cholesterol-graft-hyaluronic acid (HA-CH), both biocompatible conjugates self-assemble in aqueous solutions (biocompatible hydrogel). Recently, a novel superparamagnetic maghemite nanoparticles (SAMNs, surface active maghemite nanoparticles) were modified with BSAO, using rhodamine-isothiocyanate adduct as fluorescent spacer arm. We suggest that samn@ritc-bsao complex, characterized by a high specific activity, could be used, in the presence of exogenous/endogenous polyamines, as fluorescent magnetically drivable H<sub>2</sub>O<sub>2</sub> and aldehydes producing system. Future applications in selective tumour cell destruction can be suggested. In fact, DrAgostinelli intend to evaluate these approaches in clinical trials in the near future.

## B. Positions and Honors

### **Positions and Employment**

Dr Enzo Agostinelli is Professor of Biochemistry and Molecular Biology at the Faculty of Pharmacy and Medicine at the SAPIENZA University of Rome, Italy. He is Professor of Biochemistry in Specialized School of Endocrinology, Faculty of Medicine and Surgery and in the College Ph.D. course in Pharmacology and Toxicology in the same University.

Postdoctoral and researcher training was carried out in several Universities in the European Union, Canada and USA, where he improved his knowledge on intracellular microinjection/electroporation techniques and cancer research.

*Dr Agostinelli was visiting scientist in several research centres and Universities:*

1988 : Centre d'Etudes Nucléaires de Grenoble, France

1988 : Biotechnology Centre-Cranfield Institute of Technology, England

1988-1995 and 2002: Université du Québec à Montréal, Canada

1992: Department of Oncology, Tucson, University of Arizona, USA

1994: Department of Radiation Oncology/Research Laboratories, William Beaumont Hospital", Royal Oak Michigan, USA

1995: Department of Pharmacology in Albert Einstein, New York, USA

*and Visiting Professor in numerous Universities:*

2004-2005: Department of Biochemistry and Molecular Biology, Universities of Osaka, Hiroshima, Kanazawa, Tokio, Chiba and Himeji, Japan, within the collaboration of using copper-enzymes as new approach in anticancer therapy,

2005: Department of Oncology, Nerhu University, New Dehli (India)

2006: Laboratory of Nutritional Cancer Prevention, ULP-EA3430, Institut de Recherche contre les Cancers de l'Appareil Digestif (IRCAD), University of Strasbourg, France

2009: Department of Biochemistry and Molecular Biology, University of Pretoria, South Africa

2010: Department of Biochemistry, Universities of Osaka and Tokio and Department of Biology in Kanazawa University

2011-2012: Department of Genetic and Molecular Biology; Istanbul Kultur University, Istanbul, Turkey

2012: Faculty of Medicine, Hebrew University, Jerusalem, Israel

2012: Weizmann Institute, Rehovot, Israel

2012: Faculty of Medicine, University of Nis, Serbia

2000-2007 : Erasmus-Socrates scientific coordinator Faculty of Pharmacy and member of the Commission European Community Programs;

He has organized 18 International Congresses on Amine Oxidases, Polyamines/Cancer, Copper in Biological Systems (in Italy, USA, Japan, China, Austria, Turkey). In 2009 and 2011: Chair and Organizer of Gordon Research Conference on Polyamines in USA-New Hampshire. He is currently organizing the 13<sup>o</sup> International Congress on Amino Acids and Proteins that will be held in Texas the next October 2013 and the "Third International Conference on Polyamines: Biochemical, Physiological and Clinical Perspectives", that will be in Ubatuba, Brazil on September 2014. Dr Agostinelli was member of the Organizing Committee of several International meetings on cancer and translational research, and was also member of the Scientific Advisory Boards.

### **Representative Honors**

Professor Agostinelli is member of the editorial board of the journals: Amino Acids, Molecular Medicine Reports, International Journal of Oncology.

He was regularly invited, both as speaker and as chairman, in many International meetings (more than 60) in USA, Japan, China, India, Canada, South Africa and in many countries of the European Union, and in Russia and Turkey. Dr Agostinelli has delivered plenary lectures (some of them are reported below) in numerous congresses and seminars in many Universities.

He's a member of the Italian Biochemical and Molecular Biology Society (SIBMB), Italian Association of Cellular Cultures (AICC) and of the Bioinorganic Chemistry Society (SBIC); from 2002 to 2007 he was coordinator of the "Biogenic Amines" group of the Italian Biochemical and Molecular Biology Society and in 2006-2009 member of the Committee for Research Projects evaluation at "La Sapienza" University of Rome.

2008 Opening Plenary Talk, International Congress on Biogenic Amines, Trento, Italy

2009 Vice-Chair Gordon Research Conference on Polyamines

2010 Awarded with Medal of honors from Mayor of Rome

2011 Co-Chair Gordon Research Conference on Polyamines

2011 Award in Oncology, XVI International Congress on Advanced Oncology, Rhodes (Greece)

2012 Plenary Speaker, International Congress on Polyamines: Biological and Clinical Perspectives Istanbul (Turkey)

2012 Award from Faculty of Medicine and Surgery University of NIS (Serbia)

2013 For the study in Oncology has deserved the cover of the volume published on July 1<sup>st</sup> by Intern. Journal of Oncology

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### C. Selected recent Peer-reviewed Publications relevant to this proposal(limited to 15)

Dr Agostinelli's career has been dedicated to the development of novel and future therapeutic strategies with the aim to improve the quality of life for people with malignant diseases. To date, his efforts resulted in over 110 peer-reviewed publications on International journals and book chapters. Moreover, he has edited 4 special journal issues on "Polyamines and their Analogues in Cancer and other Diseases: Biological and Clinical Perspectives" published on Amino Acids, Springer – Verlag; he has also edited the Proceedings of numerous International meetings.

1) Iron nanoparticles from animal blood for cellular imaging and targeted delivery for cancer treatment.

Chamundeeswari M, Sastry TP, Lakshmi BS, Senthil V, **Agostinelli E**.

Biochim Biophys Acta. 2013; 1830(4):3005-10. doi: 10.1016/j.bbagen.2012.12.031. Epub 2013

2) Reactive oxygen species spermine metabolites generated from amine oxidases and radiation represent a therapeutic gain in cancer treatments.

Amendola R, Cervelli M, Fratini E, Sallustio DE, Tempera G, Ueshima T, Mariottini P, **Agostinelli E**.

Int J Oncol. 2013 Sep;43(3):813-20. doi: 10.3892/ijo.2013.2013. Epub 2013 Jul 12.

3) An Eudesman Derivative From *Verbena persicifolia* D.C. as a Natural Mild Uncoupler In Liver Mitochondria. A New Potential Anti-Obesity Agent?

Dalla Via L, García-Argáez AN, Braga A, Martínez-Vázquez M, Grancara S, Martinis P, **Agostinelli E**, Toninello A.

Curr Pharm Des. 2013 May 16. [Epub ahead of print]

4) CDK Inhibitors Induce Mitochondria-Mediated Apoptosis Through The Activation Of Polyamine Catabolic Pathway in LNCaP, DU145 and PC3 Prostate Cancer Cells.

Arisan ED, Obakan P, Coker-Gürkan A, Calcabrini A, **Agostinelli E**, Unsal NP.

Curr Pharm Des. 2013 May 16. [Epub ahead of print]

5) Hyaluronic Acid Nanohydrogels as a Useful Tool for BSAO Immobilization in the Treatment of Melanoma Cancer Cells.

Montanari E, Capece S, Di Meo C, Meringolo M, Coviello T, **Agostinelli E**, Matricardi P.

Macromol Biosci. 2013 Jul 8. doi: 10.1002/mabi.201300114. [Epub ahead of print]

**6. Agostinelli E**, Toninello A, Vianello F, Stevanato R. (2012). Do mammalian amine oxidases and the mitochondrial polyamine transporter have similar protein structures?

AMINO ACIDS, vol. 42, p. 725-731, ISSN: 0939-4451, doi: 10.1007/s00726-011-0988-x

**7. Agostinelli E**. (2012). Role of polyamines, their analogs and transglutaminases in biological and clinical perspectives.

AMINO ACIDS, vol. 42, p. 397-409, ISSN: 0939-4451, doi: 10.1007/s00726-011-1129-2

**8. Sinigaglia G**, Magro M, Miotto G, Cardillo S, **Agostinelli E**, Zboril R, Bidollari E, Vianello F. (2012). Catalytically active bovine serum amine oxidase bound to fluorescent and magnetically drivable nanoparticles..

INTERNATIONAL JOURNAL OF NANOMEDICINE, vol.7, p. 2249-2259, ISSN: 1178-2013, doi: 10.2147/IJN.S28237

**9. Tavladoraki P**, Cona A, Federico R, Tempera G, Viceconte N, Saccoccio S, Battaglia V, Toninello A, **Agostinelli E**. (2012).

Polyamine catabolism: target for antiproliferative therapies in animals and stress tolerance strategies in plants.

AMINO ACIDS, vol. 42, p. 411-426, ISSN: 0939-4451, doi: 10.1007/s00726-011-1012-1

**10. DALLA VIA L**, SANTI S, DI NOTO V, VENZO A, **E. AGOSTINELLI**, CALCABRINI A, CONDELLO M, TONINELLO A (2011). Platinum(II) chloride indenyl complexes: electrochemical and biological evaluation. JBIC, vol. 16, p. 695-713, ISSN: 0949-8257, doi:10.1007/s00775-011-0771-1

**11. KAISER A**, KHOMUTOV AR, SIMONIAN A, **E. AGOSTINELLI** (2011). A rapid and robust assay for the determination of the amino acid hypusine as a possible biomarker for a high-throughput screening of antimalarials and for the diagnosis and therapy of different diseases. AMINO ACIDS, vol. 42, p. 1651-1659, ISSN: 0939-4451, doi: 10.1007/s00726-011-0859-5

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- 12.** Valente S, Tomassi S, Tempera G, Saccoccio S, **Agostinelli E**, Mai A. (2011). Novel reversible monoamine oxidase A inhibitors: highly potent and selective 3-(1H-pyrrol-3-yl)-2-oxazolidinones. *JOURNAL OF MEDICINAL CHEMISTRY*, vol. 54, p. 8228-8232, ISSN: 0022-2623, doi: 10.1021/jm201011x
- 13.** E. AGOSTINELLI, MARQUES MP, CALHEIROS R, GIL FP, TEMPERA G, VICECONTE N, BATTAGLIA V, GRANCARA S, TONINELLO A (2010). Polyamines: fundamental characters in chemistry and biology. *AMINO ACIDS*, vol. 38(2), p. 393-403, ISSN: 0939-4451, doi: 10.1007/s00726-009-0396-7
- 14. E. AGOSTINELLI**, TEMPERA G, VICECONTE N, SACCOCCIO S, BATTAGLIA V, GRANCARA S, TONINELLO A, STEVANATOR (2010). Potential anticancer application of polyamine oxidation products formed by amine oxidase: a new therapeutic approach. *AMINOACIDS*, vol. 38(2), p. 353-368, ISSN: 0939-4451, doi: 10.1007/s00726-009-0431-8
- 15. E. AGOSTINELLI**, CONDELLO M, MOLINARI A, TEMPERA G, VICECONTE N, ARANCIA G (2009). Cytotoxicity of spermineoxidation products to multidrug resistant melanoma M14 ADR2 cells: sensitization by the MDL 72527 lysosomotropic compound. *INTERNATIONAL JOURNAL OF ONCOLOGY*, vol. 35(3), p. 485-498, ISSN: 1019-6439, doi: 10.3892/ijo\_00000360

## **D. Research Support**

Dr Agostinelli research has been awarded:

from 1989 to 1996 Canadian Medical Research Cancer (CMRC)  
from 1990 to 2006 Italian National Research Council (CNR),  
1993 and 1995 Italian Ministry of Foreign Affairs  
1998 - up-to-day University of Rome "La Sapienza"  
from 1998 to 2011 Italian Ministry of Scientific Research (MIUR) PRIN - MIUR Projects  
from 1999 to 2009 Italian Ministry of Health  
2000 – 2006 Canadian Institution Cancer Research (NSERC)  
2003 – up-to-day Enrico and Enrica SOVENA Foundation  
2003 -2008 Canadian National Cancer Institute (NCI),  
2010-2014 NIH (USA) and Italian Ministry of Health (bilateral agreement)  
2011 – 2014 Institute Pasteur Paris-Cenci Bolognetti Foundation

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