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The Polyamines: Small Molecules in the 'Omics' Era

Edited by H. Wallace

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Contents

Preface

The aim of this volume is to provide background information on the role of the polyamines in mammalian cells as we understand it currently in a concise and easily read format. Over the years, I have had many PhD, MSc, and intercalating medical and honours students who would have benefited enormously from a volume such as this to give them the initial understanding of the field that they need to start their research projects. This volume is dedicated to all of the students who have worked in my laboratory; I am sorry this took me so long to do! My thanks go to every one of you for all your hard work, dedication and fun over the years.

Why the title? We are now in an age where unparalleled amounts of data are being generated in biological systems – so much information that we have to design bioinformatics programs to deal with the data generated. This *Essays in Biochemistry* volume aims to show that there is still a place in the 'omics' world for elegant biochemistry which can lead to a detailed understanding of a biological system.

Heather Wallace
August 2009

Authors

Heather M. Wallace graduated in Biochemistry from the University of Glasgow and obtained her Ph.D. from the University of Aberdeen, Scotland, U.K. She undertook postdoctoral research in Biochemistry at Aberdeen and was awarded a University Research Fellowship. Her first Faculty position was a Wellcome lectureship followed by a "New Blood" lectureship/senior lectureship in Molecular Pharmacology and Toxicology. In 2004, she was elected a Fellow of the Royal College of Pathologists and currently is Chair of the College Specialty Advisory Committee for Toxicology. Heather was awarded a Fellowship of the British Toxicological Society in 2005 and became a member of the U.K. Register of Toxicologists and a European Registered Toxicologist in 2006. She is on the Editorial Board and is a Deputy Chair of the *Biochemical Journal* and reviews for many journals and grant awarding agencies. She is a registered evaluator for the European Commission. Her research interests are in the mechanisms of cell death associated with anticancer drugs and potential chemopreventative agents, in particular drugs targeting the polyamine pathway, and in the use of biomarkers for diagnosis and monitoring efficacy of anticancer drug therapy.

Lo Persson obtained a Ph.D. in Physiology from Lund University, Lund, Sweden in 1982. During 1983, he worked as a postdoctoral fellow at the Department of Cellular and Molecular Physiology, Milton S. Hershey Medical Center, Pennsylvania State University, PA, U.S.A. He is currently Professor of Molecular and Cellular Physiology at the Department of Experimental Medical Science, Lund University. He has worked in the field of polyamine-related research for more than 30 years. His research interests include the regulatory mechanisms involved in the cellular control of polyamine levels, as well as the polyamine metabolic pathway as a potential target for drug development against parasitic diseases.

Anthony Pegg is the J. Lloyd Huck Professor of Molecular and Cell Biology and Evan Pugh Professor of Cellular and Molecular Physiology at Pennsylvania State University College of Medicine in Hershey, PA, U.S.A. He received his Ph.D. from Cambridge University, Cambridge, U.K. in 1966 and was a postdoctoral fellow at Johns Hopkins University, Baltimore, MD, U.S.A., from 1966–68 where he worked with Guy Williams-Ashman and characterized the enzymes in the mammalian biosynthetic pathway for polyamines. His laboratory works on polyamine metabolism and function, and on DNA repair of alkylation damage. He has published more than 500 papers on these topics.

Chaim Kahana obtained a B.Sc. in Agriculture at the Hebrew University, Jerusalem, Israel, in 1976 and a M.Sc. in Agriculture in 1978. He studied towards his Ph.D. at the Weizmann Institute of Science, Rehovot, Israel, followed by postdoctoral research at the Johns Hopkins University (Baltimore, MD, U.S.A.) with Daniel Nathans. He is currently an Associate Professor in the Department of Molecular Genetics at the Weizmann Institute of Science, with interests in molecular biology, protein degradation, regulation of polyamine metabolism and in the role polyamines exert in regulating cellular functions, particularly cell growth and proliferation.

Kersti Alm has been involved in research on polyamines and their effects on the cell cycle since she was a graduate student. She has a temporary position at the level of Associate Professor at Lund University, Lund, Sweden, which includes teaching and research. Dr Alm has been a postdoctoral fellow at Roswell Park Cancer Institute, NY, U.S.A. Here she delved deeper into the mysteries of cell-cycle regulation together with Professor Carl Porter and Dr Deborah Kramer. **Stina M. Oredsson** has been in the field of cancer cells and cell-cycle regulation since 1979. She has always been fascinated by the possibilities inherent in cellular polyamine homoeostasis for utilization in cancer treatment. In later years her research has branched into studies of treating breast cancer, bladder cancer and neuroblastoma with polyamine analogues. Besides research, she is heavily involved in teaching at Lund University.

Thulani Senanayake is currently a Postdoctoral Associate at the University of Nebraska Medical Center in Omaha, NE, U.S.A. She was instrumental in developing an efficient synthesis of polyamine-based histone deacetylase inhibitors, and also conducted their evaluation as inhibitors of individual histone deacetylases, and as antitumour agents in cell culture. Her work led to the discovery of a relationship between histone deacetylase inhibition and annexin A1-mediated apoptosis in breast tumour cells. **Hemali Anunugama** is a Ph.D. graduate from the laboratory of Patrick Woster. As a graduate student in the Woster laboratory, Hemali was responsible for the synthesis of a series of polyamine–metal complexes, and for characterizing their DNA-binding and antitumour effects. **Tracey D. Boncher** is Associate Professor of Medicinal Chemistry in the College of Pharmacy at Ferris State University, MI, U.S.A. As a graduate student in the laboratory of Patrick Woster, Tracey synthesized an extensive library of symmetrically and unsymmetrically substituted polyamine analogues, many of which have been shown to possess significant antitumour activity. **Patrick M. Woster** is Professor of Pharmaceutical Sciences in the Eugene Applebaum College of Pharmacy and Health Sciences at Wayne State University. Professor Woster is a medicinal chemist with an interest in the synthesis of molecules that modulate polyamine metabolism as potential antitumour agents. He has produced a number of inhibitors that target enzymes in the polyamine biosynthetic pathway, and

synthesized the first unsymmetrically substituted alkylpolyamine analogues. Molecules developed in the Woster laboratory have been shown to produce dramatic effects on a variety of tumour cells by initiating apoptosis, binding to DNA and by producing epigenetic changes in gene expression. Professor Woster currently serves as a consultant to Progen Pharmaceuticals.

Yi Huang is a Research Associate of Oncology in the Johns Hopkins University School of Medicine, Baltimore, MD, U.S.A. After completing his Ph.D. degree at the Medical University of South Carolina in 2001, Dr Huang joined the Breast Cancer Programme at Johns Hopkins for his postdoctoral training to study the role of polyamines in breast cancer development and the exploitation of polyamine analogues as an effective strategy in breast cancer therapy. In 2006, Dr Huang joined the faculty of the Johns Hopkins University School of Medicine to study the epigenetic regulation of histone-modifying enzymes on gene regulation and to develop effective polyamine analogues in targeting epigenetic alterations. **Laurence J. Marton** is the Chief Scientific Officer of Progen Pharmaceuticals and an Adjunct Professor in the Department of Laboratory Medicine at UCSF (University of California at San Francisco), School of Medicine During many years in academia, Professor Marton has served as Professor and Chair of the Department of Laboratory Medicine and as Professor of Neurological Surgery at UCSF, and subsequently as Dean of the Medical School at the University of Wisconsin, Madison, WI, U.S.A. More recently he co-founded a biotechnology company in order to move his work on polyamine analogues as therapeutic agents to the clinic. This work is now ongoing at Progen and as part of a number of academic collaborations. **Robert A. Casero, Jr** is a Professor of Oncology in the Johns Hopkins University School of Medicine. As a molecular pharmacologist he has spent most of the last 30 years studying the role of polyamines in normal and tumour cell growth, and devising strategies to target polyamine function and metabolism for therapeutic benefit. His laboratory was responsible for cloning several genes involved in human polyamine catabolism; genes whose expression is thought to affect cellular responses to specific polyamine analogues. Additionally, his laboratory participated in the discovery of LSD1 (lysine-specific demethylase 1). Dr Casero is also a scientific advisor to Progen Pharmaceuticals.

Nathaniel S. Rial is a graduate of The University of Arizona, College of Medicine. He also defended his dissertation at the University of Arizona, Tucson, AZ, U.S.A. in the Cancer Biology Programme. He is undertaking his residency at the University of Arizona in Internal Medicine. He is currently enrolled in the University of Arizona Mel and Enid Zuckerman College of Public Health. **Frank L. Meyskens, Jr** attended medical school at UCSF (University of California at San Francisco), then served his internship and residency at UCSF-Moffet Hospital. His haematology and oncology fellowship

was at the National Cancer Institute within the National Institutes of Health campus. He is an investigator in trials focusing on therapy and chemoprevention in a variety of cancers, including melanoma and oral, colon, prostate and cervical cancer. He is currently Professor of Medicine and Biological Chemistry and Director of the Chao Family Comprehensive Cancer Center, and Associate Vice Chancellor of Health Sciences at the College of Health Sciences University of California, Irvine. **Eugene W. Gerner** began his graduate career in 1971 as The War on Cancer was signed into policy in the United States. He was influenced by Professor Alfred Knudson's lectures at the University of Texas embarking on a career in Cancer Biology. He was the founding Chair of the Cancer Biology Program at the University of Arizona, Tucson, AZ, U.S.A., and founding Director of the Gastrointestinal Cancer Program at the Arizona Cancer Center. He is Principal Investigator of a SPORE (Specialized Programs of Research Excellence) in gastrointestinal cancer. He is currently a Professor of Cell Biology and Anatomy and Biochemistry and Molecular Biophysics.

Leena Alhonen is a Professor of Animal Biotechnology and is responsible for the operation of the transgene unit at the University of Kuopio, Kuopio, Finland. She, together with the late Professor Juhani Jänne, started the pioneering work aimed at generation of transgenic rodents with altered polyamine homoeostasis to be used as tools to study the physiological roles of polyamines. The laboratory has produced more than 80 founder animals or rodent lines carrying polyamine metabolism-related transgenes. **Anne Uimari** is a senior researcher who participates in the molecular characterization of the polyamine metabolic genes and enzymes, and in the production and characterization of transgenic mice. She is also involved in the research studying the diseases connected to altered polyamine metabolism. **Marko Pietilä** works as a senior researcher in Leena Alhonen's group. He has specialized in the production of transgenic animal models. He has been closely involved on the production and characterization of both SSAT (spermidine/spermine N^1-acetyltransferase) transgenic and knockout animals. His special interests in the polyamine field are the roles of polyamines in the physiology of the skin and energy metabolism in adipose tissue. As a follow-on to his postdoctoral studies in the laboratory of Professor Coffino at UCSF (University of California at San Francisco), San Francisco, CA, U.S.A., he has started projects to assess the roles of antizyme and antizyme inhibitor in cancer cell growth. **Mervi T. Hyvönen** is a postdoctoral researcher in the animal biotechnology group. She has been investigating a variety of polyamine-related topics, such as the role of polyamines in acute pancreatitis, the regulation of SSAT expression and the role of eIF5A (eukaryotic translation initiation factor 5A) in polyamine depletion-induced cell-growth arrest. Her current studies aim to characterize the biological properties of several novel methylated polyamine analogues in

order to develop research tools and potential therapeutics. **Eija Pirinen** is completing her Ph.D. studies in the area of molecular medicine at the University of Kuopio. Her Ph.D. studies revealed that the polyamine cycle can be considered as a futile cycle, and that activated polyamine catabolism regulates glucose and energy metabolism in mice. Her main research interest is energy metabolism in Type 2 diabetes, obesity and cardiac dysfunction. **Tuomo A. Keinänen** is a docent of chemical biology at the A.I. Virtanen Institute for Molecular Sciences, University of Kuopio. He is responsible for the analytical method development and chemical research tool development in polyamine research in the animal biotechnology group led by Professor Leena Alhonen.

Abbreviations

8-methyl-MMTA	5′-deoxy-5′-dimethylsulfonio-8-methyladenosine
AbeAdo	(5′-{[(Z)-4-amino-2-butenyl]methylamino}-5′-deoxyadenosine
AdoMet	*S*-adenosylmethionine
AdoMetDC	*S*-adenosylmethionine decarboxylase
AMA	*S*-(5′-deoxy-5′-adenosyl) methylthioethylhydroxylamine
ANXA1	annexin A1
APAO	N^1-acetylpolyamine oxidase
APC	adenomatous polyposis coli
Az	antizyme
AzI	antizyme inhibitor
CDK	cyclin-dependent kinase
CHO	Chinese hamster ovary
COX	cyclo-oxygenase
CRC	colorectal cancer
CV	cardiovascular
DAC	5-aza-2′-deoxycytidine
dcAdoMet	decarboxylated *S*-adenosylmethionine
DENSPM	diethylnorspermine
DFMO	difluoromethylornithine
EGF	epidermal growth factor
FAP	familial adenomatous polyposis
Genz-644131	5′-{[(Z)-4-amino-2-butenyl]methylamino}-5′-deoxy-8-methyladenosine
GSK-3β	glycogen synthase-3β
HAT	histone acetyl transferase
H3K4me	mono-methylated H3K4
H3K4me2	dimethylated H3K4
H3K4me3	tri-methylated H3K4
HDAC	histone deacetylase
IGF-1	insulin-like growth factor-1
Jmj C	Jumonji C
LSD1	lysine-specific demethylase 1
MAPK	mitogen-activated phosphate kinase
MAO	monoamine oxidase
MAOEA	5′-deoxy-5′-[(2-aminooxyethyl) methylamino]adenosine

MEK	MAPK (mitogen-activated protein kinase)/ERK (extracellular-signal-regulated kinase) kinase
MGBG	methylglyoxal bis(guanylhydrazone)
MHZPA	5′-deoxy-5′-[(3-hydrazinopropyl) methylamino]adenosine
MS-275	*N*-(2-aminophenyl)-4-[*N*-(pyridin-3-ylmethoxycarbonyl)-aminomethyl]benzamide
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide
NF-κB	nuclear factor κB
NMDA	*N*-methyl-D-aspartate
NO	nitric oxide
NOS-2	inducible nitric oxide synthase
NSAIDs	non-steroidal anti-inflammatory drugs
ODC	ornithine decarboxylase
ORF	open reading frame
PABA	polyaminobenzamide
PAHA	polyaminohydroxamic acid
PAO	polyamine oxidase
PDGF	platelet-derived growth factor
PGC-1α	PPARγ (peroxisome-proliferator-activated receptor γ) co-activator 1α
PGE_2	prostaglandin E_2
PI3K	phosphoinositide 3-kinase
PLP	pyridoxal phosphate
pRB	retinoblastoma protein
RNAi	RNA interference
R-point	restriction point
ROS	reactive oxygen species
SAHA	suberoylanilide hydroxamic acid
SAM486A	4-amidinoindan-1-one-2′-amidinohydrazone
SAT1	spermidine/spermine acetyltransferase (see also SSAT)
SFRP	secreted frizzle-related protein
SMO	spermine oxidase
SNP	single nucleotide polymorphism
SpdS	spermidine synthase
SpmS	spermine synthase
SSAT	spermidine/spermine N^1-acetyltransferase
SWIRM	Swi3p/Rsc8c/Moira
TCF/LEF	T-cell factor/lymphoid-enhancing factor
TRAMP	transgenic prostate adenocarcinoma model
uORF	upstream open reading frame
UTR	untranslated region