

Chemotherapy of Viral Infections

Editors

P.E. Came and L.A. Caliguiri



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Dedicated to
Bette, Paula, and Heather
and Maggy, Laura, and Anne

Preface

"... the motto for the therapeutics of the future
will have to be *de sedibus et causis pharmacorum*."
P. EHRLICH, 1909

Exciting events in the basic disciplines of virology, immunology, and pharmacology continue to advance the understanding of the pathogenesis and control of virus diseases. At the same time, the rational development of antiviral agents is attracting, to an increasing extent, the interest of workers in other disciplines. Improvements in technology facilitate the definition of potential target sites for antiviral intervention and unmask new viral and host genes. The outcome is a further steady development of new antiviral agents which approach the "magic bullets" first proposed by PAUL EHRLICH. Remarkable advances in protein synthetic methods that yield polypeptides which inhibit active sites of viral proteins have aided substantially in the basic and clinical study of these antiviral agents. In addition, the extremely rapid progression in recombinant DNA techniques, leading to the synthesis of large quantities of gene products, is also increasing our opportunities at a dashing pace. New information and developing technology facilitate research on the mechanism of action, toxicity, pharmacokinetics, and pharmacodynamics of new agents. The list of clinically effective antiviral agents is expanding and the number of potentially useful compounds is growing rapidly.

This book is a combined theoretical text and practical manual which, it is hoped, will be of use to all who have an interest in virus diseases, particularly scientists, physicians and graduate students. There are two major divisions of the volume: the first part deals with antiviral agents which are clinically effective and the second discusses compounds which are not, at present, widely used as chemotherapeutic agents, but are either currently under study as possible drugs or are used to elucidate the mechanism of virus replication. These major sections are preceded by a comprehensive chapter on current models of pathogenesis of virus disease produced by all the major groups of viruses. This updated coverage highlights the diversity of the important pathogens and offers insight into possible means of their control.

We have asked that the contributors of chapters consider the efforts and attempts of the chemists to cite important aspects of structure-activity relationships. The pharmacologic interactions including half-life, tissue distribution, and excretion rate are discussed where appropriate. The available results of clinical trials for various compounds are also discussed.

It is our goal to discuss the recent advances in historical perspective and to add a better understanding of antiviral compounds or drugs, per se. As the reader will learn, some of the chemicals which have never become drugs are the very compounds that supplied the impetus and optimism to continue the search. It is our hope that this volume will provide an awareness of previous contributions,

investigations of newer agents suitable for chemotherapy of virus infections, and the excitement of the current work with the anticipation of the viral therapeutics of the future – the seat and cause of the pharmacology of antiviral agents.

We thank our colleagues who have made contributions to this work and made this volume possible, and acknowledge the valuable assistance of Ms. KATHLEEN CAVANAGH and Ms. MARY FRAZIER who provided editorial assistance in addition to excellent secretarial skills.

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List of Abbreviations

ABPP	2-amino-5-bromo-6-phenyl-4-pyrimidinol	BVdUrd	E-5-(2-bromovinyl)-2'-deoxyuridine
ADCC	antibody-dependent cellular cytotoxicity	CA	chorioallantoic
5'-AdThd	5'-aminodeoxythymidine	cAMP	cyclic adenosine monophosphate
AHF	Argentinian hemorrhagic fever	CFA	complete Freund's adjuvant
AI dUDP	5-iodo-5'-amino-2',5'-dideoxyuridine diphosphate	CF ₃ dUMP	5-trifluoromethyl-2'-deoxyuridine monophosphate
AI dUrd	5-iodo-5'-amino-2,5'-dideoxyuridine	CF ₃ dUrd	5-trifluoromethyl-2'-deoxyuridine
AI dUTP	5-iodo-5'-amino-2,5'-dideoxyuridine triphosphate	CF ₃ dUTP	5-trifluoromethyl-2'-deoxyuridine triphosphate
AIPP	2-amino-5-iodo-6-phenyl-4-pyrimidinol	CID	cytomegalovirus inclusion disease
AMP	adenosine monophosphate	CJD	Creutzfeldt-Jakob disease
AMV	avian myeloblastosis virus	CMP	cytomegalovirus
Ara-A	arabinofuranosyladenine	CPE	cytopathic effect
Ara-ADP	arabinofuranosyladenine diphosphate	cpm	counts per minute
Ara-AMP	arabinofuranosyladenine monophosphate	dATP	deoxyadenine triphosphate
Ara-ATP	arabinofuranosyladenine triphosphate	dCTP	deoxycytidine triphosphate
Ara-C	arabinofuranosylcytosine	dCyd	deoxycytidine
Ara-Hx	arabinofuranosylhypoxanthine	DEV	duck embryo vaccine
Ara-HxMP	arabinofuranosylhypoxanthine monophosphate	dGTP	deoxyguanosine triphosphate
Ara-T	arabinofuranosylthymine	DHAdt	5,6-dihydro-5-azathymidine
Ara-TMP	arabinofuranosylthymine monophosphate	DI	defective interfering (particles)
Ara-TTP	arabinofuranosylthymine triphosphate	DMSO	dimethylsulfoxide
ATP	adenosine triphosphate	DNA	deoxyribonucleic acid
BCG	bacille Calmette-Guérin	DNAP	Dane particle associated RNA polymerase
BEV	baboon endogenous virus	DNase	deoxyribonuclease
BHF	Bolivian hemorrhagic fever	dNMP-PA	deoxynucleotide monophosphate phosphonoacetate
BHK	baby hamster kidney (cells)	dpm	disintegrations per minute
BL	Burkitt's lymphoma	DRB	5,6-dichloro-1- β -D-ribofuranosylbenzimidazole
BRU-PEL	<i>Brucella abortus</i> preparation	dThd	deoxythymidine
BSA	bovine serum albumin	dTMP	deoxythymidine monophosphate
BTV	Bluetongue virus	dTTP	deoxythymidine triphosphate
		EA	early antigen
		EBNA	Epstein-Barr nuclear antigen
		EBV	Epstein-Barr virus

EDTA	ethylenediaminetetracetic acid	LCM	lymphocytic chorio-meningitis
EEE	Eastern equine encephalo-myelitis	LHA	lower hemagglutinin
EIBT	<i>N</i> ₁ -ethylisatin- β -thiosemicarbazone	LPS	lipopolysaccharide
EMC	encephalomyocarditis	MA	membrane antigen
EtdUrd	5-ethyl-2'-deoxyuridine	MCMV	murine cytomegalovirus
2'F-Ara-IC	1-(2-deoxy-2-fluoro- β -D-arabinofuranosyl)-5-iodo-cytosine	MDMP	2-(4-methyl-2,6-dinitro-vanilino)- <i>N</i> -methylpropion-amide
FCS	fetal calf serum	MDP	muramyl dipeptide
F ₃ dThd	trifluorothymidine	MEM	minimum essential medium
FMDV	foot-and-mouth disease virus	MER	methanol-extracted residue
FPA	<i>p</i> -fluorophenylalanine	MHV	mouse hepatitis virus
FSV	feline sarcoma virus	MIBT	<i>N</i> -methylisatin- β -thiosemi-carbazone
FUDR	fluorodeoxyuridine	MIC	minimum inhibitory concentration
GMK	green monkey kidney (cells)	MLV	murine leukemia virus
HA	hemagglutinin	MMdUrd	5-methoxymethyl-2'-deoxyuridine
HBB	2-(α -hydroxybenzyl)-benzimidazole	MMTV	murine mammary tumor virus
HB _c Ag	hepatitis B core antigen	m.o.i.	multiplicity of infection
HB _e Ag	hepatitis B enzyme antigen	MRB	5-methyl-2-D-ribobenzimid-azole
HBIG	hepatitis B immune globulin	mRNA	messenger ribonucleic acid
HB _s Ag	hepatitis B surface antigen	NA	neuraminidase
HDCS	human diploid cell strain	NCV	noncapsid viral (protein)
HDL	high density lipoprotein	NDV	Newcastle diseases virus
HFI	human fibroblast interferon	NK	natural killer (cells)
HLA	human leukocyte antigen	NP	nucleoprotein
HLI	human leukocyte interferon	NPC	nasopharyngeal carcinoma
hnRNA	heterogeneous nuclear ribonucleic acid	opv	oral poliovirus vaccine
HPLC	high pressure liquid chromatography	PAS	periodic acid-Schiff
HPV	human papillomavirus	PEG	polyethylene glycol
HSV	herpes simplex virus	pfu	plaque forming unit
HVA	hepatitis virus A	PML	progressive multifocal leukoencephalopathy
HVB	hepatitis virus B	PPi	inorganic pyrophosphate (phosphodiesterase)
IBT	isatin- β -thiosemicarbazone	PrdUrd	5-propyl-2'-deoxyuridine
IBV	infectious bronchitis virus	PVM	pneumonia virus of mice
IdCyd	5-iodo-2'-deoxycytidine	RF	replicative form
IdUMP	5-iodo-2'-deoxyuridine monophosphate	RI	replicative intermediate
IdUrd	5-iodo-2'-deoxyuridine	RLV	Rauscher leukemia virus
IgG	immunoglobulin α	RNA	ribonucleic acid
IgG	immunoglobulin γ	RNP	ribonuclear protein (complex)
IgM	immunoglobulin μ	RSV	respiratory syncytial virus
IMP	inosine monophosphate	SDS	sodium dodecylsulfate
ipv	inactivated poliovirus vaccine	SFV	Semliki Forest virus
ISG	immune serum globulin	SGOT	serum glutamate-oxalo-acetate transaminase
K	killer (cells)		
KTS	kethoxal-bis-thiosemi-carbazone		

SMON	subacute myelo-optico-neuropathy	TPCK	L-1-tosylamide-2-phenylethyl-chloromethyl ketone
SRBC	sheep red blood cells	tRNA	transfer ribonucleic acid
SSPE	subacute sclerosing para-encephalitis	TSC	thiosemicarbazone
SSV	simian sarcoma virus	UHA	upper hemagglutinin
SV	simian virus	UMP	uridine monophosphate
SVP	subviral particles	VA	virus-associated
TCID ₅₀	tissue culture median infective dose	VCA	viral capsid antigen
TCT	γ -thiochromanone-1-thio-semicarbazone	VIG	vaccinia immune globulin
TdT	deoxynucleotidyl transferase	VPg	genome-linked viral protein
TGE	transmissible gastroenteric (virus of swine)	VSV	vesicular stomatitis virus
TK	thymidine kinase	VZIG	varicella zoster immune globulin
TLCK	<i>N</i> - α - <i>p</i> -tosyl-L-lysinechloromethyl ketone	VZV	varicella zoster virus
TMV	tobacco mosaic virus	WEE	Western equine encephalo-myelitis
		WT	wild-type (virus)

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