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Antiviral resistance – an emerging problem

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State-of-the-art symposium on antiviral resistance

The development of antiviral drugs has progressed rapidly over the last decade. As of 1995, the list of antiviral agents approved for use by the United States Food and Drug Administration includes acyclovir, amantadine, didanosine, famciclovir, foscarnet, ganciclovir, interferon-α, ribavirin, rimantadine, stavudine, vidarabine, zalcitabine, and zidovudine. With the increasing utilization of antiviral drugs, however, has come an enhanced appreciation for the development of antiviral resistance.

With the exception of interferon-α, the currently licensed antiviral agents generally inhibit steps in virus-specific replication, usually by targeting viral enzymes. Examples of these enzyme targets include viral reverse transcriptase [human immunodeficiency virus (HIV)] and viral DNA polymerase [herpes simplex virus (HSV), varicella zoster virus (VZV), cytomegalovirus (CMV), hepatitis B virus (HBV)]. By impairing the natural function of such viral enzymes, most of the antiviral drugs currently available interfere with viral nucleic acid synthesis. This preferential inhibition of viral replicative processes increases the therapeutic index of these antiviral drugs.

In general, mutations within the viral genome account for the acquisition of antiviral resistance. The relative susceptibilities of subpopulations of viral isolates deter-

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mine the cumulative susceptibility of the entire sample. Selective drug pressure can result in the emergence of resistant viral isolates by conferring a survival advantage to those subpopulations that are relatively less susceptible to the drug. In addition, resistant subpopulations have been found to exist naturally for virtually all viruses evaluated to date. Spontaneous mutations also may arise during drug exposure. For many viruses, in vitro passage in the presence of antiviral drugs readily selects for resistant isolates; examples include VZV, HSV, influenza A, and HIV. A single nonlethal nucleotide mutation leading to a critical amino acid substitution in viral protein often confers drug resistance. The resulting resistant phenotype possesses replicative advantages in the presence of drug. It is notable that such bacterial mechanisms of drug resistance as altered drug uptake or efflux and drug inactivation have not been identified in studies of viral resistance. The biologic consequences of these viral mutations can include alterations in viral pathogenicity, transmissibility, and genetic stability. However, the extent to which most resistant viruses are impaired in these vital functions is not fully understood at this time.

The emergence of viral resistance can manifest clinically as failure to resolve disease despite appropriate antiviral therapy, as well as an inability to decrease or eradicate viral replication in the host. Intact host defense mechanisms are essential for recovery from virtually all viral infections. In highly immunocompromised patients, for example, clinical failures frequently occur even when disease is caused by a drug-susceptible virus. Disease due to drug-resistant viruses occurs most frequently in immunocompromised patients. Circumstances which favor the selection of resistant isolates include high viral replicative loads, high intrinsic mutation rates, and prolonged drug exposure.

The in vitro assay systems utilized for the determination of antiviral susceptibility are not standardized. Results can vary from laboratory to laboratory due to differences in the assay system employed, the cell line utilized, and the viral inoculum. In addition, the correlation between in vitro drug concentration and in vivo clinical response is not established for most antiviral agents.

The problem of antiviral resistance is certain to increase as antiviral agents are utilized more widely. For this reason, a consensus symposium was developed and convened on December 8–10, 1994, by The Macrae Group to discuss state-of-the-art knowledge of antiviral resistance. Issues relating to current knowledge of molecular mechanisms of antiviral resistance, effective assays for assessing drug susceptibility, availability of animal models in investigations of viral pathogenesis, and human studies of antiviral resistance were addressed at this symposium. In addition, areas in which additional research is needed were identified and prioritized. The following five articles in this issue of *Antiviral Research* review the information presented at this symposium.

Participants at this symposium included John P. Bader, National Cancer Institute, Bethesda, MD; Roy Barzilai, Israel Institute for Biological Research, Ness Ziona, Israel; Karen K. Biron, Burroughs Wellcome, USA, Research Triangle Park,

NC; Michael Boeckh, Fred Hutchinson Cancer Research Center, Seattle WA; Donald M. Coen, Harvard Medical School, Boston, MA; Jeffrey I. Cohen, National Institutes of Health, Bethesda, MD; Richard J. Colonno, Bristol-Myers Squibb Co., Princeton, NJ; Michael Cordingley, Boehringer Ingelheim Research Inc., Laval, Quebec, Canada; Robert B. Couch, Baylor College of Medicine, Houston, TX; Susan Cox, Smittskyddsinstitute, Stockholm, Sweden; Gilbert Croteau, Boehringer Ingelheim Research, Inc., Laval, Quebec, Canada; Clyde S. Crumpacker, Beth Israel Hospital, Boston, MA; Graham Darby, Wellcome Research Laboratories, Beckenham, Kent, United Kingdom; James V. Desiderio, Bristol-Myers Squibb, Wallingford, CT; John C. Drach, University of Michigan, Ann Arbor, MI; W. Lawrence Drew, Mount Zion Medical Center of UCSF, San Francisco, CA; P. Scott Eastman, Chiron Corporation, Emeryville, CA; Emilio A. Emini, Merck Research Labs, West Point, PA; Naisheng Fan, The Upjohn Company, Kalamazoo, MI; Phillip A. Furman, Burroughs Wellcome Co., Research Triangle Park, NC; George J. Galasso, National Institutes of Health, Bethesda, MD; Phillip Gioia, Forest Labs, New York, NY; John W. Gnann, Jr., University of Alabama at Birmingham, Birmingham, AL; Neil H. Goldstein, Sterling Winthrop Inc., Collegeville, PA; Johan Harmenberg, Astra Arcus AB, Södertälje, Sweden; Alan J. Hay, National Institute for Medical Research, London, United Kingdom; Frederick G. Hayden, University of Virginia, Charlottesville, VA; Edgar L. Hill, Burroughs Wellcome, USA, Research Triangle Park, NC; Michael J. M. Hitchcock, Gilead Sciences, Foster City, CA; Louis E. Holland, IIT Research Institute, Chicago, IL; Karl Y. Hostetler, University of California San Diego, La Jolla, CA; Ronald Keeney, Glaxo Research Institute, Research Triangle Park, NC; Earl R. Kern, University of Alabama at Birmingham, Birmingham, AL; David W. Kimberlin, University of Alabama at Birmingham, Birmingham, AL; Brent E. Korba, Georgetown University, Rockville, MD; Fred Lakeman, The University of Alabama at Birmingham, Birmingham, AL; Robert A. Lamb, Howard Hughes Medical Institute and Northwestern University, Evanston, IL; Brendan Larder, The Wellcome Foundation Limited, Beckenham, Kent, United Kingdom; Catherine Laughlin, National Institute of Allergy and Infectious Diseases, Rockville, MD; Iris Long, AIDS Coalition to Unleash Power, Jackson Heights, NY; Sarah Martin-Munley, Astra USA, Inc., Westborough, MA; Suzanne Mattingly, Syntex Inc. (USA), Palo Alto, CA; Douglas L. Mayers, Walter Reed Army Institute of Research, Rockville, MD; Mark McKinlay, ViroPharma, Collegeville, PA; John W. Mellors, University of Pittsburgh Medical Center, Pittsburgh, PA; Maureen W. Myers, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; Thomas W. North, University of Montana, Missoula, MT; Judith A. Partaledis, Vertex Pharmaceuticals Inc., Cambridge, MA; Lawrence H. Pinto, Northwestern University, Evanston, IL; Douglas D. Richman, University of California San Diego, La Jolla, CA; Norman Salzman, National Cancer Institute, Frederick, MD; Raymond F. Schinazi, Emory University, Decatur, GA; William M. Shannon, Southern Research Institute, Birmingham, AL; Robert W. Sidwell, Insti-

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