Chapter 7

Virology

NIAD supports a broad spectrum of both basic and applied research in virology to expand the understanding of the biology, pathogenesis, and the immunology of viral diseases, leading to their prevention, control, and treatment, including research on (i) the viral replication cycle; (ii) the structure and function of the viral components; (iii) host virus interactions, including pathogenesis, immune evasion, and immune enhancement; (iv) viral genetics and evolution; (v) viral interference and defective interfering particles; (vi) virus vector relationships; (vii) epidemiology and natural history; and (viii) preclinical and clinical research to develop vaccines, adjuvants, therapeutics, immunomodulators, and diagnostics (http://www3.niaid.nih.gov/research/topics/viral/introduction).

In addition, research on the emergence of new epidemic viruses through *host switching* has become a major priority for NIAID-supported research (http://www3.niaid.nih.gov/research/topics/viral/newepi_wkshp.pdf).

7.1 Resources for Researchers

The most important task of the *NIAID Antiviral Testing Program* is the evaluation of the efficacy and toxicity of new antiviral agents using a broad array of *in vitro* assays and *in vivo* animal models (http://www3.niaid.nih.gov/research/topics/viral/resources.htm). The main objective of this program is to identify antiviral agents with the potential to treat viral infections of public health importance, including those for newly emerging infections and those that are not a high priority for the pharmaceutical industry. NIAID ensures that the intellectual property rights of the compound supplier are protected. The viruses and models covered under this program include:

In Vitro Screens

- *Herpesviruses*: herpes simplex virus-1 (HSV-1); herpes simplex virus-2 (HSV-2); varicella-zoster virus (VZV); Epstein-Barr virus (EBV); cytomegalovirus (CMV); human herpes virus-6 (HHV-6); and human herpes virus-8 (HH-8)
- *Respiratory Viruses*: Influenza A and B; respiratory syncytial virus (RSV); parainfluenza virus (PIV); measles; rhinoviruses; adenoviruses; and severe acute respiratory syndrome (SARS) virus
- *Papillomaviruses and BK virus*
- *Biodefense*: orthopoxviruses (vaccinia, cowpox); Venezuelan equine encephalomyelitis virus (VEE); Punta Toro virus; Pichinde virus; Yellow fever virus; West Nile virus; and dengue virus

Animal Models

- HCV/-SCID/bg/uPA chimeric model
- *Herpesviruses*: HSV-1, HSV-2, murine cytomegalovirus (MCMV), guinea pig cytomegalovirus (GPCMV), human cytomegalovirus ($HCMV_{SCID-hu}$)
- *Respiratory Viruses*: Influenza A and B, RSV, PIV-3, Maedi-Visna virus (MV)
- *Hepatitis Viruses*: woodchuck hepatitis virus (WHV) and hepatitis B ($HBV_{transgenic}$)
- *Papillomaviruses*: Shope, $HPV_{SCID-hu}$
- Hamster scrapie in hamster-prion transgenic mice
- *Biodefense*: orthopoxviruses (vaccinia, cowpox, ectromelia), Punta Toro virus, Pichinde virus, Banzi virus, Semliki Forest virus, and West Nile virus

7.1.1 The Collaborative Antiviral Study Group (CASG)

CASG is a multi-institutional collaborative network funded by NIAID to conduct clinical trials and evaluate experimental therapies for viral infections. It comprises investigators at nearly 50 clinical research institutions and a Central Unit that serves as the core administrative, research, laboratory, biostatistical, and data management component of CASG. The CASG infrastructure would allow researchers to respond expeditiously to promising new therapies and

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to unanticipated emerging clinical priorities (http://www3.niaid.nih.gov/research/topics/viral/resources.htm).

7.2 Recent Scientific Advances

- *Insulin-Degrading Enzyme Is a Cellular Receptor Mediating Varicella-Zoster Virus Infection and Cell-to-Cell Spread*. The varicella-zoster virus (VZV), which causes chickenpox and shingles, is likely spread to susceptible hosts as a cell-free virus. However, its cell-to-cell transmission in the body and *in vitro* is facilitated by the interaction of the VZV glycoprotein E (gE) with the insulin-degrading enzyme (IDE). IDE serves as a receptor through an extracellular domain. Cell-to-cell spread of the virus has been impaired by blocking IDE *(1)*. This finding suggests that IDE may become a valid target for new shingles and chickenpox treatments.
- *Structure of the Parainfluenza Virus 5 F Protein in Its Metastable, Prefusion Conformation*. Enveloped viruses have evolved complex glycoprotein machinery that drives the fusion of viral and cellular membranes, permitting the viral genome to enter the cell. For the paramyxoviruses, the fusion (F) protein catalyzes this membrane merger and entry step, and it has been postulated that the F protein undergoes complex refolding during this process. The crystal structure of the parainfluenza virus 5 F protein in its prefusion conformation and stabilized by the addition of a carboxy-terminal trimerization domain has been elucidated *(2)*. The positions and structural transitions of key parts of the fusion machinery, including the hydrophobic fusion peptide and two helical heptad repeat regions, clarified the mechanism of the F protein–mediated membrane fusion.
- *Development of a Humanized Monoclonal Antibody with Therapeutic Potential Against West Nile Virus*. Neutralization of West Nile virus (WNV) *in vivo* correlates with the development of an antibody response against the viral envelope (VE) protein. Using random mutagenesis and yeast surface display, the individual contact residues of 14 newly generated monoclonal antibodies against domain III of the WNV E protein have been defined *(3)*. One of them, a humanized version of E16 (HV-E16) retained antigen specificity, avidity, and neutralizing activity. In postexposure therapeutic trials in mice, a single dose of HV-E16 protected mice against WNV-induced mortality and may, therefore, be considered a viable treatment option against WNV infection in humans.
- *NIAID West Nile Virus (WNV) Vaccine Clinical Trial*. A small clinical trial to test the safety of an experimental vaccine against WNV was initiated in 2005 at the NIH Clinical Center. The experimental vaccine is composed of a small, circular piece of DNA plasmid that contains genes that code for two key surface proteins of WNV (niaidnews@niaid.nih.gov).

References

1. Li, Q., Ali, M. A., and Cohen, J. I. (2006) Insulin degrading enzyme is a cellular receptor mediating varicella-zoster virus infection and cell-to-cell spread, *Cell*, **127**(2), 305–316.
2. Yin, H.-S., Wen, X., Paterson, R. G., Lamb, R. A., and Jardetzky, T. S. (2006) Structure of the parainfluenza virus 5 F protein in its metastable, prefusion confirmation, *Nature*, **439**, 38–44.
3. Oliphant, T., Engle, M., Nybakken, G. E., Doane, C., Johnson, S., Huang, L., Gorlatov, S., Mehlhop, E., Marri, A., Chung, K. M., Ebel, G. D., Kramer, L. D., Fremont, D., H., and Diamond, M. S. (2005) Development of a humanized monoclonal antibody with therapeutic potential against West Nile virus, *Nat. Med.*, **11**, 522–530.