Marseilleivirus, Blood Safety, and the Human Virome

Jesse L. Goodman
Food and Drug Administration, Silver Spring, Maryland

(See the major article by Popgeorgiev et al on pages 1042–50.)

Keywords. Marseilleivirus; blood safety; organ safety; virome; microbiome; giant viruses.

MARSEILLEVIRUS: A GIANT VIRUS IN SEARCH OF DISEASE

In this issue of the Journal, Popgeorgiev et al report investigations stemming from deep sequencing to find DNA viruses too large to pass through ultrafilters typically used in virus hunting [1]. Their findings suggest the presence of a previously unknown virus in blood samples from asymptomatic French blood donors. They call the approximately 357-kb virus “giant blood Marseilleivirus” (GBM) because of its close relationship to a Marseilleivirus first isolated from Seine River water cocultivated with amoebae, within which it replicates. No Marseilleivirus has to date been shown to cause disease, although one Marseilleviridae family member, Senegalivirus, has been isolated from feces of an asymptomatic person. The Marseilleviridae family is grouped within the nucleocytoplasmic large DNA viruses (NCLDVs), a diverse order. The largest member, mimivirus, has been found in a variety of protists and has a length of 1.18 Mb, making it the largest virus discovered to date. Members of the NCLDV range from familiar viruses that can infect humans and other vertebrates, such as those of the Poxviridae and Asfarviridae (the cause of African swine fever) families, respectively, to poorly understood viruses that seem to primarily infect insects, Paramaecium, algae, or, as in the case of Marseilleviridae, amoebae. These viruses are unique both in size and genetic makeup, frequently including genes of a variety of viral, bacterial, and cellular origins, including protists. It has recently been proposed that the giant viruses, some of which also contain messenger RNA within their capsid, be reclassified as the Megaviridae and that they may even qualify as a fourth domain of life, beyond the Archaea, Bacteria, and Eukarya [2].

The intriguing findings reported by Popgeorgiev et al include not only identifying GBM DNA in pooled blood specimens from 10 donors and tracing the source to a single donor, but also evidence of viral capsids, antigens, and antibody in that donor’s serum, as well as evidence that the virus can replicate in the human Jurkat T-cell-derived cell line. Finally, the authors examined specimens from 20 further asymptomatic blood donors and found 3 to be seroreactive against antigen prepared from the related Marseilleivirus, 2 of which were also polymerase chain reaction (PCR) positive for GBM.

While these findings must be confirmed independently, they suggest that this virus may well be part of what is increasingly called the human virome—viruses associated with people. Such interactions can involve the gamut of host-microbe relationships, ranging from no discernable infection; to acute infection, that may or may not result in disease, which may then either be cleared or, instead, result in persistent productive or latent infection; to becoming part of the human genome itself (as occurs with endogenous retroviruses). The findings that 3 of 30 apparently asymptomatic blood donors were seropositive and that, of these 3, 3 were also PCR positive, while preliminary and obtained by a serologic assay with a sensitivity and specificity that are not fully characterized, are suggestive of a reasonably common persistent or latent infection of generally low virulence. There are precedents for finding blood-borne viruses that, although widespread, do not appear to be pathogenic in humans, such as Torque Teno virus and its relatives, as well as GB virus C [3]. However, given the very preliminary state of knowledge about GBM, a potential role for this virus in causing human disease, whether acute or chronic or limited to certain individuals (eg, those who have a specific genetic background or are immunocompromised), should not be excluded and is important to study, including its implications for transfusion safety. So for now, like many other microbes discovered through random searching for “foreign” nucleic acids.
(as opposed to those found while trying to understand a disease), GBM remains a virus both in search of disease(s) and of its hosts.

**GBM AND KEEPING BLOOD AND ORGAN DONATIONS SAFE**

In addition to independent confirmation of GBM in asymptomatic blood donors, development of well-characterized serologic assays will be important. If the reported findings are confirmed, seroepidemiologic studies and PCR can more broadly and accurately determine the prevalence of antibodies, suggesting exposure, and the prevalence and duration of viral DNA in the blood, suggesting exposure, and the prevalence and duration of viral DNA in the blood, suggesting exposure. However, if transfusion and/or transplantation of blood and organs obtained from GBM-positive donors was found to pose a significant health risk, it should be feasible to develop tests to screen donors. More understanding would be needed to determine whether testing for DNA, antibodies, or both is most appropriate. For example, in some circumstances nucleic acid testing (NAT) is indicated because only NAT-positive specimens pose an infectious risk (as in acute infections in which recovering individuals clear the virus, like West Nile virus) or because NAT is most sensitive, particularly early during infection, prior to development of antibodies (as seen with human immunodeficiency virus and hepatitis C virus). Whether NAT, antibody tests, or both were needed, there is ample precedent in recent years for rapid development, validation, and implementation of such tests [4], which can often use existing platform technologies and are increasingly automated and able to support testing for multiple pathogens [5]. However, such tests must be very carefully developed and evaluated, because they must not only be highly sensitive, but also, given their use in screening millions of donations annually, highly specific so as to avoid false-positive results and the potential to reduce blood and organ availability. Thus, both costs and public health consequences are not insignificant in considering adding donor testing. As diagnostic tools advance, however, it may be possible to screen donors by multiplex arrays or other assays that sensitively detect either all known pathogens or selected pathogens of concern, and to even use the same technologies to concurrently identify the immune and infection status of recipients. This could further enable what can be thought of as “personalized transfusion”, for example avoiding blood transfusion from pathogen-positive donors to pathogen-negative (ie non-immune) recipients, but allowing transfusion from positive donors to recipients who are already immune, provided such transfusion does not pose added risks. This approach is similar to the use of serologic testing to prevent transfusion of blood from CMV positive donors specifically to CMV negative immunocompromised recipients, individuals to whom it can pose a substantial risk.

**THE HUMAN VIROME: DATA, KNOWLEDGE, AND THE WEB OF LIFE WITHIN**

Whether or not GBM turns out to be a significant pathogen, the findings from this study raise a number of fascinating and important general issues. First, the power of new science to detect potential pathogens as causes of currently undiagnosed illness or contributors to chronic disease is remarkable. Second, going from discovery of a microbe to a disease may, in many cases, be more challenging than traditional disease-based pathogen discovery. In addition, akin to the challenges associated with specialization in clinical medicine, as science becomes increasingly driven by data, noise-to-signal ratios can become high, and few individuals or groups may have the knowledge, perspective, and clinical and laboratory resources to place data in perspective to best understand how to respond. Third, our horizon, whether as clinicians, researchers, or patients, must be expanded to include the understanding that we are not simply organisms locked in battle with pathogens. As has become abundantly clear as we begin to understand the microbiomes in our skin, gut, genitourinary tract, and elsewhere, our own microbial world is constantly interacting, both among its members and with our immune and other cells, and these interactions, or their disequilibrium, are
critical in causing, understanding, and treating certain diseases [6]. It is similarly likely that viruses, including many that billions of people live with for much of their lifespan, even when they do not cause a disease in the traditional sense, can interact with and affect our immune and inflammatory responses [7]. Whether GBM has such properties is unknown, but if so it could exert unique effects, whether deleterious or beneficial, based on its complement of genes of diverse origin. Whatever the conclusion to this story, just as there is a web of life and an ecosystem outside of us that we are all part of, so too is there one within and on us. These ecosystems can and do communicate, sometimes through microbes. Along with other recently appreciated influences, such as the epigenome and extracellular RNA, we clearly share pathogens and information across species and kingdoms of life. Such sharing poses both clear risks but also potential benefits, such as in our ability to better sense, respond, and adapt to our environments, thereby influencing health and disease.

**Notes**

**Acknowledgments.** I thank Drs Hira Nakhasi and Jay Epstein for helpful comments and for many years of sharing information about and protecting blood safety.

**Disclaimer.** The views expressed are the author’s and are not intended to represent those of the Food and Drug Administration or the Department of Health and Human Services.

**Potential conflicts of interest.** Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**References**