

The human cytomegalovirus: a forgotten herpesvirus

Professor Richard D. Dix specialises in ocular virology and immunology at Georgia State University. More specifically, his work focuses on mouse models of AIDS-related cytomegalovirus retinitis, and the links between chronic cytomegalovirus infection and age-related macular degeneration in the elderly. His ultimate aims are to contribute towards better diagnosis and management of several life-altering diseases of the eye.

Despite the various barriers that the body uses to preserve vision and to prevent pathogens from damaging the eye, viruses use unique mechanisms to bypass the barriers and establish infection. This infection process often leads to destruction of the structural architecture of the retina, causing retinitis, and ultimately vision loss potentially leading to blindness.

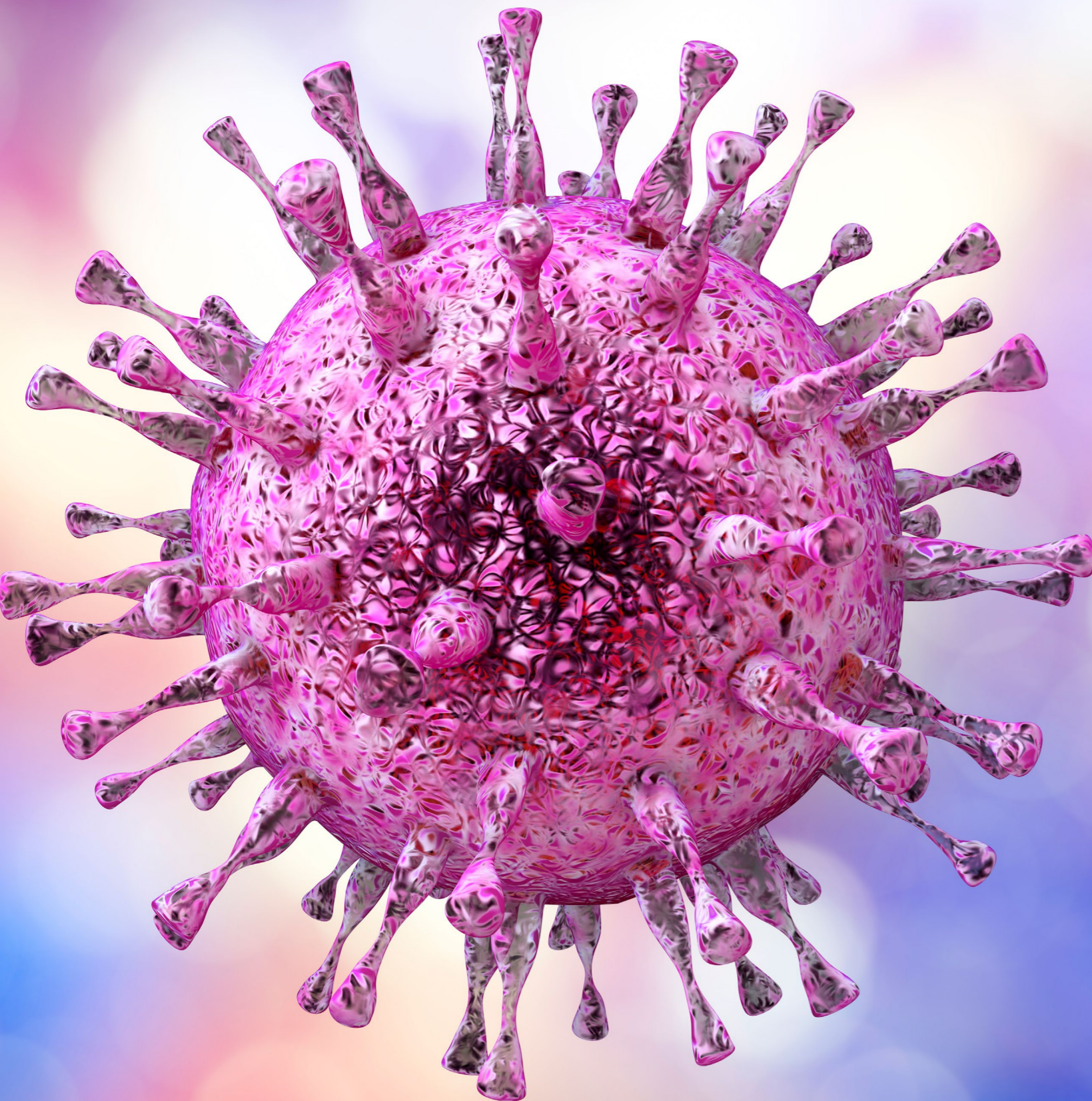
Professor Dix calls human cytomegalovirus 'the forgotten herpesvirus'. A β -herpesvirus that is capable of causing severe disease in immunocompromised individuals, human cytomegalovirus (HCMV) is acquired early in life and spreads from person to person through a range of bodily fluids. However, like other herpesviruses, it establishes a dormant infection in healthy individuals that can reactivate later in life to cause disease. Approximately 80% of adults are likely to be infected with the virus, but it rarely causes problems unless the immune system declines. HCMV retinitis is thought to originate from virus that invades the retina from the blood during systemic infection in severely immunocompromised individuals. For example, patients treated with immunosuppressive drugs to prevent rejection of solid-organ and bone marrow transplants are especially at risk for developing HCMV retinitis at an incidence of approximately 5%.

Alongside the increased appearance of AIDS, AIDS-related HCMV retinitis also became more commonly observed, a disease which caused vision loss and blindness in up to 30% of AIDS patients. As combination anti-retroviral therapy (ART) has improved, and the number of opportunistic infections decreased, so has the incidence of AIDS-related HCMV retinitis. However, it still remains a major problem in HIV-infected patients who do not have access to ART in many parts of the world, or do not respond to ART.

Dix's research on AIDS-related HCMV retinitis uses a unique mouse model of retrovirus-induced immunosuppression, called murine acquired immunodeficiency syndrome (MAIDS). In fact, a recent paper published by Alston and Dix compares expression of suppressors of cytokine signalling (SOCS) in the eye for two different mouse models of experimental MCMV retinitis. The study concluded that using different methods of immune suppression prior to injection with MCMV yielded slightly different results. Although in both models, two forms of SOCS were stimulated, they increased to a lesser extent when immune suppression was induced by corticosteroids, as compared to retinitis-susceptible MAIDS mice.

Present work is looking at how cell death pathways, such as apoptosis, necroptosis

Cytomegalovirus is capable of causing severe disease in the immunocompromised



and pyroptosis may combine with virus-induced cell death to cause the severe and irreversible retinal cell destruction associated with retinitis. It is not yet clear whether these pathways are operating simultaneously within individual retinal cells to induce intermediate forms of cell death, or whether they occur independently of one another.

CHRONIC VIRAL INFECTION AS A CO-FACTOR FOR VISION LOSS IN THE ELDERLY

Age-related macular degeneration (AMD) occurs in two forms; wet and dry. Wet AMD is the leading cause of severe irreversible vision loss in the ever-growing elderly population. It is characterised by formation of new blood vessels, a process called neovascularisation, within the macula of the retina. This disrupts the architectural structure and contributes to loss of sight. Several co-factors are already known, including smoking, genetics and a high fat diet. Chronic cytomegalovirus infection in immunologically normal individuals can affect the retina, and because of this, may also be a co-factor in the pathogenesis of AMD.

Dix's research group has worked with a team at Duke University to utilise a mouse model of wet AMD to provide evidence that chronic cytomegalovirus infection of circulating monocytes in the blood may be an additional co-factor for the disease. In order to show this, the team used an established mouse model of choroidal neovascularisation (CNV). They infected the mice with MCMV and induced CNV at various timepoints. Compared to the control animals, those infected with MCMV developed more severe CNV. This was particularly poignant in mice with a chronic MCMV infection. It was hypothesised that a potential mechanism may involve stimulation of macrophages to make pro-angiogenic factors, for example vascular endothelial growth factor (VEGF), which would result in formation of new blood vessels, and that this process requires active virus replication. Furthermore, depletion of macrophages has been shown to significantly decrease the size and severity of lesions in the eye following experimentally induced CNV.

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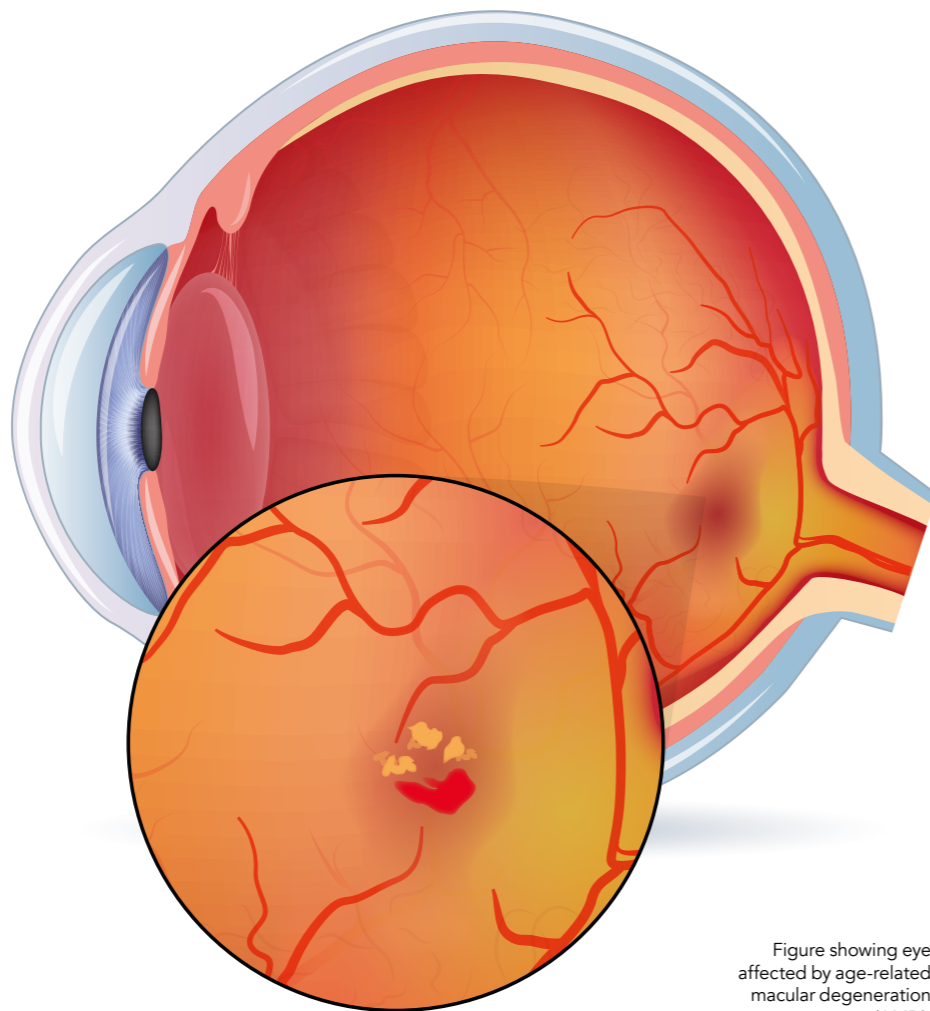
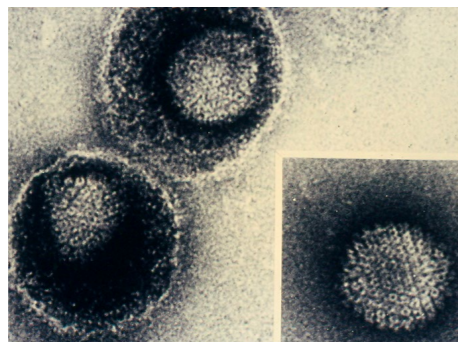


Figure showing eye affected by age-related macular degeneration (AMD).



An electron micrograph showing herpesvirus particles. Insert shows a naked nucleocapsid without envelope.

This work means that it may be possible to predict that patients with low levels of circulating HCMV may develop less severe AMD than those with high levels of circulating virus, or those in which the virus has recently undergone a re-activation event. Therefore, as with AIDS-related HCMV retinitis, it is possible that antiviral treatment may be effective in suppressing

the choroidal neovascularisation associated with the development of wet AMD. The current treatment for wet AMD is an artificial antibody against VEGF, in an attempt to prevent the formation of new blood vessels in the eye. However, 25-40% of patients will not respond to this treatment and it will only reduce the symptoms, rather than cure the disease.

TRAINING THE NEXT GENERATION

As well as producing world class scientific findings, Professor Dix is committed to training the next generation of vision scientists. Through his research programme, he mentors graduate students seeking M.S. and Ph.D. degrees in ocular virology and immunology.

In the future, Dix and his collaborators would like to explore predictors of AMD, as well as potential treatment options. For example, viral load may be a way to predict who is more susceptible to developing AMD, and therefore antivirals may be an option to tackle AMD in some cases. Firstly though, Dix has a new \$1.48 million grant from the National Institute of Health to spend on investigating another blindness-causing disease also caused by cytomegalovirus in patients with AIDS.

Q&A

Many of your studies focus on female mice, are there differences between how males and females respond? Is this a phenomenon seen in humans?

There is no difference between how male mice versus female mice respond to development of MAIDS or development of experimental cytomegalovirus retinitis in our MAIDS model of AIDS-related HCMV retinitis. This observation is true in humans for development of AIDS and development of HCMV retinitis during HIV-induced immunosuppression.

Your studies, and those of others, use a laboratory adapted version of MCMV, how similar is this to a current wild type, circulating HCMV i.e. have any genome comparisons been done?

HCMV is highly species-specific, a barrier that contributed to the initial lack of development of animal models for study of HCMV retinal disease. Investigators eventually turned to MCMV, a mouse herpesvirus whose genomic structure and cellular/tissue tropisms parallel those of HCMV. In fact, the determination of the nucleotide sequence of both HCMV (strain AD169) and MCMV (strain Smith) has allowed analysis of the biological importance of a number of virus genes shared between HCMV and MCMV. The similarities between HCMV and MCMV gene expression are striking, especially among those involved in the pathogenesis and immunology of the viruses. Our understanding of many of the basic mechanisms underlying the pathogenicity of HCMV has been strengthened considerably by a large body of experimental data using MCMV.

Can virus pass between the two eyes of an individual? Many studies use the contralateral eye as a control, so this must assume there is no transfer of the CMV either from the infected eye of the mouse, or from its cage mates.

Following unioocular injection of MCMV subretinally, the eyes are collected no later than ten days after injection. We do not detect evidence of MCMV infection

of the contralateral eye tissues at this time.

Whilst in humans, HCMV invades the retina from a systemic infection, in mice an experimental, local ocular infection is induced. Although the histopathological features of the two forms of retinitis may look similar, is there a possibility that two different sets of pathways and mechanisms are at play here?

My laboratory, as well as other laboratories, have attempted to induce retinitis in immunosuppressed mice (corticosteroid treated or mice with MAIDS) following systemic MCMV infection (intraperitoneal or tail vein injection). Use of tracer viruses have shown that virus does indeed travel to the eye and can infect retinal pigmented epithelial cells. However, virus rarely infects cells of the neurosensory retinal tissues, and retinitis fails to develop. Moreover, retinitis rarely develops if virus is inoculated into the anterior chamber or vitreous cavity of eyes of immunosuppressed mice. Only injection of virus by the subretinal route (other laboratories call it the supraciliary route) results in a high percentage of eyes with reproducible retinal disease that mimics that observed in humans with AIDS-related HCMV retinitis. We believe that these observations suggest that virus invades the retina via the retinal pigmented epithelium from the choroidal vasculature during onset and development of AIDS-related HCMV retinitis in humans.

What is the one piece of advice that you give to all graduate students that you mentor?

Quantify, quantify, quantify when obtaining data!! I also promote professionalism, i.e., always take the high road when dealing with colleagues and (especially) competitors/rivals or you may be splashed with mud if you lower your standards.

Detail

RESEARCH OBJECTIVES

Professor Dix's research explores the key events that take place during onset and development of retinal diseases caused by human herpesviruses, with a particular focus on human cytomegalovirus.

FUNDING

- National Eye Institute, National Institutes of Health (NIH)

COLLABORATORS

- Julia Hilliard, Ph.D., Georgia State University
- Scott Cousins, M.D., Duke University School of Medicine, Durham, North Carolina
- Colleagues of the Atlanta Vision Research Center and Emory Eye Institute, Emory University School of Medicine, Atlanta, Georgia

BIO

Professor Richard Dix obtained his BS in Biological Sciences from Youngstown State University and his PhD in Virology from Baylor College of Medicine.

Following his postdoctoral training in neurovirology and AIDS in San Francisco, Richard moved to Bascom Palmer Eye Institute, University of Miami School of Medicine, where he became full Professor in 1998.



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