Herpes virus infection and immunity

‘Les Pensières’
Fondation Mérieux Conference Centre
Veyrier du Lac – France

June 18-20, 2012

Steering Committee:

• Jeffrey COHEN
• Catherine DUTEL
• Simon DELAGRAVE
• David KNIPE
• Jacques LOUIS
June 18, 2012

Dear participants,

It is our pleasure to welcome you to the symposium entitled:

‘Herpes Virus Infection and Immunity’

in Fondation Mérieux’s Conference Centre ‘Les Pensières’. We hope you will enjoy this meeting, which brings together some of the world’s foremost experts. The format of the discussion is intended to generate discussion and interaction among participants and to foster the dissemination of new information on this topic. The conference will provide an opportunity for specialists to exchange their knowledge and experience through collaboration with researchers from around the world.

Over the next three days, the team at Les Pensières will be on hand to help you with any questions you may have and to make your stay and conference as comfortable and valuable as possible.

Yours sincerely,

Benoît Miribel
Director General
Fondation Mérieux
Among the herpesviridae family, five viral species are of particular importance to human health: herpes simplex virus (HSV) types 1 and 2, varicella virus (VZV), Epstein-Barr virus (EBV) and cytomegalovirus (CMV). All of these are highly prevalent throughout the world; however, the high socioeconomic cost of disease due to HSV, its transmission to newborns at birth, and its enhancement of susceptibility to HIV infection, make it a particularly pressing target for vaccine development. While vaccines are available to prevent varicella in children and zoster in older adults, there has been very limited progress in developing an effective vaccine against HSV.

Latest developments in virology:
A long-term study of HSV-infected individuals has recently confirmed prior findings that the virus is shed frequently regardless of whether the infected individual is symptomatic or not. What is the latest model of latency at the cellular and molecular levels? Where are the gaps in our understanding of this phenomenon, and what will it take to fill them? What technological and scientific advances will be required to enable the elimination of a latent infection?

Our understanding of the function of the glycoproteins involved in membrane fusion has advanced significantly in recent years with the solution of the atomic structures of gD, gB, gH and gL, and the biochemical analysis of their interactions. What have we learned and what are the implications for vaccine development?

Latest developments in immunobiology:
It is clear that innate immunity plays a role in responding to HSV infections. And the role of T cell immunity in sensory ganglia as well as peripheral tissues is under investigation. What progress have we made in studying these phenomena and in determining the correlates of protection against HSV infection? What is known about the immune evasion mechanisms that HSV has evolved?

Molecular epidemiology:
The Knipe lab has identified a South African strain of HSV-2 showing evidence of immunological divergence from North American strains. HSV-2 is highly prevalent in sub-Saharan Africa and is known to increase susceptibility to HIV infection. With the availability of next-generation sequencing technology, could a systematic survey of HSV-2 and -1 isolates be carried out?

Prophylactic vaccines:
GSK recently announced the failure of their Simplirix vaccine. What is the latest information available on this trial? Are there lessons to be learned which could be applied to future vaccine development efforts? What are our options for modelling natural HSV infections? What alternatives are there?

Immunotherapy:
Therapeutic vaccines comprising gD have shown some weak but statistically significant benefits in human clinical trials. What must be achieved immunologically in order to effect a sufficiently beneficial clinical outcome?

Comparative virology:
What can be learned from other vaccines for sexually transmitted diseases like human papillomavirus in terms of virology, immunology, and vaccinology?

The aim of this conference is to stimulate an exchange of information and ideas on herpes simplex with the hope that this will result in new insights that can be applied to the development of novel immunotherapeutic and immunoprophylactic approaches.

Simon Delagrave, Ph.D.
Scientific Programme

**Monday 18 June 2012**

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**Tuesday 19 June 2012**

**Session 1**

**Burden of diseases due to HSV infections, medical needs**

**Chair:** David Knipe

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**Immunobiology of HSV infections**
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Chair: Jeffrey Cohen

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Keynote lecture

Past lessons and application of new knowledge about immunology of HSV infection on the development of HSV vaccines
Past lessons and application of new knowledge about immunology of HSV infection on the development of HSV vaccines

Lawrence COREY
Fred Hutchinson Cancer Research Center - USA

The predominant thinking in HSV biology for over 50 years has been that once HSV-2 established latency in the sacral nerve root ganglia, reactivation was infrequent and invariably led to genital lesions. On a mechanistic level, the major regulator of reactivation was viral host interaction within the neuron. In the mid-1990’s, studies using PCR based technologies demonstrated asymptomatic reactivation of HSV-2 in the genital tract was the predominant form of reactivation in humans. Concomitantly, Hendricks, et al demonstrated that HSV specific T cells were present in ganglia and their removal was associated with reactivation of latent infection, suggesting control of reactivation was at least in part immune mediated by T cells in the neural ganglia. Over the last 5 years, detailed studies of the kinetics of subclinical viral reactivation indicate most subclinical HSV-2 reactivations last only 2-6 hours. These subclinical reactivations are multifocal and widely spread anatomically; hence, involving several different individual ganglia. The abrupt onset and clearance of such multifocal reactivations on a nearly daily basis requires a reassessment of the operant mechanisms behind HSV reactivation. In 2007, we demonstrated that CD8+ T cells, including HSV-2 specific CD8+ T cells, were present and localized at the dermal-epidermal junction, adjacent to sensory nerve endings where reactivating virion particles are released. These cells persisted at the dermal-epidermal junction for months. More recently, we have used a laser capture microdissection method in combination with transcriptional profiles and RT PCR to evaluate the function of these CD8+ T cells in situ. These analyses indicate significantly higher expression levels of genes with a cytotoxic effector function, such as those encoding perforin, granzyme A, granzyme B and interferon γ, in CD8+ T cells captured from the dural-epidermal junction of biopsies at clinically quiescent time periods as compared to CD8+ T cells captured from control biopsies of normal arm tissue or genital skin from the contralateral side. Moreover, many of the glycolytic and fatty acid metabolism transcripts detected have half lives of <24 hours; suggesting that exposure to cognate antigen has occurred recently.
The expression of cytolytic granules in these cells was also demonstrated at the protein level. Most recent, these cells appear to be able to contain HSV-2 antigen before lesion onset. These data provide evidence of a new conceptual model of HSV-2 pathogenesis in which viral host interactions occurs frequently and in which host mucosal immune responses are the primary determinants of reactivation location and frequency. The spatial kinetics between host response and viral reactivation are the major determinants of containment versus non-containment. These insights provide optimism that novel immunological approaches to HSV therapy can be developed.
Session 1

Burden of diseases due to HSV infections, medical needs
Neonatal Herpes Simplex Virus Infections: Improving Outcomes – Need to do Better

Richard J. WHITLEY
The University of Alabama - USA

In developed societies, the incidence of neonatal herpes simplex virus (HSV) infections varies between 1 in 2500 to 30,000 deliveries. This discrepancy is a function of definition of disease in different countries. The most severe forms of disease manifest as involving either the central nervous system (CNS) or multiorgan disseminated disease with or without skin involvement, accounting for approximately 60% of all infected children. The remaining 40% of infected newborns will have disease localized to the skin, eye or mouth. Overall, approximately 50% of all babies with this disease will have CNS involvement, resulting in significant morbidity. Four areas warrant special attention. First, high dose acyclovir has decreased mortality significantly; however, morbidity remains high, especially in children with CNS disease. Second, the application of PCR evaluation of cerebrospinal fluid at the completion of treatment correlates with long term neurological outcome. Third, evaluation of viral load in the cerebrospinal fluid provides a marker suggesting the development of resistance to acyclovir in a small percentage of children. Lastly, long term suppressive therapy not only improves neurologic outcome but suggests chronic replication versus asymptomatic recurrence of HSV in the brain. The future requires the evaluation of combination therapies with drugs that have different mechanisms of action as well as considering suppressive therapy with drugs that have improved pharmacokinetics.
Global Epidemiology of HSV infections, the links between HSV and HIV

Helen WEISS
London School of Hygiene & Tropical Medicine - UK

Infection with herpes simplex viruses type-1 (HSV-1) and type 2 (HSV-2) is very common worldwide. HSV-2 is almost always sexually transmitted, whereas HSV-1 is usually acquired during childhood via nonsexual contacts. After primary infection, both types remain latently present in the body and lead to the production of lifelong antibodies, and periodic symptomatic reactivation. In general, HSV-1 causes oral lesions, and HSV-2 causes genital lesions. For both types, the clinical spectrum includes recurrent episodes of lesions or vesicles, and subclinical episodes of infectious viral shedding. Prevalence of HSV-1 is estimated at around 60% in the United States, and is almost universal in parts of sub-Saharan Africa. HSV-2 prevalence in the United States has decreased slightly (from 21% in 1988-1994 to 17% in 1999-2004), and again tends to be higher sub-Saharan Africa (30%-80% in women, 10%-50% in men). Prevalence of both infections tends to be higher in women than in men, and to increase with age. Many studies have shown that HSV-2 infection increases risk of acquiring HIV infection, even in the absence of HSV-2 symptoms. However, standard dose acyclovir has not been effective in preventing HIV infection or transmission. In this talk we will review the global epidemiology of HSV-1 and HSV-2, including the association with HIV infection, discussing the suite of randomised controlled trials that have assessed the impact of suppressive and episodic HSV therapy on HIV acquisition and transmission.
Considerations in Estimating the Economic Burden of Genital Herpes Simplex Virus Infections

David FISMAN
University of Toronto - Canada

Genital tract infection with herpes simplex viruses is highly prevalent worldwide, but associated with an extraordinary degree of heterogeneity in clinical manifestations, ranging from asymptomatic infection to severe primary infection with frequent recurrences. Perinatal and obstetrical complications of infection, and enhanced risk of HIV acquisition and transmission further broaden this clinical spectrum. Financial stresses on healthcare providers mean that emerging strategies and interventions to prevent HSV infection must be considered in light of effectiveness and cost-effectiveness, and such analyses depend on estimates of costs of HSV in the absence of intervention. Economic valuation of disease burden is based on three core elements: "costs" (whether estimated in monetary units or in terms of reduced quality-adjusted health) need to be (i) identified; (ii) measured; and (iii) valued. There have been few studies that have sought to estimate HSV-attributable costs directly, and consequently estimation of the economic burden of genital HSV infection depends on synthesis of empirical data from multiple sources, using modeling techniques. For genital HSV infection, identification and measurement of costs are facilitated by large longitudinal cohort studies that have generated important insights into disease natural history. Limitations in measurement of costs derive from the non-notifiable nature of genital HSV infections, lack of granularity in medical billings databases, and difficulties in estimating the fraction of HIV infections that are HSV-attributable. Valuation of HSV-attributable costs and reduction in health-related quality of life is complex, in part because of the relapsing-remitting nature of disease, and in part because many important elements of the genital HSV disease experience are intangible: for example, comprehensive valuation health states needs to consider not only physical manifestations of disease during symptomatic periods, but also such elements as feelings of shame, and concern about transmission to partners, which may be present during asymptomatic periods. I will discuss the challenges outlined above, and also introduce research methodologies, including contingent valuation and conjoint analysis, which may be used to value intangible aspects of genital HSV infection.
Session 2

Epidemiology of HSV infections
Changing Epidemiology of HSV infections in Developed Countries

Fujie Xu
Centers for Disease Control and Prevention - USA

HSV epidemiology has been studied by serologic surveys of HSV-1 and HSV-2 as well as virologic studies of genital herpes. Data from developed countries suggest that the epidemiology of HSV infections is changing. Some of the best serologic data from developed countries come from population-based surveys in the US.

In the United States, the NHANES surveys, nationally representative sero-surveys since the late 1970s monitored trends of HSV-1 and HSV-2 infections over time. Most recent data showed that approximately 1 in 6 Americans 14-49 years of age (16.2%) were infected with HSV-2 during the survey period from 2005 to 2008, making it one of the most common sexually transmitted infections (STI) in the US and representing among the highest seroprevalence in the general population in developed countries. Although there was no significant change in seroprevalence from the previous period, measured during 1999-2004 at 17%, HSV-2 seroprevalence was higher in the past (21% in 1988-1994). Globally, the lowest HSV-2 seroprevalence was in western Europe, where prevalence reached a maximum of around 18% among women and 13% among men.

Among women aged 15–49 years in the United States, we estimated that there were 15.9 million prevalent HSV-2 infections in 2008 (prevalence: 21.7%); among men, there were an estimated 8.2 million HSV-2 infections (prevalence: 11.3%). Assuming that HSV-2 prevalence in people ≥50 years of age was the same as that among 45-49-year-olds, there were an estimated 48.5 million prevalent HSV-2 infections in the U.S. population. In the 15–24 year-old age group, there were an estimated 1.7 million prevalent infections among women (prevalence: 8.2%) and 812,000 infections among men (prevalence: 3.9%). Preliminary findings from catalytic models fitted to HSV-2 seroprevalence data from NHANES surveys (1988–2008) showed that there were estimated 356,000 new HSV-2 infections among women aged 15–49 years in 2008 (incidence: 0.49%) and 420,000 incident infections among men (incidence: 0.58%). Among women aged 15–24 years, there were an estimated 208,000 incident infections in 2008 (incidence: 1.01%); among men, there were an estimated 144,000 infections (incidence: 0.69%).
Continued

The models also showed that over the last twenty years, age-adjusted HSV-2 incidence rates were stable for all sex-race/ethnicity groups examined except for non-Hispanic white and Mexican-American women, in which there were decreases after 2002 and 2001, respectively. HSV-1 seroprevalence in the US was much higher than HSV-2. In children age 6 to 13 years, HSV-1 seroprevalence was 31.1% (95% confidence interval [CI], 28.6% to 33.9%).

Virologic studies in both the US and elsewhere suggest that the etiologies of genital herpes is changing. A recent randomized, double-blind trial in women 18 to 30 years of age in the United States and Canada observed an attack rate of 3.2% for HSV-1 and 1.5% for HSV-2 in the control group of 3,076 women over a 20-month period, and HSV-1 was a more common cause for symptomatic genital herpes. Compared to Canadian women, U.S. women were more likely to acquire HSV-2 (hazard ratio, 2.7; 95% CI, 1.2 to 6.2), but not HSV-1 infection. A recent study in US young, adult military population reported seroincidence rates of 9.1 per 100 person-years for HSV-1 and 6.2 for HSV-2. HSV-1 as the main cause of genital herpes has been reported in other developed countries, including Sweden, Norway, and Australia.

In conclusion, HSV-2 remains a common STI, especially in women, in developing countries. However, the increasing burden of HSV-1 as the cause of genital herpes disease warrants renewed attention.
Genetic and phenotypic diversity of HSV strains; the issue of protection against the African strains

David M. KNIFE
Harvard Medical School - USA

Most animal model studies of génital herpes vaccines have used laboratory strains for challenge infections. Our studies with the dl5-29 vaccine virus have shown protection against the low passage HSV-2 G strain isolated in the US. However, there are epidemics of génital herpes in several parts of the world, and several studies have shown that viruses from these areas can be more genetically diverse and more pathogenic than viruses from the US or Europe. To test whether the dl5-29 vaccine strain can protect against HSV-2 from Sub-Saharan Africa, we examined the ability of an HSV-2 vaccine strain, dl5-29, and other HSV-2 replication-defective mutant strains to protect against genital challenge with US or South African strains in a murine model (Dudek et al., 2011). Immunization with dl5-29 reduces infection by both viruses but is significantly more efficacious against the US virus than against the African virus. Furthermore, another US vaccine strain was more efficacious against US than against African viruses, and the converse was observed for the parallel African vaccine strain. Nevertheless, protection against the African viruses was significantly less with all vaccines used in this study. We concluded that there may be differences in protective epitopes and pathogenesis between the US and African strains that raise the need for increased doses of the existing vaccine candidate or an HSV-2 vaccine strain based on viruses from that region.

Further studies are investigating the factors needed to achieve better protection against the South African viruses, including route of immunization, genetic background of the vaccine strain, and introduction of additional mutations to reduce immune evasion. Sequencing studies of the South African virus genomes have shown limited genetic diversity from the US/European viruses, and we have nearly completed the assembly of the genome for the African SD-90 HSV-2 strain. This may provide a more representative reference strain than the attenuated HSV-2 HG-52 virus. An expanded genomic comparison is continuing on a set of HSV-2 isolates in collaboration with the Broad Institute. Phenotypic studies have found the African HSV-2 viruses may be more effective in blocking innate responses than the US viruses, which could contribute to their pathogenicity. In summary, there may be key differences between the African and the US/European HSV-2 strains that will need to be considered in design of genital herpes vaccines for international use.
Session 3

Virology
The strategy of herpes simplex virus (HSV) in productive and latent infections

Bernard ROIZMAN
The University of Chicago - USA

The mission of HSV is to replicate and disseminate with minimal harm to the infected individual. The strategy involves (a) complete control of the infected cells during replication at the portal of entry (b) invasion and maintenance of the genome in neuronal cells innervating the site of initial infection, (c) a dynamic equilibrium between a state of silence and minimal gene expression that can lead to reactivation, and (d) transmission to the body surface and dissemination to contacts. The highlights are as follows:

**Productive infection:**

1. Susceptible cells respond immediately to the entry of HSV into cells. In the cytoplasm sensors respond by activation of NFKB and ultimately IRF3. In the nucleus viral DNA is coated by histones, repressed by HDAC1-2/CoREST/REST complex, and induces the assembly of ND10 bodies.

2. Pre synthesis of viral gene products, an endoribonuclease encoded by UL41 gene and known as VHS-RNase introduced into the cells during infection rapidly degrades 5'→3' stable mrNAs, (b) inactivates by 3' UTr cleavage most NFKB dependent mrNAs but largely spares viral mrNAs. In addition VP16 recruits several host proteins including LSD1 to derepress α (immediate early) promoters.

3. Post synthesis of α proteins (a) ICP27 blocks the splicing of cellular mrNAs, (b) ICP0 mediates the degradation of PML and other proteins thereby precluding exogenous interferon from blocking viral replication. ICP0 also dislodges HDAC1-2 from CoREST thereby enabling the derepression of β and γ promoters. (c) Viral protein kinases introduced into the cell during infection accelerate the process of acquiring total control of the infected cell. ICP0 in the cytoplasm interacts with Cin85, EF-18, src, etc. to both block responses to infection and to enable efficient synthesis of viral proteins.

**Bottom Line:** The fundamental strategy of HSV is (a) preemptive strike – block the cell before it can react to the virus (b) sequential derepression of viral genes to maximize the size of progeny and (c) recruit cellular proteins known to regulate the key proteins of interest (e.g. ICP0 binds cyclin D3 to recruit CDK4, Bmal1 to recruit CLOCK, Cin85 to recruit Cbl, etc.)
The net effect is that the cell cannot possibly recover following viral replication.

Establishment of Latency and Reactivation

Overwhelming evidence indicates that HSV is repressed in sensory neurons by repressive histones, and repressors. The data indicate that the establishment of latent state involves a slow progression from an initial silencing to a state that may be controlled by LAT and miRNAs.

The key issue is the mechanism of derepression of viral DNA in the absence of VP16. Studies based on neuronal cultures suggest that VP16 is made first. Studies based on ganglionic organ cultures within the time frame of a single round of viral replication indicate activation of viral gene expression follows a potentially "catastrophic" event leading to the derepression of all viral genes at once, and degradation of LAT and miRNAs.

Bottom Line: The biochemical changes accompanying viral gene expression are fatal to the neuron. The finding of low level viral DNA in genital track of HSV-2 infected women most likely represents chronic low level replication and not frequent activation of virus replication by the same neurons.
Herpes Simplex virus fusion and entry: A pathway governed by four viral glycoproteins

Roselyn EISENBERG
University of Pennsylvania - USA

Herpesviridae comprise a large family of enveloped DNA viruses all of which employ orthologs of three glycoproteins, gB, gH and gL. Additionally, herpesviruses often employ accessory proteins to bind receptors and/or bind the heterodimer gH/gL or even to determine cell tropism. For herpes simplex virus, this key accessory protein is gD which binds one of two protein receptors. Sorting out how these proteins function for HSV induced cell fusion and virus entry has been resolved to a large extent by structural biology coupled with supporting biochemical and biologic evidence. Together with the G protein of vesicular stomatitis virus (which is in an entirely different family of viruses), gB is a charter member of the Class III fusion proteins. These two proteins share remarkable domain structure despite the absence of any sequence similarities. Importantly, G can carry out fusion on its own while gB only functions when partnered with gH/gL. However, gH/gL does not resemble any known viral fusion protein and therefore it is unlikely to act as a co-fusogen with gB. We have uncovered evidence that the function of gH/gL is to up-regulate the fusogenic activity of gB. Moreover, gH/gL itself is up-regulated into an active state by conformational changes that occur when gD binds either one of its receptors. Although we understand that fusion occurs in this stepwise fashion, we are now focusing on the details of each step. It is notable that gD, gB and gH/gL are important targets of the host’s immune response. Thus these proteins are key components of any new anti-HSV vaccine. Moreover, it is our hypothesis that the steps involved in fusion and entry will be important targets for developing new therapeutics directed at virus entry. I will present data to support our current model for how herpes simplex virus (HSV) accomplishes fusion in a series of highly regulated steps. This model will highlight what is known and will also provide a framework to address mechanistic questions about fusion by HSV.
An immunization strategy to block HSV-2 immune evasion and cell-to-cell spread

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Mouse and guinea pig animal models for HSV-2 vaccine development remain valuable tools to assess novel vaccine candidates. The animal models are useful to insure that new vaccine candidates outperform earlier formulations that did not yield the intended results in human trials, to evaluate whether the desired outcomes in humans, such as preventing acute and recurrent genital lesions, can be achieved by new candidate vaccines in animal models, and to define immune correlates of vaccine efficacy. Our approach to a subunit vaccine for genital herpes is to induce potent immune responses to multiple glycoproteins that are involved in virus entry (gD2), cell-to-cell spread (gD2 and gE2) and immune evasion (gC2 and gE2) with the goal of blocking activities mediated by the glycoproteins.

We reported that a HSV-2 bivalent subunit glycoprotein vaccine containing gC2 and gD2 administered with CpG and alum was highly protective against HSV-2 vaginal infection in mice and guinea pigs; however, protection of the dorsal root ganglia (DRG) was not complete, which we consider an important outcome for a HSV-2 vaccine. The rationale for immunizing with gC2 was based on producing antibodies to block gC2-mediated immune evasion from complement. HSV-2 gE2 is an immune evasion molecule that binds the Fc domain of IgG and acts in synergy with gC2 to protect HSV-2 from antibody and complement neutralization. HSV-2 gE2 is also required for efficient virus spread from cell to cell.

HSV-2 gE2 antigen was purified from the supernatant fluids of baculovirus-infected cells and antibodies were prepared by immunizing rabbits, which resulted in ELISA titers >1:400,000. When the rabbit serum was used at a 1:20 dilution, it failed to neutralize HSV-2; however, at a 1:40 dilution, the serum markedly reduced plaque size of HSV-2 infected cells, demonstrating that gE2 antibodies blocked cell-to-cell spread. HSV-2 gE2 antibody also blocked rosetting of IgG-coated red blood cells to HSV-2 infected cells in a dose-dependent manner, indicating that the antibodies blocked HSV-2 IgG Fc receptor activity. As further evidence for blocking IgG Fc receptor activity, we evaluated whether rabbit gE2 antibodies enhanced the neutralizing ability of gD2 antibodies obtained from humans immunized with the GSK gD2 vaccine or gC2 antibodies obtained from immunized rabbits.
The addition of gE2 to gC2 or gD2 antibodies, each used at a 1:40 dilution, enhanced neutralization by 1.5 to 2 log10 in the presence of human complement, suggesting that anti-gE2 blocked gE2 mediated immune evasion. Therefore, antibodies to gE2 blocked both immune evasion from antibody and cell-to-cell spread. Studies are in progress using the murine vaginal infection model to assess the benefits of adding gE2 to gC2 and gD2 with CpG and alum as adjuvants in a trivalent subunit antigen vaccine.
Session 4

Immunology of HSV infections
How does Herpes Simplex Virus Enter a Mammalian Cell?
Targets for Intervention by Vaccination

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In the polyclonal humoral response of humans to natural infection by HSV, little is known about antibodies to particular epitopes, especially those of the glycoproteins responsible for entry. However for vaccine design or evaluation, it is important to identify those epitopes on the entry glycoproteins (gD, gB and gH/gL) that stimulate neutralizing antibody. Indeed, we know little about which epitopes of particular glycoproteins are critical for inducing a protective response or for clearing infectious HSV from the host. We have used a structure-function and immunological approaches to dissect the polyclonal response of rabbits to gD, gB, and gH/gL. Our studies rely on the fact that we in collaboration with crystallographers (D. Wiley, A. Carfi, S. Harrison and K. Heldwein) have solved the crystal structures of the four entry glycoproteins, as well as that of gD bound to each of its protein receptors, HVEM and Nectin-1. Over the years, we have assembled panels of monoclonal antibodies to each of these proteins and we are now applying them to this new goal. As a proof of concept our initial studies have focused on rabbit sera directed at gD. We have developed a competition study using the monoclonal antibodies to detect particular epitopes and we have also begun to separate antibodies to individual epitopes by biochemical methods. These studies have revealed interesting data that may serve as proof of concept for evaluating anti-HSV activity in human sera. Thus far, we have focused on the cell-receptor binding protein gD and the humoral response in rabbits to different forms of this antigen. Using this approach we are now studying the contributions of particular functional domains of gB and gH/gL to humoral immunity. Lastly, we hope to be able to determine whether our approaches can be applied to sera of human who have been vaccinated against HSV and to humans who have acquired humoral immunity by natural infection. Our hope is that our studies will help form new conceptual approaches for vaccine development against HSV.
T-cell responses to HSV-1 and HSV-2 in the whole genome/whole proteome era

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Specific T-cells play important roles in host defence against HSV infections, albeit correlates of protection or disease severity have remained elusive. In unpublished cross-sectional studies, we examined if blood levels of HSV-2-reactive CD4 cells, or HLA class I type as a surrogate marker for CD8 responses, correlate with HSV-2 genital shedding or lesion rates in chronically infected persons. Circulating CD4 T-cells varied over a 100-fold dynamic range in the study population but did not correlate with severity. Specific HLA class I alleles correlated with more severe genital herpes and HSV shedding, indicating a possible role for CD8 T-cells. Immunodominant and immunoprevalent CD8 T-cell antigens, especially if they could be administered to deposit cells in the skin/mucosa, would be rational as components of subunit vaccines. We are therefore dissecting the T-cell response to the entire HSV proteome, starting with HSV-1. In a small sample, open reading frames UL39 and UL46 were immunoprevalent for CD8 responses in the blood. The overall diversity per person for both CD4s and CD8s was on the order of 20 HSV-1 genes per person. A few CD8 responses are above the threshold required for direct ex vivo detection and single tetramer (+) populations of up to 2% have been observed. The CD8 diversity data may favour a whole virus vaccine approach. CD4 immunodominance data show that membrane glycoprotein and immediate early proteins elicit the most numerically abundant CD4 T-cells. Initial data from parallel genome-wide HSV-2 studies applied to CD4 T-cells from skin and from sero-negative persons will also be introduced.
Tissue-resident memory CD8+ T cells and protection against HSV infection

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HSV infection primes CD8+ T cells that are recruited to sites of infection as part of the immune response involved in control of virus replication. Not surprisingly, these T cells persist in sensory ganglia after the cessation of lytic replication, where they are thought to suppress virus reactivation as a consequence of ongoing activation. However, similar populations of T cells can be found persisting at initial sites of peripheral infection, in barrier tissues such as skin and mucosal surfaces. These cells have a unique phenotype and behave as a permanent resident sessile population, distinct from the memory T cells found in the circulation. Most recently, we have developed an approach that allows site-directed lodgment of these permanently tissue-resident CD8+ memory T (TRM) cells in barrier tissues in the absence of infection or antigenic stimulation. Importantly, TRM cells formed in this fashion afford superior local anti-viral immunity compared to their circulating counterparts. As a consequence, this targeting of CD8+ TRM cells to peripheral tissues provides effective barrier protection against infection without the need for persistent T cell activation.
Herpes simplex encephalitis in children: central nervous system specific inborn errors of TLR3-IFN-mediated immunity

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Childhood HSE is a life-threatening complication of primary infection by HSV-1, a common virus which causes only innocuous infection in most children. HSE is however the most common sporadic viral encephalitis in Western countries, and most acyclovir-treated survivors suffer from severe neurological sequelae. HSE has an incidence of about 2-4 cases per 1,000,000 individuals per year, and peaks between the ages of three months and six years, earlier than the peak of HSV-1 primary infection. HSV-1 is a double-stranded enveloped DNA virus. More than 85% of healthy adults worldwide are serologically positive for HSV-1, yet HSV-1 causes HSE only in rare cases, strongly suggesting that host susceptibility to HSV-1 plays a key role in the pathogenesis of HSE. The pathogenesis of HSE has long remained unclear. HSE has never been reported in patients with known primary immune deficiencies (PIDs). Remarkably, children with HSE are normally resistant to other infectious agents. Moreover, the lesions observed are restricted to the central nervous system (CNS) and there is no detectable viremia. In the course of HSE, the virus reaches the CNS via the trigeminal nerve and the olfactory bulb. No overt immunological abnormalities have been detected in affected children. Children with HSE do not generally suffer from subsequent recurrences of HSE and, following infection, HSV-1-specific T and B cells are detectable. These features suggested that human immune defects affect an HSV-1-specific host defense pathway in the CNS may underlie the pathogenesis of childhood HSE. We recently showed that HSE may result from single-gene mutations impairing intrinsic immunity to HSV-1 in the central nervous system (CNS). By following a candidate gene approach, we described six HSE-determining inborn errors of TLR3 immunity: autosomal recessive (AR) UNC-93B deficiency, AR and autosomal dominant (AD) TLR3 deficiencies, AD TRAF3 deficiency, and AR and AD TRIF deficiencies. By differentiating and testing CNS resident cells from UNC-93B-deficient patients’ fibroblast-derived induced pluripotent stem (IPS) cells, we further deciphered the cellular basis of HSE, which involves impaired interferon (IFN)-α/β and -γ production, upon stimulation of TLR3 by dsRNA viral intermediates in CNS resident cells, resulting in increased virus replication. Our findings demonstrated that a TLR can play a non-redundant role in host defense in a naturally occurring infection. Our findings also paved the way of treatment of HSE patients with IFN-α, in addition to acyclovir.
Dissecting the human B cell response to pathogens

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Memory B lymphocytes and long lived plasma cells represent the repository of the antigenic experience of an individual. By analyzing their specificity we can gain insights into the human immune response to foreign and self antigens, identify correlates of protection and isolate therapeutic antibodies. We have developed two culture-based high-throughput methods to interrogate human memory B cells and plasma cell repertoires. Using these methods we have analyzed the human antibody response to viruses, bacteria and parasites as well as the repertoire of autoantibodies in autoimmune diseases. In particular we have isolated and characterized a number of potent and broadly neutralizing antibodies that identify conserved targets in otherwise very variable pathogens. Some of these antibodies neutralize all serotypes and even distantly related viruses. Specific examples regarding HIV, influenza, DENV, RSV and MPV will be provided. I will also discuss how neutralizing antibodies can be used for the design of improved subunit vaccines, and provide such an example for HCMV.
Session 5

Interventions against HSV infections
Animal models of HSV infection and vaccine development

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A number of small animal models have been used for analyzing HSV infection including mice, rabbits, guinea pigs, and cotton rats. HSV inoculation of the eye, flank, or genital tract of mice results in local replication, local disease, and latency in sensory ganglia. HSV reactivation can be induced in mice with hyperthermia or ultraviolet irradiation. Reactivation is more readily induced after ex vivo explant cocultivation. Ocular inoculation of rabbits with HSV results in latency and reactivation of the virus from the eye. Vaginal inoculation of guinea pigs or cotton rats with HSV-2 causes acute infection, latency, and recurrent genital herpes with virus shedding.

Vaccines which were effective in preventing infection in mice and guinea pigs, such as those containing recombinant HSV gD, have been unsuccessful in phase 3 human trials. Similarly, therapeutic vaccines that were effective in preventing recurrences in guinea pigs, including a disabled infectious single cycle virus, were also unsuccessful in human trials. Thus, small animal models do not reliably predict the success of HSV vaccines in humans.

There are several limitations to small animal models for HSV. First, HSV naturally infects only humans, and viral proteins that elicit B and T cell responses have coevolved with their human hosts. Infection of small animals results in presentation of viral epitopes to hosts that have not seen these proteins; therefore recognition of HSV proteins may be different in small animals than in humans. Second, HSV encodes several proteins that evade the host immune response, and many of these viral proteins are less effective at inhibiting the orthologous cellular proteins in small animals. Third, it is estimated that over 20 sexual exposures are required for the uninfected partner of an HSV-2 infected partner to become infected. Since most infections occur during asymptomatic shedding which occurs very frequently, this suggests that the infectious dose may be relatively low. In contrast, most experiments in mice and guinea pigs use an infectious dose well above that needed to infect 100% of animals. Fourth, if an HSV vaccine will be targeted to prepubertal children, like the age group for which human papillomavirus vaccine is recommended, an HSV vaccine will need to be remain protective for many months to years. In contrast, most mouse and guinea pig studies challenge animals within a few weeks to months of vaccination. Fifth, most vaccine and challenge protocols use viruses of American or European ancestry that have been passaged many times in cell culture. Recent studies from the Knipe laboratory indicate that low passage viruses from Africa may be more difficult to protect against in small animal models.
Continued

In view of the disparity between the success of HSV vaccines in small animal models and their failure in human clinical trials, more stringent animal models are needed for preclinical testing of HSV vaccines.
Vaccine development against HSV - Past, Current and Future

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The history of HSV vaccine development dates from the 1930’s. The initial work focused on therapeutic vaccines intended for the control of recurrent mucocutaneous HSV infections. Clinical assessment of prophylactic vaccines did not begin until the late 1940’s. Two major problems hampered early research: the lack of defined vaccine products and fatally flawed design of clinical trials. Seven different types of vaccines have been investigated: 1. inactivated whole virus vaccines; 2. virion component or subunit vaccines; 3. attenuated live virus vaccines; 4. vaccines consisting of replication-limited or replication-impaired virus mutants; 5. replicating non-pathogenic vectors that express one or more HSV antigens; 6. Peptide vaccines; and 7. DNA vaccines, i.e., plasmids expressing one or more HSV genes.

HSV vaccine development begun in the modern era (1980’s and 1990’s) has been largely unsuccessful. However, studies conducted in the 1990’s were successful in establishing the feasibility of developing therapeutic and prophylactic HSV vaccines. Vaccines currently in clinical development or advancing towards commercial development include HSV peptides vaccines (Agenus and Genocea) and replications defective mutants (Sanofi-Pasteur).

Until a proven effective vaccine is on the market there will be continued preclinical exploration of existing platforms (sub-unit vaccines and replication impaired mutants) likely with new twists (e.g. nasal administration with mucosal adjuvants). Likewise newer approaches that have not been explored in a clinical setting for HSV control will advance in development including DNA vaccines, prime-boost strategies, and vectored vaccines including use of the neonatal Fc receptor for mucosal immunization.
The Herpevac Trial for Women: Efficacy Results

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Methods: A randomized, double-blind efficacy field trial vaccinated 8323 women 18 to 30 years of age who were negative for antibodies to HSV-1 and HSV-2. At months 0, 1 and 6, some subjects received the investigational vaccine, consisting of 20 µg of glycoprotein D from HSV-2 with alum and 3-0-deacylated-monophosphoryl lipid A as an adjuvant (AS04, GSK); control subjects received hepatitis A vaccine, at a dose of 720 ELISA units. The primary endpoint was occurrence of genital herpes disease due to either HSV-1 or HSV-2 between month 2 (1 month after dose 2) through month 20. Secondary endpoints included prevention of HSV-1 or HSV-2 infection (with or without disease) from month 2 through month 20 (two-dose efficacy) or month 7 through month 20 (three-dose efficacy) and prevention of genital herpes infection and disease caused by individual HSV types. Cases of infection and disease were determined centrally by an independent, blinded end-point review committee with the use of documented criteria.

Results: Fifty clinical sites in the United States and Canada screened a total of 31,770 women for antibodies to HSV-1 and HSV-2; 12,468 women were seronegative for both HSV-1 and HSV-2, of whom 8,323 met the other eligibility criteria and were enrolled and randomized. The two study groups were well balanced with respect to demographic characteristics and risk behaviour at study entry. The HSV vaccine was associated with an increased risk of local reactions as compared with the control vaccine, and it elicited ELISA and neutralizing antibodies to HSV-2. Overall, the vaccine was not efficacious; vaccine efficacy was 20% (95% confidence interval [CI], -29 to 50) against genital herpes disease. However, efficacy against HSV-1 genital disease was 58% (95% CI, 12 to 80). Vaccine efficacy against HSV-1 infection (with or without disease) was 35% (95% CI, 13 to 52), but efficacy against HSV-2 infection was not observed (-8%; 95% CI, -59 to 26).

Conclusions: In a study population that was representative of the general population of HSV-1 and HSV-2-seronegative young adult women, the investigational vaccine was effective in preventing HSV-1 genital disease and infection but not in preventing HSV-2 disease or infection. (Funded by the National Institute of Allergy and Infectious Diseases and GlaxoSmithKline; ClinicalTrials.gov number, NCT00057330.)
Lessons learned from HPV vaccines

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HPV infection induces virtually all cases of cervical cancer, and a proportion of other non-cervical malignancies, including vulvar, vaginal, penile, anal, and oropharyngeal cancer. Together, they account for about 5% of human cancer worldwide. HPV16/18 causes ~70% of cervical cancer and more than 90% of non-cervical cancer. Infection by HPV6 and 11 causes most cases of most cases of genital warts and recurrent respiratory papillomatosis.

The importance of HPV as human pathogen stimulated development of prophylactic HPV vaccines, based on the observation that the L1 main structural protein of the HPV virion can self-assemble into empty virus-like particles (VLPs) which contain the conformationally-dependent neutralization epitopes of L1 and can induce high levels of neutralizing antibodies. There are two FDA/EMEA-approved commercial versions of the VLP vaccine. Merck’s is a quadrivalent vaccine composed of VLPs from HPV6, 11, 16, and 18, while GlaxoSmithKline’s is a bivalent vaccine composed of VLPs from HPV16 and 18. Both vaccines are administered in three doses, given over 6 months. Efficacy trials in young adults showed that, for fully vaccinated subjects, both vaccines induce almost complete protection against incident persistent anogenital infection and the associated lesions attributable to the HPV types targeted by the vaccine. Immunogenicity and protection induced by the vaccines are so strong that a two dose regimen is being used in some countries. Experimental studies indicate that the neutralizing antibodies induced by the VLP vaccine are the main mechanism by which it protects against infection and disease.

There are at least three possible implications for HSV vaccine development. First, the HPV vaccine indicates it is possible to develop an effective vaccine against a viral agent that causes a local genital mucosal and cutaneous infection. Second, the repetitive display of the L1 immunogen in the VLP contributes to the high immunogenicity of the HPV vaccine. In principle, any antigen, including a Herpesvirus antigen, can be similarly displayed, either in the VLP (whether the VLP is from HPV or another virus) or conjugated to it, which should induce a stronger humoral response than from antigenic monomers.
Continued

Third, our experimental mouse studies with HPV pseudoviruses (which contain the two viral capsid proteins, L1 and L2, and an encapsidated reporter plasmid, and mimics the pathway of authentic virus infection) indicate that infection requires transient abrogation of the intact female mucosal epithelium. Under these conditions, infection leads to the induction of strong cellular and humoral responses in the genital tract against a foreign gene encoded by the reporter plasmid. Such immune responses might be induced if Herpesvirus antigens were delivered by this approach.
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