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T-cell immunity to human alphaherpesviruses

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Human alphaherpesviruses (αHHV) — herpes simplex virus type 1 (HSV-1), HSV-2, and varicella-zoster virus (VZV) — infect mucosal epithelial cells, establish a lifelong latent infection of sensory neurons, and reactivate intermittingly to cause recrudescent disease. Although chronic αHHV infections co-exist with brisk T-cell responses, T-cell immune suppression is associated with worsened recurrent infection. Induction of αHHV-specific T-cell immunity is complex and results in poly-specific CD4 and CD8 T-cell responses in peripheral blood. Specific T-cells are localized to ganglia during the chronic phase of HSV infection and to several infected areas during recurrences, and persist long after viral clearance. These recent advances hold promise in the design of new vaccine candidates.

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Introduction

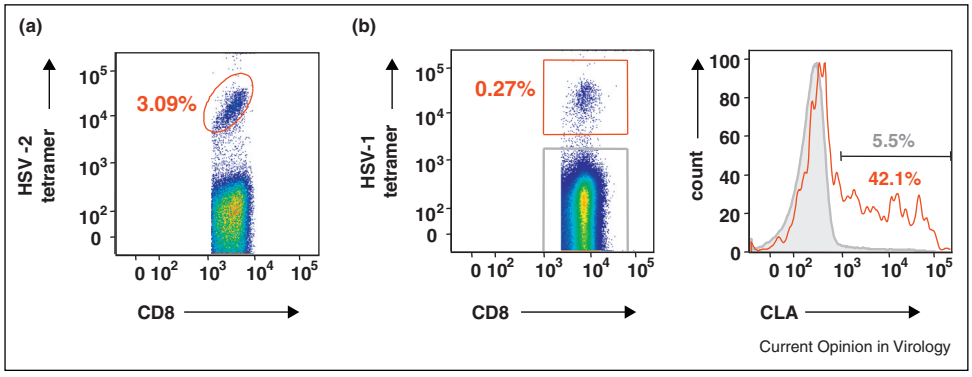
Herpes simplex virus type 1 (HSV-1), HSV-2 and varicella-zoster virus (VZV) are closely related human neurotropic alphaherpesviruses (αHHV) that are endemic worldwide. Primary αHHV infections are acquired through the orofacial (HSV-1) and genital epithelia (HSV-2), albeit HSV-1 is a prominent cause of genital herpes in some settings, or via aerosols (VZV) [1,2]. Upon primary infection, αHHV establish a latent infection in sensory ganglion neurons, allowing the virus to reactivate and cause recrudescent disease [1,2]. Although frequently asymptomatic, HSV-1 and HSV-2 infections may cause herpes labialis (cold sores) and genital herpes [1]. HSV reaches the ganglia via axonal transport thereby restricting HSV infections and recurrences — that arise from neuronal reactivation and axonal transport — to the same areas [1]. VZV causes varicella (chickenpox) as a primary infection and herpes zoster (HZ; shingles) upon reactivation [2]. Memory T-cells are postulated to traffic VZV during the viremic phase of primary infection to the skin and ganglia leading to widespread cutaneous varicella lesions and neuronal latency [2]. HZ results from VZV reactivation and axonal transport to skin causing dermatomal skin rash, frequently followed by postherpetic neuralgia (PHN) [2]. Adaptive immunity is pivotal for uncomplicated recovery from αHHV infection, illustrated by severe complications observed in immunocompromised individuals [1,2]. A live-attenuated VZV vaccine has been licensed for both preventive (varicella) and immunotherapeutic (HZ) use [2]. However, there is no vaccine for prevention or treatment of HSV-1 or HSV-2. Recent advances in the field have shed new light on the priming, specificity, and function of αHHV-specific T-cells. This review will summarize and discuss current understanding of the role of T-cell immunity in αHHV infections, with an emphasis on the virus' natural human host.

HSV-1 and HSV-2

Most of our current understanding αHHV-specific T-cell immunity is based on HSV-1 and HSV-2, largely due to their recurrent nature and availability of small animal models that recapitulate some aspects of human HSV infection. While HSV-1 and HSV-2 are antigenically and biologically distinct and have separate disease profiles in humans, specific immune responses directed at them are generally similar and partially overlap at both the B-cell and T-cell level [3,4], such that data are largely interwoven and summarized rather than separated in this review.

HSV-induced priming of naïve T-cells during primary infection has only been studied in mice. During primary HSV infection, antigen is acquired by mobile, but uninfected, dendritic cells (DCs) and transported from epithelial sites to draining lymph nodes [5,6]. Handoff to lymph-node resident DCs may occur before contact with naïve CD8 T-cells [7] and different DCs may prime CD4 and CD8 T-cells [8,9]. Depending on kinetics, classic dermal $CD8\alpha^+$ DC or $CD8\alpha^+CD103^+$ DC may dominate CD8 T-cell priming [8,10]. DC may mediate antigen uptake by the receptor DNGR1 and by means of toll-like receptor 3, DC may sense HSV as a danger signal to

Figure 1



HSV-specific CD8 T-cells in PBMC of HSV-seropositive immunocompetent individuals. **(a)** Cells specific for amino acids 49–57 of HSV-2 gene *UL49* and restricted by HLA B*0702 can represent up to 3.09% of circulating CD8 T-cells. **(b)** CD8 T-cells specific for amino acids 90–99 of HSV-1 gene *UL48*, restricted by HLA A*0101, overexpress CLA (red histogram) compared to the remaining CD8 T-cells (gray histogram).

facilitate crosspriming [11,12]. Autophagy is involved in priming of CD4 T-cells [13]. DCs are variably permissive for HSV infection *in vitro* [14], and immune evasion molecules encoded by HSV inhibit direct antigen presentation by virus-infected DC [10]. For example, the γ34.5 protein may inhibit antigen presentation via disruption of autophagy [15], and the *vhs* protein encoded by *UL41* counteracts NFκB translocation [16]. To date, however, little evidence implicates direct infection of DC as an important component of pathogenesis or immunity *in vivo*. Adequate priming of naïve HSV-specific CD8 T-cells during primary infection likely depends on cognate virus-specific CD4 T-cells acting via licensure of DCs [17]. HSV-specific CD4 T-cells may also be necessary for the transition of primed CD8 T-cells into memory T-cells [17] and may prolong DC survival during CD8 T-cell priming [18].

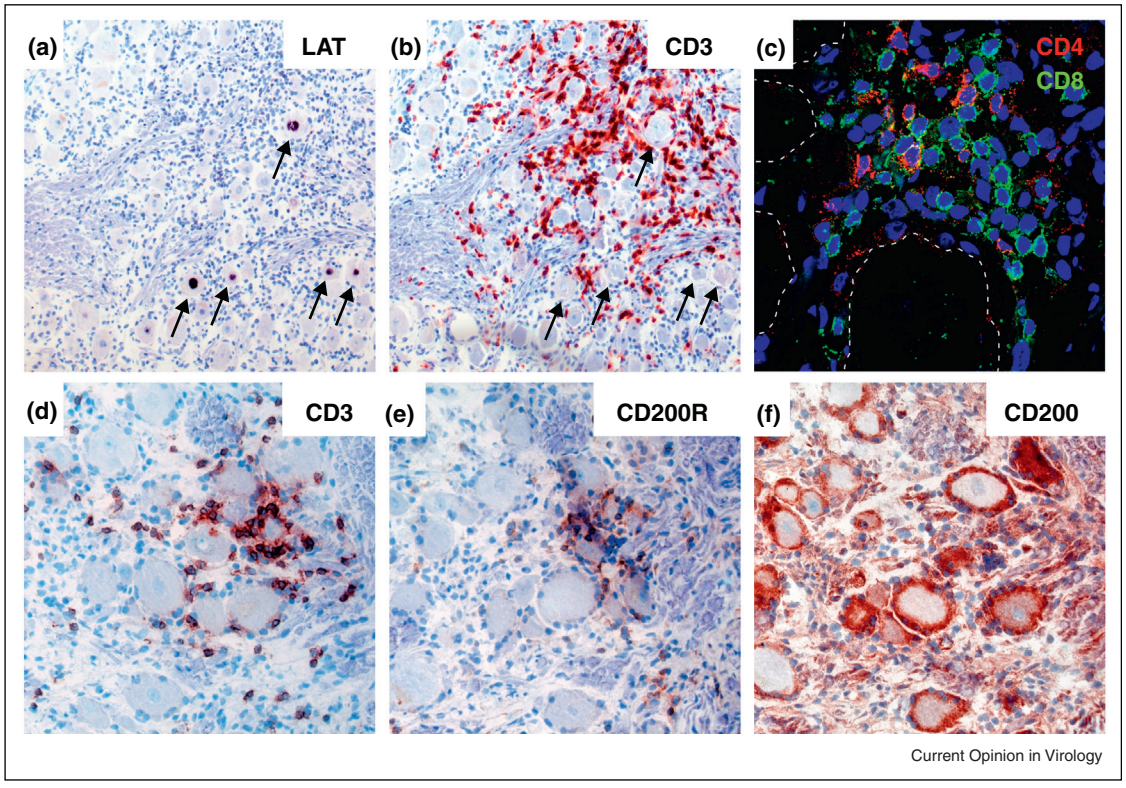
The kinetics and specificity of HSV-specific T-cells during primary infection are largely unknown in humans. After resolution of acute infection, HSV-specific memory T-cells are detected at moderate levels of 0.1–1% in blood of immunocompetent individuals [19••,20]. Exceptionally, single HSV-2 peptide may be recognized by up to 3% of blood CD8 T-cells; the relationship of such expansions to disease severity is unknown (Figure 1a). Recently, we have defined the specificity of peripheral blood HSV-1-specific CD4 and CD8 T-cells towards 77 distinct proteins in healthy individuals [19••,21•]. The emerging picture is of a complex, poly-specific CD4 and CD8 T-cell response with recognition of a median of 22 and 17 distinct HSV-1 proteins, respectively. T-cell targets include HSV proteins present in large quantities in the virion (e.g. viral envelope, tegument, capsid, and regulatory proteins), as well as enzymes [19••,21•]. We find striking immunodominance of HSV-1 glycoprotein or regulatory protein-reactive CD4 T-cells, with rapid tapering to a large number of low-abundance responses recognizing many viral proteins. Interestingly, this HSV-specific CD4 T-cell immunodominance profile is mathematically identical to that observed for vaccinia virus (VV) [21•], which causes an acute viral infection and is completely cleared from the host, in contrast to αHHV that cause chronic infections [21•]. Notably, HSV proteins encoded by genes *UL39* (an enzyme) and *UL46* (a tegument protein) are prominent CD4 T-cell targets, equivalent to the vaccine candidates glycoprotein B (gB) and gD in terms of population prevalence [19••]. For HSV-specific CD8 T-cells, typically only a few fine specificities are detectable either using direct *ex vivo* ELISPOT [19••] or after enrichment by selection of CLA-positive T-cells [22]. The immunodominant high magnitude CD8 T-cell responses detected to date are specific for viral tegument and capsid proteins [4,23]. HSV-2-specific CD8 T-cells in herpetic skin lesions are predominately directed to tegument proteins and confirm the antigenicity of immediate early (IE) proteins and glycoproteins deduced from studies using blood [24,25]. CD8 T-cells recognizing tegument protein VP22 have public T-cell receptor αβ (TCRαβ) pairings [26], and HSV-specific CD8 clonotypes, defined by TCR sequencing, appear to be long-lasting and traffic from blood to cervix and skin [27]. HSV-specific CD4 T-cells are typically multifunctional for Th1/Th0-like cytokines and, after expansion, have brisk cytolytic potential [3,20]. Blood HSV-specific CD8 T-cells can express high levels of cytolytic molecules and secrete IFN-γ upon antigenic recall [4]. Counterbalancing roles for regulatory T-cells or inhibitory receptors such as PD-1 remain largely unexplored in humans [28] but can have profound effects in mice [29].

HSV-specific T-cells profoundly localize to sites of primary and recurrent infection such as skin, cervix and eye, and to sites of chronic latent infection in trigeminal ganglia (TG). Recurrent HSV infections result in 10–40% of local CD8 T-cells being HSV-specific in herpetic eye disease and skin at

crust stage [24,30,31]. Oligoclonal virus-specific CD4 and CD8 T-cells, mostly recognizing tegument proteins (including the *UL46* and *UL47* products) were detected in the HSV-affected eye [30–33]. HSV-specific cytotoxic CD8 T-cells accumulate near sensory nerve endings in HSV-2-infected human skin biopsies [34,35]. Murine data support and extend the human observations, with HSV-specific CD8 T-cells localizing to infected skin and to latently infected ganglia [36••,37]. Tissue persistence of HSV-specific CD8 T-cells in murine skin after viral clearance correlated with local protection from exogenous re-inoculation [36••]. HSV-specific CD8 T-cells retained in murine skin continuously patrol the epidermis and recognize rare antigen-expressing keratinocytes [38•]. In humans, CD8 T-cells show prolonged localization to the dermo-epidermal junction after HSV-2 healing and have an activated and antiviral phenotype [39,40]. Like CD8 T-cells, HSV-2-specific CD4 T-cells also display the tissue-resident memory (T_{RM}) phenotype, persistently localizing to sites of previously infected recurrent skin infection in humans [40]. In the uterine cervix, HSV-2-specific CD4 T-cells are abundant even when the virus is suppressed with antivirals [23]. Both HSV-2-specific CD4 and CD8 T-cells preferentially express CLA, and its ligand E-selectin is upregulated in herpetic skin [23,41]. Recent data with HSV-1-specific tetramers show that HSV-1-reactive CD8 T-cells in blood also express this homing receptor (Figure 1b). It is unclear if this adhesion molecule is important in inflammatory homing at times of overt HSV recurrence or is also involved in local T-cell retention. Taken together, these and data from other viral systems [42••] are consistent with a T_{RM} phenotype as a specialized subset of memory T-cells, and current efforts with vaccines seek to optimize the generation and guidance of these cells to the preferred anatomic site: the virus' port d'entree [43].

HSV-1, but not VZV, infection of human TG is associated with chronic inflammation [44,45]. Ganglion-infiltrating T-cells are oligoclonal in nature and preferentially recognize HSV-1 [45,46]. These CD8 T-cells have an activated late-effector memory phenotype and form rosettes around neurons including those that express HSV-1

Figure 2



Clusters of CD4 and CD8 T-cells surround HSV-1 LAT-positive neurons in human TG. Consecutive TG sections were stained for HSV-1 LAT by *in situ* hybdrization **(a)** and CD3 by immunohistochemistry **(b)**, showing that T-cell clusters surround HSV-1 LAT+ neurons. Arrows indicate LAT+ neurons. **(c)** Human TG immunofluorescently stained for CD4 (red) and CD8 (green), showing that ganglionic T-cell clusters are composed of both CD4 and CD8 T-cells. Dashed lines indicate neurons. Nuclei were counterstained with 4′,6-diamino-2-phenylindole. Consecutive TG sections were stained for CD3 **(d)**, CD200R **(e)** and CD200 **(f)** by immunohistochemistry. Ganglion-infiltrating T-cells express CD200R, whereas neuron-interacting satellite glial cells express its ligand CD200. (a, b, d–f) Sections were developed with 5-bromo-4-chloro-3-indolyl-phosphate (LAT; black color) and 3-amino-9-ethylcarbazole chromogen (CD3, CD69, CD200R and CD200; red color); nuclei were counterstained with hematoxylin. Magnification: (a, b) 100×, (c) 400×, and (d–f) 200×.

latency-associated transcript (LAT) (Figure 2a,b). CD4 T-cells are less abundant than CD8 T-cells and appear both in neuron-surrounding T-cell coronas as well as along axons (Figure 2c) [45,46]. Neuron-surrounding satellite glial cells (SGC) function as TG-resident antigen presenting cells and express the T-cell inhibitory molecules HLA-E and PD-L1 that interact with their receptors CD94/NKG2A and PD-1 on ganglionic T-cells to control HSV latency without neuronal damage [47]. In addition, we recently demonstrated the potential role of the T-cell inhibitory CD200/CD200R axis in human TG: TG-resident SGC expressed CD200 and the interacting T-cells expressed the cognate receptor CD200R (Figure 2d–f). The human intra-TG HSV-specific T-cell response, involving both CD4 and CD8 T-cells, is directed to a limited set of viral antigens (Van Velzen *et al.*, abstract 5.05, International Herpesvirus Workshop, Calgary, August 2012). The current data suggest that persistent local HSV-specific T-cell responses control viral latency and reactivation in ganglia and skin, respectively. Alternatively, rather than recognizing latently infected neurons, ganglionic virus-specific T-cells may be 'mopping-up' an HSV reactivation that has bypassed innate immune control by SGC. Murine studies demonstrate that deposition [48] or attraction [49••] of antigen-specific T-cells at anatomic sites of challenge protects from exogenous infection, but it is possible that ganglion-resident T-cells also serve as sentinels to modulate and limit endogenous reactivation or resultant centripetal spread, epithelial shedding, recrudescent lesions and transmission.

VZV

Compared to HSV, VZV is human-restricted pathogen. Simian varicella virus (SVV) infection of nonhuman primates closely resembles VZV pathogenesis in humans and is currently being used to define T-cell immunity in its natural host. VZV-specific T-cells are considered essential for recovery from varicella and for prevention of and resurgence from HZ. Varicella has an incubation period of 10–21 days [2] and VZV-specific T-cells become detectable one to three days after the appearance of skin rash [50]. The site and cells involved in priming of naïve T-cells are unknown. VZV decreases the capacity of DC to induce specific T-cell responses by reducing surface expression of both T-cell costimulatory molecules (i.e. CD80, CD83 and CD86) and human leukocyte antigen type I (HLA-I) and human leukocyte antigen type II (HLA-II) [51,52]. In addition, the virus reduces HLA-I expression and inhibits IFN-γ-induced HLA-II expression on VZV-infected cells to escape CD8 and CD4 T-cell recognition, respectively [53–56]. VZV hinders T-cell recognition of VZV-infected keratinocytes by inhibiting intercellular adhesion molecule 1 (ICAM-1) expression [57].

The magnitude of the VZV-specific T-cell response initiated during primary infection inversely correlates with the severity of varicella and termination of viremia [50,58]. Studies on SVV indicate that CD4 T-cell immunity plays a more critical role than antibody and CD8 T-cell responses to control varicella [59••]. Compared to HSV, studies on local tissue-restricted VZV-specific T-cells are scarce. Yet, both CD4 and CD8 T-cells are known to infiltrate the dermis of varicella and HZ patients [57,60–62], possibly relocating via skin-homing receptors [58]. The local VZV-specific T-cell response in patients with VZV-induced uveitis is more comprehensively characterized. Intra-ocular T-cells recognize a wide variety of VZV proteins, secrete Th1/Th0-like cytokines, have cytolytic potential, and are able to inhibit virus replication in retinal pigmented epithelial cells [63–65]. The combined data suggest a detrimental role of VZV-specific T-cells in the pathology of VZV uveitis.

Memory VZV-specific T-cells are maintained at a low frequency [66], likely involving exogenous re-exposure to VZV or endogenous (subclinical) reactivation, and have a mixed central and effector memory phenotype [52,58,67,68]. Circulating VZV-specific memory CD4 T-cells are commonly CLA-negative and preferentially express CD38 and PD-1 [67,68], suggesting recent antigenic stimulation and/or exhaustion. Although similar frequencies of circulating VZV-specific CD4 and CD8 cytotoxic T-cells have been reported [69,70], recent studies indicate that VZV-specific CD8 T-cells are less abundant than CD4 T-cells [52,71,72]. T-cell reactivity to VZV antigens include structural proteins including the glycoproteins gB, gC, gE, gH, gI and the IE proteins IE4, IE62 and IE63 [67–70,72–77]. However, the latter studies were restricted to the analysis of only a limited set of virus proteins, which does not allow identification of the immunodominant T-cell antigens involved in protection and immunopathogenesis.

It is well established that the risk of HZ increases with age [78]. This is largely attributed to the decline of VZV-specific T-cell immunity, but not humoral immunity, with progressing age [79–81]. Notably, the frequency of IL-4 producing VZV-specific T-cells remains unaltered [52,73,80,82,83,84•,85,86]. Whether waning of VZV-specific T-cell immunity reflects quantitative or qualitative changes in circulating virus-specific T-cells is unknown. Regardless, HZ induces rapid, profound and sustained T-cell responses [87,88], so that individuals typically develop zoster only once during their life. The magnitude of the VZV-specific T-cell immunity after HZ is inversely correlated with disease severity and the risk of developing PHN [88]. Despite their protective role in preventing reactivation, VZV-specific T-cells have not been detected in latently infected ganglia [45]. The data suggest that during VZV latency no viral proteins are expressed or that the proteins are not

efficiently presented for T-cell recognition *in situ* [45,89,90]. During VZV and SVV reactivation, however, dense CD8 T-cell infiltrates have been detected in ganglia. The limited expression of granzyme B by infiltrating T-cells, combined with the overt expression of CXCL10, suggest a chemokine rather than an antigen-driven infiltration and accumulation of CD8 T-cells in reactivated ganglia [91•,92•,93].

Vaccines

The only human herpesvirus vaccine available to date is the live-attenuated VZV vaccine, which induces both B-cell-mediated and T-cell-mediated immune responses in vaccinated children and the elderly, thereby preventing varicella and HZ, respectively [94–97]. However, the current VZV vaccine protects only 80–87% and 51% of the vaccinees against varicella and HZ, respectively [96,98], indicating an unmet need for an improved VZV vaccine with a higher efficacy. Furthermore, the vaccine contains an attenuated virus that may cause mild varicella and establishes a latent infection posing the risk of reactivation and dissemination in the population. Full VZV genome-wide screens of the VZV-specific CD4 and CD8 T-cell repertoire, such as performed recently by our groups for HSV-1 [19••,21•], are warranted to decipher the immunodominance of VZV proteins targeted by circulating and lesion-infiltrating virus-specific T-cells. These studies will lead to rational choice of candidate virus proteins for a safe and efficacious VZV vaccine.

There is no licensed preventive or therapeutic HSV vaccine. Although variable formulations of HSV vaccines induced protective immunity in mice [99], success in the vaccine arena is yet to translate to humans. Earlier HSV-2 glycoprotein vaccines were not active to prevent primary infection despite antibody and CD4 T-cell immunogenicity [100,101]. Three trials with truncated HSV-2 gD adjuvanted with alum and 3′-*O*-deacylated-monophosphoryl lipid A showed contrasting results [102,103]. Initial studies suggested that the vaccine was efficacious in women with no known prior HSV-1 or HSV-2 infection, but a confirmatory study (whose endpoints included both seroconversion and disease) showed only partial efficacy against HSV-1 but not HSV-2 in this population. Provision of multiple effector T-cell populations with diverse specificity seems attractive given recent data that the CD8 and CD4 T-cell response to natural infection with HSV-1 targets 17 and 22 proteins, respectively [19••,21•]. Replication-incompetent whole virus formats are advancing to clinical trials [104], while replication-competent candidates — which are highly active in challenge-escalation animal models — remain interesting if safety concerns can be overcome [105]. An inherently lower immunogenicity observed with replication-incompetent viruses relative to wild-type viruses can be overcome with additional vaccine doses, at least in the case of orthopoxviruses such as VV [106]. It remains to be seen if a similar strategy can be used for HSV. Therapeutic vaccination remains a goal as an alternative to small-molecule antivirals for the treatment of recurrent lesions and the reduction of transmission of HSV. While a replication-incompetent whole virus candidate was inactive in a phase 2b therapeutic clinical trial [107], a multipeptide approach was recently shown to increase CD4 and CD8 T-cell responses in HSV-2 infected persons [108] and a multivalent subunit candidate is under evaluation (Skoberne *et al.*, abstract 6.05, International Herpesvirus Workshop, Calgary, August 2012).

Conclusions

The T-cell responses to HSV and VZV have interesting similarities, but also striking differences. The development of a potent αHHV-specific T-cell immunity relies on multifaceted DC priming of T-cells and CD4/CD8 T-cell cooperation at several stages and anatomic sites, thus favoring vaccines that elicit complex T-cell responses, and likely also B-cell responses to generate long-lasting virus-neutralizing antibodies. We do not yet know if the same T-cell antigens that are immunodominant in naturally infected humans are best for vaccines, but population prevalence at least indicates the potential for T-cell responses and is a reasonable criteria for candidate subunit approaches. Fascinating recent work comparing HSV-1 seropositive persons with and without histories of symptomatic orolabial herpes raises the possibility that humoral response patterns to specific proteins, or T-cell response patterns to defined epitopes within HSV glycoproteins, may correlate with clinical severity, offering a set of criteria for rational down-selection of vaccine candidates [109,110]. While poly-specific responses such as that elicited by the live-attenuated VZV vaccine are attractive, safety concerns persist and replication-incompetent viruses, or a multivalent subunit approach based on whole proteome-covering data sets, hold promise for both HSV, and for next-generation VZV vaccines that are safe enough for immunocompromised recipients. Apart from eliciting T-cell responses to viral proteins, the emerging picture for HSV is that one must also create a virus-specific T_{RM} population in both the ganglia and in the orofacial and anogenital mucosa. In that regard, promising results of a recent study showed that T_{RM} can be 'pulled' to the site of vaginal challenge by priming with replication-competent virus at a remote site and subsequently administering CXCR3 agonist chemokines vaginally [49••]. Considering therapeutic vaccination, a more thorough understanding of the T-cell response to zoster vaccine in adults with regards to specificity, T-cell levels and homing, and new priming versus re-stimulation of memory, and for HSV, detailed searches for T-cell correlates of severity, may give clues to extending and improving the success of the existing attenuated VZV vaccine and extending it to HSV.

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- • of special interest
- •• of outstanding interest

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