Herpes simplex virus (HSV) causes life-long, recurrent oral and genital infection in humans. The outcome of HSV infection varies widely among the general healthy population, and the determinant of HSV disease remains to be elucidated. We have developed several tissue-based technologies, including cell-type-specific laser capture microdissection, to dissect protective immune responses in sequential human biopsies, during the course of HSV recurrence. We have learned that tissue resident memory (TRM) CD8 T cells function in immune surveillance and rapid containment. Through active communication with neighboring keratinocytes, the TRM CD8 cells link adaptive and innate immune responses to convey a broad antiviral protection in the tissue microenvironment. We have recently bioengineered a 3D ‘skin-on-chip’ platform to mimic normal human skin architecture and to enable immune cells and drug perfusion. The utility of this novel system to model viral-host interactions in HSV infection and to inform future therapeutic development will be discussed.