# Abstract

The World Health Organization (WHO) estimates that 340 million new cases of sexually transmitted diseases (STDs) occur every year worldwide, 75-85% of which in developing countries. Among the different STDs genital herpes, generally caused by herpes simplex virus-2 (HSV-2), is one of the most prevalent. Generally herpes simplex virus-1 (HSV-1), which is serologically distinguished from HSV-2, is associated with *herpes labialis*, but nowadays it is also responsible of 35-50% new cases *herpes genitalis* probably due to sexual behavior changes.

Primary infection, which lasts up to 21 days, is characterized by the presence of vesicles, followed by ulcers and crusts in the genital area; these symptoms can be also associated with pain, lymphadenopathy, dysuria, systemic symptoms and meningitis. Following primary infection the virus establishes latency in the dorsal root ganglion where it can reactivate because of hormonal or environmental stress. In immunocompromised patients lesions are more extensive and have longer permanence and they can lead to a disease similar to varicella with multiple organ involvement. Recently it has been demonstrated that genital herpes can also increase susceptibility to secondary infections and in particular the risk to acquire the human immunodeficiency virus (HIV) is 3 times fold higher. If the infection is contracted during pregnancy, it can be transmitted from mother to child increasing the risk of miscarriage, congenital defects, blindness, encephalitis and disseminated disease with multiple organ disfunction.

On these premises and due to the onset of drug resistant strains, vaccination seems to be the most preventive and effective tool to prevent the disease.

Unfortunately vaccines tested so far (inactivated, attenuated, subunit, recombinant vaccines) didn't show promising results.

The work carried out in this thesis aims to develop an anti-herpes vaccine using a viral vector. In fact viruses, because of their ability to transfer genetic material in the host cell, can be used to vehiculate genes of therapeutic interest into specific target cells (transduction). Among them, lentiviral vectors offer further advantages, because they allow a long-lasting gene expression and they can transduce also non-proliferating cells. In our laboratory we are carrying out an *in vivo* study based on a vector derived from the feline immunodeficiency virus (FIV) whose genomic organization and delivery capabilities are similar to HIV, but which is considerably safer compared to the latter for human applications. Our vaccine vector delivers the glycoprotein B1 (gB1) inserted in HSV-1 envelope, which can induce an immune response against both HSV-1 and HSV-2. This vector was previously tested *in vitro*, demonstrating its ability in transducing different cellular histotypes.

In this study a vaccine protocol against HSV-2 is described, it is based on a previous protocol against HSV-1, that showed positive results in term of protection. C57BL/6 mice were inoculated with HSV-1 gB1 expressing vector (LAW34-gB1) or with the empty control vector, LAW34. The vaccine schedule consisted of 2 injections in the footpad, one week apart and a third intradermal injection 2 weeks after the second one. Following each injection some animals were sacrificed and the antibody and cell-mediated immune response evaluated through different immunological tests. Three weeks after the last injection mice were challenged intravaginally with HSV-2 strain. Mice were monitored daily, evaluating the different steps of the disease through a predefined score and the results of the macroscopical analysis were confirmed through different *in vitro*

tests. The strong and durable immune response induced by our vector led to an efficient protection against the infection.