MVA-HPV-IL2
A Therapeutic Vaccine to Treat HPV-induced Cervical Cancer and Precancerous Pathologies

MARKET
Human papillomaviruses (HPV) have been associated with a variety of epithelial proliferative diseases, including cutaneous warts, anogenital condylomas, and epithelial cancers of the cervix, penis and anus. The pathogenesis of cervical neoplasms follows a natural history characterized by HPV infection, a long latent period, and then proceeding in a fraction of patients through dysplasia (CIN), carcinoma-in-situ, to invasive cancer and metastatic disease. Few viral strains only are specifically responsible for cervical neoplasms, of which, HPV16, accounts for more than half of reported cases. Approximately half a million new cases of cervical cancer are observed each year, world-wide. Cervical cancer remains an important cause of death for women in many economically underprivileged countries. Incidence and death are particularly high in Latin America, and in some countries from Eastern Europe and Asia, where cervical cancer represents the second most common cancer among women.

All HPV-related disorders represent an attractive target for therapies up-regulating immune response. Estimations give 10% of sexually active adults aged 15-49 infected with HPV, with only 1% displaying condyloma acuminata and about 20-30% of patients with condyloma experiencing spontaneous regression. These data suggest that most people develop appropriate immunity in order to control viral infection, while others may benefit from therapies stimulating their immune system. It is in this context that MVA-HPV-IL2 is developed for the treatment of pathologies related to HPV16 infection.

PRODUCT RATIONALE
The onset of HPV-induced neoplasia involves the interaction of E6 and E7 early gene products with the proteins encoded by the tumor suppressor genes p53 and Rb, respectively. To increase the antigenic response against HPV infection, Transgene developed MVA-HPV-IL2, a frozen suspension of recombinant vector particles, which harbor nucleotidic sequences encoding modified HPV-16 E6 and E7 antigens, and human IL-2. The vector is based on the Modified Virus Ankara (MVA), a non propagative highly attenuated vaccinia virus (VV) strain which was especially developed when immunizing high risk patients (e.g. nervous system disorder, allergy or skin disease) against smallpox.

PRODUCT DESCRIPTION
MVA-HPV-IL2 stimulates the immune system to induce tumor rejection. MVA-HPV-IL2 is a recombinant vaccinia virus containing nucleotidic sequences encoding HPV type 16 E6 and E7 antigens, and the immuno regulatory cytokine interleukin-2 (IL-2). MVA-HPV-IL2 initiates immune responses to eradicate HPV16-induced cancers and precancerous lesions.

DEVELOPMENT STATUS: PHASE II
Three phase II studies are currently in progress with MVA-HPV-IL2 in patients at different stages of cervical lesions: from cervical intraepithelial neoplasia grade 3 to advanced cancer:

- **Cervical Cancer**: Stage IIb-IVa, HPV16 positive, resistant to or relapse after radiotherapy
- **CIN 2-3**: HPV16 positive and no previous treatment for CIN
- **VIN 3**: HPV16 positive vulvar lesions greater than 1 cm² after biopsies at baseline

IP POSITION
MVA-HPV-IL2 is covered by a series of issued patents in the US, in Europe and Japan as well as Transgene know-how.

BUSINESS STRATEGY
Transgene is looking for partnerships either with pharmaceutical or biopharmaceutical companies, to develop and market MVA-HPV-IL2 world-wide.
The E6 and E7 proteins cognate nucleotidic sequences were modified prior to placing them into the vector, by removal of sequences encoding interfaces in contact with p53 or pRb. Furthermore, to improve the immunogenicity of modified E6 and E7 proteins, the respective genes were fused to heterologous sequences encoding secretion signal- and membrane anchoring-domains. IL-2 is naturally secreted by antigen-stimulated T-lymphocytes, and mediates the proliferation and the differentiation of all lymphoid cells by binding to specific cell surface receptors. IL-2 enhances both specific and non-specific cellular responses.

PRECLINICAL DATA
The antitumoral efficacy was investigated in several mice models, where both immunoprophylaxis and immunotherapeutic activities were confirmed.

Fig. 1 : Immunotherapy of metastases : percentage of survival in C57BL6 mice infused IV with TC1 tumor cells and subsequently immunized 3 times SC with TG4001 MVATG8042), MVAN33 (MVAcontrol) or vehicle (SO8 formulation buffer).

Fig. 2 : Immune response memory : percentage of tumor free animals in mice IP immunized 3 times with MVA vectors prior to SC inoculation of TC1 cells. Tumor challenge was performed 82 days after the last immunizing injection.

CLINICAL DATA
Following phase I studies where the product showed safety and preliminary efficacy, MVA-HPV-IL2 is currently assessed for clinical efficacy in 3 Phase II trials for the following indications : cervical cancer, cervical dysplasia (CIN) and vulvar intraepithelial neoplasia (VIN). The main objectives of this Phase II program are to confirm the efficacy of the product and to define the most appropriate dose and dosing schedule to be used for Phase III studies.

In mid-course of the 3 phase II studies, we can mention several promising findings :

- For CIN, viral clearance and lesion regression are observed at the highest dose,
- For cervical cancer, promising remissions have been found when the treatment is combined with chemotherapy.

Final results are scheduled for the first half of 2004.

KEY STRENGTHS
- Potent immuno-potentiator based on MVA vaccinia virus.
- Highly stable vector.
- Long-lasting immunity in comparison with non-living vectors.
- Easy to administer by subcutaneous injection.
- Strong IP position on the expression of HPV early genes using vaccinia virus systems.
- Robust manufacturing process.
- E6 and E7 proteins expressed as membrane-anchored tumor antigens to enhance vaccinal potency by promoting MHC class II antigen presentation. The chosen vector was the most efficient (100% tumor rejection) of the viruses tested both in therapeutic and prophylactic conditions, as compared with recombinant viruses producing intra-cytoplasmic forms of the same antigens.
- Improved safety of the viral vector when vaccinating humans due to the mutation of E6 and E7 genes to abolish the oncogenic potential of cognate proteins.

CONTACT
Michel Hubert
VP, Business Development.
Tel : +33 3 88 27 91 12
Fax : +33 3 88 27 91 11
e-mail : hubert@transgene.fr