NON-CLINICAL AND CLINICAL SAFETY OF MVA-BASED IMMUNOTHERAPY PRODUCTS TARGETING CANCER AND INFECTIOUS DISEASES

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ABSTRACT

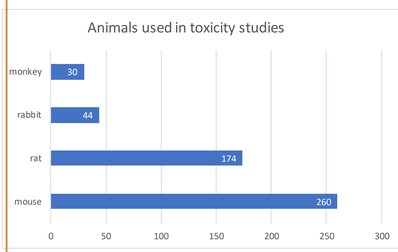
Transgene is developing specific MVA-based immunotherapy products targeting the tumor-associated MUC-1 antigen (TG4010) and Human Papilloma Virus (HPV)16 E6-E7 oncoproteins (TG4001) in cancer indications. A therapeutic MVA vaccine expressing hepatitis C antigens (TG4040) was stopped after a phase II. Taken together Transgene has a very strong safety record in animal and human mainly after local administration of MVA for long-term treatment periods. The toxicity profiles of TG4010, TG4001 and TG4040 were first investigated in more than 500 animals (mice, rats, rabbits and primates) following single and/or repeated administrations. All MVA constructs were well tolerated. Hematology and histo-pathology did not reveal any signs of potential immunotoxicity, alteration in immune system organs (e.g., thymus, spleen, lymph nodes and bone marrow) or sign of amyloidosis. Minor local reactions were observed at the injection sites. In addition, TG4001 did not show any maternal toxicity or adverse effects on embryo-foetal, or pre- and post natal development. To date, 800 patients received at least one dose of MVA-based product, regardless of the indication and/or the route of administration. Tolerance of MVA immunotherapeutics was good and side effects mainly consisted of injection site pain and influenza- like symptoms. The well-established tolerance of recombinant MVA both in animal and human along with the scientific rationale to combine MVA-based immunotherapeutics with anti-PD1 or anti-PDL1 supported the ongoing evaluation of TG4010 in combination with Nivolumab and TG4001 in combination with Avelumab. MVA could also be assessed as a potential safe platform for patient specific neoantigen directed immunotherapy.

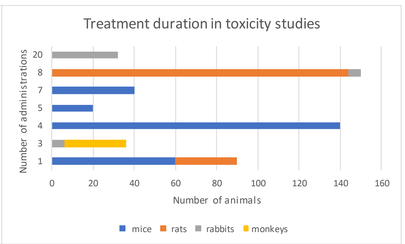
INTRODUCTION

The modified vaccinia strain Ankara (MVA) is a highly attenuated strain of vaccinia virus that does not replicate in human cells. Its large DNA genome allows the insertion of large coding sequences for disease associated antigens. The absence of adverse effects among vaccinated individuals make MVA a safe platform to use in immunotherapeutic approaches against cancer. MVA-based targeted immunotherapeutics are designed to induce a cytolytic cellular immune response.

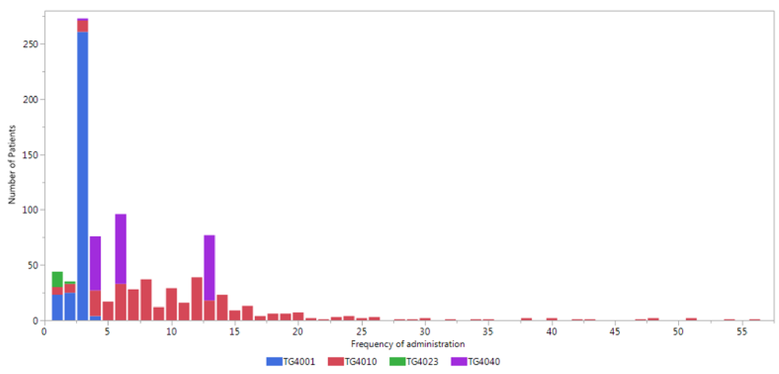
MATERIAL AND METHODS

- **Animal toxicity studies**: Thirteen (13) GLP-compliant single or multiple-administration toxicity studies involving a total of 508 treated animals from various species were carried out at doses ranging from 10^5 to 10^8 pfu/animal given subcutaneously, intramuscularly or intravenously.





- **Clinical studies**: Twenty-one (21) clinical studies involving a total of 882 healthy, cancer or Hepatitis C volunteers received MVA-based immunotherapies up to 56 administrations at doses ranging from $5x10^5$ to 10^9 pfu mainly subcutaneously, or intramuscularly.



RESULTS

- Animal toxicology results supported the good tolerance of sustained iterative administrations of MVA-based products without risk of immunotoxicity or inflammatory illnesses (e.g. amyloidosis)

Parameters examined	Outcome
Mortality and Clinical Observations	No effect
Evaluation of the injection site for local reactions	Occasional acanthosis and inflammatory cell infiltration at the injection site
Body Temperature	No effect
Body weight	No effect
Hematology	Dose-dependent increase in neutrophils (up to 3-fold) indicative of viral infection
Blood chemistry	Dose-dependent increase in α1-globulin, α2-globulin, β1-globulin,β2-globulin and γ-globulin indicative of immune host response and viral infection
Urinalysis	No effect
Histopathology	Increased formation of secondary lymphoid follicles in the superficial lymph nodes (axillary, inguinal, mandibular and popliteal), representing a stimulation of B-cells in response to injections.
Signs of potential immunotoxicity	No relevant toxic effect on hematology, serum globulins, immune system organs weights and histology (e.g., thymus, spleen, lymph nodes and bone marrow)
Amyloidosis	No amyloid deposit in heart, aorta, liver and kidney

- In animals, MVA DNA was limited to the injection site, without spreading to organs or persistence supporting the absence of risk of accumulation in organs

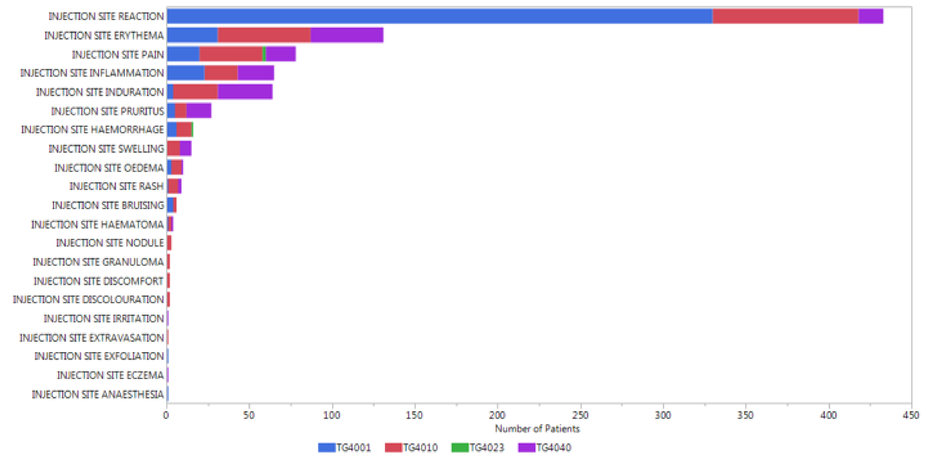
Injection site						> Limit of Quantification
Brain	Lung	Blood	Heart	Lymph nodes	Urine - Feces	< Limit of Quantification
Liver	Spleen	Bone Marrow	Kidney	Gonads		Not detected

- In human, blood and urine samples of 154 patients were negative for MVA DNA. Traces of MVA DNA (~0,6 % of the dose) was found in injection site swabs up to 2 weeks supporting the absence of risk of viral shedding

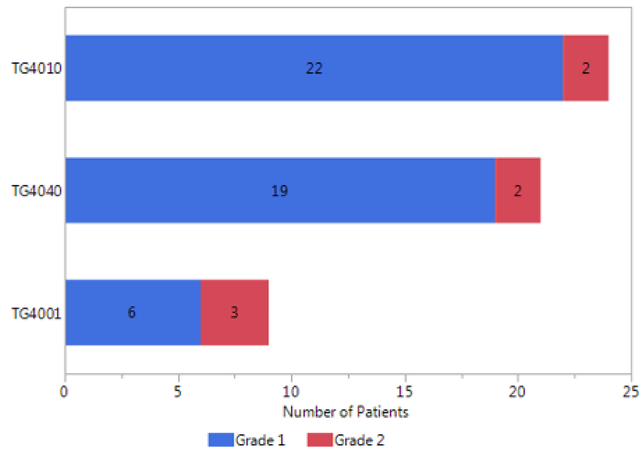
- Although MVA-based therapies should not be administered to pregnant women and to breast feeding women, the risk of unintentional exposure of an embryo/fetus was assessed in a Embryo-fetal and pre-and post-natal development study in mice:
  - No maternal toxicity on clinical maternal condition, body weight, maternal performance (pregnancy rate, ovarian and uterine examinations) and gross pathology findings
  - No effects upon embryo-fetal and pre- and post-natal development on F1 generation pup viability, clinical condition or pup weights and the incidence of fetuses with abnormalities

- In clinical trials, the safety profile was consistent with injection site reactions and influenza like illness

Distribution of MVA-treated patients with at least one reaction at injection site



Distribution of MVA-treated patients with at least one Influenza-like illness



CONCLUSION

- MVA-based products developed by Transgene in cancer or hepatitis C disease were well tolerated in animal species as well as in human
- The main adverse findings consisted in irritation at the injection site which is very common. Influenza-like illness occurred occasionally.
- Long-term treatment did not reveal any immunotoxic concern or amyloid deposits in tissues from potential immunoglobulin fragments due to iterative administration of viruses.
- The good tolerance of recombinant MVA along with the scientific rationale to combine MVA-based immunotherapeutics with anti-PD1 or anti-PDL1 supported the ongoing evaluation of TG4010 in combination with Nivolumab and TG4001 in combination with Avelumab
- MVA could also be assessed as a potential safe platform for patient specific neoantigen directed immunotherapy.

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