TG6050, an oncolytic vaccinia virus encoding interleukin-12 and anti-CTLA-4 antibody, favors tumor regression via profound immune remodeling of the tumor microenvironment

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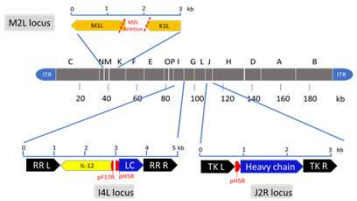
BACKGROUND

Oncolytic virotherapy has reached maturity in the recent years, with several products having obtained market approval or being engaged in advanced clinical trials. Among them, Vaccinia Virus has an interesting positioning in terms of tumor selectivity, safety, and engineering possibility. In this respect, TG6050 was designed as an improved oncolytic vector, combining the intrinsic properties of vaccinia virus to selectively replicate in tumors with the tumor-restricted expression of IL-12 and anti-CTLA4 to modify the tumor immune phenotype. These properties might be of particular interest for "cold" tumors, either poorly infiltrated or infiltrated with anergic T cells. A clinical trial (Delivir) is in progress, assessing intravenous TG6050 alone, then in combination with an ICI, in metastatic non-small cell lung cancer (NCT05788926).

METHODS

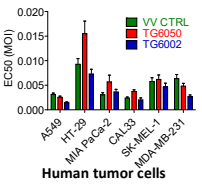
TG6050, an oncolytic vaccinia virus encodes single-chain human interleukin-12 (hIL-12) and full length anti-cytotoxic T-lymphocyte-associated antigen-4 (@CTLA-4) monoclonal antibody. The relevant properties of TG6050 (replication, cytopathy, transgenes expression and functionality) were extensively characterized *in vitro*. The biodistribution and pharmacokinetics of both the viral vector, @CTLA-4 and IL-12, as well as antitumoral activities (alone or combined with immune checkpoint inhibitors) were investigated in several "hot" (highly infiltered) and "cold" (poorly infiltered) syngeneic murine tumor models. The mechanism of action was deciphered by monitoring both systemic and intratumoral immune responses, and by tumor transcriptome analysis. The safety of TG6050 after repeated intravenous administrations was evaluated in cynomolgus monkeys with a focus on the level of circulating IL-12.



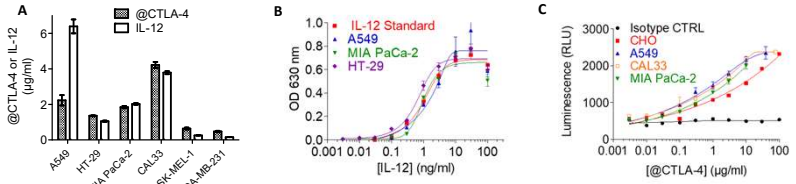
Schematic representation of TG6050's genome

TG6050 : AN ONCOLYTIC VIRUS EXPRESSING FUNCTIONAL IL-12 AND ANTI-CTLA4

TG6050 is as oncolytic as benchmark viruses

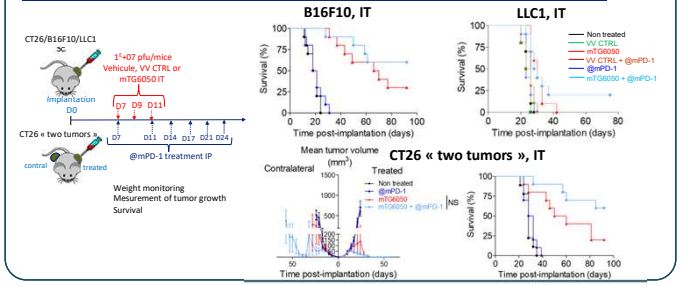


IL-12 and anti-CTLA4 are expressed at high level and are functional

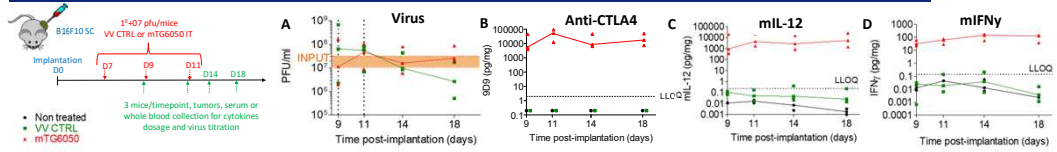


A: Expression level of transgenes by different infected human tumor cells; B-C: IL-12 and anti-CTLA4 functionalities vs benchmarks (red)

COMBINATION WITH ICI IMPROVED ANTITUMORAL ACTIVITY



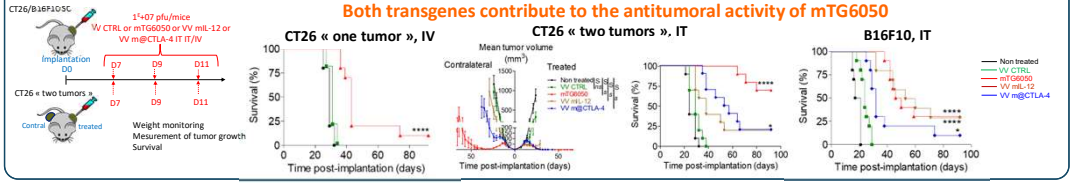
mTG6050 INJECTION INDUCED A SUSTAINED EXPRESSION OF IL-12, ANTI-CTLA4 AND IFNg IN TUMOR



Tumor pharmacokinetics of virus (A), anti-CTLA4 (B), IL-12 (C) and IFNg (D) after mTG6050 injection

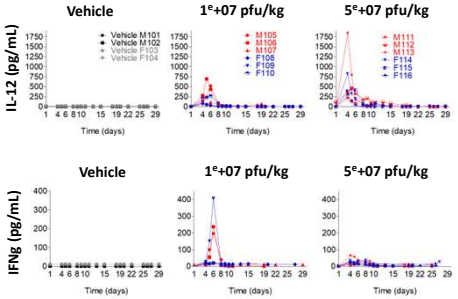
mTG6050 INJECTION INDUCED ANTITUMORAL ACTIVITY IN « HOT » AND « COLD » TUMORS

Both transgenes contribute to the antitumoral activity of mTG6050



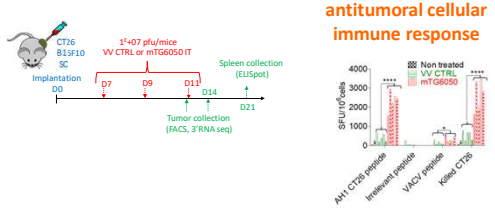
TG6050 (IV) WAS WELL TOLERATED IN CYNOMOLGUS MONKEY

Increase in IL-12 and IFNg after TG6050 injection but concentrations were more than 15-fold lower than those measured after administration of a therapeutic dose of IL-12

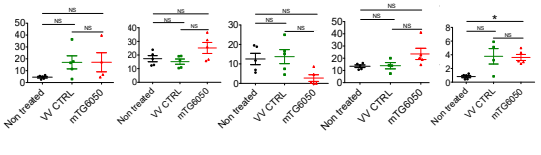


mTG6050 TREATMENT INDUCED MASSIVE INFILTRATION OF TME BY INNATE AND ADAPTIVE IMMUNE CELLS

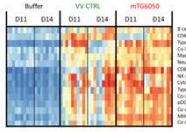
Strong systemic and specific antitumoral cellular immune response



mTG6050 treatment increased CD8 + T cells and decreased Treg infiltration Both M1/M2 ratio and PD-L1 on tumor cells increased



TG6050 induced a strong increase of expression of genes in most immune pathways



Gene expression levels were analyzed by 3' RNA seq followed by gene set variation analysis (GSVA)

CONCLUSION & PERSEPECTIVES

- TG6050 effectively delivers **functional IL-12 and @CTLA-4** into tumor, resulting in a **strong antitumor activity**
- The shift towards an **inflamed TME** correlated with **a boost of the systemic antitumor T cells**
- The **solid preclinical data**, and **favorable risk/benefit ratio** paved the way for clinical evaluation of TG6050 in metastatic NSCLC (**NCT05788926 trial ongoing**)
- **Azar F et al; Journal for ImmunoTherapy of Cancer 2024; 12:e009302. DOI: 10.1136/jitc-2024-009302**

DISCLOSURES

All authors are or were employees of Transgene SA the manufacturer of TG6050