MVdeltaC: A new therapeutic vaccine with promising preclinical immuno-oncolytic activities

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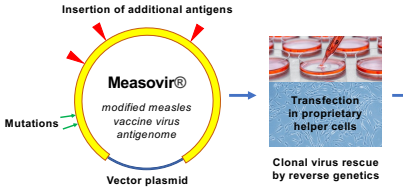
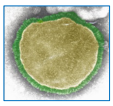
ONCOVITA is a biotech company that emerged as a spin-off from Institut Pasteur. Our primary focus is the development of a therapeutic anti-cancer vaccine based on the Measovir™ platform, a proprietary technology derived from the safe and highly immunogenic measles vaccine virus (MV), an attenuated negative strand RNA paramyxovirus. MVdeltaC was generated by deleting the virulence factor C of MV. It exhibits specific tropism for cancer cells due to the overexpression of its entry receptor CD46 on the surface of a wide array of cancer cells. The anti-cancer efficacy of MVdeltaC was evaluated *in vitro* on human tumor cell lines (mesothelioma, lung adenocarcinoma, hepatocarcinoma, bladder, ovarian, cervical cancers), and *in vivo* by local administration in mesothelioma PDX, and in a syngeneic neuroblastoma model in immunocompetent A/J mice.

Measovir® is a unique viral vector platform derived from the Schwarz measles vaccine virus capable of delivering large quantities of additional genetic material (up to 7.5 kb) in the form of RNA and antigenic proteins. This platform has previously generated several recombinant vaccines that have demonstrated their safety and immunogenicity in numerous preclinical and clinical trials despite pre-existing anti-measles immunity.





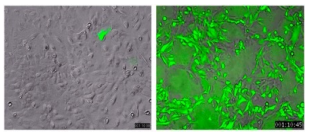
- Single dose
- Lifelong protective immunity
- Safety / efficacy track record over 2 billion children vaccinated
- High genetic stability
- Well established manufacturing

Measles vaccine: a live attenuated negative-sense RNA virus. Attenuated by more than 150 passages in culture on chicken embryonic cells, the virus has accumulated around 50 mutations scattered along its genome of approximately 16 kb. It is one of the safest and most effective human vaccines widely used in preventive medicine for more than 50 years.

Natural ability: the measles virus has the natural ability to kill cancer cells (regression of Burkitt's lymphoma observed during infectious measles).

Specific targeting: the entry receptor of attenuated measles vaccine virus is **CD46**, a molecule that tumor cells over-express on their surface to protect themselves from attacks by the immune system.

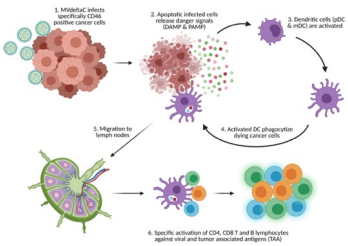
Anti-tumor activity validated: the oncolytic capacity of the attenuated measles vaccine virus (MV) was previously clinically validated by a team from the Mayo Clinic.

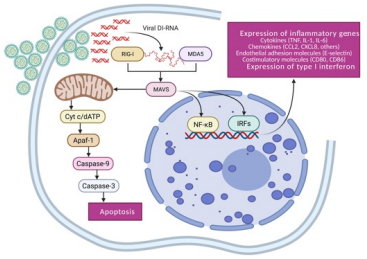


Infection of normal (left) or cancerous (right) mesothelial cells demonstrating CD46 specificity on cancer cells.

Mechanism of immuno-oncolytic action of MVdeltaC

MVdeltaC combines the known oncolytic safety and efficacy of measles vaccine virus with a specifically enhanced ability to induce immunogenic cell death and reactivate "cold" tumors.





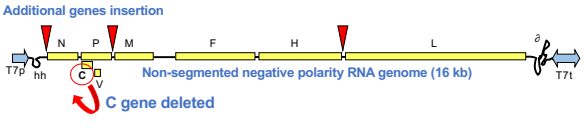
Immune activation: MVdeltaC-induced immunogenic cell death releases danger signals (DAMP, PAMP) and tumor associated antigens (TAA), activates dendritic cells (mDC & pDC), phagocytosis of dying cancer cells and cross-presentation of TAA to T and B cells.

A RIG-I agonist: MVdeltaC replication in cancer cells produces large amounts of RNA and 5'copy-back defective genomes that are potent agonists of RIG-I and MDA5 receptors. Their binding rapidly triggers apoptosis and activates the expression of inflammatory genes and type I interferons.

Conclusion & perspectives: MVdeltaC demonstrated a robust oncolytic capacity against various human tumor cell lines, with 70% of the tested cell lines displaying sensitivity to treatment. *In vivo* studies in NOD/SCID mice with human mesothelioma grafts revealed a significant reduction in tumor mass two weeks after a single low-dose i.p. treatment. This potential was further confirmed in PDX models of mesothelioma and bladder tumors. In immunocompetent A/J mice three intratumoral administrations resulted in complete tumor rejection in 72% of the mice. The *ex-vivo* infection of cancer cells by MVdeltaC triggered the release of danger signals and tumor associated antigens (TAA), the activation of mDC and pDC, and cross-presentation of TAA to autologous T lymphocytes. Based on these preclinical data, Oncovita now plans to initiate a FIH trial in patients with solid tumors. The activity on ICI resistant tumors will be of particular interest to investigate. We have already improved the mode of production of genetically stable MVdeltaC with high titers.

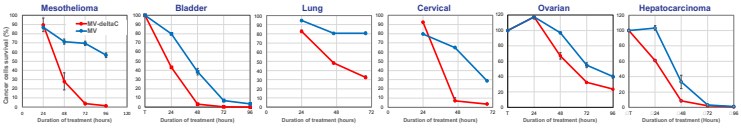
Gauvrit A. et al., Cancer Res, 2008; Guillerme JB et al., Clin Cancer Res, 2013; Delaunay T. et al., Oncoimmunology, 2018; R. Sanchez & F. Tangy, eLife, 2016; M. Mura & F. Tangy, JVI, 2017

MVdeltaC : an innovative immuno-oncolytic virus



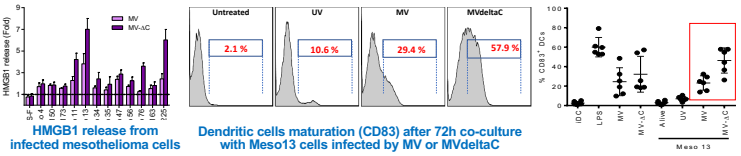
We have constructed the MVdeltaC virus from the MeasoVir™ platform by deleting the **viral factor C** which controls apoptosis and viral replication in infected cells. This deletion gives the virus a significantly increased potential to induce immunogenic death of cancer cells **while sparing healthy cells** as MVdeltaC is hyper-attenuated and does not propagate.

in vitro oncolytic activity on human tumor cells



MVdeltaC oncolytic activity *in vitro* was evaluated on 127 cell lines of 8 cancer types. Over 70% of cancers tested respond to treatment. The oncolytic activity of MVdeltaC is enhanced and faster as compared to standard unmodified measles vaccine virus.

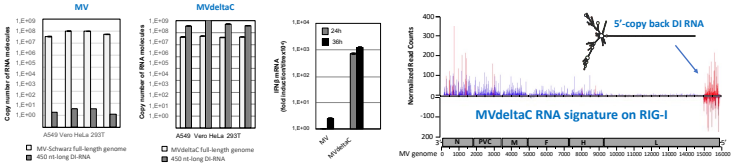
MVdeltaC induces DAMPs and activates dendritic cells



HMGB1 release from infected mesothelioma cells

Dendritic cells maturation (CD83) after 72h co-culture with Meso13 cells infected by MV or MVdeltaC

Generation of 5'copy-back defective genomes agonists of RIG-I

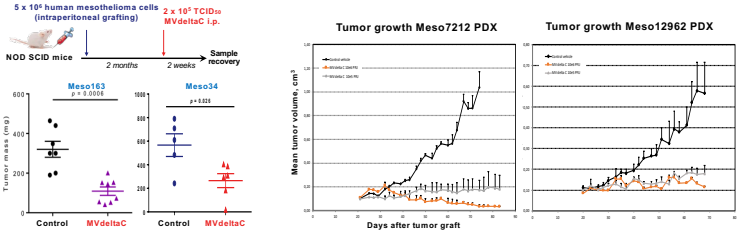


Strong induction of 5'-copy back defective interfering genomes (450 nt-long DI-RNA) by MVdeltaC infection as compared to MV and subsequent strong induction of type-I interferon response.

Identification by NGS of 5'-copy back defective interfering genomes derived from MVdeltaC containing dsRNA (in red) specifically bound to RIG-I receptor.

MVdeltaC inhibits PDX tumor growth *in vivo*

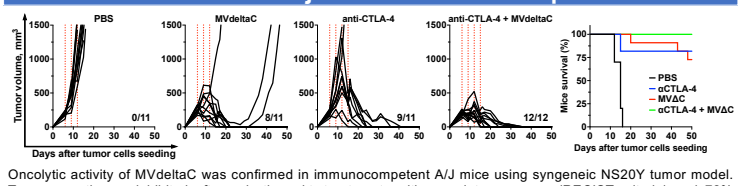
The anti-tumor activity of MVdeltaC is confirmed in patient-derived xenografts (PDX) mice models.



60-70% tumor reduction two weeks after a single intraperitoneal administration

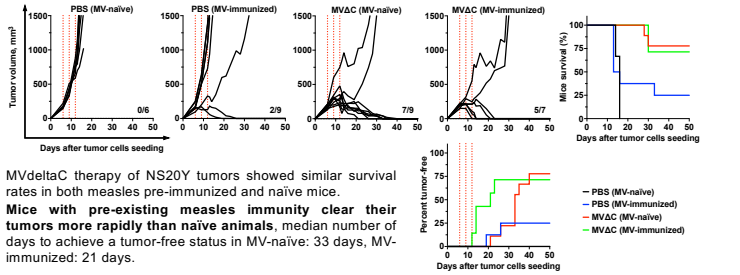
Weekly intratumoral injections of MVdeltaC in PDX mesothelioma strongly inhibit tumor growth in nude mice

MVdeltaC induces tumor rejection in immunocompetent mice



Oncolytic activity of MVdeltaC was confirmed in immunocompetent A/J mice using syngeneic NS20Y tumor model. Tumor growth was inhibited after only three i.t. treatments with complete response (RECIST criteria) and 72% survival rate in MVdeltaC treated animals. Co-administration of MVdeltaC with anti-CTLA-4 antibody resulted in a 100% survival rate

Preexisting immunity to measles is beneficial in MVdeltaC therapy



MVdeltaC therapy of NS20Y tumors showed similar survival rates in both measles pre-immunized and naïve mice.

Mice with pre-existing measles immunity clear their tumors more rapidly than naïve animals, median number of days to achieve a tumor-free status in MV-naïve: 33 days, MV-immunized: 21 days.