Measles virus vaccine induces oncolysis of tumor cells and activates immune responses.

Marc Grégoire*, J.-F. Fonteneau, N. Boisgerault, J.-B. Guillerme and F. Tangy¤.

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Anti-tumor Virotherapy using oncolytic virus



Oncolytic virus

Infection



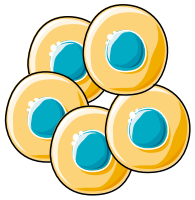
Tumor cells

apoptosis



Activation of the immune system

~~**Infection**~~



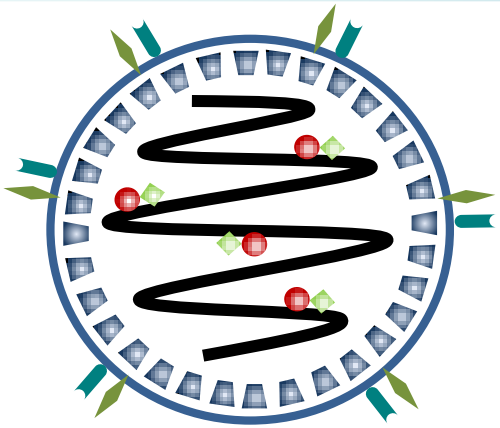
Healthy cells

Ideal replicating oncolytic virus:

Russell SJ, *Nature biotechnol,* 2012
Vacchelli E et al, *Oncoimmunology*, 2013

- **Infects exclusively or preferentially tumor cells**
- **Kills efficiently tumor cells** (apoptosis)
- **No toxicity** (genetically stable, minor side effects)
- **High viral concentration production capability**
- **Induction or stimulation of an anti-tumor immune response.**

Measles virus vaccine (MV) based anti-tumoral virotherapy



- Hémagglutinine (H)
- Protéine de Fusion (F)
- Protéine de Matrice (M)
- Protéine L
- Phosphoprotéine (P)
- ARN + Nucléoprotéine (N)
- Double membrane lipidique

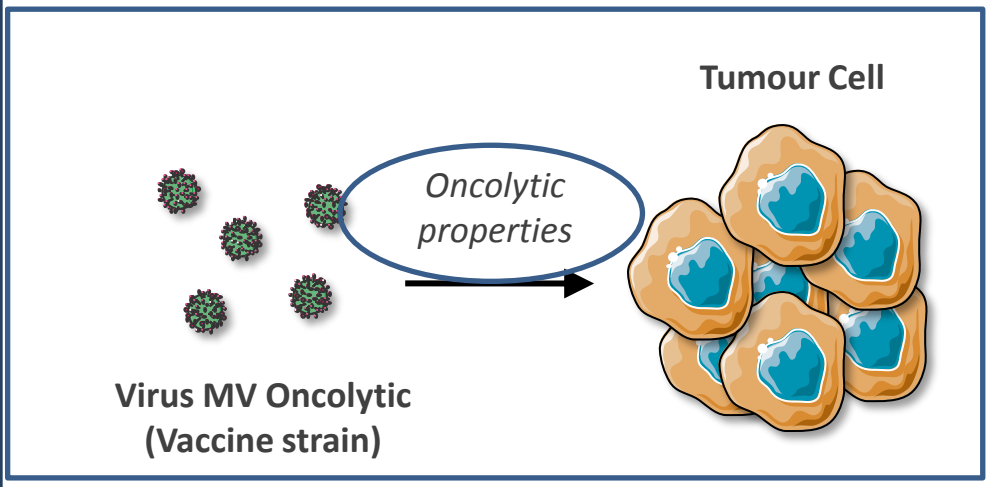
Guillerme JB et al, *Biology*, 2013

Measles virus vaccine, Schwarz strain (MV):
Dr Frédéric Tangy (Viral genomics and Vaccination laboratory, Pasteur Institut, Paris)

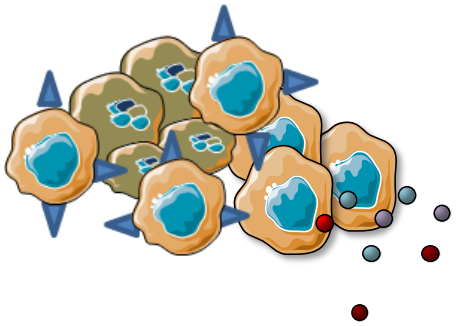
- **Enveloped, non-segmented, negative-sense, single-stranded RNA (ssRNA) paramyxovirus of the genus Morbillivirus**
- **Attenuated replicating vaccine strain of measles virus: Schwarz** (MMR vaccine)
- **Targets CD46, complement regulatory protein** (wt MV targets CD150/SLAM)
- **CD46 is expressed at low level by healthy cells**
- **CD46 is often found overexpressed on tumor cells**
- **antiviral pathway defects are often found in tumor cells**
- **Spontaneously oncolytic:**
  - Lymphoma, glioma, breast, ovary, prostate … (Russell SJ, Mayo Clinic, USA)
  - MPM, colon and lung adenocarcinoma

Gauvrit A et al, Cancer Research, 2008; Boisgerault N et al, Biomed Res Int, 2013

Oncovirotherapy – Oncolytic properties of Measles Vaccine



Immunogenic apoptotic cell death

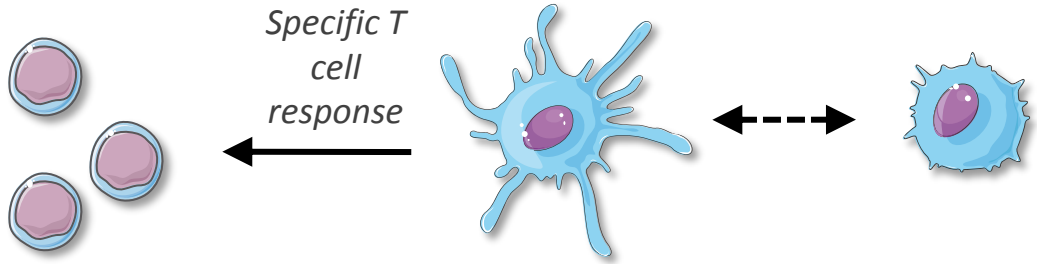


immunogenic molecules
DAMP & PAMP

Ideal replicating oncolytic virus: *(Fielding AK, 2005)*:

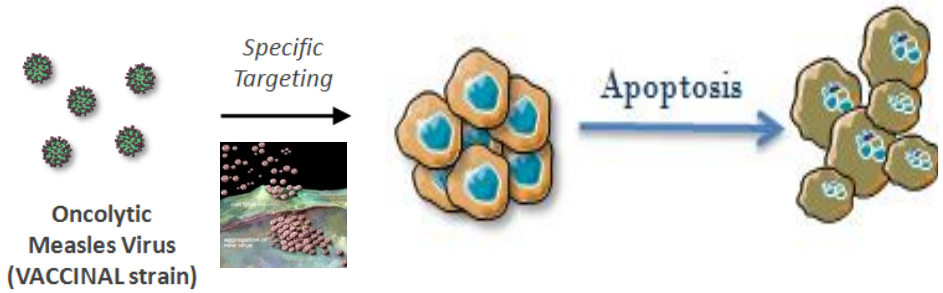
- ✓ Infects exclusively or preferentially tumor cells
- ✓ Kills efficiently tumor cells (apoptosis)
- ✓ No toxicity (genetically stable, minor side effects)
- ✓ High viral titre production capability
- ✓ Induction of an immune response.

Specific T cell response



T Lymphocytes | **Myéloïd DC** | **Plasmacytoïd DC**

Tumour cell infection (mesothelioma)

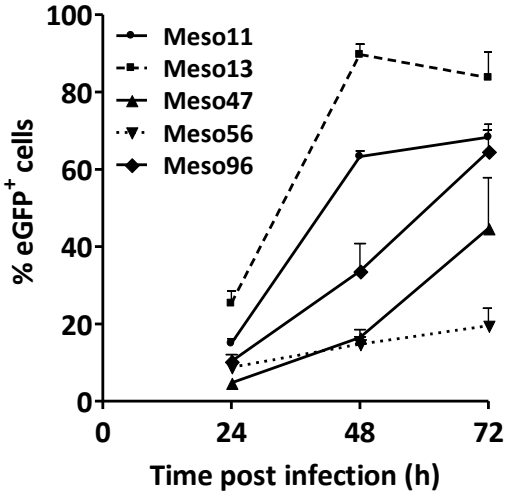


INFECTION

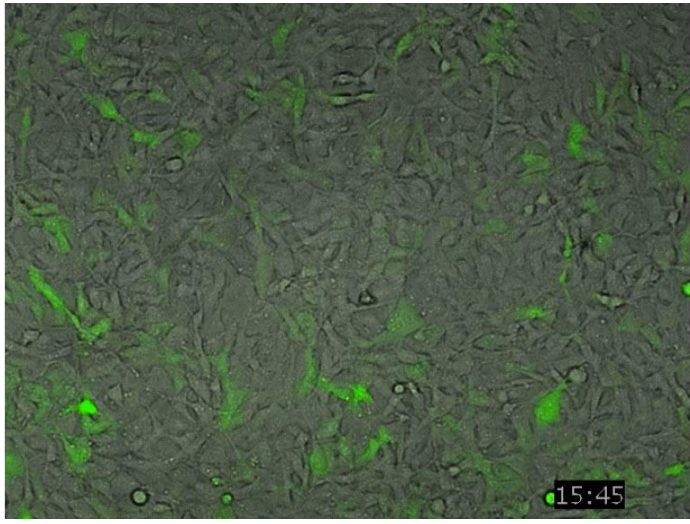
Others

- Mesothelioma : 14/18
- Melanoma : 7/8
- Lung : 3/4
- Colorectal : 4/4

Mesothelioma

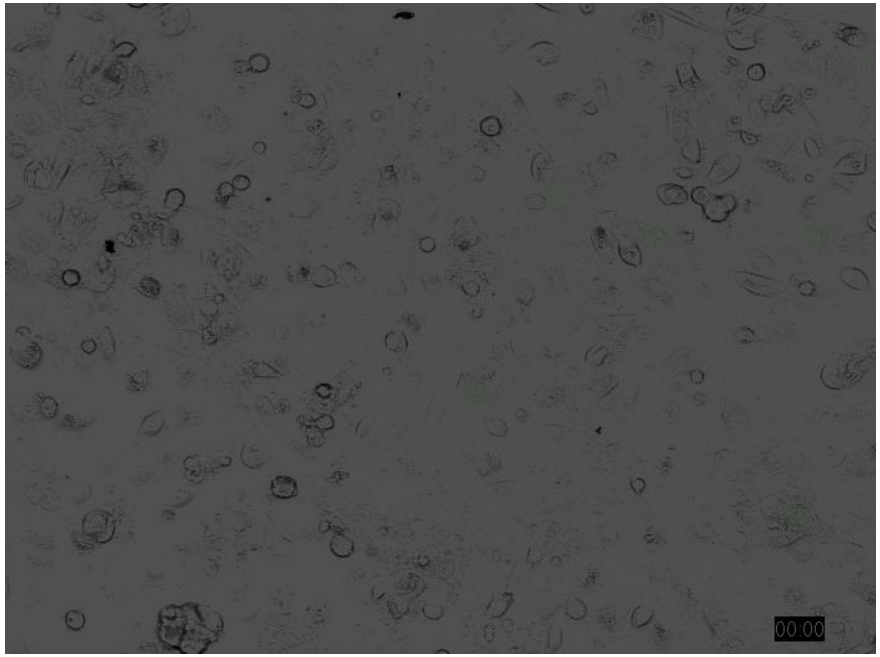


Infected cells MV-eGFP

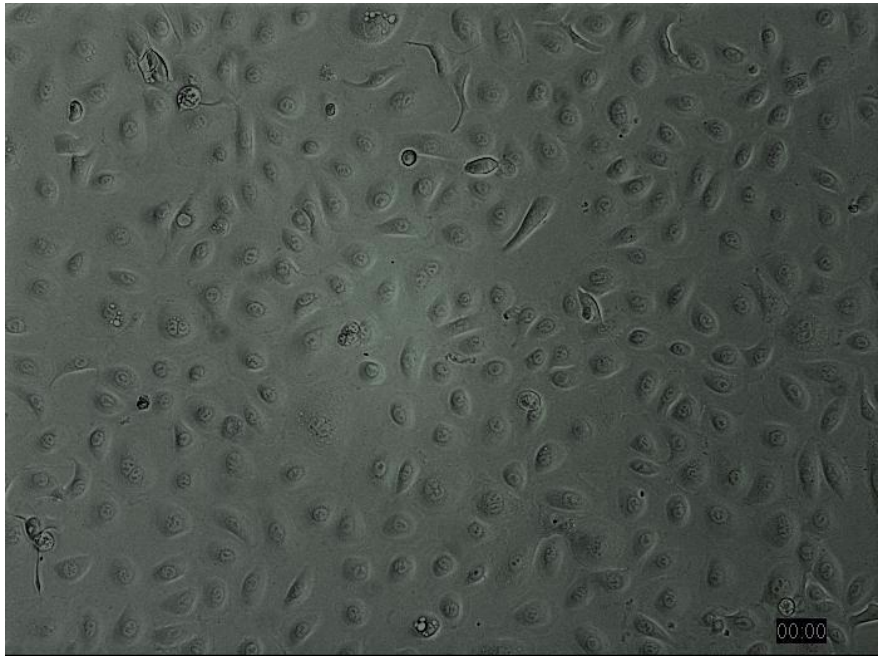


- ✓ Mesothelioma *(Gauvrit A et al, Cancer Research, 2008)*
- ✓ Lung, Colorectal adenocarcinoma (*N. Boisgerault et al., Biomed. Res. Int., 2013*)

Normal cells: mesothelial and lung cells



Mesothelial cells

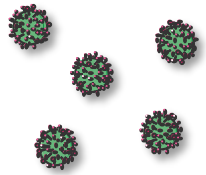


Lung cells

Also for :

- Fibroblasts
- Endothelial cells

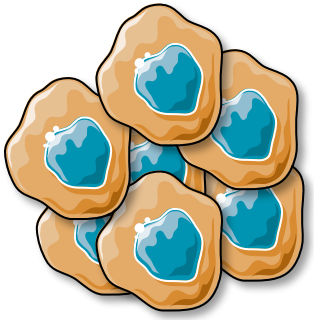
Oncovirotherapy - Live attenuated Schwarz Measles Vaccine



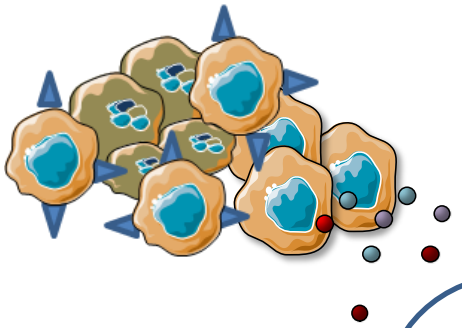
Virus MV Oncolytic
(Vaccine strain)

Oncolytic properties

Tumour Cell



Immunogenic apoptotic cell death

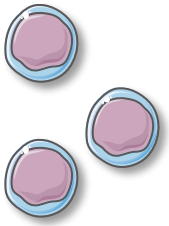


immunogenic molecules
DAMP
& PAMP

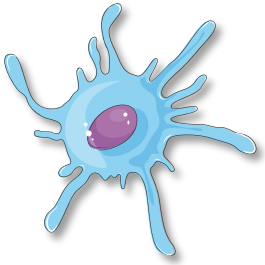
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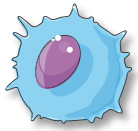
Specific T cell response



T Lymphocytes

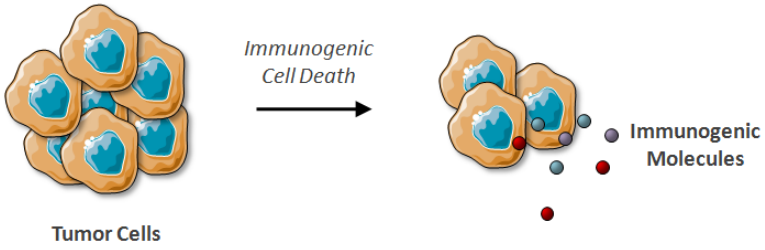


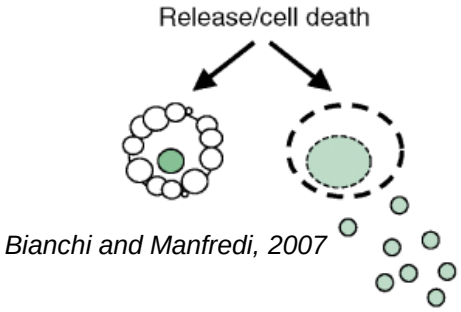
Myéloïd DC



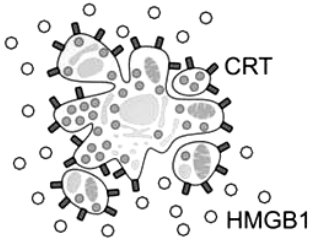
Plasmacytoïd DC

Danger Signals: Damage Associated Molecular Patterns





Bianchi and Manfredi, 2007



Kepp et al., 2009

HSP70

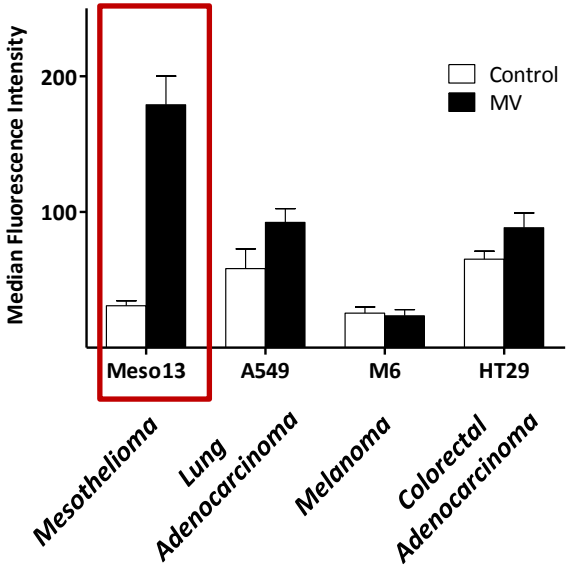
➢*Cross-presentation of tumor-derived antigens*

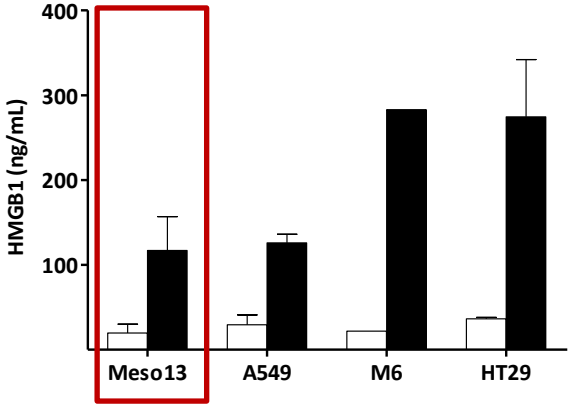
HMGB1

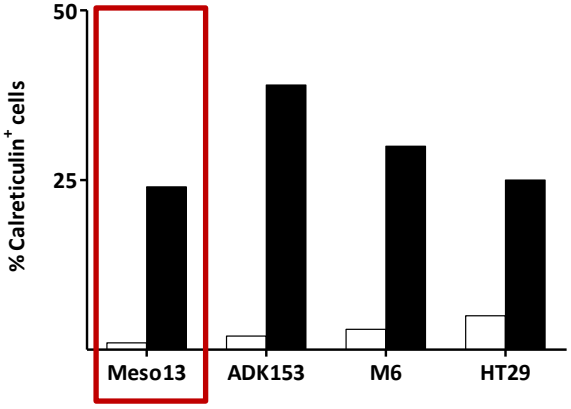
➢*Antigen processing and presentation*

Calreticulin

➢*Phagocytosis*

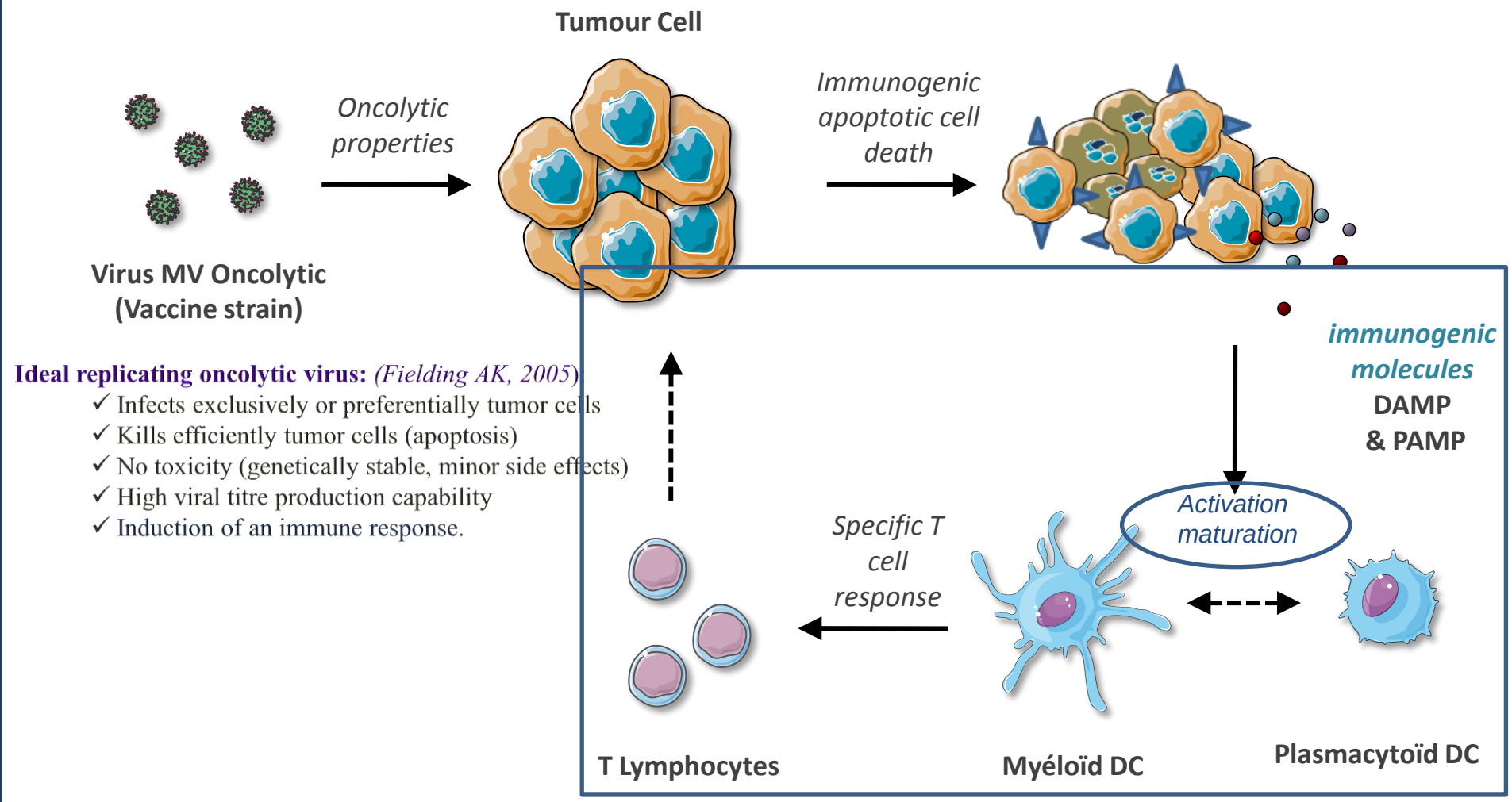






Gregoire et al, *in preparation*

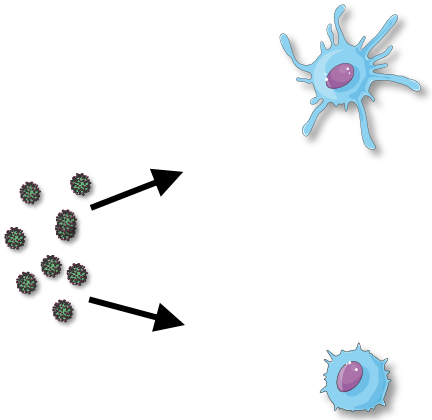
Immune response with Live attenuated Schwarz Measles Vaccine

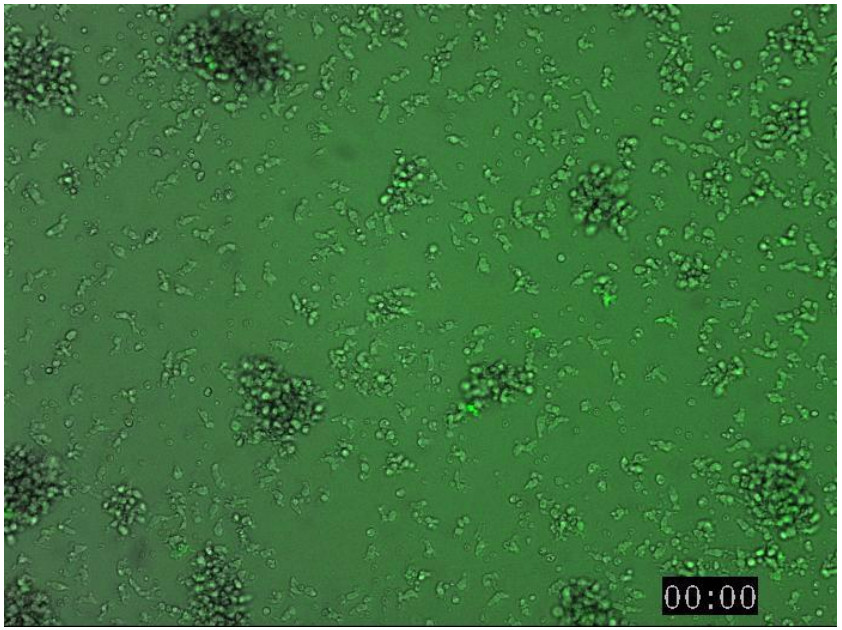


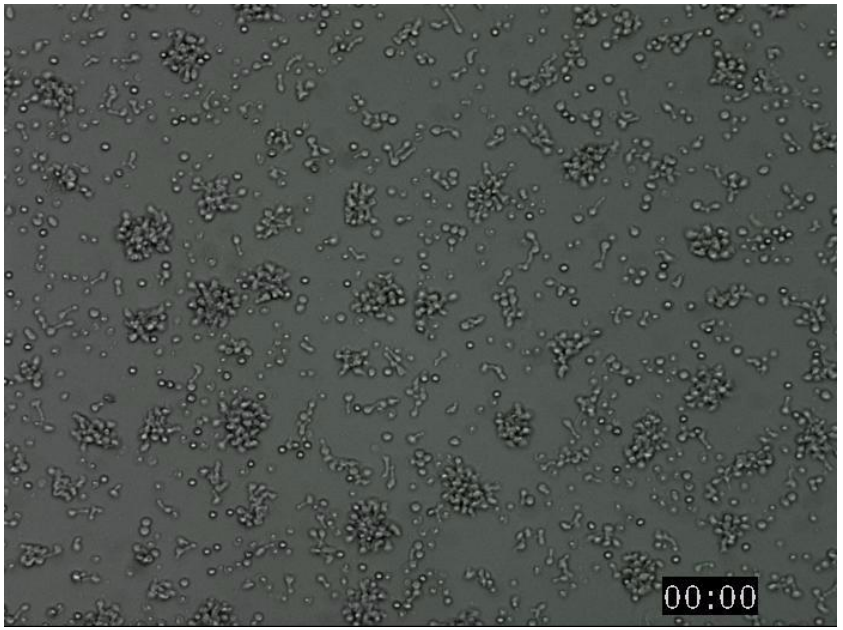
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MV preserves dendritic cells







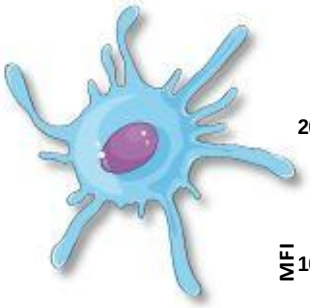
Myeloid dendritic cells

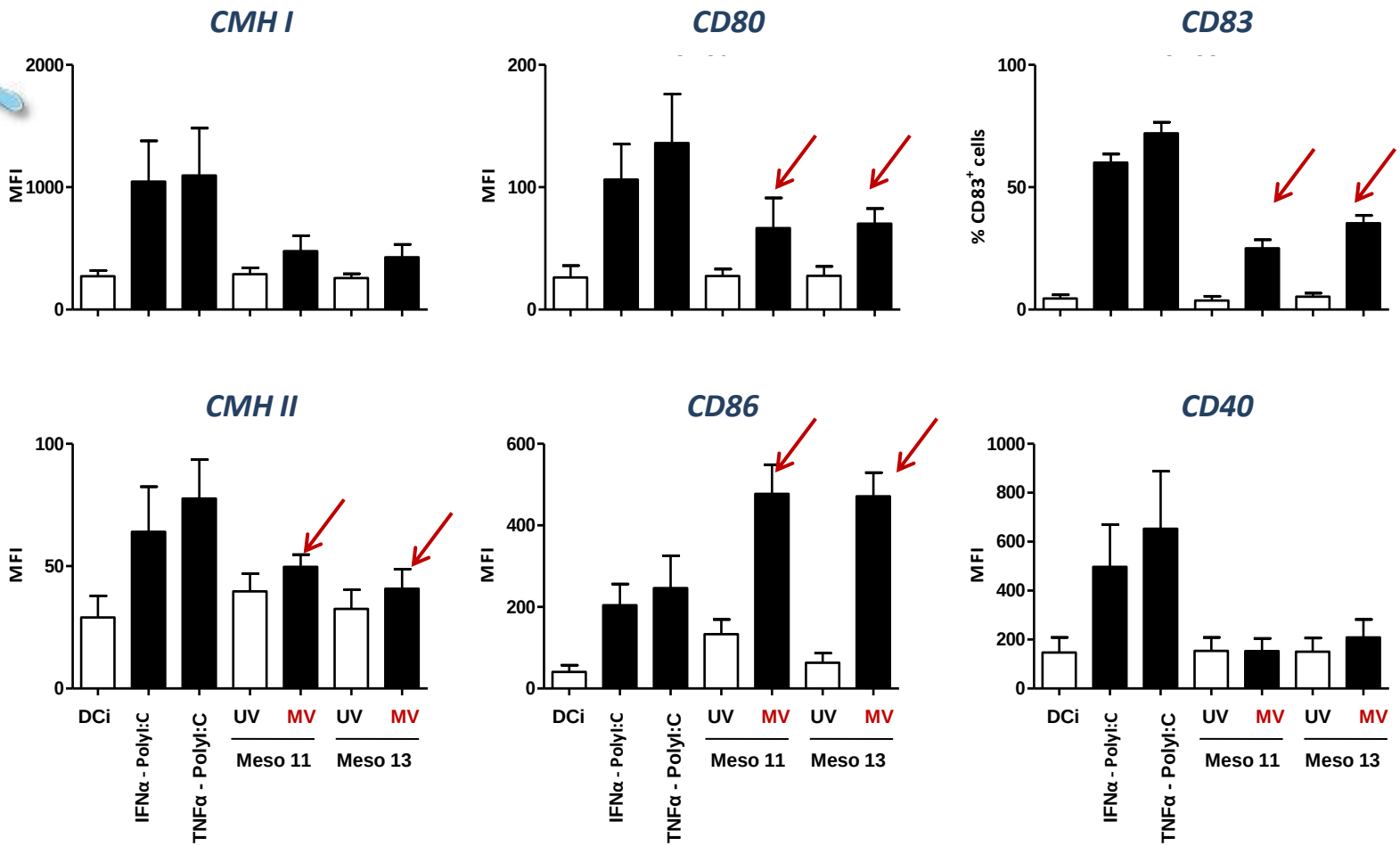
(Gauvrit A et al., 2008, Cancer Research)

Plasmacytoid dendritic cells

(Guillerme JB et al., 2013, Clinical Cancer Research)

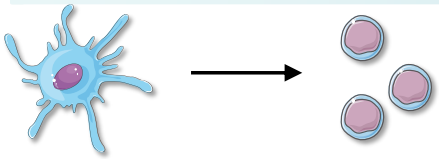
MV-infected tumor cells induced Mo-DC Maturation



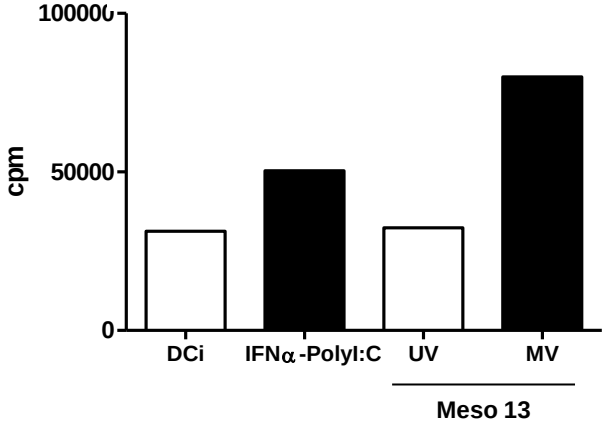


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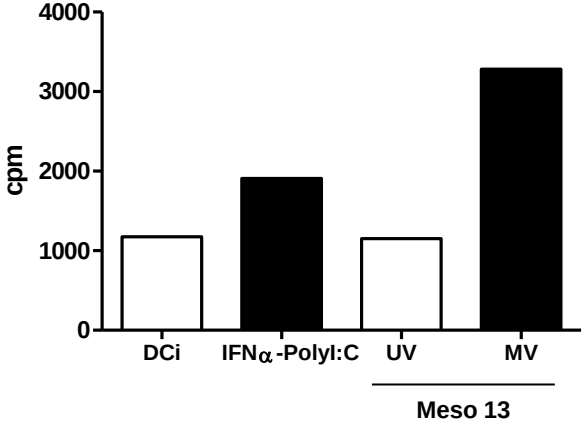
MUC-1 or mesothelin +Mo-DC



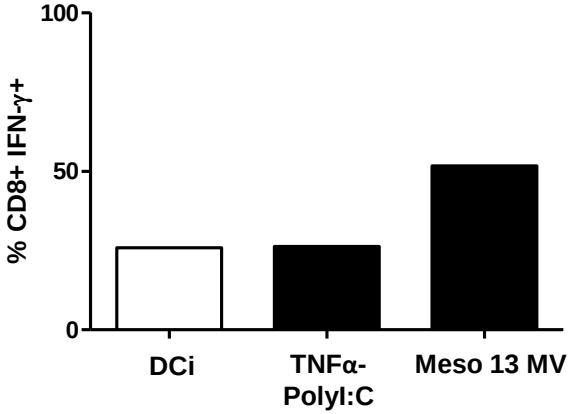
T CD4 Proliferation



T CD8 Proliferation

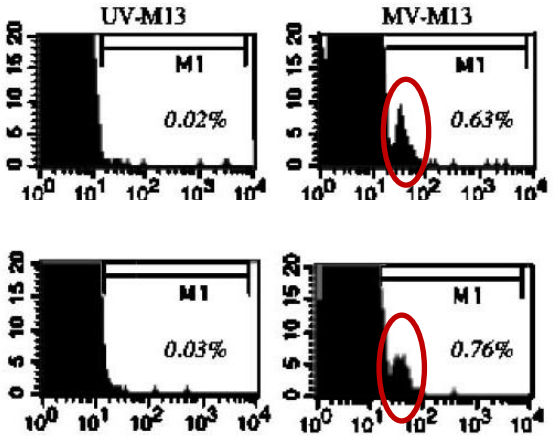


Clone T CD8 anti-MUC-1



(Gauvrit A et al., 2008, Cancer Research)

Cross-presentation (mesothelin)

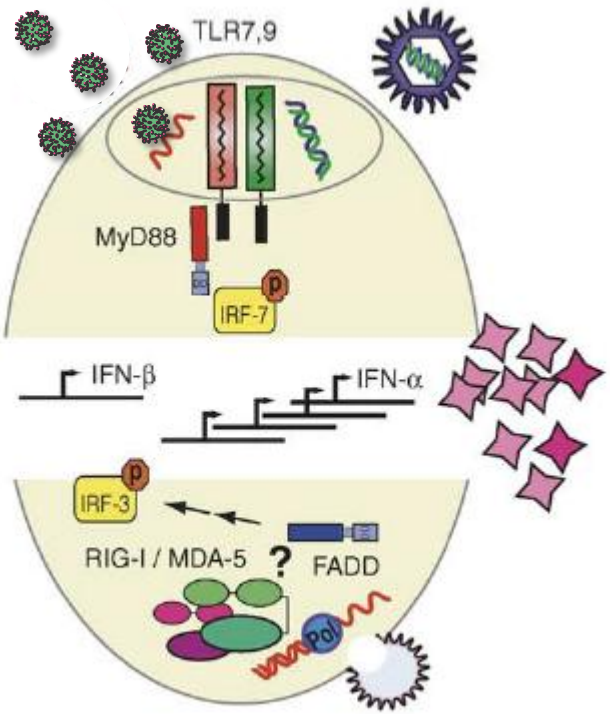


(Gauvrit et al., 2008)

Plasmacytoid dendritic cells



MV
ARNsb



- **Expression of TLR7 et TLR9**
  => specialized in recognition of viral nucleic acids

- **Produce huge quantities of Type I IFN (-α and –β) in response to virus**

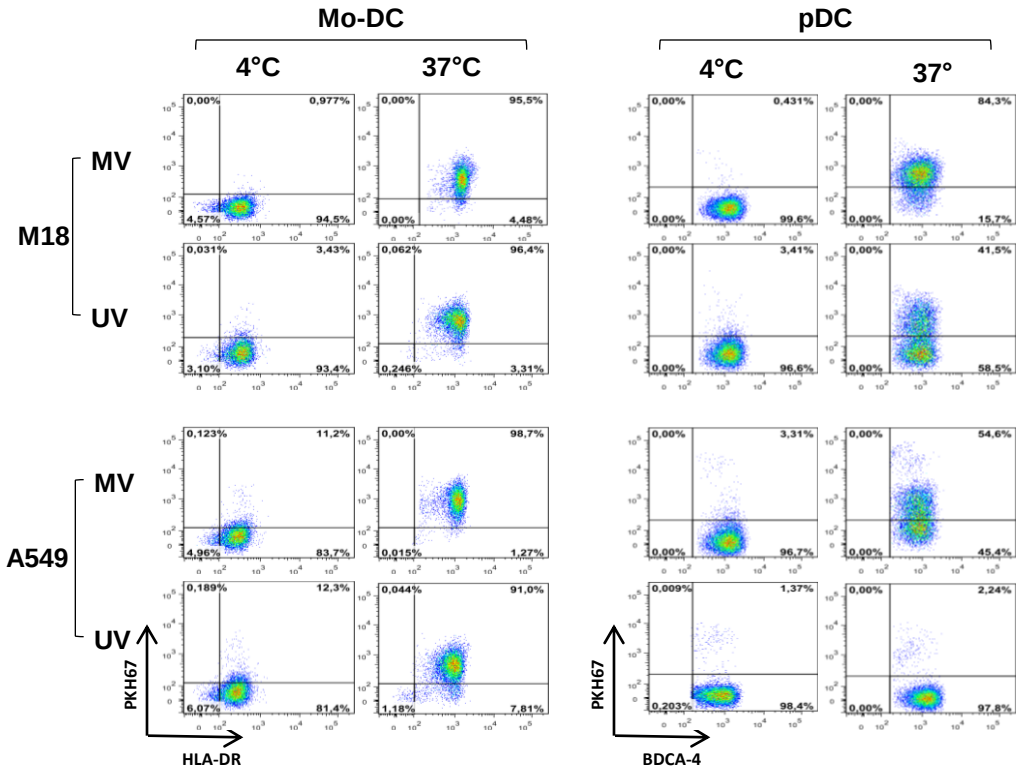
- **Antigen cross presentation in human:**
  - **HIV** *(Hoeffel, G,.Immunity, 2007) (Crozat, K., J Exp Med, 2010)*
  - **Influenza** *(Lui, G., PLoS One, 2009)*

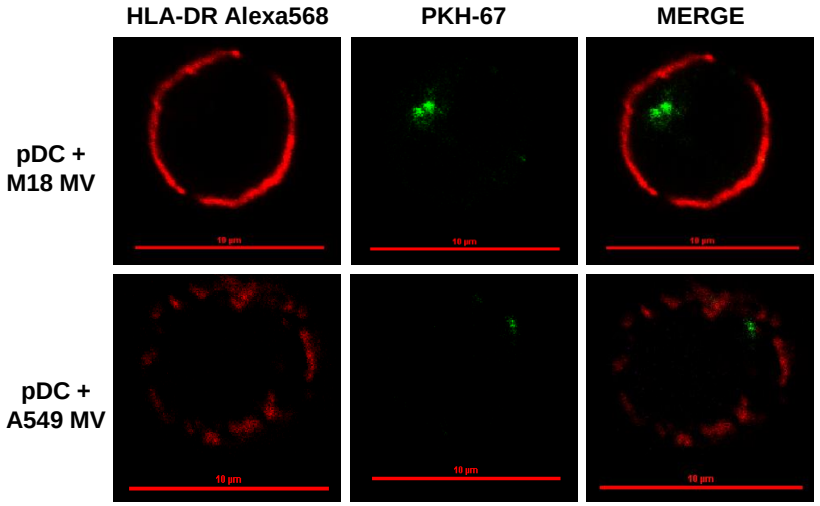
- **Antigen cross presentation in mice:**
  - **Cross-tolérance** (Goubier, A., Dubois, B., *Immunity, 2008)*
  - **OVA** (Mouries, J., Blood, 2008)

- **One of the target of imiquimod (R837, TLR7 ligand) in the treatment of basal cell carcinoma with Aldara.**

IFN-α Production and tumor antigen cross-presentation by pDC exposed to MV infected tumor cells?

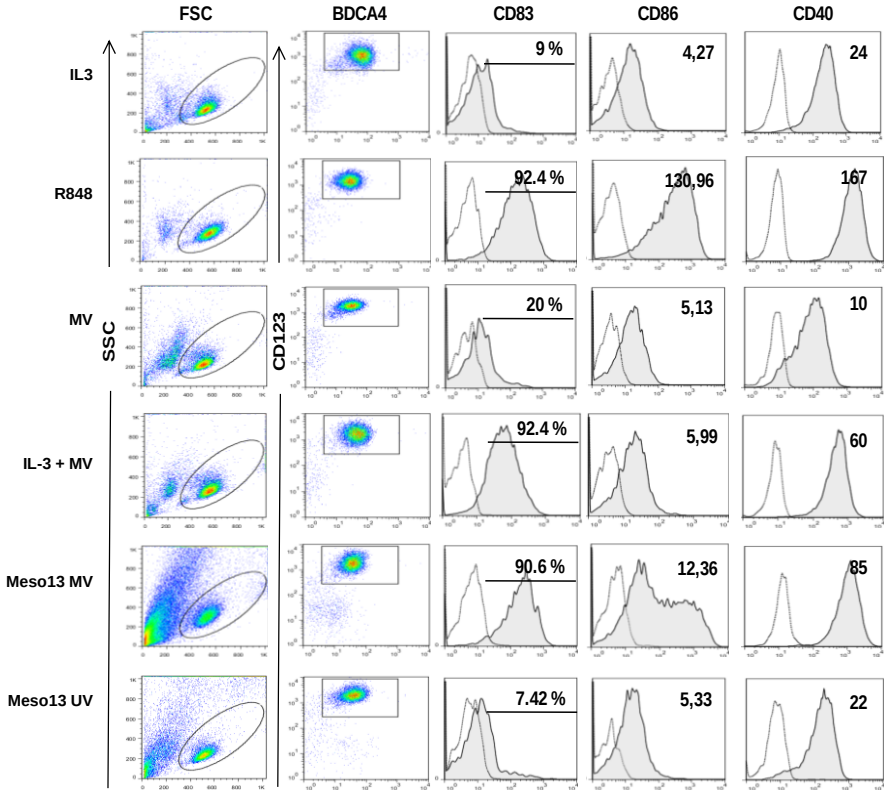
MV infected tumor cells are internalized by Plasmacytoid dendritic cells

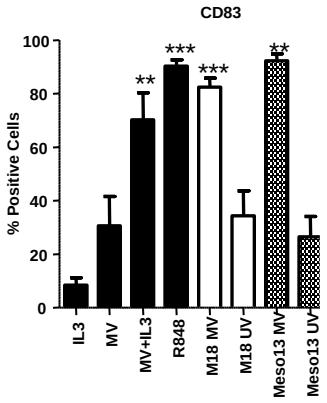


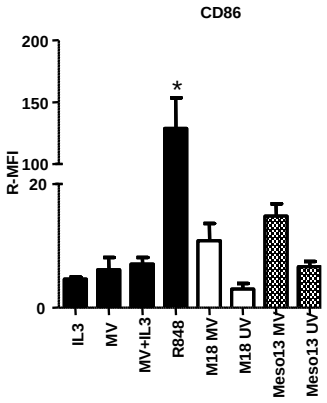


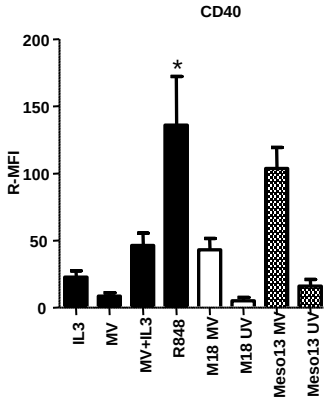
MV infected tumor cells induce Plasmacytoid dendritic cells maturation



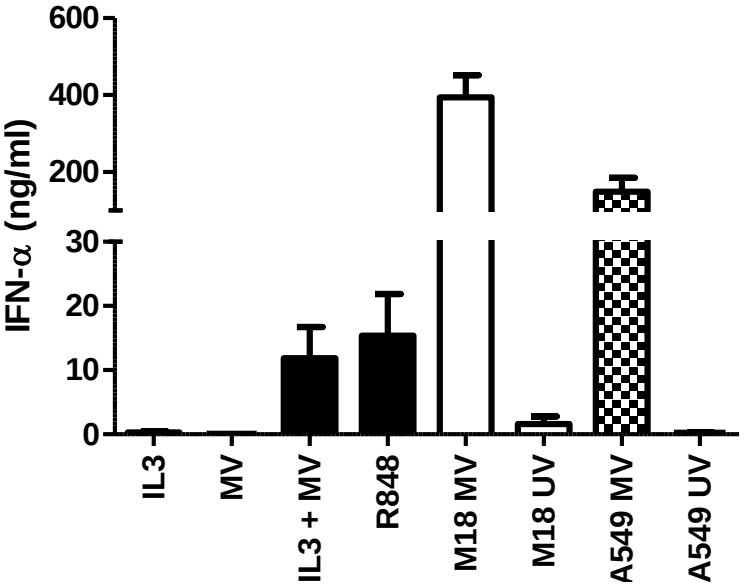


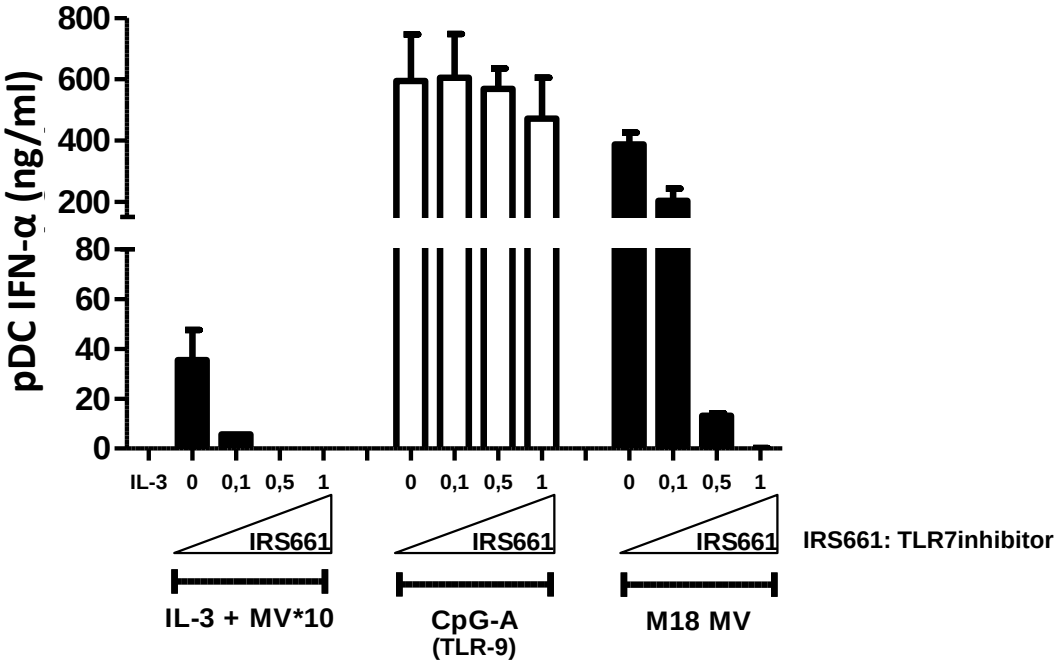




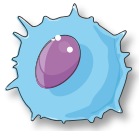


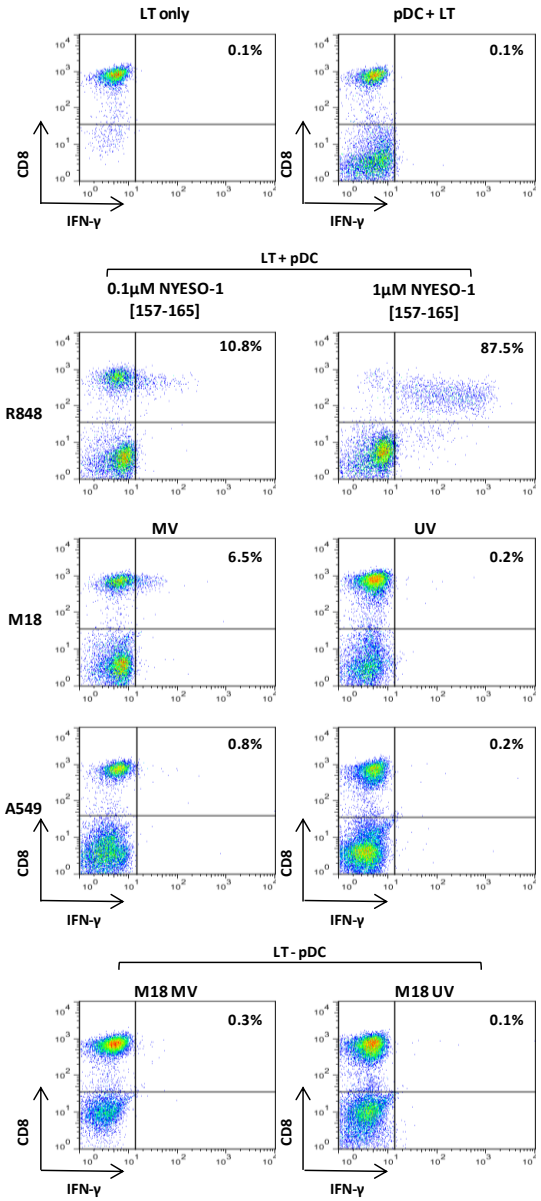
MV infected tumor cells induce production of INF type I by pDC

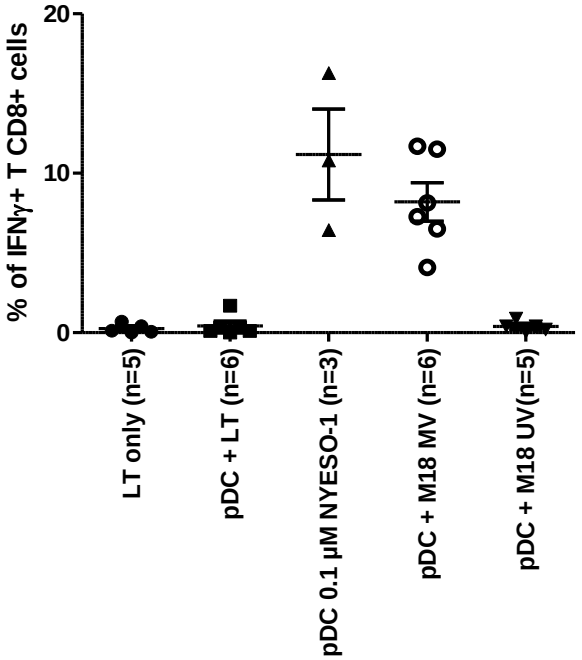




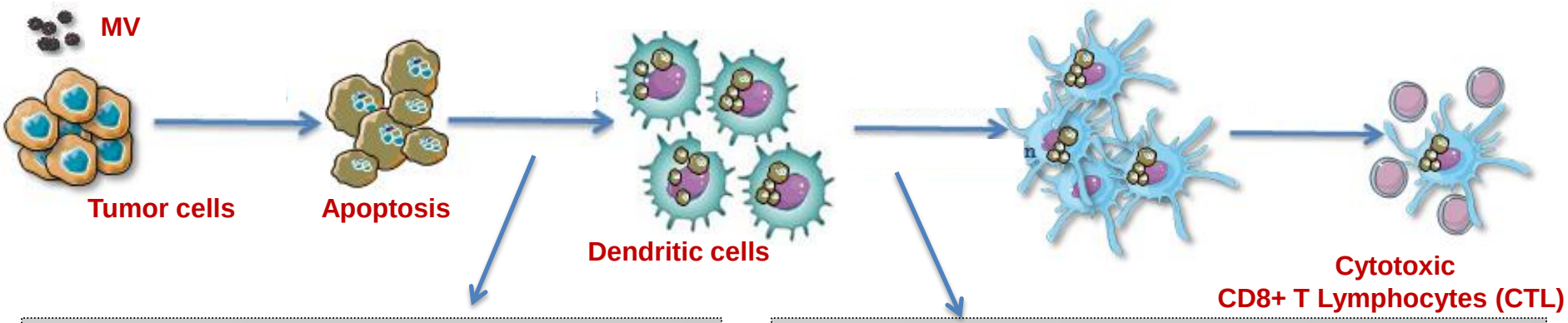
MV infected tumor cells induce NY-ESO-1 cross-presentation by pDC







In conclusion: Virotherapy and DC activations



✓ **Dangers signal expression**

- **HMGB1**
- **Calreticuline**
- **HSP**
- **inflammasome, caspase1, IL-1b**

Boisgerault N et al, *in preparation*

✓ **Immune system activation**

- **Activation of myeloïd DC**
- **Activation of tumor antigen specific CD8+ T lymphocytes**

Gauvrit A et al, *Cancer Research,* 2008

✓ **Immune system activation**

- **Activation of plasmacytoid DC (production of type I interferon)**

Guillerme JB et al, *Clin. Cancer Res., 2013*

IMMUNOGENIC PROPERTIES OF DEAD CELLS

CANCER RESEARCH CENTER, NANTES, FRANCE

MARC GREGOIRE

JEAN-FRANÇOIS FONTENEAU

ANNE GAUVRIT

JEAN-BAPTISTE GUILLERME

NICOLAS BOISGERAULT



VIRAL GENOMICS AND VACCINATION LABORATORY

PASTEUR INSTITUTE, PARIS, FRANCE

FRÉDÉRIC TANGY

MARIANA MESEL-LEMOINE

"DEVELOPMENT AND CLINICAL TRANSFER" CORE FACILITY PLATFORM

DELPHINE COULAIS

CLARISSE PANTERNE