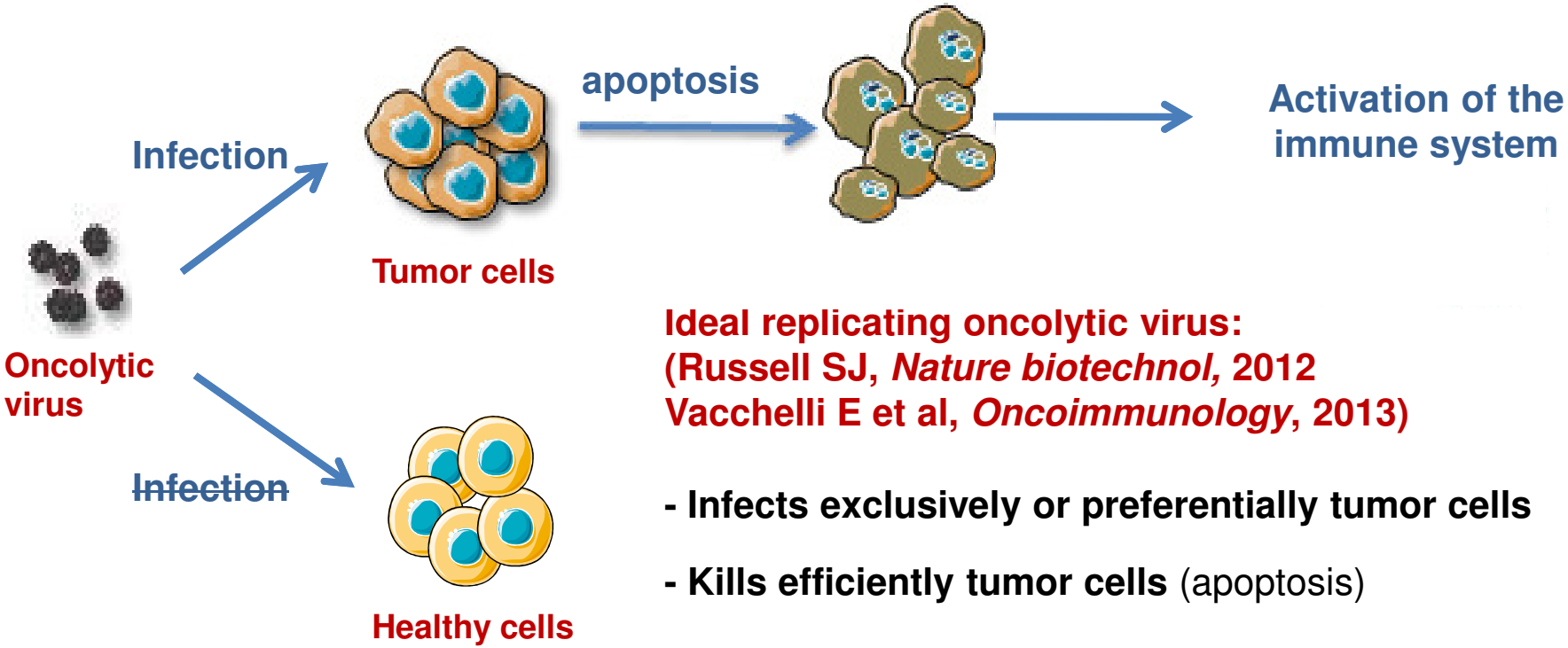
Immunoadjuvant Properties of Oncolytic Schwarz Measles Virus

Dr Jean-François Fonteneau
Institut de Recherche en Santé de
l'Université de Nantes
INSERM UMR892, CNRS UMR6299
Nantes, France

Anti-tumor Virotherapy using oncolytic virus



Ideal replicating oncolytic virus:
(Russell SJ, *Nature biotechnol,* 2012
Vacchelli E et al, *Oncoimmunology*, 2013)

- Infects exclusively or preferentially tumor cells

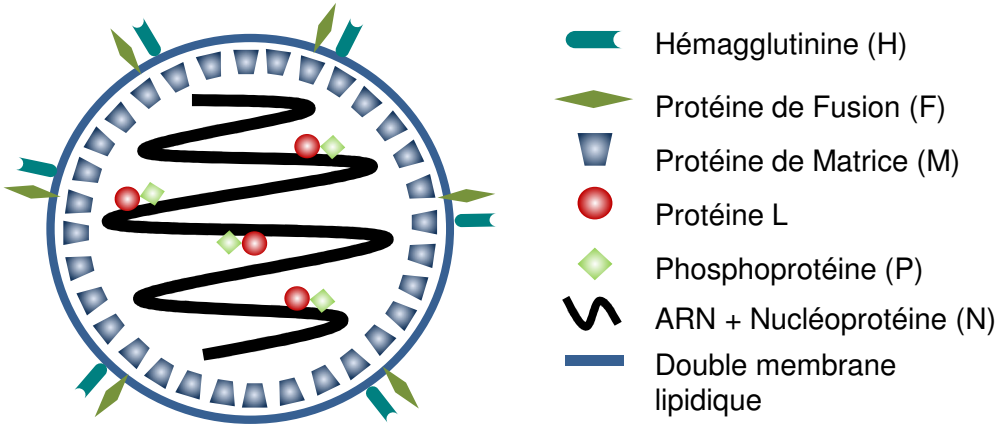
- Kills efficiently tumor cells (apoptosis)

- 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



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

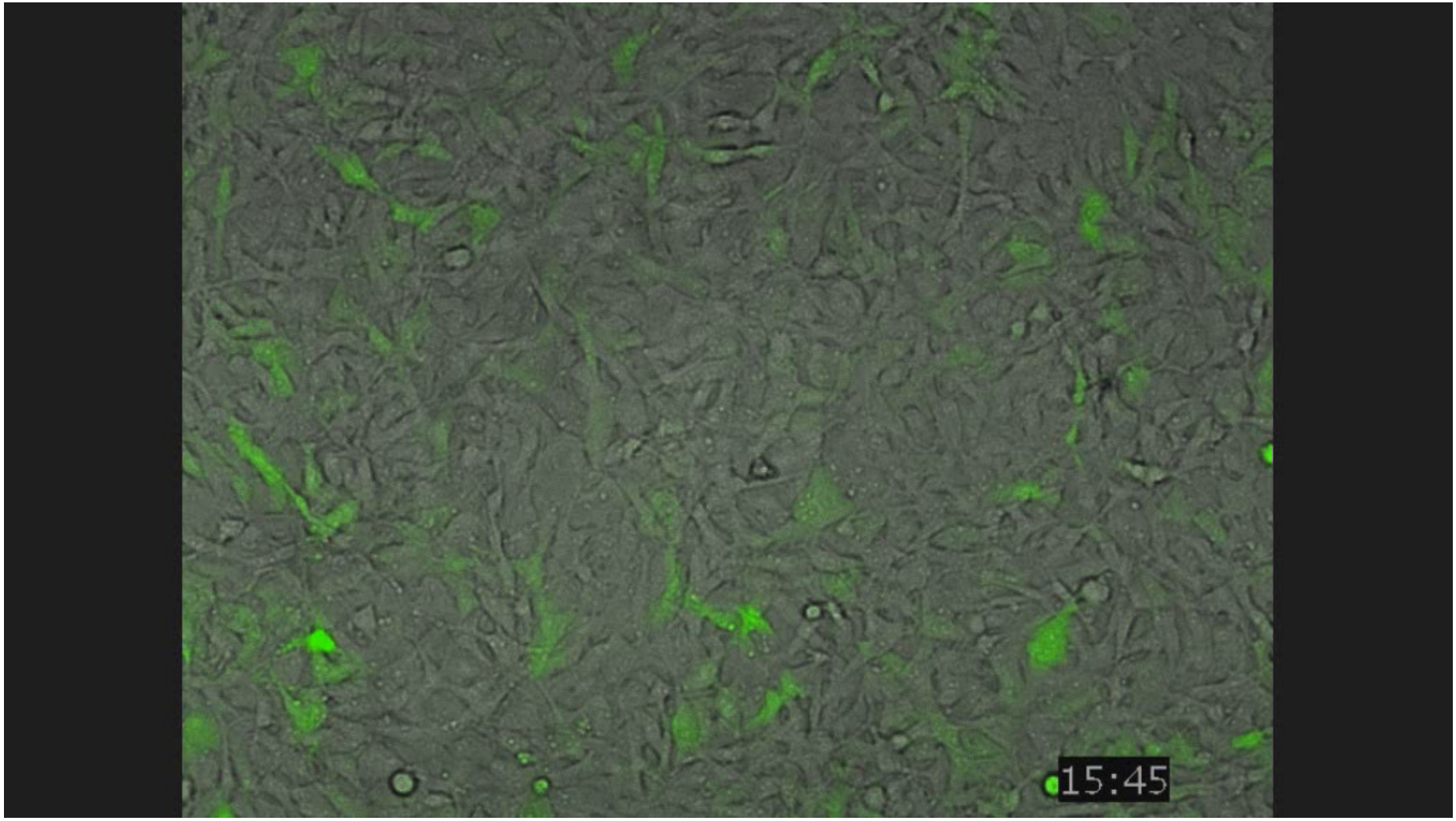
- Spontaneously oncolytic:

- 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*)*

MV infection of Malignant Pleural Mesothelioma tumor cells

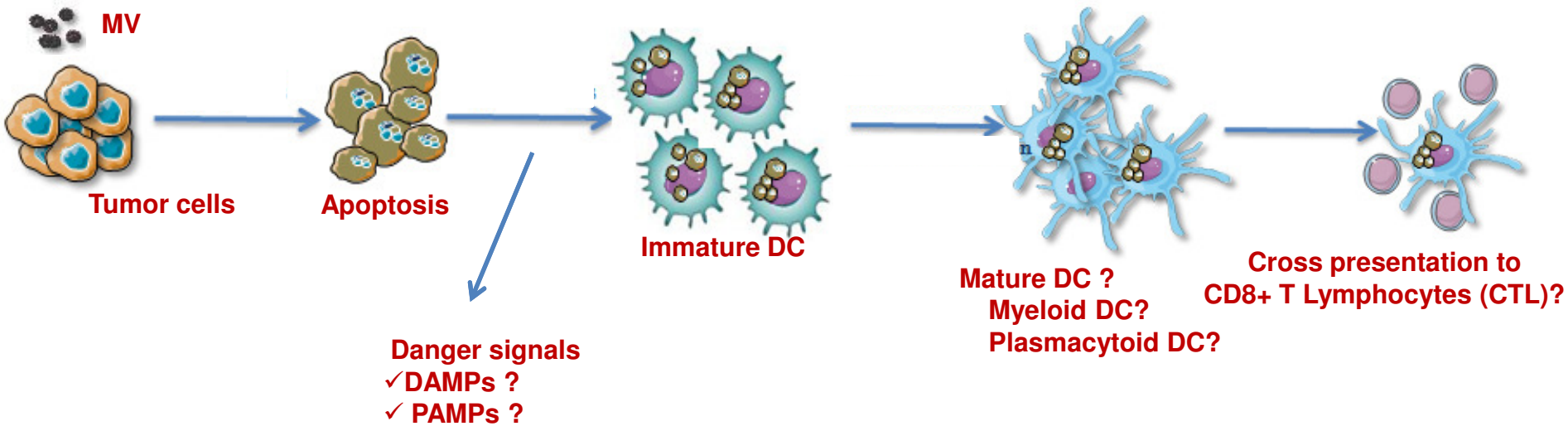
Video : MV infection of meso13 by MV-eGFP (enhanced green fluorescent protein)



Limited MV infection of healthy mesothelial cells

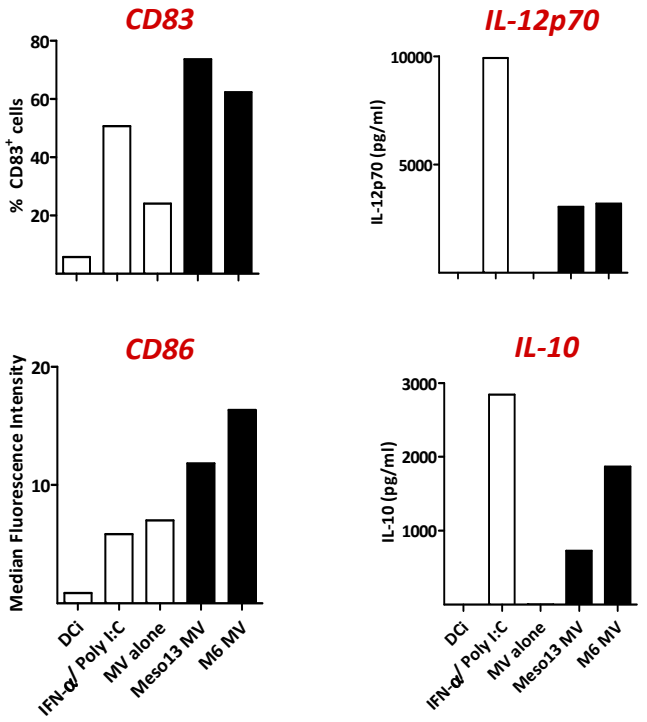
Video : healthy mesothelial cells exposed to MV-eGFP

Activation of the immune system by MV infected tumor cells ?



Activation of monocyte derived DC (Mo-DC) and tumor antigen cross-priming by MV infected tumor cells

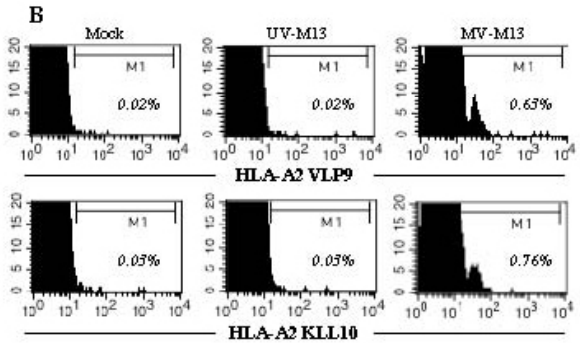
Mo-DC activation



Tumor antigen cross-priming

A

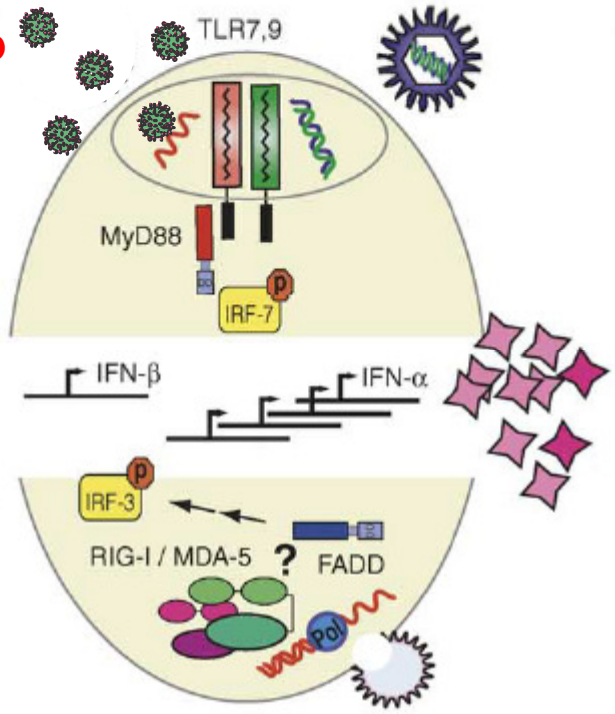
Name	Position	Sequence	Restriction	SYFPEITHI Score	BIMAS Score	Reference
VLP9	531-539	VLPLTVAEV	HLA-A2	29/30	272/285	(24)
KLL10	541-550	KLLGPHVEGL	HLA-A2	30/31	312/312	(25)



Gauvrit et al, *Cancer Research*, 2008

Plasmacytoid Dendritic Cells (pDC)

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)*

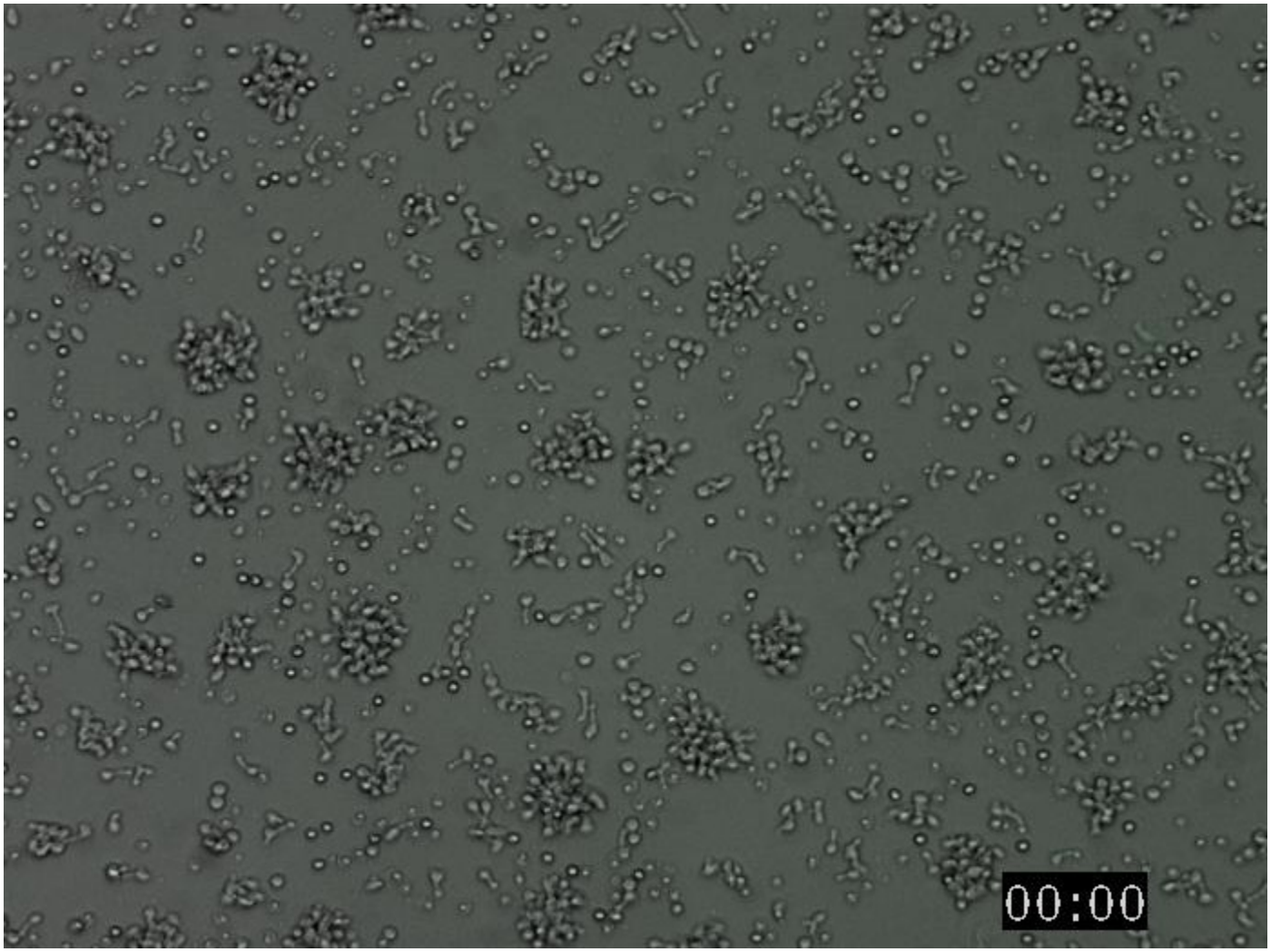
- **Antigen cross presentation in mice:**
  - **Cross-tolérance** (Goubier, A., Dubois, B., *Immunity, 2008)*
  - **OVA** (Mouries, J., Blood, 2008)

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

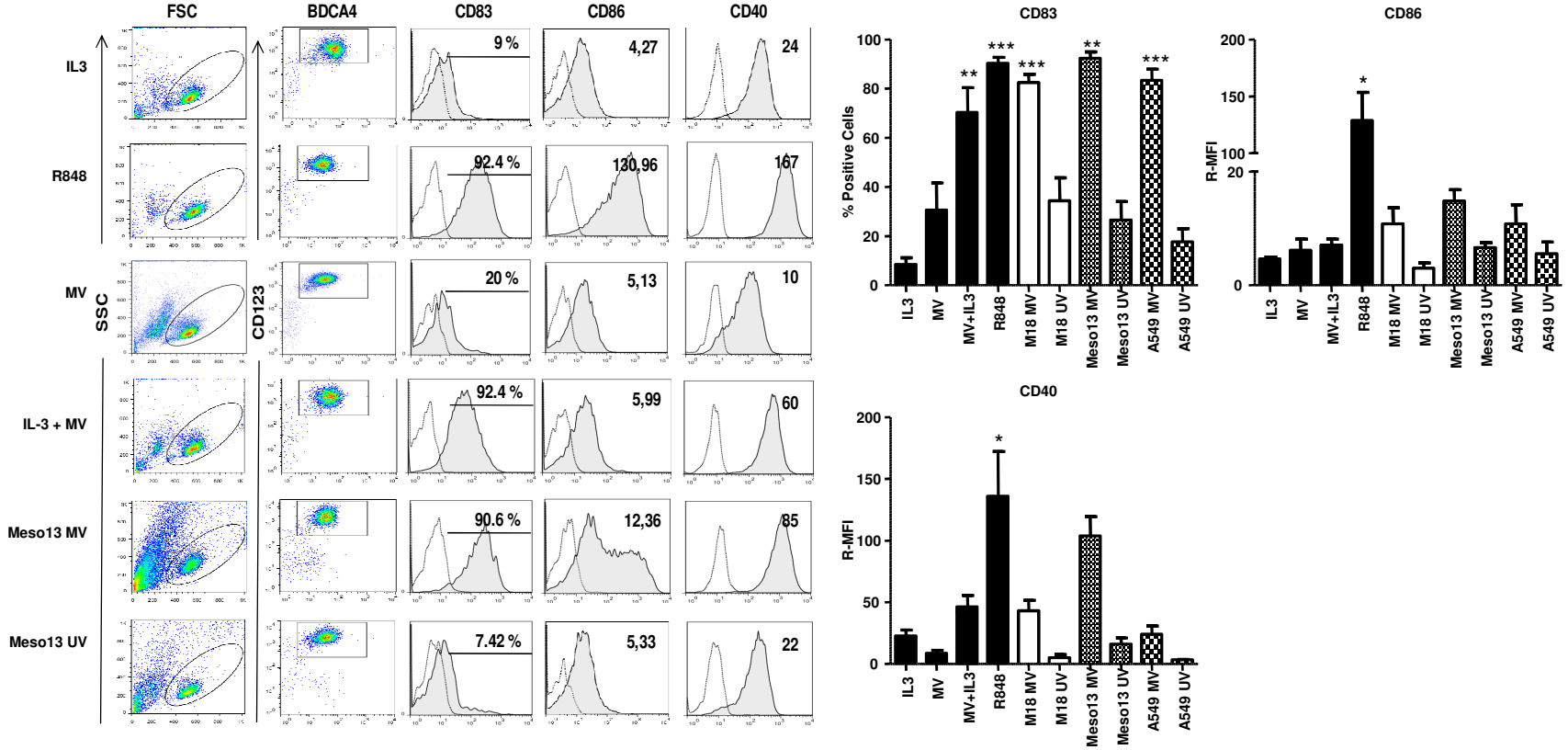
IFN-α Production and tumor antigen cross-presentation by pDC exposed to MV infected tumor cells?

pDC are not infected by Schwarz MV

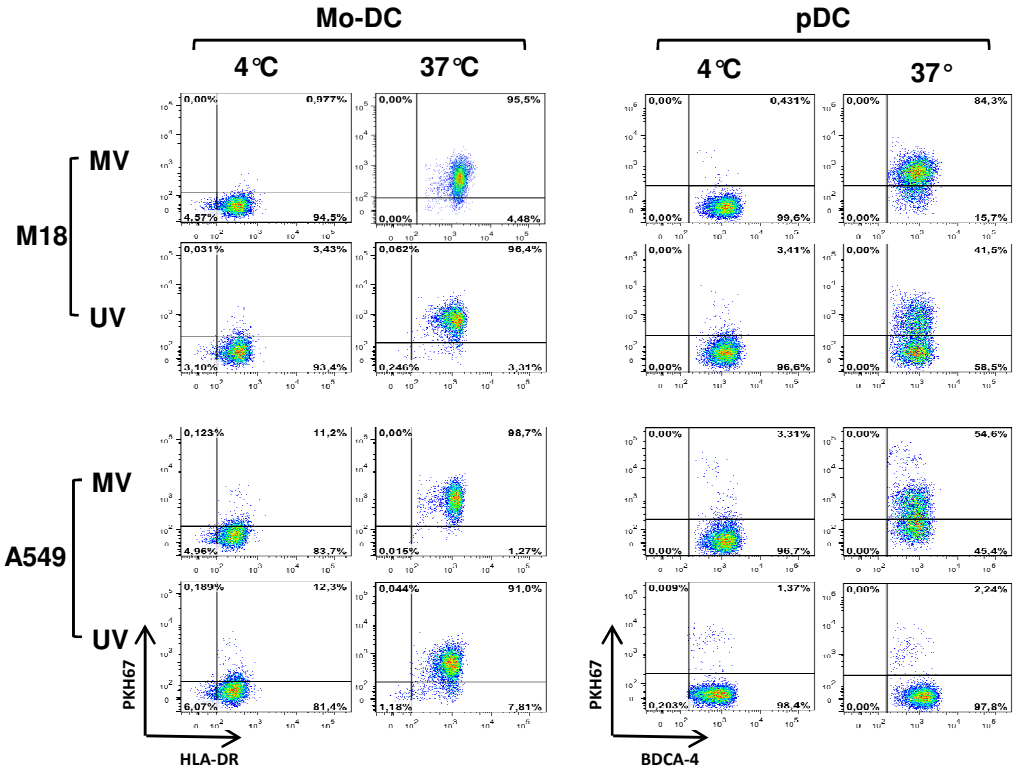
Video : pDC exposed to MV-eGFP

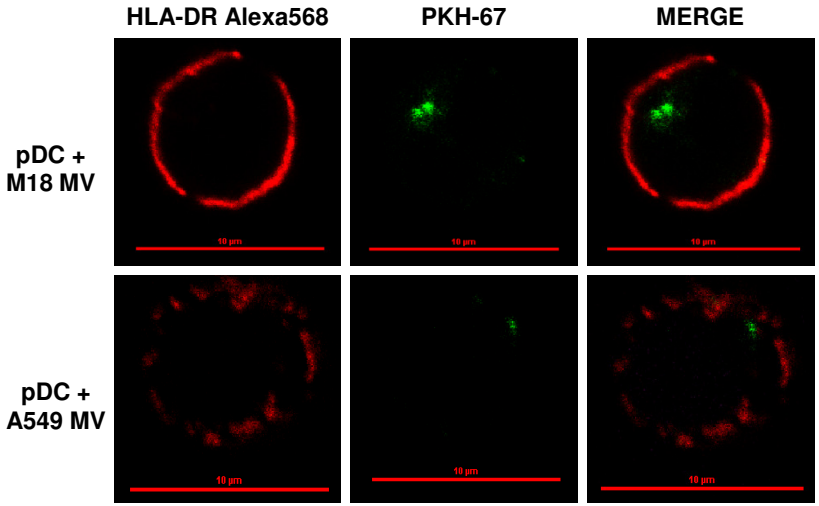


MV infected tumor cells induce maturation of plasmacytoid DC

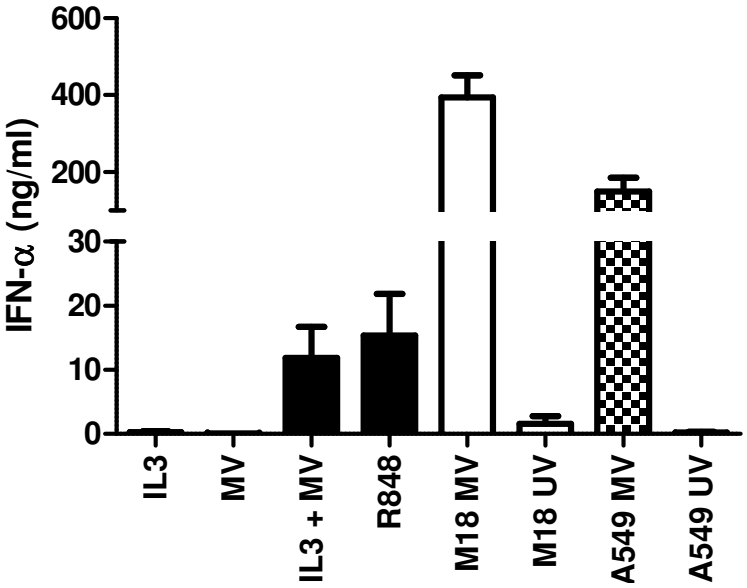


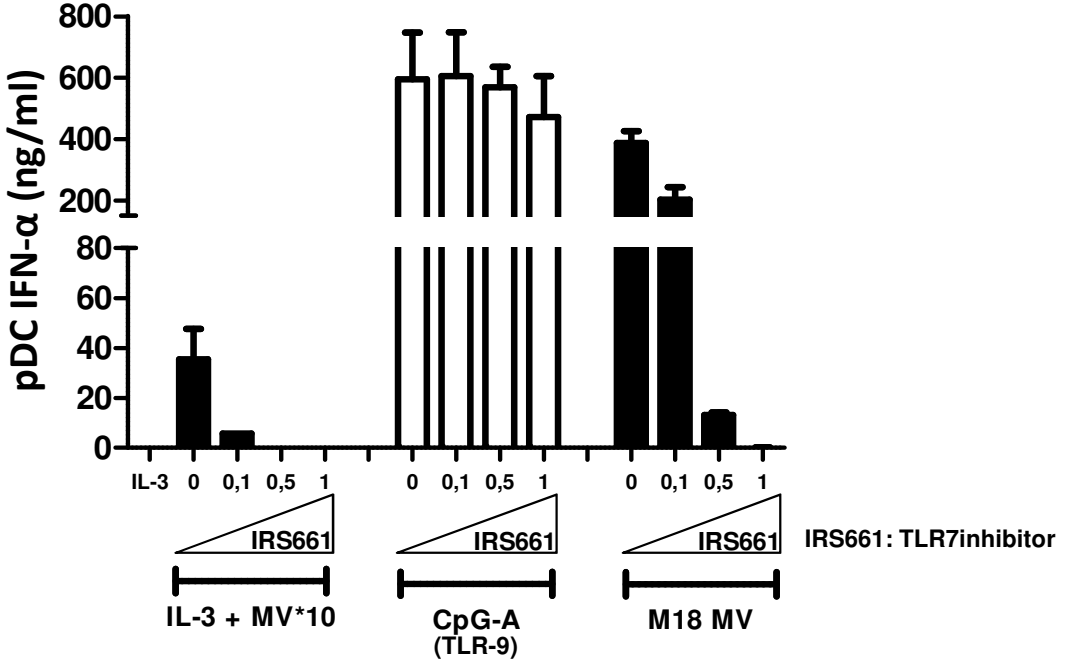
MV infected tumor cells are internalized by plasmacytoid DC





MV activates pDC IFN-α production by TLR7

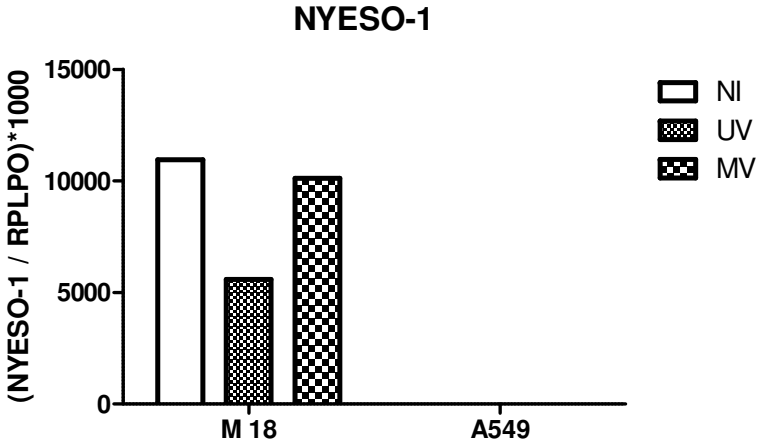




MV probably activates pDC via TLR7 in early endosome

CpG-A (TLR9) -> High IFN-α -> Low costimulation (CD80, CD86) -> Low inflammatory molecules secretion (IL-8)	**CpG-B (TLR9)** -> Low IFN-α -> High costimulation (CD80, CD86) -> High inflammatory molecules secretion (IL-8)	Kerkmann M et al, *J Immunol*, 2003
Early endosome	Late endosome	Honda K et al, *Nature*, 2005 Guiducci C et al, *J Exp Med*, 2006
IRF7 pathway	NF-κB pathway	Sadaka C et al, *Blood*, 2009 Kubo-Murai M et al, *Blood*, 2008
HIV (TLR7)	R848 (TLR7/TLR8) CpG-B (TLR9)	O'brien M et al, *J Clin Invest*, 2011
MV (TLR7)	R848 (TLR7/TLR8)	Guillerme JB et al, clin cancer Res, 2013

NYESO-1 cross-presentation by pDC exposed to MV infected tumor cells



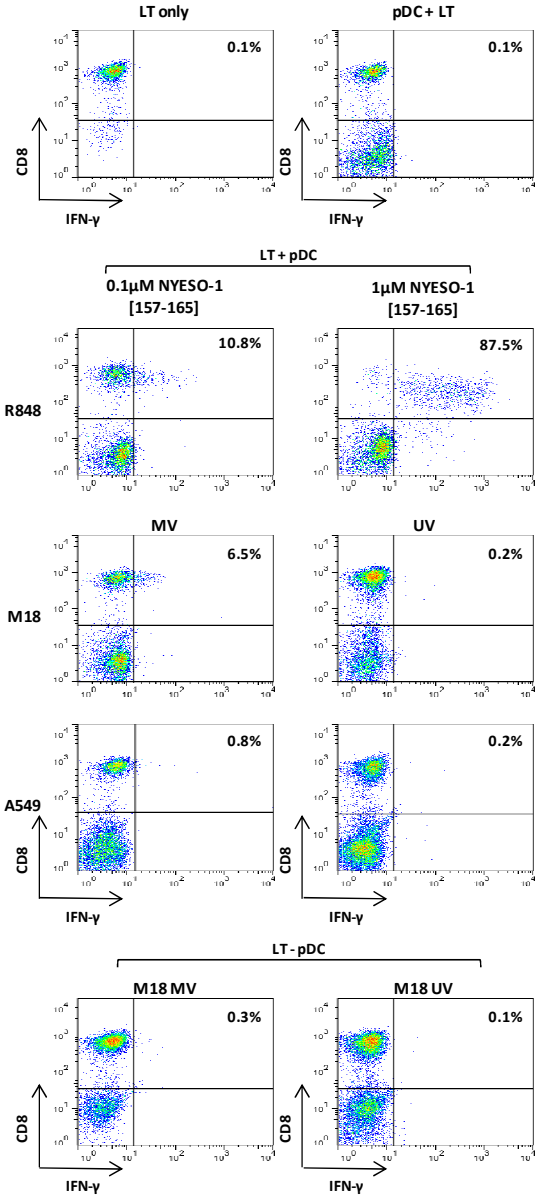
M18 : HLA-A*0201- , NYESO-1+

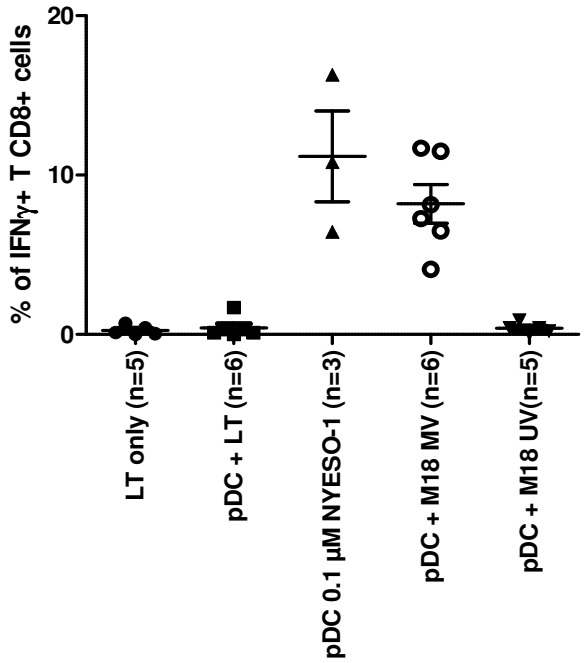
A549 : HLA-A*0201- , NYESO-1-

pDC : HLA-A*0201+ , NYESO-1-

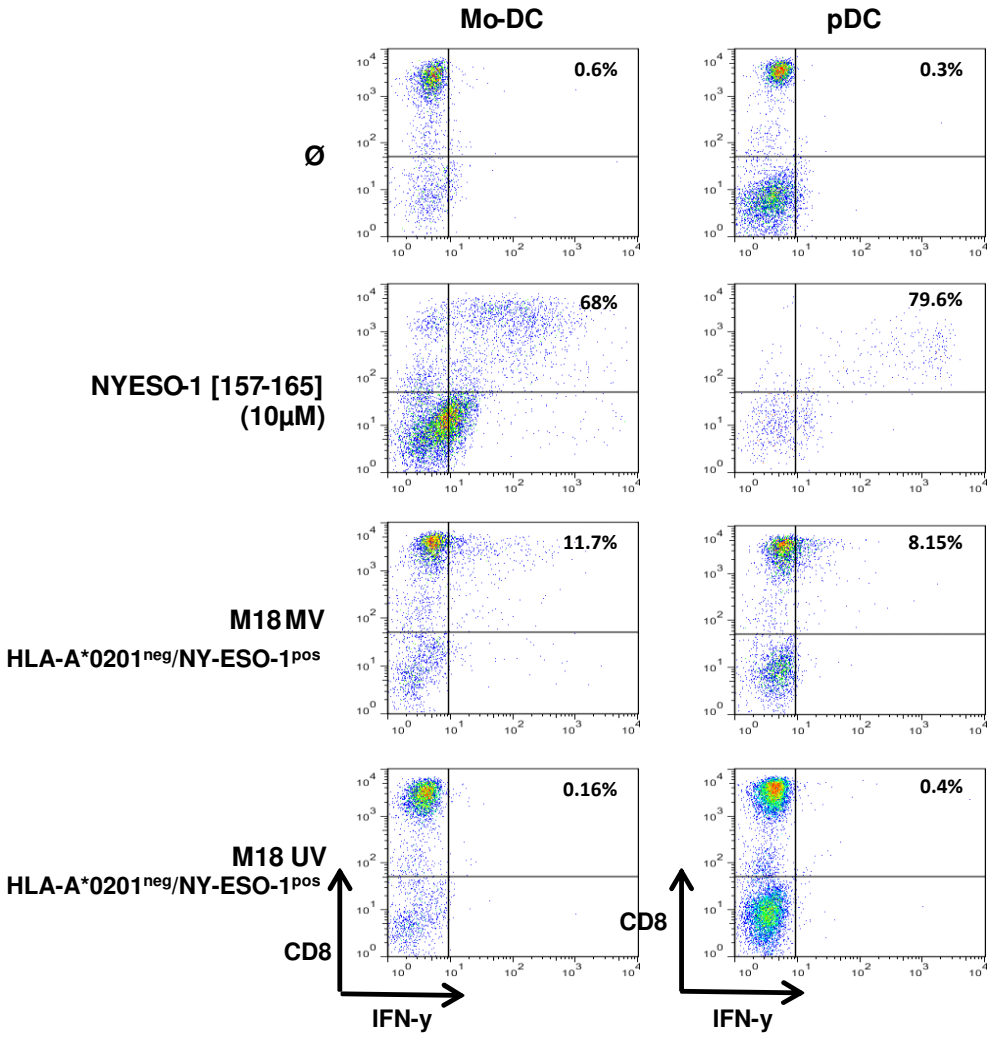
M117.167 : HLA-A*0201/NYESO-1(157-165) specific CD8+ T cell clone

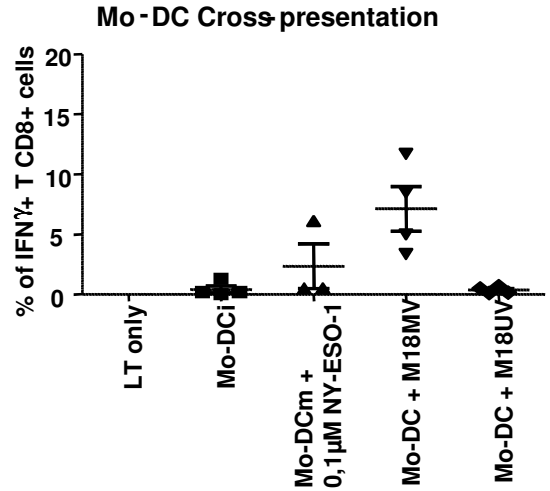
NYESO-1 cross-presentation by pDC exposed to MV infected tumor cells

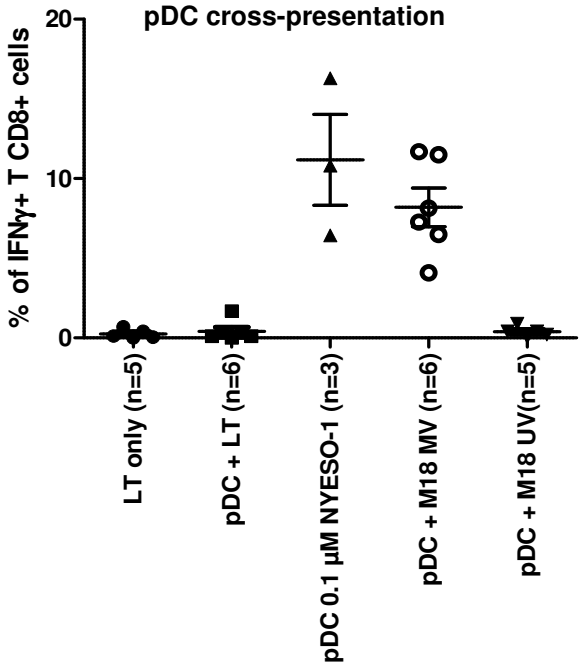




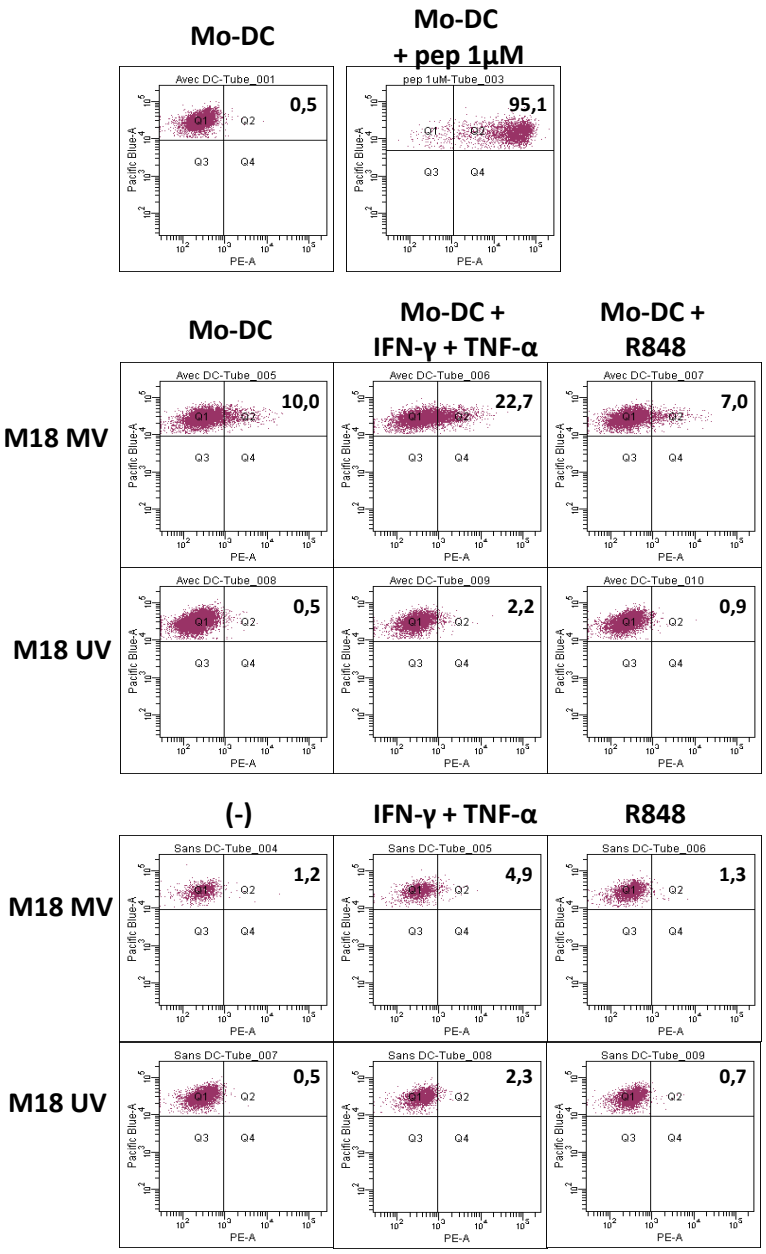
NYESO-1 cross-presentation by pDC and Mo-DC exposed to MV infected tumor cells

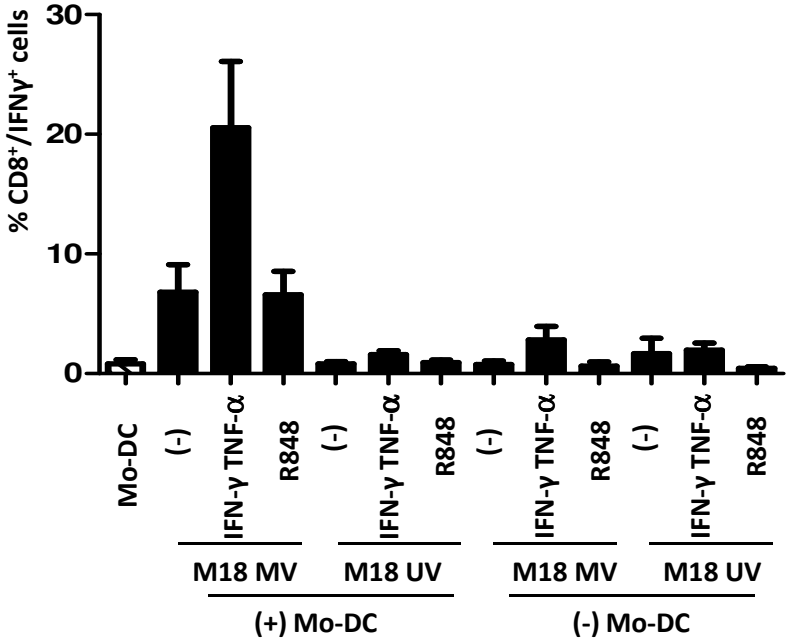






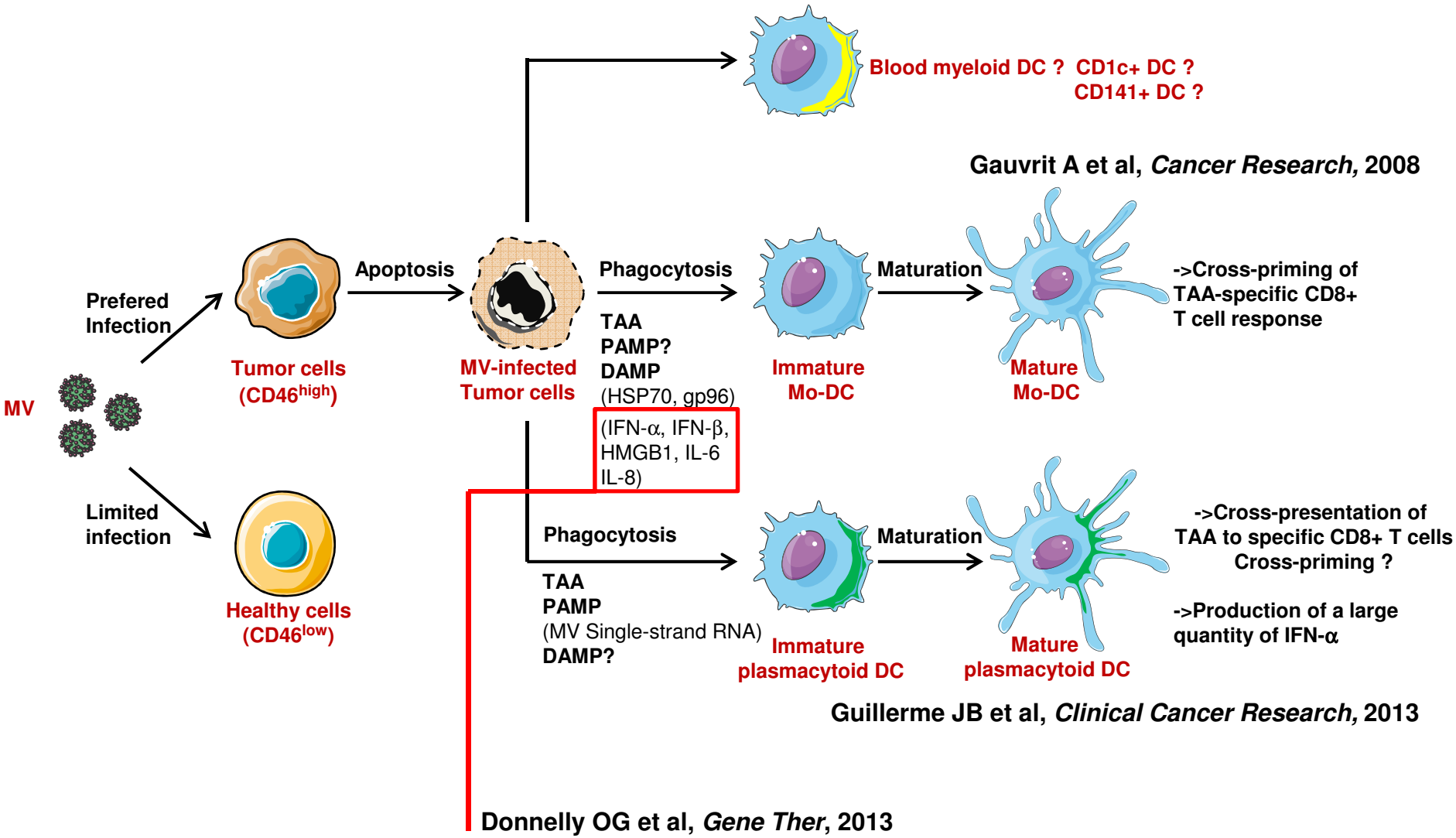
NYESO-1 cross-presentation by Mo-DC is increased by TNF-α/IFN-γ





Deauvieau F et al, *Int J Cancer,* 2014

Conclusions



Collaborations

Plateforme de dévelopement et de transfert à la clinique (CHU Nantes) :
Delphine Coulais, ingénieur
Clarisse Panterne, ingénieur

Service de pneumologie du CHU de Nantes
Laurent Cellerin,
Christine Sagan
Antoine Magnan

Service de pneumologie du CHU de Lille
Arnaud Scherpereel

Institut Pasteur, Viral genomics and Vaccination laboratory
Frédéric Tangy
Mariana Mesel-Lemoine

Centre de Recherche en cancérologie de Lyon
Jenny Valladeau
Christophe Caux

Team (Inserm U892,Nantes)

Marc Grégoire, INSERM
Christophe Blanquart, CNRS
Daniel Pouliquen, INSERM
Jean-François Fonteneau, INSERM
Nicolas Boisgerault
Jean-Baptiste Guillerme
Carole Achard,
~~Ferdaous Allagui~~
Iza Denis
Clarisse Panterne
Sophie Deshayes

Funding

FONDATION RECHERCHE MÉDICALE
CONTRE LE CANCER LA LIGUE
Association pour la Recherche sur le Cancer
le souffle c'est la vie — Fondation du Souffle contre les maladies respiratoires — www.lesouffle.org
SPLF — SOCIÉTÉ DE PNEUMOLOGIE DE LANGUE FRANÇAISE