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Control of oncolytic rodent protoparvoviruses over the innate immunity machinery: impact on their use in cancer immunotherapy

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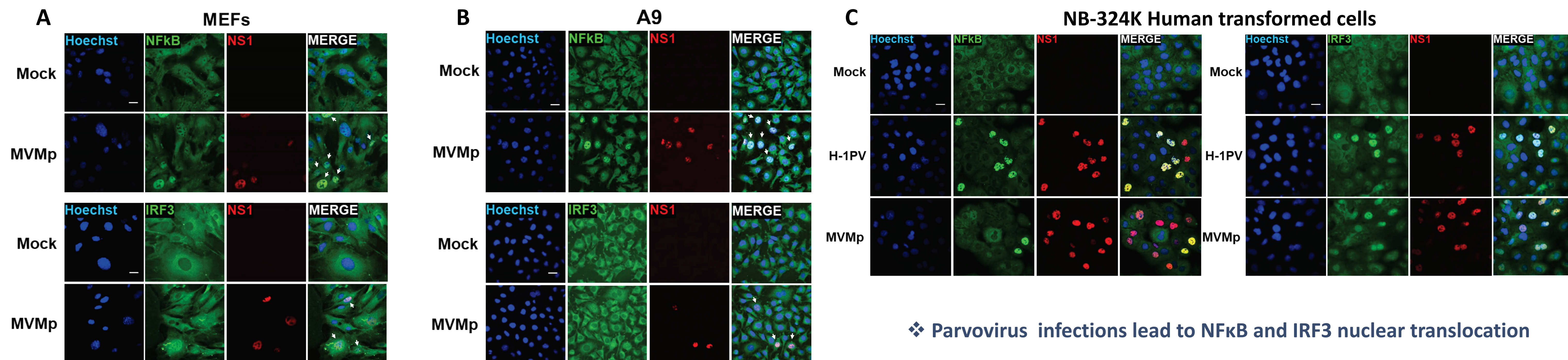
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Abstract

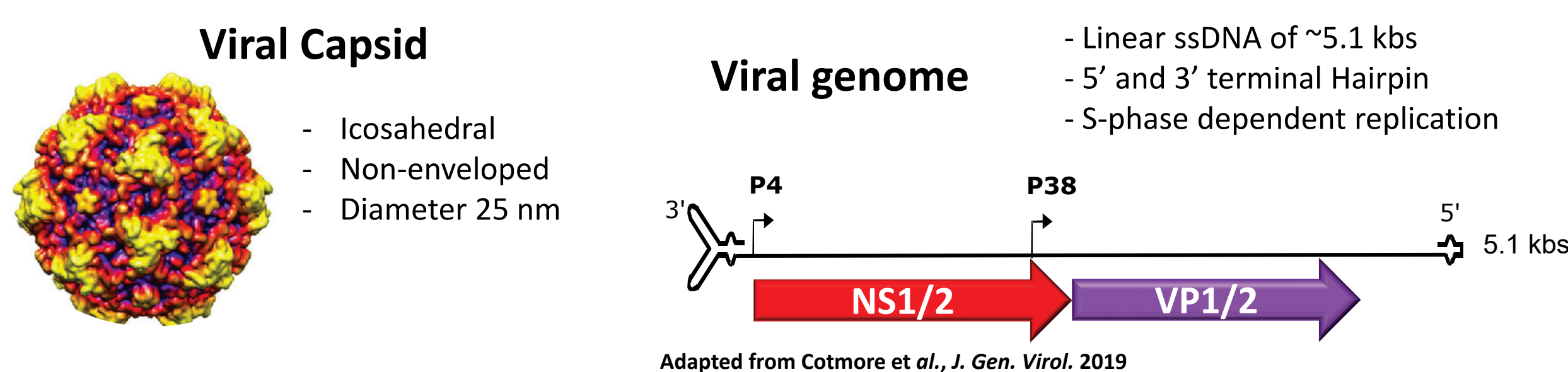
The oncolytic rodent protoparvoviruses (PV) MVMp and H-1PV are under investigation for their immunotherapeutic potential. The presence of interferon- β (IFN- β), a type-I IFN cytokine, and the activation of IFN- β signaling pathways in the tumor microenvironment are considered instrumental for favorable long-term outcomes of several types of cancer treatments. PV-induced IFN- β production was shown to be significant, yet weak in infected normal cells, including immune cells and fibroblasts, but could not be detected in infected neoplastic cells even though these cells were intrinsically competent in this process. The evasion of PV-infected tumor cells from IFN- β production may limit the immunostimulatory and oncosuppressive potential of these viruses. This prompted us to further characterize the molecular mechanisms underlying the PV modulation of IFN- β expression in infected cells. PV induction of IFN- β was found among others (i) to be independent of various known pattern recognition receptor pathways, (ii) to be initiated (NF κ B and IRF3 nuclear translocation) in both normal and tumor cells concomitantly with the nuclear accumulation of PV-encoded dsRNA molecules, but (iii) to go to completion (IFN- β production and release) only in normal cells while IFN- β mRNA transcription was blocked in transformed cells. This intriguing PV suppression of a late step in IFN- β induction in infected tumor cells leads us to speculate as to whether this inhibition may be prevented through viral genome manipulation in order to restore the PV-initiated production of immunogenic IFN- β , and/or be taken advantage of in treatments combining PV with other IFN- β -sensitive oncolytic agents.

Result 1 : MVMp & H-1PV infections engage an antiviral response by both normal and transformed cells

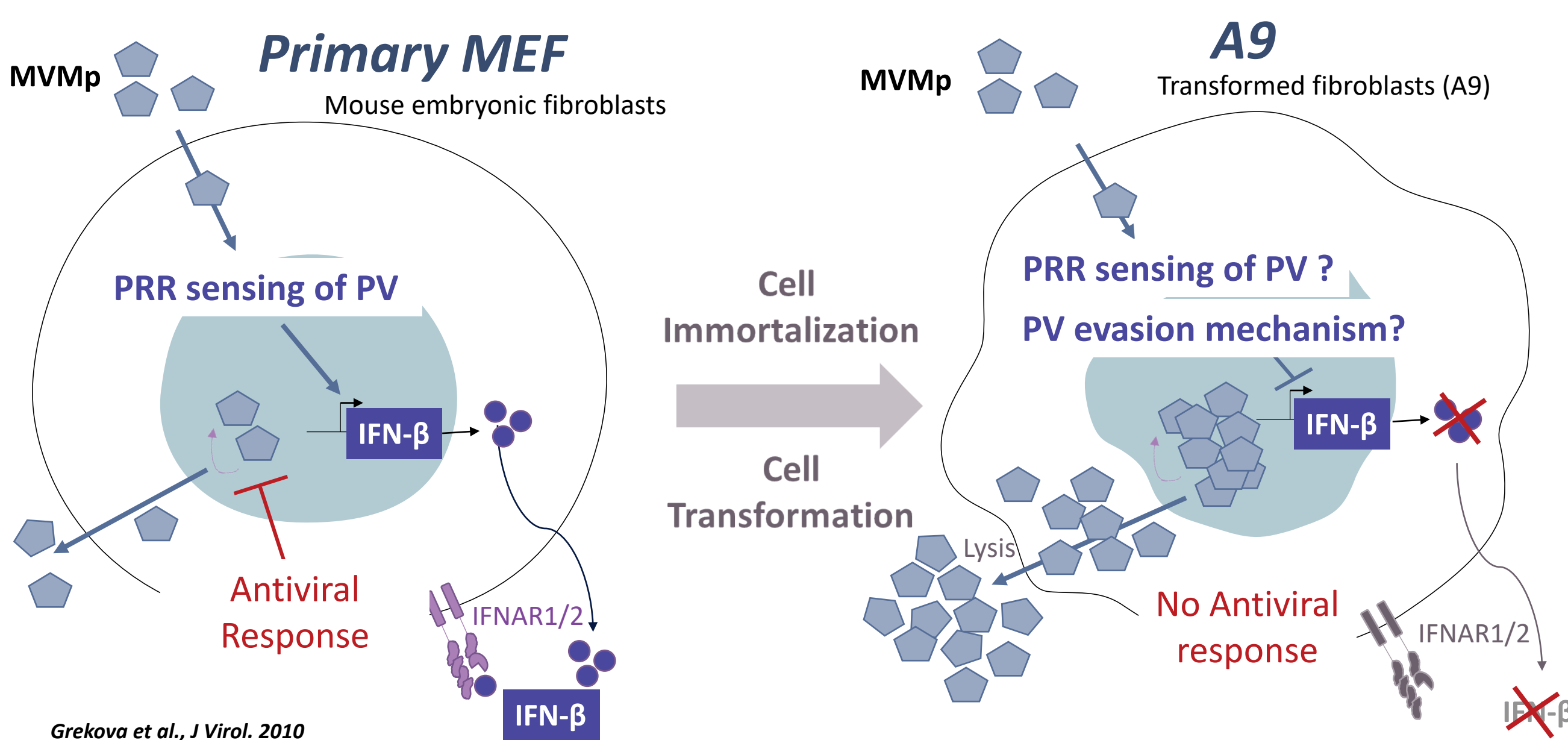


Introduction

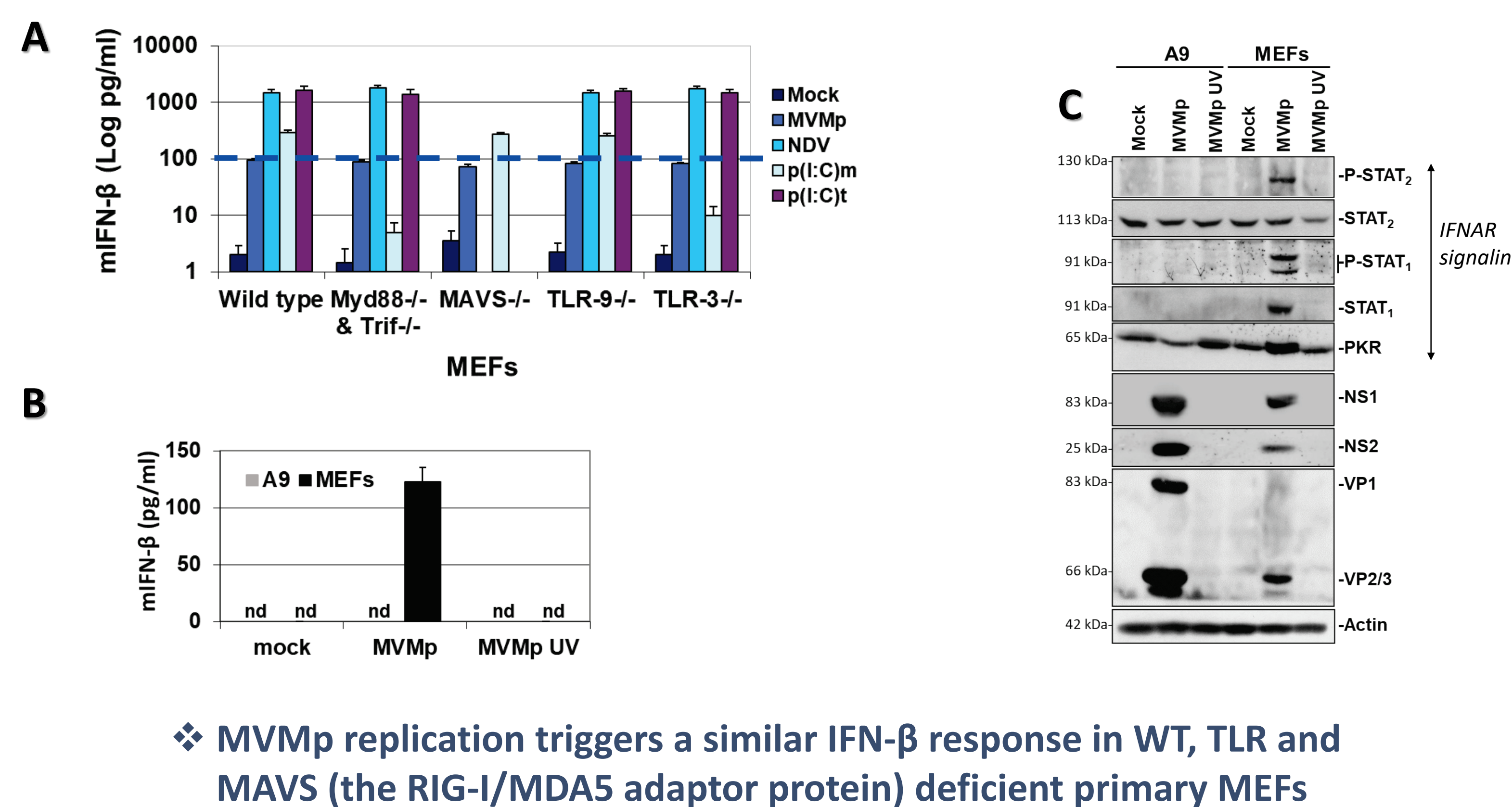
Rodent Protoparvoviruses (PV) MVMp (mouse) & H-1PV (rat)



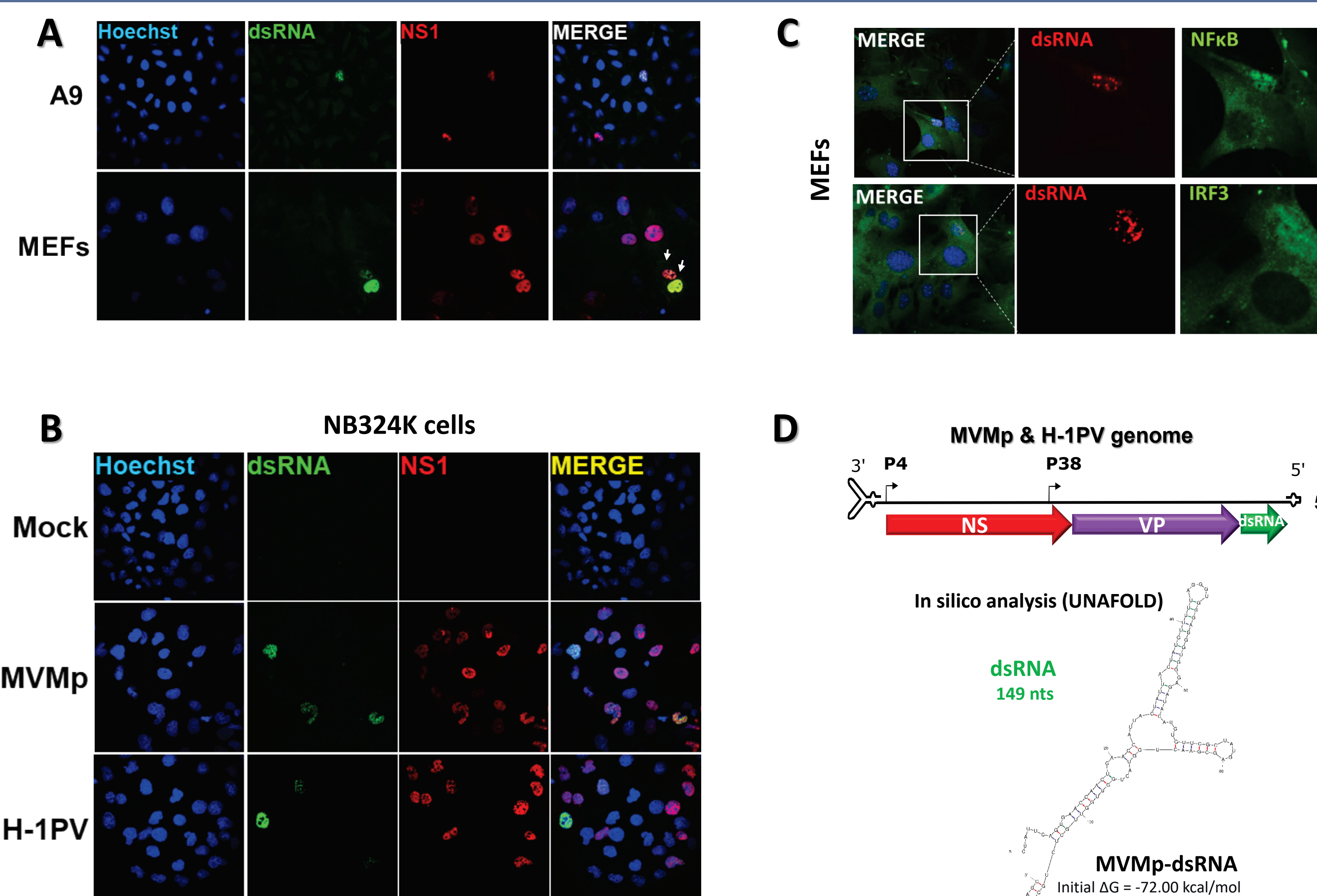
PV life cycle in normal and transformed fibroblasts



Result 2 : The immune response is TLR & RLR independent (A) but requires PV replication (B,C)

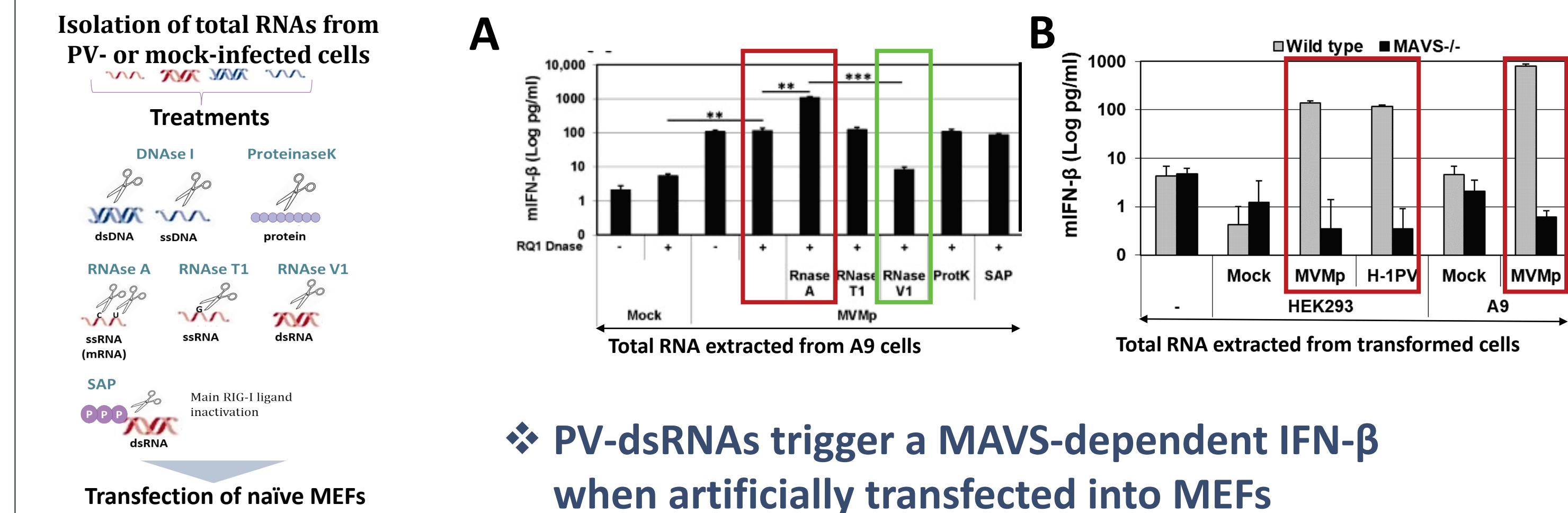


Result 3 : PV infections lead to the concomitant nuclear accumulation of PV-dsRNAs, IRF3 and NFkB

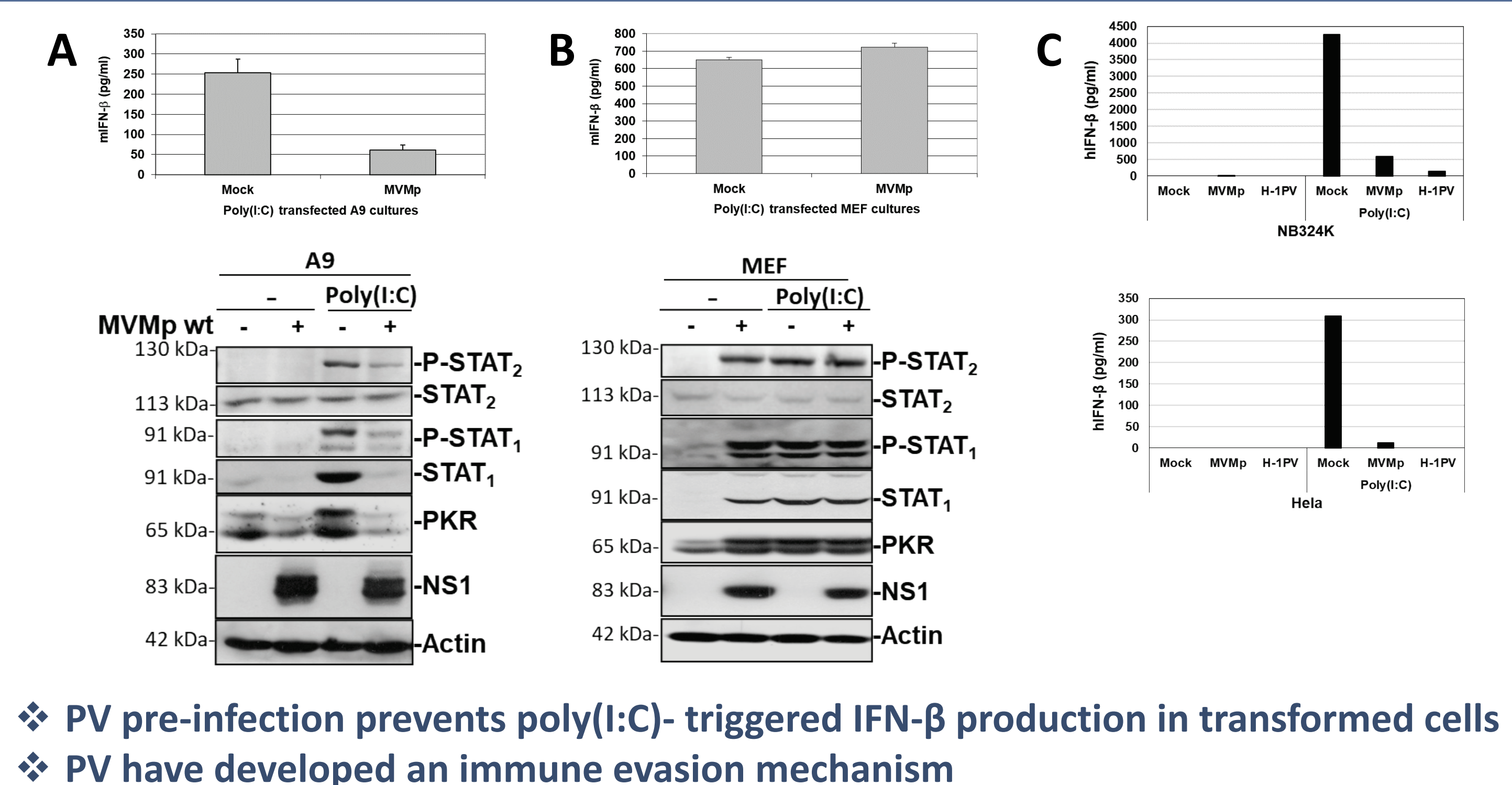


❖ PV replication produces nuclear viral dsRNA molecules (PV-dsRNAs)

Result 4 : PV-dsRNAs behave as PAMPs for RLR, in artificial conditions



Result 5 : IFN-β production is prevented in transformed cells upon PV infections

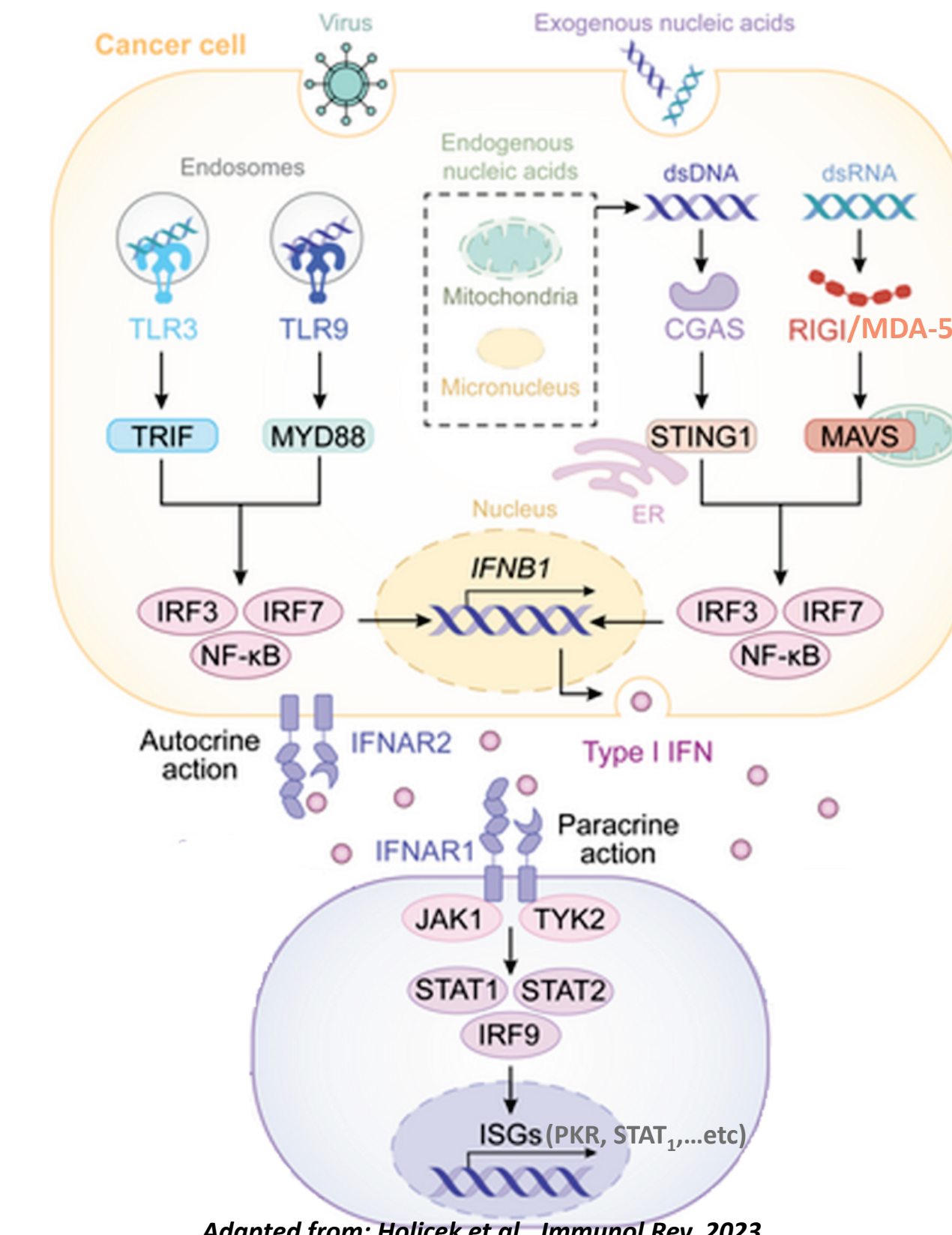


Conclusions & Perspectives

- PV infections engage an antiviral immune pathway in all permissive cells
- PV replication allows accumulation of nuclear dsRNA molecules encoded by their genome in all permissive cells
- PV prevent the fulfillment of type-I IFN production most efficiently in transformed cells by triggering a potential nuclear evasion mechanism
- Is the dsRNA behaving as a PAMP during natural PV infections?
- Beside being RLR ligands, are PV-dsRNAs also TLR3 activators?
- Which PRR senses PV infections (cGAS-Sting)/PV-dsRNAs?
- In which cellular compartment does the PAMP-PRR interaction occur?
- Which PV factor triggers the evasion mechanism?

Could this PV-triggered evasion mechanism be used in treatments combining PV with other IFN- β -sensitive oncolytic agents?

Antiviral Innate Immune signaling pathways



Questions

- 1) Why is IFN- β not produced in PV-infected transformed cells?
- 2) Is an antiviral pathway at all engaged in PV-infected transformed cells?
- 3) Do PV block most efficiently innate immune pathways in transformed cells (evasion mechanism)?
- 4) Which PRR senses PV infections?
- 5) Which viral factor behaves as a PAMP?