**Pintel, 2002**

A **mutation that disrupts the interaction between the NS2 protein of minute virus of mice and the nuclear export factor Crm1** results in a **block to egress of mutant-generated full virions** from the nucleus of infected murine cells. These mutants produce wild-type levels of monomer and dimer replicative DNA forms but are impaired in their ability to generate progeny single-stranded DNA in restrictive murine cells in the first round of infection. The NS2-Crm1 interaction mutant can be distinguished phenotypically from an NS2-null mutant and reveals a **role for the Crm1-mediated export pathway at a late step in viral infection**.

**Almendral 2004**

It is uncertain whether nonenveloped karyophilic virus particles may actively traffic from the nucleus

outward. The unordered amino-terminal domain of the VP2 major structural protein (2Nt) of the icosahedral parvovirus minute virus of mice (MVM) is internal in empty capsids, but it is exposed outside of the shell through the fivefold axis of symmetry in virions with an encapsidated single-stranded DNA genome, as well as in empty capsids subjected to a heat-induced structural transition. In productive infections of transformed and normal fibroblasts, mature MVM virions were found to efficiently exit from the nucleus prior to cell lysis, in contrast to the extended nuclear accumulation of empty capsids. Newly formed mutant viruses **lacking the three phosphorylated serine residues of 2Nt were hampered in their exit from the human transformed NB324K nucleus**, in correspondence with the capacity of 2Nt to drive microinjected phosphorylated heated capsids out of the nucleus. However, in normal mouse A9 fibroblasts, in which the MVM capsid was phosphorylated at similar sites but with a much lower rate, the nuclear exit of virions and microinjected capsids harbouring exposed 2Nt required the infection process and was **highly sensitive to inhibition of the exportin CRM1** in the absence of a demonstrable interaction. Thus, the MVM virion exits the nucleus by accessing **nonconventional export pathways relying on cell physiology** that can be intensified by infection but in which the exposure of 2Nt remains essential for transport. The flexible 2Nt nuclear transport signal may illustrate a common structural solution used by nonenveloped spherical viruses to propagate in undamaged host tissues.

**Nüesch 2008**

The autonomous parvovirus Minute Virus of Mice (MVM) **induces specific changes in the cytoskeleton filaments of infected permissive cells**, causing in particular the degradation of actin fibers and the generation of ‘‘actin patches.’’ This is attributed to a **virus-induced imbalance between the polymerization factor N-WASP (Wiscott-Aldrich syndrome protein) and gelsolin**, a multifunctional protein cleaving actin filaments. Here, the focus is on the involvement of gelsolin in parvovirus propagation and virus-induced actin processing. Gelsolin activity was knocked-down, and consequences thereof were determined for virus replication and egress and for actin network integrity. Though not required for virus replication or progeny particle assembly, **gelsolin was found to control MVM (and related H1-PV) transport from the nucleus to the cell periphery and release into the culture medium**. Gelsolin-dependent actin degradation and progeny virus release were both **controlled by (NS1)/CKIIa,** a recently identified complex between a cellular protein kinase and a MVM non-structural protein. Furthermore , the export of newly synthesized virions through the cytoplasm appeared to be mediated by (virus-modified) lysomal/late endosomal vesicles. By showing that MVM release, like entry, is guided by the cytoskeleton and mediated by vesicles, these results challenge the current view that egress of non-enveloped lytic viruses is a passive process.

**Salomé Almendral 2008**

Regular NESs must have low affinity for CRM1 to function optimally. We previously generated artificial NESs with higher affinities for CRM1, termed supraphysiological NESs. **Here we identify a supraphysiological NES in an endogenous protein, the NS2 protein of parvovirus Minute Virus of Mice (MVM).** NS2 interacts with CRM1 without the requirement of RanGTP, whereas addition of RanGTP renders the complex highly stable. Mutation of a single hydrophobic residue that inactivates regular NESs lowers the affinity of the NS2 NES for CRM1 from supraphysiological to regular. Mutant MVM harboring this regular NES is **compromised in viral nuclear export and productivity**. In virus-infected mouse fibroblasts we observe colocalization of NS2, CRM1 and mature virions, which is dependent on the supraphysiological NS2 NES. **We conclude that supraphysiological NESs exist in nature and that the supraphysiological NS2 NES has a critical role in active nuclear export of mature MVM particles before cell lysis.**

**Salomé 2012**

An in-frame, 114-nucleotide-long deletion that affects the NS-coding sequence was created in the infectious molecular clone of the standard parvovirus H-1PV, thereby generating Del H-1PV. The plasmid was transfected and further propagated in permissive human cell lines in order to analyze the effects of the deletion on virus fitness. Our results show key benefits of this deletion, as Del H-1PV proved to exhibit (i) **higher infectivity (lower particle-to-infectivity ratio) *in vitro* and (ii) enhanced tumor growth suppression *in vivo* compared to wild-type H-1PV. This increased infectivity correlated with an accelerated egress of Del H-1PV progeny virions in producer cells and with an overall stimulation of the viral life cycle in subsequently infected cells.** Indeed, virus adsorption and internalization were significantly improved with Del H-1PV, which may account for the earlier appearance of viral DNA replicative forms that was observed with Del H-1PV than wild-type H-1PV. We hypothesize that the internal deletion within the NS2 and/or NS1 protein expressed by Del H-1PV results in the stimulation of some step(s) of the viral life cycle, **in particular, a maturation step(s), leading to more efficient nuclear export of infectious viral particles and increased fitness of the virus produced.**

**Nüesch 2013**

Progeny particles of non-enveloped lytic parvoviruses were previously shown to be actively transported to the cell periphery through vesicles in a gelsolin-dependent manner. This process involves rearrangement and destruction of actin filaments, while microtubules become protected throughout the infection. Here the focus is on the intracellular egress pathway, as well as its impact on the properties and release of progeny virions. By colocalization with cellular marker proteins and specific modulation of the pathways through over-expression of variant effector genes transduced by recombinant adeno-associated virus vectors, we show that progeny PV particles become **engulfed into COPII-vesicles in the endoplasmic reticulum (ER)** and are transported **through the Golgi** to the plasma membrane. Besides known factors like **sar1, sec24, rab1, the ERM family proteins, radixin and moesin play (an) essential role(s) in the formation/loading and targeting of virus-containing COPII-vesicles.** These proteins also contribute to the transport through ER and Golgi of the well described analogue of cellular proteins, the secreted Gaussia luciferase in absence of virus infection. It is therefore likely that radixin and moesin also serve for a more general function in cellular exocytosis. Finally, parvovirus egress via ER and Golgi appears to be necessary for virions to gain full infectivity through post-assembly modifications (e.g. phosphorylation). While not being absolutely required for cytolysis and progeny virus release, vesicular transport of parvoviruses through ER and Golgi significantly accelerates these processes pointing to a regulatory role of this transport pathway.